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HIV patients in Africa with a specific genetic variant have much lower rate of tuberculosis

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In the first known discovery of its kind, a Case Western Reserve University School of Medicine-led team has found that HIV patients in Africa with a certain genetic variant have a 63-percent lower chance of developing tuberculosis than HIV patients without the genetic variant.

"This finding could pave the way for the development of new TB treatments, which may be effective in both HIV-positive individuals and the general population," said the study's lead author, Scott M. Williams, PhD, visiting professor in the department of epidemiology and biostatistics at Case Western Reserve University School of Medicine.

In the study, published in the March issue of The *American Journal of Human Genetics*, a team of researchers from the United States, Africa, Japan, and Europe studied the genetic profiles of 581 HIV-positive Ugandans and Tanzanians, 267 of whom developed active TB, and 314 who did not. They found that the latter group was significantly more likely to carry a genetic variant near the IL12B gene that codes for a protein called interleukin 12, which is present in all people and helps kill off pathogens by stimulating the immune response that fights the infection. In fact, those who carried the variant had a 63 percent reduction in risk of TB when exposed to the bacteria that causes TB. "The genetic variation that we found appears to affect this important protein by either producing more interleukin 12 or a different version of it—or perhaps a combination of the two," said Williams. "We think this may be the reason for the much greater level of resistance to TB that we found. We will be carrying out further work to determine which of these

three possible explanations is correct."

Previous studies have shown that a deficient IL12B gene predisposes patients to TB. This is the first known study to find that patients with a genetic variation of the gene are associated with protection from TB. All previous studies of human genetic susceptibility to TB have excluded HIV patients or adjusted for it as a potential confounder in the analyses; the School of Medicine-led study is the first to focus exclusively on HIV patients in relation to TB.

The present study is also unique in demonstrating that a relatively small sample size can generate a statistically significant finding of such magnitude. "Typically studies of the genetic relation to TB entail 10,000 patients or more," said Williams. "In those cases, genetic effects have been associated with five-percent to twenty-percent change in the risk for TB. Our findings of a 63-percent increase in protection from TB are a significant departure from these other studies."

The study population comprised HIV patients from Tanzania who were likely to have been exposed to TB since they were living in a crowded urban area in a country with high incidence of TB, and HIV patients from Uganda living with family members diagnosed with TB (meaning the study group was exposed to TB on a regular basis).

Tuberculosis is caused by a bacterium called *Mycobacterium tuberculosis* (MTB). The bacteria usually attack the lungs, but other parts of the body such as the kidney, spine, and brain are susceptible as well. If not treated appropriately, TB can be deadly. The disease is spread through the air when a person with TB of the lungs or throat coughs, sneezes, speaks, spits, or sings. People close by may breathe in these bacteria and become infected. TB is not spread by shaking hands, sharing food or drink, or kissing.

According to the World Health Organization, in 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease. About one-third of the world's population has latent MTB infection, which means they have been infected by MTB bacteria but are not (yet) sick with the disease and cannot spread it. These people have a ten-percent lifetime risk of developing TB. However, those with compromised immune systems, such as those living with HIV, malnutrition, or diabetes, or people who use tobacco, have a much higher risk of falling ill. People who are infected with HIV are 20 to 30 times more likely to develop active TB and one in three HIV deaths globally are estimated to be due to TB. The disease occurs in every part of the world but is most prevalent in Africa, with 281 cases per 100,000 people in 2014 (compared with a global average of 133).

Provided by Case Western Reserve University

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