EURETINA – Review

Ophthalmologica

Ophthalmologica 2011;225:127–134
DOI: 10.1159/000317072

Received: March 3, 2010
Accepted after revision: June 3, 2010
Published online: October 16, 2010

Axial Length of Myopia: A Review of Current Research

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Key Words
Axial length · Myopia · Genetics · Refractive error · Endophenotype

Abstract
Myopia, or nearsightedness, is a worldwide common type of refractive error. It is a non-life-threatening disorder with huge social and economic consequences due to its increasing prevalence. Axial length (AL) is the primary determinant of non-syndromic myopia. It is a parameter representing the combination of anterior chamber depth, lens thickness and vitreous chamber depth of the eye. AL can also be treated as an endophenotype of myopia and may provide extra advantages in the investigation of its genetic basis. The study of AL will not only identify the determinants of eye elongation, but also provide aetiological evidence for myopia. The purpose of this review is to outline the current state of AL research. Epidemiological evidence, genetic determinants, the relationship with other eye components and relative animal models of AL are summarised.

Introduction

Myopia is a major threat for vision health across the world. It is responsible for around 75% of the refractive-error-related complications, with serious social and economical consequences [1, 2]. Patients with severe forms of myopia or high myopia are more susceptible to other ocular abnormalities such as lacquer cracks, retinal detachment, chorioretinal atrophy and glaucoma [3]. In Western Europe, the estimated prevalence of myopia is over 25% [3]. Similar results have been reported in some regions such as the Middle East and South America. Table 1 summarises myopia prevalences of middle-aged groups in different areas [3–12]. Those studies revealed a relatively higher morbidity of myopia in some East Asian countries. The difference was found to be greater if preschool and school age children were evaluated (table 2) [13–24]. Studies on schoolchildren in Hong Kong and medical students in Singapore even revealed extremely high prevalences of 82% and 90% [25, 26]. According to a recent report from the World Health Organisation, the number of people who have visual impairment caused by myopia and other ocular disorders reached over 161 million in 2002 whereas some researchers worried that this figure was greatly underestimated [27, 28].

Myopia can be classified using different criteria [29]. For example, physiological myopia and pathological myopia are differentiated by the presence of degenerative changes and the value of the refractive error (normally in diopters). Based on the age of onset, myopia can also be divided into 3 groups: youth-onset myopia (less than 20 years old), early adult-onset myopia (aged between 20 and 40) and late adult-onset myopia (over 40 years old). Other classifications include: axial myopia and non-axial my-

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Table 1. Prevalence of myopia and high myopia in middle-aged populations

Country or region	Sample number	Age distribution, years	Definition of		Prevalence of	
			myopia, dpt	high myopia, dpt	myopia, %	high myopia, %
Japan [4]	3,021	58.4 ± 11.8	<–0.5	<–5	41.8	8.2
Iran [5]	1,367	63.7 ± 7.1	<–0.5		27.2	
Bangladesh [6]	11,624	44 ± 12.6	<–0.5	<–5	22.1	1.8
China, north [7]	6,491	>30	<–0.5	<–5	26.7	1.8
China, south [8]	1,269	>50	<–0.5	<–5	32.3	5
India [9]	3,642	>40	<–0.5	<–5	34.6	4.5
Singapore [10]	1,113	>40	<–0.5	<–5	38.7	9.1
Europe, west [3]	6,543	>40	<–1	<–5	26.6	4.6
USA [3]	14,414	>40	<–1	<–5	25.4	4.5
Australia [3]	8,324	>40	<–1	<–5	16.4	2.8
Norway [11]	1,889	40–45	<–0.5		30.3	
Spain [12]	417	40–79	<–0.5		25.4	

Age distribution is preferred to be presented as means ± standard deviation. If the references did not provide such information, then other forms of age range are shown.

opia; low myopia (0 to –3 dpt), moderate myopia (–3 to –6 dpt) and high myopia (<–6 dpt); syndromic myopia and non-syndromic myopia. To some extent, a graded classification is artificial. In the genetic domain, non-syndromic myopia can be separated into 2 categories: myopia following complex traits, which is determined by both genetic and environmental factors; myopia showing a mendelian pattern of inheritance (autosomal dominant, autosomal recessive and so on), which is normally found by family studies and mainly caused by genetic mutations.

Axial Length

There are 4 ocular structures contributing to the refractive status of a given human eye, including the cornea, aqueous humour, lens and the vitreous humour. Myopia and other refractive-error disorders are consequences of uncoordinated contributions of ocular components to overall eye structures. In other words, the cornea and lens fail to compensate for axial length (AL) elongation (myopia) or shortening (hyperopia). Thus, parameters closely linked to measurements of these parts such as corneal curvature, anterior chamber depth (ACD), lens thickness, vitreous chamber depth and AL are widely evaluated in the study of eye diseases [30]. Among these components, AL received most attention since it is a main parameter for both myopia and hypermyopia [30].

As early as the mid last century, researchers found that AL showed a bimodal distribution in an adult myopic population [31]. When grouping samples in 2 categories, a first peak appears around the AL of 24 mm for low myopia (–6 dpt < refractive error < 0 dpt) while the second peak appears roughly at the AL of 30 mm for high myopia (refractive error <–6 dpt). This indicates that the physiopathological mechanisms of different severities of myopia may differ and partly explains why it is necessary to separate myopia cases according to the severity to explore its genetic basis. Meanwhile, the distribution of AL is reported to be positively skewed in the general population, and it is under a normal distribution in some selected cohorts [32, 33]. Table 3 shows a summary of AL and its corresponding refractive error in multiple populations from different countries [33–39]. Nowadays, ophthalmologists use ultrasound velocity reading machinery and optical partial coherence interferometry to determine the AL of their patients to clarify the severity of myopia. Most agree that AL is the largest determinant of refractive error [40]. A great number of reports have shown a negative relationship between AL and myopia. In other words, the longer the AL, the severer the myopia [41, 42]. Olsen et al. [35] found that when considering the contribution of AL, lens power and corneal power together, using multiple linear regression analyses, it can explain up to 96% of the variation of refraction in populations. Age-related AL differences were discovered in some investigations. Older people were likely to have shorter AL than younger par-

Table 2. Prevalence of myopia in preschool and school age children

Country or region	Sample number	Age distribution	Definition of myopia dpt	Prevalence of myopia %
Singapore [13]	3,009	6–72 months	<–0.5	11.0
USA				
Urban and white [14]	1,030	6–71 months	<–1	0.7
African [15]	2,994	6–72 months	<–1	6.6
Hispanic [15]	3,030			3.7
Australia [16]				
Urban	322	11–14 years	<–0.5	17.8
Rural	270			6.9
China [17]	1,892	14.7 ± 0.8 years	<–0.5	*62.3*
Iran [18]	815	6 years	<–0.5	1.7
UK [19]	7,600	7 years	<–1	1.1
Singapore [20]	631	7 years	<–0.5	29.0
	470	8 years		34.7
	352	9 years		*53.1*
Poland [21]				
Urban	1,200	11.9 ± 1.4 years	<–0.5	13.7
Rural	1,006			7.5
Indian [22]				
Urban	1,789	7–15 years	<–0.5	*51.4*
Rural	1,525			16.7
Sweden [23]	143	4–15 years	<–0.5	6.0
Malaysia [24]	705	6–12 years	<–0.5	5.4

Age distribution is preferred to be presented as means ± standard deviation. If the references did not provide such information, then other forms of age range are shown. The highest 3 are italicised.

ticipants [38]. Warrier et al. [34] suggested that these differences were related to cohort effects. For example, near work was more intensive in the younger age group, which is a factor increasing AL probably due to a defocus-induced disturbance of emmetropisation [43]. However, the Los Angeles Latino Eye Study did not reveal an age-related AL difference based on a population of 5,588 participants over a period of 40 years [44]. Meanwhile, it is well agreed that women tend to have a shorter AL [34, 35], partly explained by stature [45]. AL has some predicted values for the onset of myopia but only within the 2–4 years preceding onset [46]. It reaches its fastest rate of change during the year before the onset of myopia and then axial elongation follows relatively slowly, with more stable rates of change after onset [46].

AL and Ocular Biometric Components

The visual system is not well developed until 3 years of age. In general, AL increases rapidly in the early stage of life, then slowly increases until adulthood, then decreases in old age. Data from Biino et al. [33] showed a quadratic relationship between AL and age. A cohort study reported that the average axial length for full-term infants increases from 16.8 to 23.6 mm when they become adults [47]. This increase in AL would cause a serious shift to myopia, which was however offset by corresponding changes in other parts of the eye structure. For example, the lens will reduce its refractive power when AL increases [48]. A 1-mm elongation of AL without other compensation is equivalent to a myopia shift of –2 or –2.5 dpt. Evidence shows that each component of the visual system has close interaction with the other components during the maturation process. Lambert [49] deduced from animal experiments that if the lens were removed from human eyes at an early stage (within the first 2 months), a retardation of eye growth would occur. Human data also support the contention that the AL of eyes after cataract surgery is shorter than in age-matched controls [50, 51], although some authors have observed opposite effects [52]. A decrease in lens power is correlated with the elongation of AL but knowledge on whether this is an active or a passive emmetropisation process is rather limited to make a decisive conclusion [53]. AL was also reported to be significantly negatively correlated with corneal power and documented to have a positive correlation with ACD and a negative correlation with lens thickness [35, 54–56]. Osuobeni [55] suggested that the ratio between AL and corneal radius may be a better indicator of myopia. AL undergoes diurnal fluctuation of around 15–40 μm, with a mean period of approximately 21 h [57]. The maximum AL appears at midday. It is reasonable to hypothesise that this phenomenon is caused by the daily change of intraocular pressure (IOP) since IOP follows diurnal fluctuation as well [58]. However, this assumption is under debate [58, 59]. Read et al. [59] found the association between the change in AL and the change in IOP while no evidence was found by Wilson et al. [58] that IOP fluctuation appears to cause diurnal AL fluctuation.

AL and Genetic Determinants

Myopia can be treated as a mendelian trait, caused by a single gene, or a complex trait, affected by multiple genetic factors and environmental factors depending on the

Table 3. AL information and its corresponding refractive error in middle-aged populations

Country or region	Supplemental information	Age distribution years	Study type	Sample number	AL mm	Corresponding refractive error dpt
Sardinia, Italy [33]	right eye left eye	41 ± 19	family	741	23.57 ± 1.15 23.51 ± 1.06	–0.27 ± 2.11 –0.24 ± 1.78
Myanmar [34]	male female	56.2 ± 11.5	population	605 893	23.12 ± 0.98 22.54 ± 1.04	–1.33 ± 3.40 –1.16 ± 3.12
Denmark [35]	male female	67.9 68.1	population	325 398	23.74 ± 1.01 23.20 ± 0.98	1.05 ± 2.19 1.28 ± 2.12
Mongolia [36]	male female	40–49	population	241 368	23.40 ± 1.30 23.00 ± 1.30	0.10 ± 1.80 –0.30 ± 1.60
Jordan [37]	male female	29.3 ± 7.45 27.4 ± 6.45	population	450 643	23.33 ± 1.02 22.99 ± 0.97	–0.74 ± 1.84 –0.95 ± 1.58
Singapore [38]	male female	>40	population	457 547	23.54 ± 1.10 22.98 ± 1.16	–0.40 ± 2.41 –0.56 ± 2.89
Australia [39]		46.5 ± 19.6	family	723	25.53 ± 1.50	–2.10 ± 3.12

Age distribution is preferred to be presented as means ± standard deviation. If the references did not provide such information, then other forms of age range are shown.

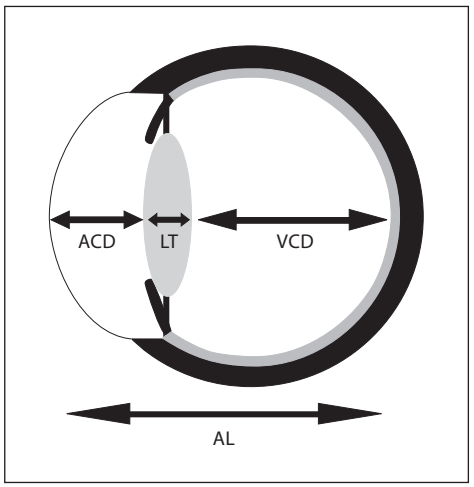

Fig. 1. Illustration of AL. ACD = Anterior chamber depth; LT = Lens thickness; VCD = vitreous chamber depth.

underlying mechanism. So far, more than 20 chromosomal areas have been proposed to contain potential myopia genes, but further attempts need to narrow down these regions and pinpoint the corresponding genes [60]. Evidence supports strong genetic components in the determination of AL. Children with myopic parents have a higher chance of being affected and have longer AL than those without myopic parents [61]. Twin studies also demonstrated that AL is highly heritable and genetic effects can explain up to 88% of this parameter [62, 63]. Segregation analyses suggested that AL is under polygenic control [64]. Moreover, a large proportion of correlation between AL and myopia can be explained by these genetic effects, which indicates that AL and myopia may share common genes [65]. AL reflects the sum of the thickness of the lens, ACD and the length of the vitreous chamber (fig. 1) [66]. Research has shown that part of the heritability of AL is mediated by ACD [67]. In 2004, Biino et al. [33] performed a linkage analysis on extended pedigrees and discovered a locus on 2p24 possibly containing a gene for AL. Afterwards, using twin samples, Zhu et al. [68] reported the evidence for linkage of AL to the long arm of chromosome 5. To our knowledge, these were the only 2 regions reported so far for AL and have not been fine mapped yet.

AL is an endophenotype of myopia. Both AL and myopia (in refractive error) can be analysed as a quantitative trait using linkage studies. However, AL is much more suitable. The phenotype of myopia, especially high myopia, is commonly accompanied with other eye disorders

Table 4. Heritability comparisons between AL and myopia

Trait	Heritability		
	twins	sibs	nuclear families
AL [65]	0.88	0.73	0.75
Myopia [39]	0.82	0.50	0.21

Table 5. Comparison between heritability of AL and heritability of refractive error (RE)

Country or region	Study type	Heritability of AL, %	Heritability of RE, %
Sardinia, Italy [33]			
Male	family	60	18–27
Female	family	31	
Taiwan [70]	twin	67	33
	twin	94	89–91
USA [67]	population	67	58
France [64]	family	20	20

Only references containing both AL and RE heritability information are selected.

such as cataract, glaucoma and chorioretinal abnormalities [69], thus would inevitably involve some confounders and may lead to biased conclusions. However, AL, as a clean trait, could be studied in general optical healthy populations and subjects with low myopia to avoid those confounders. Some reported that the heritability of myopia varies significantly among studies with different family structures, while the heritability of AL remains quite consistent (table 4) [39, 65]. Trait variance of AL caused by environmental factors was only around 6% contrasting that of myopia from 14 to 33% [39, 65]. Thus, using AL as an endophenotype could avoid or minimise the substantial bias caused by a more complex myopic trait due to instability of heritability. Table 5 summarises the studies that calculated both heritability of AL and heritability of refractive error [33, 64, 67, 70]. Most studies showed a higher heritability of AL than refractive error. AL as a clean and simple endophenotype may bring some advantages to the research field of myopia. This conclusion was partly supported by the first genome-wide association study (GWAS) on myopia performed by a Japanese group [71]. In addition to using general populations as controls, they defined high myopia as AL >28 mm regardless of refractive error information. A susceptible locus on 11q24.1 was then discovered by this case-control GWAS approach.

AL and Myopia Animal Models

It is well confirmed that ocular growth is affected by the quality of visual experience during early life. Failure to induce myopia in dark-reared animals suggests that visual experience is a trigger of eye growth [72]. Animal models of myopia have been successfully established in several species including the monkey, tree shrew, marmoset, chick and the pig [30]. Various methods can be applied to achieve myopia, such as form deprivation, minus lens-induced optical defocus and restricted visual environment conditions [30]. Eyes with induced myopia were observed to have longer AL. For example, negative lenses produce hyperopic defocus and increase the rate of eye growth in monkeys [73]. Conversely, positive lenses lead to myopic defocus and decrease eye growth [74]. It is worth mentioning that such eyes with induced myopia showed evidence of recovery when the inducing factors were removed, and this recovery was inversely related to age [75, 76]. The monkey eyes showed evidence of strong recovery ability. Even 1 h/day of unrestricted viewing can reduce around 50% of the myopia induced by a 17-week period of deprivation [77]. This suggests the existence of an active emmetropisation mechanism, which controls the location of the retina by remodelling of the sclera so that images can be focused on the focal plane [78]. A molecular signalling cascade seems to be involved in this process. This is probably through the neuro-epithelium and the choroid, and involves a remodelling of the scleral extracellular matrix. In turn, this would cause AL to increase due to lengthening of the vitreous chamber [79, 80]. Scientists are working on strengthening the sclera in order to prevent the elongation of AL. One method is called collagen cross-linking, which will generate a more stable internal structure of the sclera by inducing intra- and interfibrillar collagen cross-links [81]. Physical cross-linking by combined riboflavin-ultraviolet or riboflavin-blue light and chemical cross-linking by glyceraldehydes, glutaraldehyde and aliphatic β-nitro alcohols were proven to increase biomechanical strength in both human and animal sclera [81–85]. Compared with other treatments of myopia, cross-linking would correct a cause instead of an effect. However, severe side effects can happen to other ocular structures such as the retina and cornea when cross-linking [81, 82]. Recently, successful cross-

linking approaches without severe side effects were reported by Wollensak and Iomdina [86, 87]. Chick models on axial myopia also suggested the involvement of genes controlling body size [88].

Questions Requiring Answers in the Future

Myopia, as a complex trait, is influenced by both genetic and environmental factors. However, none of the myopia genes have been confirmed so far despite multiple candidate loci being proposed. Currently, 18 regions from MYP1 to MYP18 have been approved by the HUGO Gene Nomenclature Committee. These regions were well described by Tang et al. [60] except the latest one – the MYP18 region. This spans from 14q21.1 to 14q24.2 and was recently found in a consanguineous Chinese family [89]. This is the first report of an autosomal recessive inheritance model of high myopia.

Candidate genes such as *PAX6, MFRP, MYOC, MMP, UMODL1* and collagen genes have been studied on single or multiple single-nucleotide polymorphism bases [90]. These candidates have good biological evidence to participate in the process of myopia genesis or progression. For example, polymorphisms in the *MMP* genes may affect the activities of enzymes degrading matrix proteins and modulate sclera extensibility. However, lessons from GWAS studies on other complex traits such as coronary heart disease showed that most of the traditional candidate genes with solid biological connection with the trait could not be replicated in the GWAS [91]. And those discovered loci were not previously suspected as candidates [91]. GWAS is a good approach to detect major genes for myopia and sheds light on the molecular basis of this disorder as well as identifies possible pathways. However, special care needs to be taken when designing GWAS to avoid possible confounders.

It still remains unclear as to what roles the environmental factors play in relation to human myopia. Are they only triggers or decisive factors? It has been suggested that environmental factors such as extensive near work act as triggers of myopia [29]. The expression of *AL* genes activated by environmental factors leads to the elongation of AL. In environments of extensive near work, such as some high schools in East Asia, where students perform more reading and writing due to higher education pressure, a case-control GWAS study design would be helpful to discover trigger genes for axial myopia or in other words, genes for AL. Sorsby and Leary [92] suggested that ocular growth ceases around the age of 14–15 years based on a cross-section study involving 1,500 individuals aged from 3 to 22 years. On the other hand, myopia progress will not stop until the mid twenties for those hard-working students. In these 10 years, adolescents will experience significant changes due to pubertal development. Then the question is whether anything related to puberty, for example endocrine changes, will also affect the progress of myopia or the elongation of AL. If the extensive near work occurs after the age of 30 years, will it have the same consequence as when it occurs in teenagers? Why does AL generally decrease in the old? Is this process a simple reversal of axial elongation or completely caused by a different mechanism?

Animal models have provided useful and interesting theories concerning myopia and AL but species-specific differences in ocular structures make current extrapolations to human eye development somewhat tenuous. Creative new studies of myopia and its primary determinant, AL, will be able to provide valuable predictive information and effective treatment of this widespread disorder.

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