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# High polygenic risk is associated with earlier treatment initiation and escalation in glaucoma suspects

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## Abstract

**Purpose :** To assess whether a polygenic risk score for primary open angle glaucoma predicts treatment commencement amongst treatment naive glaucoma suspects.

**Methods :** A prospective, longitudinal genetic association study combining a discovery cohort of glaucoma suspects who were treatment naive at enrollment into the Predicting Risk of Glaucoma: RElevant SNPs with Significant Association (PROGRESSA) study, and a replication cohort comprising of treated early manifest and suspect glaucoma cases.

In the discovery phase, a per-allele weighted polygenic risk score was calculated for 301 glaucoma suspects who were treatment naive at enrollment into the PROGRESSA study. Multivariable cox proportional regression analysis assessed the correlation between polygenic risk score and time to initiation of Intraocular pressure (IOP) lowering therapy. A replication analysis assessed the correlation between polygenic risk score and time to escalation of IOP lowering therapy amongst 539 suspect and manifest glaucoma cases who were on IOP lowering therapy at study enrolment.

**Results :** A higher glaucoma PRS was correlated with earlier initiation of IOP-lowering therapy after adjustments for age, gender, IOP, and family history of glaucoma (adjusted HR: 1.43/SD 95% CI: [1.04, 1.95] P=0.024). Participants in the highest normative population quintile demonstrated a 3.4-fold likelihood of requiring IOP-lowering therapy within 5

years than participants in the lowest quintile (HR: 3.38/SD 95% CI [1.12, 10.20] P=0.017).

A replication analysis then evaluated the correlation between polygenic risk score and escalation of therapy amongst participants on therapy at enrolment. A higher polygenic risk score for glaucoma was correlated with a greater risk of requiring treatment escalation (HR: 1.24 95% CI: [1.05, 1.24] P=0.009), and was correlated with maximum number of required IOP-lowering agents during monitoring (beta: 0.17/SD 95% CI: [0.07, 0.26] P<0.001).

Conclusions : This study demonstrates novel associations between polygenic risk of primary open angle glaucoma and time to initiation of IOP lowering therapy. It builds upon previous work highlighting the therapeutic utility of genetic risk stratification in glaucoma.

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