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Analyses of the UK Biobank data highlights hundreds of genetic loci and pathways associated with refractive error and myopia

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Footnotes

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Abstract

Purpose : Refractive error (RE) is a highly heritable complex trait. Genetic studies to date have identified many associated genetic loci, yet they explain a small proportion of the trait's heritability, have poor predictive value and have only allowed a cursory reconstruction of the biological pathways involved. Our purpose is to identify novel genetic factors and mechanisms involved in RE, taking advantage of the power of a large, homogeneous British Cohort.

Methods : The UK Biobank is a cohort of half a million mostly British subjects. We ran a genome-wide association study (GWAS) in this cohort. The outcomes for this study were refractive status, based on the direct autorefractor measurements of 120,000 subjects and refractive status inferred by self-reported information (including age of first spectacle wear) from an additional 320,000 additional subjects. Linear mixed model regressions controlling for potential structure were carried out in each stratum, and results were standardized prior to a meta-analysis. Previously published analyses were used to replicate and validate these findings.

Results : Over 200 genetic loci were significantly associated with refractive status in the UK Biobank, over one third of which are novel and not described in previous GWAS, largely driven by age- of-onset of myopia. In addition to confirming association with known myopia genes (e.g. LAMA2 $p=6 \times 10^{-140}$, GOLGA8/GJD2 $p=7 \times 10^{-114}$), association was found also for genes where rare mutations cause syndromic eye disease such as microphthalmia (e.g. BMP4, 6×10^{-25} , MFRP $p=2 \times 10^{-12}$). Interestingly association was also found at the LOXL1 gene locus ($p=6 \times 10^{-14}$) previously associated with pseudoexfoliation. Among biological pathways, there is emerging evidence for the involvement of *Wnt* signaling pathways, with several key genes strongly associated with the outcome.

There were also highly significant ($p < 1 \times 10^{-10}$) genetic correlations between refractive error and measures of intelligence, body mass, and cataract.

Conclusions : Our work suggests there are many more interesting and important genes that play key roles over refractive error and myopia. Analyses in large and homogeneous cohorts, exploring relevant refractive phenotypes, will improve our understanding of how they develop and perhaps lead to personalized risk profiles and better clinical management in the future.

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