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New study quadruples known genetic risk factors for Fuchs dystrophy

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Researchers discovered three novel genetic mutations associated with Fuchs endothelial corneal dystrophy, the most common corneal disorder requiring transplantation.

The study is published in *Nature Communications*. Sudha K. Iyengar, PhD, Professor of Epidemiology and Biostatistics, Vice Chair for Research at Case Western Reserve University School of Medicine, and member of the Case Comprehensive Cancer Center in Cleveland, Ohio is the lead author.

Corneal diseases are common causes of blindness worldwide. One highly heritable disease, Fuchs endothelial corneal dystrophy, causes painful corneal swelling and blurred vision. The disease commonly requires corneal transplant from a deceased donor. Approximately 4% of United States adults age 40 and older develop Fuchs dystrophy.

Only one gene—TCF4—has been successfully associated with Fuchs dystrophy in genetic studies. Iyengar and her team set out to perform the largest genetic scan to date for the disease, to identify other genetic risk factors that could inform treatment efforts.

An international team of 36 researchers compared DNA sequences from 2,075 people with Fuchs dystrophy and 3,342 without the disease. They generated a list of 18 genetic variations found only in people with Fuchs dystrophy, later narrowing the list to three most relevant to disease with the help of corneal laboratory models.

The team spanned 16 institutions and included first authors Robert Igo, PhD, Assistant Professor of Epidemiology and Biostatistics at Case Western Reserve University School of Medicine and Natalie Afshari, MD, FACS, Professor of Opthalmology at University of California San Diego. Iyengar led the study alongside Yi-Ju Li, PhD, Associate Professor at Duke University School of Medicine, and Jonathan Lass, MD, Charles I Thomas Professor of Ophthalmology and Visual Sciences at Case Western Reserve University School of Medicine.

The study revealed three novel variations in the human genome that increase risk of Fuchs dystrophy. The variations—KANK4, LAMC1, and ATP1B1—have never before been associated with Fuchs dystrophy. The new study quadruples the number of known genetic risk factors for Fuchs dystrophy, and helps explain its genetic etiology.

The researchers also discovered the first sex-specific differences in Fuchs dystrophy genetics. They found men with a specific variation in the well-known TCF4 gene have a higher risk of disease, while women with variations in one of the newly identified genes, LAMC1, have an increased risk. The genes can help predict a person's risk of developing disease with approximately 78% accuracy, and could be targeted by molecular diagnostic tests.

"In most individuals with Fuchs Endothelial Corneal Dystrophy (FECD) the cause of the disease is unknown. It was thought that genetics only played a role in those with a family history of FECD. Our results pointed to three new genetic markers for FECD and confirmed the vital role of a previously known marker even among those who did not have a previously known family history of the disease. Thus, our work showed that knowing the genetic architecture is key to understanding this disease," Iyengar said.

"The markers we identified can be used to develop a biomarker panel

for pre-symptomatic testing even among people who did not have a family history," Iyengar indicated.

"The cornea is the clear tissue in the front of the eye that lets light into the eye so we can see. FECD is the most common reason older individuals get a corneal transplant when their cornea starts to loses transparency," explained Iyengar. "There is no cure other than surgery. Therefore, other ways to help cure this disease are necessary as the US population gets older.

"Considering that there is currently no clinical screening tool other than family history, this is a significant advance for development of molecular diagnostic tests," Iyengar said.

The researchers used corneal tissue samples to identify biologic roles for the new genes. While their preliminary experiments suggest the genes help control fluid levels in the cornea, Iyengar cautions that additional laboratory models will be needed to pinpoint their precise functions.

More information: Natalie A. Afshari et al, Genome-wide association study identifies three novel loci in Fuchs endothelial corneal dystrophy, *Nature Communications* (2017). DOI: 10.1038/ncomms14898

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