Understanding the Evolution of Human Pigmentation: Recent Contributions from Population Genetics

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Variation in human skin and hair color is one of the most striking aspects of human variability, and explaining this diversity is one of the central questions of human biology. Only in the last decade or so has it been realistically possible to address this question experimentally using population genetic approaches. On the basis of earlier studies in mice, and on studies in humans with various Mendelian disorders, many of the genes underpinning population variation in skin color have been identified. More recently, genome-wide approaches have identified other loci that appear to contribute to pigmented variation. The ability to study sequence diversity from world populations has allowed examination of whether the observed variability is due to random genetic drift or is a result of natural selection. The genetic evidence taken as a whole provides strong evidence for natural selection, functioning so as to increase pigment diversity across the world’s populations. Future larger studies are likely to provide more details of this process and may provide evidence for exactly which mechanistic pathways have mediated selection.

Defining the role of natural selection in explaining variation in human skin and hair color is one of the classic problems of human biology (Cavalli-Sforza, 2001; Barsh, 2003; Rees, 2003; Jablonksi, 2004; Diamond, 2005; Robins, 2005, 2009; Parra, 2007). Why exactly do humans vary in skin and hair color, and what explains the longstanding correlations between skin pigmentation and geographical and genetic ancestry? Is this variation a reflection of physiological necessity or merely a reflection of the play of chance in the development and growth of our species? To put the question provocatively, what exactly are red hair and freckles for?

In this article, we set out to review how recent work on human population genetics affects our knowledge of human evolution. Our target is the nonspecialist skin biologist and dermatologist. Understanding human evolution is in part a historical science, and answering many questions requires contributions from many fields—genetics, physiology, animal evolution, anthropology, human history and geography, and medicine to name but a few. Our aim is to produce a coherent overview of what we take to be some of the key findings of recent work—but with the emphasis on how modern population genetics has provided strong evidence for natural selection contributing to human skin pigment diversity. Even within this narrow field, we have had to choose breadth over depth, although we have tried to provide appropriate references for those wishing to pursue the topic more deeply. There are three issues worth flagging up. First, using genetic techniques to address evidence for, or against, natural selection is a problem that requires a reasonable level of statistical insight. This is unavoidable. Second, we do not discuss in any depth the cell biology or physiology of pigmentation, as there are several pertinent reviews available (Nordlund et al., 2006; Costin and Hearing, 2007; Sturm, 2009). Furthermore, we would argue that one virtue of the recent work in population genetics is to allow (and presage further) experimental testing of the various competing hypotheses that physiologists and cell biologists have proposed. Finally, we do not discuss the relationship between skin color and society, or the role of sexual selection in explaining skin color diversity (Aoki, 2002; Jablonski, 2004; Robins, 2005).

**WHY NOW?**

Natural selection functions on genetic variability such that, depending on an individual’s genotype, an individual either produces more or fewer offspring. That is, the level of fitness varies between individuals. It is self-evident in humans—unlike say in some model organisms—that we cannot distinguish fitness differences easily: the contribution of genetic inheritance may be small compared with the importance of social, cultural, environmental, or chance factors that influence reproductive success. Our task, then, is to infer selection from the evidence detected in a range of data. What has markedly changed the nature of this task is our increased ability to produce and interpret genetic data and sequence variation. There are two reasons for this change with respect to human pigmentation. First, the combination
of preexisting resources such as the mouse fancy (and more recently zebrafish), coupled with both positional cloning in humans and candidate gene approaches based on work in mice, has allowed the identification of many genes involved in human pigmentation (Sturm, 2009). This initially took the form of finding the genes that caused the highly penetrant Mendelian disorders such as the various types of albinism (Sturm, 2009). Subsequently, variants of some of these genes or single-nucleotide polymorphisms (SNPs) close to these genes (see Table 1 for a list of relevant loci) were found to contribute to normal variation in pigmented phenotype within a Mendelian framework (the distinction here is between Mendelian traits and complex traits). For instance, the melanocortin 1 receptor (MC1R) was found to not only explain the quasi-Mendelian trait of red hair (Valverde et al., 1995) but also contribute to skin color, sun sensitivity, and other pigimentary traits such as freckling in the wider non-red-haired population (Flanagan et al., 2000; Healy et al., 2000). Second, high-throughput sequencing has allowed rapid examination of associations between pigmentation traits and multiple loci across whole genomes. In the span of 20 years, we have gone from knowing little about any of the genes involved in human pigmentation to a position where quantitative models of the contribution of loci to human pigmentation are available (Naysmith et al., 2004; Oh et al., 2004; Lamason et al., 2005). This area of pigment biology has been well reviewed (Sturm, 2009). Assessing evidence of evolution and natural selection requires the analysis of the basic unit of genetic change—sequence diversity. The knowledge of many more genetic variants associated with diversity in human pigmentation has opened up new opportunities for assessing the role of selection in their evolution.

**HOW IS NATURAL SELECTION DETECTED BASED ON ANALYSIS OF GENETIC SEQUENCE?**

It may appear counterintuitive, but a large part, if not the majority, of genetic change in human populations is not thought to be due to natural selection but rather due to the play of chance (genetic drift; Harris and Meyer, 2006; Li et al., 2008; see Table 2 for a glossary of terms frequently used in population genetics). Many opportunities for chance can occur in the transmission of alleles from parents to offspring, and evidently did occur as part of the demographic process of dispersal out of Africa. Thus, finding differences in the frequency of alleles at a particular locus between populations is not an evidence of natural selection per se. The default position is that of neutral theory, whereby chance events account for most patterns of genetic diversity (Harris and Meyer, 2006). Of course, deleterious mutations will be selected against (purifying selection) and beneficial mutations may increase in frequency to fixation, but overall these events will contribute little to explaining the presence of most polymorphisms. One advantage of this framework is that it makes testable theoretical predictions about sequence diversity. When sequence data are examined for evidence of selection, we seek statistical evidence for departures from what we would have expected under neutral theory. This will be familiar to most experimentalists in the way that classical-frequentist statistics test whether the evidence is strong enough to allow the “null hypothesis” to be rejected. In the case under discussion here, an expectation under neutral theory is the null hypothesis. If the distribution of the data is such that it would rarely occur under neutral theory, then the data are taken as providing evidence for selection. Note that finding evidence for selection does not in itself determine what selective factors are operating. Harris and Meyer (2006) provide a simple taxonomy of available statistical procedures accessible to the nonexpert, but we would highlight some of the key points below.

- Ratios of nonsynonymous (NS) to synonymous (S) change. NS and S changes will affect function differently, with NS change much more likely to affect function. Although high rates of NS/S provide evidence of positive selection and low rates of NS/S provide evidence of purifying selection, under strict neutrality the predicted ratio would be close to unity. Where these ratios differ for diversity within species in comparison with divergence between species, changes in selective pressures are implicated.
- Levels of neutral polymorphism depend on mutation rate and evolutionary population size. Alleles change frequency under genetic drift in random trajectories over time spans predicted by the evolutionary population size. Polymorphism at any particular site is a transient state, but the time taken for a new variant to replace its

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**Table 1. The full names or associated clinical syndromes for some abbreviations used in the text with selected OMIM (Online Mendelian Inheritance in Man) numbers**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full name or associated clinical syndrome</th>
<th>OMIM number</th>
</tr>
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<tbody>
<tr>
<td>ASIP</td>
<td>Agouti signaling protein</td>
<td>600201</td>
</tr>
<tr>
<td>ATN</td>
<td>Attractin</td>
<td>603130</td>
</tr>
<tr>
<td>DTNB1</td>
<td>Hermansky-Pudlak type 7</td>
<td>614076</td>
</tr>
<tr>
<td>HERC2</td>
<td>Noncoding downstream of OCA2. Affects expression of OCA2</td>
<td>227220</td>
</tr>
<tr>
<td>KITLG</td>
<td>Kit ligand</td>
<td>184745</td>
</tr>
<tr>
<td>MC1R</td>
<td>Melanocortin-1-receptor</td>
<td>155555</td>
</tr>
<tr>
<td>MYO5A</td>
<td>Myosin V (Griscelli syndrome 1)</td>
<td>160777</td>
</tr>
<tr>
<td>OCA2</td>
<td>Oculocutaneous albinism 2</td>
<td>611409</td>
</tr>
<tr>
<td>RAB27A</td>
<td>Griscelli syndrome 1</td>
<td>607674</td>
</tr>
<tr>
<td>SILV</td>
<td>Melanoocyte protein 17</td>
<td>155550</td>
</tr>
<tr>
<td>SLC24A5</td>
<td>Solute carrier family 24, member 5</td>
<td>609802</td>
</tr>
<tr>
<td>SLC45A2</td>
<td>Solute carrier family 45, member 2</td>
<td>606202</td>
</tr>
<tr>
<td>TYRP1</td>
<td>Tyrosinase related protein 1</td>
<td>203290</td>
</tr>
<tr>
<td>TRPM1</td>
<td>Melastatin</td>
<td>603576</td>
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ancestors (fixation) is typically long. Under positive selection, a favored mutation has a rapid rise in frequency, which will also lead to a reduction in overall diversity close to the site, a change known as a selective sweep. New mutations will eventually restore the neighborhood heterozygosity; however, as this occurs at the slower pace of neutral evolution, a detectable footprint of selection remains for some time. 

- Differences in the fixation index between populations within a species. If a particular allele increases fitness in one population but is either not present in another population or was not selected for in this other population, then the differentiation between the populations is increased. Outliers in the distribution of the fixation index can be judged using predictions based on neutrality.
- Linkage disequilibrium. Over many meiotic stages, regions within a chromosome are shuffled (recombined) between homologs such that the farther they are from each other the less likely they are to stay together. This process breaks up any physical linkage between the segregating sites of multiple polymorphisms. The older any sequence variants are the more likely that they will have been shuffled (and hence may attain “linkage equilibrium with each other”). However, if the time taken to become shuffled is longer than the time taken for variants to be lost by genetic drift, then linkage equilibrium may not be attained, and the resulting linkage disequilibrium establishes haplotypes. Different human populations typically differ in haplotype composition through the interplay of mutation, recombination, and genetic drift. If a mutation arises that improves fitness, then a selective sweep occurs. The rapid increase in frequency extends the typical haplotype length over what we would have expected if there were no change in fitness. As part of the same process, the local diversity is reduced. These properties lend themselves to whole-genome SNP-based analyses that examine the extended structure of haplotypes.
haplotype homozygosity (EHH; Sabeti et al., 2002). A selective sweep increases the favored haplotype to a high frequency and extends the surrounding haplotype, generating high EHH values, compared with patterns seen elsewhere in the genome as a result of drift. Note that such approaches allow scanning of the entire genome and identification of areas that might be under selection without prior knowledge of what functions particular loci serve.

The above principles guide interpretation of sequence data, but of course rely on certain assumptions. Population expansion or bottlenecking will lead to violations of neutral models that assume constant population size (Harris and Meyer, 2006; Tang et al., 2007; Laval et al., 2010). One major advantage of genomic scans is that they inform the neutral “null” model and reveal evidence for selection. The principle here is that demographic changes should affect all neutral loci, whereas the focus of selection will be on particular physiological pathways. Whole-genome scans also allow empirical testing where literally tens of thousands of SNPs are examined, and results that appear to be outliers in terms of change are viewed as candidates for evidence of having undergone selection (Voight et al., 2006; Tang et al., 2007).

**SELECTION AT THE MC1R**

The MC1R was the first gene identified in humans that determined normal variation in pigmentation characteristics (Rees, 2000). It encodes a seven-pass transmembrane receptor that signals via cAMP and alters (at least in hair if not skin) the ratio of pheomelanin to eumelanin. The gene was identified in mouse and underpinned the previously described extension locus. The α-melanocyte-stimulating hormone functions as an agonist at the mc1r; in the mouse, at least there is clear evidence that agouti antagonizes this effect (Robbins et al., 1993). For a recent review, see Beaumont et al. (2011). The fact that the MC1R is under 1 kb and is devoid of introns facilitated analyses with the sequencing technology available at that time (Rees, 2000).

Early studies showed that the MC1R was highly polymorphic in Northern European populations, with many loss-of-function alleles or diminished-function alleles present at high frequency (Smith et al., 1998). The majority of those with red hair were compound heterozygotes for two of these alleles, but there was also a clear effect of single alleles on freckling, skin color, scalp hair color, and beard color (Flanagan et al., 2000). Chemical analyses of hair melamins showed this heterozygote effect (Naysmith et al., 2004). However, the limited studies in human skin found that only homozygotes with diminished-function alleles tended to have lower amounts of both pheomelanin and eumelanin, rather than a simple alteration in the ratio as with hair (Hennessy et al., 2005; for the situation in mouse, see Van Raamsdonk et al., 2009). Individuals harboring one of a range of variant alleles are predisposed to both non-melanoma skin cancer and melanoma skin cancer, as well as freckling (Valverde et al., 1996; Smith et al., 1998). Subsequent functional studies and population studies have further defined the functional status of a range (but not all) of these alleles, which today number over 65 (Wong and Rees, 2005). Studies of Neanderthal DNA have also shown changes in MC1R that would be predicted to lead to a red-haired phenotype (the particular mutation seen has not been found in modern-day humans).

The degree of variation at MC1R was unexpected and subsequent population studies by Harding et al. (2000) and Rana et al. (1999) showed that this variation was largely restricted to European populations when compared with African or Asian samples (nucleotide diversity rates of 0.12%, 0.09%, and 0.07%, respectively). What was equally striking was that the pattern of nucleotide change differed between Northern European populations and the others examined. In the European populations, NS changes predominated, whereas the majority of changes seen in African populations were synonymous. Subsequent studies (John et al., 2003) have detected some NS changes, although the African populations sampled were from South Africa rather than the populations from central and western Africa in the earlier studies.

This pattern of diversity is of course unusual in that for most genetic loci diversity within African populations is higher than the diversity in other world populations (Cavalli-Sforza, 2001). Both Harding et al. (2000) and Rana et al. (1999) analyzed the pattern of MC1R diversity, and agreed that there was functional constraint on MC1R in African populations. However, they proposed different interpretations of the reason for diversity in Northern European populations. Harding et al. (2000) argued that NS mutations of this gene diminished fitness and were therefore selected against in Africa, but that relaxation of this constraint outside of Africa was sufficient to explain the observed diversity (Robbins et al., 1993). Conversely, Rana et al. (1999) argued in favor of diversifying selection. In other words, Harding et al. (2000) argued that the diversity seen in Europe was not a result of selection (for loss-of-function or diminished-function alleles), but because there was little fitness difference between any of these alleles. The observed data were not sufficient to reject the neutral theory hypothesis. In contrast, Rana et al. (1999) argued that the role of mutation at MC1R was such as to have actively been selected for presumably on the basis of a fitness advantage of a paler skin color. Harris and Meyer (2006) provide a critical review of these two papers. Large studies with greater population sampling might resolve some of these differences in interpretation. As we will see, the MC1R data are of interest in themselves because not all pigment genes show the same evolutionary patterns, and also because the pleitropy of MC1R cautions against evidence based on one gene only.

**SLC24A5**

Differences in pigmentation are clearly not just due to alterations in the ratio of eumelanin to pheomelanin (“pigment switch”). Indeed, as previously mentioned, although this switch is clearly evident in studies of mouse or human hair, studies in human skin are less convincing.

Pigmentation in human skin reflects a complex series of cellular processes, which at the least involve the production
of a myriad of different melanin polymers, the packaging of these products into melanosomes, and the transfer of these melanosomes into the surrounding keratinocytes. The pattern adopted by these melanosomes after they have been taken up by keratinocytes may also be important in photoprotection, and it is well known that the size and shape of melanosomes differ between people with differences in skin color (Nordlund et al., 2006).

Although, historically, mouse mutants have been the focus of comparative pigment geneticists, the zebrafish have also in recent years provided important insights. Zebrafish that are homozygous for the golden mutation show hypopigmentation of the skin and retinal pigmented epithelium. The pigment granules in these tissues are less dense and smaller. Lamason et al. (2005), using linkage and morpholino knockdown experiments, cloned and identified the golden gene, which in humans is known as SLC24A5. SLC24A5 based on sequence is a member of the family of potassium-dependent sodium-calcium exchangers. Lamason et al. (2005) noted a polymorphism in the gene with the G and A alleles of the SNP rs1426654 encoding alanine or threonine, respectively, at amino acid 111 in the third exon. This SNP had previously been shown to vary in frequency between populations with different ancestries, ranging from over 98 to 100% for the Thr111 variant in European populations, whereas in African or East Asian populations the Ala111 allele had a frequency of 93–100%. These differences are striking, highly unusual for the vast majority of SNPs, and of course compatible with selection to almost fixation. To confirm the role of selection, the authors noted that the pattern of heterozygosity around SLC24A5 was less compatible with a selective sweep having taken place under positive selection in European populations. Physiological studies in admixed populations showed that the allele has a direct effect on skin color, measured spectrophotometrically (Lamason et al., 2005). Differences in SLC24A5 do not, however, account for differences in skin color between Africans and East Asians because the ancestral allele (Ala111) is found in both.

**SLC45A2 (ALSO KNOWN AS THE MEMBRANE-ASSOCIATED TRANSPORTER PROTEIN (MATP))**

Mutations of SLC45A2, another solute carrier similar to SLC24A5, underlie oculocutaneous albinism type 4 (OCA4; Newton et al., 2001). Other polymorphisms have also been detected in this gene and are associated with pigmentation phenotypes (Graf et al., 2005), as well as with ancestry. Soejima et al. (2006) studied the pattern of diversity in this gene within the coding and exon-flanking regions. They found lower diversity than expected under neutrality only in those of European descent; they also found that one haplotype was overrepresented in European populations, in keeping with a positive selective sweep (for lightening of skin color; Soejima et al., 2006). As for MC1R, SLC45A2 was under constraint in African populations.

**WHOLE-GENOME STUDIES AND RELATED METHODS**

The studies described above have focused on single genes. The MC1R is small and easily sequenced, and coding region variants are very frequent in European populations. SLC24A5 and SLC45A2 were identified on the basis of work in model systems and human studies that examined candidate SNPs in terms of effect on phenotype, ancestral distribution, and subsequently whether there was evidence for selection.

The development of high-throughput sequencing methods over the past 10 years has, however, allowed new approaches to the study of genes involved in human pigmentation. Genome-wide scans have both confirmed a role for a number of candidate genes in human pigmentation—previously identified on the basis of work in the mouse or other model systems—and identified new loci, which with further work are likely to be found to be causal in explaining human pigmentation differences (Sulem et al., 2007, 2008; Han et al., 2008). These include, as well as the ones discussed above, TYR, TYRP1, OCA2, ASIP, KITLG, and loci that were previously not suspected to harbor a role in pigmentation, including SLC24A4, IRF4, HERC2, and TPCN2 (for a review of relevant cell biology, see Sturm, 2009).

Knowledge of the loci implicated in determining pigmentation characteristics coupled with the statistical methods described earlier has allowed several groups to seek evidence for natural selection at a number of different candidate loci. Examples include Lao et al. (2007), who used EHH evidence for inferring positive selection in European populations at a number of pigmentation loci including at OCA2, TYRP1, and KITLG, as well as in Asians (OCA2, DCT, KITLG, EGC3, and DRD2); Izagirre et al. (2006), who have conducted similar candidate-based studies, although their results differ from some others in the literature (see Lao et al. 2007 for a critique); and Norton et al. (2007), who analyzed FST for known pigmentation genes to suggest that ASIP and OCA2 may be involved globally in explaining skin color adaptations, whereas other loci, such as SLC24A5, MATP, and TYR, may have contributed to adaptation in European populations but not in East Asian populations.

However, the most powerful approaches have scanned the whole genome, looking for evidence of loci that, on the basis of EHH statistics, look as though they have been subjected to selective sweeps (Sabeti et al., 2002, 2007). One advantage of this approach is that it allows the distribution of values across the genome for EHH to be calculated and then interest focused on those loci that show extreme values, the assumption being that if EHH values are unusually high then selection is likely. The resulting areas can then be summarized and interpreted on the basis of likely physiological functions. Thus, if a screen finds that many of the genes with high EHH values are involved in pigmentation, or immunity, or absorption of dietary products, then it is possible to paint a picture of how our environment has shaped our recent biological history.

Voight et al. (2006) used data from the International HapMap Project to create a first-generation map of selection across the human genome. Their chief test statistics were derived from the EHH principle. They showed, as expected, that genes involved in fertility and reproduction are subject to rapid adaptive evolution, but that some of the strongest signals of recent selection were for genes involved in...
pigmentation in Europeans, including OCA2, MYO5A, DTNBP1, and TYRP1. The technique they used has limited power where alleles have achieved fixation or are close to fixation, but signals for SLC24A5 were also strong. These signals of selection for pigmentation postdated the divergence of the three main population groups around the world (Africa, Europe, and Asia). Other statistical analyses—but still based on EHH—have also confirmed some of these same pigmentation loci (MYO5A and SLC24A5) as being under selection using data sets from both the HapMap Project and Perlegen Sciences (Tang et al., 2007), and SLC24A5 and SLC45A2 as being under positive selection in Europe (Sabeti et al., 2007; Barreiro et al., 2008). Loci identified as being related to pigmentation and showing evidence of selection in one or more studies include OCA2, TYRP1, DNTPB1, SLC24A5, MYO5A, SLC45A2, ABCC11, KITLG, MATP, HERC2, SILV, TRPM1, RAB27A, and ATRN. The HapMap and Perlegen data sets have limited sampling with only one or two populations from within the main regions (Africa, Europe, and East Asia). Pickrell et al. (2009) therefore looked at just under 1000 individuals from 53 world populations using the Human Genome Diversity—CEPH Panel. They used EHH and related statistics, as well as looked at FST. For some population comparisons (e.g., Europe vs. Africa), differences in allele frequencies were much greater for various, previously identified, pigmentation genes than those typically found for other loci, and haplotype analyses again showed evidence for selection of SLC24A5 and KITLG. They also found evidence for selection of genes such as MLPH and RGS19, which are known to have a role in pigmentation in other mammals, but not to date in humans. Finally, echoing some of the work of Norton et al. (2007), they note that different genes may cause skin lightening in different parts of the world (i.e., the causes of lightening in European populations may differ genetically from lightening in East Asians).

Linking Genes with the Physical Environment

Another powerful use of whole-genome SNP analysis has been an attempt to link markers of selection with measures of climatic change directly. It has been long known that climatic factors are important determinants of species distribution and are likely key determinants of phenotypic variation. Examples would include change in body shape and mass with temperature, and of course skin pigmentation. Hancock et al. (2011) have correlated allele frequencies at a range of SNPs and climate variables such as solar radiation, humidity, precipitation, and so on. They report a striking enrichment of genic and nonsynonymous SNPs relative to nongenic SNPs among those that are correlated with climate variables. Changes in SLC24A2 and OCA2 were particularly noteworthy, but also of relevance was a SNP in keratin 77 (KRT77), a gene that is expressed in sweat glands, and genes involved in UVR-related DNA repair. As they state, a common theme of their analyses and other similar analyses is that genes involved in pigmentation and UV radiation are among those with the strongest signals of selection.

What Drives Natural Selection?

Just over 10 years ago, the world literature on genetic evidence for natural selection on human pigmentation comprised only two papers, both dealing with sequence diversity in the only gene then known to have a role in normal (rather than pathological) pigmentation variation, the MC1R. Rana et al. (1999; Harding et al., 2000). Subsequent candidate-based approaches show evidence for SLC24A5 (Lamason et al., 2005) and SLC45A2 (Soejima et al., 2006). Unbiased scans using a range of techniques to detect selection have now involved a range of loci including OCA2, TYRP1, DNTPB1, SLC24A5%, MYO5A, SLC45A2, ABCC11, KITLG, MATP, HERC2, SILV, TRPM1, RAB27A, and ATRN (Hancock and Rienzo, 2008).

The breadth of this evidence is important (Pritchard et al., 2010). The pattern of selection is not the same in all populations studied, with different alleles being selected for skin lightness in some European and Asian populations, and evidence of sweeps for many but not for MC1R. For technical reasons relating to the diversity and representation present in many genome-wide studies, there may be a bias toward genes important in European populations rather than African populations (Pritchard et al., 2010; Casto and Feldman, 2011). African populations remain under strong selective forces, and although the majority of pigment diversity is between continents, there remains substantial pigmentation variation within Africa (Relethford, 2002), which is as yet largely unexplained in genetic terms.

Ascribing single functions to some genes may on occasions also be premature. Perhaps the clearest example is again the MC1R. The MC1R was identified on the basis of its coat color phenotype in the mouse. Human studies reasonably focused on association studies between allelic variants and the pigmentary phenotype, and particularly, given the thrust of this essay, the relationship between its evolution and ambient UVR exposure. The fact that MC1R has a role in photoprotection is compelling, but should we necessarily attribute MC1R diversity to the inverse of the same selective pressures? Consider the unexpected findings in 2005 of pain researchers who found that in the mouse,_mc1r_had pronounced effects on responses to some types of pain stimuli (Mogil et al., 2003). Subsequent studies have extended this work into humans, and although the effect on phenotype appears complex and confined to the females, the effect appears real, although the mechanism is unknown (Mogil et al., 2003; Delaney et al., 2010). This inevitably emphasizes the importance of studying groups of genes sharing some commonality or overlap of function over evidence from just a single locus, where unexpected phenotypes could undermine what appear to be clearcut conclusions. Similarly, the study by Hancock et al. (2011) relating selection to measures of ambient UVR allows not only the study of pigmentation phenotypes but also of genes that have a role in UVR-induced DNA repair. Furthermore, thinking in terms of physiological pathways seems appropriate. However, another caveat here is required; although sequence changes over a range of genes that affect pigmentation may strengthen the overall case for selection
on pigmentation, one can also ask—as for MC1R and pain—whether other factors could be driving changes in some genes independently of affects on skin color and photoprotection. To speculate beyond the remit of this essay, do changes in MC1R reflect some form of sexual selection for red hair and porcelain skin? It is beyond the nature of the evidence available to us to make a reply.

The available studies do not tell us why pigmentation has been the subject of natural selection, why dark skin has been selected for in sub-Saharan populations, or why lighter skin has been selected in European populations and in some of the Asian populations (Relethford, 2002). The conventional explanation is of course that this variation is related to ambient UVR, and indeed studies such as those of Hancock et al. (2011) are quite compatible with this. Of course, compatible does not mean that they are correct. Nevertheless, most opinion converges on the idea that human interfollicular pigmentation evolved to compensate the loss of body hair in our ancestors, driven by the need for effective sweating, an activity that is severely limited by a dense coat or sunburn. The evidence presented strongly argues that the skin color of ancestral modern humans was dark, and this pigmentation provided a defense against UVR damage. As our ancestors migrated out of Africa, the need for such effective protection diminished and indeed as we have learned, paler skin—skin that receives more damage from UVR—was favored. The time course of these latter changes are not known with any confidence (ranging from 6,000 years to over 50,000 years), nor is there tight agreement on the time course of our recent demographic history (Laval et al., 2010).

The principal theories relating to variation in pigmentation and UVR relate to vitamin D biosynthesis, folate depletion, sunburn, skin cancer dysfunction (reviewed by Robins, 2005; Juzeniene et al., 2009), or barrier dysfunction (Elia et al., 2009). The presence of dark skin protects against sunburn and possibly folate deficiency, whereas in areas with less ambient UVR, lightening of the skin is necessary to allow sufficient vitamin D biosynthesis, and the problem of sunburn or skin cancer or folate deficiency is relatively less (Robins, 2005). It is difficult, however, to conjure up experiments to meaningfully test these various hypotheses. For instance, skin cancer is often judged to be irrelevant because it affects individuals usually of a post-reproductive age. However, we know that extreme syndromes such as xeroderma pigmentosum and albinism (Robins, 2005; Parra, 2007) show markedly impaired fitness, and quantitative data on how those with pale skin would manage in equatorial regions without the coat or sunburn. The evidence presented strongly argues that the skin color of ancestral modern humans was dark, and this pigmentation provided a defense against UVR damage. As our ancestors migrated out of Africa, the need for such effective protection diminished and indeed as we have learned, paler skin—skin that receives more damage from UVR—was favored. The time course of these latter changes are not known with any confidence (ranging from 6,000 years to over 50,000 years), nor is there tight agreement on the time course of our recent demographic history (Laval et al., 2010).

The role of vitamin D in our physiology over our evolutionary past is hard to definitively judge. It is clear that our cereal-based diet in historically recent times coupled with life at Northern latitudes provides a vitamin D-poor diet. However, problems remain as to whether this is the explanation for skin lightening in earlier periods. Whereas we have a good idea of what levels of vitamin D are required for bone health early in life, we are uncertain about what levels are needed for a number of other putative biological functions, including resistance to infectious diseases. Our knowledge of how these various factors affected over the past 5–50,000 years is scant, as is direct evidence of our vitamin D status over all but recent historical times. There are similar gaps in our knowledge about whether variation in pigmentation can be accounted for in terms of selection against UVR degradation of folate.

Given the historical nature of the subject matter, it may seem easy to be pessimistic that we will obtain answers to these questions. However, just over 10 years ago it was hard to imagine the results we have now: that merely by relating patterns of DNA variation to population and to measures of environmental stress (and there is no good reason to imagine there have been significant global changes in UVR over the last millions of years), clusters of genes involved not only in pigmentation but also in cellular responses to UVR DNA damage would be flagged up by tests for selection. It seems possible at least that as we learn to burrow down further into our shared DNA that other footprints of physiological stress—vitamin D deficiency or folate deficiency—might have caused patterns of diversity that function as tracers for those forces that have shaped us. Finally, our knowledge of the genes underpinning pigmentation, and the technical ability to identify DNA from Neanderthals and other hominins (Laleuza-Fox et al., 2011), means that there may still be a lot to learn about why we look the way we do. As is often repeated, evolution is the greatest story ever told, and there will surely be more episodes, if not surprises, to follow.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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