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Gene implicated in human pigment variation

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A pigmentation gene first identified in zebrafish helps explain skin color differences between human European and African populations, a new *Science*study shows. A derived variant of the *slc24a5* gene, which is correlated with light skin color and differs from the ancestral allele by only one nucleotide, seems to have undergone strong natural selection in European populations.

While scientists had previously found pigmentation genes that contribute to variations within populations, said senior author Keith Cheng, "it's been a complete mystery" as to what drives major variations in human skin color. "It's remarkable that this difference in skin color that has historically been partly responsible for a great deal of problems in our civilization is due to this one nucleotide out of 3 billion," Cheng told *The Scientist*.

"What these findings speak to is the molecular differences that explain differences in skin color. That is very different than what people refer to as race," said Greg Barsh at Stanford University, who did not participate in this study.

Cheng's team at the Pennsylvania State University College of Medicine in Hershey was studying the *golden* mutation in zebrafish—characterized by lighter-colored stripes than the wild type—when the researchers noticed that the phenotypes were distinguished by differences in the number, size, and density of melanosomes (melanin-producing granules) in the stripes. "That was to our amazement," Cheng told *The Scientist*, "because those types of changes are the same types of changes that we see between darker and lighter human beings."

Using positional cloning, the researchers isolated *slc24a5* as the gene responsible for the *golden* phenotype in zebrafish and pinpointed its mutation as a stop codon that truncates the translated protein by 40%. BLAST searches confirmed their suspicion that this zebrafish gene has a closely related counterpart not only in many other vertebrates but in humans, with 69% sequence homology.

When the researchers injected human *slc24a5* mRNA into *golden* zebrafish embryos, the wild type stripes were restored. The results showed that the gene's function has been conserved over vertebrate evolution, what Barsh called a perfect demonstration "that nature doesn't reinvent the wheel."

The scientists found *slc24a5* to be highly expressed in the melanin-producing cells of both zebrafish and mammals. In an effort to determine what role the previously uncharacterized protein might play in pigmentation, the team localized it to intracellular, membrane-bound structures—likely melanosomes. Further observations based on structure and related proteins led them to conclude that SLC24A5 may be involved in organellar calcium uptake, though Cheng said that much remains to be determined about the protein's mechanism.

The team then turned to genomics to see how the protein might be important in humans. When they consulted the recently published HapMap, they discovered that there were two primary alleles, varying at only one locus. And while nearly all East Asian and African genomes had a site containing alanine, the ancestral allele shared by other vertebrates, 99% of the Europeans had threonine, representing a derived allele. This striking bifurcation, coupled with a marked decrease in heterozygosity in nearby

genes within the European genomes, led the group to conclude that the threonine variant has been the target of strong natural or sexual selection in European populations.

As a functional test of their findings, Cheng's group was able to correlate *slc24a5* genotype to skin color—measured by reflectance—in 308 individuals with mixed African and European ancestry. Homozygotes for each allele tended to be either light-skinned or dark-skinned, respectively, with heterozygotes falling in the middle. The researchers determined that the threonine (skin-lightening) allele is partially dominant to the alanine allele, and that the gene accounts for between 25% and 38% of European-African differences in melanin levels.

While Cheng said they have "identified the probable largest impact gene explaining the difference between Europeans and Africans," they are curious about other genes in play that would explain pigmentation differences between East Asian and African populations. On a biochemical level, Barsh said, other proteins that have been implicated in pigmentation seem to have similar biochemical mechanisms to SLC24A5, highlighting the need to determine how SLC24A5 interacts with these proteins and with ones that have yet to be identified.

Cheng's findings are consistent with what he said is the prevailing evolutionary wisdom: melanin blocks UV light, and while darker skin is advantageous under strong sunlight because it reduces the destructive effects of UV rays, lighter skin is adaptive in less sunny climates since it allows more sunlight absorption for the production of vitamin D.

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