Rare genetic disease may protect Ashkenazi Jews against TB

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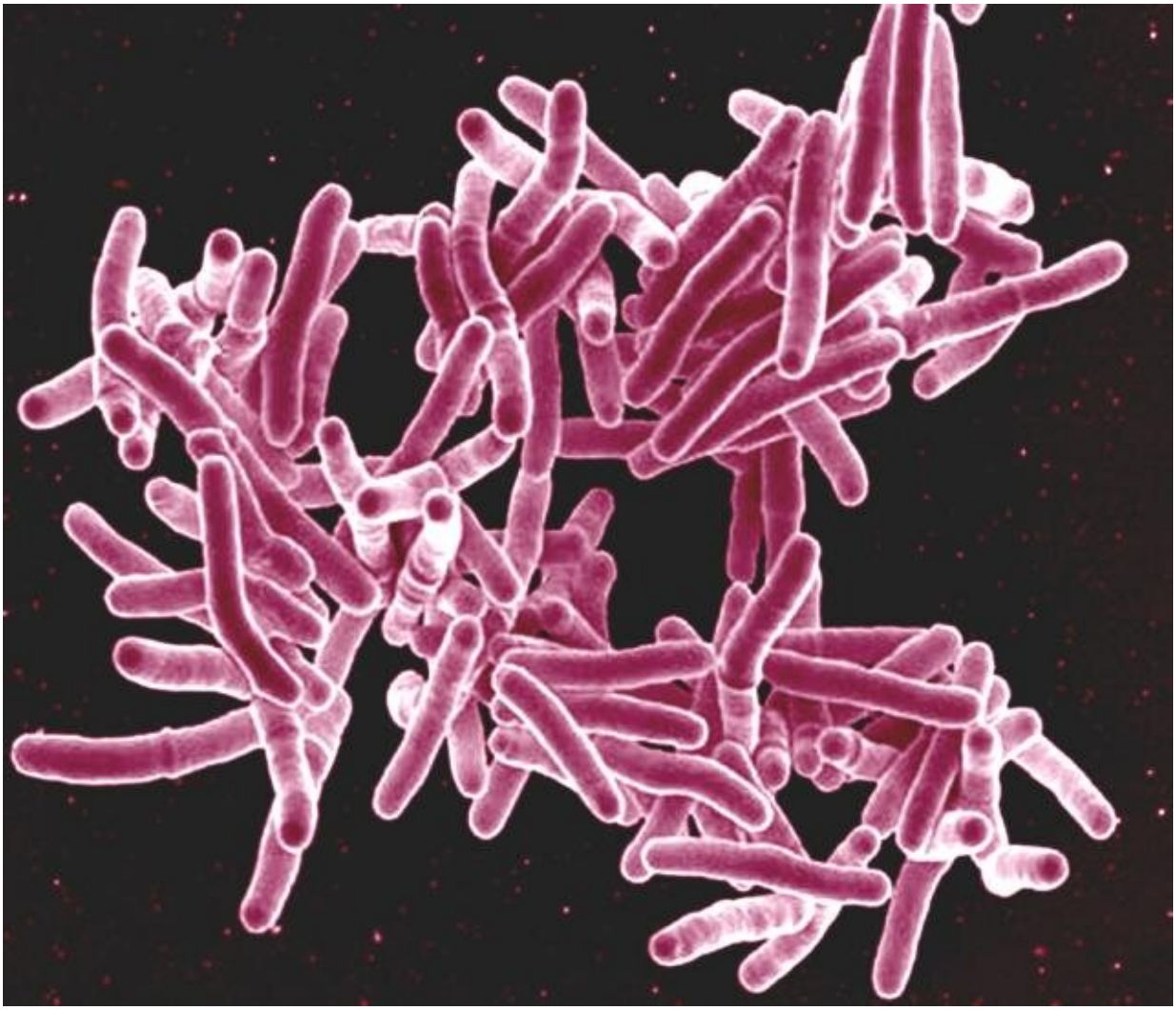

Scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, which cause TB. Credit: NIAID

Scientists may have solved the question of why Ashkenazi Jews are significantly more susceptible to a rare genetic disorder known as Gaucher disease—and the answer may help settle the debate about whether they are less susceptible to tuberculosis (TB).

In research published today (February 6) in *Proceedings of the National Academy of Sciences* (*PNAS*), Cambridge scientists, with colleagues in the Netherlands, Spain, and Pennsylvania, U.S., show that the same biological mechanisms that underlie Gaucher disease are also effective at clearing TB infection.

The discovery, made while studying TB susceptibility in zebrafish, suggests that genetic variants that increase the risk of Gaucher also protect against TB, giving them a selective advantage—that is, making the variants more likely to be passed down from generation to generation.

In 2021, an estimated 10.6 million people worldwide fell ill with TB and 1.6 million people died from the disease. Most people manage to clear the infection themselves, however, only around 1 in 10 to 20 people will go on to develop the disease.

Professor Lalita Ramakrishnan and colleagues from the University of Cambridge and the Medical Research Council Laboratory of Molecular Biology, Cambridge, are interested in what makes some people susceptible to TB while others appear to be protected. She uses zebrafish to model human disease as it is relatively easy to manipulate zebrafish's genetics, and their immune systems share many similarities with those of humans.

During their research, her team had previously found that zebrafish with mutations that impaired the digestion of proteins by lysosomes became more susceptible to TB. Lysosomes are components of our cells that

break down unwanted materials, including proteins and fats, using enzymes. When a mutation affects the production of these enzymes, it can lead to a build-up of toxic materials.

One type of cell that is vulnerable to this build-up is the macrophage, a type of immune cell that 'eats' toxic material, including bacteria and waste products. In lysosomal disorders, the macrophages become enlarged because of accumulation of undigested material in their lysosomes and move slowly, hampering their ability to fight infection.

Professor Ramakrishnan said, "Macrophages need to move quickly to attack invading bacteria and viruses. Their name means 'big eater,' and this is exactly what they do. But with lysosomal disorders, they're unable to break down the food they eat, which makes them bloated and sluggish, unable to perform their duties."

However, when Ramakrishnan and colleagues modeled a lysosomal storage disease known as Gaucher disease, they found something unexpected: TB resistance rather than susceptibility.

Gaucher disease is a rare disease, affecting around one in 40,000 to 60,000 births in the general population, but rates are significantly higher among Ashkenazi Jews—around one in 800 births. In most cases, the disease can be relatively mild—with symptoms including enlarged spleen and liver, and anemia—and around two-thirds of people carrying two copies of the most common genetic variant are unaware they are carriers.

When the researchers genetically engineered zebrafish with genetic variants causing Gaucher disease that are common among Ashkenazi Jews, as anticipated their macrophages became enlarged and unable to break down the toxic materials, in this case an unusual type of fat (called sphingolipids) rather than protein. But when the team exposed the fish to

TB, they discovered unexpectedly that the fish were resistant to infection, not susceptible.

The reason for this resistance to infection was because of the fatty chemical that accumulates within the macrophages in Gaucher disease, called glucosylsphingosine. Glucosylsphingosine was found to act as a detergent-like microbicide that kills TB mycobacteria within minutes by disrupting their cell walls.

Professor Ramakrishnan added, "We'd unknowingly landed in a debate that's been going on in human genetics for decades: are Ashkenazi Jews—who we know are at a much greater risk of Gaucher disease—somehow less likely to get TB infection? The answer appears to be yes."

The Ashkenazi Jewish diaspora has experienced centuries of persecution, often forced to live in ghettos and migrate from country to country. They would almost certainly have been exposed to TB, which spreads more widely among poorer living conditions and densely-populated urban areas.

Although this genetic mutation is associated with Gaucher disease, the fact that it makes people more resistant to TB would likely have outweighed the potential fitness cost of Gaucher disease. This would have increased the likelihood of affected individuals passing on their genes to future generations and therefore spread the mutation within the population. A similar phenomenon is seen among some individuals who carry genetic variants that protect them from malaria but, when more than one copy is present, cause harmful anemia or even sickle cell disease.

Unlike the example of sickle cell anemia, however, only individuals who carry two copies of the Gaucher genetic variant—one from each

parent—are likely to be protected against TB. That's because the one "healthy" gene generates enough of the enzyme to clear the macrophages of their accumulating material—and hence gets rid of the antimicrobial substrate.

Professor Timothy Cox from the University of Cambridge, a co-author on the paper, added, "Our discovery may provide clues to possible new treatments for TB. Drugs that mimic the effects of Gaucher disease—specifically the build-up of glucosylsphingosine—might offer antimicrobial effects against TB."

Several such drugs have already been designed by Professor Hans Aerts from Leiden University, another co-author on the paper. Because these drugs would only need to be administered for a relatively short amount of time, any side-effects should be limited and temporary.

More information: Fan, Jingwen et al, Gaucher disease protects against tuberculosis, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2217673120.
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