

# The complexities of genetic susceptibility to tuberculosis revealed

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Researchers working in Vietnam have identified a genetic variant that predisposes people to developing a lethal form of tuberculosis (TB), tuberculous meningitis, if they are infected with a strain of TB known as the Beijing strain. The work, described in a study published March 28th in the open-access journal *PLoS Pathogens*, underlines the importance of studying both sides of the complex host-pathogen interaction and its role in susceptibility to disease.

TB, which is caused by the bacterium *Mycobacterium tuberculosis*, kills over 2 million people each year. It is estimated that well over 2 million people are infected with *M. tuberculosis*, though the majority will never show symptoms. Some will develop a latent infection, with symptoms only showing if they become sick or immunocompromised, for example through HIV infection. A small number will develop an active TB infection, usually in their lungs, occasionally progressing to "disseminated TB" – a condition in which failure of the immune system to control the infection allows its spread to other parts of the body.

Some of the risk factors that determine whether individuals develop active TB following exposure are well known; these include HIV infection, malnutrition and smoking. Sarah Dunstan and colleagues from the Wellcome Trust Major Overseas Programme based at the Hospital for Tropical Diseases and the Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Vietnam previously identified the link between TB susceptibility and the role of a gene involved in the immune system, known as TLR2, which is important for recognising and

initiating the defensive response when the bacterium enters the body.

People with a particular variant of TLR2, commonly found in the Vietnamese population, are particularly susceptible to developing the most severe form of TB, in which the infection spreads to the meninges, the membranes that envelope the brain and the spinal cord. One in three people who develop TB meningitis die, even amongst those who receive hospital treatment.

Now, Caws and her colleagues have shown that the predisposition to developing TB meningitis appears to be strongest in people who carry the variant of TLR2 and who are infected with the specific Beijing strain of TB.

"We are seeing an increasing number of cases of the Beijing strain worldwide, a strain that is becoming more and more resistant to drugs," says Dr Caws.

The World Health Organisation estimates that around 5% of the TB cases in the world are now multi-drug resistant. In people who have multi-drug resistant TB meningitis mortality approaches 100% because there are no effective treatment regimens.

"Our findings are important because they show that we need to look at both the patient's susceptibility to the disease and the genetics of the pathogen that is infecting them at the same time," says Dr Caws. "Many studies have shown a genetic association with disease in one population but the finding has not been repeated in different populations. This might be not only because of ethnic differences in the population, but also because the pathogen populations are different.

"Understanding the mechanisms that influence our susceptibility to infectious diseases may allow us to develop more sophisticated and

targeted treatments and vaccines. This is particularly important in this era of emerging 'untreatable' bacterial infections due to antibiotic resistance."

Citation: Caws M, Thwaites G, Dunstan S, Hawn TR, Lan NTN, et al. (2008) The Influence of Host and Bacterial Genotype on the Development of Disseminated Disease with Mycobacterium tuberculosis. PLoS Pathog 4(3): e1000034. doi:10.1371/journal.ppat.1000034

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