Published in final edited form as:

Retina. 2018 January ; 38(1): 91–101. doi:10.1097/IAE.0000000000001518.

Involvement of multiple molecular pathways in the genetics of ocular refraction and myopia

Robert Wojciechowski, OD, PhD^{1,2,3} and Ching-Yu Cheng, MD, PhD^{4,5,6}

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

²Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, MD

³Computation Genomics Branch, National Human Genome Research Institute, Baltimore, MD, USA

⁴Singapore Eye Research Institute, Singapore National Eye Centre, Singapore

⁵Duke-NUS Graduate Medical School, Singapore

⁶Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Abstract

The prevalence of myopia has increased dramatically worldwide within the last three decades, and has reached epidemic proportions in some parts of East Asia. Recent experimental and epidemiological studies have shown that refractive development is influenced by environmental, behavioral, and inherited factors. Large epidemiological studies (mainly genome-wide association studies) have increased our understanding of the genetics involved in refractive error and myopia. Affordable sequencing has enabled investigation of the human exome for rare mutations causing extreme myopia. These studies have identified interesting candidate genes, and will no doubt continue to discover many more. All the genetic loci discovered to date indicate that refractive development is a complex heterogeneous process mediated by a number of often overlapping biological processes. The exact mechanisms by which these biological networks regulate eye growth are poorly understood. Although several individual genes and/or molecular pathways have been investigated in animal models, a systematic network-based approach in modeling human refractive development and experimental myopia is necessary to understand the complex interplay between genes and environment in refractive error. New biomedical technologies and better-designed studies will continue to refine our understanding of refractive error, and may lead to preventative and therapeutic measures to combat the myopia epidemic.

Correspondence to: Dr. Robert Wojciechowski, 615 N. Wolfe Street, Room E6516, Baltimore, Maryland 21205, USA. Tel: +1-410-614-5041; kassaq@jhu.edu, Dr. Ching-Yu Cheng, 20 College Road, The Academia, Level 6, Discovery Tower, Singapore 169856, Tel: +65 6576 7277; chingyu.cheng@duke-nus.edu.sg.

Conflict of interest statement: Dr Wojciechowski reports no conflict of interest in relation to the present manuscript.

Keywords

axial length; genome-wide association study; myopia; sequencing

Introduction

Over the last three decades, the world has experienced a dramatic increase in the incidence of myopia. This so-called “myopia epidemic” has been particularly acute in urban areas of East Asia, where multiple population-based surveys have estimated that over 80% of individuals are myopic by early adulthood. Moreover, the prevalence of a high degree of myopia (typically defined as a spherical equivalent correction of -6 diopters (D) or less) has increased disproportionately compared with low and moderate myopia. Given that the genetic composition of the population has remained unchanged for the last 2–3 generations, the trends in the incidence of myopia must be attributable to changing environmental and behavioral factors. Nevertheless, estimates of the proportion of the variation of refractive error within a population due to genetic factors (i.e., its heritability) have remained high across multiple populations.

Genome-wide association studies (GWAS) have identified numerous loci harboring genes that influence refractive development.^{1–5} Nevertheless, these variants combined have been estimated to account for less than 5% of the population variation in ocular refraction,⁴ (well below heritability estimates for the same trait, which typically range from 50% to over 90% across disparate populations).^{6–11} This is a common phenomenon in GWAS that has been termed the “missing heritability” problem. Missing heritability is likely the result of a variety of causes including limited statistical power in association studies, overestimated heritabilities from studies of relatives, linkage disequilibrium, and the presence of a large number of rare causal variants that have not been identified in standard GWAS.

Missing heritability suggests that additional loci will be discovered with ever-larger GWAS, next-generation sequencing approaches, and novel analytical strategies. Most currently-identified loci for refractive error are extremely robust,¹² and unlikely to be falsified in future studies. Moreover, the genes harbored within these loci indicate that common and biologically-plausible mechanisms underlie the development of human refractive error.

Large epidemiological studies in a number of human populations have demonstrated that genetics, environment, and behavioral factors have important roles in refractive variation. A number of excellent reviews have summarized these epidemiological studies (see, for example, refs^{13–15}). Here, we restrict our review to recent developments in human genetic association and sequencing studies.

Importance of study design in genetics studies

Large GWAS have become feasible only within the last decade, and next-generation sequencing has recently become the standard technology for rare-variant discovery in Mendelian genetics. Different study designs, however, have different strengths and limitations,¹⁶ which should be taken into consideration when interpreting their results.

GWAS were initially proposed as a powerful alternative to linkage studies under the common disease-common variant hypothesis of complex disease.¹⁷ Because the statistical power of GWAS decays exponentially with decreasing (minor) allele frequency, traditional GWAS are not well suited to identify rare variants. Thus, GWAS have principally identified common variants with relatively small effects.

Figure 1 illustrates the strengths of GWAS in identifying common loci for refractive error. It plots effect sizes at genome-wide significant loci from two large GWAS (see below) of refractive error⁴ and age-at-onset of myopia² against the minor allele frequency at the most significant marker at each locus. Despite large sample sizes of >40,000 individuals, all significant markers were common variants (minor allele frequency 0.05 or more) with small-to-modest effect. Moreover, no common marker had a strong effect on these refractive phenotypes. This implies that common variants of large effect are unlikely to exist in these (mainly European) populations, and that larger GWAS currently under way will mainly uncover less-frequent variants and variants with small effects. Figure 1 also emphasizes the well-acknowledged theoretical limits of GWAS: an 80% power curve for a sample size of 40,000 (dashed red line) indicates that all but very large effects (from rare variants) are detectable via traditional GWAS. This relative lack of power has been demonstrated by study data that precisely follow the power curve. Thus, genetic studies of high or pathological myopia should attempt to enrich their data for highly-penetrant forms of myopia or utilize family-based study designs, such as case-parent trios or linkage analysis in extended pedigrees, which are more suitable for identifying rare variants of large effect.

Because they survey a finite sample of genetic markers, GWAS rely on between-marker linkage disequilibrium (i.e., correlations between nearby markers) to achieve sufficient statistical power to identify associated loci. Most positive GWAS associations are found in intergenic regions, and the genes annotated to these loci are often chosen based on their proximity to the marker(s) yielding the most significant association signals. Therefore, statistical evidence of association to particular genes should be supplemented with evidence of functionality and biological relevance.

Genetics of ocular refraction

GWAS have identified numerous loci for a variety of refractive error traits and endophenotypes (such as axial length and corneal curvature). Population-based GWAS for common (non-pathological) refractive errors were first published by groups in the United Kingdom¹ and the Netherlands.³ These studies identified and mutually replicated genome-wide significant associations to two separate regions on chromosome 15q closest to the genes *RASGRF1* (rs939658; $p = 2.07 \times 10^{-9}$),¹ and *GJD2* (rs634990; $p = 2.21 \times 10^{-14}$).³

Most insights into the genetics of refractive error have been provided by two landmark studies of >40,000 participants (Table 1).^{2,4} The size of these studies underscores the idea that large samples are often necessary for variant discovery in complex traits such as refractive error, in which many variants have individually small effects on the trait. The Consortium for Refractive Error and Myopia (CREAM), an international group of investigators representing over 30 individual studies, identified 16 novel quantitative trait

loci for refractive error in a large meta-analysis of 37,382 participants of European descent, and in 8,376 East Asians.⁴ A combined analysis of European and Asian cohorts identified 8 additional loci for ocular refraction. Subsequently, Kiefer et al from the personal genetics company 23andMe published results of a survival analysis GWAS of myopia age-of-onset in 45,771 people of European ancestry.² In addition to replicating previous results for the *RASGRF1* and *GJD2* loci, they reported 20 new loci for myopia age-at-onset. An analysis of the most significant markers ($p < 1 \times 10^{-4}$) from both the CREAM and 23andMe studies showed a strong overlap between studies wherein the majority of loci discovered in one study were replicated in the other.¹² Moreover, the estimated effect sizes at markers common to both studies were strongly linearly related despite being measured on different scales. This interesting result suggests that the genetic architecture of the onset of myopia early in life overlaps significantly with refractive error severity. Moreover, the influence of these genes can be measured well past middle age despite the cumulative effects of aging and extrinsic environmental factors. Table 1 summarizes results from both studies and shows the top genome-wide significant markers within 100 kb of genes (or pseudogenes) in 23andMe and CREAM. Of the 68 unique markers, 40 (59%) are intragenic. In total, 51 genes are within 100 kb of these markers. When adjacent single-nucleotide polymorphism (SNPs) are grouped by separating them by at least 100 kb, 33 unique loci can be identified (represented by locus number column in Table 1). Fourteen of these loci contain SNPs that were highly significant in both studies. Recently, 15 loci from CREAM and 23andMe were replicated in a cohort of 3712 volunteers from the Nagahama Study in Japan.¹⁸

Genes in close proximity to markers associated with refractive error appear to cluster into a limited number of functional classes or pathways (Table 2). Mutations in genes in several refractive error-associated loci have been reported in human inherited ophthalmic and retinal disease. These include genes involved in diseases of eye growth and development: *SIX6*,¹⁹ *BMP4*,²⁰ and *PRSS56*,²¹ (anophthalmia, microphthalmia, and nanophthalmos) as well as retinal dystrophies: *RGR*,²² (retinitis pigmentosa) and *CDHR1*,^{23,24} (cone-rod dystrophy, retinitis pigmentosa). It should also be noted that some candidate genes for refractive error occupy the same locus (for example, *CDHR1*, *LRIT1*, *LRIT2*, and *RGR* at 10q23.1), and it is unclear whether one or more of these genes contribute to refractive development.

These varied mechanisms suggest that genes involved in refractive variation are not isolated to a specific tissue in the retinoscleral signaling cascade, which is thought to regulate refractive development. In addition, although discrete mechanisms for refractive error control can be hypothesized from loci discovered via GWAS, the pathways involved likely overlap considerably. The difficulty in inferring regulatory networks from GWAS data alone is compounded because single genes are involved in multiple biological processes (pleiotropy), and their expression and functions can be highly tissue- and context-dependent. For example, *GJD2* codes a gap junction protein, Connexin-36, which regulates electrical coupling between cells in the inner and outer retina. Gap junction conductance between rod and cone photoreceptors is, in turn, regulated by a dopamine-dependent circadian clock.²⁵ Thus, differential refractive control via *GJD2* may possibly be mediated by the circadian rhythm and dopamine. It has been suggested that light- and dopamine-modulated electrical coupling of horizontal cells via gap junctions underlies contrast detection,²⁶ providing

another putative mechanism by which *GJD2*-mediated refractive control may depend on environmental (lighting) conditions.

Risk of myopia and genomic heritability of refractive error

Multiple family-based studies have estimated the heritability of refractive error (i.e., the proportion of the phenotypic variance due to inherited factors) to range from 50% to more than 90%.^{6,8,10,13,14,27} These estimates are consistent with those obtained for other complex traits such as human height.^{28,29} Despite having identified more than two dozen loci for refractive error in the CREAM GWAS, the implicated variants explained only 3.4% of the phenotypic variance (or ~5% of the heritability) in 9,307 participants in the Rotterdam Eye Study.⁴ This proportion of variance explained is similar to estimates of highly significant environmental predictors such as educational attainment (partial $r^2=1.9-2.6\%$ in AREDS;³⁰ partial $r^2=1.3-2.3\%$ in the Framingham Eye Study [unpublished data]). Nevertheless, a low proportion of variance explained is a recurring and well-described phenomenon in complex trait genomics dubbed the “missing heritability” problem.³¹ We should note that genomic heritabilities based on a limited number of genome-wide significant markers can be severely underestimated, particularly when the causal variants are not directly typed, as is invariably the case in GWAS. For example, while the ~50 independent variants initially identified for human height accounted for ~5% of its phenotypic variance, the variance explained reached 45% when ~300,000 common SNPs were simultaneously modeled in genomic heritability estimates.^{32,33} A similar pattern is almost certainly the case for refractive error.

Gene–environment interactions in refractive error development

Gene–environment (G×E) interaction can be defined as a differential effect of genetic variants depending on environmental conditions. This statistical concept of G×E interaction (or effect modification) is fundamentally different from biological interactions, and the presence of one does not necessarily imply the presence of the other.

Environmental effect modification of genetic polymorphisms on refractive phenotypes have been difficult to demonstrate convincingly, in part because of a lack of statistical power of even the largest refractive error GWAS to detect statistical interactions. Nevertheless, a study of five Singapore cohorts,³³ reported that the effect of variants at three loci (*SHISA6-DNAH9*, *GJD2* and *ZMAT4-SFRP1*) showed strong associations with refractive error in highly educated individuals. The effect was not seen in their less-educated counterparts, suggesting that environmental context is important in modulating the effects of these loci on refraction. Such G×E interactions with education have also been suggested for polymorphisms in the matrix metalloproteinase cluster on chromosome 11q22.2.³⁰ Recently, Tkatchenko et al. used lens-induced mouse myopia models and human GWAS data to demonstrate an interaction between *APLP2* variants and environment on myopia development.³⁴ While statistical G×E interactions on refractive error are likely to exist in greater numbers than have been reported to date, successfully mapping interacting loci using GWAS will likely depend on improved measures of relevant exposures at appropriate sampling periods. For detailed discussions on study design and statistical considerations for

G×E GWAS, we direct the reader to excellent reviews on the topic (see, for example, refs^{35,36}).

Genetics of ocular axial length

Refractive errors result from a misalignment between the focal point of an eye and the retinal plane. It is well recognized that most myopia is caused by a relative elongation of the eye's axial length (more specifically, its posterior segment) through scleral remodeling. A few studies have reported results from GWAS on refraction-related phenotypes (endophenotypes) such as ocular axial length.

Fan et al.³⁷ identified a locus on chromosome 1q41 associated with axial length in three Singapore cohorts and high myopia in a Japanese case-control sample. Subsequently, using a subset of CREAM studies, Cheng et al.³⁸ replicated the findings at 1q41 near the pseudogene *ZC3H11B*, and identified another 8 significant loci for axial length across the genome: *RSPO1*, *C3orf26*, *LAMA2*, *GJD2*, *ZNRF3*, *CD55*, *MIP*, and *ALPPL2*. Of these, five were associated with refraction in 18 independent cohorts (n = 23,591) and/or had already been reported in CREAM,⁴ or 23andMe.² *MIP*, a member of the water-transporting aquaporins, expresses the *Lens Fiber Major Intrinsic Protein* (NCBI reference sequence NP_036196.1) and is associated with cataracts.^{39,40} Its relationship to axial length is unknown. Importantly, two of the axial length genes (*RSPO1* and *ZNRF3*) along with refractive error loci *CHD7* and *DLG6* are part of the Wnt/Frizzled signal transduction pathway, which plays a major role in ocular tissue development.⁴¹

Genetics of high and pathological myopia

The genetic basis of high myopia has been investigated for decades. Indeed, hereditary forms of syndromic and isolated myopia have been well-described in the medical literature since the 1930s.⁴² It was not until late 1998 that Young et al.⁴³ mapped the first genetic loci in families displaying non-syndromic high myopia to chromosome 18p11.31 (MYP2; OMIM:160700; <http://omim.org/entry/160700>). Subsequent linkage analyses identified numerous additional loci for hereditary high myopia, although these chromosomal regions were generally quite wide and contained dozens to hundreds of genes. Despite evidence that more extreme refractive errors were more highly heritable,^{6,44} “high myopia genes” were more elusive than genetic variants associated with more common refractive errors. This might be explained by a lack of power in traditional GWAS in mapping rare variants (Figure 1). Although pathological forms of myopia are more likely to present as Mendelian disorders, mutations causing severe visual disability have undoubtedly been under considerable purifying selection, leading to a depletion of severe-disease causing alleles. Moreover, the definition of “high myopia” is inconsistent, somewhat arbitrary, and may lead to significant misclassification because of the presence of phenocopies. Case-control studies of high myopia may therefore suffer from high genetic and phenotypic heterogeneity. Nevertheless, population-based GWAS of refractive errors contain individuals from across the spectrum of refractive errors, and individuals with extreme phenotypes have disproportionate leverage on quantitative trait association statistics. Thus, association signals

from the CREAM and 23andMe analyses implicitly include information from high-myopia loci.

Many successes in mapping loci for high myopia has come from linkage analysis, in which cosegregation of phenotype and marker loci is followed and quantified in pedigrees. To date, more than 12 loci for high myopia have been mapped using linkage studies or simpler segregation analyses (Table 3). Although linkage studies have poor spatial resolution (linkage peaks typically span several megabases), they are well suited to uncover loci harboring rare variants of strong effect (Figure 1), which is expected in inherited forms of high myopia. Linkage analysis also facilitates the discovery of causal variants by limiting the search from the whole genome to relatively narrow candidate regions. Moreover, Mendelian inheritance patterns are highly evocative of single-gene disorders within families, therefore minimizing the confounding effect of genetic locus heterogeneity or multilinear transmission of dominant disease in any given pedigree.

Case-control GWAS have been less successful in mapping loci for high myopia. The two-stage GWAS by Nakanishi et al.⁴⁵ included 830 cases and 1,911 general population controls in stage-1, and 533 cases and 977 controls in a replication set. Although rs577948 (close to the *BLID* gene) was nominally significant for association with high myopia in the combined analysis ($p = 2.22 \times 10^{-7}$), no marker attained genome-wide significance levels.

Studies that mapped loci for high myopia using a combination of methods including next-generation sequencing of whole exomes or candidate genes showed some mechanistic overlap with known refractive error loci. In general, however, whole-exome sequencing in small samples followed by aggressive *ad hoc* variant filtering and comparisons with reference samples provides limited support for implicating particular genes and/or variants.⁴⁶ In addition, contrary to GWAS and linkage analysis, robust statistical and computational methods for quantifying uncertainty in variant-dredging studies have not been developed. In the absence of such statistical support, much care should be taken in interpreting results from studies that rely heavily on “variant-filtering” procedures. Ideally, researchers should support their findings with functional studies of the molecular and physiological consequences of candidate gene/protein manipulation. Because thousands of genes are expressed in the retina alone, expression in the eye and retina should be considered insufficient as supporting evidence. However, differential expression in relevant ocular tissues in well-controlled animal experiments provides biological support for a role of specific genes in high myopia.

MYP21 and ZNF644

Whole exome sequencing with next-generation technologies offers an opportunity to identify exonic variants of large effect (or, equivalently, of high penetrance), especially in large pedigrees exhibiting clear Mendelian transmission. Using a combination of variant filtering and segregation, Shi et al.⁴⁷ identified a putative locus for high myopia (*MYP21*) in a multigenerational Han Chinese pedigree that was autosomal dominant for high myopia. A mutation in *ZNF644* segregated with 6 affected family members, but was absent in 7 unaffected relatives. Screening for *ZNF644* mutations in singletons by Shi et al.⁴⁷ and Tran-Viet et al.⁴⁸ identified additional variants possibly associated with high myopia.

MYP22 and PRIMPOL

Whole exome sequencing was also used by Zhao et al.⁴⁹ to map a novel missense variant in *CCDC111* (current HGNC symbol *PRIMPOL*) on chromosome 4q35.1 (*MYP22*) in a high myopia pedigree. The variant was also identified in 4 of 270 sporadic high myopia patients, but was not present in 270 controls. Little is known about the function of *PRIMPOL*, and its association with myopia should be considered tentative.

MYP6 and SCO2

Similarly, Tran-Viet et al. found a rare nonsense mutation in the *SCO2* gene (*MYP6*) that segregated with autosomal dominant high myopia (2-point LOD = 1.49) in a three-generation pedigree. The putative causal allele c.157C>T (rs74315510) leads to a stop gain on all known transcripts of the *SCO2* cytochrome C oxidase assembly protein (canonical transcript ENST00000543927). They also identified three rare *SCO2* mutations in 140 unrelated high-grade myopia cases. Real-time PCR and immunofluorescence labeling showed that levels of *Sco2* messenger RNA were significantly reduced in the retina, retinal pigment epithelial cells, and sclera of induced-myopia mouse models compared with control eyes. The authors hypothesized that *Sco2* deficiency may affect normal copper metabolism in ocular tissues, resulting in increased oxidative stress, altered retinal function, and high myopia. It should be noted that Stambolian et al.⁵⁰ initially mapped *MYP6* to a locus at 22q12 in a large cohort of Ashkenazi Jewish families with varying degrees of myopia. Klein et al.⁵¹ later replicated this result by mapping a quantitative trait locus for spherical equivalent refractive error centered at 22q11.23 in families from the Beaver Dam Eye Study. Although these loci have been merged into *MYP6* by OMIM (OMIM #608908; <http://omim.org/entry/608908>), it is unlikely that they represent the same underlying locus as *SCO2*.

MYP23 and LRPAP1

Aldahmesh et al.⁵² used autozygosity (linkage) analysis to map mutations for severe myopia in consanguineous Saudi families, and identified homozygous truncating variants in *LRPAP1* and *CTSH* as probable causal mutations. Interestingly, *LRPAP1* encodes a chaperone of LRP1 whose deficiency upregulated transforming growth factor (TGF)- β in cells from affected individuals.⁵² Another study by Guo et al.⁵³ found a nonsense mutation (c.141C>G;p.Y47*) in *SLC39A5* co-segregating (multipoint LOD = 1.42) with the phenotype in a family with non-syndromic severe myopia. Functional experiments showed that mutations of the zinc transporter encoded by the gene dysregulated the BMP/TGF- β pathway. This possible mechanism for altered eye growth is consistent with GWAS findings of an association of refractive error with bone morphogenic protein genes (*BMP2*, *BMP3*, and *BMP4*),^{2,4} which are involved in the TGF- β signaling and differentiation pathway. It is also consistent with findings from experimental animal myopia models that implicated TGF- β in eye growth regulation.^{54,55} Moreover, *in silico* analyses of protein-protein interactions involving products of genes identified through GWAS showed that many genes were related to cell cycle and growth networks such as the MAPK and TGF- β SMAD pathways.⁵⁶ This is consistent with a view of myopia as a dysregulation of eye growth and suggests that common molecular mechanisms underlie normal eye development and refractive error.

Summary

Within the last five years, gene mapping in humans has been highly successful in discovering genetic loci implicated in refractive error development and high myopia. Altogether, more than 30 loci for refractive phenotypes have been mapped with high confidence. Common quantitative trait variants for refraction have small effects consistent with the common disease–common variant hypothesis. The genetic heterogeneity uncovered by GWAS confirms that refractive error is a complex phenotype influenced by numerous genes and environmental factors. Many of these genes, however, can be clustered into broad, yet overlapping, functional categories. The search for variants that cause high or pathological myopia has been hindered by the inherent constraints of GWAS, in addition to a general lack of statistical and computational methods to comprehensively analyze sequencing data. These constraints include genetic heterogeneity, small sample sizes, noncoding loci that contain many variants that are difficult to place in a biological context, a lack of reproducibility of GWAS results across studies and populations, and rare variants of small effect that might be involved in the heritability of disease phenotypes. Increasing the sample size of GWAS might improve the predictive power of such studies, although different study designs should also be considered.

Hybrid study designs that capitalize on familial segregation and high-throughput sequencing have identified several mutations in genes putatively associated with high myopia. Some of these genes are known to be involved in functional pathways implicated in refractive error development in humans (through GWAS) and experimental myopia in animals. Discrepancies between heritability estimates and the proportion of variance explained by known refractive error loci suggest that many (perhaps most) variants associated with refractive phenotypes remain to be discovered. These discoveries will likely be obtained through a combination of ever-larger GWAS, better computational and statistical tools for rare-variant discovery, and appropriate study designs for whole-genome or whole-exome sequencing data.

Acknowledgments

Funding source: C. Y. Cheng is supported by an award from the National Medical Research Council, Singapore (CSA/033/2012). R. Wojciechowski is supported by a Clinical Investigator Award (1K08EY022943), from the US National Eye Institute (NIH).

Dr Cheng has received support for travel to the 2nd International Conference of Pathologic Myopia, Kyoto, Japan, from Novartis Pharma K. K., Japan.

References

1. Hysi PG, Young TL, Mackey DA, et al. A genome-wide association study for myopia and refractive error identifies a susceptibility locus at 15q25. *Nature Genetics*. 2010; 42:902–905. [PubMed: 20835236]
2. Kiefer AK, Tung JY, Do CB, et al. Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. *PLoS genetics*. 2013; 9
3. Solouki AM, Verhoeven VJ, van Duijn CM, et al. A genome-wide association study identifies a susceptibility locus for refractive errors and myopia at 15q14. *Nature Genetics*. 2010; 42:897–901. [PubMed: 20835239]

4. Verhoeven VJ, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multi-ancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat Genet.* 2013; 45:314–318. [PubMed: 23396134]
5. Stambolian D, Wojciechowski R, Oexle K, et al. Meta-analysis of genome-wide association studies in five cohorts reveals common variants in RBFOX1, a regulator of tissue-specific splicing, associated with refractive error. *Human Molecular Genetics.* 2013; 22:2754–2764. [PubMed: 23474815]
6. Wojciechowski R, Congdon N, Bowie H, Munoz B, Gilbert D, West SK. Heritability of refractive error and familial aggregation of myopia in an elderly American population. *Investigative Ophthalmology & Visual Science.* 2005; 46:1588–1592. [PubMed: 15851555]
7. Dirani M, Chamberlain M, Shekar SN, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. *Investigative Ophthalmology & Visual Science.* 2006; 47:4756–4761. [PubMed: 17065484]
8. Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: the twin eye study. *Investigative Ophthalmology & Visual Science.* 2001; 42:1232–1236. [PubMed: 11328732]
9. Kim MH, Zhao D, Kim W, et al. Heritability of myopia and ocular biometrics in Koreans: the healthy twin study. *Investigative Ophthalmology & Visual Science.* 2013; 54:3644–3649. [PubMed: 23620424]
10. Peet JA, Cotch MF, Wojciechowski R, Bailey-Wilson JE, Stambolian D. Heritability and familial aggregation of refractive error in the Old Order Amish. *Investigative Ophthalmology & Visual Science.* 2007; 48:4002–4006. [PubMed: 17724179]
11. Teikari JM, Kaprio J, Koskenvuo M, O'Donnell J. Heritability of defects of far vision in young adults--a twin study. *Scand J Soc Med.* 1992; 20:73–78. [PubMed: 1496333]
12. Wojciechowski R, Hysi PG. Focusing in on the complex genetics of myopia. *PLoS Genet.* 2013; 9:e1003442. [PubMed: 23593034]
13. Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res.* 2005; 24:1–38. [PubMed: 15555525]
14. Wojciechowski R. Nature and nurture: the complex genetics of myopia and refractive error. *Clinical Genetics.* 2011; 79:301–320. [PubMed: 21155761]
15. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet.* 2012; 379:1739–1748. [PubMed: 22559900]
16. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet.* 2008; 9:356–369. [PubMed: 18398418]
17. Risch N, Merikangas K. The future of genetic studies of complex human diseases. *Science.* 1996; 273:1516–1517. [PubMed: 8801636]
18. Yoshikawa M, Yamashiro K, Miyake M, et al. Comprehensive replication of the relationship between myopia-related genes and refractive errors in a large Japanese cohort. *Investigative Ophthalmology & Visual Science.* 2014; 55:7343–7354. [PubMed: 25335978]
19. Ahmad ME, Dada R, Dada T, Kucheria K. 14q(22) deletion in a familial case of anophthalmia with polydactyly. *Am J Med Genet A.* 2003; 120A:117–122. [PubMed: 12794703]
20. Bakrania P, Efthymiou M, Klein JC, et al. Mutations in BMP4 cause eye, brain, and digit developmental anomalies: overlap between the BMP4 and hedgehog signaling pathways. *Am J Hum Genet.* 2008; 82:304–319. [PubMed: 18252212]
21. Gal A, Rau I, El Matri L, et al. Autosomal-recessive posterior microphthalmos is caused by mutations in PRSS56, a gene encoding a trypsin-like serine protease. *Am J Hum Genet.* 2011; 88:382–390. [PubMed: 21397065]
22. Morimura H, Saindelle-Ribeaudeau F, Berson EL, Dryja TP. Mutations in RGR, encoding a light-sensitive opsin homologue, in patients with retinitis pigmentosa. *Nat Genet.* 1999; 23:393–394. [PubMed: 10581022]
23. Henderson RH, Li Z, Abd El Aziz MM, et al. Biallelic mutation of protocadherin-21 (PCDH21) causes retinal degeneration in humans. *Mol Vis.* 2010; 16:46–52. [PubMed: 20087419]

24. Ostergaard E, Batbayli M, Duno M, Vilhelmsen K, Rosenberg T. Mutations in PCDH21 cause autosomal recessive cone-rod dystrophy. *J Med Genet.* 2010; 47:665–669. [PubMed: 20805371]
25. Ribelayga C, Cao Y, Mangel SC. The circadian clock in the retina controls rod-cone coupling. *Neuron.* 2008; 59:790–801. [PubMed: 18786362]
26. Bloomfield SA, Volgyi B. The diverse functional roles and regulation of neuronal gap junctions in the retina. *Nat Rev Neurosci.* 2009; 10:495–506. [PubMed: 19491906]
27. Guggenheim JA, Pong-Wong R, Haley CS, Gazzard G, Saw SM. Correlations in refractive errors between siblings in the Singapore Cohort Study of Risk factors for Myopia. *The British Journal Of Ophthalmology.* 2007; 91:781–784. [PubMed: 17135339]
28. Macgregor S, Cornes BK, Martin NG, Visscher PM. Bias, precision and heritability of self-reported and clinically measured height in Australian twins. *Human Genetics.* 2006; 120:571–580. [PubMed: 16933140]
29. Ronald FA. The Correlation between Relatives on the Supposition of Mendelian Inheritance. *Transactions of the Royal Society of Edinburgh.* 52 0400.
30. Wojciechowski R, Yee SS, Simpson CL, Bailey-Wilson JE, Stambolian D. Matrix metalloproteinases and educational attainment in refractive error: evidence of gene-environment interactions in the Age-Related Eye Disease Study. *Ophthalmology.* 2013; 120:298–305. [PubMed: 23098370]
31. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature.* 2009; 461:747–753. [PubMed: 19812666]
32. Yang J, Benyamin B, McEvoy BP, et al. Common SNPs explain a large proportion of the heritability for human height. *Nature Genetics.* 2010; 42:565–569. [PubMed: 20562875]
33. Fan Q, Wojciechowski R, Kamran Ikram M, et al. Education influences the association between genetic variants and refractive error: a meta-analysis of five Singapore studies. *Human Molecular Genetics.* 2014; 23:546–554. [PubMed: 24014484]
34. Tkatchenko AV, Tkatchenko TV, Guggenheim JA, et al. APLP2 Regulates Refractive Error and Myopia Development in Mice and Humans. *PLOS Genetics.* 2015; 11
35. Aschard H, Lutz S, Maus B, et al. Challenges and opportunities in genome-wide environmental interaction (GWEI) studies. *Human Genetics.* 2012; 131:1591–1613. [PubMed: 22760307]
36. Thomas D. Gene–environment-wide association studies: emerging approaches. *Nature Reviews Genetics.* 2010; 11:259–272.
37. Fan Q, Barathi VA, Cheng CY, et al. Genetic variants on chromosome 1q41 influence ocular axial length and high myopia. *PLoS Genet.* 2012; 8:e1002753. [PubMed: 22685421]
38. Cheng CY, Schache M, Ikram MK, et al. Nine loci for ocular axial length identified through genome-wide association studies, including shared loci with refractive error. *Am J Hum Genet.* 2013; 93:264–277. [PubMed: 24144296]
39. Berry V, Francis P, Kaushal S, Moore A, Bhattacharya S. Missense mutations in MIP underlie autosomal dominant 'polymorphic' and lamellar cataracts linked to 12q. *Nat Genet.* 2000; 25:15–17. [PubMed: 10802646]
40. Geyer DD, Spence MA, Johannes M, et al. Novel single-base deletional mutation in major intrinsic protein (MIP) in autosomal dominant cataract. *Am J Ophthalmol.* 2006; 141:761–763. [PubMed: 16564824]
41. Fuhrmann S. Wnt signaling in eye organogenesis. *Organogenesis.* 2008; 4:60–67. [PubMed: 19122781]
42. Wold KC. Hereditary myopia. *Archives of Ophthalmology (Chicago, Ill : 1929).* 1949; 42:225–237.
43. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. *Am J Hum Genet.* 1998; 63:109–119. [PubMed: 9634508]
44. Farbrother JE, Kirov G, Owen MJ, Guggenheim JA. Family aggregation of high myopia: estimation of the sibling recurrence risk ratio. *Investigative Ophthalmology & Visual Science.* 2004; 45:2873–2878. [PubMed: 15326097]
45. Nakanishi H, Yamada R, Gotoh N, et al. A genome-wide association analysis identified a novel susceptible locus for pathological myopia at 11q24.1. *PLoS Genetics.* 2009; 5

46. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015; 17:405–424. [PubMed: 25741868]
47. Shi Y, Li Y, Zhang D, et al. Exome sequencing identifies ZNF644 mutations in high myopia. *PLoS Genet*. 2011; 7:e1002084. [PubMed: 21695231]
48. Tran-Viet KN, St Germain E, Soler V, et al. Study of a US cohort supports the role of ZNF644 and high-grade myopia susceptibility. *Mol Vis*. 2012; 18:937–944. [PubMed: 22539872]
49. Zhao F, Wu J, Xue A, et al. Exome sequencing reveals CCDC111 mutation associated with high myopia. *Hum Genet*. 2013; 132:913–921. [PubMed: 23579484]
50. Stambolian D, Ibay G, Reider L, et al. Genomewide linkage scan for myopia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 22q12. *Am J Hum Genet*. 2004; 75:448–459. [PubMed: 15273935]
51. Klein AP, Duggal P, Lee KE, Klein R, Bailey-Wilson JE, Klein BE. Confirmation of linkage to ocular refraction on chromosome 22q and identification of a novel linkage region on 1q. *Arch Ophthalmol*. 2007; 125:80–85. [PubMed: 17210856]
52. Aldahmesh MA, Khan AO, Alkuraya H, et al. Mutations in LRPAP1 are associated with severe myopia in humans. *Am J Hum Genet*. 2013; 93:313–320. [PubMed: 23830514]
53. Guo H, Jin X, Zhu T, et al. SLC39A5 mutations interfering with the BMP/TGF-beta pathway in non-syndromic high myopia. *J Med Genet*. 2014; 51:518–525. [PubMed: 24891338]
54. Chen BY, Wang CY, Chen WY, Ma JX. Altered TGF-beta2 and bFGF expression in scleral desmocytes from an experimentally-induced myopia guinea pig model. *Graefes Arch Clin Exp Ophthalmol*. 2013; 251:1133–1144. [PubMed: 23381656]
55. Jobling AI, Wan R, Gentle A, Bui BV, McBrien NA. Retinal and choroidal TGF-beta in the tree shrew model of myopia: isoform expression, activation and effects on function. *Exp Eye Res*. 2009; 88:458–466. [PubMed: 19046968]
56. Hysi PG, Wojciechowski R, Rahi JS, Hammond CJ. Genome-wide association studies of refractive error and myopia, lessons learned, and implications for the future. *Investigative Ophthalmology & Visual Science*. 2014; 55:3344–3351. [PubMed: 24876304]

Summary statement

Here, we review the results of recent epidemiological and genome-wide association studies into the molecular pathways and genetics underlying ocular refraction and myopia, the prevalence of which is reaching epidemic proportions in East Asia. We examine the complex mixture of factors contributing to myopia and discuss strategies for future research.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Left panel: Effect sizes vs. minor allele frequencies (MAF) of identified genetic loci from the genome-wide association studies on refractive error,⁴ and age-at-onset of myopia,² conducted by the CREAM Consortium (red circles) and 23andMe (blue circles), respectively. Circle diameters are proportional to $-\log_{10}(p\text{-values})$. Data on effect sizes and minor allele frequencies were obtained from the most significant genetic marker at each locus. Top markers for LAMA2 and GJD2 loci are shown for both studies. Other locus names are omitted for clarity. The dashed red line represents the 80% power curve to detect genetic effects for a sample size of 40,000 in genome-wide association studies ($\alpha = 5 \times 10^{-8}$). Effect sizes between CREAM and 23andMe were scaled by regressing variants common to both studies. Right panel: Pictorial representation of variant frequencies vs. expected effect size (or disease penetrance). The blue-red gradients represent the expected effect-size and allele frequencies identified in GWAS: GWAS usually identify common variants of mild-to-moderate effect. Common variants of strong effect are rare because of purifying selection. The green-yellow gradient shows the expected effect/variant frequency combinations in the low-frequency allelic spectrum: rare variants of strong effect generally cause Mendelian disorders that are better suited for linkage analysis, whereas rare variants of small or intermediate effects are difficult to detect genetically because of a lack of statistical power of traditional analytical methods. The right panel was adapted from McCarthy et al.¹⁶ with permission from Nature Publishing Group.

Table 1

Loci for refractive error and myopia age-of-onset in CREAM⁴ and 23andMe² studies, respectively

Locus number	Study	Top SNP	Chr	Position (bp)	Nearest gene	Dist. to nearest gene (kb)	Location	CREAM p-value	23andMe p-value	Replicated
1	CREAM	rs1346720	1	207387766	C4BPA	69	DOWNSTREAM	6.31E-13		
1	CREAM	rs1652333	1	207470460	CD55	-24	UPSTREAM	1.14E-12		
2	23andMe	rs57718990	2	172662614	SLC25A12	0	INTRAGENIC		3.70E-08	
2	23andMe	rs17428076	2	172851936	HAT1	3	DOWNSTREAM		2.80E-09	
2	23andMe	rs6704590	2	172878554	METAP1D	0	INTRAGENIC		3.20E-09	
3	23andMe	rs17400325	2	178565913	PDE11A	0	INTRAGENIC		1.90E-09	
4	CREAM	rs2139026	2	233264910	ALPL2	-7	UPSTREAM	4.45E-08		†
4	23andMe	rs1550094	2	233385396	PRSS56	0	INTRAGENIC		1.30E-15	†
4	BOTH	rs733603	2	233387635	PRSS56	0	INTRAGENIC	7.75E-13	8.20E-11	**
4	BOTH	rs1881492	2	233406998	CHRNA1D	0	INTRAGENIC	5.15E-11	8.80E-09	**
4	23andMe	rs2573206	2	233408239	CHRNA1D	0	INTRAGENIC		2.20E-09	†
4	CREAM	rs1568830	2	233446725	EIF4E2	0	INTRAGENIC	1.90E-07		†
4	23andMe	rs7607107	2	233452344	EIF4E2	4	DOWNSTREAM		2.30E-09	†
5	CREAM	rs14165	3	53847408	CACNA1D	1	DOWNSTREAM	2.14E-08		
6	BOTH	rs6764769	3	141100280	ZBTB38	0	INTRAGENIC	9.25E-08	4.10E-08	**
6	23andMe	rs13091182	3	141133960	ZBTB38	0	INTRAGENIC		9.00E-10	†
7	CREAM	rs9307551	4	80530671	LINC00989	33	DOWNSTREAM	1.09E-08		†
7	23andMe	rs62297622	4	80563489	LINC00989	66	DOWNSTREAM		2.90E-07	†
8	23andMe	rs7692381	4	81903049	C4orf22	18	DOWNSTREAM		4.80E-08	†

Locus number	Study	Top SNP	Chr	Position (bp)	Nearest gene	Dist. to nearest gene (kb)	Location	CREAM p-value	23andMe p-value	Replicated
8	BOTH	rs7667446	4	81906024	C4orf22	21	DOWNSTREAM	9.43E-08	5.90E-07	*
8	23andMe	rs5022942	4	81959966	BMP3	0	INTRAGENIC		1.40E-10	*
9	BOTH	rs7744813	6	73643289	KCNQ5	0	INTRAGENIC	4.18E-09	6.60E-22	**
10	BOTH	rs12193446	6	129820038	LAMA2	0	INTRAGENIC	3.08E-12	1.38E-45	**
10	BOTH	rs12205363	6	129834629	LAMA2	0	INTRAGENIC	1.79E-12	4.60E-27	**
11	BOTH	rs7829127	8	40726394	ZMAT4	0	INTRAGENIC	3.69E-10	7.10E-16	**
11	BOTH	rs2137277	8	40734662	ZMAT4	0	INTRAGENIC	4.08E-09	4.70E-16	**
12	BOTH	rs3110155	8	60078114	TOX	46	DOWNSTREAM	2.33E-08	2.50E-12	**
12	23andMe	rs4531042	8	60088688	TOX	57	DOWNSTREAM		6.30E-16	*
13	CREAM	rs4237036	8	61701057	CHD7	0	INTRAGENIC	1.82E-08		
14	23andMe	rs7026057	9	71720024	FXN	5	DOWNSTREAM		3.10E-08	*
14	23andMe	rs11145261	9	71720422	FXN	5	DOWNSTREAM		3.10E-08	*
14	23andMe	rs62567093	9	71721719	FXN	7	DOWNSTREAM		3.10E-08	*
14	BOTH	rs11145465	9	71766593	TJP2	0	INTRAGENIC	7.26E-09	4.40E-10	*
14	BOTH	rs11145746	9	71834380	TJP2	0	INTRAGENIC	8.83E-08	2.30E-11	*
15	CREAM	rs7042950	9	77149837	RORB	0	INTRAGENIC	2.59E-08		
15	CREAM	rs7042950	9	77149837	MIR6130	0	INTRAGENIC	2.59E-08		
16	CREAM	rs7084402	10	60265404	BICC1	-7	UPSTREAM	2.06E-13		
16	BOTH	rs4245599	10	60365755	BICC1	0	INTRAGENIC	4.55E-10	6.90E-07	*
17	23andMe	rs6480859	10	79081948	KCNMA1	0	INTRAGENIC		1.20E-08	

Locus number	Study	Top SNP	Chr	Position (bp)	Nearest gene	Dist. to nearest gene (kb)	Location	CREAM p-value	23andMe p-value	Replicated
18	23andMe	rs3814213	10	85974236	CDHR1	0	INTRAGENIC		1.10E-09	
18	23andMe	rs745480	10	85986554	LRIT2	1	DOWNSTREAM		2.50E-10	
18	23andMe	rs11200931	10	85989879	LRIT1	-1	UPSTREAM		5.50E-10	
18	23andMe	rs1042454	10	86012713	RGR	0	INTRAGENIC		4.40E-09	
19	CREAM	rs10882165	10	94924324	CYP26A1	87	DOWNSTREAM	1.03E-11		
20	23andMe	rs1381566	11	40149607	LRRCC4C	0	INTRAGENIC		3.00E-26	
21	23andMe	rs2155413	11	84634790	DLG2	0	INTRAGENIC		4.70E-10	
22	CREAM	rs495498	11	105575774	GRIA4	0	INTRAGENIC	1.98E-10		
23	BOTH	rs3138144	12	56114769	BLOC1S1-RDH5	0	INTRAGENIC	4.44E-12	8.80E-10	**
23	BOTH	rs3138144	12	56114769	RDH5	0	INTRAGENIC	4.44E-12	8.80E-10	**
23	BOTH	rs3138142	12	56115585	BLOC1S1-RDH5	0	INTRAGENIC	6.99E-07	1.80E-20	*
23	BOTH	rs3138142	12	56115585	RDH5	0	INTRAGENIC	6.99E-07	1.80E-20	*
23	23andMe	rs35746357	12	56120096	CD63	0	INTRAGENIC		4.80E-11	†
24	CREAM	rs12229663	12	71249996	PTPRR	0	INTRAGENIC	5.47E-09		
25	23andMe	rs4291789	13	100672921	LINC00554	23	DOWNSTREAM		2.10E-08	†
25	CREAM	rs8000973	13	100691367	LINC00554	41	DOWNSTREAM	8.13E-08		†
25	23andMe	rs35266498	13	100705065	PCCA	-36	UPSTREAM		2.40E-08	†
25	CREAM	rs2184971	13	100818092	PCCA	0	INTRAGENIC	2.11E-08		†
26	23andMe	chr14:54413001	14	54413001	MIR5580	-2	UPSTREAM		1.70E-08	
26	23andMe	rs2738265	14	54422399	BMP4	0	INTRAGENIC		1.90E-08	
27	CREAM	rs1254319	14	60903757	C14orf39	0	INTRAGENIC	1.00E-08		

Locus number	Study	Top SNP	Chr	Position (bp)	Nearest gene	Dist. to nearest gene (kb)	Location	CREAM p-value	23andMe p-value	Replicated
27	CREAM	rs1018533	14	60971137	SIX6	-5	UPSTREAM	1.95E-08		
28	BOTH	rs524952	15	35005886	GJD2	-39	UPSTREAM	5.00E-16	5.60E-19	**
28	BOTH	rs636751	15	35012584	GJD2	-32	UPSTREAM	4.97E-18	5.90E-14	**
29	BOTH	rs4778879	15	79372875	RASGRF1	0	INTRAGENIC	4.25E-11	1.10E-10	**
29	23andMe	rs28412916	15	79378167	RASGRF1	0	INTRAGENIC		3.50E-11	†
30	BOTH	rs17648524	16	7459683	RBOF1	0	INTRAGENIC	5.64E-10	1.30E-22	**
31	BOTH	rs2908972	17	11407259	SHISA6	0	INTRAGENIC	9.28E-09	4.50E-13	**
31	BOTH	rs2969180	17	11407901	SHISA6	0	INTRAGENIC	7.29E-11	4.80E-08	**
32	CREAM	rs17183295	17	31078272	MYO1D	0	INTRAGENIC	9.66E-11		†
32	BOTH	rs10512441	17	31239645	TMEM98	-15	UPSTREAM	2.12E-10	7.70E-07	**
33	CREAM	rs235770	20	6761765	BMP2	1	DOWNSTREAM	1.57E-08		

Top SNP: Most highly significant marker at locus; Chr: Chromosome; Position Hg19; Position, in base pairs, on human reference genome Hg19 (GRCh37); Nearest gene: closest gene or pseudogene on human reference genome Hg19; Dist. to nearest gene: distance, in Kb, from top SNP to nearest gene. Negative numbers indicate that SNPs are upstream (5') of the gene, 0 indicates that the SNP is intragenic; Location: location of top SNP relative to the nearest gene; Locus number: individual locus obtained by separating SNPs with p-values of 1×10^{-5} or less in both studies by at least 100 kb. Loci are numbered from 1 to 33. CREAM p-value: p-value in CREAM data using all European and Asian populations combined; 23andMe p-value: p-value in 23andMe, adjusted for variance inflation; Replicated: indicates whether:

** the same SNP was genome-wide significant in both studies,

* one SNP was genome-wide significant in one study and $p < 1 \times 10^{-6}$ in the other, or

† the SNP was genome-wide significant in one study and the locus contained a different genome-wide significant SNP in the other study.

Table 2

Functional classes of genes influencing refractive error identified through genome-wide association studies

Functional classes	Genes [*]
Neurotransmission	<i>GJD2, RASGRF1, GRIA4</i>
Photoreceptor morphogenesis and retinoic acid metabolism	<i>CDHR1, CHRNG, CYP26A1, RDH5, RGR, RORB</i>
Ion channel activity	<i>KCNQ5, KCNJ2, KCNMA1, CACNA1D, RASGRF1</i>
Ocular and central nervous system development	<i>SIX6, CHD7, ZIC2, BICC1, LRRC4C, TMEM98, PRSS56</i>
Extracellular matrix development and remodeling	<i>BMP2, BMP3, BMP4, CD63, LAMA2</i>

^{*} Genes in close proximity to markers associated with refractive error.

Loci for inherited refractive errors and myopia (adapted from OMIM phenotypic series Myopia - PS160700; <http://www.omim.org/phenotypicSeries/PS160700>)

Table 3

Location	Phenotype mapping key*	Locus	Gene(s)	Gene/ Locus MIM number	Phenotype**	Trait presumed mode of transmission***	Reference
1p36	2	MYP14		610320	HM	QTL	Wojciechowski ⁴⁷
1p22.2	3	MYP21	<i>ZNF644</i>	614159	HM	AD	Shi ³⁷ ; Tran-Viet ³⁸
2q37.1	2	MYP12		609995	HM	AD	Paluru ⁴⁸
3q26	2	MYP8		609257	RE	QTL	Hammond ⁴⁹
4p16.3	3	MYP23	<i>LRPAP1</i> , <i>A2MRAP</i>	104225	HM	AR	Aldamesh ⁴² ; Jiang ⁵⁰
4q12	2	MYP9		609258	RE	QTL	Hammond ⁴⁹
4q22-q27	2	MYP11		609994	HM	AD	Zhang ⁵¹
4q35.1	3	MYP22	<i>CCDC111</i>	615421	HM	AD	Zhao ³⁹
5p15.33-p15.2	2	MYP16		612554	HM	AD	Lam ⁵²
5p15.1-p13.3	2	MYP19		613969	HM	AD	Ma ⁵³
7p15	2	MYP17		608367	RE	QTL	Cinert ⁵⁴
7q36	2	MYP4, [†]		608367	HM	MIXED	Naiglin ⁵⁵ ; Paget ⁵⁶
8p23	2	MYP10		609259	RE	QTL	Hammond ⁴⁹
10q21.1	2	MYP15		612717	HM	AD	Nallasamy ⁵⁷
11p13	2	MYP7		609256	RE	QTL	Hammond ⁴⁹
12q13.3	3	MYP24	<i>SLC39A5</i>	608730	HM	AD	Guo ⁴³
12q21-q23	2	MYP3		603221	HM	AD	Young ⁵⁸
13q12.12	2	MYP20		614166	HM	AD	Shi ⁵⁹
14q22.1-q24.2	2	MYP18		255500	HM	AR	Yang ⁶⁰
17q21-q22	2	MYP5		608474	HM	AD	Paluru ⁴⁸
18p11.31	2	MYP2		160700	HM	AD	Young ³³

Location	Phenotype mapping key*	Locus	Gene(s)	Gene/Locus MIM number	Phenotype**	Trait presumed mode of transmission***	Reference
22q13.33	3	MYP6	SCO2, CEMCOX1	604272	HM	AD	Tran-Viet ⁶¹ , Stambolian ⁴⁰
Xq23-q27.2	2	MYP13		300613	HM	XR	Zhang ⁶²
Xq28	2	MYP1		310460	Mixed	XR syndromic ^{††}	Haim ⁶³ , Young ⁶⁴ , Michaelides ⁶⁵

* Phenotype Mapping Key: 1 - the disorder is placed on the map because of its association with a gene, but the underlying defect is not known; 2 - the disorder was placed on the map by statistical methods; 3 - the molecular basis of the disorder is known; 4 - a contiguous gene duplication or deletion syndrome in which multiple genes are involved.

** Phenotype: HM – High Myopia; RE – Refractive Error; Mixed: Moderate to High myopia.

*** Trait presumed mode of transmission: AD – Autosomal Dominant; AR – Autosomal Recessive; XR – X-linked Recessive; MIXED – Variable transmission pattern; QTL – Quantitative Trait Locus.

[†]MYP4 is deprecated and has been combined with MYP17 by OMIM.

^{††}Syndromic myopia accompanied with cone dysfunction.