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International Team Sheds New Light on Biology Underlying Schizophrenia

Genes, pathways identified could inform new approaches to treatment

A group of researchers from the Institute of Mental Health (IMH) and A*STAR's Genome Institute of Singapore (GIS) has helped identify over 100 locations in the human genome associated with the risk of developing schizophrenia in what is the largest genomic study published on any psychiatric disorder to date. They were part of the Schizophrenia Working Group of the Psychiatric Genomics Consortium, and the study was part of the 5-year Translational Clinical Research in Neuroscience which is funded by the National Research Foundation.

"The main aim of this 5-year project was to identify the markers that will enable the better and early identification of those who might develop schizophrenia and these include genetic markers," said Professor Chong Siow Ann, Vice Chairman Medical Board (Research), IMH, who is the Principal Investigator of this project.

These latest findings, which are published online in *Nature*, point to biological mechanisms and pathways that may underlie schizophrenia, and could lead to new approaches to treating the disorder, which has seen little innovation in drug development in more than 60 years.

Schizophrenia, a debilitating psychiatric disorder that affects approximately 1 out of every 100 people worldwide, is characterized by hallucinations, paranoia, and a breakdown of thought processes, and often emerges in the teens and early 20s. Its lifetime impact on individuals and society is high, both in terms of years of healthy life lost to disability and in terms of financial cost.

Despite the pressing need for treatment, medications currently on the market treat only one of the symptoms of the disorder (psychosis), and do not address the debilitating negative and cognitive symptoms of schizophrenia. In part, treatment options are limited because the biological mechanisms underlying schizophrenia have not been understood. The sole drug target for existing treatments was found serendipitously, and no medications with fundamentally new mechanisms of action have been developed since the 1950s.

In the genomics era, research has focused on the genetic underpinnings of schizophrenia because of the disorder's high heritability. Previous studies have revealed the complexity of the disease (with evidence suggesting that it is caused by

the combined effects of many genes), and roughly two dozen genomic regions have been found to be associated with the disorder. The new study confirms those earlier findings, and expands our understanding of the genetic basis of schizophrenia and its underlying biology.

In the genome-wide association study (GWAS) published in *Nature*, the authors looked at over 80,000 genetic samples from schizophrenia patients and healthy volunteers and found 108 specific locations in the human genome associated with risk for schizophrenia. Eighty-three of those loci had not previously been linked to the disorder.

The study implicates genes expressed in brain tissue, particularly those related to neuronal and synaptic function. These include genes that are active in pathways controlling that are implicated in learning and memory – and pathways involved in signaling between cells in the brain.

Additionally, the researchers found a smaller number of genes associated with schizophrenia that are active in the immune system, a discovery that offers some support for a previously hypothesized link between schizophrenia and immunological processes. The study also found an association between the disorder and the region of the genome that holds *DRD2* – the gene that produces the dopamine receptor targeted by all approved medications for schizophrenia – suggesting that other loci uncovered in the study may point to additional therapeutic targets.

“The discovery of these 108 genomic regions has opened the door for further biological and clinical research to discover the genes that are directly linked with schizophrenia development and further understand the molecular mechanisms underneath the association of these genes with schizophrenia. The scientific breakthrough made by this study is a great demonstration that large-scale genetic association study is a powerful tool for understanding disease genetic susceptibility and revealing novel biological insight into disease mechanism” said Professor Jianjun Liu, Deputy Director, Research Programmes, and Senior Group Leader, Human Genetics, from the Genome Institute of Singapore who is the Co-Principal Investigator of this project and the leader of the genetic study program of the project.

The other co-investigators of the project and co-authors of the paper from IMH’s Research Division are Adj Asst Prof Mythily Subramanian, Adj Assoc Prof Sim Kang and Dr Jimmy Lee. “These new findings will also open doors to allow researchers to examine and better clarify the underlying brain connectivity changes associated with these genes and genetic mechanisms. A better understanding of the genetic mechanism and underlying brain changes can potentially allow better detection of illness, monitoring of response with treatment and progression over time,” added Adj Assoc Prof Sim Kang.

This study is the result of several years of work by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC, http://pgc.unc.edu) which is an international, multi-institutional collaboration founded in 2007 to conduct broad-scale analyses of genetic data for psychiatric disease.

The 80,000 samples used in this study represent all of the genotyped datasets for schizophrenia that the consortium has amassed to date. The PGC is currently

genotyping new samples to further study schizophrenia and additional psychiatric diseases, including autism and bipolar disorder.

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About the Institute of Mental Health, Singapore
The Institute of Mental Health (IMH) is the only tertiary psychiatric care institution in Singapore. Located on the sprawling 25-hectare campus of Buangkok Green Medical Park in the north-eastern part of Singapore, IMH offers a multidisciplinary and comprehensive range of psychiatric, rehabilitative and counseling services. The 2010-bedded hospital aims to meet the needs of three groups of patients – children and adolescents (age below 19 years), adults and the elderly. Besides providing clinical services, IMH also leads in mental health research and training the next generation of mental health professionals in Singapore.
For more information, visit: www.imh.com.sg

About the 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.
www.gis.a-star.edu.sg

About the Agency for Science, Technology and Research (A*STAR)
The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector agency that fosters world-class scientific research and talent to drive economic growth and transform Singapore into a vibrant knowledge-based and innovation driven economy.

In line with its mission-oriented mandate, A*STAR spearheads research and development in fields that are essential to growing Singapore's manufacturing sector and catalysing new growth industries. A*STAR supports these economic clusters by providing intellectual, human and industrial capital to its partners in industry.

A*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities, located in Biopolis and Fusionopolis, as well as their vicinity. These two R&D hubs house a bustling and diverse community of local and international research scientists and engineers from A*STAR's research entities as well as a growing number of corporate laboratories.
www.a-star.edu.sg

About GWAS
Genome-wide association studies (GWAS) examine the frequency of common variations within the human genome to determine which locations in the genome may be linked to a specific phenotype,or trait (usually, a disease). To study these variations, researchers scan strategically selected sites of the genome that are known to vary considerably across the population, taking note of single nucleotide polymorphisms (SNPs) – single-letter variations in the genetic code. SNPs found to be significantly more common in people with a trait than in those without are considered to be "associated" with that phenotype. Where the associated SNP resides in the genome can provide valuable clues about the genes and mechanisms that may be contributing to the phenotype being studied.

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ENGLISH-CHINESE GLOSSARY **Annex 1**

Associate Professor Chong Siow Ann Vice Chairman, Medical Board (Research) Institute of Mental Health	莊紹安临床副教授 医疗委员会副主席(研究) 心理卫生学院
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Institute of Mental Health	心理卫生学院
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Genome Institute of Singapore	新加坡基因组研究院