Study reveals genetic link to infectious disease susceptibility

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Researchers from the Wellcome Trust Centre for Human Genetics at the University of Oxford, Singapore's Agency for Science, Technology and Research (A*STAR) and National University Health System (NUHS) have identified new genetic variants that increase susceptibility to several infectious diseases including tuberculosis and malaria.

With greater understanding of the role of the gene implicated, it is hoped the findings could one day lead to better therapies and vaccines.

Environmental factors such as malnutrition and poor hygiene can account for a large proportion of an individual person's susceptibility to infectious diseases, but it's clear that this is not the whole story. Studies of twins and adopted persons indicate that genetics also plays a role.

The team analysed genes from over 8,000 people at clinical sites in Malawi, Kenya, Vietnam, Hong Kong and The Gambia, over a period of 5 years. In particular, they were looking for genetic variants that might contribute to susceptibility to tuberculosis, malaria and serious bacterial infections of the blood, or bacteraemia.

Their findings reveal a striking association with a gene called CISH and increased risk of susceptibility to these infectious diseases. CISH encodes a protein that is involved in the immune response to infectious diseases. It plays a role in dampening down messaging signals between cells of the immune system.

A panel of five different genetic variants was identified within the CISH gene. Within the population studied, having just one of these variants increased susceptibility to disease by 18% compared with somebody who does not have any 'risk' variants. "That is a substantial effect size for a single gene," commented Dr Fredrik Vannberg of the Wellcome Trust Centre for Human Genetics.

"What the results tell us is that CISH is well worth following up with more research to understand better how the immune system responds to these infectious diseases, and how this can contribute to disease risk," explains Professor Adrian Hill from the Wellcome Trust Centre for Human Genetics.

One variant in particular (-292) accounted for most of the genetic association with disease. Functional studies carried out in Singapore showed that blood cells from healthy Chinese volunteers carrying the -292 variant had lower levels of the CISH protein overall than individuals with the normal variant. This suggests that CISH exerts a significant genetic influence on our immune response.

Dr Chiea C. Khor from A*STAR's Singapore Institute for Clinical Sciences (SICS), who co-led the studies in Singapore, commented: "It's not clear from our study why having a reduced level of CISH associates with increased susceptibility to multiple infectious diseases, but it does suggest that CISH is a key regulator of the immune system. We hope that our findings will encourage clinical research to better understand the immunological processes that are going on, with a view to identifying targets for therapeutic intervention and the development of better therapies and vaccines."

Infectious diseases represent a significant proportion of loss of life in the developed world, but this is even more pronounced in the developing world. New treatments and vaccines are urgently needed to help stem

these preventable deaths.

Professor Judith Swain, Executive Director of SICS, said: "That one small gene can be involved in multiple infectious diseases at a very fundamental level is a rare and unexpected finding. This work has far-reaching implications in that it provides a better understanding of the mechanisms of infectious disease, which in turns guides our selection of drug targets for disease treatment. A*STAR hopes to groom even more scientists, clinicians, and clinician-scientists to work together at the international level to ease the global burden of disease."

More information: Chiea C. Khor et al. CISH and Susceptibility to Infectious Diseases. The New England Journal of Medicine 2010 [Epub ahead of print]

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