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MEDIA RELEASE
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STUDY FINDS STRONG GENETIC RISK FACTOR FOR KIDNEY DISEASE

Discovery opens up possibilities for new potential therapeutic target for the disease and related renal dysfunction

SINGAPORE – An international research collaboration has discovered a strong genetic risk factor for IgA nephropathy (IgAN) – the most common inflammatory kidney disease worldwide – and related renal dysfunction. Published in *Science Translational Medicine*, the discovery has advanced the researchers' understanding of IgAN.

The prevalence of IgAN is higher in Asia than Western countries, and 15-40% of the patients will eventually progress to end-stage renal diseases within 20 years of the disease onset. Despite its global prevalence, IgAN's pathogenesis is not well understood. By investigating copy number variations (CNVs) of the α-defensin gene in Chinese patients with IgAN and healthy controls as well as a Caucasian cohort with IgAN, the researchers found that a low copy number of the α-defensin gene increases the risk of IgAN, and the CNV of α-defensin gene can explain the 4.96% of disease risk.

In addition, the researchers also found that the low copy number of the α-defensin gene also increases the risk of renal dysfunction in IgAN patients and shows negative correlations with serum IgA1 and galactose-deficient IgA1. This is the first study that demonstrates the vital role of α-defensin gene in IgAN development and related renal dysfunction, suggesting the gene to be a potential therapeutic target for this important kidney disease.

This collaboration was led by Prof Liu Jianjun, Deputy Director for Research Programmes and Senior Group Leader of Human Genetics at A*STAR's Genome Institute of Singapore (GIS), and Prof Yu Xueqing, Professor of Medicine and Director of the Institute of Nephrology at the First Affiliated Hospital of Sun Yat-sen University (SYSU), and the current President of the Chinese Society of Nephrology. To date, the collaborative research team from GIS and SYSU have already discovered five novel genetic risk loci for IgAN.

"As a major source of genetic variation, CNVs have long been suggested to play important roles in disease development, but only a few specific CNVs have demonstrated convincing evidence. This CNV contributes more genetic risk to IgAN than the cumulative effect of all the other loci we have discovered. So, this discovery is truly exciting," said Prof Liu.

Prof Yu added, “IgAN is the most common primary glomerulonephritis worldwide. However, no disease-specific treatment agents have been developed yet, due to the unknown pathogenesis of IgAN. Our findings revealed the important role of α-defensin gene in the development and renal progression of IgAN. It will help in exploring the specific intervention target for IgAN, and provide a solid work for the future development of disease specific targeted drugs.”

GIS Executive Director Prof Ng Huck Hui said, “The positive correlation between α-defensin gene and risk for IgAN identified in this study is a significant discovery. The translation of these findings have the potential to be beneficial to IgAN patients worldwide.”

"This paper provides important insights into the genetics and root causes of the world’s most common primary disease of the kidney glomerulus, IgAN. The identification of a copy number variant as a genetic mechanism of disease is novel and the discovery of altered activity of α-defensins in IgAN pathogenesis suggests potential new avenues for therapy," said Prof Thomas Coffman, Dean of the Duke-NUS Medical School.

“The discovery of IgAN susceptibility gene, α-defensin, is a major breakthrough in the fight against the disease. It will pave the way for identifying individuals at high risk for IgAN. It may also reveal new treatment target (i.e. its protein product - human neutrophil peptides) to prevent the onset and progression of IgAN,” said Dr Lim Su Chi, Clinical Director, Clinical Research Unit at the Khoo Teck Puat Hospital.

Notes to Editor:

The research findings described in this media release can be found in the scientific journal *Science Translational Medicine,* under the title, “Low α-defensin gene copy number increases the risk for IgA nephropathy and renal dysfunction” by Zhen Ai[1,2*], Ming Li[1,2*], Wenting Liu[1,2*], Jia-Nee Foo[3], Omniah Mansouri[4], Peiran Yin[1,2], Qian Zhou[1,2], Xueqing Tang[1,2], Xiuqing Dong[1,2], Shaozhen Feng[1,2], Ricong Xu[1,2], Zhong Zhong[1,2], Jian Chen[5], Jianxin Wan[6], Tanqi Lou[7], Jianwen Yu[1,2], Qin Zhou[1,2], Jinjin Fan[1,2], Haiping Mao[1,2], Daniel Gale[8], Jonathan Barratt[9], John A. L. Armour[4], Jianjun Liu[3,10,11†], Xueqing Yu[1,2†]

[1]Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510080, China.
[2]Key Laboratory of Nephrology, Ministry of Health and Guangdong Province, Guangzhou, Guangdong 510080, China.
[3]Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore.
[4]School of Life Sciences, University of Nottingham, Queen’s Medical Centre, Nottingham NG7 2UH, UK.
[5]Department of Nephrology, Fuzhou General Hospital of Nanjing Military Command, Fuzhou, Fujian 350025, China.

[6]Department of Nephrology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350005, China.
[7]Department of Nephrology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510630, China.
[8]University College London Centre for Nephrology, Royal Free Hospital, London NW3 2PF, UK.
[9]Department of Infection, Immunity and Inflammation, University of Leicester, Leicester LE1 9HN, UK.
[10]School of Biological Sciences, Anhui Medical University, Hefei, Anhui 230032, China.
[11]Saw Swee Hock School of Public Health, National University of Singapore, Singapore 119077, Singapore.
*These authors contributed equally to this work.
†Corresponding author. Email: yuxq@mail.sysu.edu.cn (X.Y.); liuj3@gis.a-star.edu.sg (J.L.)

Full text of the *Science Translational Medicine* paper can be accessed online from: http://stm.sciencemag.org/content/8/345/345ra88

For media queries and clarifications, please contact:

Joyce Ang
Senior Officer, Office of Corporate Communications
Genome Institute of Singapore, A*STAR
Tel: +65 6808 8101
Email: angjj@gis.a-star.edu.sg

About A*STAR's Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology, Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit www.gis.a-star.edu.sg

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