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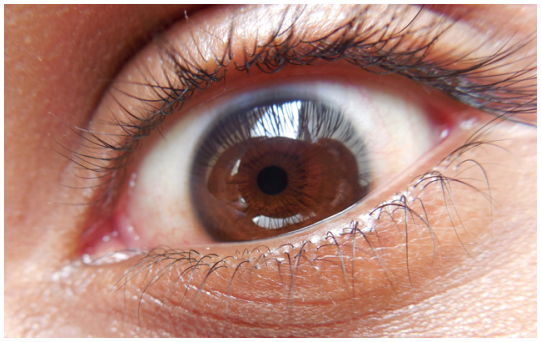
Researchers Find New Genetic Links Underlying Progressively Blinding Eye Disease

Using genome-wide association data, they deepen understanding of Fuchs endothelial corneal dystrophy, the most common cause for corneal transplants

Corneal diseases are among the most common causes of visual impairment and blindness, with Fuchs endothelial corneal dystrophy (FECD), a gradual swelling and clouding of the cornea, being the most common reason for eventual corneal transplants.



The cornea is the transparent front part of the eye covering the iris, pupil and anterior chamber. In Fuchs endothelial corneal dystrophy, the innermost cell layer of the cornea begins to progressively deteriorate, eventually resulting in severe vision impairment and blindness.

Writing in the March 30 online issue of *Nature Communications*, researchers at University of California San Diego School of Medicine, with colleagues at Case Western University, Duke University, the National Institutes of Health and elsewhere, have identified three novel genomic loci — distinct stretches of genetic material on chromosomes — linked to FECD, which often clusters in families and is roughly 39 percent heritable.

“Previously, there was one known FECD locus. We’ve expanded that number to four,” said the study’s first author Natalie A. Afshari, MD, professor of ophthalmology, Stuart Brown MD Chair in Ophthalmology in Memory of Donald Shiley and chief of cornea and refractive surgery at Shiley Eye Institute at UC San Diego Health. “These findings provide a deeper understanding of the pathology of FECD, which in turn will help us develop better therapies for treating or preventing this disabling disease.”

FECD affects the innermost layer of cells in the cornea (the transparent front cover of the eye), called the endothelium. The endothelium is responsible for maintaining the proper amount of fluid in the cornea, keeping it clear. FECD is a progressive disorder in which the endothelium

slowly degrades, with lost clarity, pain and severely impaired vision. It affects 4 percent of the U.S. population above age 40 and worsens with age. Women are two to four times more affected than men. While there is symptomatic treatment in early stages, surgery — often a corneal transplant — is the only remedy after significant vision loss occurs.

The research team conducted a genome-wide association study, an analytical approach in which scientists look for genetic variants in individuals associated with a particular disease. This study involved 1,404 patients with FECD and 2,564 controls of European ancestry.

The results confirmed the known role of the *TCF4* gene, but also revealed associations with three other loci: *KANK4*, *LAMC1* and *LINC009970/ATPB1*. Researchers also found some genomic markers that were more associated by gender, with *LAMC1* increasing FECD risk in women while *TCF4* increased risk in men.

“While more work must be done to precisely elucidate what these proteins do,” said Afshari, “the results suggest they have essential roles in sustaining and maintaining the health of the corneal endothelium. This knowledge improves our understanding of the genetic risk factors for FECD and gives us new therapeutic targets.”

Co-authors include: senior author Sudha K. Iyengar, Robert P. Igo, Nathan J. Morris, V. Lakshmi Pulagam, Barbara J. Truitt and Jonathan H. Lass, Case Western Reserve University; Dwight Stambolian, University of Pennsylvania; Shiwani Sharma, Richard Mills Abraham Kuot, Sonja Klebe and Jamie E. Craig, Flinders University, Australia; Steven Dunn, Michigan Cornea Consultants; John F. Stamler and John H. Fingert, University of Iowa; Jacqueline Rimmler, Xuejin Qin, Mollie A. Minear, Elmer Balajonda, Simon G. Gregory, Gordon K. Klintworth and Yi-Ju Li, Duke University Medical Center; Christopher R. Croasdale, Davis Duer Dean Clinic, Madison, WI; Kathryn P. Burdon, Flinders University and University of Tasmania; S. Amer Riazuddin and John D. Gottsch, Johns Hopkins University School of Medicine; Jiagang Zhao, UC San Diego; George O. Rosenwasser, Central Pennsylvania Eye Institute; Keith H. Baratz and Sanjay V. Patel, Mayo Clinic; V. Vinod Mootha, University of Texas Southwestern Medical Center; Joan E. Bailey-Wilson, NIH; Marianne O. Price and Francis W. Price, Price Vision Group; and Anthony Aldave, UCLA.

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MEDIA CONTACT

Scott LaFee, 858-249-0456, slafee@ucsd.edu

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