Fish gene sheds light on human skin color variation mystery

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The genetic determination of human skin color is one of biology's enduring mysteries. With help from a common aquarium pet and a recently released online database of human genetic variation, a collaborative team of Penn State researchers has found what could be the most important skin color gene identified to date.

The team, led by cancer geneticist Keith Cheng, M.D., Ph.D., a Jake Gittlen Cancer Research Foundation researcher in the Penn State Cancer Institute, at Penn State College of Medicine, Penn State Milton S. Hershey Medical Center, in collaboration with University Park anthropologist Mark Shriver, Ph.D., found that a change in just one amino acid in one gene plays a major role in determining why people of

European descent have lighter skin than people of African descent.

The find could lead to further research using the protein coded by the pigmentation gene as a target for treatment of malignant melanoma, the most deadly form of skin cancer, as well as to research on ways to modify skin color without damaging it by tanning or using harsh chemical lighteners.

The findings will be published as the cover story in the December 16 edition of *Science* magazine.

Previous studies on pigmentation have identified more than 100 genes involved in pigment production. Alterations in some of these genes are associated with disorders such as albinism, which causes very light skin, but also vision problems. However, most of the genes responsible for normal differences in skin pigmentation remained unknown. The gene identified by Cheng's team – called SLC24A5 – previously had not been suspected to be involved in pigmentation.

The pigmentation discovery was an unexpected offshoot of cancer research Cheng began a decade ago using zebrafish, a common aquarium pet that is widely used as a model organism for studying the genetics of development. The zebrafish reproduces rapidly, and many of its genes are similar to humans, which makes it a good model for studying genetic alterations and their roles in cancer, Cheng said.

The similarities between fish and humans extend to the pigment cells, which contain pigment granules called melanosomes. In people of European descent, the melanosomes are fewer, smaller, and lighter than those from people of West African ancestry, while the melanosomes of East Asians show intermediate properties. Cheng's team found that a zebrafish variant called "golden" also had fewer, smaller, and less heavily pigmented melanosomes than normal fish. This clue suggested

the gene mechanisms responsible for the change in zebrafish also might be involved in variation in human skin color.

The researchers found that the lighter pigmentation of golden zebrafish is caused by a mutation that cuts short a certain protein – referred to as slc24a5. Adding the normal zebrafish protein to the golden version resulted in fish with darker coloring. Victor Canfield, Ph.D., an assistant professor of pharmacology at the College of Medicine, found that the closely related genes were present in all vertebrates. The team asked whether the human version of the gene could also work in zebrafish and found that it did.

Cheng then sought Shriver's help in determining whether this gene plays a role in human pigmentation. Shriver's group has been focused for the past eight years on the evolutionary genetics and physiology of normal variation in human pigmentation.

The importance of the work extends beyond pigmentation, Cheng and Shriver say.

"We know so little about the genetic and evolutionary architecture of human traits," said Shriver, associate professor of anthropology. "We can not expect to use human genetics to understand complex diseases most effectively without first working out how fundamental characteristics, such as eye, hair, and skin color, are determined."

"Working out the details of pigmentation with help from model systems like zebrafish is a great paradigm for seeking understanding of other complex diseases such as diabetes or heart disease," Cheng said.

The team started with the recently released HapMap – a free and publicly accessible database of DNA sequence variation in the human genome. When researchers looked at variations within the human

SLC24A5 gene, they found that the protein specified by the gene was identical in all populations studied, except for the amino acid at one position. At that position, West Africans and East Asians shared the same ancestral sequence with other vertebrates, including zebrafish and chimpanzees. In contrast, all individuals in the European population tested showed a change in one amino acid.

According to Shriver, the results are indicative of a "selective sweep," which is a signal of selection for a particular gene variant.

Either a variant is selected for because the trait produced is better suited to the current environment than other traits and other traits are less capable of competing, or the variant is sexually selected. Sexual selection occurs because individuals choose mates with certain characteristics that are more attractive or that indicate better reproductive potential.

To verify the importance of the amino acid change, Shriver examined the SLC24A5 gene in populations of mixed European and West African ancestry. Individuals with the European form of SLC24A5 tended to have lighter skin than those with the ancestral form of the gene. Those findings suggested that this variation contributes between 25 to 38 percent of the range of skin color in this population.

The team speculates that well-known variations in European eye and hair color may have been made possible by the alteration in SLC24A5. However, they say that the patterns of DNA variation indicate that the lighter skin color of East Asians is due to variation in genes that have yet to be identified.

Scientists have long hypothesized that decreased skin pigmentation was an adaptive change that made it possible for humans to live outside the tropics, since sunlight is essential to generate the vitamin D required to prevent rickets, a condition causing bones to become weak. Team

members suggest that the gene they have identified played an important role in that adaptation in Europeans.

Source: Penn State

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