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Ophthalmology Update

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Expanded Trinucleotide Repeat in *TCF4*, E2-2 May Be a Functional Cause of Fuchs Corneal Dystrophy

INSIDE THIS ISSUE

Keith H. Baratz, MD

Fuchs corneal dystrophy (FCD) is the most common indication for corneal transplant. Its cause remains unknown, and its pathophysiology has not been clarified.

In 2010, research conducted at Mayo Clinic in Rochester, Minnesota, showed that genetic variation across the transcription factor 4 gene (*TCF4*) encoding the basic helix-loop helix DNA-binding protein E2-2 is a major contributor to FCD. "The study identified a primary gene involved with FCD and the protein that might lead us to that pathophysiology," says Keith H. Baratz, MD, with the Department of Ophthalmology.

In a 2011 study, "An Association Between an Expanded Trinucleotide Repeat in Transcription Factor 4 (*TCF4*, E2-2) and Fuchs Corneal Dystrophy," a research team from the departments of ophthalmology and molecular biology explored whether a known region of nucleotide triplet repeat expansion may explain the association between *TCF4* and FCD.

The research team examined corneas of 35 patients with FCD and 32 patients with normal corneas, graded the corneas for FCD severity, and measured the length of the CTG trinucleotide repeat in all subjects. Results indicated that expansion of a CTG trinucleotide repeat in intron 2 of the *TCF4* gene was associated with FCD, with a positive predictive value of 93%. The results have been replicated in 60 additional study subjects.

"These results indicate that expansion of trinucleotide repeats should be explored as a frequent functional cause of FCD and as a target for identifying at-risk individuals," says Dr Baratz. "Our ultimate goal is to develop a medical treatment for patients who are identified with FCD, rather than just observing until they need corneal transplant."

Trinucleotide Repeats

Trinucleotide repeats are segments of DNA in which a pattern of 3 nucleotide residues continues for a given length. Short segments of repeats are not problematic, but long segments of repeats may ultimately cause structural alterations of protein, affect the regulation of gene transcription, prevent DNA repair mechanisms, or impair transcription of other genes by

George B. Bartley, MD, Appointed Editor-in-Chief of *Ophthalmology*

George B. Bartley, MD, with the Department of Ophthalmology at Mayo Clinic in Rochester, Minnesota, has been appointed editor-in-chief of *Ophthalmology*, the official journal of the American Academy of Ophthalmology. He succeeds Andrew P. Schachat, MD, who has served in the role for the past 10 years.

Dr Bartley brings a wealth of experience to his new position. He joined the board of the *American Journal of Ophthalmology* in 1992 and served as abstract editor and ultimately as senior associate editor. Dr Bartley was appointed to the *Ophthalmology* editorial board from 1996 to 2002 and has been an active member of the *Archives of Ophthalmology* editorial board since 2004.

Additionally, Dr Bartley has been on the board of *Ophthalmic Plastic and Reconstructive Surgery* since 1993 and served as editor-in-chief of that journal from 1999 to 2002, when he stepped down when appointed chief executive officer for Mayo Clinic in Florida. Dr Bartley's term as editor-in-chief of *Ophthalmology* will commence in January 2013.

For More Information

"An Association Between an Expanded Trinucleotide Repeat in Transcription Factor 4 (*TCF4*, E2-2) and Fuchs Corneal Dystrophy" was presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting in May 2012. Read the abstract at www.arvo.org/eweb/StartPage.aspx?Site=arvo2.

View video of Dr Baratz discussing the study that indicates that a genetic variation in *TCF4* contributes to the development of FCD at physicianupdate.mayoclinic.org/.

sequestering proteins involved in the transcription process.

Trinucleotide repeat disorders are adult-onset, progressive degenerations. Several dozen diseases have been attributed to trinucleotide repeat expansion, including Huntington disease, Friedreich ataxia, fragile X syndrome, and myotonic dystrophy. Fuchs dystrophy appears to be the first disease attributable to trinucleotide repeat expansion that is not a neurologic or neuromuscular degeneration.

Studies Shed Light on the Role Episcleral Venous Pressure Plays in Intraocular Pressure Variation

Arthur J. Sit, SM, MD

Glaucoma is the leading cause of preventable blindness. Elevated intraocular pressure (IOP) is its primary risk factor, and lowering IOP is the only known effective treatment for glaucoma.

IOP, however, varies, with random fluctuations as well as circadian rhythm. Peak IOP occurs during sleeping hours. The physiologic reasons for these IOP variations are also poorly understood. Arthur J. Sit, SM, MD, with the Department of Ophthalmology at Mayo Clinic in Rochester, Minnesota, leads a team of researchers that focuses on understanding the clinical importance and basic mechanisms of circadian IOP variation.

"Variations in IOP are assumed to be at least partially due to changes in episcleral venous pressure, or EVP," says Dr Sit. His research team recently completed 2 studies that explored the relationship between EVP and IOP: "Variations of Episcleral Venous Pressure With Body Position in Healthy Subjects" and "Relationships Between Episcleral Venous Pressure and Ocular and Systemic Variables in Healthy Subjects."

Figure 1. *Computerized episcleral venomanometer for automated, objective, noninvasive measurement of episcleral venous pressure.*

EVP and Body Position

"We know that IOP varies with body position, but the effect of body position on EVP is poorly understood. When we investigated changes in EVP between 2 body positions, sitting and prone, we found that other factors in addition to EVP may contribute to IOP variation," says Dr Sit.

Using a pneumatonometer, the research team measured IOP in 25 eyes of 13 healthy volunteers in a seated position. The team then measured EVP 4 times in a selected vein using a computerized venomanometer mounted on a slit lamp. This device, designed and built at Mayo Clinic, enables objective, noninvasive measurements of EVP. After 30 minutes, the subjects were placed in a prone position for 5 minutes. IOP was remeasured, and EVP in the same vein was measured twice, with the subject's neck extended and the head resting on the chin rest of the slit lamp.

"Results showed that IOP and EVP were higher for volunteers in the prone position than in the sitting position. The rise in EVP when volunteers changed from the upright to prone position could partly explain the rise in IOP," says Dr Sit. "The Goldmann equation, however, predicts that the change in IOP should be equal to the change in EVP if aqueous humor flow, outflow facility, and uveoscleral flow remain constant. This outcome suggests that other factors, in addition to the increase in EVP, may contribute to the rise in IOP that occurs with a recumbent body position."

Mayo Clinic's Venomanometer

Read "A Novel Method for Computerized Measurement of Episcleral Venous Pressure in Humans," published in *Experimental Eye Research*, Volume 92, No. 6, June 2011, at www.journals.elsevier.com/experimental-eye-research.

The Modified Goldmann Equation

$$Po = (Q - U)/c + Pv$$

Po is IOP in millimeters of mercury (mm Hg), Q is the rate of aqueous formation, U is the rate of uveoscleral drainage, c is the facility of outflow, and Pv is episcleral venous pressure.

For More Information

"Variations of Episcleral Venous Pressure With Body Position in Healthy Subjects" and "Relationships Between Episcleral Venous Pressure and Ocular and Systemic Variables in Healthy Subjects" were presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting in May 2012. Read the abstracts at http://www.arvo.org/eweb/StartPage.aspx?Site=arvo2.

EVP and Ocular and Systemic Variables

The research team also examined the relationships between EVP and physiologic parameters, including blood pressure, ocular characteristics, and systemic variables. In this study, the research team measured EVP in 74 eyes of 37 healthy volunteers using Mayo's computerized venomanometer. Age, central corneal thickness (CCT) by ultrasonic pachymetry, IOP, refractive error, height, weight, and blood pressure in the seated position were recorded for all participants. Correlations between EVP and these variables were examined to account for possible correlations between eyes from the same subjects.

"EVP was not significantly correlated with age, CCT, IOP, body mass index, or pulse pressure. It was weakly correlated with refractive error, systolic blood pressure, and diastolic blood pressure, but these factors determine only a small percentage of the overall variability in EVP," says Dr Sit. "This relationship suggests that IOP may be affected by blood pressure through EVP, but research is needed to fully understand the factors that determine variations in EVP and IOP."

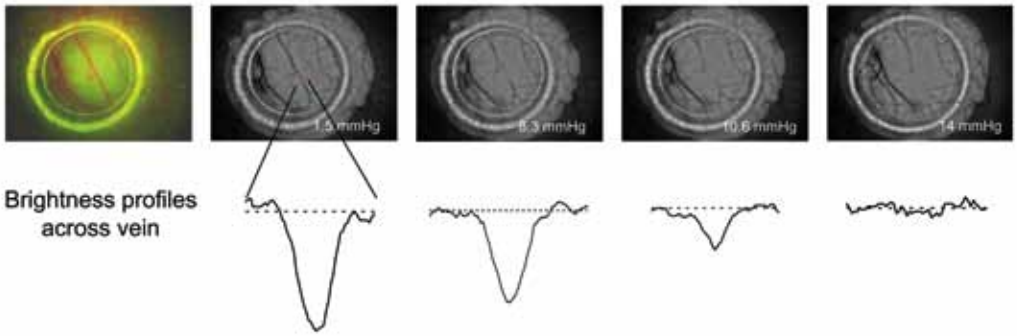

Figure 2. *Image sequence from the computerized episcleral venomanometer. The balloon tip of the venomanometer is placed on the sclera against an episcleral vein, and the pressure is steadily increased. A high-definition video camera records the images of the vein as it is compressed. Each image is synchronized with a pressure reading from a transducer. Image analysis software is used to evaluate the brightness profiles of the vein and determine the point at which the vein first starts to collapse, which corresponds to the episcleral venous pressure.*

K_{ATP} Channel Opener Diazoxide Shows Potential as a Modality for Treatment of Glaucoma

In 2011, research conducted in the Department of Ophthalmology at Mayo Clinic in Rochester, Minnesota, suggested that adenosine triphosphate–sensitive potassium K_{ATP} channels play a prominent role in the regulation of intraocular pressure (IOP) and so may have the potential to become a future treatment modality for glaucoma. "We identified several K_{ATP} channel openers, including diazoxide (DZ), nicorandil, and P1075, as novel agents capable of decreasing pressure in an ex vivo human anterior segment organ culture," says Michael P. Fautsch, PhD.

Dr Fautsch and his fellow researchers have continued their studies on K_{ATP} channel openers by evaluating DZ-induced outflow facility change in vivo and identifying the extracellular signal–regulated kinase (ERK) 1/2 pathway as a critical mediator of DZ-induced pressure reduction.

Confirmation of DZ-Mediated Pressure Reduction in Vivo

"Our previous studies published in *Investigative Ophthalmology & Visual Science* in 2011 showed that DZ increased outflow facility in an ex vivo human anterior segment culture model," says Dr Fautsch. To evaluate the role of K_{ATP} channel openers in vivo, C57BL/6 mice were treated with DZ. One eye of each animal received DZ while the contralateral eye received vehicle, both administered topically, once daily for 14 consecutive days. In eyes that received DZ, IOP was 20% lower than the vehicle control eye. To verify the specificity of the K_{ATP} channel involvement in IOP reduction, a similar experiment was performed with C57BL/6 mice that lacked a subunit of K_{ATP} channels called Kir6.2 (Kir6.2 knockout mice). These mice had no change in IOP when treated with DZ, confirming a role for K_{ATP} channels in IOP regulation.

Michael P. Fautsch, PhD

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DZ-ERK1/2 Connection

Several different signaling mechanisms have been associated with K_{ATP} channel opening. In studies performed in cultured primary human trabecular meshwork cells, the Fautsch lab found that opening of the K_{ATP} channels by DZ induced ERK1/2 phosphorylation within 15 minutes. To assess the role of ERK1/2 in IOP modulation, cultured human anterior segments were treated with DZ alone or in combination with U0126, an ERK1/2 phosphorylation inhibitor. As previously shown by the Fautsch lab, DZ reduced pressure in human anterior segments. The action of DZ was inhibited, however, when DZ was added in combination with U0126. Similar results were observed in vivo, where mice eyes treated with DZ had lower IOP than eyes treated with DZ and U0126.

"DZ shows potential as a future therapeutic modality for the treatment of ocular hypertensive diseases like glaucoma," says Dr Fautsch. "This study indicates that the K_{ATP} channel opener DZ lowers IOP in both ex vivo perfusion cultures of human eyes and in vivo murine models by activating the ERK1/2 signaling pathway."

For More Information

"ATP-Sensitive Potassium (K_{ATP}) Channel Activation Decreases Intraocular Pressure in the Anterior Chamber of the Eye" was published in Investigative *Ophthalmology & Visual Science*, Volume 52, No. 9, August 2011. Read the article at www.iovs.org.

"The ATP-Sensitive Potassium (K_{ATP}) Channel Opener Diazoxide Increases Outflow Facility by Activating the ERK1/2 Signaling Pathway" was presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting in May 2012. Read the abstract at www.arvo.org/eweb/StartPage.aspx?Site=arvo2.

AAO Leaders Featured in Video Interviews

Interviewers, bloggers, and videographers from the Department of Ophthalmology at Mayo Clinic spoke with key American Academy of Ophthalmology (AAO) leaders about current issues and the future of the specialty at the 2011 AAO annual meeting. Watch featured interviews on YouTube at http://www.mayoclinic.org/ophthalmology-rst/aao.html.

Raymond Iezzi Jr, MD, Receives Visionary Award

Dr Iezzi, a consultant in the Department of Ophthalmology at Mayo Clinic in Rochester, Minnesota, was recognized for his research in neuroprotectants and ocular applications of nanotechnology at the Foundation Fighting Blindness inaugural dinner May 23, 2012. Dr Iezzi holds the academic rank of associate professor of ophthalmology at Mayo Clinic. The Foundation Fighting Blindness is a national nonprofit organization focused on sight-saving research.

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Department of Ophthalmology Ranks Fourth in RPB-Cited Publications for 2011

In the Research to Prevent Blindness (RPB) publication rankings of 2011 unrestricted grant recipients, the Mayo Clinic Department of Ophthalmology tied 2 other medical schools with 52 articles each to rank fourth in the year-end summary. The department includes 27 MDs and 1 PhD with primary appointments in ophthalmology, plus 7 optometrists. Research focuses on cornea, glaucoma, retinal degeneration, and pediatric ophthalmology.

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