Complex Trait Genetics of Refractive Error

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Refractive errors (myopia, hyperopia, and astigmatism) are complex heterogeneous disorders of the human eye and are ideal for genetic investigation. Moderate to severe refractive errors can predispose individuals to poor visual development, various types of glaucoma, misshapen corneal surfaces, premature cataracts, and loss of retinal integrity, which can lead to detachment. Knowledge of genetic mechanisms involved in refractive error susceptibility may allow treatment to prevent progression or to further examine gene-environment interactions. Early genetic predisposition detection for developing severe refractive errors may be useful for efficient and cost-effective screening program design. This review explores the genetic mechanisms associated with nonsyndromic refractive error development known to date.

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The concepts of polygenic and multifactorial inheritance provide an explanation for disorders that tend to cluster in families but do not conform to single-gene mendelian inheritance. The expression of a disease may depend on the presence of a critical number of genes that are inherited independently. Such a disorder would be *polygenic,* and the genetic risk factors would be additive. If environmental factors affect the outcome, the term *multifactorial* is used. Examples of diseases that cluster in families but are not proved to be single-gene defects and are not purely environmental include refractive error, strabismus, glaucoma, diabetes mellitus, cleft lip, and spina bifida. In this review article, we briefly discuss the genetics of nonsyndromic refractive error.

DETERMINANTS OF REFRACTIVE STATUS

The refractive status of a given human eye depends on the coordinated contributions of the refractive powers of the cornea and lens, the axial length (AL), the refractive indices of the aqueous and vitreous, and the age of the person.[1] Usually the effects of the aqueous and vitreous humors are constant, with each having a refractive index of 1.33620. Thus, the major refractive components are the cornea, the lens, and the AL. The size, shape, and power of all are determined largely by inheritance.[2] Conformational factors, such as intrauterine environment and the bony orbits and eyelids, can also affect eye shape and growth.[3]

Spherical refractive error usually represents a mismatch between AL and the combined dioptric powers of the cornea and lens. Several studies[2-6] have shown that the refractive status of the eye is determined primarily by variation in AL. The average refractive error at birth is approximately 1 to 2 diopters (D) of hyperopia, and the AL measures approximately 17 mm. By adulthood, the AL grows to approximately 24 mm. The corneal diameter of the infant is 10 mm compared with the adult size of 12 mm. Owing to the steep curvature, corneal power averages 51 D at birth and flattens to approximately 44 D by 6 weeks of age.[7] Lenticular power averages 34 D at birth and decreases to 28 D by 6 months of age and to 21 D by adult-

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hood.[7] The process of emmetropization, in which the refractive components change in a complementary and coordinated manner as the eye grows, results in minimal changes in refractive error; as the radius of the curvature of the cornea decreases, the refractive powers of the lens and cornea decrease, and AL increases.[4,6] The postnatal human eye normally maintains an AL within 2% of its optimal focal point.[1,2,4] Usually emmetropia, where a clear image is focused on the retina, is reached at approximately 9 to 14 years of age, with no refractive change in normal eyes after 16 years.[7]

Refractive error distribution in the adult population follows a bell-shaped curve, with the peak around emmetropia (plano spherical refraction).[3] The individual refractive components, such as dioptric lenticular and corneal powers, anterior chamber depth, and AL, also follow bell-shaped distributions. Moderate ametropia results from moderate failure of correlation of components where in general all components are within their respective reference ranges but are borderline high or low. High refractive error, described as +4.00 to −6.00 D, is usually the result of correlation ametropia, and values higher than this range are due to component ametropia.[1,3] These categories may have different genetic causes.

OCULAR REFRACTIVE COMPONENT GENETICS

Refraction is determined by means of the coordinated contributions of ocular biometric components, such as AL, anterior chamber depth, corneal curvature, and lens thickness. Separately, these components may be assessed as quantitative traits intimately related to the clinical phenotype of myopia. Multiple articles[8-17] have examined the familial aggregation and heritability of ocular components.

Axial length is the largest contributor to the determination of refractive error. Several studies[10-14] have reported an inverse relationship of AL to refraction (the longer the eye, the more myopic the refractive error). Axial lengths in a myopic adult population may show a bimodal distribution, with a second peak of increased AL relating to high myopia (<−6 D at 24 mm and >−6 D at 30 mm) when plotted as a distribution curve.[2] This suggests that myopia of −6 D or greater represents a deviation from the normal distribution of AL and is not physiologic.

Estimates of heritability for AL range from 40% to 94%.[8,15-17] A study[17] of 3 large Sardinian families found modest evidence of linkage on chromosome 2p24, with a likelihood of the odds (LOD) score of 2.64. Axial length includes anterior chamber depth, and studies have shown that increased anterior chamber depth has an inverse relationship as well to refractive error.[14] Heritability estimates for anterior chamber depth range from 70% to 94%,[9,15-17] and the same Sardinian study[17] found evidence of modest linkage with chromosome 1p32.2, with a LOD score of 2.32.

The steeper the corneal curvature, the more likely that the resulting refractive error is myopic; eyes with hyperopia are more likely to have flatter corneal curvature readings by means of keratometry.[10,18,19] Heritability estimates for corneal curvature range from 60% to 92%.[9,15-17] The Sardinian family study[17] noted evidence of modest linkage between corneal curvature and chromosomes 2p25, 3p26, and 7q22, with LOD scores ranging from 2.34 to 2.50. Increased lens thickness correlates with increased myopia.[14] A dizygotic and monozygotic twin study[15] reported 90% to 93% heritability for lens thickness.

MYOPIA GENETICS

Types and Prevalence

Of all the types of refractive error, the most widely studied is myopia. Myopia is the most common human eye disorder in the world, and its public health and economic impact are considerable.[4,20-31] The prevalence of myopia varies because of varying definitions of myopia, but in the US adult population, the estimated prevalence of 25% is supported by multiple studies.[4,25-28] Females are reported to have an earlier onset and a slightly higher prevalence than males,[24,27-29] US Asians and Hispanics have a higher prevalence than whites or African Americans,[26] Chinese and Japanese populations have very high myopia prevalences of greater than 50% to 70%,[28-31] and Ashkenazi Jews, especially Orthodox males, have shown a higher prevalence than other white US and European populations.[31]

"Juvenile-onset" myopia most often develops and progresses between the ages of 10 and 16 years, whereas "pathologic" or high-grade myopia usually begins to develop in the perinatal period and is associated with rapid refractive error myopic shifts before 10 to 12 years of age.[4,20-22,24] Juvenile-onset or moderate myopia most often develops and progresses between the ages of 8 and 16 years.[4,5,22-24]

Pathologic or high myopia (refractive spherical dioptric power of −5 or higher) is a major cause of legal blindness in many developed countries.[20,27,31-35] It affects 27% to 33% of all myopic eyes, corresponding to a prevalence of 1.7% to 2.0% in the general population of the United States.[4,26] High myopia is especially common in Asia.[33,34,36] In Japan, pathologic or high myopia reportedly affects 6% to 18% of the myopic population and 1% to 2% of the general population.[33] Comparative prevalence rates from different countries show considerable variability but confirm that myopia affects a significant proportion of the population in many countries.[20,25,33-36]

Ocular Morbidity

Many investigators have reported on the association of high myopia with cataract, glaucoma, retinal detachment, and posterior staphyloma with retinal degenerative changes.[4,37-53] High myopia is associated with progressive and excessive elongation of the globe, which may be accompanied by degenerative changes in the sclera, choroid, Bruch membrane, retinal pigment epithelium (RPE), and neural retina. Various funduscopic changes in the posterior staphyloma develop in highly myopic eyes, including atrophy of the RPE and choroid, lacquer cracks in the Bruch membrane, subretinal hemorrhage, and choroidal neovascu-

larization (CNV). Of these various fundus lesions, macular CNV is the most common vision-threatening complication of high myopia.[40,41,43-45,47] Clinical and histopathologic studies have documented CNV in 4% to 11% of highly myopic eyes. Relative to emmetropic eyes, an approximate 2-fold increased risk of CNV was estimated for eyes with 1 to 2 D of myopia, a 4-fold increase with 3 to 4 D of myopia, and a 9-fold increase with 5 to 6 D of myopia.[40,47,53,54] Poor visual outcome after CNV in myopic eyes is not uncommon and often affects relatively young patients.

The risk of retinal detachment is estimated to be 3 to 7 times greater for persons with myopia greater than 5 D than for those with myopia of less than 5 D.[6,50,53] Myopia between 5 and 10 D was associated with a 15- to 35-fold greater risk of retinal detachment relative to that associated with low levels of hyperopia.[6,50,53] The lifetime risk of retinal detachment was estimated to be 1.6% for patients with less than 3 D of myopia and 9.3% for those with more than 5 D of myopia.[50,51] A subgroup with lattice degeneration and greater than 5 D of myopia had an estimated lifetime risk of 35.9%.[51] The prevalence of lattice degeneration increases with increasing levels of myopia as measured by AL.[6,53,55,56] Glaucoma was observed in 3% of patients with myopia who had ALs of less than 26.5 mm, in 11% with ALs between 26.5 and 33.5 mm, and in 28% with longer ALs.[52]

Role of Environment in Myopia Development

The prevalence of myopia in some populations seems to have increased dramatically from one generation to the next in progressively industrialized settings or with increased educational achievement.[53,57-60] Assessing the impact of inheritance on myopia development may be confounded by children adopting parental behavioral traits associated with myopia, such as higher-than-average near-work activities (ie, reading).[61] Observational studies of this risk factor do not fully explain the excessive familial clustering of myopia, how-

ever. A detailed assessment of confounding effects and interactions between hereditary and environmental effects in juvenile-onset myopia has shown that near-work activities describes very little of the variance in refractive error compared with parental myopia.[62] In addition, near-work activities exerted no confounding effect on the association between parent and child myopia, indicating that children do not become myopic by adopting parental reading habits. More important, there was no significant interaction between parental myopia and near-work activities; reading was weakly and equally associated with myopia regardless of the number of myopic parents. This finding indicates that children could inherit myopia as a trait from parents.

In addition to genetics, moderate to severe myopia can be induced by local optical alterations in the developing eye. Image quality seems to determine focal length and is commandeered by the retina, which then provides signals to underlying ocular tissues to promote or restrict axial elongation of the globe. This is exemplified by experimental modulation of refractive error in the developing eyes of several animal models (mammalian and avian)[63-65] and the development of myopia in young children with media irregularities that prevent a focused retinal image.[66-68] There are uncertainties about the applicability of these experimental paradigms to physiologic human myopia. For example, artificial alterations to visual experience, such as form deprivation, can be compared with conditions such as unilateral ptosis and congenital cataracts. However, these patients do not always develop myopia as a result of such deprivation.[67]

Role of Genetics in Myopia Development

Multiple familial aggregation studies[69-73] report a positive correlation between parental myopia and myopia in their children, indicating a hereditary factor in myopia susceptibility. Children with a family history of myopia had, on average, less hyperopia, deeper anterior chambers, and longer vitreous chambers even

before becoming myopic. Yap and colleagues[73] noted a prevalence of myopia in 7-year-old children of 7.3% when neither parent was myopic, 26.2% when 1 parent was myopic, and 45% when both parents were myopic, implying a strong role for genetics in myopia.

Multiple familial studies[74-77] support a high genetic effect for myopia. Naiglin and colleagues[78] performed segregation analysis on 32 French multiplex families with high myopia and determined an autosomal dominant (AD) mode of inheritance. The λ_s for myopia (the increase in risk to siblings of a person with a disease compared with the population prevalence) has been estimated to be approximately 4.9 to 19.8 for high myopia (≥ -6.00 spherical D) and approximately 1.5 to 3.0 for low or common myopia (approximately -1.00 to -3.00 spherical D), suggesting a definite genetic basis for high myopia and a strong genetic basis for low myopia.[79,80] A high degree of familial aggregation of refraction, particularly myopia, was recently reported in the Beaver Dam Eye Study population after accounting for the effects of age, sex, and education.[81] Segregation analysis suggested the involvement of multiple genes rather than a single major gene effect.

Twin studies[3,8,15,75,82] provide the most compelling evidence that myopia is inherited. Multiple studies[3,15,75,83] note an increased concordance of refractive error and refractive components (AL, corneal curvature, and lens power) in monozygotic twins compared with dizygotic twins. Sorsby et al[83] noted a correlation coefficient for myopia of 0 for control pairs, 0.5 for dizygotic twins (40 pairs), and almost 1.0 for monozygotic twins (78 pairs). Twin studies[8,15,75,82,83] estimate a high heritability value for myopia (the proportion of the total phenotypic variance that is attributed to genetic variance) of 0.5 to 0.96.

Molecular Genetic Studies of Human Myopia

Much of the current information on the molecular genetics of nonsyndromic human myopia can be drawn from studies of relatively few fami-

lies affected by high myopia, usually defined as a spherical refractive error greater than −6 D. An X-linked recessive form of myopia, the Bornholm (Denmark) eye disease, was designated the first myopia locus in the Online Mendelian Inheritance in Man (OMIM) (available at http://www.ncbi.nlm.nih.gov/omim/) on chromosome Xq28 (*MYP1*; OMIM 310460).[84] Collaborating with Bornholm eye disease researchers, we made comparative molecular genetic haplotype and sequence analyses of a large Minnesota family of Danish descent that showed significant linkage of myopia to chromosome Xq27.3-q28. The phenotype of both families seems to be due to a novel cone dysfunction and not simple myopia. The genetic origin in each family seems to be distinct because the haplotypes are different.[85] A recent study by Michaelides et al[86] confirms that the different X-linked cone dysfunction syndrome with an associated high myopia phenotype is distinct from the Bornholm eye disease in 4 families. Our group[87] identified the first AD locus for nonsyndromic high myopia in a 7.6-centimorgan (cM) region on chromosome 18p11.31 (*MYP2*; OMIM 160700) in 7 US families. This locus was confirmed in Chinese Hong Kong and Italian Sardinian cohorts.[88,89] Using the Hong Kong cohort, investigators[90] identified transforming growth factor β–induced factor (*TGIF*β) as the implicated gene for *MYP1* using limited single nucleotide polymorphism (SNP) association studies and exonic sequencing. Our group[91] fully sequenced *TGIF*β in a cohort of original *MYP1* families and found no associations with high myopia status. A second locus for AD high myopia was mapped to a 30.1-cM region on chromosome 12q21-q23 (*MYP3*; OMIM 603221) in an American family of German-Italian descent also in our laboratory.[92] This locus was confirmed in a high myopia white British cohort, although the *MYP2* and *MYP5* loci showed no statistically significant linkage.[80] A statistically significant third locus suggestive of AD high myopia was reported on chromosome 7q36 in a white French cohort (*MYP4*; OMIM 608367).[93] A

fourth AD locus on chromosome 17q21-q22 (*MYP5*; OMIM 608474) was determined in a large multigenerational English-Canadian family.[94] Our group[95] recently identified a locus for AD high myopia on chromosome 2q37 in a large, multigenerational white US family. Loci on chromosome Xq23-q25 and 4q have also recently been identified by Zhang et al[96,97] in ethnic Chinese families. All loci identified to date for isolated nonsyndromic high myopia are either AD or X-linked and highly penetrant.

At least 2 studies[98,99] have shown nominal or no linkage of juvenile-onset myopia (low to moderate myopia) to many of the known high myopia loci. Mutti et al[98] genotyped 53 common myopia families (at least 1 child with more myopia than −0.75 D in each meridian) using the highest intrainterval LOD score microsatellite markers for the 18p and 12q loci and did not establish linkage. Ibay et al[99] found no strong evidence of linkage to chromosome arms 18p, 12q, 17q, and 7q in a cohort of 38 Ashkenazi Jewish families with mild or moderate myopia (≥−1.00 D). These studies suggest that different genes account for mild or moderate myopia susceptibility or development or that the effect of these genes is too small to be detected with the relatively small sample sizes.

Three whole-genome mapping studies have identified several candidate gene intervals for common juvenile-onset myopia using spherical refractive error data. The results of these studies demonstrate the potential for determining molecular genetic factors implicated in myopia at all levels of severity. These studies, however, used microsatellite genotyping instead of SNP technology and a limited cohort sample size. Two of the 3 studies used homogenous isolated populations, which introduces uncertainty regarding generalizing these findings. One study was a genome screen of 44 families of Ashkenazi Jewish descent.[100] Individuals with at least −1.00 D of myopic spherical refractive error were classified as affected. Their strongest signal localized to chromosome 22q12 (logarithm of the odds [LOD] = 3.56; nonparametric linkage = 4.62). Eight additional

regions (14q, 4q22-q28, 8q22.2, 10q22, 11q23, 13q22, 14q32, and 17qter) showed nominal linkage evidence. Hammond and colleagues[9] evaluated 221 dizygotic twin pairs with moderate myopia and found significant linkage to 4 loci, with a maximum LOD score of 6.1 on chromosome 11p13. Other identified loci mapped to chromosomes 3q26 (LOD score, 3.7), 4q12 (LOD score, 3.3), 8p23 (LOD score, 4.1), and 11q23-24 (LOD score, 2.9). This group found that the paired box gene 6 (aniridia, keratitis) gene (*PAX6*) at the chromosome 11p13 locus showed linkage with 5 SNPs but no association. They suggested that *PAX6* (a major eye development gene) may play a role in myopia development, possibly due to genetic variation in an upstream promoter or regulator. A recent study[101] confirmed the myopia locus at chromosome 8p23 in an isolated Pennsylvania Old Order Amish population of 34 families.

Another recent article[102] found significant genomewide evidence for linkage of refractive error to a novel quantitative trait locus on chromosome 1p36 in an Ashkenazi Jewish population. Wojciechowski et al[102] performed regression-based quantitative trait locus linkage analysis on 49 Ashkenazi Jewish families with at least 2 myopic members. Maximum LOD scores of 9.5 for ocular refraction and 8.7 for log-transformed refraction were observed at 49.1 cM on chromosome 1p36 between markers D1S552 and D1S1622. The empirical genomewide significance levels were *P* = .07 for ocular refraction and *P* < .005 for log-transformed refraction, providing strong evidence for linkage of refraction to this locus. **Table 1** lists the identified myopia loci as posted in OMIM.
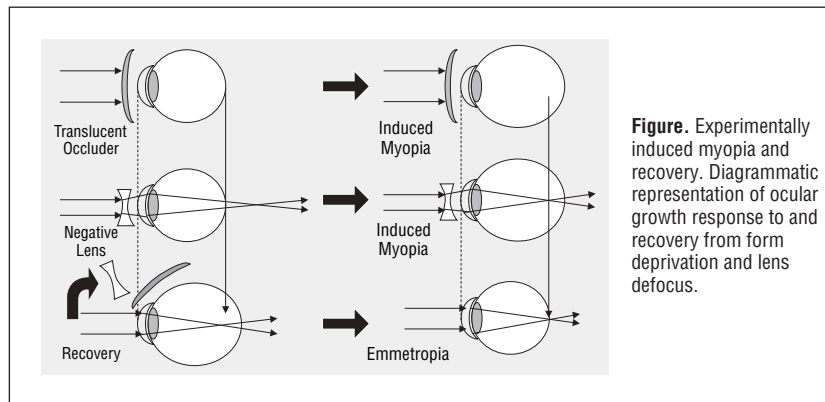
ANIMAL MODEL STUDIES RELATED TO MYOPIA AND EYE GROWTH

One impediment to correlating genotypic data with actual tissue histopathologic findings in human myopia is that the tissue of interest (ie, retina/sclera) cannot be directly sampled. Animal models of myopia have been developed to be used as surrogates, although it is un-

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Table 1. Identified Myopia Loci as Approved by the HGNC

Myopia Locus	OMIM	Cytogenetic Location	Source	Myopia Severity Age at Onset
MYP1	310460	Xq28	84-86	High: −6.75 to −11.25 D Early: 1.5-5 y
MYP2	160700	18p11.31	87-89	High: −6 to −21 D Early: 6.8 y (average)
MYP3	603221	12q21-q23	80, 92	High: −6.25 to −15 D Early: 5.9 y (average)
MYP4	608367	7q36	94	High: −13.05 D (average)
MYP5	608474	17q21-q22	95	High: −5.5 to −50 D Early: 8.9 y (average)
MYP6	608908	22q12	101	Mild-moderate: −1.00 D or lower
MYP7	609256	11p13	9	−12.12 to +7.25 D
MYP8	609257	3q26	9	−12.12 to +7.25 D
MYP9	609258	4q12	9	−12.12 to +7.25 D
MYP10	609259	8p23	9, 102	−12.12 to +7.25 D
MYP11	609994	4q22-q27	98	High: −5 to −20 D Early: before school age
MYP12	609995	2q37.1	96	High: −7.25 to −27 D Early: before 12 y
MYP13	300613	Xq23-q25	97	High: −6 to −20 D Early: before school age

Abbreviations: D, diopters; HGNC, HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl); OMIM, Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Figure. Experimentally induced myopia and recovery. Diagrammatic representation of ocular growth response to and recovery from form deprivation and lens defocus.

clear how correlative induced myopia in animals may be to physiologic myopia in humans. In 1977, Wiesel and Raviola[64] reported axial myopia in rhesus macaques and stump-tailed macaques after unilateral tarsorrhaphy. Subsequent examination showed typical myopic fundus changes. Although several species have been explored, only a few have emerged as primary animal models of myopia, such as the monkey,[64] tree shrew,[65] marmoset,[103] and chick.[104]

Animal studies[65,104-108] during 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 AL to optical power so that the photoreceptors are in focus for distant objects. All the studies support the observation that ocular growth is affected by the quality of visual experience in early life. It was also discovered that myopia could not be induced in dark-reared animals, suggesting that visual experience plays an important role in eye growth.[109]

Experimentally induced myopia is achieved by various means, such as form deprivation, lens-induced optical defocus, and restricted visual environment conditions.[65,104-110] Form deprivation induced by unilateral lid suturing or by the placement of a translucent occluder eliminates higher spatial frequencies and decreases the contrast of the image projected onto the retina yet still al-

lows limited transmission of light to the retina. Form deprivation has been extensively used for experimentally inducing myopia and is consistently successful in producing increases in AL by elongating the vitreous chamber depth.

The initial lid suturing technique was improvised owing to the confounding effects of alterations in corneal curvature.[110] The placement of translucent occluders has become the method of choice (**Figure**). Lens-induced optical defocus is based on shifting the focal plane of the eye posteriorly (with minus lenses) or anteriorly (with plus lenses) (Figure 1). Minus lenses produce axial elongation of the eye, which grows until the retinal location has shifted by the amount that approximately matches the shift of the focal plane.[111] Plus lenses have been shown to act inversely to decrease the AL elongation rate in tree shrews[112] and chicks.[113]

The idea of recovery from induced myopia emerged when it was reported that induced chick axial elongation due to form deprivation showed recovery when patterned light was restored in young animals.[114] These researchers also suggested that this recovery is inversely related to age and hinted at the existence of an active emmetropization mechanism. The same phenomenon has been observed and reported in tree shrews.[115] This paradigm is detailed in Figure 1. The emmetropization mechanism exists with visually driven challenges occurring in either refractive error direction. This control mechanism begins in the retina, where neurons (perhaps a subset of amacrine cells) detect focused vs defocused images.[116] Constant hyperopic defocus uniformly (across species) produces retinal signals that pass, in a signaling cascade that is not well understood, through the RPE and choroid[117] to remodel the scleral extracellular matrix and cause axial elongation.[118,119] This, in turn, reduces the hyperopic defocus so that this feedback system is self-limiting, resulting in a match of AL to optical power. Genes expressed in the retina, RPE, choroid, or sclera that are involved in the normal emmetropization process could be in-

volved in myopia development with irregular expression so that the emmetropization mechanism is disrupted, causing the eye to elongate and become myopic.[117,120-122]

Factors that regulate the rate and duration of eye growth in mice have revealed 2 loci (*Eye1* and *Eye2*) that may be responsible for genetic factors that affect myopia.[123-125] Human homologous regions of synteny are chromosomes 6p, 16q13.3, and 19q13 for *Eye2* and chromosome 7q for *Eye1*. These human loci have been scrutinized for potential candidate genes in myopia genetic studies.

Two independent groups[126,127] recently interrogated candidate genes highlighted from animal model studies and found statistically significant associations of candidate gene SNPs with high myopia in their respective human study cohorts. Han et al[126] performed a family-based association analysis of hepatocyte growth factor gene (*HGF*) polymorphisms using 128 nuclear Han Chinese families and 133 severely myopic offspring. Hepatocyte growth factor is an important multifunctional cytokine, is expressed in the eye, and maps to the chromosome 7q21.1 locus of *Eye1*.[128] The HGF5-5b–tagged SNP selected for association study was found to be significantly associated with high myopia as a quantitative trait in additive, dominant, and recessive models and with high myopia considered as a dichotomous qualitative trait. Lin et al[127] performed a case-control SNP association analysis of transforming growth factor β1 comparing 201 high-myopic Chinese Taiwanese adults with 86 nonmyopic controls. Transforming growth factor β1 is a transcription factor and modulates the production of extracellular matrix.[129] It is a growth regulator of scleral chondrocytes and scleral fibroblasts that in turn affects scleral shape, such as AL.[129] The *TGFB1* gene maps to chromosome 19q13.1-q13.3 of the *Eye2* locus.

HYPEROPIA GENETICS

Role of Genetics in Hyperopic Development

Pedigrees have been reported primarily for autosomal recessive (AR) high hyperopia.[130,131] Variable levels of expressivity have been seen in the same pedigree. The relative frequency of inheritance mode and the refractive component contributions are not known.

Special Form of Extreme Hyperopia: Nanophthalmos

Nanophthalmos is a rare disorder of eye development characterized by extreme hyperopia (farsightedness), with refractive error in the range of +8.00 to +25.00 D.[130] The cornea and lens are normal in size and shape. Hyperopia occurs because insufficient growth along the visual axis places the focal image behind the retina.[13] Nanophthalmic eyes show considerable thickening of the choroidal vascular bed and scleral coat, which provide nutritive and structural support for the retina.[132] Thickening of these tissues is a general feature of axial hyperopia, whereas the opposite occurs in myopia.

Two genetic loci have been identified in conjunction with isolated high hyperopia: AD nanophthalmos (*NNO1*; OMIM 600165) on chromosome arm 11p[133] and AR nanophthalmos *NNO2* (OMIM 609549) on chromosome 11q23.3.[134]

Autosomal dominant nanophthalmos is characterized by a small eye, as indicated by short AL, high hyperopia, high lens–eye volume ratio, and a high incidence of angle-closure glaucoma. Othman et al[133] performed clinical and genetic evaluations of members of a large family with the dominant form of nanophthalmos. Hyperopia ranged from +7.25 to +13.00 D, with a mean of +9.88 D in 22 affected members. Twelve affected members had angle-closure glaucoma or shallow anterior chamber angles. Linkage analysis assigned the locus *NNO1* to chromosome 11p in a 14.7-cM interval. The master control gene *PAX6* (OMIM 607108) located on 11p was thought to be excluded because it does not map within the *NNO1* genetic inclusion interval. The *PAX6* mouse mutants develop small, microphthalmic eyes.

An AR form of nanophthalmos (*NNO2*) is caused by mutations in the gene encoding the membrane-type frizzled-related protein (*MFRP*; OMIM 606227). In 4 individuals with nanophthalmos from the Amish-Mennonite kindred originally reported by Cross and Yoder,[134] Sundin et al[135] mapped AR nanophthalmos to a unique locus at 11q23.3 and identified 4 independent mutations in *MFRP*, a gene that is selectively expressed in the ciliary body and RPE of the eye and that encodes a protein with homology to Tolloid proteases and the Wnt-binding domain of the frizzled transmembrane receptors. This gene is not critical for retinal function, as patients entirely lacking *MFRP* can still have good refraction-corrected vision, have clinically normal electroretinographic findings, and show only modest dark-adaptation responses of the photoreceptors. The *MFRP* gene seems to be primarily devoted to regulating the AL of the eye. On the basis of changes in collagen fibril ultrastructure and sulfated proteoglycan metabolism documented in scleral explants, nanophthalmos had previously been considered a primary defect of connective tissue.[132] This finding introduces a different perspective on eye growth regulation. **Table 2** lists identified hyperopia/nanophthalmos loci as posted in OMIM.

Table 2. Identified Hyperopia/Nanophthalmos Loci or Genes as Approved by the HUGO Gene Nomenclature Committee

Gene or Locus	OMIM	Cytogenetic Location	Source	Myopia Severity
NNO1	600165	11p	135	High: +7.75 to +22 D
NNO2	605738	11q23.3	136 137	
MFRP	609549	11q23.3	137	High: +8 to +25 D

Abbreviations: D, diopters; *MFRP*, membrane-type frizzled-related protein; *NNO1*, autosomal dominant nanophthalmos; *NNO2*, autosomal recessive nanophthalmos; OMIM, Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Astigmatism Genetics

Astigmatism (from the Greek "a" meaning absence and "stigma" meaning point) is a refractive condition in which the parallel rays of light entering the eye through aberrant refractive media do not focus on a single point. Corneal and noncorneal factors contribute to refractive astigmatism.[1-4] Corneal astigmatism is mainly due to an aspheric corneal anterior surface.[19] In 10% of people the effect is neutralized by the back surface.[19,82,83] The curvature of the back surface of the cornea is not considered in most studies because it is more difficult to measure. Noncorneal factors can be due to errors in the curvature of the anterior and posterior crystalline lens surfaces, an irregularity in the refractive index of the lens, or an eccentric lens position.[1-3,7]

Role of Genetics in Astigmatic Development

Mash et al[136] calculated heritability estimates for corneal power in 2 populations that differed in their incidence of esotropia. The estimates were found to be similar for the 2 populations. The heritability estimates for corneal astigmatism were, in most cases, rather low. The patterns of population and sex differences among heritability estimates were consistent with those in previous population studies[17,19,82,83] for cylindrical refractive error.

Teikari et al[16] used data from the Finnish Twin Cohort Study to compile twin pairs in whom 1 or both members had astigmatism. Seventy-two pairs of twins (42 monozygotic and 30 dizygotic) were studied. Refractive error and astigmatism information was obtained by asking the twins to send their last prescription for glasses to the authors. The correlations between monozygotic twins for astigmatism were not higher than the correlations between dizygotic twins. The difference in the amount of astigmatism in monozygotic twins was not statistically significantly different than that in dizygotic twins. This suggested that genetic factors do not contribute to astigmatism, leaving environmental causes as major contributors.

Clementi et al[137] performed complex segregation analysis using data from a geographically well-defined sample of 125 nuclear families of individuals affected by astigmatism. Their analytical programs could not distinguish between alternative genetic models, and only the hypothesis of no familial transmission could be rejected. After inclusion of the severity variable, they obtained results that defined a genetic model for corneal astigmatism and provided evidence of single-major-locus inheritance. These results suggest that genetic linkage studies could be implemented and that they should be limited to multiplex families with severely affected individuals. Autosomal dominant inheritance was favored.

Special Form of Corneal Astigmatism: Keratoconus

Keratoconus is a disorder in which progressive corneal thinning and protuberance and increased astigmatism with visual acuity loss are the clinical characteristics. It is a major indication for cornea transplantation in the Western world.[138,139]

Several pedigree studies[138-141] suggest an AD or AR inheritance transmission pattern for keratoconus. Ihalainen[138] found multiple keratoconus cases in 19 of 101 families studied in the north of Finland and in 5 of 58 families in the south. In 24 of 28 multiplex families, the pattern of inheritance was AD, with incomplete penetrance. Kennedy et al[139] found keratoconus in less than 6% of the relatives of affected probands. Rabinowitz et al[140] studied a 3-generation family. Keratoconus was detected in 8 of 15 family members, with vertical transmission consistent with AD inheritance. Wang et al[141] conducted a family study to investigate genetic contributions to the development of keratoconus. The estimated prevalence in first-degree relatives was 3.34% (41/1226), which is 15 to 67 times higher than that in the general population (0.05%-0.23%). The correlation in sibling and parent-offspring pairs ($r=0.30$ and 0.22, respectively) was significantly greater than that in marital pairs ($r=0.14$), and the latter was not significantly different from zero. Segre-gation analysis in 95 families did not reject a major gene model; the most parsimonious model was AR inheritance.

Several loci for keratoconus have been identified, and 1 gene has been discovered. One form of keratoconus (*KTCN1*) is caused by mutations in the visual system homeobox 1 gene (*VSX1*; OMIM 605020) on chromosome 20.[142] Mutations in this gene are also associated with posterior polymorphous dystrophy.[142] Other loci for keratoconus have been mapped to chromosomes 16q22.3-q23.1 (*KTCN2*; OMIM 608932), 3p14-q13 (*KTCN3*; OMIM 608586), and 2p24 (*KTCN4*; OMIM 609271).[143-145]

Special Form of Corneal Astigmatism: Cornea Plana

Cornea plana is a rare condition in which the corneal curvature is excessively flat.[146,147] There are 2 forms, AD (*CNA1*; OMIM 121400) and, more commonly, AR (*CNA2*; OMIM 217300), which maps to chromosome 12q22.[146-149] Tahvanainen et al[149,150] compared the AD and AR forms of cornea plana congenita and found that they are distinct clinically and genetically. By comparing dioptric keratometry measurements, his team noted a control population (n=473) mean (SD) value of 43.4 (1.5) D for men and 43.7 (1.6) D for women, whereas in 51 subjects affected with *CNA2*, the AR form, the mean (SD) value was 29.9 (5.1) D and in 5 subjects affected with *CNA1*, the mean (SD) value was 37.8 (1.6) D. Mapping studies in 2 *CNA1* families excluded linkage in the *CNA2* locus interval.[150]

As noted previously herein, by the degree of corneal flattening, the AD form of cornea plana is milder than the AR form. Clinical features shared by the AD and AR forms include reduced corneal curvature, an indistinct corneal limbus border, and early-onset arcus lipoides.[149,150] An opaque central thickening occurs in most cases of the AR form but never in the AD form. Iris malformations such as a slitlike pupil and iris-corneal adhesions are more prevalent in the AR form.

Mutations in the keratocan gene (*KERA*; OMIM 603288) on chromo-

Table 3. Identified Loci or Genes for Astigmatism/Keratoconus/Cornea Plana as Approved by the HUGO Gene Nomenclature Committee

Gene or Locus	OMIM	Cytogenetic Location	Source
VSX1	605020	20p11.2	144
KTCN2	608932	16q22.3-q23.1	145
KTCN3	608586	3p14-q13	146
KTCN4	609271	2p24	147
CNA1	121400	129	148, 152
CNA2	127300	12q22	152
KERA	603288	12q22	153-156

Abbreviations: *CNA*, cornea plana; *KERA*, keratocan; *KTCN*, keratoconus; OMIM, Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM); *VSX1*, visual system homeobox 1.

some 12q22 have been associated with *CNA2*, primarily in the Finnish population and in 1 Hispanic family and 1 Saudi Arabian family.[151-154] Keratocan is a member of the small leucine-rich proteoglycan family.[155] Keratocan is expressed selectively in the eye early in neural crest development and later in corneal stromal cells.[155,156] This molecule is thought to be important in developing and maintaining corneal transparency. **Table 3** lists identified astigmatic/keratoconus/cornea plana loci as posted in OMIM.

Future Directions

It is clear from these data that (1) refractive error of all types is heritable and contains a significant genetic etiologic component; (2) the quantitative traits underlying refractive error (spherical dioptric power, AL, corneal curvature, etc) are also heritable and may be used as quantitative trait loci in gene mapping studies; (3) several linkage and association studies establish the feasibility of the positional cloning/candidate gene analysis approach for the identification of genes for these complex ocular phenotypes; and (4) disease expression of refractive errors involves more than 1 gene, of which some may display incomplete penetrance or variable expressivity.

The expanding use of SNP technology for linkage and association studies may provide the necessary platform for finding the genes of large effects for these complex traits. The use of SNPs for haplotype-based association studies offers advantages over the use of conventional microsatellite markers.[157-163]

Genomic regions can be tested for association without requiring discovery of the functional variants. The SNPs are more densely distributed and abundant, spaced approximately every 1000 base pairs along the human genome. The SNPs occur in gene coding regions and in the intervening regions (introns). The SNPs are binary and thus well-suited to automated, high-throughput genotyping. Finally, in contrast to more mutable markers, such as microsatellites, SNPs have a low rate of recurrent mutation, making them stable indicators of human history. More than 4 million SNPs have been identified and are available through public and commercial databases, such as dbSNP (available at http://www.ncbi.nlm.nih.gov/SNP/). More than a million SNPs have now been confirmed. The efforts of the International HapMap Project continue to rapidly generate new sets of validated SNPs for analysis.[164,165]

The SNP-based strategies for complex diseases have had recent success in the ophthalmologic community. Using a "genomic convergence" approach[166] to localize genes that affect age-related macular degeneration, the complement factor H gene was identified through initial family-based linkage analysis, followed by an "unbiased" association of a fine-mapping component and a triage component analyzing candidate genes suggested by expression studies of ocular tissues.[167-169]

CONCLUSION

In summary, the various refractive errors are ideal disorders for ge-

netic investigation. Genetic mechanisms have unequivocally been associated with these disorders. The identification of refractive error susceptibility disease genes will not only provide insight into the molecular basis of these significant eye disorders but will also identify pathways that are involved in eye growth and development. This effort may lead to effective therapies for these potentially blinding disorders.

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