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Introduction to the Special Section on Genomics

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The debate about the relevance of human genetics knowledge to everyday life has been marked by fluctuations of interest and enthusiasm. The negative impact of eugenics on the public consciousness suppressed dialogue between geneticists and the public for most of the second half of the 20th century (Ridley, 1999). For the most part, non-geneticists did not follow the development of the science of genetics closely, even with regard to the discovery of the genetic code, during this period. Research on genetics was often not considered relevant for public health because genetic disorders were thought to be rare (Thomas, 2004). All of this changed, however, with the sequencing of the full genome by the Human Genome Project in 2003 (Human Genome Program, 2008)

Many scientists and laypeople expected that the completion of the sequencing of the genome might provide clear information about disease liability, and quickly usher in an era of personalized medicine (Collins, 2010). Although some of the initial expectations have not been fully realized in this first decade since the completion of the sequencing of the genome (Nature, 2011), the landscape has nonetheless changed markedly. The Human Genome Project led to the transformation of the science of genetics, which blended with and has been enriched by molecular biology, biochemistry, and systems theories, to form the science of genomics. Genomics, the science of the genome, is unfolding at a unique level of comprehensiveness, scale, and technology development, with related social and ethical implications (Green & Guyer, 2011). The Human Genome Project brought to the surface longstanding sociological and ethical concerns about the social consequences of obtaining such biological information (Duster, 2006), generating charged discussions of the value and usability of this information (Lander, 2011), and eliciting a spectrum of opinions on the relevance of the Project to societal discourse and policy. These opinions were marked by extreme views on the value of genetic knowledge as “geneticization” to the celebratory reference to the completion of the Project as a “genomic revolution” (Weinshilboum, 2002).

The Human Genome Project triggered discussion in numerous spheres, including medicine (e.g., Weinshilboum, 2002), law (e.g., Torrance, 2010) and biotechnology (e.g., Herring, 2007). Yet, relatively little of this discussion has penetrated the field of developmental science, with some notable exceptions (e.g., Plomin, DeFries, Craig, & McGuffin, 2003; Plomin & Rutter, 1998), including Plomin’s contribution to this special section. The medical, legal, and technological literatures discuss a wide variety of issues pertaining to the connections between the Project and everyday life, such as the clinical translation of discoveries (Schully, Benedicto, Gillanders, Wang, & Khoury, 2011), evidence of improved outcomes based on new knowledge (Botkin, et al., 2010), apparent challenges in incorporating new knowledge into practice due to deficits in provider and client education (Guttmacher, Porteous, & McInerney, 2007), concerns about privacy and discrimination associated with accumulation of personal genetic data (Silvers & Stein, 2003), and issues pertaining to insurance and reimbursement (Williams, 2007). Developmental science is just beginning to address the implications of the genomic revolution.

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This special section of *Child Development* was designed to stimulate this discussion, a discussion that is ripe for at least three reasons. First, the completion of the Human Genome Project has led to the generation of fundamental knowledge about biology and its alteration in disease. Yet, despite advances in knowledge, the Human Genome Project has also established boundaries that have slowed the immediate translation of its discoveries into health and well-being benefits (Feero & Green, 2011). This natural pause has provided a window of opportunity to engage in a discussion of the utility and usability of the Human Genome Project discoveries within the field of developmental science. Second, unlike the end of the last century when it was rare to come across an article within developmental psychology using genetic concepts and measures, there is now a substantial body of literature in which traits and abilities are contextualized by genetic terminology and interrogated with genetic methods. In other words, developmental scientists are using genetic methods in their work. Third, paralleling the need to practice medicine at the frontiers of the genomic sciences (Rubinstein & Roy, 2005), there is an emergent need to ask developmental questions at the frontiers of the genomic sciences.

The papers included in this special section could only be possible in the postgenomic era. The section starts with a discussion of what was one of the most immediate accomplishments of the Human Genome Project. In this paper, Connolly, Glessner, and Hakonarson (this issue) provide an example of a genome-wide association study, the very promise of which is the abundance in the human genome of a particular type of genetic polymorphism, that is, the single nucleotide polymorphism (SNP). In the next paper, Zhang et al. (this issue) venture into a presentation and discussion of a variety of other types of genetic variation, including structural variation. Next, Szyf and Bick present an overview of epigenetic studies, and Essex et al. present an illustration. Then, Naumova et al. present an overview of expression studies, followed by Hu's integral (systemic) illustration of the utilization of multiple types and levels of genomic analyses. Finally, the section closes with Plomin's overview of the field and directions for the future. In this Introduction we briefly provide context for the contributions that follow in this issue, and, hopefully, will continue to be seen in *Child Development* as the junction between developmental science and the genetic and genomic sciences broadens.

Genome-Wide Association Studies

Genome-Wide Association Studies were among the most immediate benefits of the Human Genome Project. As the machines plugged through the uncovering of the genome, a startling frequency of a particular form of variation across human genomes was noted. Single nucleotide polymorphisms (SNP) are single base changes in the DNA that have since been carefully catalogued throughout the genome. SNP variants tend to be common in different human populations, although specific allele frequencies vary dramatically. Along with the development of the relevant technology (see Plomin, this issue), the cataloging of SNP has spurred a string of large-scale studies capitalizing on the abundance of SNP in the human genome. In GWAS, the DNA aliquots collected from individuals with a particular disorder and their matched controls are placed on a microarray (as described by Plomin), and genotyped. The Human Genome Project has identified the SNP, and the private biotechnology sector has provided multiple platforms on which such genotyping can be completed (the current chip, for example, can fit as many as 2.5M SNP).

The rationale for this work is based on what is known as the common disease-common variant (CD-CV) hypothesis. This hypothesis predicts that common disease-causing alleles (or variants) will be, first, found in all human populations that display a given condition (i.e., disease or disorder) and, second, found at higher frequency in the subpopulation that manifests the condition compared to those in the population that do not. In other words, the

hypothesis posits that genetic susceptibility to common diseases (e.g., hypertension and diabetes) is largely due to alleles that occur with moderate frequency in the population. Of note is the assumption that the causal alleles of interest can be found regardless of whether they are found on the microarrays. It was assumed that the constellation of the human genome and the nature of the distribution of these polymorphisms within it (i.e., the observation that sizable chunks of genetic material on a chromosome are packaged in the linkage disequilibrium blocks that tend to be transmitted between generations as a unit) would permit researchers to identify causal variants. To verify this and other related assumptions, the International HapMap Consortium was established which has produced the HapMap. The HapMap is a useful resource for the design of large-scale association studies identifying common variants, but less useful for studies attempting to identify rare variants. Thus, the Human Genome Project created the impetus for GWAS, which then served as the impetus for HapMap. Both the Human Genome Project and HapMap substantiated hundreds of GWAS for a variety of phenotypes, many of which are of direct interest to developmental science.

The contribution of Connolly et al. (this issue) exemplifies this type of research. The manuscript is a spin-off of a large-scale genome-wide association study (GWAS) of 2,165 participants from the Autism Genetic Resource Exchange (AGRE). In addition to featuring critical characteristics of a representative GWAS (i.e., large target and replication samples of clinical families, and a dense microarray of 500,000+ SNP), the manuscript introduces an analysis that is unusual in the GWAS literature. Specifically, it attempts to mark genes (or specific polymorphisms, SNP) that are associated with diagnostic assessment items of Autism Spectrum Disorders (ASD). Included among these are items from the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), and the Social Responsiveness Scale (SRS). The researchers identified a number of genes that correlate significantly with assessment items, including *KCND2* (associated with overly serious facial expressions), *NOS2A* (associated with loss of motor skills), and *NELL* (associated with faints/fits/blackouts). These findings may help prioritize study designs and directions for future genomic efforts, and suggest the usefulness of the concept of endophenotype for studying complex heterogeneous conditions.

As a good example of the GWAS paradigm in general, this study also exemplifies difficulties faced by researchers working to reconcile findings from their GWAS with the field. The incorporation of the results from hundreds of GWAS into the field has not been a seamless task. On the contrary, it has triggered much heated discussion in the literature. This discussion is multifaceted, concerning both the premise of the GWAS approach and the pattern of findings that thus far has emerged. The first point of contention stemmed from the introduction of case-control GWAS, when fervent endorsement of the methodology paved the way (Lander & Schork, 1994), ultimately contextualizing the GWAS methodology within the HapMap Project (Gabriel, et al., 2002). Even more criticism arose when findings were more inconsistent than first expected (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). Nonetheless, the GWAS approach was supported by an unprecedented development of both the relevant technologies and the statistical apparatuses needed to generate and process the corresponding data rapidly and effectively. Although there have always been voices in the field that have been cautious about the “association fashion,” the wave of enthusiasm generated numerous GWAS with a large variety of phenotypes (for an ongoing update, see http://www.genome.gov/gwastudies/).

There have been different interpretations of the emerging picture resulting from GWAS studies. Arguably the most profound concern is the problem of missing heritability. The problem of missing heritability refers to the observation that when actually “measured” (i.e., captured through common SNP on microarrays), the genetic variance does not account for

the previously observed heritability estimated (see Plomin, this issue). In fact, the heritability estimated is typically large and the genetic variance accounted for is typically small, which introduces a puzzle of how to match the findings from quantitative (i.e., heritability-based) and molecular (i.e., specific polymorphism-based) genetics. Since first identified as a problem, the missing heritability issue has not been resolved, although there have been multiple attempts to solve it. These attempts can be broadly categorized in three lines of argument. According to the first line, common variants are the wrong place to look: GWAS "… have not explained as much of the genetic component of many diseases and conditions as was anticipated. We must therefore turn more sharply toward the study of rare variants" (Goldstein, 2009, p. 1698). According to the second line of argument, heritability coefficients have been overestimated for a number of reasons (Zuk, Hechter, Sunyaev, & Lander, 2012). Moreover, it has been argued that the central assumptions of the traditional quantitative behavior-genetic paradigm are discordant with those of the systems perspective (Fogel, 2011). Specific examples include such characteristics of developmental systems as: non-independence of genetic and environmental sources of variance; the capacity for integrating variance from multiple levels of analysis, unfolding in a minimum of two dimensions, spatial and temporal; nonlinearity of the structural relationships between systemic elements; and changeability (rather than invariance) of systemic elements in time (Boker, Molenaar, & Nesselroade, 2009). Thus, if the very assumptions of quantitative genetics are in question, so are the heritability estimates generated within the corresponding framework. As evidenced in the discussion of the missing heritability issue in Plomin, this debate is far from resolved. The third line appears to be the most conciliatory one, suggesting that the initial outcry for missing heritability might have been premature and, in fact, more and more things fall into place as GWAS findings are generated within studies with large samples and good designs (Lander, 2011). In fact, missing heritability has been gradually found and its portions will continue to be recovered as the field continues with well-designed large-scale GWAS.

The second concern with regard to GWAS is that hundreds (and perhaps even thousands) of SNP that have been reported to be associated with phenotypes of interest are located in noncoding genomic regions (Manolio, 2010). This issue is a considerable challenge, as it is not easy to track the phenotype causality with such SNP, as it is with SNP in protein-coding DNA sequences (Green & Guyer, 2011). Given everything that has been revealed by the Human Genome Project and related research, this finding is not surprising. The field's previous accentuation of the protein-coding sources of variation and lack of such in non-coding (junk) sources of variation is no longer appropriate. Rather, non-coding (especially conserved non-coding) regions of the genome are now central to exciting lines of investigation, in the context of which GWAS-featured noncoding SNP cannot be dismissed. It is anticipated that when these SNP are carefully catalogued and investigated in the context of system studies a larger picture of the patterning of the germline variants (both common and rare) that confer risk for inherited disease will emerge (Green & Guyer, 2011). The cataloging of somatic mutations will also be important for understanding tumor biology, as well as the emergence of developmental neuropsychiatric conditions (Hardy & Singleton, 2009).

The third important concern is that, to this point, GWAS have been carried out primarily in developed countries and primarily with samples from Europe (predominantly Western and Northern Europe) or of European descent (as is characteristic of GWAS samples from Canada and the USA). There are obvious reasons for this, including: awareness and readiness to donate DNA specimens; particular patterns of linkage disequilibrium in specific European populations; concerns about genetic stratification; distributions of resources for DNA collection, processing, storage, and genotyping; and funding mechanisms. Nonetheless, the resulting configuration of GWAS "hot spots" is geographically limited.

This configuration, due to its biases, has the potential danger of contributing to healthcare disparities rather than equalities (Need & Goldstein, 2009). The search for genetic mechanisms of disease susceptibility and response to specific pharmacological treatment should be carried out both within and across racial groups (Risch, Burchard, Ziv, & Tang, 2007).

Finally, it is important to mention that the field has experienced some spectacular successes with this type of research and the disease-common variant hypotheses, specifically, for studies of age-related macular degeneration (see Manolio, 2010), Crohn's disease (see Green & Guyer, 2011), and epilepsy research (see Shostak, Zarhin, & Ottman, 2011). In these cases, the relatively unbiased nature of GWAS in their approach to surveying a genome that is hypothesis-free, has allowed the identification of previously unsuspected genetic variants that account for a nontrivial amount of variance in the general population. This knowledge, in turn, has permitted the development of cellular models, provided suitable targets for therapeutic intervention in animal models, and resulted in the ultimate delivery of effective interventions.

"Other" Types of DNA Sequence Variation

Another outcome of the Human Genome Project that has both conceptual and technological facets pertains to the enhanced realization of the role of "other" (compared to SNP) types of variation in the human genome. The discussion of this line of research is exemplified in this special section by contributions from Zhang et al. and Beaudet. Zhang et al. provide a more general overview of these "other" types of variation, whereas Beaudet focuses more on a particular variation, namely, Copy Number Variation (CNV). Zhang and colleagues share insights on the quantity and mechanism of the emergence of different types of sequence variation, and briefly describe technologies that are used for their detection, focusing primarily on the role of 2nd-generation sequencing. Beaudet focuses primarily on arrays, considering ease of use and interpretation, and the capacity to "upscale" their utilization to the level of routine prenatal screening. In this context, he briefly discusses ethical and legal issues related to such an upscale. Zhang et al. and Beaudet provide excellent representations of the field's current landscape; we present only a brief overview here.

Structural DNA sequence variation in the human genome is viewed as contributing to the etiology of three categories of human diseases and disorders, reflecting the extent of genetic determinism. The first category encompasses disorders that are manifested prenatally and at birth. These disorders are typically related to at least one (and often more) specific lesion in the genome and are referred to as genomic syndromes. Zhang et al. and Beaudet (both in this issue) provide multiple examples of such syndromes. What is particularly interesting is the amount of inter-individual variation that is present at the levels of the genome (i.e., structural variants within specific syndromes) and at the level of clinical manifestation (i.e., cognitive and behavioral profiles) of a particular syndrome. Thus, although the presence of large structural events in the DNA sequence (i.e., either deletions or insertions of a substantial amount of genetic material) deterministically results in a behavioral manifestation, the degree of phenotypic variability among individuals who are carriers of such events is remarkable. What appears to be deterministic is the behavioral manifestation of large chromosomal events, but not specific characteristics of this manifestation. As pointed out by Zhang et al., Beaudet, and Plomin (all in this issue), the field is in a very good position to offer insightful prenatal screening and counseling for these types of genomic lesions. Beaudet suggests that such practices should become routine practice in pregnancy monitoring. However, the question remains of whether the professionals who will order and receive the results of such testing, the families themselves, and representatives of corresponding social services are ready to deal with such type of screening on a large scale.

The second category of disorders for which the genome plays the defining role includes single-gene disorders that are manifested at some point before puberty. Similar to the improved understanding of the role of various sequence variations in human diseases and disorders, the field's knowledge of single-gene (Mendelian) conditions has also been greatly enhanced by the Human Genome Project. In 1990, the genetic and molecular basis was understood for fewer than 2% of the estimated 7,000 Mendelian conditions (e.g., phenylketonuria); this had increased to more than 40% in 2011 (Feero & Green, 2011).

The third category consists of multifactorial (polygenic) diseases that typically manifest during or after puberty. This category includes what are typically referred to as complex common disorders (e.g., diabetes, depression). Although these diseases may have precursors that can be identified prenatally, they cannot be diagnosed early in development. Additionally, there is growing interest in the role of so-called somatic cell genetic defects that might constitute a fourth group of disorders in this classification.

In discussing DNA sequence variation, Zhang et al., Beaudet, and Plomin (all in this issue) use the concept of "rare" variants. This label of "rareness" is derived from the frequency with which a particular type of event occurs in the general population. The abundance of this type of sequence variation (i.e., there are many such variants, each of which is rare or even unique) has permitted the formulation of a hypothesis competing with the common disease-common variant (CD-CV) hypothesis. This hypothesis is referred to as the common disease-rare variant (CD-RV) hypothesis, and it suggests that multiple rare variants underlie susceptibility to a disorder in question.

In 2010, when the field was marking the 10-year anniversary of the completion of the first draft of the Human Genome Project, new expectations were articulated for the Human Genome Project and its numerous affiliates (e.g., the HapMap Project, the 1000 Genomes Project, The Encyclopedia of DNA Elements (ENCODE) Consortium, the International Rare Disease Research Consortium, the Human Epigenome Project), serving as the vision statement of the National Human Genome Research Institute (NHGRI). These expectations were organized around the central premise that understanding normal biology is the foundation for disease biology (Green & Guyer, 2011), and consisted of the following five domains of science: (1) understanding the structure of the genomes, (2) understanding the biology of the genomes, (3) understanding the biology of disease, (4) advancing the science of medicine, and (5) improving the effectiveness of health care. This change of practice—originating from the Human Genome Project and, as envisioned by Beaudet (this issue)—has and will more fully penetrate the routine of pediatric (both medical and nonmedical) services, when referrals are made for screening purposes (Levy, 2010), medical problems (Miller, et al., 2010) and/or for developmental (Willemsen, et al., 2012) and educational issues (Ercan-Sencicek, et al., 2012).

These changes in practices are inevitably coupled with anticipated changes in technology. The human genome is not homogeneous and it contains structurally complex regions that are either known or likely to have a role in disease (see Zhang et al, this issue). Our current methods are unable to untangle this complexity. Moreover, as the field anticipates routine clinical use of genome sequencing, speed is an important issue for clinical applications; although the first sequence of the human genome took years, and it now takes weeks, the target is hours. Another pending demand is for specificity of tests of genetic markers that may be available for different genome products, in different tissues, in response to different exogenous agents, and in conjunction with the prescription of different pharmacological agents (Frueh, et al., 2008). These technological developments are in the works and some have been demonstrated to be effective in case studies (DeFrancesco & Subbaraman, 2011).

Epigenetics and Epigenomics

Although the Human Genome Project has focused on the structure of the genome, it reconfirms that the genome is both structurally malleable and functionally dynamic within ontogenesis; in other words, the genome changes across the lifespan. The Human Genome Project has captured spatial and temporal dynamics of the genome and readdressed the question of what is controlled by the genome. These issues appear to be of direct relevance to developmental research as they pertain to the redefinition of the concept of phenotype.

Nonetheless, research into DNA structural variation provides only a limited set of answers. For example, it does not address such questions as how the brain develops from the same DNA sequence as other tissues, or how a single zygote with a finite DNA reservoir gives rise to more than 200 different cell types. This process of developmental specification is addressed largely by epigenetics (or epigenomics, with these terms used here interchangeably). This type of postgenomic research was not fully appreciated from the1940s, when it was first defined by Waddington (Van Speybroeck, 2002), until the late years of the 20th century. Two convergent factors have determined the recent interest in epigenetic research. First, there is a growing accumulation of data stressing the association between various epigenetic mechanisms, especially those in action early in life, and long-term developmental and health outcomes (e.g., Bird, 2007; Feinberg, 2007; Szyf & Bick, this issue). Second, there is a growing realization in the field that inquiries into the structural variation in DNA sequencing pose new questions regarding how genetic and genomic processes are integrated into the overall process of typical and atypical development. It is this tension that puts epigenetic research at the forefront of the field today.

It is important to note that there are many definitions of epigenetics. The literal meaning of the term is “outside conventional genetics.” The term “epigenesis” originally referred to the interpretation of the genotype into a phenotype occurring during development (Waddington, 1940). The modern definition of epigenetics uses the term as the study of heritable (i.e., transmittable from one generation of cells to the next generation of cells) changes in gene expression that cannot be accounted for by changes in DNA sequence (Bird, 2007). These changes are vital for development and differentiation, but can also arise in adult organisms due to random factors of environmental influences (Issa, 2000). Also of note is that these changes substantiate differential expression in a highly localized manner, commanding specific genes (or genetic loci) either to silence (i.e., no transcription) or to activity (i.e., transcription) by chemically modifying either the DNA itself or the proteins associated with these loci.

Epigenetic research is represented in the special section by two contributions, a literature review by Szyf and Bick and an empirical study by Essex and colleagues. Both articles illustrate the current state of the field, as well as future possibilities. Although these contributions cannot be comprehensive in what they cover, they provide contextual and empirical illustration of the potential of epigenetic research for the field of child development. Several issues of particular concern for developmental research are described briefly below.

First, it is not possible to generate a single reference epigenome, similar to what has been assembled for the genome. However, there are massive efforts underway to catalog variation in the typical (i.e., not challenged by a known disease or disorder) epigenome. In the future, it should be possible to specify a minimum epigenome, which, in its integrity, could characterize epigenetic profiles of an individual for different cell types and tissues at different stages of development. Members of The NIH Roadmap Epigenomic Mapping Consortium (Bernstein, et al., 2010) are in the process of defining and characterizing such an

epigenome. The Consortium has initially identified DNA methylation, six major histone modifications (H3K4me1, H3K4me3, H3K9me3, H3K9ac, H3K27me3 and H3K36me3), chromatin accessibility, and RNA as essential features of the human epigenome. In addition, the Consortium is building a database to capture characteristics of the minimum epigenome in a variety of cell and tissue types in normative development to provide a reference point for subsequent studies of diseases and disorders. This resource will be of great interest to developmental scientists, as it calibrates the "allowable" amount of epigenetic variation specifying typical development.

Second, there appears to be no unique path through which epigenetic mechanisms act throughout the lifespan. For example, both hypo- and hyper-methylation have been associated with aging (Jaenisch & Bird, 2003). Thus, mechanisms of both gain and loss of function might prove to be important for studies of epigenetics. A common feature that appears to be central to the manifestation of an atypical "epi" phenotype is "…the disruption of phenotypic plasticity — the ability of cells to change their behaviour in response to internal or external environmental cues" (Feinberg, 2007, p. 433). It is critical to explore the variety of "influences" (i.e., both endogenous and exogenous to a person) that trigger epigenetic changes. One such mechanism that is currently being closely investigated is diet. Dietary supplements such as folate or vitamins affecting the activity of enzymes are intimately involved in various cellular processes substantiating DNA methylation. It has been shown that a limited amount of folate is associated with genomic instability (Jacob, 1999), neural tube defects (Heseker, 2011) and genomic hypo-methylation (Friso, et al., 2002). It has also been reported that early starvation (and, perhaps, subsequent dietary practices) can result in the accumulation of epigenetic changes over time, which can manifest in particular disease/disorder-related phenotypes. There is also a tremendous amount of interest in early indicators of social environment, rearing practices, and other factors that are known to influence child development and have been marked as epigenetic triggers. In this issue, Essex and colleagues exemplify such triggers by studying parental reports of adversity during infancy and preschool stages as related to the epigenome. The hope is by cataloguing such triggers and understanding the reaction of the epigenome, the field will be able to understand and perhaps influence how the genome is affected by experience.

Third, the field has yet to determine which epigenetic causal elements relate to the manifestation of disorders. With regard to the structure of DNA, such causal elements are defined as genetic lesions, that is, sequence changes (i.e., breakages, deletions, insertions, translocation, nucleotide substitutions). It is unclear at this stage what will define comparable epigenetic lesions. Plausible candidates are changes in the local or global density of DNA methylation and incorrect histone modification. Relatedly, a pathway connecting the genome, the epigenome, and the phenotype (i.e., a clinical disease/disorder phenotype) is also unknown. In fact, common diseases may have causal roots in both the genome (i.e., caused, at least partially, by some form of structural variation) and epigenome (i.e., caused, at least partially, by epigenetic changes that modulate the effects of DNA sequence variation). The CD-CV and CD-RV hypotheses can be further developed into a common disease genetic and epigenetic (CD-GE) hypothesis. According to this hypothesis, epigenetic mechanisms provide an additional layer of variation that alters the relationship between the genotype and the phenotype as it is modulated by the environment (Bjornsson, Fallin, & Feinberg, 2004). The CD-GE hypothesis appears to be particularly relevant for understanding the increased number of common diseases among the aging (Fraga, et al., 2005). Specifically, aging is often conceptualized as a general loss of phenotypic plasticity and responsiveness to the environment. This concept can be understood in terms of the development of an imbalance between gene-promoting and gene-silencing factors occurring throughout the genome, such as increased variance of total DNA methylation and histone

H3K9 acetylation in older monozygotic twins than in younger twins (Fraga, et al., 2005). The CD-GE can also be useful in understanding the phenomenon of discordance of diseases, such as bipolar disorder between monozygotic twins (Kato, Iwamoto, Kakiuchi, Kuratomi, & Okazaki, 2005).

Finally, there have been hopes raised that epigenetic changes may contribute to finding an explanation for the "missing heritability" problem. Inherited epigenetic changes that contribute to disease risk would not be measurable in GWAS, but may have the potential to contribute to average risk and to similarities among relatives. Yet, as it stands now, initial analytical treatments and simulation studies suggest that epigenetic mechanisms can be considered as causal mechanisms for complex diseases, but not for the problem of missing heritability, unless the acquired epigenetic modifications have been persistent within families for many generations (Slatkin, 2009).

In sum, the epigenome holds much promise for enhancing the field's understanding of the biology underlying typical and atypical development and translating this understanding into prevention and treatment. Moreover, epigenetics also offers an important window to understanding the role of the environment's interactions with the genome in causing disease, and in modulating those interactions to enhance normative development and compensate for atypical development.

Transcriptomics and Other '-Omics'

One of the most often cited discoveries of the Human Genome Project is the fact that the genome has many fewer genes than was initially anticipated. Specifically, the genome is estimated to consist of only ~21,000 distinct protein-coding genes (Clamp, et al., 2007). However, many more proteins have been cataloged (using RNA-Seq technology, see below), especially if alternative splicing is taken into account (Lander, 2011). This challenged the central dogma of the field of genetics that there was a one-to-one correspondence between a portion of DNA referred to as a gene, an mRNA transcribed off this gene, and a protein encoded by this mRNA. Correspondingly, the products of each expressed gene, their type (ribosomal RNA--80–90%, rRNA; transfer RNA--5–15%, tRNA; mRNA--2–4%; and a small fraction of intragenic (i.e., intronic) and intergenic noncoding RNA--1%, ncRNA; Lindberg & Lundeberg, 2010) and amount, were referred to as the "transcriptome" (Velculescu, et al., 1997). Many "other" things were also known to exist (e.g., intragenic and intergenic sequences, enriched in repetitive elements), but their role was not understood and, collectively they were referred to as "junk" (Doolittle & Sapienza, 1980). As the field has learned, the amount of noncoding DNA (ncDNA) increases with organism complexity, ranging from 0.25% of prokaryotes' genome to 98.8% of humans (Taft, Pheasant, & Mattick, 2007), and therefore is probably highly important for whatever those complex organisms do (Costa, Angelini, De Feis, & Ciccodicola, 2011).

Although it is not yet clear what should replace the central dogma of genetics or how it should be modified, it is clear that there are many types of "other" RNA that do not fit the dogma, but are nonetheless important and should be counted as part of the transcriptome. Among these are small interfering RNA (siRNA), microRNA (miRNA), long interspersed noncoding RNA (lincRNA), promoter and terminator-associated small RNA (PASR and TASR, respectively), transcription start site-associated RNA (TSSa-RNA), transcription initiation RNA (tiRNA), and many others (Jacquier, 2009). In addition, many transcripts are tissue-/cell-type-specific. In this context, whole transcriptome analyses to discover and catalog all the transcripts found within any studied tissue/cell-type at a particular moment in time (Martin & Wang, 2011; Wang, Gerstein, & Snyder, 2009) are particularly crucial. Such analyses that identify and catalog the different transcripts (Ozsolak & Milos, 2011), not only

permit their study in isolation, but also allow an investigation of their interactions (i.e., their systemic influences). This is especially applicable to studying the brain, which is discussed in this special section by Naumova and colleagues (this issue).

RNA-based analyses are just entering the field of child development, and the body of empirical literature reviewed by Naumova et al. (this issue) is necessarily limited. Nonetheless, the use of genomic methods such as RNA microarrays and RNA-Seq described by Naumova et al. is highly promising because it allows a focus on changes in gene expression. This diverts attention from “causative gene (or genes)” to “causative change,” redefining the system and substantiating both typical and atypical development. RNA-based approaches also allow a focus on the patterns of gene regulation, gene expression, and systems that generate these patterns. Courtney, Kornfeld, Janitz, and Janitz (2010) argued that single-gene research approaches to complex diseases are not sufficient for understanding pathogenic processes resulting in a manifestation of a particular disorder (or a comorbid cluster of disorders). Such approaches are being superseded by those that rely on systems (Hawkins, Hon, & Ren, 2010). An illustration of such a systemic approach is provided by Hu (this issue) in her review of the field of studies of Autism Spectrum Disorders (ASD). She proposes understanding these disorders at a systemic level by integrating findings from types of “omics” science (including genomics, epigenomics, transcriptomics, proteomics, and/or interactomics), instead of focusing on a single isolated field.

Conclusion

This Introduction to the special section briefly contextualizes the contributions presented, and attempts to capture the current general parameters of the fields of genetics and genomics and their junctions with the field of child development. Both the Introduction and the section do not do justice to many aspects of genetics and genomics. Among issues not covered are those pertaining to: managing (Hawkins, et al., 2010) genomic data, as this poses a unique challenge to protecting participant confidentiality; using genomic testing for diagnostic and predictive purposes, as well as direct-to-consumer genetic testing (Gollust, Hull, & Wilfond, 2002); educating the public and various professionals who will need to understand and interpret various genetic tests; handling ethical considerations pertaining to a near-ubiquitous presence of new information related to or generated by the Human Genome Project, and numerous other topics introduced or crystallized by the Project. We are hopeful that this special section will have multiple sequels.

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