

Of Fish and Men

THE SAME GENE DRIVES SKIN COLOR EVOLUTION IN STICKLEBACK FISH AND HUMANS.

At the end of the Ice Age, 10,000 years ago, marine stickleback fish colonized the newly formed freshwater lakes and streams that dotted North America, Europe, and Asia. In each new, isolated habitat, the fish evolved traits that would help them thrive.

Among these changes were darkening and lightening of skin color, helping fish blend in or stand out in different water colors. By comparing modern-day stickleback from around the globe, HHMI investigator David Kingsley of Stanford University has revealed a gene responsible for those color changes. What's more, he discovered that the same gene has likely played a role in changing skin color during human evolution.

Taking advantage of genetic crosses and the recently sequenced stickleback genome, Kingsley and colleagues first identified a region of a chromosome, encompassing 12 genes, that seemed to differ distinctly in fish of varying shades. From there, they narrowed the color control down to one gene, *Kitlg*, which is involved in a number of developmental processes—including the development of pigment cells.

The researchers found that lighter-colored fish had a mutation in the regulatory part of the gene, which decreased the gene's expression in gills and skin cells. Since skin color can be slightly affected by many genes, it was surprising that one single gene could have such a large effect.

"If we look at multiple [stickleback populations] along the West Coast where light skin color had evolved, the same mechanism was used over and over," says Kingsley. Such a striking pattern suggested to him that perhaps the gene was involved in skin color evolution of other species, including humans.

Indeed, when the scientists compared the *Kitlg* gene sequence of Africans and Europeans, they found regulatory differences in *Kitlg* that contribute to skin color variety. They reported the work in the December 14, 2007, issue of *Cell*.

"It may be that the general mechanisms producing major changes during adaptation to a new environment are pretty constrained," says Kingsley. "Mechanisms you find when studying how one organism has evolved may help predict mechanisms used in very different animals." ■ —SARAH C.P. WILLIAMS



A stickleback from the ocean (upper) and one from a freshwater creek (lower) show different skin colors and body types.

IN BRIEF

MALARIA PARASITES PUNCH THROUGH SKIN CELLS

Detailed observations of malaria parasites moving through mice have revealed that the parasites power straight through cells on their journey from the skin to the liver. While scientists had previously observed the parasites jabbing through liver cells, the new work led by HHMI international research scholar Robert Ménard is the first to show that this so-called cell traversal begins at the skin.

Ménard, of the Pasteur Institute in Paris, and his colleagues took advantage of a mutant form of *Plasmodium berghei*—the malaria parasite that infects mice—which cannot make holes in cells. They engineered these mutated parasites to carry a fluorescent molecule they could follow in the mice.

The parasites, which were expected to travel through the body, got immediately stuck in skin cells, the researchers reported February 14, 2008, in *Cell Host & Microbe*. When they were injected straight into the liver, the parasites had no problem growing, dividing, and making the mice sick—obliterating the theory that the ability to dive through liver cells is vital to the parasites' life cycles, and instead suggesting that the long-overlooked skin phase of the malaria parasite deserves closer scrutiny.

Ducking in and out of cells likely helps the parasite avoid immune cells, says Ménard, who next hopes to deduce exactly how the parasites are able to punch through the cells. "It's a pretty aggressive behavior," he says, "and we have no idea yet how they do it."

TRACING THE PATH TO A MELANOMA

Scientists trying to determine what makes a benign mole different from a deadly skin cancer have found a protein that halts the growth of tumors.

Moles and cancerous melanomas both start out as melanocytes—pigment-producing skin cells. When a mutation in melanocytes causes an increase in expression of a protein called BRAF, the cells proliferate faster. This abnormal growth sends cells down one of two routes—it either shuts the cells down and forms a mole, or triggers an unstoppable cancer.

Researchers led by HHMI investigator Michael Green, of the University of Massachusetts Medical School, searched the genome for proteins needed to send cells down the more tame pathway. Their search led them to insulin-like growth factor binding protein 7 (IGFBP7), a protein that melanocytes make when BRAF expression increases. The IGFBP7, it turns out, leaves

the cell where it's made and signals neighboring cells to enter hibernation, preventing tumor formation.

When the researchers injected IGFBP7 into mice that already had tumors, the protein stopped tumor growth. The tumor cells, Green found, had turned off production of IGFBP7. Moles, on the other hand, actively expressed the protein, keeping surrounding cells from becoming cancerous. "It's an extremely powerful anti-cancer mechanism," says Green, who hopes the findings, published in *Cell* on February 8, 2008, will lead to a new melanoma treatment.

SYNDROME CAUSED BY MISSING CHROMOSOME SEGMENT

A chunk of missing DNA explains some cases of mental retardation that have never before been diagnosable, a team of scientists, led by HHMI investigator Evan E. Eichler of the University of Washington School of Medicine, has discovered.

While screening 700 people with mental retardation and seizure disorders, the researchers noticed two unrelated patients with identical large missing areas on chromosome 15. When the researchers looked at a larger group of patients—more than 2,000—nine people turned up with the same missing genetic material. Tests of