Myopia: Gene-environment Interaction

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Abstract

Introduction*: Myopia has reached epidemic proportions in Japan, Hong Kong, Taiwan and Singapore. This review summarises the evidence for environmental and genetic factors as well as gene-environment interaction for myopia for both epidemiologic studies as well as animal models. *Methods*: A literature review was conducted after a Medline search on articles on the genetic or environmental aetiology of myopia in animal or epidemiologic studies. Articles on the methodology of gene-environment studies were also reviewed. All articles reviewed were articles published in peer-reviewed journals. *Results*: Cross-sectional studies have found a positive association between myopia and near work activity such as reading and writing. Likewise, laboratory research has shown that environmental factors such as visual deprivation may lead to the development of myopia in animals. While linkage studies in humans are currently being conducted to identify possible markers for myopia in the human genome, several neurotransmitters, modulators and growth factors that influence refractive development have already been identified in animal models that may help identify candidate genes. Epidemiologic studies have also evaluated the combined effects of hereditary factors, environmental factors and gene-environment interaction on myopia development. *Conclusions*: Both genes and environmental factors may be related to myopia. There are no conclusive studies at present, however, that identify the nature and extent of possible gene-environment interaction. Further linkage analysis, affected sib-pair studies, and family-based association studies may better identify the nature of gene-environment interaction.

***Ann Acad Med Singapore* 2000; 29:290-7**

Key words: Animal models, Epidemiology, Near work activity, Refractive errors, Twin studies

Introduction

Myopia affects up to 70% of adults in Singapore, Taiwan, Hong Kong and Japan.[1,2] The prevalence rates in these Asian countries are higher than those among Caucasians and Blacks in the United States and Europe.[3-5] All myopes, even those with the lowest degree of myopia, are encumbered with both the physical and financial burden of wearing spectacles or contact lenses as well as frequent optometry visits.[6] In addition, myopia, especially high myopia (<–6.0 diopters), may be associated with myopic macular degeneration, retinal detachment, glaucoma, and cataract.[7]

Interpretation of population-based studies is hampered by issues of definition. When treated as a qualitative trait, there is no uniformly accepted definition of myopia.[7] Generally in different reports, the mean spherical equivalent refraction defining myopia varies between less than –0.25 to less than –1.0 diopters. Rather than defining myopia as a qualitative trait, other researchers have evaluated refractive errors measured as a continuum and examined factors that shift the population curve. In myopes, biometrics information has shown that there is vitreous chamber elongation, deeper anterior chambers and thinner crystalline lenses.[8] Central corneal curvature may also vary with

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refractive error.[9-11] No uniform classification system exists for myopia either, with current schemes variably based on severity of myopia, the co-existence of retinal pathology, age of onset or hypothesised mechanisms of pathogenesis.[12] We know little about the factors involved in eye growth. There are several conflicting and diverse theories on the pathogenesis of myopia. The "nature versus nurture" debate continues whereby some myopia researchers have found that myopia is due to both genetic and environmental influences.[13-15] Environmental influences such as reading, writing, distance, and posture may work in tandem with genetic factors to cause myopia. No genetic or environmental factor works in isolation, and most now accept that the aetiology of myopia is complex in nature, involving the interaction of environment and genetics.[7] It seems probable that gene-environment interaction exists where genetically predisposed children are influenced by environmental factors in modern society resulting in high rates of myopia.[15,16]

In this review, evidence from epidemiologic studies and laboratory research studies for specific environmental and genetic factors in the development of myopia are summarised. We also explored the epidemiologic studies that have examined possible gene-environmental risk factors for myopia. This review is based on published studies in Medline.

Environmental Factors

The concept that environment factors influence ocular development and contribute to the development of myopia is well supported by both clinical and laboratory studies.

Epidemiological Data

Many societies have experienced a period in which the prevalence of myopia increased at a rate too rapid to be explained solely by genetic factors. For the Asian countries of Japan, Taiwan, Hong Kong and Singapore, this rise in myopia prevalence has been marked over the last few decades.[1,2] Among Eskimos in the Arctic regions of Alaska and Canada, there similarly has been a striking increase in the prevalence of myopia.[17-19] Such rapid prevalence shifts in defined populations provide the strongest argument for an environmental factor in the aetiology of myopia.[20] An environmental factor responsible for increased myopia is commonly hypothesised to be use of the eyes for near work.[21] Typically, myopia begins to become manifest at ages when children start attending school and become involved in reading and other near work activities.[21] Myopia is also more prevalent and has a higher incidence in certain occupations such as microscopists, visual display terminal workers, and carpet weavers.[22-25]

Most epidemiologic studies that have been conducted are cross-sectional in nature and have not been able to establish whether near work may result in myopia or whether children with myopia have difficulty seeing far and thus tend to do more near work.[26-29] Furthermore, the measures of near work e.g. school attendance, reading a paper or book in the past week, are crude estimates at best. A questionnaire has been developed by Saw et al[30] to document the different types of near work activity during the different times of the year, distances of the object from the eyes, posture, and lighting conditions.

Table I provides examples of epidemiologic studies that have examined the relationship between near work activity or its parameters such as night light and myopia. In Jerusalem, the prevalence of myopia in 175 males from orthodox schools was 81.3% compared to 27.4% in 193

TABLE I: SUMMARY OF EPIDEMIOLOGIC STUDIES OF READING, WRITING AND MYOPIA

Author (year)	Type of study	Exposure measurement	Disease/Health outcome measurement	Study results
Richler (1980)	Cross-sectional (n = 957)	Near work as hours per day on reading, sewing, knitting	Retinoscopy with fogging	For every hour increase in near work per day, the refractive error increases by –0.22diopters, adjusting for age, sex, and education
Zylbermann (1993)	Cross-sectional (n = 870)	Type of school attended: orthodox versus general	Refraction using the fogging technique (refractive error at least –0.50 diopters)	81.3% of orthodox males are myopic compared to 27.4% of males in general schools
Wong (1993)	Cross-sectional (n = 408)	School attendance	Retinoscopy with fogging (refractive error at least –1.0 diopter)	Odds ratio of myopia for school attendees was 1.7 (95% confidence interval 1.0,3.0)
Parssinen (1993)	Cohort study (n = 238)	Reading and writing (hours per day)	Cycloplegic refraction	Myopia progression was faster for children who spent time on reading and writing (P = 0.004)
Quin (1999)	Cross-sectional (n = 479)	Night time light during the first two years of age	Cycloplegic refraction	Myopia rates are higher for children with night time light

males from general schools.[29] The authors attributed the higher myopia rate in students from orthodox schools to the variety of print size, frequent swaying habits during study, and the increased number of study hours. In a cross-sectional study of 408 men and women aged 15 to 39 years in a Hong Kong fishing harbour during the Chinese New Year period, the odds ratio of school attendance in myopes was 1.7 (95% confidence interval 1.0,3.0).[28] The refraction errors were measured without cycloplegia and the measures of near work were crude. In a population-based study of 957 persons aged 5 years and above in Newfoundland, the partial correlation coefficient for refraction and near work, controlling for age, sex and education, was –0.38 for subjects aged 30 to 44 years, and –0.21 for those aged 45 to 59 years.[27]

Many environmental factors other than near work activity and their parameters may be at work. It has been suggested that personality, intelligence and stress may be related to myopia development. However, the results from the different studies are conflicting.[31-33] The evidence for diet, height, and prematurity and myopia onset is also not convincing.[34-36]

A recent report has proposed that artificial lighting at night might constitute a new potential risk factor for myopia. The prevalence of myopia including high myopia was found to be higher in children who slept at night with room lighting during the first two years of life.[37] This study suggests that the lack of absolute darkness at night may lead to the development of myopia in very young children. This study is limited by its cross-sectional nature, and it needs to be generalised to other population groups. Nonetheless, it does identify another feature of the environment in modern societies that might adversely affect eye growth and could provide a stimulus for productive future research.

Laboratory Research

Besides the above clinical findings, observations from animal experimentation also lend credibility to the hypothesis that the environment may have some influence on myopia development. By employing different experimental methods, researchers have successfully induced myopia in many animal species including chickens, squirrels, cats, tree shrews and several types of monkeys.[38-41]

Initial efforts to induce myopia in animals were based on the near work hypothesis derived from clinical studies. In a series of experiments on monkeys, Young[42] induced only a modest amount of myopia by rearing monkeys in an environment with restricted visual space limited to a mean distance of 38 cm. More pronounced myopia can be induced in juvenile animals by depriving the eyes of clear visual input. This so-called form deprivation myopia has been studied in chicks, squirrels, tree shrews and monkeys.[38-41] This model has established that the control mechanism for eye growth is dependent on vision, largely local within the eye and likely involves the participation of specific retinal neurons. When subsequently studied in children, it was found that human disorders obstructing visual input such as ptosis or vitreous haemorrhage also induced eye growth and myopia in early childhood.[43-46] Thus, while not the mechanism for the common myopias, form-deprivation myopia can develop in humans. It has actually been hypothesised that reading might be a form of visual deprivation because printed material fails to stimulate retinal photoreceptors other than those in the macular area and hence human myopia occurring as a result of prolonged reading may be due to an absence of neural activity.[36,47]

The relevance of form-deprivation myopia to the common human condition has been questioned because it is most robust in the neonatal and early juvenile ages and progresses at a very rapid rate.[48] Recent studies have, however, demonstrated that form-deprivation myopia can be induced at later developmental stages in chicks, monkeys and marmosets and progresses at a rate more compatible with the clinical course of human myopia.[49-51]

Further support for the concept that visual input guides refractive development comes from wearing of spectacle lenses in chicks, tree shrews and monkeys alters ocular growth. Specifically, the wearing of concave lenses to displace distant images behind the retina stimulates ocular growth, and the wearing of convex lenses to displace distant images in front of the retina retards ocular growth.[52]

As an experimental model, form-deprivation myopia has facilitated direct study of the retina to try to understand the biological mechanisms regulating eye growth. Varying degrees of evidence implicate a broad range of retinal neurotransmitters and modulators in the mechanism regulating eye growth, such as dopamine, acetylcholine, glutamate, vasoactive intestinal peptide and basic fibroblast growth factor.[53-60] The available evidence cannot easily be incorporated into a model explaining the retinal circuitry controlling eye growth. Nor is it now known how these data in animals with form-deprivation myopia relate to the mechanisms underlying the common human myopias. Nonetheless, such findings might provide clues to help identify candidate genes that explain the environmental/genetic interactions in myopia pathogenesis.

Form-deprivation myopia in animals has also enabled the study of biochemical changes in the sclera and choroid. In myopic chick eyes, synthesis and accumulation in extracellular matrix protein and collagen as well as proteoglycans in the posterior sclera were significantly increased.[61-63] In tree shrews, active scleral metalloproteinase MMP-2 level increased 3-folds in myopic eyes and reduced

5-folds in recovering eyes.[64] The content and concentration of basic fibroblast growth factor (bFGF) and transforming growth factor -beta (TGF) were significantly changed in the sclera in the posterior region of the myopic eyes compared with those in control eyes.[65-67] Thus, the work in animals has studied biochemical responses in the sclera. Once there is human linkage to chromosome sites, candidate genes might be suggested by this work.

Genetic Factors

Epidemiologic Studies

There is little doubt that genetics play an important role in the growth and development of the eye. Inter-ethnic differences such as a higher prevalence rate of myopia in Chinese and Japanese compared to Africans and African Americans suggest that genetic factors contribute to myopia development.[21] The prevalence of myopia in Hawaii varied between a rate of 17% in Chinese, to 13% in Koreans, to 12% in Japanese, and 12% in Caucasians.[68] In a recent study by Lin et al[69] in Taiwan, they found that the myopia rate in aboriginals was 13% compared to 65% in children of Chinese descent.

Several family studies and twin studies have demonstrated that hereditary factors are important for myopia development. Table II summarises the findings from twin, family studies, and linkage analysis studies. One of the first twin studies was conducted by Sorsby where the coefficients of correlation approached unity for the 78 pairs of uniovular twins, 0.5 for the 40 pairs of biovular twins and zero in the 48 unrelated subjects.[70] In several later twin studies, monozygotic twins who share 100% of the genes had a higher concordance rate for myopia compared to dizygotic twins who share 50% of the genes.[71-74] Proof for heritability of myopia comes from two sources: 1) a greater percentage of concordant pairs among monozygotic twins was found compared to dizygotic twins;[75] 2) the correlation in liability was higher (0.94) among monozygotic twins compared to a 0.65 among dizygotic pairs. Liability refers to the genetic predisposition and the environmental circumstances which render a person to develop a disorder.

Parental history of myopia is also another risk factor for myopia development. The prevalence of larger eyes is greatest in children with both myopic parents (40%), and least in children with no myopic parents (10%).[76] The prevalence of myopia in the children with one or two myopic parents is 2- to 4-fold higher than that of children with no myopic parents.[77,78] Sorsby et al reported that correlations for refractive error were 0.07-0.25 and 0.25-0.45 for parent-offspring and siblings, respectively.[79-83]

Based on work on the retinal and scleral biochemistry in animals, chromosomal linkages may be made, genes related to either the retinal or scleral biochemistry in those chromosome areas might be useful as candidate genes. Recently, Young et al[84,85] mapped two genetic loci for high myopia to 18p11.31 and 12q21-23, respectively. They conducted a genome-wide screen for myopia susceptibility loci in families with an autosomal dominant pattern of myopia. The definition of myopia (myopia <–4.5 diopters), however, does not conform with the usual criteria and the sample size was small. Significant linkages to 18p11.31 and 12q21-23 were found, with the maximum lod score of 9.59 (= 0.0010) and 3.85 (= 0.0010), respectively. Evidence of genetic heterogeneity was demonstrated.

Laboratory Research

Data from several animal studies highlight the likely importance of both breed and strain, and hence genes, as factors influencing susceptibility to alterations in the environment such as form-deprivation.[86-88]

Results from chick studies indicate that genes can influence the eye's susceptibility to environmental factors that alter refractive development. Marked strain and/or breed differences have been detected in the ocular growth response to visual form deprivation and to changes in photoperiod.[87] These genetic differences are manifest not only in overall refraction but by complex effects on anterior chamber depth, vitreous chamber length and axial length. These strain and breed differences presumably reflect underlying genetic differences.

Zhu et al[89] evaluated the eye growth and refractive

TABLE II: SUMMARY OF SELECTED TWIN STUDIES AND FAMILY LINKAGE STUDIES FOR MYOPIA

Author (year)	Type of study	Sample size	Observation
Hu (1981)	Twin study	49 monozygotic twins; 37 dizygotic twins	Concordance rate of myopia in monozygotic and dizygotic twins is 0.82 and 0.25, respectively. The heritability index is 0.6.
Lin & Chen (1987)	Twin study	90 monozygotic twins; 36 dizygotic twins	Concordance rate of myopia in monozygotic and dizygotic twins is 0.65 and 0.46, respectively. The heritability index is 0.24.
Telkari (1991)	Twin study	54 monozygotic twins; 55 dizygotic twins	Concordance rate of myopia in monozygotic and dizygotic twins is 0.8 and 0.51, respectively. The heritability index is 0.58.
Young (1998)	Family linkage analysis	8 families with at least 2 affected subjects	Significant linkages to 18p11.31 and 12q21-23 were found with the maximum lod score of 9.59 and 3.85, respectively.

development of male and female chicks. The visually deprived eyes of male chicks developed more myopia and had deeper vitreous chambers than female chicks. The finding of sex-based differences in ocular reactivity to visual deprivation may add to the evidence that genetic factors, in addition to possible endocrine factors, may play a part in myopia development. In summary, the strongest argument from animal studies for a genetic component comes from strain/breed effects in chicks and perhaps sex differences.

Gene-environment Interaction

Introduction

New tools have been developed to assess both environmental risk factors as well as genetic factors for disease whereby traditional epidemiologic methods are now combined with new advances in molecular genetic techniques such as linkage analysis to determine possible gene-environment interaction.[90-92] Gene-environment interaction has been defined as "a different effect of an environmental exposure on disease risk in persons with different genotype."[93]

Epidemiologic Studies

Studies of possible gene-environment interaction for myopia are limited (Table III). To date, the most conclusive evidence is from the study by Chen et al[74] wherein 361 same-sex twin pairs aged 10 to 15 years were recruited from preliminary and junior mid-schools in Taiwan. The study examined 122 male monozygotic, 116 female monozygotic, 61 male dizygotic, and 58 female dizygotic twin pairs. Myopia was diagnosed by retinoscopy after cycloplegia, and any twin pair with a difference in myopia of less than 0.5 diopters was defined as concordant; otherwise all other twin pairs were defined as discordant for myopia. Questions on the number of hours of studying and reading per day were asked and twin pairs with a difference of less than one hour were classified as concordant; otherwise the twin pairs were classified as discordant for reading and writing. A higher myopia concordance rate (92.2%) was found in monozygotic twins with concordant reading and writing habits than in monozygotic twins with discordant reading and writing habits (79.3%). There was significant additive interaction as the myopia concordance rate for monozygotic twins concordant for reading and writing was 92.4%, monozygotic twins discordant for reading and writing was 79.1%, dizygotic twins concordant for reading and writing was 62.03%, and dizygotic twins discordant for reading and writing was 37.8%.

A cross-sectional study was nested in a cohort study of 716 children in Orinda, California.[76] A mailed questionnaire was used to document the number of hours spent on reading, watching television and video games. The refractive errors and biometry of the children were measured using autorefractors and A-scan ultrasound, respectively. In this study, prevalent cases of myopia were excluded and children with two myopic parents had longer eyes. There was no statistically significant association between near work and myopia or any statistically significant interaction between near work or parental history of myopia in the pre-myopic school children.

Suggested Future Studies on Gene-Environment Interaction

Traditional Epidemiologic Studies

A cohort study may be designed wherein environmental factors such as reading and writing, and genetic factors such as genetic markers are concurrently measured in the same population. Statistical techniques may then be used to examine the interaction between environmental and genetic factors for myopia in the same subjects.

Case-control Studies with Two Types of Controls

Case-control studies of myopia where controls are chosen from relatives of cases as well as unaffected persons in the population or hospital may demonstrate gene-environment interaction.[90] In the study design, the genetic markers and relevant environmental risk factors are examined as independent factors and as interacting factors. The odds ratios of environmental factors such as reading and writing for relatives as controls may be different compared to using population-based controls if there is an interaction between genes and reading or writing.

TABLE III: SUMMARY OF STUDIES OF GENE-ENVIRONMENT INTERACTION FOR MYOPIA

Author (year)	Type of study	Genotype assessment	Environment assessment	Evidence of gene-environment interaction?
Chen (1985)	Twin study (361 same-sex twins)	Monozygotic and dizygotic twins (zygosity)	Number of hours studying and reading per day in a questionnaire	Yes. Monozygotic twins with concordant reading habits were significantly more concordant in myopia than dizygotic twins
Zadnik (1994)	Cross-sectional study	Parental history of myopia	"Diopter hours" for reading, writing, video games, and watching television	No gene-environment interaction found

Family-based Association Study

Association analysis may be a more sensitive test for linkage between genetic markers and disease. The case–parental study design considers the alleles found in the parents of an affected offspring, and compares the alleles from parents transmitted (case alleles) and untransmitted (control alleles) to the offspring (transmission disequilibrium tests). To study gene-environment interaction, the offspring (case alleles) are stratified according to their environmental exposure status (e.g. reading and writing), and any difference in odds ratios will demonstrate a multiplicative effect.[94-96]

Affected Sib-pair Studies

Affected sib-pair studies test for increased marker similarity in affected sib pairs. Under random segregation, the expected distribution of sharing 0, 1 or 2 alleles is 25%, 50% and 25%, respectively, between the siblings identical by descent. Departure from this distribution suggests linkage between the disease and the genetic marker.[97] The odds ratio of myopia for individuals who read and write more is calculated for different strata of allele sharing. Difference in odds ratios of myopia for individuals who read and write more in the various strata of allele sharing (0, 1 or 2) may indicate an interaction between genes (allele sharing) and environment (reading and writing).

Studies of Twins Reared Apart and Together

The concordance for myopia for monozygotic twins reared together, monozygotic twins reared apart, dizygotic twins reared together, and dizygotic twins reared apart may be additionally assessed to evaluate for interaction.[98] If gene-environment interaction is present, the concordance rate for myopia for monozygotic twins reared together would be higher than expected. There may be larger variation in environmental influences for twins reared apart. The possible diverse differences of environmental factors for twins reared apart may be essential in examining the influences of genes and the environment.

Conclusion

On-going research studies have examined the possible environmental and genetic factors that may be related to myopia. Many questions remain unanswered. Are there other risk factors besides near work that may cause myopia? Do different environmental risk factors act at different ages? Are there different genetic determinants for the different environmental risk factors? Both gene and environmental factors appear to work in tandem to cause myopia. The exact nature and contribution of the genetic and environmental factors is still a puzzle. We also believe that identifying the gene-environment interaction may be possible and that we need to systematically evaluate the evidence in animal model work and human studies. In Asian societies, the demands of an increasingly vigorous educational system coupled with possible genetic predisposition may result in escalating myopia rates in the region.

There are several limitations of studies to determine the gene-environment interaction.[98] There may be misclassification of environmental factors (reading and writing) or inaccuracies related to the measurement of genetic markers. In reported family history, there may be misclassification of siblings as non-myopic children at a young age may develop myopia later in life. There may also be confounding of gene-environment interaction whereby other factors such as age or ethnicity may act as a confounder resulting in a spurious relationship.

How would a better understanding of gene-environment interaction for myopia have public health implications in society? Preventable environmental risk factors such as posture or lighting conditions in society may also be identified and therefore, we may introduce changes in behaviour in individuals who are genetically susceptible to the disease. A good understanding of the nature of the interaction will allow us to provide health education messages for disease prevention in persons with the high-risk genotype and who spend large amounts of time reading and writing.

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