Large-scale study reveals genetic link to infectious disease susceptibility

Researchers from the Wellcome Trust Centre for Human Genetics and 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 is 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 tuberculous, 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.

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 CISH overall than individuals with the normal variant. There was likely influence from the nearby -163 variant as well. This suggests that CISH exerts a significant genetic influence on our immune response.

The studies in Singapore were co-led by Dr Khor Chiea Chuen from A*STAR’s Singapore Institute for Clinical Sciences (SICS) and and A/Prof Denise Goh from SICS and the Department of Paediatrics, NUS Yong Loo Lin School of Medicine (YLLSoM).

Said Prof Judith Swain, Executive Director of SICS: “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.”
“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 Prof Adrian Hill from the Wellcome Trust Centre for Human Genetics.

SICS’ Dr Khor 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.”

NUHS’ A/Prof Goh also believes that “such functional studies done using human cells will provide greater insight into the biology of how these variants work.”

Drs Khor and Goh are clinician-scientists working in Singapore. Dr Khor was one of the pioneer recipients of A*STAR’s MBBS-PhD scholarship, which trains clinician-scientists to undertake world-class translational research in Singapore. Added Prof Swain: “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.”

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.

A/Prof Daniel Goh, Head of Paediatrics at the University Children’s Medical Institute, National University Hospital, added: “The research findings will have a significant impact on our understanding and management of patients with infectious diseases and help us better appreciate the genetic basis of their response (or otherwise) to therapy. This is yet another example of the impactful and clinically relevant research that is the focus of NUHS.”

The study is published today in The New England Journal of Medicine and is supported by the Wellcome Trust and A*STAR.

For media queries, please contact:

Ms Adela Foo  
Senior Officer, Corporate Communications  
Agency for Science, Technology and Research (A*STAR)  
DID: (+65) 6826 6218 | Fax: (+65) 6478 9593  
Email: adela_foo@a-star.edu.sg

Zaki Amrullah  
Assistant Manager, Communications & Development Office  
National University Health System  
DID: 6516 5894  
Email: zaki_amrullah@nuhs.edu.sg

Jen Middleton  
Media Officer, Wellcome Trust  
T: 020 7611 7262  
E: j.middleton@wellcome.ac.uk
Notes To Editors

The **Agency for Science, Technology and Research** (A*STAR) is the lead agency for fostering world-class scientific research and talent for a vibrant knowledge-based and innovation-driven Singapore. A*STAR oversees 14 biomedical sciences, and physical sciences and engineering research institutes, and nine consortia & centres, which are located in Biopolis and Fusionopolis, as well as their immediate vicinity.

A*STAR supports Singapore's key economic clusters by providing intellectual, human and industrial capital to its partners in industry. It also supports extramural research in the universities, hospitals, research centres, and with other local and international partners.

For more information on A*STAR, please visit [www.a-star.edu.sg](http://www.a-star.edu.sg).

Established in 2007, the **Singapore Institute for Clinical Sciences** (SICS) is an institute within A*STAR. Its mission is to develop disease-oriented clinical and translational research programmes in focused disease areas. SICS is distinguished by its focus on clinical sciences and the use of innovative approaches and technologies that enable the efficient and effective study of human health and diseases. The clinical scientists in SICS conduct the full spectrum of “bench to bedside” research activities in genetic medicine, infectious diseases and metabolic diseases (including diabetes/obesity/insulin resistance). SICS aims to attract, train and nurture clinician-scientists and serves as a critical bridge linking basic research undertaken by A*STAR Research Institutes and clinical research programmes in Singapore's public hospitals, disease centres and universities.

For more information on SICS, please visit: [www.sics.a-star.edu.sg](http://www.sics.a-star.edu.sg).

The **National University Health System** (NUHS) was established in January 2008. It is jointly owned by the Ministry of Health Holdings and National University of Singapore (NUS), and groups the National University Hospital, NUS Yong Loo Lin School of Medicine (YLLSoM) and NUS Faculty of Dentistry (FoD) under a common governance structure to create synergies to advance health by integrating excellent clinical care, research and education.

The enhanced capabilities and capacity will enable the NUHS to deliver better patient care, train future generations of doctors more effectively and bring innovative treatments to patients through groundbreaking research. For more on the NUHS, please visit [www.nuhs.edu.sg](http://www.nuhs.edu.sg).

A leading global university centred in Asia, the **National University of Singapore** (NUS) is Singapore’s flagship university which offers a global approach to education and research, with a focus on Asian perspectives and expertise.

NUS has 14 faculties and schools across three campuses. Its transformative education includes a broad-based curriculum underscored by multi-disciplinary courses and cross-faculty enrichment. Over 30,000 students from 100 countries enrich the community with their diverse social and cultural perspectives.

Well-known for its research strengths in engineering, life sciences and biomedicine, social sciences and natural sciences, NUS shares a close affiliation with 23 university-level, 16 national-level and more than 80 faculty-based research institutes and centres. The University also strives to create a supportive and innovative environment to promote creative enterprise within its community.

For more information, please visit [www.nus.edu.sg](http://www.nus.edu.sg).
The National University Hospital (NUH), a member of the National University Health System (NUHS), is a tertiary specialist hospital that provides advanced, leading-edge medical care and services. Equipped with state-of-the-art facilities as well as dedicated and well-trained staff, the NUH is a major referral centre that delivers tertiary care for a wide range of medical and dental specialties including Cardiology, Gastroenterology & Hepatology, Obstetrics & Gynaecology, Oncology, Ophthalmology, Paediatrics and Orthopaedic Surgery. It is the principal teaching hospital of the NUS Yong Loo Lin School of Medicine.

With combined resources (from the teaching hospital and NUS Yong Loo Lin School of Medicine and Faculty of Dentistry), the NUH will be able to meet the healthcare needs of patients, train future generations of doctors more effectively, and help develop solutions to our healthcare problems through research.

Backed by substantive expertise and experience, the NUH was chosen by the Ministry of Health to develop two new national specialist centres, the National University Heart Centre, Singapore and National University Cancer Institute, Singapore to meet the growing need for cardiac and cancer treatments.

In 2004, the NUH became the first Singapore hospital to receive Joint Commission International (JCI) Accreditation, an international stamp for excellent clinical practices in patient care and safety. It was also the first hospital in Singapore to receive a triple ISO certification concurrently for Quality, Environmental, and Occupational Health & Safety Management Systems in 2002.

For more information, please visit www.nuh.com.sg.

The Wellcome Trust is a global charity dedicated to achieving extraordinary improvements in human and animal health. It supports the brightest minds in biomedical research and the medical humanities. The Trust's breadth of support includes public engagement, education and the application of research to improve health. It is independent of both political and commercial interests.

For more information, please visit http://www.wellcome.ac.uk.

The Wellcome Trust Centre for Human Genetics was established to undertake research into the genetic basis of common diseases. The scientific objective of the Centre is to explore all aspects of the genetic susceptibility of disease. The Centre houses multi-disciplinary research teams in human genetics, functional genomics, bioinformatics, statistical genetics and structural biology.

For more information, please visit http://www.well.ox.ac.uk/home.