Human Lineage-specific Gene Inactivation

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Pseudogenes are nonfunctional vestiges of genes. Investigating genes that were inactivated specifically on the human lineage can reveal the genetic basis of inter-species differences between humans and chimpanzees and inter-individual differences within humans. It can also help to understand the specific selective pressures that were altered during human evolution.

Advanced article

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Introduction

Pseudogenization is an evolutionary phenomenon whereby a gene loses its function by disruption to its regulatory or coding sequence. Such loss of function is generally thought to be detrimental to an organism and selectively disadvantageous. Since gene loss leads to immediate loss of gene function, it probably affects organisms to a greater extent than do most amino acid replacements. However, if a non-essential gene is pseudogenized, there may be no selective disadvantage and such pseudogenization can be selectively neutral. Recently, Olson proposed the 'less-is-more' hypothesis, suggesting that gene loss may serve as an engine of evolutionary change (Olson, 1999). This hypothesis is particularly intriguing for human evolution, as several human gene losses have been proposed to provide opportunities for adaptations and be responsible for human-specific phenotypes. Thus, studies identifying gene losses specific to the human lineage could help unravel the genetic basis for the biological differences between humans and their close primate relatives and determine how selection influenced these genetic changes. **See also**: Pseudogenes and their Evolution

Currently, over 16 000 pseudogenes are estimated to be present in the human genome (http://www.pseudogene.org). Many of these are unprocessed pseudogenes, meaning that they contain remnants of the exon–intron structure of a functional gene but that have insertion, deletion or substitution mutations that eliminate their ability to produce a complete functional protein. These pseudogenes represent previously functional genes in the genome that have been lost during evolution. Humans share the majority of these unprocessed pseudogenes with our close primate relatives, such as chimpanzee or gorilla, because many pseudogenization events occurred in the common ancestor of these primates. However, pseudogenization events that occurred along the human lineage since the human–chimpanzee split can divulge information about selection pressures and genetic changes unique to our species. **See also**: Genome Organization: Human

Pseudogenization is an ongoing process in genome evolution, and many human genes have segregating pseudogenes, meaning that some human individuals contain functional alleles while others have nonfunctional alleles. The presence of segregating pseudogenes in the human genome reveals that these gene inactivation events occurred relatively recently. The segregating pseudogenes allow for different individuals to have different sets of functional genes and thus may explain inter-individual differences in phenotype. Additionally, they allow the use of population genetics to determine the evolutionary forces driving the spread of the pseudogenized allele in the population.

Human-specific pseudogenes, with putatively functional chimpanzee orthologues, have been identified with both systematic comparative genomic studies and in individual case studies. Both types of studies reveal an overwhelming overrepresentation of genes of chemosensory or immune response function that became pseudogenized in humans. They also identified human-specific pseudogenes that explain some of our obvious phenotypic differences from our primate relatives. **See also**: Chemosensory Systems; Divergence between Human and Chimpanzee Genomes and its Impact on Protein and Transcriptome Evolution; Gene Deletions in Evolution; Primate Evolution: Gene Loss and Inactivation; Vertebrate Immune System: Evolution

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Chemosensory Gene Loss in the Human Lineage

In a systematic identification of 67 human-specific pseudogenes, Wang and colleagues found that over half were odourant receptors and two were bitter taste receptors (Wang *et al.*, 2006). Massive loss of odourant receptor

genes appears to have also occurred in nonhuman Old World primates, although the extent may be smaller in these species than in humans (Gilad *et al*., 2004). Genes responsible for vomeronasal olfactory sensitivity have also been inactivated in Old World primates (Zhang and Webb, 2003). The loss of these olfaction-related genes may reflect a shift from relying on olfactory cues as a means of communication to relying more on visual cues with the acquisition of a full trichromatic vision in the common ancestor of Old World primates (Zhang and Webb, 2003; Gilad *et al*., 2004). **See also**: Olfaction; Olfactory Receptors

While there was no survey of population variation in the odourant receptor pseudogenes identified from the systematic study, many segregating odourant receptor pseudogenes have been previously observed in humans, suggesting vast intra-population and inter-population differences in human olfactory ability. For example, Menashe and colleagues surveyed 51 odourant receptor pseudogene loci in 189 individuals of different ethnic descent (Menashe *et al*., 2003). Twenty-six of the 51 loci were found to have segregating alleles resulting in 178 different combinations of functional and nonfunctional odourant receptors at these 51 loci. These authors estimated that the human genome contains at least 60 segregating odourant receptor pseudogenes. Consistent with this estimate, the Human Olfactory Receptor Database Exploratorium (HORDE; http://bioportal.weizmann.ac.il/HORDE/) reports 61 segregating pseudogenes. It is unclear as whether the inter-individual and inter-population differences in human functional odourant receptor repertoire are shaped entirely by random inactivation mutations and genetic drift or are in part due to differential natural selection in different geographic regions and environments.

Similar to odourant receptor gene loss, pseudogenization of bitter taste receptors appears to be increased in the human lineage compared to other primate lineages. Since the last common ancestor of humans and chimpanzees, two bitter receptors have become fixed pseudogenes in the human lineage, but none in the chimpanzee lineage (Wang *et al*., 2004). Because bitter taste receptors are mainly used to detect toxic compounds in diet, loss of bitter receptors likely reflects a change in diet behaviour in human evolution, such as the reduction in the consumption of plant tissues, which contain more toxins than animal tissues, and the use of fire for cooking and detoxification. However, some bitter receptors were also lost in other primate lineages and the causal relationship between diet and bitter receptor pseudogenization is not always clear. Also, similar to odourant receptors, not all gene loss in bitter receptors has been fixed. For example, two human segregating bitter receptor pseudogenes of low to moderate frequency of pseudogenized allele (2.3 and 25%) have been reported (Wang *et al*., 2004). These fixed and segregating pseudogenes reflect a relaxation from purifying selection on bitter receptors that occurred in human evolution. Although some studies have found positive selection acting at some human bitter receptor genes, the majority of the human bitter receptors appear to be evolving neutrally (Wang *et al*., 2004). **See also**: Taste: Cellular Basis

Immune Response Gene Loss in the Human Lineage

Besides the overrepresented inactivation of chemosensory genes, human-specific pseudogenization is frequent in genes that had a function in immune response and host defence. An additional 10 pseudogenes identified in Wang *et al*.'s systematic study had function in immune response or host defence (Wang *et al*., 2006). This overrepresentation is also observed in the individual case studies. For example, the human-specific inactivation of the gene encoding the enzyme cytidine monophosphate (CMP)-*N*-acetylneuraminic acid hydroxylase (CMAH) led to the deficiency of the mammalian common sialic acid Neu5Gc (*N*-glycolylneuraminic acid) on the human cell surface. This inactivation was due to an Alu-mediated sequence replacement that occurred about 2.7 million years ago and may have had several important consequences to human biology and evolution (Chou *et al*., 1998, 2002), such as malaria susceptibility. Interestingly, parallel loss has occurred in the sialic acid binding immunoglobulin (Ig)-like lectin (SIGLEC) gene family, and SIGLEC13 has been lost in the human lineage (Angata *et al*., 2001). Additionally, one human-specific pseudogene is similar in sequence to the mannose-binding lectin genes, which mediate responses against invading microorganisms as part of the innate immune system (Wang *et al*., 2006). Another gene in this gene family, *MBL1*, is a pseudogene in all hominoid primates and a third gene, *MBL2*, is a segregating pseudogene in humans. Interestingly, mice deficient for *Mbl1* have increased survival rate for peritoneal sepsis, suggesting a possible selective agent for this gene loss in primates. However, these mice also had a greater risk of infection following a burn. This negative pressure was likely not a factor in the pseudogenization of *MBL1* because it was pseudogenized in primate evolution much earlier than humans were able to domesticate fire use.

There are other immune differences between humans and our primate relatives that are likely mediated through human-specific gene loss events. For example, the napsin B peptidase gene (*NAPSB*) lacks an in-frame stop codon and has a missense mutation at a crucial catalytic site, yielding no protein product despite abundant transcription in cell lines derived from immune cells (Tatnell *et al*., 1998). Additionally, the haptoglobin gene cluster has undergone parallel gene deletion events during primate evolution that likely resulted in differences in immune response in humans and other primates (Puente *et al*., 2005). Humans and chimpanzees each have a unique two gene combination of an ancestral three gene locus. The gene lost in chimpanzees, *HPR*, could contribute to chimpanzee susceptibility to Trypanosome parasites, and the parallel loss of the *HPP* gene in humans likely has similar immune effects (Puente *et al*., 2005). Further effects of gene loss on unique aspects of human immunity could result from the human-specific inactivation of epidermal growth factor (EGF)-like module containing, mucin-like, hormone receptor-like 4 (*EMR4*), a member of the EMR gene family that is

expressed in leukocytes (Hamann *et al*., 2003). *BASE*, a gene of unknown function expressed in breast cancer tissue and the salivary gland, has been inactivated in the human lineage (Hahn and Lee, 2005). This gene is homologous to members of the gene family PLUNC, which is a host-defence gene family in mammalian upper respiratory systems (Bingle *et al*., 2004). Another example is flavin-containing monooxygenase 2 (*FMO2*). This gene has been almost completely pseudogenized, although the functional copy has a 4% frequency in African populations (Dolphin *et al*., 1998). This gene is the pulmonary member of the FMO gene family that catalyse the oxidation of xenobiotics and drugs (Dolphin *et al*., 1998). Similarly, two genes involved in drug metabolism, the putative *N*-acetyl transferase Camello-like 2 (*CML2*) and transporter 2, adenosine triphosphate (ATP)-binding cassette, subfamily B (*TAP2*), are segregating pseudogenes in humans (Hahn and Lee, 2006). Many other human-specific pseudogenes belong to gene families related to immune response or host defence, such as T-cell receptors and immunoglobulins. This abundance of pseudogenes suggests a shift in pathogen infection and susceptibility in the human lineage since its divergence from the chimpanzee lineage, as reflected by the difference in susceptibility to human immunodeficiency virus/simian immunodeficiency virus (HIV/SIV), malaria and other diseases between humans and their great ape relatives. Additionally, inter-population differences in the frequency of pseudogenized alleles for genes in these gene families suggest population differences in encounters with certain pathogens. **See also**: ATP-Binding Cassette (ABC) Transporter Supergene Family: Genetics and Evolution; Immunology: Comparative Immunology of Mammals; Simian Retroviruses

Although loss-of-function mutations are generally thought to be deleterious, some are observed at high frequencies. These high-frequency pseudogene alleles might indicate that the pseudogenization is beneficial and the pseudogenized allele might be increasing in frequency by positive selection. The best example of this type is the pseudogenization of *CASPASE12*. Outside of Africa, all human populations have a pseudogene allele of *CASPASE12*. However, in African populations there is still a 10% incidence of the functional version of this gene. Interestingly, it was found that those with the functional alleles are more likely to suffer from severe sepsis than those with pseudogenized alleles. To investigate if the pseudogene allele increased in frequency by positive selection for its ability to reduce severe sepsis or if it increased by chance, Wang and colleagues investigated the nucleotide sequence variation in functional and pseudogenized alleles (Wang *et al*., 2006). Based on decreased nucleotide variation in the pseudogenized allele near the pseudogenizing mutation (**Figure 1**) and other population genetic evidence, the authors inferred that the spread of the pseudogenized allele was promoted by positive selection. They also estimated that *CASPASE12* became a pseudogene shortly before the out-of-Africa migration of modern humans. The functional human CASPASE12 acts as a dominant-negative regulator of essential cellular responses including the nuclear factor-kappa B (NF-κB) and interleukin (IL)-1 pathways; it attenuates the inflammatory and innate immune response to endotoxins. Because an appropriate level of immune response that is neither excessive nor insufficient is important to an organism, the immune suppression function of CASPASE12 likely become harmful when the immune system cannot fully respond to a challenge. It is possible that during human evolution alterations in our genetic and/or environmental background resulted in a malfunction of the immune response to endotoxins, which rendered the previously necessary function of CASPASE12 deleterious in humans and the pseudogenized allele advantageous over the functional one. **See also**: Cytokines as Mediators of Disease

While the selective pressure for the spread of the *CASPASE12* pseudogenized allele has been discerned, not all such pseudogenes have an obvious selective advantage. For example, a pseudogenized allele for the chemokine receptor *CCR5* was thought to have increased its frequency by positive selection. The pseudogenized allele *CCR5Δ32* is present at relatively high frequencies in some European populations (up to 16%). Homozygotes for this pseudogenized allele are resistant to certain infectious diseases such as acquired immunodeficiency syndrome (AIDS). Since HIV has been around for less than a century, its impact on the frequency of *CCR5Δ32* is minimal. Thus, it was hypothesized that resistance to diseases earlier in human history, such as the bubonic plague or smallpox, led to selection for *CCR5Δ32*. However, further population genetic studies and allele frequencies for this gene from Bronze Age samples (long before *CCR5Δ32* was thought to have arisen) suggest that there was no positive selection promoting the spread of *CCR5Δ32* and that its relatively high frequency among Europeans was simply due to chance (Sabeti *et al*., 2005). **See also**: Human Immunodeficiency Virus (HIV) Infection: Genetics

Morphological Impacts of Gene Loss in the Human Lineage

Other human-specific pseudogenes help discern some of the physical differences between humans and chimpanzees. For example, the pseudogenization of the sarcomeric myosin gene *MYH16* at the time of the emergence of the genus *Homo* is thought to be responsible for the marked size reduction in hominin masticatory muscles, which may have allowed the brain size expansion in *Homo* (Stedman *et al*., 2004). However, a subsequent study gave a much earlier time for the pseudogenization event, yielding it unrelated to the brain size expansion (Perry *et al*., 2005). Regardless of its effect on brain size, the pseudogenization of *MYH16* probably resulted in distinct craniofacial muscle and skeletal structure in humans compared to other primates (**Figure 2**). Additionally, human type I hair keratin is a pseudogene with functional orthologues in chimpanzee and gorilla (Winter *et al*., 2001). Loss of this gene in the

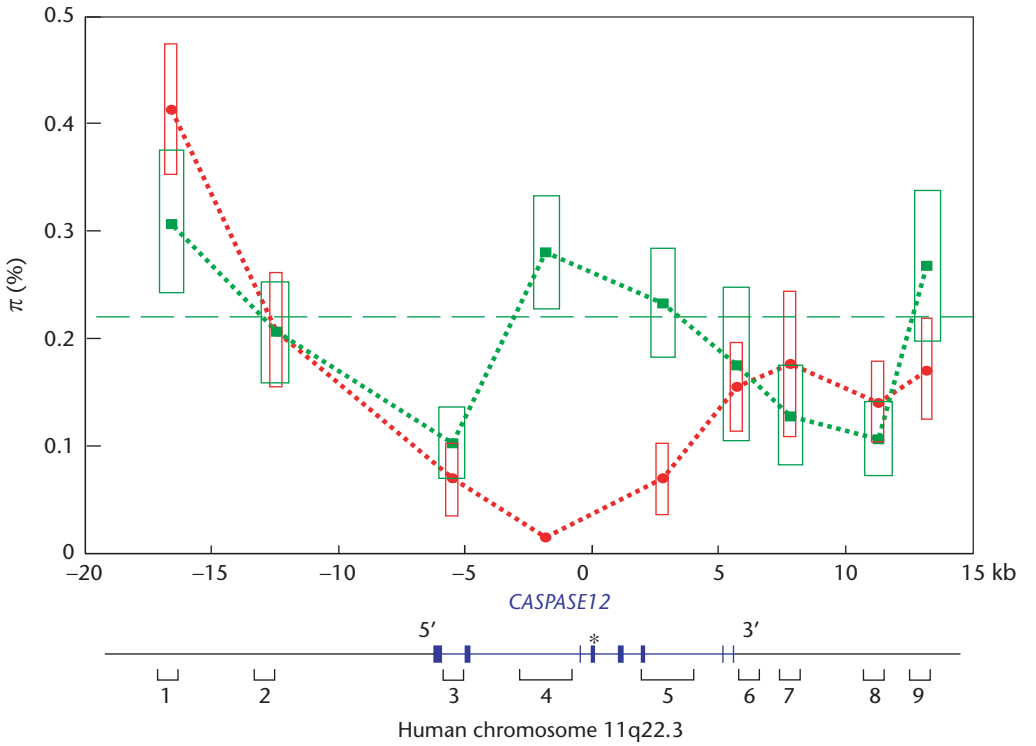

Figure 1 Nucleotide diversity in the CASPASE12 gene in noncoding regions of the pseudogenized allele and functional allele. The exon structure for CASPASE12 is shown in thick blue bars. Nucleotide diversity (π) is significantly lower near the disrupting mutation (*) in exon 4 of the CASPASE12 pseudogenized allele (red) than is observed in the functional allele (green). Red circles and green dots show the percent nucleotide diversity in the pseudogenized and functional alleles, respectively, at each of nine noncoding regions within and around the gene (black bars). The rectangles surrounding the dots and squares show ± 1 standard error. The green dotted line is the average nucleotide diversity for the functional allele. The decreased diversity in the pseudogenized allele near the disrupting mutation is indicative of a selective sweep for this pseudogenized allele. Adapted from Wang *et al.* (2006).

human may reflect the difference in body hair patterns between humans and their great ape relatives. **See also**: Keratins and Keratin Diseases; Myosin Superfamily

Gene Loss of Unknown Biological Relevance

Some segregating pseudogenes have relatively high frequency in human populations and population genetic analysis of the locus indicates that the pseudogenized allele is favoured by positive selection. However, unlike the case of *CASPASE12* where the pseudogenized allele decreased the risk for severe sepsis, there is no documented physiological benefit gained by the pseudogenized allele in these cases. For example, the fast skeletal muscle fibre protein α-actinin-3 (ACTN3) has a pseudogenized allele that has a frequency of 10–50% in different human populations. Homozygotes for the pseudogenized allele are overrepresented in endurance runner athletes, but not sprinters or power athletes. Interestingly, mice that are deficient for Actn3 can run 33% further than wildtype mice (MacArthur *et al.*, 2007). A population survey in humans indicates that selective sweeps for the pseudogenized allele occurred 15 000 and 33 000 years ago for European and Asian populations, respectively. While MacArthur and colleagues suggested positive selection for more efficient aerobic muscle metabolism as the driver of these sweeps, the direct benefit of this physiological difference to humans remains unclear.

Another example of an increase in pseudogene frequency in human evolution is in the *SERPINA2* locus, which encodes a serpin peptidase inhibitor (Seixas *et al.*, 2007). A population genetic survey reveals that the frequency of a *SERPINA2* pseudogenized allele is 85% in Sao Tome, West Africa and 67.5% in Portugal. Linkage disequilibrium studies reveal decreased polymorphism in the pseudogenized allele haplotypes indicative of a selective sweep increasing their frequencies. However, the physiological benefit of this pseudogenized allele remains unclear. Based on the expression patterns of the functional alleles, this gene may have been involved in reproduction. Consistent with this explanation, comparative genomics studies of proteases and protease inhibitors reveal many lineage-specific gene gains and losses in protein families including serine protease inhibitor (SERPIN) that could reflect differences in reproduction. Alternatively, the loss of *SERPINA2* might reflect differences in host–pathogen interactions, especially pathogens found in the reproductive tract.

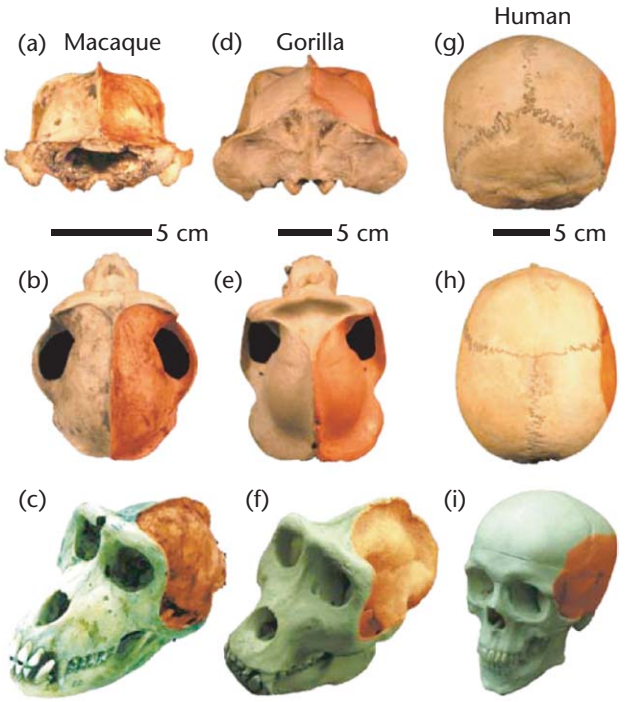

Figure 2 The relative size of chewing muscles differs greatly between humans and their primate relatives as a result of pseudogenization of human MYH16. The differences in musculature are reflected in the morphology of such craniofacial features as the temporal fossa and zygomatic arch (highlighted in red) in skulls from macaque (a–c), gorilla (d–f) and human (g–i). Adapted by permission from Macmillan Publishers Ltd., Stedman *et al.*, Copyright (2004).

Interestingly, the *Serpina2* locus has been independently pseudogenized in the chimpanzee lineage, suggesting that similar selective pressures affect this locus in other primates. **See also**: Serpins: Evolution

In some cases, 'inactivating mutations' do not seem to result in loss of function. For example, the secretoglobin *SCGB1D4* has a frameshift mutation in the *C*-terminal end of the coding region that does not affect the important functional domains of the protein, and the protein has been shown to be functional in experimental assays (Hahn and Lee, 2005). Similarly, the mutations occurred in the *C*-terminus of neurotensin receptor *NTSR2*, phosphodiesterase *PDE3B* and ubiquitin *C*-terminal hydrolase (UCH)-interacting protein *UIP1*, reducing the lengths of these proteins by less than 10 amino acid residues (Hahn and Lee, 2005, 2006). However, a mutation in the *C*-terminal region of a protein is not always benign. For example, a mutation in the stop codon of the natriuretic peptide (*NPPA*) gene increases the protein length by just two amino acids, but this lengthened form of NPPA is associated with increased risk of stroke (Rubattu *et al*., 2004). Besides coding region changes, human-specific inactivating mutations have occurred in the regulatory regions. The promoter and enhancer regions of human pancreatic elastase 1 (*ELA1*) gene has acquired many mutations compared to other mammals and it is no longer expressed in the pancreas (Rose and MacDonald, 1997). However, the coding region of human *ELA1* remains intact suggesting that this gene might be expressed elsewhere (Rose and MacDonald, 1997). Indeed, human *ELA1* was found to be expressed in skin cells (Talas *et al*., 2000). Since other ELA genes are expressed in the human pancreas, the functional consequences of this human-specific expression change are unknown (Talas *et al*., 2000).

Conclusions

Gene loss that occurred specifically in the human lineage reveals much about the evolutionary history of our lineage. The overrepresentation of human-specific pseudogenes of chemosensory and host-defence functions suggests that many of the differences between human and chimpanzee stem from our different environments. Segregating pseudogenes offer a more recent glimpse of human evolution. With the increased amount of polymorphism data generated from human population genomic studies, more functional variation will be identified in human populations. These differences may help identify the genetic mechanisms underlying the phenotypic variations among major ethnic groups.

Genetic differences between humans and their close primate relatives and those among human individuals have significant biomedical implications. First, these lineage-specific genetic changes present potential restrictions to using model organisms for understanding human biology. Second, the inter-individual genetic differences resulting from segregating pseudogenes impact the efficacy of some medical treatments. This complication is exemplified by the inter-individual variation in cytochrome P450 (*CYP450*) genes. These genes are involved in the metabolism of xenotoxins in most vertebrates. Many human *CYP450* genes are segregating pseudogenes with variable frequencies of pseudogenized alleles in different populations. These population differences likely reflect the varied presence of different xenotoxins in different geographical regions. However, CYP450 genes often aid in metabolism of modern drugs and the variation in CYP450 function results in a wide range of individual response to certain drugs (Lynch and Price, 2007). This problem is beginning to be addressed by the fields of pharmacogenetics and individualized medicine and exemplifies the importance of understanding our past genes to maintain our future survival. **See also**: Cytochrome P450 (*CYP*) Gene Superfamily; Drug Metabolic Enzymes: Genetic Polymorphisms; Pharmacogenetics and Pharmacogenomics

References

Angata T, Varki NM and Varki A (2001) A second uniquely human mutation affecting sialic acid biology. *Journal of Biological Chemistry* **276**: 40282–40287.

Bingle CD, LeClair EE, Havard S *et al*. (2004) Phylogenetic and evolutionary analysis of the PLUNC gene family. *Protein Science* **13**: 422–430.

Chou HH, Hayakawa T, Diaz S *et al*. (2002) Inactivation of CMP-*N*-acetylneuraminic acid hydroxylase occurred prior to brain

expansion during human evolution. *Proceedings of the National Academy of Sciences of the USA* **99**: 11736–11741.

Chou HH, Takematsu H, Diaz S *et al*. (1998) A mutation in human CMP-sialic acid hydroxylase occurred after the Homo–Pan divergence. *Proceedings of the National Academy of Sciences of the USA* **95**: 11751–11756.

Dolphin CT, Beckett DJ, Janmohamed A *et al*. (1998) The flavin-containing monooxygenase 2 gene (FMO2) of humans, but not of other primates, encodes a truncated, nonfunctional protein. *Journal of Biological Chemistry* **273**: 30599–30607.

Gilad Y, Przeworski M and Lancet D (2004) Loss of olfactory receptor genes coincides with the acquisition of full trichromatic vision in primates. *PLoS Biology* **2**: E5.

Hahn Y and Lee B (2005) Identification of nine human-specific frameshift mutations by comparative analysis of the human and the chimpanzee genome sequences. *Bioinformatics* **21**(suppl. 1): i186–i194.

Hahn Y and Lee B (2006) Human-specific nonsense mutations identified by genome sequence comparisons. *Human Genetics* **119**: 169–178.

Hamann J, Kwakkenbos MJ, de Jong EC *et al*. (2003) Inactivation of the EGF-TM7 receptor EMR4 after the Pan–Homo divergence. *European Journal of Immunology* **33**: 1365–1371.

Lynch T and Price A (2007) The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *American Family Physician* **76**: 391–396.

MacArthur DG, Seto JT, Raftery JM *et al*. (2007) Loss of ACTN3 gene function alters mouse muscle metabolism and shows evidence of positive selection in humans. *Nature Genetics* **39**: 1261–1265.

Menashe I, Man O, Lancet D and Gilad Y (2003) Different noses for different people. *Nature Genetics* **34**: 143–144.

Olson MV (1999) When less is more: gene loss as an engine of evolutionary change. *American Journal of Human Genetics* **64**: 18–23.

Perry GH, Verrelli BC and Stone AC (2005) Comparative analyses reveal a complex history of molecular evolution for human MYH16. *Molecular Biology and Evolution* **22**: 379–382.

Puente XS, Gutierrez-Fernandez A, Ordonez GR, Hillier LW and Lopez-Otin C (2005) Comparative genomic analysis of human and chimpanzee proteases. *Genomics* **86**: 638–647.

Rose SD and MacDonald RJ (1997) Evolutionary silencing of the human elastase I gene (ELA1). *Human Molecular Genetics* **6**: 897–903.

Rubattu S, Stanzione R, Di Angelantonio E *et al*. (2004) Atrial natriuretic peptide gene polymorphisms and risk of ischemic stroke in humans. *Stroke* **35**: 814–818.

Sabeti PC, Walsh E, Schaffner SF *et al*. (2005) The case for selection at CCR5-Delta32. *PLoS Biology* **3**: e378.

Seixas S, Suriano G, Carvalho F *et al*. (2007) Sequence diversity at the proximal 14q32.1 SERPIN subcluster: evidence for natural selection favoring the pseudogenization of SERPINA2. *Molecular Biology and Evolution* **24**: 587–598.

Stedman HH, Kozyak BW, Nelson A *et al*. (2004) Myosin gene mutation correlates with anatomical changes in the human lineage. *Nature* **428**: 415–418.

Talas U, Dunlop J, Khalaf S, Leigh IM and Kelsell DP (2000) Human elastase 1: evidence for expression in the skin and the identification of a frequent frameshift polymorphism. *Journal of Investigative Dermatology* **114**: 165–170.

Tatnell PJ, Powell DJ, Hill J *et al*. (1998) Napsins: new human aspartic proteinases. Distinction between two closely related genes. *FEBS Letters* **441**: 43–48.

Wang X, Grus WE and Zhang J (2006) Gene losses during human origins. *PLoS Biology* **4**: e52.

Wang X, Thomas SD and Zhang J (2004) Relaxation of selective constraint and loss of function in the evolution of human bitter taste receptor genes. *Human Molecular Genetics* **13**: 2671–2678.

Winter H, Langbein L, Krawczak M *et al*. (2001) Human type I hair keratin pseudogene phihHaA has functional orthologs in the chimpanzee and gorilla: evidence for recent inactivation of the human gene after the Pan–Homo divergence. *Human Genetics* **108**: 37–42.

Zhang J and Webb DM (2003) Evolutionary deterioration of the vomeronasal pheromone transduction pathway in catarrhine primates. *Proceedings of the National Academy of Sciences of the USA* **100**: 8337–8341.

Further Reading

Balakirev ES and Ayala FJ (2003) Pseudogenes: are they "junk" or functional DNA. *Annual Review of Genetics* **37**: 123–151.

Chimpanzee Sequencing and Analysis Consortium (2005) Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature* **437**: 69–87.

Clarke B (2006) Pharmacogenetics and cytochrome P450. *The Biomedical Scientist* 38–40.

Gerstein M and Zheng D (2006) The real life of pseudogenes. *Scientific American* **295**: 48–55.

Xue Y, Daly A, Yngvadottir B *et al*. (2006) Spread of an inactive form of caspase-12 in humans is due to recent positive selection. *American Journal of Human Genetics* **78**: 659–670.

Web Links

Comprehensive pseudogene database http://www.pseudogene.org

Human Olfactory Receptor Database Exploratorium http://bioportal.weizmann.ac.il/HORDE/