Association of High Polygenic Risk With Visual Field Worsening Despite Treatment in Early Primary Open-Angle Glaucoma

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IMPORTANCE: Irreversible vision loss from primary open-angle glaucoma (POAG) can be prevented through timely diagnosis and treatment, although definitive diagnosis can be difficult in early-stage disease. As a consequence, large numbers of individuals with suspected glaucoma require regular monitoring, even though many of these may never develop disease and other high-risk individuals with suspected glaucoma may have delayed or inadequate treatment. POAG is one of the most heritable common diseases, and this provides an opportunity to use genetic instruments in risk-stratified screening, diagnosis, and treatment of early glaucoma.

OBJECTIVE: To assess the association of glaucoma polygenic risk with glaucoma progression in early-stage disease.

DESIGN, SETTING, AND PARTICIPANTS: This cohort study used clinical and genetic data obtained from a longitudinal cohort study, Progression Risk of Glaucoma: Relevant SNPs With Significant Association (PROGRESSA) . Participants of European ancestry with characteristic optic nerve head changes suggestive of glaucoma were included. Data were collected between February 2012 and June 2020. Analysis took place between July 2020 and April 2022.

MAIN OUTCOMES AND MEASURES: The association of a glaucoma polygenic risk score (PRS) (2673 uncorrelated variants) with rate of peripapillary retinal nerve fiber layer thinning on optical coherence tomography and progression of visual field loss on 24-2 Humphrey visual fields.

RESULTS: A total of 1777 eyes from 896 individuals had sufficient data for structural progression analyses and 1563 eyes from 808 individuals for functional progression analyses. The mean (SD) age was 62.1 (9.9) years, 488 (44%) were male, and 1087 of 1103 individuals (98.5%) had European ancestry. An ancestrally matched normative population cohort (n = 17 642) was used for PRS reference. Individuals in the top 5% PRS risk group were at a higher risk of visual field progression compared with the remaining 95% after 5 years (hazard ratio, 1.5; 95% CI, 1.13-1.97; P = .005) . Conversely, those in the bottom 20% PRS risk group

were at a lower risk of visual field progression compared with an intermediate risk group over 3 years (hazard ratio, 0.52; 95% CI, 0.28-0.96; P = .04) .

CONCLUSIONS AND RELEVANCE: In this study, high polygenic risk was associated with more rapid structural and functional progression in early POAG, despite more intensive treatment. A PRS may serve as a valuable adjunct to identify individuals who stand to benefit the most from more frequent surveillance and earlier or more intensive treatment.

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