# Researchers identify 135 new melanin genes responsible for pigmentation

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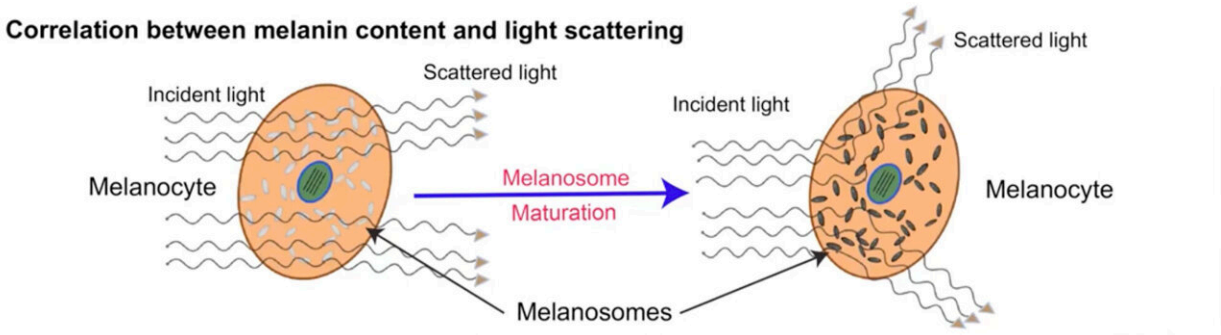


Light scattering process used to identify melanin-producing melanosomes. Credit: Vivek K. Bajpai et al., A genome-wide genetic screen uncovers determinants of human pigmentation. *Science*. DOI:10.1126/science.ade6289

Melanin is produced within special structures called melanosomes. Melanosomes are found inside melanin-producing pigment cells called melanocytes. Although all humans have the same number of melanocytes, the amount of melanin they produce differs and gives rise to the variation in human skin color.

"To understand what actually causes different amounts of melanin to be produced, we used a technology called CRISPR-Cas9 to genetically engineer cells," Bajpai said. "Using CRISPR, we systematically removed more than 20,000 genes from hundreds of millions of melanocytes and observed the impact on melanin production."

To identify which genes influence melanin production, cells that lost melanin during the gene removal process needed to be separated from millions of other cells that did not. Using in vitro cell cultures, Bajpai developed a novel method to achieve this goal that detects and quantifies the melanin-producing activity of melanocytes. By passing light through the melanocytes, he could record if the light was either absorbed or scattered by the melanin inside.

"If there are a lot of melanin-producing melanosomes, the light will scatter much more than in cells with little melanin," Bajpai said. "Using a process called side-scatter of flow cytometry, we were able to separate cells with more or less melanin. These separated cells were then analyzed to determine the identity of melanin-modifying genes. We identified both new and previously known genes that play important roles in regulating melanin production in humans."

The researchers found 169 functionally diverse genes that impacted melanin production. Of those, 135 were not previously associated with pigmentation. They further identified the function of two newly discovered genes: KLF6 and COMMD3. The DNA-binding protein KLF6 led to a loss of melanin production in humans and animals, confirming the role KLF6 plays in melanin production in other species as well. The COMMD3 protein regulated melanin synthesis by controlling the acidity of melanosomes.

Historically, darker pigmentation has been needed to protect against ultraviolet radiation in areas closer to the equator and for people who spend hours in direct sunlight. As humans moved into areas with less direct sunlight or fewer hours of daylight overall, less melanin was needed. Over time, this resulted in melanosomes that produced less melanin, thus absorbing more sunlight.

"By understanding what regulates melanin, we can help protect lighter-

skinned people from melanoma, or skin cancer," Bajpai said. "By targeting these new melanin genes, we could also develop melanin-modifying drugs for vitiligo and other pigmentation diseases."

The technological processes developed and used by the research team could also be applied to identify genes that regulate melanin production in fungi and bacteria. Melanin production in fungi and bacteria enables them to be more pathogenic to humans or crops. Researchers could develop effective interventions against these microbes and their diseases by discovering and targeting such melanin-producing genes.

Bajpai's role in the study was completed during his professorship at the University of Oklahoma. However, a portion of this research took place during his postdoctoral research fellowship at Stanford University.

The article, "A genome-wide genetic screen uncovers determinants of human pigmentation," is published in the journal *Science*.

**More information:** Vivek K. Bajpai et al, A genome-wide genetic screen uncovers determinants of human pigmentation, *Science* (2023). DOI: 10.1126/science.ade6289

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