deCODE discovers cause of major subtype of glaucoma

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In a paper published today in the journal *Science*, scientists from deCODE genetics and academic colleagues from the National University Hospital in Reykjavik and Uppsala University in Sweden report the discovery of two common single letter variations (SNPs) in the sequence of the human genome that appear to account for virtually all cases of a major subtype of glaucoma.

The SNPs are located in the LOXL1 gene on chromosome 15, and confer respectively 26-fold and 8-fold increases in risk of exfoliation glaucoma compared to the low-risk versions of the same markers.

Approximately 25% of those in the Icelandic and Swedish study cohorts were found to have two copies of the highest risk variant, putting them at approximately 100 times the likelihood of developing exfoliation glaucoma (XFG) as are individuals with the low risk version of the same SNP. The LOXL1 protein encoded by the gene is involved in the formation of elastin fibers which, when they accumulate in the eye, cause XFG.

The paper, entitled “Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma,” is published today in the online edition of *Science*, and will appear in an upcoming print edition of the journal.

“This discovery is remarkable and important because the genetics has led us directly to what appears to be the sole cause of a devastating common

disease. The risk conferred by these variants is such that it accounts for virtually all cases of exfoliation glaucoma, meaning that if we can neutralize the impact of these variants we might eliminate the disease. The LOXL1 protein made by this gene appears to play a role in the accumulation of microfibullar deposits that causes XFG, providing a promising mechanism to target for developing therapy. We plan to conduct additional studies to examine how we can take advantage of this finding to begin drug discovery," said Kari Stefansson, CEO of deCODE.

The deCODE team discovered the variants by first analyzing more than 300,000 SNPs in Icelandic and Swedish glaucoma patients and control subjects, utilizing the Illumina Hap300 SNP chip. One SNP was strongly linked to exfoliation syndrome, in which fibrous deposits begin to accumulate in the front of the eye but have not yet begun to impair vision. Analysis of additional SNPs in public databases and which were not included on the chip led to the identification of the two risk variants – allele G of rs1048661 and allele G of rs3825942 – strongly linked to XFG in Icelandic and Swedish case-control cohorts. A combined total of some 16,000 patients and control subjects participated in the study.

Glaucoma is one of the most common causes of blindness worldwide. There are various types of glaucoma, all of which lead to damage in the optic nerve and progressive loss of vision. Exfoliation glaucoma is caused by the buildup of fibrous deposits on the surfaces on the front of the eye. Between 10-20% of people over the age of 60 are believed to have some degree of exfoliation syndrome, and perhaps more than half of these individuals will go on to develop exfoliation glaucoma.

The progression of glaucoma can be slowed using various medications that promote the drainage of fluids from the eye and reduce pressure on the optic nerve. However, exfoliation glaucoma is often resistant to drug treatment. Little has been understood to date about the pathophysiology

of the disease and there are no treatments targeting the underlying causes of the condition.

Source: deCODE genetics