

## CLINICAL SUMMARY

# IMI Myopia Genetics Report

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## INTRODUCTION

**T**his report details the current genetic findings in myopia and the future research directions. Both genetic and environmental factors can govern common refractive error, especially myopia. With the introduction of large genome-wide association studies (GWAS), identification of refractive error genes associated with myopia is flourishing.

## KEY FINDINGS

Refractive errors including myopia are caused by a complex interplay between many common genetic factors and environmental factors (near work, outdoor exposure). Almost 200 genetic loci have now been published for refractive error and myopia, which mostly carry low risk but are commonly found in the general population. The identified genes have a wide variety of functions, and all retinal layers appear to be sites of expression, with roles in synaptic transmission, cell-cell adhesion, calcium ion binding, cation channel activity, and extra-cellular matrix components. Many are light-dependent and related to cell cycle and growth pathways. A GWAS meta-analysis confirmed a light-dependent retina-to-sclera signaling cascade for myopia development and marked out potential pathological molecular drivers.

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Eighty years ago, Sir Duke-Elder was one of the first to recognize a “hereditary tendency to myopia” and twin studies show high heritability of refractive error (90%), but this varies widely across other familial studies, with reports of as low as 10%. In the general population, only 5% to 35% of the variation in refractive error was explained by heritability. People at high genetic risk, based on the polygenetic risk scores (risk determined by all the genes that contribute to a trait) can have up to 40 times greater risk of myopia than people at low genetic risk.

Recently, the international Consortium for Refractive Error And Myopia (CREAM) and the personal genomic company 23andMe identified many more genetic variants, and combining their findings, the 161 common variants identified for refractive error explained approximately 8% of the variance. This further suggests that environment plays a key role in the recent epidemic rise in the prevalence of myopia.

Genome-environment-wide interaction studies (GEWIS) revealed gene-environment interaction; those who are highly educated with a high genetic load appeared to have a far greater risk of myopia. To date, there is a lack of strong evidence to suggest that the myopia genetic risk between Europeans and Asians is profoundly different. And that the recent global rise of myopia prevalence is unlikely due to genetic factors, although the degree of myopia may still be under genetic control.

The secondary myopias, those that can accompany other systemic or ocular abnormalities for which there is a strong genetic basis, are generally monogenic (involved or controlled by a single gene). Most genes causing syndromic forms of myopia have not (yet) been implicated in common forms of myopia, despite some slight overlap.

Whole-exome sequencing (WES) and whole-genome sequencing (WGS), Mendelian randomization (MR), and epigenetics have also been used to further shed light on myopia genetics.

## CONCLUSION

Research on myopia genetics, genetic epidemiology, and epigenetics is growing and providing a wealth of insights into new molecules involved in myopia genesis. As most of the phenotypic variance of refractive errors is still unexplained, larger scale studies are required with deeper coverage of the genome, using the latest novel technological advances, multi-source study populations, environmental genomics and systems biology to integrate all the findings via big data analytics. Expanding our knowledge of pathological mechanisms and ability to identify at risk individuals for targeted therapy would improve patient management, and, ultimately, the prevention of complications and visual impairment from myopia.

**Reference:** Tedja MS, Haarman AEG, Meester-Smoor MA, Kaprio J, Mackey DA, Guggenheim JA, et al. IMI - Myopia Genetics Report. Invest Ophthalmol Vis Sci. 2019;60(3):M89-M105. <https://iovs.arvojournals.org/issues.aspx?issueid=937872#issueid=937872>

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