BEHAVIORAL AND BRAIN SCIENCES (2012) **35**, 331–410
doi:10.1017/S0140525X11002226

# Behavior genetics and postgenomics

**Evan Charney**
*Department of Public Policy and Political Science, Duke Institute for Brain Sciences, Duke Institute for Genome Sciences and Policy, Duke University, Durham, NC 90239*
**http://fds.duke.edu/db/Sanford/faculty/echar**

**Abstract:** The science of genetics is undergoing a paradigm shift. Recent discoveries, including the activity of retrotransposons, the extent of copy number variations, somatic and chromosomal mosaicism, and the nature of the epigenome as a regulator of DNA expressivity, are challenging a series of dogmas concerning the nature of the genome and the relationship between genotype and phenotype. According to three widely held dogmas, DNA is the unchanging template of heredity, is identical in all the cells and tissues of the body, and is the sole agent of inheritance. Rather than being an unchanging template, DNA appears subject to a good deal of environmentally induced change. Instead of identical DNA in all the cells of the body, somatic mosaicism appears to be the normal human condition. And DNA can no longer be considered the sole agent of inheritance. We now know that the epigenome, which regulates gene expressivity, can be inherited via the germline. These developments are particularly significant for behavior genetics for at least three reasons: First, epigenetic regulation, DNA variability, and somatic mosaicism appear to be particularly prevalent in the human brain and probably are involved in much of human behavior; second, they have important implications for the validity of heritability and gene association studies, the methodologies that largely define the discipline of behavior genetics; and third, they appear to play a critical role in development during the perinatal period and, in particular, in enabling phenotypic plasticity in offspring. I examine one of the central claims to emerge from the use of heritability studies in the behavioral sciences, the principle of minimal shared maternal effects, in light of the growing awareness that the maternal perinatal environment is a critical venue for the exercise of adaptive phenotypic plasticity. This consideration has important implications for both developmental and evolutionary biology.

**Keywords:** behavior genetics; developmental biology; evolutionary developmental biology; epigenetics; evo-devo; gene association studies; genetics; heritability; maternal effects; phenotypic plasticity; stochasticity; twin studies

## 1. A paradigm shift

It is one of the aims of any scientific discipline to construct models that will account for as many observations as possible within a coherent framework. These models, and the framework of which they are a part, constitute a scientific paradigm. A paradigm commonly includes a set of dogmas, or key assumptions concerning both the nature of certain phenomena and the methodologies employed to study them that are never doubted as long as the paradigm appears to work well. The history of science, as it turns out, is a history of overturned dogmas and supplanted paradigms (Kuhn 1970). The discovery of new phenomena – anomalies – that appear to violate a central dogma or dogmas – perhaps, according to the paradigm, they have been deemed incapable of existing – can constitute a serious challenge to a paradigm. Sometimes, these phenomena can successfully be accounted for by the current paradigm and incorporated into it. But when they cannot, a new paradigm will emerge from new models constructed to better explain the phenomena. This is the process that Thomas Kuhn (1970) famously called a "paradigm shift" or a scientific revolution.

The science of genetics is undergoing a paradigm shift (Dear 2009; Gressler & Haslberger 2010; McClellan & King 2010; Ooi & Wood 2008; Petronis 2010; Sgaramella & Astolfi 2010; Whitelaw & Whitelaw 2006). Consider the following developments:

1. It has been a long-standing dogma in molecular genetics that an individual's genome, his or her entire DNA sequence, is fixed at the moment of conception and, with the exception of the occasional point mutation or mutations associated with, for example, cancer, does not change throughout life. It has become increasingly clear that DNA is dynamic rather than static, being subject to a wide array of rearrangements, insertions, and deletions. During embryogenesis, the genome is altered by such phenomena as retrotransposons, or "jumping genes," which are mobile DNA elements that "copy and paste" themselves at various positions in an individual's DNA sequence; *de novo* copy number variations – deletions, insertions, and duplications in segments of DNA; and aneuploidy, alterations in the number of copies of chromosomes per cell. Some of these phenomena, such as retrotransposition, likely continue throughout the course of life and may be environmentally responsive.

2. These same phenomena challenge another long-standing dogma – that persons have identical DNA in all

EVAN CHARNEY is an associate professor of the practice of public policy and political science at the Sanford School of Public Policy at Duke University, a faculty fellow at the Duke Institute for Brain Sciences, and a faculty researcher at the Duke Institute for Genome Sciences and Policy. He received his Ph.D. in political science from Harvard University in 2000 with a focus in political theory. His research focuses on genetic, biological, and evolutionary explanations of human behavior, ranging from personality to political orientation.

 0140-525X/12 $40.00

the cells and tissues of their bodies (with the exception of germ cells, red blood cells, and certain cells in the immune system). It is appearing more and more likely that the normal human condition is one of somatic and chromosomal mosaicism, that is, different genomes in different cells and tissues of the same individual.

3. Since DNA's discovery in 1953, it has been a key dogma of molecular genetics that DNA is the sole biological agent of heritability, and it is still commonly treated as such. We now know, however, that it is not. The epigenome, that is, the complex biochemical system that regulates DNA expression, turning genes on and off and modulating their "transcribability," has been found to be heritable, both somatically and intergenerationally via the germline, enabling the biological inheritance of traits with no changes to the DNA sequence. Furthermore, the epigenome is highly environmentally responsive. Environmentally induced changes in gene transcribability can have long-term – sometimes lifelong – phenotypic consequences.

4. The idea that environmentally induced phenotypic changes can be inherited transgenerationally violates a central dogma of neo-Darwinism, which insists that this is an impossibility. It bespeaks (to neo-Darwinists) a resurrection of the "Lamarckian heresy" – Lamarck, a predecessor of Darwin, having proposed just such a possibility. It is not uncommon nowadays to encounter in respected scientific journals defenses of "neo-Lamarckianism" – minus Lamarck's quasi-teleological ideas (Gissis & Jablonka 2011; Champagne 2008; Ho & Burggren 2010; Lemke et al. 2004).

What are the implications of these recent paradigm-shifting developments in genetics for behavior genetics? This article is an attempt to answer this question. As we shall see, the cumulative evidence of recent discoveries in genetics and epigenetics calls into question the validity of two classes of methodologies that are central to the discipline: twin, family, and adoption studies, which are used to derive heritability estimates, and gene association studies, which include both genome-wide and candidate-gene association studies. In fact, what the cumulative evidence calls into question is a paradigm of the relationship between genotype and phenotype. Let us call this the genetic paradigm. Some of the elements of this paradigm have already been mentioned, and others will be considered below.

Contrasting with the genetic paradigm is what I shall call the postgenomic view. I do not call it a paradigm because it has not yet coalesced around a core set of principles or assumptions characteristic of a paradigm. Despite its nascent state, it is nonetheless capable of being characterized largely on the basis of the developments in genetics and epigenetics that I examine in this article. In the most general terms, the biological worldview of postgenomics is characterized by extreme complexity, variability, multilevel reciprocal interactionism, and stochasticity as an inherent property of biological systems, which all contribute to what might be called the blurring of boundaries, in particular, the boundary between genes and environment.

While the developments to be considered have implications for all of genetics, they are particularly significant for behavior genetics for at least three reasons: First, phenomena that are transforming our conception of the genome – epigenetics, retrotransposons, copy number variations, chromosomal aneuploidy – seem to be particularly prevalent in the human brain and are likely relevant for a good deal of human behavior. Epigenetics, for example, represents a new frontier in the study of mammalian behavior. Second, heritability and gene association studies are the two methodologies in genetics that are most dependent upon the genetic paradigm. Because these methodologies in large measure define the discipline of behavior genetics, the impact of these developments upon this discipline is likely to be most profound. Third, these developments have important implications for one of the most influential generalizations in behavior genetics concerning human behavior to emerge from the use of heritability studies. This can be referred to as the principle of minimal shared maternal effects, according to which the early (primarily maternal) rearing environment, prenatal and postnatal, is not a cause of phenotypic concordance among offspring but, if anything, a cause of phenotypic *discordance*.

As it turns out, the phenomena we shall consider have a significant bearing upon the validity of this principle, and for reasons independent of the soundness of the methodology used to derive it. This is because these same phenomena appear to play a number of critical roles in embryogenesis, fetal development, and the early postnatal period. One of these roles is in enabling what is termed "adaptive phenotypic plasticity." As we shall see, the principle of adaptive phenotypic plasticity is fundamentally at odds with the principle of minimal shared maternal effects, with implications not only for the sources of behavioral variation but for developmental and evolutionary biology as well.

Finally, although my focus is on behavior genetics throughout, the phenomena I shall consider have profound implications for all of genetics and for the ongoing search for the role of genes in any number of human diseases. Heritability and gene association studies have been employed, and continue to be employed, in the search for the causes of cancer, heart disease, and diabetes, among other phenotypes.

## 2. Genes, heritability, and gene association studies: A few basics

### 2.1. Genes and alleles

Genes are segments of DNA coded for the production of RNA molecules and proteins. Transcription is the process in which the DNA molecule is used (by a cell) as a template to produce messenger RNA (mRNA), which in turn serves as a template for protein synthesis (translation). Persons possess two copies of each gene in the cells of their bodies (except for sperm and egg cells, red blood cells, and genes located on the X and Y chromosomes in males), one copy of which comes from the mother and one from the father. Each of the copies of a gene is called an *allele* of the gene. Alleles of a gene from the two parents may be identical, or they may differ slightly, sometimes differing by only a single nucleotide substitution (nucleotides are the basic subunits that make up the DNA molecule). These minor structural differences between alleles can be found in many different configurations or versions. When two or more versions of an allele for a single gene occur in greater than 1% of a given population, it is referred to as a *polymorphism*. A version of an allele that occurs in less than 1% of the population is called a *mutation*. When both of the alleles for a given gene are identical, then one is *homozygous* for that gene; when the alleles differ, one is *heterozygous*.

Individual alleles are inherited in a *Mendelian* manner, which can be best illustrated by considering the inheritance of single-gene or monogenic disorders (e.g., cystic fibrosis, sickle cell anemia), a discrete class of disorders caused by mutations on one or both alleles of the same gene. If the disorder is dominant, then only one mutated allele is necessary to present the disease phenotype; if the disorder is recessive, then both alleles must have mutations. When a monogenic disorder is completely penetrant (i.e., those who present the mutated allele[s] always have the disease phenotype) and the gene mutation known, then based upon the genotype of the parents and whether or not the disorder is dominant or recessive, the odds that the child will inherit the disorder (the risk factor) can be calculated precisely according to the simple rules of Mendelian inheritance. Because the vast majority of human traits are not caused by variations on one or two alleles, they are not inherited in a Mendelian manner.

### 2.2. Heritability studies

Heritability is defined as the proportion of phenotypic variance attributable to genotypic variance in a given population at a given time. According to the prevailing methodological approach, the heritability of a given trait is ascertained by comparing phenotypic concordances and discordances between subjects relative to their presumed degree of genetic similarity. For example, monozygotic (MZ) twins, inasmuch as they are derived from the division of a single fertilized egg cell, are assumed to share 100% of their segregating genes (genes shared by descent) – that is, they are genetically identical. Dizygotic (DZ) twins, on the other hand, are derived from two separate fertilized egg cells and share on average 50% of their segregating genes, the same percentage as non-twin siblings. Assuming that the environments of MZ and DZ twins do not differ in any systematic ways that would affect the trait under consideration – the so-called trait-specific equal environment assumption (Guo 2001) – greater phenotypic concordance between MZ twins as opposed to DZ twins is taken as evidence of a genetic component. The same principles underlie family and adoption studies: Siblings (or singletons) share on average 50% of their segregating genes; half siblings share 25%; and adopted siblings do not share any segregating genes with their (non-adopted) siblings.

One of the simplest and most widely used modeling techniques for estimating heritability partitions total phenotypic variation for a trait ($V_P$) into a contribution attributable to genotypic variation ($V_G$) and a contribution attributable to environmental variation ($V_E$): $V_P = V_G + V_E$. This model assumes additive genetic variance (A) – that is, independent genetic effects are fully transmitted from parent to offspring, and each allele adds a fixed amount to the genetic component of a given trait. As many researchers in behavior genetics acknowledge, the genetic contributors to variation in behavioral phenotypes likely do not act in this simple manner (Plomin 2004), and additional terms can be added for non-additive genetic effects including interactions among alleles at a single locus (dominance-recessiveness), interactions among alleles at a different locus (epistasis), and interactions between alleles and the environment (gene by environment [G × E] interaction).

### 2.3. Gene association studies

Gene association studies typically involve the search for statistically significant differences in the prevalence of a polymorphism between individuals who possess a trait of interest and those without the trait. In a candidate-gene association study, an association is proposed between a particular allelic variant and a given phenotype. Suppose that gene A comes in two common forms (polymorphisms), allele $A_1$ and allele $A_2$. A claim for an association in a candidate-gene association study generally takes the following form: Those with allele $A_1$ are more likely to display behavior X than those with allele $A_2$ (or vice versa); or, those homozygous for gene A (alleles $A_1A_1$ or $A_2A_2$) are more likely to display behavior X than those who are heterozygous (alleles $A_1A_2$),[1] or vice versa. Candidate-gene association studies are hypothesis driven, the hypothesis depending upon an assumption concerning the manner in which the protein for which the candidate gene is encoded affects behavior. The hypothesis is commonly tested in behavior genetics by the use of large data sets that contain both a certain amount of genetic data as well as behavioral data (usually in the form of subject responses to a questionnaire). Genome-wide association studies are non-hypothesis driven and involve sequencing all or most of the entire genome, typically of hundreds or thousands of individuals who possess a given phenotype. The researcher looks for any single nucleotide polymorphisms that those who exhibit the trait of interest possess in statistically significant numbers relative to those without the trait. Recently, the use of genome-wide studies has expanded to include a variety of other common (and uncommon) forms of DNA variation, including many of those we consider below.

## 3. Six basic assumptions

Heritability and gene association studies depend upon the following set of assumptions (among others) that I would like to highlight. These assumptions can be broken into two groups on the basis of their relevance for either heritability or association studies.

Heritability studies (HS):

1. HS1. 100% of the genes of MZ twins are genetically identical. On average, 50% of the genes of DZ twins are genetically identical. On average, 50% of the genes of non-twin siblings are genetically identical.

2. HS2. The percentages of genetic identity in H1 *never change* (i.e., they are unvarying). That is, MZ twins, from conception to death, are always 100% genetically identical; DZ twins are always ~50% genetically identical; and non-twin siblings are always ~50% genetically identical (heritability, however, can change over the life course).

3. HS3. All causes of phenotypic variation that impact human behavior can be attributed to a latent genetic (G) or environmental (E) parameter, or the interaction of the two (G × E).

HS1 sets out the relations of genetic identity upon which heritability estimates depend. HS2 ensures that these relations of genetic identity remain constant over the life course. HS3 ensures that the categories used to explain the causes of phenotypic variation are sufficient and complete.

Gene association studies (GAS):

1. GAS1. Persons have identical DNA in all of the cells and tissues of their bodies (with the exception of germ cells, red blood cells, and certain cells in the immune system).
2. GAS2. The presence of a particular genotype (polymorphism or mutation) entails that it is turned on, that is, it is capable of being transcribed in a manner associated with that polymorphism or mutation. Hence, the same two polymorphisms in any given two individuals will have the same capacity to be transcribed in the same manner (precisely what this entails will be considered below, but it empathically does not mean that any two polymorphisms in any two individuals are always being transcribed to the same extent).
3. GAS3. Specific genes are coded for the production of specific proteins.

GAS1 ensures that any tissue that is genotyped (e.g., buccal cells) yields a genome that is present in all other cells and tissues of the body (e.g., neurons). GAS2 ensures that genes that are associated with phenotypes are in fact capable of being transcribed. GAS3 ensures that genes that are associated with phenotypes are in fact associated with whatever intermediate protein is associated with the phenotype. (GAS3 is likely more relevant for candidate gene than for genome-wide association studies [GWAS], inasmuch as the former are hypothesis driven and the latter are not. That is, the hypothesis in candidate-gene association studies depends upon an assumption concerning the manner in which the protein for which the candidate gene is encoded affects behavior).

As we shall see, recent developments in molecular genetics call into question the validity of every one of these assumptions.

## 4. The genome

Because the distinction between germline and somatic inheritance will be important for much that follows, it might be useful to clarify this distinction. Germline inheritance refers to the process whereby genetic information is transmitted to offspring through sexual reproduction via germ cells or gametes (egg and sperm). By contrast, somatic inheritance occurs postconception when changes to DNA in somatic (i.e., non-gametic) cells are transmitted to daughter cells through the process of mitotic cellular division. An example of somatic inheritance is the reproduction of specialized cell types during embryogenesis and throughout the life course; for example, kidney cells produce only kidney cells, and any given kidney cell inherits the (epi)genetic markings of its progenitor. Another example would be an error in DNA replication during embryogenesis that gives rise to a mutation in stem cells destined to become kidney cells, with the result that only kidney cells contain this mutation. Inasmuch as somatic mutations do not affect the germline, they cannot be inherited from parents and cannot be transmitted to offspring. Although germline and somatic inheritance are treated as two distinct modes of inheritance, the distinction between the two is not hard and fast, and they are not always easy to differentiate (Notini et al. 2008). Heritability studies in behavior genetics are intended to measure solely germline inheritance – that is, the behavioral effects of the genes one inherits from one's parents and can transmit to one's offspring. Finally, *de novo* mutations refer to mutations that appear for the first time in the DNA of a particular cell, often as a result of an error or errors in replication. Such mutations can arise in germ cells as well as postconception in the somatic cells of the embryo.

### 4.1. Transposable elements

One striking finding to emerge from the completion of the human genome sequencing project is that an astonishing ~48% of the genome is composed of transposable elements, repetitive mobile DNA sequences – "jumping genes" – dispersed throughout the genome (Gibbs 2003). Although there are many different kinds of transposable elements, they are divided into two classes according to their movement strategies. Class I elements are made up of DNA transposons, composing 3% of the human genome, which move as segments of DNA by a cut-and-paste mechanism, "cutting" themselves out of their current genomic location and "pasting" themselves into a new location (Craig et al. 2002). Class II elements are retrotransposons, which compose ~45% of the genome and move by a replicative copy-and-paste mechanism: They copy themselves to RNA, and the original DNA copy is maintained at the same location. The RNA copy is then reverse-transcribed into DNA – that is, RNA→DNA (the standard direction of transcription in the synthesis of proteins being DNA→RNA→protein[2]), and the DNA is inserted into the genome at a new location. Hence, these elements expand in number as they retrotranspose, leading to an increase in genomic DNA content and a change in DNA sequence and structure at the region of insertion (Goodier & Kazazian 2008).

Conventional wisdom holds that transposable elements are "selfish" DNA parasites living within the genomes of organisms in a manner analogous to viruses (Dawkins 2006; Orgel & Crick 1980). And indeed, the activity of transposable elements can disrupt gene transcription and cause a variety of pathogenic conditions (more than 70 known diseases involve heritable and *de novo* retrotransposition events (Cordaux & Batzer 2009). Over time, mutations and truncations of transposable elements have rendered many of them inactive. Class I elements – transposons – are, for the most part, inert fossil remains of ancient elements in human DNA (Lander 2001). And many Class II elements – retrotransposons – have been rendered incapable of retrotransposition; that is, they are *transpositionally incompetent*, which means they can no longer move about the genome, copying and inserting themselves (Gilbert et al. 2005), while those that remain *transpositionally competent* are often associated with pathogenesis and normally immobilized by epigenetic gene-silencing mechanisms (Callinan & Batzer 2006). The one-sided view of retrotransposons as wholly destructive DNA parasites or as "junk DNA," however, is giving way to a much more complex picture.

Recent evidence indicates that three types of retrotransposons retain the capacity to retrotranspose (Ostertag & Kazazian 2001; Ostertag et al. 2003; Rowold & Herrera 2000). A base pair is a pair of conjoined DNA bases (the steps of the DNA spiral staircase, i.e., double-helix) and is used as a unit of DNA measurement. A long interspersed nucleotide element (LINE-1 or L1), is a transposition-competent retrotransposon greater than or equal to 7,000 base

pairs in length (= 7 kilobases). L1 is the most widespread class of transposable elements in mammals, constituting ~20% of mammalian genomic DNA. While most L1 sequences are transpositionally incompetent, ~100–150 retrotransposons in the human genome retain the capacity to retrotranspose and of these, 10% are classified as highly active or hot (Brouha 2003). Alu elements are members of the class of short (100–300 base pairs) interspersed nucleotide elements (SINEs). Alu elements are a class of *primate-specific*[3] retrotransposons constituting the most prevalent repetitive element in the human genome (more than one million in number) and accounting for ~11% of genomic DNA. The human genome contains on average 2,000–3,000 transposition competent Alu elements (unlike L1s, which can autonomously retrotranspose, Alu elements require certain functional products of L1s to retrotranspose). SVA elements are hybrid transposable elements, ranging from 700 to 4,000 base pairs and combining features of both short and long interspersed nucleotide elements (though like Alu elements, they are non-autonomous). Approximately 3,000 active SVA elements have been identified in the human genome, and they are believed to be the youngest primate specific family of retrotransposons (Hancks & Kazazian 2010; Wang et al. 2005).

Consider first transpositionally incompetent L-1s, Alu elements, and SVAs. That a retrotransposon is transpositionally incompetent does not mean that is has no effect upon gene transcription. Diverse DNA regions are involved in the process of gene transcription, including promoter and regulatory regions, exons and introns, stop and start sites, as well as histone proteins, and transpositionally incompetent transposable elements can affect each of these:

1. A promoter is a region of DNA where specific proteins – transcription factors – bind to initiate the process of gene transcription. Transpositionally incompetent L1s that act as alternate promoters have been identified thus far for over 40 human protein-coding genes (Matlik et al. 2006). The activity of an alternate promoter can impact gene transcription in a number of ways, including overexpression: higher rates of gene transcription than would occur with only a single promoter, resulting in higher levels of protein synthesis.

2. A regulatory region is a segment of DNA where transcription factors and other regulatory proteins preferentially bind, and genome-wide scans have identified some 23,000 candidate regulatory regions derived from transpositionally incompetent L1s (Faulkner et al. 2009).

3. Human genes typically contain several DNA sequences that code for amino acids (the building blocks of proteins) known as exons, interspersed with several introns, non-coding regions, and transpositionally incompetent L1s and Alu elements can function as both exons and introns (Muotri et al. 2007; Zhang & Chasin 2006).

4. Transpositionally incompetent L1s and Alu elements can function as stop sites, which are DNA regions that indicate the termination point for transcription of a particular DNA sequence (Muotri et al. 2007; Zhang & Chasin 2006). About 250,000 retrotransposon-derived transcription start sites, which are DNA sequences where gene transcription commences, have been identified (Faulkner et al. 2009).

5. DNA is organized into units known as nucleosomes, each of which consists of a segment of DNA of ~145–150 base pairs wound around a histone protein core (Richmond & Davey 2003). Recent research indicates that Alu elements play a critical role in the positioning of nucleosomes (Tanaka et al. 2010), and the configuration of histones plays a critical role in the extent to which any given gene can be transcribed.

Hence, retrotransposons probably have a key influence upon the transcriptional output (the transcriptome) of the mammalian genome (Faulkner 2011).

In contrast to transpositionally incompetent retrotransposons, transpositionally competent L1s, Alu elements, and SVAs are continually expanding in number in the human genome through ongoing *germline retrotransposition* (Batzer & Deininger 2002; Ostertag & Kazazian 2001). Some new (i.e., *de novo*) germline (hence heritable) L1 and Alu retrotransposition insertions have been generated so recently that they are found in only a single individual and are designated private *de novo* insertions (Conrad et al. 2011; Mills et al. 2007). Humans harbor a large genetic load of recent transposon insertions along with several million fixed (transpositionally incompetent) insertions: Estimates suggest that up to 600 million of these private germline insertions have been generated in human genomes throughout the world (Cordaux & Batzer 2009; Mills et al. 2007; Xing et al. 2009). This represents a significant mutagenesis of the genome, collectively equivalent to one insertion for every five base pairs of chromosomal DNA, and these mutations are expected to influence a wide range of human phenotypes (Iskow et al. 2010). The ability of transposable elements to move within the genome gives them an intrinsic propensity to affect genome evolution through the creation of new DNA sequences and structures and ultimately, to affect the evolution of species (Cordaux & Batzer 2009; Rebollo et al. 2010).

Transpositionally incompetent retrotransposons, the positions of which are fixed within the genome, can be inherited, like other alleles, according to the principles of Mendelian inheritance. Such does not appear to be the case regarding active retrotransposons. One unusual mode of active retrotransposon inheritance involves the inheritance not of DNA, but of RNA. It will be recalled that L1s retrotranspose by copying themselves to an RNA molecule that is then reverse transcribed (RNA→DNA) to form a copy of the original L1 retrotransposon. Kano et al. (2009) reported that the RNA of L1 elements is abundant in both germ cells and embryos and that L1 RNA transcribed in male or female germ cells can be carried over through fertilization and integrate in daughter cells during embryogenesis. This RNA is then reverse transcribed creating a *de novo* L1 retrotransposition insertion in the genome of offspring. In other words, active L1s exhibit a non-Mendelian RNA-based inheritance.

*De novo* somatic retrotransposition also occurs postconception in the somatic cells of the zygote. The activity of L1s capable of retrotransposition is regulated by the epigenome (Ostertag & Kazazian 2001) which regulates the expressional activity of genes by a number of processes, one of which is DNA methylation (see sect. 5). During gamete formation and in early embryogenesis, short waves of demethylation in a region of the L1 that serves as a promoter of expression allows L1s to escape epigenetic silencing (Beraldi et al. 2006), and research suggests that activated retrotransposons play a critical role in the development of the human brain.

Neural precursor cells have the capacity to develop into any kind of neuron (out of an estimated 10,000 different

kinds) as well as other nervous system cells. Coufal et al. (2009) demonstrated that human neural precursor cells, whether derived from fetal brains or from cultured embryonic stem cells, support the retrotransposition of an introduced human L1, and cells into which L1s were introduced generated distinct types of functional neurons. Using advanced DNA analysis on biopsied human heart, skin, liver, and brain cells, Coufal et al. detected more L1s in the genome of adult human brain cells than in the genomes of heart or liver cells from the same individual – as many as 100 extra copies per neuron tested relative to other organs, and they estimated 80–800 new insertions per cell in some brain regions. This is consistent with both somatic retrotransposition and with neural precursor cells having undergone more retrotransposition events than other tissues.

Applying high-throughput sequencing techniques to study somatic retrotransposition in human brain tissue, Baillie et al. (2011) identified 7,743 L1 insertions, 13,692 Alu insertions, and 1,350 SVA insertions in the hippocampus and caudate nucleus of three healthy individuals. A number of key loci were found to contain somatic L1 insertions, including dopamine receptors and serotonin neurotransmitter transporters. Baillie et al. also identified a disproportionate number of intronic L1 insertions, which is noteworthy inasmuch as introns are the protein-coding loci of DNA, and determined that genes containing intronic insertions were twice as likely to be differentially overexpressed (i.e., overtranscribed) in the brain. As they note of their findings: "The hippocampus seems to be predisposed to somatic L1 retrotransposition, which is intriguing given that [it] is a main source of adult neurogenesis" (Baillie et al. 2011, pp. 3–4). For more on the hippocampus and neurogenesis, see section 4.1.1.

Given that each retrotransposition event that occurs in a cell results both in an increase in nuclear DNA (nDNA) and a change in DNA sequence, the discovery of 80 new retrotransposon insertions in some neurons, 800 in others, and more in the brain than in other tissues, entails *somatic mosaicism*, the existence in one and the same individual of two or more distinct genomes. It has been a long-standing dogma that humans have identical copies of DNA – identical genomes – in the nucleus (i.e., nDNA) of all the cells of their bodies (with the usual exceptions):

> Fortunately, in the face of ever-increasing levels of variation being discovered in the human genome, there is at least one touchstone: The genomes of all the cells in a cancer-free individual are the same.… [A]side from … peculiar exceptions, and barring mutations accumulated as part of the ageing process, the genomes in all of your cells are identical. Or are they? (Dear 2009, p. 452)

As the author of this quote notes, *they are not*. In fact, as we shall see, all of the genetic phenomena to be considered in this article contribute, in one way or another, to widespread somatic mosaicism.

**4.1.1. Postnatal retrotransposition.** For approximately one hundred years it was a central dogma of neuroscience that adult neurogenesis was impossible – that humans were born with all of the brain neurons they would ever possess (Cajal 1899). By 1992, this dogma was effectively overturned (Reynolds & Weiss 1992). New neurons are continually generated throughout adulthood predominantly in two regions of the brain: the dentate gyrus in the hippocampus (a paired brain structure involved in memory, learning, and emotion) and the subventricular zone (a layer of cells found along the brain's lateral ventricles) (Fuchs & Gould 2000; Kuhn et al. 1996). The newly generated neurons form synapses and are functionally integrated into existing neuronal circuits. There is evidence that adult neurogenesis is important for synaptic plasticity – that is, the ability of synaptic connections between neurons to change in response to changes in their level of activity, learning, and memory (Bruel-Jungerman et al. 2005; Kitamura et al. 2009; Neves et al. 2008).

The level of adult hippocampal neurogenesis is positively and negatively modulated by environmental conditions, including environmental enrichment, physical activity, stress, and aging (Kuzumaki et al. 2010; Lista & Sorrentino 2009; Zhao et al. 2008). Exercise is known to have a significant impact upon hippocampal neurogenesis: It significantly increases the amount of brain-derived neurotropic factor (BDNF) in the hippocampus, a protein that supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses (Bednarczyk et al. 2009; Borght et al. 2009; Cotman & Berchtold 2002). Figure 1A shows that the levels of hippocampal BDNF are significantly higher in wheel-running as opposed to sedentary rodents after five days; Figure 1B shows that the levels of hippocampal BDNF correlate with the level of activity; and Figure 1C shows a 3.1-fold increase in the number of new neurons in the dentate gyrus of running as opposed to non-running mice.

Given that retrotransposon activity has been associated with neurogenesis, we would expect environmental events known to increase hippocampal neurogenesis to increase hippocampal L1 retrotransposition as well. This is precisely what was demonstrated by Muotri et al. (2009): Voluntary running in rodents doubled L1 retrotransposition in the hippocampus of the rodent brain (Fig. 1D). As was noted above (sect. 4.1), Baillie et al. (2011) found an elevated number of retrotransposition events in the human brain relative to other regions, which is consistent with increased retrotransposition during neurogenesis in adult humans. Muotri et al. (2009) also reported an increase in L1 retrotransposition not only in neurogenic areas but also in non-neurogenic areas, such as the cerebellum. This finding indicates that running not only increases the number of new L1 insertions in the brain but also activates silenced L1 insertions in other non-neurogenic brain regions. In humans, depending on its impact upon the brain, L1-induced somatic DNA variability might induce behavioral changes that could help the individual to adapt better to changing environments or, alternatively, increase the risk of neuropsychiatric disorders (Marchetto et al. 2010; and sect. 7).

Because where retrotransposons activated in neural precursor cells ultimately end up in the brain is largely a result of stochastic factors (or perhaps, controlled stochasticity), the brains of MZ twins will exhibit retrotransposon induced intertwin (in addition to intratwin) genetic heterogeneity (Marchetto et al. 2010; Martin 2009; Singer et al. 2010). Such heterogeneity will result not only from brain-wide retrotransposition during embryogenesis, but from ongoing neurogenesis in the hippocampus that occurs throughout life. It is entirely conceivable that differences in lifestyle, such as one twin exercising more than another, could further contribute to an already existing neuronal genetic heterogeneity. As Martin (2009, p. 1088) observes of retrotransposition in the human

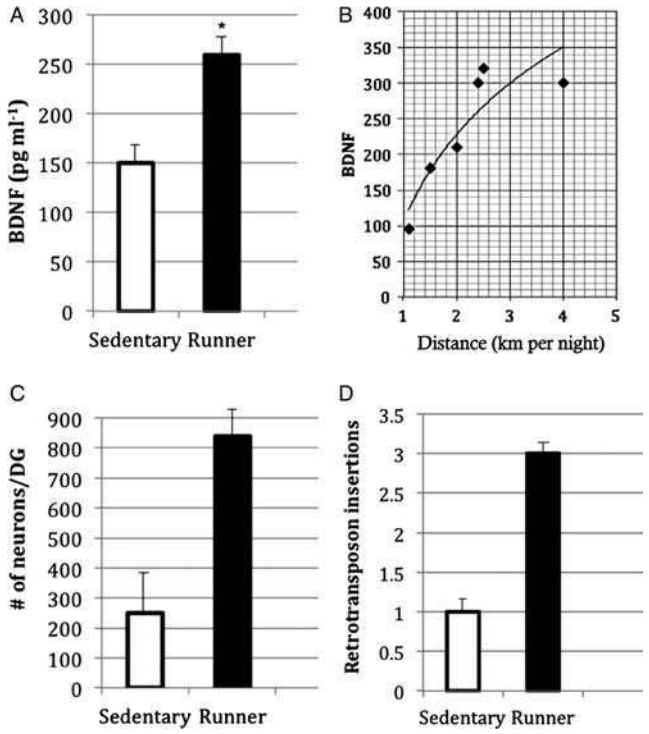


Figure 1. Exercise alters levels of BDNF, number of new neurons in the hippocampus, and neuronal DNA. A. Quantification of hippocampal brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus of sedentary and exercising animals after 5 days of wheel-running. B. Rats and mice acclimate rapidly to the running wheel and progressively increase their extent of daily running, in some cases up to 20 kilometers (~12–13 miles) per night. BDNF protein levels correlate with running distance (average over 14 days running). A & B adapted from Cotman and Berchtold (2002, p. 297), with permission from Elsevier. C. Running significantly increases the total number of newborn neural cells. D. Differences in degree of retrotransposition in the hippocampus of sedentary and running mice. Mice were assigned to either control non-runner ($n = 7$) or runner ($n = 7$) conditions. Mice in the runner group ran an average distance of $5.1 \pm 0.8$ kilometers per day. Running mice showed a threefold increase of retrotransposition events in the dentate gyrus of the hippocampus. C & D adapted from Muotri et al. (2009, p. 1004–5). Reprinted with permission.

brain and retrotransposon induced genetic heterogeneity in MZ twins: "These findings challenge the notion of the genome as a constant entity with limited impact on neuronal plasticity, and blur the distinction between genetic and environmental effects on the nervous system."

**4.1.2. Retrotransposons and behavior genetics.** Following are several examples of studies that identify retrotransposons as a potential causal element in specific behavioral disorders. (A similar list is presented for CNVs, aneuploidy, copy number variation, and mtDNA).

1. Rett syndrome is a neurodevelopmental disorder characterized by loss of speech, stereotypic movements, mental retardation, and social-behavioral problems (Chahrour & Zoghbi 2007). Studies have linked many Rett syndrome cases to a defect in the methyl-CpG-binding protein 2 (MeCP2) gene, MeCP2 being a protein involved in DNA regulation and numerous human neurodevelopmental disorders. Muotri et al. (2010) recently discovered that L1 neuronal transcription and retrotransposition are increased up to sixfold in rodents lacking MeCP2 (MeCP2 null mice) compared to normal controls. Using neural precursor cells derived from human stem cells and human tissues, they demonstrated that patients with Rett syndrome who carry specific MeCP2 mutations have increased susceptibility for L1 retrotransposition activity specific to certain brain regions correlated with brain regions in MeCP2 null mice.

2. Huang et al. (2010),[4] in a study of X-chromosome L1 sites in 69 males with clinically defined X-linked intellectual disability, verified six novel, relatively uncommon L1 insertions and three private (i.e., unique) insertions within this group. Three were located in or near brain-expressed genes or genes with known roles in central nervous system development.

### 4.2. Copy number variations

The single nucleotide polymorphism (SNP) is the most familiar form of DNA variation. Approximately 10 million SNPs have been identified in the human population, and many more are being discovered with the determination of each personal genome sequence (Wheeler et al. 2008). Until recently, SNPs were thought to be the predominant form of genomic variation and to account for most normal, as well as abnormal, phenotypic variation in human phenotypes with a genetic component. A recent and important development in human molecular genetics has been the discovery of the ubiquitousness of a variety of structural variations (SVs) in DNA – deletions, insertions, duplications, and inversions – as well as more complex multisite variants of varying sizes that change the chromosomal architecture (Redon et al. 2006). It is now apparent that human genomes differ more as a consequence of structural variation than from differences in single nucleotides (i.e., SNPs) (Alkan et al. 2011; Conrad et al. 2010; Li et al. 2011).

The most extensively studied of these SVs are submicroscopic copy number variations (CNVs), defined as stretches of DNA at least 1,000 base pairs (1 kilobase) long and extending up to several million base pairs, that are either deleted or present in multiple copies relative to a model normal genome (Feuk et al. 2006; Iafrate 2004; Redon et al. 2006). Many CNVs discovered thus far have a population frequency of greater than 1%, in which case they are referred to as copy number polymorphisms. In 2006, Redon et al. (2006) constructed a first-generation CNV map of the human genome, showing that 2,900 genes, or 10% of the total number of genes in the human genome, are encompassed by CNVs. The average size of the CNVs was 250,000 base pairs. Since the average nuclear gene is 27,000–60,000 base pairs long (Alberts et al. 2002), many of the CNVs were composed of multiple copies (or deletions) of entire genes, in some cases exceeding 12 copies of a single gene, challenging the dogma that individuals possess two copies of each gene (i.e., two alleles) in their nDNA.

The functional impact of CNVs on gene transcription has been demonstrated across the full range of biology (Conrad et al. 2010; Hurles et al. 2008). They can alter the expression of multiple genes located in the region of variable copy number simultaneously – approximately half of CNVs identified thus far overlap protein-coding genes

(Sebat et al. 2004) – allowing expression levels to be higher or lower than could be achieved by a single copy gene (Hastings et al. 2009; Stranger 2007). And while CNVs can affect the activity of neighboring genes, they can also have an equivalent effect at a distance: There is now substantial evidence that regulatory elements of genes can reside up to a million base pairs or more away (Nobrega et al. 2003).

CNVs can be inherited via the germline in the manner of SNPs, while exhibiting mutation rates from 100 to 10,000 times greater across the human genome (Zhang et al. 2009). This accelerated rate of mutation may help explain several unique characteristics of CNVs. First, CNVs comprise a large percentage of the genetic differences between humans and apes, and appear to be a major driving force in evolution, especially in the rapid evolution that has occurred, and continues to occur, within the human and great ape lineages (Bailey et al. 2008). Second, CNVs display extremely high interindividual variation: Studies indicate that the total amount of DNA sequence variation involving CNVs between two normal subjects is actually higher than for SNPs (Korbel 2007). Third, and even more surprising, this variation appears to be intraindividual as well as interindividual. In other words, CNVs are another source of *somatic mosaicism*.

For example, in an analysis of 34 tissue samples from healthy subjects, Piotrowski et al. (2008) observed at least six CNVs affecting a single organ of one or more tissues of the same subject. These findings were recently confirmed by Rodríguez-Santiago et al. (2010), who, as part of a genome-wide survey of mosaic genomic variation, analyzed blood or buccal DNA samples of 1,991 adult individuals. They found copy number mosaicism in 1.7% of tissue samples from the same individual, and these variants were present in anywhere from 17% to 98% of all cells from the same tissue. Liang et al. (2008) demonstrated that CNVs involving gains or losses of millions of base pairs occur during mitotic divisions of mouse embryonic stem cells during routine culture involving relatively few cellular divisions. The frequency and extent of these genomic changes in embryonic stem cells suggest that most somatic tissues will be mosaics composed of variants of the zygotic genome (Dear 2009).

If copy number somatic mosaicism occurs intraindividually in healthy individuals during embryogenesis, then since MZ twins begin as a single individual (a single zygote), somatic mosaicism should occur between healthy MZ twins as well, resulting in inter-MZ twin genetic discordance. Bruder et al. (2008) confirmed this in a study of 29 pairs of MZ twins using peripheral blood-derived DNA samples. The study included 10 phenotypically unselected normal MZ twins and 19 twin pairs both concordant and discordant for Parkinson's disease, parkinsonianism, and Lewy body dementia. They discovered large-scale CNVs among all the twins, healthy and diseased, with *an estimated frequency of up to 10% variation per twin pair.*[5]

It should be emphasized that these variations were found in a single tissue (i.e., blood). Given somatic mosaicism, the actual total percentage is likely much higher, and it is for this reason that Bruder et al. (2008, p. 766) note: "It is likely that the confirmed CNVs shown here represent the 'tip of the iceberg' of all CNVs that are actually present in the studied twins."

Finally, it is important to keep in mind that CNVs are not the only kind of structural variation common in the human genome. For example, there are more than one million microsatellites, variable numbers of 1–6 base pair repeats that account for 3% of the DNA sequence (Weber et al. 2002); about 150,000 minisatellites and variable number tandem repeats, polymorphic sequences containing 20–50 copies of 6–100 base pair repeats (Naslund et al. 2005); and about one million deletions and insertions of DNA base pairs (Weber et al. 2002). Therefore, CNV mosaicism itself likely represents the tip of the mosaic iceberg.

**4.2.1. CNVs and behavior genetics.** Examples of studies that identify CNVs as a potential causal element in specific behavioral disorders.

1. In a genome-wide association study (GWAS) of rare (<1% frequency) CNVs involving 996 individuals with autism spectrum disorder and 1,287 matched controls, Pinto et al. (2010) found that cases carried a higher global burden of rare CNV variants (1.19 fold, $P = 0.012$), especially for loci previously implicated in either autism and/or intellectual disability (1.69 fold, $P = 3.4 \times 10(-4)$). Among the CNVs there were numerous somatic *de novo* and inherited events, sometimes in combination in a given family. They also discovered an enrichment of CNVs disrupting functional gene sets involved in cellular proliferation, projection and motility, and intercellular signaling. Other studies have also reported an association between *de novo* CNVs and autism (Glessner et al. 2009; Marshall et al. 2008; Sebat et al. 2007).

2. Several genome-wide association studies (GWAS) of individuals with schizophrenia have found a higher number of individually rare CNVs in cases versus controls, and these CNVs disproportionately disrupted genes known to be involved in neurodevelopment (Buizer-Voskamp et al. 2011; Kirov et al. 2009; Stefansson et al. 2008; Walsh et al. 2008).

3. In a GWAS of children with attention-deficit/hyperactivity disorder (ADHD) involving 366 cases and 1,047 controls, Williams et al. (2010) reported a significantly increased rate of CNVs in children with ADHD, with 57 large, rare CNVs identified in cases and 78 in controls.[6]

In addition, CNVs have been associated with numerous classes of human disease with an underlying genetic basis (Almal & Padh 2012; Buchanan & Scherer 2008).

### 4.3. Aneuploidy

Humans possess 23 pairs of chromosomes, with each parent providing one chromosome in each pair, a condition referred to as diploidy (excepting male sex chromosomes: males contain a single X and a single Y chromosome). Any variation in the number of chromosomes, either more or less, is typically associated with pathogenesis. For example, trisomies are characterized by an extra chromosome (e.g., trisomy 21, or Down syndrome, and trisomy 18, or Edward syndrome); monosomies are characterized by the complete or partial absence of a chromosome (e.g., Turner syndrome, characterized by a single X chromosome instead of an XX or XY). Despite this association with pathogenesis, there is a surprisingly high degree of germline and somatic chromosomal mosaicism in healthy individuals.

It is estimated that 2–5% of healthy male sperm exhibit one or another form of aneuploidy, with significant intra-

and interindividual variations (Tempest et al. 2009; Templado et al. 2011). Approximately 2.26% of healthy sperm exhibits disomy (sperm should exhibit monosomy), while the estimated rate of 2× disomy is 4.5%. Longitudinal analysis in which sperm samples were obtained from healthy males, ages 18–32, every 6 months for 18 months, revealed significant time dependent intraindividual fluctuations in both the total amount of aneuploidy and in the chromosomes affected (Tempest et al. 2009). Studies have associated increases in sperm aneuploidy frequency with a variety of environmental factors, including increases in consumption of caffeine, alcohol, drugs, and smoking; increased exposure to pesticides and endocrine compounds; and infection or illness (Härkönen 2005; Robbins et al. 2005; Shi et al. 2001). In oocytes of healthy females, the rate of aneuploidy is much higher: Cytogenetic analysis places the aneuploidy rate at anywhere from 20% to 25% (Templado et al. 2011).

Distinguishing between germline and somatic chromosomal mosaicism is complicated because some chromosomal abnormalities, although the result of an abnormality in the parental gamete, are not considered inherited in the usual sense of that term. For example, a common form of trisomy 21 is the result of an error during meiosis – that is, during the formation of the maternal ovum. Because this error affects only one or several ova, the child who develops trisomy 21 has not inherited the mother's genotype (which is normal) but rather has developed from a defective ovum (Antonarakis et al. 2004; Hassold & Hunt 2001). Hence, this form of aneuploidy is not considered germline aneuploidy. By contrast, *germline aneuploidy* has been thought to be a rare cause of aneuploidy in the human population, but recent evidence from cytological and population studies suggests otherwise. Molecular and cytogenic analyses have revealed that approximately 5% of young couples with a Down syndrome child show evidence of trisomies on chromosomes 13 and 19 (Kovaleva & Tahmasebi-Hesari 2007). Most recently, direct analysis of fetal ovarian premeiotic, meiotic, and stromal cells (i.e., connective tissue) *in normal offspring* showed low-level trisomy 21 aneuploidy in every sample tested (Delhanty 2011; Hulten et al. 2010; Kovaleva 2010). This has led to the suggestion that the apparently universal trisomy 21 germline mosaicism in females may account for the relatively high occurrence of Down syndrome in the human population. As Delhanty (2011, p. 136) notes, "Based upon this evidence, germinal or gonadal mosaicism is likely to make a significant contribution to aneuploidy in the human population."

Recent conservative estimates place the overall percentage of aneuploid neural cells in the normal adult brain at an astonishing 10%, involving monosomy, trisomy, tetrasomy, polyploidy (greater than four chromosomes), and uniparental disomy, that is, two copies of a chromosome from one parent (Iourov et al. 2006; 2009; Rehen 2005). This is an indication of widespread *chromosomal somatic mosaicism* in the human brain (see Table 1). Given an estimated 100 billion neurons in the adult brain, this yields a rough (conservative) estimate of 10 billion neurons and 100–500 billion glial cells (neural cells that do not transmit electrical impulses but play an essential role in neuronal structure and function) with one or another form of chromosomal aneuploidy. It is estimated that roughly 28% of embryonic neural precursor cells exhibit chromosomal aneuploidy in one form or another (Iourov et al. 2009). This chromosomal diversity appears to result from a high frequency of stochastic postzygotic chromosome mutations in somatic cells, whereby neuroprogenitor cells in numerous regions of the embryonic brain display cell division defects in normal cells that result in aneuploid adult cell progeny.

Various lines of evidence indicate that brain tissues may be more prone to aneuploidy than other tissues (Rehen 2005). Mature aneuploid neurons are functionally active and integrated into brain circuitry, showing distant axonal connections (Kingsbury 2005). One likely result of this is neuronal signaling differences caused by altered gene expression, as documented in mammalian neural cells (Kaushal et al. 2003). Thus, a network composed of intermixed diploid and aneuploid neurons might produce unique signaling properties distinct from a network composed purely of diploid cells (Pavelka et al. 2010; Westra et al. 2010). Once again, the highly stochastic nature of chromosomal aneuploidy and resulting chromosomal mosaicism ensures that MZ twins will have differences in their neuronal chromosomes and that siblings will depart from a presumed 50% possession of the parental nuclear genome. MZ twins discordant for aneuploidy have been recognized for several decades: Discordant MZ twins have been reported for monosomy X, trisomy 1, trisomy 13, trisomy 21, and uniparental disomy (Gilgenkrantz & Janot 1983; Nieuwint et al. 1999; Rogers et al. 1982; Uchida et al. 1983; Weiss et al. 1982).

Table 1. *Percentage of whole chromosome 21 gain and loss in the normal brain varies within and among individuals*

| Age (years) | Cell Type | % Disomy | %Tetrasomy | %Monosomy | %Trisomy | %Aneuploidy |
|---|---|---|---|---|---|---|
| 2 | Frontal cortex cells | 94.3 | 2.5 | 1.7 | 1.5 | 3.2 |
| 5 | Occipital cortex cells | 93.8 | 2.4 | 2.2 | 1.6 | 3.8 |
| 35 | Frontal cortex cells | 93.9 | 2.4 | 1.8 | 1.8 | 3.6 |
| 48 | Frontal cortex cells | 93.8 | 2.6 | 1.6 | 2.0 | 3.6 |
| 77 | Hippocampal cells | 91.5 | 3.8 | 2.6 | 2.3 | 4.8 |
| 86 | Hippocampal cells | 91.5 | 2.4 | 3.0 | 2.2 | 5.2 |
| Average | Brain cells | 93.3 | 2.7 | 2.1 | 1.9 | 4.0 |
| 33 | Lymphocytes | 99.8 | 0.2 | 0.4 | 0.2 | 0.6 |
| <0 | Down's syndrome neural cells | 7.1 | 3.6 | 3.6 | 89.3 | 89.3 |

Note: Lymphocytes and Down syndrome cells were used to validate the counting criteria. Adapted from Rehen et. al. (2005, p. 2178). Reprinted with permission.

**4.3.1. Aneuploidy and behavior genetics.** Many, if not most, of the disorders associated with aneuploidy affect cognitive functioning and behavior in one way or another (Borgaonkar 1997; Gersen & Keagle 2005).

Examples of studies that identify aneuploidy as a potential causal element in specific behavioral disorders

1. Comparing aneuploidy frequency in 12 control and 12 schizophrenia brains by scoring more than 50,000 individual brain cells, Yurov et al. (2008) detected an approximately twofold increase of stochastic aneuploidy levels on chromosome 1 in the schizophrenia brain relative to controls.

2. Iourov et al. (2009) monitored aneuploidy in the cerebral cortex of normal and Alzheimer's disease brains by molecular cytogenetic approaches scoring more than 480,000 neural cells, using sets of DNA probes for chromosomes 1, 7, 11, 13, 14, 17, 18, 21, X, and Y. They found a 10-fold increase of chromosome 21-specific aneuploidy – both hypoploidy (<2 chromosomes per cell) and hyperploidy (>2 chromosomes) were detected in the Alzheimer's cerebral cortex (6–15% versus 0.8–1.8% in control). They concluded that somatic mosaic aneuploidy differentially contributes to intercellular genomic variation in the normal and Alzheimer's brain and noted that neural aneuploidy leading to altered cellular physiology may significantly contribute to the pathogenesis of neurodegenerative diseases.

### *4.4. Mitochondrial DNA*

We are accustomed to discussing *the* human genome – the familiar double-stranded helix that exists in identical form in all the cells of our bodies. Humans, however, do not have *a* genome, but at least two entirely distinct genomes, differing not only in structure, but also in the manner in which they are inherited.

Mitochondria are intracellular organelles, small membrane-enclosed structures within the cell, in which the end product of the breakdown of glucose in cells is processed to form the primary source of cellular energy, adenosine triphosphate (ATP). Hence, mitochondria are commonly characterized as the powerhouses of the cell (McBride et al. 2006). However, mitochondria also play a central role in a number of critical cellular and metabolic processes, including cellular proliferation; apoptosis or programmed cell death (cellular suicide), a process aimed at destroying a physiologically unwanted cell (Desagher & Martinou 2000); the regulation and homeostasis of intracellular calcium, which acts as an intracellular signal involved in numerous cellular processes including cellular expression and metabolism; fertilization and embryonic development (Cao & Chen 2009); DNA repair (DNA is constantly exposed to endogenous and exogenous agents that generate DNA lesions and induce DNA instability; see Gredilla et al. 2010); aging (Salvioli et al. 2001); the regulation of steroid hormone synthesis in the adrenal cortex, including estrogen, testosterone, and cortisol (Almahbobi et al. 1992); synthesis of heme, one of the components of hemoglobin (Atamna 2004); and detoxification of ammonia from the liver (Jackson et al. 1986). Mitochondria also play a critically important role in the brain and are involved in the regulation of brain function, including synaptic plasticity and brain size (Chada & Hollenbeck 2004).

Mitochondria possess their own genome composed of mitochondrial DNA (mtDNA), a circular structure of double-stranded DNA located within the mitochondrion itself and separate from the more familiar genome located in the cell's nucleus, that is, nuclear DNA (nDNA). Mitochondrial DNA exhibits a number of properties that distinguish it from nDNA. First, mtDNA is not inherited in Mendelian fashion, but rather, it is inherited from the mother; that is, it is exclusively transmitted by the oocytes. Second, mtDNA exhibits *polyploidy*, numerous multiple copies of the complete mitochondrial genome in a single cell that occur in variable numbers both within individual mitochondria, which possess 2–10 copies of mtDNA each, and in individual cells, which vary significantly in the amount of mitochondria, and hence mtDNA, that they contain, on the basis of cell-type (Clay Montier et al. 2009). For example, there are 1,075–2,794 copies of mtDNA per cell in muscle cells, 1,200–10,800 in neurons, and up to 25,000 in liver cells. Studies have shown differences in the mtDNA content of different oocytes *from the same female* ranging from 11,000–903,000 mtDNA molecules per oocyte (May-Panloup et al. 2007). Third, mtDNA exhibits *heteroplasmy*, the occurrence of allelic differences between the multiple copies of mtDNA in the same individual that often segregate differentially in different tissues (Pfeiffer et al. 2004). Fourth, the mtDNA mutation rate is anywhere from ~9 to 25 times greater than that for nDNA, and mutations are commonly inherited both somatically and via the germline (Lynch et al. 2006).

The association between human mtDNA mutations and phenotype is significantly complicated by the dual features of polyploidy and heteroplasmy. Due to heteroplasmy, not all copies of mutated mtDNA will exist in all of the copies of the mtDNA genome; due to polyploidy, the number of copies of the mtDNA genome possessing the mutation will vary in different cells and tissues of the body and may be preferentially segregated in certain tissue types. In the case of diseases known to be associated with a mtDNA mutation, whether or not the phenotype is expressed depends upon whether the mtDNA is localized in certain cells and tissues of the body, and if so, which cells and tissues, and whether the amount of mutated mtDNA surpasses a certain threshold level necessary for the appearance of the phenotype (Taylor & Turnbull 2005).

Because oocytes from the same mother can differ dramatically in the amount of mtDNA they contain and likewise in the amount of mutated mtDNA they contain, the amount of mtDNA any given sibling possesses is a result of whatever maternal oocyte he or she happened to develop from, as well as a host of other stochastic processes that occur during embryogenesis. Hence, siblings will not possess 50% of their mother's mtDNA, and although MZ twins develop from a single fertilized oocyte, mtDNA is stochastically partitioned with the first mitotic cell division. Suppose we are concerned with the heritability of a trait associated with a certain mtDNA mutation. It is possible for one MZ twin to receive more than half mutant mtDNA molecules while the other twin receives only a tiny fraction, depending on how the twins divide from each other and how much mutant mtDNA happens to be on each side of the division. Even with an even division, the mutant mtDNA in one twin may end up in cells that eventually die during normal development, while the mutant mtDNA in the other twin may end up in cells that differentiate into brain tissue (Clay Montier et al. 2009).

**4.4.1. Mitochondrial DNA and behavior genetics.** Polymorphic variation in mtDNA has been associated with the increased likelihood of developing various psychiatric disorders (Hroudová & Fišar 2011) including autism (Giulivi et al. 2010), schizophrenia (Clay et al. 2011), bipolar disorder (Rollins et al. 2009), depression (Kato et al. 2011), Parkinson's disease (Shinohara 2001), and Alzheimer's (Coskun 2004), and has been associated with differences in cognitive ability (Dimauro & Davidzon 2005).

## 5. The epigenome

Epigenetics is the study of heritable changes – both germline and somatic – in gene transcribability[7] and phenotype that occur without changes in DNA sequence (Bollati & Baccarelli 2010). For the most part, genes are transcribed to produce RNA and proteins, but before a gene can be transcribed, it must be *turned on* – that is, activated (Martienssen et al. 1996). Genes are not self-activating, and the mere presence of a gene as part of an individual's genotype does not entail that it is capable of being transcribed. Rather, genes are turned on and off by the epigenome, the complex biochemical regulatory system that silences, activates, and changes the transcriptional activity of genes without any change to the DNA sequence itself (Bernstein et al. 2007). Just how significant these changes can be phenotypically can be illustrated by considering the role of the epigenome in cellular differentiation: A heart cell, for example, differs from a neuron not because of differences in DNA sequence or structure, but (in part) because of differences in epigenetic programming between the two cell types. While epigenetic modifications of the genome can be stable throughout the life course, such as the epigenetic modifications that contribute to cellular differentiation during embryogenesis, they can also be environmentally responsive, changing the transcribability of the genome in response to environmental input. The term *environmental epigenomics* reflects the constant interplay between the environment, which includes both endogenous (e.g., hormone levels or immune status) and exogenous (e.g., the perinatal environment) factors, and the epigenome (Jirtle & Skinner 2007).

While new epigenetic mechanisms are being uncovered, the best characterized are histone modification, DNA methylation, and the expression of non-coding micro RNAs (Chuang & Jones 2007; Kim et al. 2009). Within the cell's nucleus, nDNA is wrapped around a core of histone proteins that exhibit histone tails, which are histone strands that extend outside the nucleosome core and wrap around the DNA molecule. In histone modification, a variety of chemical modifications to the histone tails (e.g., acetylation, methylation, and phosphorylation) change the structure of histones in such a way as to make the DNA either more or less accessible to transcription factors. In DNA methylation, the addition of a methyl group to CpG dinucleotides (sites in the DNA molecule where a cytosine base is followed by a guanine base) acts as a physical barrier to transcription factors and attracts enzymes and proteins that further reduce the transcriptional activity of a gene. Non-coding RNAs (ncRNAs) are not involved in gene transcription, like the more familiar messenger RNA (mRNA), but function instead as a vast system for posttranscriptional regulation of DNA, regulating gene silencing by binding to mRNAs. Non-coding RNAs include at least 1,000 different kinds of micro RNA (miRNAs) – and the number may be as high as 20,000 – short RNA molecules approximately 22 nucleotides long. It was once believed that DNA was involved primarily in the transcription of proteins, but in fact, 97–98% of the transcriptional activity of the human genome is devoted to non-protein-coding RNA (Mattick 2001).

Studies indicate that epigenetic changes can be inherited via the germline as well as somatically, resulting in the intergenerational non-genomic inheritance of epigenetic states (Anway et al. 2008; Crews et al. 2007; Cuzin et al. 2008; Jablonka & Raz 2009; Pentinat et al. 2010; Skinner et al. 2008; Stouder & Paoloni-Giacobino 2010; Walker & Gore 2011). It was once believed that genome-wide epigenetic reprogramming during gametogenesis and early embryogenesis would erase epigenetic modifications acquired during the life of the animal in order to restore the totipotency of the fertilized egg (i.e., the ability of fetal stem cells to become any cell type) (Allegrucci et al. 2005). This epigenetic reprogramming, however, is not complete. Modifications at variably expressed alleles are not completely erased during gametogenesis and embryogenesis while other epigenetic markings are reestablished as part of the developmental process (Jablonka & Raz 2009).

A much studied example of the intergenerational transmission of epigenetic programming and associated phenotypes[8] concerns endocrine disruptors, synthetic chemicals that can have disruptive effects upon the mammalian endocrine system (National Institute of Environmental Health 2010). Studies have demonstrated that embryonic exposure to the endocrine disruptor vinclozolin (a common fungicide) during gonadal sex determination in rodents induces a transgenerational phenotype characterized by spermatogenic cell defects and subfertility in the $F_1$ (first) through $F_3$ (third) generations (Anway et al. 2008; Clement et al. 2010; Nilsson et al. 2008; Stouder & Paoloni-Giacobino 2010; Uzumcu et al. 2008). This exposure has also been associated with a decrease in anxiety-like behavior in third-generation males (Skinner et al. 2008). The transmission of these phenotypes is not associated with any changes in DNA sequence; rather, it is associated with changes in DNA methylation at specific genes known to be involved in spermatogenesis.

Imprinting is an epigenetic process, essential to normal development, in which genes are preferentially expressed in a parent-of-origin manner. For example, the maternal allele may be highly methylated (and effectively silenced), while the paternal allele is largely unmethylated (Beard & Jaenisch 1993; Kaneda et al. 2004; Kato et al. 2007). Decreases in human spermatogenesis are associated with imprinting defects on a number of the same genes that have shown abnormal methylation patterns in vinclozolin studies (Stouder & Paoloni-Giacobino 2010). This is particularly suggestive given that in the past century a significant decline in sperm count has been documented in young, healthy males in industrialized countries, a finding that may in part explain a parallel decline in birthrates (Andersson et al. 2008; Joffe 2010). The rapidity of these changes strongly suggests that environmental factors play a role. Endocrine disruptors are a plausible contributing factor given their ubiquitousness in the environment in the form of herbicides, insecticides, and fungicides,

resulting in daily exposure for many human populations (Sultan et al. 2001).

### 5.1. Epigenetics and monozygotic twins

Monozygotic twins exhibit significant intertwin epigenetic differences, and these differences may play an important role in intertwin phenotypic differences (Fraga et al. 2005; Kaminsky et al. 2009; Poulsen et al. 2007). MZ intertwin differences in DNA methylation and histone modification profiles have been reported in whole-genome-wide scans, select tissues samples, and specific genomic regions (Boks et al. 2009; Fraga et al. 2005; Kaminsky et al. 2009; Wong et al. 2010). In a comparison of gene expression of 3-year-old and 50-year-old MZ twins, Fraga et al. (2005) identified a fourfold increase in epigenetic discordance in older versus younger twins. And in a recent study, Ollikainen et al. (2010) analyzed DNA methylation levels in five different tissues from 56 MZ and 35 DZ newborns. In examining individual CpG dinucleotides, they found up to 82% discordance in DZ twin pairs and up to 54% in MZ twin pairs. They note that their findings "demonstrate that the intrauterine period is a sensitive time for the establishment of epigenetic variability in humans, with implications for the effects of maternal environment in addition to genetics on the development of the newborn epigenome and potentially for programming of later disease risk" (Ollikainen et al. 2010, p. 4176). (For more on epigenetics and the intrauterine environment, see sect. 7.)

### 5.2. Behavioral epigenetics

There is growing evidence for the role of epigenetic modifications in all aspects of normal neural development and functioning including perception, memory, cognition and learning, emotion, and neural and behavioral plasticity (Allen 2008; Champagne 2010b; Crews 2008; Day & Sweatt 2011; Gao 2008; Keverne & Curley 2008; Kuss & Chen 2008; Mehler 2008; Meza-Sosa et al. 2012; Molfese 2011; Nelson et al. 2010; Roth et al. 2010). Epigenetic disregulation may contribute to abnormal gene expression in a range of neuropsychiatric disorders and neurodegenerative diseases, including autism, schizophrenia, depression, and Alzheimer's disease (Abdolmaleky et al. 2011; Akbarian 2010; Coppieters & Dragunow 2011; Gruber 2011; Nelson et al. 2008; Paslakis et al. 2011; Grafodatskaya et al. 2010).

**5.2.1. Behavioral epigenetics and the perinatal environment.** A number of studies have demonstrated how the perinatal environment can program the epigenome with potentially lifelong behavioral consequences (Cameron et al. 2008; Champagne & Curley 2008; 2009; Darnaudery & Maccari 2008; Goyal et al. 2010; Ho & Burggren 2010; McGowan & Szyf 2010; McGowan et al. 2008; 2009; Mueller & Bale 2008; Murgatroyd & Spengler 2011; Oberlander et al. 2008; Reyes-Castro et al. 2011; Sakhai et al. 2011; Szyf 2009; Vucetic et al. 2010; Walker & McCormick 2009; Weaver 2009; Weaver et al. 2004; Weinstock 2008). A notable example from animal studies concerns the relationship between maternal rearing behavior and the stress response. Mother rats exhibit stable interindividual differences in the amount of licking and grooming (LG) behavior they display toward offspring (Liu et al. 1997). Pups raised by high-LG dams consistently exhibit, as adults, lower levels of stress as measured both physiologically and behaviorally, while pups raised by low-LG dams exhibit, as adults, high levels of stress. Furthermore, the female offspring of high-LG mothers become, as adults, high-LG mothers themselves, while the female offspring of low-LG mothers become low-LG mothers. Cross-fostering studies have consistently indicted that adult offspring are more likely to resemble their foster as opposed to biological mothers in stress-related behavioral phenotypes and in rearing behavior (Barha et al. 2007; Caldji et al. 2003; Champagne & Curley 2009; Fish et al. 2004; Francis & Meaney 1999; Liu et al. 1997; Menard & Hakvoort 2007; Weaver et al. 2004).

In mammals, the stress response involves a complex series of neurological, cardiovascular, respiratory, gastrointestinal, renal, endocrine, and immunological processes. A central component of this response involves the hypothalamo-pituitary-adrenal (HPA) axis (Tsigos & Chrousos 2002). The hypothalamus releases corticotrophin-releasing factor (CRF), which stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary glands into the general bloodstream. ACTH in turn stimulates the release of the glucocorticoid hormones (cortisol in humans, corticosterone in rodents) and the neurotransmitters/hormones epinephrine and norepinephrine (the catecholamines). Epinephrine and norepinephrine increase heart rate, contract blood vessels, and dilate air passages. Increased adrenal glucocorticoids orchestrate, along with the catecholamines, a mobilization of lipid and glucose reserves combined with insulin antagonism to increase the available energy supply (Sapolsky et al. 2000). Glucocorticoid receptor (GR) is a transcription factor involved in the regulation of the HPA stress response through a negative feedback relationship. It is coded by the GR gene; higher levels of GR transcription are associated with lower levels of stress responsivity, and lower levels of transcription are associated with higher levels of stress (Jacobson & Saplosky 1991).

In a study by Weaver et al. (2004), analysis of a specific region of the GR gene in hippocampal neurons, the exon $1_7$ glucocorticoid receptor promoter ($GR1_7$), several weeks after the birth of pups raised by low- and high-LG mothers revealed significant differences in degree of methylation: High maternal LG was associated with decreased $GR1_7$ methylation in pups, corresponding to elevated levels of GR transcription in the hippocampus and decreased HPA stress response. Strikingly, just before birth at embryonic day 20 (E20), the hippocampal GR promoter in the fetuses of both high and low-LG mothers was unmethylated. One day after birth – postnatal day 1 (P1) – the exon $1_7$ GR promoter was *de novo* methylated in both groups of pups to the same extent. By P6, however, the promoter was effectively demethylated in pups reared by high-, but not low-, LG mothers. These differences in methylation remained consistent through to adulthood and were associated with corresponding differences in stress reactivity. These findings suggest that the group difference in DNA methylation occurred as a function of maternal behavior over the first week of life.

In mammals, neuroendocrine regulation of maternal care is dependent on estrogen–oxytocin interactions involving hypothalamic estrogen receptors (Gimpl &

Fahrenholz 2001). In the rat, central oxytocin receptor levels are functionally linked to behavioral differences in maternal care. Dams who display high levels of maternal LG behavior exhibit elevated expression of the estrogen receptor α (ERα) in a region of the hypothalamus known as the medial preoptic area, whereas low-LG mothers exhibit decreased ERα expression (Champagne et al. 2003b; Westberry et al. 2010). These differences in turn are associated with differences in DNA methylation: High-LG behavior is associated with lower levels of

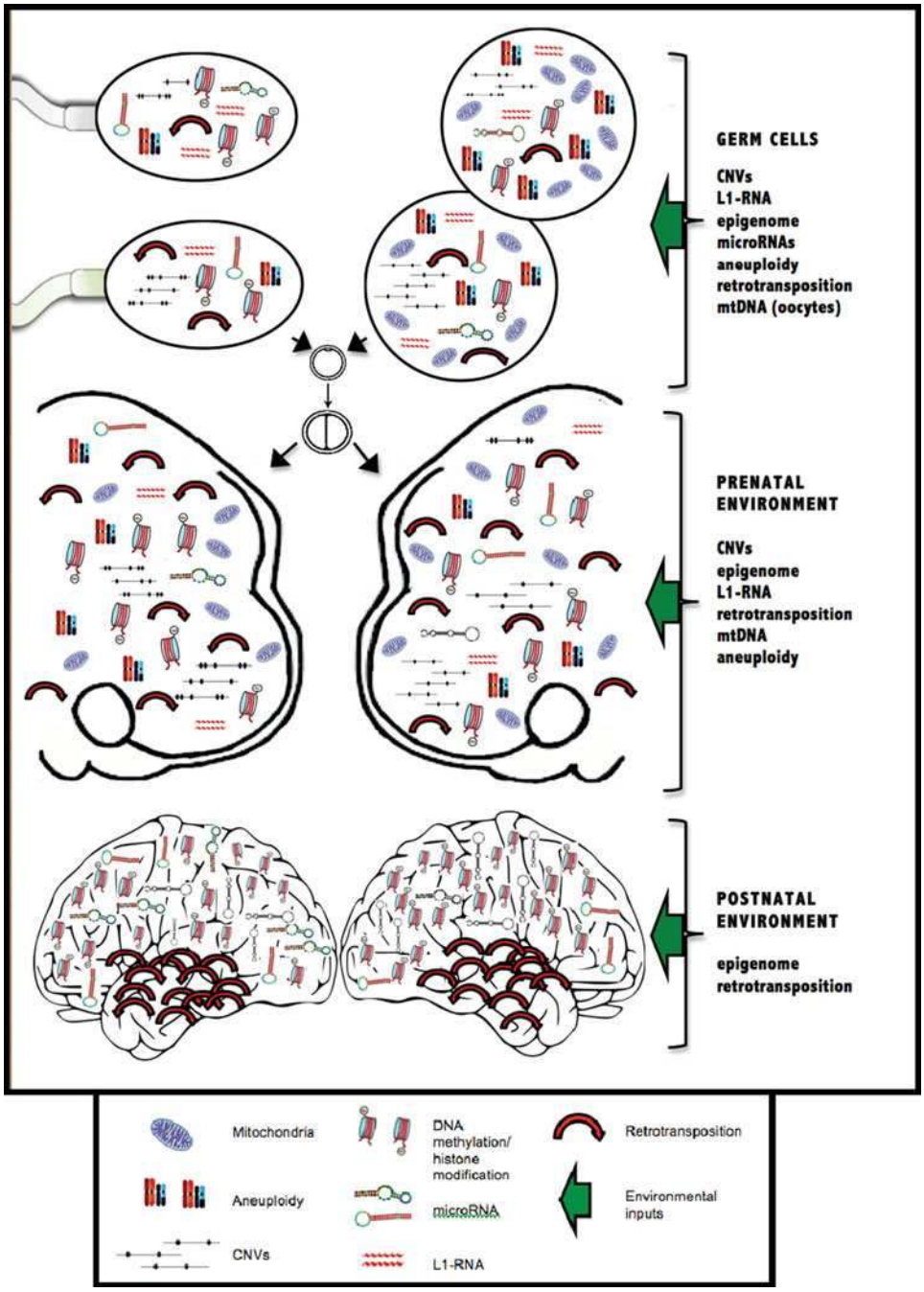


Figure 2. Overview of several sources of genetic and epigenetic heterogeneity between germ cells of the same two individuals and between monozygotic cotwins. Germ cells: Spermatocytes exhibit interindividual variation in L1-RNA, copy number variations (CNVs), epigenetic profiles, and microRNAs (miRNAs) (as well as smaller differences in aneuploidy). Oocytes exhibit interindividual variation in L1-RNA, CNVs, epigenetic profiles, and miRNAs, as well as significant differences in mitochondrial DNA (mtDNA) and aneuploidy. Environmental inputs influencing germ cell variation may include maternal stress, activity, diet, and environmental toxins. Prenatal environment: Splitting of the zygote into two (monozygotic twins): CNVs, aneuploidy, mtDNA partitioning and heteroplasmy, L1 retrotransposition, and the epigenome develop non-identically in the two twin embryos. Prenatal environmental inputs that may affect any of these phenomena in the prenatal environment may include maternal stress, anxiety, depression, diet, activity, (prenatal) environmental toxins, intrauterine position effects, and chorion effects. Postnatal environment: Intertwin discordance due to different epigenomes and differences in ongoing retrotransposition resulting from neurogenesis in the hippocampus. The epigenomes of the twins are depicted as being substantially different due to differences in life experiences and environments.

methylation of the ERα gene, which is associated with higher levels of ERα transcription; low-LG behavior is associated with higher levels of ERα gene methylation and lower levels of gene transcription. Female offspring of high- and low-LG mothers exhibit, on average, the same methylation patterns, levels of gene transcription, and LG behavior as their mothers. Cross-fostering studies have associated these changes with both the rearing mother and potential prenatal environmental effects (Cameron et al. 2008).

As the authors of these studies emphasize, it is not their claim that behaviors such as high or low stress reactivity and maternal rearing behavior are in effect caused by changes in the methylation status of one or two genes. In studying the epigenetics of the maternal environment, Weaver et al. (2006) identified more than 900 genes as being stably regulated by maternal care. Using microarrays to monitor changes in hippocampal expression of 31,099 unique mRNA transcripts, they identified 253 transcripts that were up-regulated (increased transcription) and 50 transcripts that were down-regulated (decreased transcription) in the offspring of high- versus low-LG mothers. Inasmuch as the authors only included genes with known biological function in their analysis, and only studied gene expression in the hippocampus, it is likely that a far greater number of genes are differentially transcribed.

Figure 2 illustrates some of the genetic and epigenetic differences between germ cells of the same individual and between the brains of MZ cotwins. Many of the same processes that lead to the genetic and epigenetic heterogeneity of intra-individual germ cells are depicted as contributing to the heterogeneity of MZ cotwins. This heterogeneity of MZ twins commences with the first division of the zygote and continues throughout the life course.

## 6. Implications for twin studies

Two preliminary terminological points: Henceforth, the phenomena that I have considered – retrotransposons, CNVs, mtDNA, aneuploidy, and epigenetics – will be referred to collectively by the term *neogenome* (neogenomics, neogenetics). The Genome (capital "G") will be used to refer to both the various different mitochondrial and nuclear genomes that exist (in different forms and quantities) in different cells and tissues of the body. In this sense, it will be used analogously to the term *epigenome*: Persons do not have a single epigenome, but rather different epigenomes in different cells and tissues.

Let us now reconsider the assumptions identified as central to the twin study methodology:

*HS1.* 100% of the genes of MZ twins are identical; on average, 50% of the genes of DZ twins and singletons are identical; singletons possess ~50% of their parental DNA.

MZ twins, in addition to not possessing identical mtDNA, do not possess identical nDNA. Their Genomes differ in the polyploidy and heteroplasmy of their mtDNA, number and location of retrotransposition events, number and location of CNVs, replications and deletions of whole or partial chromosomes, and their epigenomes. To the extent that heritability estimates depend upon an assumption of enduring genetic identity, they will be unable to provide reliable estimates. If MZ twins are discordant for a trait that does have a heritable component to a greater extent than DZ twins, it is possible that such discordance is the result of genetic discordance. If MZ twins are concordant for this trait to a greater extent than DZ twins, this greater concordance cannot confidently be attributed to genetic concordance, since they may be genetically discordant. Furthermore, it is important to keep in mind that epigenetic discordance can be every bit as significant as genetic discordance in considering heritability. Suppose that cotwins A and B both possess the same allele of gene Z. If, as a result of different environmental exposures, Z is epigenetically silenced in A but not in B, the functional result can be equivalent to A not possessing allele Z at all.

*HS2.* The relationships of genetic identity in H1 *never change* (i.e., they are unvarying). That is, MZ twins, from conception to death, are always 100% genetically identical; DZ twins and singletons are always ~50% genetically identical, and singletons always possess ~50% of their parental DNA.

The presumed percentages of genetic identity between MZ twins, DZ twins, and non-twin siblings are not fixed, but are likely a moving target. One twin exercising and the other being sedentary can lead to differences not only in the number of new neurons formed in the hippocampus, but also in the genetic identity of those neurons due to differences in L1 retrotransposition. Hence, in longitudinal heritability studies, for example, presumed genetic identity will not be constant.

*HS3.* All causes of phenotypic variation that impact human behavior can be attributed to a latent genetic (G) or environmental (E) parameter, or the interaction of the two (G × E).

The neogenome constitutes a class of heritable agents that does not fall into either category.

All of this places in doubt the validity of heritability estimates in all but a small class of traits (i.e., so-called monogenic disorders; see sect. 8.1). What this does not call into doubt, however, is the following: MZ twins are significantly more genetically concordant than DZ twins (and are likely most concordant in relation to SNPs), and this greater genetic concordance plays an important role in a wide range of intertwin phenotypic concordances. As we shall see, however, this fact may end up being of limited practical application, at least within the framework of the conventional genetic paradigm.

### 6.1. Three objections

**6.1.1. Objection 1: Biometric versus biomolecular genetics.** "Defense by distinction" is an expression coined by Tabery (2007; Tabery & Griffiths 2010) to characterize the manner in which defenders of the use of heritability estimates in behavior genetics have responded to objections by assorted developmentalists, including developmental psychologists, biologists, and embryologists. The distinction at issue could be characterized as that between a biometric analysis of the causes of phenotypic variation on the one hand and a biochemical analysis on the other. Let us call the former type of analysis *biometric* genetics, and the latter, *biomolecular* genetics. Biometric genetics is concerned with the question, *how much* do

various causal agents (genes and environment) contribute to phenotypic variation? Biomolecular genetics is concerned with the question, *how* do various causal agents contribute to phenotypic variation (or phenotype in general); for example, what are the particular physical causal mechanisms or pathways – genetic→biochemical→neurological→behavioral – by which a particular genotype contributes to a particular phenotype (Tabery & Griffiths 2010)? This distinction forms the basis of the following objection: In considering the ways in which the neogenome affects phenotype, I have been focusing on biomolecular genetics, something appropriately outside the purview of biometric genetics. In effect, I have been confusing different levels of analysis (Bouchard & Segal 1985; Plomin et al. 1977; Scarr 1995).

Although employing statistical analysis, biometric genetics must make contact with the natural world at some point. If it did not, it would have nothing to tell us about genetics. The assumptions of heritability studies (HS) 1–3 are three points of contact. They are not assumptions about variance or the proper application of statistical methods; rather, they are contingent *empirical* assumptions that form the basis for the application of those methods. For example, the assumption that MZ twins are genetically identical (HS1) is an empirical claim about the natural world. The *demonstration*[9] of why HS1 is invalid involves a consideration of those natural phenomena – neogenomic processes – the existence of which entails the non-genetic identity of MZ twins. This demonstration must also show *how* the neogenome entails the non-genetic identity of MZ twins. The answer to this *how* question involves an elaboration of the causal networks of physical entities: MZ twins are not genetically identical *because* of the stochastic partitioning of mtDNA, retrotransposition in the germline and somatic cells, and so on. In other words, it requires a detailed consideration of *biomolecular genetics*.

The assumption that the causes of variation in behavior can be partitioned between the latent parameters, genes (G) and environment (E) (HS3) – while itself an assumption about variance, depends upon the following assumption: G and E are exhaustive categories, and from the standpoint of heritability estimates, everything in the natural world that is relevant to phenotypic variance ($V_P$) can be partitioned into G, E, or G × E. Note that the assumption that causes of variance can be partitioned into the categories G, E, and G × E, does not entail that G *be* (Mendelian) genes and E the environment (everything else), but rather that they behave in the manner in which G and E are assumed to behave when estimating heritability. The problem is that the neogenome behaves like neither category.

Some germline neogenomic phenomena are transmitted according to the principles of Mendelian inheritance, for example, fixed germline CNVs, fixed retrotransposon insertions in the genome; others are not, for example, mtDNA, germline retrotransposition, intergenerationally transmitted epigenetic marks, and miRNAs. Variation in the latter cannot be assimilated to measurements of genetic variation ($V_G$): The *extent* to which $V_P$ is due to variation in germline retrotransposition, or germline epigenetic variation, cannot be estimated according to the principles of Mendelian inheritance, or dominance-recessiveness, or allelic epistasis, or G×E interaction. Why not? How do we know this? Not as a matter of traditional quantitative genetics, which if anything has concealed the extent to which phenomena that behave like neither G nor E influence $V_P$. Instead, we know this because of years of research in molecular genetics, biochemistry, and biology, and experiments with microorganisms, plants, and animals, that is, because of biomolecular genetics.

**6.1.2. Objection 2: Underestimated heritability.** If anything, genetic discordance between MZ twins entails that phenotype heritability has been *underestimated* (and therefore, current heritability estimates are conservative). This objection assumes what can be called the principle of causal ascription: Phenotypic concordances of MZ cotwins not ascribed to shared environment are ascribable to shared alleles. And this, in turn, depends on, first, the assumption that alleles that are the same will behave in the same manner, that is, assumption gene association studies (GAS) 2; and second, that all causes of phenotypic variation that impact human behavior can be partitioned between genetic variation (G) and environmental variation (E), or the interaction of the two (G × E), that is, assumption HS2. GAS2 will be considered later when we turn to gene association studies. As we have just seen, HS2 is invalid. It might be argued, however, that inasmuch as neogenetics is a cause of co-twin phenotypic *discordance*, HS2 is still relevant, that is, there are still two possible causes of phenotypic *concordance*: genes and environment.

The epigenome, however, can be a non-genomic cause of phenotypic concordance as well as phenotypic discordance, and studies have shown that discordance in methylation patterns is greater among DZ as opposed to MZ twin pairs (Fraga et al. 2005; Kaminsky et al. 2009). Greater discordances in DZ twin methylation profiles may be due to their having originated from two distinct oocytes and two distinct sperm bearing different epigenetic markings. Studies have shown that in healthy human subjects, the majority of sperm cells *of the same individual* exhibit different DNA methylation profiles (Flanagan et al. 2006). Male germ cells undergo unique and extensive epigenetic remodeling soon after their specification in embryonic stem cells and during the differentiation process to become mature spermatozoa (Puri et al. 2010; Seki et al. 2005). There are several lines of evidence that the epigenetic markings in sperm can influence embryonic development. For example, analysis of DNA methylation in sperm has identified hypomethylated promoters that reveal patterns of methylation similar to those found in embryonic stem cells (Farthing et al. 2008; Fouse et al. 2008).

There is also growing evidence for the role of miRNA in sperm as an agent for the intergenerational transfer of phenotype (Brykczynska et al. 2010; Cuzin & Rassoulzadegan 2010; Dadoune 2009; Grandjean et al. 2009). The development and function of the nervous system is orchestrated by a plethora of gene regulatory mechanisms, and miRNAs are emerging as important posttranscriptional regulators of gene expression in the brain (Gao 2008; Krichevsky et al. 2003; Meza-Sosa et al. 2012; Nelson et al. 2010). Micro RNAs function at all stages of neuronal development, ranging from the initial specification of neuronal cell types to the formation and plasticity of synaptic connections between individual neurons. Moreover, links between miRNA dysfunction and neurological diseases are becoming more apparent (Kuss & Chen 2008; Meza-Sosa et al. 2012; Nelson et al. 2008). One of the most abundantly

expressed miRNAs in the mammalian brain is the brain-specific miR-124 (Lagos-Quintana et al. 2002). In the mouse, miR-124 acts as a switch to induce neuronal differentiation: Its expression increases sharply during brain development and is maintained in differentiated neurons (Cheng et al. 2009; Krichevsky et al. 2003). Interestingly, the experimentally initiated expression of a miR-124 in non-neural cells results in a dramatic change of global gene transcribability toward a pattern usually found in neural cells (Lim et al. 2005; Makeyev et al. 2007).

In sum, there is growing evidence that heritable epigenetic elements, which are not transmitted in Mendelian fashion, can be an important component of phenotypic variation. Because MZ twins are derived from a single egg and sperm cell, and because epigenetic elements can vary significantly between individual germ cells of the same individual, greater phenotypic concordances of MZ twins could also be caused, in part, by greater epigenetic concordance. This conclusion might appear, if anything, to support an argument for the underestimation of heritability, albeit a different kind of heritability not based exclusively upon traditional principles of Mendelian genetic inheritance. As we shall see, however, neogenetics also likely play an important role in translating commonly overlooked environmental concordances into phenotypic concordances.

**6.1.3. Objection 3: Similar average effects.** If the neogenome affects the phenotypes of MZ twins, DZ twins, and siblings to the same extent, then the result will be similar average phenotypic differences (or similarities). In other words, the presumed ratio of genetic identity between MZ and DZ twins (1 to 0.5) and between siblings (0.5 to 0.5) will be preserved, on average, over time.

First, given all that we now know about genomic variation in germ cells and throughout the developmental process and the life course, there is no reason to assume that these ratios are preserved because there is no reason to assume that they ever existed. Second, to the extent that neogenetic phenomena appear to occur at a high rate during embryogenesis, differences in the intrauterine environment could differentially impact how the neogenome influences the phenotypes of MZ versus DZ twins. This point will require a more extended defense and will provide the opportunity to consider important aspects of the interplay between genes, the epigenome, and the environment, as well as the validity of the equal environment assumption. Recall that the attribution of MZ phenotypic concordance to genes depends upon an assumption of (trait-specific) equal environments: The environments of MZ and DZ twins are not considered to vary in a manner that would result in greater phenotypic concordance among MZ twins. As we shall see, this assumption clearly does not hold prenatally.

## 7. The maternal environment (maternal effects I)

It is well established that the prenatal environment can have profound influences on development with long-term metabolic and neurological consequences (Coe et al. 2003; Champagne 2010a; Field et al. 2004a; 2004b; Gluckman & Hanson 2006; Horton 2005; Heijmans et al. 2008; Huizink et al. 2002; Kemme et al. 2007; Langley-Evans et al. 1999; Lui et al. 2011; Maccari et al. 2003; Oberlander et al. 2008; O'Connor et al. 2005; Painter et al. 2005; Parnpiansil et al. 2003; Ryan & Vandenbergh 2002; Sandman et al. 2011; Schneider et al. 1999; Waterland & Michels 2007; Welberg & Seckl 2001; Weinstock 2008; Tamashiro & Moran 2010; Thompson 1957). The maternal environment begins prior to conception (during the formation of the oocyte), and the effects of this environment (maternal effects) begin at conception. Early embryonic development is not primarily controlled by the embryo's genome, but by the products of maternal genes deposited into the oocyte during oogenesis (Bettegowda et al. 2008; Johnson 2007). Fundamental early decisions of zygotic cell fate are controlled by factors within the oocytic cytoplasm (and it is hard to imagine an environment of greater developmental importance than that which determines cellular fate). This early phase of development is referred to as *maternal cytoplasmic control* (Evsikov et al. 2006).

The concept of developmental programming was put forward to explain the association between environmental challenge during pregnancy and later pathophysiology (Seckl 1998). During prenatal programming, environmental adversity is transmitted to the fetus and acts on specific tissues during critical developmental periods, changing their developmental trajectories (Harris & Seckl 2011). For example, epidemiological studies have shown that even moderately insufficient prenatal protein availability has detrimental effects on offspring brain development and subsequent behavior, cognition, and emotional reactivity (Almeida et al. 1993; Coupé et al. 2009; Galler et al. 1983; Reyes-Castro et al. 2011; Trzctńska et al. 1999; Watkins et al. 2008). In studies with baboons, Antonow-Schlorke et al. (2011) reported that moderate maternal undernutrition in early pregnancy led to major disturbances in the architecture of the fetal subventricular zone, a brain region critical for the birth of nerve cells, along with delayed maturation of the brain cortical-neuronal network.

Maternal stress during pregnancy – prenatal stress – has been associated in animal studies with abnormally high levels of fetal blood cortisol, which alters the development of neurons in the brain leading to many of the same morphological effects and behaviors that are observed in suboptimal prenatal maternal nutrition (Brown 2002; Brunton & Russell 2011; Lui et al. 2011; Mueller & Bale 2008; Reyes-Castro et al. 2011), including lifelong compromised neurodevelopment, enhanced stress reactivity, and increased fearful or anxious behavior. Coe et al. (2003) evaluated the behavior of juvenile monkeys whose mothers were subjected to stress induction during pregnancy as compared to controls. To induce stress, the pregnant female was acutely disturbed 5 days per week by being moved to a darkened test room and intermittently aroused with an acoustical startle protocol. At ages 2–3 years old, juvenile monkeys from undisturbed, normal pregnancies (control) were compared with offspring from mothers who were disturbed for 6 weeks during the 24-week pregnancy, either early (days 50–92 postconception) or late (days 105–147) (these periods correspond to two distinct stages of cell growth and synaptogenesis in the fetal monkey cortex) (Bourgeois et al. 2000). Offspring of both early and late prenatally disturbed pregnancies engaged in significantly lower levels of focused exploration (Fig. 3A), in line with prior research showing altered offspring emotionality after similar types of gestational

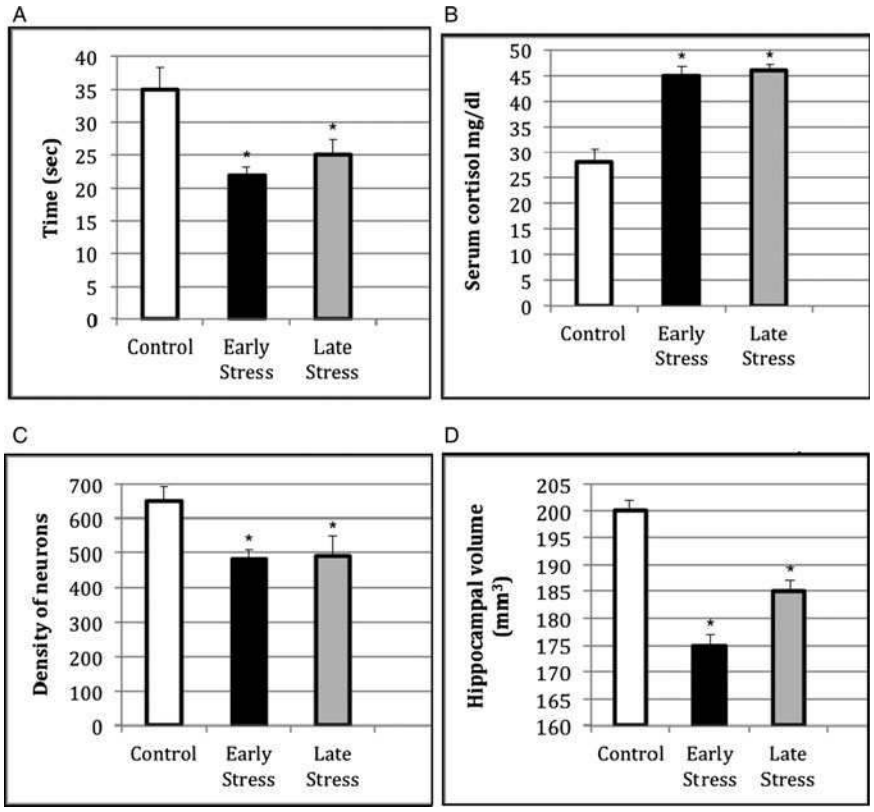


Figure 3. Differences in hippocampal volume and production of new neurons, serum cortisol, and exploratory behavior in monkeys from early- and late-stress pregnancies compared with controls. A. Exploratory behavior based on 12 observation sessions of 5 minutes each. Time spent in focused environmental exploration was significantly decreased in both the early- and late-stress monkeys as compared with control monkeys. B. Basal cortisol levels. C. Postnatal hippocampal neurogenesis. Cell proliferation in the dentate gyrus was significantly less in monkeys from both early- and late-stress pregnancies. D. Hippocampal volume measurements. Postmortem hippocampal volumetry revealed that prenatal stress resulted in a significantly reduced hippocampal volume in both early- (−12%) and late-stress monkeys (−10%). Adapted from Coe et al. (2003, pp. 1028–1029), with permission from Elsevier.

manipulations in monkeys (Clarke & Schneider 1993; Clarke et al. 1994; Schneider 1992). Monkeys generated from the early- and late-stress pregnancies had significantly higher cortisol levels than did controls (Fig. 3B), significantly reduced hippocampal neurogenesis (Fig. 3C), and significantly reduced hippocampal volume in both early (−12%) and late (−10%) stress protocols (Fig. 3D). In humans, prenatal stress has been associated with a wide array of adverse developmental outcomes and numerous cognitive and behavioral disorders including autism, depression, ADHD, schizophrenia, learning disabilities, and cognitive impairment (Beversdorf et al. 2005; Brouwers et al. 2001; Charil et al. 2010; Grizenko et al. 2008; Kinney et al. 2008; Lazinski et al. 2008; Li et al. 2010; Raikkonen et al. 2011; Sandman et al. 2011).

### 7.1. Neogenetics and prenatal stress

There is growing evidence that epigenetic programming by the prenatal maternal environment is an important mechanism in such phenotypic changes, involving processes similar to those implicated in postnatal epigenetic reprogramming by the maternal environment (Lillycrop & Burdge 2011; Lillycrop et al. 2008; Mesquita et al. 2009; Oberlander et al. 2008; Weaver et al. 2007). In animal models, exposure to chronic variable stress during the first trimester is associated with hypermethylation of the GR promoter in the hypothalamus, reduced methylation of the CRF promoter in the amygdala, increased HPA reactivity as measured by stress-induced corticosterone levels, and increased stress associated behaviors and anhedonia (Mueller & Bale 2008). Prenatal stress has also been associated with significant changes in specific miRNAs in the brains of male offspring and reduced anogenital distance and adult testes weight, which is consistent with decreased testosterone exposure *in utero* (Morgan & Bale 2011). In a study of 82 pregnant women, Oberlander et al. (2008) found increased levels of GR neonatal promoter methylation in infants born to depressed mothers and increased HPA stress reactivity at age 3 months in response to visual novel stimuli.

Offspring of female rats placed on a protein deficient diet throughout gestation exhibit elevated hepatic GR gene transcription associated with decreased DNA methylation, and decreased methylation and increased transcription of the peroxisomal proliferator-activated receptor (PPAR) gene, which codes for proteins that act as transcription factors (Mueller & Bale 2008; Oberlander et al. 2008), as well as epigenetic modifications to the renin-angiotensin system, a hormonal system that regulates blood pressure (Bogdarina et al. 2007; Goyal et al. 2010). These epigenetic changes have been associated with, among other phenotypes, offspring hypertension, insulin resistance, and obesity (Lillycrop & Burdge 2011).

A well-known example of epigenetic/phenotypic reprogramming via maternal prenatal diet concerns Agouti mice. Mice carrying the dominant *Agouti* allele $A^{vy}$ develop a complex set of traits collectively referred to as the yellow obese or yellow mouse syndrome, characterized by yellow fur, obesity, insulin resistance, and hyperglycemia (Miltenberger et al. 1997). Inbred $A^{vy}$ rodents raised in identical environments nonetheless exhibit significant variation in the severity of their agouti symptoms due to epigenetic differences. Mice with high levels of CpG methylation of the $A^{vy}$ allele exhibit fewer and milder symptoms (a phenotype referred to as pseudoagouti): The higher methylation levels reduce the levels of transcription of the abnormal $A^{vy}$ allele and consequently, the severity of the symptoms (Jirtle & Skinner 2007). When pregnant agouti mice are fed a diet supplemented with methyl donors (folate, choline, and vitamin B12), the phenotype of the offspring is shifted away from yellow to pseudoagouti (Dolinoy 2008; Waterland & Jirtle 2003; Wolff et al. 1998). The methyl supplements that the pup receives from the mother in the womb reprogram the pup's epigenome, effectively silencing the abnormal *Agouti* gene. Agouti offspring whose mothers receive no methyl supplementation exhibit no corresponding phenotypic shift.

Other neogenetic phenomena are likely involved in maternal programming in stressful prenatal environments. For example, in rats, prenatal stress has been shown to be associated with an increase in oxidative damage to mtDNA in fetal neural stem cells, leading to changes in their differentiation into distinct classes of neurons in the hippocampus (Cai et al. 2007; Song et al. 2009). Physiological cell stressors and viral infection can demethylate Alu elements, enabling them to retrotranspose (Li et al. 1999). Transposed elements can confer stress-inducibility to genes in their proximity (Naito et al. 2006) or protect those genes against stress via a small-RNA-mediated mechanism (Hilbricht et al. 2008). L1 mRNA and proteins can accumulate in stress granules, providing a cellular reservoir that could be quickly activated in response to environmental stimuli (Krichevsky & Kosik 2001). Moreover, androgenic steroids and steroid-like compounds involved in embryonic brain development, stress responses, and behavior can induce L1 activity (Zuloaga et al. 2008). A burst of retrotransposon activity may aid in rapidly generating genetic diversity in changing environments and in mammalian brain development, and maternal stress could impact L1 mobility in newly born neurons during embryonic development (Faulkner 2011; Marchetto et al. 2010; Singer et al. 2010). Hence, maternal diet and stress could affect the activation of transposable elements via reprogramming of the embryonic epigenome.

### *7.2. Twins and the prenatal environment*

**7.2.1. Twins versus singletons.** The prenatal environment of twins is on average more stressful than that of singletons. Twins have a death rate four times higher than singletons, and this figure is six times higher for triplets (Sutcliffe & Derom 2006). Twins are seven times more likely than singletons to die within a month of birth (Weber & Sebire 2010). The main reason for this elevated perinatal mortality is preterm and very preterm birth, resulting in low and very low birth weight. In singletons, twins, and triplets the frequency of low birth weight (<2,500 g) is 3.9%, 42.7%, and 64%; and for very low birth weight (<1,500 g), it is 0.7%, 7%, and 27% (Gielen et al. 2010). In singletons, the risk of childhood and adult disease is inversely related to birth weight across the birth weight spectrum (Larios-Del Toro et al. 2011; Richmond 1990), and extremely low birth weight is associated with poorer neurobehavioral and cognitive outcomes (Aarnoudse-Moens et al. 2009; Anderson & Doyle 2003; 2004; Orchinik et al. 2011; Taylor et al. 2009). While low birth weight is a consequence of prematurity, twins also exhibit lower gestational birth weight in the womb relative to singletons beginning in the third trimester (Blickstein et al. 2000). One likely cause of lower gestational weight is adaptive growth restriction, in which the restricted *in utero* environment results in the down-regulation of the growth of multiple fetuses early in gestation (Maulik 2006; Siddiqui & McEwan 2007).

Premature birth is associated with maternal stress (Dole et al. 2003; Dunkel Schetter 2011; Roy-Matton et al. 2011), as is gestational age at birth (Wadhwa et al. 1993). One reason for the higher level of prematurity among twins is the effect that a twin pregnancy has on the mother; in other words, a twin pregnancy is a cause of maternal physiological stress. Women pregnant with twins are 2.5 times more likely to develop preeclampsia (Sibai et al. 2000), a condition characterized by high blood pressure and protein excretion in the urine (proteinuria) that can lead to premature separation of the placenta from the uterus (placental abruption). Even in normal twin pregnancies without preeclampsia, the rate of maternal protein excretion is significantly elevated relative to singleton pregnancies, which translates into twins having significantly elevated levels of protein excretion relative to singletons (Smith et al. 2010). Mothers in twin pregnancies are also twice as likely to develop gestational diabetes, which is associated with increased risk of newborn death and stillbirth and an increased risk of offspring developing diabetes later in life. In the broadest sense, a congenital anomaly is an abnormality present at or before birth, usually as a result of faulty development, infection, or heredity. In a study of 2,329 twin pregnancies (4,658 twins) and 147,655 singletons delivered in the Northeast of England during 1998–2002, Glinianaia et al. (2008) reported that rates of congenital anomalies for twins were 405.8 per 10,000 twins versus 238.2 per 10,000 for singletons. The most common types of congenital anomalies were cardiovascular anomalies (28.0%), anomalies of the central nervous system (13.2%), genito-urinary system (13.7%), chromosomal anomalies (11.5%), musculoskeletal (10.4%), and others (17.0%). Twins showed higher rates of all major types of congenital anomalies than singletons except for chromosomal anomalies.

The principal neurological disability seen in twins is cerebral palsy (Ingram Cooke 2010). Petterson et al. (1993) reported cerebral palsy rates from the 1980s in Western Australia: Triplets had a rate of 28 per 1,000 live births; twins, 7 per 1,000; and singletons, 1.6 per 1,000. The risk for cerebral palsy was similar at low gestational ages but became higher for multiples as gestation approached term when rates were 4 per 1,000 for twins and 1.1 per 1,000 for singletons. When one twin died *in utero*, the cerebral palsy rate was 96 per 1,000 compared to 12 per 1,000 when both were born alive. Similarly, Scher et al. (2002) studied data from the 1980s on more than one million

births in the United States and Australia, of whom more than 25,000 were twins. Twins had a fivefold risk of fetal death, sevenfold risk of neonatal death, and fourfold risk of cerebral palsy compared with singletons.

Twins are not only at a greater risk for congenital disorders, but also for language delays. For example, since early last century, numerous studies have documented slower rates of language development in twins compared to singletons (Conway et al. 1980; Day 1932; Hay et al. 1987; McEvoy & Dodd 1992; Rutter et al. 2003; Thorpe 2006). On average, twins score lower than singletons on a range of tests of verbal competence, and this effect is more evident in male twins. The finding of language delay is significant behaviorally inasmuch as studies of singletons indicate that language delay has long-term consequences for children's academic attainment and emotional well-being (Rutter & Mawhood 1991).

**7.2.2. Monozygotic versus dizygotic twins.** Are MZ and DZ twins exposed, on average, to the same levels of prenatal stress? Clearly, they are not, and much of this difference is due to chorionicity. Monozygotic twinning occurs when a single fertilized egg gives rise to two separate embryos (the cause is unknown). If twinning takes place prior to the first 4 days after conception, two separate placentas and chorions, the outermost of two fetal membranes that surround the embryo (the amnion being the innermost), are formed, one for each embryo. Such twins are called dichorionic (DC) MZ twins and account for about one-third of all MZ twins.[10] If twinning occurs after this, a single placenta will develop. This single monochorionic (MC) placenta serves both embryos, and in 90% of cases, contains a network of blood vessels (placental anastomoses) that connect both twins, enabling ~1% of the total twin blood volume to be exchanged daily (Umur et al. 2001). About two-thirds of all MZ twins are MC. If twinning occurs after the eighth day of conception, the MC–MZ pair will also share a common amniotic sac in addition to a common placenta and chorion. About 5% of MZ twins are monochorinoic (MC) and monoamniotic (Machin & Keith 1999). Dizygotic twins, by contrast, are usually DC and diamniotic.[11] The varying patterns of blood vessels that connect MC twins commonly result in their receiving an unequal *in utero* blood supply resulting in unequal growth rates: 22% of MC twin pairs exhibit birth weight discordances greater than or equal to 20% total body mass (Senoo et al. 2000), and 10–15% of MC twins experience twin-twin transfusion syndrome (TTTS), which occurs as the result of a net transfer of blood from a donor twin to a recipient twin.

As Blickstein (2006, p. 235) notes of monochorionic twin pregnancies: "It is well accepted that monochorionic twin gestations – a subset of the monozygotic twinning phenomenon – carry a significantly higher perinatal risk compared with dichorionic ones." Chorionicity is one of the main predictors of perinatal mortality in twins: Monochorionic twins have a sixfold loss rate before 24 weeks gestation and two- to threefold increased risk of stillbirth and early neonatal deaths when compared with DC twins (Gibson & Cameron 2008; Glinianaia et al. 2011; Sebire et al. 1997). In a study of 2,329 twin births, Glinianaia et al. (2008) reported that the prevalence of congenital anomalies in MC twins (633.6 per 10,000) was nearly twice that in DC twins (343.7 per 10,000). Preterm delivery at less than 32 weeks occurs in 1% of singleton pregnancies, 5% of DC–MZ twins, and 10% of MC–MZ twins (Gibson & Cameron 2008). Fetal growth restriction complicates approximately 5% of all singleton pregnancies, 20% of DC–MZ pregnancies, and 30% of MC–MZ pregnancies. Ultrasonographic brain scans have indicated that MC twins have a sevenfold higher risk than DC twins of developing cerebral white matter lesions, which have been associated with increased risk of cerebral palsy, early cognitive impairment, and Alzheimer's disease (Adegbite et al. 2005). In regard to TTTS, a study by Dickinson et al. (2005), reported that the mean IQ score in TTTS twins born before 33 weeks, both donor *and* recipient, was 8 points lower compared with a non-TTTS comparison cohort.

Awareness of all of the risks associated with MC pregnancies is an established part of medical practice:

> Monochorionic twin pregnancies are at high risk of adverse foetal and neonatal outcomes. The chorionicity of a twin pregnancy can be diagnosed with a high degree of accuracy by ultrasound in the first and early second trimesters of pregnancy. Failure to diagnose monochorionic twin pregnancy is substandard care, as identification is required to plan intensive surveillance for complications throughout pregnancy. (Gibson & Cameron 2008, p. 572)

These are unambiguous indications that on average, the prenatal MZ twin environment is significantly more stressful than that of DZ twins, in large part because of differences in chorionicity (Acosta-Rojas et al. 2007; Adegbite et al. 2004; Carroll et al. 2005; Gibson & Cameron 2008; Hack et al. 2008). To the extent that the prenatal environment of MC–MZ twins results in unequal birth weight, it is a clear cause of phenotypic discordance. The effects of the maternal environment, however, cannot simply be classified as discordance producing (i.e., non-shared; Bouchard & McGue 2003). This is because the prenatal environment can be a cause of phenotypic *concordance* for MZ twins inasmuch as they are more likely to be exposed to the forms of prenatal programming – and to exhibit the corresponding phenotypes – that are associated with higher levels of prenatal stress. Furthermore, neogenetics appears to play a significant role in prenatal programming.

Let us recall objection 3 in section 6.1.3 – similar average effects: If the neogenome affects MZ twins, DZ twins, and siblings to the same extent, then the result will be similar average neogenomic differences (or average similarities), which would effectively preserve the presumed ratios of genetic identity. If the prenatal MZ twin environment is on average more stressful than that of DZ twins, and the DZ twin environment more stressful than that of singletons, and if neogenomics plays a role in translating these environmental differences into phenotypic variation, we would not expect neogenome-induced phenotypic differences (or similarities) to be the same among MZ twins, DZ twins, and singletons. In this regard, consider the following studies.

1. In a study of 2,329 twin births (mentioned earlier), Glinianaia et al. (2008) reported that the prevalence of congenital anomalies was nearly twice as great for MC (633.6 per 10,000) as DC (343.7 per 10,000) twins, while the rate for singletons was 283.2 per 10,000.

2. In a recent study, characterized as "the largest population based study of autism that used contemporary standards for the diagnosis of autism," Hallmayer et al. (2011) reported that when one MZ twin develops autism, the chance of the other twin developing the disorder is 70%.

They also found a sizable 35% overlap among DZ twins, which is notably higher than the 3–14% overlap between singletons.[12] According to Hallmayer et al. (2011, p. E7).

> Our study provides evidence that the rate of concordance in dizygotic twins may have been seriously underestimated in previous studies and the influence of genetic factors on the susceptibility to develop autism, overestimated.… Because the prenatal environment and early postnatal environment are shared between twin individuals, we hypothesize that at least some of the environmental factors impacting susceptibility to autism exert their effect during this critical period of life.

3. Knickmeyer et al. (2011) compared brain volumes and the relationship of brain volumes to gestational age in 136 singleton and 154 twin pairs neonates (82 DZ, 72 MZ) using high-resolution magnetic resonance imaging (MRI), and examined differences between the three groups, adjusting for gestational age at birth. Singletons had significantly larger estimated gray matter volumes (total, cortical, and parietal) at birth than DZ twins ($p < 0.001$, 7–9% difference), who had significantly larger gray matter volumes than MZ twins ($p < 0.001$, 20–25% difference). At the same time, total gray matter and cortical gray matter increased at a greater rate in MZ than DZ twins, and parietal gray matter increased at a greater rate in MZ twins than in DZ twins or singletons. The authors hypothesized that gray matter development is delayed *in utero* in MZ twins and that they experience a period of antenatal catch-up. This is consistent with postnatal correction for a process of prenatal adaptive growth restriction.

These studies point to the significance of variations in the prenatal environment – and prenatal neogenomics – in influencing twin phenotypes. While it is always possible that greater concordance rates among MZ versus DZ twins and singletons are due to greater genetic concordance, it is also possible that they are due to greater prenatal environmental concordance. This could account, at least in part, for the pattern that appears in several studies: MZ twin concordance>DZ twin concordance>singleton concordance.

There are three further implications of this that are relevant for heritability studies. First, to the extent that both MZ and DZ twins experience prenatal environments that are more stressful than that of singletons, the generalizability of twin studies is called into question. Second, to the extent that the prenatal environment of MZ twins (and MC–MZ twins in particular) can be significantly more stressful than that of DZ twins, and hence a cause of greater stress-related phenotypic concordance, the equal environment assumption will not hold in relation to behavioral phenotypes potentially associated with prenatal stress. Third, studies of twins raised apart are intended to eliminate possible confounding effects due to a shared environment,[13] but cannot eliminate the potential confounding effects of a shared prenatal environment (Table 2). This applies to singletons as well, inasmuch as adopted singletons have still experienced their biological mothers' prenatal environment.

Table 2. *Comparison between rat and human age*

| Rat Age | Effect on Hippocampal GR | Approximate Human Age |
|---|---|---|
| 1–7 days | Maximal effect | 2.4 months–1.6 years |
| 8–14 days | Moderate effect | 1.9 months–3.3 years |
| 15–21 days | No effect | 3.5–5 years |

## 8. Implications for gene association studies

Let us reconsider three assumptions of association studies (AS) 1–3:

*AS1.* Persons have identical DNA in all of the cells and tissues of their bodies (with the exception of germ cells and certain cells in the immune system).

Persons do not have identical DNA in all the cells and tissues of their bodies due to widespread somatic mosaicism.

*AS2.* The presence of a particular gene (polymorphism or mutation) entails that it is turned on – that is, it is capable of being transcribed in a manner that is associated with that polymorphism or mutation. Hence, the same two polymorphisms in any given two individuals will have the same capacity to be transcribed in the same manner (i.e., they will both be turned on).

The presence of a particular allele does not entail that it is capable of being transcribed in the manner associated with that allele, because it may be epigenetically silenced. In a characteristic candidate-gene association study, for example, allelic variants of a given gene are associated with variations in phenotype. The hypothesized causal link between the allele and phenotype is often expressed in terms of allelic differences in transcriptional efficiency or expression. For example, certain alleles of the monoamine oxidase A gene (MAOA) are deemed less transcriptionally efficient than others, with the more transcriptionally efficient alleles designated as high and the less transcriptionally efficient as low (Sabol et al. 1998), and have been associated with a host of behavioral (and non-behavioral) phenotypes (Caspi et al. 2002; Filonzi et al. 2009; Frydman et al. 2011; Fuemmeler et al. 2008; Tu et al. 2010).[14] Such studies depend upon the assumption that the high and low alleles of all who possess them are turned on, that is, they are capable of being transcribed in the manner associated with those alleles (or in a manner associated with those alleles interacting with a particular environment [$G \times E$]).

Suppose that persons A and B both possess the same allele of gene Z. However, due to differing early environmental effects (perhaps perinatal maternal effects), Z is hypermethylated (turned off) in person A and hypomethylated (readily transcribed) in person B. This could be functionally equivalent to A not possessing Z. The effects of methylation, however, are not simply binary (i.e., on/off). It is possible to talk about degrees of transcribability, with higher methylation being associated with lower transcribability and lower methylation with higher transcribability. Suppose that gene Z exhibits three allelic variations: long Z, associated with highly efficient transcription; intermediate Z, associated with intermediate transcription; and short Z, associated with inefficient transcription. Persons A and B both possess the intermediate allele of gene Z. However, due to differing environmental effects, intermediate Z is hypomethylated (higher transcribability) in A and hypermethylated (lower transcribability) in B. This could be functionally equivalent to A possessing the allele long Z and B possessing short Z.

*AS3.* Specific genes (polymorphisms/mutations) are coded for the production of specific proteins.

Specific alleles are not coded for the production of specific proteins or RNA molecules for a reason that has not yet been examined. The discovery that the human genome contains ~25–30,000 genes, as compared to, for example, greater than 32,000 genes in maize, that is, corn (Schnable et al. 2009), necessitated a rethinking of the assumption that for every protein there is a specific gene and each gene contains the instructions for making just one protein, inasmuch as there are likely over one million proteins in the human organism (Bernot 2004).

As noted earlier (sect. 4.1), human genes typically contain several DNA sequences that code for amino acids, known as exons, interspersed with several introns, non-coding regions. In gene transcription, the intron and exons are first copied to create what is known as pre-messenger RNA (pre-mRNA). *Alternative splicing* occurs when pre-mRNA exons are combined in various ways to form different proteins, called isoforms (Chen & Manley 2009; Nilsen & Graveley 2010). For example, the human fibronectin gene is translated into pre-mRNA that can be alternatively spliced into mRNAs that specify more than 20 different fibronectin proteins, each having different phenotypic characteristics, functions, and locations (Kornblihtt et al. 1996). Hence, *a single gene can code for multiple proteins,* something that is estimated to occur in 90% of all human genes (Yeo et al. 2004). The spatial and temporal control of alternative splicing is a major mechanism used to generate protein diversity in the brain and is regulated, in part, by miRNAs during neuronal development (Grabowski 2011; Makeyev et al. 2007), as well as by histone modification (Luco et al. 2010). Activity-dependent changes in alternative splicing have been noted in the rat brain, "indicating that the coordinated change of alternative splicing might contribute to the molecular plasticity in the brain" (Daoud et al. 1999, p. 788).

### 8.1. Multifactorialism

Most human traits with a genetic component are multifactorial (or complex), that is, they are polygenic, involving the biochemical products of hundreds and even thousands of genes (see below) interacting with each other and the environment in complex ways. Widespread epistasis, pleiotropy, the epigenome, retrotransposons, CNVs, aneuploidy, mtDNA, and alternative splicing render such traits even more complex. Consider the following:

1. Height is a highly heritable trait: 80% of the variation in height in a given population is attributable to genetic factors. A new, exceptionally large study involving full genome scans (genome-wide association studies, or GWAS) of more than 180,000 individuals identified 180 genomic regions that influence adult height (Lango et al. 2010). The variants on these 180 genes, however, explain only 10% of the heritable phenotypic variation in height in a given population. Current estimates are that anywhere from 1,485 to more than 7,244 polymorphisms are necessary to explain 45% of the variance of height.[15]

2. The largest genetic effects that have been identified for common psychological disorders via GWAS account, all together, for less than 1% of genetic variance (Franke et al. 2009; Plomin & Davis 2009). As Plomin and Davis (2009, p. 63) note:

> GWA studies suggest that for most complex traits and common disorders genetic effects are much smaller than previously considered.… This finding [of small genetic effects] implies that hundreds of genes are responsible for the heritability of behavioural problems in childhood, and that it will be difficult to identify these genes of small effect.

3. Researchers performed complete genome-wide gene expression and GWA scans of 40 lines of inbred *Drosophila melanogaster* (fruit flies), and their analysis implicated at least 266 unique candidate genes associated with natural variation in aggressive behavior (Edwards et al. 2006; 2009a; 2009b). The candidate genes were involved in a broad spectrum of biological processes, including vision, olfaction, learning and memory, and the development and function of the nervous system, as well as basic cellular processes including transcription, protein modification, and mitosis, indicating that the single alleles involved in aggression have pleiotropic effects on multiple traits. Furthermore, the findings are consistent with extensive epistasis. At the same time, the heritability of aggressive behavior in *Drosophila* is relatively low (~0.1). Expressing the genetic and environmental variances of aggressive behavior as genetic and environmental coefficients of variation ($CV_G$ and $CV_E$, respectively), they found that $CV_G = 23.2$ and $CV_E = 71.9$. Thus, the low heritability is not due to a lack of segregating genetic variation, which is abundant, but to a high level of environmental variance.

Given this, we would not expect to find among common gene variants single gene effects that confer a sufficiently high odds ratio to be predictive of a phenotype: If a common polymorphism conferred a high odds ratio, it would have to be the principal contributor to the overall prevalence of the phenotype (Galvan et al. 2010; Hirschhorn et al. 2002; Ioannidis et al. 2006; Zondervan & Cardon 2004). The discovery that many genes of small effect size contribute to traits known to be highly heritable (such as height) helps toward explaining the so-called missing heritability problem (Manolio et al. 2009). This refers to the fact that despite thousands of genome-wide and candidate-gene association studies, very few genes have been identified that are reliably (i.e., consistently) associated with complex phenotypes (Need & Goldstein 2010). In the words of Conrad et al. (2010), to date, GWAS have left a "heritability void." Retrotransposition, CNVs, aneuploidy, mtDNA, and the epigenome, doubtless all contribute to missing heritability (Slatkin 2009). It is unlikely however, that methylation on a single gene, or a single CNV, or a single retrotransposon insertion will be the principal genetic contributor to a complex trait any more than an SNP.

These phenomena are also likely part of the answer to another absence of correlation, namely, that between human phenotypic complexity and genome size (e.g., humans possess fewer genes than corn). This lack of correlation is referred to as the C-paradox (the C-value refers to the amount of DNA contained in a gamete, or one-half the amount of DNA contained in the nucleus of a somatic cell) (Biemont & Vieira 2006). Most of the differences in genome size between species reside in the non-coding parts (such as the 45% of the human genome that is composed of transposable elements). For example, the human genome is composed of 98% non-coding regions of DNA (International Human Genome Sequencing Consortium 2004), whereas the fruit fly, *Drosophila melanogaster*, has

a very compact genome with fewer sequences of this kind (Clark et al. 2007; Dowsett & Young 1982; Hoskins et al. 2002; Rebollo et al. 2010). This is highly suggestive, especially if we consider that two major classes of retrotransposons are *primate specific* (see sect. 4.1).

**8.1.1. Monogenics.** There are, of course, exceptions to what might be called the non-predictiveness of SNPs. The most obvious example concerns not SNPs, but mutations associated with so-called monogenic disorders. However, even in completely penetrant monogenic disorders, the poster child for Mendelian inheritance, things are turning out to be a lot more complicated than once thought. One reason concerns the possibility of many different allelic mutations on the same gene locus being associated with the disorder, for example, more than 1,400 different mutations on the cystic fibrosis transmembrane conductance regulator (CFTR) gene have been identified thus far that can cause cystic fibrosis, a recessive disorder, and different mutations have been associated with differences in disease phenotype (Bobadilla et al. 2002). More important, even when two individuals have the same mutation for the same completely penetrant monogenic disorder, it is often extremely difficult to predict phenotype on the basis of genotype alone. Consider the following two quotes from researchers in this field:

> An African American male infant with sickle cell disease has a devastating stroke; an African American soldier is surprised when he is informed that he has sickle cell disease. They are both homozygous for the same mutation. An Ashkenazi Jewish woman with Gaucher disease has a huge spleen and severe thrombocytopenia; her older brother, homozygous for the same … mutation, is found on routine examination to have a barely palpable spleen tip.… Such siblings must surely be carrying the same 2 disease-producing alleles. With the advent of sequence analysis of genes, the great extent of phenotype variation in patients with the same genotype has come to be more fully appreciated, but understanding of why it occurs continues to be meager. (Beutler 2001, p. 2597)

> The dogma in molecular genetics until the 1990s was that genotype would predict phenotype. We thought that once we cloned and characterized the gene, then the nature of the mutation in the gene would specify the individual's phenotype.… This concept celebrated reductionism. However, nature had not informed the patients and their biology of this belief system. Not only could we not predict phenotype for genotype for GK [glycerolkinease deficiency] and AHC [congenital adrenal hypoplasia], similar observations were being made by others for many rare [monogenic] genetic disorders. (McCabe & McCabe 2006, p. 160)

What this indicates is that the *phenotypes* of single gene disorders *are in fact complex traits* (Nagel 2005; Weatherall 2000), influenced by multiple genetic, epigenetic, and environmental factors:

> One promise of molecular genetics for many of us was that a detailed knowledge of mutant alleles would permit accurate prediction of prognosis and better selection of therapeutic strategies for Mendelian disorders. This presumed predictive promise was naive and was based on a reductionist view of genotype-phenotype correlations, i.e., that a refined and specific knowledge of a mutation's impact on protein structure and function would permit extrapolation to the phenotype of the intact organism. The reality of molecular genetics, however, is that for many diseases only a subset of mutations reliably predicts phenotype. This lack of genotype-phenotype correlation for many Mendelian disorders shows us that the clinical phenotypes of "simple" Mendelian disorders are complex traits. (Dipple et al. 2001, p. 45)

Nonetheless, for the most part, completely penetrant monogenic disorders entail that two individuals with the same mutation will have the disease, even if they exhibit significant *phenotypic* differences.

There are exceptions to the non-predictiveness of SNPs in relation to polygenic traits, in the sense that the association between a polymorphism and a complex trait appears to be reliably reproduced, and the association is of such a magnitude that the polymorphism can be deemed a risk factor. The most reliably reproduced are: The E4 variant of the apolipoprotein E gene, ApoE, which greatly increases the risk of Alzheimer's disease; the association of an amino acid substitution in the complement factor H gene, CFH, with age-related macular degeneration; and a variant in the LOXL1 gene with exfoliation glaucoma, a common form of age-related blindness (in the case of the latter two, however, the SNPs are so prevalent in the population that they lack predictive value) (Need & Goldstein 2010). Why these are exceptions is not entirely clear, although it may be an indication that they are *oligogenic* disorders involving polymorphisms on a small number of genes and hence are more akin to monogenic disorders than to most human traits. As such, they are exceptions that prove the rule.

## 9. Phenotypic plasticity

The inability to predict complex phenotypes on the basis of genotype alone is precisely what we would expect in an organism possessed of any degree of *phenotypic plasticity*. Phenotypic plasticity can be defined broadly as the ability of an organism to change phenotype in response to its environment (Pigliucci et al. 2006). This includes the possibility of modifying developmental trajectories in response to specific environmental cues, and the ability of an individual organism to change its phenotypic state or activity in response to variations in environmental conditions (Garland & Kelly 2006). Modern evolutionary biology reflects the idea that adaptation is not limited to the process of natural selection (i.e., adaptation at the level of the species), but includes adaptation of the individual organism to its *ecological niche*. Offspring do not inherit simply genes from their parents, but also an environment (Gluckman et al. 2009; West-Eberhard 2003; West & King 1987). Developmental plasticity evolved because it is *adaptive*, promoting Darwinian fitness by enhancement of survival and reproductive success by using environmental cues to optimize the life-course strategy. As Pigliucci (2010, p. 357) notes, "Phenotypic plasticity is now the paradigmatic way of thinking about gene-environment interactions (the so-called nature–nurture problem) and one of the best studied biological phenomena in the evolutionary literature, with knowledge steadily advancing about its genetic molecular underpinnings (Schlichting & Smith 2002; Suzuki & Nijhout 2008), ecological role (Callahan & Pigliucci 2002; Nussey et al. 2007), and evolution (Paenke et al. 2007; Pigliucci & Murren 2003)."

### 9.1. Maternal effects II

Adaptive phenotypic plasticity is apparent in plants, invertebrates, amphibians, reptiles, fishes, birds, and mammals.

What unites almost all species is the centrality of maternal effects – or maternal programming – as a mechanism of phenotypic plasticity (Bernardo 1996; Maestripieri & Mateo 2009; Mousseau & Fox 1998; Wade 1998; Zhang et al. 2006). Maternal effects are the effects of a mother's phenotype upon the phenotype of offspring and are distinguished from direct genetic effects, that is, the phenotypic effect upon offspring of inheriting maternal genes (Mousseau & Fox 1998). Offspring behavioral plasticity enables the mother to adjust the phenotype of offspring in response to the environment she inhabits and, in doing so, in effect transmit to them information about the environment they will inhabit. If the mother's adjustments to the environment are adaptive, and if the environment is stable across generations, that is, if the cues from the mother's environment are a good predictor of the environment in which offspring will find themselves, then the offspring's phenotypic adjustments are adaptive (Badyaev & Oh 2008; Qvarnstrom & Price 2001). A high degree of phenotypic plasticity may also imply that sometimes maternal effects can be maladaptive. For example, if the environment changes in relevant respects, maternal modifications of offspring phenotype may be maladaptive. Therefore, maternal effects may also provide a mechanism by which maladaptive phenotypic traits are transmitted across generations (Gluckman et al. 2009; Mastripieri & Mateo 2009).

Consider a few examples across species:

1. Storm and Lima (2010) studied differences in the behavior of offspring of gravid crickets from two different environments. In one environment, the gravid mothers were regularly exposed to a predator, the wolf spider *Hogna helluo,* while the other environment was predator free. The offspring of *Hogna*-exposed gravid mothers displayed increased antipredator immobility in response to *Hogna* chemical cues and significantly higher survival rates in the presence of *Hogna* relative to the offspring of non-exposed mothers. According to Storm and Lima (2010, p. 383), this was an example of "a transgenerational maternal effect in antipredator behavior that takes the form of a 'warning' about predators that female fall field crickets *Gryllus pennsylvanicus* transmit to their offspring."

2. Female birds are able to alter many aspects of egg composition, including nutrients, hormones, antioxidants, immunoglobulins, and even embryo sex, in response to food availability, levels of sibling competition, and the quality of their mates (Adkinsregan et al. 1995; Groothuis & Schwabl 2008; Horváthová et al. 2012; von Engelhardt et al. 2006). Such maternal effects can result in the influence of a particular environmental factor on phenotypic development persisting across a number of generations, even if the factor itself has altered.

3. In mammals, including humans, any imbalance of nutrient intake, such that one or more nutrients is limiting, will produce adaptive responses in the developing fetus (Bellinger et al. 2004; 2006; Godfrey et al. 2011; Wiedmeier et al. 2011). These metabolic adaptations ensure the immediate survival of the fetus in a less than optimal fetal environment, while long-term modifications to organ structure, hormone responsiveness, or gene expression may predispose to metabolic disorders in later life (Godfrey et al. 2011; Lillycrop & Burdge 2011; Tamashiro & Moran 2010). This is precisely what we saw in examining the prenatal environment of twins (sect. 7.2) in which an adaptive response – growth restriction – ensures the survival of twins in a suboptimal prenatal environment.

4. Numerous studies have shown that offspring olfactory cues and food preferences in both humans and other mammals can be shaped by the maternal prenatal diet *in utero* and the postnatal environment during lactation (Becques et al. 2010; Bilkó et al. 1994; Cooke & Fildes 2011; Hausner et al. 2010; Hepper 1995; 1988; March et al. 2009; Pedersen & Blass 1982; Schaal et al. 1995; 2000; Semke et al. 1995; Simitzis et al. 2008; Smotherman 1982). For example, a recent study with mice examined whether maternal exposure to the artificial sweetener acesulfame-K (AK) during pregnancy or lactation affected the sweet preference of adult offspring (Zhang et al. 2011). At 8 weeks after birth, preference scores for AK and sucrose were significantly elevated among exposed – both in utero and via nursing – as opposed to non-exposed offspring. The researchers were also able to correlate maternal ingestion of AK with AK in both amniotic fluid and breast milk. Human infants whose mothers consumed, for example, carrots, anise, garlic, and fruits during breastfeeding (Mennella & Beauchamp 1999; Mennella et al. 2001; Schaal et al. 2000) (Cooke & Fildes 2011), or who were fed vanilla-flavored (Gerrish & Mennella 2001) or vegetable-flavored (Mennella et al. 2006) formula showed marked preferences for these foods and flavors. Furthermore, studies have shown that breast-fed, as opposed to formula-fed, infants are more receptive to diverse food flavors (Forestell & Mennella 2007; Maier et al. 2007; 2008). This may be due to the greater variety of flavors to which an infant is exposed via mother's milk (which can transmit a variety of flavors from the mother's diet).

Adversity during perinatal development can forecast an increased level of demand in the environment the offspring will occupy. Under such conditions, the animal's best interest is to enhance its behavioral (e.g., vigilance, fearfulness) and endocrine (HPA and metabolic) responsiveness to stress (Champagne et al. 2003a). These responses promote detection of potential threat, avoidance learning, and metabolic/cardiovascular responses that are essential under the increased demands of the stressor. In regard to maternal rearing behavior, under high-risk conditions, when the probability of extended periods of growth and survival are low, the optimal strategy is to maximize the number of offspring through accelerated mating, increasing the chances that at least some offspring will survive to reproductive maturity (Cameron et al. 2008). Moreover, since adverse environments are characterized by high, unavoidable risks and thus increased mortality, parental investment in offspring quality may be futile (Gangestad & Simpson 2000). Such conditions favor a shift in reproductive investment toward quantity. In contrast, more favorable environmental conditions favor greater investment in individual offspring at the cost of mating, since offspring quality predicts successful competition for available resources and reproductive fitness.

We saw (sect. 5.2.1) how maternal rearing behavior can shape the rearing behavior of offspring through epigenetic reprogramming. Further studies with rodents have shown that the female offspring of low-LG mothers exhibit, in addition to changes in levels of estrogen receptor α (ERα) expression, increased sexual receptivity; increased levels of plasma luteinizing hormone, which regulates a number of aspects of the female menstrual cycle; increased

levels of fetal testosterone at embryonic day 20; and accelerated puberty compared to offspring of high-LG mothers (Cameron et al. 2008; 2011; Jia et al. 2011; Sakhai et al. 2011). These changes were associated with earlier puberty and earlier and increased sexual activity in the female offspring of low-LG versus high-LG mothers. There is evidence that human reproductive strategies in adverse environments exhibit a similar dynamic. Studies have shown that stressful early life conditions, including family relations, are associated with earlier age at menarche (Chisholm et al. 2005; Ellis 2004; Ellis & Garber 2000; Graber et al. 1995; Moffitt et al. 1992; Saxbe & Repetti 2009), and earlier age at menarche is associated with earlier onset of sexual behavior and reproduction (Andersson-Ellström et al. 1996; De Genna et al. 2011). In other words, being raised in a stressful environment is associated with accelerated mating.

### 9.2. Human exceptionalism?

On the basis of several highly influential studies of twins raised apart conducted in the 1980s, researchers concluded that when it comes to behavioral concordances, the shared rearing environment has an effect statistically indistinguishable from 0 (Plomin & Daniels 1987). Genetic factors were almost wholly responsible for behavioral concordances. Rearing environmental influences were instead largely a cause of *discordance* (i.e., were non-shared):

> [W]hen the genetic basis of parent-offspring resemblance is controlled by studying adoptive families, the association between child-rearing strategies and offspring behavior (McGue et al. 1996) and the relationship between home characteristics and intellectual achievement (Scarr 1997) are nearly eliminated. Behavioral genetic research on the minimal effect of shared environmental factors … challenges the validity of a vast amount of psychological research aimed at identifying environmental risk. (McGue & Bouchard 1998, pp. 14–15)

This absence of shared environmental influence led some behavioral geneticists to conclude that to the extent that parents impact child outcomes, they do so at a child-specific, rather than a family-wide, level:

> Quantitative genetic methods, such as twin and adoption methods, were designed to tease apart nature and nurture in order to explain family resemblance. For nearly all complex phenotypes, it has emerged that the answer to the question of the origins of family resemblance is nature – things run in families primarily for genetic reasons.… If genetics explains why siblings growing up in the same family are similar, but the environment is important, then it must be the case that the salient environmental effects do not make siblings similar. That is, they are not shared by children growing up in the same family – they must be "non-shared".… "Nurture" in the nature–nurture debate was implicitly taken to mean shared environment because from Freud onwards, theories of socialization had assumed that children's environments are doled out on a family-by-family basis. In contrast, the point of non-shared environment is that environments are doled out on a child-by-child basis. (Plomin 2011, p. 582)

Plomin's point, however, is not that all environmental influences are non-shared, but that "most environmental influence for most traits is non-shared" (Plomin 2011, p. 583). Although, as behavior geneticists have themselves noted, such a finding challenges the validity of a vast amount of psychological research (McGue & Bouchard 1998; Bouchard 2004), nonetheless, it has been widely accepted (Burt 2009). Maternal effects, prenatal and postnatal, are phenotypic concordance-producing effects; or in the language of behavior genetics, they are *shared environmental effects.* As Mateo (2009, p. 134) notes: "Parental effects lead to parent-offspring resemblance, which can be adaptive if offspring encounter similar social and environmental features as adults." For example, all of the studies cited earlier concerning postnatal epigenetic reprogramming of offspring via maternal rearing behavior demonstrated the *transmission* of maternal behavior on both the molecular and phenotypic level; that is, offspring came to resemble their (rearing) mothers. In doing so, they also came to resemble each other. Of course, offspring may differ in the degree or manner in which specific behavioral phenotypes are shaped by the perinatal environment due to any number of genetic, epigenetic, and micro-environmental differences (such as fetal position), or on the basis of sex. These same differences, and countless others, entail that the maternal environment can simultaneously be a cause of phenotypic discordance. Nonetheless, particularly in animal studies where the typical litter may contain up to 10 pups, the concordance-producing effects of the maternal environment on offspring behavior are obvious (Champagne 2010a; Champagne et al. 2003a).

Were it true that there were no (or minimal) maternal effects upon the behavior of human offspring, then humans would indeed be exceptional among all animal taxa. What this would entail is that humans possessed less behavioral phenotypic plasticity, were less capable of being behaviorally shaped by maternal effects, than rodents. Any assumption of the absence of maternal effects, both prenatally and postnatally, seems doubly counterintuitive given that maternal effects appear to play a larger role in the evolutionary dynamics and adaptation of mammals than in any other animal taxa (Fusco & Minelli 2010; Mastripieri & Mateo 2009; Uller 2008). As Chevrud and Wolf (2009, pp. 13–14) note:

> Maternal effects are particularly important for mammals where the maternal-offspring relationship is prolonged and intimate. Indeed, the very name of the class Mammalia refers to the specialized organ by which the mother feeds her offspring at birth.… From the time of implantation to birth, the fetus will draw nutrients, oxygen, and hormones and dispel wastes through the placenta rather than processing them through its own immature organs.… The period prior to weaning provides some of the greatest opportunity for survival selection (Crow & Kimura 1970) on the offspring during life.… Thus, the joint evolution of maternal effects and offspring phenotypes plays a critical role in mammalian evolution.

As mammals, humans have extended and intimate maternal associations, both pre- and postnatal, lasting many years. Yet, in the absence of maternal effects, *what is this commitment for,* involving as it does an enormous expenditure of maternal time and energy? Just as pressing is the question as to what possible *adaptive advantage* could accrue to the human species by lacking the plasticity to be behaviorally shaped by maternal effects to better meet the demands of its environment, when such a lack is clearly maladaptive. To see just how maladaptive, consider the following three examples:

1. A gravid mother rabbit consumes throughout the perinatal period a berry that is nutritious and grows in

abundance in an environment that has an otherwise limited food supply (Bilkó et al. 1994; Semke et al. 1995). Given minimal maternal effects, her offspring have no predilection for the berries. Postweaning, they die of starvation.

2. A dam inhabits a very dangerous environment beset by numerous predators. She has high levels of circulating corticosterone and behaviorally displays heightened reactions to stress. She devotes less time to maternal care and more time to being vigilant against predators. Given minimal maternal effects, her offspring, postweaning, exhibit modest stress responses and moderate levels of fearfulness. They are eaten in short order.

3. The major histocompatibility complex (MHC) is a set of molecules on the surface of cells that play a central role in the immune system and self- or non-self-recognition. The genes coded for MHC molecules are among the most polymorphic coding loci known among vertebrates (Klein 1986). Differences in the MHC are associated with different odors, and studies in both animals and humans have indicated a mating preference for individuals whose odor is associated with dissimilar histocompatibility genes (Havlicek & Roberts 2009; Wedekind & Furi 1997). It is hypothesized that MHC dissociative mating preferences function to produce disease-resistant, MHC-heterozygous offspring, or to reduce inbreeding, or both (Apanius et al. 1997; Brown & Eklund 1994; Potts & Wakeland 1993). Cross-fostering studies with animals have shown that histocompatibility scent preferences are determined by the scent of the rearing, not the biological mother (Ihara & Feldman 2003; Penn & Potts 1998). Given minimal maternal effects, offspring are not affected by their mother's scent one way or another. They inbreed and produce a line of disease-ridden offspring that will die out in several generations.

## 10. Postgenomics

One of the major theoretical conclusions to emerge from the growing field of systems biology – a self-professed postgenomic discipline that attempts to mathematically model biological networks – is that causation in biological systems runs in both directions: upward from the molecular level (which includes the genome), and downward from all other levels – cellular, tissue, organ, organism, external environment (Noble 2010; Shapiro 2009). There are feedback and feed-forward loops between different levels, and developing the mathematical and computational tools to deal with these multiple levels of causation is a major challenge (Srividhya et al. 2011). No one level is privileged or controlling. DNA is no longer privileged as the sole carrier of information (Jablonka & Lamb 2005).[16] Identical DNA sequences exist in phenotypically different cell types: These phenotypic differences are due to epigenetic programming of DNA, which carries the information as to which genes can be transcribed and proteins synthesized in a given cell. Which protein is produced from a given genomic sequence is not determined by the sequence itself, but by the cell, which through alternative splicing determines which isoforms will be produced in response to external and internal signals. Neither the genome nor the epigenome determine the nature of the prenatal environment that will induce changes in both.

For phenotypes of any degree of complexity, DNA does not contain a determinate genetic program (analogous to the digital code of a computer) from which we can predict phenotype. If DNA were the sole carrier of information relevant to phenotype formation, and contained a genetic program sufficiently determinate that solely by reading it we could predict phenotype, then humans (and all other organisms) would be largely lacking in phenotypic plasticity. Phenotypic plasticity is one of the keys to adaptation and species survival. However, to state that the Genome is not the sole biological agent of heritability or the sole carrier of information and hence not privileged among other heritable biological agents, the environment (at all levels), and the developmental process is of course not to claim that it is *less* critical than any of these. It is, rather, to claim that it is an integral component of an exceedingly complex, integrated, interactive, multilevel process.

What, then, are the implications of all of this for the future of the two methodologies in behavior genetics that I have considered? The challenges for traditional heritability estimates are formidable (Richards 2009; Wells & Stock 2011). How might we go about incorporating neogenomic phenomena into heritability estimates? Here is a description of just such an endeavor in relation to epigenetic inheritance:

> Interindividual differences in chromatin states at a locus (epialleles) can result in gene expression changes that are sometimes transmitted across generations. In this way, they can contribute to heritable phenotypic variation in natural and experimental populations independent of DNA sequence. Recent molecular evidence shows that epialleles often display high levels of transgenerational instability. This property gives rise to a dynamic dimension in phenotypic inheritance. To be able to incorporate these non-Mendelian features into quantitative genetic models, it is necessary to study the induction and the transgenerational behavior of epialleles in controlled settings. Here we outline a general experimental approach for achieving this using crosses of epigenomically perturbed isogenic lines in mammalian and plant species. We develop a theoretical description of such crosses and model the relationship between epiallelic instability, recombination, parent-of-origin effects, as well as transgressive segregation and their joint impact on phenotypic variation across generations. In the limiting case of fully stable epialleles our approach reduces to the classical theory of experimental line crosses and thus illustrates a fundamental continuity between genetic and epigenetic inheritance. We consider data from a panel of *Arabidopsis* [a plant frequently used as a model organism in research] epigenetic recombinant inbred lines [epiRILs] and explore estimates of the number of quantitative trait loci for plant height that resulted from a manipulation of DNA methylation levels in one of the two isogenic founder strains. (Johannes & Colome-Tatche 2011, p. 215)

It should be noted that the path ahead travels through biomolecular genetics. Nonetheless, if the objective is to incorporate neogenomics into heritability estimates, this passage also indicates some of the obstacles. To begin with, even inbred *Arabidopsis* are not genetically identical and their genetic identity is not fixed, as researchers employing *Arabidopsis* for the same purpose of analyzing epigenetic heritability have noted. Johannes et al. (2009) and Reinders et al. (2009) created two inbred lines of *Arabidopsis*, each containing different mutations that would disrupt methylation at specific epialleles (epiRILs):

> Standard … approaches to identify important epialleles affecting complex traits using these epiRILs will be frustrated by

> the fact that the new epigenetic variation is often unstable and not sequestered in tidy blocks that can be traced unambiguously to one or the other parent. Confounding matters further, there is another type of variation generated in the epiRIL lines that undermines the premise of the lines' construction. In both the *met1*- and *ddm1*-derived epiRILs, two lines with defective genes … transposons are mobilized.… These DNA elements lose epigenetic silencing and are activated in the *ddm1* mutant parents (Miura et al. 2001). Once these elements shed their epigenetic silencing, they continue to jump in the different *ddm1*-derived epiRIL lineages. (Richards 2009, p. 1604)

The mobilization of transposons is not, however, a phenomenon that results only from defective genes. In humans, their mobilization is a normal part of embryogenesis, leading to their jumping around in the brains of MZ twins, altering their neural genomes. Furthermore, active transposons are present in the germline and L1 RNA is heritable, but in a non-Mendelian manner. Nor are methylation and histone remodeling the only heritable forms of epigenetic regulation. The vast system of miRNA posttranscriptional regulation of DNA is also heritable via the germline, and although it appears to affect every aspect of human development and functioning, we still have very little knowledge as to its manner of inheritance, how it operates, and how it affects phenotypes. This passage also shows, in a very clear way, that although epialleles, their methylation patterns, and transposons may all be inherited, albeit according to different processes and principles, *they do not act as separate lines of causal influence.* Rather, they continually interact because their interaction is essential to normal organismic development and functioning (i.e., if methylation did not repress transposition, it would run amuck with fatal consequences; if the waves of demethylation that occur during human embryogenesis did not allow the activation of retrotransposons, the consequences would also be fatal).

Attempting to compose a formula that could be used to estimate the extent to which variation in anything inherited via the germline could affect phenotype shows the nature of the problem. We would need to begin by identifying each of those heritable agents, for example, $V_{TE}$ (transposable elements), $V_{miRNA}$ (miRNA), $V_{METH}$ (methylation profile), $V_{HM}$ (histone modification), $V_{L1\text{-}RNA}$ (L-1 RNA), $V_{mtDNA}$ (mtDNA), and $V_{ANEU}$ (aneuploidy). It is likely that not all transposable elements, and not all miRNAs, are heritable to the same extent or in the same way, so we might need to break them into subcategories. Alongside the question of measurement is the question as to how these terms should be related. We know that there are innumerable interactions, for example, $V_{TE} \times V_{METH}$, $V_{TE} \times V_{HM}$, $V_{TE} \times V_{L1\text{-}RNA}$, $V_A \times V_{miRNA}$, $V_A \times V_{METH}$, $V_A \times V_{L1\text{-}RNA}$, $V_A \times V_{ANEU}$, $V_{mtDNA} \times V_{METH}$, $V_{mtDNA} \times V_{miRNA}$, $V_{mtDNA} \times V_{TE}$, and so on (this is of course a highly simplified schematic, since the effects of interaction between two sources of variance can interact with a third source of variance, and so on). Every one of these agents interacts with the environment, prior to conception (in the germ cells) and during embryogenesis. I suggest that in a situation such as this, this question does not make a lot of sense: "Which contributes more to variation in a complex behavior, genes or environment?" (And if the reader is inclined to doubt the relevance of all of these nongenomic heritable agents for human behavior, recall that humans possess fewer genes than corn, and although possessing only ~25,000 genes, the human organism produces well over a million proteins.)

Gene association studies, particularly with advances that will allow parallel sequencing of multiple tissues simultaneously and the simultaneous search for multiple genetic markers – SNPs, CNVs, and transposon insertions – hold out promise for future research. However, from a postgenomic perspective, the operating assumption should be that in most cases, genotype alone will not predict phenotype. Even when what seem to be statistically significant correlations have been found, they must always be considered within a wider context of research, and ideally combined with other levels of analysis. These include global and tissue-specific methylation profile and miRNA analysis, as well as the analysis of mRNA and protein levels. The analysis of mRNA and proteins has the advantage of showing DNA transcription in action, reflecting the combined inputs and decisions of multiple physiological and environmental players whose behavior is not entirely determined or regulated by DNA itself. This has sparked the development of new research methodologies in which, for example, the transcriptome and the proteome are viewed as modes (or levels) of analysis more productive than an exclusive focus on the genome (Crameri et al. 2005; Martin & Wang 2011; Nagaraj et al. 2011; Yu et al. 2004).

The incorporation of newly discovered heritable agents and assorted *-omics* is still likely to yield insufficient predictive capacity, however, without a thorough consideration of possible environmental factors as contributing agents. From the postgenomics perspective, the environment is as much a carrier of information as the DNA sequence, both for shaping phenotype and as a source of information in trying to predict phenotype. An awareness of developmental biology and the concept of phenotypic plasticity needs to inform any search for predictors of behavior, and known domains and mechanisms of plasticity should be a part of every investigation. This begins, naturally, with the fetal environment. Hence, researchers need to examine not just the parents' genomes, but the mother's behavior during pregnancy and birth – her nutrition, stress levels, lifestyle, mode of interaction with offspring, levels of maternal care, breast-feeding behavior, and so on. There are many studies of this sort; but more are needed, and they need to be integrated with, for example, genomics, epigenomics, and proteomics.

Finally, one of the key insights to emerge from the resurrection of developmental biology as a central focus in evolutionary theory is that development occurs not simply in the mother's womb, but in an ecological niche (West & King 1987). For better or worse, the ecological environment of the mother impacts the perinatal environment. Hence, we also need to incorporate into an expanded synthesis an understanding of the broader ecological factors: socioeconomic status, environmental toxins, health care provision, and even weather and light and day cycles (Brook et al. 2009; Skinner et al. 2010), all of which can also shape phenotype. In contemporary evolutionary theory, an ambitious synthesis of all of these forces has been fashioned into an area of research dubbed ecological developmental biology (Gilbert & Epel 2009). I suggest that a parallel approach in the behavioral sciences will yield many valuable insights.

Nonetheless, understanding and prediction are not the same thing, and if the goal is the latter, it may prove

elusive, at least for the immediate future, especially when we add the omnipresence of stochasticity to the mix. Considered for a long time to be insignificant variations around a significant mean, stochasticity in gene expression clearly plays an important role in biological processes, and the molecular bases of such stochasticity are now a major area of investigation (Coulon et al. 2010; Feinberg & Irizarry 2010; Kaufmann & van Oudenaarden 2007; Lipniacki et al. 2006; Paulsson 2005; Raj & van Oudenaarden 2008; Shahrezaei & Swain 2008; van Oudenaarden 2009). Biology creates order from stochastic processes, but biological systems can never overcome stochasticity, which persists at every level of biological organization. In fact, constrained randomness, intermediate between rigid determinism and complete disorder, is probably the best way to characterize the relationship between biological systems and stochasticity (Theise & Harris 2006). While stochasticity continually threatens to undermine the order imposed by biological systems, those same systems can exploit stochasticity for their own advantage. Consider, for example, the manner in which the cells of the immune system anticipate a highly variable environment, a process to which some researchers have compared the activity of retrotransposons in the human brain and neuronal somatic and chromosomal mosaicism (Sciamanna et al. 2009).

Cells of the immune system protect the body against disease by identifying and destroying pathogens such as viruses and bacteria. They do this by identifying antigens, sites on pathogens that antibodies can recognize as the biochemical mark of an intruder and to which they can bind. Finding and destroying pathogens is made vastly more difficult by the fact that pathogens can rapidly evolve, producing adaptations that allow them to change the structure of their antigens to avoid detection. Since only immune cells with the right configuration can bind to antigens with a complementary configuration via a "lock-and-key" process, this creates a significant problem for the immune system. To combat this problem, immune cells exhibit somatic hypermutation. For example, it has been estimated that lymphocytes are capable of producing about $10^{15}$ different antibody variable regions (B cells) and a similar number of T-cell receptor variable regions. This allows for the creation of as many antibody "keys" as there are antigen "locks." Remarkably, this vast diversity of the immune repertoire originates from fewer than 400 genes (Abbas et al. 2010). For the immune system, stochastic genomic recombination creates genetic hyperdiversity, which leads to phenotypic hyperdiversity (antibody configurations), and this phenotypic hyperdiversity enables immune cells to better respond to hypervariable threats in the environment.

In an analogous fashion, genetic hyperdiversity in neurons in the brain may lead to phenotypic hyperdiversity, that is, hyperdiversity of neuronal morphology and function between individual neurons, and this diversity may better enable the brain to respond adaptively to the demands of a diverse and variable environment. Similarly, the manner in which the epigenome functions is also highly stochastic: "Gene promoters can be in various epigenetic states and undergo interactions with many molecules in a highly transient, probabilistic and combinatorial way, resulting in a complex global dynamics as observed experimentally" (Coulon et al. 2010, p. 1). That highly stochastic processes such as epigenetic reprogramming, retrotransposition, chromosomal somatic mosaicism, and CNV appear to be particularly prevalent in the human brain is likely no evolutionary accident. CNVs, which exhibit mutation rates anywhere from 100–10,000 times greater than SNPs, are believed to have been a driving force in the rapid evolution from the great apes to humans; Alu elements, which use the products of retrotransposons to transpose, are unique to apes and humans; and the ability of transposable elements to move within genomes gives them an intrinsic propensity to affect genome evolution (Cordaux & Batzer 2009; Rebollo et al. 2010). The same stochastic processes that enable rapid mutation can also enable rapid evolution (Feinberg & Irizarry 2010).

Niels Bohr argued for the intrinsic stochasticity of nature, and the shift from the genetic to the postgenomic paradigm has been compared to the shift from the Newtonian paradigm to that of relativity theory and quantum mechanics (Noble 2010). Beyond analogies, systems modeled on quantum mechanics are now being employed in the study of probability landscapes of heritable epigenetic states:

> Computational studies of biological networks can help to identify components and wirings responsible for observed phenotypes. However, studying stochastic networks controlling many biological processes is challenging. Similar to Schrödinger's equation in quantum mechanics, the chemical master equation (CME) provides a basic framework for understanding stochastic networks. (Cao et al. 2010)

Hence, it is well to keep in mind what Bohr himself said with a refreshing spirit of scientific humility: "Prediction is very difficult, especially if it's about the future."

## NOTES

**1.** In discussing the alleles of a gene, for the most part order does not matter – that is, $A_1A_2$ is equivalent to $A_2A_1$.

**2.** In 1952, Francis Crick declared that "the central dogma of molecular biology" was that information flows from DNA to RNA to protein, which determines the cellular and organismal phenotype (Crick 1958). The copying of RNA to DNA was predicted by Temin (1964) on the basis of studies of RNA tumor viruses that gave rise to DNA through a latent stage. Crick (1970) published a reformulation of the central dogma in response to the findings of Temin, acknowledging that information can flow from RNA to DNA. Reverse transcription is now known to be an essential process that fulfills a number of different functions related to the modification or addition of genomic sequences, and genomic sequencing has revealed abundant evidence of the importance of reverse transcription in genome evolution (Brosius 1999; 2003).

**3.** For the potential evolutionary significance of the primate specificity of Alu elements and SVAs, see the discussion in sections 8.1 and 10.

**4.** This study, and a number of other studies cited throughout section 4, are association studies of one form or another. For the most part, association studies in behavior genetics (and in most other areas of genetic research) either fail to be replicated, or are replicated inconsistently (Bosker et al. 2011; Chanock et al. 2007; Colhoun et al. 2003; Elbaz et al. 2006; Hirschhorn et al. 2002; Ioannidis 2006; Little et al. 2009; Lucentini 2004; Need et al. 2009a; 2009b; Redden & Allison 2003; Shen et al. 2005). The likely reason for this will be considered below (sect. 8.1). The point of this comment is not to cast doubt on the relevance of these phenomena for human behavior, both normal and abnormal, but rather to note that given the extraordinary levels of complexity they introduce, caution is warranted in making inferences of causality solely from observed correlation in one or even several studies. At the same time, these studies are representative of association studies in behavior genetics in general.

**5.** A listing of the genetic discordances the authors found is available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427204/bin/mmc1.pdf

**6.** However, as Morrow (2010, p. 1099) notes of these studies: "Several important questions emerge from these CNV studies.… The first relates to just how much of the phenotype may be attributable to rare CNVs. Indeed, the frequency of these (generally large) CNVs across the genome is highly variable from study to study."

**7.** For the most part, I employ that term *transcribability* in place of the more common *expressivity* for the following reason: Genes does not "express themselves" in response to environmental signals and "produce" more or less of an RNA or protein as a "response." Hence, genes do not exhibit expressivity. It is, rather, the *cell* that expresses itself, mobilizing numerous responses to internal and external environmental stimuli that will enable it to produce more of a given RNA or protein that is coded for in one of its genes. On its own, DNA is incapable of producing anything or expressing anything: All the biochemical machinery necessary for transcribing DNA is external to it.

**8.** The intergenerational transfer of epigenetic programming is distinct from intrauterine epigenetic programming of offspring by the maternal environment (sect. 7). Consider a gestating female ($F_0$ – the initial parental generation) exposed to an environmental agent that reprograms the epigenome of the embryo. This constitutes direct exposure of the $F_0$ generation female, the $F_1$ (first) generation embryo, and the germline of the $F_1$ generation embryo that will generate the $F_2$ (second) generation (Skinner et al. 2008). Hence, designating a phenotype as an example of environmentally induced transgenerational epigenetic inheritance requires the *absence* of a direct environmental exposure beyond the $F_0$ generation and transmission of the phenotype to at least the $F_3$ (third) generation.

**9.** "The demonstration" can be taken as a proxy for "this article."

**10.** Parents of like-sexed DC–MZ twins are frequently misinformed that their twins are necessarily DZ (Shur 2009).

**11.** It is important to note that DZ twins can be MC as well. Although still considered extremely rare, it may in fact be somewhat more common (Boklage 2009). Nonetheless, MC–DZ twins are likely a small percentage of all MC twins.

**12.** An earlier study of twins ascertained from a clinical sample consisting of 36 MZ and 30 DZ twin pairs reported a 72% concordance rates for MZ twins and a 0% concordance rate for DZ twins. This study estimated the heritability of autism at about 90% (Bailey et al. 1995).

**13.** No classical study of twins raised apart has ever been conducted in which only twins separated immediately after birth were studied (Horwitz et al. 2003; Joseph 2004; Kamin & Goldberger 2002). For example, a study based on data from the much utilized Swedish study of twins raised apart (Swedish Adoption/Twin Study of Aging, or SATSA) reports the ages of separation for studies of twins raised apart as follows (Pederson et al. 1988): 48% of the twins raised apart were separated before their first birthday, 64% by their second birthday, and 82% by the age of 5. Hence, 48% were separated at less than age 1 (how much less than age 1 is not clear), 16% at ages 1–2, 18% at ages 2–5, and 18% at age >5 (how much greater than age 5 is not clear). In total, 52% were separated after age 1. Furthermore, separation at an age <1 is not equivalent to separation immediately after birth. This is representative of all studies of twins raised apart (Farber 1981; Kamin & Goldberger 2002). This entails that the majority of the twins in these studies inhabited *the same environment* during the period of maximal phenotypic plasticity in the brains of developing mammals, and during the period when we would expect parental effects to exert a strong and lasting influence on behavioral phenotypes.

Consider the following example: Brief, daily handling of rat pups for the first 21 days postnatally has been found to permanently increase glucocorticoid receptor (GR) concentrations within the hippocampus (Meaney & Aitken 1985), alter serotonin (5-HT) turnover and 5-$HT_2$ receptor binding in selected brain regions (Laplante et al. 2002; Smythe et al. 1994), and reduce HPA stress response (Weaver et al. 2001). Thus, the development of this neural receptor system is modifiable by environmental stimulation. The handling effect on hippocampal GR concentrations is apparent as early as Day 7 of life. Moreover, handling on Days 1–7 shows the largest increase in GR concentrations and the most pronounced behavioral changes; handling on Days 8–14 is somewhat less effective; and handling on Days 15–21 is without effect. Thus, the sensitivity of the hippocampal GR system to this early manipulation wanes through the first 3 weeks of life as GR concentrations reach adult levels, suggesting that handling may directly alter the number of receptor sites per cell (Weaver et al. 2001). A rough comparison between rat and human age yields the results shown in Table 2. Clearly, a behavioral cross-fostering study with inbred rats, in which some of the rats were separated from their mother at Day 1, others at Day 10, and the majority at Day 20, would be of limited scientific value.

**14.** For a list of some of the phenotypes that have been associated with the same polymorphisms of MAOA (as well as polymorphisms of three other genes commonly found in large behavioral data sets) see Charney and English (2012).

**15.** According to Yang et al. (2010), who employed a model of effect sizes based on the assumption that the variance explained by genetic markers (Vg) follows an exponential distribution, the susceptibility SNPs for height predict that a total of 1,485 SNPs would be needed to explain 45% of variance of height. However, according to Park et al. (2011), a mixture of two exponential distributions provides a much better fit to the data, yielding an estimation that at least 7,244 SNPs would be needed to explain the same fraction of heritability.

**16.** Additional inheritance systems, in the specific sense of transmitters of *information*, include self-sustaining metabolic loops, which through positive feedback enable the long-term perpetuation of alternative cellular states (Ferrell 2002; Thieffry & Sanchez 2002); structural inheritance, which involves three-dimensional architectural templating, as seen in complex membrane systems and cortical structures (Cavalier-Smith 2004; Grimes & Aufderheide 1991), and in the self-perpetuating activities of prions (Collinge 2001). In a more general sense of the term, these are all examples of (non-genomic) epigenetic inheritance systems (Jablonka 2004).

# Open Peer Commentary

## Clinicians learn less and less about more and more until they know nothing about everything; researchers learn more and more about less and less until they know everything about nothing: Discuss

doi:10.1017/S0140525X12001367

Kenneth John Aitken

*Psychology Department, Hillside, Aberdour, Fife KY3 0RH, Scotland.*
**drken.aitken@btinternet.com**

**Abstract:** A number of recent developments in our understanding of the biology of heritability question commonly held views on the immutability of genetic factors. These have numerous potential implications for

improving understanding and practice in pre- and postconceptional care and for infant and child mental health, and they carry a cautionary message against overgeneralization.

A rapid paradigm shift has taken place over the past decade that fundamentally alters the field of behavioral genetics. We have moved from viewing DNA sequences as somehow providing the fixed, immutable, predetermined basis to behavior to viewing these as interacting components, albeit critical ones, in the complex systems that underpin physical and behavioral development (Jaenisch & Bird 2003).

The specialism of epigenetics has developed rapidly (Bird 2007; Jablonka & Lamb 2008) and did not even warrant mention in a major behavioral genetics text as recently as 2003 (Plomin et al. 2003). Genetics and epigenetics interact – epigenetic processes are in part regulated by genetic mechanisms (Yuan 2012), whereas gene functions are themselves epigenetically regulated (Trakhtenberg & Goldberg 2012).

Prenatal and perinatal exposures alter development, and the effects may persist over generations (Bloomfield 2011; Gicquel et al. 2008; Gluckman & Hanson 2005; Gudsnuk & Champagne 2011). Epigenetic marking and gene methylation are keys in this process (Chatterjee & Morison 2011; LaSalle 2011; Szyf 2011; van Ijzendoorn et al. 2011) and can help to explain developmental commonalities and individual differences (Mehler 2008). Placental nutrition and intrauterine environment influence the fetal phenotype. Charney rightly highlights this as one important aspect that has not received its due attention in genetic analyses and draws our attention to other factors such as parent-of-origin effects.

A further limitation in classic genetic studies is that data analyses often minimize complexity. While Occam's razor has its place, there is seldom appropriate consideration of issues like multicollinearity (Rahbar et al. 2012).

Many genetic issues influence behavioral development, including differences in microsatellite DNA (Hammock & Young 2005) that are themselves affected by factors like diet (McGowan et al. 2008). Various genetic anomalies have been linked to specific developmental psychopathologies (Aitken 2010; Geschwind 2009).

Social behavior directly affects gene expression, with implications for infant development and animal models (Branchi et al. 2011; Meaney 2001). The ways in which such influences operate are complex (Lee et al. 2012) and are interlinked with many other aspects of the biopsychosocial environment. Where genetic anomalies are known, or in laboratory environments where effects can be evaluated *ceteris paribus*, the strength of specific contributions may be readily demonstrable. In most real-world situations, however, the effects of specific factors are harder to deconstruct (Robinson et al. 2008).

Some brief examples indicate the range and complexity of issues that can influence developmental processes. In humans, (1) maternal immune status can affect the likelihood of seizures developing in a child with fragile-X syndrome (Chonchaiya et al. 2010); (2) particular patterns of nutrient intake during pregnancy can alter the course of fetal brain development (Brantsæter et al. 2011); (3) maternal consumption of foodstuffs (such as licorice) can affect the human fetus, impairing placental barrier protection by lowering 11ß-HSD2 levels against circulating maternal glucocorticoids (Räikkönen et al. 2009); and (4) the effects of maternal stress on the fetus during pregnancy partly results from differences in placental gene activation (Gheorghe et al. 2011). In other animals, (1) dietary supplements can prevent fetal hypomethylation otherwise resulting from exposure to neurotoxic factors like bisphenol-A (Dolinoy et al. 2007); and (2) lab chow differences can have major effects on gene expression in mice (Kozul et al. 2008).

Twin studies have been a fundamental source of information in human behavioral genetics (Bell & Saffery 2012; Boomsma et al. 2002). The validity of simple monozygotic–dizygotic (MZ–DZ) comparison studies that form the bulk of this work has been questioned for various reasons. For example, fetal growth differences result from monoplacental twinning, and there are implications of mono versus dichorionicity (Nikkels et al. 2008). Simple mechanical factors like chord entanglement and more complex issues like transfusion syndromes are only found with monochorionic pregnancies (Machin 2004), and they are consequently far more likely to affect MZ than DZ twins. In more general ways multiparity increases risks to offspring. They are typically born earlier and have a higher rate of other perinatal complications, with a three- to sevenfold increased rate of morbidity and mortality as compared to singletons (Sherer 2001). Many twin similarities lessen with age, resulting from factors such as divergence of methylation status (Wong et al. 2010). Methylation status is, however, unlikely to account for most such MZ twin discordance (Chatterjee & Morison 2011). Overall, such findings show that the MZ–DZ gene research is unduly simplistic and question the generalizability of many results from twin populations. By inverting the typical paradigm and investigating sources of discordance, research on twins may help us to identify epigenetic mechanisms (Bell & Spector 2011).

Knowledge of these mechanisms is an important component to understanding developmental psychopathologies. This is complementary to and highlights the limitations of purely "gene-centric" models. These neurobiological processes are relevant to the assessment and focused treatment of many conditions where diagnosis and management have more traditionally been based only on history and presenting behavior. This point applies particularly to people with attention-deficit/hyperactivity disorder (ADHD; Archer et al. 2011) and autism spectrum disorder (ASD; Coleman & Gillberg 2012; Grafodatskaya et al. 2010).

Rett syndrome is a paradigm condition (Chahrour & Zoghbi 2007), having been identified as a disorder linked to dysfunction of the methyl-CpG binding protein MeCP2 involved in chromatin remodeling and RNA splicing (Amir et al. 1999). Knowledge of the mechanism has enabled a reversible loc-cassette model to be developed (Guy et al. 2007).

In both ASD and ADHD there are a wide range of genetic and epigenetic anomalies and a range of comorbidities. Many overrepresented differences such as mitochondrial abnormalities demonstrate compromised metabolism (Rossignol & Frye 2012; Weissman et al. 2008). Other neuro-metabolic disorders such as sleep difficulties (Aitken 2012), neuromuscular dysfunction (Marrone & Shcherbata 2011), and seizure disorders (Qureshi & Mehler 2010) are also more common than in the general population.

Despite the broadening range of sufficient neurobiologies, clinical classification is becoming steadily more broad-based and homogenized ("lumping," not "splitting"). In part, this facilitates large-N research on otherwise heterogeneous conditions like ASD (Hus et al. 2007). Through this process, however, there is a danger of marginalizing the relevance of much of the rich information on subgroup-specific neurobiology being generated through research. I have tried to illustrate this in the examples above. This obvious divergence should serve as a wake-up call before the increasing specificity of bioscience and the broadening generalization of clinical practice become an irreparable barrier to progress. It should help us to focus on the need for more informative multidisciplinary approaches, increasing the scope for collaborative, focused research relevant to clinical management and treatment. Recognizing and acknowledging such complexities should enable us to progress from the current unrealistic emphasis placed in clinical practice on an increasingly incompatible research-evidence base to one with a greater focus on practice-relevant evidence (Green 2006). This should in turn inform a more valid and fit-for-purpose research paradigm that would mutually enhance both academic research and clinical practice (Ioannidis 2006; Sidman 2011).

## Is behavioral genetics 'too-big-to-know' science?

doi:10.1017/S0140525X12001331

Marco Battaglia

*Academic Centre for the Study of Behavioural Plasticity, Vita-Salute San Raffaele University, 20127 Milan, Italy; Institut Universitaire en Santé Mentale de Québec, Universitè Laval, Québec, QC G1J 2G3, Canada.*
**marco.battaglia@unisr.it**

**Abstract:** Several new molecular findings and concepts furnish evidence in support of gene–environment interdependence, challenging some of the current tenets and basic statistics of behavioral genetics. I, however, argue that (1) some of the expectations evoked by "neogenomics" are contradicted by findings; and (2) while epigenetic and gene expression effects are complex, they can to some extent be incorporated into "classical" behavioral genetics modeling.

Through a review of molecular findings, Charney revisits the important topic of gene–environment interdependence in behavioral traits. While a need for the revision of some concepts, and perhaps tenets, of behavioral genetics was recently heralded by geneticists (Petronis 2010), developmentalists (Rutter 2012), and social scientists (Tabery 2007), earlier contributions identified genetic influences upon environmental measures (Plomin & Bergeman 1991), and long before the bioinformatics era, behavioral geneticists had hypothesized epigenetic mechanisms to account for deviations from linear-additive genetic effects (Gottesman & Shields 1982). So the issue does not seem to be whether the arguments presented by Charney and several other before him should influence behavioral genetics' concepts and methods, but rather *how*, and in what specific circumstances, this should take place.

Below, while focusing on epigenetics and gene expression, I provide some examples of how predictions stemming from Charney's treatment of "neogenomics" are at odds with empirical findings, and I underline that while epigenetic and gene expression effects are complex, they are partially predictable by the degree of genetic relatedness between individuals. By these arguments, I wish to emphasize that neogenomic effects do not always need to have pervasive and relevant consequences on phenotypes, nor do they necessarily contradict "classic" behavioral genetics' tenets. Hence, their action can at least in part be conceptualized, modeled, and incorporated into classic methods (Battaglia 2012).

First, the relationship between widespread epigenetic marks and genetic expression is still controversial. Zhou et al. (2011) showed that H3K4me3 changes of histonic profiles in the hippocampus of substance-addicted humans do not predict gene expression at the individual gene promoter level. Instead, H3K4me3 changes appeared to highlight macroscopic alterations of histone structure probably induced by addiction. Therefore, while epigenetic effects are potentially important, the individual and specific impact on brain and behavior is neither well understood nor unambiguously linked to gene expression data.

Second, according to Charney, through the effects of neogenomic forces (e.g., transposons), the degree of genetic heterogeneity between monozygotic (MZ) cotwins is expected to increase in time, as they experience increasingly different environments and lifestyles. Contrary to this prediction, for several phenotypes (e.g., general cognitive abilities) the degree of similarity among MZ pairs increases in time, even among more elderly (age>80) individuals (McClearn et al. 1997; Plomin 1986).

Third, based on the premise that physical exercise promotes hippocampal neurogenesis in laboratory animals, Charney concludes that this same mechanism is transferrable and relevant to humans, with the expectation that exercise can impact causally upon mental health and increase twins' genetic heterogeneity. This is based on the intuition that, following differential physical exercise, MZ twins' brains will exhibit enhanced, retrotransposon-induced genetic heterogeneity. Experimental observations contradict these hypotheses. De Moor et al. (2008) data show that the cross-sectional bivariate genetic correlations between indexes of physical exercise and symptoms of anxiety/depression differ quite remarkably from the longitudinal correlations. Among the longitudinal bivariate correlations between exercise and anxiety/depression, the only significant were the genetic, not the environmental correlations. Even in the presence of biased assumptions of genetic–environmental monozygotic–dizygotic (MZ–DZ) correlations, these data are inconsistent with an augmentation of intrapair genetic heterogeneity for the traits under scrutiny. Moreover, a series of tests of the association between exercise and mental health did not support a causal link. Instead, De Moor et al.'s data were consistent with shared genetic factors having opposite effects upon exercise and anxiety/depression.

The above examples show that while the field of neogenomics is conceptually interesting, some predictions are hardly generalizable or are contradicted by findings. It is argued that the parsimonious, classical behavioral genetic models that rely on simpler (occasionally even simplistic) assumptions and theory often prove quite effective in explaining empirical data. In evaluating the trade-offs between conceptual and computational parsimony and explanatory power, it should be remembered that the Slatkin (2009) study, which included within the same model both epigenetic and genetic factors to estimate complex traits' susceptibility, suggested a role for epigenetic changes in explaining individual risk, but not necessarily heritability. Thus, the power of epigenetic changes to explain important issues such as the "missing heritability" in genome-wide association (GWA) studies is currently unknown (Bell & Spector 2011).

So can epigenetic and gene expression effects, together with their inherent variability, be at least partially ascribed to generalizable concepts, and thus studied?

There is wide individual variability for gene expression, even when measured in the same cell types at the same developmental stage; some genes show little, and other genes conspicuous, variation of expression levels. Since in these experiments (Cheung & Spielman 2009) the non-genetic sources of variation are maintained the same for all the genes, and the measured degree of variability is less pronounced among related – compared to unrelated – individuals, it can be argued that we are facing yet another measure of heritability here, with the measure of expression (e.g., mRNA) becoming the phenotype under scrutiny. Thus, gene expression is itself a heritable quantitative trait, and the statistical power to detect gene variants that affect gene expression depends on such heritability (Visscher et al. 2008). Analogously, DNA methylation profiles (Kaminsky et al. 2009) are significantly more similar among MZ than DZ twin pairs. Thus, methylation per se could become the object of modeling: The methylation status of an individual in a given genomic region can be conceived as the result of linear-additive genetic and environmental effects plus a latent *Ep* causal component, the latter term indicating heritable and stable DNA-sequence independent epigenetic factors (Bell & Spector 2011). Likewise, one may devise the incorporation of epigenetic effects into structural equation modeling of twin data. Inevitably, in the light of high indetermination and lack of robust findings, fixing intrapair correlations for methylation with certainty would not be easy (Bell & Spector [2011] proposed 0.4(CI: 0.5, 1) and 0.2 (CI: 0.7, 1) for MZ and DZ pairs, respectively).

Although several technical challenges remain, adding epigenetic effects to the classic behavioral genetics arsenal is conceivable. This could open new and conceptually fascinating avenues; for instance, stochastic and environmentally induced epigenetic variation could explain a sizable proportion of the effects currently attributed to non-shared environment.

ACKNOWLEDGMENTS

This research was supported in part by a grant by the Italian Ministry of University and Research, Rome (PRIN 2008-SCYLW9), and a grant by The Region Lombardy Grant Funding for Scientific and Technological Partnerships grant SAL-25/16848.

## Twin and family studies are actually more important than ever

doi:10.1017/S0140525X12000969

S. Alexandra Burt

*Department of Psychology, Michigan State University, East Lansing, MI 48824.*

**burts@msu.edu**

**Abstract:** Charney argues that the presence of inherited epigenetic effects makes twin, family, and adoption studies obsolete. This argument relies on both a faulty characterization of these studies and indirect comparisons of DNA and "neogenetic" factors. I argue that twin and family studies will in fact serve a necessary and vital role in the study of epigenetic and neogenetic processes.

Charney provided us with a comprehensive review of "neogenetic" phenomena – retrotransposons, copy number variations, mitochondrial DNA, aneuploidy, and epigenetics. It was a fascinating read and highlights the many exciting breakthroughs in our understanding of the human genome. Unfortunately, these scientific advances were used to argue that twin and family studies are therefore obsolete. This conclusion misses the mark, for a number of reasons.

1. A core premise of his argument was that the "neogenome behaves like neither category," that is, neither genetic (G) nor environmental (E) parameter. Based on his descriptions, this does not appear to be true – instead, it behaves like both G and E. To the extent that monozygotic (MZ) twins are more phenotypically similar than are dizygotic (DZ) twins because of their neogenetic profiles, the neogenome will be absorbed into G. To the extent that MZ twins also differ phenotypically because of differences in their neogenetic profiles, the neogenome will be absorbed in E. The key here is that both can happen simultaneously (e.g., parenting has been shown to influence twin outcomes at genetic and environmental levels simultaneously; Burt et al. 2003; 2007). Loading on more than one component of variance in no way means that they are somehow omitted from heritability estimates – indeed, to the extent that they contribute to outcomes, neogenetic effects are already necessarily being included in the G and E estimates we obtain. This is not the first time our understanding of the specific effects within a component of variance has changed. The same thing happened with G × E (contrary to Charney's claim, G × E are not estimated in traditional heritability estimates, which in fact explicitly assume that there are no G × E) – we now know that G × E are included in our simple estimates of G and E (Purcell 2002).

2. Charney's gestalt argument was that Mendelian models of familial resemblance should be discarded in favor of Lamarckian models. Put differently, he argued that the similarity of sibling's DNA matters less than their neogenetic (including environmental) similarity. Although he offered circumstantial support for his hypothesis, he was unable to point to studies directly testing this proposition. Why is this? Because neogenetic effects are tissue specific, most cannot be examined until after death, a fact that makes research very difficult to do in humans. How should we resolve this? Are we doomed to an endless cycle of back-and-forths where we argue about whether genetic or neogenetic resemblance matters more? No, and it turns out that the empirical answer will likely be found in the "natural experiments" that Charney would have us discard. Twin and family studies make use of naturally varying degrees of genetic and environmental relationships to infer general patterns of etiology. What sorts of family studies might allow us to test Charney's overall hypothesis that genetics matter less than neogenetics? There are many possibilities. Half-siblings would be useful, for example, in that we could compare siblings who were reared together with a common mother (but different fathers; these siblings share their family environment, an average of 25% of their nuclear DNA, their mitochondrial DNA, and many aspects of their prenatal environment) to those with a common father (but different mothers; who share their family environment and 25% of their DNA but not their mitochondrial DNA or their prenatal environment). Should half-siblings who share a mother be more similar to one another than those who share a father, it would argue for the importance of the prenatal environment/mitochondrial DNA.

An even stronger design might seek to disaggregate genetic resemblance and (most) neogenetic resemblance via a sample of children adopted as embryos. Embryos created via IVF (in vitro fertilization) are three days old when they are frozen and so consist of only eight undifferentiated cells. One could thus compare siblings (conceived via IVF) born to their biological mother to biological siblings adopted as embryos and born to another family (all siblings would share their DNA and any neogenetic effects that preceded the third day of embryonic life, but only some would also share their prenatal and familial environments). The children adopted as embryos could be further compared to other siblings adopted as embryos, but with different biological parents (in this case, the siblings would share only prenatal and familial environments). To the extent that biological siblings are more similar to each other when born to the same mother as when born to different mothers, it would highlight neogenetic/prenatal and environmental processes. To the extent that sibling similarity varied instead with degree of genetic relatedness, it would argue for the importance of DNA to sibling similarity.

Yet another design might take advantage of the fact that some MZ twins have different chorions, while others do not, thereby allowing researchers to examine the consequences of different degrees of prenatal sharing while controlling for the general effects of DNA. In fact, some such studies have already been done (Jacobs et al. 2001; Reise 1999) and have revealed minimal/inconsistent effects of chorion type on personality and cognitive ability. Jacobs et al. (2001), for example, found that whereas genetic effects accounted for more than 60% of the variance in cognitive abilities, chorion type accounted for less than 15% (and typically 0–2%). Although the above results begin to argue against prominent prenatal effects on normal-range outcomes (and moreover, suggest that the equal environments assumption need not be violated), future research should clearly seek to examine this possibility in more detail.

In closing, I would further note that discordant MZ twins may prove to be the most useful research design for examining neogenetic processes in humans, because controlling for the basic effects of DNA allows for particularly strong counterfactual inferences regarding neogenetic effects on outcome (stronger in fact than within a given person). This is particularly the case because, despite the exceptions noted by Charney, twins are comparable to singletons (Moilanen et al. 1999; Robbers et al. 2010; van den Oord et al. 1995) for the majority of psychological and behavioral outcomes. Future work should seek to do just this.

## Heritability estimates in behavior genetics: Wasn't that station passed long ago?

doi:10.1017/S0140525X12000970

Wim E. Crusio

*Institute of Cognitive and Integrative Neuroscience, University of Bordeaux and CNRS, F-33400 Talence, France.*

**wim_crusio@yahoo.com**

**http://www.incia.u-bordeaux1.fr/spip.php?article168**

**Abstract:** Charney describes several mechanisms that will bias estimates of heritability in unpredictable directions. In addition, the mechanisms described by Charney explain the puzzling fact that research in human-behavior genetics routinely reports higher heritabilities than animal

studies do. However, I argue that the concept of heritability has no real place in human research anyway.

It is now 22 years since I wrote my first open-peer commentary for *Behavioral and Brain Sciences* (Crusio 1990). How much has changed since. And how much has stayed the same. In that commentary, I argued that heritability estimates had only a very limited value, namely, that of predicting the response to selection. Being young and bold (or perhaps young and reckless), I asserted that "these estimates have only a very limited value for researchers investigating animal behavior and are without purpose in human-behavior research." Significantly older now and perhaps even more reckless but certainly more stubborn, I still maintain that heritability estimates have only a very limited value and I still don't see much use for them in human research.

Perhaps it would be good to recall the definition of heritability: the proportion of the phenotypical variance that is attributable to genetic variation in a given population in a given environment or set of environments. (Depending on whether or not only additive-genetic variation is taken into account, we may distinguish between heritability in the broad sense or in the narrow sense, but that distinction is not important for this discussion.) The crucial words here are "in a given" population or environment. If our population is an inbred mouse strain, heritability will be zero for every measurable phenotype, as there is no genetic variation present. In a population with limited genetic variability, heritability may be relatively small, while a genetically more variable population would show a higher heritability even if it was living in exactly the same environment. Similarly, if two populations had identical levels of genetic variability, but were exposed to different environments, then they would almost certainly also show different heritabilities. In short, in human populations, where we cannot experimentally control either environments or levels of genetic variation, heritability estimates have no inherent theoretical value (as opposed to *practical* uses, such as determining the number of subjects needed to localize genes). As far as I can see, the only questions of theoretical import would be whether heritability is significantly different from 0 (i.e., genetic effects on the phenotype of interest exist) and from 1 (i.e., significant effects of the environment exist). The often-heard argument that higher heritabilities would mean that a trait (or disorder) will be less responsive to (therapeutic) interventions is obviously flawed.

It should perhaps be noted that the foregoing holds even in the idealized simplified situation where there is no interaction or covariation between genotype and environment. Taking into account also those effects, as well as the molecular processes so skillfully described by Charney in the current target article, really should be the final nail in heritability's coffin. It is true that the effects and processes that Charney describes can be included in quantitative-genetic models: Whatever can be measured can also be modeled. But given the foregoing, such an exercise would seem to be a waste of time and effort. In short, my only beef with Charney's criticism of heritability is the same as the one I raised in my commentary on Wahlsten's (1990) target article, namely, that they both criticize the concept of heritability on technical points, whereas *even if those could be solved*, there are still much more fundamental inherent problems with the use of this construct in human-behavior genetics. That Charney nevertheless apparently felt that he had to pay the attention that he did to such a useless notion is an apt testimony of the amount of reification that the concept of heritability has undergone in the field of human quantitative behavior genetics.

Despite the foregoing, I would like to bring up one more point about heritability estimates. Animal studies are designed to "boost" heritability: All animals are raised as much as possible in uniform environments in an attempt to reduce the amount of phenotypical variance attributable to variation induced by environmental variations. The end result should be that genetic causes would become relatively more important, leading to higher heritabilities, compared to uncontrolled situations such as encountered in human studies. Yet, studies in human-behavior genetics routinely report heritabilities over 50%, whereas studies in animal genetics generally yield much more modest values, a point that has always puzzled me. The explanation for this paradox may lie in the different processes described by Charney. First of all, although their effects may result in both over- and underestimates of the heritability of a character, the general tendency seems to be to inflate these values. Second, thinking about the way animal studies are set up (e.g., comparisons of inbred strains of mice, or a species always giving birth to multiple offspring), it would appear that there are less confounding effects in these studies and, hence, a lower possibility of arriving at an overestimate.

A final, more minor, point that I would like to make concerns phenotypic plasticity. The situation here is actually even more complex than Charney describes: There is experimental evidence that the amount of phenotypical plasticity that a certain organism is capable of is itself under genetic control (Crusio 2006), an idea that has been around for a considerable time (Hyde 1973).

Summarizing, Charney raises many important points with far-reaching implications for research in human-behavior genetics and offers explanations for a number of its more puzzling findings, from heritability estimates that often are much higher than those found in animal studies to the baffling difficulties encountered when attempting to identify genes for most complex phenotypes in this field, be they psychiatric pathologies or behaviors in the normal range.

## Postgenomics and genetic essentialism

doi:10.1017/S0140525X12000982

Ilan Dar-Nimrod

*School of Psychology, University of Sydney, Sydney, NSW 2006, Australia.*
**ilan.dar-nimrod@sydney.edu.au**

**Abstract:** Traditional lay perceptions of genetics are plagued with essentialist biases leading to some unfortunate consequences. Changes in the scientific understanding of heredity in general, and in genotype–phenotype relationships more specifically, provide a vital basis for shifting public understanding of genetics. Facilitating postgenomic literacy among the public has the potential to have translational implications in diminishing deleterious attitudes, beliefs, and behaviors.

In the target article, Charney delineates some of the most central traditional assumptions which have guided the conceptualization of heredity in the past century. Much research in recent years has provided many challenges to these traditional assumptions as Charney convincingly articulated. Woven together, these challenges present an appealing basis for a new paradigmatic conceptualization of the etiology of phenotypic manifestations. The emerging scientific picture provides a more complex, rich, and ultimately probabilistic portrayal of the integration between nature and nurture, which will undoubtedly guide future heredity research. It is paramount that this paradigmatic shift will also reach the lay public in its complexity for more than just scientific literacy reasons.

Whereas the majority of people are unlikely to summon terminology from advanced, complex scientific theories such as quantum mechanics or the string theories, most individuals seem to hold mental representations of genetics (Henderson & Maguire 2000) and even preschoolers invoke the concept of genes to explain human phenotypes (Heyman & Gelman 2000). These mental representations are quite limited and inaccurate even when they are assessed relatively close to the time when most individuals learn about genetics (i.e., high school; see Henderson & Maguire 2000). The mental representations of genetics

are not only inaccurate, but they also seem to provoke cognitive fallacies collectively termed genetic essentialist biases (Dar-Nimrod & Heine 2011).

The genetic essentialist biases contribute to an increase in the likelihood that specific outcomes/phenotypes will be viewed more deterministically while alternative etiological explanations will be devalued (for a review, see Dar-Nimrod & Heine 2011). Demonstrating some of the effects of these biases, empirical research showed that exposure to genetic etiological accounts affects a slew of outcomes ranging from dislike of ethnically dissimilar individuals (Keller 2005) and increased gender stereotyping (Brescoll & LaFrance 2004) to altered moral evaluations (Dar-Nimrod et al. 2011; Monterosso et al. 2005), academic underperformance (Dar-Nimrod & Heine 2006; Moè & Pazzaglia 2010), and adverse health behavior intentions (Beauchamp et al. 2011). These findings demonstrate that laypeople's perceptions of genetic etiology for various human phenotypes are not only incongruent with the current scientific picture of genotype-phenotype relationships (Charney), but they may also facilitate undesirable beliefs and suboptimal behaviors.

Although the mass media may have been the main contributor to the simplistic and deterministic lay representations of genetics (Conrad 1997; 2001), scientists have arguably contributed to this distortion unwittingly (Dar-Nimrod & Heine 2011). As gatekeepers of much of the new knowledge that originates on heredity, one may argue that we have a responsibility to portray our findings in a manner that minimizes activation of deeply rooted biases, which seem to be exacerbated by the public's misguided yet impactful understanding of genetics (Dar-Nimrod 2007).

The postgenomic paradigm that emerges from Charney's account challenges some of the last strongholds, which facilitate genetic essentialist biases, portraying a system in which the genome loses its primacy in favor of dynamic interactions between various heredity and environmental components. Staying true to these intricacies may have great potential in reducing the adverse effects of the perceived genetic attributions among the lay public by minimizing essentialist cognitions. To facilitate such a shift it is necessary for researchers and journalists to work together to reduce deterministic portrayals of genetic research. It is also advisable to target the first systematic exposure to heredity science in our society – the science curriculum in schools.

Currently, Mendelian inheritance and the ubiquitous Punnett squares seem to be the focus of much of the schools' science curriculum involving heredity (Dougherty 2009). As a result, these conceptualizations arguably dominate individuals' mental representations of heredity after graduation (Henderson & Maguire 2000). However, as Charney observed, Mendelian inheritance is only one part of a much larger picture connecting heredity to phenotypes. By favoring these narrow exemplars of heredity science above all others, the majority of people, whose only in-depth knowledge of scientific accounts of genes comes during school, are left with an oversimplified understanding of genetics, an erroneous understanding that promotes the assumption of a one-to-one relationship between genes and phenotypes. To reflect our current understanding of the genotype–phenotype relationships, there is a need to overhaul the current genetic module in science education. Revamping this curriculum is especially pertinent given the cognitive biases and deleterious outcomes that seem to arise from misconceptions about heredity. This suggestion is not designed to advocate abolishment of Mendelian inheritance from the curriculum altogether but rather to place it in its appropriate context as only one of many processes that shape human phenotypes. As some of the most unfortunate misrepresentations of genetic science relate to behaviors and diseases, it is prudent to emphasize how largely irrelevant the simplified portrayals of Mendelian inheritance processes are for the majority of these outcomes.

The paradigmatic changes in the scientific understanding of genetics do not make us immune to essentialism. For example, in reviewing research on copy number variation, (CNVs) and behavior genetics, Charney cites findings that reported increased CNVs in children with attention-deficit/hyperactivity disorder (ADHD; Williams et al. 2010). Although this research may be part of the new paradigm that challenges the traditional genetic research assumptions, the article itself is plagued by essentialist-promoting language. Williams et al. argue that their findings "allow us to refute the hypothesis that ADHD is purely a social construct" (p. 1407). The use of such language, which is reminiscent of the commonplace inclination to pit nature against nurture, was exacerbated in the media coverage of the research. In one such article, the reporter teamed with a genetic scientist to suggest that these reported genetic underpinnings indicate that ADHD is "a real hard and true disorder" (Landau 2010). Such statements evoke blatant essentialist cognitions placing the ultimate test for "real hard disorders" in our genes and imply that disorders that cannot be traced to the genome are "not true" or just "social constructs." To make a true paradigmatic shift in our accounts of heredity, we should all be best advised to avoid falling into the old essentialist traps in the new postgenomic era.

## Non-Mendelian etiologic factors in neuropsychiatric illness: Pleiotropy, epigenetics, and convergence

doi:10.1017/S0140525X12001392

Curtis K. Deutsch and William J. McIlvane

*Eunice Kennedy Shriver Center, University of Massachusetts Medical School, Waltham, MA 02452.*

**curtis.deutsch@umassmed.edu william.mcilvane@umassmed.edu**

**Abstract:** The target article by Charney on behavior genetics/genomics discusses how numerous molecular factors can inform heritability estimations and genetic association studies. These factors find application in the search for genes for behavioral phenotypes, including neuropsychiatric disorders. We elaborate upon how single causal factors can generate multiple phenotypes, and discuss how multiple causal factors may converge on common neurodevelopmental mechanisms.

Behavior genetics takes into account several sources of complexity in estimating heritability, including genetic and environmental factors, their interaction, and covariance. Charney argues that a fully realized model would ideally take into account not only these sources of variance but also numerous molecular features. Charney's discussion is wide-ranging, with an emphasis on the inclusion of both Mendelian and non-Mendelian factors in heritability estimations and how these issues impact genetic association studies.

These molecular genetic and genomic factors are central to gene discovery for behavioral phenotypes. This is keenly felt in medical behavior genetics, notably in the search for genetic factors underlying neuropsychiatric illness. Gene discovery has been frustrated by difficulties in the modeling of genetic architecture of complex disorders (Psychiatric GWAS Consortium Coordinating Committee 2009; Cichon et al. 2009; Gejman et al. 2011; Kendler et al. 2011; Yeo 2011). Further, the confounding of heterogeneous etiologies and phenotypes for a disorder can undermine the statistical power to identify genes (Deutsch et al. 2008).

In this discussion, we expand upon the role played by some of these factors. We consider the role of pleiotropy in gene identification for brain-based disorders; a shorthand for this source of complexity is *one gene, multiple phenotypes*. We also discuss the converse association: *one phenotype, multiple genetic factors*, adding a consideration of epigenetic factors as well. Finally, we examine how multiple, heterogeneous effects may disrupt common underlying molecular pathways for brain-based disorders.

***Pleiotropy.*** This signifies multiple manifestations stemming from a single causal factor. Take, for example, the effects of the phosphatase and tensin homolog (PTEN) gene, located at 10q23.31. It encodes a tumor suppressor phosphatase that antagonizes the PI3K signaling pathway, which contributes to a variety of conditions. These include specific clinical genetic syndromes (e.g., Bannayan-Riley-Ruvalcaba), macrocephaly, autism, and malignant melanoma (Nadeau & Topol 2006). These multiple manifestations are conceptually unified when the underlying mechanism is revealed.

A single etiologic factor can have multiple phenotypes, present in some but not all gene carriers. This genetic heterogeneity, combined with reduced penetrance for a diagnosis, may increase the risk of false negatives in gene discovery; the power to detect linkage on the basis of the disease phenotype alone is limited. Thus, there is a potential boon in studying not only the psychiatric illness, but also alternative phenotypes that provide a more complete picture of pleiotropic manifestations.

There can be marked statistical power benefits to this pleiotropic approach (Sunga et al. 2009). For example, in schizophrenia, common underlying causal factor(s) may generate not only the clinical diagnosis, but also eye movement disorders, which are present in the majority of schizophrenia patients (Holzman et al. 1988). Matthysse et al. (2004) modeled the cotransmission of both phenotypes, schizophrenia and eye movement disorders, among probands and their relatives, yielding a linkage analysis that identified a locus on chromosome 6.

***Copy number variants (CNVs).*** Recent genetic studies have heralded the importance of genetic CNVs in brain-based disorders, as Charney describes. Pleiotropy is increasingly discussed with respect to CNVs (e.g., Poot et al. 2011), and single microdeletions and microduplications have been found to have a variety of manifestations. For example, a cluster of rare disorder-associated CNVs on chromosome 9 (containing the microdeletion 9q33.1, which includes neurodevelopmental genes astrotactin 2 [ASTN2] and tripartite motif-containing 32 [TRIM32]) has been associated with a variety of conditions: bipolar disorder, schizophrenia, and autism spectrum disorder (ASD; Lionel et al. 2011). A similar phenomenon exists for the microdeletion of 16p11.2, observed in ASD (McCarthy et al. 2009); the same CNV is also seen among individuals with intellectual disability in the absence of ASD (Bijlsma et al. 2009). The association of *both* intellectual disability and psychiatric illness with a single CNV is seen for a number of other novel recurrent copy number changes, including 1q21.1 deletion and duplication, 3q29 deletion, 15q11.2 deletion, 15q13.3 deletion, 15q24 deletion, 16p13.11 deletion and duplication, and 17q12 deletion (Mefford et al. 2012).

***Single genes.*** A limitation to gene discovery in CNVs is the sheer magnitude of genetic material within many deleted or duplicated regions; yet the chief pathogenic genes may isolated to a small subset of this region. Without a comprehensive genetic dissection of the region, strong inference about associations with phenotypes is impossible. A more direct approach is to delineate genotype-phenotype relationships for a single gene.

Many genes are associated with the diagnosis of autism. This is best illustrated by the long list of *de novo* single nucleotide variants (SNVs) now emerging in autism within the Simons Simplex Collection of families (Neale et al. 2012; O'Roak et al. 2012a; 2012b; Sanders et al. 2012). These SNVs may be found to have broad pleiotropic manifestations beyond ASD *per se*. An example of classical pleiotropy for psychiatric diagnosis can be found for the gene diacylglycerol kinase eta (DGKH). It has been implicated in not only bipolar disorder, but also unipolar depression and attention-deficit/hyperactivity disorder (ADHD; Weber et al. 2011). Also, the gene synaptosomal-associated protein 25 (SNAP25) has been associated with ADHD and antisocial disorders, and it may be associated with lower reward dependence and higher novelty seeking (Basoglu et al. 2011).

***Epigenesis.*** Dysregulation of DNA methylation and histone modification are likely to play a major role in the pathophysiology of ASD and other neuropsychiatric illness (Shulha et al. 2012). Studies of post-mortem prefrontal brain tissue have revealed epigenetic profile alteration for literally hundreds of loci, notably, ones implicated in neurodevelopment. These epigenetic effects may converge on common developmental pathways in autism.

***Convergent neurodevelopmental pathogenesis.*** There is also strong evidence from post-mortem brain studies that multiple genes may disrupt common neurodevelopmental pathways in autism. Voineagu et al. (2011) found that gene expression influencing cortical patterning is markedly altered in ASD. Their findings, taken as a whole, indicate that heterogeneous gene splicing and transcriptional dysregulation may underlie neurodevelopmental pathogenesis in autism.

***Summary.*** The enterprise of gene discovery for neuropsychiatric disorders is revealing how multiple etiologies can contribute to one phenotype and multiple phenotypes can be manifested for one etiology. Once causal factors for brain-based disorders are identified, a new challenge emerges: determining how multiple pathogenetic factors conspire to disrupt common underlying neurodevelopmental mechanisms.

## Is genomics bad for you?

doi:10.1017/S0140525X12000994

Benjamin J. A. Dickins

*Biology Department, Pennsylvania State University, University Park, PA 16802.*

**ben@bx.psu.edu http://www.bendickins.com/**

**Abstract:** The plasticity of the genome complicates genetic causation but should be investigated from a functional perspective. Specific adaptive hypotheses are referenced in the target article, but it is also necessary to explain how the integrity of the genome is maintained despite processes that tend towards its diversification and degradation. These include the accumulation of deleterious changes and intragenomic conflict.

Most of the phenomena Charney terms "neogenetic" entail changes to the genetic substrate and are therefore classifiable as kinds of mutation. Epigenetic marks differ because they influence gene expression, not sequence. Somatic mutations during development can lead to genetic mosaicism, while epigenetic modifications presumably underlie cellular differentiation (Ng & Gurdon 2008). Mutations in the germline can lead to non-Mendelian inheritance of portions of the genome (reviewed in Burt & Trivers 2006), and epigenetic changes can create unusual patterns of expression such as polar overdominance (Cockett et al. 1996). Charney argues that these peculiarities undermine genotype to phenotype maps implicit in the statistical frameworks of behavior genetics. Rather than venture criticism, I here expand on the theoretical challenge presented by one aspect of mutation, simply that of its ubiquity.

Mutations can be understood as products either of necessity or chance. Charney's emphasis on adaptive phenotypic plasticity is apposite. To the extent that mutations are functional, they are instances of adaptedness per se, rather than drivers of adaptation (for an explanation of this perspective, see Dickins & Dickins 2008). Charney also describes well the manner in which adventitious changes are harnessed through somatic hypermutation in the immune system. But he says "stochasticity continually threatens to undermine the order imposed by biological systems." This is surely so: Severe and multifarious mutations affecting the genome within lineages (at least some of which are associated with behavioral dysfunction: e.g., Stewart et al. 2011) would seem to threaten extinction. How, for example, does a brain maintain its function or a population of organisms preserve its genomic integrity, despite frequent aneuploidy?

Let us consider only "conventional" mutations, namely, single nucleotide changes or indels (insertions and deletions), of the kind that can be associated with Mendelian disorders. Many such mutations are deleterious, and even mildly deleterious mutations can lead to extinction when they accumulate under the influence of genetic drift (Muller 1964). Even assuming an infinite population size, mutation accumulation can lead to population extinction with a probability that depends not on the average effect size of mutations but on their rate of occurrence and on the intrinsic fecundity of individuals (Bull et al. 2007). Humans have slow life histories (Robson & Wood 2008), a low effective population size (Yu et al. 2004), and a relatively high mutation rate (Kondrashov 2003; Lynch 2010), although they benefit from recombination. Given the proportion of *de novo* mutations expected to be deleterious, and with advances in medical care that plausibly entail a relaxation of negative selection, these parameters have led to concerns about population fitness in the medium term (Lynch 2010; but see Keightley 2012). Low frequency alleles with relatively large effect sizes may also underlie at least some of the missing heritability in genome-wide association studies (Manolio et al. 2009), thereby contributing to the burden of disease at this time.

The reduction in the mean fitness of a population caused by mutations (the mutation load) is attenuated when the fitness of an individual depends on others around it; this is so-called soft selection (Wallace 1975). Alternatively, germline viability selection can expurgate deleterious alleles, an observation made plausible in humans by the seemingly high rate of "occult" pregnancies (Edmonds et al. 1982), with many aborted concepti manifesting aneuploidies (Macklon et al. 2002). The occurrence of mitotic and meiotic cell divisions in the germline of "sexual" species has significant population genetic consequences (Hastings 1991). For example, when germline selection is soft, this can favor the evolution of "anti-robustness" in which genotypes readily suffer reduced fitness when mutated (Archetti 2009). Anti-robust genotypes are also expected in regenerative tissues for theoretical reasons (Krakauer & Plotkin 2002) paradoxically contributing to robustness at the level of the organism.

Emerging evidence supports purifying selection in the mammalian mitochondrial genome (Fan et al. 2008; Stewart et al. 2008), which is probably facilitated by a germline bottleneck in copy number. We are beginning to understand how cell lineages behave in mammalian oogenesis (Reizel et al. 2012), but important details are unresolved. In the male germline, recent evidence suggests positive selection *for* specific genetic disorders (Choi et al. 2012; Goriely et al. 2003). One response to these preliminary data is to conceive of disease as an outcome of a breakdown in the regulation and control of deleterious mutations. Focusing on the regulation of mitochondrial function, one colorful review elaborates such a "quality-control" perspective (Braschi & McBride 2010). Although Charney suggests that transposon activation in the brain might be positively associated with neural plasticity and flexibility, it may prove necessary to consider how neural networks buffer themselves from the deleterious effects of mutations or even how behavior itself might modulate mutational effects.

Some of the phenomena Charney describes might threaten stability, not because of their passive accumulation but because they are selected for independently of their effect on the rest of the genome. For example, transposons active in the germline increase their contribution to posterity by overreplication, but can damage genes if they "jump" close by or into them. When intragenomic conflict occurs, and a component of the genome acts against the wider coalition, the evolution of repressors is favored by natural selection (Burt & Trivers 2006). Aspects of meiosis such as reduction division and recombination may have evolved to restrain selfish genetic elements.

Many forms of epigenetic regulation were revealed during research into genomic imprinting. Imprinted gene expression can be explained by conflict between paternally and maternally derived alleles within offspring (Haig & Westoby 1989) or as a consequence of maternal–fetal co-adaptation (Keverne & Curley 2008). From the conflict perspective, imprinted gene expression does not benefit the organism, but potentially creates problems in the event of epigenetic dsyregulation or mutation (due to haploinsufficiency at the expressing allele). Aberrant patterns of imprinted gene expression are implicated in intrauterine growth restriction (Tycko 2006), but recent screens (reviewed in Kelsey 2011) have suggested abundant imprinted expression in the brain. Trivers (2000) has also outlined ways in which intragenomic conflict can manifest itself in the behavior of individuals.

## Preventing a paradigm shift: A plea for the computational genome

doi:10.1017/S0140525X12001355

Carmine Garzillo[a] and Giuseppe Trautteur[b]

[a]*Dipartimento di Scienze mediche preventive;* [b]*Dipartimento di Scienze fisiche, Università di Napoli Federico II, 80138 Naples, Italy.*

**carmine.garzillo@unina.it trau@na.infn.it**

**Abstract:** Against the opinion that DNA as program is not sufficiently explanatory, we maintain that the cellular machinery is entirely computational, and we identify the crucial notion of the interpreter that expresses the gene with the minimal gene set. Epigenetics research does not so much need paradigm shifts as the unraveling of an exceedingly complex computational machine.

The target article displays a thorough and impressive gathering of cellular phenomena that cannot be accounted for by "classical" genetics. Such phenomena are then rallied against the fact that "it has been a key dogma of molecular genetics that DNA is the sole biological agent of heritability, and it is still commonly treated as such." Such state of affairs, the author intimates, implies a Kuhnian paradigm shift towards a "postgenomic view" which, nevertheless, Charney does "not call … a paradigm because it has not yet coalesced around a core set of principles or assumptions characteristic of a paradigm."

Two lines of study are identified in the target article: heritability studies and gene association studies. Out of both these lines, a feeling oozes that the implicit debate underlying the contrast between dogmatic biology and the more permissive postgenomics has been replacing the now largely obsolete nature–nurture dispute. Günther Stent (1975), through his dissatisfaction with the unique agency of the genome and his assertion of an implicit role of the cell, anticipated the essential uneasiness of the actual epigenetics movement.

So what is it this further element, over and above the dogmatic centrality of the DNA, which is alleged by the epigenetics community? We think it is the computational nature of the cell.

This runs contrary to Charney's statement: "DNA does not contain a determinate genetic program (analogous to the digital code of a computer) from which we can predict phenotype." And it might well be true that the phenotype is not predictable, but rather more because generally program behavior is undecidable (Davis 2004), hence unpredictable, than because the genome is a program, or rather a computational structure.

There is a lack of appreciation that the computational and information theoretic talk about the cell, current since the very beginning of molecular biology, is not metaphoric but literal, and that cellular processes are primarily computational rather than biochemical ones, in the same sense that the CPU chip of a PC is primarily a computational apparatus rather than a solid-state physics device.

As stressed ubiquitously in the epigenetics domain, the gene does not express the protein by itself. The author states as much

in Note 6, and indeed, the fact that the strings of genetic material are not self-operating, autonomous entities has been overlooked by the dogmatic attitude of molecular biology (but not by Stent). We analyzed this empirical fact (Garzillo & Trautteur 2009) and proposed that what those biological strings needed in order to beget expressive behavior was what in computer science parlance is an interpreter.

The core cellular machinery appears to consist of two parts: (1) the sequence of bases of the coding genes, which constitute a text specifying the structure of the proteins, and (2) the basic machinery of the cell, which we identify with the minimal gene set (Koonin 2000; Gil et al. 2004; Glass et al. 2006) together with the expressed enzymes coded by the minimal gene set itself.

Such an entity, that is, the minimal gene set encompassed with the expressed proteins that allow its own operation, is a biological forerunner of the universal Turing machine (Herken 1988; Turing 1936) and of the essentially equivalent *stored program* computer, soon to become the CPU chip of the PC. The core interpretive machine is made up of the coalescing within the same cytoplasm of the minimal gene set DNA *together* with the expressed enzymes coded for by the same minimal gene set. How it came to be that an active structure (ribosomes, etc.) evolved together with its own effective description (the genes coding for them) is at the core of the problem of the origin of life and of the genetic code. Suffice it to say that at present things are this way and allow for a computational interpretation. It is intriguing to note that this copresence of both the genic specification of the enzymes and the enzymes themselves had been "naturally" devised in the artificial, and computational, self-reproducing machine by John von Neumann (1966), a consequence of the 2nd Kleene recursion theorem (Rogers 1967). As a further remark, the epigenetics possibility that an initial self-reproducing genome may keep "improving" itself indefinitely had already been delineated by John Myhill (1970).

The gist of our commentary is that the cell being an universal Turing machine entails that the genome, besides coding for structural proteins, does also code for "functional" proteins, whose enzymatic activities amount to program execution: Some fulfill control actions on metabolic pathways, thus interfering with the external milieu – the nutrients or signaling molecules – and some act upon the genome itself. For instance, in the case of the transposases, the enzyme recognizes the ends of the transposon and cuts it off a chromosome. That freed-up piece of DNA, with the transposase still attached, does move to a new place thus preparing on the fly a new genic string, which gets expressed in turn, always through the operation of the universal Turing machine–like minimal gene set. Such activities parallel common programming practices such as code displacement, code modification, or creation at execution time.

We discussed elsewhere the action of the genome upon itself (Garzillo & Trautteur 2009) with examples overlapping many examples of the target article. In particular, we considered the treatment of the transposable elements and some further examples concerning the ciliates.

If systems biology concludes "that causation in biological systems runs in both directions: upward … and downward," that "there are feedback and feed-forward loops between different levels," and that "DNA is no longer privileged as the sole carrier of information" (all quoted from target article sect. 10, para. 1), it need not worry about causation, levels, and the nebulous notion of information more than it is done in computer science.

No further entity or phenomenon, beyond the genome, needs to be looked for in epigenetic research. Nor is a paradigm shift in the offing, unless one would call paradigm shift the interdisciplinary usage of established concepts in a different discipline. Epigenomics' travail (Ferguson-Smith et al. 2009) consists in the painful and, let us not forget, therapeutically invaluable unraveling of an exceedingly complex *computational* machine.

## Biology trumps statistics in the postgenomic era

doi:10.1017/S0140525X12001008

Charles E. Glatt

*Department of Psychiatry, Weill Cornell Medical College, New York, NY 10065.*
**ceg2004@med.cornell.edu**

**Abstract:** Charney discusses the growing realization in the postgenomic era that genomic biology deviates from Mendelian assumptions at the heart of genetic heritability and association studies. Given the complexity of genomic biology, how are we to identify meaningful genetic factors that contribute to behavioral? One response is to make genetic variants the focus of biological rather than statistical analyses of behavior.

The promise of behavior genetics in the genomic era was that the molecular basis of the major psychiatric disorders could be identified in the absence of a detailed understanding of the biology of the brain. That is, the logic of genome-wide association studies (GWAS) is *hypothesis free,* requiring only that the target disorder display substantial heritability for statistical associations between specific polymorphisms and the target phenotype to be identified. This was a powerful promise in the face of the vast complexity of the brain and our rudimentary understanding of how molecules lead to mind. Moreover, genetic risk factors, once identified, would be powerful translational tools providing an easy manner of assessing an individual's risk for psychiatric disease and perhaps allowing for rational targeting of treatments to the individuals most likely to respond based on their genetic profile.

Unfortunately, now that large-scale, statistically powerful GWAS have been conducted for all of the major psychiatric disorders, it has become clear that common, large-effect genetic risk factors for behavioral disorders do not exist. Despite heritability estimates of 40–90% for psychiatric disorders including depression, autism, schizophrenia, and bipolar disorder (Burmeister et al. 2008), only minor risk factors of minute effect size have been identified. Taken in aggregate, these risk factors only account for ~1% of the estimated genetic variance (Plomin & Davis 2009). The small effect size of identified risk factors and substantial missing heritability in behavior genetics have limited the value of this approach both in terms of the predictive value of genetic testing in clinical application and in understanding the molecular basis of behavior.

Charney describes a number of biological mechanisms by which the simple logic of behavior genetics is violated. The manner in which these factors violate the Mendelian assumptions of behavior genetics vary and have different implications for the design and success of behavior genetic studies. Phenomena such as somatic mutation, chimerism, and heteroplasmy of mitochondrial DNA all mean that monozygotic twins are more genetically discordant than has been assumed. This will lead to underestimates of the heritability of diseases or traits. In contrast, the systematic concordance of non-genetic factors in monozygotic versus dizygotic twins, such as prenatal stress in Charney's example, leads to exaggerated estimates of heritability. These deviations from Mendelian principles highlight that, rather than removing biology from behavior genetics, postgenomics requires that polymorphisms themselves become the focus of biological analysis. Statistics alone cannot bridge the gap from molecule to mind; instead, the biology of polymorphisms must be studied systematically in the context of non-genetic factors that might modify their biological properties to make meaningful and informative genotype-phenotype relationships.

How does a biologically focused analysis of a polymorphism work? First and foremost, it involves identifying the molecular effects of a polymorphism. This process is straightforward for polymorphisms that result in an amino acid substitution in the peptide sequence coded for by a gene. Such polymorphisms can be identified by applying the genetic code to the ancestral and

variant codons, and the effects of the substitution on protein function can be assessed through in vitro assays. Taking the polymorphism out of the human context and studying it in molecular assays allow controlled experiments in which the alleles of the polymorphism are the only variable. Moreover, controlled experiments allow for the systematic study of physiologic factors that modify the effects of the polymorphism, and this information can be applied upwards into studies of more complex phenotypes. An example of this approach was applied to a common valine to methionine substitution in the human gene for brain-derived neurotrophic factor (BDNF). BDNF is a secreted signaling molecule that facilitates neuronal growth and synaptic plasticity (Autry & Monteggia 2012). Expression of the recombinant ancestral and variant proteins in neuronal cultures revealed that the polymorphism altered activity-dependent but not constitutive secretion of BDNF (Chen et al. 2004; Egan et al. 2003). This result demonstrated that the polymorphism has a molecular phenotype and suggests specific domains of neuronal function that might be affected such as activity-dependent learning. This hypothesis was confirmed by creating a transgenic mouse in which the conserved ancestral valine was replaced with the variant methionine (Chen et al. 2006). When the two strains were compared for their ability to extinguish a learned fear association, the methionine-expressing strain displayed an extinction-learning deficit (Soliman et al. 2010). This finding motivated the collection and assessment of human subjects for extinction learning in a parallel paradigm as a function of the BDNF polymorphism. Humans with the methionine allele of the BDNF polymorphism also displayed less efficient extinction learning (Soliman et al. 2010). This finding has clear implications for the genetic basis of anxiety, but anxiety is so imprecisely measured in humans that further characterization of the BDNF polymorphism is needed to meaningfully refine the anxiety phenotype. These refinements can be modeled in the transgenic mice and then applied to human studies. Ultimately, the goal of this approach is to identify biologically defined subtypes of behavioral disorders in which the effect size of individual polymorphisms are large and reliably assessed. At that point the polymorphism might be of practical predictive value as a genetic test.

There are many caveats to this biological approach. It is far from guaranteed that model systems will adequately recapitulate the complex biology of human brain. As Charney points out in the target article, abundant forms of genetic variability are unique to primates and even humans. Biological characterization of polymorphisms is also an extremely labor-intensive process that cannot be applied in a genome-wide manner, and thus choices must be made about which polymorphisms to study. One approach to integrating biometric and biomolecular genetics, to use Charney's terms, would be to perform biological characterization of variants that show greatest association in GWAS and then use the characterization of the variants' biology to refine target phenotypes for subsequent GWAS to increase the effect size of the variants to the point that they could be useful in clinical practice.

## Affirmation of a developmental systems approach to genetics

doi:10.1017/S0140525X12001124

Carolyn Tucker Halpern

*Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599.*
**carolyn_halpern@unc.edu**

**Abstract:** More than 40 years ago, Gilbert Gottlieb and like-minded scholars argued for the philosophical necessity of approaching genetic contributions to development through a multilevel, bidirectional systems perspective. Charney's target article builds on this heritage in significant ways, offering more recent examples of the interactions of biology and context, as well as the diversity of developmental mechanisms, and reaffirming a way forward for genetic research.

> A virtual revolution has taken place in our knowledge of environmental influences on gene expression that has not yet seeped into the social sciences in general and the behavioral sciences in particular. Aside from the feared misinterpretation of Lamarckian mechanisms at work, there is an explicit dogma, formulated as such, that does not permit environmental influences on gene activity: the "central dogma of molecular biology," first enunciated by Crick in 1958. (Gottlieb 1998, p. 792)

More than 40 years ago, Gilbert Gottlieb (along with like-minded predecessors and colleagues such as T. C. Schneirla and Zing-Yang Kuo) began a career-long effort to convince scholars from a variety of disciplines that real and lasting scientific progress in our understanding of development, and genetic contributions to development, would not be possible until a relational, developmental systems approach was adopted and routinely applied in research. Gottlieb's meta-theory of a dynamic, coactional system spanning genetic, neural, behavioral, and environmental contributions to growth and development defied the central dogma of genetics (Gottlieb 1998). He offered support for this systems perspective in the form of extensive comparative data that he generated himself, as well as compelling examples of phenotypic plasticity reflecting species ranging from wasps to humans (e.g., see Gottlieb 1998).

Gottlieb offered a cutting-edge, probabilistic conception of epigenesis (see Gottlieb [1992] for his figurative framework) with a focus on relational, bidirectional causes of developmental processes that are non-linear and sometimes not obvious (Gottlieb 1997). "The cause of development – what makes development happen – is the relationship of the components, not the components themselves" (Gottlieb 1997, p. 91). Sadly, when he passed away in 2006, Gottlieb was unconvinced that his years of writing and accumulation of evidence had made a real impact on the way scientists, and certainly the broader population, think about genetic processes and their coactional contributions to health and development. I think he would be very pleased to see that a new generation of scholars continues to advocate for this coactional paradigm of genetic research, marshaling extraordinary data made possible through new technology to demonstrate the poverty of dualistic, reductionist approaches to development and the wealth of insight to be gained from a complex, multilevel, bidirectional systems model.

Charney's target article is a welcome contribution to this tradition, using both older and new empirical examples to demonstrate the necessity of thinking about genetics from a systems perspective. Using insights from next-generation studies, Charney compellingly reasserts the paradigmatic assumption that DNA is dynamic and environmentally responsive, not the static starting point for fixed development processes. Charney notes that although there may be long distances between genes and regulatory elements, and between life experience and biological processes, there is in reality no boundary between genes and the environment.

I'm not quite sure why Charney chose to include a discussion of how behavioral genetics might fit the new paradigm. As Gottlieb often noted, the notion of partitioning variation into discrete biological and contextual elements is philosophically incompatible with the assumptions of the postgenomic paradigm proposed in the target article. However, that seeming inconsistency aside, with the persistent and convincing arguments offered in insightful articles like Charney's, the field will continue to move to the probabilistic, multilevel systems paradigm envisioned by multiple generations of visionary scientists.

## Genetic sensitivity to the environment, across lifetime

doi:10.1017/S0140525X1200101X

Judith R. Homberg

*Donders Institute for Brain, Cognition, and Behaviour, Centre for Neuroscience, Department of Cognitive Neuroscience, Radboud University Nijmegen Medical Centre, 6525 EZ Nijmegen, The Netherlands.*

**j.homberg@cns.umcn.nl**

**Abstract:** The target article by Charney convincingly argues that genomic plasticity perinatally induced by the environment creates a complication in determining which parts of behavior are attributed to nature and which to nurture. I argue that real life is even more complex because (1) genotype influences sensitivity to environmental stimuli, and (2) the genome continues to be modified throughout life.

The terms *nature* and *nurture* are used as popular terms for the roles of, respectively, heredity and environment in human development. One extreme view is that our behavior is determined solely by genetic factors, which is referred to as the nature theory of human behavior. The other extreme view is the nurture theory of human behavior, which poses that our behavior is entirely shaped by the environment through experiences. Recently, both theories have been reconciled by assuming that nature and nurture contribute to human behavior, although it is unclear what aspect of behavior is determined by genetic factors and what part by environmental factors. As elegantly described by Charney, the complication to dissect nature *versus* nurture may be because our genome can change under influence of environmental factors. The genomic plasticity, that is, variability in copy number variations, retrotransposons, and epigenomic variability, may significantly impact genome-wide association studies, which rely on genomic stability. Indeed, these phenomena may account for the so-called missing heritability, which is seen in many complex traits, including behavior and psychiatric conditions. Yet, beyond the important message of Charney, there are two factors that need to be included in the understanding of this missing heritability.

First, not only do environmental stimuli influence the genome, the genome also influences the impact of environmental stimuli. Whereas the "static" diathesis–stress/dual risk view (Monroe & Simons 1991) adheres to the theory that some individuals are disproportionately likely to be affected adversely by environmental stressors because of a genetic "vulnerability," the recently introduced "for-better-and-for-worse" concept postulates that "vulnerability" genes actually function as plasticity genes (Belsky et al. 2009). These plasticity genes may turn out maladaptive in aversive environments, but adaptive in favorable environments (Belsky et al. 2009). A well-known example is the common serotonin transporter-linked polymorphic region (5-HTTLPR). Individuals carrying the short allelic variant of this polymorphism showed maladaptive behavior (e.g., depression) when they were exposed to an aversive environment, but also showed increased adaptive behavior (e.g., improved decision making) in response to a favorable environment (Homberg & Lesch 2010). Long-allele carriers, on the other hand, show resilience to aversive environments, but also benefit less from a favorable environment. For instance, female short- (but not long-) allele carriers have increased risk of postpartum depression under poor socioeconomic conditions and less under high socioeconomic conditions (Mitchell et al. 2011). Similarly, in adopted adults with the dopamine D4 receptor (DRD4) 7 repeat (7R) allele, experience with parental problems had the highest scores for trauma, whereas subjects with DRD4-7R who did not experience parental problems showed the lowest ratings. Among participants without this allele, the parental problems during childhood did not make a difference (Bakermans-Kranenburg et al. 2011). The most plausible explanation for these observations is that plasticity genes shape the sensitivity to environmental stimuli (Belsky et al. 2009). Hence, individuals differ by genotype in the extent to which they are affected (either positively or negatively) by environmental exposures. Interestingly, one study showed that the long-allele in combination with high *5-HTT* promoter DNA methylation (a type of epigenetic modification) predicted more trauma compared to long-allele subjects with low levels of methylation. On the other hand, the short-allele predicted more trauma, but only when levels of methylation were low (van Ijzendoorn et al. 2010). Although it is impossible to dissociate the "chicken and the egg" in cross-sectional association studies, it is tempting to speculate that the impact of early life trauma on DNA methylation varied as function of 5-HTTLPR genotype, and that the level of *5-HTT* gene suppression as a consequence of DNA methylation influenced the responses of the children to trauma. The lesson that can be drawn here is that besides that the environment affects the genome (see Charney), the genome also affects the impact of the environment (presumably due to epigenetic processes).

Second, whereas Charney focuses on the importance of the intrauterine and early postnatal environment on changes in the genome and phenotypic plasticity, the impact of later life environment on the genome should not be overlooked. For instance, adult desert locusts have the ability to switch from the solitary phase to the swarming phase depending on population density (Anstey et al. 2009) through epigenetic modifications (Boerjan et al. 2011). This also makes sense from an evolutionary point of view: If early life (epi)genetic programming were unchangeable, the organism would be less able to adapt to environmental changes in later life. Although much of our behavior has been acquired and/or shaped by experiences and epigenetic modifications in early life, it is not the case that these processes end in later life. There is indeed evidence that fear learning, memory, and extinction in adult rodents are associated with histone (Stafford et al. 2012), and DNA methylation (Lubin et al. 2008) modifications. As stated by Charney, mothers may prepare their offspring for expected future environmental conditions, and if these conditions change, maternal modifications of the offspring's phenotype may turn out to be maladaptive. This may explain common diseases with late-onset phenotypes (Feinberg 2007). However, if the epigenome continues to be vulnerable to change by environmental influences throughout life, the epigenome associated with a particular disease may also be "treatable." In support, the histone deacetylase inhibitor trichostatin A rescued impaired fear memory in a mouse model for Alzheimer's disease (Francis et al. 2009), several pharmacological agents currently used in the treatment of psychiatric disorders act through the epigenome (Wilkinson et al. 2009), and teenagers carrying the 7-repeat version of *DRD4* were more positively affected than controls by an intervention targeting substance use (Beach et al. 2010). An intriguing question that arises from this discussion is whether later life environmental factors differentially affect the early life (epi) genetic programming when they match or mismatch the maternal environment. In any case, the examples above clearly illustrate that gene x environment interactions are more complex than described in Charney's article. Combining different theories is necessary to fully understand the "case of the missing heritability."

## A call for an expanded synthesis of developmental and evolutionary paradigms

doi:10.1017/S0140525X12001021

Andrew J. Lewis

*School of Psychology, Faculty of Health, Deakin University, Burwood, Victoria 3125, Australia.*

**andrew.lewis@deakin.edu.au**

**www.deakin.edu.au/hmnbs/staffprofiles/index.php?username=andlewis**

**Abstract:** Charney's target article continues a critique of genetic blueprint models of development that suggests reconsideration of concepts of

adaptation, inheritance, and environment, which can be well illustrated in current research on infant attachment. The concepts of development and adaptation are so heavily based on the model of genetics and inheritance forged in the modern synthesis that they will require reconsideration to accommodate epigenetic inheritance.

Charney's target article is an important synthesis of work that has led to calls for a paradigm shift beyond the modern synthesis underpinning evolutionary, genetic, and developmental sciences (Jablonka & Lamb 2007; Mattick 2009; Müller 2007) and furthers a crucial critique of genetic "blueprint" models of development – which can be traced back as far as the work of Schneirla (1957) and Lehrman (1970). At stake in this debate are assumptions underpinning the dominant models of child clinical psychological and preventative research that seeks to improve developmental outcomes by identifying and reducing environment risk factors. The focus of my commentary is to suggest areas where Charney's model can be further extended.

Although the focus of the target article is on implications for behavioural genetics, a model that includes a role for the intergenerational transmission of environmental influences via the epigenome could have major implications for an emerging developmental science by integrating findings from the genetic, epigenetic, and psychosocial domains. However, one of the problems occurs in the translation of the language of maternal effects (Mousseau & Fox 1998) – derived from evo-devo research – into human developmental psychology. To argue that maternal effects do reliably shape development in adaptive ways and that this applies as much to human development as other organisms, Charney argues that "maternal effects … are phenotypic concordance-producing effects." He appears to be stressing this point to counter Plomin (2011), who argues that variance in phenotypic outcome in children is derived from mostly genetic or non-shared environment. This is where it is a real pity that Charney did not consider research findings on infant attachment in humans. Maternal effects on offspring phenotypes can be measured in terms of the attachment patterns in infants, which can differ among offspring of the same mother – and so too an infant can develop different attachment patterns for mother and father. This suggests that, despite sharing the same family environment, the attachment *relationship* is unique to each child–caregiver dyad. Against the trend of many findings in child development, behavioural genetic studies of concordance of attachment status in twin studies suggest that differences in attachment patterns have very minimal genetic contribution but are largely due to both shared and non-shared environmental factors. An important distinction derived from such research is that while family environments may be shared by children – and this includes the sharing of maternal effects – the translation of this concept into human social ecologies requires consideration of the *relationships* among children, parents, and siblings. Attachment findings seem to suggest that each child's developmental context is unique at the level of the relationship it has with available caregivers. This more complex social network influences the child's developing biology via the emergence of a sense of self that comes to mediate the experience of that environment (Fonagy et al. 2007). The notable absence of any consideration of attachment theory and research in Charney's target article forecloses an opportunity to consider a field in which maternal sensitivity has been well measured in humans and so too development of psychopathology as a function of disturbance in the social environment (Lewis & Tooley 2009).

The concept of "adaptive phenotypic plasticity" is insufficiently elaborated upon in Charney's target article, and in the end, the concept may be inadequate for an epigenomic paradigm of inheritance. First, with respect to the notion of phenotypic plasticity, it is important to note not only how shaping effects occur from the "maternal perinatal environment" to offspring, but also how an offspring actively shapes its environment. Such maternal programming has an effect because of a certain mode of responsivity to very specific cues in the environment. Learning is a prime example of such responsivity. Rapid learning in the form of visual or olfactory imprinting is particularly relevant to recognition and proximity seeking of offspring to caregiver, such that an offspring may benefit from maternal investment – particularly in mammals. While learning suggests a degree of targeted receptivity to environmental signals, infants also show a range of seemingly highly preprogrammed behaviours. Infant attachment behaviours – such as crying, clinging, and proximity seeking – appear to be designed to elicit maternal care and investment. There can be variation in both maternal sensitivity and infant attachment behaviour, as well as feedback loops between the two. These species-specific signalling functions, which serve to elicit parental investment, can be manipulated by both parent and offspring so as to elicit additional care or parental investment – leading to parent–offspring conflict within the maternal shaping of development (Trivers 1974). Instead of this complex and systemic interaction, Charney's model of development tends to assume a degree of passivity of the offspring in its shaping by the maternal environment.

Second, the notion of *adaptation* implied in the concept of adaptive phenotypic plasticity quickly shows its limitations. The traditional, and Neo-Darwinian, concept of adaptation is so heavily based on the model of genetics and inheritance forged in the modern synthesis that, without substantial reconsideration, it will prove inadequate to accommodate epigenomic heritability. Certainly genetic change at a population level is slow to react to environmental change, so it makes sense that more fine-grained modifications of the biological systems underpinning phenotypic outcomes are responsive to environmentally derived programming effects. Nevertheless, Charney's model of adaptation seems to be a "fit to the environment," which has been criticised some time ago by Lewontin, suggesting instead that organisms co-construct and co-define their ecological niche, and this becomes increasingly the case as social ecologies take on greater complexity (Lewontin 2001; Griffiths & Gray 2005). Both an infant and its (maternal) environment undergo their own developmental processes that require systemic interaction. So too it is necessary to rethink the notion of heritability because, in effect, an offspring inherits genetic information, but so too epigenetic information and interacts with an environment provided by other dynamic and developing organic organisms – to which it is often genetically related. Not only the concepts of inheritance and environment, but also adaptation and development, will need to be transformed.

## From gene activity to behavior (and back again)

doi:10.1017/S0140525X12001033

Robert Lickliter

*Department of Psychology, Florida International University, Miami, FL 33199.*
**licklite@fiu.edu dpblab.fiu.edu**

**Abstract:** Documenting the bidirectional traffic from gene action to the external environment and its effects on behavior remains a major conceptual, empirical, and analytical challenge for developmental science. Charney has provided an instructive snapshot of where we are in meeting this challenge and, in so doing, exposes the considerable shortcomings of the traditional genomic model employed by behavior genetics.

A revolution has been taking place in the biological sciences regarding how to conceptualize genes, development, inheritance, and evolution. This revolution has contributed to the rapid growth of areas such as epigenetics, evolutionary developmental biology, and systems biology. In an extension of this ongoing revolution, Charney has presented a detailed and comprehensive critique of

the genomic model underlying contemporary behavior genetics. I was impressed with the range of topics covered and the clear and appropriately detailed presentation of the implications of recent findings across the life sciences for how we think about heritability, gene expression, the use of twin studies, and gene association studies. Although his detailed examples of the remarkably fluid nature of the genome will likely challenge many non-biologists, these examples provide a solid and necessary empirical basis for the "postgenomic" paradigm shift outlined by Charney in his target article.

I entirely agree with Charney that the traditional genomic model promoted for much of the twentieth century across the life sciences is no longer viable. The idea of a fixed genome that is the sole source of heritable traits is simply not plausible, given advances over the last several decades in genetics, molecular biology, and the like. The mind-boggling combinatorial complexity of the bidirectional traffic inherent in the process of development, a key point of Charney's arguments against old-fashioned behavior genetics, blurs the boundary between genes and environment and highlights the dynamic fusion of biology and ecology that is proving key to our understanding of both development and evolution.

A key point of Charney's argument is that genes do not stand outside the developmental system (of which they are a part), acting as independent causes of traits or characters. Their expression, whether they are active or inactive, is determined by an array of influences from other levels of the system. This idea of distributed control, that direction for the emergence and development of traits resides in the nature of the relationships between internal genetic and non-genetic factors and external environmental variables, is a key principle of a developmental point of view. This point of view is in sharp contrast to the concept of the additivity of genes and environment, a key assumption of traditional heritability analysis. A developmental point of view shifts the focus from population statistics to the study of individual development, because it is only through the study of the *process* of development that we can understand the dynamics of developmental (and evolutionary) change. In this light, it important to emphasize that there is no direct connection between genetic activity and behavior. All genetic effects on behavior are mediated through the cell membrane and subsequent coactions among cells and neural networks (Johnston & Edwards 2002).

Documenting the bidirectional relations from gene action to the external environment and their effects on behavior over the life course, including the prenatal period, remains a major conceptual, empirical, and analytical challenge for developmental science. Charney has provided a useful and instructive snapshot of where we are in meeting this challenge. His review of the wide range of factors that are participants in gene activity and expression, in some cases well beyond the timescale of individual development, supports the view that the organism–environment system is the fundamental level of analysis in our efforts to understand the links among development, heredity, and evolution (Lickliter 2009). An organism and its environment are fundamentally connected, and the epigenetic research considered by Charney is providing powerful evidence that they cannot be functionally separated.

One implication of this insight for behavior genetics seems clear – linking genotypes to behavioral outcomes requires developmental investigation. As pointed out by Gottlieb (1995; 2003) some years ago, the population view of behavioral genetics is not developmental. It is based on the assumption that a quantitative analysis of the genetic and environmental contributions to individual differences can contribute to an understanding of the developmental process of individuals. However, it is clear that individual development is the result of organism–environment relationships in which the quantitative contribution of either cannot be specified. Charney has provided a scholarly and integrative review of why this is the case, and I applaud his accomplishment.

Further, Charney's review demonstrates that because of the variability of relevant resources across different environments and because only a portion of the genome is expressed in any individual, what is actually realized during the course of individual development is only one of many possibilities. This is a core tenet of probabilistic epigenesis (Gottlieb 2007), the view of development and evolution that emphasizes that because of the multiplicity of levels, factors, and interactions involved and because of its history-dependent and situated nature, neither physical nor behavioral development can have a predetermined outcome. To understand the origin, maintenance, or transformation of any phenotypic trait, it is necessary to study its development. This is the challenge now facing behavior genetics, and we will have to see if the field is up to the task of achieving a science grounded in developmental processes.

My lone reservation regarding Charney's exposure of the shortcomings of the basic assumptions of behavior genetics is that he has not gone far enough in exploring the implications of what this means for the future of behavior genetics, as well as biology and psychology more generally. I have emphasized the need for assuming a developmental point of view, but there are a number of other concerns that remain, including whether it will be possible for the field to reinvent itself in light of the range of molecular findings that appear to be undermining its conceptual foundation, a foundation rooted in the assumptions of Mendelian genetics. More broadly, Charney hints at but does not directly address the possibility that given that phenotypic development is a multidetermined phenomenon involving systemic complexity over time, the number of variables, interactions, and contingencies involved from fertilized egg to functional adult may well put its full understanding beyond human comprehension. Explanatory and predictive power are hard to come by when dealing with complex systems.

## The fate of heritability in the postgenomic era

doi:10.1017/S0140525X12001045

Kevin MacDonald[a] and Peter J. LaFreniere[b]

[a]*Department of Psychology, California State University–Long Beach, Long Beach, CA 90840*; [b]*Department of Psychology, University of Maine, Orone, ME 04469.*

**kevin.macdonald@csulb.edu Peter_LaFreniere@umit.maine.edu**

**Abstract:** This commentary argues that age changes in heritability are incompatible with Charney's theory. The new genetics must be tempered by the findings that many epigenetic phenomena are random and are linked to pathology, thus making them peripheral to the design of complex adaptations. Behavior-genetic findings are compatible with strong maternal effects; G × E correlations likely underestimate environmental effects; and G × E interactions are unlikely to be an important aspect of normal development.

This commentary reflects an evolutionary perspective on behavioral development that defends the utility of heritability estimates but also acknowledges limitations of the standard behavior-genetic model.

***Age changes in heritability are incompatible with Charney's theory.*** There is substantial evidence that heritability of cognitive ability increases with age (Deary et al. 2006; Haworth et al. 2010), but Charney emphasizes that monozygotic (MZ) twins become increasingly unlike each other in terms of epigenetic profile as they get older, either because of stochastic errors in cell division or because of encountering different environments. Thus older twins are more discordant for epigenetic factors, but they are more concordant for IQ and a variety of other traits than younger twins. Indeed, IQ has relatively low heritability in early childhood, with linear increases into the young adult period (Haworth et al. 2010).

Thus the relatively greater genetic discordance of older MZ twins for epigenetic factors does not make them less alike in IQ; rather they become more alike.

Charney argues that perinatal stress makes MZ twins more similar. But being concordant for epigenetic factors due to prenatal stress does not increase MZ concordance for IQ early in life when concordance for IQ is relatively low; and relative discordance for epigenetic factors in adulthood does not decrease concordance for IQ in adulthood. These results are clearly independent of any greater similarity MZ twins may have because they are exposed to more stress in utero – Charney's suggested explanation for MZ twin similarity.

***Phylogenetic adaptations and contingent alternate strategies.*** As Charney notes, a great many epigenetic events are random or are linked to pathology. As indicated by the IQ example above, Charney does not present a case that there are important epigenetic effects on adaptive traits like cognitive ability or personality.

Many of the processes highlighted by Charney are stochastic. But phylogenetic adaptations reliably arise across the range of environments normally encountered by a given species. Like genetic point mutations, most of these stochastic events are likely to be maladaptive or neutral. The development of adaptations requires the smooth meshing of genes. Thus it is not surprising that many epigenetic events are linked with pathology.

However, some adaptations function as contingent strategies in which genes are turned on or off depending on environmental triggers (e.g., as a result of maternal influence). Behavior-genetic studies of contingent adaptive strategies should result in evidence for substantial shared environmental influence and low heritability if mothers treat offspring the same, as indicated by the mouse maternal licking studies. Charney challenges "the principle of minimal shared maternal effects." However, recent studies of attachment – a central developmental construct (e.g., Sroufe et al. 2005) – show strong effects of shared maternal environment (Bakermans-Kranenburg et al. 2004; Bokhorst et al. 2003; O'Connor & Croft 2001; Pasco Fearon et al. 2006; Roisman & Fraley 2008). For example, Roisman & Fraley found that shared environment explained 53% of the variance in attachment security, unshared environment explained 30%, and the remaining 17% were due to additive genetic variance.

Behavior-genetic models can thus be quite informative on variation resulting from environmental programming of adaptive systems. Moreover, lack of maternal effects would be surprising given evolutionary and life history perspectives on the importance of maternal care, particularly in mammals. Research indicates large intercorrelations between markers of high-quality environments (including secure attachment, delayed maturation, low fertility) and adaptive outcomes in children, with parenting variables accounting for 20%–50% of the variance in child outcomes (Maccoby 2000).

Finally, minimal maternal effects are logically inconsistent with behavioral data on parent–child interaction showing bidirectional influence between child and parent. If the child's behavior shapes the parent's behavior, how is it possible that the parent's behavior has no effect on the child?

This type of adaptive phenotypic plasticity makes great sense to us as evolutionists. Epigenetic processes grant the genome greater flexibility than a rigid DNA code. Its great adaptive advantage stems from its sensitivity to fluctuating environmental conditions such as the availability of food. Nature and nurture in concert shape developmental pathways and outcomes, resulting in a "blurring of boundaries" between genes and environment.

***G × E Interactions are unlikely design features of complex adaptations.*** Charney continues in the tradition of earlier critics of behavior genetics who emphasize the possibility of extensive G × E interactions (Gottlieb 1997; Meaney 2010; Wahlsten 1990). Currently all G × E interactions that have been identified involve single genes that have multiple variants and are linked with pathology. These findings provide clear cases in which one allele is less functional than the more common allele, predisposing people carrying the allele towards pathological outcomes in normal environments (e.g., the PKU gene or the alanine allele associated with diabetes). However, caution should be exercised in extrapolating these findings to complex polygenic traits such as IQ, where no such G × E interactions have ever been identified, despite repeated attempts to do so. Whereas genotype-environment correlation (Cov[G,E]) results in maximizing the fit between organisms to environments, G×E interactions actually imply a genetic load, as there is selection against some variants in some normal environments (MacDonald & Hershberger 2005).

In general, findings support the importance of additive genes. For example, Hill et al. (2008) summarized data from animal and human genetics indicating that for fitness-related traits, typically around 50% of the phenotypic variation is due to additive genetic variation and that about 80% of genetic variation is additive. Additive genes have their effects on a wide range of normal genetic backgrounds and across a wide range of normal environments, thus fitting easily into the architecture of complex adaptations. The presence of complex, unpredictable, or idiosyncratic interactions would make it very difficult for natural selection to construct complex adaptations.

Despite this, it remains true that some genes may produce G×E interactions important for psychiatry and medicine because they result in pathology in some environments. The point here is that such genes are not likely to be part of the story of normal development of complex adaptations in the Environment of Evolutionary Adaptedness or even in the vast majority of contemporary environments.

## A developmental science commentary on Charney's "Behavior genetics and postgenomics"

doi:10.1017/S0140525X12001057

George F. Michel

*Psychology Department, University of North Carolina at Greensboro, Greensboro, NC 27402.*

**gfmichel@uncg.edu**

**Abstract:** Charney's target article convincingly demonstrates the need for the discipline of quantitative human behavior genetics to discard its false assumptions and to employ the techniques, assumptions, and research program characteristic of modern developmental psychobiology.

Charney provides a timely assessment of how research in molecular genetics challenges most of the assumptions of the quantitative behavior genetics of humans and requires a reorientation of that research program (a paradigm shift). The physical instantiation in the DNA of the hypothetical gene of quantitative genetics has altered notions of how genes work and these changes affect how genes can be used as descriptive and explanatory constructs in quantitative genetics. I propose that the research program of developmental psychobiology can serve as the context for the "new" paradigm.

The discipline of *quantitative* genetics was proposed as an alternative to the qualitative/descriptive approach of Darwinian theory. The interpretation offered for Mendel's research proposed that the hypothetical hereditary elements (genes), provided by the parent population, specified the particular characters of individuals. These genes segregated independently to produce the offspring's characters and linked the offspring's and parents' features. The genotype–phenotype distinction highlighted the hypothetical aspect of the "gene" construct and its incomplete relation to observable traits. Quantitative genetics became the discipline capable of characterizing the heredity of traits and

predicting their distribution in an offspring population given knowledge of their distribution in the parent population and who mated with whom.

Before the establishment of quantitative genetics, Galton (1869/1891) proposed the techniques (e.g., comparison of the correlations among monozygotic [MZ] and dizygotic [DZ] twins) for investigating the heredity of human psychological traits (e.g., intelligence, personality). Galton's techniques were combined with those of quantitative genetics to create quantitative human behavior genetics. Given the individualistic character of Western cultures (which values the notion that the individual's self, personality, and abilities owe little to cultural and social contexts), a popular belief in genetic determinism became the context in which human quantitative behavior genetics flourished.

The modern synthesis combined Darwinian theory of evolution by natural selection with quantitative genetics. Natural selection worked on phenotypic traits, but these traits reflected the combination of specific genes inherited from the parents that governed their developmental manifestation. The modern synthesis supposedly incorporated developmental phenomena by acknowledging that genes and the environment interact to create the traits. Fisher's analysis of variance techniques estimated the influence of genetic and environmental factors and the interaction of genes and environment on phenotypic variability (Fisher 1925). Some developmental scientists argued that complex organisms develop through interactions at many levels of organization within the organism and in relation to the external environment in ways not captured by Fisher's technique.

Quantitative geneticists developed procedures that permitted them to ignore research attempting to characterize mechanisms responsible for the development of traits. They assigned such mechanisms to only three sources of variance: genetic influences, environmental influences (including shared and non-shared environments), and the influences of genetic × environmental interactions. Behavioral genetic research on humans used the same models to create the impression of a genetic predisposition and susceptibility of individuals to certain environmental risk factors in the development of particular psychological phenotypes. Unfortunately, these models do not account for how some individuals with both the presumed predisposition and exposure to the environmental risk do not manifest the phenotype. Nor do the models account for how other individuals, with neither the presumed predisposition nor the environmental risk, nonetheless manifest the phenotype. In contrast, developmental scientists were seeking to account for those changes in developmental trajectories that characterize the manifestation of all such types of phenotypic traits (developmental psychobiology).

Meanwhile, as researchers tried to instantiate the hypothetical genes, chromosomes became the first candidate. Discovery that chromosomes are composed partly of the DNA molecule and that DNA was a double helix whose strands could unwind and separate to form two identical DNA molecules demonstrated how gametes could retain hereditary components from each parent. Further discovery that particular triplet sequences of the four bases of the DNA could "code" for a specific amino acid and that proteins were specific combinations of amino acids gave the promise of a complete material instantiation of genes. As Charney's article nicely illuminates, molecular instantiation of genes began to create problems for the quantitative geneticists' assumptions about how genes operate.

When molecular genetics failed to provide evidence of direct relations of genes to behavioral phenotypes, quantitative geneticists proposed that complex traits could be connected to genes via endophenotypes. The term *endophenotype* describes the various physiological pathways that relate the genotype to behavioral phenotypes (Gottesman & Gould 2003). Brain structure and functioning were key endophenotypes that were "causal mechanisms leading to specific [psychological] outcomes" (Maheu & Macdonald 2011, p 20). Genes would affect mechanisms of cellular functioning which, in turn, would bias developmental trajectories via their influence on protein production and subsequently on neural structure and function. Thus, the endophenotype acknowledges that a complex pathway (developmental) channels genotypes into a delimited range of possible phenotypes.

Of course, endophenotypes are themselves affected by environmental factors. Elucidation of such patterns of organism–environment interaction during development is the research program of developmental psychobiologists (Michel & Moore 1995). Developmental psychobiology provides research strategies that reveal the dynamic bidirectional relationships between the individual's biological processes (including molecular genetics) and the individual's social and physical environment at all levels of organization in the developing individual. Research in developmental psychobiology demonstrates how specific behavioral characteristics derive from trajectories that represent transitions in the individual's biological processes as these are affected by the individual's environmental conditions, at each specific phase of the trajectory.

Epigenetic regulations of gene activity and expression are only one manifestation of this organism–environment interplay during development. Deconstructing the various contributions to the dynamic of this developmental process has been the activity of developmental psychobiologists. Genes (molecular cellular processes) play a part throughout these developmental trajectories. However, developmental psychobiologists have demonstrated that the offspring also inherit an ecological habitat (niche), a pattern of parental care for many species, and the epigenetic factors created by the parents' life conditions. Thus, someone's psychological phenotype is a product of a uterine and postnatal nurturing environment that is influenced by nutritional, stressful, and particular social and physical experiences operating within specific cultural and societal conditions.

Developmental psychobiological research strategies require elaborate and extensive longitudinal research designs using robust statistical tools. However, they produce advances in knowledge of what maintains consistency across development and what produces changes in trajectories and this knowledge will eventually reveal effective intervention techniques for prevention and rehabilitation of certain psychological phenotypes. This knowledge will inform social-policy-relevant discussions (e.g., for educational programs, treatment of disorders, adjusting social stratification, decision making and conflict resolution).

## Assumptions in studies of heritability and genotype–phenotype association

doi:10.1017/S0140525X12001380

Michael B. Miller,[a] Colin G. DeYoung,[a] and Matt McGue[a,b]

[a]*Department of Psychology, University of Minnesota, Minneapolis, MN 55455*; [b]*Department of Epidemiology, University of Southern Denmark, DK-5000 Odense C, Denmark.*

**mbmiller@umn.edu cdeyoung@umn.edu mcgue001@umn.edu**
**http://scholar.google.com/citations?user=EV_phq4AAAAJ&hl=en**
**http://www.tc.umn.edu/~cdeyoung/**
**http://www.psych.umn.edu/people/faculty/mcgue.htm**

**Abstract:** Charney's dismissal of well-established methods in behavioral genetic research is misguided. He claims that studies of heritability and genetic association depend for their validity on six assumptions, but he cites no sources to support this claim. We explain why none of the six assumptions is strictly necessary for the utility of either method of genetic analysis.

The target article is to be commended for highlighting exciting new developments in molecular genetics, but its dismissal of the

better-established methods in behavioral genetics research misses the big picture, the goals of these methods. The biometric analysis of behavioral phenotypes ("heritability studies") was never meant to specify a theory of human behavior. Rather, biometry provides a useful, and approximate, characterization of the nature of familial resemblance that implicates the importance of heritable factors and provides a foundation for targeted examination of those factors. Similarly, the investigation of genotype–phenotype association is not intended to specify the exact mechanisms by which the genotype is translated into the phenotype, but rather to examine the phenotypic consequences of variation in DNA. Research on mechanisms intermediary between genotype and phenotype builds on rather than competes with genetic association studies. All models of family resemblance and genotype–phenotype relations are imperfect, but that does not mean they are not useful.

Charney claims, without citing any evidence, that "heritability and gene association studies depend" on "six basic assumptions" (HS1–HS3, for heritability studies, and GAS1–GAS3 for genetic association studies).

Assumption HS1 asserts that heritability estimation assumes MZ (monozygotic) twins are genetically identical. Charney aims to refute this assumption by referring to studies that suggest MZ twins ought to differ in their DNA in somatic cells and in mitochondrial DNA. Most of the MZ twin differences he cites have nothing to do with heritability because they are acquired and are not differences in inherited DNA. We have known about genetic differences between MZ twins for decades (Zwijnenburg et al. 2010), but we also know that MZ twins rarely differ in measured genotypes. CNVs (copy number variations) and methylation patterns are more promising fronts that are being vigorously explored as a basis for MZ twin discordance (Bell & Spector 2011).

Charney's definition and discussion of HS2 and HS3 reveal his misunderstanding of biometric studies. Heritability indicates the percentage of variance in a phenotype that is due to inheritance, not due to variations in DNA. There is an important difference because, as Charney points out, many new variations in DNA may arise during development and certain epigenetic changes are heritable. The first model for heritability estimation was proposed by Sewall Wright (1920), years before the importance of DNA to genetics was understood. Biometrical models have become progressively more sophisticated over the years, and as new kinds of genetic and environmental phenomena are discovered, their effects can be incorporated into the models. Models include much more than G, E and G × E. We also model age and sex effects on heritability (Haworth et al. 2010), effects of assortative mating (Vinkhuyzen et al. 2012), the prenatal environment (Devlin et al. 1997), sex-specific effects, social interactions such as sibling competition and sibling cooperation, measured genotypes, and measured environment effects (Neale & Cardon 1992). Factors that cannot be modeled well today because we lack good data, such as cytosine methylation or retrotransposons, may be incorporated someday and the effects of these factors on model parameters can already be investigated through simulation.

Like HS1, GAS1 (persons having identical DNA in all cells) need only be accurate in a limited sense for genetic association studies to be valid, and considerable evidence supports this validity. We typically extract DNA from white blood cells or from cells in saliva. DNA in those cells is not necessarily the same as DNA in other cells. However, several types of evidence suggest that DNA extracted from different cell types is nearly identical. MZ twins are nearly as alike in their SNP (single nucleotide polymorphism) genotypes as are two DNA samples from the same person; we see the expected patterns of haplotype sharing for pairs of relatives (e.g., siblings or parent–offspring pairs); and there is very little evidence of Mendelian inconsistency in GWAS (genome-wide association studies) of parents and their offspring. In all of these cases, the differences we observe occur at the rate we would expect due to genotyping error, indicating that the rare changes that do occur are inconsequential for an association study.

Neither GAS2 nor GAS3 are assumed in genetic association research. In typical genotype–phenotype association research (including GWAS), one tests the association of a measured genotype with a phenotype. This method has very few assumptions, only an association test followed by the challenge of interpreting the result. If an association is found, this means that genotype predicts phenotype regardless of epigenetic moderation of gene expression or any of the intermediary processes that Charney describes. Genetic association studies should not be abandoned, even if they are made more powerful through the addition of analyses of CNVs, gene expression, and so forth.

Charney's greatest mistake is his misunderstanding of the role of quantitative genetic models. One of the most salient features of human behavior is that it is familial. Indeed, despite Charney's focus on differences, MZ twins are strikingly similar: correlated approximately .80 for IQ (Bouchard & McGue 1981), .50 on diverse personality characteristics (Bouchard & Loehlin 2001), and for a trait of particular interest to political scientists like Charney, .50 in their political ideologies (Alford et al. 2005). It is hard to imagine that the investigation of how MZ twins come to be so similar would provide no insights into the nature of the development of these fundamental human traits. Quantitative genetics is a powerful tool for initiating a program of research aimed ultimately at explicating the mechanisms leading to familial resemblance: Behavior is heritable, implying inherited differences in DNA sequence contribute in some way to behavioral differences. DNA sequence markers are associated (albeit weakly) with some behavioral phenotypes, implying that variants in the region of these markers are likely causal. It is not that the phenomena that draw Charney's interest – retrotransposons, mosaicism, and structural variation – are unimportant. They clearly are important. Rather, what these diverse phenomena do not provide is a coherent alternative paradigm for what remains one of the most important observations about human behavior, namely, that it is transmitted within families in a predictable manner.

## Estimating the actual subject-specific genetic correlations in behavior genetics

doi:10.1017/S0140525X12001069

Peter C. M. Molenaar

*Human Development & Family Studies, The Pennsylvania State University, University Park, PA 16802.*

**pxm21@psu.edu**

**http://www.hhdev.psu.edu/hdfs/directory/Bio.aspx?id=PeterMolenaar**

**Abstract:** Generalization of the standard behavior longitudinal genetic factor model for the analysis of interindividual phenotypic variation to a genetic state space model for the analysis of intraindividual variation enables the possibility to estimate subject-specific heritabilities.

The target article by Charney discusses what is called a paradigm shift in genomics and its significance for behavior genetics and gene association studies. In what follows I will focus on some of the implications for behavior genetics, in particular assumption HS1 (100% of the genes of MZ [monozygotic] twins are genetically identical, on average 50% of the genes of DZ [dizygotic] twins and non-twin siblings are genetically identical) and to a lesser degree on assumption HS2 (the percentages of genetic identity in HS1 never change).

The implications of the paradigm shift concerned are summarized in the target paper as follows: MZ twins, in addition to not possessing identical mitochondrial DNA, do not possess identical nuclear DNA. Their genomes differ in the polyploidy and

heteroplasmy of their mitochondrial DNA, in the number and location of retrotransposition events and copy number variations, in replications and deletions of whole or partial chromosomes, and in their epigenomes. To the extent that heritability estimates depend upon HS1, they will be unable to provide reliable estimates. Moreover, the presumed percentages of genetic identity between MZ twins, DZ twins and non-twin siblings are likely a moving target, thus violating HS2.

The standard behavior genetic model for the analysis of p-variate phenotypes of MZ and DZ twins is the genetic factor model of Martin & Eaves (1977), composed of additive genetic, common environmental, and specific environmental factors. The p-variate phenotypes of each member of a twin pair are stacked in a 2p-variate supervector, while the correlation of the additive genetic factors within twin pairs is fixed at 1.0 for MZ twins and 0.5 for DZ twins. The factor loadings of the additive genetic factors are assumed to be equal within and across all twin pairs. The extension of the standard genetic factor model to p-variate phenotypes obtained with MZ and DZ twins in a longitudinal design with T repeated measurement occasions is straightforward, again consisting of the stacking of the observations in a 2pT-dimensional supervector. At each measurement occasion the factor model described above obtains, while the relationships between measurement occasions are explained by regressing the additive genetic, common environmental, and specific environmental factors on their analogs at earlier measurement occasions (cf. Molenaar 2010).

The consequence of violation of HS1 is that the correlation of the additive genetic factor within MZ twin pairs in the standard genetic factor model no longer can be fixed at 1.0. Given the dependence on environmental contingencies of several of the causes, which according to the target paper underlie this violation (e.g., DNA methylation, maternal effects), it also would seem that the degrees of violation of HS1 are subject-specific, that is, yielding different genomes for different twins. This would imply that the correlation of the additive genetic factors in the standard genetic factor model becomes subject-specific. Violation of HS1 also would seem to lead to a decrease in the average correlation of the additive genetic factors of DZ twin pairs. Furthermore, the dependence on environmental contingencies then also yields subject-specific violations of HS2 with the same consequences for the standard longitudinal genetic factor model.

We have emphasized that the consequences of nonlinear epigenetic processes for the standard (longitudinal) genetic factor model may even be more severe in that not only the genetic correlations, but also the genetic factor loadings, become subject-specific (cf. Kan et al. 2010; Molenaar 2007; 2010; Molenaar et al. 1993). The standard (longitudinal) genetic factor model is fitted to the data by pooling across twin pairs (analysis of interindividual variation). It was shown in simulation studies (Molenaar et al. 2003) and by analytic proof (Kelderman & Molenaar 2007) that such subject-specific variation of factor loadings is invisible standard factor analyses of interindividual variation.

The only principled way to identify subject-specific variation in genetic correlations and factor loadings is to accommodate the standard genetic longitudinal factor model for applications to multivariate phenotypic time series (intraindividual variation) obtained with a single pair of genetically related subjects (e.g., a single MZ or DZ twin pair). Therefore the standard genetic longitudinal factor model was generalized as a genetic state space model for multivariate phenotypic time series (Molenaar 2010). A special feature of this so-called iFACE model is that the correlation between the additive genetic factor series is estimated (not fixed a priori). Moreover, the model allows for subject-specific factor loadings for the additive genetic, common environmental, and specific environmental factors. It turns out that this iFACE model is almost always identifiable (i.e., the derivative of its likelihood function with respect to the free parameters has null space of dimension zero; cf. Bekker et al. 1994).

The iFACE was applied to the quantitative genetic analysis of multilead event-related potentials obtained with a single DZ twin pair (Molenaar et al. 2011). It was found that the correlation between the additive genetic factors is about 0.40. Moreover, importantly, it was found that the patterns of genetic factor loadings differ substantially between twin 1 and twin 2. Heritability is high for twin 1 at the central parietal lead, whereas it is high for twin 2 at the left and right lateral parietal leads.

In conclusion, the iFACE – a direct generalization of the standard longitudinal genetic factor model for the analysis of interindividual phenotypic variation to the subject-specific analysis of intraindividual variation – can accommodate the implications of violations of HS1 and HS2 for behavior genetic analyses.

## Gene-independent heritability of behavioural traits: Don't we also need to rethink the "environment"?

doi:10.1017/S0140525X12001070

Christian P. Müller, Bernd Lenz, and Johannes Kornhuber

*Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, 91054 Erlangen, Germany.*

**christian.mueller@uk-erlangen.de**
**Bernd.Lenz@uk-erlangen.de**
**Johannes.Kornhuber@uk-erlangen.de**
**http://www.psychiatrie.uk-erlangen.de/wir_ueber_uns/mitarbeiter/prof_dr_rer_nat_christian_p_mueller/index_ger.html**

**Abstract:** Behavioural phenotypes have been explained by genetic and environmental factors ($E$) and their interaction. Here we suggest a rethinking of the $E$ factor. Passively incurred environmental influences ($E_{pass}$) and actively copied information and behaviour ($E_{act}$) may be distinguished at shared and non-shared level. We argue that $E_{act}$ underlies mutation and selection and is the base of gene-independent heritability.

The concept of heritability in its broadest sense attempts to explain the phenotypical similarities between generations. This refers to the physical constitutions of an organism over time as well to its behaviours. Heritability is based on the question of what are causal factors for the phenotype of a living organism, which happens to resemble that of a parent and kin (Jacquard 1983; Rose 2006). It is believed that because phenotypes cannot be passed on, these similarities are explained best by genetic factors. Genes are copied, and in that way, at least parts of their information is passed on to the next generation (Visscher et al. 2008). This constitutes a somewhat exclusive view of genetic heritability. However, it should be noted that independent from genes, behaviours can be copied as well, and large parts of an environment may remain the same between generations.

Behavioural genetics set out to explain how genes may transmit the observed similarities in adaptive and pathological behaviours from one generation to the next (Plomin et al. 2007). This approach, however, is not only based on a genetic definition of heritability, but also on several assumptions which make the DNA of an organisms its relatively solid and stable base throughout life in an ever-changing environment. Charney has now shown that this base is a much less stable and less homogeneous source for a behavioural phenotype as previously thought. In that, it may also serve less well as the unique source for behavioural similarities between parents and offspring. Here we argue that other heritable factors, which are normally the subject of behavioral neuroscience and social learning research, should also be considered more in depth than they were in behavioural neuroscience and social learning research. This may involve that the definition of heritability needs to be expanded and refined to include also

non-genetic factors contributing considerably to the similarities in behaviour within pedigrees and social groups.

To explain similarities between generations, behavioural genetics asked for the establishment of clear relationships between genetic (and epigenetic) variations of the DNA and behavioural traits (Plomin et al. 2007). While this worked out for some physiological measures, complex behavioural traits resisted a simple reduction to properties of the DNA (Maher 2008). In 2003, Caspi et al. introduced a new level of understanding when showing that a genotype (G) may result in a particular phenotype only by an interaction with the environment (E). Henceforth, a great number of studies emerged focusing on the G × E interaction. This was assuming a rather constant genotype at longitudinal (i.e., throughout lifetime) and transversal dimensions (i.e., in all cells of the organism, or at least between blood and brain). However, when considering the G×E interaction, major parts of behavioural trait variance resisted explanation (Maher 2008). One reason may be that all three components had been looked at too simplistically. In his article, Charney summarizes the evidence that suggests a major break-up in genetic dogmas. Accordingly, the genetic contribution to heritability of behaviour seems much more complex than previously thought.

It has long been known that genes constitute only a certain degree of the behavioural phenotype (Plomin 1990). This leaves considerable space for the "environment." Here we suggest that, in parallel to the diversification of genetic factors, environmental influences should be reconsidered. We propose to consider two major categories of *E*: (a) the passively incurred environmental influences ($E_{pass}$) and (b) the actively copied information and behaviour ($E_{act}$). $E_{act}$ may be not only the origin for the transmission of particular behaviours and behavioural disorders (Müller & Schumann 2011), but also the proximal cause for social interactions and culture (Danchin et al. 2004). While the ability to copy behaviour from conspecific models is genetically determined, its content (i.e., what kind of behaviours and information are copied) is most likely not (Pagel 2012).

Both environmental components have *shared* and *non-shared* components. Shared $E_{pass}$ would, for example, be the experience of a natural disaster that hits great parts of a population. Non-shared $E_{pass}$ would be, for example, domestic violence as experienced by a single child. The shared part of $E_{act}$ can be considered as "public information" – knowledge every member of a group has access to (Boyd et al. 2011; Danchin et al. 2004). Shared $E_{act}$ may also comprise "cognitive behaviours" such as verbally transmitted strategies of reasoning that form a "cognitive phenotype" (Pinker 2010). The non-shared $E_{act}$ may comprise those socially learned behaviours and information that are restricted to an individual; that is, the source is not accessible in the same way for other individuals.

The conceptual differentiation of the *E* factor in $E_{pass}$ and $E_{act}$ allows for a discussion of non-genetic heritability of behaviour. The potential advantage of a gene-independent heritability of behaviour is clear. It can mutate the behavioural phenotype at a much faster rate and to a more rigorous extent than genetic mechanisms in a changing environment. Once a particular information or behaviour is copied from a conspecific, it may still be modified and optimized by its positive or negative consequences for the single organism. By that way, particular behaviours can be completely erased from transmission, and new ones can be created and passed on. In constant or constructed "niches" (Laland et al. 2000), the advantage may be even bigger, because this way of passing knowledge to the next generation allows for an accumulation in the complexity of the behaviours (Byrne & Russon 1998). A multitude of complex human behaviours related to sophisticated technology, which essentially define cultural development, can only be passed on by copying (Boyd et al. 2011; Laland 2004). The behavioural phenotype of an individual may thus be a function of the genome, "inherited behaviours," environmental factors, and their specific interactions (Laland et al. 2010).

## Relational developmental systems: A paradigm for developmental science in the postgenomic era

doi:10.1017/S0140525X12001082

Willis F. Overton[a] and Richard M. Lerner[b]

[a]*Department of Psychology, Temple University, Philadelphia, PA 19122-6085*; [b]*Eliot-Pearson Department of Child Development, Tufts University, Medford, MA 02155.*

**Overton@temple.edu**

**Abstract:** This commentary argues that the anomalies suffered by the population behavior genetics paradigm are more widespread than suggested by Charney, including many made in the field of developmental science. Further, it is argued that, according to the criteria established by Kuhn, there is and has been available an alternative scientific paradigm that provides the formative context for Charney's postgenomic view. This is the relational developmental systems paradigm.

Charney has written a highly valuable review and analysis of the important new empirical findings in genetics and epigenetics that, as he notes, represent significant Kuhnian anomalies for the population (quantitative) behavior genetics (PBG) paradigm. This review is a major contribution and should strongly impact on the progressing general shift in the science of genetics away from the anachronistic PBG paradigm to a postgenomic view. In this commentary we focus our remarks on the nature of scientific paradigms and scientific revolutions in an effort to facilitate a generalization and consolidation of Charney's suggestion of a paradigm shift.

As a first point concerning paradigm anomalies, we highlight the long history of both conceptual and empirical critiques of the multiple flaws (anomalies) associated with the PBG paradigm. These contributions to the story of anomalies, which in Kuhn's (1970) framework lead toward a scientific crisis for the paradigm, emerged from several fields, including biology (e.g., Lewontin 1974; 1991), anthropology (e.g., Ingold 2000), experimental psychology (e.g., Hirsch 1967; Kamin 1974), and of special importance – considering its absence in Charney's review – developmental psychology/developmental science (Lerner 2006; 2012). Central to this latter field has been the conceptual and empirical work of Gilbert Gottlieb and his colleagues (e.g., Gottlieb 1997; 2003; Gottlieb et al. 2006; Wahlsten 2012). Our own work on this topic began early (e.g., Lerner 1978; Overton 1973) and has continued to the present (e.g., Lerner 2004; 2012; Overton 2004; 2011). And emerging within developmental science there has been over the past several years a series of important broadly based critiques of the PBG paradigm that are necessary readings for any full understanding of the breadth and depth of this paradigm's critical flaws (e.g., Greenberg 2011; Ho 2010; Jablonka & Lamb 2005; Joseph 2010; Lickliter & Honeycutt 2010; Meaney 2010; Moore 2001; Partridge 2005).

This wealth of historical and contemporary literature arguably presents a sufficient case for that part of a scientific revolution that Kuhn (1970) termed a *crisis* (i.e., a breakdown of normal puzzle solving within a paradigm). But a scientific crisis is not sufficient for a paradigm shift. That is, contrary to Charney's suggestion that with sufficient anomalies "a new paradigm will emerge," Kuhn points out that "once [it] … has achieved the status of a paradigm it is declared invalid only if an *alternative candidate is available* to take its place…. The decision to *reject one paradigm is* always simultaneously *the decision to accept another*" (Kuhn 1970, p. 77, emphasis added). Thus, the relevant question is whether there is currently an alternative available paradigm that provides the formative context for Charney's postgenomic view, and, if so, what is it? Our answer is that there is, and has been, such a paradigm, and it has been broadly referred to as the relational developmental systems (RDS) paradigm (Lerner 2006; 2011; Lerner & Overton 2008; Overton 2006; 2010; 2012).

For Kuhn, "paradigm" had two distinct meanings: one narrow, one broad. The narrow meaning he termed *exemplars* (i.e., "concrete problem-solutions") or methodological ways the science is actually conducted. Clearly both Charney's review and the abovementioned literature present a number of exemplars that would appear to differentiate PBG from some alternative postgenomic paradigm (e.g., the computation of heritability indices and gene association studies versus the experimental analysis of causal pathways). It is in the broader meaning of paradigm, however, that we find the specific nature of this alternative paradigm. Kuhn called this broader meaning the *disciplinary matrix*, and a key feature is that it entails shared *metaphysical beliefs* – "from heuristic to ontological models … [which] supply the group with preferred or permissible analogies and metaphors (1970, p. 184)." In other words, following Charney, here we have "key assumptions concerning … the nature of the phenomena" under study.

The PBG paradigm is framed by a Cartesian–Newtonian mechanistic ontology. According to this disciplinary matrix, the world is ultimately composed of stable split-off pure forms or elements (e.g., the genotype) that combine, always in an additive fashion, to constitute the world of appearance (e.g., the phenotype). The split-off pure forms permit context free definitions and context-free identifications of objects and events. The combining of elements is often termed *interaction*, but the meaning of this term simply entails multiple additions, as pure forms remain pure forms. In this world, activity is split off from form and treated as forces or causality that operate in a unidirectional and additive linear fashion (cause → effect). This is a world in which foundationism, atomism, and reductionism are bedrock concepts.

Contrary to Charney's suggestion that the postgenomic view "has not yet coalesced around a core set of principles or assumptions characteristic of a paradigm" RDS is exactly the disciplinary matrix that frames the postgenomic view. The RDS paradigm asserts a relational ontology. This disciplinary matrix is holistic and dynamic. The world is conceived as a spontaneously active (dynamic), changing (developing), relational, holistic (integrated) system. Stability here is the exception rather than the rule. Systems are complex rather than simply complicated, often nonlinear and nonadditive, and through processes of self-organization and self-regulation, they grow (develop) increasing complexity. The relational nature of the system emphasizes causality as bi- or multidirectional (← →). All facets of the individual and the context exist in mutually influential relations (Elder 1998; Molenaar 2007). Accordingly, the potential for plasticity of intraindividual change is a hallmark of the RDS paradigm.

Organisms within the RDS paradigm are characterized as relational, complex, spontaneously active, self-creating (autopoetic), self-organizing, and self-regulating adaptive systems, with subsystems – from the genetic to the behavioral and sociocultural levels – composed of co-acting, co-developing processes functioning according to the reciprocal causality entailed by complex positive and negative feedback action loops. A final key feature of this paradigm – derived from its relational and holistic character – is that all behavior and development is contextualized and situated. There are no split-off discrete pure forms (e.g., pure gene, pure environment) operating in isolation or additively "interacting."

## The history of the nature/nurture issue

doi:10.1017/S0140525X12001094

Csaba Pléh

*Department of Psychology, Károly Eszterházy College, Eger H-3300, Hungary.*
**pleh.csaba@ektf.hu www.plehcsaba.hu**

**Abstract:** It is worthy to supplement Charney with two historical issues: (1) There were two rival trends in the rebirth of genetic thought in the 1960s: the universal and the variation related. This traditional duality suggested that heredity cannot be equated with genetic determinism. (2) The classical debates and reinterpretation of adoption/twin studies in the 1980s regarding intelligence suggested that the environment had a more active role in unfolding the genetic program.

In addition to its specific claims regarding the dynamic nature of genetic determination of behavior, Charney's target article has done a great service in drawing our attention to the underlying principles and the history of the entire idea of the complexity of genetic determination. Charney, along with others (like Johnson et al. 2011), rightly claims that the genetic determination of (among other things) behavior is complex at least in two regards. First, besides genes, gene expression is crucial. His second claim, that psychometric heritability is not the only issue of genetic determinism, should be seen in the context of the recent past. The historical reminder here goes back to the 1960s. That was the time when genetic determination reappeared in psychology, but in two rival and different forms. One was the innatism proposed by Chomsky (1959; 1965; 1968), mainly on analogy with ethology, suggesting that complex human behaviors may be under genetic control. Innatism was one way to overcome the "empty organism" metaphor of the behaviorists.

This kind of revival of genetic determinism was entirely uninterested in individual differences, as, for example, Chomsky's (1972a) intervention in the early intelligence debates showed. Innate organizing principles of language and other complex human achievements belong to "species-specific behaviors." For Chomsky and his followers, this kind of genetic determination is by far not determinism in the traditional sense. Genetically determined language is not a constraint on thought; rather, by its structure it is unbound and unlimited, and therefore it also ensures the unlimited free development of humanity (Chomsky 1972b; 1988).

At roughly the same time, the issue of genetic determinism of human behavioral and intellectual individual differences became the focus of increasing scientific attention again. This opposing view focused on things differentiating individuals. They denied that the behaviorists' life history empiricism could be a possible way to explain individual differences. To explain individual differences, they referred to the Galtonian paradigm that proposed heredity to be crucial in determining individual differences in behavior and basically presupposed an additive role of nature (genetic) and nurture (environment). The followers of Galton considered interaction as a mere statistical term (for critical surveys, see McLafferty 2006; Richardson & Spears 1972; Taylor 1980).

There is a third aspect of Galton's theory, namely, that it assumes one single feature of excellence. As we emphasized a decade ago:

> In psychology Darwin's theory has taken two competing forms for more than a hundred years. The first is a conservative, deterministic approach based upon the theory of natural selection and the survival of the fittest. It stresses the need to reduce the dimensions of psychological variability by finding a small number of traits in which individuals differ from each other. If someone excels in these traits, he is considered to be fitter than others. The second approach is more tolerant, emphasizes development, and considers variability itself as an evolutionary asset. (Kovács & Pléh 2000, p. 1)

The hot debate regarding the validity of the Galtonian paradigm started half a century ago by Jensen (1969) claiming the genetic intellectual inferiority of African Americans. Interestingly, in addition to the social value issues, the debate concerned the statistical solidity of arguing on the basis of twin research towards the hereditary nature of individual and group differences. Way before postgenomics, the issues raised were similar to those regarding the relationships between postgenomics and heritability by Charney and by Johnson et al. (2011). Kagan (1969) suggested that twin research does not allow us to make intergroup comparisons, and curiously enough, his examples, as well as those in the books edited by Richardson and Spears (1972) and Block and Dworkin

(1976), consider the highly heritable trait of height as also being influenced and controlled by environmental factors (nutrition). The classical debate warned us that inheritance does not determine more than a mere response range (Crow 1969; Hunt 1969) and argued for taking environmental interventions seriously, not unlike the role advocated to epigenetic unfolding by Charney.

These statistical discussions raised the methodological issue that when interpreting the twin data, the shared environment (see the argument of Charney about early shared environment and the onset of separation) and environmental similarity are not considered sufficiently. A left-wing French group of sociologists of science (Chappaz et al. 1980) raised similar issues, when they criticized mixing statistical and professional regarding the additivity of variances.

Many twin researchers, who – due to their political preferences – believed in the deterministic role of environment well before postgenomics, argued for a more subtle use of twin data. Luria (1936) claimed that higher order functions are more under environmental control because identical and fraternal twins' elementary functions are more similar than their higher functions (e.g., voluntary memory). According to Luria, higher functions are under stricter environmental control and tend to converge with age. Zazzo (1955; 1962), repeatedly argued that there is an important biological discrepancy between twin and singleton pregnancies – as Charney argues as well – and twins also have a peculiar social environment. Zazzo (1960) summarized the embryological and psychological peculiarities of twin development that could have been gathered before molecular genetics and modern behavior genetics were born.

These historical remarks are by far not questioning the arguments of Charney. My intention was to indicate that several issues raised by postgenomics research were present in discussions how genetics and "embriology" contribute to the unfolding of psychological individuality. The intense study of epigenetic unfolding as shown by Charney and by reviews like that of Zhanks and Meaney (2010) indicate that to understand the implications of the striking landscape metaphor proposed by Waddington (1942; 1957) to illustrate the concept of epigenesis (see Jablonka & Lamb [2002] for a history of the concept), psychologists have to become aware of the possible new interpretation of their classical doubts regarding straightforward genetic determinism. One can find an interesting parallel between recent developments in postgenomics thought and classical issues of behavior genetics.

## Epigenetic regulation of brain-derived neurotrophic factor: Implications in neurodevelopment and behavior

doi:10.1017/S0140525X12001100

Benjamin D. Schanker

*Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02115.*

**bdschanker@gmail.com**

**http://www.massgeneral.org/psychiatry/research/pngu_home.aspx**

**Abstract:** Several recent research findings have implicated brain-derived neurotrophic factor (BDNF) as a mediator of neuronal plasticity. The *BDNF* gene is under extensive epigenetic regulation, which modulates how much or how little environmental experiences become encoded within neurons and neural circuits. Future scientific progress within the postgenomic paradigm requires elucidation of the functional trajectory in neogenetic and environment interactions.

One of the most intriguing genes highlighted by Charney (sect. 4.1.1) is that of brain-derived neurotrophic factor (BDNF), a growth factor implicated by numerous research studies as an important mediator of neuronal plasticity. Although Charney notes the impact of increased hippocampal *BDNF* expression on neurogenesis – via cell signaling that promotes neuronal survival, growth, and differentiation – it is valuable to recognize that *BDNF* is prevalently expressed not only in the hippocampus, but also in the cerebral cortex and other limbic structures. BDNF also functions in these regions as a biomolecular mediator of neural plasticity and in the corresponding development of neuroanatomical circuits and complex behavioral phenotypes. Exploring – more in-depth – the functions of BDNF provides insight into the phenotypic and behavioral significance of gene-environment interactions outlined by Charney (sect. 5.2).

Following transcription and translation of the *BDNF* gene, protein products are packaged into large vesicles within neurons and released following neuronal depolarization in an activity-dependent manner, comparable to neurotransmitter release (Mowla et al. 1999) and consistent with Hebbian theory. Deficiencies of BDNF can contribute to underdevelopment of neurons. Low levels of BDNF mediate age-related declines in hippocampal volume and memory function (Erickson et al. 2010). Moreover, the environments in utero, during early life, and in adulthood can have long-lasting effects on the methylation patterns and chromatin modeling of the *BDNF* gene in cells across the brain, affecting how much or how little growth factor is available in different neuroanatomical regions.

*BDNF* contains at least eight distinct promoter regions that together with differential alternate splicing, polyadenylation, and promoter expression can generate over 18 different isoforms. The isoforms are selectively localized within neurons, contributing to highly specific regional, spatial, and temporal regulation of neural plasticity. Epigenetic modifications, including DNA methylation and histone acetylation, meticulously regulate the *BDNF* gene. The effect Charney notes of increased hippocampal plasticity following exercise (sect. 4.1.1) has indeed been demonstrated to be mediated by chromatin remodeling of *BDNF*, including histone acetylation and demethylation of promoter regions (Gomez-Pinilla et al. 2011). Interestingly, promoters I and III have been found to be transcriptionally upregulated in the amygdala during consolidation of fear learning (Rattiner et al. 2004), and BDNF has been shown to be necessary in the hippocampus for extinction of aversive memories (Heldt et al. 2007).

Human clinical studies have found strong evidence that patients suffering from depression have lower levels of serum BDNF compared to healthy subjects, deficiencies that can be ameliorated with antidepressants (Sen et al. 2008). Other pharmaceuticals and mood stabilizers have demonstrated effects as well: Lithium, valproic acid, and several other HDAC inhibitors have been shown to upregulate *BDNF* promoter IV expression (Yasuda et al. 2009). A study of postmortem suicide victims' brains revealed hypermethylation at CpG sites in the *BDNF* promoter IV, corresponding to lower *BDNF* mRNA levels in specific brain areas (Keller et al. 2010). Using serum samples of patients living with major depression, another study recently found hypermethylation of CpG sites in *BDNF* promoter I (Fuchikami et al. 2011). These findings highlight the potential of using an individual's *BDNF* methylation profile as an epigenetic biomarker of depression. Moreover, they add credence to Charney's supposition of a paradigm shift away from the prediction of complex phenotypes using the genetic code alone, and toward greater recognition of epigenetic/neogenetic effects (sect. 10).

Highly variable levels of *BDNF* expression – across brain regions and between individuals – have implications for behavioral phenotypes. BDNF serves as a model system that exemplifies the significance of epigenetic modifications in neurodevelopment and behavioral plasticity, which Charney posits (sect. 5.2). The resemblance between high licking and grooming rat mothers and their biological or fostered pups in regard to stress-related behavioral phenotypes and subsequent rearing behavior (sect. 5.2.1) has

been further studied in relation to BDNF; findings corroborate the importance of the perinatal environment. Mice experiencing higher levels of perinatal care have demonstrated a propensity for greater social interactions in adulthood, correlated with increased hippocampal BDNF levels (Branchi 2009). Conversely, infant isolation has been associated with reduced levels of *BDNF* mRNA in the prefrontal cortex, hippocampus, and amygdala. Epigenetic studies of BDNF in rats have demonstrated an association between early life adversity and hypermethylation of *BDNF* promoter IV in the prefrontal cortex and hippocampus (Roth & Sweatt 2011). The methylation effects have been found to not only persist into adulthood, but also to be intergenerational, with significant behavioral implications.

In human studies, prenatal exposure to maternal cigarette smoking has been associated with higher rates of *BDNF* promoter VI methylation in adolescent blood samples, and these adolescents showed an increase in drug experimentation (Toledo-Rodriguez et al. 2010), a finding potentially consistent with "developmental programming" (sect. 7). Although intriguing, additional human studies are necessary to validate the numerous findings in animal models, despite the logistical challenges of robust epigenetic human studies.

Biological or statistical epistasis has been reported between *BDNF* and the serotonin transporter (*SLC6A4*) (Grabe et al. 2012), the dopamine receptor (*DRD2*) (Montag et al. 2010), and more recently the glucocorticoid receptor (Jeanneteau et al. 2012). In the latter case, *BDNF* expression was shown to regulate the release of corticotrophin-releasing hormone in the hypothalamic-pituitary-adrenal (HPA)-axis.

In essence, BDNF functions as a primary biomolecular substrate for encoding environmental experiences into neurons. The growth factor mediates the formation of neural engrams that derive from negative or positive life experiences – engrams in neural circuits and the HPA-axis that later direct adulthood stress responses and behavioral phenotypes. The epistatic and pleotropic effects of *BDNF* expression have implications for mood, temperament, behavior, and development of neuropsychiatric conditions (Boulle et al. 2012). Stress, adversity, physical activity, early environment, enrichment, aging, and trauma can all change levels of gene expression, which can subsequently mediate neurodevelopmental and behavioral changes. In Charney's postgenomic paradigm, additional human subjects research with BDNF is necessary to better elucidate the functional trajectory from biomolecular science (genetics and neogenetics) to neurodevelopment (neuroanatomical structures/circuits) to behavioral phenotypes (normal and pathologic). This understanding will illuminate better therapeutic targets and facilitate the prevention of pathologic neurodevelopment.

## Parental brain and socioeconomic epigenetic effects in human development

doi:10.1017/S0140525X12001112

James E. Swain, Suzanne C. Perkins, Carolyn J. Dayton, Eric D. Finegood, and S. Shaun Ho

*Department of Psychiatry, University of Michigan School of Medicine, Ann Arbor, MI 48109.*

**jamesswa@med.umich.edu**
**http://www2.med.umich.edu/psychiatry/psy/fac_query4.cfm?link_name=jamesswa**
**sperkinz@med.umich.edu carolynjdayton@gmail.com**
**efinegoo@med.umich.edu hosh@med.umich.edu**

**Abstract:** Critically significant parental effects in behavioral genetics may be partly understood as a consequence of maternal brain structure and function of caregiving systems recently studied in humans as well as rodents. Key parental brain areas regulate emotions, motivation/reward, and decision making, as well as more complex social-cognitive circuits. Additional key environmental factors must include socioeconomic status and paternal brain physiology. These have implications for developmental and evolutionary biology as well as public policy.

Bonding between parents and offspring constitutes the earliest and most influential relationship (Feldman 2007). Building on the work of Bowlby (1978), characterizations of this reciprocal interaction between mother and infant and the impact on infant and child development provide powerful theoretical and empirical frameworks within social and developmental psychology (Cassidy & Shaver 1999). Despite increased physiological, emotional, and economical stress (Barclay et al. 1997), both mothers and fathers typically find themselves highly motivated care for their infants' needs (Goodman 2002; Mercer 1985). Sensitive parenting can diminish anxiety and aggression (NICHD Early Care Research Network 2006) and cultivate resilience after stress (Korosi & Baram 2010). Thus, adults' caregiving for their infants may have roots in early-life experiences with parents (Swain et al. 2012). The possibility that maternal behavior depends on the simultaneous regulation of avoidance and approach motivation raises intriguing questions about possible health implications of maternal caregiving because both motivations are tied to the regulation stress response (Brown et al. 2012). In addition to early-life programming through altered expression of genes in animal models (Champagne 2010), altered brain structure and function in circuitry are directly implicated in the regulation of maternal behavior in humans (Kim et al. 2010b). However, reversal of maladaptive brain outcomes with psychotherapy remains to be shown.

Attempts to understand the human maternal brain with brain-imaging studies of mothers listening to baby stimuli highlight an array of emotion response and regulation circuits, including amygdala (alarm), striatum/nucleus accumbens (NA; motivation and reward), and cingulate (decision making). In humans, cortical regions that have not been highlighted so much in the rodent literature have also been described, including the inferior frontal gyrus (IFG), orbitofrontal cortex (OFC), insula, periaqueductal gray (PAG) and dorsomedial prefrontal cortex (dmPFC), that regulate complex social-cognitive functions that are selectively engaged when the maternal brain responds to infant stimuli. (For reviews, see Barrett & Fleming 2011; Swain 2011.) Direct studies of baby brain structure and function in response to parenting cues have not been done; however, a pioneering neuroimaging study of mothers showed how perceived maternal care (a proxy for the animal models' licking and grooming behaviors) affects both brain structures and functional response to own-baby cries (Kim et al. 2010b). In this study, mothers who reported higher maternal care in their own childhood showed higher gray-matter density, proportional to the number of neurons, in a range of higher cortical areas and executive function areas, including the insula, superior and middle frontal gyri, orbital gyrus, superior temporal gyrus, and fusiform gyrus. There were also increased functional responses in a number of frontal brain regions and the insula in response to own-baby cries.

Besides the distant effects of mothers' own early-life experiences, the transition to parenthood also involves maternal brain plasticity around childbirth. In the first prospective longitudinal study of gray-matter changes over the first few months of motherhood, gray-matter volume of the insula, prefrontal cortex, parietal lobes, and midbrain areas between 2–4 weeks and 3–4 months postpartum increased (Kim et al. 2010a). Furthermore, greater gray-matter volume in the midbrain (including the hypothalamus, substantia nigra, and amygdala) was associated with maternal positive perceptions of her baby. In contrast, the associated chronic stress of low socioeconomic status (SES) involve the amygdala, hippocampus, and PFC (Hackman et al. 2010; McEwen & Gianaros 2010). Also, young adults' recollection of lower SES from their own childhood was reported to be associated with greater amygdala reactivity to threatening but not nonthreatening faces (Gianaros et al. 2008). Interestingly, current levels of perceived

SES were unrelated to amygdala reactivity to threatening face stimuli – only perceived SES in *childhood* mattered. Indeed, low-SES parents are themselves more likely to exhibit harsh or unresponsive parenting toward their children, and poverty is also associated with a higher incidence of child abuse and neglect (Conger & Donnellan 2007; McLoyd 1998). Low-quality parenting is furthermore associated with altered neurological development, as evidenced by the effects of early-parental care on hippocampus structure. In humans, adults who experienced adverse parenting during their own childhood have significantly smaller hippocampus volumes in adulthood (Buss et al. 2007; Woon & Hedges 2008). However, these studies have not included direct measures of childhood poverty, participants' experiences of either concurrent of childhood chronic stress, or the experience of parenting behaviors. Adults with lower subjective social status had reduced gray-matter volume in the perigenual anterior cingulate cortex (ACC) region of the PFC (Gianaros et al. 2007). These environmentally sensitive brain regions are involved in many cognitive and emotional regulatory functions, including the appraisal of salient events and emotional experiences, as well as the complex behaviors and possibly cardiovascular reactivity in response to environmental demands (Evans 2003; McEwen & Gianaros 2010).

Harsh early-childhood parenting environments also show high amygdala reactivity during an emotion labeling task, positively correlated with high right-ventrolateral-prefrontal-cortex (rvlPFC) activity (Taylor et al. 2006). This can be potentially interpreted as decreased ability of rvlPFC to modulate amygdala activation. Along the same lines, exposure to parental corporal punishment in childhood is associated with reduced gray-matter volume in mPFC, dorsolateral-PFC, and ACC (Tomoda et al. 2009). On the other hand, lower social status may result in increased sensitivity of mentalization circuits some circuits (Muscatell et al. 2012). Despite a growing literature on the brain physiology important for parenting (Swain 2011), it remains to be shown how the chronic stress of poverty affects these circuits longitudinally. The environmental role of the father brain is also just beginning to be examined (Swain et al., under review). Recent studies demonstrate epigenetic paternal effects (Chong et al. 2007), including the transmission of stress-induced pathologies such as depression (Dietz et al. 2011; Dietz & Nestler 2012). The effects of early-experience on the developing brain for emotion regulation may be further linked to next generations' capacity for sensitive parental behaviors (Francis et al., 1999; Kim et al. 2010b; Meaney 2001) with resulting implications for public policy (Dawson et al. 2000).

ACKNOWLEDGMENTS

The authors are supported by grants from the National Alliance for Research on Schizophrenia and Depression (JES), the Klingenstein Third Generation Foundation (JES), NIMHD IRC2MD004767-01 (JES, SSH; EFD), the Michigan Institute for Clinical Health Research UL1RR024986 (JES, CD, SSH; SCP), and University of Michigan – Robert Wood Johnson small grant program (JES, SSH).

## Neogenomic events challenge current models of heritability, neuronal plasticity dynamics, and machine learning

doi:10.1017/S0140525X12001379

Cláudio Eduardo Corrêa Teixeira,[a,b,c] Nelson Monte de Carvalho-Filho,[a,b] and Luiz Carlos de Lima Silveira[a,b]

[a]*Instituto de Ciências Biológicas, Universidade Federal do Pará, Belém, Pará, Brazil*; [b]*Núcleo de Medicina Tropical, Universidade Federal do Pará, Belém, Pará, Brazil*; [c]*Programa de Pesquisa em Neurociências e Comportamento, Universidade da Amazônia, Belém, Pará, Brazil*.

**luiz@ufpa.br**

**Abstract:** We address current needs for neogenomics-based theoretical and computational approaches for several neuroscience research fields, from investigations of heritability properties, passing by investigations of spatiotemporal dynamics in the neuromodulatory microcircuits involved in perceptual learning and attentional shifts, to the application of genetic algorithms to create robots exhibiting ongoing emergence.

Charney draws a plausible picture about how *genome* structure, function, and heritability can be modified in a complex manner by both inner (body) and outer environments, as well as by the environment-modulated *epigenome*. The concepts raised in his article challenge the current knowledge about brain function, environment and self-representation, and human behavior. In addition, the dynamics of the *neogenome*, the active genetic material employed by the organism resulting from the interaction of the genome and epigenome, brings difficulties to intuitive understanding of cognitive processes. Thus, it becomes important for neuroscientists to develop new theoretical and computational methods to extract useful information about the influence of neogenomic regulatory networks on evolutionary and developmental processes.

The understanding of heritability studies was one of those completely changed under the neogenomics perspective, and it has direct impact on the neurosciences. For example, it is now necessary to investigate the real chance that acquired modifications at F0 male/female neogenome have to be transferred to F1 neogenome (i.e., the chance that F1 has to be a heritor of a neogenomic potential to develop F0 male/female acquired phenotypes). It is well known that acquired modifications in the somatic F0 male/female neogenome are related to F0 male/female acquired phenotypes, and that both acquired modifications cannot be transferred to F1. In contrast, acquired modifications in the neogenome of F0 male/female germ cells can be transferred to F1. What if the acquired modifications in the neogenome of F0 male/female germ cells were identical to that occurred in the neogenome of F0 male/female somatic cells related to acquired phenotypes? Could such acquired modifications in the neogenome of F0 male/female germ cells transfer to F1 a neogenomic potential to F1 to develop phenotypes acquired by F0 male/female? Theoretically, the transference of acquired phenotypes from F0 to F1 through the transference of modified neogenome of F0 male/female germ cells to F1 would be highly constrained. For example, it would require the absence of a direct environmental exposure beyond F0 male/female and transmission of a given phenotype through germ cells to at least the F3 generation (Charney's target article, note 7). In addition, the development of F0 acquired phenotypes by F1 would be highly constrained by other diverse neogenomic and environmental factors. For example, the acquired modifications in the neogenome of F0 male/female germ cells transferred to F1 should be similar in amount, extent, and specificity to the acquired modifications in the neogenome of F0 male/female somatic cells linked to the acquisition of new phenotypes. Further, instead of solely assured by the heritability of a neogenome with acquired modifications, the development of F0 male/female acquired phenotypes by F1 also should be constrained by stochastic environment-induced neogenomic events related to the regulatory dynamics of genes transcription and translation, as well as protein structure processing in F1 cells. However, despite the number and nature of constraints involved in this issue, investigation of the real chance that acquired phenotypes have to be inherited is needed.

Another field that will undergo important changes due to the introduction of neogenomics concepts is the investigation of the spatiotemporal dynamics of neuronal microcircuitry involved in the neuromodulation of cortical activity states. The neogenomic events described by Charney often are related to synaptic plasticity and neurogenesis (Allen 2008; Day & Sweatt 2011). They are events assumed to be involved in perceptual learning and attentional modulation (Day & Sweatt 2011; Feng et al. 2007). In the temporal domain, visual attention shifts can occur at a millisecond scale, while in the spatial domain the scale corresponds to a

displacement of 10° (Koenig-Robert & VanRullen 2011). Perceptual learning may early and rapidly improve performance (Hawkey et al. 2004) and is thought to be driven by external inputs controlling the ongoing cortical plasticity (Sagi 2010). These two mechanisms are also related to competition between cortical populations for specific features of sensory stimuli (Ashwin et al. 2011; Lewkowicz 2000). Neuromodulatory subcortical neurons implicated in the modulation of attentional shifts and experience-dependent cortical plasticity (Goard & Dan 2009) also play a role during neuronal competitions, contributing significantly to the decorrelation between cortical populations responses to a given stimuli. Are such decorrelations between the responses of cortical populations a result of their neogenomic regulatory systems decorrelation? Are the neogenomic regulatory systems of subcortical neuromodulatory neurons controlling the neogenomic regulatory systems of cortical populations? Are the neogenomic regulatory systems capable of implement an action in the same spatiotemporal limits of attentional shifts and perceptual learning? New theoretical and computational formal methods are demanded to answer questions currently raised under the neogenomic perspective.

Finally, a small set of canonical simple computations have been identified as the mathematical basis of neuronal population behavior, and it is interesting to consider how analogous these operations are to our original view of how the genome worked. Exponentiation, linear filtering, and divisive normalization are the operations most commonly described (Baylor & Fuortes 1970; Grossberg 1988; Heeger 1992; Lo & Wang 2006; Naka & Rushton 1966; Priebe & Ferster 2008; Stanford et al. 2010; Wang 2002). In addition, several more complex theoretical and computational formalisms also have been employed to understand how genetic events are implicated in the control of intracellular and intercellular processes: direct and indirect graphs, Bayesian networks, Boolean networks, stochastic equations, rule-based formalisms, winner takes all and winnerless competition models, and so forth (for a review, see Jong 2002). However, under the recent progress of neogenomics, algorithms based on the original genome paradigm will have to be reviewed or changed towards algorithms based on the neogenome dynamics. In this way, *epigenetic robotics* is a relatively new field of science that aims to understand the brain by constructing embodied systems and to build intelligent systems by learning from brain studies (Zlatev & Balkenius 2001). Considering the perspective of neogenomic dynamics, epigenetic robotic operations should be guided by software (genome) modifiable by both inherent reprogramming tasks (transposable elements) and developmental experiences (epigenome), which in turn should be driven by interactions with robot inner/outer environments, all contributing to the emergence of robot self-programming (Prince et al. 2005; Markman et al. 2011). Therefore, through this new modeling perspective, epigenetic robotics should provide useful explanatory neogenomic brain components and contribute to the validation and further development of machine learning foundations.

ACKNOWLEDGMENTS

The authors are supported by CNPq, FINEP, CAPES, and IBN-Net.

## A straw man's neogenome

doi:10.1017/S0140525X12001343

Oscar Vilarroya

*Unitat de Recerca en Neurociència Cognitiva, Departament de Psiquiatria i Medicina Legal, Universitat Autònoma de Barcelona, Fundació IMIM, C/ Doctor Aiguader, 88, 08003 Barcelona, Spain.*

**oscar.vilarroya@uab.cat**

**Abstract:** The neogenome has indeed changed how to understand the relationship between genotype and phenotype. However, this does not imply a paradigm shift, but simply a normal development of a young science. Charney creates a straw man out of the myth of an immutable genetics, and conveys the wrong idea that heritability studies and gene association studies are no longer valid.

I would like first to welcome Charney's target article. It is an excellent introduction to those genetic mechanisms that are most relevant for behavioral genetics, and it provides a first-class overview of the recent advances in genetics concerning the weight of epigenetic processes. I agree completely with Charney in his view that "the biological worldview of postgenomics is characterized by extreme complexity, variability, multilevel reciprocal interactionism, and stochasticity as an inherent property of biological systems, which all contribute to what might be called the blurring of boundaries, in particular, the boundary between genes and environment" (sect. 1). I also agree that the new epigenetics is changing the way we must understand the relationship between the genotype and the phenotype. I have myself tried to transmit the idea for a long time, with very little success, that this is a fact to be assumed in cognitive neuroscience (Hilferty & Vilarroya 2002; 2008; Hilferty et al. 1998).

However, if we take that the aim of the article is to convince the reader that we are in front of a paradigm shift, then I think that Charney misdirects his efforts. A paradigm shift implies a replacement of the theoretical framework and the methodologies of a discipline by new ones, such as heliocentric cosmology did to its precedent geocentric cosmology. All the mechanisms that Charney reviews are extremely relevant developments and imply important improvements in genetics theory and methodology, but they do not replace genetics with a new discipline; rather, they enrich it. These improvements are part of the normal dynamics in the development of a young discipline. In science, there are many assumptions that are modified in the course of new findings. Genetics is a growing discipline, and as such, it has undergone a great deal of change in its short life. Raising its working assumptions to the status of a dogma is, in my opinion, an exaggeration. For one thing, the idea that the genotype is not sufficient to predict phenotype, or that biological causation runs upwards and downwards, can be accommodated by a genetics framework understood as a set of scientific, and thus flexible, assumptions (e.g., Fusco & Minelli 2010).

My impression is that Charney has created a straw man out of the myth of an immutable genetics. First, he pictures genetics as embodying a fixed dogma, and then he assumes that new developments in epigenetics count as a paradigm shift. For example, he argues that the causes of phenotypic variation are attributed to genetic or environmental parameters, or to the interaction of the two, and then he advances that "the neogenome constitutes a class of heritable agents that do not fall into either category" (sect. 6). I believe that extant genetics is confidently accommodating this new notion (e.g., Bell et al. 2010; Caldji et al. 2011; Cherry & Daley 2012; Gershon et al. 2011; Hamm & Costa 2011; Oh & Petronis 2008; Pike 2011; Rutten & Mill 2009). Second, he creates artificial categorical assumptions, which later can be easily refuted with evidence. For example, the qualifications of "all" and "never" in the description of the central assumptions for twin study methodology are not common qualifications in science, nor are they a reasonable attribution to genomics. Finally, Charney reverses the burden of proof by asking extant genomics methodologies to prove their soundness. For example, Charney asserts that "although employing statistical analysis, biometric genetics must make contact with the natural world at some point" (sect. 6.1.1). It is difficult for me to see the point of such a claim. The challenge is either trivial or highly argumentative. How does one independently assess biometric genetics contact with the natural world?

Additionally to creating a straw man, I believe that some of Charney's conclusions are non sequiturs. In some places he is carried away by his paradigm shift momentum. For example, considering that the DNA is no longer privileged as the sole carrier of information does not grant the idea that the DNA is no longer a privileged carrier of information, as Charney seems to imply. In other places, he presents contentious argumentations. For

example, he argues that "if MZ [monozygotic] twins are concordant for [a specific] trait to a greater extent than DZ [dizygotic] twins, this greater concordance cannot confidently be attributed to genetic concordance, since they may be genetically discordant" (sect. 6). In view of all the evidence that Charney has brilliantly presented in his target article, we can all agree that MZ twins may be genetically discordant, but it doesn't follow that we cannot confidently attribute trait concordance to genetic concordance. The issue cannot be *all or nothing*; rather, it is a question of *degree*. Finally, and perhaps most important, the target article seems to convey the corollary that heritability studies and gene association studies are no longer valid as methodologies. For example, Charney argues that "the cumulative evidence of recent discoveries in genetics and epigenetics calls into question the validity of two classes of methodologies that are central to the discipline: Twin, family, and adoption studies, which are used to derive heritability estimates, and gene association studies, which include both genome-wide and candidate-gene association studies." My view is that the evidence presented by Charney does not support such a strong contention. It is one thing to hold that the interpretation of gene association and heritability findings should be modified, but a very different thing to aver that such methodologies are no longer valid as research tools. I think that heritability studies and gene association studies have still a role to play, albeit assuming improvements (e.g., Gershon et al. 2011).

ACKNOWLEDGMENTS

I would like to thank Cristina Pujades for a fruitful discussion on a draft of this commentary.

# Author's Response

## Humans, fruit flies, and automatons

doi:10.1017/S0140525X12001501

Evan Charney

*Department of Public Policy and Political Science, Duke Institute for Brain Sciences, Duke Institute for Genome Sciences and Policy, Duke University, Durham, NC 90239.*

**http://fds.duke.edu/db/Sanford/faculty/echar**

**Abstract:** My response is divided into four sections: (1) is devoted to a potpourri of commentaries that are essentially in agreement with the substance of my target article (with one exception); in (2) I address, in response to one of the commentaries, several issues relating to the use of candidate gene association studies in behavior genetics (in particular those proposing a specific G×E interaction); in (3) I provide a detailed response to several defenses of the twin study methodology; and in (4) I conclude with several reflections on that methodology and the conception of human nature it has fostered.

Due to limitations of space, I fear that I will not be able to comment, to the full extent warranted, on the many commentaries that essentially agree with the substance of my target article. They enrich, improve, and extend my arguments in numerous ways. However, the commentaries that, in one form or another, defend the methodologies I critique afford a rare opportunity for engagement in critical dialogue. To this end, the bulk of this response will be devoted to addressing the critical commentaries.

### R1. Assortment

**Dar-Nimrod** points out that the media (as well as researchers themselves) have shaped the public's perception of the relationship between genes and human behavior through uncritical and sensationalist reporting on the results of twin and gene association studies. Indeed, the media are enamored of reports that "two genes predict voter turnout" or whether one is a (twenty-first-century American) liberal or conservative is largely heritable. What the media do not like are disconfirming studies or studies that call reductionist models into doubt. Complexity does not sell.

**Lewis** presents several helpful critiques, two of which I mention here as additions or corrections to my overall argument: My account of the shaping of offspring behavior by the maternal environment ignores the fact that offspring actively shape that environment by eliciting maternal responses through behavior such as crying, clinging, and proximity seeking; my model of adaptation is a "fit the environment" model that ignores the extent to which organisms are active participants in the construction of their own environmental niches.

**Müller, Lenz, & Kornhuber** (**Müller et al.**) make a case for viewing what they term $E_{act}$ – which includes socially learned behaviors and information – as a non-genetic form of inherited behavior. Their characterization of $E_{act}$ is reminiscent of what Jablonka and Lamb (2006) term the (non-genetic) behavioral and symbolic inheritance systems. Human behavior does not occur in a vacuum, and to the extent that $E_{act}$ inheritance includes such things as culture, language, (cultural) history, and social norms and practices, it is essential to consider $E_{act}$ when discussing the transmission of human behavior. A noteworthy feature of behavior genetics is the widespread tendency to treat behavioral and symbolic inheritance as if they were genetic inheritance.

For example, according to a study by Alford et al. (2005), mentioned by **Miller, DeYoung, & McGue** (**Miller et al.**), population variance in (twenty-first century American) conservatism and liberalism is attributable more to genetic then environmental variance.[1] In fact, Alford et al. claimed that what they were considering was whether one was a "liberal" or "conservative," but these were measured by asking American citizens a series of questions designed to measure attitudes associated with twenty-first-century American liberalism and conservatism. The problem is that there exists no set of attitudes ("symptoms") by which we could identify a "liberal " and "conservative" in all times and places. Compare and contrast the "symptoms" of conservatism with the "symptoms" of Type I diabetes (T1D). The symptoms of T1D are basically the same, no matter where they occur, and we can discuss T1D as a disease without referring to any historical or geographical or cultural context (of course, these would be highly relevant if we were considering the etiology of T1D – e.g., the rate of T1D is 45 per 100,000 in Finland and 1 per 100,000 in Venezuela). But we cannot even coherently talk about conservatism, for example, without identifying that we are discussing the "phenotype" characterized by the "symptoms" of a twenty-first-century American conservative as opposed to the "symptoms" of an eighteenth-century German conservative or a twenty-first-century Russian conservative. This is because these

divergent "symptoms" amount to very different "phenotypes"; there does not exist (as historians will tell you) a core set of "symptoms" that all conservatives in all times and places exhibit. To assume that there is such a thing is to *reify* something inherently historical and shifting, to treat it on the model of T1D, and thereby, completely distort it.

This difficulty is rarely considered. The assumption seems to be that just as behavioral genetics need not be concerned with the molecular genetic and biological mechanisms that link genes to behavior, so too it need not be concerned with the conceptual coherence of claiming that a particular set of local and historical behaviors are genetically inherited. Apparently, whatever "phenotype" a twin study claims to be genetically heritable simply *is* genetically heritable (to think otherwise would be to doubt the methodology). This includes such things as voting behavior (Fowler et al. 2008); credit card debt (De Neve & Fowler 2010); mobile phone use (including amount of time spent texting) (Miller et al. 2012); and consumer preferences for soups and snacks, hybrid cars, science fiction movies, and jazz (Simonson & Sela 2011). One wonders whether the results of *any* twin study – a twin study concerning the heritability of speaking Chinese, or being an Anglican, or shopping at Macy's department stores – would prompt a reconsideration of the methodology (or at the very least, a critical examination as to what it makes sense to propose could be heritable, i.e., is a "phenotype," in the first place).

**Overton & Lerner** argue that a paradigm shift (in the Kuhnian sense) requires a competing paradigm, and that despite my comment that the postgenomic view has not yet coalesced into a countervailing paradigm, relational developmental systems (RDS) qualifies as just such a paradigm. I admit my unfamiliarity with this approach, but judging by Overton & Lerner's comments, it seems like a strong candidate for a countervailing paradigm. **Halpern** notes that much that I argue draws upon Gilbert Gottlieb's developmental systems approach to genetics, and indeed, I have been significantly influenced by his work (as well as by the work of Richard Lewontin). **Pléh** notes that a debate similar to that I proposed between the genomic and postgenomic worldviews, specifically in relation to the validity of the twin study methodology, existed almost half a century ago between Jenkens and his followers on the one hand and Kagan on the other.

**Dickins** shows that the flip side, as it were, of the many processes that change DNA structure, which I highlighted, are the processes that preserve DNA integrity. Although DNA mutation may be necessary for evolution, limitless mutation would result in rapid extinction. Hence, an account of the mechanisms that lead to DNA transformation should be matched with an account of those that preserve DNA stability. It is interesting to conjecture what role stability-inducing mechanisms, or their failure, have in human behavior**. Schanker** notes how brain-derived neurotropic factor (BDNF), which I mentioned as promoting neurogenesis in the hippocampus, is also expressed in the cerebral cortex and other limbic structures and likely plays a critical role in neuronal and behavioral plasticity.

**Garzillo & Trautteur** present the outlines of a case for viewing DNA, or rather DNA and the cell, as a biological "Turing machine," against my assertion that "DNA does not contain a determinate code equivalent to the digital code of a computer." They argue that the "core cellular machinery" is a Turing machine. The core cellular machinery consists of (1) the sequence of bases of the coding gene, which constitute a text specifying the structure of proteins; and (2) the basic machinery of the cell and the expressed enzymes coded by the "minimal gene set." I see a number of problems with their formulation:

1. The sequence of DNA does not constitute anything like a "text" for specifying the structure of proteins. There are ~25,000 genes in the human genome yet at least 1 million proteins in the human body. In other words, the "expressed enzymes" are not coded in the "minimal gene set." As noted in the target article, it is the cell, in response to internal and external signals, that determines which isoforms of a given protein will be produced. Furthermore, the exons that the cell combines in different ways to form proteins can be widely dispersed throughout the DNA sequence, challenging the notion of genes as either linear "letters" or "words" that constitute a "text." Hence, the cell does not function as an "interpreter," which in the computer science sense of the term either executes the source code directly (which **Garzillo & Trautteur** equate with the DNA sequence) or translates the source code into some intermediate code that it then executes. The DNA sequence better resembles a database on which the cellular system draws rather than a logical program of instructions (Noble 2010).

2. I may well have missed something, but I am not sure how one gets from the "minimal gene set" to the "expressed enzymes." Without the epigenome, nothing will be expressed (i.e., transcribed). The epigenome itself, however, is not regulated by the minimal gene set (how could it be, if the natural state of the gene set is to be in the "off" position?). Is this problem circumvented by simply postulating that the core cellular machinery includes the expressed enzymes, which then (by what appears to be definitional fiat) obviates the need to account for how these enzymes are able to be synthesized in the first place?

3. Similarly, the minimal gene set can never give rise to differentiated cell types, since what differentiates cell types is not their gene set, but rather gene set activity. Gene set activity is not coded in the gene set, since what differentiates a neuron and a heart cell is not differences in nuclear DNA (nDNA) sequence, but differences in gene transcription. Perhaps **Garzillo & Trautteur** intended to characterize a "generic cell," but generic cells do not exist.

Hence, DNA does not constitute a Turing machine, but if anything, an "interaction machine."

Furthermore, **Garzillo & Trautteur** argue that the central problem of DNA and the origins of life is how active structures such as ribosomes evolved together with the genes coding for them. However, some of these structures, such as mitochondria, plastids (chloroplasts), and possibly other organelles of eukaryotic cells likely originated as free-living bacteria that were incorporated into another cell in a symbiotic relationship (endosymbiosis). Recent evidence suggests that functionally important regions of ribosomes were recruited and could be relics of an ancient ribonucleoprotein world (Harish & Caetano-Anollés 2012), while retrotransposons are ancient viruses that became incorporated into DNA. The history of both DNA and the cell indicates that they are the products of multiple symbiotic (and non-symbiotic)

relationships whereby precursors of cellular organelles were incorporated into precursors of the cell.

**Teixeira, Carvalho-Filho, & Silveira** (**Teixeira et al.**) present an interesting overview as to how neogenomic processes might inform investigations of neuronal micro-circuitry. I mention their contribution here because their comments concerning "epigenetic robots" bear a close resemblance to the arguments of **Garzillo & Trautteur** for viewing the core cellular machinery as a Turing machine. They conjecture that an "epigenetic robot" would be "guided by software (genome) modifiable by both inherent reprogramming tasks (transposable elements) and developmental experiences (epigenome), which in turn should be driven by interactions with robot inner/outer environments, all contributing to the emergence of robot self-programming." My reservations in regard to this characterization of an epigenetic robot are essentially the same as those in regard to the characterization of the core cellular machinery as a Turing machine: The genome is not equivalent to (or not accurately analogized to) a program and/or a program that engages in (self) reprogramming. Indeed, it has been suggested that DNA be viewed as more akin to hardware and the epigenome to software (Dolinoy et al. 2007; Jammes et al. 2011), although in the final analysis, analogies to hardware and software may obscure, like a lot of other dichotomies, the complex, dynamic, multifaceted, and fluid nature of the phenomena.

I agree with **Glatt**'s assertion that "statistics alone cannot bridge the gap from molecule to mind," particularly when the statistical approach depends upon a genetic paradigm that is no longer viable. Glatt argues that attempts to relate polymorphisms to behavior should be driven not by the search for statistical correlations, but by experimentation, for example, in vitro analysis and studies of knockout and transgenic mice. Although such approaches are an important tool in trying to unravel the physiological-behavioral effects, if any, of polymorphic variations, they present a number of potential difficulties.

Consider, for example, the monoamine oxidase gene: monoamine oxidase A (MAO-A) breaks down a class of neurotransmitters known as monoamines, including adrenaline, noradrenaline, dopamine, and serotonin, thereby diminishing their bioavailability. The MAOA gene exhibits polymorphisms in its promoter region characterized by "tandem repeats," the replication of two or more nucleotide sequences directly adjacent to each other (because the tandem repeats vary in number, they are referred to as variable number tandem repeats [μVNTR]). On the basis of in vitro analysis, the 3.5- and 4-repeat MAOA-μVNTR alleles have been classified as being transcribed 2 to 10 times more efficiently than alleles containing the 3-tandem repeat (Sabol et al. 1998). Hence, the 3-repeat allele is classified as low (*l* MAOA-μVNTR), for low transcriptional efficiency, and the 3.5- and 4-repeat alleles as high (*H* MAOA-μVNTR), for high transcriptional efficiency. It is commonly assumed that the differences in in vitro transcription rates translate into different levels of bioavailable MAO-A in the brain, which in turn is presumed to translate into different levels of bioavailable serotonin (5-HT), yielding the following causal schematic: high/low MAOA-μVNTR→high/low levels of brain MAO-A→ high/low levels of brain 5-HT. Finally, the different levels of serotonin in the brain are presumed to translate into differences in behavioral phenotypes.

In fact, it is by no means clear that high and low alleles of MAOA-μVNTR correspond to higher and lower levels of brain serotonin. Studies that have attempted to demonstrate the effects of MAOA-μVNTR genotypes upon in vivo (as opposed to in vitro) brain levels of MAO-A have had mixed, largely negative results (Alia-Klein et al. 2008; Cirulli & Goldstein 2007; Fowler et al. 2007; Nordquist & Oreland 2010; ). According to a recent review (Nordquist & Oreland 2010, p. 2), "in adult humans, and monkeys with orthologous genetic polymorphisms [polymorphisms having the same function in two different species], there is no observable correlation between these functional genetic variants [of MAOA] and the amount or activity of the corresponding proteins in the brain." This is not surprising. The brain, like all other organ systems, is characterized by elaborate *homeostatic* mechanisms: Even if we assumed "greater transcriptional efficiency" of the gene for a given enzyme, we would not expect this to translate into more of that enzyme and more of the physiological effects associated with that enzyme in any straightforward manner.

Furthermore, although these polymorphisms of the MAOA gene have been associated with a bewildering array of phenotypes (see next section), the most well-known association is with aggression (Buckholtz & Meyer-Lindenberg 2008): High MAOA is associated with lower aggression and low MAOA with higher aggression (although like all candidate gene association studies, these studies have failed to be consistently replicated). This association was hypothesized on the basis of knockout studies in mice (Shih & Thompson 1999). MAOA knockout (KO) mice exhibit greater aggression (as well as a number of other behavioral abnormalities). One problem with drawing behavioral inferences from KO mice is that what KO mice manifest are in effect the *symptoms of an artificially produced monogenic disorder*. It is by no means clear that one can infer, from behavior associated with an artificial monogenic disorder, behavior associated with polymorphisms of that same gene. Finally, if we consider the differences in gene transcription associated with differences in aggression in fruit flies (see next section), it seems very unlikely that any single polymorphism will be a risk factor for behavior.

I mention this cautionary tale not to argue that experimental analysis of polymorphisms is without value, but rather to emphasize the limitations of such analysis.

## R2. Gene association studies

I agree with **Homberg** and **Crusio** that in addition to environmental stimuli affecting the genome, the genome itself can also influence the impact of environmental stimuli. I did briefly mention something to this effect in the target article, when I commented that, "Of course, offspring may differ in the degree or manner in which specific behavioral phenotypes are shaped by the perinatal environment due to any number of genetic, epigenetic, and micro-environmental differences (such as fetal position), or on the basis of sex" (sect. 9.2). The most well-known example of differences in the impact of environmental stimuli (to use Homberg's formulation) being linked to polymorphic differences concerns polymorphisms of the genes that compose the hepatic cytochrome P450 mixed-function oxidase system and drug metabolism (Wrighton & Stevens 1992).

I am, however, highly skeptical of the examples that **Homberg** presents: Vulnerability to environmental stressors being influenced by polymorphisms of 5-HTT and DRD4. What I argued in the target article in relation to candidate gene association studies applies as well to gene association studies that posit a specific G × E. Consider that the "stress response" is one of the most diffuse physiological responses in the human organism, involving the hypothalamo–pituitary–adrenal axis and immune system and changes in levels of (to name but a few), corticotropin releasing hormone, glucocorticoid receptor, adrenocorticotropic hormone, epinephrine, norepinephrine, prolactin, growth hormone, gamma-aminobutyric acid, neuropeptide Y, beta receptors, neural killer cell activity, mineralocorticoid receptor, vasopressin, proopiomelanocortin, thyroid stimulating hormone, gonadotropic hormones, luteinizing hormone, follicle stimulating hormone, and oxytocin. That a response that involves proteins coded in thousands of genes, not to mention unknown epigenetic processes, and every major organ system in the body, should be so impacted by polymorphisms on a single gene as to have significant behavioral consequences does not make a lot of sense physiologically or from the standpoint of evolutionary biology.

A good example of just how many proteins we might expect to be differentially transcribed in behavioral variation is provided by an example I considered in the target article: aggression in fruit flies (*Drosophila melanogaster*). Zwarts et al. (2011) bred a strain of hyperaggressive fruit fly. Using advanced DNA expression analysis they found differences in the transcription levels of 4,038 genes in homozygous hyperaggressive flies versus controls; 1,169 genes were coordinately up or down regulated in all hyperaggressive homozygous flies, with epistatic interactions for over 800 genes. Significant pleiotropy was also observed in that these same genes were involved in a host of basic physiological processes including olfaction, nervous system development, detoxification of xenobiotics, and sex determination, as well as genes of previously unknown origin (for the potential significance of pleiotropy in neuropsychiatric illness, see the commentary of **Deutsch & McIlvane**). In a situation such as this, no single polymorphism on a single gene (or 2 or 10 genes) could predict, or be a risk factor for, aggression in fruit flies.

**Homberg**'s characterization of polymorphisms of the serotonin transporter linked polymorphic region (5-HTTLPR) as predictors of, or risk factors for, stress-related "maladaptive" behavior draws upon a study by Caspi et al. (2003), according to which specific polymorphisms of 5-HTTLPR, combined with stressful life events, increase the risk of depression. Like most candidate gene association studies, however, this study has failed to be consistently replicated (see supplemental table for Charney & English [2012] at http://tinyurl.com/AssociationStudies), and the conclusion of a comprehensive meta-analysis published in the *New England Journal of Medicine* is as follows:

> The results of this meta-analysis clearly demonstrate that stressful life events have a potent relationship with the risk of depression, an association that has been one of the most widely studied environmental factors for a range of mental disorders. Addition of the serotonin transporter genotype did not improve the prediction of risk of depression beyond that associated with exposure to negative life events. (Risch et al. 2009, p. 2469)

Furthermore, the specific polymorphisms **Homberg** mentions are two members of a small group of polymorphisms that have been effectively data-mined for associations (see Charney & English 2012 and supplemental table at http://tinyurl.com/AssociationStudies). For example, the long and short polymorphic regions of the serotonin transporter gene have been associated with, in addition to many other behavioral and non-behavioral phenotypes, agreeableness, alcoholism, Alzheimer's disease, anger/aggression, anorexia, attachment, attention-deficit/hyperactivity disorder, autism, bipolar disorder, blushing, borderline personality disorder, brain activation by colorectal distention, brain activation in processing errors, breast cancer, bulimia, chronic fatigue syndrome, cleft lip, conscientiousness, contraception use, cooperativeness, creativity, deductive reasoning, depression, epilepsy, extraversion, fearfulness, fibromyalgia, pathological gambling, gastric emptying, harm avoidance, heroin use, attitudes toward individualism and collectivism, insomnia, intelligence, interpretive bias, irritable bowel syndrome, job satisfaction, loneliness, longevity, maternal sensitivity, migraines, neurodermatitis, neuroticism, novelty seeking, number of sexual partners, obesity, obsessive-compulsive disorder, openness, optimism, osteoporosis, panic disorder, parenting, Parkinson's disease, persistence, periodontal disease, postpartum depression, posttraumatic stress disorder, premature ejaculation, premenstrual dysphoria disorder, psoriasis, resiliency to victimization, reward dependence, schizophrenia, seasonal affective disorder, shyness, sleep apnea, smoking, social phobia, sudden infant death syndrome, suicide, utilitarian moral judgments, and well-being. (This list is by no means complete. For complete references for the associations listed here, along with a representative list of associations for three other genes – MAOA, DRD2, and DRD4 – that have been associated with a wide array of phenotypes, see the supplemental table for Charney & English [2012] at http://tinyurl.com/AssociationStudies).

How is it possible that the same polymorphisms of the same gene could simultaneously predict (or be risk factors for) so many different phenotypes (even when, as is sometimes the case, a specific G × E or G × G (gene × gene) interaction is proposed)? A common response to the question (to the extent that it is raised) is to evoke the concept, discussed by **Michel**, of an "endophenotype." As Michel characterizes it, an endophenotype describes the various physiological pathways that relate the genotype to behavioral phenotypes. Thus characterized, the concept is certainly important. However, it has been used as a way to explain how the same polymorphism could simultaneously give rise to so many diverse phenotypes (although it remains unclear as to how the same polymorphism could *predict,* or be a risk factor for, so many different phenotypes). According to Gottesman and Shields (1973), an endophenotype is defined as an "intermediate trait" or an "internal phenotype," that lies "intermediate" between the genotype and phenotype. The idea is that the endophenotype, which is more "elementary" than the phenotype, can give rise to an array of phenotypes (due to interacting genetic or environmental factors) that all share something with the more primary endophenotype. Furthermore, the genetic basis of endophenotypes is assumed to be less complicated than the phenotypes to which they give rise, to involve fewer genes, and be more "direct" and "deterministic."

The idea that an endophenotype involves fewer genes and is more direct and deterministic lacks empirical support, and one suspects that this characterization justifies the results of candidate gene association studies more than anything else. If it is proposed that the proliferation of phenotypes associated with the long and short polymorphisms of 5-HTT point to an underlying endophenotype, what more elementary phenotype unites maternal sensitivity, premature ejaculation, irritable bowel syndrome, utilitarian moral judgments, schizophrenia, periodontal disease, and voting? Nor can we divide all of these "phenotypes" into those characteristic of "vulnerability" and those not, or those that that are adaptive and those that are maladaptive (are utilitarian moral judgments adaptive or maladaptive?), particularly given that one and the same trait can be adaptive in one environment and maladaptive in another.

## R3. Twin studies

In their commentary, **Miller et al.** begin with a familiar rejoinder: Those who challenge the twin study methodology from any perspective other than that of statistics – in my case, the perspectives of molecular genetics and developmental and evolutionary biology – fail to appreciate the precise nature of biometric genetics. I anticipated this rejoinder and responded to it at length in the target article (sect. 6.1.1. "Objection 1: Biometric versus biomolecular genetics"). To summarize what I said there: Although biometrical analysis is not concerned with the molecular mechanisms that underlie phenotypic variation, it nonetheless depends foundationally upon certain empirical assumptions. **Vilarroya** questions the point of my assertion that "biometric genetics must make contact with the natural world at some point." All that I meant by this was that biometric genetics depends upon certain empirical assumptions, and if these assumptions turn out not to be true, then the validity of the twin study methodology will be called into question. For example, one of the empirical assumptions of the twin study methodology is that MZ (monozygotic) twins share 100% of their segregating genes and their genetic identity remains fixed throughout the life course. To demonstrate that neither of these propositions is true, it was necessary to consider the intermediary mechanisms between genotype and phenotype. The assumption that biometric genetics need not be concerned with advances in molecular genetics (because not concerned with the underlying genetic-molecular mechanisms) has in some ways enabled a methodology developed in the late nineteenth and early twentieth centuries to persist essentially unchanged into the twenty-first (what has changed is the sophistication of the statistical analysis).

According to **Miller et al.**, most of the genetic and epigenetic MZ-twin differences I considered have nothing to do with heritability because they are acquired and not inherited. To the contrary: They can all be inherited, a point I went to great pains to demonstrate throughout the article. Because of the critical importance of this point, I repeat the relevant sections of my article here (references omitted):

> *Retrotransposons*: In contrast to transpositionally incompetent retrotransposons, transpositionally competent L1s, Alu elements, and SINE-VNTR-Alus (SVAs) are continually expanding in number in the human genome through ongoing *germline retrotransposition*.…The ability of transposable elements to move within the genome gives them an intrinsic propensity to affect genome evolution through the creation of new DNA sequences and structures and ultimately, to affect the evolution of species. (T.A. sect. 4.1)
>
> *CNVs*: CNVs (copy number variations) can be inherited via the germline in the manner of SNPs (single nucleotide polymorphisms), while exhibiting mutation rates from 100 to 10,000 times greater across the human genome. (T.A. sect. 4.2)
>
> *Aneuploidy*: *Germline* aneuploidy has been thought to be a rare cause of aneuploidy in the human population, but recent evidence from cytological and population studies suggests otherwise. As Delhanty … notes, "Based upon this evidence, germinal or gonadal mosaicism is likely to make a significant contribution to aneuploidy in the human population." (T.A. sect. 4.3)
>
> *Mitochondrial DNA*: Mitochondrial DNA (mtDNA) exhibits a number of properties that distinguish it from nDNA. First, mtDNA is not inherited in Mendelian fashion, but rather, it is inherited from the mother; that is, it is exclusively transmitted by the oocytes. (T.A. sect. 4.4)
>
> *Epigenome*: Studies indicate that epigenetic changes can be inherited via the germline as well as somatically, resulting in the intergenerational non-genomic inheritance of epigenetic states. It was once believed that genome-wide epigenetic reprogramming during gametogenesis and early embryogenesis would erase epigenetic modifications acquired during the life of the animal in order to restore the totipotency of the fertilized egg (i.e., the ability of fetal stem cells to become any cell type). This epigenetic reprogramming, however, is not complete. Modifications at variably expressed alleles are not completely erased during gametogenesis and embryogenesis while other epigenetic markings are reestablished as part of the developmental process. (T.A. sect. 5)

If **Miller et al.** believe that all of the studies in support of these statements are incorrect, then it is incumbent upon them to provide countervailing evidence in support of such a claim.

Similarly, I suspect that **Burt**'s proposal to compare children created via in vitro fertilization (IVF) and gestated and raised by biological mothers with IVF children gestated and raised by non-biological mothers, as a way to disaggregate genetic and neogenetic concordance producing effects, rests upon the assumption that neogenetic effects are solely acquired. (If such studies are undertaken, one hopes that researchers will take into account the following growing body of evidence: Children conceived through assisted reproduction technology (ART) are at an increased risk for negative health outcomes (Allen et al. 2006; McDonald et al. 2009; Wen et al. 2012); there are significant *epigenetic* differences between ART and naturally conceived children (Katari et al. 2009; Turan et al. 2010; van Montfoort et al. 2012).

In regard to the distinction **Miller et al.,** as well as **Burt,** draw between what is inherited and what is acquired, consider the following: MZ twins are genetically identical at one point in their development: before they are MZ twins (i.e., when they are still a single zygote). The moment the zygote divides, they are no longer genetically identical (this is uncontested in regard to mtDNA, but likely true in relation to several neogenetic phenomena). In a situation such as this, what precisely is inherited and what is acquired? Shall we say that what is "inherited" applies only to the predivision zygote and that everything from division on is "acquired"?

**Miller et al.** state that "several types of evidence suggest that DNA extracted from different cell types is nearly identical. MZ twins are nearly as alike in their SNP genotypes as are two DNA samples from the same person." Regarding SNPs, as I noted in the target article, "What this [neogenomics] does not call into doubt, however, is the following: MZ twins are significantly more genetically concordant than DZ [dizygotic] twins (and are likely most concordant in relation to SNPs), and this greater genetic concordance plays an important role in a wide range of intertwin phenotypic concordances" (sect. 6). SNPs of nDNA, however, do not occur in mtDNA; and retrotransposon insertions, CNVs, cellular and chromosomal aneuploidy, and the epigenome are not SNPs. We know that MZ twins differ dramatically in their mtDNA, which is inherited solely from the mother and is stochastically partitioned during the formation of the zygote. We know that MZ twins differ in their CNVs (see the findings of the study by Bruder et al. [2008]: supplemental data at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427204/bin/mmc1.pdf). We know that MZ twins differ in their epigenomes and that these differences change over the life course. And because germline retrotransposition and chromosomal aneuploidy are stochastically distributed, MZ twins are likely discordant for these as well.

Regarding the findings cited by **Miller et al.** for twin concordance for SNPs, things are likely not quite as they seem. During pregnancy, the mother and fetus exchange a certain number of cells (along with their DNA), most likely through the placenta, with the result that the mother and/or fetus exhibit *chimerism*, a form of somatic mosaicism in which the mosaic cells contain the DNA of another individual (Jonsson et al. 2008). MZ and DZ twins can exhibit, in addition to maternal–fetal chimerism, twin–twin chimerism. Theoretically, chimerism cannot occur in MZ twins, under the assumption that they are genetically identical (so that any intertwin cellular trafficking would not result in somatic mosaicism, but simply the exchange of genetically identical cells). In fact, there are a number of accounts of chimerism in MZ twins (Bourthoumieu et al. 2005; O'Donnell et al. 2004; Willer et al. 2006), and the incidence is likely significantly higher due to the fact that the possibility of chimerism is only considered (and hence investigated) in cases of dramatic disease related intertwin phenotypic discordance. Cases of inter-MZ-twin chimerism also reveal how genotyping from blood can conceal intertwin genetic discordance.

Consider the following representative (actual) case of blood chimerism between MZ-monochorionic (MZ–MC [monochorionic]) twins (O'Donnell et al. 2004): At delivery, one MZ twin exhibited a normal phenotype, and the other twin showed the dysmorphic features characteristic of trisomy 21. Blood from both twins showed an admixture of normal and trisomic cells (cells with three chromosomes, characteristic of trisomy 21). However, tissue studies of skin and buccal cells of the dysmorphic twin showed only trisomy 21 cells, whereas buccal cells from the normal twin showed only normal cells. In other words, the genetically distinct hematopoietic stem cells of the twins "fused," leading to a chimeric blood system shared by both twins. If genotyping of the twins were based solely on blood analysis, then their genetic discordances would not have been discovered. A large number of studies have highlighted the potentially confounding effects of blood chimerism when studying genomic and epigenetic variations among discordant MZ twins (Bourthoumieu et al. 2006; Kaplan et al. 2010; Machin 2009). According to a recent analysis by Erlich (2011), the effects of chimerism on the detection of variation in intertwin SNPs is substantial:

> The effect of mirrored chimerism on detection of discordant SNP variations is substantial. We found that the sensitivity dropped below 20% in the range of typical chimerism and zero sensitivity when more stringent calling was applied. [O]ur analysis proposes that blood-derived DNA is inadequate for whole genome sequencing of MZ twins. The challenge of picking the right tissue for twin genomics is twofold. First, one should avoid tissues that contain high levels of hematopoietic cell lineages due to twin chimerism. Second, any post-twinning variation is likely to show some degree of somatic mosaicism and might be found only in certain cell lineages. Thus, it is highly important to sample a tissue that shows the discordant phenotype or developmentally close tissues if the affected organ is not accessible. (Erlich 2011, p. 141)

I am aware, contrary to what **Miller et al.** say, that heritability indicates the percentage of variance in a phenotype that is due to *inheritance*, not to variations in DNA. It is precisely for this reason that I speculated in the concluding section of the target article (sect. 10, "Postgenomics") what might be involved in attempting to estimate variation due to everything inherited via the germline:

> Attempting to compose a formula that could be used to estimate the extent to which variation in anything inherited via the germline could affect phenotype shows the nature of the problem. We would need to begin by identifying each of those heritable agents, for example, $V_{TE}$ (transposable elements), $V_{miRNA}$ (miRNA), $V_{METH}$ (methylation profile), $V_{HM}$ (histone modification), $V_{L1\text{-}RNA}$ (L-1 RNA), $V_{mtDNA}$ (mtDNA), and $V_{ANEU}$ (aneuploidy).

According to **Miller et al.**, my "greatest mistake" is that I misunderstand the role of quantitative models, which are concerned with explicating the mechanisms that lead to familial resemblance. Most of the examples I considered in the target article – resemblance between mothers and their offspring in rearing behavior, stress responses, and mating behavior; and resemblances of MZ twins, DZ twins, and singletons with each other and their parents – are examples of familial resemblance. That family members resemble each other is obvious. That DNA, the epigenome, and the pre- and postnatal environment interacting with each other in complex ways contribute to these resemblances is clear.

What is not clear, what is in fact misguided, is the assumption that the twin study methodology can effectively partition and quantify the contribution to phenotypic variation between offspring that is due to differences in what is "inherited" on the one hand and what is "environmental" on the other. "Inherited versus environmental," or "nature versus nurture," are artificial and superannuated dichotomies that distort the complexity of the phenomena. Trying to fit environmentally induced epigenetic activation of retrotransposons, or intergenerationally transmitted epigenetic reprogramming, into this dichotomous worldview as represented in standard quantitative genetic models is like trying to locate black holes within Aristotle's dichotomy of the sublunar world of change and the immutable heavens.

This is a fitting place to consider **Molenaar**'s contribution. As someone who has thought long and hard about genetic modeling techniques, Molenaar illustrates the

problems that violations of HS1 (the shared genetic identity of MZ twins = 1 and DZ twins = 0.5) and HS2 (this genetic identity remains fixed over the life course) pose to standard methods of analysis in behavior genetics. In this, we are in complete agreement. Indeed, Molenaar's previous work has shown how subject-specific violations of HS1 and HS2 can lead to severely biased estimates in the standard longitudinal genetic factor model. However, where Molenaar and I disagree is in his optimism that this problem can be solved using multivariate, phenotypic, and intraindividual time series data obtained from pairs of genetically related subjects.

The iFACE model that **Molenaar** has pioneered is a significant improvement over standard quantitative genetic models to the extent that it attempts to incorporate many of the complexities that the standard model ignores. But the limitations of the iFACE model illustrate why this complexity is likely to remain intractable. Space does not permit a full examination of the statistical properties and assumptions of the iFACE model, other than to note that it likewise (and necessarily) rests on dubious empirical assumptions.

In brief, iFACE combines an idiographic filter technique with the standard genetic factor model to look for fixed patterns of factor correlations in a pair of genetically related individuals over time. One of the benefits of iFACE is that it allows genetic correlations between DZ twins to be freely estimated, rather than assumed to be 0.5 from the outset. Moreover, Monte Carlo simulations have demonstrated that iFACE yields fairly accurate estimates of data generated from known parameters (Molenaar 2010). However, the Achilles heel of iFACE lies in the assumptions it must make as to what remains fixed or constrained. The iFACE model *must* assume stability in the shared environment *or* in shared genetics in order to estimate the source of phenotypic variation over time (otherwise one could not disambiguate what is driving the variation). In fact, the iFACE model assumes identical, shared environments for DZ twins, at least as the model is presented in existing publications: "The only exception [to parameters that are allowed to be subject specific] is the set of loadings on the common environmental factor: these were constrained to be equal across the two subjects, but could freely vary across the four phenotypic time series" (Molenaar 2010, p. 644).

In other words, the model presumes an answer to the precise question that is at stake in the larger debate: What, exactly, is driving phenotypic variation? Indeed, the assumption of equivalent environmental factors across subjects is every bit as contentious as the a priori assumption of a shared genetic endowment of 0.5 for DZ twins and 1 for MZ twins. Moreover, for any real-world behavioral phenomenon of any interest, environments do differ between twins and change for both twins over time. To even begin to address the methodological problems raised by this reality, one would need reliable and comparable measures of every conceivable environmental influence acting on each of the DZ twins over the time horizon in question (and even then it is not clear how to disambiguate environmental and genetic effects).

**Molenaar**'s work has taken seriously the modeling problems posed by non-linear and non-ergodic genetic processes. However, although iFACE represents an improvement compared to the simplistic factor models used in so much research, it nonetheless assumes an answer to the real question that is at stake. In the end, iFACE shows us that in trying to deal with increasing degrees of complexity and variation in our models, we have no Archimedean point on which to stand. Violations of HS1 and HS2 present deep methodological problems for behavior genetics that cannot be resolved by any existing analytic approach. In fact, I would argue that the real problem lies not in our inability to disambiguate environmental and genetic contributions to phenotypic variation, but with the attempt to do so in the first place. In stating this, I register my agreement with **Crusio**, who avers that the difficulties that beset human heritability estimates transcend technical solutions. I also agree with **Lickliter** that we are likely dealing with a degree of complexity such that a full understanding of the route from fertilized egg to mature human exhibiting one or another behavior lies beyond the limits of human understanding.

**Burt** argues that my assertion that the neogenome behaves like neither an E (environmental) nor G (genetic) parameter is erroneous for the following reason:

> To the extent that monozygotic (MZ) twins are more phenotypically similar than are dizygotic (DZ) twins because of their neogenetic profiles, the neogenome will be absorbed into G. To the extent that MZ twins also differ phenotypically because of differences in their neogenetic profiles, the neogenome will be absorbed in E….Loading on more than one component of variance in no way means that they are somehow omitted from heritability estimates–indeed, to the extent that they contribute to outcomes, neogenetic effects are already necessarily being included in the G and E estimates we obtain.

First, what **Burt** ignores is the fact that MZ twins *are not genetically identical.* Even assuming "loading" onto G and E, heritability estimates in the twin study methodology depend upon the assumption that MZ twins share 100% of their segregating genes. Therefore, it is not the case that neogenetic processes can be partitioned into concordance-producing effects (G) and discordance-producing effects (E) within a model in which the genetic identity of MZ twins is fixed at 1. To the extent that the twin study model treats the genetic identity of MZ twins as fixed in this manner, neogenetic effects *will necessarily be excluded.*

Second, the use of the expression "absorbed" ("the neogenome will be absorbed into G") in **Burt**'s commentary is interesting because it implies that something that is not G would be treated as if it were G. So, if MZ twins are more similar because of more similar epigenetic profiles, the epigenome will be "absorbed" into G. Does it matter if the effects of the epigenome are "absorbed" into G in heritability estimates, inasmuch as heritability is concerned with what is inherited, not with DNA per se, as **Miller et al.** note? Clearly, it does. Consider the intergenerational transmission of environmentally induced changes in sperm count due to exposure to the endocrine disruptor vinclozolin (target article, sect. 5).

If MC–MZ twins were more concordant for low sperm count from vinclozolin-induced epigenetic reprogramming due to their sharing a single blood supply prenatally, and if this epigenetic programming was absorbed into G, then we would falsely conclude that the type of oligospermia we were considering was caused by an inherited defect in the genes (and would likely begin looking for the

responsible genes). In other words, the absorption of the epigenome into the genome would *mask* the true cause of the phenotype. What is more, in this case, the epigenetic reprogramming is *environmentally induced* and then intergenerationally transmitted: The phenotype itself is manifested in the *absence* of the original inducing environment. If environmentally induced, inherited epigenetic reprogramming were absorbed into G, we would never consider that the culprit might be an environmental agent. This is also an instance of boundary crossing or the blurring of boundaries, for how are we to classify the inheritance of environmentally induced epigenetic changes in the absence of the original environmental stimulus? Is E inherited? Or is E transformed into G?

Both **Battaglia** and **MacDonald & LaFreniere** argue against the claim that MZ twins become more epigenetically and genetically discordant over their lifetimes by citing studies that purport to show that heritability increases with age. I am not sure if their claim is that these studies demonstrate that epigenetic discordances of MZ twins do not, in fact, increase over time, or that, although they may increase over time, they have no effect upon phenotypes. If the former, then clearly the results of a twin study cannot refute the existence of increasing epigenetic discordance, a phenomenon that has been repeatedly demonstrated by advanced molecular techniques (Ballestar 2009; Fraga et al. 2005; Kaminsky et al. 2009; Kato et al. 2005; Martin 2005; Mill et al. 2006; Ollikainen et al. 2010; Petronis et al. 2003; Poulsen et al. 2007; Rosa et al. 2008). To deny *this* would require a refutation of these studies. So, I take the argument to be the latter, namely, that studies that purport to show that heritability increases with age demonstrate that whatever epigenetic (and genetic) changes MZ twins experience over their lifetimes have no effect upon, for example, cognitive development.

Such generalizing from one or two studies concerning one or two phenotypes to *all behavioral phenotypes* is a common practice in the twin study literature, and it is also an example of the fallacy of "hasty generalization." Given that the results of a number of other twin studies draw the opposite conclusion–that heritability *decreases* with age–including the heritability of cognitive ability, such an argument in this context is perhaps more accurately characterized as an instance of the fallacy of neglect of relevant evidence. For example, according to Reynolds et al. (2005):

> As the number of waves of data collection in longitudinal twin studies has increased, behavior genetic analyses of changes with age have begun to be conducted. Results suggest strong genetic influences on stability (Plomin et al. 1994) over the short term. Initial cohort-sequential analysis suggested a decline in heritability of IQ from age 60 to age 80 (Finkel et al. 1998), a conclusion that has been supported by cross-sectional results from other twin studies of aging (McClearn et al. 1997; McGue & Christensen 2002). (Reynolds et al. 2005, p. 3)

And as Reynolds et al. (2005, p. 13) note of their own study: "The findings of the present study can be construed as generally supportive of theories proposing the increasing importance of the environment with respect to cognitive aging: Although heritable influences are of greater relative importance for individual differences in cognitive performance, environmental variances increase steadily after age 65." Other twin studies have reported decreasing heritability for personality (Floderus-Myrhed et al. 1980; Pedersen et al. 1988), science scores (Haworth et al. 2009), extraversion and introversion (Viken et al. 1994), self-esteem (Jonassaint 2010; Raevuori et al. 2007), body mass index (Korkeila et al. 1991), and anxiety/depression (Saviouk et al. 2011).

According to **Battaglia**, though epigenetic effects are potentially important, the individual and specific impact on brain and behavior is neither well understood nor unambiguously linked to gene expression data. In support of this assertion, he mentions a study by Zhou et al. (2011). Whatever Battaglia's precise intent in mentioning this study, their conclusion unambiguously links epigenetic changes to changes in gene expression and behavior:

> In addition to histone modifications, gene expression is also regulated by many components of the complex transcriptional machinery and also involves other mechanisms such as DNA methylation. Nonetheless, our results reveal genome-wide alteration of histone H3K4 trimethylation resulting from long-term cocaine and alcohol exposure, and accompanying large-scale changes in gene expression that implicate several functional pathways in substance-shared and substance-specific fashion. (Zhou et al. 2011, p. 6631)

According to **MacDonald & LaFreniere**, "Charney does not present a case that there are important epigenetic effects on adaptive traits like cognitive ability or personality." To the contrary, all of the examples I presented concern epigenetic effects upon adaptive traits: stress responses, fearfulness, maternal rearing behavior, and mating behavior. Given MacDonald & LaFreniere's focus on cognitive ability, I add the following two excerpts from two recent studies:

> Parental enrichment, preconceptionally and prenatally, altered offspring behavior on the negative geotaxis task and open-field exploratory behavior task…Additionally, both environmental enrichment paradigms significantly decreased global methylation levels in the hippocampus and frontal cortex of male and female offspring. This study demonstrates that positive prenatal experiences; preconceptionally in fathers and prenatally in mothers, have the ability to significantly alter offspring developmental trajectories. For similar findings of the effects of prenatal enrichment on offspring hippocampal cell proliferation, see Maruoka et al. (2009). (Mychasiuk et al. 2012, p. 294)

> Recent evidence indicates that, like histone modifications, changes in DNA methylation represent a critical molecular component of both the formation and maintenance of long-term memories (Feng et al. 2010; Lubin et al. 2008; Miller et al. 2008; 2010). Interestingly, contextual fear conditioning consequently increases and decreases methylation of memory-related genes expressed in the hippocampus, implicating methylation and demethylation as a molecular mechanism underlying learning and memory. Consistent with the idea that these changes are necessary for memory formation, inhibition of DNMTs [a group of enzymes involved in the transfer of a methyl group to DNA] within the hippocampus, which produces a hypomethylated state in naive animals, results in impaired expression of contextual fear memories (Lubin et al. 2008; Miller et al. 2008). Likewise, DNMT inhibitors impair the induction of LTP at hippocampal synapses, providing an important cellular correlate of learning deficits induced by blocking DNA methylation (Levenson et al. 2006). Interestingly, DNMT inhibition in the prefrontal cortex impairs the recall of existing memories but not the formation of new memories, indicating circuit-specific roles for DNA methylation in memory formation and maintenance (Miller et al. 2010). (Day & Sweatt 2011, p. 816)

**MacDonald & LaFreniere** assert that many of the processes I highlight (such as epigenetics) are stochastic, and stochastic events are likely to be maladaptive. A direct refutation of this assumption comes from a highly stochastic mechanism that is also highly adaptive, in fact, is the sine qua non for adaptation: the immune system. As mentioned in the target article, stochastic DNA recombination allows for the creation of $\sim 10^{15}$ variable antibody regions to combat rapidly mutating antigens. Furthermore, in noting how epigenetic events have been linked with pathology – which they claim is not surprising given their stochastic nature – they ignore the fact that the epigenome is involved in every aspect of human development starting with cellular differentiation. A neuron differs from a kidney cell not because of differences in its nDNA, but because of differences in its epigenome. Epigenetic differences enable different tissue types and different organs. Hence, if epigenetic processes are maladaptive, then having a brain (as opposed to a kidney) is maladaptive.

Furthermore, stochasticity is playing an increasingly important role in theories of evolutionary adaptation. As against Fisher's standard geometric model of evolution by small steps, that is, the accumulation of many mutations with small benefit, stochastic models of evolution are increasingly being employed. According to Østman et al. (2012, p. 1):

> More modern applications use stochastic substitution models (Gillespie 1991; Kim and Orr 2005; Kryazhimskiy et al. 2009; Orr 2002). If the mutation rate is small and selection is strong, the adaptive process can explore at most a few mutational steps away from the wild-type, so that mutations are fixed sequentially and deleterious mutations play only a minor role (if any). However, if the rate of mutation is high (and/or selection is weak) mutations can interact significantly and adaptation does not proceed solely via the accumulation of only beneficial (and neutral) mutations. Instead, deleterious mutations play an important role as stepping stones of adaptive evolution that allow a population to traverse fitness valleys. Kimura (1985) for example, showed that a deleterious mutation can drift to fixation if followed by a compensatory mutation that restores fitness. Recent work using computational simulations of evolution has shown that deleterious mutations are crucial for adaptation, and interact with subsequent mutations to create substantial beneficial effects (Bridgham et al. 2006; Clune et al. 2008; Cowperthwaite et al. 2006; Lenski et al. 2003; Poelwijk et al. 2006).

**MacDonald & LaFreniere** defend the primacy of additive genes in behavioral variation (a basic assumption of the twin study methodology) by citing a statistical analysis by Vissher, according to which for fitness-related traits, "typically around 50% of the phenotypic variation is due to additive genetic variation and…about 80% of genetic variation is additive." While MacDonald & LaFreniere mention this to challenge the notion of extensive G × E (which would include epigenetic processes to the extent that the epigenome is classified as part of the environment), it is important to consider that such high figures for additive variance entail that epistasis (G × G interaction) is not an extensive feature of complex traits. While this view may be prevalent in the behavioral genetics community, it is certainly not the view of geneticists and evolutionary biologists in general (Phillips et al. 2000, pp. 26–27 [references omitted]):

> Developmental genetics also predicts variability in the ways that genes interact. The feedback mechanism, gene regulation, and activation cascades inherent in development each create interactions among alleles whose form depends on the specifics of the developmental system. Indeed, the existence of extensive epistasis has provided a useful tool for ordering genes in the developmental pathways. Recent models that attempt to integrate developmental regulation with evolutionary change have predicted the emergence of gene interactions as a major feature of the evolution of developmental systems. Developmental systems are therefore expected to display not only gene interactions per se but also an extensive range of epistatic effects.

Aggression is a universal and highly adaptive behavior. As noted above, *800 genes implicated in differences in aggression in Drosophila showed significant epistasis* (as well as pleiotropy).

**MacDonald & LaFreniere** note that contrary to my claim that twin studies are responsible for the principle of minimal maternal effects, recent twin studies of attachment have indicated strong effects of a shared maternal environment. I make two points in this regard: First, the claim of Plomin and Daniels (1987) that in relation to personality the shared rearing environment has an effect statistically indistinguishable from 0 remains highly influential and widely accepted. Second, what MacDonald & LaFreniere identify as maternal effects are effects that the researcher has classified as "shared" and then decided to classify as "maternal." Although it is true that maternal effects are "shared" (i.e., concordance-producing) environmental effects, to measure maternal effects according to a quantitative genetic model, one must incorporate models developed in animal breeding. These include a measure of maternal performance ($P'_m$) as part of the offspring's phenotype (the prime indicates that the phenotypic value is a trait possessed by a different individual – the mother – than the individual being considered). For the mathematics involved in estimating maternal effects, see, for example, Bijma (2006) and Chevrud and Wolf (2009).[2] As researchers in animal breeding have persistently noted, *direct heritability and the response to selection are overestimated when maternal effects are not considered* (Barazandeh et al. 2012; Gregory et al. 1985; Koivula et al. 2009; Maniatis and Pollott 2002; Russell & Lummaa 2009;). They also note that the genetic analysis of maternal effects has proven enormously difficult.

## R4. Concluding remarks (with emphasis on twin studies)

Consider the following account of what I have termed minimal (shared) maternal effects in regard to studies of twins (purportedly) reared apart:

> Just as interesting as the genetic results from this study are its implications concerning environmental influences. Estimates of E ["environment"], were consistently low, accounting for less than 10% of the total phenotypic variance….There appeared to be little effect of age at separation and degree of separation on twin resemblance for personality.…This result is consistent with the minimal estimates of Es ["shared environment"], which classically are conceptualized as effects of the early rearing environment. If early rearing environment has little or no effect, selective placement is unlikely to be important.… The lack of effect of selective placement and small estimates of shared environment supports the conclusion that most of the environmental variance for these self-reported measures of personality is of the nonshared variety. (Pedersen et al. 1988, pp. 955–56)

Similarly, **Burt** cites a single study of cognitive ability to suggest that the known differences between the prenatal environments of twins and singletons and between (particularly monochorionic) MZ twins and DZ twins has little effect upon behavioral phenotypes. Both **Battaglia** and **MacDonald & LaFreniere** argue that the increase of heritability with age demonstrates an imperviousness to acquired genetic or epigenetic/environmental alterations. These arguments, like almost all defenses of the twin study methodology, share one thing in common: *They are denials that one or another aspect of the environment has any effect upon individual behavior.* I shall call this "environmental imperviousness."

Environmental imperviousness actually plays an important role in the twin study methodology: *It enables the legitimacy of the equal environment assumption* (EEA), historically the most contested aspect of the twin study methodology. In its current incarnation, the EEA does not rest upon the assumption that the environments of MZ twins do not differ in systematic ways from those of DZ twins, but rather that these systematic differences have *no effect* upon the behavioral phenotype under consideration (Guo 2001). Environmental imperviousness ensures that studies of twins "raised apart" in which, for example, none of the twins are separated at birth and some are separated as late as age nine, are free of potential confounding environmental influences. Likewise, it ensures that the results of studies of twins raised together (by far the bulk of twin studies) are not confounded by shared environmental influences. And one can rest assured that if, as **Burt** suggests, behavior geneticists start using IVF-conceived and differently gestated and reared siblings in heritability studies, studies will appear demonstrating, for example, that the IQ of IVF children is no different from that of naturally conceived children. From this it will be inferred that although IVF children are at greater risk for a range of adverse health outcomes (just as MC–MZ twins are), nonetheless, behavioral geneticists can safely ignore this because none of their behavioral attributes are affected.

It is striking that what is presumed not to matter in human "cross-fostering" studies is deemed to be profoundly important in rodent cross-fostering studies. Consider a typical protocol for a rat cross-fostering study (van der Veen et al. 2008, p. 185):

> From mating until weaning, dams were fed on a diet enriched with protein (23.5%) and fat (5%). A 14-h light/10-h dark cycle was installed, as is common in reproductive facilities. Each female was paired with male of her own strain ... Cross-fostering was conducted between 4 and 7 h after both biological and adoptive dams had given birth.... The whole procedure of fostering lasted on average 2 min and never took more than 4 min… Four experimental groups per pup strain were thus constituted: pups of the C57 and DBA strains raised by their biological mother, a mother of the same strain as their biological mother, a mother of the AKR strain or a mother of the C3H strain. The breeding cage (29 × 11 × 13 cm) contained a transparent Plexiglas separation at 9 cm from the wall with a small hole to go in and out, to create a nest compartment (9 × 11 × 13 cm). This nest compartment occupied approximately one third of the cage. The breeding cages were placed in sound safe video-equipped chambers to record maternal behavior. An infrared camera was placed facing the back wall of the breeding cage where the nest compartment was located. During both the day and the night phase, a clear view of the dam–pups dyad was available and the different maternal behaviors could be clearly distinguished. Given that maternal behavior is rhythmic and might be differently organized in different mouse strains, analyses were performed over the entire light/dark (LD) cycle except for the last hour of the dark period because other cages were placed in the recording boxes during this period to allow recording on the next day.

Yet even with all of this effort to avoid potential confounding environmental influences, laboratory animal studies are plagued by unknown "cage effects" (as well as "handler effects") that appear to influence complex behavior in profound ways (Valdar et al. 2006). Perhaps the most striking example of this concerns not rodents, but fruit flies (see below). And of course, what are not controlled for in such studies are the effects of the prenatal environment.

It is a reasonable principle that any methodology, particularly one as controversial as the twin study methodology, should be evaluated both on the basis of what the methodology presupposes (e.g., do twins in fact share 100% of their segregating genomes?) and on the basis of its results (i.e., are its results in accord with everything we know thus far about the development, behavior, and evolution of life forms from paramecium to baboons?). Twin studies fail on both of these counts.

Bluntly stated, the principle of minimal maternal effects *must be wrong* because, as argued in the target article, and as helpfully expanded upon by **Swain, Perkins, Dayton, Finegood, & Ho** (**Swain et al.**) and **Aitken**, maternal effects are omnipresent and far-reaching in human development. Denial of the importance of shared maternal effects leads to an untenable form of human exceptionalism, the hallmark of which is non-adaptive environmental imperviousness (i.e., the absence of phenotypic plasticity). The complement of such environmental imperviousness is the extraordinarily high estimates of heritability that twin studies typically yield. For example, we are told that personality is around 50% heritable (with minimal shared maternal effects) (Bouchard 2004). Compare this with recent studies on aggression in fruit flies (discussed earlier). For all of the up and down regulation identified in the transcription of over 4,000 genes, *heritability estimates for aggression were only 10%* (Zwarts et al. 2011). This means that by the standard formulation of heritability, 90% of the variation in aggression was due to environment, *even though the researchers assumed that they had raised the flies in identical environments.*

Given what we now know about heritability of aggression in fruit flies and the extraordinary responsiveness of the developing fly to imperceptible differences in the environment, such high estimates of heritability for human behavior must be wrong. But why? Why not simply assume that the behavior of fruit flies develops in a more environmentally responsive manner, and that what is unique about humans (in addition to their use of language and writing and the extent of culture) is their degree of environmental imperviousness? The problem with such an assumption is that it is diametrically opposed to everything we know about the development of the human brain. Humans are born with brains that are developmentally incomplete. Most neuronal connections are made during infancy and early childhood, and by the time a child is 3 years old, he or she has formed about 1,000 trillion connections (Lagercrantz 2010). The evolutionary "purpose" of these well-known features of brain development is to enable adaptive plasticity within a particular environment. High heritability

combined with environmental imperviousness are incompatible with phenotypic plasticity.

Twin studies paint a picture of human behavior as characterized by extraordinarily high heritability (significantly higher than fruit flies), extraordinarily low environmental responsiveness (significantly lower than fruit flies), and prevalent genetic determinism (there is no other way to characterize the assumption that heritability increases with age). The answer as to why twin studies have yielded such a bizarre characterization of human behavior is not hard to find. The underlying assumptions that enable the methodology appear to be confirmed by the results of its application. In other words, the phenomena are interpreted (or distorted) in such a way as to enable (or legitimize) the methodology, while the methodology shapes (or distorts) the phenomenon.

Hence, we are told that the twin study methodology itself has demonstrated that whatever cannot be accommodated by, or whatever might undermine the validity of, the methodology *does not matter*, and it does not matter because it has no effect upon behavior. The greater similarities of pre- and postnatal environments of twins versus singletons and MZ versus DZ twins have no phenotypic effects; maternal effects, the "bane of heritability estimates," are minimal or non-existent. Inherited differences in mtDNA – which cannot be accommodated in a model that assumes that MZ twins are genetically identical – do not matter. And as **Battaglia** and **MacDonald & LaFreniere** suggest, differences in retrotransposons, CNVs, and epigenomes do not matter either. If we combine such environmental imperviousness with the assumption that all human behavior – being a twenty-first-century American liberal or conservative; amount of time spent texting on a cell phone; consumer preferences for soups and snacks, hybrid cars, science fiction movies, and jazz – is to a large extent heritable, the result is that the subject of twin studies resembles more an *automaton* than a human organism (or any organism).

The paradigm that underlies twin studies presupposes a biological world characterized by simplicity, symmetry, stability, order, and predictability. It posits a limited number of causal agents – genes, shared environment, nonshared environment – whose contributions to variance in any trait of interest can be separated by simple and intuitive "natural experiments." The principles of Mendelian inheritance ensure that genetic relatedness is a matter of simple, symmetrical fractions: MZ twins are 1 to 1, MZ twins to DZ twins are 1 to 0.5; siblings are 0.5 to 0.5; germ cells contain 50% of maternal and paternal DNA, and so on. DNA, the sole agent of heritability, is identical in all the cells and tissues of the body, is fixed at the moment of conception, and remains virtually unaffected by the environment throughout the life course, ensuring that the genetic identity of all the relevant subjects never changes. Complex phenotypes are predictable because the path from genotype to phenotype displays such regularity that by relatively simple methods (e.g., candidate gene association studies), we can predict the probability that individuals will possess complex traits on the basis of single nucleotide polymorphisms, often (though not always) without having to take into account any specific attributes of the environment.

All of these assumptions enable *statistics* to be the driving engine of discovery in behavior genetics. The result is that the ability to make profound discoveries in genetics appears deceptively simple: All that is required is a data set that contains either zygosity and/or genotype information for a handful of polymorphisms and behavioral data (usually in the form of self-reporting). Statistical analysis takes care of the rest. This elevation of statistics has led to the adoption of the methodologies of behavior genetics by researchers in an ever expanding number of disciplines: Economists, sociologists, political scientists, researchers in business, marketing, and management all regularly publish the results of twin and gene association studies that purport to identify the heritability of, and specific polymorphisms for, the behaviors associated with their respective disciplines. Nature, however, does not reveal her secrets so easily.

Why is it assumed that, often with little training beyond statistics, a researcher can in effect become a geneticist but not, for example, a *physicist*? Why is discovery in genetics deemed so much simpler than discovery in physics, particularly since DNA is a *molecule* and part of the account of the relationship between genotype and phenotype involves molecular processes? The answer depends upon the simplicity, symmetry, stability, order, and predictability characteristic of the genetic-biological worldview of behavioral genetics.[3] This worldview, however, is radically at odds with what cutting edge research in molecular genetics and developmental biology (to name two out of a number of scientific disciplines) is revealing. In the emerging postgenomic paradigm, we are confronted with a biological world that is in many ways the opposite of that which has thus far enabled the methodologies of behavioral genetics.

## NOTES

**1.** Strictly speaking, heritability in this sense is what the authors demonstrated, inasmuch as this is what twin studies are designed to measure. But even researchers tend to exhibit a certain "slippage" between two possible senses of "heritable" in characterizing their findings. In one sense, "heritable" can be construed as the adjectival form of "heritability," in which case the expression "political orientation is highly heritable," would mean that a high percentage of variance in political ideology in a given population at a given time is ascribed to "genetic" as opposed to "environmental" differences. In another sense, heritable means *inherited*, that is, transmitted via the germline from parents to offspring. The two, of course, are not the same: A trait can largely be inherited but have a heritability of 0 because there is no variation in the trait in a given population, or its heritability can change with changes in the population or environment. Furthermore, inheritance refers to *individuals* but heritability refers to *populations* (individuals do not exhibit variance). It is an illegitimate inference to assume that an assumption that *variance* for a trait is due largely to "genes" as opposed to "environment" entails that the *trait itself* is *inherited* (i.e., genetically transmitted from parents to offspring). Causes of a trait, and causes of trait variance, are not the same thing. Nonetheless, they are commonly treated as if they are. Hence, the title of the article by Alford et al. (2005) is "Are Political Orientations Genetically Transmitted?" Their presumption is that they have answered this question in the affirmative (political orientations are genetically transmitted, i.e., *inherited*) because on the basis of a twin study they have demonstrated a high heritability (percentage of *variance* in a population ascribed to genetic variance) for political orientation.

**2.** Shared maternal effects have been called the "bane of heritability estimates" (Wade 1998, p. 9): "Environmental correlations and phenotypic effects stemming from the special circumstances of the mother have been viewed as the bane of heritability estimates. They can give rise to nongenetic and somewhat uncontrollable correlations between the phenotypes of maternal full siblings and half siblings (e.g., Falconer 1989, p. 137)."

**3.** The idea that biological processes are inherently different than physical processes is likely of ancient origin. In modern times, the idea of a fundamental distinction between biology – and molecular biology in particular – and physics was reinforced by the influential ideas of Schrödinger (1944): While physics dealt with the emergence of order from disorder, such as the ordered behavior of a gas from the disordered Brownian motion of individual molecules, biology dealt with order even at the molecular level (Noble 2010). This idea has contributed to the conception of DNA as a "genetic program" with all of the presumed regularities that enable statistical analysis to be deemed a tool for such profound insights in behavior genetics. One of the insights of biophysics is that biology and physics are not distinct disciplines in the manner traditionally conceived: "There is absolutely no way in which biological systems could be immune from the stochasticity that is inherent in Brownian motion itself. It is essential therefore that biological theory, like physical theory, should take this into account" (Noble 2010, p, 1,130). For the importance of stochasticity in genetic and biological processes, see section 10 of the target article.

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**[The letters "a" and "r" before author's initials stand for target article and response references, respectively]**


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