

MEDIA RELEASE

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IMH and A*STAR researchers identify two genes associated with the risk of schizophrenia and possible cognitive dysfunction, signalling potential for novel treatment approaches

1. A global team of hundreds of researchers, including researchers from the Institute of Mental Health (IMH) and A*STAR's Genome Institute of Singapore (GIS), has demonstrated that 287 regions in the human DNA harbour genes that increase the risk of schizophrenia, one of the most debilitating psychiatric disorders, in individuals. Furthermore, they showed that genetic risk for schizophrenia is seen in genes concentrated in brain cells called neurons, but not in any other tissue or cell type, suggesting it is the biological role of these cells that is crucial in schizophrenia.
2. The team also found that in these segments of DNA, there are two genes — the glutamate receptor subunit *GRIN2A* and transcription factor *SP4* — that are associated with rare disruptive coding variants in people with schizophrenia. These genes, related to neuronal function, particularly synaptic organisation, differentiation and transmission, are also known to be linked to autism and other neurodevelopmental disorders. Such genes are expressed in the central nervous system, particularly in the brain and neurons, but not in other tissues or cell types.
3. The breakthrough discovery pushes current understanding of biological processes in the brain, in particular for psychiatric disorders, to the next level. This could potentially lead to new ways of treating schizophrenia, which has seen limited innovation in drug development in over 70 years.
4. Characterised by hallucinations, delusions and cognitive impairments, schizophrenia affects about one in 100 people globally and has a prevalence of 0.86% or one in 116 people in Singapore.¹ It is associated with elevated risk of suicide and serious physical illnesses, reduced life expectancy, and substantial health and social costs. The presence of certain genetic variants and the way such genes interact can predispose the individual to the risk of the disorder. This, coupled with various factors such as environmental stressors, could lead to the development of schizophrenia.
5. "Mental illnesses, like schizophrenia, are disorders of the brain. Since brain tissue from a living individual is not readily available for investigations, clinicians and scientists face significant challenges in advancing our understanding of mental illnesses. Knowing which parts of the brain are affected and how they are affected can focus future research efforts and help us develop more targeted and effective treatments," explains Dr Jimmy Lee, Senior Consultant, Department

¹ Singapore Mental Health Study 2016

of Psychosis and Research Division, IMH and Associate Professor at the Lee Kong Chian School of Medicine, Nanyang Technological University. “In the absence of living brain tissues and the rise of human genomics technology more than a decade ago, researchers came to a realisation that we could study brain function in an indirect way, specifically, the human DNA. Deciphering DNA codes for the structure of neurons and how they “talk” to each other in the brain is equivalent to putting together a jigsaw puzzle to understand behaviour. It took tens of thousands of participants, hundreds of scientists and doctors working together to achieve this feat.”

6. The findings were outlined in the article “Mapping genomic loci implicates genes and synaptic biology in schizophrenia” published in *Nature* this month. It involved a 13-year collection and analyses of DNA samples from more than 300,000² people around the world, including 3741 samples from Singapore, making this the largest genomic study of its kind to date. It is driven by the Schizophrenia Working Group of the Psychiatric Genomics Consortium, an international, multi-institutional collaboration founded in 2007 to conduct broad-scale analyses of genetic data for psychiatric disease.
7. The methods reported in the paper are considered the most cutting edge in genomics literature at present, and surface the key biological processes that are implicated with schizophrenia. “These biological processes have previously been speculated to be theoretically related to schizophrenia — this study is seminal in the sense that the DNA data analyses provided real evidence from real data to show it,” says Dr Max Lam, Research Fellow, IMH and National Medical Research Council (NMRC), who leads the data analysis for the Asian population and is one of the contributors of this paper. “This will set the stage for researchers to think about the next steps for clinical translation research not only for schizophrenia but also other psychiatric illnesses,” adds Dr Lam.
8. In another joint effort by IMH and GIS, supported by NMRC and the Psychiatric Genomics Consortium, Dr Lam reported in *Nature Genetics* that these results were not limited to people of European ancestry, and were seen among people suffering from schizophrenia in Singapore and the rest of Asia. “Genetic studies so far have reported primarily on European ancestry samples, potentially missing important biological insights from the Asian population, he explains. “With this study, we now know that the genetic basis of schizophrenia and its biology are broadly shared across populations,” he says.
9. With the findings, Dr Lam has also showed that genes like *GRIN2B* that predispose individuals to risk of mental illnesses also largely overlap with genes responsible for cognitive function. “This suggests that new drug development focusing on genes that lie in the intersection between risk of mental illness and cognitive function might be a crucial step in the next phase of genomics research,” he says. Decline in cognitive function is one of the core symptoms of schizophrenia, and affects the individual’s ability to live independently. Current treatment options in this area have been limited partly because biological mechanisms underlying schizophrenia have not been well understood. “If a drug is developed to target the overlapping genes, specifically aimed at arresting cognitive dysfunction, there might be a chance that the medication could at least

² Samples of 76,755 persons with schizophrenia and 243,649 controls (i.e. persons without schizophrenia)

alleviate some of the disability related to schizophrenia and individuals can go back to work or school and live as they choose to.”

10. In other parallel work, Dr Lam, together with Prof Liu Jianjun from GIS, Dr Jimmy Lee and colleagues at IMH, showed that genes such as *TNFRSF1B* and *CALCOCO1* independently conferred a three-fold increase in risk of Tardive Dyskinesia (involuntary repetitive movements that occur in the body) in people with schizophrenia, beyond the usual clinical risk factors; and that genetic liability to schizophrenia is likely to increase the risk for developing psychosis in young people. Ongoing work is currently being undertaken to understand how this new knowledge could be utilised to improve care for individuals suffering from mental illness.
11. Prof Liu Jianjun, Deputy Executive Director of GIS, said, “GIS is proud to be part of this groundbreaking discovery that could potentially lead to novel treatments for debilitating mental illnesses such as schizophrenia. As these mental illnesses have high heritability, we aim to leverage our exceptional capabilities in genetics and genomics to better understand the biological processes in the brain, and discover potential treatments.”
12. Prof Patrick Tan, Executive Director of GIS, said, “International studies and research collaboration are essential for improving global health to ensure diverse representation. A*STAR is glad to stand alongside IMH and contribute our capabilities in genomic sciences to greater understanding of mental illness like schizophrenia, which greatly affects all areas of patients’ lives.”

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About the Institute of Mental Health (IMH)

The Institute of Mental Health (IMH), a member of the National Healthcare Group, is the only tertiary psychiatric care institution in Singapore. Located on the sprawling 23-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 therapy services in hospital-based and community-based settings. The 2,000-bedded hospital aims to meet the needs of three groups of patients – children and adolescents (aged 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, please visit www.imh.com.sg or www.facebook.com/imh.singapore.

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 pursues the integration of technology, genetics and biology towards academic, economic and societal impact, with a mission to "read, reveal and write DNA for a better Singapore and world".

Key research areas at the GIS include Precision Medicine & Population Genomics, Genome Informatics, Spatial & Single Cell Systems, Epigenetic & Epitranscriptomic Regulation, Genome Architecture & Design, and Sequencing Platforms. The genomics infrastructure at the GIS is also 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.a-star.edu.sg/gis.

About the Agency for Science, Technology and Research (A*STAR)

A*STAR is Singapore's lead public sector R&D agency. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit the economy and society. As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by improving societal outcomes in healthcare, urban living, and sustainability. A*STAR plays a key role in nurturing scientific talent and leaders for the wider research community and industry. A*STAR's R&D activities span biomedical sciences to physical sciences and engineering, with research entities primarily located in Biopolis and Fusionopolis. For ongoing news, visit <https://www.a-star.edu.sg/>