MedicalXpress

Exfoliation syndrome study reveals genetic mutation that protects against glaucoma

September 20 2017

A leading cause of glaucoma and blindness is exfoliation syndrome, or XFS, an age-related disorder that results in excess fibrous material building up. Now, A*STAR scientists, along with an international research team, have found a novel mutation on the LOXL1 gene that appears to protect against XFS and glaucoma, alongside five new locations on a chromosome associated with XFS1.

"We started a large-scale, international study of XFS in November 2012," explains Chiea Chuen Khor at the A*STAR Genome Institute of Singapore, who led the research. "Despite the large sample size on this first project, we could only identify one other gene locus (CACNA1A) consistently associated with XFS to add to the known locus, LOXL1. XFS could not be explained by just LOXL1 and CACNA1A. There had to be more biological determinants."

As the body ages, molecules that provide both physical structure and biochemical support to all tissues and organs—the so-called 'extracellular matrix', or ECM—can begin to decline, resulting in abnormalities and the development of XFS. In XFS, cells are torn, or 'exfoliated', from the ECM; this is most prominent in the eye, and can severely damage the ocular nerves and tissues.

The team conducted deep-sequencing analysis of both LOXL1 and CACNA1A in samples from 5,570 XFS cases and 6,279 healthy controls from nine countries. Many of the participants were Japanese, and it was within this specific population that Khor's team found a rare, protective

mutation in the healthy control group; the p.407F allele, located at the LOXL1 gene.

"This mutation has never been seen before, and it goes some way to explain why some people appear to be resistant to XFS' effects," says Khor. "Although aging 'loads the gun' by inducing cell damage and potentially triggering the exfoliative process, the presence of the p.407F allele seems to markedly increase ECM material, and cells with the mutation bind together more strongly, delaying the progress of the disease."

The mutation at LOXL1 considerably reduces the chances of developing glaucoma, and represents a promising target for future therapies to treat this widespread, debilitating condition.

"If we can stop cells from exfoliating, we may prevent the disease from occurring," says Khor. "The data gives us clues as to how we might target LOXL1 to try to make this happen."

Khor's team also performed a genome-wide association study on a larger cohort from 24 countries, uncovering five new genetic loci associated with XFS susceptibility, which they will investigate soon.

More information: Tin Aung et al. Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci, *Nature Genetics* (2017). DOI: 10.1038/ng.3875

Provided by Agency for Science, Technology and Research (A*STAR), Singapore