Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries

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Primary open-angle glaucoma (POAG) , is a heritable common cause of blindness world-wide. To identify risk loci, we conduct a large multi-ethnic meta-analysis of genome-wide association studies on a total of 34,179 cases and 349,321 controls, identifying 44 previously unreported risk loci and confirming 83 loci that were previously known. The majority of loci have broadly consistent effects across European, Asian and African ancestries. Cross-ancestry data improve fine-mapping of causal variants for several loci. Integration of multiple lines of genetic evidence support the functional relevance of the identified POAG risk loci and highlight potential contributions of several genes to POAG pathogenesis, including SVEP1, RERE, VCAM1, ZNF638, CLIC5, SLC2A12, YAP1, MXRA5, and SMAD6. Several drug compounds targeting POAG risk genes may be potential glaucoma therapeutic candidates.

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REVIEW by Karl Mercieca

This is an important study which has identified a strong cross-ancestry genetic correlation for POAG between Europeans, Asians, and Africans. It has also identified 127 genome-wide significant loci by combining GWAS results across ancestries.

This paper was chosen because it is the largest study to date examining the genetic causes of POAG and helps to demonstrate that while there is some overlap in genetic causes between Europeans and non-Europeans, larger studies are still needed especially in African populations on the pathway to personalised glaucoma care.

The strengths of this paper include the large numbers included (>34,000 POAG and >349,000 controls) and the multi-ethnic approach to risk loci identification which is novel when compared to previous GWAS studies

that focused on a single ancestry group. The study also introduces a large number of new gene loci with most being also identified at genome-wide level. A further strength is the linking of findings to glaucoma-associated endophenotypes with consistent effects across ethnicity.

Weaknesses include the relatively low statistical power for subtype-specific analyses which limit the study's ability to identify subtype-specific loci, and the fact that a significant proportion of glaucoma cases were obtained via self-reports which has obvious limitations.

The authors themselves also highlighted other limitations, including that a subset of studies did not age-match both cases and controls, so future studies should fully investigate the effect of the identified risk loci across different age strata. Furthermore, although the functional relevance of identified risk loci was done using bioinformatic analyses, functionality in vitro and in vivo was not confirmed, leaving further work to be done on the biological roles of these risk loci with respect to POAG pathogenesis on tissue and molecular levels.