Special Issue

IMI—Myopia Genetics Report

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Purpose. The genetic landscape of myopia has advanced considerably since the previous International Myopia Institute genetics reports. This white paper provides an updated overview of current findings on myopia genetics and identifies priorities for future research.

Methods. We performed a comprehensive literature review covering genome-wide association studies (GWASs), rare variant analyses, functional genomics, and multi-omics approaches. Specific focus areas included common and high myopia, monogenic syndromes, and gene–environment interactions.

Results. Over 1000 common variants have now been associated with refractive error and myopia, implicating pathways in retinal signaling, extracellular matrix remodeling, and neurodevelopment. Whole-exome and whole-genome sequencing studies have uncovered rare variants in new candidate genes for high and syndromic myopia. Polygenic risk scores show improved predictive power when combined with environmental and demographic factors. A growing number of studies have explored gene–environment interactions, genetic pleiotropy, and causal inference using Mendelian randomization. These analyses support a role for educational attainment, screen time, physical activity, and metabolic or inflammatory biomarkers in refractive error development.

Conclusions. While a substantial portion of myopia heritability remains unexplained, future efforts should prioritize integrative approaches combining genetic, functional, and multiomics data across diverse populations. This will be essential for advancing personalized risk prediction, our understanding of gene–environment interplay, and identifying individuals most likely to benefit from targeted prevention or treatment strategies.

Keywords: myopia, refractive error, genetics, GxE, omics

Since the publication of the first International Myopia Institute (IMI) Genetics Report in 2019[1] and Genetics Update in the 2021 IMI Yearly Digest,[2] our knowledge in the genetic architecture of myopia has progressed substantially. The 2019 Genetics Report described the high heritability of refractive error, the discovery of common risk loci for myopia through large-scale genome-wide association studies (GWASs), and how studies of rare monogenic syndromes offered valuable insights into the biological pathways underlying myopization. The 2021 Yearly Digest highlighted early advances in functional interpretation, including initial uses of polygenic risk scores and emerging insights from epigenetic studies. In this Genetics update, a comprehensive overview of developments across the spectrum of genetic research is presented. Key topics, including large-scale GWASs of myopia, comprehensive rare variant analyses using whole-exome and whole-genome sequencing in patients and families with extreme phenotypes, in-

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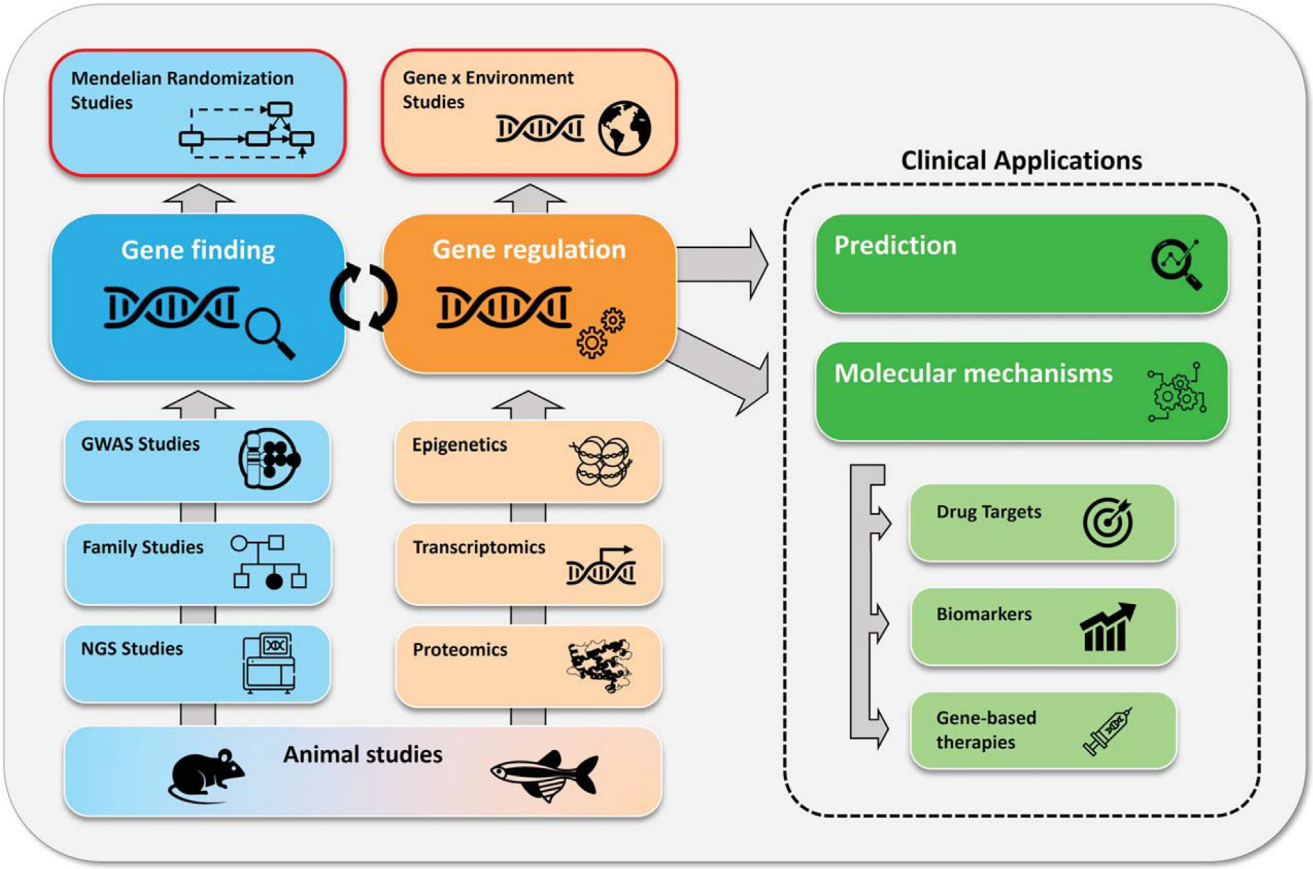

Figure. Overview of the current and ongoing myopia related human genetic research.

depth Mendelian randomization studies to establish causal links with lifestyle and systemic traits, and advanced multi-omics approaches encompassing DNA and RNA methylation, regulatory RNAs, and proteomic profiling, are covered. Although polygenic risk scores have not yet reached clinical applicability, they have drawn substantial attention as research tools. Similarly, the number of Mendelian randomization studies has grown significantly. A shift toward gene–environment interaction and omics approaches, such as transcriptomics, has also become evident. The Figure depicts an overview of the current and ongoing myopia-related human genetic research. We identified relevant papers published between February 2020 and May 2025, from a comprehensive PubMed search using MeSH terms: for example, "Myopia/genetics," "Myopia" AND "Genome Wide Association Study" or ("Myopia" OR "Spherical Equivalent" OR "Refraction") AND "Mendelian Randomization Analysis" or "Myopia" AND "epigenetics" or "Myopia" AND "transcriptomics" or "Myopia" AND "proteomics." The most significant findings and a detailed evaluation of their implications for the field are discussed.

Gene Finding

Genome-Wide Association Studies

GWASs are a powerful tool for analyzing genetic variations across the genome, typically focusing on common variants to identify those associated with specific traits or diseases. Since the 2010s, a substantial number of GWASs focusing primarily on myopia, refractive error, and eye biometry as a quantitative trait have been published.[2] It should be noted that despite the large number of associated loci identified to date, most of these loci currently lack functional validation. In recent years, two large-scale GWASs have further advanced the field.[3,4] Jiang et al.[3] conducted a large multiethnic GWAS of axial length in 19,420 individuals from the Genetic Epidemiology Research on Adult Health and Aging cohort, including participants of European, Latino, Asian, and African ancestry. Their study identified 16 genetic loci associated with axial length at genome-wide significance, including 5 novel loci, revealing potential candidate genes *SLC25A12*, *BMP3*, *RGR*, *RBFOX1*, and *MYO5B*. Two loci were available for replication in the Consortium for Refractive Error and Myopia (CREAM) data set, of which one (rs1353386 near *BMP3*) was successfully replicated. All axial length loci were also significantly associated with refractive error in the same cohort, and genetic correlation analyses revealed substantial shared heritability between axial length and myopia ($rg = 0.80$). Gene and pathway analyses further implicated mechanisms related to extracellular matrix remodeling, the visual cycle, and neuronal development, highlighting axial length as a robust endophenotype for myopia gene discovery.

Patasova et al.[4] conducted a GWAS on age of first spectacle wear (AFSW) in the UK Biobank (derivation cohort $N = 340$ K, replication cohort $N = 43$ K). This study

reinforced AFSW as a robust proxy for myopic refractive error—a concept introduced earlier by 23 and Me,[5] a direct-to-consumer company that also served as a replication for this study—further strengthening the link between specific genetic variants and age of myopia onset. Through a time-to-event analysis, the study identified 44 independent genomic loci associated with AFSW, including 6 novel loci. Among these, four loci, including the genes *NEGR1*, *TRIB2*, *TBC1D5*, and *ADAM11*, were replicated. These genes are predominantly expressed in the central nervous system and are implicated in neuronal development, cellular adhesion, signaling, and tissue remodeling.[4]

Among GWASs on refractive error, the meta-analysis by Hysi et al.[6] remains the largest up to now, with over half a million European participants. These authors found that a total of 890 genetic variants explained 12.1% of the variance of spherical equivalence and 18.4% of its heritability. Beyond single-nucleotide polymorphism (SNP) heritability, other factors such as rare variants, nonadditive genetic effects, and gene–environment interactions are likely to contribute to the overall heritability. However, it is unrealistic to expect GWASs to fully account for the 60% to 90% heritability estimated by twin studies, as these rely on different methodologies and assumptions.[7]

Regarding GWASs on eye biometry, two large studies were carried out on corneal curvature in the UK Biobank[8] and CREAM.[9] The authors evaluated the interplay between corneal curvature, axial length, and refractive error and identified a group of "eye-size" genes that appear to regulate corneal curvature as well as axial length in order to maintain emmetropia, along with another group of genes that affect refractive error primarily through corneal curvature and not axial length. Interestingly, SNPs associated with normal eye enlargement differed from those linked to myopization driven by axial length growth.[8] Furthermore, Fuse et al.[10] conducted a large GWAS of axial length in more than 33,000 Japanese individuals from the Tohoku Medical Megabank, identifying 31 loci, of which 7 were novel, while confirming known loci such as *GJD2*, *WNT7B*, and *PRSS56*. These findings emphasize both shared and ancestry-specific genetic contributions to eye growth.

In recent years, there has been a shift toward GWAS using an extreme phenotype design. There has been recognition that some children have very early-onset myopia or early childhood high myopia that may be primarily genetic rather than environmental in origin. Several GWASs on relatively large case-control studies on (very) high myopia have been conducted in Asian populations. Most of these studies identified a number of novel loci. Among the striking findings was the much higher frequency of risk alleles in East Asians versus Europeans; in addition, evidence supports the functionality of the newly associated *PDE4B* gene on scleral *COL1A1* expression and the identification of *LILRB2* as a novel susceptibility gene for pathological myopia, linking it mechanistically to lipid accumulation and choroidal dysfunction through the ERK–P38–JNK pathway.[11–16]

Several studies have focused on individual genes or loci identified in previous GWASs, often uncovering more detailed evidence supporting their associations with myopia.[17–26] Among these, many have replicated the association with the gap junction gene *GJD2*, one of the earliest genes linked to common myopia. Functional follow-up studies in mice and zebrafish models provided evidence for a role of *GJD2* in myopia development. Transcriptome data revealed that *GJD2* was most strongly expressed in cone photoreceptors, and electrophysiology studies in humans demonstrated altered electrical responses in cone-driven OFF pathways in persons with the risk allele.[27–30]

Rare Variants and Monogenic Myopia

Studies using exome array, whole-exome sequencing (WES), and whole-genome sequencing (WGS) have provided further insights into rare variants associated with myopia. Exome arrays target known variants in the exome for cost-effective genotyping, WES sequences the entire exome to capture all coding variants, and WGS sequences the full genome for the most comprehensive analysis, including both coding and noncoding regions. An exome array study from the CREAM consortium ($N = 27$K) revealed 129 unique genes associated with refractive error, including novel candidates such as the retina-expressed gene *PDCD6IP*, the circadian rhythm gene *PER3*, and the eye morphology gene *P4HTM*.[31] Patasova et al.[32] analyzed whole-exome sequencing data from nearly 51,000 UK Biobank participants and identified rare variants in *SIX6* and *CRX* significantly associated with refractive error, highlighting genes crucial for retinal and optic disc development. Simpson et al.[33] combined exome array and linkage analysis in African American families with mild myopia (average spherical equivalent −2.78 D) and were the first to identify a myopia-associated locus in this ethnicity. The candidate gene *PDE1C* within the significant linkage peak on chromosome 7 showed higher expression in retina than in blood and has been associated with retinal development in animal studies. A study by Lu et al.[34] was the first to utilize WGS data to perform a genome-wide SNP analysis in 350 individuals with an average axial length of 29.24 mm. The study identified four SNPs significantly associated with axial length. Among these, an intronic SNP was located in *ADAMTS16*, and an intergenic SNP was found near the *PIGZ* gene. Notably, both genes were significantly upregulated in the neural retina of form-deprived myopic mice, with *PIGZ* showing predominant expression in the ganglion cell layer. Interestingly, *ADAMTS* proteins are known to play a role in extracellular matrix remodeling, and other *ADAMTS* genes have been implicated in myopic complications.

Over the past years, many rare variants have been identified in genes associated with monogenic (e.g., ocular or syndromic) disorders presenting with childhood high myopia. Using WES, these have been found in genes for retinal disorders, specifically for congenital stationary night blindness (*TRPM1*, *CACNA1F*, *NYX*[35]), Bornholm eye disease (*OPN1LW/OPN1MW*[35,36]), and cone phototransduction (*ARR3*[37–41]); connective tissue diseases such as Marfan (*FBN1*), Stickler (*COL2A1*), and Knobloch syndromes (*COL18A1*[35]); and eye development (*PAX639*). The diagnostic yield of genetic testing for high myopia through WES, particularly when using gene panels for known ocular disorders, typically ranges from 12% to 23%.[32,35,42–44] This variability is influenced by factors such as the composition of the gene panels and the criteria for selecting patients. The relatively high frequency of variants identified in genes associated with retinal disorders or syndromes underscores the value of comprehensive genetic testing in high myopia, even when it presents as the only symptom. Such testing is crucial for uncovering possible related condi-

tions, which will guide management strategies and genetic counseling.[45]

Identification of Novel Risk Genes for High Myopia

A recent large-scale WES on adult patients with myopia ≤−10 D ($N = 449$) identified three deleterious variants in *KDELR3*, a gene involved in intracellular protein trafficking and protein folding within the endoplasmic reticulum. The authors found that *KDELR3* was particularly expressed in ocular fibroblasts, and functional studies in cell lines and zebrafish provided evidence that this gene affects the regulation of various collagen genes. This links the gene to scleral extracellular matrix organization.[44] The largest exome-wide study in high myopia to date (≤−6 D; $N = 9613$ cases) revealed rare variants in the promoter region of *FKBP5* in East Asians, while a rare missense variant in *FOLH1* was found only in Europeans.[46] *FKBP5* has multifunctional roles, including modulation of the glucocorticoid receptor and interaction with NF-κB and TGF-β pathways; *FOLH1* is known to regulate glutamate. In the first WGS study on extreme high myopia (≤−10 D; $N = 159$)—more challenging due to the vast number of variants—participants were selected based on low polygenic risk scores that did not explain the phenotype.[47] Besides risk variants in known ocular genes, cases carried a higher frequency of rare variants in the novel genes *HS6ST1*, *RBM20*, and *MAP7D1*, genes involved in Wnt signaling, melatonin degradation, and ocular development, respectively. Additionally, several WES family studies have identified the *AGRN43*, *FLRT3*, and *SLC35E2B45* genes as potentially new candidate genes for myopia.[48–53] These genes warrant further validation and functional evaluation to fully establish their significance for high myopia. More recently, Liu et al.[54] conducted a large-scale, sex-stratified whole-exome sequencing study in over 8000 Han Chinese individuals with high myopia. Their findings revealed significant genetic heterogeneity between males and females, with *CHRNB1* emerging as a male-specific gene associated with high myopia. Functional studies showed that *CHRNB1* deficiency disrupted mitochondrial organization specifically in male-derived cells, suggesting sex-specific pathogenic mechanisms. This study underscores the value of incorporating sex-aware analysis and rare variant testing to uncover hidden genetic architecture in high myopia.

Polygenic Risk Scores

Polygenic risk scores (PRSs) estimate an individual's genetic predisposition to a trait or disease by summing the effects of multiple genetic variants across the genome, weighted by their effect sizes. Studies have used different numbers of SNPs for calculating PRSs. One study included only a small subset,[55] while others incorporated large numbers of SNPs identified through GWAS meta-analyses.[56–60] Although the PRS for myopia reached an area under the curve (AUC) of 0.75 to 0.80, cycloplegic autorefraction remains a stronger predictor of myopia risk (AUC 0.87).[57] However, when the PRS was combined with ancestry, environmental factors such as educational attainment, and interaction terms, the AUC increased to 0.84.[58]

Two studies explored the use of the PRS for predicting myopic macular degeneration (MMD) but had discrepant results.[58,59] Further replication is needed to determine whether the PRS for refractive error can reliably predict MMD in clinical practice. Tideman et al.[61] investigated the shared genetic susceptibility between high and low myopia, emmetropia, and hyperopia in Europeans and Asians and compared a European GWAS-based PRS between these refractive error categories. Results provided evidence that highly myopic individuals inherit a higher number of variants from the same set of myopia-predisposing alleles compared to individuals with less or nonmyopic refractive errors. Cross-ancestry similarities provide further support that genetic differences are unlikely to explain the higher prevalence of myopia in East Asia compared with Europe.

Gene–Environment Interactions, Mendelian Randomization, and Genetic Pleiotropy

Many studies have sought to elucidate the complex interplay between genetic and environmental factors contributing to the development of myopia. In addition to the well-established protective association of time spent outdoors with myopia, a large study in the UK Biobank analyzed genetic and environmental interactions and found evidence for a genotype-by-education interaction for variants located near *GJD2*, *RBFOX1*, *LAMA2*, *KCNQ5*, and *LRRC4C*.[62]

Environmental influences may be determined by parental risk alleles associated with the environmental exposure—a phenomenon called genetic nurture. In this light, Guggenheim et al.[63] investigated the genetic contribution to educational attainment and refractive error using SNP heritability estimates from GWAS-based polygenic risk scores. The authors found no evidence for genetic nurture and concluded that the genetic contribution to refractive error occurs mainly through direct parent-to-child transmission of refractive error risk alleles, not by genetic variants associated with education.

Mendelian randomization has offered researchers a powerful technique to assess causal relationships between exposures and outcomes using genetic variants as instrumental variables. In myopia research, Mendelian randomization has helped establish causal relationships between education and lifestyle factors. These insights can be used for public health interventions targeting the exposure, for personalized approaches to myopia prevention, and for patient risk stratification. A substantial number of studies have been published on Mendelian randomization (MR) in relation to myopia. Below, we highlight the most relevant findings published in recent years.[64–85]

Using MR, Zhang et al.[84] provided evidence for a causal link between computer use and increased myopia risk, whereas moderate-to-vigorous physical activity and television viewing were causally associated with a lower risk of developing myopia.

Clark et al.[67] and Hartmann et al.[69] confirmed the well-known association between education and myopic refractive error. They also reported that this association is partially mediated by time spent outdoors. Wei et al.[80] found alcohol to be causally related to myopia, which may be harder to interpret, as children, particularly at young ages, will have no or low exposure to this factor. It should be noted that MR studies of behavioral exposures such as computer use and alcohol intake may not fully satisfy the underlying assumptions of MR, since the genetic instruments may

reflect broader determinants such as socioeconomic status or personality traits. Findings from these studies should therefore be interpreted with greater caution than MR analyses of biologically defined exposures. Li et al.[73] investigated causality for glycemia and found higher HbA1c levels to be significantly associated with a greater risk of myopia. Xue et al.[83] suggested a protective effect of omega-3 and docosahexaenoic acid on myopia, potentially through the modulation of choroidal blood perfusion. Another metabolomics-based study by Jiang et al.[71] linked higher levels of specific plasma metabolites—such as 4-vinylphenol sulfate and N6-methyllysine—with increased myopia risk.

Inflammatory biomarkers have also been reported to play a role in the complex and multifactorial processes of ocular growth and refractive development. Elevated levels of VEGF-A, CD6, MCP-2, IL-2, and IL-2ra have been causally related to a higher myopic refractive error, whereas increased levels of TNF-like weak inducer of apoptosis have been related to a lower myopic refractive error.[72,74] Yet, Xu et al.[85] demonstrated in a bidirectional MR study that higher circulating IL-1RA and IL-2 levels were causally associated with a decreased risk of myopic refractive error. Lv et al.[77] extended these findings regarding inflammatory biomarkers by also linking gut microbiota, blood metabolites, and immune cells to myopia. The authors identified specific gut microbial genera (e.g., *Eubacterium fissicatena*) and immune-related biomarkers such as IL-12p70, which are causally implicated in myopia pathogenesis, whereas Hui et al.[70] reported that several bacterial taxa affect myopia risk through mediation by circulating lipid metabolites. Notably, metabolites such as albumin, omega-6 fatty acids, and cholesterol esters were shown to partly mediate the effects of gut microbiota on both common and pathological myopia, suggesting possible novel targets for intervention. Qin et al.[79] further reported six putative genetically causal targets for myopia treatment (*CD34*, *CD55*, *Wnt3*, *LCAT*, *BTN3A1*, and *TSSK6*). Their analysis not only clarified underlying biological pathways, such as Wnt signaling and lipid metabolism, but also predicted candidate compounds through molecular docking.

Using myopia as an exposure, several studies have identified a causal association and shared genetic basis between myopic refractive error and primary open-angle glaucoma,[65,66] as well as vitreous disorders.[81] Additionally, a lower birth weight within the normal range has been associated with a modest increased risk of developing myopia,[78] with the risk of myopia increasing by approximately 30% for each standard deviation increase in preterm birth.[75]

Xue et al.[86] used GWASs in the UK Biobank to investigate the genetic etiology underlying five common ocular conditions: age-related macular degeneration, diabetic retinopathy, glaucoma, retinal detachment, and myopia. The authors identified three pleiotropic loci significantly associated with all five conditions and confirmed the presence of shared genetic variants between myopia and retinal detachment.

Epigenetics

Epigenetics refers to changes in gene expression and function that do not alter the DNA sequence variation itself but that impact the production of proteins that control biological processes. Key epigenetic mechanisms include DNA and RNA methylation, histone modification, and noncoding RNA regulation.[87–91] Epigenetic modifications can be influenced by development and environmental exposures, making them relevant to study in myopia.

DNA and RNA Methylation

While methylation at both the DNA and the RNA level influences gene expression, there are some differences. DNA methylation typically represses gene transcription, and RNA methylation is more complex as it alters regulation by affecting RNA stability and mRNA translation. With respect to the study of DNA methylation in myopia, Swierkowska et al.[92] analyzed genome-wide methylation patterns in highly myopic Polish children and controls and identified altered DNA methylation levels at 55 CG dinucleotides, 14 of which were located in 5′UTRs or transcription start sites. The largest difference in the decrease of DNA methylation was found in the *PCDHA* gene cluster at the 5q31 myopia-associated locus. In a subsequent study, the authors evaluated methylation of genes encoding microRNAs (miRNAs) in the same study population.[93] Increased methylation levels were identified in promoter regions of *MIR3621*, *MIR34C*, and *MIR423*; decreased levels were noted in promoter regions of *MIR1178*, *MIRLET7A2*, *MIR885*, *MIR548I3*, *MIR6854*, *MIR675*, *MIRLET7C*, and *MIR99A*. The target genes of these miRNAs were found to be enriched in several key pathways, such as axon guidance, focal adhesion, TGF-β signaling pathway, insulin, and MAPK and EGF pathways.

Regarding RNA methylation, a case-control study was performed on m^6A methylation, the most common form of RNA methylation in mRNA in eukaryotic cells, in the anterior capsule of the lens collected after cataract extraction in high myopia patients and controls.[94] More than 2000 hypermethylated and >900 hypomethylated peaks were identified. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the genes relating to the altered methylation revealed biological processes, such as anatomical morphogenesis, extracellular matrix formation, regulation of ion transport, plasma membranes, and ion channel activity. Based on conjoint analysis of differentially expressed genes and differentially methylated genes, the higher the transcription expression, the higher the methylation ratio. The authors speculate that m^6A methylation may regulate the composition of the extracellular matrix by influencing protein synthesis, thereby contributing to the altered eye anatomy observed in myopia.

Regulatory Elements and Noncoding RNAs

Regulatory elements are specific sequences of DNA that control the expression of genes, determining when, where, and how much a gene is transcribed, and include promoters, enhancers, silencers, and insulators. Noncoding RNAs are RNA molecules that are transcribed from DNA but are not translated into proteins. Among others, regulatory noncoding RNAs include miRNA and long noncoding RNA (lncRNA). Several studies have investigated genetic associations with these regulators in myopia and refractive error. Tedja et al.[95] performed a comprehensive genome-wide scan into the association between enhancers, miRNAs, miRNA binding sites, and lncRNAs and refractive error and myopia; results of this study will be discussed per regulator.

Enhancer Regions

A study performed in a large high-myopia case-control study of Han Chinese participants investigated common variants in the known refractive error gene *KCNQ5*.[96] A protective

association was found with two intronic genetic variants (rs7744813 and rs9342979) located within a region enriched for enhancer-specific histone modifications (H3K4me1 and H3K27ac). Using VISTA Enhancer Browser and FANTOM5, the large-scale study mentioned above found 18 to 25 significantly associated genetic variants in enhancer regions, and most genes flanking these regions were expressed in peripheral retinal cell types. Seven of these genes showed cell-type specificity, for instance, for fibroblasts, melanocytes, or amacrine cells. A genetic risk score (GRS) based on variants in enhancers tested in an independent children cohort showed a significant association with axial length–related parameters and refractive error.

MicroRNAs

One of the most researched miRNAs in association with myopia is hsa-miR-328. Kunceviciene et al.[97] investigated the expression of miRNA hsa-miR-328 in peripheral blood and its predicted target gene *PAX6* in a myopia case-control study. Although both were significantly associated with myopia, they were not significantly associated with each other. In a subsequent study, these authors found that increased expression of hsa-miR-328-3p resulted in a significant decrease of retinal pigment epithelium optical density in myopic individuals.[98]

Tedja et al.[95] identified two genetic variants in miRNA genes and 54 highly confident miRNA-binding sites in the aforementioned GWAS. The GRS of these miRNA-related variants and binding sites did not associate with axial length or axial length/corneal radius. To guide future research, the authors prioritized findings for functional validation using an extensive biological plausibility scoring system. Pathways of target and host genes of highly ranked variants included eye development (*BMP4*, *MPPED2*), neurogenesis (*DDIT4*, *NTM*), extracellular matrix (*ANTXR2*, *BMP3*), photoreceptor metabolism (*DNAJB12*), photoreceptor morphogenesis (*CHDR1*), neural signaling (*VIPR2*), and TGF-β signaling (*ANAPC16*).

Long NonCoding RNAs

As miRNAs, lncRNAs play a significant role in gene regulation. However, lncRNAs can act at multiple layers and can bind to proteins and DNA as well as RNA. LncRNAs can act as a skeleton frame unit to recruit transcription factors and participate in complex regulatory mechanisms. Wang et al.[99] investigated the coregulation of 13 myopia-related transcription factors and lncRNA transcripts (*EGR1*, *FOS*, *FOXO1*, *HOXA9*, *NR3C1*, *PAX6*, *PBX1*, *SRF*, *STAT2*, *STAT3*, *TFAP2A*, *TGIF1*, and *ZIC2*) selected from the literature. They found that transcription factor binding site regions of myopia-related lncRNA transcripts were disturbed, altering structural accessibility and affecting molecular binding force.

Tedja et al.[95] found 417 significant genetic variants from the GWAS residing in 245 lncRNA regions, of which 7 were top SNPs of their associated loci in the GWAS. Contrary to GRS of miRNA-related variants, the GRS of these lncRNA SNPs showed a significant association with axial length in the independent children cohort.

Extrachromosomal Circular DNA

Extrachromosomal DNA (ecDNA) is DNA that exists outside chromosomes in a cell, either the nucleus or the cytoplasm. The DNA is often circular in form, and the normal function is related to mitochondrial activity or viral replication. ecDNA can contain multiple copies of chromosomal genes but lacks their chromosomal gene regulation, making it susceptible to uncontrolled expression. Initial steps have been taken to unravel the role of extrachromosomal circular DNA (eccDNA) in myopia. Wen et al.[100] investigated eccDNA expression in the anterior lens capsule of six patients with high myopia and six patients with simple nuclear cataract undergoing cataract extraction and found increased levels of eccDNA of the myopia-related genes *CTNND2*, *UHRF1BP1L*, *LAMA3*, and *ZNF776* in the high myopes.

Transcriptomics

Transcriptomics involves the investigation of RNA transcripts to provide insight into gene expression and regulatory mechanisms. A genome-wide approach had been performed only in mice,[101] but publications on human transcriptomics in myopia have emerged.

A single-cell RNA sequencing study on eight postmortem retinas from four individuals without eye diseases investigated chromatin accessibility in retinal cells to decipher the role of noncoding risk variants associated with various ocular diseases, including myopia.[102] All genetic variants were derived from previously published GWASs up to 2020. A notable finding was that rs2730260 was found in a chromatin-accessible region in Müller glia, and variation at this SNP significantly correlated with the expression of *VIPR2*. This gene has many different functions, but one related to Müller cells may be regulating the release of glutamate and GABA, neurotransmitters that have been associated with myopia. Another noteworthy myopia-related noncoding SNP was rs1532278, which resides in an intron of the *CLU* gene encoding clusterin, a protein involved in stress responses, cell survival, and extracellular matrix regulation. Expression quantitative trait locus (eQTL) data confirmed that this SNP regulates *CLU*, and models predicted that variation at this SNP alters chromatin accessibility in, again, Müller cells. Ni et al.[103] investigated RNA sequencing data of the cornea epithelium from myopia and control subjects. Remarkably, among the differentially expressed genes in myopia, those significantly enriched in immune-related pathways stood out. Contact lens wear was not considered in this study.

Zhu et al.[104] compared lens biometry between high myopes and emmetropes on magnetic resonance imaging and verified that the former had larger equatorial lens diameter but not increased lens thickness. Analyses of RNA transcripts revealed that increased lens size was associated with upregulation of β/γ-crystallin expression. Using mouse models, the authors subsequently found evidence that the transcription factor MAF plays an essential role in upregulating β/γ-crystallins in the lens of high myopes by direct activation of the crystallin gene promoters and by indirect activation of TGF–β1–Smad signaling.

Exosomal RNAs are small regulatory RNA molecules encapsulated in exosomes and released into the extracellular space to mediate intercellular communication. You et al.[105] investigated differential expression of exosomal miRNA in vitreous humor, comparing highly myopic patients to controls, and found that miR-143-3p and miR-145-5p, miRNAs related to the insulin resistance pathway, were downregulated in participants with signs of myopic macular degeneration.

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Circular RNAs are stable, closed-loop RNAs that can act as miRNA sponges, transcriptional regulators, and scaffolds for protein complexes. Zhang et al.[106] compared the expression of circular RNA in vitreous humor from highly myopic patients undergoing surgery for epiretinal membrane or macular hole with that of emmetropic patients undergoing the same surgery for the same indication. The authors found hundreds of mRNAs and circular RNAs differentially expressed. KEGG pathway analysis showed that target genes of circular RNAs were enriched in the mTOR, insulin, cAMP, and VEGF signaling pathways, and GO analysis indicated that they mainly target transcription, cytoplasm, and protein binding.

Proteomics

The easily accessible anterior segment of the eye has been utilized to study proteomics in myopia. Yu et al.[107] sampled corneal stromal lenticules of high and low myopes after refractive surgery and conducted proteomics analysis using label-free quantitative mass spectrometry. With machine learning models, the authors found 17 proteins associated with high myopia, of which complement C5, *COL1A1*, and *CDH11* were most prominent. Expression analyses using Western blot and quantitative real-time PCR provided evidence for decreased expression of *COL1A1*, the most abundant collagen in cornea, and increased expression of cadherin-11 (*CDH11*), a calcium-dependent cell adhesion protein that is related to fibrosis, stromal remodeling, and immune activation. Whether these altered protein expression levels also play a remodeling role in the sclera at the back of the eye remains to be elucidated.

Conclusions

Since the last update on myopia genetics in IMI Digest 2021, numerous studies have advanced our understanding of genetic factors influencing the development of refractive error and myopia. While identification of novel genes through GWASs appears to have reached a plateau, GWAS meta-analyses in diverse populations remain valuable for exploring ancestry-specific genetic risk variants. As the field moves forward, the focus of myopia genetics will be shifting from gene discovery to functional implications and clinical applications. Key areas of interest include genetic contributions to treatment responses and gene–environment interaction analyses. Achieving these goals will require large, diverse data sets, for which international collaborations and consortia will be instrumental. The versatility and application of Mendelian randomization studies continue to expand, which helps to establish causality in risk profiles for myopia. This will guide the development of targeted interventions and personalized prevention strategies. Future research should determine the levels of genetic load or specific genetic predispositions at which individuals are most likely to benefit from targeted therapies. Epigenetic features are characterized by spatiotemporal and tissue-specific effects, which have posed significant challenges for research. Nevertheless, the number of epigenetic studies on myopia is steadily increasing, indicating that mechanisms such as DNA methylation, histone modifications, and noncoding RNA regulation play a large role in the pathophysiology of myopia. How epigenetic features relate to environmental stimuli and mediate their effect at the molecular level is a next research step to be taken. Finally, a systems biology approach integrating data from multiple levels, including genomic, transcriptomic, proteomic, epidemiologic, and animal studies, will be needed to tackle the complexity of myopia more effectively, ultimately improving prevention, prognosis, and treatment strategies.

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