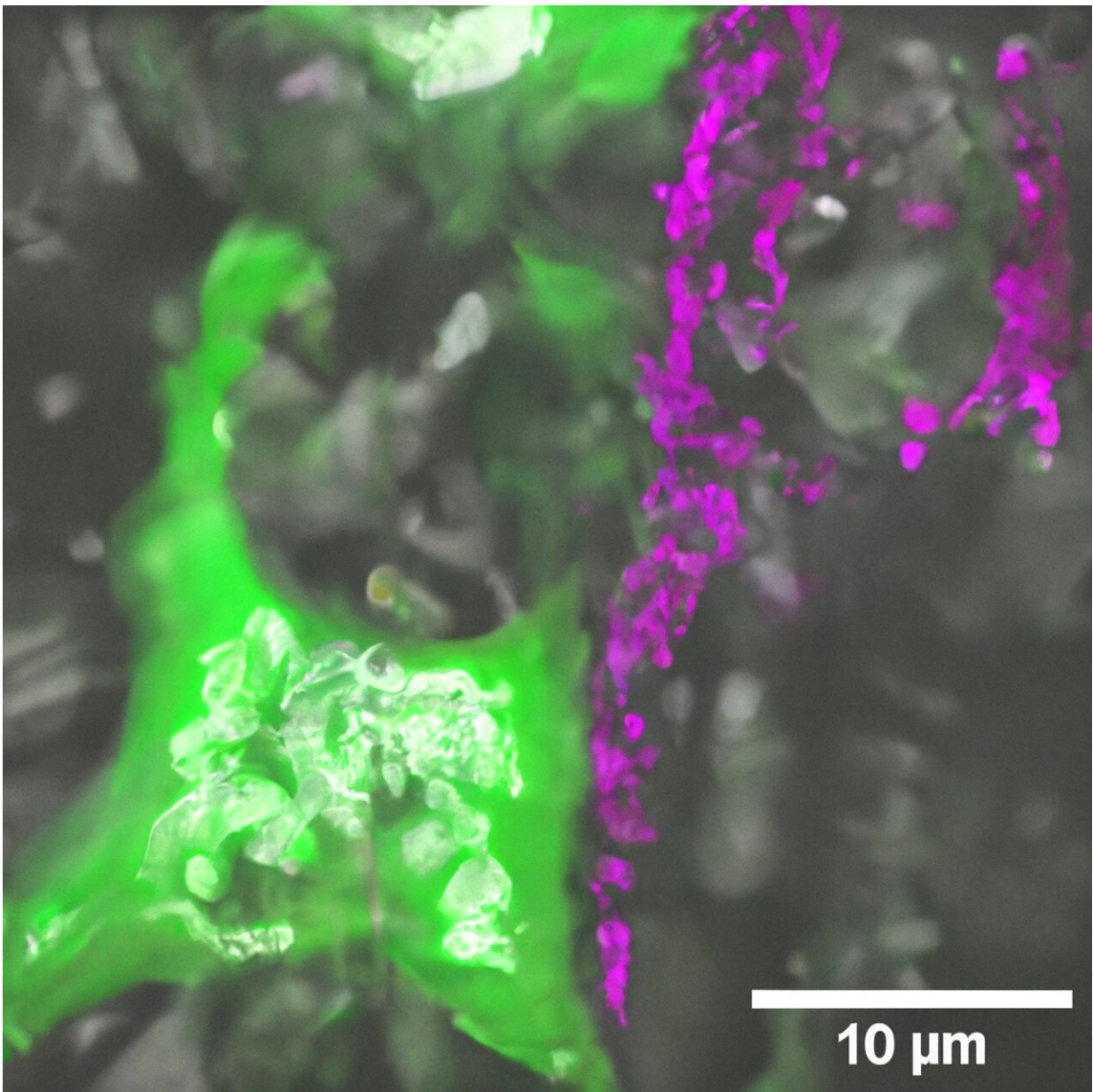


The genetic heritage of the Denisovans may have left its mark on our mental health

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Demonstration that part of the transporter is located in mitochondria by superresolution STED microscopy imaging with HEZ293 cells transfected with the zinc transporter ZnT9 (in green). In magenta the mitochondrial protein TOM 20 and in white the localization to mitochondria. Credit: Rubén Vicente. Credit: Ruben Vicente

Modern humans left Africa some 60,000 years ago in the event known as "Out-of-Africa." In Asia, they coincided with the Denisovans, and that encounter may have led to confrontations and collaborations, but also various crossbreeding. In fact, modern humans retain genetic variants of Denisovan origin in our genome, which are testimony to those initial interactions.

Now, a team led by the Institute of Evolutionary Biology (IBE), a joint center of the Spanish National Research Council (CSIC) and Pompeu Fabra University (UPF), and by the UPF Department of Medicine and Life Sciences (MELIS), has identified one of the most widespread traces of the genetic heritage of the extinct Denisovans in [modern humans](#).

The teams of Elena Bosch, IBE principal investigator, and of Rubén Vicente, MELIS-UPF principal investigator, have discovered that this genetic adaptation helped ancestral populations of Homo sapiens to adapt to the cold. The variant observed, involved in zinc regulation and with a role in cellular metabolism, could also have predisposed modern humans to [psychiatric disorders](#) such as depression or schizophrenia.

Genetic variation in zinc regulation may have meant an evolutionary advantage

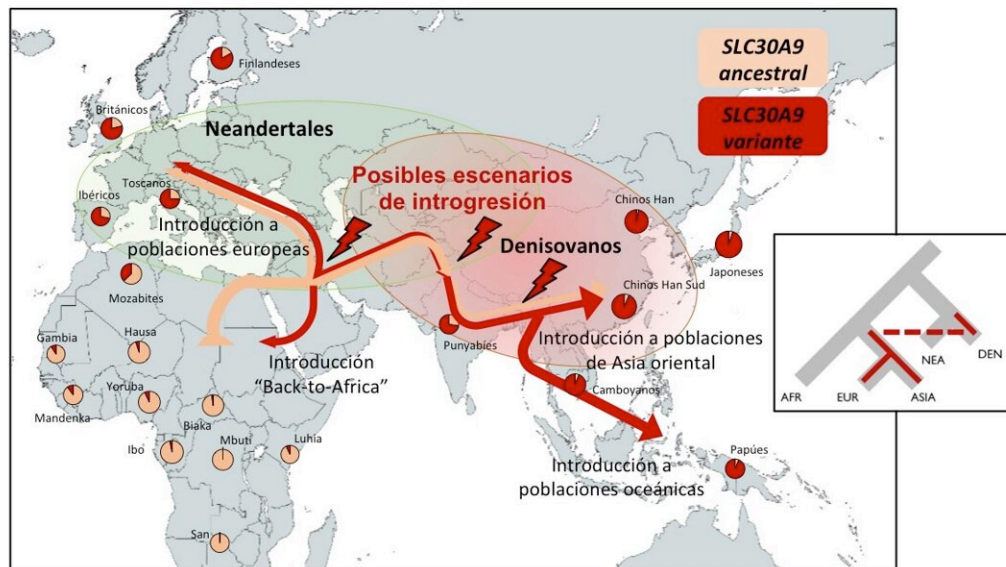
How adaptation has shaped current genetic diversity in human populations is a matter of great interest in evolutionary genetics.

Arising from this question, Elena Bosch's team identified an adaptive variant among current [human populations](#) in a region of our genome that bears great similarity to the genome of an extinct ancestral [population](#): the Denisovans.

"Through genomic analysis, we noted that the genetic variant observed came from our interbreeding with archaic humans in the past, possibly the Denisovans," says Ana Roca-Umbert, co-first author of the study. The team has ruled out Neanderthal heritage, since these populations do not have this mutation.

"Apparently, the change was beneficial and proved a selective advantage for humans. As a consequence, this variation in the SLC30A9 gene was selected and has reached current populations," adds Jorge Garcia-Calleja, co-first author of the study.

The Evolutionary Population Genetics Laboratory, directed by Bosch, wished to find out what changes are brought about by this [genetic variation](#) of Denisovan origin at the cellular level. "We discovered that this mutation surely had implications for the transport of zinc within the cell, and so we contacted Vicente's team," recalls Elena Bosch, IBE principal investigator and co-leader of the study.



Geographical distribution of the substitution identified in the SLC30A9 gene in current human populations and possible scenarios of Denisovan introgression. SLC30A9 ancestral corresponds to the version of the gene prior to the crossing between Denisovans and Sapiens. SLC30A9 variant refers to the version shared with Denisovans. Credit: Jorge Garcia and Elena Bosch. Licensed under Creative Commons 4.0. Created in mapchart. Credit: Jorge Garcia and Elena Bosch. Licensed under Creative Commons 4.0. Created in mapchart.

Zinc regulation: Key to adapting to the cold

"Elena contacted me because her team had observed a change in an amino acid in a zinc transporter, which was very different between the populations of Africa and Asia today. From there, we started asking ourselves questions and looking for answers," Rubén Vicente comments. His team, in the Biophysics of the Immune System group at the Laboratory of Molecular Physiology, undertook the technical challenge

of studying the movement of intracellular zinc.

Zinc, an essential trace element for [human health](#), is an important messenger that transfers both information from the outside to the inside of cells and between different cellular compartments. A lack of zinc causes growth, neurological and immune disorders, although "its regulation is still poorly studied due to the lack of molecular tools to follow the flow of zinc."

Vicente's laboratory identified that the observed variant causes a new zinc balance within the cell, promoting a change in metabolism. By altering the [endoplasmic reticulum](#) and mitochondria of the cells, this variation causes a possible metabolic advantage to cope with a hostile climate. "The observed phenotype leads us to think of a possible adaptation to the cold," Vicente says.

The Denisovan genetic heritage could affect the mental health of European and Asian populations

Zinc transport is also involved in nervous system excitability, and plays a role in people's mental equilibrium and health.

The team points out that the variant found in this [zinc](#) transporter, which is expressed in all tissues of the body, is associated with a greater predisposition to suffering from some psychiatric diseases. These include anorexia nervosa, hyperactivity disorder, autism spectrum disorder, bipolar disorder, depression, obsessive compulsive disorder, and schizophrenia.

"In the future, expanding this study to animal models could shed light on this predisposition to suffering from mental illnesses," Vicente notes.

The genetic variant has left a global mark, except in Africa

Although the variant was established in Asia as a result of interbreeding between Denisovans and Homo sapiens, it also spread to European and native American populations. In fact, it is found in populations all over the planet, although, in the case of African populations, it is much less frequent.

The team points out that it is probably the Denisovan [genetic adaptation](#) to have the greatest geographical scope discovered to date. "For example, a [variant](#) in the EPAS1 gene inherited from the Denisovans allows adapting to life at altitude, but is found only in Tibetans. However, in our case, the impact extends to all populations outside Africa," Bosch concludes.

The work is [published](#) in the journal *PLOS Genetics*.

More information: Ana Roca-Umbert et al, Human genetic adaptation related to cellular zinc homeostasis, *PLOS Genetics* (2023). [DOI: 10.1371/journal.pgen.1010950](#)

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