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Heritability Analysis of Spherical Equivalent, Axial Length, Corneal Curvature and Anterior Chamber Depth in the Beaver Dam Eye Study

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Abstract

Objective—Quantitative refraction and its related binary traits of myopia and hyperopia are highly correlated within families. Many linkage regions have been reported for myopia, high myopia, and quantitative refraction. However, the measured phenotype of refraction is in large part dictated by the relationship between the underlying optical components of axial length, corneal curvature, and anterior chamber depth.

Methods—Using data from the 4th visit of the Beaver Dam Eye study, we conducted familial correlation and heritability analysis of quantitative spherical equivalent, axial length, anterior chamber depth, and corneal curvature using data from 715 individuals in 189 pedigrees.

Results—Overall, every trait was highly heritable. Heritability estimates were: 0.62 (standard error (s.e.) 0.13) for spherical equivalent after adjustment for age, education and nuclear sclerosis, 0.95 (s.e 0.11) for corneal curvature after adjustment for height, 0.67 (s.e. 0.14) for axial length after adjustment for height and education, and 0.78 (s.e. 0.14) for anterior chamber depth after adjustment for age, education, height, and nuclear sclerosis.

Conclusion—Refraction and the underlying traits of axial length, corneal curvature and anterior chamber depth are highly heritable. Genetic analysis of these traits may provide greater insight into the development of refractive errors.

INTRODUCTION

Quantitative refraction is influenced by the underlying morphology of the eye: axial length, corneal curvature and anterior chamber depth. Refractive errors are common in the Beaver Dam Eye Study cohort, with 26.2% being myopic (-0.75 diopters or more negative) and 49.0% being hyperopic (+0.75 diopters or more positive). Environmental factors have been reported to be associated with refraction, the most notable being near-work or educational attainment

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which is used as a surrogate measure for nearwork[1-5]. We have recently reported that longer axial length was associated with an increase in years of education and height within this cohort. Greater corneal curvature and deeper anterior chambers were also associated with increase in height and educational attainment. (Lee, in press)

It has been well documented that refractive errors are highly correlated within families[6-9]. Twin studies have indicated a high heritability for refraction[10] and there is evidence showing that refraction is highly correlated between siblings[6, 11]. Hammond et al. reported heritabilities of 84 to 86 percent for refraction as a continuous trait in a model with additive genetic components and environmental components[10].

Numerous linkage studies of myopia and quantitative refraction have been conducted. Linkage on chromosomes 2q, 4q, 7q, 10q, 12q, 17q, 18p and Xq have been found for high myopia (≤-6D)[12-18] as well as to chromosomes 3q, 6q, 8p, 20q, 22q and Xq[19,20] for moderate myopia (≤ -1 D). It is important to note, the precise definition of myopia varies across studies. Refraction as a quantitative trait has been linked to regions on 3q, 4q, 8p and 11p[21] with confirmation of the 8p locus[20]. Additionally, we have reported regions on 1q and 22q (confirming linkage to 22q) are linked to quantitative refraction in the Beaver Dam Eye Study[22] and a 2nd region on 1q has been linked to quantitative refraction in a study of large Ashkenazi Jewish myopia families[23].

We have demonstrated strong familial correlation for refraction in the Beaver Dam Eye Study population, with a sibling correlation of 0.34 and a parent-offspring correlation of 0.17 [7] after accounting for the effects of age, sex and education. Given that refraction is influenced in large part by axial length, corneal curvature, and anterior chamber depth, we hypothesize there may be genetic components to these traits which may account for a substantial portion of the heritability of refraction. Several studies have indicated an inverse relationship between axial length and refraction (i.e. longer axial length, more myopic). Additionally these studies have shown that much of the variation in refractive error, especially in younger individuals, is due to variation in axial length.[24-28] Heritability estimates for axial length range between 40%-94% [10, 29-33] Decreases in refraction have been correlated to increases in anterior chamber depth[28]. Heritability estimates for anterior chamber depth range from 51 to 94%[10, 29-33] In addition to increased axial length and deeper anterior chambers, individuals with more myopic refraction have steeper corneal curvatures.[24, 25] Because ocular refractive errors develop when there is not balance between axial length and corneal curvature, some investigators suggest the simple ratio of axial length to corneal curvature may be a more appropriate measure. An inverse correlation between refraction and the ratio of axial length to corneal curvature has also been reported,[24, 27] however, these results were not consistent across studies[25, 26]. The heritability of corneal curvature has been estimated to be quite high, ranging from 60% to 92%[10, 29-31]. However, the Genes in Myopia study, a family study from Australia, recently reported a heritability of only 16% for corneal curvature. Modest evidence for linkage on 2p24, 5q and 14q was reported for axial length, to 2p25, 3p26 and 7q22 for corneal curvature and to 1p32 for anterior chamber depth [31, 34].

The heritability of the biometric traits underlying refraction has not been examined in a United States cohort. Therefore, to examine genetic influences for refractive error, we conducted familial correlation and heritability analysis of refraction(spherical equivalent), axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study, a large population-based sample of United States European-Americans in Wisconsin.

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METHODS

This study was reviewed and approved by the institutional review board of the University of Wisconsin School of Medicine and Public Health and informed consent was obtained from all study participants. Approval was obtained for data analyses from the institutional review boards of the Johns Hopkins School of Medicine and the National Human Genome Research Institute, NIH. Tenets of the Declaration of Helsinki were followed.

Study Population

4,926 individuals, of the 5,924 eligible individuals aged 43-86 years of age, who resided in the township of Beaver Dam, Wisconsin, participated in the baseline examination of the Beaver Dam Eye Study which was conducted between 1988 and 1990 [35]. Follow-up examinations were been conducted every five years. During, the 4th exam period, May 2003 through May 2005, 2,375 individuals were examined. Recruitment methods and study procedures have been described in detail elsewhere[35-39]. Eye examinations were performed at each examination including automated refractive error measurements as described below. Ocular biometry measurements were only available at the 4th visit.

In brief, during the 4th visit, ocular biometric measurements were obtained using partial coherence laser interferometry (IOL Master, Carl Zeiss, Germany). Standardized non-cycloplegic refraction measurements using an automated refractor (Humphrey, San Leandro, CA) was also obtained. For individuals with visual acuity of 20/40 or worse an ETDRS standards[40, 41], a refraction was performed. Eyes without a lens or eyes with an intraocular lens, or eyes with best corrected visual acuity of 20/200 or worse were excluded. Spherical equivalent (sphere power+[0.5*cylinder power] measured in diopters) was calculated from the refraction measurements. Analysis was performed using both the right eye and left eye. Both eyes yielded very similar results and only the results of the right eye are presented. Age, height, and education were obtained at all visits. Nuclear lens opacity was determined by grading of slit-lamp lens photographs using a standard protocol, resulting in a 5-level scale[42].

Family relationships were collected during the baseline examination and verified at the 1st follow-up exam. Of the 5,924 eligible individuals, 2,783 had available information on familial relationships and could be classified into one of 602 pedigrees. Of the 2,375 individuals who participated in the 4th exam, 1,032 were members of families. Analysis was limited to families where biometry measures were available on at least 2 pedigree members, resulting in 715 individuals in 189 families. Due to software limitations several of the more complex pedigrees were split.

Statistical Analysis

Familial correlation analysis was performed using FCOR, part of the S.A.G.E version 4.5 statistical package[43]. First, linear regression was used to determine whether measured covariates significantly predicted the quantitative phenotypes of the ocular biometric measures and spherical equivalent. For each of these quantitative phenotypes, familial correlations using phenotypic residuals after adjusting for statistically significant covariates ($p<0.05$) were then calculated between relative pairs, with equal weight given to each relative pair[43]. In all adjustments age, height, education and nuclear sclerosis were treated as continuous variables. The phenotypic residuals were calculated as the difference between an individual's phenotypic measurement and the predicted phenotypic value after accounting for its covariates (the summation of the products of β-coefficients for all covariates, plus the intercept). Heritability estimates (h^2) for the quantitative phenotypes were obtained using SOLAR. Bivariate heritability analysis was also conducted to determine if there is evidence of shared genetic effects across traits. Overall phenotypic correlation was derived as:

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$\rho_p=\rho_g\sqrt{h_1^2}\sqrt{h_2^2}+\rho_e\sqrt{1-h_1^2}\sqrt{1-h_2^2}$ where ρ_g is the genetic correlation between two phenotypes and $\rho_e$is the environmental correlation between two phenotypes, and h_1 and h_2 denote the heritability of phenotypes, respectively[44]. All significant covariates in our regression analysis were included in our variance component modeling using SOLAR and adjusted heritability estimates were obtained under a variance component framework by conditioning the likelihood estimate on covariates[45].

RESULTS

Of the 2,375 participants in the 4th visit of the BDES, 1,827 had data available on spherical equivalent, 1,962 on axial length and corneal curvature and 1,675 had data available on anterior chamber depth. Of these 715 participants could be classified into 189 pedigrees for familial correlation and heritability analysis. In this family subset, the mean spherical equivalent was 0.58D, mean axial length 23.56 mm, mean corneal curvature 7.69mm and mean anterior chamber depth 3.09mm. We also examined the ratio of axial length to corneal curvature (Table 1). In Table 1 we also present the distribution of these traits in the entire Beaver Dam cohort for comparison. Overall, the family subset was similar to the rest of the cohort (Table 1) and those with biometry measurements were similar to those without (Lee, in press).

We examined the intra-individual correlation between these measurements (Table 2). Spherical equivalent was strongly and inversely correlated with axial length, -0.45 (s.e. 0.04), and positively correlated with corneal curvature, 0.19 (s.e. 0.05). There was an inverse correlation between spherical equivalent and anterior chamber depth, -0.10 (s.e. 0.05). Corneal curvature was strongly and positively correlated with axial length, 0.34 (s.e. 0.04), but there was no correlation between corneal curvature and anterior chamber depth. Axial length and anterior chamber depth were strongly correlated, 0.35 (s.e. 0.04). The ratio of axial length to corneal curvature was also strongly correlated with spherical equivalent, -0.60 (s.e. 0.03), and anterior chamber depth, 0.36 (s.e. 0.04).

To examine the potential role of genetic factors in these traits we calculated familial correlations using FCOR (Table 3). Overall, all traits demonstrated a high familial correlation suggesting shared genetic and/or environmental components. For spherical equivalent, sibling correlation was high, 0.33 (s.e. 0.08), after adjustment for age, sex and education and decreased to 0.12 (s.e. 0.01) among cousin pairs. Corneal curvature demonstrated the highest sibling correlation, 0.44 (s.e. 0.07), and remarkably high correlation among cousin pairs, 0.23 (s.e. 0.07). Axial length and anterior chamber depth were also strongly correlated between siblings, 0.33 (s.e. 0.08) and 0.32 (s.e. 0.09), respectively as was the ratio of axial length to corneal curvature, 0.33 (s.e. 0.08). Twice the sibling pair correlation provides an estimate of trait heritablity. Little correlation was observed among more distant cousin pairs.

Among sibling pairs we also examined inter-trait correlation (Table 4). Spherical equivalent in one sibling was strongly inversely correlated with axial length. -0.25 (S.E 0.07), as well as the ratio of axial length to corneal curvature, -0.29 (s.e. 0.07), in the 2nd sib. There was also modest correlation between axial length in one sib and corneal curvature in the 2nd sib, 0.15 (s.e. 0.07).

Additionally, we estimated heritability using the full pedigree data with SOLAR. These results, presented in Table 3, are consistent with our correlation analysis. Overall, corneal curvature had the highest heritability, 0.95 (s.e. 0.10) after adjustment for height. Heritability for anterior chamber depth was 0.78 (s.e. 0.14) after adjustment for age, education, height and nuclear sclerosis. The heritability of axial length was slightly lower, 0.65 (s.e. 0.14) after adjustment for education and height. Consistent with our previous studies[7], as well as estimates from other

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populations, the heritability for spherical equivalent was 0.62 (s.e. 0.13), slightly lower than the individual components.

To assess the evidence for shared genetic and/or environmental components between these traits, bivariate heritability analysis using SOLAR was also performed. In these analyses, the observed phenotypic correlation was partitioned into the correlations due to genetic and to environmental factors. Analysis was performed on the unadjusted phenotype values as well as for each phenotype adjusted for statistically significant covariates ($p<0.05$). The results of our analysis for the adjusted traits are presented in Table 5. The overall estimates of phenotypic correlation were similar to those presented in Table 2 obtained using FCOR. The total phenotypic correlation between spherical equivalent and corneal curvature was 19%. This correlation was largely due to shared genetic effects, since the genetic correlation was estimated to be 0.25 ($p=0.06$) and there was no evidence of shared environmental factors between spherical equivalent and corneal curvature, with an environmental correlation of 0.01 ($p=0.98$). Overall the inverse phenotypic correlation between spherical equivalent and axial length of -0.47 was attributed to both a strong inverse genetic correlation, -0.25 ($p=0.03$), as well as strong shared environmental effects, since the environmental correlation was -0.94 ($p<0.009$). While only some of the genetic influences on spherical equivalent act via axial length, most of the environmental factors which act on spherical equivalent influence axial length.

We also assessed the role of genetic and environmental factors in the observed correlation between axial length and corneal curvature, which demonstrated a phenotypic correlation of 0.35. The phenotypic correlation was largely due to shared genetic factors, 0.40 ($p<0.001$). However, there was some suggestion, although not statistically significantly, of shared environmental factors as well, 0.26 ($p=0.72$), suggesting a role for genes that influence both axial length and corneal curvature but also genes that act independently on these traits. The strongest phenotypic correlation in all of our analyses was that of spherical equivalent and the ratio of axial length to corneal curvature, which demonstrated a -0.61 correlation. This correlation is due to strong genetic correlation, -0.47 ($p<0.001$), and strong environmental correlation, -1 ($p<0.003$) between these phenotypes. Thus, genes influencing the ratio of axial length to corneal curvature play an important role in determining spherical equivalent. There was also evidence of shared genetic effects between anterior chamber depth and axial length, 0.36 ($p=0.04$) as well as between anterior chamber depth and the ratio of axial length and corneal curvature, 0.38 ($p=0.02$). Overall, each phenotype was influenced by genetic factors and some genetic factors are shared among traits. Environmental factors seemed to play an important role in axial length and spherical equivalent, but less so for corneal curvature and anterior chamber depth.

DISCUSSION

Quantitative refraction and the related clinical phenotypes of myopia and hyperopia are under strong genetic control. However, the observed phenotype of quantitative refraction is influenced by the relationship of axial length to corneal curvature. Heritability estimates for axial length and corneal curvature were comparable or slightly higher than for quantitative refraction, suggesting that inherited genetic factors play an equally important role in the development of these components as compared to quantitative refraction (which is also influenced by phenotypic heterogeneity related to development of cataract and iatrogenic interventions such as refractive procedures). These findings suggest that understanding of the genetics of refraction should include the investigation of genetic determinants of these biometric traits.

Axial length reflects the total length of the lens, anterior chamber and vitreous chamber. Linear regression analysis of the family data used in these analyses indicated no significant association

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between spherical equivalent and anterior chamber depth (p=0.6) after adjustment for axial length. However, both anterior chamber depth and spherical equivalent are strongly associated with axial length (p-values <0.001). This suggests the heritability of axial length may in part be mediated by anterior chamber depth.

Our results were consistent with previous studies that have examined the heritability of refraction, axial length, corneal curvature and anterior chamber depth in other populations. However, unlike some previous studies our study population was limited to older, Caucasian adults. The high heritabilities observed for these phenotypes demonstrate, in our study suggest that there is evidence of strong genetic effects on these traits in older adults despite the variety of environmental exposures and other disease processes that may have occurred during these individuals' lifetimes. Because many ocular refractive errors, in particular myopia, first develop in childhood, many studies of refraction focus on young adults. However, our results indicate that genetic studies of refraction in older adults should have ample power to identify genetic loci. While more accurate measurement of early environmental factors such as childhood near-work are possible on younger cohorts, extreme values of spherical equivalent, in particular myopia, can develop into the 2nd and 3rd decade of life (excluding later myopic shifts due to factors such as nuclear sclerosis). Therefore, misclassification due to changes of spherical equivalent in these early decades is less of a concern when studying adults. Our analysis suggests that environmental factors play more of a role in determining axial length as compared to corneal curvature. The strong environmental correlation between spherical equivalent and axial length suggests a large portion of the environmental influences on spherical equivalent are mediated through axial length. This is consistent with studies that demonstrated that near-work is associated with increased axial length leading to decreased spherical equivalent[46]. While we adjusted for years of education, our analysis still suggested a significant role of environmental factors in determining spherical equivalent and axial length. This could be due to years of education not being a sufficient surrogate for total near-work such that there is significant residual confounding. However, other unmeasured factors could also be involved. The heritability of corneal curvature was higher than either axial length or spherical equivalent. These results could be due in part to a smaller role for environmental factors in determining corneal curvature as heritability is an estimate of the proportion of the total trait variation due to genetic factors.

Genetic heterogeneity, different genes that play a role in determining the same phenotype, not only make it difficult to identify genes which underlie complex traits such as spherical equivalent but also have been demonstrated to be a substantial cause of the difficulty in replicating linkage findings. Given the biological complexity of spherical equivalent and the likely substantial genetic heterogeneity of this trait, it is not surprising there have been numerous reported linkages and differences in linkage peaks when comparing high myopia, myopia, severe hyperopia, and quantitative spherical equivalent[47]. Additionally, the small to modest samples sizes of some studies may result in limited power to replicate linkage peaks.

Limitations of our study include the inability to examine the impact of near-work, other than through the surrogate measure of years of education, on our various traits. Given the association between near-work and myopia this may cause a slight underestimation of our familial correlation. Also, because measurement of axial length, corneal curvature and anterior chamber depth is only available for the 4th follow-up visit, our samples size reflects only a sub-set of the initial cohort and we cannot examine age-related changes in these traits.

The high heritability of these optical components of refraction suggest that using these traits in analysis aimed at understanding the genetic basis of ocular refractive errors may be useful. Our analysis builds on previous studies by suggesting there are genes that influence both axial length, corneal curvature and anterior chamber depth. However, our results also suggest that

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there are other genes that influence these traits independently. Since fewer genes are likely to impact axial length or corneal curvature as compared to the composite phenotype of quantitative refraction (less genetic heterogeneity), examining these traits independently is likely to result in greater power to detect genes associated with these phenotypes. Linkage studies that examine axial length, corneal curvature and anterior chamber depth as well as spherical equivalent will provide further insight into the development of ocular refraction.

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References

1. 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]
2. Wang Q, Klein BE, Klein R, Moss SE. Refractive status in the Beaver Dam Eye Study. Invest Ophthalmol VisSci 1994;35:4344–4347.
3. Wong L, Coggon D, Cruddas M, Hwang CH. Education, reading, and familial tendency as risk factors for myopia in Hong Kong fishermen. J Epidemiol Community Health 1993;47:50–53. [PubMed: 8436895]
4. Angle J, Wissmann DA. Age, reading, and myopia. American journal of optometry and physiological optics 1978;55:302–308. [PubMed: 696794]
5. Aine E. Refractive errors in a Finnish rural population. Acta Ophthalmol (Copenh) 1984;62:944–954. [PubMed: 6524319]
6. 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]
7. Klein AP, Duggal P, Lee KE, Klein R, Bailey-Wilson JE, Klein BE. Support for polygenic influences on ocular refractive error. Invest Ophthalmol VisSci 2005;46:442–446.
8. Ashton GC. Segregation analysis of ocular refraction and myopia. Human Heredity 1985;35:232–239. [PubMed: 4029963]
9. Sorsby, A.; Sheridan, M.; Leary, GA. Medical Research Council Special Report. HMSO; London: 1962. Refraction and its components in twins. Series 303
10. Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: the twin eye study. Invest Ophthalmol VisSci 2001;42:1232–1236.
11. 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]
12. 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]
13. Young TL, Ronan SM, Alvear AB, et al. A second locus for familial high myopia maps to chromosome 12q. American Journal of Human Genetics 1998;63:1419–1424. [PubMed: 9792869]
14. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. Am J HumGenet 1998;63:109–119. [PubMed: 9634508]
15. Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF. Novel locus for X linked recessive high myopia maps to Xq23-q25 but outside MYP1. Journal of medical genetics 2006;43:e20. [PubMed: 16648373]
16. Nallasamy S, Paluru PC, Devoto M, Wasserman NF, Zhou J, Young TL. Genetic linkage study of high-grade myopia in a Hutterite population from South Dakota. Molecular vision 2007;13:229–236. [PubMed: 17327828]

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17. Paluru PC, Nallasamy S, Devoto M, Rappaport EF, Young TL. Identification of a novel locus on 2q for autosomal dominant high-grade myopia. Invest Ophthalmol Vis Sci 2005;46:2300–2307. [PubMed: 15980214]

18. Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF. A new locus for autosomal dominant high myopia maps to 4q22-q27 between D4S1578 and D4S1612. Molecular vision 2005;11:554–560. [PubMed: 16052171]

19. 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. American Journal of Human Genetics 2004;75:448–459. [PubMed: 15273935]

20. Stambolian D, Ciner EB, Reider LC, et al. Genome-wide scan for myopia in the Old Order Amish. American journal of ophthalmology 2005;140:469–476. [PubMed: 16084785]

21. Hammond CJ, Andrew T, Mak YT, 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. American Journal of Human Genetics 2004;75:294–304. [PubMed: 15307048]

22. Klein AP, Duggal P, Lee KE, Klein R, Bailey-Wilson JE, Klein BE. Confirmation of linkage to ocular refraction on chromosome 22q and identification of a novel linkage region on 1q. Arch Ophthalmol 2007;125:80–85. [PubMed: 17210856]

23. Wojciechowski R, Moy C, Ciner E, et al. Genomewide scan in Ashkenazi Jewish families demonstrates evidence of linkage of ocular refraction to a QTL on chromosome 1p36. Hum Genet 2006;119:389–399. [PubMed: 16501916]

24. Carney LG, Mainstone JC, Henderson BA. Corneal topography and myopia. A cross-sectional study. Invest Ophthalmol Vis Sci 1997;38:311–320. [PubMed: 9040463]

25. Grosvenor T, Scott R. Role of the axial length/corneal radius ratio in determining the refractive state of the eye. Optom Vis Sci 1994;71:573–579. [PubMed: 7816428]

26. Mainstone JC, Carney LG, Anderson CR, Clem PM, Stephensen AL, Wilson MD. Corneal shape in hyperopia. Clin Exp Optom 1998;81:131–137. [PubMed: 12482262]

27. Strang NC, Schmid KL, Carney LG. Hyperopia is predominantly axial in nature. Current eye research 1998;17:380–383. [PubMed: 9561829]

28. Wong TY, Foster PJ, Ng TP, Tielsch JM, Johnson GJ, Seah SK. Variations in ocular biometry in an adult Chinese population in Singapore: the Tanjong Pagar Survey. Invest Ophthalmol Vis Sci 2001;42:73–80. [PubMed: 11133850]

29. 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. The British journal of ophthalmology 2001;85:1470–1476. [PubMed: 11734523]

30. Teikari J, O'Donnell JJ, Kaprio J, Koskenvuo M. Genetic and environmental effects on oculometric traits. Optom VisSci 1989;66:594–599.

31. Biino G, Palmas MA, Corona C, et al. Ocular refraction: heritability and genome-wide search for eye morphometry traits in an isolated Sardinian population. Hum Genet 2005;116:152–159. [PubMed: 15611866]

32. Chen CY, Scurrah KJ, Stankovich J, et al. Heritability and shared environment estimates for myopia and associated ocular biometric traits: the Genes in Myopia (GEM) family study. Hum Genet 2007;121:511–520. [PubMed: 17205325]

33. Dirani M, Chamberlain M, Shekar SN, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. Invest Ophthalmol Vis Sci 2006;47:4756–4761. [PubMed: 17065484]

34. Zhu G, Hewitt AW, Ruddle JB, et al. Genetic Dissection of Myopia Evidence for Linkage of Ocular Axial Length to Chromosome 5q. Ophthalmology. 2007

35. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. Ophthalmology 1991;98:1310–1315. [PubMed: 1923372]

36. Linton KL, Klein BE, Klein R. The validity of self-reported and surrogate-reported cataract and age-related macular degeneration in the Beaver Dam Eye Study. Am J Epidemiol 1991;134:1438–1446. [PubMed: 1776618]

37. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population. The Beaver Dam Eye Study. Ophthalmology 1996;103:1169–1178. [PubMed: 8764783]

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38. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: The Beaver Dam Eye Study. Ophthalmology 2001;108:1757–1766. [PubMed: 11581046]

39. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. American journal of ophthalmology 2006;142:539–549. [PubMed: 17011842]

40. Ferris FL 3rd, Bailey I. Standardizing the measurement of visual acuity for clinical research studies: Guidelines from the Eye Care Technology Forum. Ophthalmology 1996;103:181–182. [PubMed: 8628551]

41. Ferris FL 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. American journal of ophthalmology 1982;94:91–96. [PubMed: 7091289]

42. Klein BE, Klein R, Linton KL, Magli YL, Neider MW. Assessment of cataracts from photographs in the Beaver Dam Eye Study. Ophthalmology 1990;97:1428–1433. [PubMed: 2255515]

43. S.A.G.E.. Statistical analysis for genetic epidemiology. Computer program package available from Statistical Solutions Ltd; Cork, Ireland: 2002.

44. Martin LJ, Cianflone K, Zakarian R, et al. Bivariate linkage between acylation-stimulating protein and BMI and high-density lipoproteins. Obesity research 2004;12:669–678. [PubMed: 15090635]

45. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet 1998;62:1198–1211. [PubMed: 9545414]

46. Wong TY, Foster PJ, Johnson GJ, Seah SK. Education, socioeconomic status, and ocular dimensions in Chinese adults: the Tanjong Pagar Survey. The British journal of ophthalmology 2002;86:963–968. [PubMed: 12185116]

47. suarez, BK.; Hampe, GL.; VanEerdewegh, P. Problems of Replicating Linkage Claims in Psychiatry. In: Gershon, ES.; Cloning, CR., editors. Genetic Approaches to Mental Disorders. Amereican Psyscological Association; 1994. p. 23-46.

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Table 1

Overview of Study Population

	No.	Family Data Mean (S.D)	No.	Non-Family Cohort Mean (S.D)
Age (year)	690	71.58 (8.17)	1430	70.56 (8.38)
Spherical Equivalent (Diopter)	594	0.58 (2.25)	1233	0.27 (2.35)
Nuclear sclerosis (grade)	553	2.92 (0.73)	1113	2.90 (0.74)
Axial Length (mm)	642	23.56 (1.14)	1325	23.75 (1.16)
Anterior Chamber Depth (mm)	545	3.09 (0.37)	1130	3.12 (0.37)
Corneal Curvature (mm)	640	7.69 (0.26)	1322	7.71 (0.26)
AL/CC[¤]	640	3.07 (0.14)	1321	3.08 (0.14)
Education (year)[*]	687	11.95 (2.13)	1419	13.19 (2.80)
Gender (%female)	690	54%	1420	58%
Height (inch)[*]	688	65.70 (3.54)	1417	65.92 (3.63)

[*] at baseline exam,

[¤] Corneal curvature/Axial length ratio

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Table 2

Self correlations (standard error)

	Spherical Equivalent[1]	Corneal Curvature[2]	Axial Length[3]	Anterior Chamber Depth[4]	Axial Length[5]/ Corneal Curvature Ratio
Spherical Equivalent[1] (Diopter)	**1**	0.191 (0.045)	-0.446 (0.040)	-0.096 (0.047)	-0.5999 (0.0331)
Corneal Curvature[2] (mm)		1	0.344 (0.037)	-0.017 (0.047)	-0.3412 (0.0369)
Axial Length[3] (mm)			1	0.348 (0.043)	0.7626 (0.0181)
Anterior Chamber Depth[4] (mm)				1	0.3633 (0.0429)
Axial Length[5]/Corneal Curvature Ratio					1

Adjusted for

[1] age, education, nuclear sclerosis

[2] height

[3] education, height

[4] age, education, height, nuclear sclerosis

[5] education (Axial length only)

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Table 3

Family pair correlations of refraction and biometric traits using FCOR & Heritability Estimates using SOLAR

	Number pairs	Adjusted Sibling Correlation	Number pairs	Adjusted Cousin Correlation	Pedigrees	Adjusted Heritablity	Unadjusted Heritablity
Spherical Equivalent[1] (Diopter)	162	0.328 (0.083)	202	0.123 (0.008)	189	0.578 (0.127)	0.617 (0.127)
Corneal Curvature[2] (mm)	215	0.438 (0.072)	270	0.226 (0.075)	189	0.953 (0.108)	0.948 (0.104)
Axial Length[3] (mm)	215	0.335 (0.075)	273	-0.019 (0.068)	189	0.674 (0.136)	0.651 (0.137)
Anterior Chamber Depth[4] (mm)	146	0.319 (0.094)	190	0.064 (0.088)	189	0.779 (0.142)	0.732 (0.154)
Axial Length/Corneal Curvature[5] ratio	215	0.330 (0.075)	270	0.000 (0.069)	189	0.685 (0.128)	0.682 (0.127)

Adjusted for

[1] age, education, nuclear sclerosis

[2] height

[3] education, height

[4] age, education, height, nuclear sclerosis

[5] education (Axial length only)

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Table 4

Sibling pair inter-trait correlations (standard error) using FCOR

	Spherical Equivalent[1]	Corneal Curvature[2]	Axial Length[3]	Anterior Chamber Depth[4]	Axial Length[5]/ Corneal Curvature Ratio
Spherical Equivalent[1] (Diopter)	**0.328 (0.083)**	0.060(0.072)	-0.246 (0.069)	-0.077 (0.0749)	-0.294 (0.071)
Corneal Curvature[2] (mm)		**0.438 (0.072)**	0.153 (0.070)	0.002 (0.0749)	-0.141 (0.070)
Axial Length[3] (mm)			**0.335 (0.075)**	0.153 (0.0744)	0.232 (0.071)
Anterior Chamber Depth[4] (mm)				**0.319 (0.0936)**	0.153 (0.075)
Axial Length[5]/Corneal Curvature Ratio					**0.330 (0.075)**

Adjusted for

[1] age, education, nuclear sclerosis

[2] height

[3] education, height

[4] age, education, height, nuclear sclerosis

[5] education (Axial length only)

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Table 5

Bivariate heritability analysis using SOLAR

Trait1	Trait 2	Overall Phenotypic Correlation	Genetic Correlation	p-value (vs. genetic correlation equal to 0)	p-value (vs. genetic correlation equal to 1)	Environmental Correlation	p-value (vs. environmental correlation of 0)
Spherical Equivalent[1]	**Corneal curvature**[2]	0.19	0.25	0.060	<0.001	-0.01	0.98
Spherical Equivalent[1]	**Axial length**[3]	-0.47	-0.30	0.032	<0.001	0.94 (+/- 0.32)	0.009
Corneal Curvature[2]	**Axial length**[3]	0.35	0.40	<0.001	<0.001	0.26 (+/-0.60)	0.72
Spherical Equivalent[1]	**Axial Length**[5]**/Corneal Curvature**	-0.62	-0.49	<0.001	<0.001	-1 (n.a)	0.003
Anterior Chamber Depth[4]	**Axial Length**[3]	0.37	0.36	0.038	<0.001	0.38 (+/-0.32)	0.275
Anterior Chamber Depth[4]	**Axial Length**[5]**/Corneal Curvature**	0.38	0.38	0.021	<0.001	0.39 (+/-0.32)	0.282

Adjusted for:

[1] age, education, nuclear sclerosis

[2] height

[3] education, height

[4] age, education, height, nuclear sclerosis

[5] education (Axial length only)