Study discovers a genetic locus linked to higher chances of developing glaucoma

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A*STAR researchers pinpoint a genetic locus associated with an increased susceptibility to exfoliation syndrome and glaucoma. Credit: Fred Goldstein/Hemera/Thinkstock

A genome-wide significant association between a genetic locus and the development of glaucoma in people of various ethnicities has been uncovered by A*STAR researchers participating in an ambitious international project.

Glaucoma is a common eye disorder that affects eyesight. It is caused by a condition called exfoliation syndrome (XFS) that gives rise to a build-up of extracellular material on the eye lens, which exerts pressure on the optic nerve.

It has proven difficult to pinpoint the genes responsible for XFS across

different ethnic groups. This challenge galvanized Chiea-Chuen Khor from the A*STAR Genome Institute of Singapore, who along with Tin Aung from the Singapore Eye Research Institute, designed a genome-wide association study to identify genetic loci linked to XFS.

Only one genetic locus for XFS, labeled LOXL1, has been found to date. This locus is essential for the correct development of connective tissues and elastic fibers, disorders of which had previously been implicated in XFS.

"However, the effect of LOXL1 mutations on XFS is inconsistent between different ethnic groups," explains Khor. "For example, the risk alleles—or different copies of LOXL1—found in Europeans inexplicably had a protective effect in Japanese and Africans. Susceptibility to XFS is more complex than just the LOXL1 locus."

The research project, which involves scientists from 17 countries in 6 continents, seeks to pinpoint susceptibility genes across multiple ethnicities. In the first part of the study, Khor and his colleagues completed a genome-wide analysis of over 2,500 samples from Japanese XFS cases and healthy controls. They then took the most significant associations from this nationality group and examined them further in over 6,900 cases and 20,700 controls from across the globe.

The researchers uncovered a single nucleotide polymorphism mapping to CACNA1A as a genetic locus significantly associated with susceptibility to XFS across all ethnicities. The CACNA1A gene is involved in creating calcium channels. Previous studies of XFS in human eyes had found high calcium concentrations in the accumulating extracellular material. Khor and his team believe alterations to calcium channel function may exacerbate XFS material formation, thus linking CACNA1A to the disease.

By identifying genetic loci such as CACNA1A, scientists can significantly improve their understanding of XFS and the mechanisms by which it affects individual patients' susceptibility to glaucoma. Khor and colleagues now aim to identify all genetic signatures of the disease and assess whether other susceptibility genes have ethno-geographic boundaries or are common across all ethnicities.

More information: Aung, T., Ozaki, M., Mizoguchi, T., Allingham, R. R., Li, Z. et al. A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. *Nature Genetics* 47, 387–392 (2015). dx.doi.org/10.1038/ng.3226

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