Penn-led Study Identifies Genes Responsible for Diversity of Human Skin Colors

Human populations feature a broad palette of skin tones. But until now, few genes have been shown to contribute to normal variation in skin color, and these had primarily been discovered through studies of European populations.

Now, a study of diverse African groups led by University of Pennsylvania (http://www.upenn.edu) geneticists has identified new genetic variants associated with skin pigmentation. The findings help explain the vast range of skin color on the African continent, shed light on human evolution and inform an understanding of the genetic risk factors for conditions such as skin cancer.

[vimeo]237118625[/vimeo]

“We have identified new genetic variants that contribute to the genetic basis of one of the most strikingly variable traits in modern humans,” said Sarah Tishkoff (https://www.med.upenn.edu/tishkoff/Lab/Tishkoff/Tishkoff.html), a Penn Integrates Knowledge Professor (https://pikprofessors.upenn.edu/) and the David and Lyn Silfen University Professor in Genetics and Biology with appointments in the Perelman School of Medicine (http://www.med.upenn.edu) and School of Arts and Sciences (http://www.sas.upenn.edu). “When people think of skin color in Africa most would think of darker skin, but we show that within Africa there is a huge amount of variation, ranging from skin as light as some Asians to the darkest skin on a global level and everything in between. We identify genetic variants affecting these traits and show that mutations influencing light and dark skin have been around for a long time, since before the origin of modern humans.”

The findings are published in the journal *Science* (http://science.sciencemag.org/content/early/2017/10/11/science.aan8433). Tishkoff, senior author, collaborated with first author and lab member Nicholas Crawford (https://www.med.upenn.edu/tishkoff/Lab/Crawford/crawford.html), a postdoctoral fellow, and a multi-institutional, international team.

Tishkoff has long studied the genetics of African populations, looking at traits such as height (https://news.upenn.edu/news/penn-geneticists-identify-genes-linked-western-african-pygmies-small-stature), lactose tolerance (https://news.upenn.edu/news/penn-team-links-africans-ability-digest-milk-spread-cattle-raising), bitter-taste sensitivity (https://news.upenn.edu/news/penn-geneticists-help-show-bitter-taste-perception-not-just-about-flavors) and high-altitude adaptation (https://news.upenn.edu/news/penn-researchers-help-solve-questions-about-ethiopians-high-altitude-adaptations). Skin color

emerged as a trait of interest from her experience working on the continent and seeing the diversity present across groups.

“Skin color is a classic variable trait in humans, and it’s thought to be adaptive,” Tishkoff said. “Analysis of the genetic basis of variation in skin color sheds light on how adaptive traits evolve, including those that play a role in disease risk.”

Both light and dark skin pigmentations confer benefits: Darker skin, for example, is believed to help prevent some of the negative impacts of ultraviolet light exposure, while lighter skin is better able to promote synthesis of vitamin D in regions with low ultraviolet light exposure.

To objectively capture the range of skin pigmentation in Africa, Tishkoff and colleagues used a color meter to measure the light reflectance of the skin of more than 2,000 Africans from ethnically and genetically diverse populations. They took the measurement from the inner arm, when sun exposure is minimal. The measurements can be used to infer levels of the skin pigment melanin. They obtained a range of measurements; the darkest skin was observed in Nilo-Saharan pastoralist populations in eastern Africa, and the lightest skin was observed in San hunter-gatherer populations in southern Africa.

The researchers obtained genetic information from nearly 1,600 people, examining more than 4 million single nucleotide polymorphisms across the genome, places where the DNA code may differ by one “letter.” From this dataset the researchers were able to do a genome-wide association study and found four key areas of the genome where variation closely correlated with skin color differences.

The region with the strongest associations was in and around the *SLC24A5* gene, one variant of which is known to play a role in light skin color in European and some southern Asian populations and is believed to have arisen more than 30,000 years ago. This variant was common in populations in Ethiopia and Tanzania that were known to have ancestry from southeast Asia and the Middle East, suggesting it was carried into Africa from those regions and, based on its frequency, may have been positively selected.

Another region, which contains the *MFSD12* gene, had the second strongest association to skin pigmentation. This gene is expressed at low levels in depigmented skin in individuals with vitiligo, a condition where the skin loses pigment in some areas.

“I still rememeber the ‘ah ha!’ moment when we saw this gene was associated with vitiligo,” said Crawford. “That’s when we knew we’d found something new and exciting.”

The team found that mutations in and around this gene that were associated with dark pigmentation were present at high frequencies in populations of Nilo-Saharan ancestry, who tend to have very dark skin, as well as across sub-Saharan populations, except the San, who tend to have lighter skin. They also identified these variants, as well as others associated with

dark skin pigmentation, in South Asian Indian and Australo-Melanesian populations, who tend to have the darkest skin coloration outside of Africa.

“The origin of traits such as hair texture, skin color and stature, which are shared between some indigenous populations in Melanesia and Australia and some sub-Saharan Africans, has long been a mystery.” Tishkoff said. “Some have argued it’s because of convergent evolution, that they independently evolved these mutations, but our study finds that, at genes associated with skin color, they have the identical variants associated with dark skin as Africans.

“Our data are consistent with a proposed early migration event of modern humans out of Africa along the southern coast of Asia and into Australo-Melanesia and a secondary migration event into other regions. However, it is also possible that there was a single African source population that contained genetic variants associated with both light and dark skin and that the variants associated with dark pigmentation were maintained only in South Asians and Australo-Melanesians and lost in other Eurasians due to natural selection.”

Also of interest was that genetic variants at *MFSD12*, *OCA2* and *HERC2* associated with light skin pigmentation were at highest frequency in the African San population, which has the oldest genetic lineages in the world, as well as in Europeans.

MFSD12 is highly expressed in melanocytes, the cells that produce melanin. To verify the gene’s role in contributing to skin pigmentation, the researchers blocked expression of the gene in cells in culture and found an increase in production of eumelanin, the pigment type responsible for black and brown skin, hair and eye color. Knocking out the gene in zebrafish caused a loss of cells that produce yellow pigment. And in mice, knocking out the gene changed the color of their coat from agouti, caused by hairs with a red and yellow pigment, to a uniform gray by eliminating production of pheomelanin, a type of pigment also found in humans.

“Apart from one study showing that *MFSD12* was associated with vitiligo lesions, we didn’t know much else about it,” said Crawford, “so these functional assays were really crucial.”

“We went beyond most genome-wide association studies to do functional assays,” Tishkoff said, “and found that knocking out *MFSD12* dramatically impacted the pigmentation of fish and mice. It’s pointing to this being a very conserved trait across species.

“We don’t know exactly why, but blocking this gene causes a loss of pheomelanin production and an increase in eumelanin production,” Tishkoff added. “We also showed that Africans have a lower level of MFSD12 expression, which makes sense, as low levels of the gene means more eumelanin production.”

A collaborator on the work, Michael Marks (https://www.med.upenn.edu/physiol/faculty_marks.html), a professor in the departments of Pathology & Laboratory Medicine and of Physiology at Children’s Hospital of Philadelphia (http://www.chop.edu/) and at Penn Medicine, demonstrated that the *MFSD12* gene

influences eumelanin pigmentation in a novel manner. Unlike other pigmentation genes, which are expressed mainly in melanosomes, the organelle where melanin is produced, *MFSD12* is expressed in lysosomes, a distinct organelle from the melanosomes that produce eumelanin.

“Our results suggest there must be some kind of as-yet-uncharacterized form of cross-talk between lysosomes and the melanosomes that make eumelanins,” Marks said. “Figuring out how this works might provide new ideas for ways to manipulate skin pigmentation for therapeutic means.

“In addition,” Marks said, “the fact that loss of *MFSD12* expression had opposite effects on the two types of melanins, increasing eumelanin production while suppressing pheomelanin, suggests that melanosomes that make pheomelanins might be more related to lysosomes than those that make eumelanin."

Additional associations with skin color were found in the *OCA2* and *HERC2* genes, which have been linked with skin, eye and hair color variation in Europeans, though the mutations identified are novel. Mutations in *OCA2* also cause a form of albinism that is more common in Africans than in other populations. The researchers observed genetic variants in a neighboring gene, *HERC2*, which regulates the expression of *OCA2*. Within *OCA2*, they identified a variant common in Europeans and San that is associated with a shorter version of the protein, with an altered function. They observed a signal of balancing selection of *OCA2*, meaning that two different versions of the gene have been maintained, in this case for more than 600,000 years.

“What this tells us,” Tishkoff said, “is there is likely some selective force maintaining these two alleles. It is likely that this gene is playing a role in other aspects of human physiology which are important.”

A final genetic region the researchers found to be associated with skin pigmentation included genes that play a role in ultraviolet light response and melanoma risk. The top candidate gene in the region is *DDB1*, involved in repairing DNA after exposure to UV light.

“Africans don’t get melanoma very often,” Tishkoff said. “The variants near these genes are highest in populations who live in areas of the highest ultraviolet light intensity, so it makes sense that they may be playing a role in UV protection.”

The mutations identified by the team play a role in regulating expression of *DDB1* and other nearby genes.

“Though we don’t yet know the mechanism by which *DDB1* is impacting pigmentation, it is of interest to note that this gene, which is highly conserved across species, also plays a role in pigmentation in plants such as tomatoes,” said Tishkoff.

The team saw evidence that this region of the genome has been a strong target of natural selection outside of Africa; mutations associated with light skin color swept to nearly 100

percent frequency in non-Africans, one of few examples of a “selective sweep” in all Eurasians; the age of the selective sweep was estimated to be around 60,000 to 80,000 years old, around the time of migration of modern humans out of Africa.

One additional takeaway from this work is a broader picture of the evolution of skin color in humans. Most of the genetic variants associated with light and dark pigmentation from the study appear to have originated more than 300,000 years ago, and some emerged roughly 1 million years ago, well before the emergence of modern humans. The older version of these variants in many cases was the one associated with lighter skin, suggesting that perhaps the ancestral state of humans was moderately pigmented rather than darkly pigmented skin.

“If you were to shave a chimp, it has light pigmentation,” Tishkoff said, “so it makes sense that skin color in the ancestors of modern humans could have been relatively light. It is likely that when we lost the hair covering our bodies and moved from forests to the open savannah, we needed darker skin. Mutations influencing both light and dark skin have continued to evolve in humans, even within the past few thousand years.”

Tishkoff noted that the work underscores the diversity of African populations and the lack of support for biological notions of race.

“Many of the genes and new genetic variants we identified to be associated with skin color may never have been found outside of Africa, because they are not as highly variable,” Tishkoff said. “There is so much diversity in Africa that’s not often appreciated. There’s no such thing as an African race. We show that skin color is extremely variable on the African continent and that it is still evolving. Further, in most cases the genetic variants associated with light skin arose in Africa.”

In addition to Tishkoff and Crawford, study co-authors included Derek Kelly, Matthew E. B. Hansen, Marcia Holsbach, Shaohua Fan, Alessia Ranciaro, Simon Thompson, Yancy Lo, Michael Campbell, William Beggs, Shanna L. Bowman, Michael Marks and Jake Haut of Penn; Ethan Jewett and Yun S. Song of the University of California, Berkeley; Susanne P. Pfeifer and Jeffrey D. Jensen of Arizona State University; Farhad Hormozdiari, Harriet Rothschild, Leonard Zon and Yi Zhou of Harvard University; Sununguko Wata Mpoloka and George Mokone of the University of Botswana; Thomas Nyambo of Muhimbili University of Health and Allied Sciences in Tanzania; Dawit Wolde Meskel and Gurja Belay of Addis Ababa University in Ethiopia; Michael A. Kovacs, Mai Xu, Tongwu Zhang, Kevin Bishop, Jason Sinclair, Cecilia Rivas, Eugene Elliot, Jiyeon Choi, Shenchao Li, Belynda Hicks, Shawn Burgess, Chrisan Abnet, Dawk E. Watkins-Chow, Kevin M. Brown, Stacie K. Loftus, William J. Pavan, Meredith Yeager and Stephan Chanock of NIH; and Elena Oceana of Brown University. The NISC Comparative Sequencing Program of the National Institutes of Health also participated in the research.

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