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119 loci influencing intraocular pressure provide new insight into primary open angle glaucoma susceptibility and age of onset.

Jamie E. Craig; Alex W. Hewitt; David Mackey; Stuart L Graham; Paul R Healey; Andrew JR White; John Landers; Robert Casson; Emmanuelle Souzeau; Kathryn P Burdon; Puya Gharahkhani; Stuart MacGregor

+ Author Affiliations & Notes

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Abstract

Purpose : To define common genetic variation and relevant pathways associated with intraocular pressure (IOP) in normal individuals, and determine their relevance to glaucoma.

Methods : A combined analysis of IOP in participants from the UK Biobank (N = 103914) and previously published data on IOP from the International Glaucoma Genetic Consortium (N = 29578) was performed to identify genetic variation associated with IOP. Statistically significant independent regions associated with IOP were then evaluated for association with glaucoma in 11018 glaucoma cases and available controls. Gene based and pathways analyses were performed. An allele based score for glaucoma risk was evaluated in 1734 individuals with advanced glaucoma from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) to evaluate the magnitude of phenotypic effect.

Results : 101 statistically independent regions were identified which were associated with IOP at the level of genome-wide significance, of which 85 were previously unreported for either IOP or POAG. The majority (84) of identified IOP loci showed at least nominal evidence of association with POAG. Gene-based tests implicated a further 22 independent loci for IOP, with half of these also influencing glaucoma risk. Pathways analysis for the IOP loci uncovered significant associations for both suspected (extracellular matrix, collagen) and previously unreported (vascular

development and cell migration) pathways, which were also significant in the glaucoma analysis. Using the derived allelic risk score for glaucoma in combination with previously identified POAG risk alleles showed that cases in the top decile of the allelic risk score were at increased risk (OR = 5.6; 95% CI 4.1-7.6) of advanced glaucoma relative to the bottom decile, and were diagnosed 7.4 years earlier.

Conclusions : Using normal population data for IOP can define new genes and pathways relevant not only to the regulation of IOP, but also to help define risk of severe visual loss from glaucoma, and age of onset in glaucoma in a dataset recruited independent of IOP.

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