Immune properties in ancient DNA found in isolated villages might benefit humanity today

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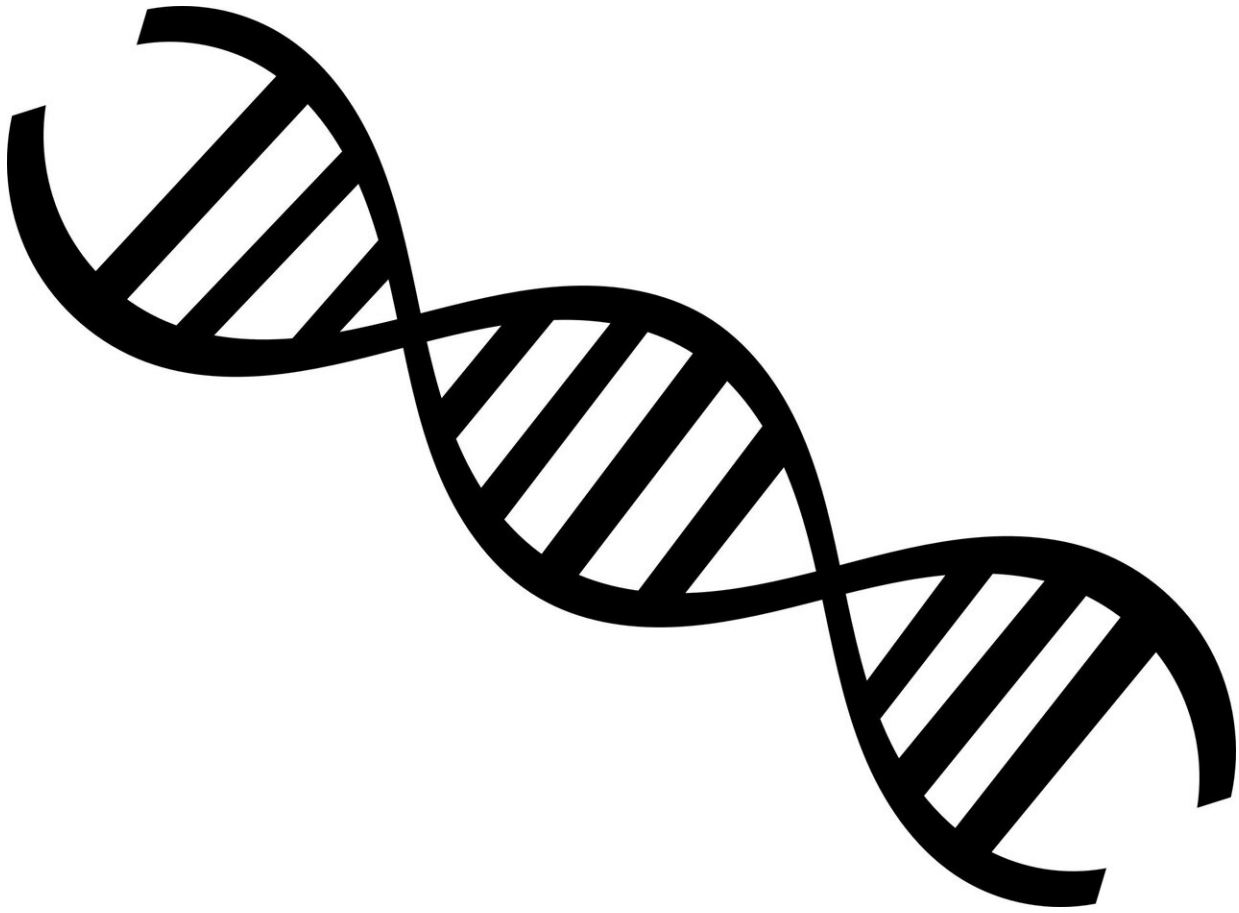

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Could remnants of DNA from a now extinct human subspecies known as the Denisovans help boost the immune functions of modern humans?

An international study co-led by the Translational Genomics Research Institute (TGen), an affiliate of City of Hope, and published in the scientific journal *PLOS Genetics*, represents the first characterizations of genes in the DNA of healthy individuals from geographically and genetically distinct populations in Indonesia.

Scientists studied genomic diversity among 116 individuals from three Indonesian populations: the Mentawai on the west coast of Sumatra; the Sumba in central Indonesia; and the Korowai, a group of hunter-gatherers from the western side of the isle of New Guinea.

The Korowai are of particular interest, as their DNA holds the world's last remaining significant remnants of genetic code—as much as 5%—from a cousin of modern humans called the Denisovans, the study says. Like the better-known Neanderthals of Europe, the Denisovans of Asia also are an extinct human subspecies who lived tens of thousands of years ago. And just as Neanderthals passed on certain immune properties to those of European ancestry, the Denisovans may have passed on protective immune genes to their southeast Asian decedents.

"Genome sequencing efforts have mainly focused on populations of European descent," said Dr. Heini Natri, a TGen postdoctoral fellow and one of the lead authors of the study. "Most of the world is deeply understudied. As we move further into the age of personalized and genomic medicine, understanding how genetics drives disease-risk across diverse populations is crucially important."

Why study Indonesia?

Spread across more than 17,000 islands between mainland Asia and

Australia, Indonesia is the world's largest archipelago. Geographically as large as the U.S. or Europe, Indonesia's 273 million inhabitants make it the world's fourth most populous nation, after China, India and the U.S. And yet, Indonesia has been largely excluded from the genomics sequencing boom of the past decade, and there previously have been no analyses of diversity in gene regulation in either Indonesia or the other island nations of southeast Asia.

"This lack of information from Indonesia is alarming as it is an epicenter of infectious disease diversity, such as malaria and other emerging tropical diseases," Dr. Natri said. "Immune pressure from infectious diseases are responsible for some of the strongest selective forces on humans throughout our species' evolutionary history, and Indonesia offers unique advantages for studying responses to these diseases."

Because of Indonesia's island environment, its many isolated villages and the relatively low population density on most of its nearly 6,000 inhabited islands, the study suggests there is low genetic diversity among those who live on each island, and even in each village, but also high genetic diversity among people from island to island, "making it a near unique study system for examining gene-by-environment interactions," the study said.

Scientists focus on immune properties of ancient human DNA

Dr. Nicholas Banovich, an Assistant Professor in TGen's Integrated Cancer Genomics Division, a human geneticist, and a senior author of this *PLOS Genetics* paper, said the study's results highlight genes involved in the function of immune cells. This suggests a potentially adaptive response to local environmental pressures, including pressures from various tropical diseases.

"One of the unique aspects of Indonesia is individuals on the island of New Guinea have high remnants of DNA from one of our extinct ancestors, the Denisovans," Dr. Banovich said. "We found these remnants of ancient DNA are driving changes in genes involved in immune function. This study demonstrates the power of including understudied populations in an effort to increase the overall understanding of human genetics."

The international team is continuing its study, integrating more genetic data, exploring patterns of local ancestry and how archaic human genes are imbedded in modern-day populations.

"We are now attempting to pinpoint individual genetic changes—in particular, those that are carried over in these remnant DNA fragments from Denisovans—which regulate how much or how little a gene is turned on, and how these genetic changes may shape immune response," Dr. Natri said.

More information: Heini M. Natri et al, Genome-wide DNA methylation and gene expression patterns reflect genetic ancestry and environmental differences across the Indonesian archipelago, *PLOS Genetics* (2020). DOI: 10.1371/journal.pgen.1008749

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