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Nature and Nurture: the complex genetics of myopia and refractive error

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Abstract

The refractive errors, myopia and hyperopia, are optical defects of the visual system that can cause blurred vision. Uncorrected refractive errors are the most common causes of visual impairment worldwide. It is estimated that 2.5 billion people will be affected by myopia alone with in the next decade. Experimental, epidemiological and clinical research has shown that refractive development is influenced by both environmental and genetic factors. Animal models have demonstrated that eye growth and refractive maturation during infancy are tightly regulated by visually-guided mechanisms. Observational data in human populations provide compelling evidence that environmental influences and individual behavioral factors play crucial roles in myopia susceptibility. Nevertheless, the majority of the variance of refractive error within populations is thought to be due to hereditary factors. Genetic linkage studies have mapped two dozen loci, while association studies have implicated more than 25 different genes in refractive variation. Many of these genes are involved in common biological pathways known to mediate extracellular matrix composition and regulate connective tissue remodeling. Other associated genomic regions suggest novel mechanisms in the etiology of human myopia, such as mitochondrial-mediated cell death or photoreceptor-mediated visual signal transmission. Taken together, observational and experimental studies have revealed the complex nature of human refractive variation, which likely involves variants in several genes and functional pathways. Multiway interactions between genes and/or environmental factors may also be important in determining individual risks of myopia, and may help explain the complex pattern of refractive error in human populations.

Keywords

myopia; refractive errors; genetics; epidemiology

Introduction

Ocular refractive errors are optical defects in which images of viewed objects do not coincide with the retinal plane, causing blurred vision. There are two forms of spherical refractive errors: myopia and hyperopia (figure 1). Because myopia has been the most widely studied refractive error, it is the primary focus of this review. Ocular refraction, defined as a quantitative measurement of the magnitude of refractive errors, will also be discussed when applicable.

Refractive errors are the most widespread human eye disorders (1). Myopia affects more than one in four people over age 40 in the United States and Western Europe while visually

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significant hyperopia afflicts about ten percent of individuals in the same age group (2). In some urban areas in East Asia, the prevalence of myopia among teenagers and young adults exceeds 70% (3–5). By the year 2020, it is estimated that 2.5 billion people--one third of the world's population--will be affected by myopia alone (2). Myopia is a risk factor for a number of ocular conditions including: peripheral retinal degenerations; age related cataracts; glaucoma; and choroidal neovascularization (6). Pathological myopia is characterized by a progressive elongation of the eye globe accompanied by potentially-blinding degenerative changes in the retina and choroid (7).

Although they can usually be corrected by optical means or with refractive surgery, uncorrected or poorly-corrected refractive errors are the most common causes of visual impairment in both industrialized and developing nations (1,8–11)_ENREF_6. Worldwide, more than 150 million people are estimated to be visually impaired because of uncorrected refractive error, of which 8 million are functionally blind (12). The global economic productivity loss due to visual impairment from uncorrected refractive error has been estimated at $268 billion (13).

It is generally accepted that the distribution of refractive errors in human populations is determined by complex interactions of biological, environmental and behavioral factors (14,15). Though numerous risk factors have been studied over decades of epidemiological and experimental research, a comprehensive mechanistic framework for 7refractive error development in humans remains elusive.

Anatomical and optical basis of refractive errors

Clear vision requires an optical system that properly focuses images of viewed objects on the eye's sensory tissue, the retina. This is accomplished through a precise coordination of the refractive components to align of the eye's focal point with the retinal plane. Any departure from a coincidence between the focal point and the retina will result in reduced image contrast at the retina and cause subjectively blurred vision. Myopia (or nearsightedness) occurs when distant objects focus anteriorly to the retina. Experimental myopia models and epidemiological data have shown that myopia is the result of a disproportionate elongation of the posterior segment of the eye, whose physical boundary is provided by the fibrous sclera (figure 1). In contrast, hyperopia (or farsightedness) is due to a relatively short eye for which the focal point is located posterior to the retina. Myopia and hyperopia together form the (spherical) refractive errors or ametropias.

The severity of refractive errors is typically quantified in terms of the optical power of a lens (in vergence diopters (D)) necessary to correct the optical defect of the myopic or hyperopic eye. By convention, myopia is quantified with negative values on the dioptric scale while hyperopia is designated by positive numbers. Most studies of myopia or hyperopia define these phenotypes as binary traits using somewhat arbitrary cutoffs of the underlying refractive values. These thresholds typically range between −0.5 D and −1D for mild myopia, −5 D to −6 D for high myopia, and −10 D or less for extreme myopia. The term "pathological myopia" is also commonly used and should be reserved for cases of high myopia characterized by extreme, progressive, ocular growth accompanied by potentially visually-devastating sequellae.

Environmental influences on refractive error

Both biological (nature) and environmental (nurture) sources of refractive variation are likely to be present in most human populations. A complete account of the research into the etiology of refractive error is beyond the scope of this review. We present below some of the

major findings supporting environmental and/or genetic effects on refractive development. A summary of these and other contributors to refractive variation are outlined in table 1.

Animal models of experimental myopia

A large body of evidence from over three decades of animal studies has shown that manipulations of the visual environment can induce predictable changes in scleral growth and lead to experimentally-induced refractive errors. In the late 1970s, three seminal papers reported that variations in the early visual experience of animal models could lead to altered eye growth and, as a result, to changes in ocular refraction (16–18). Specifically, visual form deprivation (produced by eyelid suture or via translucent occluders) induced seemingly unconstrained ocular elongation and corresponding myopic refractive changes in chick (17), tree shrew (16), and macaque monkey (18) (figure 1, bottom right). Additionally, studies in children whose vision had been disrupted during infancy confirmed that form deprivation-induced myopia can also occur in humans during susceptible periods of early ocular development (19–21).

These early animal studies spawned research into experimentally-induced refractive errors which lead to the development of a variety of vertebrate animal models, environmental manipulations and refractive error control paradigms. One of the fundamental insights of this important body of work was that changes in ocular growth patterns in a number of vertebrate species can be caused not only by visual form deprivation, but also by optical defocus (22–25). Specifically, the introduction of negatively-powered lenses in front of normally developing chick (24,25) and primate (22,23,26) ENREF 18 eyes can potentiate compensatory increases in the rate of eye growth, and cause relative myopia (compared to untreated eyes). Positive lenses, on the other hand, tend to arrest eye growth during early visual development and cause relative hyperopia.

Animal models have provided invaluable insight into the complex biological processes likely to be involved in human ocular growth and refractive development. The basic model behind refractive control during infancy involves a visually-driven feedback mechanism that modulates eye growth. In this model, environmental exposures trigger a visually-evoked signaling cascade that originates in the retina, passes through the vascular choroid (figure 1, top right), and ultimately initiates scleral remodeling (see (27–31) for reviews). The sclera is a rigid, highly-organized, connective tissue whose gene-expression profile is similar to that of cartilage (32) and is comprised of extracellular matrix (ECM) and matrix secreting fibroblasts (33). Hence, the biological mechanisms involved in refractive error are thought to ultimately act through differential effects on scleral growth via active ECM remodeling.

Age-dependent changes in refractive error

Epidemiologic data show that refractive development is a dynamic process and that refractive changes occur throughout life at variable rates. Data from human and animal studies show a highly variable distribution of refractive error during the neonatal period, typically centered in the hyperopic ranges (26,34,35). Though the human eye undergoes rapid growth during early childhood--increasing in length from approximately 18 mm at birth to 22–23 mm at three years of age--the variability of refractive error decreases progressively during this period (36–39). At age 5, most children are functionally emmetropic (39–42). This tightening of the standard deviation of refractive error during infancy and early childhood is postulated to be due to the process of “emmetropization” in which eye growth is regulated by a visually-guided feedback mechanism. After the early period of rapid eye growth, the human eye undergoes slow refractive changes that often culminate in the development of myopia (43). During school years, the distribution of refractive errors gradually shifts towards more myopia with increasing age. Corneal

curvature appears to remain relatively stable after age 6, and therefore does not play an important role in juvenile and adult-onset myopia (44). Instead, human myopia is largely the result of age-dependent increase in ocular axial length (36,45,46), corroborating evidence from animal myopia models. Although the rate of refractive change during late childhood can vary between populations and ethnicities, the incidence of myopia increases progressively from pre-school years and generally reaches its zenith around 9–12 years of age (43,47–50). By early adulthood, the rate of change in ocular refraction tends to decline and the prevalence of myopia stabilizes. During middle age (roughly between age 40 and 60), the prevalence of myopia gradually declines and mean refractive errors become more hyperopic (51–53).

Ethnic and geographic influences on refractive error

It is inherently problematic to make rigorous between-study comparisons of refractive error incidence and prevalence data because of a wide variability of sampling methodology, examination methods and diagnostic criteria utilized. The Refractive Error Study in Children (RESC) (54) was designed, in part, to assess the prevalence of refractive errors in 5 to 15 year-old children in various geographical regions while using standardized sampling, examination protocols, and diagnostic criteria. Surveys were conducted at eight locations: rural Nepal (55); rural and urban zones in India (56,57) and China (5,58); a semi-urban area in Durban, South Africa (59); and suburban districts of Santiago, Chile (60) and Kuala Lumpur, Malaysia (61). Results showed very low prevalences of myopia among 5 year-olds across study sites--ranging from 0.45% in rural Nepal (55) to 4.29% in urban New Delhi, India (56). However, the prevalence of refractive errors varied widely among fifteen year-olds (figure 2): the prevalence of myopia was 0.79% in rural Nepal (55); 48.7% in rural China (58); and 79.9% in urban Liwan District, Guangzhou, China (5). This series of studies clearly shows a wide variation in the age-specific prevalence of refractive errors between geographic regions. Interestingly, Chinese and Indian children living in urban areas showed significantly greater rates of myopia than their ethnicity-matched counterparts from more rural regions (5,56–58). A higher prevalence of myopia in urban areas has also been documented in other populations (62–65). These regional differences in the prevalence of myopia argue in favor of a strong environmental influence on refractive development.

The RESC survey of Malaysian children showed a considerably higher prevalence of myopia among ethnic Chinese than in children of Malay, and Indian ancestries (61). A similar excess risk of myopia among ethnic Chinese subjects has been observed in male military recruits (4) and school children (66) in Singapore. High risks of myopia among children of East Asian ancestry have also been reported in Australia (67), the United States (68) and the United Kingdom (69). Although estimates from individual studies vary, urban populations in East Asia show consistently high rates of myopia (often exceeding 80%)(42). Whether this is due to inter-ethnic differences in the genetic predisposition to myopia or to culture-specific environmental influences remains uncertain.

The epidemiological study of genetically or culturally isolated populations may help provide important clues about the multifactorial etiology of refractive error. For example, Orthodox Jewish communities are thought to suffer disproportionately from myopia (70,71). In a study of ocular refraction in Israel, Zylbermann et al. (71) found that teenage Jewish boys who attended Orthodox schools were, on average, 2.4 D more myopic than boys who were educated in secular school (mean refractive error = −2.9 for Orthodox school and −0.50 D for general school). In contrast, the refractive error distribution was no different between girls educated in Orthodox schools and girls who attended general schools (mean refractive error = −0.90 in both groups). Orthodox boys and girls attend separate schools with different curricula, with boys' schools emphasizing intense and prolonged study of religious texts. The authors postulated that the intensive visual demand associated with the religious

education of Orthodox males is likely responsible for high rates of myopia in the Jewish Orthodox community. Interestingly, two genetic loci for myopia susceptibility (72)(MYP6) and ocular refraction (73)(MYP14) originally identified in American Orthodox Jewish families have been replicated in linkage studies in Midwestern American pedigrees (74) (MYP6), the Old Order Amish (75)(MYP14), and in an international consortium of high-grade myopia (76)(MYP6 and MYP14).

Environmental and behavioral risk factors for refractive error

There is accumulating epidemiological evidence that the prevalence of myopia has increased appreciably in many areas across the globe within the last two-to-three decades (3,77–79). This secular trend is most marked in East Asia, where myopia now affects a significant proportion (over 80% in some areas) of young adults. Using a series of nationwide surveys, Lin et al. documented a significant increase in the prevalence of myopia among Taiwanese school children between 1983 and 2000 (3). The estimated prevalences of myopia at ages 7, 12, 15 and 18 were: 5.8%, 36.7%, 64.2% and 74% in 1983; and 21%, 61%, 81% and 84% in 2000. Moreover, the prevalence of high myopia (worse than −6 D) among 18 year-old students had increased from 10.9% in 1983 to 21% in 2000 (3). Matsumura and Hirai showed an increased prevalence of myopia, and a corresponding shift in mean refractive error towards myopia, among Japanese school children over a 12-year period from 1984 to 1996 (77). Nevertheless, the study was conducted in selected schools so their results cannot necessarily be extrapolated to the general Japanese population. The rate of myopia also appears to be increasing in some populations outside of East Asia. Vitale et al. estimated the prevalence of myopia in 12 to 54 year-old Americans to have increased from 25% to 41.6% between 1971–72 and 1999–2004 (79). Similarly, in a retrospective study of over 900,000 Israeli military recruits, Bar Dayan documented significant increases in the prevalence of high, moderate, and low myopia between 1990 and 2002 (78). Because the genetic makeup of these populations has not changed within this short time span, it is unlikely that genetic factors played a role in these trends.

In addition to documenting significant geographic and ethnic differences in refractive error distribution, epidemiological investigations have shown correlations between a variety of environmental exposures and the risk of myopia (table 1). For instance, population-based studies have reported associations between myopia and higher socioeconomic status (80) and greater levels of educational attainment (81–86). High prevalences and progression rates of myopia have been observed in individuals in visually intensive occupations such as clinical microscopists (87), carpet weavers (88) and visual display terminal workers (89). Within the context of the myopization process, education, socioeconomic status, and occupation are generally considered to be indirect surrogates for more proximal risk factors such as near-work visual demand and other unmeasured environmental variables. Studies of the effect of reading have attempted to show a more direct relationship between myopia and near work activity. Saw et al. found that myopic schoolchildren in China reported spending more time reading than non-myopic children (62). In a separate study, the same group reported that the number of books read was a better predictor of higher myopia among 7–9 year-olds than the time spent reading (90). Mutti et al. reported that children with myopia spent significantly more time studying, more time reading, and less time playing sports than non-myopic children (91). In a cross-sectional investigation of 12 year-old Australian school children, Ip et al. found no significant relationships between myopia and time spent in near work. However, they showed significant associations of myopia with close reading distance and sustained, continuous, reading (92). Studies on the effect of reading on the rate of progression of myopia have provided conflicting results. In a study of Singapore school children, near work was not associated with worsening myopia (93). On the other hand,

myopic children in Finland who spent more time reading had faster rates of myopia progression (94).

The relationship between reading and near work activity and myopia susceptibility is complex and still poorly understood. Estimates of exposure to near work are subject to considerable measurement error and are prone to bias in retrospective studies. Effect estimates may vary depending on the unit of measurement chosen (i.e., intensity, duration, reading distance or cumulative dose), outcome definitions (myopia, refractive error, rates of progression), or the ages, ethnicities and social circumstances of study subjects. These discrepancies in study characteristics can yield inconsistent results. Moreover, the current ubiquity of technologies such as computers, cellular and smart phones, and gaming devices has added a layer of complexity to the near work question. Indeed, it could be argued that the recent increase in myopia prevalence in East Asia reported in some studies may be the result of a steady rise in the use of modern electronic devices over the past three decades. Nevertheless, a direct link between the utilization of electronic devices and myopia development has yet to be convincingly established and future studies should attempt to validate and quantify this relationship.

While excessive reading or near work activity increase the risk for myopia, other environmental factors (such as participation in sports and time spent outdoors) have shown protective relationships. Recent studies have shown that time spent outdoors and participation in outdoor sports during childhood is associated with a decreased risk of myopia (95–97). Moreover, the beneficial effect of outdoor activity appears not to be the result of a concomitant reduction in near work. There is also evidence that genetic factors may interact with outdoor activity on the risk of myopia. Jones et al. (95) have shown that the inverse relationship between outdoor activity and myopia development may be limited to children with a strong familial predisposition to myopia (i.e., children with 2 myopic parents compared to children with either no or one myopic parent).

Genetic influences on refractive error

Heritability and familial aggregation of refractive errors

While behavior and environment play important, if not entirely elucidated, roles in refractive development, it has been convincingly established that heritable (presumably genetic) factors are also important in ocular refraction. Heritability studies have been conducted in a number of populations using twin data (98–101), as well as in sibship and nuclear family study designs (102–105). These reports provide consistently high heritability estimates for ocular refraction ranging from 50%to more than 90%.

Familial aggregation studies have estimated sibling recurrence risks (λ_S) of common forms of refractive errors to range from 2 to 5.61 for myopia, and 1.58 to 4.87 for hyperopia (102,103,106–108). More extreme refractive errors show even greater familial aggregation than do milder forms (107,109). Moreover, children of myopic parents tend to have longer eyes (110) and are more likely to develop myopia during childhood or adolescence (111–113). Segregation analyses of population based samples are consistent with a complex inheritance pattern for ocular refraction involving several genes and/or shared environmental factors (114,115).

The strong familial effects for refraction phenotypes (as evidenced by high heritabilities and strong familial aggregation) are present across populations with varying underlying distributions of refractive error. This observation is consistent with the hypothesis that environmental influences may drive regional and ethnic differences in refractive distribution, but that within-population variation is largely due to genetic factors. Whether

genes and environment contribute independently to the total phenotypic variance within populations, or whether gene-environment statistical interactions also play a role has remained largely unexplored in population genetic studies.

Syndromic refractive errors

Familial refractive errors can occur in simple (non-syndromic) forms or can be accompanied by other systemic or ocular abnormalities. Syndromic refractive errors are generally monogenic or oligogenic and can occur within a wide spectrum of clinical presentations. Myopia has been reported in a number of ocular syndromes including: X-linked and autosomal recessive congenital stationary night blindness (CSNB; OMIM 310500); X-linked retinitis pigmentosa 2 (RP2; OMIM 312600); and X-linked Bornholm eye disease (OMIM 310460). The myopia in X-linked ocular syndromes appears to be secondary to mutations in loci involved in retinal photoreceptor function (NYX, RP2, MYP1). Myopia can also be a characteristic feature in heritable connective tissue disorders such as: Knobloch syndrome (OMIM 267750); Marfan syndrome (OMIM 154700); and Stickler syndrome (type 1, OMIM 108300; type 2, OMIM 604841). Knobloch syndrome has been associated with mutations in COL18A1 whereas Marfan syndome is due to a defect in the fibrillin-1 gene (FBN1). These loci have not been shown to be associated with common forms of refractive error. Stickler syndrome is a phenotypically heterogeneous condition characterized by ocular abnormalities (congenital vitreous defects with myopia and/or retinal detachment) variously accompanied by auditory, musculoskeletal, craniofacial and cardiac defects. Type 1 and type 2 Stickler syndrome are caused by mutations in COL2A1 and COL11A1, respectively (116). Interestingly, two studies (117,118) have independently reported statistical associations of simple myopia phenotypes with a COL2A1 polymorphism (rs1635529), suggesting that this gene, which has been implicated in a wide variety of chondrodysplasias (OMIM 120140), may also be involved non-syndromic refractive errors.

Genetic linkage studies of myopia and ocular refraction

The first genetic locus for non-syndromic high myopia (MYP2) was mapped in 1998 to 18p11.31 by Young and her collaborators (119). A number of groups have since reported significant linkage of refractive phenotypes to several independent genetic loci; the Online Mendelian Inheritance in Man (OMIM) database (http://www.ncbi.nlm.nih.gov/omim) currently lists 16 named loci (MYP2-MYP17) for non-syndromic high myopia, common myopia or ocular refraction, distributed among 13 chromosomes (MYP1 (120) was mapped in a syndromic form of X-linked recessive myopia). At least 7 loci for refractive phenotypes (MYP1, MYP3, MYP6, MYP11, MYP12, MYP14 and MYP17) have been successfully replicated in independent linkage datasets (74–76,121–125).

Familial linkage studies highlight the heterogeneous genetic etiology of refractive errors. Familial refractive errors can exist in simple Mendelian forms (119,126), be features of systemic (7,127) or ocular (120) syndromes, or follow complex familial transmission patterns (114). Many loci for refraction traits were identified in families who segregated high myopia consistent with autosomal-dominant modes of transmission (119,123,128–132). Other loci were mapped using either binary-trait or quantitative-trait linkage analyses of milder refractive errors with complex inheritance (72,73,122,124,133,134). Though differences in phenotype definitions, modes of inheritance, and ascertainment criteria between studies limit the generalizability of linkage results, replication of linkage signals do suggest some etiological overlap. Moreover, we believe that familial linkage studies will remain important in dissecting the complex genetics of human refractive error, particularly as the rapid technological advances will allow for affordable sequencing of genomic regions under linkage peaks.

Genetic association studies of refraction phenotypes

Candidate-gene association studies—Numerous functional and positional candidate genes have been queried in genetic association studies of refractive traits. Table 2 summarizes results of studies that reported statistically significant associations to myopia or ocular refraction. Positive associations have been reported for variants in genes known to be involved in extracellular-matrix (ECM) growth and remodeling pathways. These include genes that code for a variety of extracellular constituents including: collagens (COL2A1 (117,118), COL1A1 (118)); transforming growth factors (TGFB1 (135), TGFB2 (136), TGIF1 (137)); the hepatocyte growth factor (HGF(138–140)) and its receptor (CMET(141)); insulin-like growth factor (IGF1 (142,143)); matrix metalloproteinases (144,145) (MMP1, MMP2, MMP3 and MMP9); and the proteoglycan lumican (LUM(146–148)). Figure 3 shows a first-order biological interaction network for the refraction-associated genes in table 2 (genes that do not interact directly with other genes in the network were omitted for clarity). The biological network in figure 3 was generated using the “direct interactions” network building algorithm implemented in the MetaCore software suite (GeneGo software Inc., St. Joseph, MI), which utilizes a database derived from manually-curated scientific literature on proteins and small molecules. Of particular interest is the relationship between these gene products and the collagens, which constitute over 90% of the mammalian sclera (33,149,150). As has been noted above, the sclera has been shown to undergo active growth and remodeling in animal myopia models. Hence, these association data support experimental results and provide strong evidence that the genetic basis for human refractive error is partially explained by variations in genes that directly affect ECM composition in scleral tissue, leading to differential rates of ocular enlargement and differences in susceptibility to myopia. In this partial model of refractive development, genetic variants that directly or indirectly increase ECM degradation in response to myopiagenic signals would be expected to increase the rate of eye growth and lead to relative myopia.

To date, the majority of positive candidate gene associations have been reported for high myopia (table 2). At least two of these genes, HGF (140) and COL2A1 (118), have also shown associations to milder refraction phenotypes (117,138,139). These results, and recent studies that reported genetic associations between ocular refraction and polymorphisms in matrix metalloproteinase genes (144,145)(MMP1, MMP2, MMP3 and MMP9), suggest that common biological pathways may underlie extreme myopia and milder cases of refractive error. Matrix metalloproteinases are a major group of zinc-dependent enzymes that regulate cell-matrix composition by cleaving a number of ECM constituents (151). Importantly, MMPs interact biologically with substrates of genes that have shown to be related to refractive phenotypes in association studies (table 2, figure 3). Although the simplified network presented in figure 3 is undoubtedly incomplete and represents only one potential pathway for refraction control, it does illustrate the complex relationships between genes presumed to be involved in human refractive variation, as well as how variations within these genes may interact within a common mechanistic framework.

Candidate region and genomewide association studies—Recent candidate-region (152) and genomewide association studies (GWAS) (153–155) have uncovered additional polymorphisms putatively involved in refractive regulation. These “hypothesis-free” studies have yielded genetic associations that offer novel mechanisms for the molecular basis of refractive development in human populations.

Surprisingly, two studies have implicated mitochondria-mediated cell death as a possible mechanism in ocular refraction (152,155). Using multimarker fine-scale linkage disequilibrium methods, Andrew et al.(152) showed statistical association of refractive error to loci centered on three genes on chromosome 3q: MFN1; PSARL (or PARL); and

SOX2OT. Nakashiki et al.(155) identified a polymorphism (rs577948) at 11q24.1 adjacent to the BLID gene that was associated with an elevated risk of pathological myopia (odds ratio=1.37) in a Japanese group. MFN1, PSARL and BLID are expressed in mitochondria; PSARL and BLID are involved in mitochondrial-led apoptosis, and MFN1 is involved in mitochondrial fusion. The mechanism by which mitochondrial programmed cell death can lead to myopia has not been elucidated and this pathway should be validated in additional studies. Nevertheless, these studies offer a novel mechanism for the genetic etiology of refractive error and a promising avenue for future experimental studies of myopia based on mitochondria-regulated cell apoptosis.

In a recent multi-phase GWAS of European-derived populations, Hysi et al. identified several polymorphisms in a region at 15q25 near the RASGRF1 gene in strong association with ocular refraction (153). Their reverse transcriptase experiments also showed RASGRF1 to be highly expressed in human retina. RASGRF1 expression is regulated by muscarinic receptors (156) and retinoic acid (157), both of which provide putative biological mechanisms for refractive control. Anti-muscarinic agents are effective in preventing ocular elongation in animal myopia models (158,159) and have been employed to reduce myopia progression in human clinical trials (160–162). Moreover, Lin et al.(163), reported that polymorphisms in the muscarinic acetylcholine receptor 1 gene (CHRM1) were associated with high myopia in a Taiwanese population. Retinoic acid is differentially expressed in eyes of chicks, and eutherian mammals (164,165) during experimental induction of myopia, and has been shown to induce increased MMP-2 activity in mineralizing chicken chondrocyte cultures (166)_ENREF_102. Hence, though RASGRF1 has not previously been investigated in myopia studies, it may influence ocular growth and refraction through complex biological interactions with a number of substrates known to be involved myopization.

In a companion paper to Hysi et al.(153), Solouki and collaborators mapped a susceptibility locus for refractive errors to an intergenic region at 15q14 (154). The most significant association signal was found for a polymorphism in a putative regulatory region near the genes GJD2 and ACTC1, both of which are expressed in the retina (154). GJD2 encodes a neuron-specific protein (connexin36) that is found in retinal photoreceptors, amacrine and bipolar cells. Connexin36 is essential in the transmission of rod-mediated visual signals in the mammalian retina (167,168). Evidence of photoreceptor-mediated susceptibility to myopia has previously been noted in rare X-linked disorders in which cone and/or rod function is disrupted (169–174). To our knowledge, however, the association of a variant near GJD2 is the first evidence of a possible role for modulators of retinal visual signals in susceptibility to common refractive errors.

Summary

We have shown that ocular refraction is a complex phenotype that is influenced by both environmental factors and genetic predisposition. Numerous lines of evidence from experimental myopia models and epidemiological studies have demonstrated that environmental exposures play crucial roles in ocular growth and refractive development. The precise biological mechanisms through which the environment influences ocular refraction in humans are, however, still a matter of debate. It is likely that exogenous variables interact with heritable factors to modulate eye growth during ocular development.

The evidence in favor of a role for genetic predisposition in refractive development is also convincing. A number of linkage studies have mapped almost 20 loci for high myopia, moderate myopia, and refraction as a quantitative trait. Genetic association investigations have identified variants in at least 25 genes putatively involved in ocular refraction.

However, few positive association results have been convincingly replicated in independent samples, and refractive error susceptibility alleles identified to date are generally estimated to have low or modest effect sizes. This implies that most genetic variants involved in human myopia and refractive control are yet to be discovered. It is also probable that variants in several genes interact with one-another, as well as with environmental factors, to mediate ocular growth and produce the distributions of refraction observed in human populations. To our knowledge, gene-gene and gene-environment statistical interactions have not been systematically assessed in genetic association studies of refractive phenotypes.

Many genes found to be associated with human refractive error can be clustered into common biological networks. The largest set of these genes is involved in connective tissue growth and extracellular matrix reorganization. This group includes genes that encode matrix metalloproteinases (MMP1, MMP2, MMP3, MMP9), growth factors and growth factor receptors (HGF, TGFB1, TGFB2, MET), collagens (COL1A1, COL2A1), and proteoglycans (LUM). More recently, two studies have provided evidence for mitochondrial-mediated apoptosis as a novel mechanism for refractive error regulation (152,155). Other possible sources of refractive variation in humans have been identified in recent GWAS (153,154). One novel mechanism involves a pathway that includes Ras protein-specific guanine nucleotide-releasing factor 1 (RASGRF1)(153) and muscarinic acetylcholine receptor genes (CHRM1) (163); another implicates a role for genetic modifiers of rod-mediated visual signal transmission (154). These biological mechanisms will require external validation from experimental studies, but offer solid frameworks on which to build more comprehensive models for refractive regulation in humans.

Genomewide association studies that are currently under way will help discover new variants implicated in refractive errors, clarify the relationships between known myopia susceptibility variants, and offer greater insight into the complex mechanisms underlying refractive development. Ongoing international consortia will provide the large sample sizes required to detect rare causative polymorphisms of small effect as well as gene-gene interactions. Other promising avenues for genomic research into refractive errors include pathway and gene-set enrichment analysis approaches, the study of ocular anatomical components (such as axial length and eye shape) related to refractive error, and longitudinal analyses of individual refractive changes over time. Developing the full picture of the epidemiology of refractive error in human populations, however, will necessitate that both environmental and genetic risk factors be accounted for in future genetic epidemiological studies.

References

1. Pizzarello L, Abiose A, Ffytche T, et al. VISION 2020: The Right to Sight: a global initiative to eliminate avoidable blindness. Arch Ophthalmol. 2004; 122:615–620. [PubMed: 15078680]
2. Kempen JH, Mitchell P, Lee KE, et al. The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. Arch Ophthalmol. 2004; 122:495–505. [PubMed: 15078666]
3. Lin LL, Shih YF, Hsiao CK, et al. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. Annals of the Academy of Medicine, Singapore. 2004; 33:27–33.
4. Wu HM, Seet B, Yap EP, et al. Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. Optom Vis Sci. 2001; 78:234–239. [PubMed: 11349931]
5. He M, Zeng J, Liu Y, et al. Refractive error and visual impairment in urban children in southern china. Invest Ophthalmol Vis Sci. 2004; 45:793–799. [PubMed: 14985292]

6. Saw SM, Gazzard G, Shih-Yen EC, et al. Myopia and associated pathological complications. Ophthalmic Physiol Opt. 2005; 25:381–391. [PubMed: 16101943]
7. Curtin, BJ. The Myopias: Basic Science and Clinical Management. Philadelphia: Harper & Row; 1985.
8. Munoz B, West SK, Rodriguez J, et al. Blindness, visual impairment and the problem of uncorrected refractive error in a Mexican-American population: Proyecto VER. Invest Ophthalmol Vis Sci. 2002; 43:608–614. [PubMed: 11867574]
9. Munoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. Arch Ophthalmol. 2000; 118:819–825. [PubMed: 10865321]
10. VanNewkirk MR, Weih L, McCarty CA, et al. Cause-specific prevalence of bilateral visual impairment in Victoria, Australia: the Visual Impairment Project. Ophthalmology. 2001; 108:960–967. [PubMed: 11320028]
11. Vitale S, Cotch MF, Sperduto R, et al. Costs of refractive correction of distance vision impairment in the United States, 1999–2002. Ophthalmology. 2006; 113:2163–2170. [PubMed: 16996610]
12. Holden BA, Fricke TR, Ho SM, et al. Global vision impairment due to uncorrected presbyopia. Arch Ophthalmol. 2008; 126:1731–1739. [PubMed: 19064856]
13. Smith TS, Frick KD, Holden BA, et al. Potential lost productivity resulting from the global burden of uncorrected refractive error. Bull World Health Organ. 2009; 87:431–437. [PubMed: 19565121]
14. Hornbeak DM, Young TL. Myopia genetics: a review of current research and emerging trends. Curr Opin Ophthalmol. 2009; 20:356–362. [PubMed: 19587595]
15. McBrien NA, Young TL, Pang CP, et al. Myopia: Recent Advances in Molecular Studies; Prevalence, Progression and Risk Factors; Emmetropization; Therapies; Optical Links; Peripheral Refraction; Sclera and Ocular Growth; Signalling Cascades; and Animal Models. Optom Vis Sci. 2008
16. Sherman SM, Norton TT, Casagrande VA. Myopia in the lid-sutured tree shrew (Tupaia glis). Brain Res. 1977; 124:154–157. [PubMed: 843938]
17. Wallman J, Turkel J, Trachtman J. Extreme myopia produced by modest change in early visual experience. Science. 1978; 201:1249–1251. [PubMed: 694514]
18. Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. Nature. 1977; 266:66–68. [PubMed: 402582]
19. Rabin J, Van Sluyters RC, Malach R. Emmetropization: a vision-dependent phenomenon. Invest Ophthalmol Vis Sci. 1981; 20:561–564. [PubMed: 7216673]
20. Hoyt CS, Stone RD, Fromer C, et al. Monocular axial myopia associated with neonatal eyelid closure in human infants. Am J Ophthalmol. 1981; 91:197–200. [PubMed: 7468734]
21. Meyer C, Mueller MF, Duncker GI, et al. Experimental animal myopia models are applicable to human juvenile-onset myopia. Surv Ophthalmol. 1999; 44 (Suppl 1):S93–102. [PubMed: 10548121]
22. Graham B, Judge SJ. The effects of spectacle wear in infancy on eye growth and refractive error in the marmoset (Callithrix jacchus). Vision Res. 1999; 39:189–206. [PubMed: 10326130]
23. Smith EL 3rd, Hung LF, Harwerth RS. Effects of optically induced blur on the refractive status of young monkeys. Vision Res. 1994; 34:293–301. [PubMed: 8160365]
24. Irving EL, Sivak JG, Callender MG. Refractive plasticity of the developing chick eye. Ophthalmic Physiol Opt. 1992; 12:448–456. [PubMed: 1293533]
25. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. Vision Res. 1988; 28:639–657. [PubMed: 3195068]
26. Siegwart JT Jr, Norton TT. Binocular lens treatment in tree shrews: Effect of age and comparison of plus lens wear with recovery from minus lens-induced myopia. Exp Eye Res. 2010
27. Crewther DP. The role of photoreceptors in the control of refractive state. Prog Retin Eye Res. 2000; 19:421–457. [PubMed: 10785617]
28. Nickla DL, Wallman J. The multifunctional choroid. Prog Retin Eye Res. 2010; 29:144–168. [PubMed: 20044062]

29. Rymer J, Wildsoet CF. The role of the retinal pigment epithelium in eye growth regulation and myopia: a review. Vis Neurosci. 2005; 22:251–261. [PubMed: 16079001]
30. Rada JA, Shelton S, Norton TT. The sclera and myopia. Exp Eye Res. 2006; 82:185–200. [PubMed: 16202407]
31. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. Vision Res. 1995; 35:1175–1194. [PubMed: 7610579]
32. Seko Y, Azuma N, Takahashi Y, et al. Human sclera maintains common characteristics with cartilage throughout evolution. PLoS One. 2008; 3:e3709. [PubMed: 19002264]
33. Rada, JA.; Johnson, JM. Sclera. In: Krachmer, J.; Mannis, M.; Holland, E., editors. Cornea. St. Louis: Mosby; 2004.
34. Cook RC, Glasscock RE. Refractive and ocular findings in the newborn. Am J Ophthalmol. 1951; 34:1407–1413. [PubMed: 14877971]
35. Saunders KJ. Early refractive development in humans. Surv Ophthalmol. 1995; 40:207–216. [PubMed: 8599156]
36. Larsen JS. The sagittal growth of the eye. IV. Ultrasonic measurement of the axial length of the eye from birth to puberty. Acta Ophthalmol (Copenh). 1971; 49:873–886. [PubMed: 5172264]
37. Fledelius HC, Christensen AC. Reappraisal of the human ocular growth curve in fetal life, infancy, and early childhood. Br J Ophthalmol. 1996; 80:918–921. [PubMed: 8976706]
38. Sorsby A, Benjamin B, Sheridan M, et al. Refraction and its components during the growth of the eye from the age of three. Medical Research Council Memorandum. 1961; 301:1–67. [PubMed: 13915328]
39. Gwiazda J, Thorn F, Bauer J, et al. Emmetropization and the progression of manifest refraction in children followed from infancy to puberty. Clinical Vision Sciences. 1993; 8:8.
40. Mutti DO, Mitchell GL, Jones LA, et al. Axial growth and changes in lenticular and corneal power during emmetropization in infants. Invest Ophthalmol Vis Sci. 2005; 46:3074–3080. [PubMed: 16123404]
41. Morgan IG, Rose KA, Ellwein LB. Is emmetropia the natural endpoint for human refractive development? An analysis of population-based data from the refractive error study in children (RESC). Acta Ophthalmol. 2009
42. Morgan I, Rose K. How genetic is school myopia? Prog Retin Eye Res. 2005; 24:1–38. [PubMed: 15555525]
43. Zadnik K. The Glenn A. Fry Award Lecture (1995). Myopia development in childhood. Optom Vis Sci. 1997; 74:603–608. [PubMed: 9323731]
44. Zadnik K, Manny RE, Yu JA, et al. Ocular component data in schoolchildren as a function of age and gender. Optom Vis Sci. 2003; 80:226–236. [PubMed: 12637834]
45. Fledelius HC. Ophthalmic changes from age of 10 to 18 years. A longitudinal study of sequels to low birth weight. IV. Ultrasound oculometry of vitreous and axial length. Acta ophthalmologica. 1982; 60:403–411. [PubMed: 7136552]
46. Zadnik K, Mutti DO, Mitchell GL, et al. Normal eye growth in emmetropic schoolchildren. Optom Vis Sci. 2004; 81:819–828. [PubMed: 15545807]
47. Edwards MH. The development of myopia in Hong Kong children between the ages of 7 and 12 years: a five-year longitudinal study. Ophthalmic Physiol Opt. 1999; 19:286–294. [PubMed: 10645384]
48. Zhao J, Mao J, Luo R, et al. The progression of refractive error in school-age children: Shunyi district, China. Am J Ophthalmol. 2002; 134:735–743. [PubMed: 12429251]
49. Fan DS, Lam DS, Lam RF, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. Invest Ophthalmol Vis Sci. 2004; 45:1071–1075. [PubMed: 15037570]
50. Saw SM, Tong L, Chua WH, et al. Incidence and progression of myopia in Singaporean school children. Invest Ophthalmol Vis Sci. 2005; 46:51–57. [PubMed: 15623754]
51. Lee KE, Klein BE, Klein R, et al. Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. Invest Ophthalmol Vis Sci. 2002; 43:2566–2571. [PubMed: 12147586]
52. Guzowski M, Wang JJ, Rochtchina E, et al. Five-year refractive changes in an older population: the Blue Mountains Eye Study. Ophthalmology. 2003; 110:1364–1370. [PubMed: 12867393]

53. Wu SY, Yoo YJ, Nemesure B, et al. Nine-year refractive changes in the Barbados Eye Studies. Invest Ophthalmol Vis Sci. 2005; 46:4032–4039. [PubMed: 16249477]
54. Negrel AD, Maul E, Pokharel GP, et al. Refractive Error Study in Children: sampling and measurement methods for a multi-country survey. Am J Ophthalmol. 2000; 129:421–426. [PubMed: 10764848]
55. Pokharel GP, Negrel AD, Munoz SR, et al. Refractive Error Study in Children: results from Mechi Zone, Nepal. Am J Ophthalmol. 2000; 129:436–444. [PubMed: 10764850]
56. Murthy GV, Gupta SK, Ellwein LB, et al. Refractive error in children in an urban population in New Delhi. Invest Ophthalmol Vis Sci. 2002; 43:623–631. [PubMed: 11867576]
57. Dandona R, Dandona L, Srinivas M, et al. Refractive error in children in a rural population in India. Invest Ophthalmol Vis Sci. 2002; 43:615–622. [PubMed: 11867575]
58. Zhao J, Pan X, Sui R, et al. Refractive Error Study in Children: results from Shunyi District, China. Am J Ophthalmol. 2000; 129:427–435. [PubMed: 10764849]
59. Naidoo KS, Raghunandan A, Mashige KP, et al. Refractive error and visual impairment in African children in South Africa. Invest Ophthalmol Vis Sci. 2003; 44:3764–3770. [PubMed: 12939289]
60. Maul E, Barroso S, Munoz SR, et al. Refractive Error Study in Children: results from La Florida, Chile. Am J Ophthalmol. 2000; 129:445–454. [PubMed: 10764851]
61. Goh PP, Abqariyah Y, Pokharel GP, et al. Refractive error and visual impairment in school-age children in Gombak District, Malaysia. Ophthalmology. 2005; 112:678–685. [PubMed: 15808262]
62. Saw SM, Hong RZ, Zhang MZ, et al. Near-work activity and myopia in rural and urban schoolchildren in China. J Ped Ophthalmol Strab. 2001; 38:149–155.
63. Czepita D, Mojsa A, Zejmo M. Prevalence of myopia and hyperopia among urban and rural schoolchildren in Poland. Annales Academiae Medicae Stetinensis. 2008; 54:17–21. [PubMed: 19127805]
64. Ip JM, Rose KA, Morgan IG, et al. Myopia and the urban environment: findings in a sample of 12-year-old Australian school children. Invest Ophthalmol Vis Sci. 2008; 49:3858–3863. [PubMed: 18469186]
65. Uzma N, Kumar BS, Khaja Mohinuddin Salar BM, et al. A comparative clinical survey of the prevalence of refractive errors and eye diseases in urban and rural school children. Canadian journal of ophthalmology Journal canadien d'ophtalmologie. 2009; 44:328–333. [PubMed: 19491992]
66. Saw SM, Goh PP, Cheng A, et al. Ethnicity-specific prevalences of refractive errors vary in Asian children. Br J Ophthalmol. 2006; 90:1230–1235. [PubMed: 16809384]
67. Ip JM, Huynh SC, Robaei D, et al. Ethnic differences in refraction and ocular biometry in a population-based sample of 11–15-year-old Australian children. Eye (Lond). 2008; 22:649–656. [PubMed: 17277756]
68. Kleinstein RN, Jones LA, Hullett S, et al. Refractive error and ethnicity in children. Arch Ophthalmol. 2003; 121:1141–1147. [PubMed: 12912692]
69. Rudnicka AR, Owen CG, Nightingale CM, et al. Ethnic differences in the prevalence of myopia and ocular biometry in 10–11 year old children: the Child Heart And Health Study in England (CHASE). Invest Ophthalmol Vis Sci. 2010
70. Ben-Simon GJ, Peiss M, Anis E, et al. Spectacle use and reduced unaided vision in third grade students: a comparative study in different educational settings. Clin Exp Optom: J Aus Optom Assoc. 2004; 87:175–179.
71. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. J Ped Ophthalmol Strab. 1993; 30:319–322.
72. Stambolian D, Ibay G, Reider L, et al. Genomewide linkage scan for myopia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 22q12. Am J Hum Genet. 2004; 75:448–459. [PubMed: 15273935]
73. Wojciechowski R, Moy C, Ciner E, et al. Genomewide scan in Ashkenazi Jewish families demonstrates evidence of linkage of ocular refraction to a QTL on chromosome 1p36. Hum Genet. 2006; 119:389–399. [PubMed: 16501916]

74. Klein AP, Duggal P, Lee KE, et al. Confirmation of linkage to ocular refraction on chromosome 22q and identification of a novel linkage region on 1q. Arch Ophthalmol. 2007; 125:80–85. [PubMed: 17210856]
75. Wojciechowski R, Bailey-Wilson JE, Stambolian D. Fine-mapping of candidate region in Amish and Ashkenazi families confirms linkage of refractive error to a QTL on 1p34-p36. Mol Vis. 2009; 15:1398–1406. [PubMed: 19626131]
76. Li YJ, Guggenheim JA, Bulusu A, et al. An international collaborative family-based whole-genome linkage scan for high-grade myopia. Invest Ophthalmol Vis Sci. 2009; 50:3116–3127. [PubMed: 19324860]
77. Matsumura H, Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. Surv Ophthalmol. 1999; 44 (Suppl 1):S109–115. [PubMed: 10548123]
78. Bar Dayan Y, Levin A, Morad Y, et al. The changing prevalence of myopia in young adults: a 13-year series of population-based prevalence surveys. Invest Ophthalmol Vis Sci. 2005; 46:2760–2765. [PubMed: 16043848]
79. Vitale S, Sperduto RD, Ferris FL 3rd. Increased prevalence of myopia in the United States between 1971–1972 and 1999–2004. Arch Ophthalmol. 2009; 127:1632–1639. [PubMed: 20008719]
80. Wong TY, Foster PJ, Johnson GJ, et al. Education, socioeconomic status, and ocular dimensions in Chinese adults: the Tanjong Pagar Survey. Br J Ophthalmol. 2002; 86:963–968. [PubMed: 12185116]
81. Sperduto RD, Seigel D, Roberts J, et al. Prevalence of myopia in the United States. Arch Ophthalmol. 1983; 101:405–407. [PubMed: 6830491]
82. Au Eong KG, Tay TH, Lim MK. Education and myopia in 110,236 young Singaporean males. Singapore Med J. 1993; 34:489–492. [PubMed: 8153707]
83. Wang Q, Klein BE, Klein R, et al. Refractive status in the Beaver Dam Eye Study. Invest Ophthalmol Vis Sci. 1994; 35:4344–4347. [PubMed: 8002254]
84. Katz J, Tielsch JM, Sommer A. Prevalence and risk factors for refractive errors in an adult inner city population. Invest Ophthalmol Vis Sci. 1997; 38:334–340. [PubMed: 9040465]
85. Shimizu N, Nomura H, Ando F, et al. Refractive errors and factors associated with myopia in an adult Japanese population. Japan J Ophthalmol. 2003; 47:6–12. [PubMed: 12586171]
86. Wensor M, McCarty CA, Taylor HR. Prevalence and risk factors of myopia in Victoria, Australia. Arch Ophthalmol. 1999; 117:658–663. [PubMed: 10326965]
87. McBrien NA, Adams DW. A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. Invest Ophthalmol Vis Sci. 1997; 38:321–333. [PubMed: 9040464]
88. Simensen B, Thorud LO. Adult-onset myopia and occupation. Acta ophthalmologica. 1994; 72:469–471. [PubMed: 7825415]
89. Tokoro T. Effect of visual display terminal (VDT) work on myopia progression. Acta ophthalmologica Supplement. 1988; 185:172–174. [PubMed: 2853531]
90. Saw SM, Zhang MZ, Hong RZ, et al. Near-work activity, night-lights, and myopia in the Singapore-China study. Arch Ophthalmol. 2002; 120:620–627. [PubMed: 12003612]
91. Mutti DO, Mitchell GL, Moeschberger ML, et al. Parental myopia, near work, school achievement, and children's refractive error. Invest Ophthalmol Vis Sci. 2002; 43:3633–3640. [PubMed: 12454029]
92. Ip JM, Saw SM, Rose KA, et al. Role of near work in myopia: findings in a sample of Australian school children. Invest Ophthalmol Vis Sci. 2008; 49:2903–2910. [PubMed: 18579757]
93. Saw SM, Nieto FJ, Katz J, et al. Factors related to the progression of myopia in Singaporean children. Optom Vis Sci. 2000; 77:549–554. [PubMed: 11100893]
94. Parssinen O, Hemminki E, Klemetti A. Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. Br J Ophthalmol. 1989; 73:547–551. [PubMed: 2667638]
95. Jones LA, Sinnott LT, Mutti DO, et al. Parental history of myopia, sports and outdoor activities, and future myopia. Invest Ophthalmol Vis Sci. 2007; 48:3524–3532. [PubMed: 17652719]

96. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. Ophthalmology. 2008; 115:1279–1285. [PubMed: 18294691]

97. Dirani M, Tong L, Gazzard G, et al. Outdoor activity and myopia in Singapore teenage children. Br J Ophthalmol. 2009; 93:997–1000. [PubMed: 19211608]

98. Hammond CJ, Snieder H, Gilbert CE, et al. Genes and environment in refractive error: the twin eye study. Invest Ophthalmol Vis Sci. 2001; 42:1232–1236. [PubMed: 11328732]

99. Dirani M, Chamberlain M, Shekar SN, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. Invest Ophthalmol Vis Sci. 2006; 47:4756–4761. [PubMed: 17065484]

100. Lyhne N, Sjolie AK, Kyvik KO, et al. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. Br J Ophthalmol. 2001; 85:1470–1476. [PubMed: 11734523]

101. Teikari JM, O'Donnell J, Kaprio J, et al. Impact of heredity in myopia. Hum Hered. 1991; 41:151–156. [PubMed: 1937488]

102. Wojciechowski R, Congdon N, Bowie H, et al. Heritability of refractive error and familial aggregation of myopia in an elderly American population. Invest Ophthalmol Vis Sci. 2005; 46:1588–1592. [PubMed: 15851555]

103. Peet JA, Cotch MF, Wojciechowski R, et al. Heritability and familial aggregation of refractive error in the Old Order Amish. Invest Ophthalmol Vis Sci. 2007; 48:4002–4006. [PubMed: 17724179]

104. Klein AP, Suktitipat B, Duggal P, et al. Heritability analysis of spherical equivalent, axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study. Arch Ophthalmol. 2009; 127:649–655. [PubMed: 19433716]

105. Guggenheim JA, Pong-Wong R, Haley CS, et al. Correlations in refractive errors between siblings in the Singapore Cohort Study of Risk factors for Myopia. Br J Ophthalmol. 2007; 91:781–784. [PubMed: 17135339]

106. Fotouhi A, Etemadi A, Hashemi H, et al. Familial aggregation of myopia in the Tehran eye study: estimation of the sibling and parent offspring recurrence risk ratios. Br J Ophthalmol. 2007; 91:1440–1444. [PubMed: 17494955]

107. Wojciechowski R, Congdon N, Bowie H, et al. Familial aggregation of hyperopia in an elderly population of siblings in. Ophthalmology. 2005; 112:78–83. [PubMed: 15629824]

108. Lee KE, Klein BE, Klein R, et al. Aggregation of refractive error and 5-year changes in refractive error among families in the Beaver Dam Eye Study. Arch Ophthalmol. 2001; 119:1679–1685. [PubMed: 11709020]

109. Farbrother JE, Kirov G, Owen MJ, et al. Family aggregation of high myopia: estimation of the sibling recurrence risk ratio. Invest Ophthalmol Vis Sci. 2004; 45:2873–2878. [PubMed: 15326097]

110. Zadnik K, Satariano WA, Mutti DO, et al. The effect of parental history of myopia on children's eye size. J Am Med Assoc. 1994; 271:1323–1327.

111. Saw SM, Hong CY, Chia KS, et al. Nearwork and myopia in young children. Lancet. 2001; 357:390. [PubMed: 11211020]

112. Goss DA, Jackson TW. Clinical findings before the onset of myopia in youth: 4. Parental history of myopia. Optom Vis Sci. 1996; 73:279–282. [PubMed: 8728496]

113. Wu MM, Edwards MH. The effect of having myopic parents: an analysis of myopia in three generations. Optom Vis Sci. 1999; 76:387–392. [PubMed: 10416933]

114. Klein AP, Duggal P, Lee KE, et al. Support for polygenic influences on ocular refractive error. Invest Ophthalmol Vis Sci. 2005; 46:442–446. [PubMed: 15671267]

115. Ashton GC. Segregation analysis of ocular refraction and myopia. Hum Heredity. 1985; 35:232–239. [PubMed: 4029963]

116. Rose PS, Levy HP, Liberfarb RM, et al. Stickler syndrome: clinical characteristics and diagnostic criteria. American journal of medical genetics Part A. 2005; 138A:199–207. [PubMed: 16152640]

117. Mutti DO, Cooper ME, O'Brien S, et al. Candidate gene and locus analysis of myopia. Mol Vis. 2007; 13:1012–1019. [PubMed: 17653045]

118. Metlapally R, Li YJ, Tran-Viet KN, et al. COL1A1 and COL2A1 genes and myopia susceptibility: evidence of association and suggestive linkage to the COL2A1 locus. Invest Ophthalmol Vis Sci. 2009; 50:4080–4086. [PubMed: 19387081]
119. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. Am J Hum Genet. 1998; 63:109–119. [PubMed: 9634508]
120. Schwartz M, Haim M, Skarsholm D. X-linked myopia: Bornholm eye disease. Linkage to DNA markers on the distal part of Xq. Clin Genet. 1990; 38:281–286. [PubMed: 1980096]
121. Farbrother JE, Kirov G, Owen MJ, et al. Linkage analysis of the genetic loci for high myopia on 18p, 12q, and 17q in 51 U.K. families. Invest Ophthalmol Vis Sci. 2004; 45:2879–2885. [PubMed: 15326098]
122. Wojciechowski R, Stambolian D, Ciner E, et al. Genomewide linkage scans for ocular refraction and meta-analysis of four populations in the Myopia Family Study. Invest Ophthalmol Vis Sci. 2009; 50:2024–2032. [PubMed: 19151385]
123. Zhang Q, Guo X, Xiao X, et al. A new locus for autosomal dominant high myopia maps to 4q22-q27 between D4S1578 and D4S1612. Mol Vis. 2005; 11:554–560. [PubMed: 16052171]
124. Hammond CJ, Andrew T, Mak YT, et al. A susceptibility locus for myopia in the normal population is linked to the PAX6 gene region on chromosome 11: a genomewide scan of dizygotic twins. Am J Hum Genet. 2004; 75:294–304. [PubMed: 15307048]
125. Paget S, Julia S, Vitezica ZG, et al. Linkage analysis of high myopia susceptibility locus in 26 families. Mol Vis. 2008; 14:2566–2574. [PubMed: 19122830]
126. Bartsocas CS, Kastrantas AD. X-linked form of myopia. Hum Hered. 1981; 31:199–200. [PubMed: 7262894]
127. Stickler GB, Belau PG, Farrell FJ, et al. Hereditary Progressive Arthro-Ophthalmopathy. Mayo Clin Proc. 1965; 40:433–455. [PubMed: 14299791]
128. Young TL, Ronan SM, Alvear AB, et al. A second locus for familial high myopia maps to chromosome 12q. Am J Hum Genet. 1998; 63:1419–1424. [PubMed: 9792869]
129. Naiglin L, Gazagne C, Dallongeville F, et al. A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. J Med Genet. 2002; 39:118–124. [PubMed: 11836361]
130. Paluru P, Ronan SM, Heon E, et al. New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. Invest Ophthalmol Vis Sci. 2003; 44:1830–1836. [PubMed: 12714612]
131. Nallasamy S, Paluru PC, Devoto M, et al. Genetic linkage study of high-grade myopia in a Hutterite population from South Dakota. Mol Vis. 2007; 13:229–236. [PubMed: 17327828]
132. Lam CY, Tam PO, Fan DS, et al. A genome-wide scan maps a novel high myopia locus to 5p15. Invest Ophthalmol Vis Sci. 2008; 49:3768–3778. [PubMed: 18421076]
133. Ciner E, Ibay G, Wojciechowski R, et al. Genome-wide scan of African-American and white families for linkage to myopia. Am J Ophthalmol. 2009; 147:512–517. e512. [PubMed: 19026404]
134. Ciner E, Wojciechowski R, Ibay G, et al. Genomewide scan of ocular refraction in African-American families shows significant linkage to chromosome 7p15. Genet Epidemiol. 2008; 32:454–463. [PubMed: 18293391]
135. Lin HJ, Wan L, Tsai Y, et al. The TGFbeta1 gene codon 10 polymorphism contributes to the genetic. Mol Vis. 2006; 12:698–703. [PubMed: 16807529]
136. Lin HJ, Wan L, Tsai Y, et al. Sclera-related gene polymorphisms in high myopia. Mol Vis. 2009; 15:1655–1663. [PubMed: 19710942]
137. Lam DS, Lee WS, Leung YF, et al. TGFbeta-induced factor: a candidate gene for high myopia. Invest Ophthalmol Vis Sci. 2003; 44:1012–1015. [PubMed: 12601022]
138. Veerappan S, Pertile KK, Islam AF, et al. Role of the hepatocyte growth factor gene in refractive error. Ophthalmology. 2010; 117:239–245. e231–232. [PubMed: 20005573]
139. Yanovitch T, Li YJ, Metlapally R, et al. Hepatocyte growth factor and myopia:genetic association analyses in a Caucasian population. Mol Vis. 2009; 15:1028–1035. [PubMed: 19471602]

140. Han W, Yap MK, Wang J, et al. Family-based association analysis of hepatocyte growth factor (HGF) gene. Invest Ophthalmol Vis Sci. 2006; 47:2291–2299. [PubMed: 16723436]
141. Khor CC, Grignani R, Ng DP, et al. cMET and refractive error progression in children. Ophthalmology. 2009; 116:1469–1474. 1474.e1461. [PubMed: 19500853]
142. Khor CC, Fan Q, Goh L, et al. Support for TGFB1 as a susceptibility gene for high myopia in individuals of chinese descent. Arch Ophthalmol. 2010; 128:1081–1084. [PubMed: 20697017]
143. Metlapally R, Ki CS, Li YJ, et al. Genetic association of insulin-like growth factor-1 polymorphisms with high-grade myopia in an international family cohort. Invest Ophthalmol Vis Sci. 2010; 51:4476–4479. [PubMed: 20435602]
144. Hall NF, Gale CR, Ye S, et al. Myopia and polymorphisms in genes for matrix metalloproteinases. Invest Ophthalmol Vis Sci. 2009; 50:2632–2636. [PubMed: 19279308]
145. Wojciechowski R, Bailey-Wilson JE, Stambolian D. Association of Matrix Metalloproteinase Gene Polymorphisms with Refractive Error in Amish and Ashkenazi families. Invest Ophthalmol Vis Sci. 2010
146. Chen ZT, Wang IJ, Shih YF, et al. The association of haplotype at the lumican gene with high myopia susceptibility in Taiwanese patients. Ophthalmology. 2009; 116:1920–1927. [PubMed: 19616852]
147. Lin HJ, Wan L, Tsai Y, et al. The association between lumican gene polymorphisms and high myopia. Eye (Lond). 2010; 24:1093–1101. [PubMed: 20010793]
148. Wang IJ, Chiang TH, Shih YF, et al. The association of single nucleotide polymorphisms in the 5′-regulatory region of the lumican gene with susceptibility to high myopia in Taiwan. Mol Vis. 2006; 12:852–857. [PubMed: 16902402]
149. Norton TT, Miller EJ. Collagen and protein levels in sclera during normal development, induced myopia, and recovery in tree shrews. Invest Ophthalmol Vis Sci. 1995; 36:S760.
150. Zorn N, Hernandez MR, Norton TT, et al. Collagen gene expression in the developing tree shrew sclera. Invest Ophthalmol Vis Sci. 1992; 33:S1053.
151. Somerville RP, Oblander SA, Apte SS. Matrix metalloproteinases: old dogs with new tricks. Genome Biol. 2003; 4:216. [PubMed: 12801404]
152. Andrew T, Maniatis N, Carbonaro F, et al. Identification and replication of three novel myopia common susceptibility. PLoS Genet. 2008; 4:e1000220. [PubMed: 18846214]
153. Hysi PG, Young TL, Mackey DA, et al. A genome-wide association study for myopia and refractive error identifies a susceptibility locus at 15q25. Nature genetics. 2010; 42:902–905. [PubMed: 20835236]
154. Solouki AM, Verhoeven VJ, van Duijn CM, et al. A genome-wide association study identifies a susceptibility locus for refractive errors and myopia at 15q14. Nature genetics. 2010; 42:897–901. [PubMed: 20835239]
155. Nakanishi H, Yamada R, Gotoh N, et al. A genome-wide association analysis identified a novel susceptible locus for pathological myopia at 11q24.1. PLoS Genet. 2009; 5:e1000660. [PubMed: 19779542]
156. Mattingly RR, Macara IG. Phosphorylation-dependent activation of the Ras-GRF/CDC25Mm exchange factor by muscarinic receptors and G-protein beta gamma subunits. Nature. 1996; 382:268–272. [PubMed: 8717044]
157. Tonini R, Mancinelli E, Balestrini M, et al. Expression of Ras-GRF in the SK-N-BE neuroblastoma accelerates retinoic-acid-induced neuronal differentiation and increases the functional expression of the IRK1 potassium channel. Eur J Neurosci. 1999; 11:959–966. [PubMed: 10103089]
158. Tigges M, Iuvone PM, Fernandes A, et al. Effects of muscarinic cholinergic receptor antagonists on postnatal eye growth of rhesus monkeys. Optom Vis Sci. 1999; 76:397–407. [PubMed: 10416935]
159. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. Invest Ophthalmol Vis Sci. 1993; 34:205–215. [PubMed: 8425826]
160. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. Ophthalmology. 2006; 113:2285–2291. [PubMed: 16996612]

161. Tan DT, Lam DS, Chua WH, et al. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. Ophthalmology. 2005; 112:84–91. [PubMed: 15629825]
162. Siatkowski RM, Cotter S, Miller JM, et al. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. Arch Ophthalmol. 2004; 122:1667–1674. [PubMed: 15534128]
163. Lin HJ, Wan L, Tsai Y, et al. Muscarinic acetylcholine receptor 1 gene polymorphisms associated with high myopia. Mol Vis. 2009; 15:1774–1780. [PubMed: 19753311]
164. McFadden SA, Howlett MH, Mertz JR. Retinoic acid signals the direction of ocular elongation in the guinea pig eye. Vision Res. 2004; 44:643–653. [PubMed: 14751549]
165. Mertz JR, Wallman J. Choroidal retinoic acid synthesis: a possible mediator between refractive error and compensatory eye growth. Exp Eye Res. 2000; 70:519–527. [PubMed: 10866000]
166. Nie D, Ishikawa Y, Yoshimori T, et al. Retinoic acid treatment elevates matrix metalloproteinase-2 protein and mRNA levels in avian growth plate chondrocyte cultures. J Cell Biochem. 1998; 68:90–99. [PubMed: 9407317]
167. Deans MR, Volgyi B, Goodenough DA, et al. Connexin36 is essential for transmission of rod-mediated visual signals in the mammalian retina. Neuron. 2002; 36:703–712. [PubMed: 12441058]
168. Kihara AH, Paschon V, Cardoso CM, et al. Connexin36, an essential element in the rod pathway, is highly expressed in the essentially rodless retina of Gallus gallus. J Comparative Neurol. 2009; 512:651–663.
169. Metlapally R, Michaelides M, Bulusu A, et al. Evaluation of the X-linked high-grade myopia locus (MYP1) with cone dysfunction and color vision deficiencies. Invest Ophthalmol Vis Sci. 2009; 50:1552–1558. [PubMed: 19098318]
170. Michaelides M, Johnson S, Bradshaw K, et al. X-linked cone dysfunction syndrome with myopia and protanopia. Ophthalmology. 2005; 112:1448–1454. [PubMed: 15953640]
171. Young TL, Deeb SS, Ronan SM, et al. X-linked high myopia associated with cone dysfunction. Arch Ophthalmol. 2004; 122:897–908. [PubMed: 15197065]
172. Jacobi FK, Andreasson S, Langrova H, et al. Phenotypic expression of the complete type of X-linked congenital stationary night blindness in patients with different mutations in the NYX gene. Graefe's Archive Clinical Exp Ophthalmol = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2002; 240:822–828.
173. Sui R, Li F, Zhao J, et al. Clinical and genetic characterization of a Chinese family with CSNB1. Advances in experimental medicine and biology. 2008; 613:245–252. [PubMed: 18188951]
174. Zhang Q, Xiao X, Li S, et al. Mutations in NYX of individuals with high myopia, but without night blindness. Mol Vis. 2007; 13:330–336. [PubMed: 17392683]
175. Zhou G, Williams RW. Eye1 and Eye2: gene loci that modulate eye size, lens weight, and retinal area in the mouse. Invest Ophthalmol Vis Sci. 1999; 40:817–825. [PubMed: 10102277]
176. Chakravarti S, Paul J, Roberts L, et al. Ocular and scleral alterations in gene-targeted lumican-fibromodulin double-null mice. Invest Ophthalmol Vis Sci. 2003; 44:2422–2432. [PubMed: 12766039]
177. Schippert R, Burkhardt E, Feldkaemper M, et al. Relative axial myopia in Egr-1 (ZENK) knockout mice. Invest Ophthalmol Vis Sci. 2007; 48:11–17. [PubMed: 17197510]
178. Chen YP, Prashar A, Hocking PM, et al. Sex, eye size, and the rate of myopic eye growth due to form deprivation in outbred white leghorn chickens. Invest Ophthalmol Vis Sci. 2010; 51:651–657. [PubMed: 19737880]
179. Lam CS, Goldschmidt E, Edwards MH. Prevalence of myopia in local and international schools in Hong Kong. Optom Vis Sci. 2004; 81:317–322. [PubMed: 15181356]
180. Kinge B, Midelfart A, Jacobsen G, et al. The influence of near-work on development of myopia among university students. A three-year longitudinal study among engineering students in Norway. Acta ophthalmologica Scandinavica. 2000; 78:26–29. [PubMed: 10726783]
181. Saw SM, Chua WH, Hong CY, et al. Nearwork in early-onset myopia. Invest Ophthalmol Vis Sci. 2002; 43:332–339. [PubMed: 11818374]

182. Grosvenor T. Refractive state, intelligence test scores, and academic ability. Am J Optom Arch Am Acad Optom. 1970; 47:355–361. [PubMed: 5267179]

183. Rosner M, Belkin M. Intelligence, education, and myopia in males. Arch Ophthalmol. 1987; 105:1508–1511. [PubMed: 3675282]

184. Cohn SJ, Cohn CM, Jensen AR. Myopia and intelligence: a pleiotropic relationship? Hum Genet. 1988; 80:53–58. [PubMed: 3417304]

185. Teasdale TW, Fuchs J, Goldschmidt E. Degree of myopia in relation to intelligence and educational level. Lancet. 1988; 2:1351–1354. [PubMed: 2904062]

186. Saw SM, Shankar A, Tan SB, et al. A cohort study of incident myopia in Singaporean children. Invest Ophthalmol Vis Sci. 2006; 47:1839–1844. [PubMed: 16638989]

187. Garner LF, Owens H, Kinnear RF, et al. Prevalence of myopia in Sherpa and Tibetan children in Nepal. Optom Vis Sci. 1999; 76:282–285. [PubMed: 10375242]

188. Zhan MZ, Saw SM, Hong RZ, et al. Refractive errors in Singapore and Xiamen, China--a comparative study in school children aged 6 to 7 years. Optom Vis Sci. 2000; 77:302–308. [PubMed: 10879787]

189. He M, Huang W, Zheng Y, et al. Refractive error and visual impairment in school children in rural southern China. Ophthalmology. 2007; 114:374–382. [PubMed: 17123622]

190. Zhang M, Li L, Chen L, et al. Population density and refractive error among Chinese children. Invest Ophthalmol Vis Sci. 2010; 51:4969–4976. [PubMed: 20445117]

191. Wenstrup RJ, Murad S, Pinnell SR. Ehlers-Danlos syndrome type VI: clinical manifestations of collagen lysyl hydroxylase deficiency. The Journal of pediatrics. 1989; 115:405–409. [PubMed: 2504907]

192. Westling L, Mohlin B, Bresin A. Craniofacial manifestations in the Marfan syndrome: palatal dimensions and a comparative cephalometric analysis. J Craniofacial Genet Develop Bio. 1998; 18:211–218.

193. Pacella R, McLellan J, Grice K, et al. Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. Optom Vis Sci. 1999; 76:381–386. [PubMed: 10416932]

194. Tang WC, Yap MK, Yip SP. A review of current approaches to identifying human genes involved in myopia. Clin Exp Optom. 2008; 91:4–22. [PubMed: 18045248]

195. Tang WC, Yip SP, Lo KK, et al. Linkage and association of myocilin (MYOC) polymorphisms with high myopia. Mol Vis. 2007; 13:534–544. [PubMed: 17438518]

196. Inamori Y, Ota M, Inoko H, et al. The COL1A1 gene and high myopia susceptibility in Japanese. Hum Genet. 2007; 122:151–157. [PubMed: 17557158]

197. 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. [PubMed: 19907666]

198. Han W, Leung KH, Fung WY, et al. Association of PAX6 polymorphisms with high myopia in Han Chinese nuclear families. Invest Ophthalmol Vis Sci. 2009; 50:47–56. [PubMed: 19124844]

199. Vatavuk Z, Skunca Herman J, Bencic G, et al. Common variant in myocilin gene is associated with high myopia in isolated population of Korcula Island, Croatia. Croat Med J. 2009; 50:17–22. [PubMed: 19260140]

200. Zha Y, Leung KH, Lo KK, et al. TGFB1 as a susceptibility gene for high myopia: a replication study with. Arch Ophthalmol. 2009; 127:541–548. [PubMed: 19365037]

201. Zayats T, Yanovitch T, Creer RC, et al. Myocilin polymorphisms and high myopia in subjects of European origin. Mol Vis. 2009; 15:213–222. [PubMed: 19180258]

202. Liu HP, Lin YJ, Lin WY, et al. A novel genetic variant of BMP2K contributes to high myopia. J Clin Lab Anal. 2009; 23:362–367. [PubMed: 19927351]

203. Nishizaki R, Ota M, Inoko H, et al. New susceptibility locus for high myopia is linked to the uromodulin-like (UMODL1) gene region on chromosome 21q22.3. Eye. 2009; 23:222–229. [PubMed: 18535602]

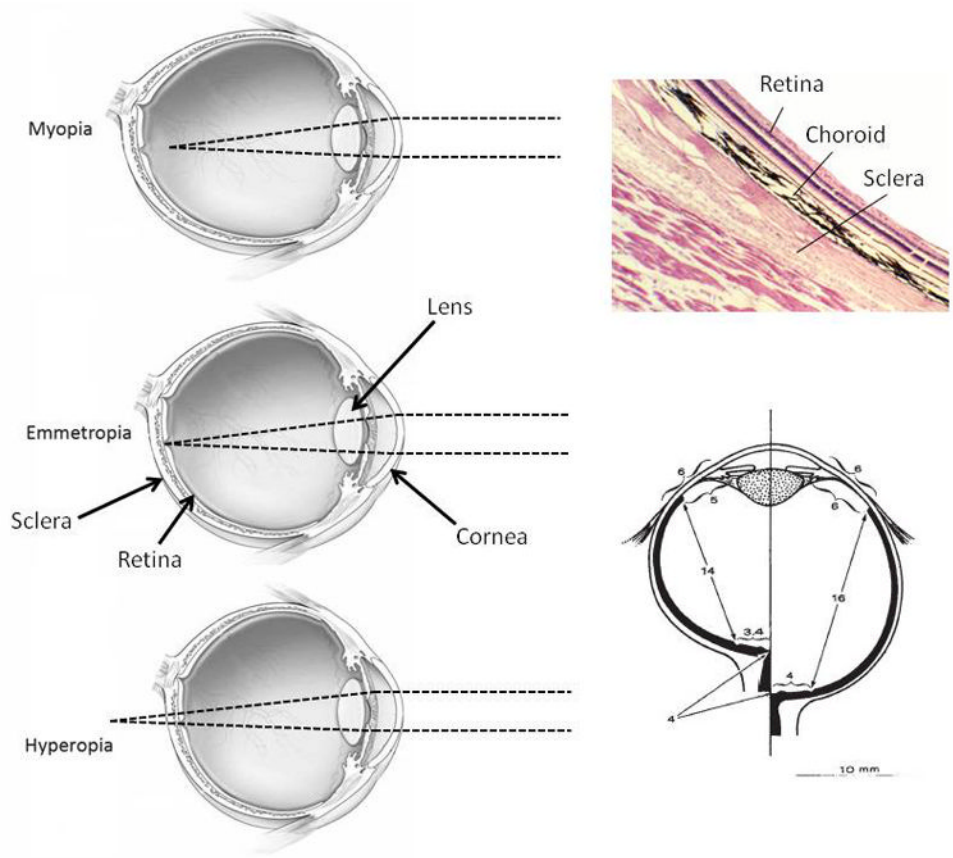

Figure 1.
The anatomical basis of refractive errors.
LEFT: Myopia or nearsightedness (top left): parallel light rays from distant objects (dashed lines) come to focus in front of the retina, causing blurred distance vision. Emmetropia or "normal" vision (middle left): incident light from distant objects are focused on the retina. Hyperopia or farsightedness (bottom left): images of distant objects are focused behind the retinal plane in an unaccommodating eye. Illustrations modified from: the National Eye Institute, National Institutes of Health (not copyrighted).
TOP RIGHT: Histological section of the posterior eye. The retina is a neurosensory tissue that detects contrast, processes the signal locally through various spatial and temporal filters, and sends the pre-processed visual signals to the visual cortex via the retinal ganglion cells. When the retina is exposed to visual signal degradation during early ocular development, it detects contrast deterioration and releases neurotransmitters to signal eye growth. These signals pass though the retinal pigmented epithelium and the vascular choroid to reach the fibrous sclera which responds with scleral tissue remodeling and axial eye growth.
BOTTOM RIGHT: Diagram illustrating the effects of form deprivation through neonatal lid fusion on various eye dimensions in rhesus monkey. The temporal halves of the eyes are juxtaposed. From Wiesel and Raviola (1977)(18), figure 2.

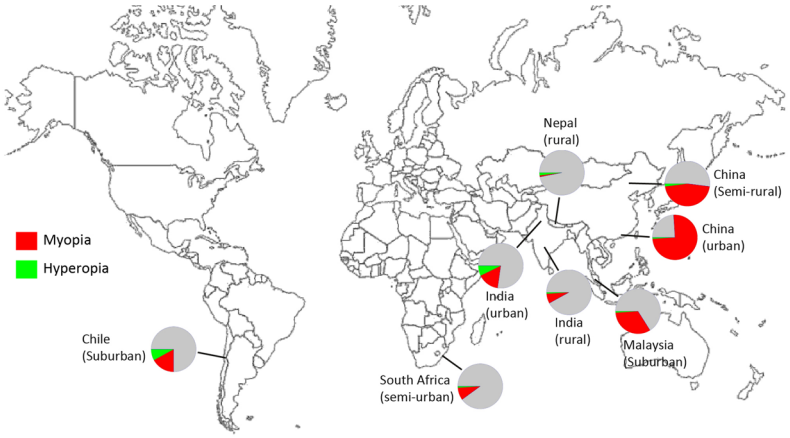

Figure 2.

Prevalence of refractive errors among 15 year-olds in the Refractive Errors Study in Children (RESC). Red shows prevalence of myopia (spherical equivalent refraction ≤ -0.5 D in both eyes); green shows prevalence of hyperopia (spherical equivalent refraction ≥ +2.50 D in both eyes); grey shows prevalence of clinical emmetropia.

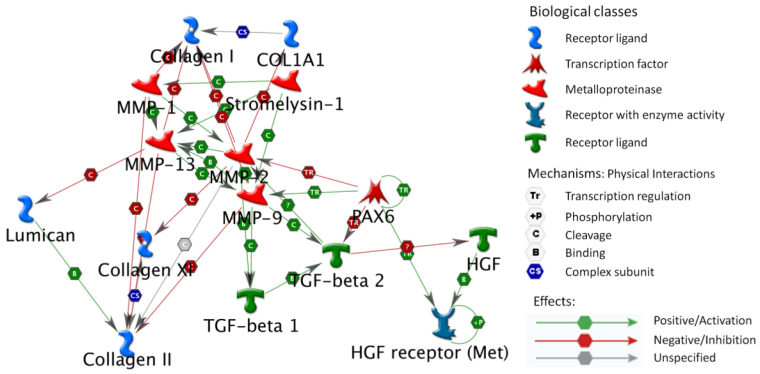

Figure 3.

First-order biological interaction network for refraction-associated genes in table 2. Genes that do not interact directly with other gene products in the network are omitted. Official gene symbol, gene names and (alternative names): COLA1A=collagen, type I, alpha 1; COL2A1= collagen, type II, alpha 1; COL11A1=collagen, type XI, alpha 1; HGF= hepatocyte growth factor (hepapoietin A; scatter factor); MET= met proto-oncogene (hepatocyte growth factor receptor); MMP1=matrix metallopeptidase 1 (interstitial collagenase); MMP2=matrix metallopeptidase 2 (gelatinase A); MMP3=matrix metallopeptidase 3 (stromelysin 1, progelatinase); MMP9=matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); MMP13= matrix metallopeptidase 13 (collagenase 3); LUM=lumican; PAX6= paired box 6; TGFB1= transforming growth factor, beta 1; TGFB2= transforming growth factor, beta 2.

Table 1

Summary of evidence supporting environmental and genetics influences on refractive error.

		Evidence supporting			
	Examples	**Environment**	**Genes**	**Comments**	**Selected references**
Animal Studies					
Form-deprivation myopia	Form deprivation through eyelid suturing or opaque lenses causes unconstrained eye growth and myopia in vertebrate models.	++		Experimental form-deprivation and lens-induced refractive error studies are generally conducted in early stages of development. Results may not be applicable to adolescent and mature animals.	Wiesel and Raviola (1977)(18); Sherman et al (1977)(16); Wallman et al. (1978)(17)
Optical defocus-induced refractive errors	Exposure to optical defocus via plus-or minus-powered lenses causes compensatory changes in eye growth and refractive state in animal models.	++		The process of emmetropization is rapid and robust during early eye development. The active emmetropization model may not be applicable to older animals.	Irving et al. (1992)(24); Smith et al. (1994)(23); Graham and Judge (1999)(22)
Knock-out models and QTL mapping in breeding experiments	Knockout and breeding experiments in mouse and chickens have identified genes involved in eye size and refractive regulation.	+	++	Few relevant knock-out animal models for refractive development exist. Visual stimuli may interact with genes in refractive control.	Zhou et al. (1999)(175); Chakravarti et al. (2003)(176); Schippert et al. (2007)(177); Chen et al (2010)(178)
Observational studies					
Form deprivation during infancy	Children suffering from conditions that cause a blurring of vision during the neonatal period often develop axial myopia.	++		Form deprivation during infancy causes axial myopia in humans and animal models. Different mechanisms may be involved in juvenile-and adult-onset refractive errors.	Rabin et al. (1981)(19); Hoyt et al (1981)(20); Meyer et al. (1999)(21);
Early ocular development in infants and children	Distribution of refractive errors during infancy and early childhood follows a pattern consistent with a visually-guided feedback mechanism found in animal studies.	++		Early refractive development (i.e., emmetropization) mechanisms may not be related to refractive errors developed later in life. Parental refractive status is associated with eye length in children.	Cook and Glasscock (1951)(34); Sorsby et al. (1961)(38); Larsen (1971)(36); Saunders (1995)(35); Fledelius and Cristensen (1996)(37); Mutti et al. (2005)(40)
Refractive development during childhood and adolescence	Prevalence of myopia increases sharply during school years through early adulthood.	++	+	Risk of myopia during school years is affected by environmental exposures. Refractive state in early childhood is predictive of future myopia development.	RESC studies (2000–2005)(48,55–61); Morgan and Rose (review; 2005)(42)
Refractive development during adulthood	"Hyperopic shift" occurs from age 40 to 60+; the prevalence of myopia decreases steadily between the 5th and 7th decades of life.	+	+	Few longitudinal studies are available in older age groups. Cross-sectional studies may be subject to confounding by cohort effects. Heritability estimates are high in older siblings.	Lee et al. (2002)(51); Guzowski et al. (2003)(52); Wu et al. (2003)(53)
***Ethnic**, geographic, sex **and temporal effects on** refractive error*					
Ethnic differences	Individuals of Chinese and East Asian descent consistently show higher rates of myopia than non-Asians.	+	+	Possible confounding between ethnicity and culturally-specific environmental factors.	RESC studies (2000–2005)(5,55–60); Wu et al. (2001)(4); Kleinstein et al. (2003); Lam et al. (2004)(179); Rudnicka et al. (2010)(69)

		Evidence supporting			
	Examples	**Environment**	**Genes**	**Comments**	**Selected references**
Geographic differences	Ethnicity-matched groups have varying rates of refractive errors depending on location of residence.	++			RESC studies (2000–2005)(5,56–58); Morgan and Rose (review; 2005)(42); Saw et al., (2006)(66)
Sex differences	No consistent pattern of sex differences in refractive errors across populations. Orthodox Jewish males have higher prevalence of myopia than females. X-linked forms of syndromic myopia have been identified.	+	+	Sex differences in refractive error likely due to differences in relevant environmental exposures. Familial X-linked myopia is rare and the result of a primary retinal abnormalities.	Zylberman et al. (1993)(71); Bartsocas and Kastrandas (1981)(126); Schwartz et al. (1990)(120);
Cohort effects and secular trends	Increase in the prevalence of myopia in some populations within the last few decades.	++		Secular trends have not been universally observed across populations. Differences in data acquisition methods limit comparability with older studies.	Matsumura and Hirai (1999)(77); Lin et al. (2004)(3); Morgan and Rose (review; 2005)(42); Bar Dayan (2005)(78); Vitale et al (2009)
Environmental and behavioral risk factors					
Education	Higher educational attainment is associated with a greater risk of myopia and myopia progression.	++		Education level is highly correlated with SES, reading/near work, measures of intelligence.	Sperduto (1983)(81); Au Eong (1993) (82); Wang (1994)(83); Katz (1997)(84); Shimizu (2003)(85); Wensor (1999)(86)
Socio-economic status	Higher SES is associated with greater risk of myopia.	++		SES is associated with many environmental factors thought to contribute to differential risk of myopia.	Wong (2002)(80);
Reading/near work/studying habits	Increased reading and near work during childhood and early adulthood increase risk of myopia.	++		Estimates of the relationship between exposure to near work and myopia are generally low. Measurement of near work exposure is difficult and prone to bias in retrospective studies.	Pärssinen (1989)(94); Zylberman (1993) (71,180); Kinge (2000); Saw (2002) (181); Mutti (2002)(91)
“Intelligence”	Positive correlation between IQ and myopia.	+	+	Possible confounding of education, school performance and reading with measures of intelligence.	Grosvenor (1970)(182); Rosner (1987) (183); Cohn (1988)(184); Teasdale (1988)(185); Saw (2006)(186)
Urbanization	Higher prevalence of myopia in urban versus rural areas	++		Urbanization is associated with many environmental factors thought to contribute to differential risk of myopia.	Garner (1999)(187); Saw (2001)(62); Zhao (2000)(58); Zhan (2000)(188); Dandona (2002)(57); Murthy (2002)(56); He (2007)(189); Zhang (2010)(190)
Outdoor activity	Increased outdoor activity and participation in sports decreases the risk of myopia.	++		The protective effect of outdoor activity on the risk of myopia may be limited to genetically susceptible individuals.	Mutti (2002)(91); Jones (2007)(95);Rose (2008)(96); Dirani (2009)(97);
Occupation	High prevalence and progression rates of myopia among occupations with high visual demand.	++			Tokoro (1988)(89); Simensen (1994) (88); McBrien (1997)(87)
Genetic studies					

	Examples	Evidence supporting: Environment	Evidence supporting: Genes	Comments	Selected references
Syndromic refractive errors	Several ocular or systemic syndromes with known genetic causes include myopia as a characteristic feature.		++	Mapped genetic syndromes suggest mechanisms of refractive control. Genes responsible for syndromic myopia may not play significant roles in non-syndromic refractive errors.	Stickler (1965)(127); Wenstrup (1989)(191); Schwartz (1990)(120); Westling (1998)(192);
Effect of parental refractive status	Number of myopic parents is associated with eye size and risk of myopia in children.		++	Relationship may be confounded with unmeasured shared environmental factors between parents and children.	Zadnik (1994)(110); Pacella (1999)(193); Saw (2006)(186); Jones (2007)(95);
Heritability and aggregation studies	Heritability and familial aggregation estimates for ocular refraction are consistently high across populations.		++	Heritability estimates may be inflated due to unaccounted-for environmental correlations within families.	Teikari (1991)(101); Hammond (2001)(98); Wojciechowski (2005)(102); Peet (2007)(103)
Genetic linkage studies	More than 17 loci for human refractive phenotypes have been mapped		++	Most linkage studies have been conducted for high myopia in highly-aggregated families. Number of loci suggests high genetic heterogeneity.	Tang (2008, review)(194), Wojciechowski (2009)
Segregation analyses	Segregation analyses of population-based samples support non-Mendelian, polygenic or shared environmental etiologies for refractive errors.	+	+	Few segregation analyses have been carried out. Segregation models are unreliable in the modeling of complex traits.	Ashton (1985)(115); Klein et al. (2005)(114)
Genetic association studies	Genetic variants in more than 25 genes have been associated with refraction phenotypes.		++	Most association studies have been conducted for high or extreme myopia. Number of genes involved suggests high genetic heterogeneity and/or polygenic effects. Common biological pathways may be involved in many refractive error. Relative paucity of GWAS studies.	See table 2

Table 2

Studies of refraction phenotypes reporting positive association results.

Candidate gene or candidate region studies								
Study 1st author	**Year**	**Geographic Region**	**Ethnicity**	**Phenotype**	**Gene symbol**	**Linkage Locus***	**Location**	**Associated marker(s)**
Lam (137)	2003	Hong Kong	Chinese	High Myopia	TGIF1	MYP2 18p11.31	18p11.3	Codon 3 657(T->G)
Han (140)	2006	China	Han Chinese	High Myopia	HGF	---	7q21.1	rs3735520
Lin (135)	2006	Taiwan	Chinese	High Myopia	TGFB1	---	19q13.1	Codon 10
Wang (148)	2006	Taiwan	Chinese	High myopia	LUM	MYP3 12q21-23	12q21.3-q22	rs3759223
Mutti (117)	2007	US	Various (62% Caucasian)	Myopia	COL2A1	STL1	12q13.11	rs1635529
Tang (195)	2007	Hong Kong	Chinese	High Myopia	MYOC	---	1q23-q24	rs235858, rs2421853
Inamori (196)	2007	Japan	Japanese	High Myopia	COL1A1	---	17q21.33	rs2075555, rs2269336
Andrew (152)	2008	UK	Caucasian	Distribution tails of refraction	MFN1 PSARL SOX2T	MYP8 3q26	3q26.33 3q27.1 3q26.3-q27	Multimarker LDU mapping
Lin (163)	2009	Taiwan	Han Chinese	High Myopia	CHRM1	---	11q13	rs544978, rs542269
Lin (136)	2009	Taiwan	Han Chinese	High Myopia	TGFB2	---	1q41	rs7550232
Ng (197)	2009	Hong Kong	Han Chinese	High Myopia	PAX6	MYP7 11p13	11p13	Dinucleotide repeats in promoter region
Yanovitch (139)	2009	US	Caucasian	Mild/Moderate Myopia	HGF	---	7q21.1	rs3735520
Han (198)	2009	Hong Kong	Han Chinese	High Myopia	PAX6	MYP7 11p13	11p13	rs3026393
Vatavuk (199)	2009	Croatia	Caucasian	High Myopia	MYOC	---	1q23-q24	rs2421853
Zha (200)	2009	Hong Kong	Chinese	High Myopia	TGFB1	---	19q13.1	rs1800470, rs4803455
Metlapally (118)	2009	US & Wales	Caucasian	High Myopia	COL2A1	STL1	12q13.11	rs1635529
Khor (141)	2009	Singapore	Chinese	Myopia/myopia progression	CMET	---	7q31	rs2073560
Chen (146)	2009	Taiwan	Han Chinese	High Myopia	LUM	MYP3 12q21-23	12q21.3-q22	rs3759223-rs3741834 haplotype block
Hall (144)	2009	UK	Caucasian	Myopia	MMP3 MMP9	--- ---	11q22.3 20q11.2-q13.1	MMP-3 gene 1612 insA MMP-9 gene exon 6 Arg->Gln
Zayats (201)	2009	US & Wales	Caucasian	High Myopia	MYOC	---	1q23-q24	rs1684720, NGA17 (microsatellite)
Liu (202)	2009	Taiwan	N/A	High Myopia	BMP2K	MYP9 4q12	4q21.21	rs2288255

Candidate gene or candidate region studies								
Study 1st author	**Year**	**Geographic Region**	**Ethnicity**	**Phenotype**	**Gene symbol**	**Linkage Locus***	**Location**	**Associated marker(s)**
Nishizaki (203)	2009	Japan	Japanese	High Myopia	UMODL1	---	21q22.3	rs2839471
Veerappan (138)	2010	Australia		Low/moderate myopia Hyperopia	HGF HGF	--- ---	7q21.1	rs1743, rs4731402, rs12536657, rs10272030, rs9642131 rs12536657, rs5745718
Metlapally (143)	2010	US, UK, Denmark, Australia, France	Caucasian	High Myopia, Myopia	IGF1	MYP3 12q21-23	12q23.2	rs6214
Wojciechowski (145)	2010	US	Amish	Ocular refraction	MMP1 MMP2	--- ---	11q22.3 16q13-q21	rs1939008 rs9928731
Lin (147)	2010	Taiwan	Chinese	High Myopia	LUM	MYP3 12q21-23	12q21.3-22	SNP haplotypes within promoter region
Khor (142)	2010	Singapore	Chinese	Myopia/High Myopia	TGFB1	---	19q13.1	rs4803455
Genomewide Association Studies (GWAS)								
Study 1st author	**Year**	**Geographic Region**	**Ethnicity**	**Phenotype**	**Gene symbol**	**Proximal Locus**	**Location**	**Associated marker(s)**
Nakanishi (155)	2009	Japan	Japanese	Pathological Myopia	BLID LOC399959	---	11q24.1	rs577948
Hysi (153)_ENREF_134_ENREF_117	2010	U.K., Netherlands, Australia	Caucasian	Ocular refraction	RASGRF1	---	15q25.1	rs939658, rs8027411
Solouki (154)	2010	Netherlands U.K. (replication)	Caucasian	Ocular refraction Myopia and Hyperopia	GJD2 ACTC1	---	15q14	rs634990

* Linkage locus indicates names and cytogenetic location of nearby linkage loci for refractive errors or myopia. STL1=Stickler Syndrome, Type 1.