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Rapid and Ongoing Darwinian Selection of the Human Genome

Bryan R. Cullen

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RAPID AND ONGOING DARWINIAN SELECTION OF THE HUMAN GENOME

While the theory of evolution, proposed by Charles Darwin in 1858, suggests that the ongoing selection of adaptive traits is a key characteristic of all living organisms, there is a tendency to view evolution as a historical phenomenon. Here, I review recent evidence that clearly reveals that humans have not only undergone positive selection for genetic mutations and biological properties that distinguish humans from apes, but have also undergone substantial positive selection since the dissemination of the human species out of Africa some 75,000 years ago. I will discuss the nature of the forces that have driven recent human evolution and provide illustrative examples of genes that distinguish human sub-populations. These findings suggest that Darwin's hypothesis that individuals who generate the largest number of viable offspring will, over time, contribute an ever greater percentage of a species' total gene pool is as relevant today for humans as it was for finches and dinosaurs in the distant past.

As first proposed by Charles Darwin and Alfred Russel Wallace in the mid-19th century, natural selection is a process by which advantageous traits – traits that increase the probability that their carriers will survive long enough to reproduce – will tend to be inherited by more offspring and will therefore become more common over time. When a specific trait has spread to all members of a given species, it is said to have gone to fixation; it becomes an invariant characteristic of that species. However, fixation is a process that takes many generations and generally many thousands of years, so that at any one timepoint many traits will not be fixed, so the species will include individuals that show different variants of a given trait. Moreover, the time to fixation will depend on the degree of advantage conferred by a particular trait, and some traits may never achieve fixation if the conferred advantage is slight, or, more importantly, if the population under selection exists in multiple environmental niches that differ in whether a specific trait is, or is not, advantageous. While Darwin and Wallace had no idea what determined the evolution and selection of the traits they were studying, we now realize that the morphology, biological and biochemical functions and, often, behaviour of animals is determined by the genes that make up the animal's genome. Changes in traits result from mutations of that genome, and these mutations can in many cases provide a mechanistic explanation for the novel trait that has appeared and been selected. While most people, and essentially all scientists, are in full agreement with the Darwinian hypothesis that species evolve by a process of random mutation followed by selection for advantageous, and selection against disadvantageous, traits, there is a tendency to think of evolution as something that occurred in the past, particularly when it comes to humans. In this review, I will present a brief overview of recent data that argue that significant human evolution has occurred over the last 5,000 to 20,000 years and that evolution is, in fact, likely to be occurring in the present time.

An Overview of Genome Function and Selection

In order to understand how mutations in the human, or any other, genome, exert their effect, it is important to understand how the genome functions. As shown in Figure 1, the genome consists of double-stranded (ds) DNA molecules that each consist of four deoxynucleotides abbreviated as G, C, T, and A. The first DNA strand predetermines the second DNA strand because G always pairs with C and A always pairs with T.

A major function for the genomic DNA is to give rise to the proteins that do the bulk of the work required to keep cells, and organisms, alive. The first step in this process is the copying or 'transcription' of one strand of the dsDNA molecule, by an enzyme called RNA polymerase, to give a messenger RNA (mRNA) molecule. Again, each nucleotide in the DNA determines the nucleotide sequence in the mRNA, with G pairing with C, C with G, T with A, and A with U (which replaces the T in RNA molecules; Figure 1).

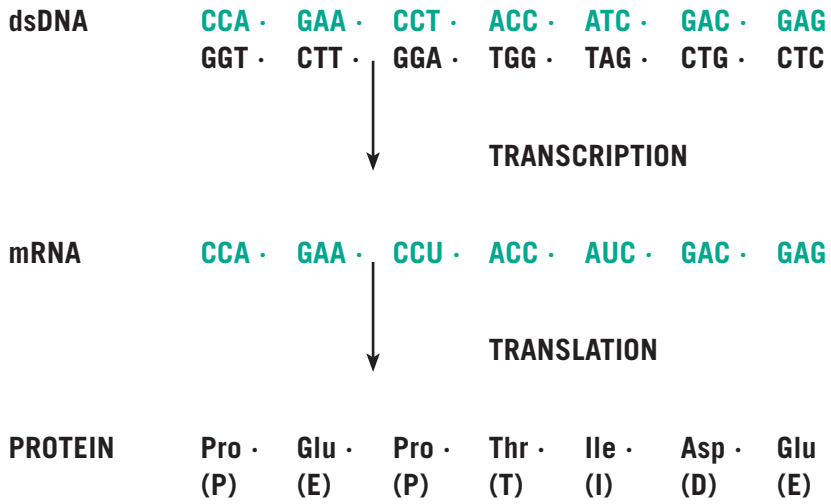

Figure 1: This figure illustrates the relationship between a double stranded DNA (dsDNA) gene, the messenger RNA (mRNA) transcribed from that gene, and the protein translated from the mRNA. The constitutive deoxynucleotides, in DNA, and ribonucleotides, in RNA, are designated by one-letter abbreviations that are here clustered into codons, each of which encodes an amino acid. The DNA 'coding' strand is shown in green. The figure shows a seven amino acid 'protein,' with three-letter and one-letter abbreviations of the constituent amino acids indicated: Pro, proline; Glu, glutamic acid; Thr, threonine; Ile, isoleucine; Asp, aspartic acid.

The mRNA molecule now recruits protein-based machines called 'ribosomes,' whose function is to synthesize proteins using the information present in the mRNA as a template, a process known as 'translation' (Figure 1). This relies on the 'triplet code' whereby each set of three nucleotides in the mRNA, a so-called 'codon,' encodes a single amino acid, the constituent molecules that make up a protein. Now, as there are four different nucleotides in the mRNA (A, U, G, and C) and there are three consecutive nucleotides in a codon, then there are 4^3, i.e., 64 potential codons. However, there are only 20 different amino acids. Therefore, even though 3 of the 64 codons actually encode 'stop' – the end of the protein being synthesized – the other 61 codons encode only 20 amino acids, so the genetic triplet code is redundant. While there are two amino acids that are specified by only a single codon, other amino acids are specified by 2, 3, 4, or even 6 different codons. In many cases, an individual amino acid will be specified by codons that are identical at positions 1 and 2 but different at position 3, the so-called, 'wobble' position. What this means is that if you randomly change (mutate) a single DNA nucleotide in a chain of DNA nucleotides that gives rise to an mRNA molecule, that change can have two effects. If the change happens to occur at position 1 or 2 of a codon, it will often change the identity of the amino acid that is incorporated into a protein

molecule when the mRNA is translated by the ribosome. A mutation that changes the amino acid incorporated during translation is called a 'non-synonymous' mutation. Conversely, if the randomly introduced single-nucleotide mutation happens to occur at position 3 in a codon, then generally this mutation will not affect the amino acid specified by this codon for incorporation into the protein during translation. Such silent mutations are referred to as 'synonymous' mutations. It is important to make the following points. Firstly, in nature, mutations are introduced randomly into the genomes of species as a result of environmental insults such as radiation or mutagenic chemicals. Secondly, once a mutation has occurred, its retention is influenced by selection based on changes in a trait. However, selection can

	mRNA sequence						protein sequence
WT SEQUENCE:	CCA ·	GAA ·	CCU ·	ACC ·	AUC ·	GAC ·	GAG	P E P T I D E
PURIFYING SELECTION:	CCA ·	GAA ·	CCA ·	ACC ·	AUC ·	GAU ·	GAG	P E P T I D E
	CCG ·	GAA ·	CCU ·	ACC ·	AUU ·	GAC ·	GAG	P E P T I D E
	CCA ·	GAG ·	UCU ·	ACG ·	AUC ·	GAC ·	GAG	P E S T I D E
dN < dS	CCU ·	GAA ·	CCC ·	ACC ·	AUC ·	GAC ·	GAA	P E P T I D E
NEUTRAL SELECTION:	CCA ·	GAG ·	CUU ·	AUC ·	AUC ·	GAU ·	GAG	P E L I I D E
	CCA ·	GAA ·	CCU ·	ACG ·	ACC ·	GAC ·	GAA	P E P T T D E
	CCG ·	GGA ·	CCU ·	ACC ·	AUC ·	GAC ·	GAG	P G P T I D E
dN = dS	UCA ·	GAA ·	CCG ·	ACC ·	AUA ·	AAC ·	CAG	S E P T I N Q
POSITIVE SELECTION:	CCA ·	GAC ·	CUU ·	ACC ·	AUC ·	GAC ·	GAG	P D L T I D E
	CCA ·	GAA ·	CCU ·	ACG ·	ACC ·	GAC ·	GAG	P E P T T D E
	CCG ·	GGA ·	CCU ·	ACC ·	AUC ·	GAC ·	GAC	P G P T I D D
dN > dS	UCA ·	GAA ·	CGU ·	ACC ·	AUC ·	AAC ·	CAG	S E R T I N Q

Figure 2: A comparison of the key characteristics of purifying selection, neutral selection, and positive selection at the molecular level. The figure shows an illustrative wild-type (WT), i.e., initial, mRNA sequence (derived from a DNA gene by transcription) and the encoded protein sequence (see Figure 1). Green letters indicate synonymous mutations and red indicates non-synonymous mutations. In fact, random mutations occur very rarely and accumulate in the genome even more slowly, so this figure greatly exaggerates the mutation rate for illustrative purposes.

only act on non-synonymous mutations, as synonymous mutations do not change protein sequences and hence do not normally exert any effect. If we then compare the sequence of a particular gene between different groups of humans, between humans and chimpanzees, or between humans and other species, we can distinguish between three forms of selection (Figure 2). The first, and most common, form of selection is 'purifying selection.' In this form of selection, the number of synonymous mutations observed exceeds the number of non-synonymous mutations. This can be expressed by the equation dN < dS, where dN is the actual number of non-synonymous mutations observed in a given gene sequence divided by the number of different possible non-synonymous mutations that could occur, while dS is the actual number of synonymous mutations divided by the potential number of synonymous mutations that could occur. The basis for purifying selection is that mutations, as noted above, occur randomly, and there is no selection against synonymous mutations. However, if the protein in question is an important contributor to the well-being of an organism, then non-synonymous mutations frequently turn out to be deleterious and are rapidly weeded out of the germ line by selection acting on the relevant trait. Because random mutations are rarely going to improve the function of a protein that acts, for example, as a structural protein or as

an enzyme, purifying selection is commonly observed over entire proteins, or at least within the key functional domains of particular proteins.

The second most common form of selection observed – neutral selection – is actually no selection at all. In neutral selection dN = dS; mutations that are non-synonymous are neither selected for nor against (Figure 2). Neutral section may be observed in unstructured regions of proteins, whose major function may only be to link two functionally relevant domains, or in proteins that have lost their functional relevance over time.

The least common, and most interesting, form of selection is positive selection, also called Darwinian or adaptive selection. In this form of selection dN > dS; non-synonymous mutations are positively selected (Figure 2). Unlike purifying selection, which selects for the maintenance of an important pre-existing function that is at or near optimum and hence resistant to change, positive selection implies acquisition of enhanced, or entirely novel, functions by a protein or a protein domain. Moreover, positive selection implies that the protein domain undergoing selection is co-evolving with a target that is exogenous to the organism whose genome is being selected, such as a pathogenic micro-organism, a predator, a food source, or members of the opposite sex. Perhaps not surprisingly, purifying selection has been found to be far more common than positive selection, as shown, for example, by a comparative analysis of the human and chimpanzee genomes (Nielsen et al., 2005), which revealed that genes undergoing strong purifying selection (dN / dS < 0.1) outnumber genes undergoing strong positive selection (dN / dS > 2.0) by ~25-fold.

Positive Selection of the Human Genome

While rare, positive selection is of great interest because positive selection can only arise by the Darwinian selection of organisms that have acquired new, advantageous traits as a result of an underlying non-synonymous mutation. Therefore, all positively selected genes must have changed some aspect of the behavior, health, or fecundity of the organism in a way that confers higher evolutionary fitness. Hence, if we can identify genes that have undergone positive selection during the evolutionary divergence of, for example, humans and chimpanzees, this can help to identify the selective pressures that led to this divergence and provide a mechanistic understanding of how this divergence came into being. Moreover, it is also possible to identify genes in the human genome that have undergone recent positive selection by comparing the genomes of geographically distinct populations of humans. This could allow the identification of selective pressures that have recently acted on, and may still be acting on, human populations.

Before describing some of the data that have been obtained, it may be useful to remind readers that anatomically modern humans, homo sapiens, are believed to have arisen in Africa some 250,000 years ago and last shared a common ancestor with chimpanzees some 5 million years ago. Humans spread from Africa to the rest of the world starting ~75,000 years ago, with a second major geographic expansion occurring after the end of the last ice age, ~14,000 years ago.

Initial efforts to define regions of positive selection in humans focused on comparisons of the human and chimpanzee genomes. For example, Nielsen et al. (2005) analyzed 20,361 primate genes and saw at least some evidence of positive selection for 3,995 of these. While most of the genomic regions undergoing positive selection encoded proteins of unknown function, or did not even coincide with known protein-coding genes, it was possible to

determine that the most common functional classes of primate genes showing evidence of positive selection included genes involved in innate or adaptive immunity (609; 15.2%), sensory perception and nutrition (206; 5.2%), or sexual reproduction (111; 2.8%). Other functional categories of genes including, perhaps surprisingly, neural function and cognition, were not over-represented among the positively selected loci.

Persuasive explanations for why genes belonging to the above three categories might be over-represented among genes undergoing positive selection can be advanced. By definition, pathogenic micro-organisms are in a state of evolutionary warfare with their potential target species, leading to an ongoing process under which host species evolve new immune defense mechanisms which are in turn countered by the evolution, by the micro-organism, of new mechanisms of immune evasion, or vice versa (Dawkins and Krebs, 1979). Species or micro-organisms that fail to keep up with this evolutionary arms race would be at a severe selective disadvantage. The hypothesis that pathogens and their targets (or predators and prey) engage in a relatively rapid form of futile antagonistic co-evolution has been termed the 'Red Queen Hypothesis' (Van Valen, 1973) based on a passage in Lewis Carroll's book 'Through the Looking Glass,' in which the Red Queen states that, 'It takes all the running you can do, to keep in the same place.' Similarly, both pathogens and target species must constantly co-evolve in order to maintain the equilibrium that allows both to exist.

In terms of sensory perception, in particular olfaction and chemosensation, it is clear that evolution can select for the ability to use – and identify – new food sources. As organisms adapt to new ecological niches or migrate into new territories, changes in available food sources are inevitable, and novel selective pressures to identify new food sources, while avoiding noxious substances, will emerge.

Finally, in terms of sexual reproduction, there is good evidence that positive selection is here driven by evolutionary competition between males to be more successful at fertilization; sperm competition (Clark and Swanson, 2005). There also may be competition between males and females, with the former benefiting from a high level of fertilization success, or from a monopoly on the available fertilizable eggs, while the latter may derive evolutionary benefits from giving birth to offspring that result from fertilization by multiple different fathers, as offspring with different fathers will show more genetic variation than offspring from only a single father and, hence, may include individuals who are fitter in an evolutionary sense.

In addition to comparing the human and chimpanzee genomes, it is also of interest to compare different human populations. Voight et al. (2006) compared the genomes of East Asians (Japanese and Chinese), Northern Europeans, and West Africans (Yoruba). These workers identified evidence for widespread positive selection in all three human populations with genes from the above three functional categories (immunity, sensory perception and nutrition, and sexual reproduction) again highly represented. In most cases, the significance of the positive selection that was observed was unclear, but a number of illustrative examples exist where the positive selection observed could be clearly linked to particular traits typical of individual human sub-populations.

i) Lactose tolerance

All mammals consume milk as infants. However, milk contains high levels of the sugar lactose, and almost all mammalian species lose their ability to digest lactose effectively once they reach adulthood. This can be viewed as the result of evolutionary selection against expression of a protein, lactose dehydrogenase (LDH), which serves no purpose once milk consumption

ceases after weaning. However, ~8,000 years ago humans succeeded in domesticating cattle in the Middle East. Domesticated cattle are, of course, useful as meat producers, but they also produce milk, a highly nutritious food whose effective digestion requires LDH. Because the ability to use this food source has the potential to confer a large selective advantage, it is perhaps not surprising that a mutation that confers LDH expression throughout life, rather than just in childhood, also arose at ~8,000 years ago in exactly the same population that had first domesticated cattle. This mutation has been selected almost to fixation in western and northern European populations (~77% penetrance) and is also found in parts of the Middle East and north India, albeit at somewhat lower levels (~30% penetrance), but is entirely lacking in sub-Saharan Africa, the Far East, and in American Indian populations (Bersaglieri et al., 2004). This is therefore an excellent example of a mutation that arose after the out-of-Africa migration and then achieved near-fixation in a sub-population of humans.

An interesting postscript arises from the fact that there are herding populations in several parts of East Africa, of whom the best known are perhaps the Masai, that also are able to consume and digest milk as adults. However, as noted above, these sub-Saharan Africans lack the mutation (the T-13910 allele) that confers LDH expression in Europeans. In fact, recent evidence (Tishkoff et al., 2007) demonstrates that in these populations lactose tolerance arises from an entirely distinct mutation in the LDH gene, termed the C-14010 allele, that nevertheless exerts the same phenotypic effect. This second mutation apparently arose independently, ~4,500 years ago, coincident with the spread of pastoralism to East Africa from Egypt, and has again been strongly positively selected. However, due perhaps to its more recent origin, the penetrance of the C-14010 allele in East Africa is only ~40%, clearly lower than that seen for the older T-13910 allele in Europe.

ii) Skin pigmentation

An obvious difference between East Asians and Northern Europeans on the one hand, and West Africans on the other, is the fact that the former have much lighter skin. Dark skin is advantageous in sunny climates, where it protects against sunburn. Conversely, light skin allows more light to penetrate, resulting in more Vitamin D production and, hence, healthier bone development. The latter trait is therefore selected in areas where sunlight is only available on a limited basis (e.g. Durham, England).

Comparative analysis of the genomes of human sub-populations reveals that light skin (as well as light hair and light eyes) results from the combined action of mutations in several genes called OCA2, MYO5A, DTNBP1, TYRP1, and SLC24A5 (Voight et al., 2006). Remarkably, mutations in each of these genes – all leading to lighter skin – can be shown to be under strong positive selection in Northern European and/or East Asian populations. In Northern Europeans, the key gene appears to be SLC24A5, which appears to have undergone a random mutation, perhaps as recently as 6,000 years ago, that has subsequently undergone strong positive selection (Lamason et al., 2005). The relevant genomic variant is now present in 98-100% of Northern Europeans, yet in less than 7% of sub-Saharan Africans or East Asians.

Of course, East Asians are also light skinned, so why do they lack this key mutation in SLC24A5? In fact, it appears that light skin in East Asians evolved essentially independently, although the mechanisms underlying this evolution are complex and remain to be fully elucidated (Norton et al., 2007). So again, we see here evidence for the recent, strong positive selection of a phenotype (light skin) that arose via distinct mechanisms in two human populations due to positive selection of different, randomly occurring mutations.

iii) Disease resistance

As noted above, disease resistance is likely to be the single most prevalent driver of positive selection and many examples of disease resistance mutations have been identified in humans. One good example relates to a mutation that confers resistance to the Plasmodium vivax strain of malaria. This mutation, termed the FY*O allele of the Duffy locus, is extremely common in Africa, having achieved full fixation in some areas, but is rarely detected outside Africa (Figure 3; Sabeti et al., 2006). This represents another good example of the rapid selection of a novel trait in quite recent human history, i.e., over the last 50,000 years or less.

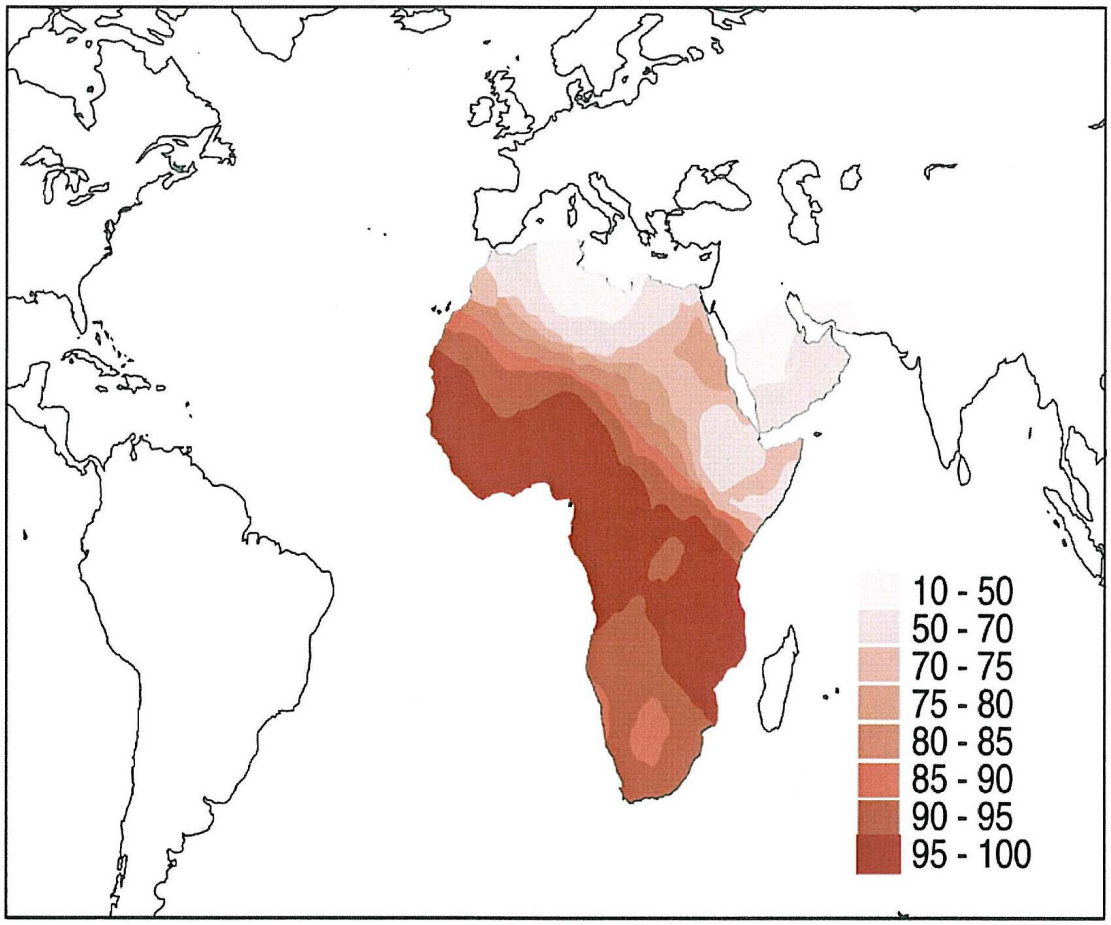

Figure 3: An example of rapid Darwinian selection of a gene in a single human sub-population. This figure presents the geographic distribution of the FY*O mutation of the Duffy locus, which confers resistance to Plasmodium vivax malaria. Note that this positively selected mutation has moved to fixation in parts of Africa but is essentially absent outside this continent. (From Sabeti P. C. et al., 2006, *Science* 312: p. 1617. Reprinted with permission from AAAS.)

A second good example of positive selection by pathogenic micro-organisms is provided by the primate APOBEC3G gene. The APOBEC3G protein can function as a potent inhibitor of pathogenic retroviruses and has the potential to block the replication of human retroviruses such as Human Immunodeficiency Virus Type 1 (HIV-1; Cullen, 2006). Unfortunately, HIV-1 has evolved a protein called Vif that binds to human APOBEC3G and induces its degradation before it can inhibit HIV-1 replication. While it might appear that APOBEC3G therefore no longer serves a useful function, this would be incorrect. In fact, human APOBEC3G retains the ability to block very effectively the replication of a wide range of retroviruses that are found in monkey and rodent species and thereby acts to prevent these retroviruses from establishing potentially serious zoonotic infection in humans (Cullen, 2006).

Interestingly, the APOBEC3G gene shows clear evidence of high levels of positive selection during primate evolution (Sawyer et al., 2004), thus suggesting that the human APOBEC3G gene has been engaged in an ongoing adversarial evolutionary struggle with potential and actual retroviral pathogens.

Conclusions

This brief overview of the current understanding of positive selection of the human genome suggests several conclusions. The first of these is that evolution is not something that occurred in the Cenozoic or Jurassic era and then stopped. Rather, ongoing evolution is a defining characteristic of all species, including humans, and continues to occur all around us. There is no doubt that 100,000 years from now there will be quite a different flora and fauna inhabiting the Earth and, if humans still exist, they will be quite different too.

A second point arises from the fact that there is clear evidence for positive selection at hundreds of loci for human populations that were, until very recently, geographically isolated. As positive selection of a random mutation can only occur if an advantageous trait is also undergoing positive selection, this implies that human sub-populations differ in multiple traits that are significant enough either to promote or hinder the survival of humans in the particular environment that they inhabit. Therefore, human sub-populations are indeed genetically somewhat different from one another, although what these encoded differences are, and whether they remain functionally significant in today's world, is currently unclear.

Acknowledgments

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Insights is edited by Susan J. Smith, IAS Director and Professor of Geography.
Correspondence should be directed to Audrey Bowron (a.e.bowron@durham.ac.uk).