

First animal model of recent human evolution

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The first animal model of recent human evolution reveals that a single mutation produced several traits common in East Asian peoples, from thicker hair to denser sweat glands, an international team of researchers reports.

The team, led by researchers from Harvard Medical School, Harvard University, the Broad Institute of MIT and Harvard, Massachusetts General Hospital, Fudan University and University College London, also modeled the spread of the [gene mutation](#) across Asia and North America, concluding that it most likely arose about 30,000 years ago in what is today central China. The findings are reported in the cover story of the Feb. 14 issue of *Cell*.

"This interdisciplinary approach yields unique insight into the generation of adaptive variation among modern humans," said Pardis Sabeti, associate professor in the Center for [Systems Biology](#) and Department of Organismic and [Evolutionary Biology](#) at Harvard University, and one of the paper's senior authors.

"This paper tells a story about [human evolution](#) in three parts," said Cliff Tabin, head of the HMS Department of Genetics and co-senior author. "The mouse model links multiple traits to a single mutation, the related association study finds these traits in humans, and computer models tell us where and when the mutation likely arose and spread."

Previous research in Sabeti's lab had identified the mutation as a strong

candidate for positive selection. That is, evidence within the genetic code suggested the mutant gene conferred an [evolutionary advantage](#), though what advantage was unclear.

The mutation was found in a gene for ectodysplasin receptor, or EDAR, part of a signaling pathway known to play a key role in the development of hair, sweat glands and other skin features. While human populations in Africa and Europe had one, ancestral, version of the gene, most East Asians had a derived variant, EDARV370A, which studies had linked to thicker scalp hair and an altered tooth shape in humans.

The ectodysplasin pathway is highly conserved across vertebrates—the same genes do the same thing in humans and mice and zebrafish. For that reason, and because its effects on skin, hair and scales can be observed directly, it is widely studied.

This evolutionary conservation led Yana Kamberov, one of two first authors on the paper, to reason that EDARV370A would exert similar biological effects in an animal model as in humans. The HMS research fellow in genetics developed a mouse model with the exact mutation of EDARV370A—a difference of one DNA letter from the original, or wild-type, population. That mouse manifested thicker hair, more densely branched mammary glands and an increased number of eccrine, or sweat, glands.

"This not only directly pointed us to the subset of organs and tissues that were sensitive to the mutation, but also gave us the key biological evidence that EDARV370A could have been acted on by natural selection," Kamberov said.

The findings prompted the team to look for similar traits in [human populations](#). When co-first author Sijia Wang and the team including collaborators at Fudan examined the fingertips of Chinese volunteers at

colleges and farming villages, they found that the sweat glands of Han Chinese, who carry the derived variant of the gene, were packed about 15 percent more densely than those of a control population with the ancestral variant.

At the same time, Wang and the team including collaborators at University College London were working to zero in on when and where the mutation arose. Computer models suggested that the derived variant of the gene emerged in central China between 13,175 and 39,575 years ago, with a median estimate of 30,925 years. Researchers concluded the derived variant is at least 15,000 years old, predating the migration from Asia by Native Americans, who also carry the mutation.

That time span suggests that different traits could have been under selection at different times. The mutation's many effects, known as pleiotropy, only complicate the question. If changes to the [sweat glands](#) conferred an advantage in new climates—one of the theories the researchers plan to explore further—changes to hair and to mammary glands could have conferred other advantages at other times.

Not all of these advantages need be direct effects on fitness. "When Pardis started this work, I would not have predicted that a gene that makes good hair would top of a list of mutations that confer evolutionary advantage among humans," said Bruce Morgan, HMS associate professor of dermatology at Massachusetts General Hospital and co-senior author on the paper. "However, in this case 'good hair' may have a biological meaning because it is genetically linked to a physiologically adaptive trait like increased sweating capacity. A cultural preference for a physically obvious trait like hair type could have arisen because individuals with it were more successful, and this would help increase selection on the new variant."

"That (pleiotropy) makes it harder for us to make a guess," Wang said.

"If there were only one associated trait, we could say with confidence that's where the selective advantage comes from. But with many traits, we don't know which is the target of selection, and which are just hitchhiking." Wang intends to focus on that question in his new role, as a Max Planck independent research group leader in dermatogenomics at Chinese Academy of Sciences – Max Planck Partner Institute for Computational Biology in Shanghai.

By leveraging the power of diverse fields, the team is piecing together the foundation for understanding how selected mutations like EDARV370A have impacted human diversity. But, they say, this is only the beginning.

"These findings point to what mutations, when, where and how," said Daniel Lieberman, a professor of human evolutionary biology at Harvard University and a co-senior author on the study. "We still want to know why."

Provided by Harvard Medical School

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