Adult-Onset Myopia: The Genes in Myopia (GEM) Twin Study

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Purpose. To report the frequency of adult-onset myopia in a large cohort of Caucasian twins that were assessed as part of the Genes in Myopia (GEM) twin study and to quantify the genetic contribution in adult-onset myopia using the classic twin model.

Methods. All twins aged 18 years or older were invited to participate in the GEM twin study through the Australian Twin Registry (ATR). Each twin completed a standard questionnaire and underwent a comprehensive eye assessment, including cycloplegic objective examination. Adult-onset myopia was defined as having the first spectacle/contact lens correction at the age of 18 years or older. Myopia was defined as spherical equivalent worse than or equal to −0.50 D.

Results. A total of 1224 twins (690 monozygotic [MZ] and 534 dizygotic [DZ]) between 18 and 86 years of age were recruited into the GEM study. A total of 96 twins (96/347 = 27.7%) comprising 50 MZ and 46 DZ twins were first prescribed optical correction for myopia at the age of 18 years or older. A significantly higher MZ intrapair correlation ($r = 0.61$) compared with that in DZ twins ($r = 0.16$, $P < 0.01$) for spherical equivalent was found in twins with adult-onset myopia.

Conclusions. Adult-onset myopia is a relatively common condition, with approximately one quarter of cases occurring in adulthood. To the authors' knowledge, the GEM twin study is the first study of its kind to provide evidence to support a genetic component in adult-onset myopia. (*Invest Ophthalmol Vis Sci.* 2008;49:3324–3327) DOI:10.1167/iovs.07-1498

Myopia is a common eye condition that affects approximately one in four individuals in Western populations.[1] However, the prevalence of myopia is markedly higher (over 80%) in urbanized regions of Southeast Asia, such as Singapore.[2] It is estimated that by 2020 approximately one third of the world's population will be affected by myopia.[1] As a consequence, the global initiative for the elimination of avoidable blindness (VISION 2020—The Right to Sight) has grouped refractive error as one of five leading causes of blindness and visual impairment in the world.[3]

Myopia can be categorized by severity and age of onset. Severity is often categorized as low myopia (between −0.50 and −2.99 D), moderate myopia (between −3.00 and −5.99 D), and high myopia as worse than or equal to −6.00 D.[4,5] On the one hand, a large proportion of myopia, known as childhood, early, youth, or school myopia, develops during the period of childhood to early teenage years (8–14 years).[2,6] On the other hand, it has been estimated that approximately 10% to 50% of myopia manifests during adulthood (18 years or older) and is thus commonly referred to as adult-onset myopia.[7–9] Individuals with adult-onset myopia tend to present with low to moderate myopia. High myopia has been reported to be less common than in childhood-onset myopia, possibly reflecting its later onset.[10] It should be noted that all previously published studies that have investigated adult-onset myopia have been undertaken either in students[11] or in individuals of certain occupational groups such as office workers[8] and clinical microscopists.[12] To our knowledge, no published study has reported the population-based frequency of myopia, and none has reported data representative of the general population.

Most epidemiologic and genetic studies conducted to investigate myopia have focused on youth/childhood-onset myopia, with little research into adult-onset disease. The prevalence of adult-onset myopia appears to vary significantly, depending on the demographics of the sample population being studied. For instance, in a recent study, Onal et al.[7] assessed refraction in 270 Turkish medical students and found that although approximately one third had myopia, adult-onset myopia (at 18 years of age or older) accounted for only 14.7% of the cases. In contrast, Iribarren et al.[8] examined refraction in 349 office workers in Argentina, and although they also found that 33.5% of individuals had myopia, almost half (47.8%) of cases were of adult onset. Moreover, it is important to ascertain whether adult-onset myopia is a different form, or subtype, of myopia than early-onset myopia or merely represents one end of the myopia spectrum.

The etiology of myopia is multifactorial, with evidence to suggest that genetic factors have a major role in its development, with studies of twins indicating that genetic factors may account for up to 80% of the variance found in myopia, irrespective of the age of onset.[11] However, to our knowledge, no twin study has assessed the genetic contribution to adult-onset myopia. Several family studies have shown that family history of myopia is similar between those with youth/childhood- and adult-onset myopia; therefore, genetic factors most likely influence myopia, regardless of the age of onset.[8,13] The findings in these studies have been challenged by Bullimore et al.,[14] who found no significant association of parental myopia with late-onset myopia.

To further investigate adult-onset myopia, we report its frequency in a sample of Caucasian twins who took part in the Genes in Myopia (GEM) twin study.[15] We believe that the generalizability of data from the cohort in the GEM twin study will provide a better insight into the frequency of adult-onset myopia in the general population, compared with that reported in prior selected cohorts. We also wanted to quantify the genetic contribution to adult-onset myopia by using a classic twin model. In brief, we intended to compare the similarity of the genetic contribution between youth/childhood- and adult-onset myopia through determining intrapair correlations in twins.

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METHODS

Recruitment

All twins in Victoria, Australia, aged 18 years or older were invited to participate in the GEM twin study through the Australian Twin Registry (ATR). Ethical approval for the GEM study was obtained through the Royal Victorian Eye and Ear Hospital (RVEEH) Human Research and Ethics Committee and the ATR. Written informed consent was obtained from each twin before any testing. The protocol adhered to the tenets of the Declaration of Helsinki and all privacy requirements were met.

Study Protocol

Each twin completed a standard questionnaire, and a comprehensive eye examination was administered that included a cycloplegic objective refraction. As part of the questionnaire, the age of onset of myopia was determined through information (self-reported) on the twins ocular history. Age of onset was defined as the age at which spectacles or contact lenses were first prescribed to correct the myopia.[10] Obtaining the age of onset through questionnaires has been shown to have high sensitivity (0.76) and specificity (0.74) as reported by Walline et al.[16] Moreover, adult-onset myopia was defined as having the first spectacle/contact lens correction at 18 years of age or older. The questionnaire covered other items, such as demographics, medical history, ocular history, and zygosity.

Cycloplegic autorefraction was performed (model KR8100 autorefractor; Device Technologies, Melbourne, Australia). Three readings were taken for each eye and the average value recorded. Results for each eye were converted to their spherical equivalent (SE) (sphere+half the cylinder). Both eyes of each individual was dilated with a single drop of tropicamide 1% (a mydriatic). To ensure maximum dilation, we performed objective refraction at least 25 minutes after instillation of the tropicamide. Myopia was defined as equal to or worse than −0.50 D.

Statistical Analyses

The premise of most twin models is to compare intrapair correlations (the degree of relatedness for a variable within monozygotic [MZ] or dizygotic [DZ] twin pairs).[17] A significantly higher correlation of disease between MZ twins and DZ twins is a strong predictor of a genetic basis for the trait. Common to most twin models is the "equal environment assumption," which assumes all twins share the same environment, irrespective of their zygosity. Structural equation modeling (SEM) was used to determine the combination of A (additive genetic), C (common environmental effects), D (nonadditive genetic), and E (unique environment and measurement error) that provided the most parsimonious model according to analysis with the statistical program Mx.[18] The best-fitting model, was assessed by the difference in the log likelihood between the sub and the full models (the best-fitting model was determined based on maximum-likelihood [ML] and χ^2 tests).[19] The ML analysis of each independent variable was used for sequential testing of the hypotheses about the means, variances, and covariances.[19] In the GEM twin study, the sex-limitation ADE model was applied in the analysis, as the variances for SE were significantly different between males and females. The ADE genetic model was applied, as MZ intrapair correlations were more than double that in DZ twin pairs, where common environmental factors ($C = 2r_{DZ} - r_{MZ}$) had no role. All other analyses were performed with commercial software (SPSS ver. 12.1; SPSS Science, Chicago, IL, and Access and Excel; Microsoft, Redmond, WA).

RESULTS

Baseline Measures

A total of 1224 twins (690 MZ twins and 534 DZ twins) between 18 and 86 years of age (mean, 52.36 ± 15.42 SD) were recruited into the GEM study. Of the twins recruited, approximately two thirds were females (n = 823l; Table 1). Most of the twins were of a Caucasian background, and therefore no ethnic comparisons could be undertaken. There was no significant difference in mean SE between MZ twin pairs (0.50 ± 2.17 D) and DZ twin pairs (−0.015 ± 2.12 D; P = 0.60). There was no statistically significant difference in mean SE between the right eyes (0.025 D; range, +6.75 to −14.50 D) and left eyes (0.104 D, range, +7.5 to −14.00 D; $P > 0.05$); therefore, statistical analysis in the GEM twin study was undertaken only for the right eye.

TABLE 1. Baseline Characteristics of Twin Pairs in the GEM Study, Defined by Zygosity

	MZ Twins	DZ Twins	*P*
Twin pairs, *n* (%)	345 (56%)	267 (44%)	—
Age (y)	52.11 ± 15.85	52.63 ± 14.96	0.56
Sex (male/total)	223/690 (32.3%)	178/534 (33.3%)	<0.05
SE (D)	0.051 ± 2.17	−0.015 ± 2.12	0.60

Frequency of Myopia

Out of the 1224 twins examined, 54 (33 MZ twins and 21 DZ twins) had no objective refraction measurements, because they left the examination before the completion of all tests. In some cases the autorefractor was not available to the primary investigator. A total of 1170 twins were included in this analysis, to estimate the frequency of myopia in the GEM twin study. Myopia (worse than or equal to −0.50 D) was found in 347 (29.66%) of the 1170 twins, with low myopia (between −0.50 and −2.99 D) accounting for 70.03% (243/347), followed by moderate myopia (between −3.00 and −5.99 D; 80/347, 23.05%), and the remaining (24/347, 6.92%) having high myopia (worse than or equal to −6.00 to −14.50 D). All adult-onset myopes (96 twins) had low/moderate myopia (range, −0.50 to −4.00 D) and approximately 70% (68/96 twins) of these had bilateral myopia.

Frequency of Adult-Onset Myopia

Of the twins that had myopia (n = 347 twins), a total of 96, 50 MZ and 46 DZ (96/347; 27.7%) were first prescribed optical correction for myopia (mean SE = −1.47 D) at the age of 18 years or older. Of the 96 twins with adult-onset myopia, 58 (60.4%) were females and 38 (39.6%) were males. In more than 90% of these twins (87/96), myopia developed between the ages of 18 to 30 years (mean SE = −1.54 D) with the remaining (9/96, 9.4%) reporting development of myopia between 31 and 45 years (mean SE = −1.42 D). In the whole GEM twin cohort (twins with refraction measurements), less than 10% of the twins (96/1170, 8.2%) had myopia defined as adult-onset.

Intrapair Twin Correlations for Adult-Onset Myopia

Intrapair correlations for SE in all twin pairs (n = 612 twin pairs) were significantly higher in MZ twin pairs (r = 0.82) than in DZ twin pairs (r = 0.36), ($P < 0.01$).[15] In data from only twins with myopia (worse than or equal to −0.50 D), the MZ intrapair correlation (r = 0.77) was significantly higher than that in DZ twin pairs (r = 0.28; $P < 0.01$). Moreover, a major genetic component of SE was found in twins with adult-onset myopia (MZ intrapair correlation, r = 0.61; DZ, r = 0.16; $P < 0.01$).

We excluded individuals with adult-onset myopia from the main analysis to determine whether this would have any effect on the overall heritability estimates. After excluding these

Table 2. Correlations for SE by Sex for Each Twin Zygosity Group without Adult-Onset Twins

Zygosity	Sex	SE (D)
Monozygotic	F/F	0.76 (0.69–0.81)
	M/M	0.88 (0.83–0.92)
Dizygotic	F/F	0.20 (0.02–0.37)
	M/M	0.31 (−0.02–0.58)
	(F/M)	0.27 (−0.04–0.53)
	(M/F)	0.39 (0.11–0.61)

twins from the main analysis, we found no significant effect on the overall heritability estimates reported in the GEM twin study.[15] With the exclusion of adult-onset myopia, the heritability estimates for SE was 74% (additive genetics, 24%; nonadditive genetics, 50%), with unique environmental effects explaining 26% of the variance in the males. Similarly, genetic factors explained 88% (A = 44%, D = 44%), and E accounted for 12% of the variance in the females. For both the males and the females, the sex limitation ADE model was found to be the best-fit genetic model to explain the variance in SE (Tables 2, 3).

Discussion

The GEM twin study is novel, in that it has provided the frequency of adult-onset myopia in a twin cohort that is more representative of the general population,[15] compared with studies that included selected participants.[12] We found that adult-onset myopia accounted for approximately one third of all myopia and was also present in 8.2% of all twins in our cohort. Our findings demonstrate that onset of myopia during adulthood is common and should be taken into account in the study of myopia, particularly in research investigating its genetic and environmental determinants. For instance, it has been postulated that perhaps some aspect of the workload or how eyes respond to various tasks in adult life accounts for adult-onset myopia.[12] Alternatively, it may be that in individuals who are genetically predisposed to development of myopia, it may develop only in their adulthood years, when they are exposed to an environmental risk factor later in life, such as greater amounts of near-work activities. In the GEM twin study, we sought to obtain information regarding the genetic basis to adult onset in a cohort who data were generalizable to the population.

In the GEM twin study, almost one quarter of clinically identified myopia was self-reported to be adult onset, occurring after the age of 18 years when glasses were first prescribed. The definition used to classify adult-onset myopia has been used extensively in the literature.[7–9] Our findings fall in the frequency range of adult-onset myopia (18 years or older) that has been reported in other studies that that have focused on specific cohorts. In a study of Turkish medical students, it was shown that the proportion of adult-onset myopia was 14.7%,[7] whereas in 133 Norwegian medical students (first received spectacles at the age of ~20 years), the rate was 43.3%.[20] In other studies, it has been shown that 47.8% of a Caucasian office worker cohort presented with adult-onset myopia,[8] whereas the incidence of adult-onset myopia was 45% in a group of 251 microscopists aged 21 to 63 years.[12] All studies have indicated a high proportion of adult-onset myopia, albeit in selected cohorts—namely, students and occupational groups. Although it is difficult to make a direct comparison with the GEM twin cohort, which is more generalizable to the population,[15] these findings all indicate that myopia can develop at a later age.

The findings of our twin study support those of family-based studies, in that they provide evidence of a genetic component to adult-onset myopia. Iribarren et al.[13] found that adult-onset myopia is significantly associated with family history ($P = 0.013$), at a level similar to that found in youth/childhood myopia.[21] In our study, we found that the MZ intrapair correlation was significant higher than that in DZ twin pairs ($P < 0.01$), thus supporting a role for genetic factors in adult-onset myopia.

For exploratory purposes, we undertook heritability analysis on our twin cohort without individuals with adult-onset myopia, to assess whether the heritability estimates would differ when compared to the analysis including all twins reported in the GEM twin study. We found that the exclusion of individuals with adult-onset myopia had no significant effect on the heritability estimates reported in the GEM twin study.[15] Moreover, the MZ intrapair correlations for adult-onset myopia was significantly different compared to that in DZ twin pairs, which provided further evidence to support a genetic component in adult-onset myopia. Therefore, it is likely that myopia has a major genetic component, irrespective of the age of onset (childhood/youth onset versus adult-onset).

A limitation in the GEM twin study is the lack of ocular history data that would have confirmed or disproved the self-reported age of myopia onset ascertained through a questionnaire. It may be argued that an individual had myopia for several years before being aware of its existence or being informed its presence, and this may have inflated the number of twins with adult-onset myopia reported in the GEM twin study. Nonetheless, it is common for studies to determine the age of onset through questionnaires, with the question of age at which one was first prescribed glasses for refractive error being the one most commonly asked. Furthermore, a study by Fledelius[10] determined the age of onset of myopia in 151 individuals aged 26 to 64 years by self-report (the age when first spectacles to correct distance vision were prescribed). They found that this method of defining age at onset was reliable and described the experience of obtaining one's first pair of glasses as a "strong emotional experience."

In conclusion, we have found that adult-onset myopia is common, with approximately one-third of myopia being acquired in adulthood years in a Caucasian twin population. In addition, all adult-onset myopia reported in the GEM twin study was low to moderate, with no cases of high myopia. Therefore, more research is needed into the biological and developmental processes involved in adult-onset myopia. To our knowledge, the GEM twin study is the first study of its kind

Table 3. Results of Sex Limitation ADE Model Fitting without Adult-Onset Twins

Variable	Model	Log-likelihood	*df*	χ^2 fit	cd.df	*P*
SE	Sex lim. ADE	4190.94	1052			
	ADE	4205.26	1055	14.33	3	<0.002
	AE	4210.15	1056	4.89	1	0.03
	E	4531.75	1057	321.597	1	<0.001

df, degrees of freedom; cd.df, difference in degrees of freedom; A, additive; D, dominant; E, unique environment.

to provide evidence to support a genetic component in adult-onset myopia. From our findings, we may postulate that both youth/childhood and adult-onset myopias are influenced similarly by genetics, with the ADE model being the most parsimonious model to explain the variance in myopia, thus indicating that myopia is most likely a spectrum with variable age of penetrance—a finding that has important implications in genetic modeling.

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