Why Do Eyes Become Myopic?

Many factors determine the route to myopia development.

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Refractive errors are the most common eye disorders worldwide and the largest source of visual impairment.[1,2] In particular, high myopia is associated with a significant risk of visual complications, such as myopic macular degeneration, glaucoma, and retinal detachment (Figure 1).[3-5] The absolute risk of severe visual impairment increases significantly with each diopter of myopic refractive error, ranging from 3% to 5% in individuals with errors of -6.00 D to more than 40% in those with -15.00 D or more (Klaver, personal communication).

Reports have shown that the prevalence of myopia is on the rise.[6-8] In the United States, the prevalence of myopia increased by 145% during the past 3 decades, and the rate of high myopia increased by 820%.[7] In South Korea, the increase in the prevalence of myopia and high myopia was 334% and 891%, respectively.[8] Although the same trends are found in African and European populations,[9-11] the prevalence of myopia is currently highest in Asians. In Singapore, 80% to 90% of young adults are myopic (Figure 2).[12]

These figures are dramatic and demand effective counteractions. The first question is, "Why do eyes become myopic?" This article summarizes current insights into the development and pathogenesis of this trait.

COURSE OF REFRACTIVE ERROR

Children are born hyperopic and become emmetropic by age 6 to 9 years due to emmetropization.[13] Although the cornea stabilizes at around age 6,[14] the power of the lens usually changes until age 12, and the eye's axis may continue to elongate up to age 20 to 25.[14,15] There is a strong correlation between the severity of adult myopia and age of onset: Onset of high myopia usually occurs in the first decade of life, while mild myopia can develop in the teenage years or even in early adulthood.

RISK FACTORS FOR MYOPIA

Genetic associations. The evidence for the heritability of refractive error and myopia stems from studies of familial clustering,[16] high heritability values in twins,[17,18] and high recurrence rates in offspring.[19,20] The search for the genes responsible for heritability was initiated by linkage (MYP 1-18) and candidate gene studies (CTNND2) performed in high-risk groups.[21-31] Although these investigations provided some success, there was a lack of validation across studies.

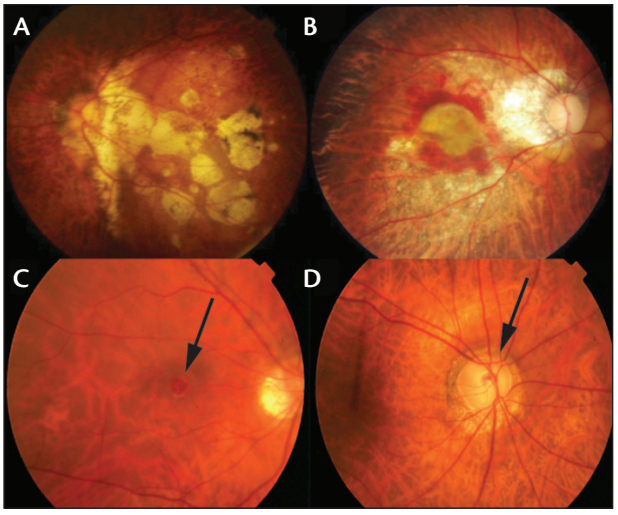

Figure 1. Myopic ocular pathology, showing chorioretinal atrophy (A), choroidal neovascularization (B), macular hole (C), and glaucoma (D).

A more powerful approach proved to be the use of genome-wide association study (GWAS) analyses, which robustly investigated numerous single nucleotide polymorphisms (SNPs) across the genome in large populations. Genomic hits for commonly occurring refractive errors were first found by Dutch and British researchers.[32-34] The loci they found were located on chromosome 15, and the closest genes were *GJD2* and *RASGRF1*, respectively. Identifying the functions of these genes opened new hypotheses on myopia development, as each plays a role in retinal neurotransmission. The *GJD2*

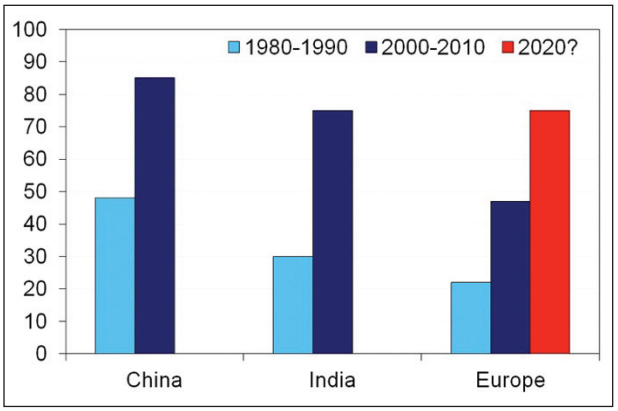

Figure 2. Increasing prevalence of myopia in Asia and Europe.[12,45]

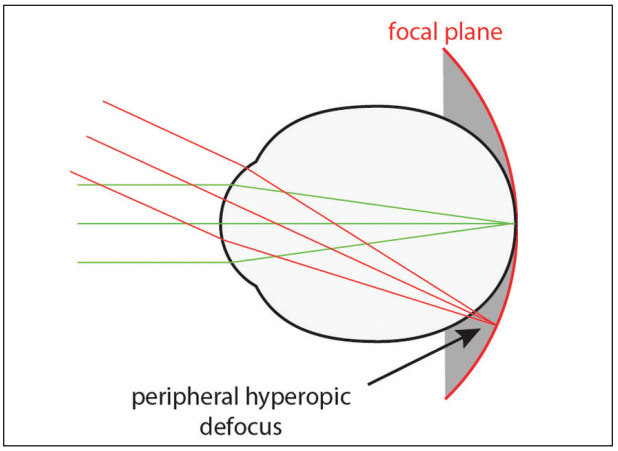

Figure 3. Prolate-shaped eyes have a relatively great depth of hyperopic defocus in the periphery. This may trigger elongation of the eye.

gene forms a gap junction between neuronal cells in the retina, enabling intracellular exchange of small molecules and ions,[35-38] while *RASGRF1* is a nuclear exchange factor involved in synaptic transmission of photoreceptor responses.[39,40] Signaling defects in the retina became a likely cause for myopia.

Following these reports, the international Consortium for Refractive Error and Myopia (CREAM) was formed to identify more genes. This group found genome-wide significance for another 24 loci in 45,758 individuals.[41] Almost simultaneously, the commercial direct-to-consumer genetic testing company 23andMe identified 22 genomic loci in 45,771 individuals using *diagnosed with myopia* and *age of first glasses* as outcome variables.[42] The results from 23andMe were strikingly similar to those of the CREAM consortium; 14 genome-wide significant hits overlapped. Additionally, the effect sizes of most of the associations were linearly related,[43] indicating that these genetic associations were robust and generalizable to other populations. The striking similarity of genetic associations between Caucasians and Asians strengthened this conception.[41]

How much risk for development of myopia do these refractive error genes convey? For individuals carrying the highest number of risk alleles, one study showed a tenfold increase over those with an average number of alleles.[41] Despite the clinical significance of this risk, the currently known 68 refractive error genes[24,44,45] explain only 5% of phenotypic variance.[41]

This leaves us with a high degree of missing heritability; in other words, many genetic risk variants are still undiscovered. Researchers are currently exploiting new avenues for gene identification, such as exome sequencing, to find the rarer genetic risk factors on coding DNA.[46-48] Interrelationships between genes and the environment also determine a large proportion of the variance in complex traits;[49] therefore, a focus on the identification of gene-environment interactions is needed as well.

Environmental risk factors. Beyond doubt, myopia is caused by nature as well as nurture. Many studies have shown that lifestyle factors play a crucial role in the onset and progression of this trait.[50,51] In particular, education is a risk factor that is highly associated with myopia; individuals with a university or higher vocational education have a five to eight times higher risk of myopia than those who have attended only primary school.[52,53] Similar effects are observed for urban versus rural areas. Urban regions have a much higher prevalence of myopia.[54]

Explanations for these risks were sought, and two observations stood out: (1) Myopic children spent less time outdoors than nonmyopic children, and (2) they performed more near work at an earlier age.[55-57] The protection conveyed by being outdoors is thought to be determined by light intensity;[58] while illuminance indoors is about 500 lux, light levels outdoors are generally greater than 20,000 lux. Higher light intensity has been associated with higher dopamine release in the retina,[59] and animal studies have shown that higher dopamine levels slow the elongation of the eyeball.[60]

The association with near work is less apparent. Type of near work has been a difficult factor to study, and factors such as use of handheld digital tablets and reading show inconsistency and low reproducibility in studies.[61,62] A current hypothesis is that near work triggers myopia due to the long duration of defocus in the peripheral retina,[63] particularly in eyes with a prolate shape (Figure 3).[64]

Gene-environment interactions. In a disease caused by both genetic and environmental factors, there is likely to be considerable interaction between these factors.[53] This is the case with myopia. Education and genetic risk have been

TABLE 1. IDENTIFIED MYOPIA GENES ANNOTATED TO GENETIC PATHWAYS[24,41,42]

Pathway/Function	Genes
Neurotransmission	*GJD2, RASGRF1, GRIA4*
Ion channels	*KCNQ5, CACNA1D, KCNJ2, KCNMA1*
Signal transduction	*GPR25, PDE11A, RBFOX1, CHRNG*
MAPK signaling	*PTPRR*
Wnt signaling	*SFRP1, BICC1, TCF7L2*
Protein processing	*MIPEP, CNDP2, NPLOC4, PZP, B4GALNT2*
Retinoic acid metabolism	*RDH5, RGR, CYP26A1*
Extracellular matrix remodeling	*LAMA2, BMP2, BMP3, BMP4, ADAMTSL1, UND*
Apoptosis	*BLID*
Cell adhesion	*LRFN5, TJP2*
Eye development	*SIX6, PRSS56, CHD7, ZNF644, CTNND2, DLX1, RORB*
Neuronal development	*LRRRC4, DLG2*
Ganglion cell growth	*ZIC2*
Complement cascade	*CD55, C1QTNF9B*
Intracellular movements	*MYO1D*
Unknown	*BI480957, CA8, EHBP1L1, PABPCP2, QKI, SETMAR, SH3GL2, SHISA6, TMEM98, TOX, ZBTB38*

shown to interact: Individuals with a high genetic load in combination with university-level education had a much higher risk of myopia than those with only one of these two factors.[65] This interaction was specifically found for the genes *SHISA6-DNAH9*, *GJD2,* and *ZMAT4-SFRP1*.[66] It is expected that many more gene-environment interactions determine the variance of refractive error and myopia.

REFRACTIVE ERROR STUDIES IN ANIMALS

Studies of refractive error in various species including chicks, rodents, marmots, guinea pigs, and monkeys have formed the foundation for our understanding of the effect of visual input on eye growth. Several strategies have been used to induce myopia in animals, including form deprivation by blurring the eye, visual deprivation by lid suture,[67-70] and placement of a negative (concave) lens in front of the eye.[71-74] Placing a positive lens in front of the eye counteracts myopia development, as it slows eye growth.[75] The lens effects appeared to be independent of visual transmission to the brain because they worked similarly in animals with a disrupted optic nerve. Recent animal studies have demonstrated that the peripheral retina is more responsive to blur than the macula,[64,76] and monkey and chicken experiments have supported the notion that peripheral retinal defocus is a stimulus for myopiagenesis.[64,77]

Chickens with negative lens wear and exposure to high illuminance showed retarded myopia progression compared with chickens with exposure to low illuminance.[78] The wavelength of light appeared to play a role as well. Chiclid fish living under red, long-wavelength light circumstances developed higher axial lengths compared with fish kept in blue, short-wavelength light.[79] Rhesus monkeys showed a significant myopic shift after growing up (for up to 51 weeks) in red light.[31] In contrast, blue light had an

TAKE-HOME MESSAGE

- There is strong correlation between age of onset and severity of adult myopia.
- Many genetic risk variants for myopia are still undiscovered, but researchers are exploiting new avenues for gene discovery, such as exome sequencing, to find rarer genetic risk factors on coding DNA.
- Numerous studies have shown that lifestyle factors, particularly education level and outdoor exposure, play a crucial role in the onset and progression of myopia.
- Future focus on the network of molecules involved in myopiagenesis and their response to environmental stimuli should open new strategies for intervention and prevention, with the ultimate aim to diminish severe visual impairment caused by myopia.

inhibiting effect on myopia development in guinea pigs.[80]

Various pharmacologic studies have been performed in animals, in particular intervention studies aimed at neurotransmitters and hormonal molecules. Many showed a potent inhibitory effect on eye growth with atropine. This effect is mediated by muscarine receptors, and the receptors M1 and M4 are most important here.[81-83] Exactly how atropine inhibits eye growth is still subject to debate, but a direct effect of these receptors on the sclera seems likely. Dopamine, like atropine, appeared to have an inhibiting effect on eye growth in rabbits and guinea pigs, and dopamine antagonists abolished the protective effect of high illuminance in chicks.[59]

Two hormones that help to balance glucose levels, glucagon and insulin,[84] were reported to play opposite roles in myopiagenesis. Glucagon inhibited eye growth, whereas insulin had a stimulatory effect. Glucagon acts via transcription factor ZENK,[85] and, interestingly, experiments showed that ZENK RNA fragments formed after lens-induced myopia rapidly down-regulated when atropine was injected into the eyes of chickens.[86] Other molecules that were investigated include retinoic acid, vasoactive intestine polypeptide, cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophospate (cGMP). Retinoic acid is a metabolite of vitamin A.[87] In form-deprived myopic chickens with accelerated axial elongation, retinoic acid appeared to be elevated in the retina. In the fellow eye (without form deprivation and inhibited axial elongation), the levels were lower.[88] cGMP, a signaling molecule in the phototransduction cascade, was shown to increase eye growth and myopia development; the antagonist inhibited the myopic effect.[89] cAMP, another signaling molecule, was also up-regulated in the retinas of form-deprived eyes.[90] Last, a vasoactive intestinal peptide receptor antagonist was shown to inhibit form-deprived myopia in chicks by counteracting the up-regulation of this neurotransmitter.[91]

Animal studies focusing on gene function are gaining popularity, and several functional studies of myopia genes have been carried out. The genes *DLX1* and *ZIC2* were shown to influence retinal development in the mouse: *DLX1* misexpression increased the number of amacrine and bipolar cells and decreased the number of cones;[92] *ZIC2*, a zinc finger gene, was shown to be capable of axonal guiding to the optic chiasm midline.[93] *RORB*, a transcription factor and member of the nuclear receptor family, was shown to be important for cone maturation and amacrine and horizontal cell development in mice.[94,95] The developmental genes *PRSS56* and *SIX6* have been associated with microphthalmus and glaucoma.[96,97]

Zebrafish studies showed that *CHD7* is also involved in determination of retinal structure.[98] In humans, this gene is mutated in the majority of patients with coloboma, heart defect, atresia choanae (CHARGE) syndrome. Interestingly, in *CHD7*-mutated mice, expression of another gene, *BMP4*, appeared down-regulated in neuronal cells.[99] *BMP4* had been shown to be up-regulated in the retinal pigment epithelium after negative lens wear.[100]

RDH5 is a gene involved in vitamin A metabolism by its ability to oxidize or reduce cis-retinoid isomers. Knockout mice of this gene mostly showed disturbance of rod function; electroretinography shows a slow recovery after bleaching,[101,102] and the dark-adapted retinoid profile shows increased levels of 11-cis retinol and cis retinyl esters. *CYP26A1* is another gene related to retinoid acid and metabolism in the retina.[103] The gene RGR is involved in rhodopsin regeneration, and, in knockout mice, this process was slowed down by a factor three.[104]

As mentioned above, *RASGRF1* is a gene related to defective neurotransmission without structural retinal defects in mutant mice.[39] The *GJD2* gene is coding for a gap junction, which appears closely related to the gap junction accessory protein *TJP2*.[105] *CACNA1D* is a calcium channel coding gene that is expressed in cones. Its function resembles that of the *CACNA1F* gene, which causes congenital stationary night blindness with high myopia.[106] *KCNQ5* is coding for an M-type potassium current in the retinal pigment epithelium and neural retina.[107] *CD55* (decay-activating factor) is increased in retinal Mueller cells in mice with mutations of complement factor H, a risk factor associated with age-related macular degeneration.[108]

DISEASE MECHANISMS

From the genes, several pathways can be annotated (Table 1). These pathways fit into the current hypothesis on myopia pathogenesis: A visually evoked signaling cascade (neurotransmission, signaling, retinoic acid genes), which originates from the retina (neuronal development, ganglion cell genes), traverses the retinal pigment epithelium and choroid (signaling, intracellular movement genes), and terminates in the sclera, where active remodelling of extracellular matrix (extracellular matrix genes, retinoic acid, apoptosis genes) results in elongation of the eye. The eye and neuronal developmental genes may have their actions at various sites in this signaling cascade.

CONCLUSION

The question of why eyes become myopic cannot be answered lightly. Many factors determine the route from emmetropization to myopiagenesis. Genetic factors provide the susceptibility, but environmental factors are key players in triggering this conversion. Future focus on the network of molecules involved and their response to environmental stimuli should open new strategies for

intervention and prevention, with the ultimate aim to diminish severe visual impairment caused by myopia. ■

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