Published in final edited form as:
Am J Hum Biol. 2011 ; 23(1): 53–64. doi:10.1002/ajhb.21132.

Comparative genetic approaches to the evolution of human brain and behavior

Eric J. Vallender*
Division of Neuroscience, New England Primate Research Center, Harvard Medical School, Southborough, MA

Abstract

With advances in genomic technologies the amount of genetic data available to scientists today is vast. Genomes are now available or planned for fourteen different primate species and complete resequencing of numerous human individuals from numerous populations is underway. Moreover, high-throughput deep sequencing is quickly making whole genome efforts within the reach of single laboratories allowing for unprecedented studies. Comparative genetic approaches to the identification of the underlying basis of human brain, behavior and cognitive ability are moving to the forefront. Two approaches predominate: inter-species divergence comparisons and intra-species polymorphism studies. These methodological differences are useful for different time scales of evolution and necessarily focus on different evolutionary events in the history of primate and hominin evolution. Inter-species divergence is more useful in studying large scale primate, or hominoid, evolution whereas intra-species polymorphism can be more illuminating of recent hominin evolution. These differences in methodological utility also extend to studies of differing genetic substrates; current divergence studies focus primarily on protein evolution while polymorphism studies are substrate ambivalent. Some of the issues inherent in these studies can be ameliorated by current sequencing capabilities while others remain intractable. New avenues are also being opened that allow for the incorporation of novel substrates and approaches. In the post-genomic era the study of human evolution, specifically as it relates to the brain, is becoming more complete focusing increasingly on the totality of the system and better conceptualizing the entirety of the genetic changes that have lead to the human phenotype today.

The human brain is an intricate organ; its complexity underlies behavior, emotion, communication, and cognition. It is the seat of our humanity, giving rise to who we are, what defines us as individuals, and what sets us apart from other species. Many approaches have emerged attempting to make sense of this complexity. One recent and promising avenue of research aims to understand the evolutionary history of brain complexity through comparative genetic approaches both between primate and mammalian species and within human populations.

To understand the genetic causes leading to the functional and anatomical changes between the human brain and the brain of apes, monkeys, and other primates divergence-based approaches are most useful and appropriate. These kinds of approaches seek to catalog the differences between species and identify positions of likely functional relevance. Even between two species as closely related as humans and chimpanzees this number of fixed differences in the genome is exceedingly large, over thirty million point mutations. Attempts to identify functionally relevant needles within this haystack have relied on tools designed for the detection of positive selection. This methodology presupposes that the changes hold

*Correspondence to E. J. Vallender, New England Primate Research Center, Harvard Medical School, Southborough Campus, Pine Hill Drive, Southborough, MA 01772. eric_vallender@hms.harvard.edu.

an evolutionarily selected advantage, a far from certain case for all functionally relevant differences between species, but perhaps more likely than not with regards to the brain. While this approach has yielded useful results, its gaps, including power issues associated with short lineages and a difficulty in operating outside of protein-coding regions, have left the story incomplete.

Studies of polymorphism within humans are substrate ambivalent, allowing them to work equally well following selection on coding or non-coding nucleotides. While divergence studies work best on time scales of tens of millions of years, polymorphism-based approaches only hold for evolutionarily recent events, perhaps within the last million years of human evolution, and are very sensitive to the effects of demography which significantly complicates interpretation. With respect to the brain and behavior, polymorphism based studies likely do not have the evolutionary reach to detect the genetic changes relating to the major structural changes that have occurred in the human brain, though perhaps they are useful for more recent subtle changes in brain function or behavior.

From the outset, evolutionary theory has been interested in understanding the emergence of the human brain. Comparative anatomists, behavioral primatologists, and paleoanthropologists have all approached these questions from diverse viewpoints. Genetic research opened the door to another approach whose promise was capitalized on by comparative genomics. As we move forward, these techniques are being integrated into a more complete picture that goes beyond merely cataloging the differences between species and actively pursues the mechanisms by which these differences have arisen. We are now transitioning into a post-genomic era where genomes for multiple species and multiple individuals within a species are available and common. This new comparative genetic landscape is strewn with potholes that must be navigated but offers the opportunity to move closer to understanding the specific changes that have occurred during the evolution from our ape-like ancestors to the modern human populations of today.

POST-GENOMIC COMPARATIVE GENETICS

Following the publication of the human genome (Lander and others 2001; Venter and others 2001), the post-genomic era largely moved in two separate directions. The first focused on the genomes of other species, while the second focused on identification of variation within human populations. Of course, neither of these approaches were novel; comparisons of inter-species divergence and intra-species variation had pre-dated genetic sequencing. Nevertheless, the explosion of genetic data and information in the post-genomic era cannot be understated. Studies that had previously focused on single or relatively modest numbers of genes could be expanded to include the entirety of the genome. Similarly regions could be expanded, allowing for a renewed focus upon non-coding regions that had too often been relegated to second-class status because of practical constraints. Study populations have expanded as well to include more sub-populations and more individuals within each sub-population. This has allowed for a better understanding of rare polymorphism as well as better type genomes for species.

Resources for comparative genetics

Numerous non-primate mammalian genomes have now become available, notably including the mouse, *Mus musculus* (Waterston and others 2002); rat, *Rattus norvegicus* (Gibbs and others 2004); dog, *Canis familiaris* (Lindblad-Toh and others 2005); cow, *Bos taurus* (Elsik and others 2009); and low-coverage genomes including the cat, *Felis catus* (Pontius and others 2007), and others (Margulies and others 2005). Many mammalian genomes are currently slated for preparation. The importance of primate genomics to understanding human biology in particular has been recognized and has resulted in an increased focus on

expanding the diversity of primate genomes available. The chimpanzee, *Pan troglodytes* (2005), and rhesus macaque, *Macaca mulatta* (Gibbs and others 2007), genomes have been published and gorilla (*Gorilla gorilla*), orangutan (*Pongo pygmaeus abelii*), and marmoset (*Callithrix jacchus*) genomes are nearing completion. There are also a handful of other non-human primate species that are currently in the sequencing pipeline at various degrees of completion (Figure 1). The current approach to non-human primate genomics has been divided between a focus on important biomedical models (including additional species from the *Macaca* genus, baboon, and vervet monkeys) and expanding our evolutionary understanding through addition of the gibbon genome and the "top-up" finishing of low-coverage genomes for the tarsier and strepsirrhine species.

Human variation studies have also greatly expanded in concert with the post-genomic explosion of data. The first major foray into human genetic variation, the Human Genome Diversity Project (HGDP), preceded the original publication of the human genome by a decade (Cavalli-Sforza and others 1991). The prescience of these efforts paved the way for the generation of a major resource incorporating more than 1000 individuals from more than 50 populations (Cann and others 2002; Rosenberg 2006). Shortly after the publication of the human genome the International HapMap Project was organized focusing on identifying common polymorphisms across the entirety of the genome as a map for association studies and for understanding population recombination rates (International HapMap Consortium 2003; International HapMap Consortium 2005). The effort used 90 individuals of Yoruban descent from Ibadan, Nigeria; 90 individuals from Utah in the Centre d'Etude du Polymorphisme Humain (CEU) collection; 45 Han Chinese individuals from Beijing; and 45 Japanese individuals from Tokyo. While chosen to broadly reflect ethnic and geographical diversity, these populations were never meant to be exhaustive. Nevertheless, despite protestations in the original publications, these populations have been too often generalized as "Sub-Saharan African", "European", and "Asian" respectively. More recent efforts from this consortium have focused on increasing genotyping depth within these populations (Frazer and others 2007). Reflecting the differences in the communities initiating these efforts it is worth noting that the anthropologists initiating the HGDP still emphasize the relative incompleteness of their collection for representing the entirety of human diversity. These efforts however were generally recognized as complementary and synergistic (Cavalli-Sforza 2005).

The practical constraints of the early post-genomic era were exemplified by these two approaches. The HGDP offered wide coverage of populations but studies generally were limited in genetic scope to single genes or relatively small subsets of loci. The HapMap project incorporated significantly more variable positions, but did so while focused on fewer individuals and populations. As next-generation sequencing technologies have driven down the costs of producing a complete genome, a project has emerged aimed at the taking the goals of both of these earlier projects and combining them. The 1000 genomes project (http://www.1000genomes.org) aims to produce the complete genomes of individuals from numerous populations. Phase one of the project aims to sequence 1100 individuals from 12 populations, with phases two and three adding 900 individuals from 10 populations and 500 individuals from 5 populations respectively. Although still in relatively early stages, this effort promises to be a major source of research innovation going forward. Interestingly, and indicative of the new challenges presented by next generation sequencing, the largest impedance emerging in the project seems to be in the data processing and analysis rather than the sequence production itself.

Inter-species comparative genetic methodologies

To date, the vast majority of inter-specific comparative genetic studies have focused on protein-coding regions. The reason for this is fairly straightforward; we have established

methodologies that support it. Most generally it is easy to identify changes between protein coding regions that are likely to have a functional significance. Mutations that change amino acids are more likely to be functionally relevant than mutations that do not, and mutations that dramatically alter the physicochemical properties of an amino acid are more likely to have a functional effect than those that do not (Grantham 1974; Graur 1985; Tang and others 2004). Mutations in regulatory regions are harder to quantify. The primary difficulty has been in identifying which nucleotides are functional in promoter or regulatory regions. This is further complicated by redundancy among regulatory regions and the lability of binding sites.

Evolutionary analyses of protein-coding regions has often focused on the relative ratio of amino acid changing mutations (variously called d_N or K_A) to the neutral mutation rate using synonymous mutations in the protein (d_S or K_S) as a proxy. These rates (d_N/d_S or K_A/K_S) can be used to infer the selective history on the proteins. A neutrally evolving sequence will show values equal to one, while proteins under negative or purifying selection (i.e. the vast majority of proteins) will show values significantly below one and those under positive selection will show values greater than one. Numerous methodologies have been implemented on this basic premise with variations that attempt to better model the mutational process or take into account added complexity and site heterogeneity (Goldman and Yang 1994; Li and others 1985; Nei and Gojobori 1986; Yang and Nielsen 2000). Other methods have compared replacement and synonymous mutations between species to polymorphism observed within species to identify differences in selective pressures (the McDonald-Kreitman test, (McDonald and Kreitman 1991)) or polymorphism and divergence between genes to identify differences in selective regimes (the HKA test, (Hudson and others 1987)). With some caveats (Vallender 2008) these methods have been largely successful in identifying protein substrates of evolutionary selection, particularly in those instances where selective pressures have been the most intense and prolonged.

Only recently have large-scale methods been successfully implemented that look at the molecular evolution of regulatory regions. One early model compared rates of substitution in non-coding regions to synonymous sites in proteins (Wong and Nielsen 2004), another compared regions immediately upstream of the transcriptional start site to surrounding intronic sequence (Haygood and others 2007). In a sense these were extensions of the protein-coding methodologies, comparing the putatively selected regions to neutral rates. While a crude approximation of the promoter sites, these approaches demonstrated some success and demonstrated a feasibility that could be built upon. More recently, a model has been developed that incorporates transcription factor binding sites into this analysis (Hoffman and Birney). This approach takes our understanding of the evolution of regulatory regions a step further but still relies on our incomplete understandings of the complexity of gene regulation. Nevertheless, it is a major step forward for the field and will likely form the basis for improved methodologies in the future.

Intra-species comparative genetic methodologies

Just as divergence between species can be used to make sense of selective pressures during speciation so too can intra-specific variation. Additionally, intra-specific variation can be used to identify differences between subpopulations of a species or to identify ongoing selective regimes. Both approaches are critically dependent on numbers of mutations for their power to be realized. This is one of the primary reasons why inter-specific comparisons between human and chimpanzees are so difficult; a paucity of changes make distinguishing signal from noise difficult. Inter-specific comparisons achieve power and best results over long evolutionary time, limiting their effectiveness to more divergent species and more ancient selective events. Intra-specific studies of variation, however, draw upon polymorphisms extant in the population. There are many more polymorphisms than fixed

differences, but they have much more recent evolutionary origins. Similarly, polymorphisms within a species are extremely dependent on demographic histories with bottlenecks and founder effects largely erasing signatures of selection preceding them. As a result of this using polymorphism for understanding selective pressures may only be relevant for fairly recent events. In humans this has the effect of limiting the usefulness of these studies to the last million years or so. While this encompasses notable differences between populations, it is difficult to use these approaches to identify those shared changes that define and separate all anatomically modern human populations.

Methodologies for detecting selective events using polymorphism data are numerous and their usage and efficacy, as well as relative strengths and weaknesses, widely debated (Nielsen 2005; Thornton and others 2007). In addition to the previously mentioned McDonald-Kreitman and HKA tests which make use of divergence data in addition to polymorphism data, tests broadly fall into three categories: those focused on the allelic frequency spectrum, those focused on population subdivision, and those focused on haplotypic structure. The first of these, epitomized by Tajima's D (Tajima 1989), compares the number of segregating sites at various frequencies to that expected under neutrality. Tests that make use of population subdivision, usually FST (Lewontin and Krakauer 1973), use exceptional differentiation between subpopulations to infer recent selection. Tests that use haplotypic structure to infer selection (reviewed in (Thornton and others 2007) have become more common recently as sequencing power and projects like HapMap offer larger data sets than were previously available.

The primary disadvantage to nearly all polymorphism-based studies is the confounding effects of demographic history. Most tests rely upon a neutral model of evolution as a null hypothesis, but it remains controversial as to what form this null model should take. This issue is ameliorated somewhat when regions are compared within a species (and thus where the demographic history of all the regions is the same if not necessarily known). Even focusing thus on outliers within a species may predispose researchers to unknown ascertainment biases. A major advantage to these approaches, however, is the lack of an *a priori* defined substrate of selection. These tests work equally well on protein-coding, regulatory, or heretofore unknown functional elements within the genome. Conversely, however, this can make it difficult to pinpoint the exact substrate of selection within the region for future study.

GENETICS AND THE EVOLUTION OF THE HUMAN BRAIN

The mid-1800's were certainly the fountainhead of much of modern biology, including the major fields of interest to us here. In 1859, Charles Darwin published *Origin of Species*, laying down the early principles of evolution and importantly beginning to build the framework for comparative studies between species. Gregor Mendel's early studies of allelic inheritance in 1866 laid the foundation for modern genetics. In one of the earliest applications of the genetic framework to the brain and behavior, Francis Galton recognized in 1869 that cognitive abilities seemed to run in families. Thus began the climb towards understanding brain evolution (Striedter 1998).

Early forays into the specific genetic differences between humans and non-human primates began in earnest in the 1980's and 1990's. A review of this early literature (Gagneux and Varki 2001) demonstrates the relative paucity of studies at the time and the focus on specific genes. Indeed a contemporaneous meta-analysis focused on genic comparisons among the great apes identified only 37 genes with available sequence in humans, chimpanzees, gorillas and orangutans (Chen and Li 2001); another identified only 88 genes with sequence in both humans and chimpanzees (Chen and others 2001). Nevertheless, despite the

relatively small genic studies, important observations were being made that have guided our current studies. Most notable among these was the observation by King and Wilson in 1975 that the similarity in genetic sequence between humans and chimpanzees was so great that regulatory changes necessarily must play a major role in phenotypic differences (King and Wilson 1975).

Today numerous studies, both single gene and whole genome, have focused on genetic evolution in humans and numerous genes have been implicated in the emergence of the human brain (Portin 2008; Vallender 2008). And while earlier studies focused almost entirely on protein-coding differences, a result of practicality rather than some dogmatic adherence, more recent studies have begun to incorporate regulatory evolution. This research has emerged from both comparative genetic traditions: inter-species and intra-species.

Evolution of human brain and behavior: Evidence from primate divergence

In studying the evolution of the human brain we are necessarily required to study it in comparison to non-human primates. The reasoning for this is simple; we are interested in the changes that have occurred that lead to the brain we currently observe in all humans. As straightforward as this may seem, it is all too common to comment on the failure to identify gene overlap when comparing divergence-based studies to polymorphism-based ones. Given the relative homogeneity of human brain architecture, it would be more surprising to find polymorphic variation associated with positive selection in brain genes compared with other categories. This belief is so strong, in fact, that we are more critical of studies appearing to support these findings. For this reason studies of how the human brain has emerged are predominantly, if not exclusively, focused on inter-species comparisons.

The human brain differs from apes in several ways. Most commonly this is thought of in terms of encephalization events, a general allometric growth of the brain usually measured through brain volumes often scaled to body size. This simplistic view can be easily conceptualized and mechanistic inferences are more straightforward, yet it does fail to account entirely for the differences observed between species. The human brain is not simply an enlarged monkey or chimpanzee brain; in fact there are notable structural and regional differences that are likely important when considering the totality of the modern human brain phenotype (Bruner 2004; Bruner and others 2003). With regards to the genetic mechanisms underlying these different kinds of changes less can be known. While it may be likely that different genes and genetic changes underlie an overall brain growth versus a specific structural change, this remains unknown and as the field moves towards regulatory changes as the salient mechanism of action the situation muddies. Nevertheless, it is clear that whatever the direct mechanism or phenotypic change, the genetic signatures of adaptation should exist in genomes.

Beyond the comparison between inter-species studies of selection and polymorphism-based studies, there are divisions to be found even among inter-species studies. When measures of the brain are compared (whether overall volume, neuronal number, cortical thickness, or other measures) it is clear that what we know recognize as the human brain has appeared in steps. Notably for our purposes here there were significant events separating the apes from old world monkeys as well as those occurring since the divergence of humans from chimpanzees (Clark and others 2001; Rilling and Insel 1999; Schoenemann and others 2005). While comparative genetics studies between humans and other ape species (particularly chimpanzee) will necessarily be focused on these most recent changes, studies that compare humans to old world monkeys (notably rhesus macaques) may instead be inadvertently identifying changes significant in the emergence of the ape brain rather than the human brain. This is particularly relevant because it is unclear what the relationships are

between the changes that generated the ape brain and those that generated the human brain. While it is possible that they should occur in the same genes or in the same systems, it is not necessarily so. This distinction need also be made because most power in evolutionary studies is derived from lineage length. The divergence time between humans and chimpanzees yields poor statistical power compared to the relative robustness of studies that include the old world monkey to ape internal branch. It is worth noting in this context as well that arguments can be made that the evolution of apes from monkeys can be better understood and interpreted compared to human evolution from apes, where perhaps historically anthropocentric biases may still be prevalent.

Studies of positive selection on protein-coding genes thought to be related to changes in the human brain have been reviewed elsewhere (Portin 2008; Vallender 2008; Vallender and others 2008a), however it is worth noting that significant recent advances have been made regarding non-coding evolution. The earliest studies found an excess of human accelerated evolution, notably not necessarily positive selection, in genes involved in neuronal cell adhesion (Prabhakar and others 2006). Contemporary studies found accelerated evolution unique to humans among primates clustering in genes associated with transcriptional regulation and DNA binding (Pollard and others 2006); a finding the authors offer in support of the earlier hypothesis of King and Wilson (King and Wilson 1975). A more explicit hypothesis of positive selection was associated with promoter regions of genes involved in neural development and function by comparing rates of evolution in these regions to nearby introns (Haygood and others 2007). It is also notable that the earliest and best characterized individual gene for positive selection on the promoter region is the opioid peptide precursor gene *PDYN* (Rockman and others 2005).

A meta-analysis of several of these studies focusing on evolution of coding and non-coding regions in the human terminal lineage from the human-chimpanzee ancestor found an overrepresentation of genes involved in neurogenesis and “other neuronal activity” in non-coding studies but an expected or underrepresentation of these categories in studies of coding regions (Haygood and others 2010). Especially notable in this study was that immune-response genes, commonly understood to be the strongest substrates for positive selection across species, showed an over-representation in both coding and non-coding studies. This highlights the relative difference in the evolution of the brain compared to other typical substrates of positive selection and again underscores the importance of gene regulation in the evolutionary history of species-specific traits in humans.

Evolution of human brain and behavior: Evidence from human polymorphism

Polymorphism-based evolutionary studies have been largely ineffective in identifying genes or characters responsible for salient human brain phenotypes. The reach of polymorphism-based approaches in humans seems unlikely to extend more than 200,000 years (Oleksyk and others 2010). By comparison, the brain size of *Homo heidelbergensis* 500,000 years ago was only slightly smaller than modern humans and the brain of *Homo neanderthalensis* appears to have been virtually identical in size (Neill 2007). The ability of polymorphism studies to detect selection may, in some cases largely bounded by stochastic effects of genetic drift and subsequent demographic events, be able to detect the most recent of these sweeps, but it is unlikely to resolve previous hominid encephalization events such as that between *Homo erectus* and *Homo heidelbergensis* during the early to mid-Pleistocene (Rightmire 2004; Ruff and others 1997). Moreover, it is important to note that the polymorphism-based studies with the greatest likelihood of detecting any such changes will almost exclusively focus on African populations that did not suffer the “Out-of-Africa” bottleneck of European and Asian populations. Simply put, polymorphism based studies as they are currently focused are unlikely to identify the changes or loci responsible for the evolutionary emergence of the modern human brain.

While it is perhaps not surprising that evolutionary selection on brain structure or intelligence (as broadly defined) is not to be found in polymorphism-based approaches, there is evidence for evolutionary action on sensory systems. The gradual decline in relative importance of the olfactory system in relation to other sensory inputs extends from throughout the evolutionary history of primates, especially anthropoids, and into more recent human history (Dong and others 2009; Gilad and others 2005; Voight and others 2006). This finding is one of the most consistent among all comparative genetic and evolutionary studies of humans and is thought to reflect an increasing reliance on visual stimuli as a means of environmental interaction. These observed chemosensory changes also include selection on bitter taste receptors (Soranzo and others 2005; Wooding and others 2006; Wooding and others 2004). Unlike the olfactory receptors, whose evolution in humans is characterized by relaxation of constraint, these bitter taste receptors seem to be undergoing positive or balancing selection, likely as a response associated with dietary adaptations.

Genetic variation has also been identified associated with behavior in humans. In addition to the aforementioned *PDYN* selection that appears to have persisted into modern populations (Rockman and others 2005), these approaches have focused largely on genes involved in the major neurotransmitter systems: dopamine, serotonin, and norepinephrine (Craig and Halton 2009; D'Souza and Craig 2008). Most notable have been findings that variability at the dopamine D4 receptor (*DRD4*) is a result of positive selection (Ding and others 2002; Wang and others 2004) possibly as a result of its association with behaviors, novelty seeking in particular (Roussos and others 2009), that facilitated the major human macro-migrations (Chen and others 1999). While this interpretation may be generous, the finding of positive selection on a major gene involved in brain physiology is not in doubt. These studies, however, do highlight a difficult reality in selection studies on human behaviors.

Most human selection work has focused on dietary adaptations (such as the lactase (Bersaglieri and others 2004) or amylase genes (Perry and others 2007)) or on adaptations to specific environmental pathogens (notably endemic malaria (Kwiatkowski 2005)). These studies benefit from being fairly quantitative and politically neutral. Behavioral studies are not. It is much more difficult to identify the phenotype under selective pressure or even how the genetic changes manifest at the organismal level. This is also complicated because behavioral genetics is often politically charged, especially when a conception of "better" is improperly inferred from selection studies. Together this has created a climate where these studies can be challenging to undertake and to interpret properly. This may perhaps account for the relative dearth in the literature especially as compares to behavioral genetics of other species. While demanding, however, this work can help to better understand recent human evolutionary history and how natural selection may have acted upon behavior when shaping the human species.

NEW DIRECTIONS IN COMPARATIVE GENETICS

Fueled by the next wave of sequencing technologies, efforts to understand the genetic substrates of selection have expanded rapidly in recent years. Up until know most of these efforts have focused on extending single gene methodologies into genomic studies. Indeed, methods for detecting positive selection either by inter-species divergence or intra-species polymorphism have long existed. In the genomic era these methodologies have been expanded to large data sets, allowing for the movement beyond candidate genes to more comprehensive studies. This is particularly important in an era that has fetishized the concept of a single "God gene" responsible for human evolution. Science has long recognized that complex phenotypes (and complex diseases) are caused by numerous different mutations in numerous different genes, with a phenotype often only developing following the emergence of particular constellations, not necessarily overlapping, of alleles.

Yet despite this theoretical understanding, practical considerations have made this concept difficult to develop. Coupled with a culture that can overvalue and overreward simple answers, it has become commonplace to emphasize the findings of specific genes (or more broadly, specific characters) at the expense of a complete picture wherein they are only a single star in a largely unexplored galaxy. In this post-genomic era, the practical limitations that have held the field to single gene studies are beginning to break down and efforts at a more gestalt understanding are intensifying.

These new opportunities go beyond simply expanding the methodologies and interpretations confined to single-gene studies to larger data sets; completely new avenues heretofore unconsidered are also opening up. This includes new sources of genetic variation within species and previously underappreciated or understudied genetic differences between species. It also allows us to take another step back and to compare patterns of 0polymorphism between multiple species at a level which was impractical prior to the genetic revolution. While these studies are not specific to the brain, they can find particular usefulness there. Perhaps nowhere will subtle changes be more strongly felt or small differences have such a great impact. Moreover, it is in the brain that genetic complex reaches its zenith and perhaps where invasive studies are most impractical.

New sources of genetic difference

One important area of new research has focused on the identification and understanding of novel evolutionary substrates. The earliest studies of copy number variations (CNVs) were associated with large-scale differences and pathological phenotypes. Chromosome 21 trisomy in Down's syndrome and the X chromosome duplications and deletions in Klinefelter's and Turner syndrome respectively are the most extreme examples of this, through it also extends to the contiguous gene syndromes such as Prader-Willi and DiGeorge. More recently it has become recognized that smaller scale copy number variation, from 1 to 1000 kb in size, is much more common and benign. Further, there has been an increased appreciation in fixed copy number differences between species. While the associated genes and phenotypes are diverse, it is noteworthy here that behavioral and neural function is featured prominently. Among pathological CNVs are those associated with mental retardation, autism, schizophrenia and neurodegenerative disorders (Zhang and others 2009). Genes containing the DUF1220 domain, expressed specifically in neurons and particularly in the hippocampus and neocortex, are notable for their fixed copy number differences among primates (Popesco and others 2006). While non-primate mammals only have one gene containing this domain, the number of genes harboring the domain increases in Old World monkeys and apes and are at their zenith in humans. Conspicuously, these genes are also in copy number variable regions associated schizophrenia (International Schizophrenia Consortium 2008; Stefansson and others 2008), microcephaly and macrocephaly (Brunetti-Pierri and others 2008). Though the associations between copy number variation and human species-unique cognitive abilities are still largely circumstantial, the pathological effects of CNVs and their association with other, non-neural, phenotypes (Gonzalez and others 2005; Perry and others 2007) make it clear that this source of genetic variation warrants further exploration.

Another area of increasing interest is in transcriptomics. While there have been attempts to identify selection on non-coding changes, we have already seen how this can be difficult especially in cross-species comparisons. Another approach has been to avoid primary sequences and instead focus on the transcriptome itself. Early studies identified differences between human and chimpanzee brain transcriptomes and from this were able to develop hypotheses of selection (Caceres and others 2003; Enard and others 2002; Khaitovich and others 2005; Khaitovich and others 2004). It is exceedingly difficult, however, to control between groups in this work. Not only is it difficult to simply obtain appropriate tissues,

especially from chimpanzees or other ape species, but it is often difficult to find appropriate humans for comparison. This work necessarily has also focused on chimpanzee brains of expedience rather than selected for maximal scientific information; chimpanzees brains are only used when a typically older adult expires precluding the study of transcriptomics during development that may better represent differences between species. More recently efforts have also begun to focus on the evolution of alternative splicing. Not only have species-specific alternative splice patterns associated with differential selection been observed in primate liver (Blekhman and others 2010), but also in the brain (Lin and others 2010). These findings are also being extended to intra-specific variation with recent evidence suggesting that, in humans, variation at intron-exon boundries is being maintained to maintain population variation in alternative splice patterns (Shimada and others 2010). It is finally of interest to note that there has also been suggestion of species-unique epigenetic differences in the brain (Enard and others 2004; Farcas and others 2009). While differences in gene regulation have long been recognized as major drivers of human phenotypic evolution, these findings have moved studies beyond cis-regulatory mutations and into new realms.

Parallel genetic variation across species

Another interesting development has focused on parallel genetic variation across species. Examples are increasingly being identified of variation in non-human primates that functionally parallels similar variation observed in humans. While not identical or evolutionarily orthologous, polymorphisms in other species are being observed with homologous functional effects. Most commonly this observation can be seen in genes affecting coloring (including hair coloring, coat coloring, and plumage) where, for instance, mutations across numerous species in the melanocortin 1 receptor (MC1R) result in similar effects (Eizirik and others 2003; Kerns and others 2007; Majerus and Mundy 2003; Mundy 2005). This commonality of polymorphism function has also been demonstrated in primate neural systems: dopamine transporter (DAT) (Madras and others 2005; Miller and others 2001; Miller and Madras 2002), opioid receptor mu (OPRM1) (Barr and others 2007; Barr and others 2008; Miller and others 2004; Vallender and others 2008b), tryptophan hydroxylase 2 (TPH2) (Chen and others 2006; Chen and others 2008), and sertotonin transporter (SLC6A4) (Bennett and others 2002; Inoue-Murayama and others 2008; Lesch and others 1997; Soeby and others 2005; Vallender and others 2008c; Wendland and others 2006). This general finding has led to the hypothesis that certain non-human primate species share with humans a constellation of functional alleles that underlie the inter-individual variability in behavior and mental health function (Miller and Mardras 2005), a concept that has included a focus on addiction disorders (Barr and Goldman 2006).

This parallel profile of functional polymorphism can be indentified in any outbred populations though notably not in the traditionally inbred, to the point of clonality, laboratory models, rats and mice. Interbreeding between strains of rodents may recapitulate some of the genetic variation from the wild populations, but it is largely incomplete. Rather, model organisms derived from large outbred populations are more likely to harbor this parallel polymorphism. These origins, coupled with close genetics, anatomical, physiological, and behavioral similarities to begin with make non-human primate model systems particularly useful in these studies. Among non-human primate model organisms, rhesus macaques may have broad applicability because of a wide geographic distribution, historically large effective population size, and generalist ecological niche that may have predisposed the species towards a maintenance of genotypic and phenotypic variation (Richard and others 1989; Suomi 2006).

The recognition that parallel phenotypic variation indeed follows from parallel genetic variation offers researchers with the opportunity of exploring cross-species evolutionary patterns. Not only does the use of model organisms allow one to better interpret the effects

of genetic polymorphism on behavior in humans, but it may also allow for a better interpretation of the fixed differences between species. To date these efforts have largely been applied to pathological conditions though they are more widely useful, especially in the case of complex phenotypes where environmental effects can have major confounding influences in human studies.

CONCLUSIONS

When studies of selection and the human brain are undertaken, there is a common complaint of anthropocentrism. It is undeniable that this work is focused on humans, but it is not because the active researchers in this area believe there is something implicitly different about the selective processes in humans. Simply, while there is a focused interest on the evolutionary history of some species, notably livestock species such as cows and pigs, largely these evolutionary studies into the genetics behind species evolution are not viewed, rightly or wrongly, as a major public interest. Studies of human evolution, including brain evolution, are primarily driven by the belief that these understandings will improve human health and well-being. At the same time, however, it must be admitted that there is an inherent, if irrational, philosophical attachment to understanding how and why humankind came to exist in its present form to the exclusion of similar questions of other species. Comparative genetics offers another tool with which we can study the evolution of the human species.

LITERATURE CITED

Barr CS, Goldman D. Non-human primate models of inheritance vulnerability to alcohol use disorders. Addict Biol. 2006; 11(3–4):374–85. [PubMed: 16961765]

Barr CS, Schwandt M, Lindell SG, Chen SA, Goldman D, Suomi SJ, Higley JD, Heilig M. Association of a functional polymorphism in the mu-opioid receptor gene with alcohol response and consumption in male rhesus macaques. Arch Gen Psychiatry. 2007; 64(3):369–76. [PubMed: 17339526]

Barr CS, Schwandt ML, Lindell SG, Higley JD, Maestripieri D, Goldman D, Suomi SJ, Heilig M. Variation at the mu-opioid receptor gene (OPRM1) influences attachment behavior in infant primates. Proc Natl Acad Sci U S A. 2008; 105(13):5277–81. [PubMed: 18378897]

Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, Champoux M, Suomi SJ, Linnoila MV, Higley JD. Early experience and serotonin transporter gene variation interact to influence primate CNS function. Mol Psychiatry. 2002; 7(1):118–22. [PubMed: 11803458]

Bersaglieri T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, Drake JA, Rhodes M, Reich DE, Hirschhorn JN. Genetic signatures of strong recent positive selection at the lactase gene. Am J Hum Genet. 2004; 74(6):1111–20. [PubMed: 15114531]

Blekhman R, Marioni JC, Zumbo P, Stephens M, Gilad Y. Sex-specific and lineage-specific alternative splicing in primates. Genome Res. 2010; 20(2):180–9. [PubMed: 20009012]

Bruner E. Geometric morphometrics and paleoneurology: brain shape evolution in the genus Homo. J Hum Evol. 2004; 47(5):279–303. [PubMed: 15530349]

Bruner E, Manzi G, Arsuaga JL. Encephalization and allometric trajectories in the genus Homo: evidence from the Neandertal and modern lineages. Proc Natl Acad Sci U S A. 2003; 100(26): 15335–40. [PubMed: 14673084]

Brunetti-Pierri N, Berg JS, Scaglia F, Belmont J, Bacino CA, Sahoo T, Lalani SR, Graham B, Lee B, Shinawi M, et al. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet. 2008; 40(12):1466–71. [PubMed: 19029900]

Caceres M, Lachuer J, Zapala MA, Redmond JC, Kudo L, Geschwind DH, Lockhart DJ, Preuss TM, Barlow C. Elevated gene expression levels distinguish human from non-human primate brains. Proc Natl Acad Sci U S A. 2003; 100(22):13030–5. [PubMed: 14557539]

Cann HM, de Toma C, Cazes L, Legrand MF, Morel V, Piouffre L, Bodmer J, Bodmer WF, Bonne-Tamir B, Cambon-Thomsen A, et al. A human genome diversity cell line panel. Science. 2002; 296(5566):261–2. [PubMed: 11954565]

Cavalli-Sforza LL. The Human Genome Diversity Project: past, present and future. Nat Rev Genet. 2005; 6(4):333–40. [PubMed: 15803201]

Cavalli-Sforza LL, Wilson AC, Cantor CR, Cook-Deegan RM, King MC. Call for a worldwide survey of human genetic diversity: a vanishing opportunity for the Human Genome Project. Genomics. 1991; 11(2):490–1. [PubMed: 1769670]

Chen C, Burton M, Greenberger E, Dmitrieva J. Population migration and the variation of dopamine D4 receptor (DRD4) allele frequencies around the globe. Evolution and Human Behavior. 1999; 20:309–324.

Chen FC, Li WH. Genomic divergences between humans and other hominoids and the effective population size of the common ancestor of humans and chimpanzees. Am J Hum Genet. 2001; 68(2):444–56. [PubMed: 11170892]

Chen FC, Vallender EJ, Wang H, Tzeng CS, Li WH. Genomic divergence between human and chimpanzee estimated from large-scale alignments of genomic sequences. J Hered. 2001; 92(6): 481–9. [PubMed: 11948215]

Chen GL, Novak MA, Hakim S, Xie Z, Miller GM. Tryptophan hydroxylase-2 gene polymorphisms in rhesus monkeys: association with hypothalamic-pituitary-adrenal axis function and in vitro gene expression. Mol Psychiatry. 2006; 11(10):914–28. [PubMed: 16847459]

Chen GL, Vallender EJ, Miller GM. Functional characterization of the human TPH2 5′ regulatory region: untranslated region and polymorphisms modulate gene expression in vitro. Hum Genet. 2008; 122(6):645–57. [PubMed: 17972101]

Chimpanzee Sequencing and Analysis Consortium. Initial sequence of the chimpanzee genome and comparison with the human genome. Nature. 2005; 437(7055):69–87. [PubMed: 16136131]

Clark DA, Mitra PP, Wang SS. Scalable architecture in mammalian brains. Nature. 2001; 411(6834): 189–93. [PubMed: 11346794]

Craig IW, Halton KE. Genetics of human aggressive behaviour. Hum Genet. 2009; 126(1):101–13. [PubMed: 19506905]

D'Souza UM, Craig IW. Functional genetic polymorphisms in serotonin and dopamine gene systems and their significance in behavioural disorders. Prog Brain Res. 2008; 172:73–98. [PubMed: 18772028]

Ding YC, Chi HC, Grady DL, Morishima A, Kidd JR, Kidd KK, Flodman P, Spence MA, Schuck S, Swanson JM, et al. Evidence of positive selection acting at the human dopamine receptor D4 gene locus. Proc Natl Acad Sci U S A. 2002; 99(1):309–14. [PubMed: 11756666]

Dong D, He G, Zhang S, Zhang Z. Evolution of olfactory receptor genes in primates dominated by birth-and-death process. Genome Biol Evol. 2009; 1:258–64. [PubMed: 20333195]

Eizirik E, Yuhki N, Johnson WE, Menotti-Raymond M, Hannah SS, O'Brien SJ. Molecular genetics and evolution of melanism in the cat family. Curr Biol. 2003; 13(5):448–53. [PubMed: 12620197]

Elsik CG, Tellam RL, Worley KC, Gibbs RA, Muzny DM, Weinstock GM, Adelson DL, Eichler EE, Elnitski L, Guigo R, et al. The genome sequence of taurine cattle: a window to ruminant biology and evolution. Science. 2009; 324(5926):522–8. [PubMed: 19390049]

Enard W, Fassbender A, Model F, Adorjan P, Paabo S, Olek A. Differences in DNA methylation patterns between humans and chimpanzees. Curr Biol. 2004; 14(4):R148–9. [PubMed: 15027464]

Enard W, Khaitovich P, Klose J, Zollner S, Heissig F, Giavalisco P, Nieselt-Struwe K, Muchmore E, Varki A, Ravid R, et al. Intra- and interspecific variation in primate gene expression patterns. Science. 2002; 296(5566):340–3. [PubMed: 11951044]

Farcas R, Schneider E, Frauenknecht K, Kondova I, Bontrop R, Bohl J, Navarro B, Metzler M, Zischler H, Zechner U, et al. Differences in DNA methylation patterns and expression of the CCRK gene in human and nonhuman primate cortices. Mol Biol Evol. 2009; 26(6):1379–89. [PubMed: 19282513]

Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, Belmont JW, Boudreau A, Hardenbol P, Leal SM, et al. A second generation human haplotype map of over 3.1 million SNPs. Nature. 2007; 449(7164):851–61. [PubMed: 17943122]

Gagneux P, Varki A. Genetic differences between humans and great apes. Mol Phylogenet Evol. 2001; 18(1):2–13. [PubMed: 11161737]

Gibbs RA, Rogers J, Katze MG, Bumgarner R, Weinstock GM, Mardis ER, Remington KA, Strausberg RL, Venter JC, Wilson RK, et al. Evolutionary and biomedical insights from the rhesus macaque genome. Science. 2007; 316(5822):222–34. [PubMed: 17431167]

Gibbs RA, Weinstock GM, Metzker ML, Muzny DM, Sodergren EJ, Scherer S, Scott G, Steffen D, Worley KC, Burch PE, et al. Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature. 2004; 428(6982):493–521. [PubMed: 15057822]

Gilad Y, Man O, Glusman G. A comparison of the human and chimpanzee olfactory receptor gene repertoires. Genome Res. 2005; 15(2):224–30. [PubMed: 15687286]

Goldman N, Yang Z. A codon-based model of nucleotide substitution for protein-coding DNA sequences. Mol Biol Evol. 1994; 11(5):725–36. [PubMed: 7968486]

Gonzalez E, Kulkarni H, Bolivar H, Mangano A, Sanchez R, Catano G, Nibbs RJ, Freedman BI, Quinones MP, Bamshad MJ, et al. The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. Science. 2005; 307(5714):1434–40. [PubMed: 15637236]

Grantham R. Amino acid difference formula to help explain protein evolution. Science. 1974; 185(4154):862–4. [PubMed: 4843792]

Graur D. Amino acid composition and the evolutionary rates of protein-coding genes. J Mol Evol. 1985; 22(1):53–62. [PubMed: 3932664]

Haygood R, Babbitt CC, Fedrigo O, Wray GA. Contrasts between adaptive coding and noncoding changes during human evolution. Proc Natl Acad Sci U S A. 2010; 107(17):7853–7. [PubMed: 20385805]

Haygood R, Fedrigo O, Hanson B, Yokoyama KD, Wray GA. Promoter regions of many neural- and nutrition-related genes have experienced positive selection during human evolution. Nat Genet. 2007; 39(9):1140–4. [PubMed: 17694055]

Hoffman MM, Birney E. An effective model for natural selection in promoters. Genome Res. 2010; 20(5):685–92. [PubMed: 20194951]

Hudson RR, Kreitman M, Aguade M. A test of neutral molecular evolution based on nucleotide data. Genetics. 1987; 116(1):153–9. [PubMed: 3110004]

Inoue-Murayama M, Hibino E, Iwatsuki H, Inoue E, Hong KW, Nishida T, Hayasaka I, Ito S, Murayama Y. Interspecies and intraspecies variations in the serotonin transporter gene intron 3 VNTR in nonhuman primates. Primates. 2008; 49(2):139–42. [PubMed: 18204817]

International HapMap Consortium. The International HapMap Project. Nature. 2003; 426(6968):789–96. [PubMed: 14685227]

International HapMap Consortium. A haplotype map of the human genome. Nature. 2005; 437(7063): 1299–320. [PubMed: 16255080]

International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature. 2008; 455(7210):237–41. [PubMed: 18668038]

Kerns JA, Cargill EJ, Clark LA, Candille SI, Berryere TG, Olivier M, Lust G, Todhunter RJ, Schmutz SM, Murphy KE, et al. Linkage and segregation analysis of black and brindle coat color in domestic dogs. Genetics. 2007; 176(3):1679–89. [PubMed: 17483404]

Khaitovich P, Hellmann I, Enard W, Nowick K, Leinweber M, Franz H, Weiss G, Lachmann M, Paabo S. Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. Science. 2005; 309(5742):1850–4. [PubMed: 16141373]

Khaitovich P, Muetzel B, She X, Lachmann M, Hellmann I, Dietzsch J, Steigele S, Do HH, Weiss G, Enard W, et al. Regional patterns of gene expression in human and chimpanzee brains. Genome Res. 2004; 14(8):1462–73. [PubMed: 15289471]

King MC, Wilson AC. Evolution at two levels in humans and chimpanzees. Science. 1975; 188(4184): 107–16. [PubMed: 1090005]

Kwiatkowski DP. How malaria has affected the human genome and what human genetics can teach us about malaria. Am J Hum Genet. 2005; 77(2):171–92. [PubMed: 16001361]

Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, et al. Initial sequencing and analysis of the human genome. Nature. 2001; 409(6822): 860–921. [PubMed: 11237011]

Lesch KP, Meyer J, Glatz K, Flugge G, Hinney A, Hebebrand J, Klauck SM, Poustka A, Poustka F, Bengel D, et al. The 5-HT transporter gene-linked polymorphic region (5-HTTLPR) in evolutionary perspective: alternative biallelic variation in rhesus monkeys. Rapid communication. J Neural Transm. 1997; 104(11–12):1259–66. [PubMed: 9503271]

Lewontin RC, Krakauer J. Distribution of gene frequency as a test of the theory of the selective neutrality of polymorphisms. Genetics. 1973; 74(1):175–95. [PubMed: 4711903]

Li WH, Wu CI, Luo CC. A new method for estimating synonymous and nonsynonymous rates of nucleotide substitution considering the relative likelihood of nucleotide and codon changes. Mol Biol Evol. 1985; 2(2):150–74. [PubMed: 3916709]

Lin L, Shen S, Jiang P, Sato S, Davidson BL, Xing Y. Evolution of alternative splicing in primate brain transcriptomes. Hum Mol Genet. 2010; 19(15):2958–73. [PubMed: 20460271]

Lindblad-Toh K, Wade CM, Mikkelsen TS, Karlsson EK, Jaffe DB, Kamal M, Clamp M, Chang JL, Kulbokas EJ 3rd, Zody MC, et al. Genome sequence, comparative analysis and haplotype structure of the domestic dog. Nature. 2005; 438(7069):803–19. [PubMed: 16341006]

Madras BK, Miller GM, Fischman AJ. The dopamine transporter and attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57(11):1397–409. [PubMed: 15950014]

Majerus ME, Mundy NI. Mammalian melanism: natural selection in black and white. Trends Genet. 2003; 19(11):585–8. [PubMed: 14585605]

Margulies EH, Vinson JP, Miller W, Jaffe DB, Lindblad-Toh K, Chang JL, Green ED, Lander ES, Mullikin JC, Clamp M. An initial strategy for the systematic identification of functional elements in the human genome by low-redundancy comparative sequencing. Proc Natl Acad Sci U S A. 2005; 102(13):4795–800. [PubMed: 15778292]

McDonald JH, Kreitman M. Adaptive protein evolution at the Adh locus in Drosophila. Nature. 1991; 351(6328):652–4. [PubMed: 1904993]

Miller GM, Bendor J, Tiefenbacher S, Yang H, Novak MA, Madras BK. A mu-opioid receptor single nucleotide polymorphism in rhesus monkey: association with stress response and aggression. Mol Psychiatry. 2004; 9(1):99–108. [PubMed: 14699447]

Miller GM, De La Garza R 2nd, Novak MA, Madras BK. Single nucleotide polymorphisms distinguish multiple dopamine transporter alleles in primates: implications for association with attention deficit hyperactivity disorder and other neuropsychiatric disorders. Mol Psychiatry. 2001; 6(1):50–8. [PubMed: 11244485]

Miller GM, Madras BK. Polymorphisms in the 3′-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. Mol Psychiatry. 2002; 7(1):44–55. [PubMed: 11803445]

Miller, GM.; Mardras, BK. Similarities of Non-human Primates to Humans: Genetic Variations and Phenotypic Associations Common to Rhesus Monkeys and Humans. In: Wolfe-Coote, S., editor. The Laboratory Primate. San Diego, CA: Elsevier Academic Press; 2005.

Mundy NI. A window on the genetics of evolution: MC1R and plumage colouration in birds. Proc Biol Sci. 2005; 272(1573):1633–40. [PubMed: 16087416]

Nei M, Gojobori T. Simple methods for estimating the numbers of synonymous and nonsynonymous nucleotide substitutions. Mol Biol Evol. 1986; 3(5):418–26. [PubMed: 3444411]

Neill D. Cortical evolution and human behaviour. Brain Res Bull. 2007; 74(4):191–205. [PubMed: 17720540]

Nielsen R. Molecular signatures of natural selection. Annu Rev Genet. 2005; 39:197–218. [PubMed: 16285858]

Oleksyk TK, Smith MW, O'Brien SJ. Genome-wide scans for footprints of natural selection. Philos Trans R Soc Lond B Biol Sci. 2010; 365(1537):185–205. [PubMed: 20008396]

Perry GH, Dominy NJ, Claw KG, Lee AS, Fiegler H, Redon R, Werner J, Villanea FA, Mountain JL, Misra R, et al. Diet and the evolution of human amylase gene copy number variation. Nat Genet. 2007; 39(10):1256–60. [PubMed: 17828263]

Pollard KS, Salama SR, King B, Kern AD, Dreszer T, Katzman S, Siepel A, Pedersen JS, Bejerano G, Baertsch R, et al. Forces shaping the fastest evolving regions in the human genome. PLoS Genet. 2006; 2(10):e168. [PubMed: 17040131]

Pontius JU, Mullikin JC, Smith DR, Lindblad-Toh K, Gnerre S, Clamp M, Chang J, Stephens R, Neelam B, Volfovsky N, et al. Initial sequence and comparative analysis of the cat genome. Genome Res. 2007; 17(11):1675–89. [PubMed: 17975172]

Popesco MC, Maclaren EJ, Hopkins J, Dumas L, Cox M, Meltesen L, McGavran L, Wyckoff GJ, Sikela JM. Human lineage-specific amplification, selection, and neuronal expression of DUF1220 domains. Science. 2006; 313(5791):1304–7. [PubMed: 16946073]

Portin P. Evolution of man in the light of molecular genetics: a review. Part II. Regulation of gene function, evolution of speech and of brains. Hereditas. 2008; 145(3):113–25. [PubMed: 18667001]

Prabhakar S, Noonan JP, Paabo S, Rubin EM. Accelerated evolution of conserved noncoding sequences in humans. Science. 2006; 314(5800):786. [PubMed: 17082449]

Richard AF, Goldstein FJ, Dewar RE. Weed macaques: the evolutionary inplications of macaque feeding ecology. Int J Primatol. 1989; 19:569–594.

Rightmire GP. Brain size and encephalization in early to Mid-Pleistocene Homo. Am J Phys Anthropol. 2004; 124(2):109–23. [PubMed: 15160365]

Rilling JK, Insel TR. The primate neocortex in comparative perspective using magnetic resonance imaging. J Hum Evol. 1999; 37(2):191–223. [PubMed: 10444351]

Rockman MV, Hahn MW, Soranzo N, Zimprich F, Goldstein DB, Wray GA. Ancient and recent positive selection transformed opioid cis-regulation in humans. PLoS Biol. 2005; 3(12):e387. [PubMed: 16274263]

Rosenberg NA. Standardized subsets of the HGDP-CEPH Human Genome Diversity Cell Line Panel, accounting for atypical and duplicated samples and pairs of close relatives. Ann Hum Genet. 2006; 70(Pt 6):841–7. [PubMed: 17044859]

Roussos P, Giakoumaki SG, Bitsios P. Cognitive and emotional processing in high novelty seeking associated with the L-DRD4 genotype. Neuropsychologia. 2009; 47(7):1654–9. [PubMed: 19397860]

Ruff CB, Trinkaus E, Holliday TW. Body mass and encephalization in Pleistocene Homo. Nature. 1997; 387(6629):173–6. [PubMed: 9144286]

Schoenemann PT, Sheehan MJ, Glotzer LD. Prefrontal white matter volume is disproportionately larger in humans than in other primates. Nat Neurosci. 2005; 8(2):242–52. [PubMed: 15665874]

Shimada MK, Hayakawa Y, Takeda J, Gojobori T, Imanishi T. A comprehensive survey of human polymorphisms at conserved splice dinucleotides and its evolutionary relationship with alternative splicing. BMC Evol Biol. 2010; 10:122. [PubMed: 20433709]

Soeby K, Larsen SA, Olsen L, Rasmussen HB, Werge T. Serotonin transporter: evolution and impact of polymorphic transcriptional regulation. Am J Med Genet B Neuropsychiatr Genet. 2005; 136B(1):53–7. [PubMed: 15858819]

Soranzo N, Bufe B, Sabeti PC, Wilson JF, Weale ME, Marguerie R, Meyerhof W, Goldstein DB. Positive selection on a high-sensitivity allele of the human bitter-taste receptor TAS2R16. Curr Biol. 2005; 15(14):1257–65. [PubMed: 16051168]

Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, et al. Large recurrent microdeletions associated with schizophrenia. Nature. 2008; 455(7210):232–6. [PubMed: 18668039]

Striedter GF. Progress in the study of brain evolution: from speculative theories to testable hypotheses. Anat Rec. 1998; 253(4):105–12. [PubMed: 9740033]

Suomi SJ. Risk, resilience, and gene x environment interactions in rhesus monkeys. Ann N Y Acad Sci. 2006; 1094:52–62. [PubMed: 17347341]

Tajima F. Statistical method for testing the neutral mutation hypothesis by DNA polymorphism. Genetics. 1989; 123(3):585–95. [PubMed: 2513255]

Tang H, Wyckoff GJ, Lu J, Wu CI. A universal evolutionary index for amino acid changes. Mol Biol Evol. 2004; 21(8):1548–56. [PubMed: 15140949]

Thornton KR, Jensen JD, Becquet C, Andolfatto P. Progress and prospects in mapping recent selection in the genome. Heredity. 2007; 98(6):340–8. [PubMed: 17473869]

Vallender EJ. Exploring the origins of the human brain through molecular evolution. Brain Behav Evol. 2008; 72(2):168–77. [PubMed: 18836262]

Vallender EJ, Mekel-Bobrov N, Lahn BT. Genetic basis of human brain evolution. Trends Neurosci. 2008a; 31(12):637–44. [PubMed: 18848363]

Vallender EJ, Priddy CM, Chen GL, Miller GM. Human expression variation in the mu-opioid receptor is paralleled in rhesus macaque. Behav Genet. 2008b; 38(4):390–5. [PubMed: 18379868]

Vallender EJ, Priddy CM, Hakim S, Yang H, Chen GL, Miller GM. Functional variation in the 3′ untranslated region of the serotonin transporter in human and rhesus macaque. Genes Brain Behav. 2008c

Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, et al. The sequence of the human genome. Science. 2001; 291(5507):1304–51. [PubMed: 11181995]

Voight BF, Kudaravalli S, Wen X, Pritchard JK. A map of recent positive selection in the human genome. PLoS Biol. 2006; 4(3):e72. [PubMed: 16494531]

Wang E, Ding YC, Flodman P, Kidd JR, Kidd KK, Grady DL, Ryder OA, Spence MA, Swanson JM, Moyzis RK. The genetic architecture of selection at the human dopamine receptor D4 (DRD4) gene locus. Am J Hum Genet. 2004; 74(5):931–44. [PubMed: 15077199]

Waterston RH, Lindblad-Toh K, Birney E, Rogers J, Abril JF, Agarwal P, Agarwala R, Ainscough R, Alexandersson M, An P, et al. Initial sequencing and comparative analysis of the mouse genome. Nature. 2002; 420(6915):520–62. [PubMed: 12466850]

Wendland JR, Lesch KP, Newman TK, Timme A, Gachot-Neveu H, Thierry B, Suomi SJ. Differential functional variability of serotonin transporter and monoamine oxidase a genes in macaque species displaying contrasting levels of aggression-related behavior. Behav Genet. 2006; 36(2): 163–72. [PubMed: 16402281]

Wong WS, Nielsen R. Detecting selection in noncoding regions of nucleotide sequences. Genetics. 2004; 167(2):949–58. [PubMed: 15238543]

Wooding S, Bufe B, Grassi C, Howard MT, Stone AC, Vazquez M, Dunn DM, Meyerhof W, Weiss RB, Bamshad MJ. Independent evolution of bitter-taste sensitivity in humans and chimpanzees. Nature. 2006; 440(7086):930–4. [PubMed: 16612383]

Wooding S, Kim UK, Bamshad MJ, Larsen J, Jorde LB, Drayna D. Natural selection and molecular evolution in PTC, a bitter-taste receptor gene. Am J Hum Genet. 2004; 74(4):637–46. [PubMed: 14997422]

Yang Z, Nielsen R. Estimating synonymous and nonsynonymous substitution rates under realistic evolutionary models. Mol Biol Evol. 2000; 17(1):32–43. [PubMed: 10666704]

Zhang F, Gu W, Hurles ME, Lupski JR. Copy number variation in human health, disease, and evolution. Annu Rev Genomics Hum Genet. 2009; 10:451–81. [PubMed: 19715442]

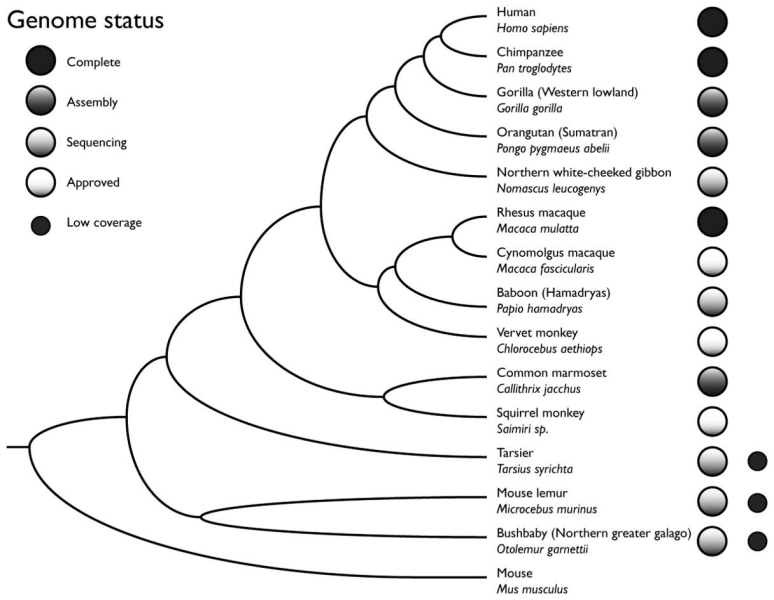

Figure 1.

Phylogeny and status of primate genomics. The status of the primate genomes currently under investigation as of summer 2010, population-specific studies are not included, nor are privately-funded efforts currently not released to the public. The phylogeny represents an approximation of primate relationships.