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THE GENE MUTATION THAT CAN PREVENT GLAUCOMA
Singapore-led discovery of rare gene mutation and identification of five new susceptibility loci will help illuminate the disease biology

Singapore – In the largest study on any cause of glaucoma to date, an international research collaboration on Exfoliation Syndrome – a major form of glaucoma – has found a mutated gene that can prevent glaucoma, the leading cause of irreversible blindness worldwide. Jointly led by A*STAR’s Genome Institute of Singapore (GIS) and the Singapore Eye Research Institute (SERI) of the Singapore National Eye Centre (SNEC), the study involved more than 120,000 individuals from 36 countries across six continents. The study has recently been published in Nature Genetics.

Exfoliation Syndrome (XFS) is an age-related eye disease where abnormal whitish flakes are deposited in the front of the eye (iris, ciliary body, lens and zonules), and abnormalities in connective tissues may appear in parts of the body. The disease occurs globally in approximately 60 to 70 million people. In the eye, the disease often leads to an increase in eye pressure, or glaucoma, which can result in visual impairment and blindness.

Since the 2007 publication of an Icelandic study and subsequent validation attempts by research groups from around the world, it is known that common genetic variants in one gene, the LOXL1 gene, show a strong association with XFS. However, the association with common genetic markers at LOXL1 are reversed depending on ethnic group, thus rendering the health implications unclear. In this latest study, the researchers uncovered a rare protective mutation in the LOXL1 gene. The mutation, p.Y407F, was found to offer protection against XFS instead, thereby leading to the prevention of secondary glaucoma. The mutation offers a 25-fold protection against XFS, the largest ever seen for a common, complex disease.

“Naturally occurring genetic variants are hard to find, but once discovered, they pinpoint potential druggable targets. These are what we call ‘accidents and experiments of nature’. The LOXL1 p.Y407F rare variant reported in this study is one of these examples,” explained Dr Khor Chiea Chuen, one of the study’s corresponding authors and Principal Investigator of Human Genetics at the GIS.

In addition, the researchers also discovered five new susceptibility gene loci in XFS – specifically POMP, TMEM136, AGPAT1, RBMS3 and SEMA6A. This will help deepen the researchers’ understanding of XFS and how the disease process works.

Prof Aung Tin, Executive Director of SERI and Deputy Medical Director of SNEC, and lead author of the paper said, “This was the largest ever genetic study for glaucoma, and with so many centres and patients from 35 countries involved, it was very challenging to coordinate the research with most of the work being done in Singapore. The findings are very exciting as it can lead to the development of new therapies for glaucoma.” Prof Aung is also Professor, Department of Ophthalmology at National University of Singapore.

Joint corresponding author Prof Janey L. Wiggs, who holds the post of Paul Austin Chandler Professor of Ophthalmology at the Harvard Medical School, commented, “This is a truly remarkable study that demonstrates the power of international collaboration. The results improve our understanding of glaucoma and also suggest important new therapeutic strategies for this common cause of blindness.” Prof Wiggs is also the Massachusetts Eye and Ear Infirmary’s Associate Chief of Ophthalmology Clinical Research, and Associate Director of Ocular Genomics Institute at Massachusetts Eye and Ear.

Executive Director of GIS, Prof Ng Huck Hui added, “By identifying the rare gene mutation, we have taken a significant step towards reducing the risk of glaucoma worldwide. A large-scale study like this reaffirms the importance and benefits of cross-institutional and cross-national collaborations, which will help us achieve improvements in human health.”
Glaucoma is the commonest cause of blindness amongst the elderly; understanding how this process happens will result in new medications to cure it.

ANNEX A – Notes to Editor

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**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](http://www.gis.a-star.edu.sg)

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**About Singapore Eye Research Institute (SERI)**
Established in 1997, the Singapore Eye Research Institute (SERI) is Singapore’s national research institute for ophthalmic and vision research. It is the research arm of
Singapore National Eye Centre, and affiliated to the National University of Singapore (NUS) and the Duke-NUS Medical School.

In two decades, SERI has grown from a team of 5 to over 225 staff, and more than 219 distinguished adjunct faculty members to become the largest eye research institute in the Asia-Pacific region. Collectively, our clinician-scientists and researchers have published more than 2,770 peer-reviewed papers supported by over S$227 million in competitive research grants. SERI has trained more than 180 current and past graduate students; and has been conferred over 407 national & international awards and 121 patents.

Today, SERI is recognized as a pioneering center for high quality eye research in Asia, with breakthrough discoveries that has translated to significant paradigm shift in eye care delivery.
ANNEX A: Notes to Editor

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