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First genome-wide association study for dengue identifies candidate susceptibility genes

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Researchers in South East Asia have identified two genetic variants associated with increased susceptibility to severe dengue. The study, funded by the Wellcome Trust and the Agency for Science, Technology, and Research, Singapore, offers clues to how the body responds to dengue infection.

Dengue is globally the most common mosquito-borne infection after malaria, with an estimated 100 million infections occurring annually. Symptoms range from mild to incapacitating high fever, with potentially life-threatening complications. No vaccine or specific treatments exist for the disease.

In children, severe dengue is characterised by increased vascular permeability, a state in which blood plasma is able to 'leak' from blood vessels to surrounding tissues. This is a potentially deadly complication that can lead to dengue shock syndrome – a life-threatening form of hypovolemic shock caused by a decrease in the volume of blood plasma. Epidemiological studies have suggested that certain populations are more susceptible to severe dengue, implying that some people's genetic make-up makes them more susceptible to the disease.

To test this hypothesis, researchers at the Wellcome Trust Vietnam Research Programme and Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam, together with researchers from the Genome

Institute of Singapore, conducted the first ever genome-wide association study to compare the genomes of children with severe dengue against population controls. Initially, they compared 2,008 patients against 2,018 controls. They then replicated their findings in an independent follow-up sample of 1,737 cases and 2,934 controls.

The findings are published today in the journal *Nature Genetics*. The researchers identified changes in the DNA code located within two genes – MICB on chromosome 6 and PLCE1 on chromosome 10 – that appeared to increase a child's susceptibility to dengue shock syndrome.

MICB is known to play a role the body's immune system and the researchers believe that a variant of this gene may affect the activation of natural killer cells or CD8 T-cells, two types of cells that play a key role in combating viral infection. If these cells are not properly functioning, their ability to rid the body of the dengue virus becomes impaired. This hypothesis is consistent with evidence that increased viral loads occur in the tissues of patients with severe dengue.

Mutations in PLCE1 have previously been linked to nephrotic syndrome, a childhood disease characterised by impairment of the normal barrier and blood filtering functions of cells in the kidney. The researchers believe that PLCE1 may also contribute to the normal functioning of the vascular endothelium, the thin layer of cells that lines the interior surface of blood vessels, with some variants of PLCE1 predisposing an individual to leakage from the blood vessels, the hallmark clinical feature of dengue shock syndrome.

Professor Cameron Simmons, senior author of the study from the Oxford University Clinical Research Unit, Vietnam, said: "Dengue is a potentially life-threatening disease. Our study confirms epidemiological evidence that some people are naturally more susceptible to severe forms of the disease than others. Our findings offer tantalising clues as to why

this should be the case and open up new avenues for us to explore to help us understand the disease."

Dr Khor Chiea Chuen, first author of the study, added: "This study implicates genetic variation in a molecule that activates natural killer cells as a culprit for increased susceptibility to severe Dengue. This is surprising as prior to this it was thought that defects in other components of the immune response, such as. T-cells, B-cells or dendritic cells, were responsible. However, they did not show up in our large, well-powered genome scan."

Combating infectious diseases is one the strategic priorities of the Wellcome Trust. Much of this work is carried out at a local level in regions where disease is endemic. This includes several major overseas programmes, including the Wellcome Trust's Vietnam Research Programme.

Commenting on the research, Professor Danny Altmann, Head of Pathogens, Immunology and Population Health at the Wellcome Trust, said: "The World Health Organization estimates that two-fifths of the world's population – 2.5 billion people – are at risk from dengue infection, yet we still do not have any specific treatments or licensed vaccines. This study, the first of its kind for dengue, is a step along the road towards understanding and eventually combating this deadly disease."

More information: Chiea Chuen Khor et al. Genome-wide association study identifies susceptibility loci for Dengue shock syndrome at MICB and PLCE1. *Nature Genetics;* e-pub Oct. 16, 2011.

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