Tuberculosis mutation discovery paves way for better treatments

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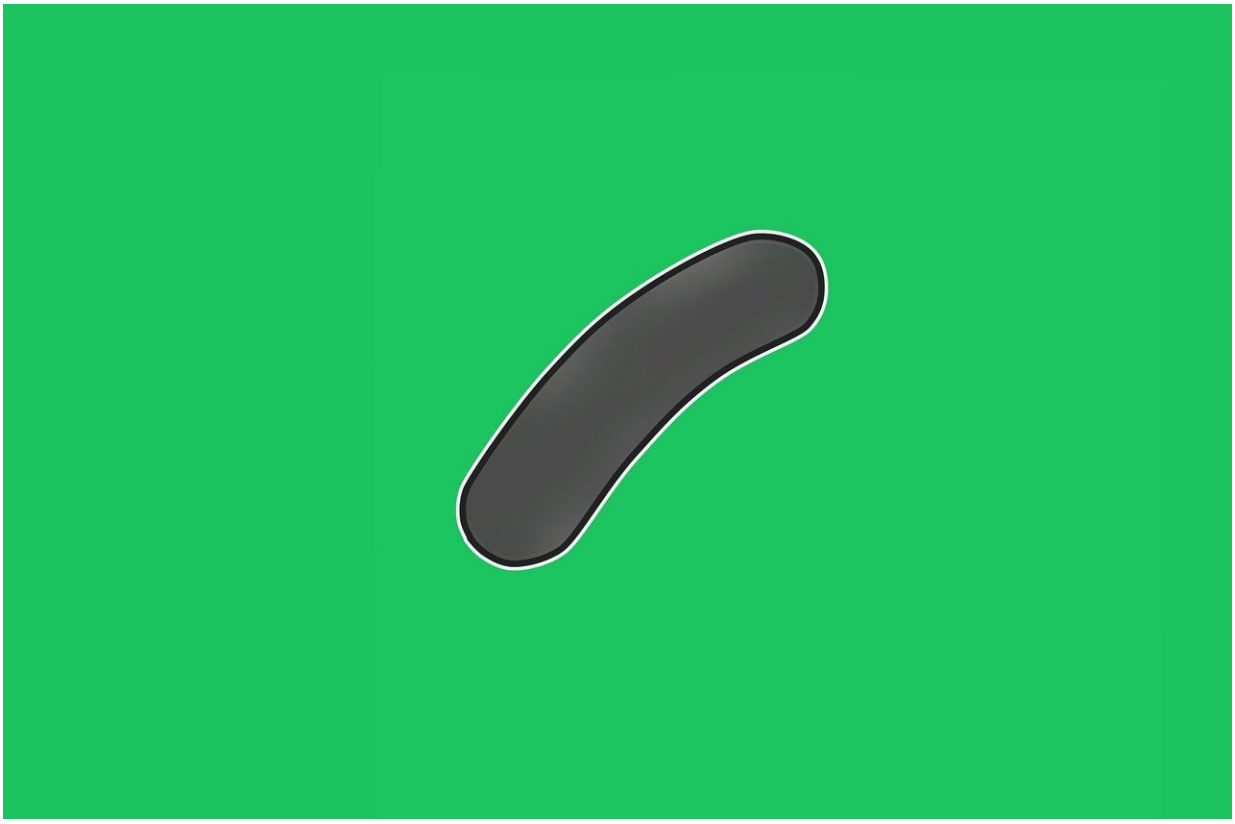

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A Rutgers New Jersey Medical School study has found a genetically tractable cause of drug tolerant tuberculosis, paving the way for researchers to develop new drugs to combat the global TB epidemic and

cure the disease.

The study, led by Drs. Hassan Safi, assistant professor of medicine, and David Alland, professor and chief of infectious disease in the department of medicine at Rutgers New Jersey Medical School, (NJMS) was published on September 5, 2019 in the scientific journal, the *Proceedings of the National Academy of Sciences (PNAS)*.

Tuberculosis is the leading cause of death from an infectious disease worldwide. One fourth of the world's population is currently infected with TB, and at least 1.3 million people died from the disease in 2017 alone, according to data from the CDC.

This new research study reveals that reversible mutations in the M.tuberculosis glpK gene, a gene responsible for an important metabolic pathway, produce a reversible form of tolerance to most of the first-line drugs used to treat TB.

"By discovering these mutants, we have pin-pointed a genetically tractable cause of drug tolerance, and as a result, we now have a unique opportunity to develop and test new treatments that are effective against drug tolerant organisms, which could lead to more rapid and effective therapies for tuberculosis," said Dr. Alland.

The study also shows that drug tolerant organisms accumulate during TB infection and accumulate even more rapidly with TB treatment. This form of drug tolerance can explain the high rates of treatment failure and relapse which occur in this disease unless it is treated for at least 6 months.

The surprising rapidly reversible nature of these mutations produce a transient form of drug tolerance that appears to disappear after the pressure of drug treatment is withdrawn. This unusual behavior likely

explains why this drug tolerance mechanism has not been discovered previously.

Despite decades of efforts to stem the tide of contagion, the length and complexity of TB therapy continue to present major barriers to global control efforts.

For example, most cases of TB must be treated for 6 months and relapses are fairly common. In fact, about 20% of patients with drug susceptible TB will experience a relapse if treated for less than 6 months and approximately 5% will relapse even when treated for a full 6 months.

Drug resistance is fixed within the TB bacterium's genetic code, but any case of TB—even cases that were previously deemed "drug susceptible"—can become drug tolerant by reversible mutations in the glpK gene.

Researchers believe drug tolerance stems from TB's ability to lie dormant in the host's immune system. This biological change allows the disease to adapt to its environment and ultimately becomes transiently resistant to traditional therapies.

Dr. Alland and his research team set out to study this phenomenon and in doing so, they discovered a new mechanism of drug tolerance caused by genetically coded, but rapidly reversable mutations in the Mycobacterium tuberculosis bacteria that could be used to develop drugs that can quickly and effectively cure drug-resistant TB.

According to this research, drugs that are effective against phase-variant M.tuberculosis can hasten TB treatment and improve cure rates.

"Because of this study, we now have the ability to track and manipulate

genetic mutations so that they have the same characteristics as drug tolerant cases of tuberculosis. That's never been done before," said Dr. Alland. "If we are going to defeat this disease, we need to find effective treatments for drug tolerant TB, and we need to do it now."

More information: Hassan Safi et al. Phase variation in Mycobacterium tuberculosis glpK produces transiently heritable drug tolerance, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1907631116

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