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Review

A genetic perspective on myopia

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Abstract. Myopia is a refractive error of the eye that has a significant socioeconomic impact due to its increasing prevalence and the fact that it causes visual impairment. Its aetiology is complex and is likely to involve the interaction of environmental and genetic influences. Tight environmental influence is exemplified by defocus-induced myopia produced in animal models, while genetic factors predominate in familial occurrence of myopia with a Mendelian inheritance pattern. The involvement of numerous mediators, such as cytokines, neurotransmitters and transcription factors, in myopia development has been indicated through various lines of investigation, particular interest focussing on scleral extracellular matrix proteins and developmental genes of the eye. As high-throughput technology for large-scale genotyping and RNA expression analysis enters the field of myopia research, a productive avenue will open up for deciphering the aetiological heterogeneity of myopia and the biological pathways underlying its development.

Key words. Myopia; candidate genes; linkage analysis; animal models; quantitative traits.

Introduction

Refractive errors are by far the most common ocular disorders in humans, with myopia (short-sightedness) alone causing approximately 25% of uncorrected decreased vision in populations of the Western world [1]. While in most cases refractive errors pose a minor restriction that can be corrected with glasses, contact lenses or refractive surgery, in some parts of the world myopic refractive errors have become a significant public health problem. Myopia is especially common in some urban Asian regions, such as Singapore, Taiwan, Japan and Hong Kong, where 60–80% of young adults are myopic [2].

Moreover, a continuous increase in the worldwide prevalence and severity of myopia has been observed over the past decades, a trend that appears to be dramatically affecting some developed Asian countries [3]. While changing lifestyle and visual experience in the industrialized world are probable factors contributing to this trend, myopic refractive errors continue to impose a major public health problem in many underdeveloped countries. Due to the inadequate medical care in many of these countries, myopia constitutes a significant cause of severe visual impairment.

The critical social and economic consequences of myopic refractive errors are one reason for widespread investigations into the origins of myopia. The other is recent progress in our understanding of the genetic basis of human disease at the molecular level and of the biological changes underlying myopia, as established through experimental animal studies. The purpose of the present review is to outline the current state of myopia research with a focus on modern genetic techniques used to identify candidate genes possibly involved in myopia development.

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Pathophysiology of myopia and eye development

Myopia defines a state of refraction where only nearby objects can be focussed to produce a clear retinal image. In terms of physical optics, myopia means a mismatch of the optical power of the eye and its axial length in such a way that essentially parallel rays from distant objects are brought into focus in front of the retina. The traditional measure of refractive errors is the power of the corrective lens expressed in diopters (dpt.) that is necessary to bring the object image back onto the retina. In the case of myopia this is a negative or diverging lens that reduces the total optical power of the eye. The more negative the value, the greater the degree of myopia.

The refractive status of a given human eye depends mainly upon three refractive elements: the refractive powers of the cornea and lens and the anterior-posterior diameter or axial length of the globe. Humans, like most animals, are frequently born with moderate hyperopic errors (far-sightedness) that are generally produced by a short axial eye length. During eye growth in the early years of life axial elongation is regulated through a process known as emmetropization that matches the refractive elements to axial length to produce normal vision or emmetropia [4]. From the frequency of observed emmetropia and from a knowledge of the visual stimuli that control refractive development in animal models, it has been concluded that emmetropization is an active feedback process with the rate of axial growth being constantly modulated in response to detected focussing errors of the eye. In contrast, the failure of emmetropization, i.e. the occurrence of refractive errors (ametropia), can be considered as a departure from this control process that may occur at any time during development [5]. In myopia, either the axial length of the eye is too long for its refractive power or the refractive power is too strong for its length. Low and moderate levels of myopic refractive errors are frequently the result of a failure of refractive components of the eye to match each other, while the magnitude of these components generally falls into the range of normal distribution [6]. In contrast, in high myopia one refractive component, usually the axial length, is clearly outside normal limits (fig. 1). Elongation of the axial length of the eye by merely 1 mm without other compensation will result in a myopia of –2.0 to –2.5 dpt.

Beside this morphological distinction of low and high grades of myopia, different levels of myopia can be distinguished clinically. For the higher levels of myopia, usually defined as axial length greater than 26 mm or a refractive error of more than –6.0 dpt., the amount of myopia correlates not only with axial length, but also with an increased risk of additional eye disorders, such as glaucoma and retinal detachment (table 1). The high grades, therefore also known as pathological myopia, though having a prevalence of only 2% in the general population in Germany, are a significant cause of visual impairment (fig. 2). High myopia complications are for instance the fourth leading cause of blindness in one regional state in southern Germany [8]. This is particularly unfortunate because myopia-related blindness, in contrast to other causes, often afflicts people earlier in life when they may still be active professionally.

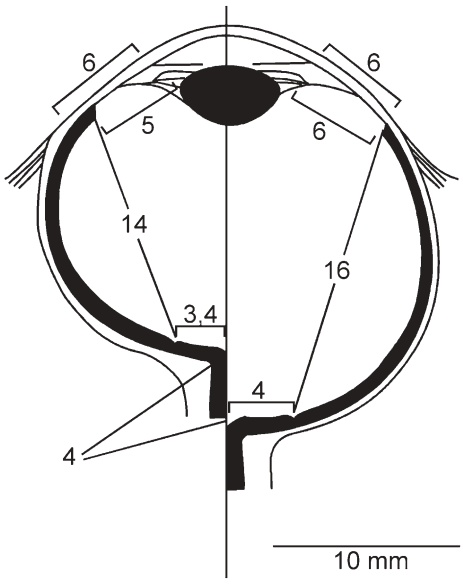

Figure 1. High grades of myopia (≥–6.0 dpt.) are commonly associated with an increased axial eye length, while other dimensions of ocular size (in mm) remain constant [7].

The classification of myopia into different orders of severity based on morphological and clinical categories should not obscure the fact that different levels of myopia, like refractive errors in general, represent a continuum of eye growth changes. In genetic studies a graded classification can be an artificial selection that reduces much important variation [13]. Refractive errors are more likely to rather behave like quantitative traits such as height and weight, except that above a certain threshold they will impede normal physiological function.

Table 1. Increased prevalence of ocular complications from high myopia.

Ocular complications	Relative frequency in high myopia (emmetropia)
Retinal tear	13% (3%); [9]
Retinal detachment	7% (0.2%); [10]
Glaucoma	11% (3%); [11]
Cataract	4–5× more frequent than in emmetropia; [12]
Myopic maculopathy	5–10% (0%); [11]
Amblyopia	5–10% (1–3%) own data
Strabism	5–10% (2–6%) own data

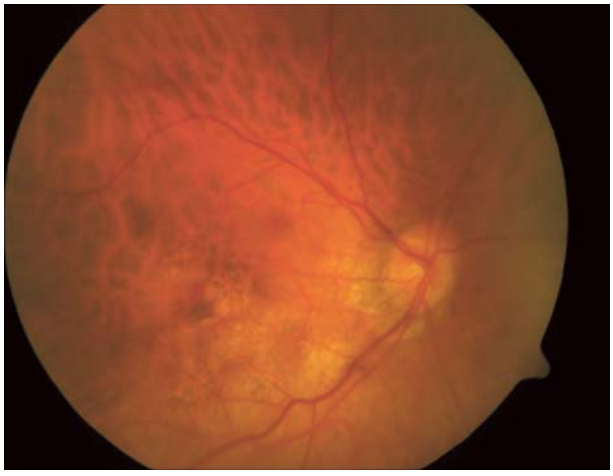

Figure 2. Characteristic ocular fundus in high myopia displaying chorioretinal atrophy and submacular choriodal neovascular membrane (Fuchs' spot).

Aetiology

Genetic versus environmental influence

Myopia is observed under a diverse set of conditions, in terms of its development and progression during lifetime and in the course of associated disorders. It may be present from birth or develop in the period up to young adulthood. Myopia, for instance, occurs more frequently in association with infant prematurity [14] and has been linked to juvenile chronic arthritis (JCA) [15]. However, in both systemic conditions a more serious ocular involvement must be feared, i.e. retinopathy of prematurity following preterm birth and anterior uveitis in JCA.

In a number of inherited, especially X-linked retinal disorders, such as retinitis pigmentosa linked to the RP2 and RP3 locus (corresponding to Xp11.23 and Xp21.1, respectively) [16, 17] and X-linked congenital stationary night blindness (CSNB1, CSNB 2) [18, 19], moderate to high levels of myopia are frequently observed both in affected males and carrier females.

In total, there are some 150 genetic syndromes, defined by specific ocular and systemic disorders, that are associated with various levels of myopia. Table 2 gives a representation of ocular and systemic syndromes and disorders associated with myopia.

This wide spectrum of myopia-associated disorders strongly argues for an aetiologically heterogeneous nature of myopic refractive errors, where multiple factors with genetic and epigenetic effects contribute at different stages during development [20]. There is a long-standing dispute on the relative role of genetic versus environmental factors in the development of myopia [21]. One source for this ongoing controversy may be a widespread but mistaken presumption, according to which myopia is considered an independent disease entity rather than a disorder marking the final outcome of a number of biological variations. Although most myopia research alludes to the juvenile form that develops during childhood and teenage years, this does not rule out aetiologic heterogeneity.

The concept that environmental factors influence ocular development has been well established in epidemiological and experimental animal studies [22, 23]. The frequent manifestation of myopia during school and college years, as well as in some occupations requiring intense and prolonged near work, has suggested the critical role of a near vision stimulus in the development of myopia. Although the precise nature of this stimulus remains elusive one current theory is that a lag in accommodation shifts the image focus during near vision behind the retina [24]. This is consistent with the observation that myopia development can be readily induced in animal experiments by hyperopic defocus, i.e. by fitting concave lenses. The chicken-and-egg dilemma in myopia genesis is highlighted by the concurring theory that assumes the opposite, i.e. that excessive rather than insufficient accommodation causes axial elongation by exerting mechanical pressure on the eye wall [25].

Despite the recognized importance of visual experience in the development of myopia there is abundant evidence for genetic factors determining refractive development [26, 27]. First, higher myopia prevalence in developed Asian countries compared to the Western world suggests a genetic susceptibility to myopia development. Further, myopic parents are more likely to give rise to offspring with myopia than non-myopic parents [28]. This finding

Table 2. Ocular and systemic syndromes associated with myopia.

Ocular syndromes	Systemic syndromes
Albinism	Down syndrome
Retinopathy of prematurity	Ehlers-Danlos syndrome
Familial exsudative vitreoretinopathy	Homocystinuria
Atrophia gyrata	Congenitale spondyloepiphyseal dysplasia
Choroideremia	Marfan syndrome
Fundus flavimaculatus	Fabry disease
Coloboma	Postaxial polydactyly with progressive myopia
Achromatopsia	Stickler syndrome
Microcornea	Turner syndrome
Myelinated nerve fibers	Noonan syndrome
Progressive bifocale chorioretinal ctrophy	De Lange syndrome
Retinitis pigmentosa	
X-chromosomal congenital stationary night blindness	
Wagner syndrome	

has been confirmed by recent large-scale epidemiological studies, according to which heritable factors account for 80% of juvenile myopia development [29]. Strong evidence for the role of inheritance is also provided by twin studies [30, 31]. According to these studies, identical twins display a higher similarity in their refractive status than fraternal twins. It should, however, be remembered that discovery of a high heritability in population and family studies only reflects a high proportion of genetic contribution to the phenotypic variation, i.e. the refractive status. The results do not indicate the degree to which myopia development is actually genetically determined.

Linkage studies and candidate gene screening

Tight genetic determination, however, is a hallmark of Mendelian genetics in which the principle of genetic linkage analysis is applied to identify gene location and subsequently mutations causing hereditary disease. Familial occurrence of myopia has been described in numerous pedigrees as a discrete, segregating phenotypic trait, mostly based on the distinction of low and high grades of myopia. All kinds of Mendelian modes of inheritance of familial myopia have been described, autosomal dominant modes being the most frequently documented. Though the definition of 'high' is arbitrary in genetic terms, high refractive errors are more likely to result from a major effect mutation than low grades of refractive error [32].

To date four loci for autosomal dominant and one for X-linked recessive familial high myopia have been listed in the Online Mendelian Inheritance in Man (OMIM) database: *MYP1* (310460) on Xq28, *MYP2* (160700) on chromosome 18p, *MYP3* (603221) on chromosome 12q, *MYP4* (608367) on chromosome 7q and *MYP5* (608474) on chromosome 17q. Determination of genetic loci for familial high myopia has generally been based on just a few families with little replication of linkage by other investigators [33, 34]. In one UK study of 306 individuals from 51 families the 12q locus was found to be responsible for high myopia in more than 25% with autosomal dominant transmission [35]. No significant contribution of either the 18p or 17q locus was found, suggesting genetic heterogeneity in familial high myopia. In another study on the genetically isolated population of Ashkenazi Jews with less severe forms of myopia, an association with the previously assigned chromosome 12 and 18 regions was excluded, but evidence was reported for locus on chromosome 22q [36].

Despite the rarity of familial high myopia with a plain Mendelian inheritance pattern and the impediments to defining high myopia as a discrete trait, it is important to search for direct myopigenic genes in order to identify possible allelic association of these genes with the more common expression of myopia. Common genetic polymorphisms – as opposed to rare mutations – generate almost all heritable differences in the size and structure of the central nervous system [37].

The genetic intervals identified by linkage analysis in families with segregating high myopia harbour a number of loci encoding structural tissue proteins that could be involved in scleral tissue remodelling during myopia development. Three genes have been localized to the vast genetic region of 30.1 cM on chromosome 12q21-q23, each encoding a member of the family of structural proteins called small leucine-rich repeat proteoglycans (SLRPs). Owing to their extracellular matrix expression in the sclera, two of these *SLRP* genes, *decorin* (12q21-22) [38] and *lumican* (12q21.3-q22) [39, 40], have been suggested as candidate genes in the aetiology of familial high myopia. The association of structural gene mutations with high myopia is well established from disease entities such as Stickler, Marfan and Ehlers-Danlos syndromes, where high myopia is part of the phenotype (see table 2). These disorders, which are associated with gene mutations in principal structural components of various extracellular matrices, provide the strongest support for the scleral theory of myopia development [41]. According to this theory, an alteration in the structure and composition of the sclera occurring on axial eye elongation may be a critical determinant or the genesis of myopia.

Results from animal studies investigating the role of decorin, one of the candidate proteins for familial high myopia mapped to 12q21-22, have been equivocal. While a nearly steady decorin synthesis in response to experimentally induced myopia was noted in neonatal primates [42], reduced proteoglycan synthesis was observed when adolescent primates were investigated [43]. Independent studies on the role of lumican in experimentally induced myopia produced more consistent results [44, 45]. Lumican-deficient mice were shown to have a disrupted collagen fibril formation of the sclera, which, based on volumetric estimations, is associated with larger eyes [46]. However, *lumican* has been excluded as the causative gene in the family with 12q21-22 linked high myopia [47]. Although the precise role of these two SLRPs is unknown, it has been suggested that *decorin* and *lumican* may play a role in scleral collagen fibril formation and organization of the extracellular matrix through inhibition of spontaneous collagen molecule assembly [48]. An increasing appreciation of the key role played by SLRPs in myopia development has prompted investigators to search for a genetic association between common myopia and other SLRP family members (keratocan, fibromodulin, biglycan, dermatan sulfate proteoglycans (DSPG)-3) [49]. To date none of these candidate proteins or loci has been found to be causally linked to common, juvenile-onset myopia [50].

Interestingly, other members of the SLRP family have recently been shown to be associated with hereditary ocu-

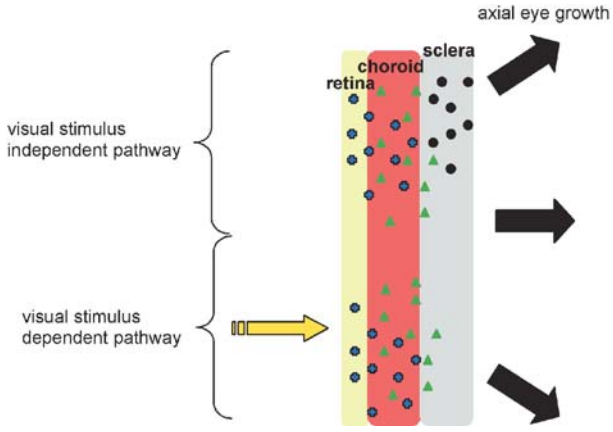

Figure 3. Schematic representation of retinal and choroidal growth signals (blue circles, green triangles) and scleral factors (black circles) inducing axial eye elongation in a visual stimulus-dependent and independent manner.

lar diseases. Thus, nyctalopin, expressed in the retina, is mutated in the retinal disorder of the complete form of congenital stationary night blindness (CSNB1) [18], and mutations in keratocan are associated with cornea plana [51], a flattening of the cornea. Disruption of nyctalopin is also frequently associated with high myopia in patients with CSNB1, while a keratocan mutation in cornea plana has been observed in combination with a reduced axial eye length or microphthalmia [52]. While these distinct lines of investigation from animal and human linkage studies pinpoint the role of scleral extracellular matrix changes, to SLRPs in particular, relatively little is known about the chemical mediators that control such changes, especially the visually-driven retinoscleral signal processes underlying myopia development (fig. 3).

Investigation of experimentally induced myopia, by means of form deprivation or hyperopic defocus and messenger RNA (mRNA) expression analysis has provided substantial data on scleral biochemical changes during axial elongation. Aside from the changes in structural components, these studies have also revealed an altered expression of a variety of growth factors and cytokines: transforming growth factor beta (TGF-β), basic fibroblast growth factor (bFGF) [53], bone morphogenic protein 2 (BMP-2) [54], sonic hedgehog (SHH) protein [55]; neurotransmitters – dopamine [56], neuroendocrine-specific proteins A and C (NSP-A and NSP-C) [57], nitric oxide [three nitric oxide synthase (NOS) isoforms] [58]; transcription factors – ZENK [59], TGF-β-induced factor (TGIF) [60]; and extracellular matrix degradative and inhibitory enzymes (MMP, TIMP) [61, 62].

Despite the extensive list of factors involved in axial eye elongation, supporting evidence for a genetic association of any of these factors with human myopia is sparse. TGF-β-induced factor (TGIF) is a transcriptional repressor which represses transcription by binding directly to DNA or interacts with TGF-β-activated intracellular signalling effectors (Smads), thereby repressing TGF-β-responsive gene expression. There is some indication that an allelic association of the *TGIF* gene to non-syndromic high myopia might exist in Chinese patients [60]. However, this finding could not be corroborated in another study of subjects from the same ethnic backround [63]. TGF-β, a cytokine with a broad range of cellular functions, regulates the metabolism of a variety of extracellular proteins, collagens, fibronectin, proteoglycans and glycosaminoglycans [64]. The *TGIF* gene was mapped to 18p11.3, rendering *TGIF* a candidate for the *MYP2* locus. However, this was recently found not to be associated with myopia by Young and co-workers [65]. *TGIF* has attained medical renown as a disease gene of the congenital brain disorder holoproencephaly. This is sometimes associated with ocular abnormalities and arises from a structural anomaly of the developing human forebrain and midface. While being an aetiologically extremely heterogeneous anomaly, with both environmental and genetic bases, holoproencephaly is causally related to mutations in a number of developmental genes, some of which are also involved in eye development [66]. Two of these genes, both encoding neurotrophic factors, have been shown experimentally to be involved in myopia: one a member of the bone morphogenetic protein family (BMP2) and the other the sonic hedgehog (SHH) protein.

Awareness that developmental genes are not only expressed during embryogenesis but also have a functional role in postnatal changes concerned with growth [67, 68] has led investigators to suspect that developmental genes may be determinants in postnatal refractive development [69]. Although eye development and growth are probably controlled by many genes, a few homeobox genes, such as paired box genes (*PAX*) or *CHX10* have been ascribed an important role in eye development [70]. The *PAX6* gene, broadly expressed during vertebrate forebrain development, is the master control gene for eye development. It is mutated in congenital aniridia, a complex developmental disorder of the eye, and has recently been suggested to have a role in myopia development in a cohort of unselected twin samples [71]. In experimental myopia, produced by hyperopic defocusing in infant rhesus monkeys, *PAX6* expression was upregulated in the retina but not the sclera or optic nerve, suggesting that *PAX6* expression may provide a retinoscleral cue to produce scleral growth. This could be mediated through direct-control matrix metalloproteinase gelatinase B expression [72], which has been shown to be associated with eye growth in experimental myopia [73].

The tendency towards excessive eye growth in myopia may be brought about by normal allelic variants at gene loci known to influence eye development. Certainly, alterations in many developmental genes, such as *CHX10*, *SHH*, *PAX2* and *PAX6*, are observed with various manifestations of microphthalmia [74–78].

Large-scale genetic analysis and QTL mapping in animal models

Most of the above knowledge of biochemical factors and their genetic variations implicated in eye growth comes from target-oriented analyses of candidates (the candidate gene approach). It is still largely unknown, however, how these factors are spatially and temporally regulated and coordinated.

Progress in techniques of genetic analysis, together with greater genome resources in humans and animal models, will significantly aid exploration of the biological pathways of eye growth regulation and myopia development [79]. For example, the rapidly expanding technology developed for DNA microarray hybridization analysis is being utilized for large-scale mRNA expression and genotype analyses. The advantage of microarray technology is that tissue-specific expression levels of several thousand genes can be obtained in a single experiment. This technology has been used to study the global expression pattern in human sceral tissue and extend the number of candidate genes potentially involved in myopia development [80]. Future research will certainly include the comparison of scleral expression profiles obtained from healthy and myopic eyes.

Another promising application of microarray technology in myopia research is the genome-wide, large-scale analysis of sequence variations used to identify the genetic variants associated with myopia. The investigations most commonly exploiting these new technologies are association studies in selected human populations, which use short tandem repeats (STRs) and single nucleotide polymorphisms (SNPs) as genetic markers and linkage disequilibrium (LD)-mapping strategies, i.e. the non-random association of alleles at neighbouring loci as a mapping tool. The general principle of LD mapping is to identify functional genetic variants or susceptibility loci by assessing how closely the trait of interest is associated with observed haplotype frequencies that differ significantly from the haplotype frequencies in the general population (i.e. case-control studies). The difficulty of the LD mapping approach is that assessment of allelic associations with the trait strongly depends on the correctness of several assumptions concerning STR and SNP variants. These include their frequency, distribution and age, the recombination frequency of neighbouring variants and whether they are evolutionarily neutral or selective.

Despite problems with the genetic design of large-scale association studies, there have been some successful attempts at gene identification using the conventional positional cloning strategy. These include *NOD2/CARD15* as a susceptibility gene for Crohn's disease [81] and the *Calpain-10* gene that influences type II diabetes [82].

Aside from human linkage studies, another approach that may profit from this technology is that of inbreeding experiments in animal models of myopia. Fundamental to this approach is the view that myopia is part of a continuous distribution of refractive errors ranging from low negative (i.e. myopia) to high plus (i.e. hyperopia). Refractive errors are viewed as the end product of the quantitative variation in eye traits that arises from the interaction of multiple, segregating genetic variants and environmental factors. Individuals inherit alleles that predispose them to grow smaller or larger eyes under different sets of environmental conditions. Zhou and Williams undertook an effort to identify quantitative trait loci (QTL) that modulate eye weight, lens weight and retinal area by performing a mapping procedure that uses experimental crosses of two inbred laboratory strains of mice [83]. By applying statistical methods to detect correlations between genotype scores and quantitative trait values in the second generation (F2) intercross progeny the authors mapped two QTL, *Eye1* and *Eye2*, that influence normal variation in eye size in mice. Several genes close to these QTL are strong candidates, including hepatocyte growth factor (*Hgf*), a potent mitogen expressed in retina and retinal pigment epithelium. The human homologue of *Eye1* should map to 7q, while the human homologue of *Eye2* should map to 6p21, 16q13.3 or 21q22.3. An additional set of QTL (*Eye3*, *Eye4* and *Eye5*) controlling eye size has been mapped recently [84]. The contention that myopia is a quantitative trait is consistent with the apparently contradictory findings of high heritability and the strong influence of environmental variables in myopia development. This is because individual eye size is determined by genetic factors, while average eye size is sensitive to environmental factors.

The variety of conditions under which myopia is studied – ranging from experimentally-induced forms in animals exhibiting no natural occurrence of myopia to familial occurrence of myopia segregating in a Mendelian inheritance pattern – reflects an aetiological spectrum ranging from totally environmental to totally genetic control of myopia development. Such marked aetiological heterogeneity demands closer definition of the phenotype. There is increasing evidence that phenotype refinement, either through the derivation of quantitative intermediate phenotypes or so-called endophenotypes (from 'endogenous', meaning somewhere along the molecular pathway) [85, 86] or through retrospective reassessment of genotype-phenotype correlations [87] may be useful for the identification of genetic heterogeneity in complex phenotypes. The broad range of biochemical factors altered in myopia development suggests that there may be candidates for an endophenotype, bridging the gap between gene and clinical phenotype.

While no biochemical endophenotypes have yet been identified for myopia, other derived quantitative phenotypes, such as axial length, corneal curvature, anterior chamber depth and lens thickness or time of myopia

onset or progression could serve as surrogate phenotypes in human linkage analyses. This corresponds to the QTL mapping approach in inbreeding experiments that dissects the phenotype into several QTL traits. The definition of more homogeneous subgroups through phenotype refinement increases the chance of detecting significant linkage [86].

Summary

In summary, we have outlined distinct lines of investigation into the genetic origin of myopia. Systematic analysis of the genetic and biological pathways involved in eye development and retinal processing of visual input to control eye growth is the most promising but also the most ambitious task in myopia research today. The identification of disease genes in the instance of familial occurrence of myopia with Mendelian inheritance, while likely to be of only minor genetic influence with regard to common forms of myopia, may reveal new pathophysiologic pathways in myopia genesis.

As we learn more about molecular pathways that regulate growth of the eye, it should be feasible to develop novel therapeutic methods to ensure normal eye growth and vision in humans.

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