The Literature

BY PRADEEP Y. RAMULU, MD, MHS, PHD

GENOME-WIDE ASSOCIATION ANALYSES IDENTIFY THREE NEW SUSCEPTIBILITY LOCI FOR PRIMARY ANGLE CLOSURE GLAUCOMA

Vithana EN, Khor C-C, Qiao C, et al[1]

ABSTRACT SUMMARY

Vithana and colleagues analyzed genetic material from nearly 4,000 individuals with primary angle-closure glaucoma (PACG) and more than 18,000 controls to identify loci potentially associated with PACG. Several loci were found in discovery samples (taken from five distinct Asian populations), and three of these loci were confirmed to be associated with PACG in replication samples (taken from five Asian and one European population). These three loci were found in *PLEKHA7* (encoding a protein critical for maintaining and stabilizing adherens junctions, which regulate paracellular permeability), *COL11A1* (encoding the alpha chain of type XI collagen, in which mutations produce axial elongation syndromes such as Stickler syndrome), and an intergenic region between *PCMTD1* and *ST18* (the *PCMTD1* gene product is more likely to be affected by this locus, and the function of its gene product is unknown).

DISCUSSION

The study expands on prior research demonstrating a strong heritability of PACG among family members. The earlier findings, along with the current report, highlight the importance of asking patients with PACG to get their family members screened for angle closure and glaucoma. The article also sheds light on the probable mechanism of PACG. *PLEKHA1* variations may produce PACG as a result of aberrant fluid dynamics in the iris and/or choroid. *COL11A1* is likely an important determinant of axial length, and some variations in the gene may result in hyperopia, a well-known risk factor for PACG. Finally, more work is necessary to explain why *PCMTD1* variations may lead to local inflammatory changes in the iris or trabecular meshwork, which are important for the progression of suspected primary angle closure to primary angle closure and PACG.

The investigators examined subjects with a wide variety of racial backgrounds and looked for genetic variations that were consistently associated with PACG across those backgrounds. As such, race-specific genetic determinants of PACG might have been overlooked.

Future research needs to explain exactly why changes in the identified loci lead to PACG. It is to be hoped that these insights will provide clinicians with a better understanding of why angle closure occurs and why some patients with iridotrabecular contact develop glaucoma whereas others do not.

BEHAVIOR OF VISUAL FIELD INDEX IN ADVANCED GLAUCOMA

Rao HL, Senthil S, Choudhari NS, et al[2]

ABSTRACT SUMMARY

Rao and colleagues evaluated the behavior of a common metric of visual field (VF) loss severity (the Visual Field Index [VFI]) in a sample of patients with stable advanced glaucoma. Specifically, the investigators hypothesized that the VFI yields unstable results as the VF mean deviation crosses the -20 dB threshold. At this level of VF loss, the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc.) switches from using the pattern deviation probability plot to the total deviation probability plot when calculating the VFI. To study this matter, the investigators identified 37 pairs of VFs in which the mean deviation of the pair spanned the -20 dB threshold (the absolute change in mean deviation was small), and they looked at how the VFI varied among those VF pairs. Twenty-eight VF pairs were also identified that spanned the -10 dB threshold, and the VFI variation in these VF pairs was used as a comparison group. The researchers found huge VFI variability in the VF pairs spanning -20 dB (median of 15%) but much less variation in the VF pairs spanning -10 dB (4%).

DISCUSSION

The study illustrates an important pitfall of relying on VFI values to determine disease progression. Clinicians may infer rapid apparent progression from an analysis of VFI values when the mean deviation crosses 20 dB, even by a small amount. They should be aware of this limitation to avoid making potentially inappropriate

decisions, particularly the decision to perform surgery on a stable eye.

The study's authors suggest a method for understanding the magnitude of the VFI differences observed in their VF pairs. It provides a theoretical understanding of why VFI variation can be seen, but the method would be difficult to apply in a busy clinical practice.

One can hope that the manufacturers of VF machines will change their VFI calculation or presentation methods to guard against poor decisions resulting from the described artifact. In the meantime, however, physicians must be aware of the artifact.

FEATURES OF OPTIC DISC PROGRESSION IN PATIENTS WITH OCULAR HYPERTENSION AND EARLY GLAUCOMA

Lloyd MJ, Mansberger SL, Fortune BA, et al[3]

ABSTRACT SUMMARY

Lloyd and colleagues evaluated the types of optic nerve changes occurring in 336 eyes of 168 patients with either ocular hypertension or early glaucoma. Alterations were defined using a pair of stereo optic nerve photographs corresponding to the first and last photographs taken several years apart (median duration of 6.1 years; range, 2.0-7.9 years). For each pair of photographs, masked graders indicated whether optic nerve progression was present or absent. Additionally, in the 92 eyes (27.4%) in which advancing disease was present, the type of progression was characterized. The investigators found increased excavation, defined as an increased depth and lateral undermining of the neuroretinal rim, to be the most common reason for diagnosed progression (89%). A majority of progressors also showed thinning of the neuroretinal rim, defined as new or increased thinning in more than 1 clock hour. Progression was infrequently the result of focal rim thinning over less than 1 clock hour (also referred to as *notching*; 16%) or new/widened defects in the nerve fiber layer. Excavation most frequently occurred in the inferotemporal quadrant (76% of eyes).

DISCUSSION

This study serves as a reminder of the continued value of stereo disc photography for the monitoring of patients with glaucoma. It also alerts practitioners to the most common types of optic nerve changes reflecting glaucomatous optic nerve progression: excavation and diffuse thinning of the rim.

The investigators are to be commended for the care taken in their optic nerve protocol, but the future of stereo optic nerve photography, at least as performed in the current study (in which printed images were viewed with a stereo viewer), is uncertain. Stereo disc photography requires pupillary dilation, a trained photographer, and viewing devices. On the other hand, computerized retinal nerve fiber layer and optic nerve head imaging devices are becoming increasingly sophisticated, are easy to use, do not require pupillary dilation in most patients, and are easily incorporated into an electronic medical record. As such, the greatest limitation of this study could be that the important clinical information it generated may be infrequently used going forward.

> "It is ... uncertain whether physicians should define all optic nerve progression equally."

The investigators defined all of the observed changes as glaucomatous progression, but it is not clear whether they all have the same visual consequences in terms of VF progression and impact on the patient. It is therefore uncertain whether physicians should define all optic nerve progression equally. Moreover, practical solutions are necessary from industry to allow physicians to obtain and easily view stereoscopic optic nerve photographs. ■

Section Editor James C. Tsai, MD, is the Robert R. Young professor of ophthalmology and visual science and the chair of the Department of Ophthalmology & Visual Science at Yale School of Medicine in New Haven, Connecticut. Dr. Tsai may be reached at (203) 785-2020; james.tsai@yale.edu.

Pradeep Y. Ramulu, MD, MHS, PhD, is an assistant professor of ophthalmology at the Wilmer Eye Institute at Johns Hopkins University School of Medicine in Baltimore. He acknowledged no financial interest in the product and company mentioned herein. Dr. Ramulu may be reached at (410) 614-1994; pramulu1@jhmi.edu.

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