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The Genetic Determinants of Axial Length: From Microphthalmia to High Myopia in Childhood

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Abstract

The axial length of the eye is critical for normal visual function by enabling light to precisely focus on the retina. The mean axial length of the adult human eye is 23.5 mm, but the molecular mechanisms regulating ocular axial length remain poorly understood. Underdevelopment can lead to microphthalmia (defined as a small eye with an axial length of less than 19 mm at 1 year of age or less than 21 mm in adulthood) within the first trimester of pregnancy. However, continued overgrowth can lead to axial high myopia (an enlarged eye with an axial length of 26.5 mm or more) at any age. Both conditions show high genetic and phenotypic heterogeneity associated with significant visual morbidity worldwide. More than 90 genes can contribute to microphthalmia, and several hundred genes are associated with myopia, yet diagnostic yields are low. Crucially, the genetic pathways underpinning the specification of eye size are only now being discovered, with evidence suggesting that shared molecular pathways regulate under- or overgrowth of the eye. Improving our mechanistic understanding of axial length determination will help better inform us of genotype–phenotype correlations in both microphthalmia and myopia, dissect gene–environment interactions in myopia, and develop postnatal therapies that may influence overall eye growth.

INTRODUCTION

Axial Length Specification: From Disrupted Early Development in Microphthalmia to Abnormal Postnatal Growth in High Axial Myopia

Early eye growth is under strict spatiotemporal control coordinated by a self-regulatory network of genes beginning from 3 weeks' gestation in humans and is specified in the anterior neuroectoderm (117). Upregulation of genes encoding eye field transcription factors, including *RAX*, *PAX6*, and *SIX3*, by *OTX2* allows for eye field specification (16, 117, 148, 152). Anterior migration of cells splits the eye field in two, evaginating toward the overlying surface ectoderm and forming two optic vesicles (76). This induces the specification of the lens placode, as well as concurrently inducing invagination of the optic vesicle to form a bilayered optic cup (16, 21, 117, 148, 152). Retinal pigment epithelium (RPE) is derived from the outer layer of the cup, while the inner layer forms the neural retina (**Figure 1*a–c***). The optic fissure forms from an opening on the ventral surface of the optic cup, allowing periocular mesenchyme to form the hyaloid vasculature to support ocular development, and closes by gestational week 7 in humans (36, 44).

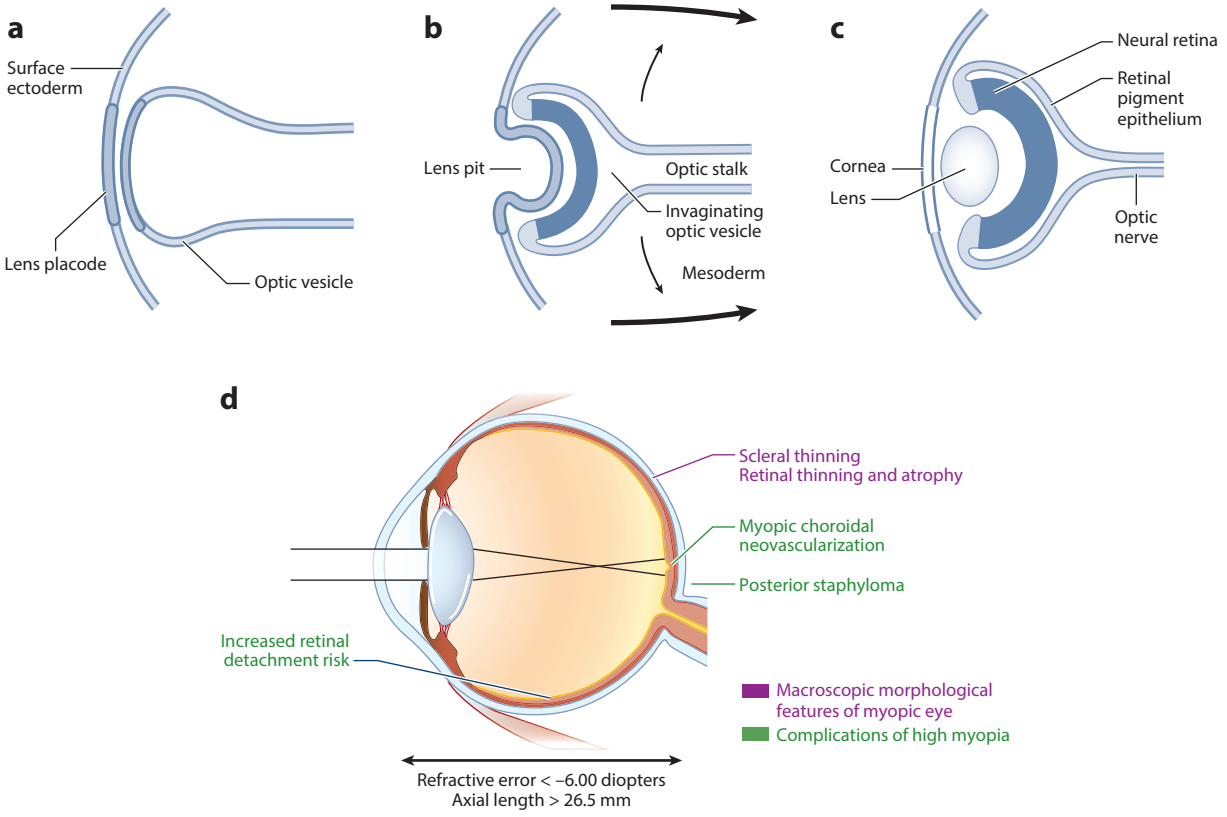

Figure 1

The development of the eye and features of the myopic eye. (*a*) Early development of the optic vesicle at gestational day 22. (*b*) Invagination of the optic vesicle, which occurs by gestational week 5, and scleral development from the embryonic mesenchyme and neural crest from inside to outside (*small arrows*) and anterior to posterior (*large arrows*), which occurs from gestational week 6 onward. (*c*) Postnatal eye with all intact structures. The bilayered optic cup with defined neural retina and retinal pigment epithelium formed at gestational week 7. The lens formed from the hollow lens vesicle, and the cornea developed from the overlying surface ectoderm. (*d*) Macroscopic morphological features of the myopic eye (*purple text*) and complications of high myopia (*green text*).

The human sclera—the dense fibrous tissue forming the outer coat of the eye—differentiates from both the neural crest (surrounding the optic cup) and the mesoderm (contributing to the vascular endothelium and extraocular muscles) in week 6 of human embryonic development (98). Differentiation occurs anterior to posterior, reaching the equator by week 8 and the posterior pole by week 12. The scleral spur can be identified by month 4, and the lamina cribosa is formed by month 5 (109). Microscopically, the sclera is a fibrous connective tissue consisting of lamellae of collagen fibrils interspersed with proteoglycans and noncollagenous glycoproteins. Type I collagen forms approximately 90% of the sclera, along with types III, IV, V, VI, VIII, XII, and XIII. Scleral connective tissue consists of extracellular matrix (ECM) and fibroblasts. Scleral fibroblasts dynamically alter the composition and biomechanical properties of the sclera by remodeling the ECM through the expression of matrix metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-9, and TIMP-1) (98). In addition to the collagen, proteoglycans consisting of a protein core and glycosaminoglycan chain form another key part of the ECM, increasing from childhood throughout life (98).

At birth, the average human eye has an axial length of approximately 16.5–17 mm, growing to 21–23.5 mm in adulthood (83). The newborn eye is hypermetropic, with changes in the cornea, lens, and axial length resulting in adjustment of the refractive state of the eye in a process called emmetropization, which occurs in childhood, with the cornea and lens undergoing the largest transition (118). The incidence of myopia, usually attributed to increased axial length, increases approximately sevenfold during puberty, peaking between ages 9 and 14, with axial length increasing by 0.5 mm (25, 29). Myopia developed during childhood or early adolescence worsens throughout adolescence, stabilizing by the early 20s. Adult-onset myopia is typically less severe compared with myopia developing in childhood. Postnatal eye growth is influenced by visual stimuli that trigger a signaling cascade initiated within the retina, passing through the RPE and choroid and resulting in scleral remodeling (91, 98, 105, 122). Evidence has been obtained largely from form-deprivation and optical-defocus animal models, which suggest that the neural retina is the source of growth-regulating signals (105). High myopia is morphologically characterized by scleral thinning and posterior scleral ectasia (98) (**Figure 1*d***).

Disorders of Axial Length

Disorders of axial length give rise to a spectrum of ocular conditions, ranging from reduced eye size arising in early development, such as microphthalmia and nanophthalmia, to pathological overgrowth resulting in axial myopia. Microphthalmia has a prevalence of 1 in 7,000 births and is defined as the presence of a small eye with an axial length of less than 19 mm at 1 year of age or less than 21 mm in an adult measured on a B-scan ultrasound, representing two or more standard deviations below normal (44, 100) (**Figure 2*a–c***). Nanophthalmia and posterior microphthalmia are rare subsets, where the eye is structurally normal overall but has a reduced axial length of less than 20 mm with high hypermetropia (more than +8.00 diopters) (58, 102).

Microphthalmia is reported in up to 11.2% of blind children and contributes up to 15% of severe visual impairment in children worldwide, with the effect on vision dependent on the severity of the abnormality, the size of the eye, and the associated ocular malformations (47, 136). Microphthalmia exhibits high phenotypic heterogeneity that is often complex and associated with other ocular abnormalities, such as anterior segment dysgenesis, ocular coloboma, cataract, or vitreoretinal dysplasia (103). Systemic malformations may be present, with up to 45% of individuals diagnosed with a recognized syndrome and up to 95% of patients having extraocular features (111, 119). There are no treatments to encourage axial growth in microphthalmic patients, and current management focuses on maximizing existing vision and enhancing cosmetic appearance.

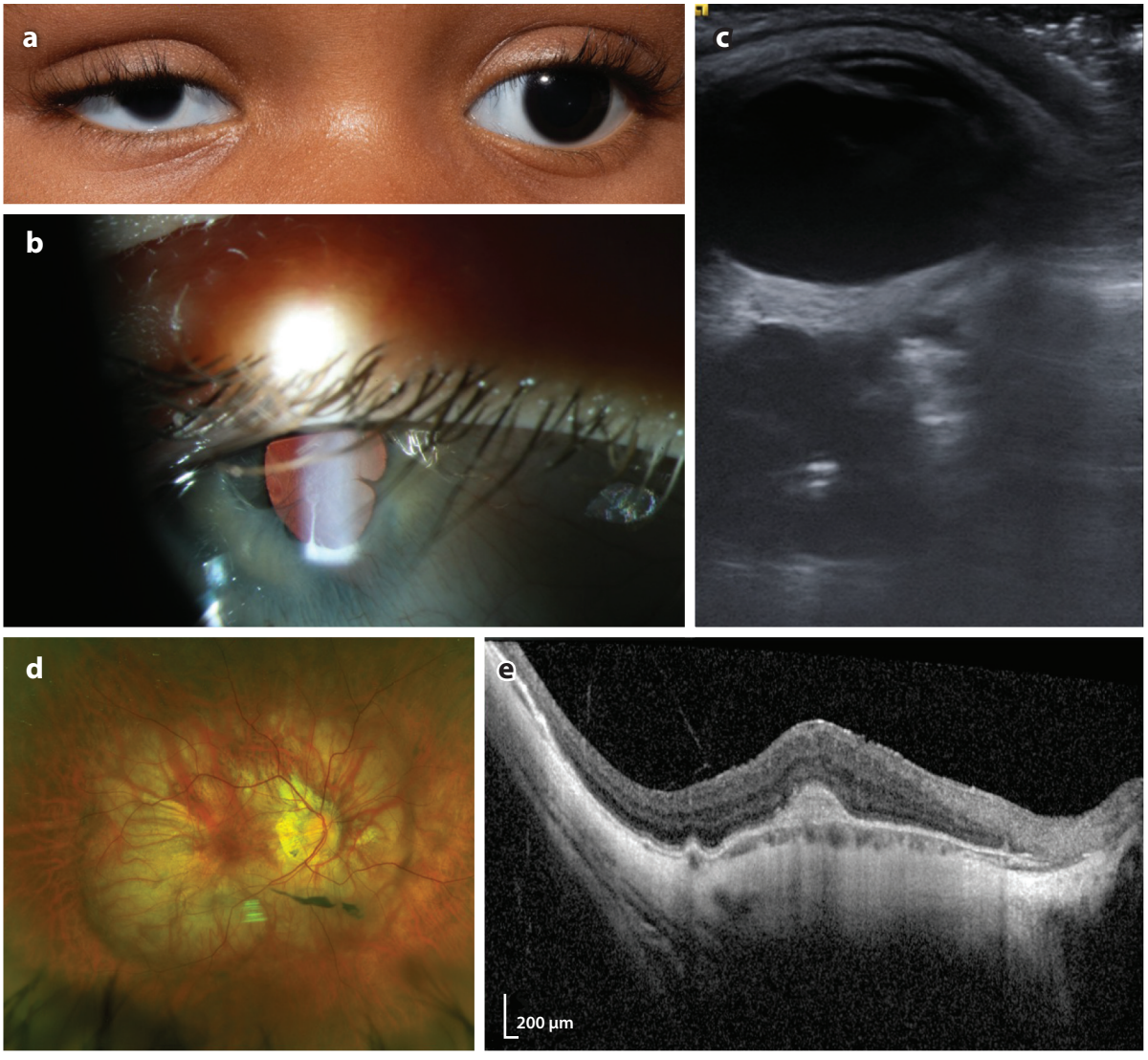

Figure 2

(*a*) External eye photograph of right-sided microphthalmia. (*b*) Slit lamp image of a microphthalmic right eye with an associated anterior segment developmental anomaly. (*c*) B-scan ultrasonography in microphthalmia, showing an axial length of 14.6 mm. (*d*) Pseudocolor fundus image from the right eye of a patient with high myopia, showing posterior pole and peripapillary retinal atrophy and vitreous opacity. (*e*) Optical coherence tomography of myopic macular degeneration with active choroidal neovascular membrane in high myopia.

Depending on methodology, phenotype, and severity, diagnostic rates vary between 33% and 80% for bilateral severe microphthalmia patients, but typically only up to 33% of unilateral patients receive a molecular diagnosis (43, 96). Improving molecular diagnostic rates through increased genetic testing and identification of novel variants will improve understanding of genotype–phenotype relationships and guide patient management and genetic counseling (136).

Refractive error is a function of corneal curvature, lens power, lens position, and axial length. Myopia is a refractive state that occurs when light focuses in front of the retina and can be either

refractive or axial. The most common form of myopia, termed axial myopia, is usually attributable to an abnormally long eye. Myopia is classified as low (or common) myopia if the refractive error is less than −6.00 diopters and as high myopia if the refractive error is −6.00 diopters or greater and/or the eye has an axial length of 26.5 mm or more. Pathological myopia is defined as high myopia with any posterior myopia-specific pathology from axial elongation, such as myopic macular degeneration, which reportedly affects 3% of the world's population and can lead to severe vision loss (30, 87, 139). Myopia can be simple or complex depending on whether the eye exhibits other abnormalities, as well as syndromic or nonsyndromic depending on whether there are extraocular features or systemic disease.

Myopia is a highly complex trait of multifactorial etiology with environmental, behavioral, and genetic influences (68, 147). The global prevalence of myopia has increased drastically over the last two decades, with 30–50% of the adult population now myopic in Europe, America, Australia, and Asia. It is predicted that by 2050, one-fifth of patients with myopia will develop high myopia (46). Refractive symptoms can be treated with glasses, contact lenses, or refractive surgery, and atropine and orthokeratology may slow or prevent axial elongation in common myopia; however, the risk of complications such as retinal detachment, glaucoma, and myopic macular degeneration increases with longer axial length (135) (**Figure 2*d*,*e***). These complications can potentially lead to visual impairment and blindness (32, 106). The development and progression of myopia occur in childhood and adolescence, with up to 16.4% of teenagers in the United Kingdom and more than 95% of those in the Far East affected (32). Emmetropization, a developmental process whereby the refractive systems of the eye balance with the axial length so that light is focused on the retina when viewing at distance, is heavily influenced by environmental factors, resulting in the development of low or moderate myopia during adolescence. Light exposure is a key component of emmetropization: Children with myopia spend less time outdoors, and a lack of sunlight linked to an increasingly urban lifestyle is a key environmental risk factor (127). Randomized controlled trials with children in East Asia demonstrated that increasing time outdoors delayed the onset of myopia and slowed down progression (143).

There is a strong genetic component to the onset and progression of myopia. Mendelian inheritance has been reported (37, 138); however, many common genetic variants (>100) have been associated with risk of refractive error and common myopia via large-scale studies, including studies performed by the Consortium for Refractive Error and Myopia in conjunction with the UK Biobank Eye and Vision Consortium and 23andMe (27, 48, 125, 126). A significant number of patients who present in early childhood (preschool) with high myopia (−6.00 diopters or more) then continue to progress, with increasing axial length and potentially pathological myopia developing over time. These patients also have a strong family history with the same presentation, highly suggestive of a genetic cause, with heritability estimated at over 90% in large twin studies (41, 74). This review focuses on the genetic basis of preschool children with high myopia as a genetic model of axial length determination.

There are an increasing number of examples of how shared genetic pathways between microphthalmia and myopia may influence axial growth. This article discusses the current understanding of the underlying genetic determinants of axial length and potential molecular mechanisms to improve our understanding of the pathology of these two conditions, with a view to developing future therapeutic interventions.

REDUCED AXIAL LENGTH: THE GENETICS OF MICROPHTHALMIA AND NANOPHTHALMIA

Microphthalmia exists on a phenotypic spectrum of ocular maldevelopment with anophthalmia, defined as aborted eye development during optic vesicle formation, leaving a cystic remnant,

and ocular coloboma, a structural malformation resulting from incomplete optic fissure fusion. There is high genotypic heterogeneity, with more than 90 monogenic causes having been identified (**Table 1**), as well as large chromosomal abnormalities in up to 8–15% of patients (55, 92, 96, 107). Environmental causes, such as maternal vitamin A deficiency and alcohol consumption, contribute to approximately 2% of microphthalmia cases (8, 13, 111). All forms of inheritance have been noted (de novo sporadic, autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive), with most pathogenic mutations associated with nonsyndromic cases that sporadically arise de novo, including missense, nonsense, frameshift, and splice-site variants. Variable expressivity and nonpenetrance have been observed, as well as germline mosaicism, creating significant challenges in counseling of patients (6, 96).

Much of our understanding of microphthalmia derives from human cellular and animal models, including mice, zebrafish, and *Xenopus*, given the challenges of studying the molecular development of the human eye at such an early gestational stage (42). The two main groups of disease-causing genes in microphthalmia are (*a*) genes encoding eye field–initiating transcription factors, including *SOX2*, *OTX2*, *RAX*, *VSX2*, and *PAX6*, which regulate further downstream signaling pathways central to tissue specialization (e.g., WNT, BMP, TGFβ, and SHH), and (*b*) the retinoic acid signaling component–encoding genes *STRA6*, *ALDH1A3*, and *RARβ*, which are key for early eye morphogenesis (44).

Heterozygous mutations of *SOX2* account for up to 40% of bilateral microphthalmia (35, 136). More than 70 disease-causing variants have been identified, 60% of which arise de novo, with autosomal dominant inheritance also being reported, leading to microphthalmia from haploinsufficiency (13, 119). *OTX2* mutations account for up to 8% of microphthalmia cases; combined with *SOX2* mutations, these account for up to 60% of bilateral microphthalmia cases (35, 136, 141). Animal modeling in *Xenopus* has shown that *Sox2* and *Otx2* play key roles in early eye specification by coordinating *Rax* signaling, positively regulating the expression of eye field transcription factors, which subsequently downregulates *OTX2* in a negative feedback loop (22, 79). Homozygous or compound heterozygous mutations in *RAX* are responsible for approximately 2% of microphthalmia cases, usually presenting with a bilateral severe phenotype, with *rx3* mutant zebrafish failing to produce optic vesicles (13, 72). *OTX2* is vital for eye development at both early and later stages, including regionalization of the optic vesicle following TGFβ signaling and RPE differentiation following *Wnt* signaling and regulation of *MITF* (148). Nonpenetrance in *OTX2* mutations is high, with 35% of mutations inherited from unaffected parents with no ocular phenotype and thought to be due to gonosomal mosaicism (35, 99, 141). *OTX2* mutations are also associated with highly variable ocular and systemic phenotypes, including anterior segment developmental abnormalities, retinal dystrophy, optic chiasm aplasia, hypopituitarism, and developmental delay, thus presenting a challenge for diagnosis and patient management (108, 124).

PAX6 is a highly conserved regulator of ocular development, mutations in which can cause numerous phenotypes, including aniridia; microphthalmia, anophthalmia, and coloboma; and optic nerve hypoplasia, with patients often having a complex phenotype (112). Most mutations in *PAX6* that cause aniridia are thought to act through a loss of function (haploinsufficiency). Mutations affecting PAX6 enhancers can also cause aniridia (5). Missense mutations, occurring in the paired-box domain that binds to SOX2 and to DNA, are more frequently associated with microphthalmia (56, 136), which has been attributed to residual DNA-binding activity of the mutant PAX6 leading to a worse-than-null phenotype (137).

Pax6 mutant mouse models exhibit small eyes; however, phenotypic severity varies in zebrafish, where missense mutations in the sunrise *pax6b* homozygous line replicate the milder microphthalmia phenotype observed in patients with some missense *PAX6* mutations, while morpholino-induced knockdown of *pax6a* results in more extreme phenotypes, including reduced

Table 1 Genes associated with microphthalmia (M) and nanophthalmia (N)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
SOX2	184429	Microphthalmia, syndromic 3	+	+	M, coloboma, microcornea, iris defect, retinal tuft, optic nerve hypoplasia, reduced palpebral fissure, congenital cataract, glaucoma, colobomatous cyst, synechiae, anterior segment dysgenesis, retinal/chorioretinal dystrophy, myopia
OTX2	600037	Microphthalmia, syndromic 5	+	+	M, coloboma, microcornea, retinal defect, optic nerve hypoplasia/aplasia, small/absent optic chiasm, Leber congenital amaurosis, early onset retinal dystrophy, hyperopia, amblyopia, cataract, focal retinal dysplasia, corectopia, synechiae, sclerocornea, persistent pupillary membrane, nystagmus, posterior vitreous opacity
RAX	601881	Microphthalmia, isolated 3	+	+	M, coloboma, sclerocornea, persistent fetal vasculature, retinal detachment, optic nerve atrophy/hypoplasia
VSX2	142993	Microphthalmia, isolated 2 Microphthalmia, isolated with coloboma 3	−	+	M, coloboma, congenital cataract/cloudy cornea, iris defect, microcornea, no pupillary aperture, retinal detachment, dislocated lens, small/underdeveloped optic nerve/chiasm, retinal dysfunction
PAX6	607108	Aniridia 1	+	+	M, coloboma, aniridia/iris hypoplasia, anterior segment dysgenesis, agenesis of optic nerve/chiasm, primary aphakia, sclerocornea, congenital glaucoma
STRA6	610745	Microphthalmia, syndromic 9	+	+	M, coloboma, cyst, retinal detachment, abnormal cornea/iris
RARβ	180220	Microphthalmia, syndromic 12	−	+	M, coloboma, sclerocornea, anterior segment dysgenesis
ALDH1A3	600463	Microphthalmia, isolated 8	+	+	M, coloboma, microcornea corectopia, cyst, hypoplastic/small optic nerve/tract/chiasm, small/short palpebral fissure, conjunctival discoloration, symblepharon, nystagmus, iris attachment to the cornea
FOXE3	601094	Anterior segment dysgenesis 2	+	+	M, coloboma, anterior segment dysgenesis, sclerocornea, aphakia, aniridia
BMP4	112262	Microphthalmia, syndromic 6	+	+	M, coloboma, microcornea, retinal dystrophy, myopia, sclerocornea, anterior segment dysgenesis, corectopia, blepharophimosis, optic nerve hypoplasia, tilted/anomalous optic disc, cyst, nystagmus, cataract, glaucoma, aphakia, embryotoxon, persistent hypoplastic primary vitreous

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
BMP7	112267	None	–	+	M, coloboma
GDF6	601147	Microphthalmia, isolated 4 Microphthalmia, isolated with coloboma 6, digenic	+	+	M, coloboma, optic nerve hypoplasia, foveal hypoplasia, nystagmus
ABCB6	605452	Microphthalmia, isolated with coloboma 7	+	–	M, coloboma
ATOH7	609875	Persistent hyperplastic primary vitreous, autosomal recessive	+	–	M, microcornea, congenital cataract/corneal opacity, optic nerve aplasia/hypoplasia, retinal detachment/nonattachment, persistent fetal vasculature, nystagmus, vitreous degeneration, glaucoma, shallow anterior chamber, anterior displacement of the iris, peripheral anterior synechiae, calcifications present on the hyaloid membranes/retina/vitreous, vitreoretinal dysplasia
C12orf57	615140	Temtamy syndrome	–	+	M, coloboma
TENM3	610083	Microphthalmia, isolated with coloboma 9	+	–	M, coloboma, microcornea, nystagmus, esotropia, myopia, retinal detachment
VAX1	604294	Microphthalmia, syndromic 11	–	+	M, optic nerve hypoplasia, small optic nerve, cyst
SMOC1	608488	Microphthalmia with limb anomalies	–	+	M, optic nerve hypoplasia
FNBP4	615265	Microphthalmia with limb anomalies	–	+	M, anophthalmia
SHH	600725	Microphthalmia, isolated with coloboma 5	+	+	M, coloboma, funnel retinal detachment with subretinal opacity, microcornea, small optic nerve, retinal dystrophy, tilted optic disc, myopia, nystagmus, glaucoma, posterior embryotoxon
NAA10	300013	Microphthalmia, syndromic 1	–	+	M, anophthalmia
BCOR	300056	Microphthalmia, syndromic 2	–	+	M, congenital cataract, microcornea, posterior embryotoxon, secondary aphakia, secondary glaucoma, retinal detachment, persistent fetal vasculature, iris heterochromia, nystagmus, myopia, iris rubeosis, flat anterior chamber
HCCS	300056	Linear skin defects with multiple congenital anomalies 1	–	+	M, corneal opacity/cloudy and vascular cornea, cyst, sclerocornea, glaucoma
MAB21L2	604357	Microphthalmia, syndromic 14	–	+	M, coloboma, microcornea, exotropia, sclerocornea, strabismus

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
RBP4	180250	Microphthalmia, isolated with coloboma 10	+	+	M, coloboma, small optic nerve/chiasm, cyst, underdeveloped extraocular muscles
GL12	165230	Holoprosencephaly 9	–	+	M, coloboma, optic nerve agenesis
PORCN	300651	Focal dermal hypoplasia	–	+	M, coloboma, aniridia, strabismus, ectopia lentis
FRAS1	607830	Fraser syndrome 1	–	+	M, fused/small palpebral fissure, cryptophthalmos
SMCHD1	614982	Bosma arrhinia microphthalmia syndrome	–	+	M, coloboma, hypertelorism, occluded or absent nasolacrimal duct, cataract
SIX6	606326	Microphthalmia, syndromic 6	–	+	M, coloboma, cataract, nystagmus, secondary glaucoma, optic nerve dysplasia/absence of optic nerve/chiasm/tract, retinal dystrophy, cyst
TFAP2A	107580	Branchiooculofacial syndrome	–	+	M, coloboma, cataract/corneal clouding, reduced corneal diameter, primary aphakia, sclerocornea, retinal detachment, lacrimal duct obstruction, cyst, subluxed cataractous lens, shallow anterior chamber, persistent pupillary membrane, iris hypoplasia, dysplastic optic disc
TCTN2	613846	Meckel syndrome, type 8	–	+	M, anophthalmia
CSPP1	611654	Joubert syndrome 21	–	+	M, anophthalmia
COL4A1	120130	Brain small vessel disease with or without ocular anomalies	–	+	M, microcornea, Peter's anomaly, retinal detachment, congenital cataract, glaucoma, anterior segment dysgenesis, hypermetropia, astigmatism
PTCH1	601309	Holoprosencephaly 7	+	+	M, coloboma, cataract, sclerocornea, anterior segment dysgenesis
TBC1D32	615867	Orofaciodigital syndrome IX	–	+	M, coloboma
CHD7	605806	CHARGE syndrome	+	+	M, coloboma, microcornea, cataract, persistent fetal vasculature
MFRP	606227	Microphthalmia, isolated 5 Nanophthalmos 2	+	–	M, nanophthalmia, retinitis pigmentosa, foveoschisis, optic disc drusen, macular edema, glaucoma, hyperopia
PRSS56	613858	Microphthalmia, isolated 6	+	–	M, N, hyperopia, elevated papillomacular retinal fold, shallow anterior chamber, thick lens, thickened scleral wall
TMEM98	615949	Nanophthalmos 4	+	–	N, hyperopia, angle closure glaucoma, narrow iridocorneal angle, shallow anterior chamber depth, optic disc drusen
HMGB3	300193	Microphthalmia, syndromic 13	–	+	M, coloboma, congenital cataract

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
PXDN	605158	Cornea opacification and other ocular anomalies	+	+	M, sclerocornea, anterior segment dysgenesis, iridocorneal dysgenesis, glaucoma, cataract
TMX3	616102	Microphthalmia with coloboma 1	+	+	M, coloboma, cyst
YAP1	606608	Coloboma, ocular, with or without hearing impairment, cleft lip/palate, and/or mental retardation	+	+	M, coloboma, extraocular muscle defect, cataract, ectopic pupil
IPO13	610411	None	+	–	M, coloboma, cataract, narrowed palpebral fissure, nystagmus, microcornea
PITX3	602669	Cataract 11, multiple types	–	+	M, cataract/corneal opacity
NDP	300658	Norrie disease	+	–	M, sclerocornea
MITF	156845	COMMAD syndrome	–	+	M, coloboma, microcornea with pannus, cataract, translucent irides, optic nerve/tract hypoplasia
FOXC1	601090	None	+	–	M, microcornea, sclerocornea, cyst, myopia, cataract, Rieger anomaly, retinal detachment
CRPPA	614631	Muscular dystrophy–dystroglycanopathy type A	–	+	M, cataract, optic nerve hypoplasia
FANCL	608111	Fanconi anemia, complementation group L	–	+	M, short upslant palpebral fissure, indiscernible pupil
SMO	601500	Curry–Jones syndrome	–	+	M, coloboma, unusually shaped pupil
DOCK6	614194	Adams–Oliver syndrome	–	+	M, retinal detachment
CRYAA	123580	Cataract 9, multiple types	+	–	M, congenital cataract
FOXL2	605597	Blepharophimosis, ptosis and epicanthus inversus	+	+	M, blepharophimosis, ptosis, epicanthus inversus, telecanthus, strabismus
CRYBA4	123631	Cataract 23, multiple types	+	–	M, enophthalmia
ERCC6	609413	Cerebrooculofacioskeletal syndrome 1	–	+	M, congenital cataract, short palpebral fissure, blepharokeratoconjunctivitis
ERCC5	133530	Cerebrooculofacioskeletal syndrome 3	–	+	M, cataract
ERCC1	126380	Cerebrooculofacioskeletal syndrome 4	–	+	M, blepharophimosis
SRD5A3	611715	Congenital disorder of glycosylation, type 1q	–	+	M, coloboma, nystagmus, cataract, optic atrophy
SALL4	607343	Duane–radial ray syndrome	–	+	M, coloboma, optic nerve hypoplasia
FREM2	610937	Fraser syndrome 2	+	+	M, coloboma, cyst
RPGRIP1L	610937	Meckel syndrome 5	+	+	M
SLC25A24	608744	Fontaine progeroid syndrome	+	+	M

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
FAM111A	615292	Gracile bone dysplasia	+	+	M
SMG9	613176	Heart and brain malformation syndrome	+	+	M
SIX3	603714	Holoprosencephaly 2	–	+	M, coloboma, myopia, astigmatism, dysplastic optic nerve, nystagmus, exotropia, cataract, hypertropia
PDE6D	602676	Joubert syndrome 22	+	+	M, coloboma
KMT2D	602113	Kabuki syndrome 1	–	+	M, cyst
PAX2	167409	Papillorenal syndrome	–	+	M, coloboma optic nerve dysplasia, retinal degeneration
TMEM216	613277	Meckel syndrome, type 2	+	+	M
CEP290	610142	Meckel syndrome, type 4	+	+	M, Leber congenital amaurosis, retinal dystrophy
KIF11	148760	Microcephaly with or without chorioretinopathy, lymphoedema, or mental retardation	+	+	M, coloboma, cataract, chorioretinopathy, hypermetropia, persistent hyaloid artery, peripheral fibrovascular proliferation, retinal detachment
SNX3	605930	None	+	+	M
ZEB2	605802	Mowat–Wilson syndrome	–	+	M, cataract, retinal aplasia, corectopia, optic nerve hypoplasia/pallor, retinal atrophy
POMT1	607423	Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type A, 1	–	+	M, anterior chamber dysgenesis, exophthalmia, buphthalmos, megalocornea, glaucoma, retinal dysplasia, congenital cataract/corneal clouding, retinal detachment
POMT2	607439	Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type A, 2	–	+	M, Peter's anomaly, cataract, buphthalmos
POMGNT1	614828	None	–	+	M, corneal opacity, cataract
FKTN	607440	Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type 4	–	+	M, retinal detachment
FKRP	606596	Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type 5	–	+	M, cataract, asymmetric pupils, persistent hyperplastic primary vitreous, anterior chamber abnormality
DAG1	128239	Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type 9	–	+	M, buphthalmos, corneal opacity, glaucoma, retinal detachment

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
B3GALNT2	610194	Muscular dystrophy–dystroglycanopathy (congenital with brain and eye anomalies), type 11	–	+	M, cataract, optic nerve hypoplasia, myopia
RAB3GAP1	602536	Warburg micro syndrome 1	–	+	M, microcornea, cataract
NHS	300457	Nance–Horan syndrome, cataract 40, X-linked	–	+	M, microcornea, congenital cataract
HMX1	142992	Oculoauricular syndrome	–	+	M, microcornea, coloboma, nystagmus, cataract, microphakia, synechiae, anterior segment dysgenesis, small dysplastic optic disc, strabismus, sclerocornea, posterior embryotoxon, stromal iris cyst, retinal dystrophy, dysplastic macropapillae, macular hypoplasia, iridocorneal adherences, enophthalmus, esotropia, calcified phthisis bulbi
GJA1	121014	Oculodentodigital dysplasia	+	+	M, cataract, uveitis, glaucoma, persistent pupillary membrane
LRP5	603506	Osteoporosis–pseudoglioma syndrome	–	+	M, retinal detachment, persistent hyperplasia of the primary vitreous
PQBP1	300463	Renpenning syndrome	–	+	M, coloboma
TUBB	191130	Symmetric circumferential skin creases, congenital 1 Cortical dysplasia, complex, with other brain malformations 6	–	+	M, short palpebral fissure, retinal dysplasia, microcornea
MAPRE2	605789	Symmetric circumferential skin creases, congenital 2	–	+	M, short/slanting palpebral fissure, strabismus, ptosis
SALL1	602218	Townes–Brocks syndrome 1	–	+	M, anophthalmia, abnormal lens, aplastic optic nerve, small optic chiasm
HDAC6	300272	Chondrodysplasia with platyspondyly, distinctive brachydactyly, hydrocephaly, and microphthalmia	+	+	M
ALX1	601527	Frontonasal dysplasia 3	–	+	M, coloboma
RERE	605226	Neurodevelopmental disorder with or without anomalies of the brain, eye or heart	–	+	M, coloboma, optic nerve hypoplasia, anisometropia
RAB18	602207	Warburg micro syndrome 3	–	+	M, microcornea, congenital cataract, small atonic pupil, progressive optic atrophy
CRB1	604210	Leber congenital amaurosis 8, pigmented paravenous chorioretinal atrophy, retinitis pigmentosa 12	+	+	M, N, retinal dystrophy

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM number	Disease	Isolated	Syndromic	Ocular abnormality
BEST1	607854	Macular dystrophy, vitelliform, 2 Bestrophinopathy, autosomal recessive Retinitis pigmentosa 50 Vitreoretinochoroidopathy	+	–	N, retinal dystrophy
MYRF	608329	Cardiac–urogenital syndrome Encephalitis/encephalopathy, mild, with reversible myelin vacuolization	+	+	N

Abbreviations: CHARGE, coloboma, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness; COMMAD, coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness.

body size and abnormal brain development. Caution is required in interpreting zebrafish models in these circumstances, as the human phenotype may not be accurately recapitulated due to gene duplication leading to role sharing among multiple orthologous genes (18, 24, 63, 104).

In addition to the eye field–initiating transcription factors, retinoic acid signaling is vital for early optic cup morphogenesis, and mutations in several stages of the pathway lead to microphthalmia. Retinoic acid is released from the developing lens placode and surrounding mesenchyme, which bind to the optic vesicle, stimulating invagination of the optic vesicle from 31 days' gestation (21). Mutations in *STRA6*—encoding a transmembrane receptor for a retinol-binding protein responsible for mediating vitamin A uptake into cells—cause variable phenotypes, ranging from anophthalmia/microphthalmia to coloboma, highlighting the importance of the retinoic acid signaling pathway in eye development (12, 14). *RARβ*, encoding one of three retinoic acid receptors that transduce retinoic acid signals, is implicated in microphthalmia and anophthalmia through missense, nonsense, and frameshift mutations (121). Mutations in *ALDH1A3*—encoding one of three human retinaldehyde dehydrogenases that are crucial to the retinoic acid synthesis pathway via oxidation of retinaldehyde acid (21)—may cause up to 10% of microphthalmia cases (119).

Abnormalities in the correct assembly of the ECM may also form an important underlying mechanism in the etiology of microphthalmia. The ECM plays a critical role in early optic vesicle development and in retinal progenitor cell differentiation (110). A notable example is *COL4A1*, encoding a subunit of type IV collagen that regulates RPE growth, mutations of which lead to a range of ocular maldevelopment issues, including microphthalmia (78). Further characterization of the role of the ECM in the developing eye is required.

Nanophthalmia can be defined as a subset of microphthalmia. Diagnostic criteria vary widely, including not only a high hypermetropic refractive error (more than +8.00 diopters) but also axial length (less than 20 mm), posterior wall thickness, and lens/eye volume ratio metrics, and there is overlap with posterior microphthalmia, in which only the posterior segment is shortened (140, 144). Clear distinctions are required in phenotyping patients, which will subsequently allow identification of genotype–phenotype correlations and improve understanding of the mechanism of genetic control of axial length. There is consensus that a nanophthalmic eye is small but structurally macroscopically normal other than thickened sclera and choroid (11, 123, 132). However, significant microscopic morphological changes underlie the pathology, with abnormal collagen fibers that are split and frayed in all scleral layers (145). Because many nanophthalmia

genes are expressed in the retina and RPE, it is unclear whether the primary pathology seen is of the sclera or a secondary abnormality within a yet-to-be-identified retina–RPE–sclera signaling cascade. Despite having a grossly normal macroscopic eye structure, patients with nanophthalmia are still at high risk of sight-threatening sequalae, including amblyopia, uveal effusion syndrome, and angle closure glaucoma (11, 90).

Nanophthalmia can be sporadic or inherited in autosomal recessive and autosomal dominant forms (3, 77, 80, 90) (**Table 1**). Six genes have now been identified in familial forms of nanophthalmia, with *PRSS56* and *MFRP* mutations being the most common (discussed further below, along with *TMEM98*) (2, 85, 97, 115). Interestingly, variants in genes usually associated with retinal dystrophy have also been associated with nanophthalmia. Mutations in *CRB1*, encoding a transmembrane protein on the photoreceptor inner segments, typically result in either Leber congenital amaurosis or retinitis pigmentosa (73). Novel homozygous missense variants have been identified in exon 5 (c.1125C>G) and exon 7 (c.2498G>A) of *CRB1* in two separate families with retinitis pigmentosa and nanophthalmia (93, 149). Additionally, mutations in *BEST1*, encoding a calcium-activated chloride channel localized to the RPE, are associated with vitelliform macular dystrophy and (rarely) autosomal dominant vitreoretinochoroidopathy; the latter occurs from mutations in splicing regulators of *BEST1* and is associated with nanophthalmia and chorioretinal atrophy (65, 146). Finally, a C-terminal mutation in the penultimate *MYRF* exon has recently been identified to cause a rare form of autosomal dominant nanophthalmia (116). One further chromosomal locus, *NNO3* (OMIM 611897), reported to be linked to chromosome 2q11–14 (66), has been associated with autosomal dominant nanophthalmia, but the gene is not yet known.

THE GENETICS OF AXIAL MYOPIA

More than 25 chromosomal loci and 100 genes are known to be associated with nonsyndromic axial high myopia, identified through linkage analysis, twin studies, candidate gene analysis, genome-wide association studies (GWASs), pathway analysis, and next-generation sequencing (9, 133). GWASs have identified many common variants and have been conducted among numerous ethnic groups with phenotypic features of high myopia, including refractive error, axial length, and decreased macular thickness. Several GWASs and meta-analyses have found that myopia or refractive error is associated with single-nucleotide polymorphisms in the vicinity of *GJD2*, *RASGRF1*, *GRIA4*, *KCNQ5*, *RDH*, *LAMA2*, *BMP25*, *SIX6*, *PRSS56*, *CTNND2*, *ZC3H11B*, *SNTB1*, *VIPR2*, and *ZFHX1B* (26, 60, 69, 113), with functional analyses producing useful subdivisions and giving insight into potential mechanisms, which include ECM remodeling, retinoic acid signaling and photoreceptor development, neurotransmission, ion channel activity, and ocular and central nervous system development (48, 49, 61, 131). The understanding of how these genes relate to axial growth and ocular development is limited, however.

To date, whole-exome sequencing has been used primarily to identify novel mutations in known high-myopia genes, with the majority of variants displaying an autosomal dominant inheritance pattern (*ZNF644*, *SCO2*, *SLC39A5*, *CCDC111*, *P4HA2*, *BSG*, *CPSF1*, *NDUFAF7*, *TNFRSF21*, *XYLT*, and *DZIP1*), but autosomal recessive inheritance (*LRPAP1*, *CTSH*, *LEPREL1*, and *LOXL3*) and X-chromosome genes (*ARR3* and *OPN1LW*) have also been reported (67) (**Table 2**). Functional division of these groups provides further insight into potential high-myopia mechanisms, including TGFβ signaling (*SLC39A5*, *LRPAP1*, and *LOXL3*), collagen synthesis (*P4HA2* and *LEPREL1*), cell signaling (*BSG*), transcription factors (*CCDC111* and *ZNF644*), retinal signal transduction (*ARR3* and *OPN1LW*), mitochondrial function (*NDUFAF7* and *SCO2*), and lysosomal protein degradation (*CTSH*). Despite this progress, a large number of unidentified genes

Table 2 Genes identified by next-generation sequencing as causing nonsyndromic high myopia

Gene	Inheritance pattern	Pathway	Mutation type(s)	Reference(s)
ZNF644	Autosomal dominant	DNA transcription	Missense	50, 114
CCDC111	Autosomal dominant	DNA transcription	Missense	151
SLC39A5	Autosomal dominant	TGFβ	Nonsense Missense	40, 50
LRPAP1	Autosomal recessive	TGFβ	Nonsense Frameshift	50
LOXL3	Autosomal recessive	TGFβ	Frameshift	1
P4HA2	Autosomal dominant	Collagen synthesis	Missense	39
LEPREL1	Autosomal recessive	Collagen synthesis	Missense Nonsense	40
ARR3	X-linked (female)	Retinal signal transduction	Missense	142
OPN1LW	X-linked	Retinal signal transduction	Missense Frameshift	67
SCO2	Autosomal dominant	Mitochondrial function	Missense Nonsense	50, 129
NDUFAF7	Autosomal dominant	Mitochondrial function	Missense	28
CTSH	Autosomal recessive	Lysosomal degradation	Nonsense	1
BSG	Autosomal dominant	Cell signaling	Missense Splicing Nonsense	52
UNC5D	Autosomal dominant	Cell signaling	Missense	28

remain, as fewer than 5% of high-myopia patients have mutations within genes that have been identified through next-generation sequencing (50).

There is increasing and reproducible evidence that the TGFβ signaling pathway is disrupted in high myopia. *LRPAP1* encodes a chaperone, LRP1, that regulates TGFβ activity, with homozygous nonsense (p.R68X) and frameshift (p.Q67Sfs*8) mutations having been identified by whole-exome sequencing in high myopia (1, 50). The regulation of TGFβ activity by *LRPAP1* is supported by the *Lrpap1* (SM22-Cre^{+};LRP$^{flox/flox}$;LDLR$^{-/-}$) knockout mouse model, which revealed activation of TGFβ target genes (*TSP1* and *PDGFRβ*) upon loss of *Lrpap1* (7). Further functional evidence that the TGFβ/BMP pathway is involved in myopia pathogenesis comes from pathogenic variants in *SLC39A5*; a total of 13 missense and 2 nonsense mutations cause high myopia (10, 28). In a lymphocyte cell line carrying the *SLC39A5*$^{p.Y47X}$ nonsense mutation, there was upregulation of *SMAD1*, which encodes a downstream transcription factor of the TGFβ/BMP pathway. *SLC39A5* encodes a zinc transport complex situated in the Golgi apparatus and is expressed in mouse sclera, inner retina, and retinal outer plexiform and ganglion cell layers. Immunofluorescence demonstrates that *SLC39A5* is detectable in both embryonic and postnatal mouse eye cryosections (38). In addition to being central to early eye development and retinal morphogenesis, TGFβ signaling is thought to modulate the postnatal scleral ECM, dysregulation of which is associated with high myopia in both tree shrew animal models and GWAS data (53, 54, 131).

Appropriate ECM remodeling is required for normal eye size development, dysregulation of which has been identified in high myopia. *P4HA2* encodes prolyl 4-hydroxylase α-polypeptide II, which catalyzes the 4-prolyl hydroxylation of collagens, a major ECM constituent. Prolyl hydroxylation is essential to correct three-dimensional folding of newly synthesized procollagen chains for collagen (84). Eight mutations in *P4HA2* associated with high myopia have been identified to

date (p.E291K, p.R451Gfs*8, p.K443X, p.Q140R, p.I150V, p.G296W, p.D128N, and p.184delH) (10, 39). Interestingly, *LEPREL1*, identified to cause autosomal recessive myopia, also encodes a collagen prolyl hydroxylase. Four homozygous mutations [two missense mutations (p.G508V and p.L349P), one nonsense mutation (p.Q5X), and one frameshift mutation in *LEPREL1*] have been identified to cause myopia (40, 52, 59, 81).

ZNF644 encodes a transcription factor that is expressed in all tissues, including human neural retina and RPE, and is postulated to regulate protein domain function. Whole-exome sequencing showed that a missense mutation in exon 3 (p.S672G) was responsible for autosomal dominant myopia in a Chinese family (114). Further heterozygous mutations in *ZNF644* responsible for high myopia following screening across different populations were also identified, implicating this gene in high myopia (128). A novel missense variant in *CCDC111* (p.Y89D) has been identified in a family with high myopia (151); *CCDC111* is highly conserved across species and ubiquitously expressed in numerous tissues, including scleral fibroblasts, RPE, and Müller cells, but its precise functions remain unknown.

BSG mutations predispose to early-onset high myopia; six missense mutations (p.P221S, p.G297S, p.G219R, p.G37R, p.G24S, and p.R129C), one nonsense mutation (p.Q69X), and one splicing defect (c.415+1G>A) in this gene have been identified (10, 52). *BSG* plays a role in developmental cell signaling, encoding a photoreceptor-specific transmembrane protein, which interacts with rod-derived cone viability factor in retinal maturation (15). The role of *BSG* in influencing axial length has been supported by a *Bsg* knock-in mouse model with a c.901G>A mutation, corresponding to the human c.889G>A p.G297S mutation, which led to an elongated axial length and myopic phenotype (50).

Retinal signal transduction has also been implicated in myopia. Three heterozygous variants in *ARR3* (p.A298D, p.R200X, and p.L80P), located on Xq13.1, have been associated with high myopia in female patients in a highly unusual pattern of X-linked female limited inheritance (142). *ARR3* encodes a cone arrestin that is enriched in the retina. *Arr4* knockout mice develop a cone-like dystrophy; however, the mechanisms and role of human *ARR3* remain poorly understood (23). *OPN1LW*, which is located on Xq28 and encodes one of three cone light-absorbing opsins, has been identified as a cause of X-linked syndromic and nonsyndromic high myopia with a frameshift p.Phe208Argfs*51 mutation (67). Investigation of a multigenerational family with X-linked high myopia and cone dystrophy showed rare exon 3 interchange haplotypes of the *OPN1LW* and *OPN1MW* genes, causing apparently nonsyndromic high myopia in young patients but leading to progressive cone–rod dystrophy with loss of color vision and visual acuity in middle-aged patients (88).

SCO2 and *NDUFAF7*, which are involved in mitochondrial function, have been reported to be responsible for pathological myopia. *SCO2* encodes a cytochrome *c* oxidase assembly protein, dysfunction in which may alter copper homeostasis in ocular tissues, resulting in axial elongation. To date, 10 mutations (including nonsense and missense variants) have been associated with autosomal dominant high myopia (129). This finding has been contested, however, as mice with p.E129K knock-in mutations (corresponding to p.E140K in humans) that result in Sco2 deficiency do not exhibit any axial elongation; therefore, it remains uncertain whether *SCO2* is related to axial or other forms of myopia (95).

CTSH encodes one of the cysteine proteases with a role in the degradation of lysosomal proteases. Whole-exome sequencing has identified a 4-bp deletion in *CTSH* causing high myopia (1). The role of *CTSH* in axial length is further supported by *Ctsb*-knockout mice that develop a markedly abnormal globe with an unusual <-shaped morphology that is thought to be due to lengthening of the posterior chamber, although the association has not been formally measured (1).

Monogenic causes of high myopia are typically complex and syndromic, caused by a highly penetrant gene. High myopia is typically a feature of Marfan syndrome (*FBN1*), Stickler syndrome (*COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3*), and several inherited retinal dystrophies (71, 75). The most common inherited retinal dystrophies include congenital stationary night blindness (*CACNA1F* and *NYX*) and X-linked retinitis pigmentosa caused by hemizygous variants in *RPGR* (45, 68). Syndromic forms of myopia are typically rare and form the exception. The association with inherited retinal dystrophies and myopia provides evidence that retinal genes are influencing scleral remodeling and eye growth. These results are further supported in form-deprivation myopia, whereby alterations of the visual stimulus trigger a signaling cascade originating in the retina. Interestingly, Stickler and Marfan syndromes are also associated with high myopia, suggesting that scleral weakness results in a mechanical stretch that causes axial elongation as part of the primary pathology. Ultimately, the role of the retina–RPE–sclera pathway and its modulators in specifying axial length requires detailed characterization.

SHARED MOLECULAR PATHWAYS SPECIFYING AXIAL LENGTH

Shared genes and molecular pathways between microphthalmia/nanophthalmia and myopia are now being identified; candidate genes are summarized in **Figure 3**. Ocular growth has been divided into two distinct phases, prenatal and postnatal. Prenatal growth, in the absence of visual stimuli, is controlled by genetic influences, perturbations of which lead to microphthalmia. Conventionally, postnatal growth is guided by visual stimuli as part of the process of emmetropization, ensuring that the axial length of the eye is appropriate for the optical power, errors in which lead to axial myopia. The presence of shared genes involved in both phases of ocular growth would suggest that there are underlying molecular pathways specifying eye size, which act both dependently and independently of visual stimuli.

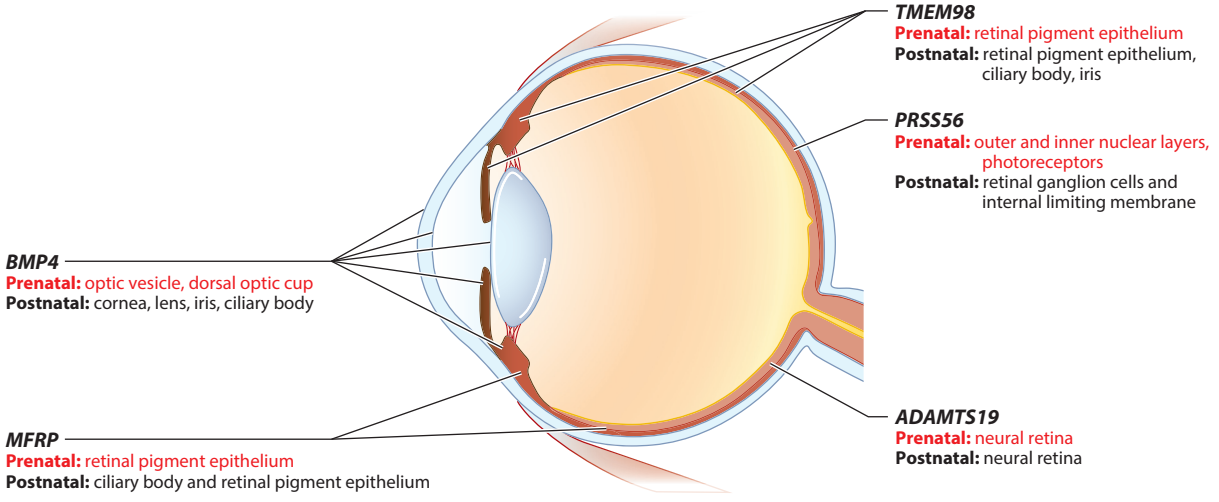

Figure 3

Shared genes involved in both microphthalmia and myopia and their expression in prenatal eye development (*red text*) and the postnatal eye (*black text and leader lines*). Further studies are required to determine the role of these genes in human early eye development and postnatal growth.

PRSS56 and *MFRP* mutations have been identified as a cause of familial autosomal recessive nanophthalmia (2, 85, 89, 97, 115). GWAS meta-analyses have also associated common single-nucleotide polymorphisms in *PRSS56* and *MFRP* (rs1550094 and rs10892353, respectively) with myopia (48, 125). Human *MFRP*, expressed in the RPE and ciliary body, encodes a transmembrane protein with an extracellular frizzled-related domain (123). Such proteins act through the Wnt signaling pathway to regulate ocular growth, differentiation, and cellular polarity (4, 57). There are at least 17 identified missense and nonsense mutations in *MFRP* in different populations leading to reduced axial length (82, 86, 134). In addition to reduced axial length, patients with *MFRP* mutations can exhibit foveoschisis, optic nerve head drusen, and retinitis pigmentosa (86, 123, 150). The phenotypic spectrum is quite varied, with no genotype–phenotype correlations yet identified (134). Both zebrafish and mouse models recapitulate the human phenotype of reduced axial length and retinal abnormalities (17, 31, 130). Interestingly, adenoviral-based gene therapy may reverse some of these pathogenic changes in $Mfrp^{rd6}/Mfrp^{rd6}$ mice, with resulting rescue of axial length in adult mice.

It is postulated that *MFRP* may act as part of a regulatory network specifying ocular axial length in conjunction with the serine protease–encoding genes *PRSS56* and *ADAMTS19* (64, 120). *PRSS56* is expressed in retinal ganglion cells and the internal limiting membrane of adult animal and embryonic eyes, at the boundary of the vitreous and retina, where a basement membrane containing laminins and type IV collagen resides (34). PRSS56 might remodel ECM via the Müller glia, which span the retina, allowing transduction to RPE. $Prss56^{-/-}$ mutant mice display a phenotype of reduced axial length and, like $Mfrp^{rd6}/Mfrp^{rd6}$ mice, demonstrate significant upregulation of Adamts19 in the retina (64, 85). Interestingly, loss of PRSS56 or MFRP function prevents excessive ocular axial growth in a mouse model of early-onset myopia caused by a null mutation in *Irbp*, further supporting the evidence of their role in axial elongation (64).

TMEM98 encodes a transmembrane protein expressed throughout the body and in the RPE, ciliary body, and iris of the adult eye (3). Two missense variants, p.A193P and p.H196P, and a small exon 4 deletion that also involves the adjacent intron are associated with autosomal dominant nanophthalmia; however, GWASs have identified 5′ variants associated with myopia (3, 61, 94, 125). One of the 5′ variants, rs10512441, located 15 kb upstream of the *TMEM98* transcription start site (70), has strong evidence of regulatory potential, locating within a DNase I hypersensitive region reported in many different cell types (70). Such potential regulatory intragenic variants may explain the divergent ocular phenotypes seen from the same gene. No dominant phenotype is seen in mice when the human disease-causing missense variants are introduced; however, mice with homozygous or compound heterozygous introduction of these mutations displayed retinal folding but otherwise normal eye size (20). Complete loss-of-function mutations in mouse *Tmem98* are lethal, but selective loss of *Tmem98* in mouse RPE produces a greatly enlarged eye phenotype, mimicking axial myopia, with expanded and thin retina and sclera, although the sclera remains microscopically normal (19). Furthermore, TMEM98 inhibits self-cleavage of MYRF, mutations in which cause nanophthalmia, as part of a postulated regulatory mechanism in eye size specification (19).

Finally, BMP4, part of the TGFβ family, is pivotal in the development of the optic vesicle and lens placode via *LHX2*-regulated expression, as demonstrated in mouse models (33, 62). Mutations in *BMP4* are typically associated with microphthalmia, syndromic 6 (MCOPS6; OMIM 112262) (101). Novel heterozygous *BMP4* truncation mutations (c.43delC, c.97A>T, c.419delT, and c.766C>T) have, however, recently been identified to cause a phenotype characterized by pathological myopia in eight patients from four Chinese families (51). The bidirectionality regarding *BMP4* and its role in axial length requires further study.

FUTURE PERSPECTIVES AND CONCLUSION

Molecular determinants of axial length remain poorly understood, although there is growing evidence for a wealth of genetic influencers. Both myopia and microphthalmia are highly genetically heterogeneous groups of diseases that display significant phenotypic variability. GWASs have provided clues to the genetic basis of myopia, but single-nucleotide polymorphisms explain only part of the heritability (i.e., the missing heritability problem), with a large proportion of variants with small effects yet to be discovered. Whole-exome sequencing has predominantly been used to investigate rare variants to date, with subsequent low diagnostic yields. Given that exomes account for only 1–2% of the human genome, patients need to be recruited for whole-genome sequencing as a priority to allow interrogation of noncoding DNA and regulatory elements. Furthermore, the complex interactions of numerous ocular tissues, along with questions about the tissue origin of the primary pathology, with much of the process occurring embryonically, make studying disorders of axial length particularly challenging. This also has implications for any potential therapy, particularly in identifying the tissue targets and age of intervention.

Much progress has been made over the last decade regarding gene discovery; however, there remains a large disconnect between these gene effectors and the actual molecular pathways involved, particularly with regard to myopia signaling cascades. Given the increasing prevalence of myopia and associated disease burden, understanding the pathways that determine eye size must be a priority.

Research on disorders of axial length has promise in elucidating the mechanisms of preschool childhood myopia, which will also better inform gene–environment interactions that underpin later-onset common myopia. In microphthalmia, many monogenic cases have been identified, but diagnostic yields remain low. Further modes of inheritance need to be considered, as well as the influence of genetic modifiers in susceptible individuals. If shared pathways are identified, then it is possible that eye growth could be manipulated using a therapy that could encourage axial growth in those with microphthalmia in the very early postnatal period; conversely, a molecular inhibitor or activator could be used to retard excessive elongation, thus reducing the morbidity of high or pathological myopia. More extensive studies identifying novel genes, expanding mutations, genotype–phenotype correlations, and biological mechanisms utilizing human and animal models are required. Such studies will ultimately provide better targeted patient management, including prevention and potential treatment of visual loss.

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LITERATURE CITED

1. Aldahmesh MA, Khan AO, Alkuraya H, Adly N, Anazi S, et al. 2013. Mutations in *LRPAP1* are associated with severe myopia in humans. *Am. J. Hum. Genet.* 93:313–20
2. Almoallem B, Arno G, De Zaeytijd J, Verdin H, Balikova I, et al. 2020. The majority of autosomal recessive nanophthalmos and posterior microphthalmia can be attributed to biallelic sequence and structural variants in *MFRP* and *PRSS56*. *Sci. Rep.* 10:1289

3. Awadalla MS, Burdon KP, Souzeau E, Landers J, Hewitt AW, et al. 2014. Mutation in *TMEM98* in a large white kindred with autosomal dominant nanophthalmos linked to 17p12-q12. *JAMA Ophthalmol.* 132:970–77
4. Bhanot P, Brink M, Samos CH, Hsieh JC, Wang Y, et al. 1996. A new member of the *frizzled* family from *Drosophila* functions as a Wingless receptor. *Nature* 382:225–30
5. Bhatia S, Bengani H, Fish M, Brown A, Divizia MT, et al. 2013. Disruption of autoregulatory feedback by a mutation in a remote, ultraconserved *PAX6* enhancer causes aniridia. *Am. J. Hum. Genet.* 93:1126–34
6. Biesecker LG, Spinner NB. 2013. A genomic view of mosaicism and human disease. *Nat. Rev. Genet.* 14:307–20
7. Boucher P, Li W-P, Matz RL, Takayama Y, Auwerx J, et al. 2007. LRP1 functions as an atheroprotective integrator of TGFβ and PDGF signals in the vascular wall: implications for Marfan syndrome. *PLOS ONE* 2:e448
8. Busby A, Dolk H, Armstrong B. 2005. Eye anomalies: seasonal variation and maternal viral infections. *Epidemiology* 16:317–22
9. Cai X-B, Shen S-R, Chen D-F, Zhang Q, Jin Z-B. 2019. An overview of myopia genetics. *Exp. Eye Res.* 188:107778
10. Cai X-B, Zheng Y-H, Chen D-F, Zhou F-Y, Xia L-Q, et al. 2019. Expanding the phenotypic and genotypic landscape of nonsyndromic high myopia: a cross-sectional study in 731 Chinese patients. *Investig. Ophthalmol. Vis. Sci.* 60:4052–62
11. Carricondo PC, Andrade T, Prasov L, Ayres BM, Moroi SE. 2018. Nanophthalmos: a review of the clinical spectrum and genetics. *J. Ophthalmol.* 2018:2735465
12. Casey J, Kawaguchi R, Morrissey M, Sun H, McGettigan P, et al. 2011. First implication of *STRA6* mutations in isolated anophthalmia, microphthalmia, and coloboma: a new dimension to the *STRA6* phenotype. *Hum. Mutat.* 32:1417–26
13. Chassaing N, Causse A, Vigouroux A, Delahaye A, Alessandri JL, et al. 2014. Molecular findings and clinical data in a cohort of 150 patients with anophthalmia/microphthalmia. *Clin. Genet.* 86:326–34
14. Chassaing N, Golzio C, Odent S, Lequeux L, Vigouroux A, et al. 2009. Phenotypic spectrum of *STRA6* mutations: from Matthew-Wood syndrome to non-lethal anophthalmia. *Hum. Mutat.* 30:E673–81
15. Chen S, Kadomatsu K, Kondo M, Toyama Y, Toshimori K, et al. 2004. Effects of flanking genes on the phenotypes of mice deficient in basigin/CD147. *Biochem. Biophys. Res. Commun.* 324:147–53
16. Chow RL, Lang RA. 2001. Early eye development in vertebrates. *Annu. Rev. Cell Dev. Biol.* 17:255–96
17. Collery RF, Volberding PJ, Bostrom JR, Link BA, Besharse JC. 2016. Loss of zebrafish Mfrp causes nanophthalmia, hyperopia, and accumulation of subretinal macrophages. *Investig. Ophthalmol. Vis. Sci.* 57:6805–14
18. Coutinho P, Pavlou S, Bhatia S, Chalmers KJ, Kleinjan DA, van Heyningen V. 2011. Discovery and assessment of conserved Pax6 target genes and enhancers. *Genome Res.* 21:1349–59
19. Cross SH, McKie L, Hurd TW, Riley S, Wills J, et al. 2020. The nanophthalmos protein TMEM98 inhibits MYRF self-cleavage and is required for eye size specification. *PLOS Genet.* 16:e1008583
20. Cross SH, McKie L, Keighren M, West K, Thaung C, et al. 2019. Missense mutations in the human nanophthalmos gene *TMEM98* cause retinal defects in the mouse. *Investig. Ophthalmol. Vis. Sci.* 60:2875–87
21. Cvekl A, Ashery-Padan R. 2014. The cellular and molecular mechanisms of vertebrate lens development. *Development* 141:4432–47
22. Danno H, Michiue T, Hitachi K, Yukita A, Ishiura S, Asashima M. 2008. Molecular links among the causative genes for ocular malformation: Otx2 and Sox2 coregulate *Rax* expression. *PNAS* 105:5408–13
23. Deming JD, Pak JS, Brown BM, Kim MK, Aung MH, et al. 2015. Visual cone arrestin 4 contributes to visual function and cone health. *Investig. Ophthalmol. Vis. Sci.* 56:5407–16
24. Deml B, Reis LM, Lemyre E, Clark RD, Kariminejad A, Semina EV. 2016. Novel mutations in *PAX6*, *OTX2* and *NDP* in anophthalmia, microphthalmia and coloboma. *Eur. J. Hum. Genet.* 24:535–41
25. Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, et al. 2004. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Investig. Ophthalmol. Vis. Sci.* 45:1071–75
26. Fan Q, Barathi VA, Cheng CY, Zhou X, Meguro A, et al. 2012. Genetic variants on chromosome 1q41 influence ocular axial length and high myopia. *PLOS Genet.* 8:e1002753

27. Fan Q, Pozarickij A, Tan NY, Guo X, Verhoeven VJ, et al. 2020. Genome-wide association meta-analysis of corneal curvature identifies novel loci and shared genetic influences across axial length and refractive error. *Commun. Biol.* 3:133
28. Feng C-Y, Huang X-Q, Cheng X-W, Wu R-H, Lu F, Jin Z-B. 2017. Mutational screening of *SLC39A5*, *LEPREL1* and *LRPAP1* in a cohort of 187 high myopia patients. *Sci. Rep.* 7:1120
29. Fledelius HC. 1982. Ophthalmic changes from age of 10 to 18 years. A longitudinal study of sequels to low birth weight. IV. Ultrasound oculometry of vitreous and axial length. *Acta Ophthalmol.* 60:403–11
30. Flitcroft DI, He M, Jonas JB, Jong M, Naidoo K, et al. 2019. IMI – defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Investig. Ophthalmol. Vis. Sci.* 60:M20–30
31. Fogerty J, Besharse JC. 2011. 174delG mutation in mouse MFRP causes photoreceptor degeneration and RPE atrophy. *Investig. Ophthalmol. Vis. Sci.* 52:7256–66
32. Foster PJ, Jiang Y. 2014. Epidemiology of myopia. *Eye* 28:202–8
33. Furuta Y, Hogan BL. 1998. BMP4 is essential for lens induction in the mouse embryo. *Genes Dev.* 12:3764–75
34. Gal A, Rau I, El Matri L, Kreienkamp HJ, Fehr S, et al. 2011. Autosomal-recessive posterior microphthalmos is caused by mutations in *PRSS56*, a gene encoding a trypsin-like serine protease. *Am. J. Hum. Genet.* 88:382–90
35. Gerth-Kahlert C, Williamson K, Ansari M, Rainger JK, Hingst V, et al. 2013. Clinical and mutation analysis of 51 probands with anophthalmia and/or severe microphthalmia from a single center. *Mol. Genet. Genom. Med.* 1:15–31
36. Gestri G, Bazin-Lopez N, Scholes C, Wilson SW. 2018. Cell behaviors during closure of the choroid fissure in the developing eye. *Front. Cell Neurosci.* 12:42
37. Guggenheim JA, Kirov G, Hodson SA. 2000. The heritability of high myopia: a reanalysis of Goldschmidt's data. *J. Med. Genet.* 37:227–31
38. Guo H, Jin X, Zhu T, Wang T, Tong P, et al. 2014. *SLC39A5* mutations interfering with the BMP/TGF-β pathway in non-syndromic high myopia. *J. Med. Genet.* 51:518–25
39. Guo H, Tong P, Liu Y, Xia L, Wang T, et al. 2015. Mutations of *P4HA2* encoding prolyl 4-hydroxylase 2 are associated with nonsyndromic high myopia. *Genet. Med.* 17:300–6
40. Guo H, Tong P, Peng Y, Wang T, Liu Y, et al. 2014. Homozygous loss-of-function mutation of the *LEPREL1* gene causes severe non-syndromic high myopia with early-onset cataract. *Clin. Genet.* 86:575–79
41. Hammond CJ, Snieder H, Gilbert CE, Spector TD. 2001. Genes and environment in refractive error: the twin eye study. *Investig. Ophthalmol. Vis. Sci.* 42:1232–36
42. Harding P, Cunha DL, Moosajee M. 2021. Animal and cellular models of microphthalmia. *Ther. Adv. Rare Dis.* 2:2633004021997447
43. Harding P, Gore S, Malka S, Rajkumar J, Oluonye N, Moosajee M. 2022. Real-world clinical and molecular management of 50 prospective patients with microphthalmia, anophthalmia and/or ocular coloboma. *Br. J. Ophthalmol.* **https://doi.org/10.1136/bjo-2022-321991**
44. Harding P, Moosajee M. 2019. The molecular basis of human anophthalmia and microphthalmia. *J. Dev. Biol.* 7:16
45. Hendriks M, Verhoeven VJM, Buitendijk GHS, Polling JR, Meester-Smoor MA, et al. 2017. Development of refractive errors—what can we learn from inherited retinal dystrophies? *Am. J. Ophthalmol.* 182:81–89
46. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, et al. 2016. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 123:1036–42
47. Hornby SJ, Gilbert CE, Rahi J, Sil AK, Xiao Y, et al. 2000. Regional variation in blindness in children due to microphthalmos, anophthalmos and coloboma. *Ophthalmic Epidemiol.* 7:127–38
48. Hysi PG, Choquet H, Khawaja AP, Wojciechowski R, Tedja MS, et al. 2020. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat. Genet.* 52:401–7
49. Hysi PG, Young TL, Mackey DA, Andrew T, Fernández-Medarde A, et al. 2010. A genome-wide association study for myopia and refractive error identifies a susceptibility locus at 15q25. *Nat. Genet.* 42:902–5

50. Jiang D, Li J, Xiao X, Li S, Jia X, et al. 2015. Detection of mutations in *LRPAP1*, *CTSH*, *LEPREL1*, *ZNF644*, *SLC39A5*, and *SCO2* in 298 families with early-onset high myopia by exome sequencing. *Investig. Ophthalmol. Vis. Sci.* 56:339–45
51. Jiang Y, Ouyang J, Li X, Wang Y, Zhou L, et al. 2021. Novel BMP4 truncations resulted in opposite ocular anomalies: pathologic myopia rather than microphthalmia. *Front. Cell Dev. Biol.* 9:769636
52. Jin Z-B, Wu J, Huang X-F, Feng C-Y, Cai X-B, et al. 2017. Trio-based exome sequencing arrests de novo mutations in early-onset high myopia. *PNAS* 114:4219–24
53. Jobling AI, Nguyen M, Gentle A, McBrien NA. 2004. Isoform-specific changes in scleral transforming growth factor-β expression and the regulation of collagen synthesis during myopia progression. *J. Biol. Chem.* 279:18121–26
54. Jobling AI, Wan R, Gentle A, Bui BV, McBrien NA. 2009. Retinal and choroidal TGF-β in the tree shrew model of myopia: isoform expression, activation and effects on function. *Exp. Eye Res.* 88:458–66
55. Källén B, Tornqvist K. 2005. The epidemiology of anophthalmia and microphthalmia in Sweden. *Eur. J. Epidemiol.* 20:345–50
56. Kamachi Y, Uchikawa M, Tanouchi A, Sekido R, Kondoh H. 2001. Pax6 and SOX2 form a co-DNA-binding partner complex that regulates initiation of lens development. *Genes Dev.* 15:1272–86
57. Katoh M. 2001. Molecular cloning and characterization of *MFRP*, a novel gene encoding a membrane-type Frizzled-related protein. *Biochem. Biophys. Res. Commun.* 282:116–23
58. Khan AO. 2008. Posterior microphthalmos versus nanophthalmos. *Ophthalmic Genet.* 29:189
59. Khan AO, Aldahmesh MA, Alsharif H, Alkuraya FS. 2015. Recessive mutations in *LEPREL1* underlie a recognizable lens subluxation phenotype. *Ophthalmic Genet.* 36:58–63
60. Khor CC, Miyake M, Chen LJ, Shi Y, Barathi VA, et al. 2013. Genome-wide association study identifies *ZFHX1B* as a susceptibility locus for severe myopia. *Hum. Mol. Genet.* 22:5288–94
61. Kiefer AK, Tung JY, Do CB, Hinds DA, Mountain JL, et al. 2013. Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. *PLOS Genet.* 9:e1003299
62. Kim HT, Kim JW. 2012. Compartmentalization of vertebrate optic neuroephithelium: external cues and transcription factors. *Mol. Cells* 33:317–24
63. Kleinjan DA, Bancewicz RM, Gautier P, Dahm R, Schonthaler HB, et al. 2008. Subfunctionalization of duplicated zebrafish *pax6* genes by *cis*-regulatory divergence. *PLOS Genet.* 4:e29
64. Koli S, Labelle-Dumais C, Zhao Y, Paylakhi S, Nair KS. 2021. Identification of MFRP and the secreted serine proteases PRSS56 and ADAMTS19 as part of a molecular network involved in ocular growth regulation. *PLOS Genet.* 17:e1009458
65. Lafaut BA, Loeys B, Leroy BP, Spileers W, De Laey JJ, Kestelyn P. 2001. Clinical and electrophysiological findings in autosomal dominant vitreoretinochoroidopathy: report of a new pedigree. *Graefe's Arch. Clin. Exp. Ophthalmol.* 239:575–82
66. Li H, Wang JX, Wang CY, Yu P, Zhou Q, et al. 2008. Localization of a novel gene for congenital nonsyndromic simple microphthalmia to chromosome 2q11–14. *Hum. Genet.* 122:589–93
67. Li J, Gao B, Guan L, Xiao X, Zhang J, et al. 2015. Unique variants in *OPN1LW* cause both syndromic and nonsyndromic X-linked high myopia mapped to MYP1. *Investig. Ophthalmol. Vis. Sci.* 56:4150–55
68. Li J, Zhang Q. 2017. Insight into the molecular genetics of myopia. *Mol. Vis.* 23:1048–80
69. Li Y-J, Goh L, Khor CC, Fan Q, Yu M, et al. 2011. Genome-wide association studies reveal genetic variants in *CTNND2* for high myopia in Singapore Chinese. *Ophthalmology* 118:368–75
70. Liao X, Lan C, Liao D, Tian J, Huang X. 2016. Exploration and detection of potential regulatory variants in refractive error GWAS. *Sci. Rep.* 6:33090
71. Logan NS, Gilmartin B, Marr JE, Stevenson MR, Ainsworth JR. 2004. Community-based study of the association of high myopia in children with ocular and systemic disease. *Optom. Vis. Sci.* 81:11–13
72. Loosli F, Staub W, Finger-Baier KC, Ober EA, Verkade H, et al. 2003. Loss of eyes in zebrafish caused by mutation of *chokh/rx3*. *EMBO Rep.* 4:894–99
73. Lotery AJ, Jacobson SG, Fishman GA, Weleber RG, Fulton AB, et al. 2001. Mutations in the CRB1 gene cause Leber congenital amaurosis. *Arch. Ophthalmol.* 119:415–20

74. Lyhne N, Sjølie AK, Kyvik KO, Green A. 2001. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. *Br. J. Ophthalmol.* 85:1470–76
75. Marr JE, Halliwell-Ewen J, Fisher B, Soler L, Ainsworth JR. 2001. Associations of high myopia in childhood. *Eye* 15:70–74
76. Martinez-Morales JR, Cavodeassi F, Bovolenta P. 2017. Coordinated morphogenetic mechanisms shape the vertebrate eye. *Front. Neurosci.* 11:721
77. Martorina M. 1988. Nanophtalmie familiale. *J. Fr. Ophtalmol.* 11:357–61
78. Matías-Pérez D, García-Montaño LA, Cruz-Aguilar M, García-Montalvo IA, Nava-Valdéz J, et al. 2018. Identification of novel pathogenic variants and novel gene-phenotype correlations in Mexican subjects with microphthalmia and/or anophthalmia by next-generation sequencing. *J. Hum. Genet.* 63:1169–80
79. Medina-Martinez O, Amaya-Manzanares F, Liu C, Mendoza M, Shah R, et al. 2009. Cell-autonomous requirement for *Rx* function in the mammalian retina and posterior pituitary. *PLOS ONE* 4:e4513
80. Moradian S, Kanani A, Esfandiari H. 2011. Nanophthalmos. *J. Ophthalmic Vis. Res.* 6:145–46
81. Mordechai S, Gradstein L, Pasanen A, Ofir R, El Amour K, et al. 2011. High myopia caused by a mutation in *LEPREL1*, encoding prolyl 3-hydroxylase 2. *Am. J. Hum. Genet.* 89:438–45
82. Mukhopadhyay R, Sergouniotis PI, Mackay DS, Day AC, Wright G, et al. 2010. A detailed phenotypic assessment of individuals affected by MFRP-related oculopathy. *Mol. Vis.* 16:540–48
83. Mutti DO, Zadnik K, Adams AJ. 1996. Myopia: The nature versus nurture debate goes on. *Investig. Ophthalmol. Vis. Sci.* 37:952–57
84. Myllyharju J. 2008. Prolyl 4-hydroxylases, key enzymes in the synthesis of collagens and regulation of the response to hypoxia, and their roles as treatment targets. *Ann. Med.* 40:402–17
85. Nair KS, Hmani-Aifa M, Ali Z, Kearney AL, Ben Salem S, et al. 2011. Alteration of the serine protease PRSS56 causes angle-closure glaucoma in mice and posterior microphthalmia in humans and mice. *Nat. Genet.* 43:579–84
86. Neri A, Leaci R, Zenteno JC, Casubolo C, Delfini E, Macaluso C. 2012. Membrane frizzled-related protein gene–related ophthalmological syndrome: 30-month follow-up of a sporadic case and review of genotype-phenotype correlation in the literature. *Mol. Vis.* 18:2623–32
87. Ohno-Matsui K, Wu P-C, Yamashiro K, Vutipongsatorn K, Fang Y, et al. 2021. IMI pathologic myopia. *Investig. Ophthalmol. Vis. Sci.* 62:5. Erratum. 2021. *Investig. Ophthalmol. Vis. Sci.* 62:17
88. Orosz O, Rajta I, Vajas A, Takács L, Csutak A, et al. 2017. Myopia and late-onset progressive cone dystrophy associate to LVAVA/MVAVA exon 3 interchange haplotypes of opsin genes on chromosome X. *Investig. Ophthalmol. Vis. Sci.* 58:1834–42
89. Orr A, Dubé MP, Zenteno JC, Jiang H, Asselin G, et al. 2011. Mutations in a novel serine protease *PRSS56* in families with nanophthalmos. *Mol. Vis.* 17:1850–61
90. Othman MI, Sullivan SA, Skuta GL, Cockrell DA, Stringham HM, et al. 1998. Autosomal dominant nanophthalmos (*NNO1*) with high hyperopia and angle-closure glaucoma maps to chromosome 11. *Am. J. Hum. Genet.* 63:1411–18
91. Pardue MT, Stone RA, Iuvone PM. 2013. Investigating mechanisms of myopia in mice. *Exp. Eye Res.* 114:96–105
92. Patel A, Hayward JD, Tailor V, Nyanhete R, Ahlfors H, et al. 2019. The Oculome panel test: next-generation sequencing to diagnose a diverse range of genetic developmental eye disorders. *Ophthalmology* 126:888–907
93. Paun CC, Pijl BJ, Siemiatkowska AM, Collin RW, Cremers FP, et al. 2012. A novel crumbs homolog 1 mutation in a family with retinitis pigmentosa, nanophthalmos, and optic disc drusen. *Mol. Vis.* 18:2447–53
94. Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA. 2016. Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* 48:709–17
95. Piekutowska-Abramczuk D, Kocyła-Karczmarewicz B, Małkowska M, Łuczak S, Iwanicka-Pronicka K, et al. 2015. No evidence for association of *SCO2* heterozygosity with high-grade myopia or other diseases with possible mitochondrial dysfunction. *JIMD Rep.* 27:63–68
96. Plaisancie J, Calvas P, Chassaing N. 2016. Genetic advances in microphthalmia. *J. Pediatr. Genet.* 5:184–88

97. Prasov L, Guan B, Ullah E, Archer SM, Ayres BM, et al. 2020. Novel *TMEM98*, *MFRP*, *PRSS56* variants in a large United States high hyperopia and nanophthalmos cohort. *Sci. Rep.* 10:19986
98. Rada JA, Shelton S, Norton TT. 2006. The sclera and myopia. *Exp. Eye Res.* 82:185–200
99. Ragge NK, Brown AG, Poloschek CM, Lorenz B, Henderson RA, et al. 2005. Heterozygous mutations of *OTX2* cause severe ocular malformations. *Am. J. Hum. Genet.* 76:1008–22
100. Ragge NK, Subak-Sharpe ID, Collin JR. 2007. A practical guide to the management of anophthalmia and microphthalmia. *Eye* 21:1290–300
101. Reis LM, Tyler RC, Schilter KF, Abdul-Rahman O, Innis JW, et al. 2011. *BMP4* loss-of-function mutations in developmental eye disorders including SHORT syndrome. *Hum. Genet.* 130:495–504
102. Relhan N, Jalali S, Pehre N, Rao HL, Manusani U, Bodduluri L. 2016. High-hyperopia database, part I: clinical characterisation including morphometric (biometric) differentiation of posterior microphthalmos from nanophthalmos. *Eye* 30:120–26
103. Richardson R, Sowden J, Gerth-Kahlert C, Moore AT, Moosajee M. 2017. Clinical utility gene card for: non-syndromic microphthalmia including next-generation sequencing-based approaches. *Eur. J. Hum. Genet.* 25:512
104. Richardson R, Tracey-White D, Webster A, Moosajee M. 2017. The zebrafish eye—a paradigm for investigating human ocular genetics. *Eye* 31:68–86
105. Rymer J, Wildsoet CF. 2005. The role of the retinal pigment epithelium in eye growth regulation and myopia: a review. *Vis. Neurosci.* 22:251–61
106. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. 2005. Myopia and associated pathological complications. *Ophthalmic Physiol. Opt.* 25:381–91
107. Schilter KF, Reis LM, Schneider A, Bardakjian TM, Abdul-Rahman O, et al. 2013. Whole-genome copy number variation analysis in anophthalmia and microphthalmia. *Clin. Genet.* 84:473–81
108. Schilter KF, Schneider A, Bardakjian T, Soucy JF, Tyler RC, et al. 2011. *OTX2* microphthalmia syndrome: four novel mutations and delineation of a phenotype. *Clin. Genet.* 79:158–68
109. Sellheyer K, Spitznas M. 1988. Development of the human sclera. *Graefe's Arch. Clin. Exp. Ophthalmol.* 226:89–100
110. Serjanov D, Bachay G, Hunter DD, Brunken WJ. 2018. Laminin β2 chain regulates retinal progenitor cell mitotic spindle orientation via dystroglycan. *J. Neurosci.* 38:5996–6010
111. Shah SP, Taylor AE, Sowden JC, Ragge N, Russell-Eggitt I, et al. 2012. Anophthalmos, microphthalmos, and coloboma in the United Kingdom: clinical features, results of investigations, and early management. *Ophthalmology* 119:362–68
112. Shaham O, Menuchin Y, Farhy C, Ashery-Padan R. 2012. Pax6: a multi-level regulator of ocular development. *Prog. Retin. Eye Res.* 31:351–76
113. Shi Y, Gong B, Chen L, Zuo X, Liu X, et al. 2013. A genome-wide meta-analysis identifies two novel loci associated with high myopia in the Han Chinese population. *Hum. Mol. Genet.* 22:2325–33
114. Shi Y, Li Y, Zhang D, Zhang H, Li Y, et al. 2011. Exome sequencing identifies *ZNF644* mutations in high myopia. *PLOS Genet.* 7:e1002084
115. Siggs OM, Awadalla MS, Souzeau E, Staffieri SE, Kearns LS, et al. 2020. The genetic and clinical landscape of nanophthalmos and posterior microphthalmos in an Australian cohort. *Clin. Genet.* 97:764–69
116. Siggs OM, Souzeau E, Breen J, Qassim A, Zhou T, et al. 2019. Autosomal dominant nanophthalmos and high hyperopia associated with a C-terminal frameshift variant in MYRF. *Mol. Vis.* 25:527–34
117. Sinn R, Wittbrodt J. 2013. An eye on eye development. *Mech. Dev.* 130:347–58
118. Sivak JG. 2008. The role of the lens in refractive development of the eye: animal models of ametropia. *Exp. Eye Res.* 87:3–8
119. Slavotinek A. 2019. Genetics of anophthalmia and microphthalmia. Part 2: syndromes associated with anophthalmia–microphthalmia. *Hum. Genet.* 138:831–46
120. Soundararajan R, Won J, Stearns TM, Charette JR, Hicks WL, et al. 2014. Gene profiling of postnatal *Mfrp*^{rd6} mutant eyes reveals differential accumulation of *Prss56*, visual cycle and phototransduction mRNAs. *PLOS ONE* 9:e110299

121. Srour M, Chitayat D, Caron V, Chassaing N, Bitoun P, et al. 2013. Recessive and dominant mutations in retinoic acid receptor beta in cases with microphthalmia and diaphragmatic hernia. *Am. J. Hum. Genet.* 93:765–72
122. Stone RA, Pardue MT, Iuvone PM, Khurana TS. 2013. Pharmacology of myopia and potential role for intrinsic retinal circadian rhythms. *Exp. Eye Res.* 114:35–47
123. Sundin OH, Dharmaraj S, Bhutto IA, Hasegawa T, McLeod DS, et al. 2008. Developmental basis of nanophthalmos: *MFRP* is required for both prenatal ocular growth and postnatal emmetropization. *Ophthalmic Genet.* 29:1–9
124. Tajima T, Ishizu K, Nakamura A. 2013. Molecular and clinical findings in patients with *LHX4* and *OTX2* mutations. *Clin. Pediatr. Endocrinol.* 22:15–23
125. Tedja MS, Wojciechowski R, Hysi PG, Eriksson N, Furlotte NA, et al. 2018. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat. Genet.* 50:834–48
126. Tideman JWL, Pärssinen O, Haarman AEG, Khawaja AP, Wedenoja J, et al. 2021. Evaluation of shared genetic susceptibility to high and low myopia and hyperopia. *JAMA Ophthalmol.* 139:601–9
127. Tideman JWL, Polling JR, Jaddoe VWV, Vingerling JR, Klaver CCW. 2019. Environmental risk factors can reduce axial length elongation and myopia incidence in 6- to 9-year-old children. *Ophthalmology* 126:127–36
128. Tran-Viet K-N, Germain ES, Soler V, Powell C, Lim S-H, et al. 2012. Study of a US cohort supports the role of ZNF644 and high-grade myopia susceptibility. *Mol. Vis.* 18:937
129. Tran-Viet K-N, Powell C, Barathi VA, Klemm T, Maurer-Stroh S, et al. 2013. Mutations in *SCO2* are associated with autosomal-dominant high-grade myopia. *Am. J. Hum. Genet.* 92:820–26
130. Velez G, Tsang SH, Tsai YT, Hsu CW, Gore A, et al. 2017. Gene therapy restores *Mfrp* and corrects axial eye length. *Sci. Rep.* 7:16151
131. Verhoeven VJ, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, et al. 2013. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat. Genet.* 45:314–18
132. Verma AS, Fitzpatrick DR. 2007. Anophthalmia and microphthalmia. *Orphanet J. Rare Dis.* 2:47
133. Wang Y-M, Lu S-Y, Zhang X-J, Chen L-J, Pang C-P, Yam JC. 2022. Myopia genetics and heredity. *Children* 9:382
134. Wasmann RA, Wassink-Ruiter JS, Sundin OH, Morales E, Verheij JB, Pott JW. 2014. Novel membrane frizzled-related protein gene mutation as cause of posterior microphthalmia resulting in high hyperopia with macular folds. *Acta Ophthalmol.* 92:276–81
135. Williams KM, Bertelsen G, Cumberland P, Wolfram C, Verhoeven VJ, et al. 2015. Increasing prevalence of myopia in Europe and the impact of education. *Ophthalmology* 122:1489–97
136. Williamson KA, FitzPatrick DR. 2014. The genetic architecture of microphthalmia, anophthalmia and coloboma. *Eur. J. Med. Genet.* 57:369–80
137. Williamson KA, Hall HN, Owen LJ, Livesey BJ, Hanson IM, et al. 2020. Recurrent heterozygous *PAX6* missense variants cause severe bilateral microphthalmia via predictable effects on DNA-protein interaction. *Genet. Med.* 22:598–609
138. Wojciechowski R, Congdon N, Bowie H, Munoz B, Gilbert D, West SK. 2005. Heritability of refractive error and familial aggregation of myopia in an elderly American population. *Investig. Ophthalmol. Vis. Sci.* 46:1588–92
139. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. 2014. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am. J. Ophthalmol.* 157:9–25.e12
140. Wu W, Dawson DG, Sugar A, Elner SG, Meyer KA, et al. 2004. Cataract surgery in patients with nanophthalmos: results and complications. *J. Cataract Refract. Surg.* 30:584–90
141. Wyatt A, Bakrania P, Bunyan DJ, Osborne RJ, Crolla JA, et al. 2008. Novel heterozygous *OTX2* mutations and whole gene deletions in anophthalmia, microphthalmia and coloboma. *Hum. Mutat.* 29:E278–83
142. Xiao X, Li S, Jia X, Guo X, Zhang Q. 2016. X-linked heterozygous mutations in *ARR3* cause female-limited early onset high myopia. *Mol. Vis.* 22:1257

143. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, et al. 2017. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol.* 95:551–66
144. Yalvac IS, Satana B, Ozkan G, Eksioglu U, Duman S. 2008. Management of glaucoma in patients with nanophthalmos. *Eye* 22:838–43
145. Yamani A, Wood I, Sugino I, Wanner M, Zarbin MA. 1999. Abnormal collagen fibrils in nanophthalmos: a clinical and histologic study. *Am. J. Ophthalmol.* 127:106–8
146. Yardley J, Leroy BP, Hart-Holden N, Lafaut BA, Loeys B, et al. 2004. Mutations of *VMD2* splicing regulators cause nanophthalmos and autosomal dominant vitreoretinochoroidopathy (ADVIRC). *Investig. Ophthalmol. Vis. Sci.* 45:3683–89
147. Young TL, Metlapally R, Shay AE. 2007. Complex trait genetics of refractive error. *Arch. Ophthalmol.* 125:38–48
148. Zagozewski JL, Zhang Q, Eisenstat DD. 2014. Genetic regulation of vertebrate eye development. *Clin. Genet.* 86:453–60
149. Zenteno JC, Buentello-Volante B, Ayala-Ramirez R, Villanueva-Mendoza C. 2011. Homozygosity mapping identifies the Crumbs homologue 1 (*Crb1*) gene as responsible for a recessive syndrome of retinitis pigmentosa and nanophthalmos. *Am. J. Med. Genet. A* 155A:1001–6
150. Zenteno JC, Buentello-Volante B, Quiroz-González MA, Quiroz-Reyes MA. 2009. Compound heterozygosity for a novel and a recurrent *MFRP* gene mutation in a family with the nanophthalmos-retinitis pigmentosa complex. *Mol. Vis.* 15:1794–98
151. Zhao F, Wu J, Xue A, Su Y, Wang X, et al. 2013. Exome sequencing reveals CCDC111 mutation associated with high myopia. *Hum. Genet.* 132:913–21
152. Zuber ME, Gestri G, Viczian AS, Barsacchi G, Harris WA. 2003. Specification of the vertebrate eye by a network of eye field transcription factors. *Development* 130:5155–67

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Contents

Errata

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