EVOLUTION

Skin color variation in Africa

Genetics of skin color has implications for pigmentary biology and human evolution

By **Hua Tang**[1] *and* **Gregory S. Barsh**[2]

The remarkable genetic diversity within African populations is both a signature and a storybook of human origins because descendants of the earliest humans who lived in Africa nearly 200,000 years ago have had the longest time to accumulate genetic variation. Although studying genetic diversity in African populations tells us a great deal about human history, there is even more to learn by juxtaposing the genetic diversity with the diversity of heritable traits (phenotypes). Yet, there is a paucity of such studies involving continental Africans (*1*). On page 887 of this issue, Crawford *et al.* (*2*) demonstrate the potential insights that can come from ameliorating this disparity. They examined skin color variation in 2000 African individuals from different geographic locations and ethnic groups; the range, from light-skinned San hunter-gatherer populations in southern Africa to dark-skinned pastoralist populations in eastern Africa, far exceeds pigmentary diversity anywhere else on the planet (see the figure). Using a genome-wide association study (GWAS) that includes 1600 individuals living in Tanzania, Botswana, or Ethiopia, the authors identified regions of the genome that contribute to skin color variation and carried out a series of analyses to pinpoint the responsible genes.

Studying the genetics of human pigmentation can provide fundamental insight into the genetic architecture of complex traits and the relationship between adaptive variation and population history, and reveal new aspects of cell biology. Although more than a hundred genes are known to influence pigmentary traits in plants and animals, only a handful have been implicated in humans. Of note, until now, all human pigmentation genes were originally discovered in nonhuman organisms.

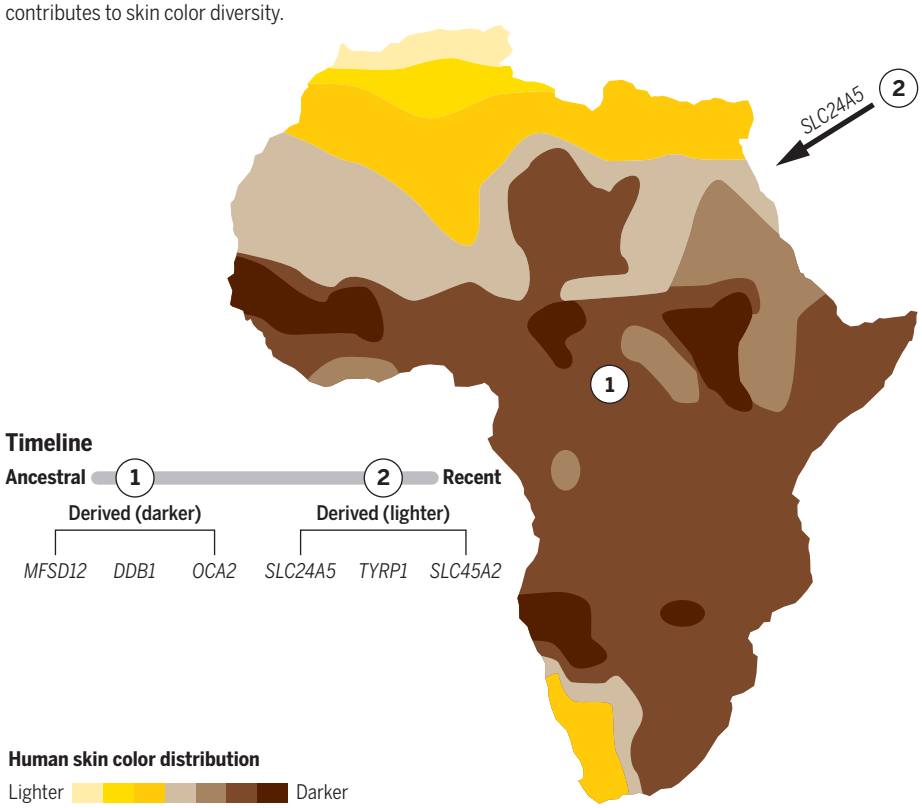
In Crawford *et al.*, the GWAS in the African cohort identifies four regions in which single nucleotide polymorphisms (SNPs) are significantly associated with skin color variation: Two of these occur in the well-known pigmentation genes *SLC24A5* (solute carrier family 24 member 5) and *OCA2* (oculocutaneous albinism 2), and a third is close to *DDB1* (damage-specific DNA binding protein 1). *SLC24A5* was first identified in zebrafish, where it is responsible for the *golden* mutation, which results in lighter pigmentation of the zebrafish stripes (*3*). In humans, a mutated, or derived, *SLC24A5* variant contributes to light skin. Complete loss of function for *OCA2* causes severe albinism (*4*, *5*), but partial loss of function due to alterations in *OCA2* expression is the major cause of blue-versus-brown eye color (*6*). *DDB1* is widely expressed, but is involved in the DNA damage response to ultraviolet (UV) radiation (*7*, *8*).

Although *SLC24A5*, *OCA2*, and *DDB1* were strong candidate genes on the basis of prior nonhuman studies, the fourth region uncovered by the GWAS harbors a series of mostly noncoding SNPs and no known pigmentation genes. The attention of Crawford *et al.* was drawn to the gene *MFSD12* (major facilitator superfamily domain containing 12) because several SNPs in the surrounding genomic region are not only associated with skin color, but also affect the expression of adjacent genes, of which several are highly expressed in melanocytes (the skin cells that produce melanin pigment). A series of experiments provided compelling support for the hypothesis that reduced expression of *MFSD12* causes darker skin in African populations. *MFSD12* encodes a transmembrane protein localized to lysosomes; therefore, this finding offers clues to how intracellular organelles may communicate and affect each other's function.

Furthermore, the association of *MFSD12* provides insight on the long-standing mystery of a mouse coat-color mutation known as *grizzled* (which refers to the streaky appearance of hairs), for which the responsible gene has not been found (*9*). Like humans, normal mice have two kinds of pigment, black-brown eumelanin and red-yellow pheomelanin. However, laboratory mice with an

Skin color variants during human history

A skin color map of indigenous African people, based on data collected by the Italian geographer Renato Biasutti *et al.* (*16*). Some variants associated with *MFSD12*, *DDB1*, and *OCA2* occurred more than 500,000 years ago. Variants associated with *SLC24A5*, *TYRP1* (tyrosinase-related protein 1), and *SLC45A2* (solute carrier family 45 member 2) are more recent, but *SLC24A5* has been introduced by migration back into Africa, where it contributes to skin color diversity.



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experimentally induced mutation of *Mfsd12* feature streaky hairs that contain eumelanin, but not pheomelanin, identical to what has been described for *grizzled*. Indeed, Crawford *et al.* demonstrate that *Mfsd12* mutant mice are unable to produce pheomelanin and that *grizzled* mice have a deletion of *Mfsd12*. Hence, the identification of *MFSD12* marks a victory for phenotype-driven human genetics.

The *MFSD12* findings from Crawford *et al.* raise several intriguing questions. How does this transporter-like protein expressed in lysosomes affect what happens in melanosomes (the organelle that stores and transports melanin)? Why does reduced expression of *MFSD12* cause increased synthesis of black-brown eumelanin in humans, but loss of *Mfsd12* in mice does not affect eumelanin synthesis? Finally, is it a coincidence that human *MFSD12* variants affect gene expression rather than protein structure? A potential answer to the last question is apparent from *grizzled* mice, which not only exhibit streaky hair but also have occasional developmental and growth abnormalities (*9*). It seems possible that regulatory variants in *MFSD12* that reduce, but do not ablate, protein function confer positive selection due to the ability of dark skin to block the damaging effects of UV radiation, but avoid negative selection due to impaired development and/or growth.

It is interesting to contrast *MFSD12* selection in African populations with that for *SLC24A5* in European populations. The regions surrounding both genes exhibit strong divergence between continents, but the derived variant of *SLC24A5*, which occurs mostly in Europe and South Asia, contributes to lighter skin color, whereas the derived variant of *MFSD12*, largely maintained in Africa, contributes to darker skin color (see the figure). Although the evidence for positive selection of the dark skin–associated *MFSD12* variants in Africans is not as strong as it is for the light-skinned variants of *SLC24A5* in Europeans, this may reflect the age of the mutations—light-skinned variation in *SLC24A5* is ~30,000 years old (*10*, *11*), whereas dark skin–associated variation in *MFSD12* is estimated to have occurred more than 500,000 years ago (*2*). Like *MFSD12*, many of the variants at the other three loci identified by Crawford *et al.* as associated with dark skin are also derived—other hominid and primate genomes carry variants associated with lighter skin at these loci. Taken together, these observations suggest that skin pigmentation of ancestral humans was intermediate, with darker pigmentation providing adaptive protection against UV radiation in east African ancestors.

Studying the genetic architecture of skin pigmentation could provide a platform to explore the extent to which interaction between genes and interaction between genes and environment contribute to phenotypic variation. But such studies require larger samples and new analytic frameworks: Like other studies on skin pigmentation (*12*–*14*), Crawford *et al.* focus on additive effects across loci—approximately one-third of the total phenotypic variation was accounted for by four loci. What accounts for the other two-thirds? Some of the "missing" heritability could represent measurement noise or environmental factors. A study of an African-European cohort from the Cape Verde Islands points to an oligogenic model with four major gene variants and many additional gene variants of small effect (*14*). It should be emphasized, however, that estimates of heritability are meaningful only to the population being studied. For example, Crawford *et al.* estimate that 12.8% of the phenotypic variance in skin pigmentation in Africans is attributable to *SLC24A5*, which reflects both the strength of allelic substitution and allele frequency. By contrast, *SLC24A5* contributes almost nothing to skin color variation in Europeans because the derived allele occurs essentially at a frequency of one. Success of the endeavor described in Crawford *et al.* depends on a diversity of approaches, diversity of genetic variation, and, especially, diversity of phenotypic variation. Perhaps paradoxically, the strongest association signal for skin color comes from *SLC24A5*, for which variation is of relatively recent origin in Europe. Thus, the power of continental Africa as a substrate for human genetics is enhanced by human migration and gene flow not only out of, but, more recently, back into Africa (*15*). Ultimately, human genetic and phenotypic variation is not captured in any single continent, and likewise, a complete picture of the genetic architecture of a complex trait—pigmentation or otherwise—cannot be gleaned through studying a single population. As in all things, diversity matters. ■

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POLYMER CHEMISTRY

The promise of plastics from plants

Plant-derived feedstocks are increasingly competitive in plastics production

By **Marc A. Hillmyer**

Polymers protect us from the elements, increase the fuel efficiency of cars, protect food from pathogens, help cure disease, and enable renewable-energy technologies. To promote, foster, and enable a sustainable society, we need polymers. Yet polymers can also create serious environmental challenges. Nearly all plastic packaging produced—more than 80 billion kg annually—originates from fossil resources and is disposed of after a relatively short period of use (*1*, *2*). An increasing fraction of plastic is recycled or incinerated to recover energy, but most ends up in landfills, littering cities or landscapes, and in the oceans (*3*). New recycling concepts (*4*), clean incineration, and the development of polymers that can rapidly degrade (*5*) will be key to addressing these problems. Shifting from petrochemical feedstocks to renewable resources—making plastics from plants—can also rectify some environmental challenges associated with petrochemical extraction and render plastics production sustainable (see the figure).

A nearly inexhaustible supply of annually renewable carbon is embedded in plant-derived macromolecules (including cellulose, lignin, and other polysaccharides) and small molecules (including sugars, vegetable oils, and terpenes). Carbon dioxide is also overly abundant. From these renewable feedstocks, it is possible to prepare nearly all of today's polymers. From a chemistry perspective, the main challenge is to establish efficient and commercially competitive transformations of these abundant resources into the set of compounds that are useful for plastics, elastomers, coatings, thermosets, and other polymeric materials. Efficiency is crucial because large-scale commodity chemicals must be produced for a few dollars per kilogram. And

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