An out-of-Africa story hiding in our DNA

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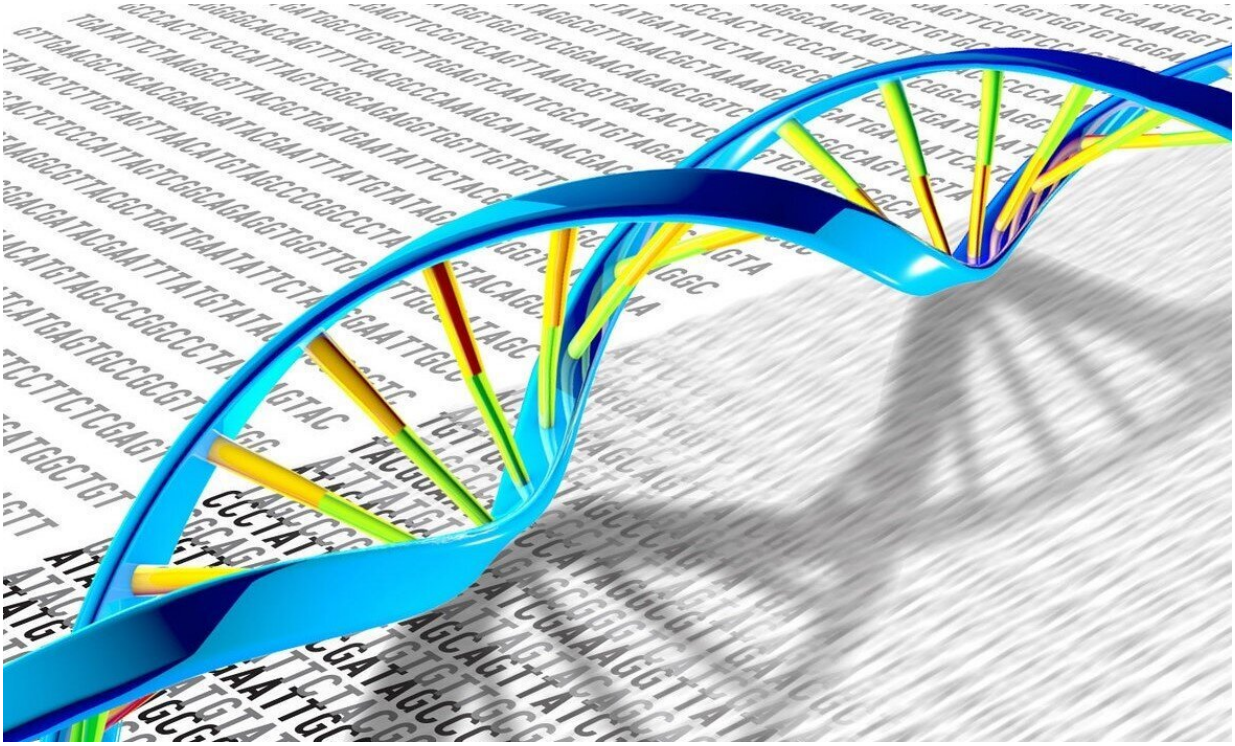

DNA, which has a double-helix structure, can have many genetic mutations and variations. Credit: NIH

"Who are we and where do we come from?" This quintessential question has intrigued humanity for millennia. Currently, the "Out-of-Africa (OOA) theory" is prevailingly accepted regarding the origin of modern humans, as a line of evidence indicates that Homo sapiens originated in Africa.

It is inferred that a small group of modern humans migrated out of Africa ~70,000 years ago, and nearly all humans outside of Africa today are considered as descendants of these early pioneers. Serving as a shelter, Africa protected modern humans from extreme cold conditions during repeated ice ages.

Early humans adapted to the heat dissipation requirements of running on the East African grasslands by losing their thick body hair. However, when the ancestors of modern humans left Africa, they encountered the same survival challenges as previous pioneers did: how to keep their bodies warm in extremely cold climates.

Are there remnants in the human genome that reflect the evolutionary adaptations of our ancestors who endured extreme environments?

Genome-wide association studies (GWAS) have significantly advanced disease genetics and provided invaluable tools for exploring human evolutionary events.

In 2007, a cluster of single nucleotide polymorphisms (SNPs) within intron 1 of the FTO (fat mass and obesity-associated) gene was identified as being most strongly associated with obesity risk. However, it remained unclear whether these SNPs directly contribute to the development of obesity.

The turning point came in 2015 when Claussnitzer and others published a milestone article in the *New England Journal of Medicine*. The study pinpointed the rs1421085 T>C variant within the FTO SNP cluster for the first time, showing that this variant inhibited the expression of UCP1 (uncoupling protein 1), a core gene of thermogenesis, and reduced thermogenic capacity of differentiated human beige fat cells.

While this study appears to elucidate the molecular mechanism of FTO

variants in obesity, it is noted that there is a lack of direct in vivo evidence to support these findings.

In 2023, a group published a paper in *Nature Metabolism* that challenged the above conclusions. Their findings revealed that mice carrying the homozygous CC-alleles exhibit enhanced brown adipose tissue (BAT) thermogenesis and resistance to high-fat diet-induced obesity.

Notably, mice harboring the CC-alleles showed ~6 °C higher than those with TT-alleles when exposed to a cold room (4°C). These results led researchers to speculate that the rs1421085 T>C variant might be related to mammals' adaptation to cold environments.

To further investigate whether the rs1421085 T>C variant affects thermogenesis in humans, researchers conducted a study, now published in *Life Metabolism*, using human fetal BAT obtained from aborted samples due to developmental defects.

The results demonstrate that TC-allele carriers owed higher expression of UCP1 in BAT than TT-allele carriers, aligning with previous observations in mice. This discovery prompted researchers to reassess the connection among the rs1421085 T>C variant, obesity, and human evolutionary processes. Could the expansion of this variant be attributed to positive selection for human adaptation to cold environments?

Over the last 100,000 years, modern humans have migrated from low latitudes to high latitudes, transitioning from tropical and temperate zones to colder regions, and shifting from hunter-gatherer societies to agricultural and pastoral lifestyles. These environmental changes have imposed evolutionary pressures that have played a pivotal role in shaping phenotypic diversity across diverse populations.

For instance, the Inuit population residing in the frigid Arctic region

heavily rely on marine fish abundant in omega-3 polyunsaturated fatty acids (PUFAs) for their diet. The most prominent signal of positive selection is observed within the fatty acid desaturase (FADS) gene. Notably, these genetic variants were initially associated with height traits in general populations. Could a comparable mechanism of positive selection elucidate the narrative behind the rs1421085 T>C variant?

Thus, using a systematic analysis of the rs1421085 C-allele frequency among diverse ancestral groups, they observed a remarked inverse correlation between the C-allele frequency and mean earth skin temperatures in January. This observed pattern indicates that "the colder the location, the higher the frequency of this variant."

In contrast, no correlation was found between the frequency and longitudes or altitudes among populations. Interestingly, the step-by-step shift of the C-allele frequency tracked the "modern human migration route map" documented previously.

Building on these human and mouse results, encompassing both in vitro and in vivo experiments, and considering the genetic distribution patterns of Eurasian and African populations, the researchers proposed a hypothesis that the substantial variance in the C-allele frequency across populations from Africa to Eurasia might be driven by positive selection mechanisms linked to varying levels of cold stress.

During the peer review process, reviewers noted some deviations in the correlation analysis, particularly regarding the high frequency of the C-allele in populations from the Indian subcontinent, which did not correspond with local ambient temperatures. Back to human genetic studies, a range of Eurasian-related ancestry varies from 20% to 80% across diverse Indian ethnic populations.

The potential influx of populations or migrations from the north and

west, known as the "Aryan invasion theory," may have contributed to the ancient Indian civilizations' decline. They speculated that historical invasions or migrations may have altered the original gene frequencies of ancient Indian populations by introducing high-frequency C-alleles from cold high-altitude regions. Therefore, major historical events may underlie these seemingly contradictory genetic findings.

Despite the absence of direct evidence from ancient human fossils, the significance of this study lies in pinpointing the functional FTO variant—rs1421085 T>C—as potentially the inaugural locus established to enhance the expression of human thermogenic genes and be positively selected in response to cold temperatures.

Their speculation suggests that this variant could confer newborn carriers a substantial survival advantage in cold climates, particularly during the short term after birth, by enhancing BAT thermogenesis. This genetic adaptation may represent just one of the numerous variants early humans employed to acclimate to harsh cold environments. The team anticipates that further genetic variants relevant to this intricate evolutionary trajectory will be unraveled in the future.

The team has devoted extensive effort over more than a decade to delve into obesity genetics, particularly focusing on the FTO SNP through functional studies. Initially, they aimed to decipher the role of this pivotal variant in obesity. As investigations have progressed, a realization has emerged that "genetic signals affecting the development of obesity in modern humans may have been destined since the moment human pioneers migrated out of Africa."

Delving into genetic studies on modern complex diseases often entails a lengthy and arduous journey to unveil the narrative's origin, given the myriad of accidental or inevitable, random or intentional factors at play. This process mirrors the tale of "the blind men and the elephant,"

marked by debates, contradictions, and crucially, collaborative support.

While the question of "where do we come from?" remains enigmatic, this research provides a glimpse of intrepid pioneers navigating within the winds and snows of distant eras and realms.

The intricacies of human genetics likely harbor numerous undisclosed secrets regarding cold resistance, alongside countless ancient narratives revolving around survival and demise. Much like the rock paintings adorning the walls of the Blombos Cave, our DNA serves as a faithful recorder of every notable event along the intricate path of human evolution.

This enduring repository of our history calls for ceaseless exploration and investigation, offering insights into our complex journey through time and adaptation.

More information: Nan Yin et al, The FTO variant with enhanced UCP1 expression is linked to human migration out of Africa, *Life Metabolism* (2024). DOI: 10.1093/lifemeta/loae027

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