Evolution of the Human Genome: Adaptive Changes

Advanced article

Article Contents

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The study of human evolution is of interest to many both for the potential it has to improve our understanding of heritable disease, as well as for the possibility of illuminating evidence for adaptations that may help to tell the story of our origin. But uncovering evidence of positive selection at the genetic level has been a challenge. It remains unclear how much of the human genome has been affected by positive selection, what the main mechanism of selection is, and what types of patterns we should be looking for to identify adaptations. With whole-genome sequencing and high performance computation, we are quickly shifting to a field in which data is no longer a limiting factor. Here we will discuss the progress that has been made towards these ends, explore the best examples of human-specific adaptations to date, and discuss the implications of these findings within the context of classical population genetic theory.

Background

Historically, human evolution was studied using a phenotype-first approach – relating phenotypic differences in populations to underlying genotypes. Perhaps the best-known example is the Duffy blood antigen, believed to be driven by selection for resistance to malaria. Individuals lacking the Duffy blood antigens are resistant to infection by *Plasmodium vivax*, and this phenotype is correlated with regions in Africa where transmission of *P. vivax* is high (Miller *et al*., 1975). Despite the intuitive appeal of this approach, it is focusing only upon phenotypic variation, which may or may not have been influenced by positive selection. In fact, perhaps the true advantage of the genomic age is the ability to take a genotype-first approach – to scan the genome for adaptive mutations, using signature patterns of positive selection, in a fashion that is blind to underlying phenotype.

But this approach has its own caveats. Firstly, different mechanisms of selection leave different signatures in the genome, and it is unclear how much each of these processes affects human populations. Also, identified selective targets do not always have an obvious phenotypic consequence or advantage. If, for example, an identified gene plays a role in many cellular processes, it is difficult to determine which of these may have been targeted, and it is dangerous to assume that the one that makes the most 'sense' from an evolutionary standpoint must be the right process. This leads to questions of whether the signals we are finding are, in fact, real indicators of selection or artifacts neutral processes. Finally, despite a proliferation of statistics designed for scanning genomes for evidence of selection (for a review see Crisci *et al*., 2012) there is alarmingly little overlap between such studies and methodologies. This raises important questions both about the mode and tempo of human evolution, as well as the efficiency of the statistics themselves. Thus, we have only a handful of convincing examples of adaptations in human populations, largely arrived at using a phenotype-first approach – suggesting that the full benefit of population genomics has yet to be realised.

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Evidence of Adaptations in Humans

Adaptation in humans is generally presented in two forms: population-specific changes that are segregating at some frequency in the species, and species-specific changes that have arisen since the split with our closest relatives (generally the chimpanzee, but recently ancient hominids as well, see below). The latter are more likely to explain distinctive neurological traits in humans, like language, learning and memory – but few convincing examples have been found to date. Thus, most examples of human adaptation are population-specific that most likely arose in response to environmental changes as humans spread to nearly every continent in the world. Common phenotypic traits affected are disease resistance, and metabolism in response to changes in diet.

Population specific adaptations

In addition to the Duffy blood group discussed above, malaria has driven selection of other traits in populations where transmission is prevalent, including sickle cell anaemia (Allison, 1954). Sickle cells are caused by a variant in the human haemoglobin gene (*HbS*). Individuals who are heterozygous for the trait are more resistant to infection by *Plasmodium falciparum*, whereas those who are homozygous have higher mortality rates. The resistance this variant confers on heterozygotes explains why the trait remains at a frequency of approximately 10% in African populations, even when it appeared at a first glance to be deleterious. This allele has both a beneficial and a deleterious phenotype, and is indeed one of the classic examples of balancing selection. Malaria remains today a selective pressure in many extant populations, and is thought to have driven selection on multiple variants of the haemoglobin gene that cause human blood disorders (for a review see Kwiatkowski, 2005). **See also**: Balancing Selection in the Human Genome; Balancing Selection in Human Evolution; Susceptibility to Malaria, Genetics of

Many diseases act as selective pressure on the immune system, promoting the evolution of resistance mutations. For instance, the CCR5 receptor is normally expressed on the membranes of CD4 T cells and provides entry for the HIV virus. A 32bp deletion in this gene in individuals of European descent prevents this receptor from being expressed on the membranes of CD4 T cells, and confers resistance to HIV infection (Samson *et al*., 1996). This deletion is present in approximately 10% of Caucasian Europeans. The age of the variant allele has been estimated to be approximately 1000–2000 years (for a review, see Galvani and Novembre, 2005); if this age were correct, it would be unlikely for this mutation to have reached this appreciable frequency by genetic drift alone (Stephens *et al*., 1998). And since HIV is believed to be a modern disease in humans, it is an unlikely explanation for the observed frequency. Initially, the Bubonic Plague was named as the selective pressure on the variant allele for CCR5 because of the timing of the mutation, but studies have subsequently demonstrated that this variant does not provide resistance to plague infection (Elvin *et al*., 2004; Mecsas *et al*., 2004). A more likely culprit is small pox, since it was highly transmissible for a long period of human history – and a relative of poxvirus infects cells using the CCR5 receptor (Lalani *et al*., 1999).

Another instance of population-specific selection as a result of environmental pressure is adaptation to a low oxygen environment in Tibetan populations – with modern populations living at approximately 2.5 miles above sea level, and thus at a 40% oxygen deficiency. Several recent papers have compared genetic data between Tibetan and Han populations to try and elucidate changes that could allow humans to live at such altitudes (Beall *et al*., 2010; Yi *et al*., 2010; Peng *et al*., 2011; Xu *et al*., 2011). All of these studies consistently highlight one gene, *EPAS1*, as being highly differentiated in the Tibetan population. *EPAS1* is responsible for regulating factors in response to hypoxia, including erythropoiesis (Patel and Simon, 2008). Additionally, Yi *et al*. (2010) find that *EPAS1* is correlated with haemoglobin levels in the blood and could explain why Tibetans have lower levels of haemoglobin at high altitudes than lowland populations.

An example of a metabolic adaptation in response to diet is the lactose tolerance phenotype. Being the only mammal to continue milk consumption after infancy, humans exhibit lactose tolerance, or lactase persistence, which results from the continual expression of lactase-phlorizin hydrolase (LPH) (*LCT*) into adulthood. Normally, levels of this enzyme decrease after infancy, and adults lose their ability to digest lactose in the intestines. The lactase persistence trait is present at a frequency between 40% and 90% in European and African populations that raise cattle (Swallow, 2003). Tishkoff *et al*. (2006) demonstrated that this was indeed an example of convergent evolution – with two different alleles conferring the phenotype between populations.

Human specific adaptations

The availability of both the Neanderthal (Green *et al*., 2010) and Denisovan (Reich *et al*., 2010) genomic sequences is a noteworthy milestone in the study of human evolution. These two populations are much more closely related to human than chimpanzee (**Figure 1**), and can provide unique insight into genomic changes that occurred during early human evolution. By comparing the Neanderthal genome sequence with the genomes of five humans from various populations and using chimpanzee as an ancestor, Green *et al*. (2010) identified putatively selected regions in humans. They looked for large regions of the human genome where Neanderthal had the ancestral state at polymorphic sites in humans, with the logic being that these mutations in humans must have occurred and rose in frequency after the split between humans and Neanderthal. Crisci *et al*. (2011) further show that this scan is capable of detecting selection in regions that would have been missed using site frequency spectrum- and divergence-based approaches – with the most interesting candidates

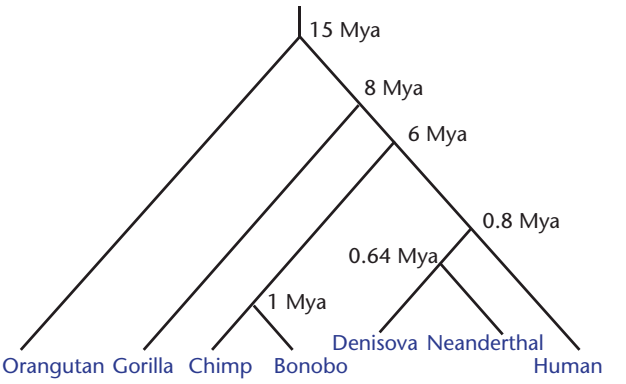

Figure 1 Phylogeny of the great apes and approximate divergence times. Branches are not drawn to scale. The Neanderthal and Denisova branches are intentionally truncated to indicate extinct versus extant.

being: *CADPS2*, mutations which are linked with autism; *NRG3*, which is expressed in the brain and located within a susceptibility locus for schizophrenia; and *DYRK1A*, also expressed in the brain and believed to be involved in learning and memory.

One interesting discovery from sequencing the genomes of these two hominins is that both populations appear to have interbred with human populations. Green *et al*. (2010) show that Neanderthals contributed up to 3% of their genomes to modern day Eurasians by comparing the Neanderthal genome to modern European, Asian, and African populations, finding that Neanderthals were more genetically similar to Eurasians than to Africans, suggesting gene flow. Reich *et al*. (2010) performed a similar analysis with the Denisovan genome and found that this population contributed 4–6% of its genome to modern day Melanesians.

This discovery of admixture raises some interesting questions regarding the evolutionary trajectory of humans. It is possible that since these two populations were present in Europe and Asia before modern humans, they could have acquired adaptive mutations in response to environmental and dietary changes, and passed them on to human ancestors as they began migrating out of Africa. A potential example of this is the controversial evolution of the *FOXP2* gene. This gene has apparent functions in speech and language (Fisher *et al*., 1998; Lai *et al*., 2001), and contains two SNPs initially found to be unique to humans that have been argued to be under positive selection (Enard *et al*., 2002). Later Krause *et al*. (2007) discovered that these SNPs were also present in the human-derived state in two Neanderthal individuals, and suggested that there was a common mutation in the ancestor of humans and Neanderthals before the two populations split over 300 Kya. But Coop *et al*. (2008) argue that the selective signature in humans is much too young to have occurred in an ancestor of human and Neanderthal, and that if the sweep was that old, new mutations would have returned local diversity levels back to neutral expectations. However, if there was in fact admixture between human and Neanderthal populations approximately 50 Kya (Green *et al*., 2010), then this selected loci very well could have arisen and swept in humans, and then the haplotype could have been passed to Neanderthals (or vice versa).

Datasets and Methodology

With many genomes now being sequenced and the ability to process large amounts of data using high-performance computing, the time required to perform large genome scans of many individuals and compare polymorphism between populations is trivial. We now have genomic sequences of the extant great apes, including human (International Human Genome Sequencing Consortium, 2001; Venter *et al*., 2001), chimpanzee (The Chimpanzee Sequencing and Analysis Consortium, 2005), gorilla (Scally *et al*., 2012), orangutan (Locke *et al*., 2011) and most recently bonobo (unpublished). Also, the draft genomes of two extinct hominins have been completed within the last year: Neanderthal (Green *et al*., 2010) and an individual from Denisova cave in Siberia (Reich *et al*., 2010). This divergence data facilitates the discovery of human-specific adaptations – often by making simple comparisons of the rate of fixation between branches. Commonly the ratio of nonsynonymous changes (d_N) to synonymous (d_S) is used as a measure of the direction of selection across a gene; with $d_N/d_S = 1$ being consistent with neutrality, $d_N/d_S > 1$ consistent with recurrent positive selection, and $d_N/d_S < 1$ consistent with recurrent purifying selection (Nei and Gojobori, 1986).

Combining this divergence-based approach with polymorphism data, the McDonald–Kretiman (MK) test performs a 2×2 contingency test between fixed versus segregating synonymous and nonsynonymous sites. Under the assumption that synonymous sites are neutral, an increased rate of fixation of nonsynonymous changes between species is generally taken as evidence of recurrent adaptive fixations (McDonald and Kreitman, 1991).

There are also methods that utilise polymorphism within a single species to identify patterns of selection. Next-generation genome-sequencing technology has made it faster and more cost effective to sequence entire genomes of many individuals, leading to large-scale polymorphism datasets. Indeed, the 1000 genomes project has provided scientists with the most complete set of genome-wide SNP information in humans to date (Durbin *et al*., 2010). All such tests rely on the patterns of variation produced by a hitchhiking event – the process by which a new beneficial allele rises quickly within a population due to positive selection, altering the frequency of linked neutral variation (Maynard Smith and Haigh, 1974; Kaplan *et al*., 1989; **Figure 2**). For the fixation of a single beneficial mutation – these patterns are well described, including a decrease in local heterozygosity, an excess of rare mutations around the fixation, and an excess of high frequency derived mutation and linkage disequilibrium in flanking regions owing to recombination events (**Figure 3**). These changes are captured in the site frequency spectrum and may be detected in polymorphism for approximately N generations (where N is the effective population size) before becoming obscured by subsequent mutation and recombination events (Przeworski, 2002) – or approximately 2 50 000 years for humans. **See also**: Identifying Regions of the Human Genome that Exhibit Evidence for Positive Selection

Mechanisms of human evolution

Positive selection can leave many different signatures in the human genome depending on the targets it acts upon – and there are many different models of selection. Selection can act on a single new beneficial mutation (discussed above), also known as a 'hard' or 'classic' sweep. Another alternative is that selection can act on multiple copies of a beneficial mutation or standing variation (Orr and

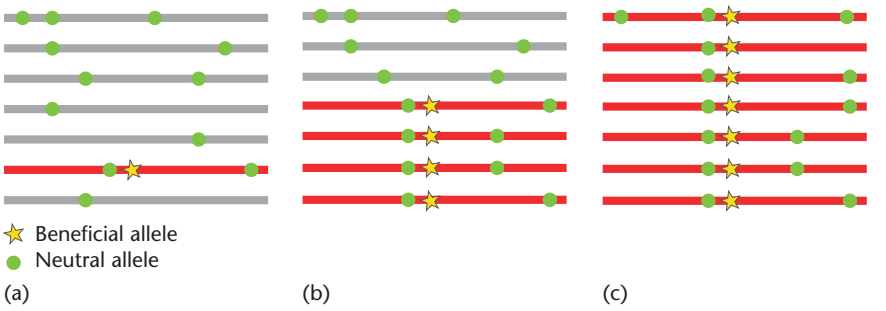

Figure 2 The hitchhiking effect. Each grey or red line represents a chromosome from a single individual. (a) A beneficial mutation arises in the population and is closely linked to a neutral allele. (b) As the mutation rises in frequency, it brings with it linked neutral alleles. Only alleles that recombine onto the beneficial haplotype are not lost from the sample. (c) After the sweep is completed the closely linked allele is fixed. Thus only high frequency alleles that have 'hitchhiked' with the beneficial mutation are visible as variation within the sample, and subsequent new mutations appear as rare variants.

Betancourt, 2001; Hermisson and Pennings, 2005). This is referred to as a 'soft' sweep since the beneficial mutations are present at some interemediate frequency before they begin sweeping. There are also models for incomplete sweeps – a classic sweep that has not reached fixation – which may be detectable with haplotype patterns (Kim and Nielsen, 2004; Sabeti *et al*., 2007). Selection can also act on polygenic (Turelli and Barton, 1990) or epigenetic traits (Jablonka *et al*., 1998; Feinberg and Irizarry, 2010). The patterns produced under all of these models differ depending on the timing, strength, and rate of selection. These all can be very confusing when attempting to scan the genome for evidence of adaptations, and contributes to the lack of concrete examples of selection at the genomic level.

The classic sweep is, perhaps, the most commonly looked for signature of selection in humans. Numerous statistics have been developed that make use of different aspects of the classic sweep pattern to try and find evidence of selection in the human genome (for a review, see Crisci *et al*., 2012). But the results of these scans offer minimal overlap of selective targets. This is further complicated by the fact that expected sweep patterns are difficult to distinguish from background selection, that is, the continuous removal of neutral mutations though linkage with deleterious haplotypes. This process creates a reduced level of neutral variation as is seen with a sweep (**Figure 3**). Indeed, even though coding regions genome-wide show this pattern, it is unclear whether selective sweeps are responsible, or background selection. For example, Cai *et al*. (2009) show that the level of neutral polymorphism in the human genome is negatively correlated with both functional constraint and divergence from chimpanzee – pointing out that this would be consistent with either recurrent selective sweeps or background selection. Hernandez *et al*. (2011) found a similar negative correlation between polymorphism and functionally conserved regions, and further add that the average reduction in diversity around human amino acid substitutions is no different from reduced diversity at synonymous substitutions, suggesting that classic sweeps could not be the cause of these amino acid substitutions.

Consider also the wait time for a beneficial mutation to occur. In order for a new beneficial mutation to fix in a population via the classic sweep model, the mutation must overcome being lost by genetic drift, and reach a high enough initial frequency for selection to act on it (Kimura, 1983). Thus, the waiting time for a new beneficial mutation to arise could be very long. If the primary driver of selection in humans were environmental change, selection on standing variation would allow for adaptations to fix more readily, alleviating the issue of wait time. Since multiple haplotypes are brought to fixation under both soft and standing models, this mechanism of evolution leaves a different genomic signature than classic sweeps – increasing intermediate frequency mutations and creating distinctive haplotype blocks (Przeworski *et al*., 2005; Pennings and Hermisson, 2006).

There is also recent and intriguing evidence that selection can shape epigenetic interactions, although the details have yet to be well resolved. For example, *PRDM9* encodes a zinc finger protein that influences where recombination hotspots occur during meiosis (Baudat *et al*., 2010). The location of these hotpots differs widely between humans and other species, and the binding domain of PRDM9 is diverse across humans, possibly owing to a selection mechanism (for a review, see Ségurel *et al*., 2011). Another example is the recent discovery of species-specific methylation patterns in sperm cells between humans and chimpanzees (Molaro *et al*., 2011). While appealing as a potential mode of rapid adaptation in natural populations, the details of epigenetic inheritance and modelling remains as a field in need of further study, though progress is beginning to be made (Geoghegan and Spencer, 2011).

The Future of Human Evolution

The role of selection on genetic variation in humans has been reconciled with many different models of selection – ranging from completely neutral (Kimura, 1968, 1983) to weakly deleterious (Ohta, 1973) to weakly advantageous (Gillespie, 1977). The extent to which positive selection affects the human genome and its primary mechanism remains unclear.

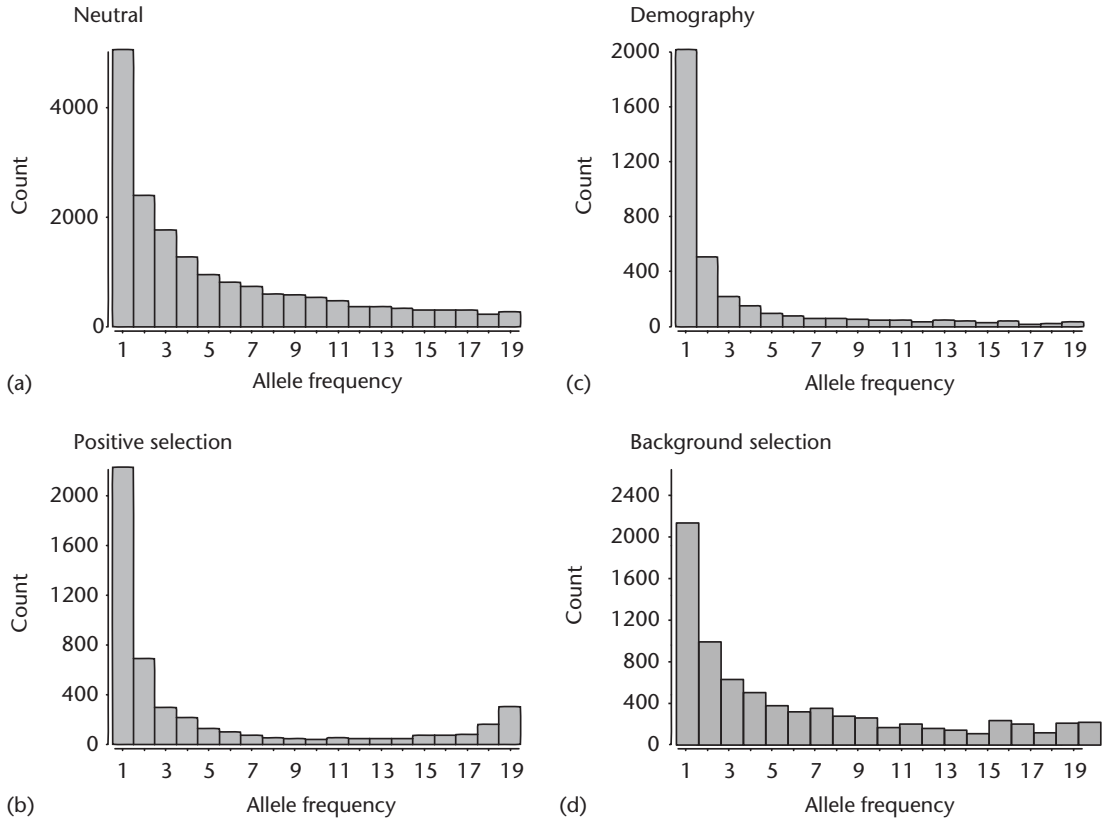

Figure 3 A comparison of the site frequency spectrum under equilibrium and nonequilibrium conditions. Plots are based on simulation of a 5 Kb region using either msms (a–c) or sfscode (d) with human-like parameters (effective population size of 10 000, per site mutation rate of 2.35×10^{-8}, and per site recombination rate of 2.56×10^{-8}). Counts on the *y*-axis are the total number of mutations based on 1000 iterations. (a) Equilibrium neutral population. (b) 1% positive selection at a single locus. (c) Nonequilibrium neutral population. Demographic parameters include an 80% reduction in population size 50 Kya, with an exponential growth of 5% for the last 1000 years. (d) Background selection, with 80% of sites experiencing negative selection (coefficient of selection = 0.01). It is apparent from this figure that both demography and selection greatly reduce the number of mutations compared to neutrality.

This currently hinders genome-wide searches for targets of positive selection in humans. Another problem often ignored is the confounding effect that demography has when estimating selection (Thornton *et al*., 2007). Human populations violate the equilibrium assumptions underlying most tests of selection, being a nonrandomly mating population that has experienced past bottlenecks and growth, as well as subdivision and migration.

All of these neutral processes shape the frequency spectrum (**Figure 3**). In order to better characterize the effects of positive selection in the human genome and it is essential that next generation modelling and method development be focused around jointly estimating selection and demography, rather than simply one or the other.

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