Over time, cryo-EM images of this lactase protein have sharpened from blobs (left) to filigrees (right).

images. In work from 1975 to 1986, Frank came up with a way to make sense of the data, by using algorithms to sort the images into related groups and then averaging each one. This not only sharpened the 2D images, but also allowed them to be combined into a 3D structure.

In the early 1980s, Dubochet sharpened the resolution further by freezing the samples, locking the biomolecules into place. Freezing biological samples ordinarily produces ice crystals, which diffract the electron beam and blur the image. Dubochet realized that if the water was frozen quickly enough—vitrified, like glass—ice crystals wouldn't form. By cooling samples with liquid nitrogen to –196°C, Dubochet created breathtakingly sharp images. Because the molecules are flash-frozen in a variety of states, researchers can assemble these pictures into movies that reveal how the shape of the protein changes as it does its work in the cell.

These advances brought the resolution of cryo-EM to 0.5 nanometers. That still couldn't match x-ray crystallography, which today achieves a resolution of 0.2 nanometers or better. "We kind of got stuck," Frank says. But Henderson pushed to replace film-based detectors with digital ones, and today's cryo-EM machines can get 0.25-nanometer resolution. "That brought us into the realm of x-ray crystallography," Frank says.

Cryo-EM techniques are revealing the structures of ever-larger complexes including the ribosome, the cellular factory that produces proteins, and the spliceosome, the complex that trims noncoding material out of RNA. Within reach is a vast world of membrane-bound proteins and protein complexes that can't be crystallized, Henderson says. "In a few years, perhaps 5 years, we might know most of the structures, at least in humans and pathogenic bacteria," he says. "It's really quite an exciting time."

The U.S. National Institutes of Health and other funding agencies are spending tens of millions of dollars to build new cryo-EM centers to expand access to the machines. One upshot, Ramakrishnan says, is that structural biologists like himself are getting out of the business of x-ray crystallography. "Nobody in my lab wanted to set up crystallization trays anymore," he says.

The exodus could have an impact on the billion-dollar, stadium-sized synchrotrons that generate the x-ray light for crystallography experiments. If structural biologists turn en masse to cryo-EM, "there might soon be too many synchrotrons around," Stark says. "That could happen." ■

PHOTOS: ALESSIA RANCIARO AND SIMON R. THOMPSON

HUMAN GENETICS

How Africans evolved a palette of skin tones

Gene variants show that the evolution of skin color was anything but black and white

By **Ann Gibbons**

Most people associate Africans with dark skin. But different groups of people in Africa have almost every skin color on the planet, from deepest black in the Dinka of South Sudan to beige in the San of South Africa. Now, researchers have discovered a handful of new gene variants responsible for this palette of tones.

Researchers have identified genes that help create diverse skin tones, such as those seen in the Agaw (top) and Surma (bottom) peoples of Africa.

The study, published online this week in *Science*, traces the evolution of these genes and how they traveled around the world. While the dark skin of some Pacific Islanders can be traced to Africa, gene variants from Eurasia also seem to have made their way back to Africa. And surprisingly, some of the mutations responsible for lighter skin in Europeans turn out to have an ancient African origin.

"This is really a landmark study of skin color diversity," says geneticist Greg Barsh of the HudsonAlpha Institute for Biotechnology in Huntsville, Alabama.

Researchers agree that our early australopithecine ancestors in Africa probably had light skin beneath hairy pelts. "If you shave a chimpanzee, its skin is light," says evolutionary geneticist Sarah Tishkoff of the University of Pennsylvania, the lead author of the new study. "If you have body hair, you don't need dark skin to protect you from ultraviolet [UV] radiation."

Until recently, researchers assumed that after human ancestors shed most body hair, sometime before 2 million years ago, they quickly evolved dark skin for protection from skin cancer and other harmful effects of UV radiation. Then, when humans migrated out of Africa and headed to the far north, they evolved lighter skin as an adaptation to limited sunlight. (Pale skin synthesizes more vitamin D when light is scarce; *Science*, 21 November 2014, p. 934.)

Previous research on skin-color genes fit that picture. For example, a "depigmentation gene" called *SLC24A5* linked to pale skin swept through European populations in the past 6000 years.

But Tishkoff's team found that the story of skin color evolution isn't so black and white. Her team, including African researchers, used a light meter to measure skin reflectance in 2092 people in Ethiopia, Tanzania, and Botswana. They found the darkest skin in the Nilo-Saharan pastoralist populations of eastern Africa, such as the Mursi and Surma, and the lightest skin in the San of southern Africa, as well as many shades in between, as in the Agaw people of Ethiopia.

At the same time, they collected blood samples for genetic studies. They sequenced more than 4 million single nucleotide polymorphisms (SNPs)—places where a single letter of the genetic code varies across the genomes of 1570 of these Africans. They found four key areas of the genome where specific SNPs correlate with skin color.

The first surprise was that *SLC24A5,* which swept Europe, is also common in East Africa—found in as many as half the members of some Ethiopian groups. This variant arose 30,000 years ago and was probably brought to eastern Africa by people migrating from the Middle East, Tishkoff says.

But though many East Africans have this gene, they don't have white skin, probably because it is just one of several genes that shape their skin color.

The team also found variants of two neighboring genes, *HERC2* and *OCA2*, which are associated with light skin, eyes, and hair in Europeans but arose in Africa; these variants are ancient and common in the light-skinned San people. The team proposes that the variants arose in Africa as early as 1 million years ago and spread later to Europeans and Asians. "Many of the gene variants that cause light skin in Europe have origins in Africa," Tishkoff says.

The most dramatic discovery concerned a gene known as *MFSD12*. Two mutations that decrease expression of this gene were found in high frequencies in people with the darkest skin. These variants arose about a half-million years ago, suggesting that human ancestors before that time may have had moderately dark skin, rather than the deep black hue created today by these mutations.

These same two variants are found in Melanesians, Australian Aborigines, and some Indians. These people may have inherited the variants from ancient migrants from Africa who followed a "southern route" out of East Africa, along the southern coast of India to Melanesia and Australia, Tishkoff says. That idea, however, counters three genetic studies that concluded last year that Australians, Melanesians, and Eurasians all descend from a single migration out of Africa. Alternatively, this great migration may have included people carrying variants for both light and dark skin, but the dark variants later were lost in Eurasians.

To understand how the *MFSD12* mutations help make darker skin, the researchers reduced expression of the gene in cultured cells, mimicking the action of the variants in dark-skinned people. The cells produced more eumelanin, the pigment responsible for black and brown skin, hair, and eyes. The mutations may also change skin color by blocking yellow pigments: When the researchers knocked out *MFSD12* in zebrafish and mice, red and yellow pigments were lost, and the mice's light brown coats turned gray. "This new mechanism for producing intensely dark pigmentation is really the big story," says Nina Jablonski, an anthropologist at Pennsylvania State University in State College.

The study adds to established research undercutting old notions of race. You can't use skin color to classify humans, any more than you can use other complex traits like height, Tishkoff says. "There is so much diversity in Africans that there is no such thing as an African race." ■

Manatees and the seagrass they graze on brought innovations from the land back to the sea.

PHOTO: AURORA PHOTOS/ALAMY STOCK PHOTO

PALEONTOLOGY

Evolution accelerated when life set foot on land

Opportunities of terrestrial living sped innovation

By **Elizabeth Pennisi**

Life probably originated in water, but nature did some of its best work once organisms made landfall. That's what Geerat Vermeij has concluded after surveying fossils and family trees to discover where and when some of life's greatest modern advances evolved. Almost all of these seemingly out-of-the-blue innovations, from fungus farming by insects to the water transport systems that made tall trees possible, came about after plants and animals learned how to survive on land some 440 million years ago, Vermeij, an evolutionary biologist at the University of California, Davis, reported last week in *Current Biology*.

"The idea that a dramatic 'pivot' in the locus and tempo of biological innovation occurred once complex life colonized the land surface is quite profound," says Stefan Lalonde, a geobiologist at the European Institute for Marine Studies in Plouzané, France.

Many researchers have focused on how newly land-based organisms coped with gravity and the threat of desiccation. But Vermeij wondered instead how the move to land might have changed the pace of evolution. He compiled a list of key innovations that showed up in several groups of organisms and provided a big competitive edge, such as herbivory by vertebrates, flight, echolocation, and warm-bloodedness. Existing fossil evidence enabled him to date the origin of a dozen of these adaptations.

Nine appeared first on land and later in the sea, he reported. "Once they evolved on land, they could re-enter the oceans," where they had a big effect on the ecosystems there, comments Nick Lane, a biochemist at University College London. For example, seagrasses brought land plants' systems for transporting water and acquiring nutrients back to the marine environment. Vermeij found two other traits that are still restricted to land. Another, the tendency of animals to guard their plant or plantlike food sources—appeared about 50 million years ago in both places. Just one, the ability to use electrical currents for communication and hunting—think electric eels—happened first, and only, in water.

Lalonde, too, has found evidence of differences in evolution on land and in the sea by studying land-based and sea-going microbes that produced oxygen billions of years ago. But he and some others are not convinced that Vermeij has found a real pattern. "A major difficulty is avoiding bias in the selection of the set of major innovations," Lalonde says. Many innovations, such as long-distance migration and color vision, don't show up in the fossil record and so were not counted.

Still, the work "will encourage us to think about whether there is something special about the terrestrial environment," says Charles Delwiche, an evolutionary biologist at the University of Maryland in College Park. Vermeij thinks life on land was less constrained because air is easier to move around in than water, but Charles Wellman, a paleontologist at the University of Sheffield in the United Kingdom, wonders whether the terrestrial environment was more stressful, forcing organisms to innovate to survive. And Delwiche suggests that the availability of new places to live was what fueled the surge of innovation following the conquest of the land.

"I don't know if I believe" the article, Delwiche says. "But the thing that I love about it is it gets me thinking." ■

Published by AAAS

Science

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Science **358** (6360), 157-158.
DOI: 10.1126/science.358.6360.157
