·Review·

Epidemiology, genetics and treatments for myopia

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Abstract

• Myopia is a significant public health problem and its prevalence is increasing over time and genetic factors in disease development are important. The prevalence and incidence of myopia within sampled population often varies with age, country, sex, race, ethnicity, occupation, environment, and other factors. Myopia growth is under a combination of genes and their products in time and space to complete the coordination role of the guidance. Myopia-related genes include about 70 genetic loci to which primary myopias have been mapped, although the number is constantly increasing and depends to some extent on definition. Of these, several are associated with additional abnormalities, mostly as part of developmental syndromes. These tend to result from mutations in genes encoding transcriptional activators, and most of these have been identified by sequencing candidate genes in patients with developmental anomalies. Currently, collagen alpha-1 chain of type I(COL1A1), collagen alpha-1 chain of type II(COL2A1), actin, alpha, cardiac muscle 1 (ACTC1), paired box gene 6 (PAX6) and NIPBL (nipped-B homolog), and so on have been mapped. Myopia is most commonly treated with spectacles or glasses. The most common surgical procedure performed to correct myopia is laser keratomileusis (LASIK). This review of the recent advances on epidemiology, genetic locations and treatments of myopia are summarized.

• KEYWORDS: myopia; refractive error; refractive correction; epidemiology; genes; genetics; treatment
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INTRODUCTION

Myopia, or nearsightedness, as it is medically termed, is a vision condition in which close objects are seen clearly, but objects farther away appear blurred. Myopia occurs if the eyeball is too long or the cornea, the clear front cover of the eye, has too much curvature. As a result, the light entering the eye isn't focused correctly and distant objects look blurred (Figure 1, from the Wikimedia Commons). Myopia is a very common vision condition affecting nearly 30 percent of population in the USA. Some research supports the theory that myopia is hereditary. There is also growing evidence that it is influenced by the visual stress of too much close work. Generally, myopia first occurs in school-age children. Because the eye continues to grow during childhood, it typically progresses until about the age of 20. However, myopia may also develop in adults due to visual stress or health conditions such as diabetes [1-4]. A comprehensive optometric examination will include testing for myopia. A common sign of myopia is difficulty with the clarity of distant objects like a movie or TV screen or the chalkboard in school. An optometrist can prescribe eyeglasses or contact lenses that correct myopia by bending the visual images that enter the eyes, focusing the images correctly at the back of the eye [4-6]. Depending on the amount of myopia, you may only need to wear glasses or contact lenses for certain activities, like watching a movie or driving a car. Or, if you are very nearsighted, they may need to be worn all the time [5-8].

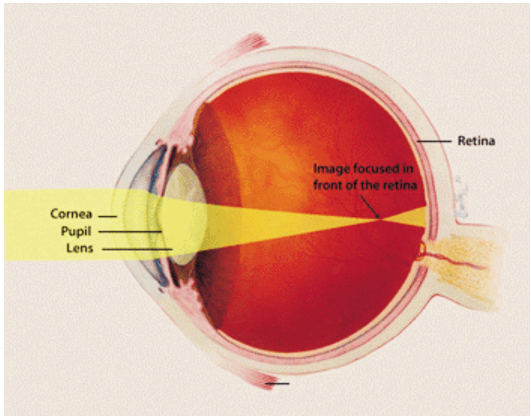

Figure 1 Schematic diagram of myopia

Table 1 The epidemiology of myopia [10-19]

Age at onset	Congenital myopia: present at birth and persists through infancy Youth onset myopia: prior to age 20 (school myopia appears during childhood, particularly the school-age years) Adult onset myopia: aged 20 - 40 Late adult onset myopia: after age 40
Region	Asia Singapore: up to 80% China: 77.3% in high school, more than 80% in college India and Malaysia: up to 41-80% Jordanian: 53.7% aged 17 to 40 Europe United Kingdom: 50% of British whites and 53.4% of British Asians Greece: 36.8% at aged 15-18 in students United States: 25.0% at aged 12-54 Australia: 2.5-17.0% Brazil: 6.4% at aged 12 to 59
Ethnicity and race	For myopia Asians: 18.5% Hispanics: 13.2% Caucasians: 4.4% African American: 6.6% For astigmatism Asians: 33.6% Hispanics: 36.9% Caucasians: 26.4% African American: 20.0%
Education and IQ	The incidence of myopia increases with level of education. A correlation between myopia and a higher intelligence quotient (IQ)
Society and culture	Metaphorically to refer to cognitive thinking and decision making

The severe myopia (high degree myopia) has more likely to develop eye disorders in later life. These might include: 1) Retinal detachment- the retina begins to pull away from the blood vessels that supply it with oxygen and nutrients; left untreated, retinal detachment can cause permanent vision loss; 2) Glaucoma-fluid builds up inside the eye which, if left untreated, can also pose a threat to your vision; 3) Cataracts-cloudy patches that develop inside the lens of the eye; 4) Macular degeneration-the central section of the retina (the macular) becomes damaged, leading to some loss of central vision.

For individuals who have difficulty with convergence or focusing or who are esophoric, close work may increase myopia. Children diagnosed with these problems would benefit from frequent breaks while doing close work. Increases in myopia for these children may be slowed with bifocals and/or removal of glasses for reading and homework.

EPIDEMIOLOGY

Myopia is a most common human eye disorder. With its increasing prevalence and earlier age-of-onset in recent birth cohorts, myopia now affects almost 33% of adults in the United States, and epidemic proportions of adults from 85% to 90% in Asian cities. Unlike children in Western populations, where the prevalence of myopia is very low (less than 5%), Asian children have prevalence as high as 29% in 7-year-old [9]. Myopia has become increasingly more common over the past 50 years, and it is estimated to now affect around 1.6 billion people worldwide, with numbers expected to climb to 2.5 billion by 2020, according to the Institute of Eye Research.In the United States, nearsightedness (myopia) affects nearly 30 percent of the population. The increase in myopia cases is thought by a team of Australian researchers to be a result of more children being raised in environments where they donot see objects far away and their eyes aren't adapted to focus on distant objects as they develop. Global myopia cases are most prevalent in societies where children watch television and play computer games instead of playing outside. In cities like Hong Kong and Tokyo, 30 to 50 percent of 12-year-old children are myopic; in the United States, it is around 20 percent for this age group [1,9-11]. Information about the epidemiology of myopia is shown in Table 1.

According to WHO estimates: 1) Approximately 285 million people worldwide live with serious vision impairment; 2) Of these, 39 million people are blind and 246 million have moderate to severe visual impairment; 3) Also included, 153 million people are visually impaired due to uncorrected refractive errors (near-sightedness, far-sightedness or astigmatism). In most cases, normal vision could be restored with eyeglasses or contact lenses; 4)Yet 75% of blindness is avoidable, i.e. treatable and/or

preventable; 5) 90% of blind people live in low-income countries; 6)Restorations of sight, and blindness prevention strategies are among the most cost-effective interventions in health care; 7)Infectious causes of blindness are decreasing as a result of public health interventions and socio-economic development; 8)Blinding trachoma now affects fewer than 80 million people, compared to 360 million in 1985; 9) Aging populations and life style changes mean that chronic blinding conditions such as diabetic retinopathy are projected to rise exponentially; 10)Women face a significantly greater risk of vision loss than men; Without effective, major intervention, the number of blind people worldwide has been projected to increase to 76 million by 2020.

Prevalence and Incidence The prevalence and incidence of myopia within sampled population often varies with age, country, sex, race, ethnicity, occupation, environment, and other factors. Variability in testing and data collection methods makes comparisons of prevalence and progression difficult. The global prevalence of refractive errors has been estimated from 800 million to 2.3 billion in 2006 [1,10,11]. In some areas, such as China, India and Malaysia, up to 41% of the adult population is myopic to-1diopters, up to 80% to -0.50 diopters [3-5,12].A study involving first-year undergraduate students in the United Kingdom found that 50% of British whites and 53.4% of British Asians were myopic [13]. In Australia, the overall prevalence of myopia (worse than -0.50 diopters) has been estimated to be 17% [14]. In another study, less than 1 in 10 (8.4%) Australian children between the ages of 4 and 12 were found to have myopia greater than -0.50 diopters [15]. A review found that 16.4% of Australians aged 40 or over have at least -1.00 diopters of myopia and 2.5% have at least -5.00 diopters [16]. The following statistics relate to the prevalence of myopia: 1 685 000 men 18.3% of male population short-sightedness, 2 257 000 women, 20.9% of population, 23.5% of female population self- reported having short-sightedness in Australia 2001.

In the United States, the prevalence of myopia has been estimated at 20%. Nearly 1 in 10 (9.2%) American children between the ages of 5 and 17 have myopia. Approximately 25% of Americans between the ages of 12 and 54 have the condition. A recent review found that 25.4% of Americans aged 40 or over have at least -1.00 diopters of myopia and 4.5% have at least -5.00 diopters [16]. In Brazil, the study estimated that 6.4% of Brazilians between the ages of 12 and 59 had -1.00 diopter of myopia or more, compared with 2.7% of the indigenous people in northwestern Brazil [17]. Another study found that nearly 1 in 8 (13.3%) of the students in the city of Natal were myopic [18]. In Greece, the prevalence of myopia among 15 to 18 year old students was found to be 36.8% [19]. In India, the prevalence of myopia in the general population has been reported to be only 6.9% [19]. A recent review found that 26.6% of Western Europeans aged 40 or over have at least -1.00 diopters of myopia and 4.6% have at least -5.00 diopters [16]. A study of Jordanian adults aged 17 to 40 found that over half (53.7%) were myopic [19]. In China, myopia rate was the highest in the world: 400 million people are myopic out of its 1.3 billion people. The prevalence of myopia is 77.3% in high school students in China, and is more than 80% in college students [19]. The prevalence of myopia has been reported as high as 70%-90% in some Asian countries, 30%-40% in Europe and the United States, and 10%-20% in Africa [11].

Ethnicity and Race Myopia is less common in African people and associated diaspora. In Americans between the age of 12 and 54, myopia has been found to affect African Americans less than Caucasians. Asians had the highest prevalence(18.5%), followed by Hispanics(13.2%). Caucasians had the lowest prevalence of myopia (4.4%), which was not significantly different from African Americans (6.6%). For hyperopia, Caucasians had the highest prevalence (19.3%), followed by Hispanics (12.7%). Asians had the lowest prevalence of hyperopia (6.3%) and were not significantly different from African Americans (6.4%). For astigmatism, Asians and Hispanics had the highest prevalences (33.6% and 36.9%, respectively) and did not differ from each other (P=0.17). African Americans had the lowest prevalence of astigmatism (20.0%), followed by Caucasians (26.4%) [19].

Education and IQ A 2008 literature review revealed that studies in several nations have found a relationship between myopia and higher intelligence quotient (IQ) and between myopia and school achievement. Several, but not all, studies have found hyperopia to be associated with lower IQ and school achievements. A common explanation for myopia is near-work. Regarding the relationship to IQ, several explanations have been proposed. The reverse explanation is that the intelligent and studious child reads more which causes myopia. One explanation is that the myopic child is better adapted at reading, and reads and studies more, which increases intelligence. Another explanation is that the myopic children have an advantage at IQ testing which is near work because of less eye strain. Still another explanation is that pleiotropic gene(s) affect the size of both brain and eyes simultaneously. According to the two most recent studies, higher IQ may be associated with myopia in school children, independent of books read per week [10-13].

A number of studies have shown that the incidence of myopia increases with level of education and many studies have shown a correlation between myopia and a higher IQ, possibly due to the confounding factor of formal

education [2-5]. Other personal characteristics, such as value systems, school achievements, time spent in reading for pleasure, language abilities and time spent in sport activities correlated to the occurrence of myopia in the students. However, the eye condition hyperopia has been linked with low IQ levels and Caucasians had the highest prevalence (19.3%). African-Americans had one of the lowest rates (6.4%) along with Asians (6.3%)[14-16,19].

Society and Culture Hyperopia, the biological opposite of myopia, is also used as a metaphor for those who exhibit "far-sighted" behavior; that is, over-prioritizing long-term interests at the expense of present enjoyment [4-6]. The terms myopia and myopic (or the common terms short sightedness or short sighted) have been used metaphorically to refer to cognitive thinking and decision making that is narrow sighted or lacking in concern for wider interests or longer-term consequences [9-11]. It is often used to describe a decision that may be beneficial in the present but detrimental in the future, or a viewpoint that fails to consider anything outside a very narrow and limited range.

There have been many instances of myopic individuals emerging in popular culture, though not always accurately. One such instance is in William Golding's Nobel Prize-winning novel Lord of the Flies, which features a character named Piggy who is very near-sighted and as a result of wearing thick glasses. The children (who are marooned on an isolated island alone) use Piggy's glasses in the same manner as a magnifying glass might be to start fires. However, if Piggy is truly myopic and not hyperopic, starting fires with his glasses would be impossible. Myopia is corrected through the use of diverging lenses to properly focus light on the retina. These lenses do not converge light in a single point-as would be required to start a fire-but rather scatter it. If Piggy were hyperopic, he would have convex, converging lenses and thus he would theoretically be able to serve this purpose[7-10].

GENETICS CHANGES

There are many factors that may affect the status of the eyes. An example of them is myopia gene. Myopia gene is not the most important issue to know about. For example, eyes are also threatened by the effects of getting older.As age begins to affect the eyes, they become more susceptible to wear and tear.Some frequent problems older patients encounter are cataracts, a shift in parts of the eye, and hardening of the muscle and fat that support the eye. Myopia can occur in association with a large number of genetic syndromes [1-3,21]. Currently, there are about 70 genetic loci to which primary myopias have been mapped, although the number is constantly increasing and depends to some extent on definition (Table 2). Of these, several are associated with additional abnormalities, mostly as part of developmental syndromes. These tend to result from mutations in genes encoding transcriptional activators, and most of these have been identified by sequencing candidate genes in patients with developmental anomalies.

Scientists have uncovered a new gene linked to the development of myopia or nearsightedness, according to a new report published today in the online journal Nature Genetics. Myopia is thought to affect up to one in every three people. Eye care experts hope that identifying the gene may help to develop successful gene therapies that may help to remedy the eye condition in future[21].

COL1A1 (collagen alpha-1 chain of type I) Collagen alpha-1 chain of type I, also known as COL1A1, is a human gene that encodes the major component of type I collagen, the fibrillar collagen found in most connective tissues, including cartilage. This gene encodes the pro-alpha1 chains of type I collagen whose triple helix comprises two alpha1 chains and one alpha2 chain. Type I am a fibril-forming collagen found in most connective tissues and is abundant in bone, cornea, dermis and tendon. Mutations in this gene are associated with osteogenesis imperfecta types I-IV, Ehlers-Danlos syndrome type VIIA, Ehlers-Danlos syndrome classical type, Caffey disease and idiopathic osteoporosis. Reciprocal translocations between chromosomes 17 and 22, where this gene and the gene for platelet-derived growth factor beta are located, are associated with a particular type of skin tumor called dermatofibrosarcoma protuberans, resulting from unregulated expression of the growth factor. Two transcripts, resulting from the use of alternate polyadenylation signals, have been identified for this gene [21-23].

Collagen is a protein that strengthens and supports many tissues in the body, including cartilage, bone, tendon, skin and the white part of the eye (sclera). The COL1A1 gene produces a component of type I collagen, called the pro-alpha1 (I) chain. This chain combines with another pro-alpha1 (I) chain and also with a pro-alpha2 (I) chain (produced by the COL1A2 gene) to make a molecule of type I procollagen. These triple-stranded, rope-like procollagen molecules must be processed by enzymes outside the cell. Once these molecules are processed, they arrange themselves into long, thin fibrils that cross-link to one another in the spaces around cells. The cross-links result in the formation of very strong mature type I collagen fibers[21,22].

The COL1A1 gene is located on the long (q) arm of chromosome 17 between positions 21.3 and 22.1, from base pair 45 616 455 to base pair 45 633 991 [23].

Table 2 Mapped human myopia

Locus	Official symbol	Chrom	MIM	ID
ACTC1	Actin, alpha, cardiac muscle 1	15q11-q14	102540	70
ADAMTS10	ADAM metallopeptidase with thrombospondin type 1 motif, 10	19p13.2	608990	81794
ADAMTS17	ADAM metallopeptidase with thrombospondin type 1 motif, 17	15q24	607511	170691
Adora2a	Adenosine A2a receptor	10		11540
ARMS2	Age-related maculopathy susceptibility 2	10q26.13	611313	387715
BFSP2	Beaded filament structural protein 2, phakinin	3q22.1	603212	8419
BLID	BH3-like motif containing, cell death inducer	11q24.1	608853	414899
BMP2K	BMP2 inducible kinase	4q21.21		55589
C1QTNF9B	C1q and tumor necrosis factor related protein 9B	13q12.12		387911
CBS	Cystathionine-beta-synthase	21q22.3	613381	875
CFH	Complement factor H	1q32	134370	3075
CHRM1	Cholinergic receptor, muscarinic 1	11q13	118510	1128
CLDN19	Claudin 19	1p34.2	610036	149461
COL1A1	Collagen, type I, alpha 1	17q21.33	120150	1277
COL2A1	Collagen, type II, alpha 1	12q13.11	120140	1280
CTNND2	Catenin(cadherin-associated protein),delta 2 (neural plakophilin-related arm-repeat protein)	5p15.2	604275	1501
EGR1	Early growth response 1	5q31.1	128990	1958
EPYC	Epiphycan	12q21	601657	1833
FBN1	Fibrillin 1	15q21.1	134797	2200
GJD2	Ap junction protein, delta 2, 36 kDa	15q14	607058	57369
GOLGA8B	Golgin A8 family, member B	15q14	609619	440270
GRM6	glutamate receptor, metabotropic 6	5q35	604096	916
HGF	Hepatocyte growth factor	7q21.1	142409	3082
IGF1	Insulin-like growth factor 1	12q23.2	147440	3479
LPIN2	Lipin 2	18p11.31	605519	9663
LRP2	Low density lipoprotein receptor-related protein 2	2q24-q31	600073	4036
LUM	Lumican	12q21.3-q22	600616	4060
MET	Met proto-oncogene	7q31	164860	4233
MIPEP	Mitochondrial intermediate peptidase	13q12	602241	4285
MIR100HG	Mir-100-let-7a-2 cluster host gene	11q24.1		399959
MMP1	Matrix metallopeptidase 1	11q22.3	120353	4312
MMP2	Matrix metallopeptidase 2	16q13-q21	120360	4313
MMP3	Matrix metallopeptidase 3	11q22.3	185250	4314
MMP9	Matrix metallopeptidase 9	20q11.2-q13.1	120361	4318
MYOC	Myocilin, trabecular meshwork inducible glucocorticoid response	1q23-q24	601652	4653
MYP1	Myopia 1	Xq28	310460	4657
MYP2	Myopia 2	18p11.31	160700	4658
MYP3	Myopia 3	12q21-q23	603221	8782
MYP4	Myopia 4	7q36		393093
MYP5	Myopia 5	17q21-q22	608474	404682
MYP6	Myopia 6	22q12	608908	450094
MYP7	Myopia 7	11p13	609256	553190
MYP8	Myopia 8	3q26	609257	553192
MYP9	Myopia 9	4q12	609258	553194
MYP10	Myopia 10	8p23	609259	553195
MYP11	Myopia 11	4q22-q27	609994	594832

MYP12	Myopia 12	2q37.1	609995	664780
MYP13	Myopia 13	Xq23-q25	300613	677764
MYP14	Myopia 14	1p36	610320	100359407
MYP15	Myopia 15	10q21.1	612717	100294716
MYP16	Myopia 16	5p15.33-p15.2	612554	100270641
MYP17	Myopia 17	7p15	608367	100359401
MYP18	Myopia 18	14q22.1-q24.2	613626	100359406
RARA	Retinoic acid receptor, alpha	17q21	180240	5914
RARB	Retinoic acid receptor, beta	3p24	180220	5915
RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1	15q24.2	606600	5923
RDH8	Retinol dehydrogenase 8	19p13.2	608575	50700
Shh	Sonic hedgehog	5 16.0 cM		20423
TEX28	Testis expressed 28	Xq28	300092	1527
TGFB1	Transforming growth factor, beta 1	19q13.1	190180	7040
TGIF1	TGFB-induced factor homeobox 1	18p11.3	602630	7050
TIMP1	TIMP metallopeptidase inhibitor 1	Xp11.3-p11.23	305370	7076
UMODL1	Uromodulin-like 1	21q22.3	613859	89766
VPS13B	Vacuolar protein sorting 13 homolog B	8q22.2	607817	157680

Specific mutations are described below the entry for the gene or locus. Chrom: chromosomal location, MIM: Mendelian Inheritance in Man reference. Specific mutations identified are listed below the gene. Genes and loci are shown in bold, while individual mutations and their descriptions are shown in small lettering below (from www.ncbi.nlm.nih.gov/pubmed/)

Location: 17q21.33

Sequence: Chromosome 17; NC_000017.10 (48261457.. 48279000, complement)

COL2A1 (collagen alpha-1 chain of type II) COL2A1 gene provides instructions for making one component of type II collagen, called the pro-alpha1 (II) chain. Type II collagen adds structure and strength to the connective tissues that support the body's muscles, joints, organs, and skin. Type II collagen is found primarily in cartilage, a tough but flexible tissue that makes up much of the skeleton during early development. Most cartilage is later converted to bone, except for the cartilage that continues to cover and protect the ends of bones and is present in the nose and external ears. Type II collagen is also a part of the clear gel that fills the eyeball (the vitreous), the inner ear, and the center portion of the discs between the vertebrae in the spine (nucleus pulposus). To construct type II collagen, three pro-alpha1 (II) chains twist together to form a triple-stranded, ropelike procollagen molecule. Procollagen molecules are then processed by enzymes in the cell. Once processed, the molecules leave the cell and arrange themselves into long, thin fibrils that link to one another (cross-link) in the spaces around cells. The cross-linkages result in the formation of very strong, mature type II collagen fibers [1,22].

This gene encodes the alpha-1 chain of type II collagen (COL2A1), a fibrillar collagen found in cartilage and the vitreous humor of the eye. Mutations in this gene are associated with achondrogenesis, chondrodysplasia, early onset of familial osteoarthritis, SED congenita, Langer-Saldino achondrogenesis, Kniest dysplasia, Stickler syndrome type I, and spondyloepimetaphyseal dysplasia Strudwick type. In addition, defects in processing chondrocalcin, a calcium binding protein that is the C-propeptide of this collagen molecule, are also associated with chondrodysplasia [6,23-25]. There are two transcripts identified for this gene. The COL2A1 gene is located on the long (q) arm of chromosome 12 between positions 13.11 and 13.2, from base pair 46 653 017 to base pair 46 684 527[26].

Location: 12q13.11

Sequence: Chromosome 12; NC_000012.11 (48366748.. 48398285, complement)

ACTC1 (actin, alpha, cardiac muscle 1) Actins are highly conserved proteins that are involved in various types of cell motility. Polymerization of globular actin (G-actin) leads to a structural filament (F-actin) in the form of a two-stranded helix. Each actin can bind to four others. The protein encoded by this gene belongs to the actin family which is comprised of three main groups of actin isoforms, alpha, beta, and gamma. The alpha actins are found in muscle tissues and are a major constituent of the contractile apparatus. Defects in this gene have been associated with

idiopathic dilated cardiomyopathy (IDC) and familial hypertrophic cardiomyopathy (FHC) [4,24].

Alpha actins are differentially found in the contractile apparatus of the three muscle cell types; sarcomeric (striated) skeletal and cardiac muscle cells and non-sarcomeric smooth muscle cells. Alpha cardiac muscle actin, caActin, alpha-cardiac actin, is a 42 kDa, 375 amino acids long protein coded by the ACTC1 gene (Gene map locus 15q11-q14) that is post-translationally modified (PTM) by N-terminal acetylation and methylation (tele-His75). It is one of six actin proteins coded by the highly conserved actin gene family. This family also includes: alpha skeletal, skActin (ACTA1); alpha vascular, SMactin, (ACTA2); beta-actin (ACTB); gamma 1, gamma (cyto) (ACTG1) and gamma enteric, SMGA (ACTG2) actin genes. Actin isotypes are sequence diverse primarily in their N-terminal regions. Alpha caActin is the monomeric (G-Actin) component of the two-stranded helix structural filament, filamentous actin (F-actin) of cardiac muscle. F-actin composed of caActin monomers is principle components of the thin filament components of cardiac muscle (cardiac myocyte) myofibrils and sarcomeres. The sarcomere is the basic structural element that mediates the contraction of cardiac muscle. Mutations of the ACTC1 gene compromise the structure and function of cardiac muscle myofibrils and their sarcomeres. ACTA1 mutations have been linked to hereditary hypertrophic (HCM) and dilated (DCM) cardiomyopathies which result in defective sarcomere contraction or force transmission, respectively. DCM is a common cause of heart failure in the young. More specifically, ACTC1 mutations have been linked to familial hypertrophic cardiomyopathy (CMH, FHC, HCM) and to an inherited form of dilated cardiomyopathy (CMDIR) [21,24-27].

Location: 15q11-q14

Sequence: Chromosome 15; NC_000015.9 (35080297.. 35087927, complement)

Refractive errors are the most common ocular disorders worldwide and may lead to blindness. Although this trait is highly heritable, identification of susceptibility genes has been challenging. Solouki *et al*[27] conducted a genome-wide association study for refractive error in 5 328 individuals from a Dutch population-based study with replication in four independent cohorts (combined 10 280 individuals in the replication stage). The odds ratio of myopia compared to hyperopia for the minor allele (minor allele frequency = 0.47)was 1.41(95% CI 1.16-1.70) for individuals heterozygous for the allele and 1.83 (95% CI 1.42-2.36) for individuals homozygous for the allele. The associated locus is near two genes that are expressed in the retina, GJD2 and ACTC1, and appears to harbor regulatory elements which may influence transcription of these genes. These data suggest that common variants at 15q14 influence susceptibility for refractive errors in the general population.

PAX6 (paired box gene 6) This gene encodes paired box gene 6, one of many human homologs of the Drosophila melanogaster gene prd. The PAX6 gene is a homeobox gene involved in oculogenesis, ocular growth, and form-deprivation myopia. In addition to the hallmark feature of this gene family, a conserved paired box domain, the encoded protein also contains a homeo box domain. Both domains are known to bind DNA, and function as regulators of gene transcription. This gene is expressed in the developing nervous system, and in developing eyes. Mutations in this gene are known to cause ocular disorders such as aniridia and Peter's anomaly. Alternatively spliced transcript variants encoding either the same or different isoform have been found for this gene [28-30].

No significant difference in genotype and allelic frequency at this position between the study and control groups was detected by Tsai *et al* [31].However, there was a significantly higher frequency of the CC genotype in extremely myopic patients (P <0.001). Furthermore, there was a higher frequency of the C allele in the extreme myopia group than in the control group (P=0.002). The elevated frequency of the CC genotype within the extreme myopia group indicated that the CC genotype could act as a genetic marker, identifying patients predisposed to develop extreme myopia. Varied expression of this genotype may contribute to the genetic predisposition to high myopia in Chinese Taiwanese [31].

There are transcription factor with important functions in the development of the eye, nose, central nervous system and pancreas for PAX6. It was required for the differentiation of pancreatic islet alpha cells. Competes with PAX4 in binding to a common element in the glucagon, insulin and somatostatin promoters was established, and which was regulated specification of the ventral neuron subtypes by establishing the correct progenitor domains. Isoform 5a appears to function as a molecular switch that specifies target genes [28-30].

The PAX6 gene is involved in ocular morphogenesis and is expressed in the developing central nervous system and numerous ocular tissues during development. PAX6 mutations have been detected in various ocular anomalies, including aniridia, Peters anomaly, corneal dystrophy, congenital cataracts, and foveal hypoplasia. However, it has not been identified in patients with optic-nerve malformations. Here, Azuma *et al* [32] identified novel

mutations in eight pedigrees with optic-nerve malformations, including coloboma, morning glory disc anomaly, optic-nerve hypoplasia/aplasia, and persistent hyperplastic primary vitreous. A functional assay demonstrated that each mutation decreased the transcriptional activation potential of PAX6 through the paired DNA-binding domain. PAX6 and PAX2 are each thought to down-regulate the expression of the other. Four of the detected mutations affected PAX6-mediated transcriptional repression of the PAX2 promoter in a reporter assay. Because PAX2 gene mutations were detected in papillorenal syndrome, alter nation of PAX2 function by PAX6 mutations may affect phenotypic manifestations of optic-nerve malformations.

Location: 11p13

Sequence: Chromosome 11; NC_000011.9 (31806340.. 31839509, complement)

NIPBL (nipped -B homolog) This gene encodes the homolog of the Drosophila melanogaster Nipped-B gene product and fungal Scc2-type sister chromatid cohesion proteins. The Drosophila protein facilitates enhancer-promoter communication of remote enhancers and plays a role in developmental regulation. It is also homologous to a family of chromosomal adherins with broad roles in sister chromatid cohesion, chromosome condensation, and DNA repair. The human protein has a bipartite nuclear targeting sequence and a putative HEAT repeat. Condensins, cohesins and other complexes with chromosome-related functions also contain HEAT repeats. Mutations in this gene result in Cornelia de Lange syndrome, a disorder characterized by dysmorphic facial features, growth delay, limb reduction defects, and mental retardation. Two transcript variants encoding different isoforms have been found for this gene [33].

In embryos, NIPBL is expressed in developing limbs and later in cartilage primordia of the ulna and various hand bones. Sites of craniofacial expression include the cartilage primordium of the basioccipital and basisphenoid skull bones and elsewhere in the head and face, including a region encompassing the mesenchyme adjacent to the cochlear canal. In the spinal column, notochord and surface ectoderm sclerotome were expressed, which seem to be migrating myoblasts. It expressed in the developing heart in the atrial and ventricular myocardium and in the ventricular tubeculae but absent in the endocardial cushions. Also, NIPBL is expressed in the developing esophagus, trachea and midgut loops, in the bronchi of the lung and in the tubules of the metanephros. NIPBL expression in organs and tissues not typically affected in CDL (e.g., the developing trachea, bronchi, esophagus, heart and kidney) may reflect a bias towards underreporting of more subtle aspects of the phenotype or problems that typically present later in life. NIPBL expressed in the mesenchyme surrounding the cochlear canal possibly reflecting the hearing impairment, and it is weakly or not expressed in embryonic brain [21,33,34].

Location: 5p13.2

Sequence: Chromosome 5; NC_000005.9 (36876861.. 37065921)

Other Genes The new genes that cause myopias are constantly discovered. Scientists have discovered strands of genetic code linked to myopia, the most common eye disorder in the world. Usually, myopia starts to manifest early in life. For those with the worst vision, around 80% of the condition is caused by genetic factors [21]. Two separate studies, published in *Nature Genetics Journal*, found variations in DNA that were more common in people with short sight. Chris Hammond, at King's College, London, found one section of DNA on chromosome 15 was more common in people with myopia. Caroline Klaver, at Erasmus Medical Centre in Rotterdam, found another strand, also on chromosome 15, linked to short sight (Table 2). The variations in DNA amount to misspellings in the genetic code. These alter the activity of three genes that control the growth of the eyeball and ensure light entering the eye is converted into electrical pulses in the retina. The discovery helps scientists piece together how a healthy eye becomes short-sighted and points the way to medicines to prevent it in children.

TREATMENTS

Myopia is one of the three major visual refractive errors, and so common today that it is estimated to affect one third of the population in the world [19]. In contrast to hyperopia which deprives people from close vision, people with myopia can see close objects but can not manage distant things such as highway signs. As people age, myopia will stop progressing and become stable, although sometimes it performs myopic creep. The other two conditions are hyperopia and astigmatism. Belonging to a same category of eye problems, both myopia and hyperopia involve irregular eyeball shapes. People with myopia have longer eyeballs than normal people, so that light rays are focused in front of the retina. Hyperopic patients have eyeballs with an opposite abnormality. It is well-known that normal, clear vision requires a light focus right on the retina. Without external interference, myopic people always squint to see distant objects and may suffer from headache or eye strain [35-39].

What's more, people who wear eyeglasses or contact lenses with an improper prescription are also bothered by these symptoms.

Prescription Eyewear Products The most popular choice is to wear prescription eyewear including eyeglasses and contact lenses for myopia. People with myopia have prescriptions with negative numbers, and a larger number represents a heavier myopia. As a common vision condition in modern times, myopia is well-known and scientists have developed a couple of solutions to its correction. Once a myopic patient's eyes are precisely tested and measured, prescription lenses can be customized according to his or her vision demand and clear vision will "return". Whether it is necessary to wear prescription eye glasses or contact lenses full-time depends on the degree or severity of myopia [1-3,40-42].

Available Surgical Treatments Refractive surgeries are becoming popular since they can reshape the cornea of a myopic patient and eliminate the need for Rx eyewear. PRK and LASIK are two of the available refractive surgeries, both of which use an excimer laser. While PRK just removes a layer of corneal tissues and flattens the cornea, a LASIK procedure involves a flap cut through the top of the cornea. Other laser eye surgeries for vision correction include by LASIK, LASEK, and Epi-LASIK *etc*: Each of these surgeries costs several thousand dollars per eye [43-46].

Ortho –k Contact Lenses and Phakic Intraocular Lenses For night wear, special contact lenses applying orthokeratology (ortho-k) technology can reshape the cornea overnight and provide clear vision during daytime without the help of Rx contact lenses or glasses. As implantable lenses, phakic intraocular lenses (IOLs) can deal with special situations that are beyond LASIK and PRK. These IOLs are permanently placed in the eye during a surgery, eliminating any maintenance [46-48].

Slowing the Myopia Progression Treatments that are currently available for slowing the progression of myopia include spectacle lenses, contact lenses, and pharmaceutical agents [3-5]. Many of the intervention studies evaluating these treatments have had methodological limitations, and their results should be interpreted with caution. In order to consider seriously, the treatment trial should include the following features: a concurrent control group, random assignment to the treatment and control groups, masking of investigators who collect the outcome data, standardized measurements, a large enough sample size, and a small loss to follow-up. The bulk of evidence from well-designed studies with proper controls shows that most therapies for myopia have small treatment benefits that last for a relatively short period of time or have significant side effects. This review of treatment options for myopia will emphasize recent results from well-designed clinical studies [49].

Single Vision Lenses An active emmetropization mechanism regulated by optical defocus is supported by results of numerous studies [50]. Strong evidence is provided by compensatory ocular growth seen in response to lens-induced defocus in animal models [51]. Based on these results, it has been suggested that spectacle intervention in myopic children with the commonly prescribed single vision lenses (SVLs) might lead to increased progression and axial elongation. Patterns of lens wear in myopic patients can vary from full-time wear, to the use of lenses for distance viewing only, to non-wear of prescribed lenses. Limited data are available on myopia progression by pattern of lens wear, though pilot data suggest that progression is similar for the different patterns [52]. Additional investigation using a large sample of children randomly assigned to a lens wear regimen is warranted.

Bifocals and Progressive Addition Lenses The use of bifocals or progressive addition lenses (PALs), sometimes called no-line bifocals, for slowing the progression of myopia has produced relatively small treatment effects overall, on the order of 0.15 to 0.50 D over 1.5 to 3 years, although treatment effects are reported to be larger in certain subgroups of myopic children, as described below [53]. The largest of the treatment trials with this type of lens was the Correction of Myopia Evaluation Trial (COMET), a multi-center, randomized, double-masked clinical trial to evaluate whether PALs slow the rate of progression of myopia compared to conventional SVLs [51,54].

Contact Lenses Many early investigations of rigid gas permeable contact lenses (RGP) for myopia control suffered from lack of randomization and a high drop out rate from the contact lens group [48-50]. In an attempt to eliminate the high loss to follow-up found in previous studies, a recent randomized clinical trial, the Contact Lens and Myopia Progression (CLAMP) study, implemented a run-in period to ensure good compliance with rigid contact lens wear.

Hotodynamic Therapy There is also pathologic myopia, which is extremely severe and can not be corrected by any of the above treatments. This type of myopia occurs in children with extremely elongated eyeball by age 12. The situation will worsen as children age and unfortunately develop abnormal growth of new blood vessels. There was no effective treatment during a long period until the approval of drug Visudyne along with non-thermal laser application in 2001. This treatment named photodynamic therapy has been proved to be effective [47-49].

Pharmaceutical Agents

Atropine Recent well-designed studies using topical atropine, a non-selective muscarinic antagonist, have

demonstrated statistically and clinic ally significant reductions in the progression of myopia [55]. For atropine treatment of myopia, the main contraindication is glaucoma. Controlled clinical trials were retrospectively analyzed to compare atropine and placebo for the treatment of myopia. The primary outcome measure was annual rate of myopia progression after daily atropine application over 1 year. Data were extracted from 6 randomized clinical trials and analyzed using standard meta-analysis and meta-regression methods. No serious adverse event was reported during the period of treatment. The results show that 0.5% and 1% atropine was demonstrated to be effective and safe to ameliorate myopia progression in childhood with low-to-moderate myopia [55,56].

Pirenzepine Pirenzepine, like atropine, is a muscarinic antagonist but it is less likely to produce mydriasis and cycloplegia [56]. Two clinical trials of pirenzepine have been conducted, one in Singapore, Hong Kong, and Thailand [57] and the other in the United States. However, these results from the U.S. study must be interpreted with caution since the study was designed as a one-year study and only 84 of the originally enrolled 174 subjects (48%) agreed to continue for a second year [58].

Therapeutic Effect and Future Treatments Many of the studies summarized above show statistically significant differences between experimental and control treatments for slowing the progression of myopia, but most of the results are not considered to be clinically meaningful. Another reason why treatments may show limited benefits is because inclusion criteria for the clinical trials typically are quite broad, and all treatments, especially lenses, are not likely to work for all myopes. In part that is because many of the treatments are effective early on, but after the initial months the treatment effects may increase only minimally or not at all. It may be helpful to take into account factors such as the amount of myopia, oculomotor characteristics (e.g., accommodation, phoria), and parental refractive state when considering treatment options for a particular patient. For example, COMET showed that PALs were more effective than SVLs in children with low myopia, large accommodative lags, and two myopic parents [51,53,59].

Multiple investigations of these treatment options are presently underway for myopia. Recent animal work has suggested that visual signals from the fovea may not be essential for normal eye growth since the peripheral retina appears to be able to regulate emmetropization and induce myopia in response to abnormal visual input [59]. Treatment options not previously discussed and likely to hold promise are correction of peripheral ametropia/aberrations and provision of extensive outdoor activity. Correction of peripheral ametropia/ aberrations may be achieved by specially designed contact lenses worn during the day or by orthokeratology.

Several large studies conducted in different parts of the world have reported that the prevalence of myopia in children with more outdoor activity hours is lower than in children with fewer hours [1,61-63]. One of the simplest therapies for retarding myopia, yet to be tested in a rigorous study, could turn out to be providing children with substantial hours of outdoor activity each week, though much more needs to be learned about possible underlying mechanisms. It appears that being outdoors is more important than being active since no association has been reported between indoor sports and myopia [61]. Eventually a clinical trial evaluating outdoor activity as a possible therapy for myopia may be conducted, but this effort should wait until more is known about the source of the protective effect.

SUMMARY

Uncorrected refractive errors (e.g. myopia and hyperopia) are the most common causes of visual impairment worldwide. It is estimated that 2.5 billion people will be affected by myopia alone within the next decade. Experimental, epidemiological and clinical research has shown that refractive development is influenced by both environmental and genetic factors for the refractive errors, myopia and hyperopia. Observational data in human populations provide compelling evidence that environmental influences and individual behavioral factors play crucial roles in myopia susceptibility. Myopia, the majority of the variance of refractive error within populations is thought to be because of hereditary factors. Genetic linkage studies have mapped the dozen loci, while association studies have implicated more than 70 different genes in refractive variation. Many of these genes are involved in common biological pathways known to mediate extracellular matrix (ECM) composition and regulate connective tissue remodeling. Other associated genomic regions suggest novel mechanisms in the etiology of human myopia, such as mitochondrial-mediated cell death or photoreceptor-mediated visual signal transmission [21,64-67].

In the last years, new ideas based on animal research have emerged; Current methods have been improved and old ways rediscovered. Some of the most promising way leads to slow myopia progression. Several of those treatments have already shown good results on isolated patients or in small sample studies, such as soft bifocal contact lenses, orthokeratology or prismatic additions [68-70]. However，those findings have to be confirmed in large controlled clinical studies. Finally, as the ultimate goal of clinicians is to avoid any onset of myopia, the specific case of Pre-Myopes is discussed [71]. In a word, observational and experimental

studies have revealed the complex nature of human refractive variation, which likely involves variants in several genes and functional pathways [72,73]. Multiway interactions between genes and/or environmental factors may also be important in determining individual risks of myopia, and may help explain the complex pattern and treatments of myopia in human populations.

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