MELANOCYTES/MELANOGENESIS

Unpacking Human Evolution to Find the Genetic Determinants of Human Skin Pigmentation

Ellen E. Quillen[1] and Mark D. Shriver[2]

[1]Department of Genetics, Texas Biomedical Research Institute, San Antonio, Texas, USA and [2]Department of Anthropology, Penn State University, University Park, Pennsylvania, USA

Correspondence: Mark D. Shriver, E-mail: mds17@psu.edu

doi:10.1038/skinbio.2011.3

How many genes determine variation in human skin color? The apparent simplicity of the question is belied by the complex evolutionary history of our species with regard to this trait. This question was first addressed in a seminal 1964 paper, ''On the inheritance of human skin colour,'' by Harrison and Owen (1964). This work is notable in (1) using reflectance spectroscopy to quantify skin pigmentation; (2) focusing on population samples with varying levels of genetic admixture; and (3) using a genetic approach to investigate evolutionary questions.

Prior to the adoption of reflectometry-based measurements of skin pigmentation, researchers relied on subjective assessments of pigmentation using reference tiles like those produced by Felix von Luschen. Although they have been widely used for 50 years, these tiles result in rough categorical estimates with large inter-observer error (unpublished data) unsuitable for quantitative genetic analysis. Harrison and Owen, on the other hand, measured reflected light across the visible spectrum in relatively unadmixed West Africans and Europeans, as well as in four admixed groups (F_1 hybrid, European backcross, West African backcross, and F_2 hybrid). By using measurements that were truly continuous and considering both population means and variance, these investigators were able to estimate the quantitative genetic underpinnings of this trait and, in doing so, established the importance of admixed human populations in studies of skin color. Without this innovative approach to measuring skin color in appropriately identified admixed populations, many of the recent advances in our understanding of the genetics of human skin color would not have been possible.

Human skin color may be the most rapidly evolving trait in our species, with relatively closely related populations showing quite large differences in average pigmentation levels. One study has estimated the interpopulation variation in pigmentation at 88%, compared to 10–15% for arbitrarily selected genetic markers (Relethford, 2002). Variation in both cellular structure and biochemical pathways underlies pigmentary differences among groups. For example, while all humans have approximately the same number of melanosomes, the melanosomes of darkly pigmented individuals contain more melanin, are larger, and are distributed singly instead of being grouped into a membrane (Sturm *et al.*, 1998). Additional variation stems from mutations in the many genes that compose the pigmentation pathway, including differences in tyrosinase activity (encoded by the *TYR* gene), which is the rate-limiting enzyme for melanogenesis (Fuller *et al.*, 2001).

In the past few years we have made dramatic advances in our understanding of the genetic basis of normal pigmentation variation (for reviews, see Parra, 2007; Sturm, 2009). To date, 11 genes are known to influence skin pigmentation levels within and between various human populations. Studies have focused largely on candidate genes or admixture linkage in recently admixed populations (primarily with West African/European or Indigenous American/European parental populations) and genome-wide association studies in non-admixed populations. One exception is a genome-wide association study in South Asians—a population that has substantial old admixture (Stokowski *et al.*, 2007). As Harrison and Owen realized, admixed populations are essential for understanding pigmentation differences among populations, since the alleles at many of the functional loci are fixed or nearly fixed. In the absence of genetic variation, it is impossible to map the effect of a locus.

Based on their partitioning of variance using data from F_1, backcrossed, and F_2 individuals, Harrison and Owen predicted that a minimum of six to eight genes underlie the skin color differences between European and West African populations. More recently, researchers considering contemporary admixed populations, which had undergone admixture for many more generations, estimated that at least 10 genes contribute to population-level differences between European and West African populations (Parra *et al.*, 2004). At present, *SLC24A5*, *SLC45A2* (*MATP*), *KITLG*, *OCA2*, *TYR*, and *ASIP* have been implicated (reviewed in Sturm, 2009). Additional genes and separate mutations likely are responsible for the differences between Indigenous Americans and Europeans. Ancestry informative markers in *CYP19A1*, *MYO5A*, and *SLC24A5* have shown admixture linkage in Hispanic populations (Hoggart et al., 2003). However, many more genes must be identified to account for the full

range of variation within and among all human populations.

Through analysis in admixed populations, rather than through the more widely used genome-wide association study approach, a picture of the evolutionary genetic architecture of human skin pigmentation is emerging and proving to be quite intricate. Lamason *et al*. (2005) identified a mutation in *SLC24A5* associated with the golden phenotype in zebrafish. An amino-acid substitution in the human homolog (*SLC24A5**Thr111), discovered by the HapMap project, was found to have the single largest effect of any known gene on skin color differences between Europeans and West Africans. Interestingly, this mutation, which is fixed across most of Europe, is rare (~2.5%) in East Asia, suggesting that the mutations responsible for lighter skin pigmentation are not shared across these populations. *SLC45A2* has also been shown to have a pattern or variation similar to *SLC24A5*, with the European skin-lightening allele being largely restricted to Europe and not found in East Asian populations (Norton *et al.*, 2007). This finding suggests that the mutation rose to fixation in Europe relatively recently, possibly under substantial selective pressure. To determine if the *SLC24A5**Thr111 allele found in European populations has a functional effect on melanogenesis, Ginger *et al*. (2008) inserted it into the DNA of cultured melanocytes. The resulting modification in the *trans*-Golgi network-associated protein NCKX5 showed both a substantial decrease in cation exchange and downregulation of melanin production. Based on these observations, Ginger *et al*. hypothesize that this mutation could change the acidity in the *trans*-Golgi network, thereby modifying the activity of tyrosine, or, based on the timing of *SLC24A5* expression during cell proliferation, it could modulate the trafficking of pre-melanosomes. These functional and admixture-based studies have been supplemented recently by several studies of genomic selection at pigmentation genes.

The distributions of *SLC24A5* and *SLC45A2*, in particular, and skin pigmentation more generally, show a steeper cline than is found for most human genes and phenotypes. This raises questions about the types of evolutionary forces that would give rise to such a pattern. Harrison and Owen were among the first to take a genetic approach to this question by examining the differences in skin reflectance levels (and, by inference, the genes of persons of known admixture). The variation among these admixed individuals sheds light on the differences that have evolved between West African and European populations. Recently, dozens of scans for selection across the human genome have confirmed strong, repeated selection on skin pigmentation genes in nearly every population considered (see Figure 1). This evidence is found more frequently in non-African populations than in African populations. This finding may be associated with the relatively recent colonization of new environments by these populations, as older selection is often more difficult to detect. In the Old World, a few genes show selection in both East Asian and European populations (e.g., *KITLG*), but there is also evidence of independent evolution of light skin pigmentation in European and East Asian populations—meaning the shared phenotype does not result from a shared ancestral mutation. This is illustrated in the example of *SLC24A5* and *SLC45A2*, both of which show signatures of selection in Europe, but not elsewhere. These selective events mirror the migration of humans into Europe and Asia within the past 50,000 years. However, not all selective events were recent. For example, patterns of genetic variation at *EDN3* support selection on pigmentation in the common ancestors of all humans prior to their divergence (McEvoy *et al.*, 2006). Some researchers have suggested that this may reflect the initial darkening of skin pigmentation in pre-human ancestors as they lost the fur that protects the light skin of our chimpanzee cousins.

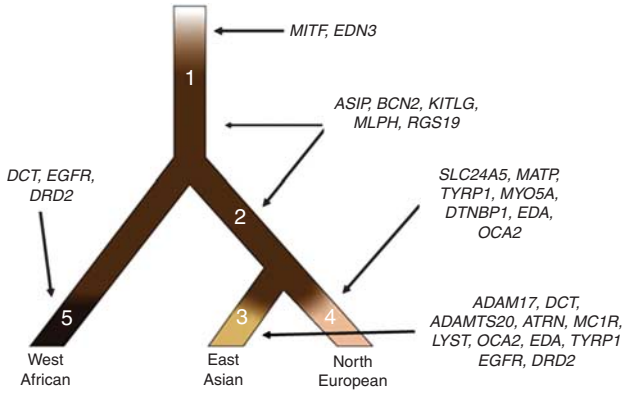

Figure 1. The evolutionary genetic architecture of skin pigmentation in three populations. Although gene flow has occurred among human populations, differences in the allele frequencies at pigmentation genes are observed among. The genes listed have demonstrated signatures of selection as (1) shared among all humans, (2) shared between East Asian and European populations, (3) unique to East Asian populations, (4) unique to European populations, and (5) unique to West African populations.

Among the most striking findings of many of these studies is the magnitude of the selection seen at skin pigmentation genes. A detailed description of the evolutionary pressures influencing skin pigmentation can be found in Jablonski and Chaplin (2000). Briefly, most research supports the hypothesis that darker skin pigmentation evolved—possibly more than once—because it reduces photolysis of folic acid, which protects against neural tube defects and is essential in DNA replication and repair, among other functions. There is more controversy surrounding the prevailing hypotheses for the adaptive benefit of lighter skin pigmentation. In a low UVR environment, less dermal melanin allows for the production of more vitamin D_3 (needed for normal skeletal development as well as proper functioning of the immune and cardiovascular systems). However, there is ongoing debate over the primacy of vitamin D in contributing to differential fitness (Robins, 2009; Chaplin and Jablonski, 2010).

Despite the ongoing investigations into the most likely pressures, what is clear is that selection on skin pigmentation has been as strong as or stronger than the selection on genes involved in immunity, reproduction, and diet—all of which are essential for human fitness. Several groups found marked over-representations of pigmentation genes among the strongest genomic signatures of selection in Europeans (Lao *et al.*, 2006; Voight *et al.*, 2006; Myles *et al.*, 2007). Pigmentation genes are more than twice as likely to show evidence of selection than randomly selected genes in both Chinese and European populations (Williamson *et al.*, 2007), and are significantly more likely to have high F_{ST}, a measure of the genetic distance between two populations, than randomly chosen regions of the genome (Pickrell *et al.*, 2009). Taken together, the more than 25 pigmentation genes showing evidence of selection suggest a history of selection on skin color that likely stretches back to before the emergence of the first anatomically modern *Homo sapiens.*

Despite the many genes already implicated in human skin color variation, a substantial number of the differences among populations cannot be explained. There are more than 350 putative pigmentation loci identified in mouse models and cataloged in the IFPCS color genes database (http://www.espcr.org/micemut/); what, if any, role these genes play in the unexplained variation in human pigmentation remains unknown. The size of this database gives credence to the hypothesis that many rare variants may contribute to pigmentation variation in humans. Identifying these rare variants will only be possible with the increased use of dense marker panels and sequencing to assess non-European and admixed populations. Moreover, it is essential that genome sequences be associated with phenotypes. Identification of variation among populations or individuals at known pigmentation genes fails to demonstrate that this variation manifests in phenotypic differences.

Unpacking the ramifications of human evolution in shaping the genetic architecture and distribution of human skin pigmentation requires accurate and objective measurement techniques. Although self-report and subjective assessments may be sufficiently informative to identify genes for some traits (e.g., albinism, red hair, and blue eye color), more complete quantitative genetic analyses require measurements of the skin using reflectometry at specific wavelengths. As a larger fraction of the variation in human skin color is distributed across rather than within populations, admixed populations are an efficient means to discover genes and to study their combined effects. These components, employed together in Harrison and Owen more than 45 years ago, have shaped modern research into the evolutionary genetics of human skin pigmentation.

CONFLICT OF INTEREST

The authors state no conflict of interest.

TO CITE THIS ARTICLE

Quillen EE, Shriver MD (2011). Unpacking human evolution to find the genetic determinants of human skin pigmentation. *J Invest Dermatol* 131: E5–E7

REFERENCES

Chaplin G, Jablonski NG (2010) Human skin pigmentation as an adaptation to UV radiation. *Proc Natl Acad Sci USA* 107:8962–8

Fuller BB, Spaulding DT, Smith DR (2001) Regulation of the catalytic activity of preexisting tyrosinase in black and Caucasian human melanocyte cell cultures. *Exp Cell Res* 262:197–208

Ginger RS, Askew SE, Ogborne RM *et al.* (2008) SLC24A5 encodes a trans-Golgi network protein with potassium-dependent sodium-calcium exchange activity that regulates human epidermal melanogenesis. *J Biol Chem* 283:5486–95

Harrison GA, Owen JJT (1964) Studies on the inheritance of human skin colour. *Ann Hum Genet Lond* 28:27–37

Hoggart CL, Parra EJ, Shriver MD *et al.* (2003) Control of confounding of genetic associations in stratified populations. *Am J Hum Genet* 72: 1492–504

Jablonski NG, Chaplin G (2000) The evolution of human skin coloration. *J Hum Evol* 39:57–106

Lamason RL, Mohideen M-L, Mest J *et al.* (2005) SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science* 310:1782–6

Lao O, de Gruijter JM, van Duijn K *et al.* (2006) Signatures of positive selection in genes associated with human skin pigmentation as revealed from analyses of single nucleotide polymorphisms. *Ann Hum Genet* 71:354–69

McEvoy B, Beleza S, Shriver MD (2006) The genetic architecture of normal variation in human pigmentation: an evolutionary perspective and model. *Hum Mol Genet* Spec No. 2: R176–81

Myles S, Somel M, Tang K *et al.* (2007) Identifying genes underlying skin pigmentation differences among human populations. *Hum Genet* 120:613–21

Norton HL, Kittles RA, Parra EJ *et al.* (2007) Genetic evidence for the convergent evolution of light skin in Europeans and East Asians. *Mol Biol Evol* 24:710–22

Parra EJ (2007) Human pigmentation variation: evolution, genetic basis, and implications for public health. *Yearbook Phys Anthropol* 50: 85–105

Parra EJ, Kittles RA, Shriver MD (2004) Implications of correlations between skin color and genetic ancestry for biomedical research. *Nat Genet* 36:S54– S60

Pickrell JK, Coop G, Novembre J *et al.* (2009) Signals of recent positive selection in a worldwide sample of human populations. *Genome Res* 19:826–37

Relethford JH (2002) Apportionment of global human genetic diversity based on craniometrics and skin color. *Am J Phys Anthropol* 118: 393–8

Robins AH (2009) The evolution of light skin color: role of vitamin D disputed. *Am J Phys Anthropol* 139:447–50

Stokowski RP, Pant PV, Dadd T *et al.* (2007) A genomewide association study of skin pigmentation in a South Asian population. *Am J Hum Genet* 81:1119–32

Sturm RA (2009) Molecular genetics of human pigmentation diversity. *Hum Mol Gen* 18:R9–17

Sturm RA, Box NF, Ramsay M (1998) Human pigmentation genetics: the difference is only skin deep. *Bioessays* 20:712–21

Voight BF, Kudaravalli S, Wen X *et al.* (2006) A map of recent positive selection in the human genome. *PLoS Biol* 4:e72

Williamson SH, Hubisz MJ, Clark AG *et al.* (2007) Localizing recent adaptive evolution in the human genome. *PLoS Genet* 3:e90