Review

Animal modeling for myopia

Lingman Zheng [a], Zhiyong Liao [a,**], Jian Zou [b,*]

[a] *Zhejiang Provincial Key Laboratory for Water Environment and Marine Biological Resources Protection, College of Life and Environmental Science, Wenzhou University, Wenzhou, China*

[b] *Eye Center of the Second Affiliated Hospital, Center for Genetic Medicine, Zhejiang University International Institute of Medicine, Zhejiang University School of Medicine, Hangzhou, China*

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ABSTRACT

Background: Myopia is one of the most common eye diseases globally, and has become an increasingly serious health concern among adolescents. Understanding the factors contributing to the onset of myopia and the strategies to slow its progression is critical to reducing its prevalence.

Main text: Animal models are key to understanding of the etiology of human diseases. Various experimental animal models have been developed to mimic human myopia, including chickens, rhesus monkeys, marmosets, mice, tree shrews, guinea pigs and zebrafish. Studies using these animal models have provided evidences and perspectives on the regulation of eye growth and refractive development. This review summarizes the characteristics of these models, the induction methods, common indicators of myopia in animal models, and recent findings on the pathogenic mechanism of myopia.

Conclusions: Investigations using experimental animal models have provided valuable information and insights into the pathogenic mechanisms of human myopia and its treatment strategies.

1. Introduction

Myopia, also known as nearsightedness, is a common refractive error, characterized by the inability of the crystalline lens to accurately focus parallel light on the retina in a relaxed state, leading to visual problems.[1] Myopia tends to develop primarily and progress fastest during childhood and early adulthood, affecting a board age range.[2] In the past three decades, the prevalence of myopia has continued to rise. Holden et al. estimated 1.406 billion people had myopia (22.9% of the world population) and 163 million people had high myopia (2.7% of the world population) in 2000. By 2050, the number of myopia cases is projected to rise to 4.758 billion (49.8% of the global population), and high myopia cases will increase to 938 million (9.8% of the global population).[3]

The vast majority of myopia is associated with excessive axial eye growth, hence the term axial myopia. In rare cases, myopia may be caused by an overly curved cornea and/or a lens with increased optical power, associated with other diseases such as keratoconus, cataracts, and intraocular inflammation.[4–6] Visual regulation plays an important role in eye growth and refractive development.[7] Retinal defocus and visual deprivation lead to blurred retinal imaging, which triggers compensatory axial growth and the scleral remodeling, thereby promoting the development of myopia.[7–9]

Myopia is a multifactorial disease. It is widely recognized that myopia results from a combination of environmental and genetic factors. Human genetic linkage studies have identified 27 loci across the genome linked to myopia (*MYP1-28*, Online Mendelian Inheritance in Man database).[10,11] Large genome-wide association studies (GWAS) in myopia patients have identified hundreds of loci associated with refractive error.[12–15] Furthermore, metabolomics and proteomics studies have suggested several dozen potentially involved metabolic pathways, most of which were carried out on animal models.[16,17] However, the epidemic of myopia in recent decades may be related to environmental factors, as genetic susceptibility has not substantially changed.

Myopia is not merely a refractive error; it often involves pathological changes such as elongation of the eyeball, enlargement of the eye, and thinning of the sclera.[18,19] As the degree of myopia increases, high myopia is prone to serious complications, including retinal detachment, cataracts, glaucoma, posterior staphyloma, myopic maculopathy, and in severe cases, it can lead to blindness.[20,21] Pathological myopia may become the second leading cause of visual impairment.[19–22]

Since the 1970s, researchers have successively established various animal models for myopia by manipulating the visual condition during

early development, either by depriving the eye of clear vision or by using defocusing lenses.[23] Although there are differences between animal models and humans, analyzing the characteristics of pathological myopia developed in animal models alongside features observed in myopic patients has provided scientists with insights into the regulation of eye growth and refractive development. In this review, we summarize the characteristics of the common myopia models, the induction methods, measurable indicators of myopia in these models, and discuss the recent progress in understanding the pathogenic mechanisms of myopia.

2. Experimental models for myopia

The general structure of the eye, the role of photopic vision in emmetropization, and the visual signaling circuitry, as well as the types and patterning of retinal neurons, are highly conserved among vertebrates, making it possible to simulate human myopia in animal models. Indeed, induced myopia and the visual regulation of eye growth have been demonstrated in a wide variety of species, from primates to fish (Fig. 1). However, due to the differences in evolutionary routes and habits, there are considerable variations between species.

2.1. Chicken

The chick is the most common animal model for studying refractive development. Chick eyes exhibit highly sensitive control of refractive status, excellent optical performance, active accommodative ability, and high visual acuity. However, there are significantly differences between chick and human eyes in aspects such as scleral structure, refractive adjustment system, and photoreceptor organization.[24] Chicks have a more cartilaginous sclera and possess an active accommodative system achieved through changes in both corneal and lens surface curvatures.[25] Chick retinas contain rods, four single cone photoreceptors, and one double cone photoreceptor.[26,27] Chick retinas do not have a fovea, but have a largely rod photoreceptor-free area centralis.[28] Unlike mammals, where the lens becomes more spherical through the relaxation of the suspensory ligament, in birds, the ciliary body compresses the lens against the "annular pad" to regulate lens shape. Moreover, the avian ciliary body is composed of striated muscle, possibly mediating the rapid and brief adjustment responses observed in birds and some reptiles, while mammals have smooth muscle. The avian ciliary muscle contains nicotinic receptors instead of muscarinic receptors, making atropine
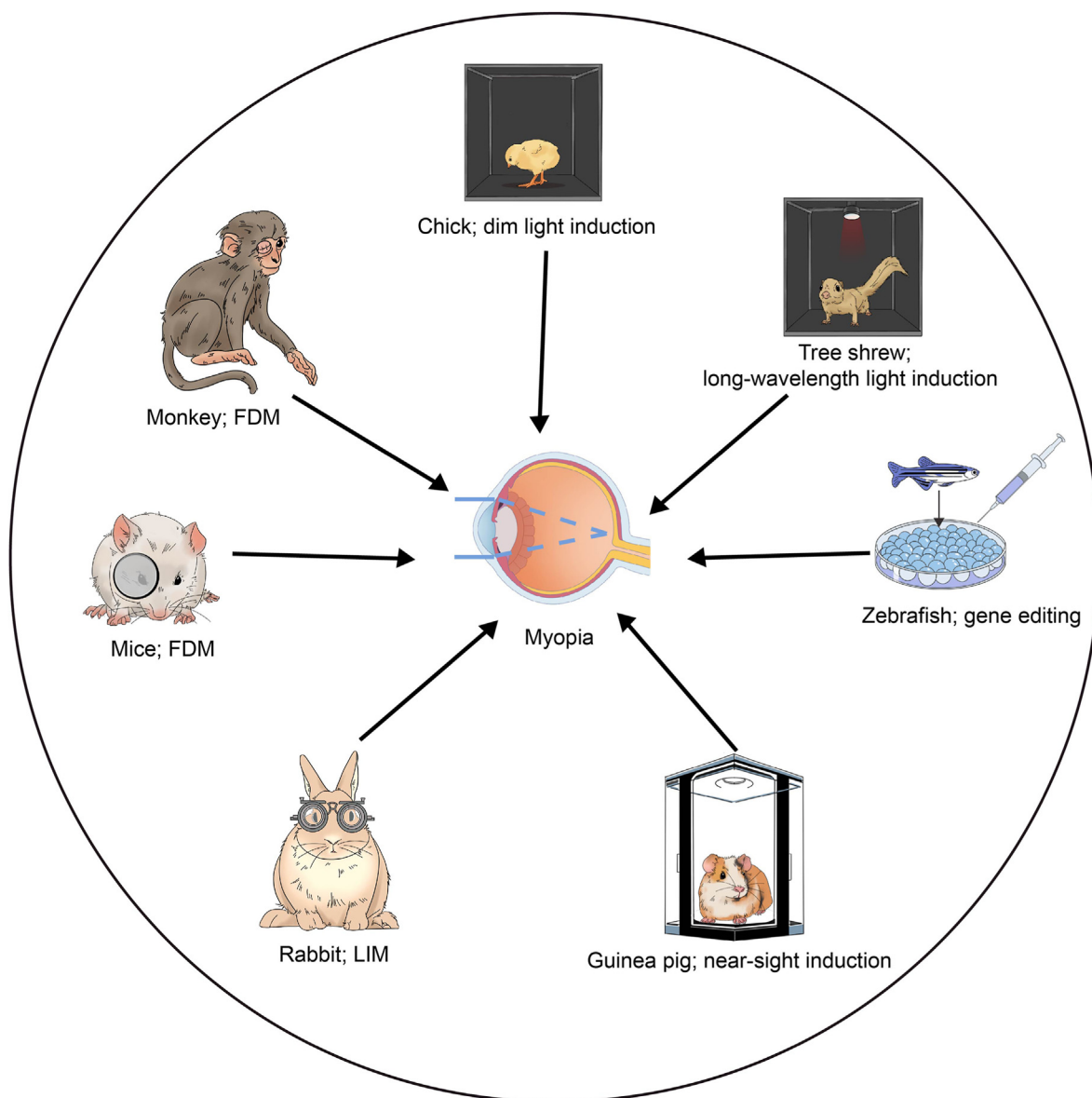

Fig. 1. The common experimental myopic animal models and induction approaches.

ineffective for paralyzing the chick ciliary muscle.[29]

2.2. Monkey

Monkeys, including marmoset monkeys and rhesus macaques, have been used in myopia studies. Monkeys share the highest similarity with humans in many aspects, such as accommodative system, the ciliary muscle and its pharmacology, and photoreceptor organization.[30,31] The monkey retina is rod-dominated with a cone-dominated fovea, and its ocular structure and developmental characteristics are closest to those of humans.[32,33] Similar to the humans, the rhesus monkey retina possesses three types of cones with short-, middle- and long-wavelength sensitivities. The marmoset retina exhibits a polymorphism of visual pigments, either dichromatic or trichromatic. The high similarity between monkeys and humans allows the monkey model to better study the mechanisms of myopia, the visual regulation of eye growth, and reactions to medicine. Zeng et al. suggested that elderly monkeys could serve as a model for pathological features similar to age-related macular degeneration and high myopia in humans.[34] However, the limitations of the monkey model, including long experimental cycles, high costs, poor compliance, and difficulties in conducting experiments with large scale sample, restrict its application.

2.3. Mouse

The mouse is a well-established animal model for human diseases. Similar to other vertebrate species, mice developed experimental myopia in response to both visual form deprivation and imposed optical defocus,[35] and photopic visual input is necessary for mouse emmetropization.[36] Both the guinea pig and mouse are rodents. Like the guinea pig, the mouse retina is dichromatic and lacks a fovea.[37] Unlike diurnal guinea pigs, mice are classified as nocturnal animals, although they are also active during the day.[38] 97% of photoreceptors in the mouse retina are rods.[39] Mice have poor optical performance, lack of accommodative ability, and do not have a fovea in the retina.[40] Compared to chickens and guinea pigs, changes in refractive power and eye growth due to visual experience in mice are slow.[41,42] Additionally, mice have relatively poor spatial vision, at least 60 times worse than humans.[43] Mouse eyes are small (approximately 3.3 mm in axial length), making accurate measurements of axial length and refractive power challenging without high resolution.[41,44]

2.4. Rabbit

Rabbits also serve as a common animal model for myopia through the application of form-deprivation or defocusing lenses.[45] The rabbit retina is dichromatic and lacks of fovea.[46] The size and anatomy of rabbit eyeballs are similar to those of humans. Ophthalmic surgery and examination methods used for humans can be directly applied to rabbits. The cost is affordable and these features facilitate the frequent use of rabbits in the preclinical assessment of ophthalmic drugs and surgical strategies.[47,48]

2.5. Fish

Teleost fish offer a unique vertebrate model for studying eye diseases and development. Unlike mammals, fish eyes and retinas can continuously grow throughout life. The fish cornea is essentially nonrefractive due to the aquatic environment. The refractive power of the fish eye is provided by moving the lens along the pupillary plane or pupillary axis,[49] rather than by deforming the lens in birds and mammals. Furthermore, fish exhibits significant differences from human in photoreceptors. Zebrafish have tetrachromatic vision. The four types of cones are organized into precise two-dimensional arrays called cone mosaics across almost the entire retina,[50,51] which is associated with the fish visual acuity and distance perception.[52,53] Despite these differences from

humans, fish offer numerous advantages as a vertebrate model with eyes similar to human in structure and function. These advantages include rapid growth and regeneration, transparent eye structures, the feasibility of large-scale screening, the availability of genetic and gene-editing tools, and low cost. These features make fish models widely used in ophthalmic research.

Refractive errors can be induced in tilapia fish through both form-deprivation and imposed defocus, and these errors can be reversed when the inducing conditions are discontinued.[54] Currently, there is limited literature on induced myopia models in zebrafish. However, a series of zebrafish genetic models demonstrate myopia-like features. Knockout of genes in zebrafish, such as *lrpap1*, *lrp2*, *bugeye*, and *lumican*, leads to increased eye axial length and disorders in the sclera.[55–57] Disruption of cone mosaics caused by *crb2b* gene knockout induces myopia phenotypes in zebrafish.[52] A zebrafish model with excessive expansion of sclera, generated by morpholino injection targeting *lumican*, has been successfully used for drug screening.[58] GWAS studies have identified hundreds of genes potentially associated with myopia. The ease of genetic manipulation in zebrafish makes it possible to analyze the function of these genes in myopia using this model. Quint et al. have tested nine genes identified by GWAS and showed that three of them (*LAMA2*, *LRRC4C*, and *KCNQ5*) play roles in refractive development.[59]

2.6. Other species

Myopia has been induced in other species, such as tree shrew,[60,61] guinea pig,[62,63] grey squirrel,[64] and cat,[65] dog,[66–68] and sheep.[69]

Tree shrews can develop myopia under conditions of visual deprivation.[61] Tree shrews are dichromatic, possessing cones sensitive to short and long wavelengths.[70] The tree shrew retina does not have a central fovea. The central region of the retina mainly consists of cones, with rods accounting for about 1%–14% of the total photoreceptors.[71] Furthermore, the breeding limitation of tree shrews also restricts their use as a model organism.

Guinea pigs develop fast from deprivation myopia and corneal curvature regulation, and their ocular growth and refractive error are visually regulated in response to imposed myopic and hyperopic defocus.[63] Guinea pigs have the advantage of high reproductive capacity and cost-effective. Compared to other animal models like chickens and mice, guinea pigs have a larger body size, making them easier to handle surgically. However, the guinea pig model has its limitations. Guinea pigs are dichromatic and do not have a fovea.[72] They may not exhibit an active accommodative response, and their vision is relatively weak.[73]

The domestic dog is a dichromatic vision animal,[66] and has been proven to be an important large animal model for many human genetic retinal diseases.[67] It has been reported that spontaneous myopia is very common in certain breeds of dogs. However, the cause of the myopia appears to be refractive, stemming from a steeper, more powerful crystalline lens and an elongated vitreous chamber depth, rather than from excess axial elongation. The axial length and corneal curvature of myopic eyes did not differ significantly from non-myopic eyes.[68]

A recent study reported a spontaneous myopia and loss of cone function in a sheep model of achromatopsia caused by *CNGA3* mutation. The day-blind sheep had a significantly longer vitreous axial length compared to WT.[69]

3. Induction of myopia in animal models

Since 1970s, researchers have developed several methods to induce myopia in animal models. The classic methods are form-deprivation myopia (FDM) and lens-induced myopia (LIM).

3.1. Form-deprivation myopia (FDM)

Form-deprivation myopia develops when light is blocked from reaching the retina through the use of eyelid sutures, diffusion eyepieces,

headgear, or lenses, thus preventing the formation of a clear image. The FDM model was first established by Wiesel et al., in 1977 by suturing the eyelids of young monkeys[23] and has since been widely applied in various animal models, such as chick,[74] monkey,[75] mouse,[35] rabbit,[45] tree shrew,[61] guinea pig[63] and tilapia fish.[76] Eyelid suturing may lead to eyelid adhesion, corneal compression, infections, and other adverse reactions, affecting experimental outcomes and making it challenging to create a model of myopia recovery. In contrast, diffuser goggles do not compress the cornea, are easy to use, and are widely applied in FDM models.

3.2. Lens-induced myopia (LIM)

Lens-induced myopia develops by placing negative lenses on animals, causing images to form behind the retina and inducing compensatory elongation of the eye axis. In 1983, Williams et al. successfully established the LIM model by fitting negative lenses on marmosets.[77] More recently, methods such as laser surgery,[78] wearing concave lenses,[79] and others have been used to defocus the retina, leading to the development of LIM.

In recent years, multiple studies suggest that peripheral hyperopic defocus can stimulate eye growth and is one of the risk factors for the onset and progression of myopia.[80] Lenses with special peripheral optical designs or bifocal lenses are used in animal models to investigate the roles of peripheral defocus in myopia. These studies indicate that peripheral hyperopic defocus induces a decrease in central refractive power and an increase in eye axial length, whereas peripheral myopic defocus slows myopia progression.[81–83]

3.3. Light induction

Myopia models can also be induced by rearing animals in dim light conditions. Epidemiological studies and experiments in animal models support the association between light intensity and myopia.[84] Chicks reared under continuous dim light developed the eye enlargement and suppressed corneal growth.[85] In primates, She et al.[75] suggested that dim light was not a strong myopia stimulus by itself, but it can impair the optical regulation of refractive development. In mice, Landis et al.[86] showed that animals exposed to either scotopic or photopic lighting developed significantly less severe myopic refractive shifts than mice exposed to mesopic lighting.

Several animal studies show that monochromatic light of different wavelengths regulates eye growth and development. She et al.[61] reported that long-wavelength monochromatic light inhibited myopia development in tree shrews. Strickland et al.[87] discovered that short-wavelength ultraviolet light could slow down the development of mouse eye refraction, producing hyperopic responses, and also inhibit lens-induced myopia. Tian et al.[88] reported that green light at lower temporal frequency led to myopia and longer axial length, while blue light at a higher temporal frequency resulted in hyperopia and shorter axial length in guinea pigs. Quint et al.[89] reported exposure to cyan or red light inhibited the axial growth of zebrafish.

3.4. Behavior induction

Near-work is considered as an important factor for myopia development.[90] Fu et al.[62] established a near-work behavior animal model for myopia using guinea pigs. Animals were placed in cylindrical cages with vertical square wave gratings, providing an average viewing distance for short, medium, and long distances, while maintaining the same light intensity for 14 days of treatment. The results showed that guinea pigs in the near-work group exhibited a shift towards myopia. However, there are currently few established behavioral animal models for myopia.

3.5. Genetic models

Given the importance of genetic factors in myopia, the genetic models are irreplaceable for the functional analysis of candidate genes for myopia. Genetic linkage studies have identified a series of myopia associated genes.[91–98] Genetic evidence in animals has confirmed the roles of certain genes in myopia, including *lumican* (*MYP3*),[99] *VIPR2* (*MYP17*),[100] *ZNF644* (*MYP21*),[101] and *LRPAP1* (*MYP23*).[57] Mutations in genes associated with complete congenital stationary night blindness (cCSNB), such as *GPR179*, *NYX*, *LRIT33*, *TRPM1* and *GRM6*, present with high myopia. Loss of these genes in mice promotes susceptibility to myopia induction.[102] Mutations in genes causing disorders in photoreceptors, such as *OPN1LW* (*MYP1*),[103] *ARR3* (*MYP26*),[104] *GNAT1*[105] and *GNAT2*,[106] and *GLRA2*,[107] can also be associated with high myopia in humans and mice by impairing photoperception and visual transmission. Depletion of matrix metalloproteinases (MMPs), which mediate scleral extracellular matrix (ECM) degradation and scleral thinning, relieved FDM-induced myopia in mice, and vice versa.[108] Knockout of TGF-β regulators such as *A2AR*[109] and *LRPAP1*[110] promotes development of myopia with increased axial length and altered scleral collagen fiber structure in mice. More genes have been identified as myopia-associated genes by GWAS. Knockout of a portion of these genes presents a myopic phenotype and can serve as genetic models for myopia. For example, depletion of myopia-associated genes *LAMA2*, *LRRC4C*, and *KCNQ5* identified by GWAS affected the refractive development in zebrafish.[59]

4. Common measurable indicators for myopia

Refraction is determined by the coordinated contributions of ocular biometric components such as axial length, anterior chamber depth, vitreous chamber depth, corneal curvature, and lens shape and thickness. Thus, these ocular biometric components are used as the indicators for myopia in animal models.

Typically, the axial distance from the cornea to the retina is referred to as the axial length of the eye. The distance from the posterior corneal surface to the anterior lens surface is referred to as anterior chamber depth. The distance from the posterior lens surface to the vitreous-retina interface is referred as vitreous chamber depth. Optical coherence tomography, as well as A- or B- scan ultrasonography technologies, is frequently employed for imaging the eyeball and measuring ocular biometry in experimental myopic animals.[17,52,89,111–113] Autorefractor keratometry is usually used to measure the corneal curvature in myopic animals. Blood flow within the choroid can be assessed using laser doppler velocimetry and flowmetry, laser interferometry, and laser speckle flowgraphy.[114] The ultrastructure of the corneal extracellular matrix can be visualized using a transmission electron microscope. In zebrafish, methods to measure visual acuity and visual distance have been established.[52,115] Furthermore, a series of studies has identified dopamine in the retina as an important neurotransmitter regulating the ocular refractive development in humans and animals.[116–119] Levels of dopamine and its primary metabolite, 3,4-dihydroxyphenylacetic acid, are used as a molecular indicators in myopic animals.

5. Cellular and molecular biology of myopia

Although myopia can be triggered by an overly curved cornea and other factors,[4,5,120] which have been also observed in some animal models of myopia,[7] axial myopia is primarily caused by excessive axial growth of the eyeball under visual accommodation. The signaling for eye growth and refractive development in visual accommodation appears to be located within the eye. Surgical or pharmacologic blockade of vision, such as transection of the optic nerve, bilateral surgical removal of the striate cortices, and sensory deafferentation by sectioning the trigeminal nerve, did not prevent induced myopia or its recovery when the induction was terminated in multiple animals.[7] It is currently believed that the shape and size of the eyeball are primarily determined by the sclera,[18]

with a possible contribution from the choroid.[121]

The sclera is a layer of dense connective tissue that forms the outermost layer of the eyeball. Human scleral tissue is composed of collagen fibrils embedded in a matrix of elastin, proteoglycans and non-collagenous glycoproteins.[18] The sclera is a dynamic tissue. The components, thickness, and ultrastructure of the scleral ECM undergo remodeling to adapt to the state of the eye. ECM remodeling leads to changes in scleral biomechanical properties, which in turn define the eye size and refraction. ECM loss and scleral thinning (especially at the posterior pole) are observed in both in highly myopic human eyes and experimental myopic animal eyes.[18,122–124] ECM loss and scleral thinning result in an increase of viscoelasticity and an decreased tensile strength of the sclera, allowing for the elongation of the eye axis.

Scleral remodeling is a dynamic process involving the continuous synthesis and degradation of the ECM. Any alterations in the scleral ECM components or the regulation of scleral ECM synthesis and degradation may lead to changes in scleral shape, which in turn could dramatically affect vision. Indeed, mutations in collagen genes, including *COL1A1*,[125] *COL2A1*,[126] *COL18A1*[127] have been identified as high risk factors for myopia. Transforming growth factor β (TGF-β), MMPs and tissue inhibitors of metalloproteinases (TIMPs) play a central role in scleral remodeling. TGF-β is a multipotent growth factor that plays a critical role in embryo development and tissue homeostasis by regulating cell growth, inflammation, apoptosis, and extracellular matrix synthesis.[128] TGF-β is essential in regulating the production of the scleral extracellular matrix.[129,130] TGF-β is also known to modulate the expression of MMPs, which can cleave collagens and degrade ECM, resulting in scleral remodeling.[131] Clinical and animal studies have shown increased expression of TGF-β2, MMPs and TIMPs in myopic eye tissues.[108,132,133]

More signaling pathways have been identified as the critical regulators of myopia (Fig. 2).[134] Dopamine is widely known as a key neurotransmitter regulating ocular refractive development in humans and animals.[116] Other transmitters and signaling molecules are involved in eye growth and refractive development include GABAb,[135] nitric oxide,[136] and adenosine.[137] Cytokines, including fibroblast growth factor

(FGF),[138] insulin like growth factor (IGF),[139] bone morphogenetic protein (BMPs),[140] vascular endothelial growth factor (VEGF),[141] retinoic acid (RA),[142] and WNT[143] are also known to participate in the process. Cellular responses, such as scleral hypoxia,[144,145] oxidative stress,[146] and endoplasmic reticulum stress[147–149] are also involved in the regulation of scleral remodeling and myopia development. Lin et al. have reported that augmentation of scleral glycolysis promotes myopia via the scleral glycolysis-lactate-histone lactylation pathway.[150] Pan et al. has reported that dietary ω-3 polyunsaturated fatty acids play a protective role against myopia.[151] Moreover, miRNAs, circRNAs and epigenetic regulation have been shown to regulate scleral remodeling.[150,152–157] These signaling molecules are primarily derived from retina, RPE, choroid and sclera.

The choroid is a highly vascularized connective tissue located between the RPE and the sclera.[158] It is a dynamic structure, and its thickness is modulated in response to various cues, including physiological and pharmacological influences, circadian rhythm and optical defocus.[112,159,160] Choroidal thickness has been shown to predict myopia development. Thinner choroids are always associated with higher degree the myopia.[8] Anti-myopia treatments have induced significant increases in choroidal thickness in several clinical studies.[161,162] The choroid provides nutrients and oxygen to the sclera and retina, influences their metabolism. Increased choroidal blood perfusion induced by the vasodilator prazosin treatment inhibited FDM myopia in guinea pigs, and vice versa.[163,164] Choroidal thickness and choroidal blood perfusion were significantly decreased in both spontaneous and induced myopic guinea pigs.[165] Pharmacological anti-myopia treatments or intense light significantly inhibited myopia development and the decrease in choroidal blood perfusion in FDM-induced myopic eyes in guinea pigs.[163] Moreover, the choroid can secrete a variety of factors involved in scleral remodeling during myopia development, including TGF-β, VEGF, hepatocyte growth factor (HGF), RA, FGF, nitric oxide, dopamine, MMPs and TMIPs, and acetylcholine.

The first signals that visually regulate eye growth may originate from the retina since the retina is the only organ that senses light. Evidences have shown that the retina plays an important role in the development of
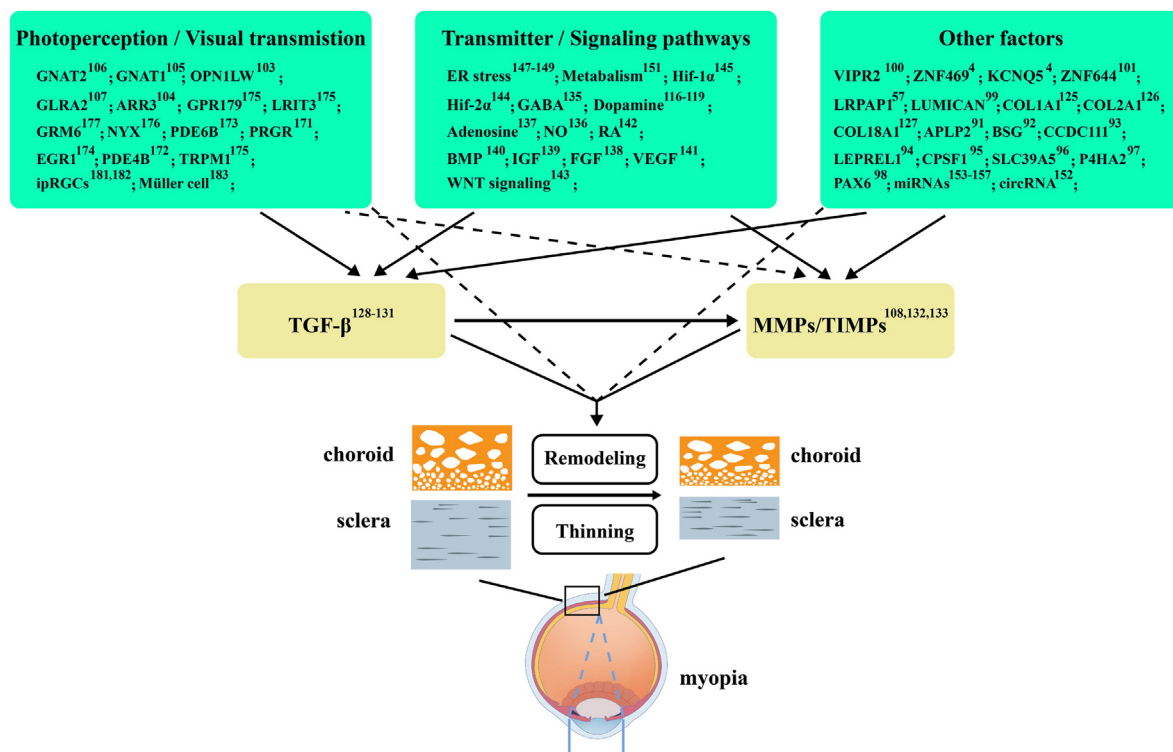

Fig. 2. The regulators of scleral ECM remodeling and myopia development. TGF-β and MMPs/TIMPs are the key regulators of scleral ECM remodeling. Arrows represents causal relationships supported with published evidences. Dasharrwos represents possible causal relationships without evidence yet.

myopia through various mechanisms. It is widely accepted that light conditions, such as light intensity, light wavelength, and intermittent/continuous light exposure, affect on eye axis growth and myopia development.[166–168] Outdoor exposure and repeated low-level red-light treatment are effective therapeutic approaches for the retardation of myopia.[168–170] Impaired photoperception and visual transmission are risk factors of high myopia. Photoreceptor disorders caused by dysfunction of genes, including *OPN1LW* (*MYP1*),[103] *ARR3* (*MYP26*),[104] *PRGR*,[171] *GNAT1*[105] and *GNAT2*,[106] *GLRA2*,[107] *PDE4B*,[172] *PDE6B*,[173] and *EGR1*,[174] are also associated with high myopia in humans and mice. Mutations in cCSNB associated genes, such as *GPR179*,[175] *NYX*,[176] *LRIT3*,[175] *TRPM1*[175] and *GRM6*,[177] presents ON-biplaor cells dysfunction with high myopia. Loss of these genes in mice promotes susceptibility to myopic induction.[102] Disruption of amacrine cells using colchicine suppresses axial growth of the eye in chicks.[178] Intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin have been identified as novel photosensitive cells in the retina.[179,180] Ablation of ipRGC or melanopsin attenuated FDM induced myopia in mice, and vice versa.[181,182] Additionally, it has been reported that Müller cells and astrocytes, which can secrete a variety of factors, are activated in myopic eyes.[183] Omics studies in human and animal myopic eyes have shown that the expression patterns of hundreds of genes are significantly altered, with both up-regulated and down-regulated expression.[16] However, the causal relationships between gene expression alterations and myopia development need further investigated.

6. Conclusions

In summary, visual regulation plays an important role in eye growth and refractive development, and myopia can be effectively induced by FDM and LIM in all these animal models. These animal models offer researchers a controlled experimental platform to gain deeper insight into the development of myopia. Studies in experimental myopic animals have provided valuable insights into the mechanisms, risk factors, and treatment for myopia. However, each animal model has its own advantages and disadvantages due to species differences. For example, chicks and rabbits exhibit excellent optical performance and are frequently used in the preclinical assessment of ophthalmic drugs and surgical strategies. Monkeys can serve as the best model for pathological features similar to humans. Mouse model is widely used to explore the cellular and molecular mechanism of myopia. Zebrafish model is suitable for the large screening of candidate genes and drugs. It is worth to note that the findings from animal models may sometimes differ significantly from those observed in human myopia.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Baird PN, Saw SM, Lanca C, et al. Myopia. *Nat Rev Dis Prim*. 2020;6(1):99. https://doi.org/10.1038/s41572-020-00231-4.
2. Wolffsohn JS, Flitcroft DI, Gifford KL, et al. Imi - myopia control reports overview and introduction. *Invest Ophthalmol Vis Sci*. 2019;60(3):M1–m19. https://doi.org/10.1167/iovs.18-25980.
3. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036–1042. https://doi.org/10.1016/j.ophtha.2016.01.006.
4. Hashemi H, Heydarian S, Hooshmand E, et al. The prevalence and risk factors for keratoconus: a systematic review and meta-analysis. *Cornea*. 2020;39(2):263–270. https://doi.org/10.1097/ico.0000000000002150.
5. Díez Ajenjo MA, García Domene MC, Peris Martínez C. Refractive changes in nuclear, cortical and posterior subcapsular cataracts. effect of the type and grade. *J Opt*. 2015;8(2):86–92. https://doi.org/10.1016/j.optom.2014.07.006.
6. Wei CC, Kung YJ, Chen CS, et al. Allergic conjunctivitis-induced retinal inflammation promotes myopia progression. *EBioMedicine*. 2018;28:274–286. https://doi.org/10.1016/j.ebiom.2018.01.024.
7. Troilo D, Smith 3rd EL, Nickla DL, et al. Imi - report on experimental models of emmetropization and myopia. *Invest Ophthalmol Vis Sci*. 2019;60(3):M31–m88. https://doi.org/10.1167/iovs.18-25967.
8. Ostrin LA, Harb E, Nickla DL, et al. IMI-the dynamic choroid: new insights, challenges, and potential significance for human myopia. *Invest Ophthalmol Vis Sci*. 2023;64(6):4. https://doi.org/10.1167/iovs.64.6.4.
9. Rada JA, Shelton S, Norton TT. The sclera and myopia. *Exp Eye Res*. 2006;82(2):185–200. https://doi.org/10.1016/j.exer.2005.08.009.
10. Baird PN, Schäche M, Dirani M. The GEnes in Myopia (GEM) study in understanding the aetiology of refractive errors. *Prog Retin Eye Res*. 2010;29(6):520–542. https://doi.org/10.1016/j.preteyeres.2010.05.004.
11. Tedja MS, Haarman AEG, Meester-Smoor MA, et al. Imi - myopia genetics report. *Invest Ophthalmol Vis Sci*. 2019;60(3):M89–m105. https://doi.org/10.1167/iovs.18-25965.
12. Verhoeven VJ, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat Genet*. 2013;45(3):314–318. https://doi.org/10.1038/ng.2554.
13. Tedja MS, Wojciechowski R, Hysi PG, et al. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat Genet*. 2018;50(6):834–848. https://doi.org/10.1038/s41588-018-0127-7.
14. Ghorbani Mojarrad N, Plotnikov D, Williams C, et al. Association between polygenic risk score and risk of myopia. *JAMA Ophthalmol*. 2020;138(1):7–13. https://doi.org/10.1001/jamaophthalmol.2019.4421.
15. Hysi PG, Choquet H, Khawaja AP, et al. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat Genet*. 2020;52(4):401–407. https://doi.org/10.1038/s41588-020-0599-0.
16. Grochowski ET, Pietrowska K, Kowalczyk T, et al. Omics in myopia. *J Clin Med*. 2020;9(11). https://doi.org/10.3390/jcm9113464.
17. Liang C, Li F, Gu C, et al. Metabolomic profiling of ocular tissues in rabbit myopia: uncovering differential metabolites and pathways. *Exp Eye Res*. 2024;240:109796. https://doi.org/10.1016/j.exer.2024.109796.
18. Harper AR, Summers JA. The dynamic sclera: extracellular matrix remodeling in normal ocular growth and myopia development. *Exp Eye Res*. 2015;133:100–111. https://doi.org/10.1016/j.exer.2014.07.015.
19. Ueta T, Makino S, Yamamoto Y, et al. Pathologic myopia: an overview of the current understanding and interventions. *Glob Health Med*. 2020;2(3):151–155. https://doi.org/10.35772/ghm.2020.01007.
20. Koh V, Tan C, Tan PT, et al. Myopic maculopathy and optic disc changes in highly myopic young asian eyes and impact on visual acuity REPLY. *Am J Ophthalmol*. 2016;168, 296-296.
21. Ohno-Matsui K, Lai TYY, Lai CC, et al. Updates of pathologic myopia. *Prog Retin Eye Res*. 2016;52:156–187. https://doi.org/10.1016/j.preteyeres.2015.12.001.
22. Ohno-Matsui K, Wu PC, Yamashiro K, et al. IMI pathologic myopia. *Invest Ophthalmol Vis Sci*. 2021;62(5):5. https://doi.org/10.1167/iovs.62.5.5.
23. Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature*. 1977;266(5597):66–68.
24. Glasser A, Murphy CJ, Troilo D, et al. The mechanism of lenticular accommodation in chicks. *Vis Res*. 1995;35(11):1525–1540.
25. Ostrin LA, Liu Y, Choh V, et al. The role of the iris in chick accommodation. *Invest Ophthalmol Vis Sci*. 2011;52(7):4710–4716. https://doi.org/10.1167/iovs.10-6819.
26. Bruhn SL, Cepko CL. Development of the pattern of photoreceptors in the chick retina. *J Neurosci*. 1996;16(4):1430–1439. https://doi.org/10.1523/jneurosci.16-04-01430.1996.
27. Kram YA, Mantey S, Corbo JC. Avian cone photoreceptors tile the retina as five independent, self-organizing mosaics. *PLoS One*. 2010;5(2):e8992. https://doi.org/10.1371/journal.pone.0008992.
28. Morris VB. An afoveate area centralis in the chick retina. *J Comp Neurol*. 1982;210(2):198–203. https://doi.org/10.1002/cne.902100210.
29. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci*. 1993;34(1):205–215.
30. Ostrin LA, Glasser A. Autonomic drugs and the accommodative system in rhesus monkeys. *Exp Eye Res*. 2010;90(1):104–112. https://doi.org/10.1016/j.exer.2009.09.015.
31. Troilo D, Quinn N, Baker K. Accommodation and induced myopia in marmosets. *Vis Res*. 2007;47(9):1228–1244. https://doi.org/10.1016/j.visres.2007.01.018.
32. Lin KH, Tran T, Kim S, et al. Advanced retinal imaging and ocular parameters of the rhesus macaque eye. *Transl Vis Sci Technol*. 2021;10(6):7. https://doi.org/10.1167/tvst.10.6.7.
33. Hendrickson A, Troilo D, Possin D, et al. Development of the neural retina and its vasculature in the marmoset Callithrix jacchus. *J Comp Neurol*. 2006;497(2):270–286. https://doi.org/10.1002/cne.20996.

34. Zeng B, Zhang H, Peng Y, et al. Spontaneous fundus lesions in elderly monkeys: an ideal model for age-related macular degeneration and high myopia clinical research. *Life Sci.* 2021;282:119811. https://doi.org/10.1016/j.lfs.2021.119811.

35. Barathi VA, Boopathi VG, Yap EP, et al. Two models of experimental myopia in the mouse. *Vis Res.* 2008;48(7):904–916. https://doi.org/10.1016/j.visres.2008.01.004.

36. Tkatchenko TV, Shen Y, Braun RD, et al. Photopic visual input is necessary for emmetropization in mice. *Exp Eye Res.* 2013;115:87–95. https://doi.org/10.1016/j.exer.2013.06.025.

37. Applebury ML, Antoch MP, Baxter LC, et al. The murine cone photoreceptor: a single cone type expresses both S and M opsins with retinal spatial patterning. *Neuron.* 2000;27(3):513–523. https://doi.org/10.1016/s0896-6273(00)00062-3.

38. Yang HS, Vitaterna MH, Laposky AD, et al. Genetic analysis of daily physical activity using a mouse chromosome substitution strain. *Physiol Genom.* 2009;39(1):47–55. https://doi.org/10.1152/physiolgenomics.00066.2009.

39. Kee CS, Hung LF, Qiao Y, et al. Astigmatism in infant monkeys reared with cylindrical lenses. *Vis Res.* 2003;43(26):2721–2739. https://doi.org/10.1016/S0042-6989(03)00469-3.

40. Geng Y, Schery LA, Sharma R, et al. Optical properties of the mouse eye. *Biomed Opt Express.* 2011;2(4):717–738. https://doi.org/10.1364/boe.2.000717.

41. Schaeffel F, Burkhardt E, Howland HC, et al. Measurement of refractive state and deprivation myopia in two strains of mice. *Optom Vis Sci.* 2004;81(2):99–110.

42. Tkatchenko TV, Shen Y, Tkatchenko AV. Mouse experimental myopia has features of primate myopia. *Invest Ophthalmol Vis Sci.* 2010;51(3):1297–1303. https://doi.org/10.1167/iovs.09-4153.

43. Geng Y, Schery LA, Sharma R, et al. Optical properties of the mouse eye. *Biomed Opt Express.* 2011;2(4):717–738.

44. Tkatchenko TV, Shen Y, Tkatchenko AV. Analysis of postnatal eye development in the mouse with high-resolution small animal magnetic resonance imaging. *Invest Ophthalmol Vis Sci.* 2010;51(1):21–27. https://doi.org/10.1167/iovs.08-2767.

45. Lin X, Wang BJ, Wang YC, et al. Scleral ultrastructure and biomechanical changes in rabbits after negative lens application. *Int J Ophthalmol.* 2018;11(3):354–362. https://doi.org/10.18240/ijo.2018.03.02.

46. Juliusson B, Bergström A, Röhlich P, et al. Complementary cone fields of the rabbit retina. *Invest Ophthalmol Vis Sci.* 1994;35(3):811–818.

47. Ji M, Liu H, Ma S, et al. Stable atropine loaded film as a potential ocular delivery system for treatment of myopia. *Pharm Res (N Y).* 2021;38(11):1931–1946. https://doi.org/10.1007/s11095-021-03135-4.

48. Tong L, Cui D, Zeng J. Topical bendazol inhibits experimental myopia progression and decreases the ocular accumulation of HIF-1α protein in young rabbits. *Ophthalmic Physiol Opt.* 2020;40(5):567–576. https://doi.org/10.1111/opo.12717.

49. Somiya H. Dynamic mechanism of visual accommodation in teleosts: structure of the lens muscle and its nerve control. *Proc R Soc Lond B Biol Sci.* 1987;230(1258):77–91. https://doi.org/10.1098/rspb.1987.0010.

50. Raymond PA, Barthel LK. A moving wave patterns the cone photoreceptor mosaic array in the zebrafish retina. *Int J Dev Biol.* 2004;48(8-9):935–945. https://doi.org/10.1387/ijdb.041873pr.

51. Zou J, Wang X, Wei X. Crb apical polarity proteins maintain zebrafish retinal cone mosaics via intercellular binding of their extracellular domains. *Dev Cell.* 2012;22(6):1261–1274. https://doi.org/10.1016/j.devcel.2012.03.007.

52. Hao Q, Zheng M, Weng K, et al. Crumbs proteins stabilize the cone mosaics of photoreceptors and improve vision in zebrafish. *J Genet Genomics.* 2021;48(1):52–62. https://doi.org/10.1016/j.jgg.2020.12.002.

53. Brainard DH. Color and the cone mosaic. *Annu Rev Vis Sci.* 2015;1:519–546. https://doi.org/10.1146/annurev-vision-082114-035341.

54. Shen W, Sivak JG. Eyes of a lower vertebrate are susceptible to the visual environment. *Invest Ophthalmol Vis Sci.* 2007;48(10):4829–4837. https://doi.org/10.1167/iovs.06-1273.

55. Yeh LK, Liu CY, Kao WWY, et al. Knockdown of zebrafish lumican gene (zlum) causes scleral thinning and increased size of scleral coats. *J Biol Chem.* 2010;285(36):28141–28155. https://doi.org/10.1074/jbc.M109.043679.

56. Veth KN, Willer JR, Collery RF, et al. Mutations in zebrafish lrp2 result in adult-onset ocular pathogenesis that models myopia and other risk factors for glaucoma. *PLoS Genet.* 2011;7(2):e1001310. https://doi.org/10.1371/journal.pgen.1001310.

57. Liu S, Chen T, Chen B, et al. Lrpap1 deficiency leads to myopia through TGF-β-induced apoptosis in zebrafish. *Cell Commun Signal.* 2022;20(1):162. https://doi.org/10.1186/s12964-022-00970-9.

58. Lin MY, Lin IT, Wu YC, et al. Stepwise candidate drug screening for myopia control by using zebrafish, mouse, and Golden Syrian Hamster myopia models. *EBioMedicine.* 2021;65:103263. https://doi.org/10.1016/j.ebiom.2021.103263.

59. Quint WH, Tadema KCD, Kokke N, et al. Post-GWAS screening of candidate genes for refractive error in mutant zebrafish models. *Sci Rep.* 2023;13(1):2017. https://doi.org/10.1038/s41598-023-28944-y.

60. Ku H, Chen JJ, Hu M, et al. Myopia development in tree shrew is associated with chronic inflammatory reactions. *Curr Issues Mol Biol.* 2022;44(9):4303–4313. https://doi.org/10.3390/cimb44090296.

61. She Z, Ward AH, Gawne TJ. The effects of ambient narrowband long-wavelength light on lens-induced myopia and form-deprivation myopia in tree shrews. *Exp Eye Res.* 2023;234:109593. https://doi.org/10.1016/j.exer.2023.109593.

62. Fu Q, Zhang Y, Chen L, et al. Near work induces myopia in Guinea pigs. *Exp Eye Res.* 2022;224:109202. https://doi.org/10.1016/j.exer.2022.109202.

63. Howlett MH, McFadden SA. Form-deprivation myopia in the Guinea pig (Cavia porcellus). *Vis Res.* 2006;46(1-2):267–283. https://doi.org/10.1016/j.visres.2005.06.036.

64. McBrien NA, Moghaddam HO, New R, et al. Experimental myopia in a diurnal mammal (Sciurus carolinensis) with no accommodative ability. *J Physiol.* 1993;469:427–441. https://doi.org/10.1113/jphysiol.1993.sp019821.

65. Smith EL, Maguire GW, Watson JT. Axial lengths and refractive errors in kittens reared with an optically induced anisometropia. *Invest Ophthalmol Vis Sci.* 1980;19(10):1250–1255.

66. Kasparson AA, Badridze J, Maximov VV. Colour cues proved to be more informative for dogs than brightness. *Proc Biol Sci.* 2013;280(1766):20131356. https://doi.org/10.1098/rspb.2013.1356.

67. Slijkerman RW, Song F, Astuti GD, et al. The pros and cons of vertebrate animal models for functional and therapeutic research on inherited retinal dystrophies. *Prog Retin Eye Res.* 2015;48:137–159. https://doi.org/10.1016/j.preteyeres.2015.04.004.

68. Williams LA, Kubai MA, Murphy CJ, et al. Ocular components in three breeds of dogs with high prevalence of myopia. *Optom Vis Sci.* 2011;88(2):269–274. https://doi.org/10.1097/OPX.0b013e3182058ff0.

69. Ross M, Ofri R, Aizenberg I, et al. Naturally-occurring myopia and loss of cone function in a sheep model of achromatopsia. *Sci Rep.* 2020;10(1):19314. https://doi.org/10.1038/s41598-020-76205-z.

70. Cheng RSY, Wai MSM, Leung GCT, et al. Different types of visual cells in the photoreceptor layer of the retinae of the treeshrew (Tupaia belangeri chinensis) as revealed by scanning microscopy. *Folia Morphol.* 2022. https://doi.org/10.5603/FM.a2022.0099.

71. Müller B, Peichl L. Topography of cones and rods in the tree shrew retina. *J Comp Neurol.* 1989;282(4):581–594. https://doi.org/10.1002/cne.902820409.

72. Jacobs GH, Deegan 2nd JF. Spectral sensitivity, photopigments, and color vision in the Guinea pig (Cavia porcellus). *Behav Neurosci.* 1994;108(5):993–1004. https://doi.org/10.1037//0735-7044.108.5.993.

73. Jiang L, Schaeffel F, Zhou X, et al. Spontaneous axial myopia and emmetropization in a strain of wild-type Guinea pig (Cavia porcellus). *Invest Ophthalmol Vis Sci.* 2009;50(3):1013–1019. https://doi.org/10.1167/iovs.08-2463.

74. Thomson K, Karouta C, Ashby R. Form-deprivation and lens-induced myopia are similarly affected by pharmacological manipulation of the dopaminergic system in chicks. *Invest Ophthalmol Vis Sci.* 2020;61(12):4. https://doi.org/10.1167/iovs.61.12.4.

75. She Z, Hung LF, Arumugam B, et al. The development of and recovery from form-deprivation myopia in infant rhesus monkeys reared under reduced ambient lighting. *Vis Res.* 2021;183:106–117. https://doi.org/10.1016/j.visres.2021.02.004.

76. Shen W, Vijayan M, Sivak JG. Inducing form-deprivation myopia in fish. *Invest Ophthalmol Vis Sci.* 2005;46(5):1797–1803. https://doi.org/10.1167/iovs.04-1318.

77. Williams RA, Boothe RG. Effects of defocus on monkey (Macaca-Nemestrina) contrast sensitivity - behavioral measurements and predictions. *Am J Optom Physiol Opt.* 1983;60(2):106–111.

78. Zhong XW, Ge J, Nie HH, et al. Effects of photorefractive keratectomy-induced defocus on emmetropization of infant rhesus monkeys. *Invest Ophthalmol Vis Sci.* 2004;45(10):3806–3811. https://doi.org/10.1167/iovs.03-0326.

79. Xu Y, Lai L, Chen Z, et al. Scleral remolding-related gene expression after scleral collagen cross-linking using ultraviolet A and riboflavin in myopic Guinea pig model. *Curr Eye Res.* 2023;48(4):392–401. https://doi.org/10.1080/02713683.2022.2156549.

80. Erdinest N, London N, Lavy I, et al. Peripheral defocus and myopia management: a mini-review. *Kor J Ophthalmol.* 2023;37(1):70–81. https://doi.org/10.3341/kjo.2022.0125.

81. Smith EL, Hung LF, Huang J, et al. Effects of local myopic defocus on refractive development in monkeys. *Optom Vis Sci.* 2013;90(11):1176–1186.

82. El-Nimri NW, Zhang H, Wildsoet CF. The effect of part-time wear of 2-zone concentric bifocal spectacle lenses on refractive error development & eye growth in young chicks. *Exp Eye Res.* 2019;180:184–191. https://doi.org/10.1016/j.exer.2018.12.010.

83. Bowrey HE, Zeng G, Tse DY, et al. The effect of spectacle lenses containing peripheral defocus on refractive error and horizontal eye shape in the Guinea pig. *Invest Ophthalmol Vis Sci.* 2017;58(5):2705–2714. https://doi.org/10.1167/iovs.16-20240.

84. Muralidharan AR, Lança C, Biswas S, et al. Light and myopia: from epidemiological studies to neurobiological mechanisms. *Ther Adv Ophthalmol.* 2021;13:25158414211059246. https://doi.org/10.1177/25158414211059246.

85. Liu J, Pendrak K, Capehart C, et al. Emmetropisation under continuous but non-constant light in chicks. *Exp Eye Res.* 2004;79(5):719–728. https://doi.org/10.1016/j.exer.2004.08.007.

86. Landis EG, Park HN, Chrenek M, et al. Ambient light regulates retinal dopamine signaling and myopia susceptibility. *Invest Ophthalmol Vis Sci.* 2021;62(1):28. https://doi.org/10.1167/iovs.62.1.28.

87. Strickland R, Landis EG, Pardue MT. Short-wavelength (violet) light protects mice from myopia through cone signaling. *Invest Ophthalmol Vis Sci.* 2020;61(2):13. https://doi.org/10.1167/iovs.61.2.13.

88. Tian T, Zou L, Wu S, et al. Wavelength defocus and temporal sensitivity affect refractive development in Guinea pigs. *Invest Ophthalmol Vis Sci.* 2019;60(6):2173–2180. https://doi.org/10.1167/iovs.18-25228.

89. Quint WH, van Buuren R, Kokke N, et al. Exposure to cyan or red light inhibits the axial growth of zebrafish eyes. *Exp Eye Res.* 2023;230:109437. https://doi.org/10.1016/j.exer.2023.109437.

90. Dutheil F, Oueslati T, Delamarre L, et al. Myopia and near work: a systematic review and meta-analysis. *Int J Environ Res Publ Health.* 2023;20(1). https://doi.org/10.3390/ijerph20010875.

91. Tkatchenko AV, Tkatchenko TV, Guggenheim JA, et al. APLP2 regulates refractive error and myopia development in mice and humans. *PLoS Genet.* 2015;11(8): e1005432. https://doi.org/10.1371/journal.pgen.1005432.

92. Jin ZB, Wu J, Huang XF, et al. Trio-based exome sequencing arrests de novo mutations in early-onset high myopia. *Proc Natl Acad Sci U S A.* 2017;114(16): 4219–4224. https://doi.org/10.1073/pnas.1615970114.

93. Zhao F, Wu J, Xue A, et al. Exome sequencing reveals CCDC111 mutation associated with high myopia. *Hum Genet.* 2013;132(8):913–921. https://doi.org/10.1007/s00439-013-1303-6.

94. Hudson DM, Joeng KS, Werther R, et al. Post-translationally abnormal collagens of prolyl 3-hydroxylase-2 null mice offer a pathobiological mechanism for the high myopia linked to human LEPREL1 mutations. *J Biol Chem.* 2015;290(13): 8613–8622. https://doi.org/10.1074/jbc.M114.634915.

95. Ouyang J, Sun W, Xiao X, et al. CPSF1 mutations are associated with early-onset high myopia and involved in retinal ganglion cell axon projection. *Hum Mol Genet.* 2019;28(12):1959–1970. https://doi.org/10.1093/hmg/ddz029.

96. Dong S, Tian Q, Zhu T, et al. SLC39A5 dysfunction impairs extracellular matrix synthesis in high myopia pathogenesis. *J Cell Mol Med.* 2021;25(17):8432–8441. https://doi.org/10.1111/jcmm.16803.

97. Napolitano F, Di Iorio V, Testa F, et al. Autosomal-dominant myopia associated to a novel P4HA2 missense variant and defective collagen hydroxylation. *Clin Genet.* 2018;93(5):982–991. https://doi.org/10.1111/cge.13217.

98. Ng TK, Lam CY, Lam DS, et al. AC and AG dinucleotide repeats in the PAX6 P1 promoter are associated with high myopia. *Mol Vis.* 2009;15:2239–2248.

99. Song Y, Zhang F, Zhao Y, et al. Enlargement of the axial length and altered ultrastructural features of the sclera in a mutant lumican transgenic mouse model. *PLoS One.* 2016;11(10):e0163165. https://doi.org/10.1371/journal.pone.0163165.

100. Zhao F, Li Q, Chen W, et al. Dysfunction of VIPR2 leads to myopia in humans and mice. *J Med Genet.* 2022;59(1):88–100. https://doi.org/10.1136/jmedgenet-2020-107220.

101. Szczerkowska KI, Petrezselyova S, Lindovsky J, et al. Myopia disease mouse models: a missense point mutation (S673G) and a protein-truncating mutation of the Zfp644 mimic human disease phenotype. *Cell Biosci.* 2019;9:21. https://doi.org/10.1186/s13578-019-0280-4.

102. Zeitz C, Roger JE, Audo I, et al. Shedding light on myopia by studying complete congenital stationary night blindness. *Prog Retin Eye Res.* 2023;93:101155. https://doi.org/10.1016/j.preteyeres.2022.101155.

103. Neitz M, Neitz J. Intermixing the OPN1LW and OPN1MW genes disrupts the exonic splicing code causing an array of vision disorders. *Genes.* 2021;12(8). https://doi.org/10.3390/genes12081180.

104. van Mazijk R, Haarman AEG, Hoefsloot LH, et al. Early onset X-linked female limited high myopia in three multigenerational families caused by novel mutations in the ARR3 gene. *Hum Mutat.* 2022;43(3):380–388. https://doi.org/10.1002/humu.24327.

105. Park H, Jabbar SB, Tan CC, et al. Visually-driven ocular growth in mice requires functional rod photoreceptors. *Invest Ophthalmol Vis Sci.* 2014;55(10):6272–6279. https://doi.org/10.1167/iovs.14-14648.

106. Chakraborty R, Yang V, Park HN, et al. Lack of cone mediated retinal function increases susceptibility to form-deprivation myopia in mice. *Exp Eye Res.* 2019;180: 226–230. https://doi.org/10.1016/j.exer.2018.12.021.

107. Tian Q, Tong P, Chen G, et al. GLRA2 gene mutations cause high myopia in humans and mice. *J Med Genet.* 2023;60(2):193–203. https://doi.org/10.1136/jmedgenet-2022-108425.

108. Zhao F, Wu H, Reinach PS, et al. Up-regulation of matrix metalloproteinase-2 by scleral monocyte-derived macrophages contributes to myopia development. *Am J Pathol.* 2020;190(9):1888–1908. https://doi.org/10.1016/j.ajpath.2020.06.002.

109. Zhou X, Huang Q, An J, et al. Genetic deletion of the adenosine A2A receptor confers postnatal development of relative myopia in mice. *Invest Ophthalmol Vis Sci.* 2010;51(9):4362–4370. https://doi.org/10.1167/iovs.09-3998.

110. Aldahmesh MA, Khan AO, Alkuraya H, et al. Mutations in LRPAP1 are associated with severe myopia in humans. *Am J Hum Genet.* 2013;93(2):313–320. https://doi.org/10.1016/j.ajhg.2013.06.002.

111. Ma Y, Lin Q, Zhao Q, et al. Prevalence and characteristics of myopia in adult rhesus macaques in southwest China. *Transl Vis Sci Technol.* 2023;12(3):21. https://doi.org/10.1167/tvst.12.3.21.

112. Ablordeppey RK, Lin CR, Song B, et al. Choroidal morphology and photoreceptor activity are related and affected by myopia development. *Invest Ophthalmol Vis Sci.* 2024;65(2):3. https://doi.org/10.1167/iovs.65.2.3.

113. Spaide RF, Fujimoto JG, Waheed NK, et al. Optical coherence tomography angiography. *Prog Retin Eye Res.* 2018;64:1–55. https://doi.org/10.1016/j.preteyeres.2017.11.003.

114. Wei X, Balne PK, Meissner KE, et al. Assessment of flow dynamics in retinal and choroidal microcirculation. *Surv Ophthalmol.* 2018;63(5):646–664. https://doi.org/10.1016/j.survophthal.2018.03.003.

115. Rinner O, Rick JM, Neuhauss SC. Contrast sensitivity, spatial and temporal tuning of the larval zebrafish optokinetic response. *Invest Ophthalmol Vis Sci.* 2005;46(1): 137–142. https://doi.org/10.1167/iovs.04-0682.

116. Zhou X, Pardue MT, Iuvone PM, et al. Dopamine signaling and myopia development: what are the key challenges. *Prog Retin Eye Res.* 2017;61:60–71. https://doi.org/10.1016/j.preteyeres.2017.06.003.

117. Tian T, Zou L, Wang S, et al. The role of dopamine in emmetropization modulated by wavelength and temporal frequency in Guinea pigs. *Invest Ophthalmol Vis Sci.* 2021;62(12):20. https://doi.org/10.1167/iovs.62.12.20.

118. Wei P, Han G, Wang Y. Effects of dopamine D2 receptor antagonists on retinal pigment epithelial/choroid complex metabolism in form-deprived myopic Guinea

pigs. *Proteomics.* 2023;23(18):e2200325. https://doi.org/10.1002/pmic.202200325.

119. Shu Z, Chen K, Wang Q, et al. The role of retinal dopamine D1 receptors in ocular growth and myopia development in mice. *J Neurosci.* 2023;43(48):8231–8242. https://doi.org/10.1523/jneurosci.1196-23.2023.

120. Pesudovs K, Elliott DB. Refractive error changes in cortical, nuclear, and posterior subcapsular cataracts. *Br J Ophthalmol.* 2003;87(8):964–967. https://doi.org/10.1136/bjo.87.8.964.

121. van Alphen GW. Choroidal stress and emmetropization. *Vis Res.* 1986;26(5): 723–734. https://doi.org/10.1016/0042-6989(86)90086-6.

122. Campbell DG. Pigmentary dispersion and glaucoma. A new theory. *Arch Ophthalmol.* 1979;97(9):1667–1672. https://doi.org/10.1001/archopht.1979.01020020235011.

123. McBrien NA, Cornell LM, Gentle A. Structural and ultrastructural changes to the sclera in a mammalian model of high myopia. *Invest Ophthalmol Vis Sci.* 2001; 42(10):2179–2187.

124. Gentle A, Liu Y, Martin JE, et al. Collagen gene expression and the altered accumulation of scleral collagen during the development of high myopia. *J Biol Chem.* 2003;278(16):16587–16594. https://doi.org/10.1074/jbc.M300970200.

125. Liang CL, Hung KS, Tsai YY, et al. Systematic assessment of the tagging polymorphisms of the COL1A1 gene for high myopia. *J Hum Genet.* 2007;52(4): 374–377. https://doi.org/10.1007/s10038-007-0117-6.

126. Jacobson A, Besirli CG, Bohnsack BL. Characteristics of a three-generation family with stickler syndrome type I carrying two different COL2A1 mutations. *Genes.* 2023;14(4). https://doi.org/10.3390/genes14040847.

127. Levinger N, Hendler K, Banin E, et al. Variable phenotype of Knobloch syndrome due to biallelic COL18A1 mutations in children. *Eur J Ophthalmol.* 2021;31(6): 3349–3354. https://doi.org/10.1177/1120672120977343.

128. Massagué J, Sheppard D. TGF-β signaling in health and disease. *Cell.* 2023;186(19): 4007–4037. https://doi.org/10.1016/j.cell.2023.07.036.

129. Zhu X, Du Y, Li D, et al. Aberrant TGF-β1 signaling activation by MAF underlies pathological lens growth in high myopia. *Nat Commun.* 2021;12(1):2102. https://doi.org/10.1038/s41467-021-22041-2.

130. Ku H, Chen JJ, Chen W, et al. The role of transforming growth factor beta in myopia development. *Mol Immunol.* 2024;167:34–42. https://doi.org/10.1016/j.molimm.2024.01.011.

131. Kerkvliet EH, Jansen IC, Schoenmaker T, et al. Collagen type I, III and V differently modulate synthesis and activation of matrix metalloproteinases by cultured rabbit periosteal fibroblasts. *Matrix Biol.* 2003;22(3):217–227. https://doi.org/10.1016/s0945-053x(03)00035-0.

132. Wojciechowski R, Yee SS, Simpson CL, et al. Matrix metalloproteinases and educational attainment in refractive error: evidence of gene-environment interactions in the Age-Related Eye Disease Study. *Ophthalmology.* 2013;120(2): 298–305. https://doi.org/10.1016/j.ophtha.2012.07.078.

133. Liu HH, Kenning MS, Jobling AI, et al. Reduced scleral TIMP-2 expression is associated with myopia development: TIMP-2 supplementation stabilizes scleral biomarkers of myopia and limits myopia development. *Invest Ophthalmol Vis Sci.* 2017;58(4):1971–1981. https://doi.org/10.1167/iovs.16-21181.

134. Brown DM, Mazade R, Clarkson-Townsend D, et al. Candidate pathways for retina to scleral signaling in refractive eye growth. *Exp Eye Res.* 2022;219:109071. https://doi.org/10.1016/j.exer.2022.109071.

135. Liu H, Schaeffel F, Yang Z, et al. GABA(B) receptor activation affects eye growth in chickens with visually induced refractive errors. *Biomolecules.* 2023;13(3). https://doi.org/10.3390/biom13030434.

136. Carr BJ, Stell WK. Nitric oxide (NO) mediates the inhibition of form-deprivation myopia by atropine in chicks. *Sci Rep.* 2016;6(1):9. https://doi.org/10.1038/s41598-016-0002-7.

137. Tao Y, Pan M, Liu S, et al. cAMP level modulates scleral collagen remodeling, a critical step in the development of myopia. *PLoS One.* 2013;8(8):e71441. https://doi.org/10.1371/journal.pone.0071441.

138. Qin Y, Liu T, Zhang Z, et al. Scleral remodeling in early adulthood: the role of FGF-2. *Sci Rep.* 2023;13(1):20779. https://doi.org/10.1038/s41598-023-48264-5.

139. Liu YX, Sun Y. MMP-2 participates in the sclera of Guinea pig with form-deprivation myopia via IGF-1/STAT3 pathway. *Eur Rev Med Pharmacol Sci.* 2018;22(9): 2541–2548. https://doi.org/10.26355/eurrev_201805_14945.

140. Li H, Cui D, Zhao F, et al. BMP-2 is involved in scleral remodeling in myopia development. *PLoS One.* 2015;10(5):e0125219. https://doi.org/10.1371/journal.pone.0125219.

141. Wong CG, Taban M, Osann K, et al. Subchoroidal release of VEGF and bFGF produces choroidal neovascularization in rabbit. *Curr Eye Res.* 2017;42(2):237–243. https://doi.org/10.1080/02713683.2016.1227448.

142. Brown DM, Yu J, Kumar P, et al. Exogenous all-trans retinoic acid induces myopia and alters scleral biomechanics in mice. *Invest Ophthalmol Vis Sci.* 2023;64(5):22. https://doi.org/10.1167/iovs.64.5.22.

143. Hu S, Ouyang S, Liu H, et al. The effect of Wnt/β-catenin pathway on the scleral remolding in the mouse during form deprivation. *Int Ophthalmol.* 2021;41(9): 3099–3107. https://doi.org/10.1007/s10792-021-01875-1.

144. Wu W, Su Y, Hu C, et al. Hypoxia-induced scleral HIF-2α upregulation contributes to rises in MMP-2 expression and myopia development in mice. *Invest Ophthalmol Vis Sci.* 2022;63(8):2. https://doi.org/10.1167/iovs.63.8.2.

145. Ren Y, Yang X, Luo Z, et al. HIF-1α aggravates pathologic myopia through the miR-150-5p/LAMA4/p38 MAPK signaling axis. *Mol Cell Biochem.* 2022;477(4): 1065–1074. https://doi.org/10.1007/s11010-021-04305-z.

146. Wei Q, Zhang T, Fan J, et al. Pathological myopia-induced antioxidative proteins in the vitreous humor. *Ann Transl Med.* 2020;8(5):193. https://doi.org/10.21037/atm.2020.01.63.

147. Kang L, Ikeda SI, Yang Y, et al. Establishment of a novel ER-stress induced myopia model in mice. *Eye Vis (Lond)*. 2023;10(1):44. https://doi.org/10.1186/s40662-023-00361-2.

148. Zhu C, Chen Q, Yuan Y, et al. Endoplasmic reticulum stress regulates scleral remodeling in a Guinea pig model of form-deprivation myopia. *J Ophthalmol*. 2020. 2020:3264525. https://doi.org/10.1155/2020/3264525.

149. Ikeda SI, Kurihara T, Jiang X, et al. Scleral PERK and ATF6 as targets of myopic axial elongation of mouse eyes. *Nat Commun*. 2022;13(1):5859. https://doi.org/10.1038/s41467-022-33605-1.

150. Lin X, Lei Y, Pan M, et al. Augmentation of scleral glycolysis promotes myopia through histone lactylation. *Cell Metabol*. 2024;36(3):511–525.e7. https://doi.org/10.1016/j.cmet.2023.12.023.

151. Pan M, Zhao F, Xie B, et al. Dietary ω-3 polyunsaturated fatty acids are protective for myopia. *Proc Natl Acad Sci U S A*. 2021;118(43). https://doi.org/10.1073/pnas.2104689118.

152. Zhang L, Yu X, Hong N, et al. CircRNA expression profiles and regulatory networks in the vitreous humor of people with high myopia. *Exp Eye Res*. 2024;241:109827. https://doi.org/10.1016/j.exer.2024.109827.

153. Cui Z, Huang Y, Chen X, et al. Identification of miR-671-5p and its related pathways as general mechanisms of both form-deprivation and lens-induced myopia in mice. *Curr Issues Mol Biol*. 2023;45(3):2060–2072. https://doi.org/10.3390/cimb45030132.

154. Jiang B, Hong N, Zhang L, et al. MiR-181a-5p may regulate cell proliferation and autophagy in myopia and the associated retinopathy. *Exp Eye Res*. 2024;241:109829. https://doi.org/10.1016/j.exer.2024.109829.

155. Liang CL, Chen KC, Hsi E, et al. miR-328-3p affects axial length via multiple routes and anti-miR-328-3p possesses a potential to control myopia progression. *Invest Ophthalmol Vis Sci*. 2022;63(12):11. https://doi.org/10.1167/iovs.63.12.11.

156. Li T, Li X, Hao Y, et al. Inhibitory effect of miR-138-5p on choroidal fibrosis in lens-induced myopia Guinea pigs via suppressing the HIF-1α signaling pathway. *Biochem Pharmacol*. 2023;211:115517. https://doi.org/10.1016/j.bcp.2023.115517.

157. Li Q, Zheng Q, He J, et al. Hsa-miR-142-3p reduces collagen I in human scleral fibroblasts by targeting TGF-β1 in high myopia. *Exp Eye Res*. 2022;219:109023. https://doi.org/10.1016/j.exer.2022.109023.

158. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res*. 2010;29(2):144–168. https://doi.org/10.1016/j.preteyeres.2009.12.002.

159. Burfield HJ, Patel NB, Ostrin LA. Ocular biometric diurnal rhythms in emmetropic and myopic adults. *Invest Ophthalmol Vis Sci*. 2018;59(12):5176–5187. https://doi.org/10.1167/iovs.18-25389.

160. Yu T, Xie X, Wei H, et al. Choroidal changes in lens-induced myopia in Guinea pigs. *Microvasc Res*. 2021;138:104213. https://doi.org/10.1016/j.mvr.2021.104213.

161. Huang Y, Li X, Wu J, et al. Effect of spectacle lenses with aspherical lenslets on choroidal thickness in myopic children: a 2-year randomised clinical trial. *Br J Ophthalmol*. 2023;107(12):1806–1811. https://doi.org/10.1136/bjo-2022-321815.

162. Chun RK-m, Liu Z, Tang WC, et al. Effect of defocus incorporated multiple segments (DIMS) lenses on choroidal thickness in schoolchildren. *Invest Ophthalmol Vis Sci*. 2021;62(8), 1389-1389.

163. Zhou X, Zhang S, Zhang G, et al. Increased choroidal blood perfusion can inhibit form deprivation myopia in Guinea pigs. *Invest Ophthalmol Vis Sci*. 2020;61(13):25. https://doi.org/10.1167/iovs.61.13.25.

164. Zhou X, Zhang S, Yang F, et al. Decreased choroidal blood perfusion induces myopia in Guinea pigs. *Invest Ophthalmol Vis Sci*. 2021;62(15):30. https://doi.org/10.1167/iovs.62.15.30.

165. Zhang S, Zhang G, Zhou X, et al. Changes in choroidal thickness and choroidal blood perfusion in Guinea pig myopia. *Invest Ophthalmol Vis Sci*. 2019;60(8):3074–3083. https://doi.org/10.1167/iovs.18-26397.

166. Jiang X, Pardue MT, Mori K, et al. Violet light suppresses lens-induced myopia via neuropsin (OPN5) in mice. *Proc Natl Acad Sci U S A*. 2021;118(22). https://doi.org/10.1073/pnas.2018840118.

167. Carpena-Torres C, Schilling T, Huete-Toral F, et al. Increased ocular dopamine levels in rabbits after blue light stimulation of the optic nerve head. *Exp Eye Res*. 2023;234:109604. https://doi.org/10.1016/j.exer.2023.109604.

168. Zhang P, Zhu H. Light signaling and myopia development: a review. *Ophthalmol Ther*. 2022;11(3):939–957. https://doi.org/10.1007/s40123-022-00490-2.

169. Wolffsohn JS, Kollbaum PS, Berntsen DA, et al. Imi - clinical myopia control trials and instrumentation report. *Invest Ophthalmol Vis Sci*. 2019;60(3):M132–m160. https://doi.org/10.1167/iovs.18-25955.

170. Zhu Q, Cao X, Zhang Y, et al. Repeated low-level red-light therapy for controlling onset and progression of myopia-a review. *Int J Med Sci*. 2023;20(10):1363–1376. https://doi.org/10.7150/ijms.85746.

171. Sanchez Tocino H, Diez Montero C, Villanueva Gómez A, et al. Phenotypic high myopia in X-linked retinitis pigmentosa secondary to a novel mutation in the RPGR gene. *Ophthalmic Genet*. 2019;40(2):170–176. https://doi.org/10.1080/13816810.2019.1605385.

172. Zhao F, Zhou H, Chen W, et al. Declines in PDE4B activity promote myopia progression through downregulation of scleral collagen expression. *Exp Eye Res*. 2021;212:108758. https://doi.org/10.1016/j.exer.2021.108758.

173. Manes G, Cheguru P, Majumder A, et al. A truncated form of rod photoreceptor PDE6 β-subunit causes autosomal dominant congenital stationary night blindness by interfering with the inhibitory activity of the γ-subunit. *PLoS One*. 2014;9(4):e95768. https://doi.org/10.1371/journal.pone.0095768.

174. Schippert R, Burkhardt E, Feldkaemper M, et al. Relative axial myopia in Egr-1 (ZENK) knockout mice. *Invest Ophthalmol Vis Sci*. 2007;48(1):11–17. https://doi.org/10.1167/iovs.06-0851.

175. Orhan E, Neuillé M, de Sousa Dias M, et al. A new mouse model for complete congenital stationary night blindness due to Gpr179 deficiency. *Int J Mol Sci*. 2021;22(9). https://doi.org/10.3390/ijms22094424.

176. Gregg RG, Mukhopadhyay S, Candille SI, et al. Identification of the gene and the mutation responsible for the mouse nob phenotype. *Invest Ophthalmol Vis Sci*. 2003;44(1):378–384. https://doi.org/10.1167/iovs.02-0501.

177. Hölzel MB, Kamermans M, Winkelman BHJ, et al. A common cause for nystagmus in different congenital stationary night blindness mouse models. *J Physiol*. 2023;601(23):5317–5340. https://doi.org/10.1113/jp284965.

178. Fischer AJ, Morgan IG, Stell WK. Colchicine causes excessive ocular growth and myopia in chicks. *Vis Res*. 1999;39(4):685–697. https://doi.org/10.1016/s0042-6989(98)00178-3.

179. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*. 2002;295(5557):1070–1073. https://doi.org/10.1126/science.1067262.

180. Hattar S, Liao HW, Takao M, et al. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*. 2002;295(5557):1065–1070. https://doi.org/10.1126/science.1069609.

181. Liu AL, Liu YF, Wang G, et al. The role of ipRGCs in ocular growth and myopia development. *Sci Adv*. 2022;8(23):eabm9027. https://doi.org/10.1126/sciadv.abm9027.

182. Li L, Yu Y, Zhuang Z, et al. Circadian rhythm, ipRGCs, and dopamine signalling in myopia. *Graefes Arch Clin Exp Ophthalmol*. 2024;262(3):983–990. https://doi.org/10.1007/s00417-023-06276-x.

183. Zhang X, Yu X, Wen Y, et al. Functions of retinal astrocytes and Müller cells in mammalian myopia. *BMC Ophthalmol*. 2022;22(1):451. https://doi.org/10.1186/s12886-022-02643-0.