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Update on the epidemiology and genetics of myopic refractive error


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While myopia is an increasingly common refractive error worldwide, its prevalence is greatest in urbanized regions in east Asia. Myopia is a complex multifactorial ocular disorder governed by both genetic and environmental factors and possibly their interplay. Evidence for a genetic role in myopia has been derived from studies of syndromal myopia, familial correlation studies and linkage analyses. More recently, candidate gene and genome-wide association studies have been utilized. However, a high proportion of the heritability of myopia remains unexplained. Most genetic discoveries have been for high myopia, with the search for genes underpinning myopia of lesser severity yielding fewer positive associations. This may soon change with the use of next-generation sequencing, as well as the use of epigenetics and proteomic approaches.

Refraction & its components

Four ocular structures contribute to the refractive apparatus of the human eye: cornea, lens, and aqueous and vitreous humors. Incoming light rays are refracted onto the retina, which then transmits an impulse along the optic nerve to the brain for processing. Refractive error arises when the eye is unable to perform this accurately. Most commonly, refractive error arises due to excessive axial length (AL), and less frequently, because the main refractive structure of the eye – the cornea and lens – lack the required refractive power. Blurred vision ensues. Myopia (‘short-sightedness’) results when light is focused in front of the retina rather than on the retina. Astigmatism may occur in conjunction with myopia. Without correction, myopia causes distant objects to appear blurred but near objects are viewed clearly. Blurred vision may be associated with squinting and eye rubbing, which may prompt a vision assessment.

Using a country-level analysis, refractive error was responsible for 27.7 million disability-adjusted life years worldwide in 2004, which was the highest of any eye disease and remained the highest of any eye disease separately across low/medium- and high-income countries [1]. The burden of refractive errors predominately affects the World Bank regions of east Asia and Pacific, and south Asia, as well as high-income economies [1]. Myopia is the most common refractive error globally, and it is estimated that there are 1.44 billion people affected, equal to 22.6% of the world’s population [2]. The prevalence of correction for myopia is lowest in areas of sub-Saharan Africa and south Asia (including India, Pakistan and Bangladesh) [2]. Myopia prevalence has been increasing worldwide throughout the 20th century, especially in some populations in east Asia, where it is also associated with an increased prevalence of high myopia [3,4]. The reasons underlying this increase are not entirely understood.

Uncorrected refractive error (URE) represents the most common cause of visual impairment worldwide and the second leading cause of blindness [5]. URE does not always correlate positively with myopia severity [6], as it is a reflection of the available health system’s capacity to provide refractive services to a population. Therefore, in low- and middle-income countries, the proportion of individuals with refractive error who are uncorrected may be higher than in high-income countries. URE is a leading cause of visual impairment in urban China, where over 70% of 15-year-olds have myopia [7], and in adults in sub-Saharan Africa, where the prevalence of myopia and other refractive error is far less [8].
A systematic review identified social factors (including socioeconomic status, isolation and education), treatment/service factors (rural domicile, access among minority groups and access to health insurance) and individual factors (including psychological factors) as being associated with URE [9]. It has been shown that uncorrected myopia is associated with poorer overall visual function and having difficulty with specific activities including reading street signs, recognizing friends and watching television [10]. However, separate research found that lower quality-of-life (QoL) scores were associated with myopia irrespective of correction status [11]. In children and younger adults, myopia has little or no impact on general health, but a positive relationship exists between increasing severity of myopia and poorer vision-specific functioning; myopia may cause visual deficits that transcend decreased visual acuity [12].

Although mild myopia has a relatively uncomplicated and benign natural history, the potential for sight loss in patients with severe (high) myopia is substantial, with the risk increasing with worsening degree of myopic refractive error. High myopia may be associated with sight-threatening cataract, open-angle glaucoma, maculopathy and choroidal neovascularization, peripheral retinal changes (such as lattice degeneration), retinal holes and tears, as well as retinal detachment [13–15]. In adults, severe myopia may affect more adversely on QoL than myopia of lesser severity [16]. Pathology associated with higher degrees of myopia is chronic, progressive and more prevalent with increasing age; this may account for the minimal impact on QoL of myopia in children. As myopia is often present during the majority of one’s lifespan, this may explain why refractive error is a greater contributor to the overall global burden of eye disease than chronic, age-related eye diseases such as cataract and macular degeneration [1].

The economic consequences of myopia at a population level are extensive. Assuming myopic individuals receive appropriate refraction and correction, the global burden of myopia has been estimated at approximately US$45 billion [2]. However, this estimate does not take into account the difference in spectacle price according to region, intercountry differences in health systems, the cost of alternative forms of myopic correction (e.g., refractive surgery), or the direct and indirect cost of treatments for consequences of pathological (high) myopia. At a country level, the mean annual direct cost of myopia for Singapore school children was US$148 per child, with greater costs associated with the use of contact lenses, higher family income and paternal education [17].

Management of myopia
Myopia may be corrected with spectacles, contact lenses, orthokeratology or surgical means including laser refractive surgery and intraocular lens implantation. Correction of myopia can result in ocular morbidity, including keratitis secondary to contact lens wear and corneal scarring and persistent corneal haze following refractive surgery. At present, there is no widely used intervention to prevent myopia from occurring or progressing. Randomized controlled trials (RCTs) of several interventions to prevent myopic progression, including bifocal lenses, progressive additional lenses and contact lenses have failed to show major promise [18]. The use of atropine drops for controlling myopic progression is hopeful and has been shown to be superior to placebo for children with mild-to-moderate myopia in several recent meta-analyses [19–21]. However, owing to several common adverse effects (including near blur, light sensitivity, dermatitis and allergic conjunctivitis), the uptake of this intervention has been sluggish. This may change, as a recent RCT demonstrated doses as low as 0.01% may be better tolerated without limiting clinical efficacy [22]. Increasing time outdoors may be a suitable intervention to prevent myopia and its progression [23] but ongoing RCTs must first be assessed and prescribing a lifestyle intervention has inherent challenges.

It is important to acknowledge that correction of refractive error by means of spectacles, refractive surgery or otherwise does not negate the elevated risk of pathology associated with severe myopia. In the majority of affected individuals with early-onset nonsyndromic high myopia, loss of vision during working life is minimal [24]. Nevertheless, high myopia remains a major cause of blindness and visual impairment in older adults [25,26]. Novel treatments that may improve the visual outcome of those affected with myopic sequelae such as choroidal neovascularization, a major cause of visual loss in high myopia, are being developed [15].

Epidemiology of myopia
Refracton across the lifespan
Refraction is dynamic throughout a lifespan. Newborns are usually hyperopic; over the first few years after birth the prevalence of myopia increases in conjunction with axial elongation, thinning of the lens and flattening of the cornea [15]. There is no simple relationship between lens thickness and lens power. The crystalline lens continues to become thinner and although it starts to thicken early in the second decade of life, it continues to lose power [27,28]. Children with longer AL, vitreous chamber depth and thinner crystalline lenses are more likely to develop myopia [29]. Myopic eye growth associated with an increased AL induces the lens to compensate by becoming much thinner [28]. In adults above 40 years of age, increasing age is often associated with a hyperopic shift, unless nuclear sclerosis/cataract is present, which leads to a late-aged myopic shift [30,33]. There is also evidence that suggests that a hyperopic shift can start in earlier years [32].

Prevalence of myopia
The highest prevalence estimates for myopia are for young adults in east Asia, with estimates enroaching 90% in some urbanized and highly educated populations [33]. Using pooled data and a standardized definition of myopia (standard error [SE]: ≤1.0 D), the crude prevalence of myopia in adults aged ≥40 years in USA, western Europe and Australia was 25.4, 26.6 and 16.4%, respectively [34]. In adults aged ≥40 years in east Asia, the prevalence tends to be higher than in other ethnic populations, but the disparity is less marked than in younger cohorts (Table 1). It is noteworthy that in many studies, participants were often excluded from refraction analyses because of reduced vision and/or if pseudophakic. Adult-onset myopia is not uncommon [35], although it does not usually progress to the same extent as myopia that arises in childhood. Data from population-based...
studies in adults do not support a consistently higher prevalence of myopia for either males or females [36–40]. High myopia affects approximately 1–4% of adults aged ≥ 40 years [41–46], but is higher in some studies of east Asian adults [47] and in younger east Asian populations [3,4]. Furthermore, the growth rate of high myopia in young adults clearly exceeds that of ‘any myopia’ in parts of east Asia [3].

The prevalence of myopia in children and young adults varies according to ethnicity, which could represent inter-ethnic genetic and/or environmental variation. Data from population-based studies performed in children propose that Asian populations, especially of Chinese ethnicity, may possess an inherent susceptibility to myopia compared with western populations [48]. Multiethnic studies of refractive error highlight inter-ethnic differences in the prevalence of refractive error. In Singaporean males aged 15–25 years, the prevalence of myopia was 48.5% in Chinese, 34.7% in Eurasians (mostly white Caucasian), 30.4% in Indians and 24.5% in Malays [49]. In a group of American school children aged 5–17 years, the prevalence of myopia was highest amongst Asians (19.8%) followed by Hispanics (14.5%), African–Americans (8.6%) and whites (5.2%) [50]. Inter-ethnic differences persisted even following adjustment for age and sex.
The Refractive Error Study in Children (RESC) examined the prevalence of refractive error in children aged 5–15 years in eight locations using a standardized protocol and diagnostic criteria. Across RESC locations in subjects aged 15 years, the prevalence of myopia ranged from less than 1% (0.79%) in rural Nepal [51] to nearly 80% (79.9%) in Guangzhou, China [7]. Such differences in myopia prevalence usually reflect differences in the respective population distributions of AL [52].

Significant insight into the etiology of myopia can be gained by studying the correlation with migration [53]. Myopia prevalence is higher among second- or later generation Indian immigrants in Singapore than the first-generation immigrants, suggesting that country-specific environmental factors may contribute to the increasing prevalence of myopia in Asia [54]. Rose et al. compared the prevalence and associations of myopia of children of Chinese ethnicity in both Singapore and Sydney [59]. They found a much lower prevalence in Sydney (3.3% vs 29.1%), with the Sydney children spending much more time outdoors per week (mean: 13.75 vs 3.05 h). Reduced time spent outdoors compared with Caucasians was also shown in a clinic-based sample of Chinese–Canadian children with a high prevalence of myopia (64.1% at 12 years of age) [56].

Incidence & progression of myopia
Several studies in children and adults have investigated longitudinal changes in refraction. The annual incidence of myopia in Hong Kong was 144.1 cases per 1000 primary school children per annum and was significantly associated with increasing age [57]. The annual mean change in refraction was greater in myopes compared with nonmyopes [57]. An earlier study from Hong Kong showed the incidence of myopia at age 7–8 years and 11–12 years to be 9% and 18–20%, respectively [58]. In Singapore, the 3-year cumulative incidence rates were 47.7 and 32.4% for 7- and 9-year-old children, respectively [29].

In the Barbados Eye Study (BES), the overall 9-year incidence in adults aged ≥40 years was 12.0% for myopia (2.0% moderate-high myopia) and 29.5% for hypermetropia [59]. The degree of shift in refraction in older adults was age associated, and it can be shown that a myopic shift is more apparent in older adults beginning at approximately 60–70 years of age, which may be due to increasing lenticular nuclear sclerosis [60,61]. At 10 years of follow-up in the Blue Mountains Eye Study (BMES), the gender-adjusted changes in refraction were 0.40, 0.33, -0.02 and -0.65 diopters (D) in persons with baseline ages 49–54, 55–64, 65–74 and ≥75 years, respectively [34]. In the Beaver Dam Eye Study (BDES) there was a mean change of +0.48, +0.03 and -0.19 D for persons aged 43–59, 60–69 and ≥70 years at the baseline examination, respectively [60].

Cohort effects on refraction
In the BDES, participants born in more recent years were more likely to have myopia than those born in earlier years [60]. Here it was shown that the mean refractions in persons 55–59 years at an examination were +0.20, -0.13 and -0.50 D for those born in the years 1928–1932, 1933–1937 and 1938–1942, respectively [60]. A cohort effect has also been suggested in Sweden where a decreased spherical equivalent (more myopic refraction) in 65- to 74-year-olds was observed over time [62]. Further evidence of a cohort effect has been demonstrated in Australian population-based studies [31,63]. There is also evidence of a myopic shift in indigenous Australians over time [64]. Mutti and Zadnik concluded that while most studies have indicated a reduced prevalence of myopia and shortened AL with increasing age in older adults, this is better explained by an intrinsic age-related decrease in an individual’s myopia over time rather than a cohort effect [65].

Results from cross-sectional surveys of younger adults at different time points provide further evidence of cohort effects in refraction. In a study of 421,116 Singaporean military conscripts aged 15–25 years, the estimated prevalence of myopia increased from 26.3% in 1974–1984 to 43.3% in 1987–1991 [66]. A further study has been undertaken involving 15,086 new male Singaporean military conscripts aged 16–26 years in 1996 and a repeat survey of 29,170 similarly aged males in 2009–2010 [67]. Overall myopia prevalence increased from 79.3 to 81.3% between 1996 and 2009, with a concomitant increase in prevalence of high myopia (13.1–14.8%). In Taiwan, the mean refraction in 4686 freshmen was -4.25 ± 2.74 D in 1988 and -4.93 ± 2.82 D in 2005 among 3709 freshman [4]. Similarly, in a series of cross-sectional surveys of 919,929 Israeli Army conscripts, the overall prevalence of myopia increased from 20.3% in 1990 to 28.3% in 2002 [68].

Notably in east Asia, the population distribution of refractive error has undergone a myopic shift in only a few generations. Even those children without myopic parents will likely become myopic, some severely. The large and rapid increase in myopia prevalence in recent birth cohorts of east Asian origin and elsewhere where large differences in environmental pressures have been observed, coupled with the lower heritability estimates and parent–offspring correlations obtained from parent and sibling–offspring correlations in such populations, supports an important and major role for environmental factors influencing myopia [33,69–71].

AL: the major endophenotype of refractive error
AL is composed of the sum of anterior and vitreous chamber depths and lens thickness. In emmetropic, pretreated eyes AL does not correlate with myopia susceptibility; in a study of chicks it was shown that the correlation between genetic variants controlling susceptibility to visually induced myopia and variants controlling normal eye size was negligible [72]. However, when looking at a whole population containing both emmetropes and ametropes, increasing AL is associated with an increasingly myopic refraction, suggesting that factors leading to an increasing AL may share homology with those contributing to myopia and a myopic refraction [73,74].

AL reaches its fastest rate of growth in the year prior to myopia onset before growing at a much slower pace following onset [75]. In Caucasian children before myopia onset, children with myopic parents display a longer AL than children with no positive family history, even after adjustment for environmental covariates [76]. Notably, parental history of myopia influenced the eye’s growth rate rather than size in a study of Chinese children.
Peripheral hyperopia may stimulate the axial elongation in myopia [78]. Greatly increased AL is characteristic of individuals with high myopia, and the degree of AL correlates strongly with high myopia severity [79]. In some adults with high myopia, the AL continues to increase, especially in those who develop posterior staphyloma [80]. One benefit of using AL in analyses is that it remains relatively constant following cataract or refractive surgery, which is not true for refractive readings.

AL does not represent a perfect surrogate for refraction. Male sex is associated with a longer AL than female sex [81,82], which may reflect differences in stature, but this does not translate into a higher prevalence of myopia [42,83,84]. Furthermore, the inter-ethnic variation in height with resulting longer ALs does not simply translate into a higher prevalence of myopia in taller populations. For example, the prevalence of myopia in the Dutch adult population [34], widely believed to be among the tallest population in the world, is much less than in the adult Chinese [47].

Environmental, socioeconomic & lifestyle risk factors of myopia
Environmental and lifestyle factors have strongly influenced the rapid increases in the prevalence of myopia over time in some populations [42,71]. Using a lifecourse epidemiological approach, several novel putative risk factors were identified from the 1958 British Birth Cohort Study, which support the overall global increase in myopia prevalence. These factors include increasing maternal age, increasing rates of intraterine growth retardation, persistence of smoking during pregnancy, changing socioeconomic status and reduced rates of breastfeeding [85].

Socioeconomic factors
In ethnically homogenous populations, people growing up in an urban environment have a higher risk of myopia than people from rural regions [45,86–88]. This incongruity may reflect differences in educational level and socioeconomic class rather than the effect of the environment itself. Other explanations may relate to long-distance viewing, differences in light intensity and optical field, and changes in levels of physical and outdoor activity [33].

One of the strongest environmental determinants of myopia is educational attainment. Prevalence of myopia increases and overall mean spherical error decreases (becomes more myopic) with increasing years of formal education [89,90]. Educational attainment is associated with higher income and decreased unemployment [91], factors that are also associated with refractive error. In an adult Japanese population, risk of myopia is higher in professional occupations with higher incomes and higher educational attainment [37]. In the 1958 British Birth Cohort study, the association between social class and myopia was significantly attenuated in the later life-stage models, thereby suggesting social class was mediated through other relevant childhood factors, which may include education, growth and reduced time spent outdoors [85]. It is important to acknowledge that educational attainment is also influenced by genetic factors and should not be regarded as merely environmental [92].

Diet
Studies of the relationship between diet and refraction have been limited by small sample sizes and imprecise methods of dietary assessment. No dietary factor appears relevant in myopia development or its progression. Malnutrition does not appear to be associated with refractive error [93]. Children with vegetarian diets had an increased prevalence of refractive errors compared with omnivorous children [94], but reasons to account for this are not clear. Using food records, Edwards found statistically significant differences in energy intake, protein, fat, vitamins B1, B2 and C, phosphorus, iron and cholesterol between 24 children who became myopic between 7 and 10 years of age and 68 controls [95]. However, there were no differences in height or weight of cases and controls, and the study was not population-based. No dietary factors for myopia, as assessed by food-frequency questionnaire, were identified in a cross-sectional sample of 851 Chinese school students aged 12.81 ± 0.83 years and, although some dietary components (cholesterol and fat) were associated with AL, multiple testing was not accounted for in analyses [96]. Several studies have shown that being breastfed as an infant is associated with increased hyperopic refraction [97,98], but this finding is not consistently replicated [99].

Diabetes & glycermia
The relationship between diabetes, acute and chronic changes in glycermia and refractive error is complex. Acutely transient changes of refraction due to hyperglycemia could lead to either a myopic or hyperopic shift, depending on whether changes occur in the refractive indices or in the lens. Hyperglycemia-associated changes in the lens nucleus and cortex often lead to transient myopia and hyperopia, respectively; corneal edema often also ensues [100]. In the cross-sectional Handan Eye Study and Los Angeles Latino Eye Study (LALES), diabetes was significantly associated with myopia [41,46]. These results have not been well supported by longitudinal studies. Diabetes was not associated with incident myopia in a 5-year follow-up study of the BMES [101]. The 9-year follow-up of the BES showed that diabetes was not significantly associated with any myopia, but was predictive of moderate-to-severe myopia (spherical equivalent ≤–3 D) [59]. Furthermore, the BDES found that people with diabetes even underwent a hyperopic shift over time [60]. In a cross-sectional study of subjects with Type 2 diabetes in an urban Indian population aged ≥40 years, poor glycemic control was associated with myopia [102]. In a Danish population, increasing HbA1c was associated with an increased odds of myopia, and risk of myopic shift was increased with HbA1c ≥8.8 compared with HbA1c <8.8, suggesting that myopia may be associated with chronic hyperglycemia [103]. By contrast, other studies have found that hyperglycemia and elevated HbA1c have been associated with a hyperopic refraction [104,105].

Smoking & alcohol
Parental smoking is independently associated with reduced myopia and increased hyperopic refraction [106]. For adults, higher frequency of personal smoking is independently associated with
hyperopic refraction [107]. In a population-based cross-sectional study of 6491 adults aged 30–99 years in China, smoking was protectively associated with myopia, following adjustment for age, diabetes, reading and family history of myopia [46]. In the Beijing Eye Study, subjects who consumed alcohol had less myopic refraction than those who did not, but this association was attenuated following adjustment for possible confounders [108].

Anthropometric measures
The finding that body stature is associated with myopia is unconvincing. Although in some studies myopes were significantly taller than nonmyopes [109,110], many studies found only a weak or negligible association [111,112]. In the Genes in Myopia study, following adjustment for age, gender, educational attainment and ocular biometric characteristics, height was not associated with myopic refraction [113]. In a study of 106,926 consecutive Israeli male military recruits aged 17–19 years, myopia was not associated with taller height, and indeed an association in the opposite direction was found [114]. Because genetic coregulation exists between stature and AL, taller people have longer eyes [115], yet because the same genes also appear to control other ocular component dimensions [116] the eyes still end up emmetropic in general.

Myopia has also been associated with low birthweight for gestational age [85]. The relationship between myopia and BMI is absent [117] or negligible [114]. Elsewhere in Asian populations, a higher BMI has been associated with hyperopic refraction in children [110] and adults [107].

Physical & sporting activity
In a 2-year prospective study of Caucasian Danish medical students, duration of physical activity was associated with a myopic refraction (0.175 D per hour of physical activity per day; p = 0.015) after multivariate adjustment [118]. Adult physical activity levels do not appear to show the same association [119]. Using objective measurements of physical activity, 12-year-old children with myopia spent less time in moderate–vigorous physical activity than other children, and also increased time in sedentary behavior, even following adjustment for social and behavioral confounders [120]. Playing sports is inversely associated with myopia [121,122], but not indoor sports [123], suggesting exposure to an outdoor environment may be more important than the exercise component.

Time spent outdoors
The current available evidence favors time spent outdoors, rather than time spent in physical activity, as being protective against myopia. A systematic review and meta-analysis has demonstrated a small but significant association between reduced time outdoors and myopia in children and young adults in observational studies [23]. Time spent outdoors is protective against incident myopia independently of physical activity level [124], and before becoming myopic, children spend less time outdoors than those who do not become myopic [125]. Accordingly, findings from a small RCT [126] have been encouraging, and several other RCTs investigating the effect of time spent outdoors, of which several are currently underway, will shed further important insights. Why being outside is protective is incompletely understood, although exposure to natural light outdoors represents a possible mechanism. This has been supported by a protective association of myopia with increasing conjunctival ultraviolet autofluorescence [127], a novel biomarker of time spent outdoors [128,129].

Near work
Traditionally, time spent doing activities involving near work has been regarded as an important risk factor for myopia, although animal data and epidemiological data are inconsistent [130]. Some studies have demonstrated that increased time spent on activities involving near vision is associated with myopia in primary school children [131]. Further, myopia is associated with proxy measures of near work in adults [85,132], but reverse causality is likely. In any case, there appears to be little difference in near work activity between and after development of myopia compared with emmetropia, suggesting other factors may be more important [133]. A number of studies have found that television watching is not associated with myopia in children [122,134,135]. Television viewing habits also do not appear to differ before and after the onset of myopia [133].

Genetic etiology of myopia
Approach to gene finding in myopia
Ocular and systemic syndromes associated with myopia, and results from familial aggregation studies, heritability estimates, segregation analyses, linkage studies and, more recently, genome-wide association studies (GWAS) provide weight to a genetic basis of myopia. Inter-ethnic differences in refractive error support a genetic etiology further (see section ‘Prevalence of myopia’). Elucidating the genetic determinants of a disease involves several steps [136]. Until recently, the main approach to identify susceptibility chromosomal regions associated with disease was linkage analysis of related individuals (either using parametric or nonparametric approaches), followed by gene localization and sequencing techniques. Candidate gene and GWAS can be performed on unrelated individuals with no specific hypothesis about which single-nucleotide polymorphism (SNP) may be involved, thus necessitating large sample sizes and strict p-value thresholds to determine statistically associations between gene variants and myopia. Once a possible causal gene variant is identified, functional studies can be conducted to identify the consequence(s) of changes in gene expression.

Animal studies
Samples of ocular tissue that might be of interest in myopia research, such as the retina and sclera, cannot be obtained from living humans thus animal models are required. There are several ways of inducing myopia experimentally: form deprivation (eyelid suturing or placing opaque lenses in the anterior eye causing axial elongation and myopia), lens-induced optical defocus (exposure to optical defocus via plus- or minus-powered lenses leading to compensatory changes in AL and refraction) and restricted visual environment conditions. Knockout, breeding experiments and
In syndromal myopia, the degree of offspring when either one or both parents are myopic compared to the general population is at a higher risk, even after controlling for environmental risk factors [121]. Failure of emmetropization could arise from irregular expression of genes in the retina, retinal pigment epithelium, lens, choroid and/or sclera, resulting in axial elongation and myopia.

**Familial aggregation analysis**

Given that families share environments, difficulty exists in differentiating the degree of familial clustering that is due to shared genes and shared environments. The intrapair correlation coefficient for spherical equivalent is significantly higher in monozygotic than dizygotic twins [35]. Studies have shown that the recurrence risk for siblings of individuals with myopia (\(\lambda_s\)) varies between 1.5 and 3.0 for low myopia and several-fold higher for high myopia [141]. This increased risk persists even after controlling for environmental risk factors [121]. In a cross-sectional study of individuals aged 17–45 years in Singapore, the odds ratio (OR) for having mild/moderate myopia was between 2.5 and 3.7, and for high myopia was 5.5; there was also a strong association between family history of myopia and having a longer AL (p < 0.001) [142]. In a study of Singaporean preschool children, subjects with two myopic parents were more likely to be myopic and to have a more myopic refraction than children without myopic parents [143]. Children with myopic parents may be predisposed to myopia because of inheriting factors associated with a longer AL [76].

**Heritability studies**

The genetic contribution to a trait/disease can be divided into an additive (A) genetic variance component and a nonadditive (D) genetic variance component – dominance and epistasis (where the effects of one gene are modified by one or several other genes). Heritability can be defined as the proportion of variance of a disease or trait due to additive genetic factors. Determination of heritability can be through either regression/correlation methods or variance component equations/structural equation modeling using modern computer software packages. Novel estimation methods of heritability analysis can employ high-density genetic marker technologies [144]. In twin studies, the most reported approximation of heritability using regression methods (Falconer’s formula) represents twice the difference in the correlation of monozygotic (MZ) and dizygotic (DZ) twin pairs; to be valid it needs to satisfy the assumptions of a classical twin study [145]. If a genetic basis for a disease or trait exists, MZ twins should be more similar as they share 100% of their genetic material, as opposed to DZ twins who on average share only 50%. Other assumptions of twin studies include the equal environment assumption, trait normality, homoscedasticity (equality) of trait, variances between zygosity groups and accurate zygosity classification. Reduced variation in the range of environmental variation in twin pairs compared with other family relationships may explain why heritability estimates from twin studies are higher than from other study designs. Within a population, heritability is not always constant, and may be altered by changes in measurement methods and environmental factors, as well as effects of migration, selection and inbreeding [144].

A meta-analysis found that the pooled heritability estimate of both refractive error (six studies) and AL (seven studies) was 0.71 (71%), even though there was very high interstudy heterogeneity [146]. However, as the study designs contributing heritability measurements were different, the interpretation of such findings is unclear even with a random-effects model. In that study [146], the individual heritability estimates for refractive error were broad, ranging from 0.2 to 0.91, with the highest estimates derived from twin studies. Most large studies, using quantitative data and structural equation techniques, showed that refractive error is largely genetic in origin (heritability >50%). A high heritability of other refractive error endophenotypes, including AL, anterior chamber depth and corneal curvature, has also been demonstrated [146,147]. Investigation of myopia endophenotypes may provide a useful strategy for unraveling the genetic risk factors of myopia [148]. Classical twin studies are potentially biased towards finding a genetic basis of disease or trait as heritability estimates are often inflated due to the failure to model shared environmental effects, following on from the assumption that any excess correlation in MZ twins compared with DZ twins only represents genetic effects. This may explain why heritability estimates from twin studies tend to be higher than those obtained from family-based designs [147]. Even when researchers attempt to model shared environmental effects, studies are often underpowered to detect them [149].

**Segregation analyses**

Segregation analysis, that is, using maximum likelihood analysis to estimate transmission probabilities of the observed data, is a valuable statistical method to determine the way complex disorders such as myopia are inherited. Multiple different inheritance modes for myopia have been proposed, including recessive, dominant and X-linked forms, providing further evidence of disease heterogeneity. Findings from 602 pedigrees encompassing 2138 BDES participants revealed that a multifactorial mode of inheritance was the most parsimonious [150], a finding that has been shown elsewhere [91].

**Syndromal myopia**

There are many ocular and systemic syndromes that are associated with myopia (Table 2). In syndromal myopia, the degree of myopia is usually severe and characterized by an early age of onset and clearly recognized familial pattern. A search of OMIM and PubMed databases performed in November 2012 revealed more than 250 individual syndromes in which myopia has been described. The probability that the myopia results from the underlying genetic mutation is elevated in cases when the myopia is severe, the myopia is highly penetrant and when the gene(s) involved has a plausible role in refraction. Furthermore, most
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<td>literature</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cornelia De Lange syndrome</td>
<td>Possibly affects one in 10,000–30,000</td>
<td>NIPBL (50–60% of cases), DXS423E, CSPG6,</td>
<td>Most cases are sporadic</td>
<td>12247 (type 1); 300590 (type 2); 610759 (type 3); 614701 (type 4)</td>
</tr>
<tr>
<td></td>
<td>newborns</td>
<td>RAD21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danon disease</td>
<td>Rare: exact prevalence unknown</td>
<td>LAMP2</td>
<td>X-linked dominant</td>
<td>300257</td>
</tr>
<tr>
<td>Ehlers Danlos syndrome</td>
<td>Combined (all types) one in 5000, with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypermobility and classic forms more common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Most common form affects at least one in</td>
<td>CBS, MTHFR, MTR, MTRR and MMADHC genes</td>
<td>Autosomal recessive</td>
<td>Several</td>
</tr>
<tr>
<td></td>
<td>200,000–335,000 people worldwide and more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>common in some countries (e.g., Qatar)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kniest syndrome</td>
<td>Rare: exact incidence is unknown</td>
<td>COL2A1</td>
<td>Autosomal dominant</td>
<td>156550</td>
</tr>
<tr>
<td>Knobloch syndrome</td>
<td>Rare</td>
<td>COL18A1 (type 1); ADAMS18 (type 2)</td>
<td>Autosomal recessive</td>
<td>267750 (type 1); 608454 (type 2)</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>One in 5000</td>
<td>FBN1</td>
<td>Autosomal recessive has</td>
<td>154700</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>been confirmed in some</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>instances. Approximately</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25% arise from new</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mutations</td>
<td></td>
</tr>
<tr>
<td>Marshall syndrome</td>
<td>Unknown</td>
<td>COL11A1</td>
<td>Autosomal dominant</td>
<td>154780</td>
</tr>
<tr>
<td>McCune–Albright syndrome</td>
<td>Between one in 100,000 and one in 1,000,000</td>
<td>GNAS</td>
<td>Not inherited. Random</td>
<td>174800</td>
</tr>
<tr>
<td></td>
<td>worldwide</td>
<td></td>
<td>mutation that occurs early</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in development (mosaicism)</td>
<td></td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>One in 1000 to one in 2500 people</td>
<td>PTPN11, SOS1, KRAS, NRAS and BRAF genes</td>
<td>Autosomal dominant</td>
<td>Several</td>
</tr>
<tr>
<td>Pitt–Hopkins syndrome</td>
<td>Rare: at least 50 people worldwide</td>
<td>TCF4</td>
<td>Autosomal dominant</td>
<td>610954</td>
</tr>
<tr>
<td>Potocki–Shaffer syndrome</td>
<td>Rare</td>
<td>ALX4</td>
<td>Proximal 11p deletion</td>
<td>601224</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>syndrome</td>
<td></td>
</tr>
<tr>
<td>Rubinstein–Taybi syndrome</td>
<td>One in 100,000 to one in 125,000 newborns</td>
<td>When identified (half people no mutation)</td>
<td>Autosomal dominant pattern</td>
<td>180849 (type 1); 613684 (type 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in CREBBP or EB300 or deletion on chromosome 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz–Jampel syndrome</td>
<td>Rare</td>
<td>SHSPG2 or LIFR</td>
<td>Either autosomal dominant</td>
<td>255800 (type 1); 601559 (type 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or heterozygote</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>manifestation</td>
<td></td>
</tr>
</tbody>
</table>

Data from OMIM [301] and the National Organization for Rare Disorders [302]. MIM: Mendelian inheritance in man; NA: Not applicable.
cases of high myopia are not associated with a syndrome. In a community-based UK population of children with high myopia who were identified from optometric and orthoptic practice records, 56% had no associated ocular or systemic condition [152], less than in a US study [153].

Many mutations leading to syndromes that are associated with myopia are in connective tissues or extracellular matrix (ECM) components. This is unsurprising as the majority of the sclera is composed of collagen, and the growth and remodeling of the sclera is increasingly recognized as playing an important role in human refraction [154]. Numerous inherited syndromes are associated with high myopia and abnormal vitreous that predisposes to rhegmatogenous retinal detachment: Stickler's syndrome, Wagner disease and erosive vitreoretinopathy, Knobloch syndrome and Marfan syndrome [155]. Identification of mutations involved with syndromic myopia led many researchers to hypothesize that these genes would be involved in cases of nonsyndromic myopia [138]. Thereafter, a candidate gene approach could be employed. Polymorphisms in the collagen type 2 α1 (COL2A1) gene, mutations of which are associated with Stickler syndrome [156], have been associated with nonsyndromic myopia [157].

### Linkage studies

The role of genetic factors is likely to be stronger in cases of nonsyndromic high myopia of early onset in contrast to cases of low/moderate myopia in which the environmental influence is likely to be more apparent [158]. Indeed, many of the loci found for myopia apply to high myopia only; 20 loci for myopia (MYPI-3;
### Table 3. List of genetic loci for myopia/refractive error.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Locus</th>
<th>MIM ID</th>
<th>Location</th>
<th>Inheritance Pattern</th>
<th>Myopia severity</th>
<th>Age of onset</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwart et al. (1990)</td>
<td>MYP1</td>
<td>310460</td>
<td>Xq28</td>
<td>X-linked recessive</td>
<td>High: -6.75 to -11.25 D</td>
<td>Early: 1.5–5 years</td>
<td>[229]</td>
</tr>
<tr>
<td>Young et al. (1998)</td>
<td>MYP2</td>
<td>160700</td>
<td>18p11.31</td>
<td>Autosomal dominant</td>
<td>High: -6 to -21 D</td>
<td>Early: 6.8 years</td>
<td>[230]</td>
</tr>
<tr>
<td>Young et al. (1998)</td>
<td>MYP3</td>
<td>603221</td>
<td>12q21-q23</td>
<td>Autosomal dominant</td>
<td>High: -6.25 to -15 D</td>
<td>Early: 5.9 years</td>
<td>[230]</td>
</tr>
<tr>
<td>Paluru et al. (2003)</td>
<td>MYP5</td>
<td>608474</td>
<td>17q21-q22</td>
<td>Autosomal dominant</td>
<td>High: -5.5 to -50 D</td>
<td>Early: 8.9 years</td>
<td>[231]</td>
</tr>
<tr>
<td>Stambolian et al. (2004)</td>
<td>MYP6</td>
<td>608908</td>
<td>22q12</td>
<td>NA</td>
<td>Mild-to-moderate: -1.00 D or lower</td>
<td>NA</td>
<td>[232]</td>
</tr>
<tr>
<td>Hammond et al. (2004)</td>
<td>MYP7</td>
<td>609256</td>
<td>11p13</td>
<td>NA</td>
<td>-12.12 to +7.25 D Mean SE: +0.39 D</td>
<td>NA</td>
<td>[233]</td>
</tr>
<tr>
<td>Hammond et al. (2004); Andrew et al. (2008)</td>
<td>MYP8</td>
<td>609257</td>
<td>3q26</td>
<td>NA</td>
<td>-12.12 to +7.25 D Mean SE: +0.39 D Range: -20 to +8.75 D</td>
<td>NA</td>
<td>[233,234]</td>
</tr>
<tr>
<td>Hammond et al. (2004)</td>
<td>MYP9</td>
<td>609258</td>
<td>4q12</td>
<td>NA</td>
<td>-12.12 to +7.25 D Mean SE: +0.39 D</td>
<td>NA</td>
<td>[233]</td>
</tr>
<tr>
<td>Hammond et al. (2004)</td>
<td>MYP10</td>
<td>609259</td>
<td>8p23</td>
<td>NA</td>
<td>-12.12 to +7.25 D Mean SE: +0.39 D</td>
<td>NA</td>
<td>[233]</td>
</tr>
<tr>
<td>Zhang et al. (2005)</td>
<td>MYP11</td>
<td>609994</td>
<td>4q22-q27</td>
<td>Autosomal dominant</td>
<td>High: -5 to -20 D</td>
<td>Early: before school age</td>
<td>[235]</td>
</tr>
<tr>
<td>Paluru et al. (2005)</td>
<td>MYP12</td>
<td>609995</td>
<td>2q37.1</td>
<td>Autosomal dominant</td>
<td>High: -7.25 to -27 D Mean SE: -14.46 D</td>
<td>Early: before 12 years of age</td>
<td>[236]</td>
</tr>
<tr>
<td>Zhang et al. (2006)</td>
<td>MYP13</td>
<td>300613</td>
<td>Xq23-q25</td>
<td>X-linked recessive</td>
<td>High: -6 to -20 D</td>
<td>Early: before school age</td>
<td>[237]</td>
</tr>
<tr>
<td>Wojciechowski et al. (2006)</td>
<td>MYP14</td>
<td>610320</td>
<td>1p36</td>
<td>NA</td>
<td>Moderate-to-high: -3.46 D (average)</td>
<td>NA</td>
<td>[238]</td>
</tr>
<tr>
<td>Nallasamy et al. (2007)</td>
<td>MYP15</td>
<td>612717</td>
<td>10q21.1</td>
<td>Autosomal dominant</td>
<td>High: -7.04 D (average)</td>
<td>Early: 6–16 years</td>
<td>[239]</td>
</tr>
<tr>
<td>Lam et al. (2008)</td>
<td>MYP16</td>
<td>612554</td>
<td>5p15.33-p15.2</td>
<td>Autosomal dominant</td>
<td>High: -7.13 to -16.86 D (range of averages)</td>
<td>NA</td>
<td>[240]</td>
</tr>
<tr>
<td>Naiglin et al. (2002), Paget et al. (2008)</td>
<td>MYP17, formerly MYP4</td>
<td>608367</td>
<td>7q15</td>
<td>Autosomal dominant</td>
<td>High: -13.05 D (average)</td>
<td>NA</td>
<td>[159,160]</td>
</tr>
<tr>
<td>Yang et al. (2009)</td>
<td>MYP18†</td>
<td>255500</td>
<td>14q22.1-q24.2</td>
<td>Autosomal recessive</td>
<td>High: -13.5 D (average right eye)</td>
<td>Early childhood</td>
<td>[241]</td>
</tr>
<tr>
<td>Ma et al. (2010)</td>
<td>MYP19†</td>
<td>613969</td>
<td>5p13.3-p15.1</td>
<td>Autosomal dominant</td>
<td>High: -11.59 D (average)</td>
<td>Early: average age of myopia diagnosis 6.9 years (range: 4–11 years)</td>
<td>[242]</td>
</tr>
<tr>
<td>Shi et al. (2011)</td>
<td>MYP20†</td>
<td>614166</td>
<td>13q12.12</td>
<td>Autosomal dominant</td>
<td>High: -10.64 D (average right eye)</td>
<td>NA</td>
<td>[243]</td>
</tr>
<tr>
<td>Shi et al. (2011)</td>
<td>MYP21†</td>
<td>614167</td>
<td>1p22.2</td>
<td>Autosomal dominant caused by heterozygous mutation in the ZNF644 gene</td>
<td>High: -7.51 to -11.49 D (right eye)</td>
<td>Early: 3–4 years</td>
<td>[161]</td>
</tr>
</tbody>
</table>

†Not yet formally recognized by HUGO Gene Nomenclature Committee.
MIM: Mendelian Inheritance in Man; NA: Not applicable.

MYP5-21 are currently listed on OMIM (Table 3) [301]. MYP4 was originally used for the locus on 7q36, but Paget et al. [159] found no evidence of linkage to 7q36 even though they used the same families as Naiglin et al. [160]. Instead, they found significant linkage.
to 7p15, now referred to as MPY17 [159]. Most of these loci have been found through linkage analyses in highly myopic probands with multiple affected relatives, and corroborative findings from replication studies have been limited. Most of these loci have displayed an autosomal dominant inheritance pattern, but other forms of inheritance have included autosomal recessive (MYP18) and X-linked forms (MYP1 and MYP13). One locus, MYP21, represents a mutation in the zinc finger protein 644 isoform 1 (ZNF644) gene, located on chromosome 1p22.2 [160]. Shi et al. discovered heterozygosity for a 2091A>G transition in exon 3 of the ZNF644 gene in a Han-Chinese family with high myopia, leading to an ile587val (I587V) substitution [161]. ZNF644 was expressed in human liver, placenta, retina and retinal pigment epithelium, the only tissues examined. Subsequently, two novel single-nucleotide variants in ZNF644 (c.725C>T, c.821A>T) in two high-grade myopia individuals (one Caucasian and one African–American) were identified in a US cohort of individuals with high myopia [162].

Not all myopia susceptibility loci are formally recognized by HUGO but may be in due course. Researchers in the BDES identified two novel regions of suggestive linkage on chromosome 1q and 7p [163]. Ciner et al. conducted linkage analysis on 96 families containing 493 African–American individuals in the Myopia Family Study (mean SE: 2.87 D) [164]. They found significant linkage at 47 centimorgans (cM) on chromosome 7 (logarithm of the odds [LOD] score: 5.87, p = 0.00005). There were also three regions on chromosomes 2p, 3p and 10p showing suggestive evidence of linkage (LOD >2; p < 0.005) for ocular refraction. Using an additional 36 white families in addition to the African–American families, a suggestive linkage at chromosome 20 was found, which became more significant when the scores were combined for both groups [165]. Using refractive error as a continuous variable, two additional potential myopia susceptibility loci at 6q13-16.1 and 5q35.1-35.2 for myopia were found [166].

Li et al. performed whole-genome linkage scans for high myopia, using 1210 samples from five independent sites [167]. In addition to replicating several previously identified loci, they found a novel region q34.11 on chromosome 9 (max LOD: 2.07 at rs913275). Sequencing of entire coding regions and intron–exon boundaries can be performed after genome-wide linkage analysis. In Bedouin kindreds with autosomal recessive high myopia, genome-wide linkage analysis mapped the disease gene to 3q28 (LOD score of 11.5 at marker D3S1314). Six genes lying in the locus were subsequently sequenced and a single mutation (c.1523G>T) in exon 10 of LEPREL1 was identified that encodes prol 3-hydroxylase 2 (PRHS2) which is involved in the hydroxylation of collagens [168].

**Candidate gene studies**

Candidate genes are chosen for several reasons: presence within a myopia susceptibility locus, relevant structure and/or function or previously identified as having a critical role in refraction in animal studies. Only a few genes have been consistently replicated in myopia. Some candidate genes have been positively associated with both high and lesser severe forms of myopia [157], thus suggesting that common pathways underpin both forms, although evidence supporting a common pathway is weak. When a myopia susceptibility locus is identified, genes lying within that locus can be sequenced, but this approach does not always result in successful gene finding [169,170]. Next-generation sequencing strategies may improve changes of gene discovery in gene regions of interest. The interplay between different biological classes of refraction-associated genes, including generic binding proteins, transcription factors, metalloproteinases and receptors, may be important [171].

By adopting a candidate gene approach, several positive associations have been identified, especially with genes involved in ECM growth and remodeling (Table 4). In this group of genes, positive associations have been found for genes encoding collagens [172,173], proteoglycans [174,175], matrix metalloproteinases [174,175], and growth factors and their receptors [176–180]. The vitamin D receptor (VDR) gene is another example of a candidate gene. It is plausible that people who develop myopia have lower levels or function of vitamin D as this nutrient is important for eye growth in animal models [181]. Polymorphisms within the VDR gene appear to be associated with low-to-moderate myopia in white individuals [182], whereas a polymorphism in the VDR gene start codon (FokI) has been associated with high myopia [183]. These associations have not been found in recent GWAS.

It has become apparent that most of the (nonhigh myopia) candidate gene associations reported previously represent poor quality, false-positive findings. These studies are typified by small sample sizes and unfeasibly large SNP effect sizes. In addition, even where candidate gene studies have been replicated, the replication often relates to different markers from those identified originally, with the originally associated variants not being replicated. In cases of high myopia, where one would expect a stronger genetic role, replication of initial associations has also been rare. For example, the rs1635529 polymorphism in the COL2A1 gene has been associated with myopia in several Caucasian datasets [157], but was not replicated in a Chinese population with high myopia [184]. This may suggest that this SNP is only associated with only one ethnicity. However, lack of replication has also been seen in studies of populations of the same ethnicity. Four allele SNPs were previously associated with high myopia (alleles of rs2229336 in TGFβ1 [185], rs3759223 in lumican [186], rs1982073 in TGFB1 [185] and rs3735520 in HGF [178]) in Chinese people living in southeast China. However, none of these four were replicated in a study of 288 Chinese subjects with high myopia and 208 controls [187], or other populations [188–193]. Another notable example has been PAX6, for which there have been many failed attempts at replication (see Table 4).

**GWAS of myopia**

Because myopia is a complex disease in which multiple genes may contribute small effects on phenotype, case-controlled and family-based association studies represent a powerful approach to identify its associated genetic risk factors. In GWAS, myopia can be expressed as a binary trait (any degree of myopia or a category of myopia severity; e.g., high myopia) at various SE or spherical error cutoffs, or alternatively, refraction or an endophenotype of myopia (e.g., AL) can be used as quantitative traits. The number of GWAS
Table 4. Selected candidate genes and their association with myopia in studies of humans.

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Chromosomal location</th>
<th>MIM ID</th>
<th>Studies with a positive association</th>
<th>Studies with no association</th>
<th>Reason for being candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF</td>
<td>Brain derived neurotrophic factor</td>
<td>11p14.1</td>
<td>113505</td>
<td>Mutti et al. (2007) [157]</td>
<td>Function</td>
<td>Associated with syndromic myopia</td>
</tr>
<tr>
<td>BMP2</td>
<td>Bone morphogenetic protein 2</td>
<td>20p12.3</td>
<td>112261</td>
<td>Liu et al. (2009) [244]</td>
<td>Function</td>
<td></td>
</tr>
<tr>
<td>CHRM1</td>
<td>Cholinergic receptor, muscarinic 1</td>
<td>11q12.3</td>
<td>118510</td>
<td>Lin et al. (2009) [245]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COL1A1</td>
<td>Collagen type 1 α 1</td>
<td>17q21.31–q22</td>
<td>120150</td>
<td>Inamori et al. (2007) [171]</td>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>COL2A1</td>
<td>Collagen type 2 α 1</td>
<td>12q13.11–q13.2</td>
<td>120140</td>
<td>Mutti et al. (2007) [157]</td>
<td></td>
<td>Associated with syndromic myopia</td>
</tr>
<tr>
<td>COL11A1</td>
<td>Collagen type 11 α 1</td>
<td>1p21.1</td>
<td>120280</td>
<td>Yip et al. (2011) [247]</td>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>COL18A1</td>
<td>Collagen type 18 α 1</td>
<td>12q13.11–q13.2</td>
<td>120140</td>
<td>Wang et al. (2012) [184]</td>
<td></td>
<td>Associated with syndromic myopia</td>
</tr>
<tr>
<td>CRYBA4</td>
<td>Crystallin A4</td>
<td>22q11.2–q13.1</td>
<td>123631</td>
<td>Ho et al. (2012) [248]</td>
<td></td>
<td>Near MYP6 locus</td>
</tr>
<tr>
<td>DCN</td>
<td>Decorin</td>
<td>12q21.33</td>
<td>125255</td>
<td>Yip et al. (2011) [249]; Wang et al. (2006) [186]</td>
<td></td>
<td>Proteoglycan gene</td>
</tr>
<tr>
<td>EGR1</td>
<td>Early growth response 1</td>
<td>5q31.2</td>
<td>128990</td>
<td>Li et al. (2008) [251]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBN1</td>
<td>Fibrillin 1</td>
<td>15q21.1</td>
<td>134797</td>
<td>Yip et al. (2011) [247]</td>
<td></td>
<td>Associated with syndromic myopia</td>
</tr>
<tr>
<td>FMOD</td>
<td>Fibromodulin</td>
<td>1q32.1</td>
<td>600245</td>
<td>Majava et al. (2007) [173]</td>
<td>Paluru et al. (2004) [253]; Lin et al. (2009) [252]</td>
<td></td>
</tr>
<tr>
<td>IGF1</td>
<td>IGF-1</td>
<td>12q22–q24.1</td>
<td>147440</td>
<td>Mak et al. (2012) [176]; Metlapally et al. (2010) [180]</td>
<td>Rydzanicz et al. (2011) [254]</td>
<td></td>
</tr>
<tr>
<td>IGFBP3</td>
<td>IGF-binding protein 3</td>
<td>7p12.3</td>
<td>146732</td>
<td>Mak et al. (2012) [176]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGFBP4</td>
<td>IGF-binding protein 4</td>
<td>17q21.2</td>
<td>146733</td>
<td>Mak et al. (2012) [176]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMA1</td>
<td>Laminin α 1</td>
<td>18p11.31–p11.23</td>
<td>150430</td>
<td>Zhao et al. (2011) [255]</td>
<td>Sasaki et al. (2007) [256]</td>
<td></td>
</tr>
</tbody>
</table>

MIM: Mendelian Inheritance in Man.
Table 4. Selected candidate genes and their association with myopia in studies of humans (cont.).

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Chromosomal location</th>
<th>MIM ID</th>
<th>Studies with a positive association</th>
<th>Studies with no association</th>
<th>Reason for being candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP1</td>
<td>Matrix metalloproteinase 1</td>
<td>11q22.2</td>
<td>120353</td>
<td>Wojciechowski et al. (2010) [174]</td>
<td>Nakanishi et al. (2011) [259]</td>
<td>Function</td>
</tr>
<tr>
<td>MMP2</td>
<td>Matrix metalloproteinase 2</td>
<td>16q12.2</td>
<td>120360</td>
<td>Wojciechowski et al. (2010) [174]</td>
<td>Nakanishi et al. (2011) [259]; Leung et al. (2011) [260]</td>
<td>Function</td>
</tr>
<tr>
<td>MMP3</td>
<td>Matrix metalloproteinase 3</td>
<td>11q22.2</td>
<td>185250</td>
<td>Hall et al. (2009) [175]</td>
<td>Nakanishi et al. (2011) [259]; Liang et al. (2006) [261]</td>
<td>Function</td>
</tr>
<tr>
<td>MYOC</td>
<td>Myocilin</td>
<td>1q24.3</td>
<td>601652</td>
<td>Vatavuk et al. (2009) [262]</td>
<td>Nakanishi et al. (2011) [259]; Leung et al. (2011) [260]</td>
<td>Within MYOC locus</td>
</tr>
<tr>
<td>SERPIN2</td>
<td>Serine protease inhibitor member 2</td>
<td>3p26.1</td>
<td>605575</td>
<td>Hysi et al. (2012) [270]</td>
<td>Nakanishi et al. (2011) [259]; Liang et al. (2006) [261]</td>
<td>Identified through previous linkage</td>
</tr>
</tbody>
</table>

MIM: Mendelian Inheritance in Man.
being performed for complex diseases has increased exponentially in recent years, with an accompanying reduction in cost of the SNP-containing chips. The absence of successful replication of previously identified SNPs may reveal a type 1 error. In this type of study, the relative risk of a causal SNP (commonly presented as an OR) is usually modest in contrast to findings from linkage analyses. Most loci identified from GWAS have only been for high myopia, with limited findings being successfully replicated. Furthermore, some variants are home to chromosomal regions, including noncoding regions, without a plausible candidate gene.

Most GWAS have investigated subjects with high myopia (Table 5) but some success has been achieved when looking at

### Table 4. Selected candidate genes and their association with myopia in studies of humans (cont.).

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Chromosomal location</th>
<th>MIM ID</th>
<th>Studies with a positive association</th>
<th>Studies with no association</th>
<th>Reason for being candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMP2</td>
<td>Tissue inhibitor of metalloproteinase 2</td>
<td>17q25</td>
<td>188825</td>
<td>Leung et al. (2011) [260]; Wojciechowski et al. (2010) [174]</td>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>TIMP3</td>
<td>Tissue inhibitor of metalloproteinase 3</td>
<td>22q12.1–q13.2</td>
<td>188826</td>
<td>Leung et al. (2011) [260]; Wojciechowski et al. (2010) [174]</td>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>TIMP4</td>
<td>Tissue inhibitor of metalloproteinase 4</td>
<td>3q25</td>
<td>601915</td>
<td>Wojciechowski et al. (2010) [174]</td>
<td></td>
<td>Function</td>
</tr>
<tr>
<td>UMODL1</td>
<td>Uromodulin-like 1</td>
<td>21q22.3</td>
<td>613859</td>
<td>Zhu et al. (2012) [271]</td>
<td></td>
<td>Previous linkage to loci</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D receptor</td>
<td>12q13.11</td>
<td>601769</td>
<td>Mutti et al. (2011) [182]; Annananeni et al. (2011) [183]</td>
<td></td>
<td>Function</td>
</tr>
</tbody>
</table>

MIM: Mendelian Inheritance in Man.

### Table 5. Genome-wide association studies and myopia/refractive error.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Primary group</th>
<th>Replication group</th>
<th>Ethnicity</th>
<th>Phenotype</th>
<th>Gene symbol</th>
<th>Location</th>
<th>Marker(s)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan et al. (2012)</td>
<td>Singapore</td>
<td>NA</td>
<td>Chinese and Malay</td>
<td>High myopia and axial length</td>
<td>ZC3H11B</td>
<td>1q41</td>
<td>rs4373767</td>
<td>[79]</td>
</tr>
<tr>
<td>Li et al. (2011)</td>
<td>Singapore</td>
<td>Japanese other Chinese group [200]</td>
<td>Singaporean Chinese</td>
<td>High myopia</td>
<td>CTNND2</td>
<td>5p15</td>
<td>rs12716080; rs6885224</td>
<td>[199]</td>
</tr>
<tr>
<td>Li et al. (2011)</td>
<td>China</td>
<td>NA. This was replicated [273]</td>
<td>Han Chinese</td>
<td>High myopia</td>
<td>No known genes in region, but expressed sequence tags exist</td>
<td>4q25</td>
<td>rs10034228</td>
<td>[274]</td>
</tr>
<tr>
<td>Nakinishi et al. (2009)</td>
<td>Japan</td>
<td>NA</td>
<td>Japanese</td>
<td>High myopia</td>
<td>B3H LOC399959</td>
<td>11q24.1</td>
<td>rs577948</td>
<td>[210]</td>
</tr>
<tr>
<td>Shi et al. (2011)</td>
<td>China</td>
<td>NA</td>
<td>Han Chinese</td>
<td>High myopia</td>
<td>Locus contains three genes (MIPEP, C10TINF98-AS1 and C10TINF98)</td>
<td>13q12.12</td>
<td>rs9318086. Five other SNPs also significant</td>
<td>[243]</td>
</tr>
</tbody>
</table>

An unpublished GWAS recently found 19 significant (p < 5 x 10^-8) associations with myopia, 17 of which were novel [197]. Most of the associations (13; 68.4%) were located within or near genes known to be associated with eye development, neuronal development and signaling, the retinal visual cycle of the retina and general eye morphology: DLG2, KOMMA1, KCNQ1, LAMA2, LRRC34, PRSS56, REFOX1, RHDS, RGR, PRFP1, TIPS2, ZBTB36 and ZIC2. NA: Not applicable; SNP: Single-nucleotide polymorphism.
subjects with less severe refractive error. The Consortium of Refractive Error and Myopia recently published their first findings [193]. This group included 31 cohorts with a total of 55,177 individuals of Caucasian (81.5%) and Asian (18.5%) ancestry. They performed a fixed-effect meta-analysis of 14 SNPs on 15q14 and five SNPs on 15q25; these regions were previously identified as being associated with human refraction in GWAS [194,195]. Within this consortium, all of the SNPs at chromosome 15q14 were significantly replicated, with the top SNP at rs634990 [193]. An increased relative risk of myopia versus hyperopia was identified in homozygotes of the rs634990 risk allele (OR: 1.88; 95% CI: 1.64–2.16; p < 0.001) and for heterozygotes (OR: 1.33; 95% CI: 1.19–1.49; p < 0.001). However, a significant association between myopia and SNPs at locus 15q25 was not found. The 15q14 locus lies close to two genes: gap junction protein 2 (GJD2) and actin α cardiac muscle 1, both of which may have possible roles in myopia development. GJD2 encodes the connexin 36 protein and is expressed in the retina where it is involved in transmission and processing of visual signals [196]. Actin α cardiac muscle 1 may play a role in scleral remodeling [197]. Recently, a very large GWAS study, which used questionnaire-based ascertained data on myopia status, was performed in 43,360 Europeans [198]. The results from the largest myopia GWAS to date were compelling: 19 significant (p-value: < 5 × 10^{-8}) associations with myopia were elucidated, 17 out of which were novel, which explained 2.7% of the total variance of myopia. Most of the associations (13; 68.4%) were located within or near genes known to be associated with the visual cycle of the retina and general eye morphology: DLG2, KCNMA1, KCNQ5, LAMA2, LRRC4C, PRSS56, RBFOX1, RHF5, RGR, SFRP1, TJP2, ZBTB38 and ZIC2.

In a meta-analysis of two genome-wide datasets of Singapore Chinese subjects, Li et al. identified two variants (rs12716080 and rs6885224) in CNTN2 on 5p15 for high myopia [199], one of which (rs6885224) was successfully replicated in a Japanese population in the same study [199] and another Chinese population [200]. CNTN2 is a neuronal-specific protein that is involved in retinal development and whose function may be regulated by DLG2 visual cycle of the retina and general eye morphology; eye development, neuronal development and signaling, the retinal

Overall, the evidence supporting gene–environment interaction in acquired myopia in humans is weak, with the strongest evidence attributed to changes in environmental pressures leading to aberrant emmetropization [198]. Support from a recent animal study has provided an important insight into gene–environment interaction. In a study of outbred White Leghorn chicks [204], after two rounds of selective breeding for high and low susceptibility in response to 4 days of form deprivation, an established animal model for myopia [205], chicks in the high-susceptibility groups developed approximately twice the myopia as the low-susceptibility group. There was also a significant difference between the groups in AL, with additive genetic effects explaining approximately half of the interanimal variation. These results support a role for gene–environment interaction in myopia by showing that susceptibility to environmentally induced myopia in chickens is strongly genetic in origin. As form deprivation during early life has been shown to occur in humans [206], results from this work suggest a potentially major role for gene–environment interaction in human myopia.

Most evidence supporting a gene–environment interaction in cases of acquired myopia in humans has used surrogates of genotype, namely parental myopia and ethnicity. Evidence for a gene–environment interaction is supported by a differential effect of outdoor activity and risk of myopia according to levels of family history of myopia [125]. However, the relationship between parental myopia and measures of education or near work is more equivocal [121,207]. Furthermore, some modifiable environmental risk factors, including educational attainment, are strongly influenced by genetic factors [92]. Recently, an association between SNPs close to an MMP gene cluster and refractive error was identified.
after stratifying by educational attainment [208]: this may represent a gene–environment interaction. As more genetic associations are being discovered in cases of mild-to-moderate myopia, this will provide a better opportunity to investigate gene–environment interactions. Furthermore, the possibility of multiple and varied gene–gene interactions contributing to refractive phenotypes is high, and exploring this will require advanced statistical techniques in conjunction with extremely large sample sizes to permit sufficient power. It will be also necessary to collect data on environmental factors in future GWAS studies, as most current studies have limited environmental data, which could account for the dearth of literature on gene–environment interaction.

Expert commentary

Myopia is a common, complex ocular disorder that is prevalent across all ethnicities in varying proportions. In parts of east Asia, the number of children and young adults with myopia far exceeds the number without. This was not the case in previous generations. We now have populations in which myopia is essentially universal in young adults [4] and this represents a major public health concern. All of these rapid changes have occurred in the context of increased urbanization and strong pressures to attain high levels of education. A concomitant increase has been seen for high myopia, which carries an elevated risk of sight-threatening sequelae. Understanding the factors leading to high myopia and axial elongation are pivotal in this regard. Correction rates for individuals with high myopia is high [6], but those with high myopia should have regular long-term follow-up for surveillance of associated pathology. Genetic discoveries for less severe but more prevalent myopia have been less successful, but steady progress has been made in recent years.

Experimental, epidemiological and clinical studies indicate that refraction is influenced by both environmental and genetic factors and, possibly, their interaction [209]. The majority of the intra-population variance of refractive error within populations (heritability) is attributed to hereditary factors, and evidence supporting a genetic etiology for high myopia is compelling. Several syndromes, both ocular and systemic, are associated with high myopia and are commonly attributed to mutations in genes coding for ECM proteins or connective tissue components that are expressed in the eye (commonly the sclera). Many high myopia susceptibility loci have now been mapped and display different forms of inheritance. Some causative gene mutations have now been identified [164,168], allowing a closer insight into the pathogenesis.

The advent of GWAS has been instrumental in unraveling the genetic complexity of myopia, and numerous unique susceptibility variants have been identified. Without a doubt, several additional variants will be identified in the ensuing years. Fortuitously, GWAS permit the identification of potential novel pathways involved in refraction such as mitochondrial-induced apoptosis [210] and photoreceptor-mediated signal transduction [199]. On the downside, few GWAS findings have been replicated and it appears that variants in several genes interact with each other, and possibly with environmental and lifestyle factors, to influence refractive error. Elucidating the genetic causes of chronic diseases such as myopia affords the opportunity of analyzing DNA samples from patients as an adjunct to clinical diagnosis, prognosis and counseling [211], and enrolling patients in clinical trials of therapeutic agents.

Five-year view

Ophthalmic genetics is evolving rapidly and we will understand much more about the etiology of myopic refractive error over the next 5 years. Much will be achieved with the advent of new technology. The emergence of GWAS that have underpinned the discovery of variants associated with low/moderate and, more commonly, high myopia has been a major advance. Increasingly, collaboration between research groups is required for the discovery, validation and meta-analysis of genetic discoveries from GWAS. Such collaborations also vastly increase the sample sizes available – crucial for ensuring sufficient power for finding rare variants, copy number variants, SNPs of modest effect and evidence of gene–gene interaction. Chromosomal regions that have been previously identified for myopia through linkage analysis will be amenable to new-generation sequencing, thus obviating the requirement for comprehensive SNP analysis [212].

Epigenetics seeks to understand heritable changes in gene expression that cannot be attributed to changes in primary DNA nucleotide sequence. From this angle, it may be possible to further elucidate the etiology of complex non-Mendelian disease and to assist in developing therapeutic interventions [213]. One key mechanism involves methylation of cytosine–phosphate–guanine sites. It is likely that epigenetic effects play an important role in the etiology of myopic refractive error, and will be instrumental in exploring possible gene–environment interactions [214]. Now the role of such studies remains largely undefined. An example of an epigenetic approach to myopia research has demonstrated that hypermethylation of cytosine–phosphate–guanine sites promoter/exon 1 of the COL1A1 gene may be associated with reduced collagen synthesis in myopic scleras [215].

Proteomic approaches could potentially use aqueous or vitreous humor, tears or serum to identify biomarkers of myopia. Duan et al. performed a proteomic analysis by comparing the protein composition of the aqueous humor of highly myopic eyes to non-myopic eyes with cataract [216]. Interestingly, total protein concentration in the aqueous humor of highly myopic eyes was significantly greater than in controls. Analysis linked the higher protein concentration to albumin, transthyretin and a vitamin D-binding protein; these proteins may represent biomarkers that are involved in axial elongation. One limitation of proteomic analysis is the potential confounding effect of concurrent medical and/or surgical treatments, as they may also influence protein composition of the tissues under investigation.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
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Papers of special note have been highlighted as:
• of interest
**• of considerable interest
25. This long-term longitudinal study followed up Danish 14-year-olds with high myopia for 40 years, finding that the majority of subjects (32 out of the 36) still had a corrected visual acuity of LogMAR 0.5 or better.

Key issues
- Myopia is a complex and heterogeneous ocular disorder.
- Some individuals develop myopia through inheriting a single gene mutation, whereas in others myopia is probably due to the action of multiple genetic and/or environmental actions.
- Most recent success in understanding the genetic etiology of nonsyndromic myopic refractive error has been in high myopia.
- More than 20 susceptibility loci have been mapped for myopia; genome-wide association studies and candidate gene studies have implicated several gene variants.
- Several of the genes associated with myopia code for an extracellular matrix component, consistent with its role in influencing eye structure and development.
- Myopia is strongly associated with level of education in the context of increasing urbanization and reduction in time spent outdoors, but support-linking myopia to increased near work is less convincing.
- Evidence from studies in humans supporting a gene–environment interaction is not strong, but evidence from animal studies is stronger.
This major review investigated the respective genetic and environmental contributions to myopia in which the authors provide evidence to argue that a strong environmental component has driven the rapid increase in myopia prevalence in some regions in the previous few generations.


In this study, authors utilized a lifecourse epidemiological approach to investigate the factors underlying myopia at different stages of the lifecycle. Novel risk factors identified were increasing births to older mothers, increasing rates of intrauterine growth retardation and survival of affected children, increasing persistence of smoking in pregnancy and changing socioeconomic status.


131 Yingyong P. Risk factors for refractive errors in primary school children (6–12 years old) in Nakhon Pathom Province.


First GWAS to identify a significant causal variant associate with myopia (rs634990 at 15q14) using spherical equivalent as the outcome measure that did not use only subjects with high myopia. This GWAS was performed in 5328 Dutch individuals and replicated in four independent cohorts. The Consortium of Refractive Error and Myopia (CREAM) representing four different continents with 55,177 individuals have replicated this finding.


• This study using chicks demonstrated evidence of a gene–environment interaction in myopia. They demonstrated that additive genetic effects explained approximately 50% of the inter-animal variability in response to form deprivation; form deprivation during early life has been shown to occur in humans.

Review

Update on the epidemiology & genetics of myopic refractive error

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