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Heritability of Refractive Error and Familial Aggregation of Myopia in an Elderly American Population

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Abstract

Purpose—To determine the heritability of refractive error and the familial aggregation of myopia in an older population.

Methods—Seven hundred fifty-nine siblings (mean age, 73.4 years) in 241 families were recruited from the Salisbury Eye Evaluation (SEE) Study in eastern Maryland. Refractive error was determined by noncycloplegic subjective refraction (if presenting distance visual acuity was $\leq 20/40$) or lensometry (if best corrected visual acuity was $>20/40$ with spectacles). Participants were considered plano (refractive error of zero) if uncorrected visual acuity was $>20/40$. Preoperative refraction from medical records was used for pseudophakic subjects. Heritability of refractive error was calculated with multivariate linear regression and was estimated as twice the residual between-sibling correlation after adjusting for age, gender, and race. Logistic regression models were used to estimate the odds ratio (OR) of myopia, given a myopic sibling relative to having a nonmyopic sibling.

Results—The estimated heritability of refractive error was 61% (95% confidence interval [CI]: 34%–88%) in this population. The age-, race-, and sex-adjusted ORs of myopia were 2.65 (95% CI: 1.67–4.19), 2.25 (95% CI: 1.31–3.87), 3.00 (95% CI: 1.56–5.79), and 2.98 (95% CI: 1.51–5.87) for myopia thresholds of -0.50 , -1.00 , -1.50 , and -2.00 D, respectively. Neither race nor gender was significantly associated with an increased risk of myopia.

Conclusions—Refractive error and myopia are highly heritable in this elderly population.

Myopia is the leading cause of visual impairment in nearly all population-based studies of ocular disease, and correction of refractive error consumed over \$12 billion per year in the United States 10 years ago, even before the recent surge in refractive surgery.¹ In some populations of east Asia, studies suggest that the prevalence of myopia may exceed 80% among young persons,² and there is some evidence that rates may be increasing rapidly.³

There is also evidence for a recent increase in the prevalence of myopia in populations such as Eskimos, in whom myopia was rare only a few generations ago.⁴ Such apparent rapid changes in the prevalence of myopia within defined populations argue for strong

environmental influences in the development of myopia. For example, much evidence exists that implicates near work as an important determinant of myopia.^{5–10}

Nevertheless, there is also considerable evidence that myopia is under genetic control. Studies have consistently shown strong correlations between the refractive errors of first-degree relatives.^{11–13} Twin studies by Hammond et al.,¹⁴ Teikari et al.,^{15,16} and Lyhne et al.¹⁷ have suggested that the heritability—that is, the proportion of the population variance under genetic control—for refraction may exceed 80%. It is therefore likely that the development of myopia is mediated by both environmental and genetic risk factors.

At least four chromosomal locations^{18–22} have been linked to high (that is, in excess of 5 D) myopia. No such loci had been identified for moderate myopia (1–5 D), which comprises some 80% of myopia among American adults,²³ until a recent report by Stambolian et al.²⁴ who found significant genetic linkage of myopia to a region on chromosome 22 in an Ashkenazi Jewish population. Moreover, in a genome-wide scan of 221 dizygotic twin pairs, Hammond et al.²⁵ reported significant linkage signals to multiple genetic loci when analyzing refractive error as a quantitative trait. Their highest linkage peak was observed at chromosomal location 11p13 while evidence for linkage was also noted at regions 3q26, 8p23, and 4q12.

The relative paucity of evidence for linkage in lower levels of refractive error, compared with high myopia, is partly because high myopia may be more likely to present in an autosomal dominant fashion,²² whereas the genetics of lower refractive errors may be more complex and multifactorial. Nevertheless, Farbrother et al.²⁶ argue that even high myopia phenotypes are unlikely to be inherited in an autosomal dominant fashion and that a multifactorial etiology is more likely. In view of the high prevalence (some 20 million American adults²³) and the resultant significant impact on the health economy in the cost of spectacles, contact lenses, and refractive surgery, it certainly seems that moderate myopia is deserving of genetic study to elucidate its fundamental mechanisms, which may or may not be the same as those of high myopia.

Using linear regression models and generalized estimating equations (GEEs), we estimated the heritability of refractive error in a population-based sample of elderly sibships in eastern Maryland. We also used logistic regression models to calculate the odds of myopia in siblings of myopic individuals compared with siblings of nonmyopes, using four thresholds to define myopia.

Subjects and Methods

Subjects

The Salisbury Eye Evaluation (SEE) began 10 years ago as a population-based study of some 2500 individuals aged 65 to 84 years as of July 1, 1993, recruited from Medicare rolls on Maryland's Eastern Shore. At the third and fourth rounds of the on-going SEE study, all subjects with one or more siblings dwelling within 100 miles of Salisbury or Baltimore were invited to undergo venipuncture and to complete a family history questionnaire, after furnishing informed consent. Consent was further obtained to contact locally resident siblings identified in the family history questionnaire, and these individuals were then contacted by mail. Those providing consent were subsequently contacted by telephone and invited to undergo venipuncture and an examination at a central site.

Methods

Participants underwent standard distance visual acuity testing using Early Treatment Diabetic Retinopathy Study (ETDRS) charts and protocols,²⁷ wearing their habitual

spectacle refractions when available. Participants in whom presenting visual acuity was 20/40 or worse in one or both eyes underwent noncycloplegic autorefractometry (Humphrey Autorefractometer model 595; Carl Zeiss Meditec, Dublin CA) followed by binocular subjective refraction. Refractive error was defined for each phakic eye of all subjects as follows: the spectacle lensometry reading for participants whose corrected visual acuities were better than 20/40, or the noncycloplegic subjective refraction yielding best visual acuity for all others. Participants in whom uncorrected distance visual acuity in both eyes was better than 20/40 did not undergo refraction and were assigned a refractive error of zero (plano). For the 154 bilaterally pseudophakic participants, preoperative records were requested from treating physicians, and refractive error was defined for each eye as the spherical equivalent for the last refraction before cataract surgery. In unilaterally pseudophakic subjects, refractive error was defined as described earlier for the sole phakic eye, and the pseudophakic eye was excluded from analysis.

Digital slit and retroillumination lens photographs were taken of all nonpseudophakic eyes of all participants by using a previously described protocol.²³ These photographs were graded with the Wilmer Cataract Grading System²⁴ by a team of trained graders.

In addition, participants underwent a slit lamp examination of the anterior segment as well as a dilated fundus examination by the study optometrist (HB). All eyes in which disease (such as corneal opacity) could have affected refractive error or precluded an accurate measurement of the refractive status were excluded from further analysis. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Johns Hopkins Medical Institutions Institutional Review Board.

Statistical Methods

Refractive error was analyzed as a continuous variable for heritability estimation. The continuous trait was defined as the spherical equivalent refractive error, averaged between eyes. Spherical equivalent refractive error for the only eye contributing data was used in individuals with monocular pseudophakia or other conditions precluding bilateral refraction. Age was defined as the age at examination or, for bilaterally pseudophakic participants, as the age at the time of last refraction before cataract surgery (averaged between the dates for the two eyes). In addition, analyses were performed using myopia as a binary outcome. For these binary trait analyses, several thresholds were used to define myopia. These included mean spherical equivalent refractive errors lower than or equal to -0.50 , -1.00 , -1.50 , and -2.00 D. Analyses for various definitions of hyperopia were also performed and are reported elsewhere.²⁸

Heritability is estimated from the degree of resemblance in a trait between siblings, or the proportion of additive genetic variance to total phenotypic variance. Mathematically, it is calculated as twice the phenotypic correlation between siblings or, in the case of multivariate regression, as twice the residual between-sibling correlation after adjustment for other variables. We estimated between-sibling correlations using multivariate linear regression models and extended GEEs, with the clustering variable being individual families.²⁵ Only self-reported full siblings were included in the analysis. Main covariates included in the statistical models were age, gender, and race. In addition, we investigated the effect of height, weight, and body mass index (BMI) on refractive error. Cataract grade was not significantly associated with refractive error in models including age and thus was not included in the final model.

Possible modifying effects on refractive errors were assessed by including three first-order interaction terms between age, gender, and race in the regression models. However, interactions between age and gender and between age and race were minimal and are not

reported. We also performed stratified analyses to obtain race-specific heritability estimates for refractive error.

Although even large departures from multivariate normality assumptions have been shown to yield unbiased parameter estimates in heritability studies,²⁹ we also calculated the heritability of refractive error after applying a normalizing transformation, transformed refraction = $\ln(-\text{refraction} + 12)$, as suggested by Blackie and Harris.³⁰ The heritability estimate of the transformed data did not differ substantially from that obtained using the raw spherical equivalent refractive error (67% versus 62%). Hence, we report all analyses using the untrans-formed data.

For the binary trait analysis, we estimated the odds ratio (OR) of being myopic, given a myopic sibling relative to a nonmyopic sibling (i.e., recurrence OR) for our four definitions of myopia. This was accomplished by using logistic regression analysis and GEEs, as described by Liang and Beaty.³¹ Affection status was coded as a binary variable and covariates, including a first-order gender-race interaction term, were identical with those in the linear regression analysis. No ascertainment correction was used, because participants were recruited independent of refractive status.

Logistic models using GEEs are advantageous as they provide unbiased estimates of sibling correlations and ORs while allowing for the incorporation of covariates and accommodating various family sizes.²⁶ Although the statistical properties of logistic regression lead to estimates of ORs, the parameter of interest for genetic linkage and association studies for binary traits is the sibling recurrence relative risk (λ_s) which is defined as the risk of being affected, given an affected sibling relative to the risk of being affected in the population (i.e., the population prevalence). ORs are biased estimates of relative risks, and the direction of the bias is always away from the null value of unity. For rare diseases the bias is negligible. However, for more common conditions, such as myopia, the difference can be substantial. We transformed our estimated sibling recurrence ORs into λ_s using

$$\lambda_s = \frac{1}{prev} \frac{OR_s (prev / (1 - prev))}{[1 + OR_s (prev / (1 - prev))]} \quad (1)$$

where *prev* is the estimated population prevalence of myopia, and the ratio *prev*/(1–*prev*) represents the odds of myopia. Prevalences of myopia were 0.20, 0.15, 0.11, and 0.09 for myopia thresholds of –0.50, –1.00, –1.50, and –2.00 D, respectively. These population prevalence estimates were obtained from our data and are consistent with previously reported data for older populations.²³

The statistical analyses were performed in R version 1.7.1³² using the GEE library, version 4.13–8. The GEE library was extended to accommodate logistic models and provide sibling recurrence ORs.

Results

Of the 523 SEE participants who had locally residing siblings, 307 elected to participate in the study (mean age, 73.4 years). The total number of siblings residing within 100 miles of the study site was 1069. Of these, 452 agreed to participate in the study, for a total of 759 participants. Nonparticipation was due either to refusal or our inability to contact or coordinate transport for participants. Participating siblings did not differ significantly from all locally resident siblings with respect to age (70.2 ± 7.7 and 71.1 ± 9.7 years, respectively, for participant siblings and all locally resident siblings), gender (59% women for participant siblings versus 60% for all eligible siblings), or race (26.8% of persons in both groups were

black). Sibship sizes ranged from two to eight in 274 families, with a mean of 2.8 siblings per family and 860 total sibling pairs. The racial makeup was the same as reported for the original population-based SEE study.³³ The mean refractive error (spherical equivalent) for the entire cohort was $+0.65 \pm 2.00$ D, and the range of individual refractive errors was -11.875 to $+6.625$ D (Table 1).

Results for the quantitative trait linear regression analysis are shown in Table 2. Within the relatively restricted age range of our cohort, the mean gender- and race-corrected refractive error difference per decade of age was $+0.32$ D (95% CI: $+0.08$ to $+0.56$), with older persons tending to be less myopic. Refractive error was not significantly associated with gender in whites ($P = 0.539$). However, the mean age-corrected refractive error was $+0.85$ D (95% CI: $+0.19$ to $+1.51$) with more hyperopia in black women than in black men. Black men were estimated to be, on average, -1.11 D (95% CI: -0.50 to -1.70) more myopic than similar-aged white men. The estimated mean refractive error did not differ significantly between black and white women (mean difference $= -0.26$ D, 95% CI: -0.76 to $+0.25$). Cataract grade was not significantly associated with refractive error for any of the cataract subtypes in models including age ($P = 0.75$, 0.26 , and 0.78 for nuclear, cortical, and posterior subcapsular grades, respectively). Including cataract grades in the regression models did not affect heritability estimates, and they were thus omitted from the final model for the sake of parsimony.

Greater height was marginally associated with more myopic refractive error (-0.21 D per 10-cm increase in height), but this association did not attain statistical significance ($P = 0.09$). In addition, the inclusion of height in our regression models did not affect the estimated heritability of myopia. Neither weight ($P = 0.76$) nor BMI ($P = 0.31$) was significantly associated with refractive error.

The residual between-sibling correlation for refractive error in was 0.310 (95% CI: 0.175 – 0.445). Thus, the estimated heritability for refractive error in this population was 62% (95% CI: 35.0%–89%). When analyses were stratified by race, the age- and sex-adjusted estimated heritability of refractive error was 80% (95% CI: 22.9%–100%) in African American and 50% (95% CI: 30.4%–60.8%) in white participants. However, the heritability estimates for black and white participants did not differ significantly ($P = 0.32$).

Sibling recurrence ORs for myopia were estimated in logistic regression models that included age (in years), gender, and race variables as well as a gender-race interaction term. The sibling recurrence ORs for myopia ranged from 2.25 (95% CI: 1.37–3.87) to 3.00 (95% CI: 1.56–5.79) for the various myopia cutoffs (Table 3). Estimated λ_s were 2.00, 1.90, 2.45, and 2.52 for myopia thresholds of -0.50 , -1.00 , -1.50 , and -2.00 D, respectively (Table 3).

Discussion

Our results suggest that genetics play a significant role in determining refractive error, with heredity explaining approximately 62% of the variance of refractive error in this population. These results are consistent with those in previous studies in which heritabilities for refractive error ranged from 50% to 90%. In a twin-pair study, Hammond et al.¹⁴ reported a heritability estimate for refractive error of between 84% and 86%. Lyhne et al.¹⁷ reported the heritability of refractive error among 114 pairs of Danish twins to be approximately 90%. In the Beaver Dam eye study, Lee et al.¹³ found an age-adjusted sibling correlation of refractive error of 0.37, equivalent to a heritability of 74%. The sibling correlation reported by Bear et al.¹² for 76 sibships >30 years of age was 0.39 (heritability of 78%). Alsbirk⁴ estimated the sib-sib correlation for refractive error among Greenland Eskimos to be 0.25 (heritability of 50%).

It is important to note that all heritability estimates are population-specific and can show large between-population differences. Specifically, heritabilities are estimated as the proportion of the additive genetic variance to the total (environmental and genetic) variance. Hence, populations in which environmental exposures predominate will have lower heritabilities relative to groups in which these factors are absent, given similar genetic backgrounds. Another possible source of bias in our study relates to the use of correlations between full siblings to estimate heritability. In full siblings, dominance genetic effects in addition to additive effects, contribute to the phenotypic covariance between individuals.³⁴ Hence, heritabilities in studies of full siblings may be inflated relative to those estimated in monozygotic versus dizygotic twin comparisons or parent- offspring designs. We do not think that this bias is likely to have been substantial in this study, since our estimate of heritability is at the lower end of previously reported figures. In addition, substantial differences in environmental exposures may actually reduce the phenotypic resemblance between generations in parent- offspring designs, leading to reduced heritability estimates.

To our knowledge, the heritability of refractive error has never been estimated in African-American populations. The heritability of 80% for the black subcohort in this study was higher than the 50% estimated heritability for the white participants. This may be the result of a higher environmental variance contributing to the phenotype in the white participants or to differing genetic backgrounds between the races. Nevertheless, the CIs of the race-specific heritability estimates overlapped considerably and hence did not differ significantly and the difference in race-specific heritability estimates may have been the result of sampling variation.

The advantage of using linear regression to estimate residual sibling correlation is that covariates can readily be included to account for nongenetic determinants. The addition of extended GEEs (GEE2) allows for the calculation of regression coefficients while accounting for multiple within-family comparisons and families of various sizes.³¹ Our heritability estimates were age, gender, and race adjusted. Nevertheless, because environmental exposures, such as educational achievement and exposure to prolonged near-vision tasks, are likely to be correlated within sibships and were not completely accounted for in our statistical models, our estimates of heritability may have been artificially elevated in this population.

The mean age of our study population was >70 years. We can expect that nongenetic influences, especially those related to cumulative age effects, would have had a relatively large effect on refractive error in this age group, increasing the total phenotypic variance and weakening the estimated genetic effect. Furthermore, there may have been some phenotypic misclassification in our population, because participants with uncorrected visual acuities better than 20/40 were assigned a null refractive error. Any such misclassification would probably be nondifferential with respect to sibling refractive error and hence decrease the observed heritability estimate.

Physical stature has previously been found to be associated with refractive error.^{9,35,36} Our results suggest that height may be marginally associated with refractive error, although this association did not reach statistical significance ($P = 0.09$). Our age-, gender-, and race-adjusted estimate of heritability for height in this population was 92% (data not shown). Nevertheless, the addition of height in our regression models did not change our estimated heritability of refractive error. This suggests that the genetic and/or common environmental factors responsible for physical stature differ from those associated with refractive error.

The age-, gender-, and race-adjusted odds of myopia were, on average, 2.72 times higher in siblings of myopic individuals than in siblings of nonmyopic participants. Our estimates are

somewhat lower than those reported by the Lee et al.,¹³ who obtained ORs of 2.82 to 4.25 (mean, 3.42) for myopia, defined as a spherical equivalent refraction less than -0.50 D, among 100 random samples of sibling pairs from the Beaver Dam population. As with our estimate of heritability, it is likely that the older age of our population compared that of the Beaver Dam cohort (mean age, 61.5 years) would have lead to relatively larger environmental influence and thus a lower estimated OR. Although we did not find a statistically significant relationship between cataract grades and ocular refraction it is possible that more subtle lens changes and differences in the anatomic relationship between ocular components causes age-related variations in ocular refraction.

Using regression models similar to ours, the Framingham Offspring Eye Study Group¹¹ found that the recurrence OR of myopia was related to the age difference of siblings. The OR ranged from 2.50 for siblings whose ages differed by >10 years to 5.13 for siblings whose age differences were within 2 years. In our study, the mean between-sibling age difference was >4 years, and the ages of $>20\%$ of our sib pairs differed by 10 years or more. Hence, our recurrence ORs are consistent with Framingham Offspring Study results.

We have also shown that sibling recurrence ORs for myopia are largely invariant to the specific definition of refractive error used. This may reflect underlying quantitative trait loci for refractive error or an environmental dose-response relationship unaccounted for in our statistical models. Nevertheless, it is difficult to assess adequately the significance of this finding, because the tests for different myopia thresholds were correlated (i.e., the same population was used for all measures). Furthermore, we limited our analysis to low-cutoff thresholds for myopia of between -0.50 and -2.00 D, because we did not have a sufficient sample size to use more extreme definitions of the myopic phenotype.

We also provide estimates of λ_s for myopia. λ_s is more easily interpreted than the sibling recurrence OR and is the parameter of interest when calculating the power of genetic linkage and association studies for binary traits. The age-, gender-, and race-adjusted risk of myopia was 1.90 to 2.52 higher in siblings of myopic participants than in the general population. Hence, the estimated prevalence of myopia of at least -0.50 D among siblings of myopic individuals was 40%, as opposed to 20% among all study participants. Similarly, at a threshold of -2.00 D, the estimated prevalence of myopia among siblings of myopes was 23%, or 2.55 times the population prevalence of 9%.

It may be that high myopia, which can be transmitted through autosomal dominant genetic mechanisms and for which several chromosomal loci have been identified in genetic linkage studies,^{18–22,37} clusters in families to a greater extent than the more common, moderate myopia. In a reanalysis of Goldschmidt's 1968 population-based sample of Danish teenagers,³⁸ Guggenheim et al.³⁹ calculated λ_s for high myopia (i.e., refractive error ≤ -6 D) to be 20. However, this estimate was based on only 39 high myopes in a population pool of 9243 children. In a study of 296 randomly selected high myopes from British optometric practices, Farbrother et al.²⁶ estimated λ_s for high myopia to be 4.9 (95% CI: 2.8–7.6). Unfortunately, they inferred the presence of high myopia among siblings through a questionnaire to be an age of onset of spectacle wear of 9.1 years or younger, which limits the interpretation of their findings.

Our results confirm reports of previous studies that non-pathologic myopia is substantially determined by heredity.^{4,12–16} However, the genetic mechanism responsible for the development of low myopia is likely to be complex, significantly complicating the search for susceptibility loci. For example, Ashton,⁴⁰ using segregation analysis, rejected a Mendelian inheritance model for refraction in nuclear families of European and Japanese ancestries.

The current study should be understood in the context of its limitations. Less than complete levels of participation at all levels (in the parent SEE study, or in this nested genetic study) could in theory have led to selection bias with regard to refractive error. However, even if such bias occurred, it would not have biased our estimates of myopia heritability unless myopes with affected siblings were more or less likely to participate than myopes without such sibs, which does not seem likely. Numerous studies have implicated environmental factors,^{5–8,10,12,41–43} such as prolonged exposure to near work, in refractive error development. In our study, data were not available to assess these effects and their influence on the heritability of refractive error. Efforts should be made to evaluate more fully these risk factors in future genetic epidemiologic studies of refractive error.

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References

1. Javitt JC, Chiang YP. The socioeconomic aspects of laser refractive surgery. *Arch Ophthalmol*. 1994; 112:1526–1530. [PubMed: 7993206]
2. Lin LL, Shih YF, Tsai CB, et al. Epidemiologic study of ocular refraction among schoolchildren in Taiwan in 1995. *Optom Vis Sci*. 1999; 76:275–281. [PubMed: 10375241]
3. Tay MT, Au Eong KG, Ng CY, Lim MK. Myopia and educational attainment in 421,116 young Singaporean males. *Ann Acad Med Singapore*. 1992; 21:785–791. [PubMed: 1295418]
4. Alsbirk PH. Refraction in adult West Greenland Eskimos: a population study of spherical refractive errors, including oculometric and familial correlations. *Acta Ophthalmol (Copenh)*. 1979; 57:84–95. [PubMed: 419981]
5. Saw SM, Hong RZ, Zhang MZ, et al. Near-work activity and myopia in rural and urban schoolchildren in China. *J Pediatr Ophthalmol Strabismus*. 2001; 38:149–155. [PubMed: 11386647]
6. Saw SM, Wu HM, Seet B, et al. Academic achievement, close up work parameters, and myopia in Singapore military conscripts. *Br J Ophthalmol*. 2001; 85:855–860. [PubMed: 11423462]
7. Saw SM, Zhang MZ, Hong RZ, et al. Near-work activity, night-lights, and myopia in the Singapore-China study. *Arch Ophthalmol*. 2002; 120:620–627. [PubMed: 12003612]
8. Saw SM, Chua WH, Hong CY, et al. Nearwork in early-onset myopia. *Invest Ophthalmol Vis Sci*. 2002; 43:332–339. [PubMed: 11818374]
9. Saw SM, Carkeet A, Chia KS, et al. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology*. 2002; 109:2065–2071. [PubMed: 12414416]
10. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. *J Pediatr Ophthalmol Strabismus*. 1993; 30:319–322. [PubMed: 8254449]
11. The Framingham Offspring Eye Study Group. Familial aggregation and prevalence of myopia in the Framingham Offspring Eye Study. *Arch Ophthalmol*. 1996; 114:326–332. [PubMed: 8600894]
12. Bear JC, Richler A, Burke G. Nearwork and familial resemblances in ocular refraction: a population study in Newfoundland. *Clin Genet*. 1981; 19:462–472. [PubMed: 7296938]
13. Lee KE, Klein BE, Klein R, Fine JP. Aggregation of refractive error and 5-year changes in refractive error among families in the Beaver Dam Eye Study. *Arch Ophthalmol*. 2001; 119:1679–1685. [PubMed: 11709020]
14. Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: the twin eye study. *Invest Ophthalmol Vis Sci*. 2001; 42:1232–1236. [PubMed: 11328732]
15. Teikari JM, O'Donnell J, Kaprio J, Koskenvuo M. Impact of heredity in myopia. *Hum Hered*. 1991; 41:151–156. [PubMed: 1937488]

16. Teikari JM, Kaprio J, Koskenvuo M, O'Donnell J. Heritability of defects of far vision in young adults: a twin study. *Scand J Soc Med*. 1992; 20:73–78. [PubMed: 1496333]
17. Lyhne N, Sjolie AK, Kyvik KO, Green A. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. *Br J Ophthalmol*. 2001; 85:1470–1476. [PubMed: 11734523]
18. Lam DS, Tam PO, Fan DS, et al. Familial high myopia linkage to chromosome 18p. *Ophthalmologica*. 2003; 217:115–118. [PubMed: 12592049]
19. Naiglin L, Gazagne C, Dallongeville F, et al. A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. *J Med Genet*. 2002; 39:118–124. [PubMed: 11836361]
20. Paluru P, Ronan SM, Heon E, et al. New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. *Invest Ophthalmol Vis Sci*. 2003; 44:1830–1836. [PubMed: 12714612]
21. Young TL, Ronan SM, Alvear AB, et al. A second locus for familial high myopia maps to chromosome 12q. *Am J Hum Genet*. 1998; 63:1419–1424. [PubMed: 9792869]
22. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. *Am J Hum Genet*. 1998; 63:109–119. [PubMed: 9634508]
23. Kempen JH, Mitchell P, Lee KE, et al. The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. *Arch Ophthalmol*. 2004; 122:495–505. [PubMed: 15078666]
24. Stambolian D, Ibay G, Reider L, et al. Genomewide linkage scan for myopia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 22q12. *Am J Hum Genet*. 2004; 75:448–459. [PubMed: 15273935]
25. Hammond CJ, Andrew T, Tat MY, Spector TD. A susceptibility locus for myopia in the normal population is linked to the PAX6 gene region on chromosome 11: a genomewide scan of dizygotic twins. *Am J Hum Genet*. 2004; 75:294–304. [PubMed: 15307048]
26. Farbrother JE, Kirov G, Owen MJ, Guggenheim JA. Family aggregation of high myopia: estimation of the sibling recurrence risk ratio. *Invest Ophthalmol Vis Sci*. 2004; 45:2873–2878. [PubMed: 15326097]
27. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol*. 1982; 94:91–96. [PubMed: 7091289]
28. Wojciechowski R, Congdon NG, Bowie H, et al. Familial aggregation of hyperopia in an elderly population of siblings in Salisbury, Maryland. *Ophthalmology*. 2005; 112:78–83. [PubMed: 15629824]
29. Rao DC, Vogler GP, Borecki IB, et al. Robustness of path analysis of family resemblance against deviations from multivariate normality. *Hum Hered*. 1987; 37:107–112. [PubMed: 3583287]
30. Blackie CA, Harris WF. Refraction and keratometry: departures from and transformations toward multivariate normality. *Optom Vis Sci*. 1997; 74:452–458. [PubMed: 9255826]
31. Liang KY, Beaty TH. Measuring familial aggregation by using odds-ratio regression models. *Genet Epidemiol*. 1991; 8:361–370. [PubMed: 1806405]
32. Ihaka R, Gentleman R. R: a language for data analysis and graphics. *J Comput Graph Stat*. 1996; 5:299–314.
33. Munoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Arch Ophthalmol*. 2000; 118:819–825. [PubMed: 10865321]
34. Falconer, DS.; Mackay, TFC. *Introduction to Quantitative Genetics*. 4th ed.. Vol. chap 10. Prentice Hall; New York: 1996. Heritability.
35. Saw SM, Chua WH, Hong CY, et al. Height and its relationship to refraction and biometry parameters in Singapore Chinese children. *Invest Ophthalmol Vis Sci*. 2002; 43:1408–1413. [PubMed: 11980854]
36. Teikari JM. Myopia and stature. *Acta Ophthalmol (Copenh)*. 1987; 65:673–676. [PubMed: 3434232]

37. Young TL, Atwood LD, Ronan SM, et al. Further refinement of the MYP2 locus for autosomal dominant high myopia by linkage disequilibrium analysis. *Ophthalmic Genet.* 2001; 22:69–75. [PubMed: 11449316]
38. Goldschmidt E. On the etiology of myopia: an epidemiological study. *Acta Ophthalmol (Copenh).* 1968; (suppl 98):1. [PubMed: 4886009]
39. Guggenheim JA, Kirov G, Hodson SA. The heritability of high myopia: a reanalysis of Goldschmidt's data. *J Med Genet.* 2000; 37:227–231. [PubMed: 10777361]
40. Ashton GC. Segregation analysis of ocular refraction and myopia. *Hum Hered.* 1985; 35:232–239. [PubMed: 4029963]
41. Richler A, Bear JC. Refraction, nearwork and education: a population study in Newfoundland. *Acta Ophthalmol (Copenh).* 1980; 58:468–478. [PubMed: 7415832]
42. Tong L, Saw SM, Carkeet A, et al. Prevalence rates and epidemiological risk factors for astigmatism in Singapore school children. *Optom Vis Sci.* 2002; 79:606–613. [PubMed: 12322931]
43. Wu HM, Seet B, Yap EP, et al. Does education explain ethnic differences in myopia prevalence?—a population-based study of young adult males in Singapore. *Optom Vis Sci.* 2001; 78:234–239. [PubMed: 11349931]

Table 1

Population Characteristics by Race

	Black	White	Total
Subjects (<i>n</i>)	201	558	759
Sibships (<i>n</i>)	68	206	274
Mean age, y (SD)	71.8 (7.41)	74.0 (5.92)	73.4 (6.41)
Females (%)	129 (64.2)	317 (56.8)	446 (58.8)
Myopia ≤ -1.00 D (%)	26 (13.3)	77 (14.6)	103 (14.2)
Mean refractive error (SD)	0.25 (2.20)	0.80 (2.01)	0.65 (2.00)

Table 2

Estimated Linear Regression Coefficients and Standard Errors for Refractive Error (D)

Variable	Estimate	SE	P
Age (y)	0.032	0.012	0.007
Gender (female)	0.107	0.175	0.539
Race (black)	−1.109	0.301	0.001
Gender-race interaction	0.853	0.335	0.008
Residual sib-sib correlation*	0.310	0.069	<0.001

Data were obtained from the linear regression model of the mean spherical equivalent refractive error on age, race, and gender. The sample comprised 759 participants (mean age, 73.4 ± 6.5 years) in 274 sibships.

* The residual sib-sib correlation was estimated as the between-sibling correlation of the residuals of refractive error after adjusting for age, gender, and race.

Table 3

Estimated Age-, Sex-, and Race-Adjusted Sibling Recurrence ORs and Sibling Recurrence Relative Risks (λ_s) for Four Definitions of Myopia

Myopia Cutoff (D)	OR*	95% CI	$\lambda_s^\dagger$
−0.50	2.65	1.67–4.19	2.00
−1.00	2.25	1.31–3.87	1.90
−1.50	3.00	1.56–5.79	2.45
−2.00	2.98	1.51–5.87	2.52

* Odds ratios were determined by multivariate logistic regression and generalized estimating equations and are defined as the odds of myopia, given a myopic sibling, divided by the odds of myopia, given a nonmyopic sibling. All logistic regression models included age-, sex-, and race- variables, as well as a sex-race interaction term.

$^\dagger \lambda_s$ was calculated using the estimated population prevalences of 0.20, 0.15, 0.11, and 0.09 for myopia thresholds of −0.50, −1.00, −1.50, and −2.00 D, respectively.