Human Molecular Genetics, 2004, Vol. 13, No. Review Issue 2 **R245–R254**
doi:10.1093/hmg/ddh253

Positive selection on the human genome

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Received July 6, 2004; Revised and Accepted July 26, 2004

Positive selection has undoubtedly played a critical role in the evolution of *Homo sapiens*. Of the many phenotypic traits that define our species—notably the enormous brain, advanced cognitive abilities, complex vocal organs, bipedalism and opposable thumbs—most (if not all) are likely the product of strong positive selection. Many other aspects of human biology not necessarily related to the 'branding' of our species, such as host–pathogen interactions, reproduction, dietary adaptation and physical appearance, have also been the substrate of varying levels of positive selection. Comparative genetics/genomics studies in recent years have uncovered a growing list of genes that might have experienced positive selection during the evolution of human and/or primates. These genes offer valuable inroads into understanding the biological processes specific to humans, and the evolutionary forces that gave rise to them. Here, we present a comprehensive review of these genes, and their implications for human evolution.

Traditionally, studies of human biology have operated under the assumption, either explicitly or implicitly, that much of the molecular processes in humans (and the genes that underlie them) are conserved in other species. The pervasiveness of this sentiment is perhaps best reflected in the wide reliance on model organisms, from microbes all the way up to non-human primates, in the studies of human biology and disease. The assumption of evolutionary conservation, though powerful, has a key deficiency—it fails to address the many aspects of human biology and disease that differ significantly from other species. Although this deficiency has long been recognized, it is only recently that there has been an upsurge of interest in characterizing human-specific traits at the molecular and genetic levels.

In studying human-specific traits, it is necessary to investigate the selective forces that gave rise to them. Evolutionary biologists have typically invoked two types of selective forces that shape the evolution of species. One is purifying selection, which favors the conservation of existing phenotypes. The other is positive selection (also known as Darwinian selection), which promotes the emergence of new phenotypes. Positive selection can leave a set of telltale signatures in the genes under its influence, such as the rapid divergence of functional sites between species and the depression of polymorphism within species (1–3). On the basis of these signatures, investigators are beginning to identify likely target genes of positive selection in the human genome. The identification of these genes represents the first, and necessary, step toward gaining molecular and genetic insights into the evolution of human-specific traits. In this article, we review genes shown to bear evidence of having been the substrate of positive selection in the evolution of humans and/or primates (Table 1). Our emphasis is to provide a comprehensive listing of these genes, and for that reason, we will include genes even if the evidence of positive selection is only suggestive. Given that the number of genes is fairly large, the amount of discussion devoted to each gene will be limited. We therefore encourage readers to refer to the primary literature if they wish to assess the strength of evidence for any individual gene.

For clarity, we will divide genes into several functional domains and consider each domain under a separate heading. We note, however, that these genes can also be coarsely sorted into two categories on the basis of their relevance to the evolution of human-specific traits. One is genes involved in biological functions typically associated with positive selection across a wide range of species, including host–pathogen interactions, reproduction, dietary adaptation and appearance. For these genes, it should come as no surprise that they are also the target of positive selection in humans, and their involvement in human-specific traits may be limited. The other category is genes belonging to biological domains that bear defining differences between humans and other species, and for which positive selection appears to have operated more intensely in the lineage leading to

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Table 1. Genes showing evidence of positive selection in humans and/or primates

Category	Gene	Lineage	References
Host–pathogen interations	ABO blood group	Human/Primates	28,29
	APOBEC3G	Primates	25
	Beta globin (*HBB*)	Recent human	40
	Beta-defensin	Primates	14,15
	CD45	Catarrhines	12
	CD59	Humans	13
	Chemokine receptor 5 (*CCR5*)	Human	24,131
	Cytidine monophospho-*N*-acetylneuraminic acid hydroxylase (*CMAH*)	Human	34,35
	Duffy blood group	Recent human	41,42
	Eosinophil cationic protein (*ECP*)	Catarrhines	27
	Glucose-6-phosphate dehydrogenase (*G6PD*)	Recent human	43–46
	Glycophorin A	Recent human/Primates	32,33
	Immunoglobulin A	Primates	22
	Immunoglobulin heavy chain	Mammals	20,21
	Interleukin 2 (*IL2*)	Mammals	17,18
	Interleukin 4 (*IL4*)	Human	19
	Killer cell inhibitory receptors (*KIR*)	Human	23
	Major histocompatibility complex (*MHC*)	Mammals	5–8
	Pyrin	Recent human	26
	Rh blood group	Hominids	31
	Sialic acid-binding immunoglobulin-like lectin 9 (*SIGLEC9*)	Human	36
	Sialic acid-binding immunoglobulin-like lectin-like protein 1 (*SIGLECL1*)	Human	37
	Tumor necrosis factor ligand superfamily, member 5 (*TNFSF5*)	Recent human	46
Reproduction	Chorionic gonadotropin	Primates	60
	Chromodomain protein Y (*CDY*)	Primates	58
	Deleted in azoospermia (*DAZ*)	Primates	55
	Fertilin	Primates	53
	Oviductal glycoprotein 1 (*OVGP1*)	Mammals	59
	Protamine 1 (*PRM1*)	Primates/Mammals	32,49
	Protamine 2 (*PRM2*)	Primates/Mammals	32
	Semenogelin 1 and 2 (*SEMG1*, *SEMG2*)	Primates	51
	Sex-determining region Y (*SRY*)	Primates/Mammals	57
	Sperm associated cation channel 1 (*CATSPER1*)	Primates	52
	Sperm protein associated with the nucleus, X-chromosome (*SPANX*)	Hominids	56
	Transition protein 2 (*TNP2*)	Primates/Mammals	32
	Zona pellucida glycoprotein 2 (*ZP2*)	Mammals	59
	Zona pellucida glycoprotein 3 (*ZP3*)	Mammals	59
Dietary adaptation	Alanine:glyoxylate aminotransferase	Anthropoids	69
	Aldehyde dehydrogenase 2 (*ALDH2*)	Recent human	70
	Lactase (*LCT*)	Recent human	72,73
	Lysozyme (*LYZ*)	Human/Primates	64,65
Appearance	Melanocortin 1 receptor (*MC1R*)	Recent human/Mammals	79–81
Sensory systems	MAS-related genes (*MRG*)	Primates	95
	Olfactory receptors (*OR*)	Human/Primates	92,93
	Red and green opsins	Human/Primates	85,86
	Taste receptor type 1 member 3 (*TAS1R3*)	Primates	87
	Taste receptor type 2 (*TAS2R*)	Primates	88
	Taste receptor type 2 member 38 (*TAS2R38*)	Recent human	89
	Type 1 vomeronasal receptor-like (*V1RL*)	Primates	94
Behavior	Dopamine receptor D4 (*DRD4*)	Primates	97,98
	Forkhead box P2 (*FOXP2*)	Human	101,102
	Monoamine oxidase A (*MAOA*)	Human	96
Brain anatomy	Abnormal spindle-like microcephaly associated (*ASPM*)	Human	107–109
	Microcephalin (*MCPH1*)	Human	110,111
	Myosin heavy chain 16 (*MYH16*)	Hominine	112
Miscellaneous	Angiogenin (*ANG*)	Primates	115
	Breast cancer 1 (*BRCA1*)	Human	113,114
	Cytochrome *c* oxidase subunit 4 (*COX4*)	Human/Primates	117
	Cytochrome *c* oxidase subunit 7a (*COX7A*)	Primates	118
	Cytochrome *c* oxidase subunit 7c (*COX7C*)	Primates	13
	Cytochrome *c* oxidase subunit 8 (*COX8*)	Human/Primates	13
	Forkhead box D4 (*FOXD4*)	Hominids	123
	Morpheus	Hominids	121

humans than in other lineages. These include genes associated with behavior, brain anatomy, and to some extent, the sensory systems. These genes are particularly relevant to understanding the evolution of biological traits that distinguish the human species, such as increased brain size and advanced cognitive abilities.

GENES LINKED TO POSITIVE SELECTION

Host–pathogen interactions

Van Valen's Red Queen hypothesis has long served as a theoretical framework for understanding the evolutionary dynamics of host–pathogen interactions (4). It states that the coevolution of two intensely competing species resembles an arms race. Both species evolve continuously to gain advantage over their rival, and yet the long-term outcome is evolutionary stasis, whereby the two species continue to coexist (and do battle) without a clear winner. In the case of host–pathogen coevolution, the pathogen is under strong selection to constantly devise new strategies for gaining access to the host while evading its defense system, whereas the host is under selection to deny access to the pathogen and to neutralize it.

Numerous studies in diverse taxa have indeed shown that genes involved in host–pathogen interactions are a frequent substrate of intense positive selection. The first study of positive selection in humans was on the genes encoding the major histocompatibility complex (MHC), which is a group of related proteins involved in antigen presentation (5–9). Overdominant selection at the *MHC* locus has been demonstrated in many species, and the most striking manifestation in humans is the sharing of ancestral polymorphisms with other hominoid taxa (10,11). The exact nature of the selective pressure on *MHC* is not completely understood, but selection appears to favor heterozygotes and low-frequency alleles, leading to high levels of allelic diversity at the *MHC* locus.

Several leukocyte antigens have also been found to have likely experienced positive Darwinian selection. One of these is CD45, or the leukocyte common antigen, which has been shown recently to be evolving rapidly in catarrhine species (i.e. old world monkeys, apes and humans) (12). Another cell surface antigen, CD59, thought to be involved in T-cell maturation, also exhibits the signature of positive selection in the lineage leading from catarrhine ancestors to humans (13).

Selection on immune response genes is by no means limited to *MHC* and leukocyte antigens. Other examples include β-defensins, which function as antimicrobial peptides (14–16); interleukins, which provide cell–cell signaling in the immune system (17–19); immunoglobulins, which are the antibodies that neutralize foreign antigens (20–22); killer cell inhibitory receptors, which regulate early antiviral response (23); CC chemokine receptor 5 (CCR5), which regulates leukocyte activity (24) and APOBEC3G, a cytidine deaminase with apparent anti-viral function (25). The *pyrin* gene, which appears to function in innate immunity and whose mutations are associated with familial Mediterranean fever, also shows signatures of episodic positive selection (26). Eosinophil cationic protein, a novel catarrhine protein generated by a duplication event, has been show to have developed a novel anti-pathogenic function, likely as the result of positive selection (27).

Cell surface molecules, especially those on blood cells, can serve as convenient (and unwitting) gateways for pathogen entry into cells. These molecules are therefore intimately involved in host–pathogen interactions even though they do not necessarily participate directly in immune response. Not surprisingly, genes encoding these cell surface molecules are often subject to positive selection. One example is CCR5 mentioned above, which regulates immune cell activity, but is also a key receptor for entry of the HIV virus (24). The ABO blood group gene, which encodes cell surface proteins on erythrocytes (i.e. red blood cells), has long been thought to be a substrate of positive selection (28), and has recently been shown to have experienced balancing selection for the last 3 million years in many primate species (29). The Rh blood group genes, which also encode erythrocyte surface proteins, have long been studied in the context of selection (30), with recent evidence suggesting that positive selection has operated on these genes in the lineage leading to apes (31). Additional examples of cell surface molecules subject to positive selection include glycophorin A, a glycoprotein solely expressed on the erythrocyte surface and implicated in pathogen binding (32,33), and the Duffy antigen which is discussed later on the context of malaria resistance.

One striking finding concerning cell surface molecules is the complete absence in humans of *N*-glycolylneuraminic acid (Neu5Gc), one of the two major sialic acids that function as glycoconjugates on most mammalian cell surfaces (the other being *N*-acetylneuraminic acid, or Neu5Ac). Humans lack endogenous Neu5Gc (but retain Neu5Ac) owing to a loss-of-function mutation in the gene encoding one of the enzymes in the Neu5Gc synthetic pathway, CMP-Neu5Achydroxylase (CMAH). This mutation apparently occurred in the human lineage after it diverged from other great apes (34,35). Interestingly, the loss of Neu5Gc during human evolution appears to have triggered additional adaptive changes in members of the Siglec protein family known to be involved in sialic acid binding. The most notable example is Siglec-9 (and perhaps several other related members of the Siglec family), which preferentially binds Neu5Gc in non-human hominoids, but which recognizes Neu5Ac (in addition to Neu5Gc) in humans (36). Another example is Siglec-L1, for which an amino acid substitution in humans (but not in other great apes) resulted in the loss a binding specificity to Neu5Gc (37). As yet, it is not clear whether these human-specific mutations are driven by positive selection. However, the potential role of cell-surface sialic acids in host–pathogen interactions makes the scenario of positive selection a rather feasible one (38,39).

Among human parasites, those causing malaria, *Plasmodium falciparum* and *P. vivax*, seem to have accorded very recent and strong selective pressure on the cellular phenotype of human erythrocytes. The evolution of a number of erythrocyte genes have now been linked to malaria resistance. The classic example is the mutant allele of β-globin, which causes sickle-cell anemia when homozygous, but imparts some protection against malaria when heterozygous. In malaria-infested regions of the world, particularly sub-Saharan Africa, the mutant allele of β-globin has reached

appreciable frequencies under strong selection, despite its fatal effect in homozygotes (40). The Duffy antigen is present on the erythrocyte surface and serves as a receptor for *P. vivax*. Null alleles of the *Duffy* locus, which impart resistance to *P. vivax*, appear to have been driven to near fixation by positive selection in sub-Saharan Africa (41,42). Multiple G6PD-deficiency alleles, which confer some protection against malaria, seem to have emerged roughly 10 000 years ago, and rose to appreciable frequencies under positive selection in regions with high malaria prevalence (43–46). A promoter variant of the CD40 ligand gene, *TNFSF5*, which also confers some malaria resistance, was similarly shown to have risen to high frequency quickly under positive selection (46).

It is perhaps not surprising, given the potential for strong selective pressure, that genetic programs controlling host–pathogen interactions in humans and other species are littered with signatures of positive selection (47).

Reproduction

Like genes implicated in host–pathogen interactions, genes involved in reproduction have also been shown to be under strong positive selection across taxa (48). Because of the large reproductive skew in males (i.e. high variance in reproductive success from male to male), selection on male reproductive processes is particularly intense. Meta-analysis of the human sperm proteome has already provided evidence that these genes may have evolved under positive selection (32,48), and more in-depth analyses of specific sperm-related genes are confirming this pattern. Studies of protamines (32,49,50), transition protein 2 (32), semenogelins (51), sperm ion channels (52) and fertilin (53) have all shown evidence of positive selection in humans. Many other genes of lesser known biochemical functions, but which are expressed predominantly in spermatogenic cells (and are linked to male infertility in some cases), have also been suggested to be subject to positive selection (54–58). The prevalence of positive selection on male reproductive genes is therefore not unlike genes involved in host–pathogen interactions.

A number of female reproductive genes have also been shown to be under positive selection. Two of these encode the zona pellucida glyoproteins ZP2 and ZP3, which make up the egg's protective coat and are intimately involved in sperm–egg recognition during fertilization (59). Another gene encodes the oviductal glycoprotein (OGP), which is also implicated in fertilization (59). It is believed that positive selection on these fertilization-related proteins may stem from the 'arms race' between sperm and egg, whereby the rapid evolution of sperm-associated proteins involved in sperm–egg recognition drives the rapid evolution of corresponding egg proteins (59).

Another female reproductive protein under positive selection is chorionic gonadotropin (CG), which is a key hormone for establishing pregnancy in humans and other simian primates (60). Why this gene should be under positive selection is unclear. It is interesting to note, however, that one of the key reproductive changes in the evolution of humans is increased gestation time. Although there is no evidence to suggest that this has any bearing on the evolution of CG or other female reproductive proteins, the possibility of a link is tantalizing.

Dietary adaptation

The adaptation to new diet is a major driving force in the evolution of a species. Dietary changes during the evolution of various primate species, particularly humans, have been well documented over the years (61,62), and a number of genes have been implicated in diet-driven positive selection. A well-studied example can be found in a pancreatic ribonuclease in old-world monkey species (63). In this species, the protein has evolved the ability to better digest bacterial DNA as a result of the monkey's changing diet. Another example is lysozyme, which aids in the degradation of gut bacteria. This protein has been shown to be under positive selection in many primate groups including humans (64,65). The nature of this selection is understood best in the langur monkey, a species that has evolved a foregut fermentation method of digestion similar to that of ruminants (64,66). In humans, the reason for positive selection is less clear, but it has been speculated that a shift towards a more meat-based diet, which likely required changes in the ability to digest bacteria, might have played a role (67,68). This suggestion is given credence by studies of alanine-glyoxylate aminotransferase (*AGT*), a gene with seemingly divergent roles in herbivores and carnivores, and which also shows evidence of positive selection across simian primates (69).

Two other examples of positive selection on diet-related genes have captured the interest of researchers and the public alike. A common mutation allele of the *ALDH2* gene causes the inability of the body to handle large quantities of alcohol, and is thought to be responsible for low alcohol tolerance in certain East Asian populations. The *ALDH2* locus shows some signature of recent selection in humans (70). It has been speculated, though far from proven, that selection might favor the *ALDH2*-definicent allele in East Asian populations because alcohol consumption exacerbates the pathology of hepatitis B infections (which are prevalent in East Asia) (71).

In most species the ability to digest dairy ends with weaning in childhood. However, in some human populations, this ability persists in many adults. A derived allele of the lactase gene has been shown to give adults the ability to continue to process dairy. This allele has been shown to be the substrate of strong positive selection (72,73). Similar to the malaria-resistance genes, the selected allele of the lactase gene appears to have arisen very recently, about 5000–10 000 years ago, coincident with the emergence of dairy farming in Eurasia (73). This allele rose quickly in frequency, presumably because individuals with the allele had a better ability to consume dairy, a clear survival advantage at that time.

Appearance

Among genes involved in the physical appearance of humans, the one with the longest story is *MC1R*, which is involved in skin and hair coloration. The *MC1R* gene encodes the melanocortin receptor, which regulates the production of eumelanin, a cause of black pigmentation. Mutations in the gene have

been reported for many taxa in which coat color variation is observed, including rodents (74,75), cats (76), dogs (77), horses (78) and several primate species (79). As coloration has long been recognized as adaptive, it seems likely that changes in this gene are driven by positive selection. Indeed, in many of the non-human species in which the gene has been studied, coloration adaptations have been invoked as the driving selective force. In humans, however, the evolution of *MC1R* has not been credibly linked to adaptation.

Multiple studies have shown extensive polymorphism at the *MC1R* locus in human populations, most notably three separate mutations resulting in red hair in the Irish, Dutch and Swedes (80,81). However, there remains some question as to whether this polymorphism represents a relaxation of constraint on the gene outside of African populations or whether there is diversifying selection acting upon the gene. Arguing for the former is the observation that these polymorphisms are located exclusively outside of Africa, whereas the argument for the latter revolves around sexual selection (82). One possibility is that there exists an advantage to novelty in attracting mates and that with humans no longer relying on coloration for camouflage or protection against the sun, diversity was selected for. Although the answer is uncertain, it seems feasible that it lies as some combination of both relaxation of constraint and positive selection.

Sensory systems

Human sensory systems have undergone major changes from their primate ancestors, one of the most notable examples being the greater reliance on visual perception. One aspect of increased visual acuity is the emergence of trichromatic vision in great apes including humans, which is accomplished by three separate opsin genes that each preferentially absorb the red, green or blue wavelength. One of these, absorbing blue light, is autosomal and found ubiquitously among primates. The other two opsins are paralogs located on the X-chromosome, with both copies present in the catarrhine clade (old world monkeys, apes and humans) but not in the more basal platyrrhines (new world monkeys). In new world monkeys, the opsin gene on the X-chromosome is a single copy. This gene is polymorphic in some new world monkey species, creating a 'red' and a 'green' allele. Males and homozygous females are dichromatic, similar to most other mammals, whereas heterozygous females are trichromatic like their simian relatives (83,84). The two X-chromosomal paralogs in catarrhines have been suggested to be the subject of adaptive evolution (85,86).

Taste is another sensory modality for which there are ample examples of adaptive evolution. This is perhaps not surprising given the importance of dietary adaptation as we have discussed. The taste receptor for sweetness exhibits interesting functional differences among primates, with the receptor in simians (including humans) capable of recognizing more sweet compounds than is the case for prosimians (87). That this difference is driven by positive selection is not an unreasonable proposition given the dietary differences among primates, but this is yet to be formally proven. The multiple bitter taste receptors underwent amplifications in diverse mammalian lineages including humans, and the rapid sequence divergence of the ligand-binding domains between amplified paralogs is indicative of positive selection (88). It has been argued that both the diversity and the specificity of the bitter receptors in a species are driven by the need to properly discern poisons commonly encountered by the species (88). The ability to taste the bitter compound phenylthiocarbamide (PTC) is a polymorphic trait across all the major human populations. It has been suggested that this polymorphism is maintained in humans by the balancing selection on two major alleles, the taster and the non-taster, of the PTC taste receptor gene (89). As yet, it is unclear why balancing selection should favor the coexistence of both taster and non-taster phenotypes in humans.

Olfactory and pheromone receptor genes have undergone significant evolutionary changes in primates, particularly humans. However, the role of positive selection is much less clear here. In humans, olfaction remains important, but perhaps much less than that in many other mammals including non-human primates. Several studies corroborate this by showing that the human olfactory subgenome has undergone a rapid process of pseudogenization coincident with relaxed functional constraint (90,91). Some studies, however, suggest that a subset of human olfactory genes may have been the subject of positive selection (92,93). For the latter finding, it remains to be seen whether it represents real positive selection on some odorant receptors, or whether it simply reflects the difficulty in distinguishing between positive selection and relaxation of constraint. Indeed, the problem of differentiating positive selection from relaxed constraint, both of which are manifested as the rapid evolution of functional sequences, plagues all studies of positive selection, and is merely exaggerated in the context of olfactory genes. This conundrum is also found in pheromone receptors, where examples of both positive selection and relaxation of functional constraint have been reported (94). It is therefore too soon to state for certain what the overall message is for these genes.

Recent evidence has also shown the effect of positive selection on nociception (i.e. the perception of pain). The MRG nociceptive receptor family has undergone rampant amplification in both the human and murine lineages, and comparisons between paralogs in each lineage showed evidence of strong positive selection in the ligand-binding domains (95). The biological impact of this positive selection remains unclear. However, it seems plausible that selection has favored the functional evolution of this receptor family because of the need to constantly tune the nociceptive properties of a species in response to the changing environment.

Behavior

Many behavioral traits in humans have been shown to have a strong genetic basis, and some of the underlying genes are now beginning to be discovered. Some of these genes have shown evidence of positive selection. One of them was *MAO-A*, which has been associated with aggressive and impulsive behavior (96). Similarly, a gene associated with novelty-seeking and attention deficit hyperactivity disorder, *DRD4*, has also been shown to have undergone recent positive selection (97,98). It is tempting to speculate on why these

genes and their associated traits are under selection by invoking a plausible 'just-so' story, but the true reasons remain unclear and any speculation is likely premature.

One behavioral trait uniquely associated with humans is language. *FOXP2* is a gene implicated in language abilities in humans, with mutations in this gene leading to a language disorder (99). Corroborating the role of *FOXP2* in language are studies showing that the gene may also play a role in song-learning in birds (100). Evolutionary studies showed that *FOXP2* has evolved faster in the human lineage than in several other mammalian species. This, coupled with human polymorphism data, suggests positive selection on this gene during recent human evolution (101,102). This is a tantalizing finding, though additional research is needed to assess whether the gene indeed plays a role in the origin of human language.

Brain development

The evolution of human anatomy is marked most prominently by the dramatic expansion of the brain. This is especially true in the last 2–3 million years of hominid evolution, during which the brain more than tripled in size (103,104). Two genes, *ASPM* and *Microcephalin*, have been implicated in the evolution of brain size. Both genes, when mutated, cause primary microcephaly, a disease characterized by a severe reduction in brain size without any other gross abnormalities (105,106). Given the important, and specific, role of these genes in regulating brain size during development, it is enticing to hypothesize that they are also involved in changes of brain size during evolution.

Going on this hunch, several groups investigated the evolution of *ASPM* and *Microcephalin* in primates and other mammals. They found that, indeed, both genes showed robust evidence of positive selection along the primate lineage leading to humans. In particular, this lineage had much higher rates of protein sequence evolution as compared with lineages leading to non-human primates (107–111). For *ASPM*, the intensity of selection is strongest in later portions of the lineage leading to humans, i.e. from ape ancestors to humans. For *Microcephalin*, selection is most pronounced in earlier portions of the lineage, i.e. from simian ancestors to ape ancestors. This suggests that these two genes might have had differential contributions to brain evolution during different periods of the primate lineage leading to *Homo sapiens*.

Another story revolves around a gene expressed in facial musculature. Myosin heavy chain 16 (MYH16) is a muscle structural protein found primarily in masticatory muscles, and has been shown to have undergone inactivation in the human lineage, since its divergence from chimpanzees (112). This inactivation was estimated at around 2.5 million years ago, or roughly the time when *Homo erectus* arose, though there are contentions over the accuracy of this estimate. *Homo erectus* has significantly reduced masticatory musculature relative to its predecessors (and a coincident increase in cranial size). The loss of *MYH16* has therefore been speculated to have contributed to smaller jaw muscles, which would perhaps free the constraint on the growth of the brain.

Miscellaneous

A number of genes that cannot be readily assigned to the above functional domains have also been linked to positive selection. Two of these, *BRCA1* (113,114) and *angiogenin* (115), are involved in cancer. It is difficult to speculate what adaptive role these genes might have played during evolution. It is interesting to note, however, that *BRCA1* knockout mice show profound defects in nervous system development such as failure of neural tube closure and severely disorganized brain growth (116). This result raises the possibility that positive selection on *BRCA1* was actually directed towards its function in brain development rather than its activity as a tumor suppressor.

Evidence of positive selection has also been found in genes involved in energy production. Four of the cytochrome *c* oxidase subunits exhibit signatures of positive selection in primates (13,117,118). Patterns of mitochondrial DNA (mtDNA) polymorphism in humans are consistent with a role of certain mutations in mtDNA having contributed to human adaptation to northern climates (119,120).

For some genes linked to positive selection, the functions are wholly unknown. One of these is *morpheus*, a gene family found only in humans and African apes, and for which the intensity of positive selection is unrivalled by any other mammalian gene (121). It is worth noting that the *morpheus* genes reside in segmental repeat regions of the genome, where frequent rearrangements (such as duplications, deletions and transpositions) produce extraordinary evolutionary lability (122). Another example is the *FOXD4* gene family which, like *morpheus*, also reside in segmental repeat regions (123). It is possible that repeat regions of the genome, such as subtelomeric and pericentrimeric regions, may have a propensity for harboring rapidly evolving gene families.

Lately, large-scale studies have begun to uncover signatures of positive selection on a genomic scale. Two of these studies surveyed the polymorphism patterns across the human genome for signals of positive selective sweeps (124,125). Another pair of studies used human–chimpanzee comparison as a means to detect positive selection (93,126). Finally, genome-wide expression surveys suggested that the transcriptome of the brain might have changed more rapidly during human evolution than during the evolution of other lineages (127). The efficacy of this coarse-grained whole-genome studies for identifying individual positively selected genes remains to be seen. However, the approach can reveal genome-wide patterns of selection not visible to single-gene studies.

CONCLUSION

As a species, we are inherently curious about our evolutionary origins. One powerful approach for studying human origins at the molecular and genetic levels is to identify genes that have been the target of positive selection. With the rapid expansion of genomic data and the availability of increasingly sophisticated analytical tools, positively selected genes are being identified at an ever faster pace. Judging from the currently available data, it appears that these genes largely belong to a limited number of functional domains. For some of these,

such as host–pathogen interactions and reproduction, the prevalence of positively selected genes is not surprising. For others, such as the regulation of brain development and behavior, the identification of positively selected genes may offer valuable insights into the evolution of those defining human-specific traits such as enlarged brain and highly advanced cognitive abilities.

A question of particular relevance to the understanding of human origins is whether the selective regimes driving human evolution are of exceptional quality or are more typical. One reason to suspect that selection on humans is exceptional is the remarkable rapidity with which some key traits were acquired. Allometrically scaled brain size, for example, grew by an order of magnitude since the lineage leading to humans diverge from old world monkeys some 20–25 million years ago, with a tripling in size occurring in just the last 2–3 million years of hominid evolution (104). Such a dramatic change within such a short period of time is extraordinary for any tissue system, but is particularly so for the brain, an exceedingly complex organ for which the growth in size is necessarily accompanied by the increase in organizational complexity (128). In the theoretical framework of 'punctuated equilibrium' (129), the enlargement of the human brain represents no less a stunning punctuation to an evolutionary equilibrium. The identification of positively selected genes, especially those relating to brain development and cognitive abilities, may offer molecular evidence for the exceptional strength of the selective pressure driving the evolution of our species.

The identification of positively selected genes may also have important implications for human medicine. Many diseases affect humans but not other animals (130). These include infectious diseases such as AIDS, as well as non-infectious conditions such as Alzheimer's disease. Likewise, many therapeutic strategies developed in animal models fail to work in humans. These dissimilarities between humans and other species are ultimately due to molecular programs that have diverged between lineages. Genes that have experienced positive selection may underlie some of these dissimilarities, and variants of these genes in humans may even participate directly in the pathogenesis of diseases.

Although a fair number of genes have already been identified as targets of positive selection during the evolution of humans and/or primates, these are likely to be the tip of the iceberg. As more genes are added and as alterations in gene sequences are mapped to functional changes, the study of positively selected genes may become a mainstream approach to the dissection of human biology and disease.

REFERENCES

1. Kreitman, M. (2000) Methods to detect selection in populations with applications to the human. *Annu. Rev. Genomics Hum. Genet.*, **1**, 539–559.
2. Yang, Z. and Bielawski, J.P. (2000) Statistical methods for detecting molecular adaptation. *Trends Ecol. Evol.*, **15**, 496–503.
3. Bamshad, M. and Wooding, S.P. (2003) Signatures of natural selection in the human genome. *Nat. Rev. Genet.*, **4**, 99–111.
4. Van Valen, L. (1973) A new evolutionary law. *Evol. Theory*, **1**, 1–30.
5. Hughes, A.L. and Nei, M. (1988) Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals overdominant selection. *Nature*, **335**, 167–170.
6. Hughes, A.L. and Nei, M. (1989) Nucleotide substitution at major histocompatibility complex class II loci: evidence for overdominant selection. *Proc. Natl Acad. Sci. USA*, **86**, 958–962.
7. Ohta, T. (1991) Role of diversifying selection and gene conversion in evolution of major histocompatibility complex loci. *Proc. Natl Acad. Sci. USA*, **88**, 6716–6720.
8. Hughes, A.L., Hughes, M.K., Howell, C.Y. and Nei, M. (1994) Natural selection at the class II major histocompatibility complex loci of mammals. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **346**, 359–366; discussion 366–367.
9. Borghans, J.A., Beltman, J.B. and De Boer, R.J. (2004) MHC polymorphism under host-pathogen coevolution. *Immunogenetics*, **55**, 732–739.
10. Fan, W.M., Kasahara, M., Gutknecht, J., Klein, D., Mayer, W.E., Jonker, M. and Klein, J. (1989) Shared class II MHC polymorphisms between humans and chimpanzees. *Hum. Immunol.*, **26**, 107–121.
11. Kupfermann, H., Mayer, W.E., O'HUigin, C., Klein, D. and Klein, J. (1992) Shared polymorphism between gorilla and human major histocompatibility complex DRB loci. *Hum. Immunol.*, **34**, 267–278.
12. Filip, L.C. and Mundy, N.I. (2004) Rapid evolution by positive Darwinian selection in the extracellular domain of the abundant lymphocyte protein CD45 in primates. *Mol. Biol. Evol.*, **21**, 1504–1511.
13. Osada, N., Kusuda, J., Hirata, M., Tanuma, R., Hida, M., Sugano, S., Hirai, M. and Hashimoto, K. (2002) Search for genes positively selected during primate evolution by 5′-end-sequence screening of cynomolgus monkey cDNAs. *Genomics*, **79**, 657–662.
14. Semple, C.A., Rolfe, M. and Dorin, J.R. (2003) Duplication and selection in the evolution of primate beta-defensin genes. *Genome Biol.*, **4**, R31.
15. Boniotto, M., Tossi, A., DelPero, M., Sgubin, S., Antcheva, N., Santon, D., Masters, J. and Crovella, S. (2003) Evolution of the beta defensin 2 gene in primates. *Genes Immun.*, **4**, 251–257.
16. Antcheva, N., Boniotto, M., Zelezetsky, I., Pacor, S., Falzacappa, M.V., Crovella, S. and Tossi, A. (2004) Effects of positively selected sequence variations in human and Macaca fascicularis beta-defensins 2 on antimicrobial activity. *Antimicrob. Agents. Chemother.*, **48**, 685–688.
17. Zhang, J. and Nei, M. (2000) Positive selection in the evolution of mammalian interleukin-2 genes. *Mol. Biol. Evol.*, **17**, 1413–1416.
18. Zelus, D., Robinson-Rechavi, M., Delacre, M., Auriault, C. and Laudet, V. (2000) Fast evolution of interleukin-2 in mammals and positive selection in ruminants. *J. Mol. Evol.*, **51**, 234–244.
19. Rockman, M.V., Hahn, M.W., Soranzo, N., Goldstein, D.B. and Wray, G.A. (2003) Positive selection on a human-specific transcription factor binding site regulating IL4 expression. *Curr. Biol.*, **13**, 2118–2123.
20. Tanaka, T. and Nei, M. (1989) Positive darwinian selection observed at the variable-region genes of immunoglobulins. *Mol. Biol. Evol.*, **6**, 447–459.
21. Ota, T. and Nei, M. (1994) Divergent evolution and evolution by the birth-and-death process in the immunoglobulin VH gene family. *Mol. Biol. Evol.*, **11**, 469–482.
22. Sumiyama, K., Saitou, N. and Ueda, S. (2002) Adaptive evolution of the IgA hinge region in primates. *Mol. Biol. Evol.*, **19**, 1093–1099.
23. Hughes, A.L. (2002) Evolution of the human killer cell inhibitory receptor family. *Mol. Phylogenet. Evol.*, **25**, 330–340.
24. Bamshad, M.J., Mummidi, S., Gonzalez, E., Ahuja, S.S., Dunn, D.M., Watkins, W.S., Wooding, S., Stone, A.C., Jorde, L.B., Weiss, R.B. *et al.* (2002) A strong signature of balancing selection in the 5′ cis-regulatory region of CCR5. *Proc. Natl Acad. Sci. USA*, **99**, 10539–10544.
25. Zhang, J. and Webb, D.M. (2004) Rapid evolution of primate antiviral enzyme APOBEC3G. *Hum. Mol. Genet.*, **13**, 1785–1791.
26. Schaner, P., Richards, N., Wadhwa, A., Aksentijevich, I., Kastner, D., Tucker, P. and Gumucio, D. (2001) Episodic evolution of pyrin in primates: human mutations recapitulate ancestral amino acid states. *Nat. Genet.*, **27**, 318–321.
27. Zhang, J., Rosenberg, H.F. and Nei, M. (1998) Positive Darwinian selection after gene duplication in primate ribonuclease genes. *Proc. Natl Acad. Sci. USA*, **95**, 3708–3713.
28. Livingstone, F.B. (1960) Natural selection, disease, and ongoing human evolution, as illustrated by the ABO blood groups. *Hum. Biol.*, **32**, 17–27.
29. Saitou, N. and Yamamoto, F. (1997) Evolution of primate ABO blood group genes and their homologous genes. *Mol. Biol. Evol.*, **14**, 399–411.

30. Feldman, M.W., Nabholz, M. and Bodmer, W.F. (1969) Evolution of the Rh polymorphism: a model for the interaction of incompatibility, reproductive compensation, and heterozygote advantage. *Am. J. Hum. Genet.*, **21**, 171–193.
31. Kitano, T. and Saitou, N. (1999) Evolution of Rh blood group genes have experienced gene conversions and positive selection. *J. Mol. Evol.*, **49**, 615–626.
32. Wyckoff, G.J., Wang, W. and Wu, C.I. (2000) Rapid evolution of male reproductive genes in the descent of man. *Nature*, **403**, 304–309.
33. Baum, J., Ward, R.H. and Conway, D.J. (2002) Natural selection on the erythrocyte surface. *Mol. Biol. Evol.*, **19**, 223–229.
34. Chou, H.H., Takematsu, H., Diaz, S., Iber, J., Nickerson, E., Wright, K.L., Muchmore, E.A., Nelson, D.L., Warren, S.T. and Varki, A. (1998) A mutation in human CMP-sialic acid hydroxylase occurred after the Homo-Pan divergence. *Proc. Natl Acad. Sci. USA*, **95**, 11751–11756.
35. Chou, H.H., Hayakawa, T., Diaz, S., Krings, M., Indriati, E., Leakey, M., Paabo, S., Satta, Y., Takahata, N. and Varki, A. (2002) Inactivation of CMP-*N*-acetylneuraminic acid hydroxylase occurred prior to brain expansion during human evolution. *Proc. Natl Acad. Sci. USA*, **99**, 11736–11741.
36. Sonnenburg, J.L., Altheide, T.K. and Varki, A. (2004) A uniquely human consequence of domain-specific functional adaptation in a sialic acid-binding receptor. *Glycobiology*, **14**, 339–346.
37. Angata, T., Varki, N.M. and Varki, A. (2001) A second uniquely human mutation affecting sialic acid biology. *J. Biol. Chem.*, **276**, 40282–40287.
38. Gagneux, P. and Varki, A. (1999) Evolutionary considerations in relating oligosaccharide diversity to biological function. *Glycobiology*, **9**, 747–755.
39. Varki, A. (2001) Loss of N-glycolylneuraminic acid in humans: Mechanisms, consequences, and implications for hominid evolution. *Am. J. Phys. Anthropol.*, **33** (suppl.), 54–69.
40. Mears, J.G., Lachman, H.M., Cabannes, R., Amegnizin, K.P., Labie, D. and Nagel, R.L. (1981) Sickle gene. Its origin and diffusion from West Africa. *J. Clin. Invest.*, **68**, 606–610.
41. Hamblin, M.T. and Di Rienzo, A. (2000) Detection of the signature of natural selection in humans: evidence from the Duffy blood group locus. *Am. J. Hum. Genet.*, **66**, 1669–1679.
42. Hamblin, M.T., Thompson, E.E. and Di Rienzo, A. (2002) Complex signatures of natural selection at the Duffy blood group locus. *Am. J. Hum. Genet.*, **70**, 369–383.
43. Tishkoff, S.A., Varkonyi, R., Cahinhinan, N., Abbes, S., Argyropoulos, G., Destro-Bisol, G., Drousiotou, A., Dangerfield, B., Lefranc, G., Loiselet, J. *et al.* (2001) Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance. *Science*, **293**, 455–462.
44. Verrelli, B.C., McDonald, J.H., Argyropoulos, G., Destro-Bisol, G., Froment, A., Drousiotou, A., Lefranc, G., Helal, A.N., Loiselet, J. and Tishkoff, S.A. (2002) Evidence for balancing selection from nucleotide sequence analyses of human G6PD. *Am. J. Hum. Genet.*, **71**, 1112–1128.
45. Saunders, M.A., Hammer, M.F. and Nachman, M.W. (2002) Nucleotide variability at G6pd and the signature of malarial selection in humans. *Genetics*, **162**, 1849–1861.
46. Sabeti, P.C., Reich, D.E., Higgins, J.M., Levine, H.Z., Richter, D.J., Schaffner, S.F., Gabriel, S.B., Platko, J.V., Patterson, N.J., McDonald, G.J. *et al.* (2002) Detecting recent positive selection in the human genome from haplotype structure. *Nature*, **419**, 832–837.
47. Trowsdale, J. and Parham, P. (2004) Mini-review: defense strategies and immunity-related genes. *Eur. J. Immunol.*, **34**, 7–17.
48. Torgerson, D.G., Kulathinal, R.J. and Singh, R.S. (2002) Mammalian sperm proteins are rapidly evolving: evidence of positive selection in functionally diverse genes. *Mol. Biol. Evol.*, **19**, 1973–1980.
49. Rooney, A.P. and Zhang, J. (1999) Rapid evolution of a primate sperm protein: relaxation of functional constraint or positive Darwinian selection? *Mol. Biol. Evol.*, **16**, 706–710.
50. Baker, R.R. and Bellis, M.S. (1995) *Human sperm competition: copulation, masturbation, and infidelity*. Chapman and Hall, London.
51. Jensen-Seaman, M.I. and Li, W.H. (2003) Evolution of the hominoid semenogelin genes, the major proteins of ejaculated semen. *J. Mol. Evol.*, **57**, 261–270.
52. Podlaha, O. and Zhang, J. (2003) Positive selection on protein-length in the evolution of a primate sperm ion channel. *Proc. Natl Acad. Sci. USA*, **100**, 12241–12246.
53. Civetta, A. (2003) Positive selection within sperm–egg adhesion domains of fertilin: an ADAM gene with a potential role in fertilization. *Mol. Biol. Evol.*, **20**, 21–29.
54. Jobling, M.A., Williams, G.A., Schiebel, G.A., Pandya, G.A., McElreavey, G.A., Salas, G.A., Rappold, G.A., Affara, N.A. and Tyler-Smith, C. (1998) A selective difference between human Y-chromosomal DNA haplotypes. *Curr. Biol.*, **8**, 1391–1394.
55. Bielawski, J.P. and Yang, Z. (2001) Positive and negative selection in the DAZ gene family. *Mol. Biol. Evol.*, **18**, 523–529.
56. Kouprina, N., Mullokandov, M., Rogozin, I.B., Collins, N.K., Solomon, G., Otstot, J., Risinger, J.I., Koonin, E.V., Barrett, J.C. and Larionov, V. (2004) The SPANX gene family of cancer/testis-specific antigens: rapid evolution and amplification in African great apes and hominids. *Proc. Natl Acad. Sci. USA*, **101**, 3077–3082.
57. Pamilo, P. and O'Neill, R.J. (1997) Evolution of the *Sry* genes. *Mol. Biol. Evol.*, **14**, 49–55.
58. Dorus, S., Gilbert, S.L., Forster, M.L., Barndt, R.J. and Lahn, B.T. (2003) The CDY-related gene family: coordinated evolution in copy number, expression profile and protein sequence. *Hum. Mol. Genet.*, **12**, 1643–1650.
59. Swanson, W.J., Yang, Z., Wolfner, M.F. and Aquadro, C.F. (2001) Positive Darwinian selection drives the evolution of several female reproductive proteins in mammals. *Proc. Natl Acad. Sci. USA*, **98**, 2509–2514.
60. Maston, G.A. and Ruvolo, M. (2002) Chorionic gonadotropin has a recent origin within primates and an evolutionary history of selection. *Mol. Biol. Evol.*, **19**, 320–335.
61. Whiten, A. and Widdowson, E.M. (1992) *Foraging Strategies and Natural Diet of Monkeys, Apes, and Humans.* Proceedings of a Royal Society Discussion Meeting Held on 30 and 31 May 1991. Oxford University Press, New York.
62. Stanford, C.B. and Bunn, H.T. (2001) *Meat-Eating and Human Evolution.* Oxford University Press, New York.
63. Zhang, J., Zhang, Y.P. and Rosenberg, H.F. (2002) Adaptive evolution of a duplicated pancreatic ribonuclease gene in a leaf-eating monkey. *Nat. Genet.*, **30**, 411–415.
64. Messier, W. and Stewart, C.B. (1997) Episodic adaptive evolution of primate lysozymes. *Nature*, **385**, 151–154.
65. Yang, Z. (1998) Likelihood ratio tests for detecting positive selection and application to primate lysozyme evolution. *Mol. Biol. Evol.*, **15**, 568–573.
66. Swanson, K.W., Irwin, D.M. and Wilson, A.C. (1991) Stomach lysozyme gene of the langur monkey: tests for convergence and positive selection. *J. Mol. Evol.*, **33**, 418–425.
67. Leonard, W.R. (2002) Food for thought. Dietary change was a driving force in human evolution. *Sci. Am.*, **287**, 106–115.
68. Finch, C.E. and Stanford, C.B. (2004) Meat-adaptive genes and the evolution of slower aging in humans. *Q. Rev. Biol.*, **79**, 3–50.
69. Holbrook, J.D., Birdsey, G.M., Yang, Z., Bruford, M.W. and Danpure, C.J. (2000) Molecular adaptation of alanine:glyoxylate aminotransferase targeting in primates. *Mol. Biol. Evol.*, **17**, 387–400.
70. Oota, H., Pakstis, A.J., Bonne-Tamir, B., Goldman, D., Grigorenko, E., Kajuna, S.L., Karoma, N.J., Kungulilo, S., Lu, R.B., Odunsi, K. *et al.* (2004) The evolution and population genetics of the *ALDH2* locus: random genetic drift, selection, and low levels of recombination. *Ann. Hum. Genet.*, **68**, 93–109.
71. Lin, Y.P. and Cheng, T.J. (2002) Why can't Chinese Han drink alcohol? Hepatitis B virus infection and the evolution of acetaldehyde dehydrogenase deficiency. *Med. Hypotheses*, **59**, 204–207.
72. Hollox, E.J., Poulter, M., Zvarik, M., Ferak, V., Krause, A., Jenkins, T., Saha, N., Kozlov, A.I. and Swallow, D.M. (2001) Lactase haplotype diversity in the Old World. *Am. J. Hum. Genet.*, **68**, 160–172.
73. Bersaglieri, T., Sabeti, P.C., Patterson, N., Vanderploeg, T., Schaffner, S.F., Drake, J.A., Rhodes, M., Reich, D.E. and Hirschhorn, J.N. (2004) Genetic signatures of strong recent positive selection at the lactase gene. *Am. J. Hum. Genet.*, **74**, 1111–1120.
74. Robbins, L.S., Nadeau, J.H., Johnson, K.R., Kelly, M.A., Roselli-Rehfuss, L., Baack, E., Mountjoy, K.G. and Cone, R.D. (1993) Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. *Cell*, **72**, 827–834.
75. Nachman, M.W., Hoekstra, H.E. and D'Agostino, S.L. (2003) The genetic basis of adaptive melanism in pocket mice. *Proc. Natl Acad. Sci. USA*, **100**, 5268–5273.

76. Eizirik, E., Yuhki, N., Johnson, W.E., Menotti-Raymond, M., Hannah, S.S. and O'Brien, S.J. (2003) Molecular genetics and evolution of melanism in the cat family. *Curr. Biol.*, **13**, 448–453.
77. Newton, J.M., Wilkie, A.L., He, L., Jordan, S.A., Metallinos, D.L., Holmes, N.G., Jackson, I.J. and Barsh, G.S. (2000) Melanocortin 1 receptor variation in the domestic dog. *Mamm. Genome*, **11**, 24–30.
78. Rieder, S., Taourit, S., Mariat, D., Langlois, B. and Guerin, G. (2001) Mutations in the agouti (*ASIP*), the extension (*MC1R*), and the brown (*TYRP1*) loci and their association to coat color phenotypes in horses (*Equus caballus*). *Mamm. Genome*, **12**, 450–455.
79. Mundy, N.I. and Kelly, J. (2003) Evolution of a pigmentation gene, the melanocortin-1 receptor, in primates. *Am. J. Phys. Anthropol.*, **121**, 67–80.
80. Harding, R.M., Healy, E., Ray, A.J., Ellis, N.S., Flanagan, N., Todd, C., Dixon, C., Sajantila, A., Jackson, I.J., Birch-Machin, M.A. *et al.* (2000) Evidence for variable selective pressures at *MC1R*. *Am. J. Hum. Genet.*, **66**, 1351–1361.
81. Makova, K.D., Ramsay, M., Jenkins, T. and Li, W.H. (2001) Human DNA sequence variation in a 6.6-kb region containing the melanocortin 1 receptor promoter. *Genetics*, **158**, 1253–1268.
82. Aoki, K. (2002) Sexual selection as a cause of human skin colour variation: Darwin's hypothesis revisited. *Ann. Hum. Biol.*, **29**, 589–608.
83. Shyue, S.K., Hewett-Emmett, D., Sperling, H.G., Hunt, D.M., Bowmaker, J.K., Mollon, J.D. and Li, W.H. (1995) Adaptive evolution of color vision genes in higher primates. *Science*, **269**, 1265–1267.
84. Boissinot, S., Tan, Y., Shyue, S.K., Schneider, H., Sampaio, I., Neiswanger, K., Hewett-Emmett, D. and Li, W.H. (1998) Origins and antiquity of X-linked triallelic color vision systems in New World monkeys. *Proc. Natl Acad. Sci. USA*, **95**, 13749–13754.
85. Deeb, S.S., Jorgensen, A.L., Battisti, L., Iwasaki, L. and Motulsky, A.G. (1994) Sequence divergence of the red and green visual pigments in great apes and humans. *Proc. Natl Acad. Sci. USA*, **91**, 7262–7266.
86. Zhou, Y.H. and Li, W.H. (1996) Gene conversion and natural selection in the evolution of X-linked color vision genes in higher primates. *Mol. Biol. Evol.*, **13**, 780–783.
87. Glaser, D., Tinti, J.M. and Nofre, C. (1995) Evolution of the sweetness receptor in primates. I. Why does alitame taste sweet in all prosimians and simians, and aspartame only in Old World simians? *Chem. Senses*, **20**, 573–584.
88. Shi, P., Zhang, J., Yang, H. and Zhang, Y.P. (2003) Adaptive diversification of bitter taste receptor genes in Mammalian evolution. *Mol. Biol. Evol.*, **20**, 805–814.
89. Wooding, S., Kim, U.K., Bamshad, M.J., Larsen, J., Jorde, L.B. and Drayna, D. (2004) Natural selection and molecular evolution in PTC, a bitter-taste receptor gene. *Am. J. Hum. Genet.*, **74**, 637–646.
90. Glusman, G., Yanai, I., Rubin, I. and Lancet, D. (2001) The complete human olfactory subgenome. *Genome Res.*, **11**, 685–702.
91. Gimelbrant, A.A., Skaletsky, H. and Chess, A. (2004) Selective pressures on the olfactory receptor repertoire since the human-chimpanzee divergence. *Proc. Natl Acad. Sci. USA*, **101**, 9019–9022.
92. Sharon, D., Glusman, G., Pilpel, Y., Khen, M., Gruetzner, F., Haaf, T. and Lancet, D. (1999) Primate evolution of an olfactory receptor cluster: diversification by gene conversion and recent emergence of pseudogenes. *Genomics*, **61**, 24–36.
93. Clark, A.G., Glanowski, S., Nielsen, R., Thomas, P.D., Kejariwal, A., Todd, M.A., Tanenbaum, D.M., Civello, D., Lu, F., Murphy, B. *et al.* (2003) Inferring nonneutral evolution from human-chimp-mouse orthologous gene trios. *Science*, **302**, 1960–1963.
94. Mundy, N.I. and Cook, S. (2003) Positive selection during the diversification of class I vomeronasal receptor-like (V1RL) genes, putative pheromone receptor genes, in human and primate evolution. *Mol. Biol. Evol.*, **20**, 1805–1810.
95. Choi, S.S. and Lahn, B.T. (2003) Adaptive evolution of MRG, a neuron-specific gene family implicated in nociception. *Genome Res.*, **13**, 2252–2259.
96. Gilad, Y., Rosenberg, S., Przeworski, M., Lancet, D. and Skorecki, K. (2002) Evidence for positive selection and population structure at the human MAO-A gene. *Proc. Natl Acad. Sci. USA*, **99**, 862–867.
97. Seaman, M.I., Chang, F.M., Quinones, A.T. and Kidd, K.K. (2000) Evolution of exon 1 of the dopamine D4 receptor (*DRD4*) gene in primates. *J. Exp. Zool.*, **288**, 32–38.
98. Ding, Y.C., Chi, H.C., Grady, D.L., Morishima, A., Kidd, J.R., Kidd, K.K., Flodman, P., Spence, M.A., Schuck, S., Swanson, J.M. *et al.* (2002) Evidence of positive selection acting at the human dopamine receptor D4 gene locus. *Proc. Natl Acad. Sci. USA*, **99**, 309–314.
99. Fisher, S.E., Vargha-Khadem, F., Watkins, K.E., Monaco, A.P. and Pembrey, M.E. (1998) Localisation of a gene implicated in a severe speech and language disorder. *Nat. Genet.*, **18**, 168–170.
100. Haesler, S., Wada, K., Nshdejan, A., Morrisey, E.E., Lints, T., Jarvis, E.D. and Scharff, C. (2004) FoxP2 expression in avian vocal learners and non-learners. *J. Neurosci.*, **24**, 3164–3175.
101. Enard, W., Przeworski, M., Fisher, S.E., Lai, C.S., Wiebe, V., Kitano, T., Monaco, A.P. and Paabo, S. (2002) Molecular evolution of *FOXP2*, a gene involved in speech and language. *Nature*, **418**, 869–872.
102. Zhang, J., Webb, D.M. and Podlaha, O. (2002) Accelerated protein evolution and origins of human-specific features: *Foxp2* as an example. *Genetics*, **162**, 1825–1835.
103. McHenry, H.M. (1994) Tempo and mode in human evolution. *Proc. Natl Acad. Sci. USA*, **91**, 6780–6786.
104. Larson, C.S., Matter, R.M. and Gebo, D.L. (1998) *Human Origins: The Fossil Record.* Waveland Press, Prospect Heights.
105. Jackson, A.P., Eastwood, H., Bell, S.M., Adu, J., Toomes, C., Carr, I.M., Roberts, E., Hampshire, D.J., Crow, Y.J., Mighell, A.J. *et al.* (2002) Identification of microcephalin, a protein implicated in determining the size of the human brain. *Am. J. Hum. Genet.*, **71**, 136–142.
106. Bond, J., Roberts, E., Mochida, G.H., Hampshire, D.J., Scott, S., Askham, J.M., Springell, K., Mahadevan, M., Crow, Y.J., Markham, A.F. *et al.* (2002) ASPM is a major determinant of cerebral cortical size. *Nat. Genet.*, **32**, 316–320.
107. Zhang, J. (2003) Evolution of the human ASPM gene, a major determinant of brain size. *Genetics*, **165**, 2063–2070.
108. Evans, P.D., Anderson, J.R., Vallender, E.J., Gilbert, S.L., Malcom, C.M., Dorus, S. and Lahn, B.T. (2004) Adaptive evolution of ASPM, a major determinant of cerebral cortical size in humans. *Hum. Mol. Genet.*, **13**, 489–494.
109. Kouprina, N., Pavlicek, A., Mochida, G.H., Solomon, G., Gersch, W., Yoon, Y.H., Collura, R., Ruvolo, M., Barrett, J.C., Woods, C.G. *et al.* (2004) Accelerated evolution of the *ASPM* gene controlling brain size begins prior to human brain expansion. *PLoS Biol.*, **2**, E126.
110. Evans, P.D., Anderson, J.R., Vallender, E.J., Choi, S.S. and Lahn, B.T. (2004) Reconstructing the evolutionary history of microcephalin, a gene controlling human brain size. *Hum. Mol. Genet.*, **13**, 1139–1145.
111. Wang, Y.Q. and Su, B. (2004) Molecular evolution of microcephalin, a gene determining human brain size. *Hum. Mol. Genet.*, **13**, 1131–1137.
112. Stedman, H.H., Kozyak, B.W., Nelson, A., Thesier, D.M., Su, L.T., Low, D.W., Bridges, C.R., Shrager, J.B., Minugh-Purvis, N. and Mitchell, M.A. (2004) Myosin gene mutation correlates with anatomical changes in the human lineage. *Nature*, **428**, 415–418.
113. Huttley, G.A., Easteal, S., Southey, M.C., Tesoriero, A., Giles, G.G., McCredie, M.R., Hopper, J.L. and Venter, D.J. (2000) Adaptive evolution of the tumour suppressor *BRCA1* in humans and chimpanzees. Australian Breast Cancer Family Study. *Nat. Genet.*, **25**, 410–413.
114. Fleming, M.A., Potter, J.D., Ramirez, C.J., Ostrander, G.K. and Ostrander, E.A. (2003) Understanding missense mutations in the *BRCA1* gene: an evolutionary approach. *Proc. Natl Acad. Sci. USA*, **100**, 1151–1156.
115. Zhang, J. and Rosenberg, H.F. (2002) Diversifying selection of the tumor-growth promoter angiogenin in primate evolution. *Mol. Biol. Evol.*, **19**, 438–445.
116. Gowen, L.C., Johnson, B.L., Latour, A.M., Sulik, K.K. and Koller, B.H. (1996) Brca1 deficiency results in early embryonic lethality characterized by neuroepithelial abnormalities. *Nat. Genet.*, **12**, 191–194.
117. Wu, W., Goodman, M., Lomax, M.I. and Grossman, L.I. (1997) Molecular evolution of cytochrome c oxidase subunit IV: evidence for positive selection in simian primates. *J. Mol. Evol.*, **44**, 477–491.
118. Schmidt, T.R., Goodman, M. and Grossman, L.I. (1999) Molecular evolution of the COX7A gene family in primates. *Mol. Biol. Evol.*, **16**, 619–626.
119. Mishmar, D., Ruiz-Pesini, E., Golik, P., Macaulay, V., Clark, A.G., Hosseini, S., Brandon, M., Easley, K., Chen, E., Brown, M.D. *et al.* (2003) Natural selection shaped regional mtDNA variation in humans. *Proc. Natl Acad. Sci. USA*, **100**, 171–176.

120. Ruiz-Pesini, E., Mishmar, D., Brandon, M., Procaccio, V. and Wallace, D.C. (2004) Effects of purifying and adaptive selection on regional variation in human mtDNA. *Science*, **303**, 223–226.
121. Johnson, M.E., Viggiano, L., Bailey, J.A., Abdul-Rauf, M., Goodwin, G., Rocchi, M. and Eichler, E.E. (2001) Positive selection of a gene family during the emergence of humans and African apes. *Nature*, **413**, 514–519.
122. Bailey, J.A., Baertsch, R., Kent, W.J., Haussler, D. and Eichler, E.E. (2004) Hotspots of mammalian chromosomal evolution. *Genome Biol.*, **5**, R23.
123. Wong, A., Vallender, E.J., Heretis, K., Ilkin, Y., Lahn, B.T., Lese Martin, C. and Ledbetter, D.H. (2004) Diverse fates of paralogs following segmental duplication of telomeric genes. *Genomics*, **84**, 239–247.
124. Fay, J.C., Wyckoff, G.J. and Wu, C.I. (2001) Positive and negative selection on the human genome. *Genetics*, **158**, 1227–1234.
125. Akey, J.M., Zhang, G., Zhang, K., Jin, L. and Shriver, M.D. (2002) Interrogating a high-density SNP map for signatures of natural selection. *Genome Res.*, **12**, 1805–1814.
126. Hellmann, I., Zollner, S., Enard, W., Ebersberger, I., Nickel, B. and Paabo, S. (2003) Selection on human genes as revealed by comparisons to chimpanzee cDNA. *Genome Res.*, **13**, 831–837.
127. Enard, W., Khaitovich, P., Klose, J., Zollner, S., Heissig, F., Giavalisco, P., Nieselt-Struwe, K., Muchmore, E., Varki, A., Ravid, R. *et al.* (2002) Intra- and interspecific variation in primate gene expression patterns. *Science*, **296**, 340–343.
128. Brodmann, K. (1912) Ergebnisse über die vergleichende histologische Lokalisation der Grosshirnrinde mit besonderer Berücksichtigung des Stirnhirns. *Anat. Anz. Suppl.*, **41**, 157–216.
129. Eldredge, N. and Gould, S.J. (1972) Punctuated equilibria: an alternative to phyletic gradualism. In Schopf, T.J.M. (ed.), *Models in Paleobiology.* Freeman, Cooper and Company, San Francisco, pp. 82–115.
130. Olson, M.V. and Varki, A. (2003) Sequencing the chimpanzee genome: insights into human evolution and disease. *Nat. Rev. Genet.*, **4**, 20–28.
131. Stephens, J.C., Reich, D.E., Goldstein, D.B., Shin, H.D., Smith, M.W., Carrington, M., Winkler, C., Huttley, G.A., Allikmets, R., Schriml, L. *et al.* (1998) Dating the origin of the CCR5-Delta32 AIDS resistance allele by the coalescence of haplotypes. *Am. J. Hum. Genet.*, **62**, 1507–1515.