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Myopia Genetics: A Review of Current Research and Emerging Trends

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Abstract

Purpose of review—Myopia, or nearsightedness, is the most common human eye disorder in the world, and is a significant global public health concern. Along with cataract, macular degeneration, infectious disease, and vitamin A deficiency, myopia is one of the most important causes of visual impairment worldwide. Severe or high-grade myopia is a leading cause of blindness because of its associated ocular co-morbidities of retinal detachment, macular choroidal degeneration, premature cataract, and glaucoma. Ample epidemiologic and molecular genetic studies support heritability of the non-syndromic forms of this condition.

Recent findings—Multiple myopia genetic loci have been identified, establishing this entity as a common complex disorder and underscoring the suitability for gene inquiry studies. Animal model research, primarily using form-deprivation techniques, implicates multiple altered regulation of biological substances in the ocular wall layers, which provides important information for prioritizing human candidate gene studies. Recent epidemiologic work supports a greater role for outdoor activity in relieving myopia progression rather than the previous touted young- age near-work activity model.

Summary—The identification of myopia susceptibility genes will not only provide insight into the molecular basis of this significant eye disorder, but will also identify pathways involved in eye growth and development. This effort may lead to effective therapies to treat or potentially prevent this common eye condition.

Keywords

myopia; genetics; mapping studies; candidate genes; epidemiology

INTRODUCTION

Myopia, or nearsightedness, is the most common human eye disorder in the world, and is a significant global public health concern. (1–2) Along with cataract, macular degeneration, infectious disease, and vitamin A deficiency, myopia is one of the most important causes of

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visual impairment worldwide. (2–3) Severe or high-grade myopia is a leading cause of blindness because of its associated ocular co-morbidities of retinal detachment, macular choroidal degeneration, premature cataract, and glaucoma. (3) Ample evidence supports heritability of the non-syndromic forms of this condition, especially for high-grade myopia—commonly referred to as myopic spherical refractive power of 5–6 diopters or higher. (4)

Consideration is needed to assess the role of environmental factors to genetic influences, such as interactions of early-age near-work or outdoor activity with genotype. (5–9) Consideration is also needed in identifying phenotypes indicating etiologically homogeneous subgroups, e.g. early age-of-onset, with/without retinal degenerative changes, or classification by individual response to accommodation reduction treatments such as progressive addition lens use. (10)

GENETICS OF OCULAR REFRACTIVE COMPONENTS

Refraction is determined by coordinated contributions of ocular biometric components such as AL, anterior chamber depth (ACD), corneal curvature (keratometry readings in diopters), and lens thickness. The inverse relationship of AL and ACD to refraction is well documented (the longer the eye, the more myopic the refractive error). AL is estimated to be the greatest determinant of refractive error; heritability estimates for AL range from 40–94%, and most recently were reported to be 81% in a whole genome twin study in Australia. (11) This study was the first to identify a locus implicated in ocular axial length, on chromosome 5q, and it identified additional regions with suggestive multipoint logarithm of the odds (LOD) ratios on chromosomes 6, 10, and 14 linked to axial length. (11)

No new loci within the past 18 months have been identified in association with ACD, corneal curvature steepness, or lens thickness (all of which, like AL, have high heritability and an inverse relationship to refractive error).

TWIN STUDIES

Twin studies provide the strongest conclusive evidence that myopia is inherited, as background contributions are diminished. Many studies have noted an increased concordance of refractive error as well as refractive components (AL, corneal curvature, lens power) in monozygotic twins compared to dizygotic twins. Most recently, Dirani et al reported the first evidence for a genetic component in adult-onset myopia, within a large cohort study of Caucasian twins. (12) He et al estimated a high genetic contribution to axial length, anterior chamber depth, and angle opening distance in twins from the Guangzhou Twin Registry. (13)

MYOPIA LOCI

Several new loci have recently been identified with linkage to myopia. Please refer to Table 1 for full details of myopia loci to date. (14–44)

Lam et al completed one of the first genome-wide scans in an Asian population, and identified a novel autosomal dominant high myopia locus on chromosome 5p15.33-p15.2 in three Hong Kong Chinese pedigrees. (36) Ciner et al identified the first quantitative trait locus for ocular refraction in an African American population, at chromosome 7p15. (37) The group also showed evidence of linkage for regions on chromosomes 2p, 3p, and 10p. (37) In a second study, Ciner et al provided the first evidence of linkage of myopia to chromosome 20, and confirmed the existence of a myopia quantitative trait locus to chromosome 11 (MYP7, at chromosome 11p13). (38) Yang et al performed the first clinical and linkage study of a consanguineous family with autosomal recessive high myopia, and

identified the first locus implicated for this hereditary type at chromosome 14q22.1-q24.2. (39)

In addition, several previously identified loci have been replicated or refined during the review period. MYP3, the second locus for autosomal dominant (AD) high myopia (on chromosome 12q21–23, OMIM 603221) (20), was replicated in a Hong Kong Chinese cohort (21). The locus was further refined by Nürnberg et al, who contracted the initial 30.1cM MYP3 interval to 6.8cM in a German family with high myopia. (22) Wojciechowski et al performed a genome wide linkage analysis that confirmed linkage of ocular refraction to 12q24, 4q21, and 5q; the group also completed a meta-analysis confirming linkage to 4q21–22 adjacent to the previously reported MYP9 and MYP11 loci. (45) The MYP12 locus (OMIM 609994) for AD high-grade myopia on chromosome 2q37 (32), was replicated in an Australian study of three multigenerational Caucasian families with mild to moderate AD myopia. (33)

The largest linkage scan to date for familial high-grade myopia was recently published, using data from 254 families from five independent sites. (40) This study demonstrated linkage replication of the MYP1, MYP3, MYP6, MYP11, MYP12, and MYP14 loci, and identified a novel locus at chromosome 9q34.11. (40)

ANIMAL MODELS

One impediment to correlating genotypic data with tissue histopathology in human myopia is that the tissue of interest (i.e. retina/ sclera) cannot be directly sampled. Animal models of myopia have been developed to be used as surrogates, although it is unclear how correlative induced myopia in animals may be to physiologic myopia in humans. Animal studies over the past 30 years in juvenile and newborn monkey, tree shrew, and chick models have revealed an active emmetropization mechanism that normally achieves and maintains a match of the ocular AL to the eye's optical power so that the photoreceptors are in focus for distant objects. Thus genes expressed in retina, RPE, choroid, and/or sclera that control this emmetropization process, if irregularly expressed, could cause the eye to elongate and become myopic.

The first knock-out mouse model for relative myopia was based on form-deprivation experiments in chickens, mice, and rhesus macaque monkeys. (46) This model involved the immediate early gene transcription factor ZENK (also known as Egr-1), which is up-regulated in retinal amacrine cells when axial eye growth is inhibited by positive lens wear, and is down-regulated when axial growth is enhanced by negative lenses, suggesting that ZENK is linked to an axial eye growth inhibitory signal. ZENK knockout mice had longer eyes and a myopic shift relative to heterozygous and wild-type mice with identical genetic background. (46)

Zhou et al (47) provided a helpful record of refraction, corneal curvature, axial components, and the correlations between refraction and ocular growth during emmetropization in C57BL/6 mice. Refraction was most myopic at day 25, then shifted in the hyperopic direction to reach a peak at 47 days.

CANDIDATE GENE STUDIES

The list of hypothesized candidate genes for myopia is based largely on the current understanding of the pathophysiology of syndromic myopia. The majority of the work examining the relationship between myopia and individual polymorphisms in candidate genes has been performed on single candidates at a time, to the exclusion of other independent or interacting genes.

Han et al recently demonstrated an association of several PAX6 variants with susceptibility to high myopia in southern Han Chinese. (48) Both PAX 6 and SOX2, considered “master control genes” in eye development and growth, have been suggested to play a role in myopia pathogenesis, possibly due to genetic variation in an upstream promoter or regulator. However Simpson et al investigated the association of common myopia with PAX6 and SOX2 in a large population study cohort, and found no significant association. (49)

The membrane-type frizzled-related protein (MFRP) gene, hypothesized to play a role in axial length regulation, has shown similarly contradictory results in different studies. Most recently, Metlapally et al showed reported no association between 16 MFRP SNPs and non-syndromic high myopia. (50)

The myocilin myopia susceptibility gene (MYOC) was identified in a Chinese cohort using the family-based transmission disequilibrium test (TDT) approach; the gene has previously been associated with juvenile-onset glaucoma and early-onset and high myopia. (30/51)

Vatavuk et al also noted an association between high myopia and a common variant in the myocilin gene in 19 individuals in Korcula Island, Croatia. (52) However these results must be interpreted with caution, as the study was relatively under-powered and had limited SNP coverage.

Hall et al recently reported an association between common myopia and polymorphisms in three genes coding for matrix metalloproteinases (MMP-1, MMP-3, MMP-9), enzymes that degrade matrix proteins and modulate scleral extensibility. (53) In their population of Caucasian English individuals, risk of myopia increased progressively with dose of polymorphic alleles in these three genes.

The uromodulin-like 1 (UMODL1) gene, previously prioritized during a whole genome case-control association analysis in Japanese high-myopia patients, has also been identified as a potential candidate gene. Nishizaki et al identified 1 significant SNP within the frequent recombinant region of UMODL1 on chromosome 21q22.3, confirming the gene’s candidacy as a disease susceptibility gene. (41)

Andrew et al confirmed evidence for linkage to chromosome 3q26 (MYP8) and identified three loci centered on MFN1, upstream from alternate-splicing SOX20T and PSARL. (54) The fact that MFN1 and PSARL both influence mitochondrial regulatory processes in the retina is somewhat surprising, and may suggest a novel mitochondrial-related pathogenetic pathway for common myopia.

Metlapally et al reported an association between TEX28 copy number variations and the MYPI X-linked myopia phenotypes, and also revealed that a range of copies (one to five) can produce the same phenotype. (55)

The collagen-related genes have consistently been cited as potential myopia candidates. A case control study of mixed ethnicities showed an association between myopia and 2 SNPs in the collagen 2 alpha 1 gene (COL2A1), which maps to chromosome 12q13.11, a locus not associated with myopia to date.(56) Sequence analysis of three individuals with familial Stickler syndrome type I revealed another COL2A1 mutation accounting for the STL1 phenotype, which includes myopia, congenital vitreous anomaly, and orofacial, articular, and auditory manifestations. (57) A third study, a retrospective notes-review of patients with a type II collagenopathy chondrodysplasia, revealed that over 85% are myopic, thus confirming that myopia can result from defects in type II collagen. (58)

Another candidate gene is the collagen type 1 alpha 1 gene (COL1A1), an extracellular matrix gene expressed in the scleral wall which maps within the MYP5 locus for high myopia (chromosome 17q22–q23.3), and which previously has been suggested to play a role in experimental myopia. A case-control study of a Japanese cohort showed an association of high myopia with 2 SNPs for this gene, providing the first evidence for COL1A1 as a candidate gene for high myopia. (59) However, a follow-up study revealed no association, suggesting that the genetic risk associated with this gene, if any, is weaker than originally thought. (60)

Similarly, Pertile et al found no association between the transforming growth beta-induced factor (TGIF) gene and refraction or ocular biometric measures, indicating that TGIF is unlikely to play a major role in these values. (61) In addition, Wang et al reported no association of high myopia with TGIF in individuals living in southeast China. (62) These reports suggest that future studies should focus on investigating other genes in the MYP2 linkage region or in other linkage regions, rather than TGIF. In addition, Wang et al found no association between high myopia and SNPs in the previously reported candidate genes Lumican, TGFB1, and hepatocyte growth factor (HGF) genes. (62)

As demonstrated by the above studies, the results for many of the candidate myopia genes are promising and may have biological plausibility, but most are not conclusive. Functional SNP effects have not been implicated for all of these candidate genes, and it is unclear how ethnic differences play a role in the degree of associative significance.

EPIDEMIOLOGY

Recent epidemiological data has identified outdoor activity as a key environmental determinant of myopia. In both Singaporean and Australian children, total time spent outdoors was associated with less myopic refraction, independent of indoor activity, reading, and engagement in sports. (6,8) A comparative study of Chinese children in Singapore and Sydney also revealed a protective effect of outdoor activity. (7)

Previous reports of rural-urban differences in myopia prevalence have also been confirmed, with inner-city urban areas having higher odds of myopia than outer suburban areas. This data suggested that small to moderate environmental differences may affect myopia development, even within a common predominantly urban environment. (9)

Lastly, helpful epidemiological data from the National Health and Nutrition Examination Survey (NHANES) was released in August 2008. It reported myopia prevalence of 33.1% in the United States, with higher prevalence in women than in men, in younger than older persons, and in Caucasians than African Americans or Mexican Americans. (2)

CONCLUSION

Steady progress has been made in the field of human myopia genetics, but there is much still to be done. For example, no results have implicated more than just a single gene, or have expanded into an analysis of a specific pathway. This may implicate additional genes in a pathway also shown to be risk factors for myopia in validation studies, and point to potential haplotype-specific treatments. No candidate genes have been shown to account for even a modest fraction of the familial risk of myopia, and most of the data are conflicting about whether a true association exists. Consideration is needed to assess the role of environmental factors to genetic influences, such as interactions of early-age near-work or outdoor activity and genotype.

Consideration also needs to be given to the identification of phenotypes indicating etiologically homogeneous subgroups, e.g. early age-of-onset, with/without retinal degenerative changes, or classification by individual response to treatments that reduce accommodation to near objects, such as progressive addition lens use. (10)

Candidate gene studies underscore that myopia is very complex, in fact, so complex that single candidate gene studies are unlikely to demonstrate the type of relationships needed to account for the majority of susceptibility genes. Thus there is a need for a genome-wide approach, incorporating candidate genes but not restricted to the study of candidate genes, to explore the relative contributions and interactions between known candidate genes and possibly novel genes in increased myopia susceptibility.

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ANNOTATED REFERENCES

* Special interest ** Outstanding interest

INTRODUCTION

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microphthalmia/anophthalmia, or high myopia. Family based association analysis also did not reveal any association between the 17 SNPs genotyped in the larger family data set for any refractive error type. Thus the findings indicate that the MFRP gene may not play a role in regulating ocular axial length in these phenotypes.

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Table 1

Identified myopia loci as approved by the Human Organization Gene Nomenclature Committee

Locus	OMIM	Cytogenetic location	Reference study	Myopia severity: age of onset
MYP1	310460	Xq28	[14–16]	High: –6.75 to –11.25 D Early: 1.5–5 years
MYP2	160700	18p11.31	[17–19]	High: –6 to –21 D Early: 6.8 years (average)
MYP3	603221	12q21–q23	[20,21,22*,23]	High: –6.25 to –15 D Early: 5.9 years (average)
MYP4	608367	7q36	[24]	High: –13.05 D (average)
MYP5	608474	17q21–q22	[25]	High: –5.5 to –50 D Early: 8.9 years (average)
MYP6	608908	22q12	[26–28]	Mild-moderate: –1.00D or lower
MYP7	609256	11p13	[29]	–12.12 to +7.25 D
MYP8	609257	3q26	[29]	–12.12 to +7.25 D
MYP9	609258	4q12	[29]	–12.12 to +7.25 D
MYP10	609259	8p23	[29,30]	–12.12 to +7.25 D
MYP11	609994	4q22–q27	[31]	High: –5 to –20 D Early: before school age
MYP12	609995	2q37.1	[32,33]	High: –7.25 to –27 D Early: before 12 years
MYP13	HGNC:32582	Xq23–q25	[34]	High: –6 to –20 D Early: before school age
MYP14	610320	1p36	[35]	
Miscellaneous Loci			[11,36**–38**,39*,40,41*,42,43,44*]	

D, diopters; HUGO, Human Genome Organization; MYP, myopia locus; p, short arm of a chromosome; q, long arm of a chromosome. OMIM, online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>). HGNC- HUGO Gene Nomenclature Committee (<http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes>).