Ancient DNA reveals clues about how tuberculosis shaped the human immune system

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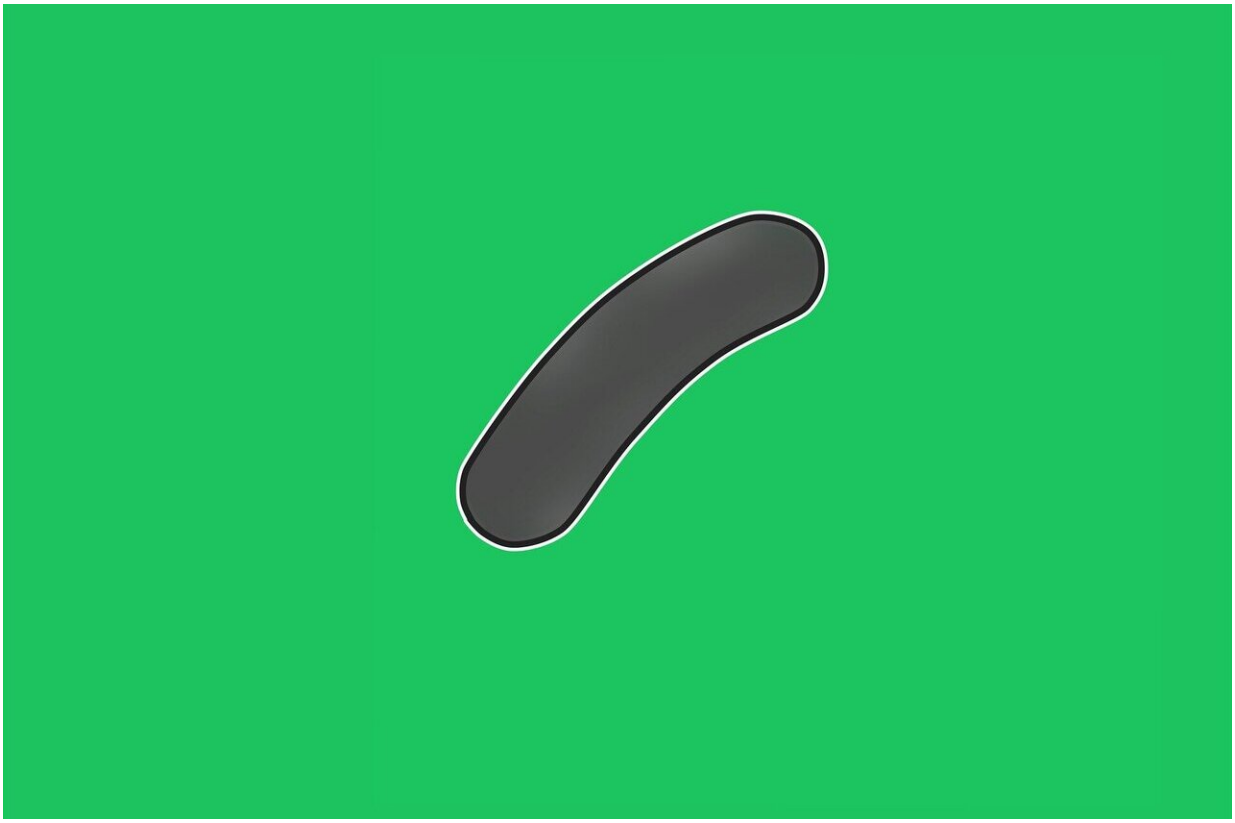

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COVID-19 is only the latest infectious disease to have had an outsized impact on human life. A new study employing ancient human DNA

reveals how tuberculosis has affected European populations over the past 2,000 years, specifically the impact that disease has had on the human genome. This work, which publishes March 4 in the *American Journal of Human Genetics*, has implications for studying not only evolutionary genetics, but also how genetics can influence the immune system.

"Present-day humans are the descendants of those who have survived many things—climate changes and big epidemics, including the Black Death, Spanish flu, and tuberculosis," says senior author Lluis Quintana-Murci of the Institut Pasteur in France. "This work uses population genetics to dissect how natural selection has acted on our genomes."

This research focused on a variant of the gene TYK2, called P1104A, which first author Gaspard Kerner had previously found to be associated with an increased risk of becoming ill after infection with Mycobacterium tuberculosis when the variant is homozygous. (TYK2 has been implicated in immune function through its effect on interferon signaling pathways.) Kerner, a Ph.D. student studying genetic diseases at the Imagine Institute of Paris University, began collaborating with Quintana-Murci, an expert in evolutionary genomics, to study the genetic determinants of human tuberculosis in the context of evolution and natural selection.

Using a large dataset of more than 1,000 European ancient human genomes, the investigators found that the P1104A variant first emerged more than 30,000 years ago. Further analysis revealed that the frequency of the variant drastically decreased about 2,000 years ago, around the time that present-day forms of infectious Mycobacterium tuberculosis strains became prevalent. The variant is not associated with other infectious bacteria or viruses.

"If you carry two copies of this variant in your genome and you encounter Mycobacterium tuberculosis, you are very likely to become

sick," Kerner says. "During the Bronze Age, this variant was much more frequent, but we saw that it started to be negatively selected at a time that correlated with the start of the tuberculosis epidemic in Europe."

"The beauty of this work is that we're using a population genetics approach to reconstruct the history of an epidemic," Quintana-Murci explains. "We can use these methods to try to understand which immune gene variants have increased the most over the last 10,000 years, indicating that they are the most beneficial, and which have decreased the most, due to negative selection."

He adds that this type of research can be complementary to other types of immunology studies, such as those performed in the laboratory. Moreover, both researchers say these tools can be used to study the history and implications of many different genetic variants for multiple infectious diseases.

More information: *American Journal of Human Genetics*, Kerner et al.: "Human ancient DNA analyses reveal the high burden of tuberculosis in Europeans over the last 2,000 years" www.cell.com/ajhg/fulltext/S0002-9297(21)00051-3 , DOI: 10.1016/j.ajhg.2021.02.009

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