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A glaucoma polygenic risk score strongly associated with disease prediction and treatment intensity.

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Abstract

Purpose : To generate an effective polygenic risk score for glaucoma and measure its efficacy for disease prediction and the intensity of treatment required.

Methods : In the discovery stage, a multi-trait analysis was conducted combining data on individuals of European descent from UK Biobank (UKBB) glaucoma case-control genome-wide association study (GWAS, 7,947 cases and 119,318 controls), VCDR (including new data on 67,040 UKBB participants, and International Glaucoma Genetics Consortium, IGGC, N = 23,899), and IOP (including data on 103,914 UKBB participants and GWAS summary statistics from IGGC, N = 29,578). Newly associated SNPs were validated in two independent case-control cohorts. A glaucoma PRS was constructed and evaluated for disease prediction and clinical covariates in independent case-control and prospective studies not used in the generation of the PRS.

Results : Multivariate genetic modelling identified 107 glauocma loci (49 novel), with high concordance in independent glaucoma cohorts. The PRS enabled effective risk stratification. In advanced glaucoma, risk was 15-fold greater in the top versus bottom PRS decile, and 21-fold greater for high tension glaucoma. The top PRS decile reach an equivalent absolute risk for glaucoma 10 years earlier than the bottom decile. This PRS predicted surgical intervention in advanced disease (P=3.6×10-6), and is associated with escalating intensity of medical therapy and disease progression in early stage glaucoma.

Conclusions : Genetic risk profiling delineates individuals at high-risk of developing advanced glaucoma, more rapid disease progression, and requirement for treatment including surgery. Glaucoma PRS profiling is likely to enable earlier screening and timely treatment of high-risk individuals, with reduced screening and monitoring costs in lower-risk groups.

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