The Genetics of Myopia

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Key Points

- While the recent global rise of myopia prevalence is primarily attributable to environmental changes, within populations inherited factors play a large role in explaining why some individuals are affected by myopia while others are not.
- Early efforts to identify the specific genes underlying the heritability of refractive error used linkage and candidate gene designs to identify up to 50 loci and genes, although most remain unconfirmed.

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- As the sample size in genome-wide association studies (GWAS) has increased, the number of implicated loci has risen steadily, with 161 variants reported in the latest meta-analysis.
- Interrogation of loci uncovered by GWAS offers insight into the molecular basis of myopia—for example, pathway analysis implicates the light induced retina-to-sclera signaling pathway in myopia development.
- Although many loci have been uncovered by GWAS, statistical modelling shows there are many more genes to find—identifying these will further illuminate the molecular pathways leading to myopia and open up new avenues for intervention.

5.1 Introduction

This chapter addresses the scientific exploration of the genetic architecture of myopia. Myopia is the most common eye condition worldwide and its prevalence is increasing. Changes in environmental conditions where time spent outdoors has reduced relative to previous generations are the main hypothesized culprit. Despite these environmental trends, within populations, myopia is highly heritable; genes explain up to 80% of the variance in refractive error. Initial attempts to identify myopia genes relied on family studies using linkage analysis or candidate gene approaches with limited progress. For the last decade, genome-wide association study (GWAS) approaches have predominated, ultimately resulting in the identification of hundreds of genes for refractive error and myopia, providing new insights into its molecular machinery. Thanks to these studies, it was revealed that myopia is a complex trait, with many genetic variants of small effect influencing retinal signaling, eye growth and the normal process of emmetropization. However, the genetic architecture and its molecular mechanisms are still to be clarified and while genetic risk score prediction models are improving, this knowledge must be expanded to have impact on clinical practice.

Some sections of this report follow the framework described in a recent International Myopia Institute Genetics report by Tedja et al. [1]

5.2 Heritability

The tendency for myopia to run in families has long been noted, suggesting genetic factors play a role in determining risk [2]. While family studies show familial aggregation, twin studies are required to reliably separate the effects of genes and familial environment [3–6]. Benchmarking of the relative contribution of genetics and environment is done by computation of heritability, the proportion of the total trait variance (here, spherical equivalent) due to additive genetic factors. Since the contributions of genes and environment can vary across human populations, heritabilities are population and

even time specific [7, 8]. The influence of environmental variance is well illustrated in the case of the heritability study in Alaskan Eskimos, where the rapid introduction of the American school system dramatically increased the contribution of the environment. As a result heritability estimates, computed based on families where the parents are less educated relative to their offspring, were very low at this time (10%) [7].

Across most human populations, environment is fairly constant and the estimates of spherical equivalent heritability are usually high (~80%) [9–11]. Although the aggregate contribution of genetic factors to variation in refractive error is high, initial studies were unable to determine the genetic architecture of myopia—that is, is myopia caused by rare mutations of large effect? Or is most variation driven by common variants, each with individually small effect on risk? With the advent of genotyping arrays, it became possible to estimate the aggregate effect of all common variants, with "array heritability" estimates of 35% from the ALSPAC study. Such estimates place a lower bound on the proportion of the heritability that is attributable to genetic variants which are common in the population. The remaining 45% (80%–35%) is likely attributable to rare genetic variants, to variants not covered by genotyping arrays or to non-additive genetic effects.

5.3 Syndromic Myopia

Syndromic myopia is generally monogenic and can occur within a wide spectrum of clinical presentations. This type of myopia is usually accompanied by other systemic or ocular disorders. Table 5.1 summarizes all syndromic and ocular conditions that present with myopia [12]. We are able to learn about myopia development by investigating these syndromes. For instance, several types of heritable syndromes result in extreme axial elongation, due to abnormalities in the development of connective tissue (i.e. Marfan syndrome, OMIM #154700; Stickler syndrome, OMIM #,108300 #604841, #614134, #614284 and Ehlers–Danlos syndrome, OMIM #225400, #601776). Similarly, inherited retinal dystrophies lead to myopia due to defects in photoreceptors, for instance, in X-linked retinitis pigmentosa (mutations in *RPGR*-gene) and congenital stationary night blindness [13].

Interestingly, several syndromic myopia genes were found in association to other ocular traits, such as CCT (*ADAMTS2*, *COL4A3*, *COL5A1*, *FBN1*) [14], and Fuchs's dystrophy (*TCF4*) [15]. However, the majority of the genes causing syndromic myopia have not been linked to common forms of myopia, except for *COL2A1* [16, 17] and *FBN1* [18, 19]. Nevertheless, a recent study found an overrepresentation for syndromic myopia genes in GWAS studies on refractive error and myopia [20], implying their important role in myopia development.

5.4 Linkage Studies

Linkage studies have been successfully applied for many Mendelian disorders, although the success has been much more limited in complex traits. The linkage approach searches for cosegregation of genetic markers with the trait of interest in

Table 5.1 Overview of syndromic forms of myopia

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
(A) Syndromes associated with myopia and associated ocular phenotype		
Acromelic frontonasal dysostosis	*ZSWIM6* (*AD*)	Telecanthus, ptosis (some patients), corneal dermoid cyst (rare), glaucoma (rare), segmental optic nerve hypoplasia (rare), persistent primary vitreous (rare)
Alagille syndrome	*JAG1* (*AD*)	Deep-set eyes, hypertelorism, upslanting palpebral fissures, posterior embryotoxon, anterior chamber anomalies, eccentric or ectopic pupils, chorioretinal atrophy, band keratopathy, cataracts, retinal pigment clumping, Axenfeld anomaly, microcornea, choroidal folds, strabismus, anomalous optic disc
Alport syndrome	*COL4A5* (*XLD*); *COL4A3* (*AR/AD*)	Anterior lenticonus, lens opacities, cataracts, pigmentary changes ("flecks") in the perimacular region, corneal endothelial vesicles, corneal erosions
Angelman syndrome	*UBE3A* (*IP*); *CH*	Strabismus (most frequently exotropia), ocular hypopigmentation, refractive errors (astigmatism, hyperopia, myopia)
Bardet–Biedl syndrome	*ARL6*; *BBS1*; *BBS2*; *BBS4*; *BBS5*; *BBS7*; *BBS9*; *BBS10*; *BBS12*; *CEP290*; *LZTFL1*; *MKKS*; *MKS1*; *SDCCAG8*; *TMEM67*; *TRIM32*; *TTC8*; *WDPCP* (*AR*)	Rod-cone dystrophy onset by end of 2nd decade, retinitis pigmentosa, retinal degeneration, strabismus, cataracts
Beals syndrome	*FBN2* (*AD*)	Ectopia lentis
Beaulieu–Boycott–Innes syndrome	*THOC6* (*AR*)	Deep-set eyes, short palpebral fissures, upslanting palpebral fissures
Bohring–Opitz syndrome	*ASXL1* (*AD*)	Prominent eyes, hypoplastic orbital ridges, hypertelorism, upslanting palpebral fissures, strabismus, retinal abnormalities, optic nerve abnormalities
Bone fragility and contractures; arterial rupture and deafness	*PLOD3* (*AR*)	Shallow orbits, cataracts
Branchiooculofacial syndrome	*TFAP2A* (*AD*)	Lacrimal sac fistula, orbital dermoid cyst, iris pigment epithelial cyst, combined hamartoma of the retina and retinal pigment epithelium, upslanting palpebral fissures, telecanthus, hypertelorism, ptosis, lacrimal duct obstruction, iris coloboma, retinal coloboma, microphthalmia, anophthalmia, cataract, strabismus

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Cardiofaciocutaneous syndrome	*MAP2K2* (*AD*)	Ptosis, nystagmus, strabismus, downslanting palpebral fissures, hypertelorism, exophthalmos, epicanthal folds, optic nerve dysplasia, oculomotor apraxia, loss of visual acuity, absence of eyebrows, absence of eyelashes
Cohen syndrome	*VPS13B* (*AR*)	Downslanting palpebral fissures, almond-shaped eyes, chorioretinal dystrophy, decreased visual acuity, optic atrophy
Cornelia de Lange syndrome	*NIPBL* (*AD*); *HDAC8* (*XLD*)	Synophrys, long curly eyelashes, ptosis
Cowden syndrome	*PTEN* (*AD*)	Cataract, angioid streaks
Cranioectodermal dysplasia	*IFT122* (*AR*)	Telecanthus, hypotelorism, epicanthal folds, myopia (1 patient), nystagmus (1 patient), retinal dystrophy (1 patient)
Cutis laxa	*ATP6V0A2*; *ALDH18A1* (*AR*)	Downslanting palpebral fissures, strabismus
Danon disease	*LAMP2* (*XLD*)	Moderate central loss of visual acuity in males, normal to near-normal visual acuity in carrier females, fine lamellar white opacities on slit lamp exam in carrier females, near complete loss of peripheral retinal pigment in males, peppered pigmentary mottling of peripheral retinal pigment in carrier females, nonspecific changes on electroretinogram in carrier females
Deafness and myopia	*SLITRK6* (*AR*)	High myopia
Desanto–Shinawi syndrome	*WAC* (*AD*)	Hypertelorism, downslanting palpebral issues, synophrys, deep-set eyes, astigmatism, strabismus
Desbuquois dysplasia	*CANT1* (*AR*)	Prominent eyes, bulging eyes, congenital glaucoma
Donnai–Barrow syndrome	*LRP2* (*AR*)	Hypertelorism, high myopia, loss of vision, iris coloboma, iris hypoplasia, cataract, enlarged globes, downslanting palpebral fissures, underorbital skin creases, retinal detachment, retinal dystrophy, prominent eyes
DOORS	*TBC1D24* (*AR*)	Optic atrophy, blindness, high myopia, cataracts
Ehlers–Danlos syndrome	*COL5A1* (*AD*); *PLOD1* (*AR*); *CHST14* (*AR*); *ADAMTS2* (*AR*); *B3GALT6* (*AR*); *FKBP14* (*AR*)	Blue sclerae, ectopia lentis, epicanthal folds

(continued)

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Emanuel syndrome	CH	Hooded eyelids, deep-set eyes, upslanting palpebral fissures, strabismus
Fibrochondrogenesis	*COL11A1* (*AR*)	–
Gyrate atrophy of choroid and retina with/without ornithinemia	*OAT* (*AR*)	Progressive chorioretinal degeneration, night blindness (onset in first decade, progressive loss of peripheral vision, blindness (onset in fourth or fifth decade), posterior subcapsular cataracts (onset in second or third decade)
Hamamy syndrome	*IRX5* (*AR*)	Severe hypertelorism, laterally sparse eyebrows, myopia (progressive severe)
Homocystinuria	*CBS* (*AR*)	Ectopia lentis, glaucoma
Joint laxity; short stature; myopia	*GZF1* (*AR*)	Exophthalmos, severe myopia, retinal detachment (some patients), iris coloboma (some patients), chorioretinal coloboma (some patients), glaucoma (1 patient)
Kaufman oculocerebrofacial syndrome	*UBE3B* (*AR*)	Blepharophimosis, ptosis, upward-slanting palpebral fissures, telecanthus, hypertelorism, astigmatism, strabismus, mild
Kenny–Caffey syndrome	*FAM111A* (*AD*)	Hyperopia (not myopia), microphthalmia, papilledema, corneal and retinal calcification, congenital cataracts (rare)
Kniest dysplasia	*COL2A1* (*AD*)	Retinal detachment, cataracts, prominent eyes
Knobloch syndrome	*COL18A1* (*AR*)	High myopia, vitreoretinal degeneration, retinal detachment (childhood), congenital cataract, syneresis, vitreous attachment at the disc, persistent foetal hyaloid vasculature, peripapillary atrophy, phthisis bulbi, band keratopathy, macular hypoplasia, irregular white dots at the vitreoretinal interface, visual loss, nystagmus
Lamb–Shaffer syndrome	*SOX5* (*AD*)	Downslanting palpebral fissures, epicanthal folds, strabismus
Lethal congenital contracture syndrome	*ERBB3* (*AR*)	High myopia, degenerative vitreoretinopathy
Leukodystrophy	*POLR1C*; *POLR3A*; *POLR3B*; *GJC2* (*AR*)	–
Linear skin defects with multiple congenital anomalies	*NDUFB11*; *COX7B* (*XLD*)	Lacrimal duct atresia, nystagmus, strabismus
Loeys–Dietz syndrome	*TGFBR1*; *TGFBR2* (*AD*)	Hypertelorism, exotropia, blue sclerae, proptosis

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Macrocephaly/ megalencephaly syndrome	*TBC1D7* (*AR*)	Astigmatism
Marfan syndrome	*FBN1* (*AD*)	Enophthalmos, ectopia lentis increased axial globe length, corneal flatness, retinal detachment, iris hypoplasia, early glaucoma, early cataracts, downslanting palpebral fissures, trabeculodysgenesis, primary (some patients), strabismus (some patients), exotropia (some patients), esotropia (rare), hypertropia (rare)
Marshall syndrome	*COL11A1* (*AD*)	congenital cataracts, esotropia, retinal detachment, glaucoma, lens dislocation, vitreoretinal degeneration, hypertelorism, epicanthal folds
Microcephaly with/ without chorioretinopathy; lymphedema; and/or mental retardation	*KIF11* (*AD*)	Upslanting palpebral fissures, downslanting palpebral fissures (some patients), epicanthal folds (some patients), nystagmus, reduced visual acuity, hypermetropia, myopic astigmatism, hypermetropic astigmatism, corneal opacity, microcornea, microphthalmia, cataract, retrolenticular fibrotic mass, chorioretinopathy, retinal folds, falciform retinal folds, retinal detachment, temporal dragging of optic disc, retinal pigment changes (some patients), optic atrophy (uncommon)
Mohr–Tranebjaerg syndrome	*TIMM8A* (*XLR*)	Photophobia, cortical blindness, decreased visual acuity, constricted visual fields, abnormal electroretinogram
Mucolipidosis	*GNPTAG* (*AR*)	Fine corneal opacities
Muscular dystrophy	*TRAPPC11*; *POMT*; *POMT1*; *POMT2*; *POMGNT1*; *B3GALNT2*; *FKRP*; *DAG1*; *FKTN*(*AR*)	Cataracts, strabismus, alacrima (some patients)
Nephrotic syndrome	*LAMB2* (*AR*)	Nystagmus, strabismus, microcoria, aplasia/atrophy of the dilatator pupillae muscle, hypoplasia of the iris and ciliary body, lenticonus posterior, blindness, decreased or absent laminin beta-2 immunoreactivity in tissues of the anterior eye

(continued)

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Noonan syndrome	*A2ML1*; *BRAF*; *CBL*; *HRAS*; *KRAS*; *MAP2K1*; *MAP2K2*; *NRAS*; *PTPN11*; *RAF1*; *RIT1*; *SOS1*; *SHOC2*; *SPRED1* (*AD*)	Ptosis, hypertelorism, downslanting palpebral fissures, epicanthal folds, blue-green irides
Oculocutaneous albinism	*TYR* (*AR*)	Absent pigment in iris and retina, translucent iris, pink irides (childhood), blue-gray irides (adult), choroidal vessels visible, foveal hypoplasia, decreased visual acuity, strabismus, nystagmus, photophobia, high refractive errors (hyperopia, myopia, with-the-rule astigmatism), albinotic optic disc, misrouting of the optic nerves at the chiasm, absent stereopsis due to anomalous decussation at the optic chiasm, positive angle kappa (appearance of exotropia but no shift on cover test), asymmetric visual evoked potentials
Oculodentodigital dysplasia	*GJA1* (*AR*)	Hypoplastic eyebrows, sparse eyelashes, telecanthus, short palpebral fissures, downslanting palpebral fissures, microphthalmia, microcornea, cataract, persistent pupillary membrane
Pallister–Killian syndrome	CH	Sparse eyebrows, sparse eyelashes, upslanting palpebral fissures, hypertelorism, ptosis, strabismus, epicanthal folds, cataracts, exophthalmos
Papillorenal syndrome	*PAX2* (*AD*)	Retinal coloboma, optic nerve anomalies (coloboma, gliosis, absent optic nerve head), optic disc anomalies (dysplasia, excavation, hyperplasia, morning glory optic disc, hypoplasia), orbital cysts, microphthalmia, abnormal retinal pigment epithelium, abnormal retinal vessels, chorioretinal degeneration, retinal detachment (rare). retinal staphyloma (rare), retinal edema (rare), macular degeneration (rare), papillomacular detachment (rare), hyperpigmentation of the macula (rare), cystic degeneration of the macula (rare), posterior lens luxation (rare), lens opacity (rare)

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Peters-plus syndrome	*B3GLCT* (*AR*)	Hypertelorism, Peter's anomaly, anterior chamber cleavage disorder, nystagmus, ptosis, glaucoma, upslanting palpebral fissures, cataract, iris coloboma, retinal coloboma
Pitt–Hopkins syndrome	*TCF4* (*AD*)	Deep-set eyes, strabismus, astigmatism, upslanting palpebral fissures
Pontocerebellar hypoplasia	*CHMP1A* (*AR*)	Astigmatism, esotropia, strabismus, hyperopia, nystagmus (some patients), cortical visual impairment (some patients), poor visual tracking (some patients)
Poretti–Boltshauser syndrome	*LAMA1* (*AR*)	Strabismus, amblyopia, oculomotor apraxia, nystagmus, retinal atrophy, retinal dystrophy, retinal dysfunction, macular heterotopia
Prader–Willi syndrome	*NDN* (PC); *SNRPN* (IP); CH	Almond-shaped eyes, strabismus, upslanting palpebral fissures, hyperopia
Pseudoxanthoma elasticum	*ABCC6* (*AR*)	Peau d'orange retinal changes (yellow-mottled retinal hyperpigmentation), angioid streaks of the retina (85% of patients), macular degeneration, visual impairment (50–70% of patients), central vision loss, colloid bodies, retinal haemorrhage, choroidal neovascularization, optic head drusen (yellowish-white irregularities of optic disc), owl's eyes (paired hyperpigmented spots)
Renal hypomagnesemia	*CLDN16*; *CLDN19* (*AR*)	Strabismus, nystagmus, hyperopia, astigmatism
SADDAN	*FGFR3* (*AD*)	High myopia, exotropia
Schaaf–Yang syndrome	*MAGEL2* (*AD*)	Esotropia, strabismus, almond-shaped eyes, short palpebral fissures, bushy eyebrows
Schimke immunoosseous dysplasia	*SMARCAL1* (*AR*)	Corneal opacities, astigmatism
Schuurs–Hoeijmakers syndrome	*PACS1* (*AD*)	Full, arched eyebrows, long eyelashes, hypertelorism, downslanting palpebral fissures, ptosis, nystagmus, strabismus
Schwartz–Jampel syndrome	*HSPG2* (*AR*)	Narrow palpebral fissures, blepharophimosis, cataract, microcornea, long eyelashes in irregular rows, ptosis
Sengers syndrome	*AGK* (*AR*)	Cataracts (infantile), strabismus, glaucoma
Short stature; hearing loss; retinitis pigmentosa and distinctive facies	*EXOSC2* (*AR*)	Deep-set eyes, short palpebral fissures, upslanting palpebral fissures, retinitis pigmentosa (2 patients), corneal dystrophy (2 patients, young-adult onset), glaucoma (1 patient), nystagmus (1 patient), strabismus (1 patient)

(continued)

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Short stature; optic nerve atrophy; and Pelger–Huet anomaly	*NBAS* (*AR*)	Thick and bush eyebrows, small orbits, bilateral exophthalmos, epicanthus, bilateral optic nerve atrophy, non-progressive decreased visual acuity, (in) complete achromatopsia, strabismus (some patients), hypertelorism (some patients), hypermetropia (rare), pigmented nevus (rare)
SHORT syndrome	*PIK3R1* (*AD*)	Deep-set eyes, Rieger anomaly, telecanthus, glaucoma, megalocornea, cataracts
Short-rib thoracic dysplasia with/without polydactyly	*WDR19* (*AR*)	Cataracts, attenuated arteries, macular anomalies
Shprintzen–Goldberg syndrome	*SKI* (*AD*)	Telecanthus, hypertelorism, proptosis, strabismus, downslanting palpebral fissures, ptosis, shallow orbits
Singleton–Merten syndrome	*IFIH1* (*AD*)	Glaucoma
Small vessel brain disease with/without ocular anomalies	*COL4A1* (*AD*)	Retinal arteriolar tortuosity, hypopigmentation of the fundus, episodic scotomas, episodic blurred vision, amblyopia (1 family), strabismus (1 family), high intraocular pressure (1 family). *Reported in some patients*: astigmatism, hyperopia, congenital cataracts, prominent or irregular Schwalbe line, iridocorneal synechiae, Axenfeld–Rieger anomalies, corneal opacities, microphthalmia, microcornea, iris hypoplasia, corectopia. *Rare*: decreased visual acuity, glaucoma, corneal neovascularization, polycoria, iridogoniodysgenesis, macular haemorrhage and Fuchs spots, peripapillary atrophy, choroidal atrophy
Smith–Magenis syndrome	*RAI1* (*AD*)	–
Spastic paraplegia and psychomotor retardation with or without seizures	*HACE1* (*AR*)	Strabismus, retinal dystrophy (some patients)
Split hand/foot malformation	CH	–
Stickler syndrome	*COL2A1* (*AD*); *COL11A1* (*AD*); *COL9A1* (*AR*); *COL9A2* (*AR*)	Retinal detachment, blindness, occasional cataracts, glaucoma, membranous (type I) vitreous phenotype

Table 5.1 (continued)

Syndrome	Gene and inheritance pattern	Ocular phenotype other than myopia
Syndromic mental retardation	*SETD5* (AD); *MBD5* (AD); *USP9X* (XLD); *NONO* (XLR); *RPL10* (XLR); *SMS* (XLR); *ELOVL4* (AR); *KDM5C* (XLR)	Synophrys, eyebrow abnormalities, upslanting and short palpebral fissures, epicanthal folds, mild hypertelorism, strabismus, cataracts, hypermetropia, astigmatism, poor vision
Syndromic microphthalmia	*OTX2*; *BMP4* (*AD*)	Uni- or bilateral microphthalmia, uni- or bilateral anophthalmia, coloboma, microcornea, cataract, retinal dystrophy, optic nerve hypoplasia or agenesis
Temtamy syndrome	*C12orf57* (*AR*)	Hypertelorism. "key-hole" iris, retina and choroid coloboma, dislocated lens (upward), downslanting palpebral fissures, arched eyebrows
White–Sutton syndrome	*POGZ* (*AD*)	Visual abnormalities, strabismus, astigmatism, hyperopia, optic atrophy, rod-cone dystrophy, cortical blindness
Zimmermann–Laband syndrome	*KCNH1* (*AD*)	Thick eyebrows, synophrys, cataracts

AD autosomal dominant, *AR* autosomal recessive, *XLR* X linked recessive, *XLD* X linked dominant, *CH* chromosomal, *IP* imprinting defect

Table 5.1A Ocular conditions associated with myopia

Ocular condition	Gene and inheritance pattern
Achromatopsia	*CNGB3* (*AR*)
Aland Island eye disease	*GPR143* (*XLR*)
Anterior segment dysgenesis	*PITX3* (*AD*)
Bietti crystalline corneoretinal dystrophy	*CYP4V2* (*AD*)
Blue cone monochromacy	*OPN1LW*; *OPN1MW* (*XLR*)
Brittle cornea syndrome	*ZNF469*; *PRDM5* (*AR*)
Cataract	*BFSP2*; *CRYBA2*; *EPHA2* (*AD*)
Colobomatous macrophthalmia with microcornea	CH
Cone dystrophy	*KCNV2* (*AD*)
Cone rod dystrophy	*C8orf37* (*AR*); *RAB28* (*AR*); *RPGR* (*XLR*); *CACNA1F* (*XLR*)
Congenital microcoria	CH
Congenital stationary night blindness	*NYX* (*XLR*); *CACNA1F* (*XLR*); *GRM6* (*AR*); *SLC24A1* (*AR*); *LRIT3* (*AR*); *GNB3* (*AR*); *GPR179* (*AR*)
Ectopia lentis et pupillae	*ADAMTSL4* (*AR*)

(continued)

Ocular condition	Gene and inheritance pattern
High myopia with cataract and vitreoretinal degeneration	*P3H2* (*AR*)
Keratoconus	*VSX1* (*AD*)
Leber congenital amaurosis	*TULP1* (*AR*)
Microcornea, myopic chorioretinal atrophy, and telecanthus	*ADAMTS18* (*AR*)
Microspherophakia and/or megalocornea, with ectopia lentis and/or secondary glaucoma	*LTBP2* (*AR*)
Ocular albinism	*OCA2* (*AR*)
Primary open angle glaucoma	*MYOC*; *OPTN* (*AD*)
Retinal cone dystrophy	*KCNV2* (*AR*)
Retinal dystrophy	*C21orf2* (*AR*); *TUB* (*AR*)
Retinitis pigmentosa	*RP1* (*AD*); *RP2* (*XLR*); *RPGR* (*XLR*); *TTC8* (*AR*)
Sveinsson chorioretinal atrophy	*TEAD1* (*AD*)
Vitreoretinopathy	*ZNF408* (*AD*)
Wagner vitreoretinopathy	*VCAN* (*AD*)
Weill–Marchesani syndrome	*ADAMTS10* (*AR*); *FBN1*(*AD*); *LTBP2* (*AR*); *ADAMTS17* (*AR*)

AD autosomal dominant, *AR* autosomal recessive, *XLR* X linked recessive, *CH* chromosomal

pedigrees [21]. Families with genetic variants which show an autosomal dominant inheritance pattern were also most successful for myopia linkage studies. Up to now, 20 MYP loci [22–25] and several other loci [26–31] are identified for (high) myopia. Fine mapping led to candidate genes, such as the *IGF1* gene located in the MYP3 locus [32]. Linkage using a complex inheritance design found five additional loci [33–37].

Validation of candidate genes often resulted in no association, but other variants appeared associated with the non-Mendelian, common form of myopia. This hints towards a genetic overlap between Mendelian and common myopia [38]. As the GWAS era progressed, linkage studies fell by the wayside. Nevertheless, segregation analyses combined with linkage and next generation sequencing (i.e. whole exome sequencing) of regions in pedigrees with high myopia are, in theory, expected to facilitate the discovery of rare variants with large effects; an aspect which cannot be distilled from GWAS.

5.5 Candidate Gene Studies

In candidate gene studies the focus is on a gene with suspected biological, physiological or functional relevance to myopia, in particular high myopia. Although sometimes effective, candidate gene studies are limited by their reliance on this existing knowledge. Table 5.2 summarizes candidate gene studies on (high) myopia. Particularly

Table 5.2 Summary of candidate gene studies reporting positive association results with myopia

Gene symbol	Gene name	Hypothesized gene function	Associated phenotype	Ethnicity	Confirmation type (PMID)	Study (PMID)	Year
APLP2	Amyloid beta precursor like protein 2	Amacrine cell function modulation	Refractive error	Caucasian	n/a	Tkatchenko et al. [39] (26313004)	2015
BMP2K	Bone morphogenic protein-2-inducible protein kinase	Ocular development (embryogenesis) and retinal tissue remodelling	High myopia	Chinese	n/a	Liu et al. [40] (19927351)	2009
CHRM1	Cholinergic receptor muscarinic 1	Target of atropine	High myopia (−6.5 dpt)	Han Chinese	Expression study found no association with CHRM1 (19262686) and finding has been debated (20414262)	Lin et al. [41, 42] (19753311)	2010
CHRM1	Cholinergic receptor muscarinic 1	Target of atropine	High myopia (−6.5 dpt)	Han Chinese	Expression study found no association with CHRM1 (19262686) and finding has been debated (20414262)	Lin et al. [43, 44] (19753311)	2009
cMET (*alias HGFR*)	Tyrosine-protein kinase met	Hepatocyte growth factor and its receptor	Paediatric myopia (<−0.5 dpt)	Chinese	Replication independent high myopia cohort (24766640)	Khor et al. [45] (19500853)	2009
COL1A1	Collagen type I alpha 1 chain	Extracellular matrix	High myopia (<−9.25 dpt)	Japanese	Multiple systemic meta-analyses with contradicting results (27162737; 26131177; 27588274)	Inamori et al. [46] (17557158)	2007
COL2A1	Collagen type II alpha 1 chain	Extracellular matrix	High myopia (−5 dpt)	Caucasian	No replication independent high myopia cohort (21993774)	Metlapally et al. [47] (19387081)	2009
COL2A1	Collagen type II alpha 1 chain	Extracellular matrix	Paediatric myopia (<−0.75 dpt)	Caucasian	No replication independent high myopia cohort (21993774)	Mutti et al. [48] (17653045)	2007

(continued)

Table 5.2 (continued)

Gene symbol	Gene name	Hypothesized gene function	Associated phenotype	Ethnicity	Confirmation type (PMID)	Study (PMID)	Year
CRYBA4	Crystallin beta A4	Retinal and scleral remodelling	High myopia (<−8 dpt)	Chinese	No replication independent high myopia cohort (29263643)	Ho et al. [49] (22792142)	2012
HGF	Hepatocyte growth factor	Hepatocyte growth factor and its receptor	High myopia	Han Chinese	No replication independent high myopia cohort (19060265)	Han et al. [50] (16723436)	2006
HGF	Hepatocyte growth factor	Hepatocyte growth factor and its receptor	Refractive error	Caucasian	No replication independent high myopia cohort (19060265)	Veerappan et al. [51] (20005573)	2010
HGF	Hepatocyte growth factor	Hepatocyte growth factor and its receptor	High Myopia (−5 dpt)	Caucasian	No replication independent high myopia cohort (19060265)	Yanovitch et al. [52] (19471602)	2009
IGF1	Insulin-like growth factor 1	Hepatocyte growth factor and its receptor	High myopia (−5 dpt)	Caucasian	Systematic review and meta-analysis of studies in high myopics resulted in no association (28135889)	Metlapally et al. [53] (20435602)	2010
LAMA1	Laminin subunit alpha 1	Extracellular matrix	High myopia (<−6 dpt and axial length >26 mm)	Chinese	No replication independent high myopia cohort (29805427; 19668483)	Zhao et al. [54] (21541277)	2011
LUM	Lumican	Scleral and extracellular matrix remodelling	Extreme high myopia	Han Chinese	Meta-analysis of studies in high myopics resulted in no association (24927138)	Chen et al. [55] (19616852)	2009
LUM	Lumican	Scleral and extracellular matrix remodelling	High myopia	Han Chinese	Meta-analysis of studies in high myopics resulted in no association (24927138) and finding has been debated (20414262)	Lin et al. [41, 42] (19643966)	2010
LUM	Lumican	Scleral and extracellular matrix remodelling	High myopia (<−6.5 dpt)	Han Chinese	Meta-analysis of studies in high myopics resulted in no association (24927138)	Lin et al. [41, 42] (20010793)	2010

LUM	Lumican	Scleral and extracellular matrix remodelling	Extreme high myopia	Han Chinese	Meta-analysis of studies in high myopics resulted in no association (24927138)	Wang et al. [56] (16902402)	2006
MFN1	Mitofusin 1	Mitochondrial remodelling and apoptosis	Myopia	Caucasian	Expression study found association with myopia (27609161) and replication independent myopia cohort (26682159)	Andrew et al. [57] (18846214)	2008
MMP1	Matrix metallopeptidase 1	Extracellular matrix	Refractive error	Amish	No replication independent high myopia cohort (20435584; 23077567)	Wojciechowski et al. [58] (20484597)	2010
MMP1	Matrix metallopeptidase 1	Extracellular matrix	Refractive error	Caucasian	No replication independent high myopia cohort (20435584; 23077567)	Wojciechowski et al. [59] (23098370)	2013
MMP10	Matrix metallopeptidase 10	Extracellular matrix	Refractive error	Caucasian	No replication independent high myopia cohort (23077567)	Wojciechowski et al. [59] (23098370)	2013
MMP2	Matrix metallopeptidase 2	Extracellular matrix	Refractive error	Amish	Expression study found association with myopia (28402202; 29803830; 28900109; 24876280); no replication independent high myopia cohort (20435584; 23378725)	Wojciechowski et al. [58] (20484597)	2010
MMP2	Matrix metallopeptidase 2	Extracellular matrix	Refractive error	Caucasian	Expression study found association with myopia (28402202; 29803830; 28900109; 24876280); no replication independent high myopia cohort (20435584; 23378725)	Wojciechowski et al. [59] (23098370)	2013

(continued)

Table 5.2 (continued)

Gene symbol	Gene name	Hypothesized gene function	Associated phenotype	Ethnicity	Confirmation type (PMID)	Study (PMID)	Year
MMP3	Matrix metallopeptidase 3	Extracellular matrix	Refractive error	Caucasian	Expression study found no association with myopia (24876280); No replication independent high myopia cohort (20435584; 23077567; 16935611)	Hall et al. [60] (19279308)	2009
MMP9	Matrix metallopeptidase 9	Extracellular matrix	Refractive error	Caucasian	No replication independent high myopia cohort (23077567)	Hall et al. [60] (19279308)	2009
MYOC	Myocilin	Cytoskeletal function	High myopia	Chinese	No replication independent high myopia cohort (22809227; 24766640)	Tang et al. [61] (17438518)	2007
MYOC	Myocilin	Cytoskeletal function	High myopia	Caucasian	No replication independent high myopia cohort (22809227; 24766640)	Vatavuk et al. [62] (19260140)	2009
MYOC	Myocilin	Cytoskeletal function	High myopia	Caucasian	No replication independent high myopia cohort (22809227; 24766640)	Zayats et al. [63] (19180258)	2009
PAX6	Paired box 6	Ocular development (embryogenesis)	High myopia	Han Chinese	Systemic review and meta-analysis of studies in high and extreme myopics resulted in replication (24637479)	Han et al. [64] (19124844)	2009
PAX6	Paired box 6	Ocular development (embryogenesis)	High myopia (<−9 dpt)	Japanese	Systemic review and meta-analysis of studies in high and extreme myopics resulted in replication (24637479)	Kanemaki et al. [65] (26604670)	2015
PAX6	Paired box 6	Ocular development (embryogenesis)	High myopia (axial length >26 mm)	Japanese	Systemic review and meta-analysis of studies in high and extreme myopics resulted in replication (24637479)	Miyake et al. [66] (23213273)	2012

PAX6	Paired box 6	Ocular development (embryogenesis)	High myopia (<−6 dpt and axial length >26 mm)	Han Chinese	Systemic review and meta-analysis of studies in high and extreme myopics resulted in replication (24637479)	Ng et al. [67] (19907666)	2009
PAX6	Paired box 6	Ocular development (embryogenesis)	Extreme high myopia	Chinese	Systemic review and meta-analysis of studies in high and extreme myopics resulted in replication (24637479)	Tsai et al. [68] (17948041)	2008
PSARL	Presenilins-associated rhomboid-like protein	Mitochondrial remodelling and apoptosis	Myopia	Caucasian	n/a	Andrew et al. [57] (18846214)	2008
SOX2OT	Sex-determining region Y-box 2 overlapping transcript	Neurogenesis and vertebrate development (embryogenesis)	Myopia	Caucasian	n/a	Andrew et al. [57] (18846214)	2008
TGFβ1	Transforming growth factor beta 1	Extracellular matrix remodelling	High myopia (<−8 dpt)	Chinese	Replication GWAS-meta-analysis on refractive error (29808027)	Khor et al. [69] (20697017)	2010
TGFβ1	Transforming growth factor beta 1	Extracellular matrix remodelling	High myopia	Chinese	Replication GWAS-meta-analysis on refractive error (29808027)	Lin et al. [70] (16807529)	2006
TGFβ1	Transforming growth factor beta 1	Extracellular matrix remodelling	High myopia	Indian	Replication GWAS-meta-analysis on refractive error (29808027)	Rasool et al. [71] (23325483)	2013
TGFβ1	Transforming growth factor beta 1	Extracellular matrix remodelling	High myopia (<−8 dpt)	Chinese	Replication GWAS-meta-analysis on refractive error (29808027)	Zha et al. [72] (19365037)	2009

(continued)

Table 5.2 (continued)

Gene symbol	Gene name	Hypothesized gene function	Associated phenotype	Ethnicity	Confirmation type (PMID)	Study (PMID)	Year
TGFβ2	Transforming growth factor beta 2	Extracellular matrix remodelling	High myopia (<−6.5 dpt)	Han Chinese	Expression study found association with myopia (28900109; 29188062; 27214233; 24967344); expression study found no association with myopia (25112847)	Lin et al. [43, 44] (19710942)	2009
TGIF (*alias TGIF1*)	TGFB induced factor homeobox 1	Extracellular matrix remodelling	High myopia	Chinese	No replication independent high myopia cohort (19060265; 18172074; 17048038; 15223781)	Lam et al. [73] (12601022)	2003
TGIF1	TGFB induced factor homeobox 1	Extracellular matrix remodelling	High myopia	Indian	No replication independent high myopia cohort (19060265; 18172074; 17048038; 15223781)	Ahmed et al. [74] (24215395)	2014
UMODL1	Uromodulin like 1	Extracellular matrix	High myopia (<−9.25 dpt)	Japanese	No replication independent high myopia cohort (22857148)	Nishizaki et al. [75] (18535602)	2009

notable are genes encoding extracellular matrix-related proteins (*COL1A1*, *COL2A*1 [16, 17] and *MMP1*, *MMP2*, *MMP3*, *MMP9*, *MMP10* [59, 60]). For candidates such as *PAX6* and *TGFB1*, the results were replicated in multiple independent extreme/high myopia studies and validated in a large GWAS meta-analysis in 2018, respectively [18, 76]. However in most other cases, the results were not independently validated: *LUM* and *IGF1* failed to confirm an association [77, 78]. Interestingly, in a few cases the candidates were subsequently implicated in GWAS of other ocular traits: *TGFβ2* and *LUM* for central corneal thickness (CCT), a glaucoma and keratoconus endophenotype [14], *PAX6* with optic disc area [79] and *HGF* [80].

5.6 Genome-Wide Association Studies

Generally, linkage studies are limited to identification of genetic variants with a large effect on myopia [81]. Given the limited number of genes identified by linkage, it became apparent in the 2000s that identifying large numbers of additional myopia genes was more practical with genome-wide association studies (GWASes), since it has dramatically higher statistical power. GWASes have greatly enhanced our knowledge of the genetic architecture of (complex) diseases [82]. Most of the variants found via GWAS reside in non-exonic regions and their effect sizes are typically small [82, 83]. For GWAS, 200 k–500 k genetic markers are usually genotyped and a further >10 million "imputed", taking advantage of the correlation structure of the genome. This approach is most effective for common variants (allele frequencies >0.01 in the population, although with larger reference panels, rarer alleles can also be detected).

Initially, GWASes for myopia were performed as a dichotomous outcome (i.e. case-control, Table 5.3). Since myopia constitutes a dichotomization of the quantitative trait spherical equivalent, considering the quantitative trait should be more informative for gene mapping. The first GWASes for spherical equivalent were conducted in 2010 [96, 97], with ~4000 individuals required to identify the first loci. The first loci to reach the genome-wide significance threshold ($P < 5 \times 10^{-8}$, the threshold reflecting the large number of statistical tests conducted genome-wide) were markers near the *RASGFR1* gene on 15q25.1 ($P = 2.70 \times 10^{-9}$) and markers near *GJD2* on 15q14 ($P = 2.21 \times 10^{-14}$). A subsequent analysis combining five cohorts ($N = 7000$) identified another locus at the *RBFOX1* gene on chromosome 16 ($P = 3.9 \times 10^{-9}$) [98].

These early efforts made it clear that individual groups would have difficulty in mapping many genes for spherical equivalent, motivating the formation of the Consortium for Refractive Error and Myopia (CREAM) in 2010, which included researchers and cohorts from the USA, Europe, Asia and Australia. They replicated SNPs in the 15q14 loci [99], which was further affirmed by other studies on both spherical equivalent and axial length alongside with the replication of the 15q25 locus [100, 101].

In 2013, two major GWAS meta-analyses on refractive error traits (spherical equivalent and age of spectacle wear) identified 37 novel loci (Table 5.4), with robust replication of *GJD2*, *RFBOX1* and *RASGFR1* in both meta-analyses. The first was the collaborative work of CREAM based on a GWAS meta-analysis on spherical equivalent, comprising 35 individual cohorts ($N_{\text{European}} = 37{,}382$; $N_{\text{SoutheastAsian}} = 12{,}332$) [108]. 23andMe, a direct-to-consumer genetic testing company, performed the second major GWAS, replicating 8 of the novel loci found by CREAM and identifying another 11 novel loci based on a GWAS survival analysis

Table 5.3 Summary of case-control design GWASs and their highest associations with myopia

Authors (year)	Study description	Associations	Ethnicity	PMID
Nakanishi et al. (2009) [84]	Genome-wide association study (GWAS) 830 cases (pathologic myopia; AL >26 mm) 1911 controls	Strongest association with 11q24.1, 44kb upstream of the *BLID* gene and in the second intron of *LOC399959*	Japanese	19779542
Li et al. (2011) [85]	GWAS 287 cases (high myopia; SE ≤ −6D) 673 controls	Strongest suggestive association ($P = 1.51 \times 10^{-5}$) with 5p15.2 for an intronic SNP within the *CTNND2* gene, but with replication in Japanese independent cohort (959 cases and 2128 controls; $P = 0.035$)	Chinese Japanese	21095009
Lu et al. (2011) [86]	GWAS 1203 cases (high myopia; SE ≤ −6D) 955 controls (SE -0.50 D to +1.00 D)	Replication ($P = 2.17 \times 10^{-5}$) with a SNP in *CTNND2* region	Chinese	21911587
Wang et al. [87] (2011)	SNP ($n = 3$) look-up in 11q24.1 and 21q22.3 regions 1255 cases (complex myopia; SE < −10.00 D <SE ≤−4.00 D) 563 cases (high myopia; SE ≤-6.00 D) 1052 controls (−0.50 D ≤ SE ≤ +2.00 D)	No statistically significant differences found for the genotype or allele frequencies of the three SNPs between the myopia cases and controls	Chinese	22194655
Yu et al. (2012) [88]	SNP ($n = 27$) look-up in 5p15 and 11q24 regions 321 cases (pathologic myopia; SE ≤ −6 D and AL > 26 mm) 310 control	Significantly associated SNPs in the *CTNND2* gene and 11q24.1 region ($P = 0.0126$ and 0.0293, respectively) with pathological myopia, replicating previous findings for these loci	Chinese	22759899
Liu et al. (2014) [89]	Meta-analysis comprising the SNPs of all 5 previously published data on the *CTNND2* gene and 11q24.1 region association with myopia 6954 cases 9346 controls	Significant association of 11q24.1 region with myopia ($P = 0.013$). No significant association with myopia for the *CTNND2* gene (two SNPs tested: $P = 0.725$, $P = 0.065$)	Chinese Japanese	24672220
Li et al. (2011) [85]	GWAS 102 cases (high myopia; SE ≤ −8 D with retinal degeneration) 335 controls	The strongest association ($P = 7.70 \times 10^{-13}$) was in a gene desert within the *MYP11* region on 4q25	Chinese	21505071

Shi et al. (2011) [90]	GWAS 419 high myopia cases (≤−6D) 669 controls	The strongest association ($P = 1.91 \times 10^{-16}$) was in an intron within the *MIPEP* gene on 13q12	Han Chinese	21640322
Shi et al. (2013) [91]	GWAS 665 cases (high myopia; SE ≤ −6D) 960 controls	The strongest association ($P = 8.95 \times 10^{-14}$) was in the *VIPR2* gene within the MYP4 locus, followed by three other variants in LD of the *SNTB1* gene region ($P = 1.13 \times 10^{-8}$ to 2.13×10^{-11})	Han Chinese	23406873
Khor et al. (2013) [92]	GWAS meta-analysis of 4 Asian studies 1603 cases ("severe" myopia; SE ≤−6 D and AL ≥26 mm) 3427 controls	The *SNTB1* gene was confirmed and a novel variant within the *ZFHX1B* gene (also known as *ZEB2*) reached genome-wide significance ($P = 5.79 \times 10^{-10}$)	East-Asian	23933737
Hosada et al. (2018) [93]	GWAS meta-analysis of 5 Asian studies 828 cases 3624 controls	Discovery ($P = 1.46 \times 10^{-10}$) and replication ($P = 2.40 \times 10^{-6}$) of the CCDC102B locus.	East-Asian	29725004
Meng et al. (2012) [94]	GWAS 192 cases (high myopia; SE ≤−6 D) 1064 controls	Confirmation of SNPs 3kb downstream of *PPP1R3B* in vicinity of MYP10 on 8p23 ($P = 6.32 \times 10^{-7}$) and MYP15 on 10q21.1 ($P = 2.17 \times 10^{-5}$)	European	23049088
Pickrell et al. (2016) [95]	GWAS 106,086 cases (Myopia "yes"; questionnaire) 85,757 controls (Myopia "no"; questionnaire)	More than 100 novel loci associated with myopia	European	27182965

Table 5.4 Overview of the 37 novel loci found in 2013 by CREAM and 23andMe and subsequent replication

Locus #	Locus name	Discovery—*P* value HapMapII CREAM (2013)	Replication—*P* value HapMapII 23andMe (2013)	Replication—individual cohort (PMID)	Replication—*P* value 1000G CREAM&23 and Me (2018)
2	*BICC1*	2.06×10^{-13}	n/a	Simpson et al. (2014) [102] (25233373), Yoshikawa et al. (2014) [103] (25335978)	1.07×10^{-18}
3	*LAMA2*	1.79×10^{-12}	6.80×10^{-53}	Cheng et al. (2013) [104] (24144296), Simpson et al. (2014) [102] (25233373)	1.91×10^{-57}
4	*CD55*	3.05×10^{-12}	n/a	Cheng et al. (2013) [104] (24144296), Yoshikawa et al. (2014) [103] (25335978)	4.42×10^{-13}
5	*TOX/CA8*	3.99×10^{-12}	4.00×10^{-22}	Simpson et al. (2014) [102] (25233373)	4.64×10^{-31}
6	*RDH5*	4.44×10^{-12}	1.30×10^{-23}		4.06×10^{-43}
7	*CYP26A1*	1.03×10^{-11}	n/a	Yoshikawa et al. (2014) [103] (25335978)	7.49×10^{-10}
8	*RASGRF1*	4.25×10^{-11}	8.20×10^{-13}	Oishi et al. (2013) [105] (24150758), Yoshikawa et al. (2014) [103] (25335978)	4.24×10^{-23}
9	*CHRNG*	5.15×10^{-11}	n/a	Tideman et al. (2016) [106] (27611182)	1.16×10^{-24}
10	*SHISA6*	7.29×10^{-11}	5.20×10^{-15}		9.46×10^{-29}
11	*PRSS56*	7.86×10^{-11}	5.80×10^{-18}	Simpson et al. (2014) [102] (25233373)	2.25×10^{-29}
12	*MYO1D*	9.66×10^{-11}	n/a		2.91×10^{-16}
13	*ZMAT4/SFRP1*	3.69×10^{-10}	1.80×10^{-18}	Simpson et al. (2014) [102] (25233373), Yoshikawa et al. (2014) [103] (25335978)	1.02×10^{-27}
14	*A2BP/RBFOX1*	5.64×10^{-10}	4.10×10^{-26}	Simpson et al. (2014) [102] (25233373), Tideman et al. (2016) [106] (27611182)	1.13×10^{-42}
15	*KCNQ5*	4.18×10^{-9}	2.70×10^{-25}	Liao et al. (2017) [107] (28884119), Yoshikawa et al. (2014) [103] (25335978), Tideman et al. (2016) [106] (27611182)	5.43×10^{-48}
16	*PTPRR*	5.47×10^{-9}	n/a		1.81×10^{-13}
17	*GRIA4*	5.92×10^{-9}	n/a	Tideman et al. (2016) [106] (27611182), Yoshikawa et al. (2014) [103] (25335978)	8.84×10^{-12}

18	*TJP2*	7.26×10^{-9}	5.20×10^{-13}		1.35×10^{-21}
19	*SIX6*	1.00×10^{-8}	n/a		2.12×10^{-8}
20	*LOC100506035*	1.09×10^{-8}	n/a		1.56×10^{-15}
21	*BMP2*	1.57×10^{-8}	n/a	Tideman et al. (2016) [106] (27611182), Yoshikawa et al. (2014) [103] (25335978)	3.11×10^{-9}
22	*CHD7*	1.82×10^{-8}	n/a		1.94×10^{-7}
23	*PCCA*	2.11×10^{-8}	n/a		1.68×10^{-7}
24	*CACNA1D*	2.14×10^{-8}	n/a	Tideman et al. (2016) [106] (27611182)	4.10×10^{-10}
25	*KCNJ2*	2.79×10^{-8}	n/a		5.53×10^{-13}
26	*RORB*	4.15×10^{-8}	n/a		1.07×10^{-11}
27	*LRRC4C*	n/a	2.30×10^{-30}	Tideman et al. (2016) [106] (27611182), Yoshikawa et al. (2014) [103] (25335978)	4.43×10^{-42}
28	*PABPCP2*	n/a	1.50×10^{-14}		1.05×10^{-17}
29	*BMP3*	n/a	4.20×10^{-12}	Simpson et al. (2014) [102] (25233373)	2.08×10^{-20}
30	*RGR*	n/a	8.00×10^{-12}		9.26×10^{-17}
31	*DLG2*	n/a	1.70×10^{-11}		8.85×10^{-15}
32	*ZBTB38*	n/a	3.60×10^{-11}		1.23×10^{-15}
33	*PDE11A*	n/a	8.70×10^{-11}		1.30×10^{-15}
34	*DLX1*	n/a	1.40×10^{-10}		2.77×10^{-16}
35	*KCNMA1*	n/a	7.30×10^{-10}		2.36×10^{-16}
36	*BMP4*	n/a	1.10×10^{-9}	Yoshikawa et al. (2014) [103] (25335978)	1.09×10^{-12}
37	*ZIC2*	n/a	2.10×10^{-8}	Oishi et al. (2013) [105] (24150758), Simpson et al. (2014) [102] (25233373), Tideman et al. (2016) [106] (27611182)	2.80×10^{-15}
S-38*	*B4GALNT2*	n/a	8.30×10^{-7}	Yoshikawa et al. (2014) [103] (25335978)	2.68×10^{-10}
S-39*	*EHBP1L1*	n/a	2.10×10^{-7}	Yoshikawa et al. (2014) [103] (25335978)	1.07×10^{-9}

*These two loci were subthreshold (S) in the analysis in 2013, but exceeded genome-wide significance in 2018 using a larger sample size

of age of spectacle wear in 55,177 participants of European ancestry. To the surprise of some in the field, the effect sizes and direction of the effects of the loci found by these two groups were concordant despite the difference in phenotype definition and in scale: dioptres for CREAM and hazard ratios for 23andMe [109]. Subsequently, replication studies provided validation for the associated loci and highlighted two other suggestive associations. At this point, the implicated loci explained 3% of the phenotypic variance in refractive error [108, 110].

The CREAM and 23andMe studies represented a large increase in sample size over the initial GWASs. Their meta-analysis approach was very effective in discovering new loci. This motivated joined efforts of CREAM and 23andMe, which resulted in a GWAS meta-analysis including 160,420 participants. Moreover, a denser imputation reference set was used (1000G phase 1 version 3), enabling better characterization of genetic variations. Although CREAM and 23andMe used different phenotypes (spherical equivalent and age at first spectacle wear, respectively) again the results were concordant and the new findings were replicated in an independent cohort with refractive error available (UK biobank, comprising 95,505 participants). Overall, this GWAS increased the number of risk loci to 161, explaining 7.8% of the phenotypic variance in refractive error. Very large sample sizes (millions) will be required to identify all of the loci contributing to myopia risk.

The genetic correlation was estimated to be 0.78 between European and Asian ancestry, suggesting that despite (1) large differences in the rate of myopia between these groups and (2) differences in the genetic ancestry of these groups, most of the genetic variation is in common. Figure 5.1 provides the chronological discovery of all associated loci and Fig. 5.2 shows the effect sizes of the established 161 loci.

Several "endophenotypes" have been considered for myopia: spherical equivalent, axial length, corneal curvature and age of diagnosis of myopia. Axial length is a well-studied "endophenotype" which correlates strongly with refractive error. The first GWAS of axial length considered 4944 Asian ancestry individuals and identified a locus at 1q41. A subsequent meta-analysis combining data on 12,531 European and 8216 Asian ancestry individuals uncovered a further eight genome-wide significant loci at *RSPO1*, *C3orf26*, *LAMA2*, *GJD2*, *ZNRF3*, *CD55*, *MIP*, *ALPPL2*, as well as confirming the 1q41 locus. Five of the axial length loci were also associated loci for refractive error. GWASs performed for corneal curvature [104, 111–114] identified the loci *FRAP1*, *CMPK1*, *RBP3* and *PDGFRA*; in the case of *PDGFRA*, associations have also been found with eye size. A study in 9804 Japanese individuals and replication in Chinese and European ancestry cohorts analysed three myopia-related traits (refractive error, axial length and corneal curvature). They replicated the association of *GJD2* and refractive error as well as the association of SNPs in *WNT7B* for axial length and corneal curvature [114, 115]

5.7 Pathway Analysis Approaches

GWAS approaches improve our understanding of the molecular basis of traits by mapping individual loci. However, it is possible to place such loci into a broader context by applying pathway analysis approaches. In myopia, a retina-to-sclera signaling cascade has been postulated, but the specific molecular components were unclear. Recent GWASs have uncovered genes which lie along this pathway [108, 110, 116]—genetic changes at individual loci only make small changes to phenotype but collectively these

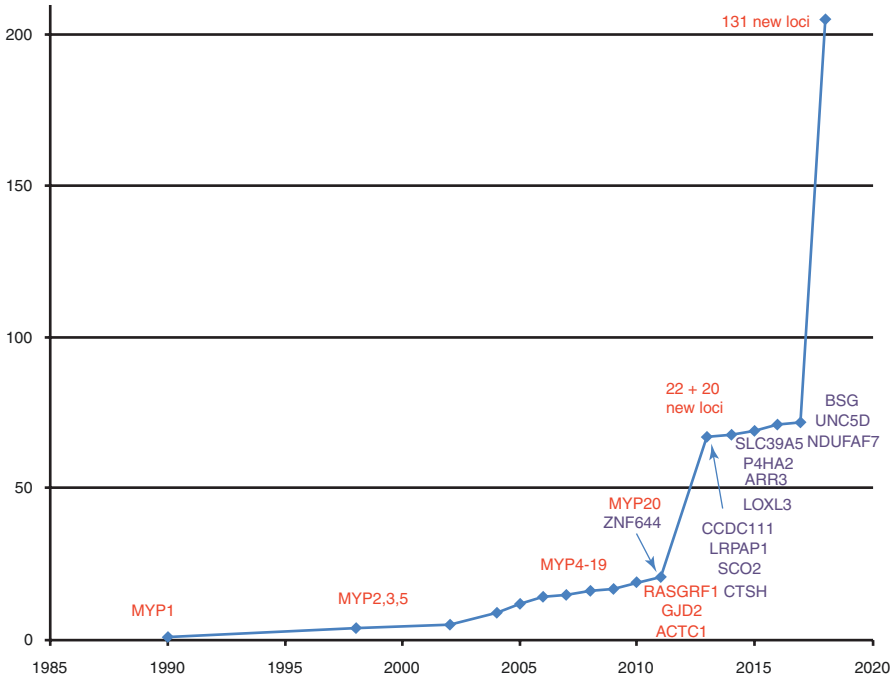

Fig. 5.1 Historic overview of myopia gene finding. Overview of myopia gene finding in historic perspective. Genes identified using whole exome sequencing are marked as purple. Other loci (linkage studies, GWAS) are marked as red

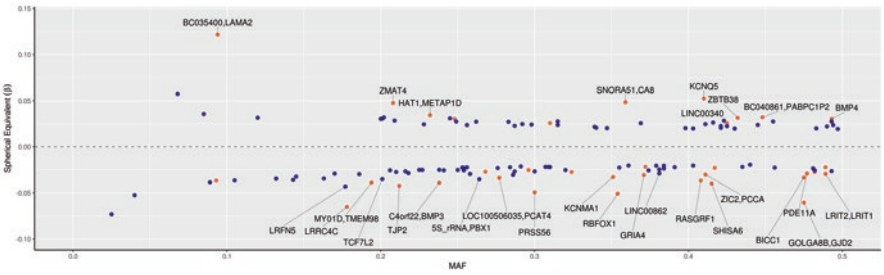

Fig. 5.2 Effect sizes of common and rare variants for myopia and refractive error. Overview of SNPs and annotated genes found in the most recent GWAS meta-analysis [18]. X-axis displays the minor allele frequency of each SNP; y-axis displays the effect size of per individual SNP. The blue dots represent the novel loci discovered by Tedja et al. [18] and the pink dots represent the loci found by Verhoeven et al. [108], which now have been replicated

perturbations are responsible for larger changes in the retina-to-sclera signaling cascade, ultimately explaining differences in refractive error from individual to individual.

Pathways inferred from the first large-scale CREAM GWAS [108, 110] included neurotransmission (*GRIA4*), ion transport (*KCNQ5*), retinoic acid metabolism (*RDH5*), extracellular matrix remodelling (*LAMA2*, *BMP2*) and eye development (*SIX6*, *PRSS56*). The 23andMe GWAS identified an overlapping set of pathways: neuronal development (*KCNMA1*, *RBFOX1*, *LRRC4C*, *NGL-1*, *DLG2*, *TJP2*),

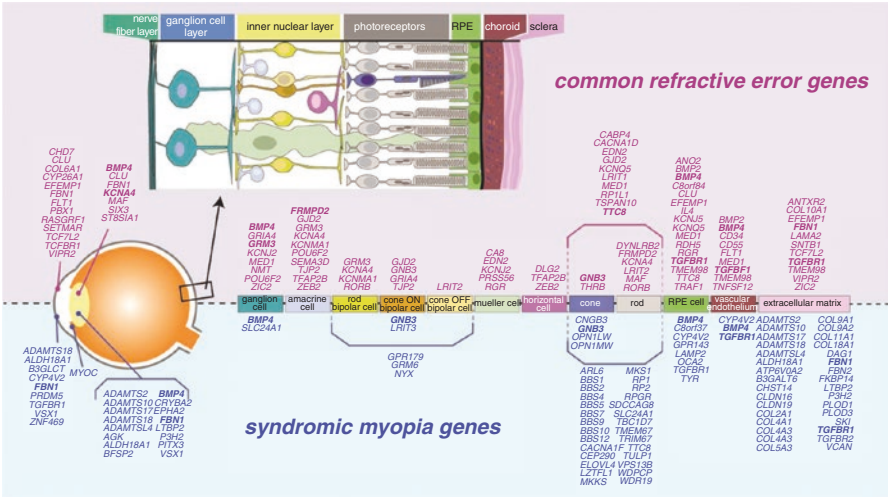

Fig. 5.3 Schematic overview of known function in retinal cell types of refractive error and syndromic myopia genes according to literature. Bold: genes identified for both common refractive error and in syndromic myopia

extracellular matrix remodelling (*ANTXR2*, *LAMA2*), the visual cycle (*RDH5*, *RGR*, *KCNQ5*), eye and body growth (*PRSS56*, *BMP4*, *ZBTB38*, *DLX1*) and retinal ganglion cell (*ZIC2*, *SFRP1*) [117]. When considered in the context of known protein–protein interactions, many genes in these pathways are related to growth and cell cycle pathways, such as the TGF-beta/SMAD and MAPK pathways [118].

The most recent meta-analysis combining data from CREAM and 23andMe data taken together confirmed previous findings and offered additional insights [18]. In a gene-set analysis, several pathways were highlighted including "abnormal photoreceptor inner segment morphology" (Mammalian Phenotype Ontology (MP) 0003730); "thin retinal outer nuclear layer" (MP 0008515); "nonmotile primary cilium" (Gene Ontology (GO) 0031513); "abnormal anterior-eye-segment morphology" (MP 0005193) and "detection of light stimulus" (GO 0009583). The genes implicated in this large-scale GWAS were distributed across all cell types in the retina-to-sclera signaling cascade (neurosensory retina, RPE, vascular endothelium and extracellular matrix, Fig. 5.3). The larger GWAS also suggested novel mechanisms, including angiogenesis, rod-and-cone bipolar synaptic neurotransmission and anterior-segment morphology. Interestingly, a novel association was found at the *DRD1* gene, supporting previous work linking the dopamine pathway to myopia.

5.8 Next Generation Sequencing

GWAS approaches have been highly effective in assessing the role of common variants in myopia but such methods cannot effectively characterize very rare genomic variants. Whole exome sequencing (WES) allows investigation of rare variants in exonic regions; due to cost, applications to date have primarily been in family studies or studies of early onset high myopia.

Studies employing WES to date have either focused on family designs (e.g. particular inheritance patterns such as X-linkage or conditions such as myopic anisometropia) or case-control studies of early onset high myopia [119–122]. The WES-based approaches identified several novel mutations in known myopia genes (Table 5.5). For instance, Kloss et al. [131] performed WES on 14 families with high myopia, identifying 104 genetic variants in both known MYP loci (e.g. *AGRN*, *EME1* and *HOXA2*) and in new loci (e.g. *ATL3* and *AKAP12*) [131]. In the family studies, most variants displayed an autosomal dominant mode of inheritance [119, 123, 124, 130] although X-linked heterozygous mutations were found in *ARR3* [126].

Both retinal dystrophies and ocular development disorders coincide with myopia. Sun et al. [132] investigated if there was a genetic link by evaluating a large number of retinal dystrophy genes in early onset high myopia. They examined 298 unrelated myopia probands and their families, identifying 29 potentially pathogenic mutations in *COL2A1*, *COL11A1*, *PRPH2*, *FBN1*, *GNAT1*, *OPA1*, *PAX2*, *GUCY2D*, *TSPAN12*, *CACNA1F* and *RPGR* with mainly an autosomal dominant pattern.

5.9 Environmental Influences Through Genetics

Although myopia is highly heritable within specific cohorts, dramatic changes in environment across many human populations have led to large changes in prevalence over time [133–136]. The role of changes in socioeconomic status, time spent outdoors, education and near-work are now well established as risk factors for myopia, based on observational studies [137–139]. Education has proven the most influential and consistent factor, with a doubling in myopia prevalence when attending higher education compared to finishing only primary education [140–142]. There are two main areas where genetic studies can inform our understanding of the role of environment. Firstly, gene–environment studies can highlight where interactions exist. Secondly, observational studies only establish association and not causation—in some circumstances genetic data can be used to strengthen the case for an environmental risk factor causally (or not) influencing myopia risk (Mendelian randomization).

Gene–environment (GxE) interaction analyses examine whether genes operate differently across varying environments. GxE studies in myopia have focused primarily on education. An early study in North American samples examined GxE for myopia and the matrix metalloproteinases genes (*MMP1-MMP10*): a subset of SNPs were only associated with refraction in the lower education level [58, 59]. A subsequent study in five Singapore cohorts found variants in *DNAH9*, *GJD2* and *ZMAT4*, which had a larger effect on myopia in a high education subset [143]. Subsequent efforts to examine GxE considered the aggregate effects of many SNPs together. A study in Europeans found that a genetic risk score comprising 26 genetic variants was most strongly associated with myopia in individuals with a university level education [144]. A study examining GxE in children considered near work and time outdoors in association with 39 SNPs and found weak evidence for an interaction with near work [144, 145]. Finally, a CREAM study was able to identify additional myopia risk loci by allowing for a GxE approach [19].

Mendelian randomization (MR) infers whether a risk factor is causally associated with a disease. MR exploits the fact that germline genotypes are randomly

Table 5.5 Overview of genes and their mutations found by next generation sequencing

Gene	Pathway	Method	Inheritance Pattern	Mutation type	Mutation	Author (Year)	PMID
CCDC111	DNA transcription	Targeted sequencing and exome sequencing	Autosomal dominant	Missense	c.265T>G:p.Y89D in *CCDC111*	Zhao et al. (2013) [120]	23579484
NDUFAF7	Mitochondrial function	Genotyping and WES	Autosomal dominant	Missense	c.798C>G:p.D266E in *NDUFAF7*	Wang et al. (2017) [121]	28837730
P4HA2	Collagen synthesis	WES	Autosomal dominant	Missense	c.1147A>G:p.(K383E) in *P4HA2*	Napolitano et al. (2018) [119]	29364500
SCO2	Mitochondrial function	WES	Autosomal dominant	Missense	c.334C>T:p.R112W; c.358C>T:p.R120W in *SCO2*	Jiang et al. (2014) [123]	25525168
SCO2	Mitochondrial function	WES	Autosomal dominant	Nonsense Missense	c.157C>T:p.Q53∗ in SCO2; c.341G>A:p.R114H; c.418G>A:p.E140K and c.776C>T:p.A259V) in *SCO2*	Tran-Viet et al. (2013) [124]	23643385
UNC5D	Cell signaling	WES	Autosomal dominant	Missense	c.1297C>T:p.R433C in *UNC5D*	Feng et al. (2017) [122]	28614238
BSG	Cell signaling	WES	Autosomal dominant	Missense Splicing Nonsense	c.889G>A:p.G297S; c.661C>T:p.P221S in *BSG* c.205C>T:p.Q69X in *BSG* c.415+1G>A in *BSG*	Jin et al. [125] (2017)	28373534
ARR3	Retina-specific signal transduction	WES	X-linked female-limited	Missense	c.893C>A:p.A298D; c.298C>T:p.R100∗ and c.239T>C:p.L80P in *ARR3*	Xiao et al. (2016) [126]	27829781

LOXL3	Transforming growth factor-beta pathway	WES	Autosomal recessive	Frameshift	c.39dup:p.L14Afs∗21; c.39dup:p.L14Afs∗21 and c.594delG:p.Q199Kfs∗35 in *LOXL3*	Li et al. [127] (2016)	26957899
SLC39A5	Transforming growth factor-beta pathway	WES	Autosome dominant Autosome dominant	Nonsense Missense	c.141C>G:p.Y47∗ in *SLC39A5* c.911T>C:p.M304T in *SLC39A5*	Guo et al. [128] (2014)	24891338
SLC39A5	Transforming growth factor-beta pathway	WES	Autosome dominant	Missense	c.1238G>C:p.G413A in *SLC39A5*	Jiang et al. (2014) [123]	25525168
LRPAP1	Transforming growth factor-beta pathway	WES	Autosomal recessive	Frameshift, truncating	N202Tfs∗8 and I288Rfs∗118 in *LRPAP1*	Aldahmesh [129] et al. (2013)	23830514
LRPAP1	Transforming growth factor-beta pathway	WES	Autosomal recessive	Truncating	c.199delC:p.Q67Sfs∗8 in *LRPAP1*	Jiang et al. (2014) [123]	25525168
CTSH	Degradation of proteins in lysosomes	WES	Autosomal recessive	Frameshift, truncating	c.485_488del in *CTSH*	Aldahmesh [129] et al. (2013)	23830514
ZNF644	DNA transcription	WES	Autosomal dominant	Missense	I587V, R680G, C699Y, 3′UTR+12 C>G, and 3′UTR+592 G>A in ZNF644	Shi et al. [130] (2011)	21695231
ZNF644	DNA transcription	WES	Autosomal dominant	Missense	c.2014A>G:p.S672G; c.2048G>C:p.R683T and c.2551G>C:p.D851H	Jiang et al. (2014) [123]	25525168
104 novel genetic variants (73 rare)	–	WES in 14 families	Autosomal dominant	Non synonymous	–	Kloss et al. (2017) [131]	28384719

assigned at meiosis, to enable a "natural" randomized controlled trial. Since the assigned genotypes are independent of non-genetic confounding and are unmodified by disease processes, MR offers a better assessment of causality than that available from observational studies [146, 147].

Two MR studies found a causal effect of education on the development of myopia. One of the MR studies tested for causality bi-directionally [148]. Both found a larger effect through MR than that estimated from observational studies suggesting that confounding in observational studies may have been obscuring the true relationship [149]. As expected, there was little evidence of myopia affecting education (−0.008 years/dioptre, $P = 0.6$). Another study focused on the causality of low vitamin D on myopia due to controversy in the literature [150]. The estimated effects of vitamin D on refractive error were so small (Caucasians: −0.02 [95% CI −0.09, 0.04] dioptres (D) per 10 nmol/l increase in vitamin D concentration; Asians: 0.01 [95% CI −0.17, 0.19] D per 10 nmol/l increase) that the authors concluded that the true contribution of vitamin D levels to degree of myopia is probably zero and that previous observational findings were likely confounded by the effects of time spent outdoors.

5.10 Epigenetics

Epigenetics in refractive error and myopia is postulated to be important due to the known effects of environmental factors on refractive error and myopia development. Nevertheless, this field is still developing and some characteristics of epigenetics render it a difficult issue to unravel. Epigenetic features can be influenced by environmental factors and are time dependent and tissue specific. This complicates the study of these effects, since myopia and refractive errors develop during childhood and young adolescence and obtaining eye tissue, preferably retinal and scleral would be unethical. Furthermore, although some epigenetic processes are conserved across species, this is not always the case: making animal studies not always translational to humans.

Non-Coding RNAs and Myopia The latest GWAS meta-analysis found 31 of 161 loci residing in or near regions transcribing (small) noncoding RNAs, thus hinting towards the importance of epigenetics [18, 151]. MicroRNAs, or miRNAs, are the best-characterized family of small non-coding RNAs. They are approximately 19–24 nucleotides in length in their mature form. They are able to bind to 3′ UTR regions on RNA polymers by sequence-specific post-transcriptional gene silencing; one miRNA can regulate the translation of many genes. MiRNAs have been a hot topic in the last years due to their potential clinical application: the accessibility of the retina for miRNA-based therapeutic delivery has great potential for the prevention and treatment of retinal pathologies [152]. Up to now, there have only been a handful of studies on miRNA and its role in myopiagenesis in humans, these are summarized in Table 5.6.

5.11 Implications for Clinical Management

Due to the high polygenicity of myopia and low explained phenotypic variance by genetic factors (7.8%), clinical applications derived from genetic analyses of myopia are currently limited. Risk predictions for myopia in children are based on

family history, education level of the parents, the amount of outdoor exposure and the easily measurable refractive error and axial length.

Currently, we are able to make a distinction between high myopes and high hyperopes based on the polygenic risk scores derived from CREAM studies: persons in the highest decile for the polygenic risk score had a 40-fold-greater risk of myopia relative to those in the lowest decile.

A prediction model including age, sex and polygenic risk score achieved an AUC of 0.77 (95% CI = 0.75–0.79) for myopia versus hyperopia in adults (Rotterdam Study I–III) [18]. This AUC is similar to that achieved by modelling environmental factors only; the AUC for myopia incidence in a European child cohort was 0.78 considering parental myopia, 1 or more books read per week, time spent reading, no participation in sports, non-European ethnicity, less time spent outdoors and baseline AL-to-CR ratio [156]. To date, one study has assessed both environmental and

Table 5.6 Overview of microRNAs associated with myopia

MiRNA	SNP	Study design	Outcome	Author
MiR-328 binding site in 3′UTR of PAX6 gene	rs662702	High myopia case-control study (Ncase = 1083, ≤−6 D; Ncontrol 1096 ≥−1.5 D)	Down regulation effect on PAX6 expression with C allele, relative to T allele. OR for CC genotype 2.1 ($P = 0.007$). This effect was significant for extreme myopia (<−10 D) and not for high myopia	Liang et al. (2011) [153]
MiR-184	n.a.	MiR-184 region sequenced in 780 unrelated keratoconus patients and 96 unrelated Han southern Chinese patients with axial myopia under the hypothesis that axial myopia is associated with keratoconus, possibly under regulation of MiR-184	No miR-184 mutations were detected in the axial myopia cohort	Lechner et al. (2013) [154]
MiR-29a	rs157907	High myopia case-control study (Ncases = 254, ≤−6 D; Ncontrols = 300, −0.5 to 0.5 D). COL1A1 is possibly targeted by MiR-29a	The G allele of the rs157907 locus was significantly associated with decreased risk of severe myopia (<10 D; $P = 0.04$), compared to the A allele. rs157907 A/G might regulate miR-29a expression levels, but no functional studies have been conducted to confirm this hypothesis	Xie et al. (2016) [155]
Let-7i	rs10877885	High myopia case-control study (Ncases = 254, ≤−6 D; Ncontrols = 300, −0.5 to 0.5 D). COL1A1 is possibly targeted by Let-7i	No significant association with rs10877885 (C/T) was found with myopia risk	Xie et al. (2016) [155]

genetic factors together and showed that modelling both genes and environment improved prediction accuracy [157]. Although these efforts to improve prediction are promising, a prediction-based approach will only be beneficial if randomized controlled trials of atropine therapy show that children with persistent myopic progression benefit from an earlier and higher dose of atropine administration. The additional costs of genetic testing and potentially invasive regime (collecting blood from children) also need to be taken into account.

5.12 Concluding Remarks

The scientific community has discovered more than 200 loci associated with myopia and its endophenotypes with a variety of approaches (linkage, candidate gene, GWAS, post-GWAS gene-based associations, next generation sequencing approaches, gene environment interactions and epigenetic approaches). With the rise of large biobanks, such as the UK Biobank [158], further GWAS meta-analyses between large consortia and companies will enable identification of many more genes. This will allow full elucidation of the molecular mechanism of myopiagenesis. Whole genome sequencing approaches will replace both GWAS and WES, and will elucidate the genetic structure which regulates the function of the myopia risk variants.

To fully understand the underlying mechanisms, the focus should lie on unraveling the genetic and epigenetic architecture of myopia by exploring interactions and effects of other "omics" in relevant tissue, i.e. multi-omics. This concept includes incorporation of methylomics, transcriptomics, proteomics and metabolomics. Future projects should focus on gathering more omics data on eye tissue. Next to the multi-omics approach, modelling gene–environment effects will tell us more about the genetic key players which are also susceptible to the environment. Furthermore, future functional studies interrogating the candidate genes and loci will point us to therapeutic solutions for myopia management.

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