Genetic variants that offered protection during Black Death are also associated with current autoimmune disorders

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Klunk et al, Skeletons uncovered in the Black Death Cemetery of East Smithfield, London. Credit: *Nature* (2022). DOI: 10.1038/s41586-022-05349-x

Infectious diseases are some of the strongest selective pressures in human evolution, selecting for genetic variants that increase resistance to infection. In the face of a pandemic, resistance to the disease undergoes strong positive selection that likely affects the genetic makeup of the population afterward.

The Black Death, otherwise known as the bubonic plague, remains the

most devastating pandemic in recorded history, reducing the European population by 30-50% within a 4-year span (1346-1350) and affecting nearly all of Afro-Eurasia. The Black Death was caused by Yersinia pestis, a highly contagious and deadly bacterium that quickly spread across the eastern continents.

How did this plague alter the population's genetic composition, and did any alleles confer protection in those that survived? These questions are explored in a new paper published in *Nature*, featuring a collaboration among the labs of Luis Barreiro, a professor of medicine at the University of Chicago; Hendrik Poinar, professor of anthropology at McMaster University; and Javier Pizarro-Cerda, Head of the World Health Organization Collaborating Research and Reference Center for Yersinia at the Pasteur Institute.

Poinar, an expert in ancient genomes and Y. pestis, and Barreiro, who has pioneered approaches to study how genetic variation affects the response to infection, are co-corresponding authors on the paper. The work was led by co-first authors Jennifer Klunk, a graduate student in Poinar's lab during the study and now a lead scientist at Daicel Arbor Biosciences, and Tauras Vilgalys, a postdoctoral fellow in Barreiro's lab.

"This was a huge interdisciplinary team that brought their experiences, their knowledge, and their questions to the project together," Klunk described. "The group was composed of historians, anthropologists, geneticists, and more, providing a wide range of perspectives and tools to work with."

The researchers collected ancient DNA across London and Denmark from individuals who died either shortly before, during, or after the Black Death. The DNA was then sequenced, and targeted immune genes were examined across the three timepoints to look for large changes in variant frequency over time.

Variants that provide protection from Y. pestis should be more frequent in post-Black Death samples compared to those that died during the plague, and variants that confer susceptibility should show the opposite pattern. The researchers found that four gene loci, including variants near ERAP2 and TICAM2, matched this pattern.

ERAP2 is active in antigen presenting cells, like macrophages, which eat and break down pathogens and present a piece of the pathogen (called an antigen) to other immune cells to help the body learn how to fight it. TICAM2 encodes an adapter protein for a macrophage surface protein called TLR4, which detects foreign gram-negative bacteria in the body, like Y. pestis.

The selected variants were associated with differences in the expression of these two genes. From the genotype data, researchers estimated that people with selected variants of these genes were 40% more likely to survive the plague.

To test how these variants favored against Y. pestis infection, monocytes were collected from the blood of living individuals with the different variants for ERAP2 and TICAM2, developed into macrophages, and exposed in vitro to Y. pestis. Macrophages with variants that caused higher expression of ERAP2 were more efficient at clearing Y. pestis than macrophages without the protective allele.

Jessica Brinkworth (IGOH, GNDP), an assistant professor of anthropology at University of Illinois Urbana-Champaign who contributed functional data to the study, described how macrophages were critical to infection of Y. pestis: "Y. pestis is really sneaky," she explained. "Once it's at 37° Celsius, it breaks down the lipopolysaccharide on its cell surface so that TLR4 can't see it anymore, basically making itself invisible. This means that there's a real clock on detecting it—it could be minutes right before these massive changes

happen. Then, it preferentially infects macrophages and turns them into little zombies, forcing them to go to the lymph nodes so Y. pestis can multiply."

Immune cells have a small window to detect Y. pestis and destroy it, and macrophages that come into contact with the bacteria need to be able to resist being hijacked to limit spread. The researchers' results show that genetic variation near ERAP2 and TICAM2 may improve detection of and resistance to Y. pestis. This likely protected people with these variants during the Black Death, increasing their chance of survival.

"I was surprised that we could actually figure out that ERAP2 has an effect on bacterial clearance in vitro," said Vilgalys. "And that's kind of surprising considering its canonical role is antigen presentation, which involves interactions of multiple cell types, not just macrophages. So what we see suggests that ERAP2 is doing something non-canonical to affect the immune response in isolated macrophages."

Variants near ERAP2 and TICAM2 also help against an array of other pathogens, but not without a trade-off. In particular, higher expression of ERAP2 is associated with autoimmune disorders in modern-day humans, including Crohn's disease. This balancing selection likely explains why different variants for these genes are still present in the population today.

"It was exciting once we delved into to the variants, to see that our variants of interest show this signal of balancing selection," Klunk said.

"We were able to say one of the variants we're looking at clearly shows a signal of selective pressure over the course of Black Death, and we showed that it's definitely involved in the immune response to Y. pestis, as well as other pathogens. But today that variant is also associated with a higher risk of autoimmune and inflammatory disorders. So being able to

make that link was like, wow, that's something special."

"I think studies like this help us understand why we're at risk for certain diseases, and how past pandemics have shaped current disease risks," Vilgalys said.

"Why does 50% of the population have these ERAP2 variants that put you at increased risk for chronic disease? Part of the reason is that our genomes have been shaped by past infectious disease, like the Black Death. Across the board, if we were to look at a lot of risk alleles for modern disorders, you're probably going to see that those are protective against some disease that we've had in the past."

The team's next steps are to look at the whole genome, rather than just immune genes, to see if any other areas were affected by the Black Death, or might have conferred resistance. Vilgalys described his excitement to look at other aspects of ancient genomes during the Black Death, such as effects of demography and migration. The team also plans to look into ERAP2 variants to better understand how it conveys protection against Y. pestis.

More information: Jennifer Klunk et al, Evolution of immune genes is associated with the Black Death, *Nature* (2022). DOI: 10.1038/s41586-022-05349-x

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