Multitrait analysis of glaucoma, intraocular pressure and vertical cup to disc ratio identifies many new loci and enables a polygenic genetic risk score strongly predictive of disease susceptibility in the population, and disease progression and treatment intensity in the clinic

Purpose: To generate an effective polygenic risk score (PRS) for glaucoma associated with disease prediction in the population, and evaluate performance in predicting progression and treatment in the clinic.

Method: In the discovery stage, a multi?trait analysis was conducted combining data from the UK Biobank (UKBB) glaucoma case–control GWAS (7947 cases vs 119?318 controls), VCDR (including data we graded on 67?040 UKBB participants, and International Glaucoma Genetics Consortium [IGGC] data N = 23?899), and IOP (103?914 UKBB participants and from IGCC N = 29 578). Newly associated SNPs were validated in two independent case?control cohorts. Then a PRS for glaucoma was constructed with a final associated set of 2673 SNPs. This was evaluated for disease prediction and clinical covariates in independent case?control studies (ANZRAG and British replication cohorts), and the prospective PROGRESSA study.

Results: Multivariate modelling identified 107 glaucoma 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 vs bottom decile of PRS, and 21?fold greater for high tension glaucoma. The PRS predicted surgical intervention in advanced disease (P