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Genome study identifies genetic variant linked to TB susceptibility in Africans

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Scientists have identified a genetic variant which increases susceptibility to tuberculosis (TB) in African populations using a technique known as a genome-wide association (GWA) study. This is the first novel disease variant to be identified using this technique in Africans and demonstrates that such studies are viable in African populations, which have a high degree of genetic diversity.

Over the past few years, GWA studies, such as the Wellcome Trust Case Control Consortium, have been increasingly effective at identifying genetic variants which increase susceptibility to diseases. The studies involve analysing hundreds of thousands of genetic markers across the human genomes in search of variants found in patients ('cases') but not in healthy volunteers ('controls').

So far, over 150 different studies have successfully identified genetic variants using this technique, but the vast majority - between 95-98% - have been only in people of European ancestry. The genetic diversity of African populations makes GWA studies far more complicated and had even led some researchers to question whether these studies would work in such populations.

Researchers carried out a GWA study, and replicated their findings, using over 11,000 samples - 3,699 cases and 7,726 controls - from Ghana, The Gambia and Malawi as part of the African TB Genetics Consortium and the Wellcome Trust Case Control Consortium in search of genetic variants that increase susceptibility to TB.

TB is one of the world's most deadly diseases, caused by the bacterium *Mycobacterium tuberculosis*. One third of the world's population are believed to be infected with *M.* tuberculosis. Each year, at least nine million people are in need of treatment for TB, and more than two million people die from the disease.

The results of the study, led by Professor Adrian Hill from the University of Oxford, UK, and Professor Rolf Horstmann from the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany, are published today in the journal *Nature Genetics*.

Dr Fredrik Vannberg from the Wellcome Trust Centre for Human Genetics at the University of Oxford says: "Our challenges here were two-fold. We were looking for human genetic variants affecting susceptibility to a pathogen which itself differs genetically from region-to-region, and we were searching for these variants in African populations, which are genetically very diverse."

The researchers identified a genetic variant on chromosome 18, located in a 'gene desert', a region composed mainly of so-called 'junk DNA', which suggested that the variant itself was not a gene, but was possibly involved in gene regulation. The surrounding area appears to be highly conserved - in other words, it is relatively unchanged across a number of species - which implies that the region plays an important role in the body's function.

Professor Adrian Hill explains: "Although we know of other genetic variants which increase susceptibility to TB, this is the first to have been identified using a genome-wide association study. This is very important as it demonstrates that we can do these studies - which have been so successful in European populations - in African populations, which suffer the greatest burden from infectious diseases."

Although African populations are genetically very complex, the researchers believe that increasing sample sizes for GWA studies in Africa will prove productive.

"African populations are highly diverse," explains Professor Rolf Horstmann from the Bernhard Nocht Institute for Tropical Medicine. "In The Gambia, for example, there are at least seven main language groups, with each bearing a slightly different ethnic background. We believe this added complexity can be overcome by increasing the number of samples in the genome-wide studies will prove even more productive."

The findings are particularly relevant to the National Institutes of Health (NIH) in the US and the Wellcome Trust, who recently announced Human Heredity and Health in Africa Project (H3Africa), an ambitious $38 million partnership to discover how genes and the environment interact in the development of cancer, heart disease, malaria and other diseases in African populations.

"This is a very important milestone in reducing the inequity that currently exists in the use of genome-wide approaches, including GWA studies, to understand the genetic basis of diseases that disproportionately affect African people," says Dr Charles Rotimi, Director of the Center for Research on Genomics and Global Health at the National Human Genome Research Institute. Dr Rotimi will provide scientific leadership for the NIH's portion of the H3Africa partnership.

"The approach and findings from this study for TB, and previous research from the MalariaGEN project, provide proof-of-principle that genome-wide approaches can yield fruitful results in African populations and sets a good precedent for the H3 Africa initiative."

More information: The African TB Genetics Consortium and The Wellcome Trust Case Control Consortium. Genome-wide association

analyses identifies a susceptibility locus for tuberculosis on chromosome 18q11.2. Nature Genetics; e-pub 8 August 2010.

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