

GENETICS

Zebrafish Researchers Hook Gene for Human Skin Color

People come in many different hues, from black to brown to white and shades in between. The chief determinant of skin color is the pigment melanin, which protects against ultraviolet rays and is found in cellular organelles called melanosomes. But the genetics behind this spectrum of skin colors have remained enigmatic.

Now, on page 1782 of this week's issue of *Science*, an international team reports the identification of a zebrafish pigmentation gene and its human counterpart, which apparently accounts for a significant part of the difference between African and European skin tones. One variant of the gene seems to have undergone strong natural selection for lighter skin in Europeans.

The new work is raising goose bumps among skin-color researchers. "Entirely origi-



Human rainbow. A newly discovered gene partly explains the light skin of Europeans, but not East Asians, as compared to Africans.

nal and groundbreaking," says molecular biologist Richard Sturm of the University of Queensland in Brisbane, Australia. Anthropologist Nina Jablonski of the California Academy of Sciences in San Francisco, California, notes that the paper "provides very strong support for positive selection" of light skin in Europeans. Researchers have not been sure whether European pale skin is the result of some selective advantage or due to a relax-

ation of selection for dark skin, after the ancestors of modern Europeans migrated out of Africa into less sunny climes.

Yet the authors agree that the new gene, *SLC24A5*, is far from the whole story:

Although at least 93% of Africans and East Asians share the same allele, East Asians are usually light skinned too. This means that variation in other genes, a handful of which have been previously identified, also affects skin color.

The *Science* paper is the culmination of a decade of work, says team leader Keith Cheng, a geneticist at Penn-

sylvania State University College of Medicine in Hershey. He and his colleagues were using the zebrafish as a model organism to search for cancer genes and became curious about a zebrafish mutation called *golden*, which lightens the fish's normally dark, melanin-rich stripes. Cheng's team identified the mutated gene and found that the zebrafish version shared about 69% of its sequence with the human gene *SLC24A5*, ▶

INDIAN SCIENCE

Booming Computer Sector Seen as a Mixed Blessing

NEW DELHI—India cemented its claim to leadership in information technology (IT) last week when three U.S. companies—Microsoft, Intel, and Advanced Micro Devices (AMD)—announced plans to spend nearly \$6 billion on research and manufacturing here over the next few years. The economy will benefit, but some scientists are concerned that the IT bonanza could drain talent away from basic research.

Microsoft chief Bill Gates announced on 7 December that his company will double its workforce in India to 7000 and increase its

R&D investment by \$1.7 billion over the next 4 years. "We depend on India for manpower, and that is why we are scaling up operations," said Gates, who unveiled plans to add a second R&D center in Bangalore to an existing one in Hyderabad.

Earlier in the week, Intel's chief executive Craig R. Barrett announced that his company will invest \$1 billion over the next 5 years, including \$200 million for development of a microprocessor being researched at its center in Bangalore. AMD is investing \$3 billion in a chip-manufacturing plant at an undisclosed location.

According to the National Association of Software and Service Companies (NASSCOM) in New Delhi, Indian software and services exports grew more than 34% from 2004 to 2005, earning revenues of \$17.2 billion over a 12-month period. India attracts IT companies, NASSCOM argues, because it has a well-educated English-speaking workforce, low labor costs, and a time zone that allows Western companies to run operations around the clock.

Although the IT sector is booming, some leaders fear

that its rapid growth could hurt other areas of research. Astrophysicist Rajesh Kochhar, former director of the National Institute of Science, Technology, and Development Studies in New Delhi, says: "There can be no doubt that information technology is acting as a brain sink." New entrants in the Indian IT sector are paid roughly three times as much as entry-level scientists, he says. The result, he argues, is that "highly qualified engineers are doing stupid, repetitive work." Echoing this view, aeronautics engineer Gangan Prathap, chief of the Centre for Mathematical Modelling and Computer Simulation in Bangalore, says foreign investments like those announced this week could "seduce" Indians into becoming "a nation of techno-coolies." He claims that academic centers already must "scrounge at the bottom of the barrel" for talent.

Other science community leaders take a more optimistic view. M. Vidyasagar, executive vice president of software company Tata Consultancy Services in Hyderabad, dismisses internal brain-drain concerns as nothing more than "disguised envy." And Raghunath Anant Mashelkar, a polymer engineer and president of the Indian National Science Academy in New Delhi, says there is undoubtedly "a war for talent at the top of the ladder." But if it leads to a stronger economy, he thinks that both commercial R&D and basic science will benefit. —PALLAVA BAGLA



Great expectations. Microsoft Chair Bill Gates meets with India's Minister of Information Technology, Dayanidhi Maran.

which is thought to be involved in ion exchange across cellular membranes—an important process in melanosome formation. And when Cheng and his co-workers injected human *SLC24A5* messenger RNA (an intermediary molecule in protein synthesis) into *golden* zebrafish embryos, wild-type pigmentation pattern was restored.

Researchers say the ability of human *SLC24A5* to “rescue” the mutant zebrafish is strong evidence that the gene has a similar function in fish and humans. “The zebrafish data are extremely compelling,” says human geneticist Neil Risch of the University of California, San Francisco.

The team then searched for genetic variants among humans. Data from the HapMap database of human genetic diversity (*Science*, 28 October, p. 601) showed that *SLC24A5* has two primary alleles, which vary by one amino acid. Nearly all Africans and East Asians have an allele with alanine in a

key locus, whereas 98% of Europeans have threonine at that locus. These marked frequency differences combined with the pattern of variation in nearby genes suggest that the threonine variant has been the target of a recent selective sweep among the ancestors of modern Europeans, Cheng’s team concluded.

Finally, the team measured the pigmentation levels of 203 African Americans and 105 African Caribbeans—groups that represent an admixture of African and European ancestry—and compared their *SLC24A5* genotypes. Subjects homozygous for the threonine allele tended to be lightest skinned, those homozygous for the alanine allele were darkest, and heterozygotes were in between, as shown by the degree of reflectance of their skin. The team concludes that between 25% and 38% of the skin-color difference between Europeans and Africans can be attributed to *SLC24A5* variants. The experiments provide “a beautiful example of the

critical role that model organism genetics continues to play for understanding human gene function,” says geneticist Gregory Barsh of Stanford University in California.

The new work doesn’t solve the question of why fair skin might have been favored among Europeans. However, it is consistent with a long-standing but unproven hypothesis that light skin allows more absorption of sunshine and so produces more vitamin D, a trait that would be favored at less sunny European latitudes.

Barsh adds that the paper “indicates how the genetics of skin-color variation is quite different from, and should not be confused with, the concept of race.” Rather, he says, “one of the most obvious characteristics that distinguishes among different humans is nothing more than a simple change in activity of a protein expressed in pigment cells.” Jablonski agrees: “Skin color does not equal race, period.” —MICHAEL BALTER

SCIENTIFIC PUBLISHING

Echoing Other Cases, *NEJM* Says Vioxx Safety Data Withheld

When the *New England Journal of Medicine* (*NEJM*) last week released a scathing editorial asserting that a study on Vioxx had omitted safety data, the episode became the latest chapter in the efforts of medical journal editors to keep what they consider misleading drug studies from their pages. The editorial contended that the authors of the influential 2000 study in *NEJM* failed to report three out of 20 heart attacks among patients treated with Vioxx and data on cardiovascular ailments such as angina.

A string of similar cases have prompted journals to tighten requirements of authors, ask increasingly pointed questions before publishing, and require that clinical trials be publicly registered before papers are reviewed. Yet those measures may not be enough, say editors. “We now hold [a paper] up to the light and say, ‘This seems like a very well done study; can we believe it?’” says Drummond Rennie, a deputy editor at the *Journal of the American Medical Association* (*JAMA*). “What can we do? ... We can’t go wired into their lab.”

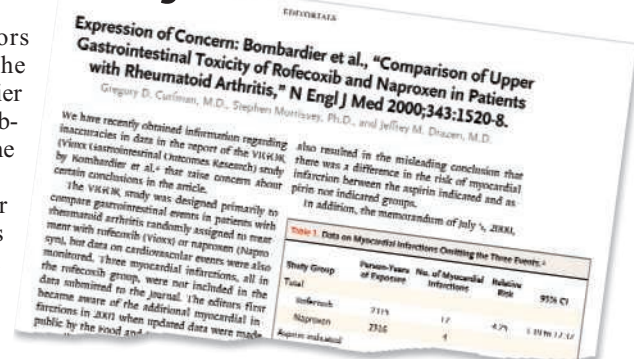
The latest case came to light when Gregory Curfman, an *NEJM* editor, was deposed on 21 November in the third Vioxx lawsuit. (The jury deadlocked, producing a mistrial this week.) Curfman learned from a Merck memo of three unreported heart attacks, which he realized had been deleted from a paper comparing the gastrointestinal effects of Vioxx with those of the anti-inflammatory naproxen, says Karen Pedersen, an *NEJM* spokesperson. (Curfman was not available for comment.) Data showing other cardiovascular problems were removed just 2 days before the manuscript was submitted, according to *NEJM*.

Pedersen says the journal’s editors crafted their editorial, sent it to the paper’s lead author Claire Bombardier of the University of Toronto, and published it online. They also invited the authors to submit a correction.

In an e-mail to *Science*, Bombardier said that she and the other authors are preparing a reply to *NEJM* and declined to comment until that’s complete. In a statement, Merck denied any wrongdoing, asserting that the three heart attacks occurred after the study’s prespecified completion and thus did not warrant inclusion. The company also noted that the heart attacks were disclosed to the Food and Drug Administration.

This new Vioxx flap produced “flashbacks,” says Christine Laine, senior deputy editor of the *Annals of Internal Medicine*. Last spring, her journal learned from a reporter that a 2003 Vioxx paper reporting several heart attacks excluded a sudden cardiac death. Because the paper was not technically in error—the cardiac death was not necessarily due to a heart attack—the journal published only a letter from the Merck co-authors. As part of its detailed author questionnaire, the *Annals* now asks whether a professional or industry writer was involved in the paper. And rather than simply asking authors what contributions they made to the research, the journal inquires at which stage they became involved.

JAMA, which was also singled by a COX-2 inhibitor paper it published in 2000, now insists on an independent statistical analysis of raw data from clinical trials and uses a ques-



Fighting back. *NEJM* released this statement about a paper it published.

tionnaire that’s increasingly specific, querying the authors about their separate contributions. The International Committee of Medical Journal Editors, a consortium of 12 medical journals and the U.S. National Library of Medicine, has also tried to tighten guidelines around conflict-of-interest disclosure and press its members to publish more negative trials.

In September, the consortium, which includes *JAMA*, *NEJM*, and *Annals*, began requiring registration of clinical trials before it would consider publishing them. The goal is to ensure that reported results conform to the trial’s design, and that there is a public record of trials whose results go unreported—often because the findings are negative. At the National Institutes of Health’s ClinicalTrials.gov, the number of trials registered shot from 12,000 in the spring to more than 30,000 today. “It really looks like the policy ... had a big impact,” says Deborah Zarin, director of the database. —JENNIFER COUZIN