New research provides a molecular look at the mechanisms behind pigmentation variation

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Sarah Tishkoff Of the University of Pennsylvania led a collaborative team of researchers who have discovered key insights into the molecular basis of skin color differences among Africans. "There's so much genetic diversity in African populations, but they've also been historically underrepresented in studies," Tishkoff says. "Our findings offer more information on these populations and paint a clearer picture of human evolution." Pictured here: Two Koesan-speaking

men pose for a photograph. Credit: Sarah Tishkoff

Researchers from the University of Pennsylvania have discovered key insights into the molecular basis of skin color variations among African populations. Their findings, published in *Nature Genetics*, broaden the understanding of human evolution and the genetics underpinning contemporary human skin color diversity.

"Despite the abundant genetic diversity within African populations, they have been historically underrepresented in genetic studies," says senior author Sarah Tishkoff, a Penn Integrates Knowledge University Professor with appointments in the Perelman School of Medicine and School of Arts & Sciences.

"Our findings offer novel information about the genetic basis and evolutionary history of skin color diversity, contributing to a clearer depiction of human evolution."

The story of human evolution is as rich and diverse as the adaptations found across the world's populations, Tishkoff says. She notes that, among many adaptive traits, skin color stands out as one of the most well-known. Darker skin tones, prevalent in equatorial regions, serve as nature's very own sunblock, evolving over millennia to shield these populations from the sun's intense ultraviolet radiation.

Conversely, lighter pigmentation, as seen in populations closer to the poles, is an adaptation to mitigate the risks of insufficient sun exposure by maximizing vitamin D production, which is triggered by UV exposure.

"Our approach involved genome-wide association studies of skin color

from more than 1,500 eastern and southern African individuals as well as scanning the genome to identify genetic variants that are highly differentiated between lightly-pigmented Khoesan-speaking San population and other darkly pigmented Africans and may play a role in local adaptation in that population," says Yuanqing Feng, first author of the paper and a postdoctoral researcher in the Tishkoff Lab.

The researchers note that pigmentation is a complex trait influenced by hundreds of variants scattered across the genome, with the majority situated in noncoding regions. These noncoding variants may affect the expression of genes located up to one million bases away.

The vast number of mutations associated with skin color and the uncertainty surrounding the target genes regulated by these mutations make it particularly arduous for researchers to find the precise genetic mechanisms governing this trait.

Feng and collaborators used massively parallel reporter assays to discern the regulatory activities of thousands of variants. This high-throughput technique narrowed down the thousands of candidates to 165 functional variants. To identify the target genes of these functional variants, Feng further constructed high-resolution chromatin interaction maps in melanocytic cells using chromatin conformation capture assays.

"This is a high-resolution 3D genome map in melanoma cells that will be valuable for gene regulation studies in pigmentation and melanoma biology," Feng says.

Using CRISPR/Cas9-based genome editing, the researchers discovered that mutations in an enhancer of OCA2, a gene associated with albinism, could lead to a 75% reduction in melanin levels when compared to control cells. Within the same OCA2 enhancer, the researchers identified two closely located regulatory variants, estimated to be 1.2

million years old and 57 thousand years old, with the latter coinciding with the period of human migration from Africa.

"This case illustrates the continuous evolution of human skin color, and it's remarkable to observe the significant effects on skin pigmentation attributed to a single enhancer," Feng says.

San people have relatively lighter pigmentation compared to other African populations and possess the oldest genetic lineages in humans. While it is hypothesized that the light skin color of the San may result from adaptation to a southern African environment, the genetic underpinnings of this adaptation remain elusive. The researchers pinpointed several crucial regulatory variants near MITF, LEF1, and TRPS1 that contribute to the skin color adaptation observed in the San.

"MITF, LEF1, and TRPS1 are involved in signaling pathways regulating both melanocyte differentiation and hair development," Tishkoff says. "This suggests that the variants influencing the lighter skin pigmentation observed in the San people may also contribute to their distinctive hair morphology."

Notably, the variant near TRPS1 associated with lighter skin color is at nearly 100% frequency in the San and in most non-Africans, whereas the variant associated with darker skin color is common in most other African populations and in the darkly pigmented Melanesian population, a striking example of global adaptations to UV exposure.

Additionally, the researchers found a novel gene impacting human skin pigmentation, CYB561A3, which regulates iron homeostasis and influences melanin levels in melanocytic cells.

"To our knowledge, the role of CYB561A3 in skin pigmentation has not been reported before. Intriguingly, there have been reports linking

intravenous iron infusion to skin hyperpigmentation. Given that CYB561A3 encodes an iron reductase, I am curious about the role of this protein in this process," Tishkoff says.

"Our findings underscore the complexity of genetic factors influencing skin color and the benefits of including ethnically diverse and underrepresented populations in genetic studies," she says. "Conducting functional studies on the impact of noncoding variants will enhance our comprehension of the genetics underlying complex human traits and disease risk."

"The populations included in this study are from remote regions of Africa and required the use of a mobile lab set up in the field sites," Tishkoff says. "The collaboration with our partners in Africa was key to the success of this research project."

In future research, the Tishkoff lab would like to use its innovative functional genomics approach to identify more genetic variants contributing to human pigmentation and other adaptive traits in a larger sample of ethnically diverse Africans.

More information: Yuanqing Feng et al, Integrative functional genomic analyses identify genetic variants influencing skin pigmentation in Africans, *Nature Genetics* (2024). DOI: 10.1038/s41588-023-01626-1

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