Gene involved in Fuchs corneal dystrophy is found

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A 13-member research team led by University of Oregon scientist Dr. Albert O. Edwards has found a gene likely responsible for Fuchs corneal dystrophy, an inheritable genetic disorder and leading cause of corneal transplant operations.

Edwards performed a genome-wide analysis comparing patients with and without typical age-related Fuchs, finding an alteration in the transcription-factor-4 gene (TCF4). Fuchs -- pronounced FEWKS or FOOKS -- generally emerges in middle-aged, roughly age 40, and older people.

The discovery appears online Wednesday, Aug. 25, ahead of regular publication in the Sept. 9 issue of the New England Journal of Medicine.

Fuchs emerges slowly with blurred or cloudy vision, tiny bumps known as guttae (GOO-tay) on the cornea's surface and, in severe stages, painful blisters on the corneal surface. The disease affects the endothelium, a thin layer of cells that line the back part of the cornea where changes result in swelling of the cornea and thickening and clouding of the cornea. Guttae are found in the corneas of an estimated 5 percent of people in the United States.

Of those diagnosed with Fuchs, only a small percentage go on to require corneal transplants, said lead author Dr. Keith H. Baratz of the Mayo Clinic ophthalmology department in Rochester, Minn. There are about 40,000 corneal transplants -- about 10,000 linked to Fuchs -- performed

annually in the United States, according to the Eye Bank Association of America. It is more common in women than in men, according to the Fuchs Corneal Dystrophy Association.

The discovery won't immediately translate into clinical benefits, but "this is the first step in identifying the pathophysiology of the disease," Baratz said. "Right now, we don't have a treatment for Fuchs dystrophy other than transplant surgery when a patient is at the end stages of the disease. The ultimate goal is to find out how the disease occurs and find a treatment to prevent or slow its progression."

Having the TCF4 gene variation has a huge impact on the risk of Fuchs disease, said Edwards, a senior research associate in the University of Oregon's Institute of Molecular Biology. "It vastly exceeds the risk found previously for the complement-factor-H gene in macular degeneration," he said. "If a person has risk variants involving TCF4, that individual is anywhere from several to a couple of hundred times more likely to have Fuchs disease."

Edwards, in 2005, when at the University of Texas Southwestern Medical Center, was lead author of a study published in the journal Science that identified complement factor H in macular degeneration. That gene discovery tied complement factor H to a five-fold increase of risk to developing macular degeneration, accounting possibly for at least 50 percent of the risk of being affected. The risk impact of TCF4 on Fuchs is much stronger, Edwards said.

While the TCF4 gene has been identified, exactly what occurs to cause a defect is not understood. The researchers found evidence that at least one transcription protein, E2-2, needs more scrutiny. "E2-2 is a transcription factor. It controls gene expression," Edwards said. "The pathway probably contains E2-2 and the protein ZEB1, but we don't really know that yet. We do find variation of expression across this

region, so it has something to do with the expression of the gene."

E2-2, important in cellular growth and differentiation, has been implicated in other disease states, including activity that promotes or suppresses cancer. It is expressed in the corneal endothelium. ZEB1, which may be regulated by E2-2, already is thought to contribute to Fuchs.

The study involved the genotyping of 280 Fuchs patients recruited in clinical settings in Minnesota and Michigan. These patients had at least Stage 1 signs of Fuchs or had received corneal replacements as a result of the disease. Their genomes were compared with 410 control patients.

"The real impact of what we've done is to determine the biological underpinnings of the disease," Edwards said. "We've identified a protein that is probably involved, and that will allow us to, hopefully, identify a method to prevent people from losing their vision."

Three other genes previously had been linked to very rare subtypes of Fuchs. In addition, early onset Fuchs has been linked to mutations in yet another gene, COL8A2, but Edwards and colleagues suggest in their paper that this may be a different disease with a different cause.

"This discovery demonstrates the value of excellent clinical phenotyping and a large-scale genetic database of genome-wide association studies (GWAS) to uncover genetic risk factors for many vision-related disorders," said co-author Anand Swaroop, chief of the National Eye Institute (NEI) Neurobiology-Neurodegeneration and Repair Laboratory. "The genetic data used in this study was obtained for GWAS of age-related macular degeneration through a scientific collaboration supported by the NEI."