# The chillest ape: How humans evolved a super-high cooling capacity

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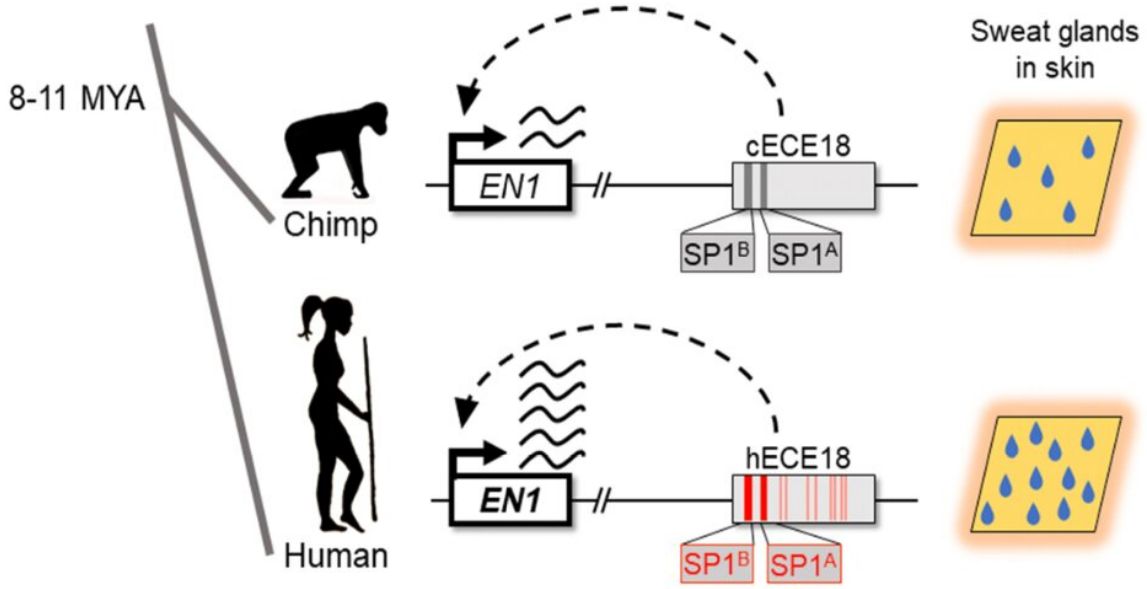


Over time, humans gradually evolved a stronger enhancer for activating Engrailed 1 gene expression, resulting in more sweat glands and making them the sweatiest of the Great Apes. Credit: Perelman School of Medicine at the University of Pennsylvania

Humans have a uniquely high density of sweat glands embedded in their

skin—10 times the density of chimpanzees and macaques. Now, researchers at Penn Medicine have discovered how this distinctive, hyper-cooling trait evolved in the human genome. In a study published today in the *Proceedings of the National Academy of Sciences,* researchers showed that the higher density of sweat glands in humans is due, to a great extent, to accumulated changes in a regulatory region of DNA—called an enhancer region—that drives the expression of a sweat gland-building gene, explaining why humans are the sweatiest of the Great Apes.

"This is one of the clearest examples I've ever seen of pinpointing the genetic basis for one of the most extreme and distinctively human evolutionary traits as a whole," said the study's senior author, Yana Kamberov, Ph.D., an assistant professor of genetics at Penn Medicine. "This kind of research is important not only because it shows how evolution actually works to produce species diversity but also because it gives us access into human biology that is often not possible to gain in other ways, essentially by learning from tweaking the biological system in a way that is actually beneficial, without breaking it."

Scientists broadly assume that humans' high density of sweat glands, also called eccrine glands, reflects an ancient evolutionary adaptation. This adaptation, coupled with the loss of fur in early hominins, which promoted cooling through sweat evaporation, is thought to have made it easier for them to run, hunt, and otherwise survive on the hot and relatively treeless African savannah, a markedly different habitat than the jungles occupied by other ape species.

Kamberov found in a 2015 study that the expression level of a gene called Engrailed 1—EN1 in humans—helps determine the density of eccrine glands in mice. EN1 encodes a transcription factor protein that, among many other functions, works during development to induce immature skin cells to form eccrine glands. Because of this property,

Kamberov and colleagues hypothesized that perhaps one way in which humans could have built more sweat glands in their skin is to evolve genetic changes that increased the production of EN1 in the skin.

The activity of a gene is often affected by nearby regions of DNA called enhancer regions, where factors that activate the gene can bind and help drive the gene's expression. In the study, Kamberov and her team identified an enhancer region called hECE18 that boosts the production of EN1 in skin, to induce the formation of more eccrine glands. The researchers showed that the human version of hECE18 is more active than that of ape or macaque versions, which would in turn drive higher levels of EN1 production.

Kamberov and her colleagues also teased apart the individual mutations that distinguish human hECE18, showing why some of them boost EN1 expression—and showing that rolling back those mutations to the chimp version of hECE18 brings the enhancer activity down to chimp levels.

Prior studies of evolved human-specific traits, such as language, generally have tied such traits to complex genetic changes involving multiple genes and regulatory regions. In contrast, the work from Kamberov and her team suggest that the human 'high-sweat' trait evolved at least in part through repeated mutations to just one regulatory region, hECE18. This means that this single regulatory element could have repeatedly contributed to a gradual evolution of higher eccrine gland density during human evolution.

While the study is mainly a feat of basic biology that shines a light on human evolution, it also should have some long-term medical relevance, Kamberov said.

"Severe wounds or burns often destroy sweat glands in skin, and so far we don't know how to regenerate them—but this study brings us closer

to discovering how to do that," she said. "The next step in this research would be to uncover how the multiple activity enhancing mutations in hECE18 interact with each other to increase EN1 expression and to use these biologically key mutations as starting points to figure out what DNA-binding factors actually bind at these sites. Basically, this provides us with a direct molecular inroad to discover the upstream factors that by activating EN1 expression get skin cells to start making sweat glands."

**More information:** Daniel Aldea et al, Repeated mutation of a developmental enhancer contributed to human thermoregulatory evolution, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2021722118

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