# Support for Polygenic Influences on Ocular Refractive Error

*Alison P. Klein,*[1] *Priya Duggal,*[1] *Kristine E. Lee,*[2] *Ronald Klein,*[2] *Joan E. Bailey-Wilson,*[1] *and Barbara E. K. Klein*[2]

**Purpose.** Refractive errors, myopia, and hyperopia are common conditions requiring corrective lenses. The familial clustering of myopia has been well established. Several chromosomal regions have been linked to high myopia (12q, 17q, and 18q), to quantitative refraction among twins (3q, 4q, 8p, and 11p), and to families with moderate myopia (22q). This study examined the familial aggregation and pattern of inheritance of ocular refraction in an adult population, by using data from the Beaver Dam Eye Study.

**Methods.** Familial correlations were examined and segregation analysis was performed on the average refractive error measurements in the right and left eyes after adjustment for age, sex, and education. Analyses were based on 2138 individuals in 620 extended pedigrees with complete data on age, sex, education, and spherical equivalent.

**Results.** Substantial positive correlation was found between siblings (0.33), parents and offspring (0.17), and cousins (0.10) and lower correlation among avuncular pairs (0.08) after adjustment for age, sex, and years of education. The results of this segregation analysis do not support the involvement of a single major locus throughout the entire range of refractive error. However, models allowing for familial correlation, attributable in part to polygenic effects, provided a better fit to the observed data than models without a polygenic component, suggesting that several genes of modest effect may influence refractive error, possibly in conjunction with environmental factors.

**Conclusions.** These results support the involvement of genetic factors in the etiology of refractive error and are consistent with reports of linkage to multiple regions of the genome. (*Invest Ophthalmol Vis Sci.* 2005;46:442–446) DOI:10.1167/iovs.04-0794

From the [1]Statistical Genetics Section, Inherited Disease Research Branch, National Human Genome Research Institute, Baltimore, Maryland; and the [2]Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, Wisconsin.

This study was supported by National Eye Institute Grants R03 EY13438 (BEKK), UIO EY06594 (RK, BEKK), and National Human Genome Research Institute Intramural Funds (JEB-W). Some of the results of this article were obtained by using the program package S.A.G.E., which is supported by a U.S. Public Health Service Resource Grant RR03655 from the National Center for Research Resources, National Institutes of Health.

Submitted for publication July 7, 2004; revised October 18, 2004; accepted October 20, 2004.

Disclosure: **A.P. Klein**, None; **P. Duggal**, None; **K.E. Lee**, None; **R. Klein**, None; **J.E. Bailey-Wilson**, None; **B.E.K. Klein**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Barbara E. K. Klein, Professor Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Ocular Epidemiology, 610 North Walnut Street, Room 409, Madison, WI 53726; kleinb@epi.ophth.wisc.edu.

Ocular refraction refers to the power of the external lens to bring images into focus on the retina. Refractive errors, myopia (nearsightedness), and hyperopia (farsightedness) are common conditions that require corrective lenses. It has been well established that myopia clusters within families, and familial high myopia (refraction of −6 D or less) has been linked to long-arm regions on chromosomes 7, 12, and 18.[1–3] Stambolian et al.[4] have shown linkage to the long arm of chromosome 22 through the study of families in which there is a high degree of aggregation of moderate myopia (<−1 D). The potential for genetic effects through the entire range of refraction has been less well studied. Twin studies have indicated a high heritability for refraction, and there is evidence showing that refraction is highly correlated between siblings.[5,6] Hammond et al.[7] reported heritabilities of 84% to 86% for refractive error as a continuous trait in a model with additive genetic components and environmental components. In addition, they reported high heritabilities for myopia and hyperopia as discrete traits (90% and 89%, respectively). Linkage analysis of quantitative refraction within the 221 dizygotic twin pairs in this same cohort provided evidence of linkage to regions on 3q, 4q, 8p, and 11p.[8]

Among the more distant family members, it has long been established that there is correlation in refractive error measurements.[9] However, the only reported segregation analysis of refraction did not support the influence of a single major gene on refraction.[10] These analyses did not take into account age, sex, and education effects. The age distribution of this study population was much broader (<10 to ~70 years) compared with the Beaver Dam Eye Study (43–84 years). In addition, Ashton[10] transformed the data before analysis, unlike in the current study, in which the best-fitting transformation is estimated as part of the model fitting process of segregation analysis.

Environmental risk factors have also been associated with refractive error, myopia, or hyperopia. Previous studies, including studies conducted within the cohort used for these analyses, The Beaver Dam Eye Study, have shown that both age and sex are associated with refractive error.[11–14] Education[15–17] and near-work[18] are both strongly associated with increasing severity of myopia. Therefore, these environmental factors must be taken into account when examining familial risk.

The goal of this study was to expand on our previous findings that refractive errors are moderately correlated among relative pairs in the following ways. First, we wanted to determine whether the observed strong familial correlations of refractive error measurements would remain after adjustment for age, education, and sex. Second, through the use of complex segregation analysis, we assessed whether these correlations between family members were due to shared environmental effects, genetic effects, or a combination of the two.

## Methods

This study was reviewed and approved by the institutional review boards of the University of Wisconsin School of Medicine and the National Human Genome Research Institute, National Institutes of



Investigative Ophthalmology & Visual Science, February 2005, Vol. 46, No. 2

Health. Appropriate informed consent was obtained from all study participants in accordance with the tenets of the Declaration of Helsinki.

## Study Population

The baseline exam of The Beaver Dam Eye Study, conducted between 1988 and 1990, involved 4926 participants (of the 5924 eligible individuals, who resided in the township of Beaver Dam).[19] Follow-up examinations have been conducted every 5 years. However, in the present study, we used only data from the baseline examination. Recruitment methods and study procedures are described in detail elsewhere.[20]

During the baseline and subsequent examinations, eye examinations were performed, including automated refractive error measurements for all participants. Family relationship information was obtained from all participants at the baseline examination. During the first follow-up visit, conducted between 1993 and 1995, family relationships, including extended pedigree information were confirmed. Of the 5924 eligible individuals, 2783 had available information on familial relationships and could be classified into one of 602 pedigrees. Of these individuals, 2138 had complete age, sex, education, and refractive error data.

However, due to the limitations of the software used to analyze these data, several of the more complex pedigrees were split into smaller pedigrees yielding the 620 pedigrees used in these analyses. In this process, no individuals for whom refraction measurements were available were duplicated and only distant relationships (i.e., cousin pairs or more distant) were severed. The resultant pedigrees did not have any individuals included more than once.

## Measurement of Refractive Error

Automated refractive error measurements were obtained from 96% of the eyes. When data were available from Early Treatment Diabetic Retinopathy Study (ETDRS) refraction, these measurements were used in the analysis (4% of eyes). When data from neither of these refractions were available, (<1% of eyes), refraction from the current prescription was used. Eyes without a lens, with an intraocular lens, or eyes with best corrected visual acuity of 20/200 or worse were excluded. Only individuals with data on both eyes were included in the analysis. Spherical equivalent (sphere power + [0.5 · cylinder power] measured in diopters) was calculated from the refraction measurements. The average of the spherical equivalent in the right and left eyes was used in these analyses.

## Statistical Analysis

Familial correlation analysis was performed with FCOR, part of the Statistical Analysis for Genetic Epidemiology S.A.G.E. (S.A.G.E., ver. 4.5) statistical package. Correlations in refractive error measurements were calculated between the following relative pairs: parents and offspring, sibling, avuncular, and cousin. Equal weight was given to each pair of relatives.[21]

Commingling analysis and segregation analysis were performed with REGC version 2.1 and REGCHUNT.[22] REGC is part of the S.A.G.E. version 2.1 statistical package.[23] For both commingling and segregation analysis, Box-Cox transformation of the data was estimated as part of the analysis, denoted by parameters $\lambda_1$ and $\lambda_2$, to ensure data were on the proper scale.[23,24] For all analyses $\lambda_1$, the power parameter, was freely estimated, whereas $\lambda_2$, the scale parameter, was fixed to 20.5 (to ensure all that adjusted trait values were non-negative before power transformation).

Commingling analysis (fitting mixtures of distributions) was used to determine whether there was a single normal distribution (described by mean and variance denoted $\mu$ and $\sigma$, respectively) that provided an adequate description of the data or if a mixture of two or three normal distributions provided a significantly better description of the data. The proportion of the population in each of the distributions is denoted by $\phi$.

Segregation analysis involves fitting a series of genetic and nongenetic models, both with and without polygenic components, to determine whether there is evidence of a major gene or polygenic components that influence refractive error. If the genetic models, models in which these parameters are fixed to what is expected under Mendelian assumptions, describe the data as well as more general models, there is support for the involvement of a single major gene associated with refractive error. The specific parameters that comprise these models are detailed herein.

REGC uses the regressive models proposed by Bonney[23,25,26] to perform segregation analysis of a continuous trait. Using these models, we tested for autosomal inheritance of a single biallelic major locus that influences refractive error as a quantitative trait by obtaining maximum-likelihood estimates for parameters designed to describe the distribution of refractive error in this population. The underling type of each individual is estimated. This represents an underlying discrete factor that influences refractive error.[27] In the models that test for inheritance of a major gene, "type" represents a genotype, but in models that test for nongenetic factors, "type" (denoted AA, AB, and BB) is interpreted as levels of exposure to an unmeasured major environmental risk factor that is not correlated between family members. Three possible types are considered, which for Mendelian inheritance represent the two homozygotes AA and BB and the heterozygote AB. The mean ($\mu$) and variance ($\sigma$) of the refractive error phenotype for each of the types is estimated. However, given that these types must sum to 1, only two parameters are estimated, denoted $q_A$ and $q_B$. When Hardy-Weinberg equilibrium is assumed, only a single parameter $q_A$ is estimated. In addition, transmission parameters (denoted by $\tau$), are estimated to test whether type is shared between parent and offspring in the proportions expected under Mendelian assumptions or whether this sharing shows patterns consistent with major random environmental exposures. The probability of a parent's transmitting factor A (or A allele for genetic models) to an offspring is represented by these parameters. Under Mendelian expectations, transmission parameters are fixed to 1 for individuals of type AA, 0.5 for individuals of type AB, and 0 for individuals of type BB, denoted as $\tau_{AA}$, $\tau_{AB}$, and $\tau_{BB}$, respectively. When these parameters are set equal to each other or equal to the type frequencies, an environmental model is represented.

These analyses were performed under the assumptions of a class-D model: Dependency between sets of siblings is equal—that is, it is not affected by birth order or other factors, but is not due to common parentage alone. In addition, familial correlations can be estimated within these analyses to account for other genes of small to modest effect (polygenes) or additional environmental factors that are shared among family members. Only correlation between members of nuclear families is estimated including: spousal ($\rho_{fm}$), parent and offspring ($\rho_{po}$), and sibling ($\rho_{ss}$). In addition, because age, sex, and education are known to influence refractive error, they were incorporated in the analysis. Age and education effects were included as covariates (influencing mean values). The variance of refractive error was allowed to be different between men and women.

The most parsimonious model that adequately described these data was selected by using likelihood ratio tests and Akaike's information criterion A (AIC). Likelihood ratio tests were computed by $-2$ times the difference in lnLikelihood between the general model and a smaller model. This was then compared to a $\chi^2$ distribution, in which the degrees of freedom were equal to the difference in the number of parameters estimated between the two models. In the situation when the parameters in the general model maximized at a boundary, a mixture of $\chi^2$ distributions were used to compute probabilities.[28] AIC allowed us to compare non-nested models by taking the $-2$ lnLikelihood of the model plus a correction of 2 times degrees of freedom of the model for estimation of additional parameters.[29] The minimum AIC indicates the most parsimonious model.

No ascertainment correction was necessary for these data, given that they were obtained through a population-based survey.

**TABLE 1.** Familial Correlation of Refractive Error Measurements Adjusted for Age, Sex and Years of Education

| | Number of Pairs | Correlation | SE |
|---|---|---|---|
| Parent-offspring | 204 | 0.171 | 0.075 |
| Sibling | 987 | 0.344 | 0.038 |
| Avuncular | 611 | 0.084 | 0.051 |
| Cousin | 1462 | 0.100 | 0.0389 |

## RESULTS

### Familial Correlation Analysis

The results of the familial correlation analysis of the sum of refraction in the right and left eyes after adjustment for age, education, and sex are presented in Table 1. Among the 2138 individuals in the 620 extended pedigrees, there was strong positive correlation between siblings (0.344) and parents and offspring (0.171). There was substantial, positive correlation between avuncular pairs and cousin pairs (0.084 and 0.100, respectively). These results are consistent with a genetic component of refractive error, with the highest correlations among closely related relative pairs and a decrease in correlations as genetic sharing between relative pairs decreases (avuncular and cousin pairs).

### Commingling Analysis

The results of the commingling analysis are presented in Table 2. This analysis indicated that three distributions provided a better fit to the data than did one or two distributions. The single- and two-distribution models were rejected in favor of the three-distribution model ($P < 0.001$). If a single-distribution model provided a better fit to the data than did the two- and three-distribution models, it suggests that an individual's refractive error being at the low (myopia) or high (hyperopia) end of the spectrum was due to chance and not due to major genetic or major environmental factors.

### Segregation Analysis

The results of the complete segregation analysis under a class D model are presented in Table 3. Models in which we did not include age and education as a covariate, did not perform a Box-Cox transformation of the data, and did not allow for sex-specific variances provided a significantly poorer fit to the observed data than did models in which we included these effects (results not shown). We present only the results of our analyses that included education and age as covariates, with sex-specific variances and a Box-Cox transformation of the data. All smaller models, single-distribution, sporadic (models A and B), Mendelian (models C–E), and environmental (model F) were rejected when compared with the general model (model I) with $P < 0.01$. Model G, which is a major gene model that allows for deviation from strict Mendelian inheritance was also rejected ($P = 0.016$). However, the models in which we estimated familial correlations, in addition to the major effects (either sporadic, major gene or environmental) provided a much better fit to the observed data than did models in which we did not estimate these correlations (model A versus B and model H versus I). These additional familial correlations represent the effect of genes of smaller effect and/or additional shared environmental factors. Overall, the most parsimonious model, that with the smallest AIC, was the general-transmission model (model I: AIC = 8548.8).

## DISCUSSION

The results of our familial correlation analysis indicate strong familial correlation throughout the entire spectrum of refractive errors. For the most part, results are consistent with a previous estimation of the correlation of refractive error in these data, using generalized estimating equations.[30] The observed high correlations between siblings compared with parents and offspring and between cousins compared with avuncular pairs (given we would anticipate correlation to be greater among avuncular pairs compared with cousin pairs because genetic sharing between avuncular pairs is higher than between cousin pairs) may indicate a cohort effect. The cohort effect could be due, in part, to an increased amount of near-work activity in younger generations. Although we included an adjustment for education, this adjustment probably only accounts for part of the true amount of near-work performed. In addition, the amount of near-work performed at a given grade level may vary between generations. The estimated familial correlations between parents and offspring were higher in the previously reported analysis 0.29 (95% confidence interval [CI] 0.15–0.42).[30] The lower correlations in these analyses could be due in part to the adjustment for age, sex, and years of education. The original report did not account for these effects. In addition, the current analysis reports modest correlations in avuncular pairs, which pairs have not been reported previously. The different analytical approaches used caused the number of relative pairs to be different in the two analyses.

Commingling analysis of these data indicated that fitting multiple distributions to the data provided a better fit to the data than did a single distribution. This suggests there is not a single distribution of refractive errors in the population, but several (at least three) that could be determined by either genetic factors, major environmental factors, or a combination of both.

The results of our segregation analysis indicated that neither a single-distribution model with polygenetic effects nor models in which there was a major environmental effect along with polygenes provided an adequate fit. However, the environmental models, which allowed for multiple underlying distributions, did provide a better fit to the data than did the single-distribution model. The models that incorporated a major gene effect with additional polygenetic effects provided a better fit to the data than did the environmental models. However, these

**TABLE 2.** Results of Commingling Analysis

| Parameter Estimated | Number of Distributions in Model | | |
|---|---|---|---|
| | One | Two | Three |
| $\phi_{AA}$ | 1.0 | 0.538 | 0.019 |
| $\phi_{AB}$ | — | 0.445 | 0.915 |
| $\phi_{BB}$ | — | 0.017 | 0.066 |
| $\mu_{AA}$ | 7.778 | 5.911 | 14.545 |
| $\mu_{AB}$ | $= \mu_{AA}$ | $= \mu_{AA}$ | 9.361 |
| $\mu_{BB}$ | $= \mu_{AA}$ | 12.704 | 5.216 |
| $\sigma^2$ | 4.28 | 3.610 | 2.697 |
| $\lambda_1$ | 2.79 | 3.713 | 2.333 |
| *df* | 4 | 2 | — |
| −2lnL | 9178.5 | 9092.9 | 9068.9 |
| *P* | <0.001 | <0.001 | — |

$\phi$ indicates the proportion of the population in each distribution (AA, AB and BB); $\mu$ indicates the mean refractive error measurement for each population; $\sigma^2$ denotes the variance of refractive error for each distribution; $\lambda_1$ denotes the power parameter for the transformation and *df* denotes the degrees of freedom between the three distribution model and each of the smaller models.

**TABLE 3.** Results of Segregation Analysis of Mean Refractive Error as a Quantitative Trait Including Age, Sex and Years of Education

| | q[a] | $\tau_{AA}$ | $\tau_{AB}$ | $\tau_{BB}$ | $\mu_{AA}$ | $\mu_{AB}$ | $\mu_{BB}$ | $\sigma_{female}$ | $\sigma_{male}$ | $\rho_{PO}$ | $\rho_{SS}$ | $\lambda_1$‡ | Age | Education | −2lnL | DF† | $\chi^2$ (*P*) | AIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. No major gene | [1.0] | | | | 6.65 | $=\mu_{AA}$ | $=\mu_{AA}$ | 4.34 | 2.78 | [0] | [0] | 2.90 | 0.06 | −0.09 | 8785.5 | 8 | 264.7 <0.0001 | 8797.5 |
| B. No major gene + correlations | [1.0] | | | | 6.49 | $=\mu_{AA}$ | $=\mu_{AA}$ | 4.24 | 2.80 | 0.28 | 0.26 | 2.94 | 0.06 | −0.09 | 8669.8 | 6 | 149.0 <0.0001 | 8687.8 |
| C. Dominant + correlations | 0.86 | [1.0] | [0.5] | [0] | 4.93 | $=\mu_{AA}$ | 11.54 | 3.36 | 2.37 | 0.23 | 0.31 | 3.89 | 0.06 | −0.08 | 8539.7 | 4 | 18.9 0.0008 | 8559.7 |
| D. Recessive + correlations | 0.14 | [1.0] | [0.5] | [0] | 11.57 | $=\mu_{BB}$ | 4.93 | 3.36 | 2.37 | 0.23 | 0.31 | 3.89 | 0.06 | −0.08 | 8538.9 | 4 | 18.1 0.0012 | 8558.9 |
| E. Co-dominant + correlations | 0.14 | [1.0] | [0.5] | [0] | 11.62 | 5.40 | 4.72 | 3.24 | 2.30 | 0.22 | 0.30 | 3.93 | 0.06 | −0.08 | 8535.8 | 3 | 15.0 0.0018 | 8557.8 |
| F. Environmental (3 means) + correlations | 0.01 | $=q_{AA}$ | $=q_{AA}$ | $=q_{AA}$ | −39,621 | 11.24 | 4.99 | 3.42 | 2.29 | 0.23 | 0.04 | 3.84 | 0.06 | −0.08 | 8531.0 | 3 | 10.3 0.0162 | 8553.0 |
| G. $\tau_{AB}$ estimated (3 means) + correlations | 0.03 | [1.0] | 0.28 | [0] | 17.72 | 10.71 | 4.66 | 3.20 | 2.32 | 0.22 | 0.32 | 4.14 | 0.06 | −0.08 | 8531.2 | 2 | 10.4 0.0055 | 8555.2 |
| H. General (3 means) + correlations | 0.13 | 0.17 | 0.51 | 0.0* | 12.37 | 4.15 | 6.80 | 2.36 | 1.43 | [0] | [0] | 2.95 | 0.06 | −0.07 | 8580.9 | 2–3 | 60.1 <0.0001 | 8604.9 |
| I. General (3 means) correlations | 0.99 | 0.99 | 0.90 | 0.92 | 4.89 | 11.00 | −37,995 | 3.35 | 2.37 | 0.23 | 0.37 | 3.93 | 0.06 | −0.09 | 8520.8 | — | — | 8548.8 |

[] Parameter fixed at value given.
* Parameter maximized at a boundary.
† Degrees of freedom.
‡ $\lambda_2$ was fixed to 20.5.

Mendelian models still did not adequately fit the data and were rejected when compared with the general transmission models. This lack of fit of the Mendelian models may be due to a cohort effect, as is indicated in the familial correlation analysis, or to other environmental factors that we have not adjusted for in the analysis or to a very complex mix of several major loci, polygenes, and environmental factors that all influence the variability of refraction in this population. Because the models we tested only examined the possibility of a single major gene that controls refraction across the entire range of refractive values (i.e., from myopia to hyperopia) the lack of fit of the single-gene Mendelian models could indicate that multiple gene(s) influence this trait. In addition, models that included a polygenic component provided a better fit to the observed data than did models that did not, which supports the involvement of several genes of modest effect in the etiology of refractive error. These results are consistent with the twin studies by Hammond et al.[7,8] and the segregation analysis by Ashton.[10]

Previous studies, including studies conducted within this cohort have demonstrated that refraction changes with age.[11,12,31] In the Beaver Dam Eye Study population, the 10-year change in refraction was approximately +0.5 D in individuals aged 43 to 59, which contrasted with a −0.41-D 10-year change in individuals aged ≥70. Little change was observed for individuals aged 60 to 69 in the 10-year follow-up period. This change in refraction over a 10-year period did not seem to differ between myopes and hyperopes. Therefore, although individuals who are classified as myopic at younger ages may no longer meet the criteria for myopia at older ages, they will still (on average) have lower refractive error than an individual of the same age who was never myopic. Thus, given that we examined refractive error as a continuous trait and adjusted for the effect of age, we feel there is minimal misclassification in these data.

We may not have removed all of the effect of age, because we assumed the relationship with age to be linear, when from the longitudinal studies we know the relationship between age and refraction is not entirely linear. We attempted to include an age-squared term in the analysis, but inclusion of this covariate overparameterized the model. However, the nonlinearity is strongest in the oldest age groups, and only 6.7% of the study population was >80 years of age.

Although the Beaver Dam Eye Study was designed as a population-based study, given that this study was conducted in a small town in Wisconsin and that a high proportion of the participants were related within extended pedigrees, provides us the unique opportunity to study the genetics of refractive error in a population of families not ascertained based on refractive error measurements. The population of the entire Beaver Dam Eye Study was comparable to those in other U.S. cities of its size for income, occupation, sex distribution, and education attainment, as described in the 1980 census (BEKK, personal communication, 2003). The current analysis was limited to study participants who were also members of families. Participants who could be classified into families tended to be a bit older, were more likely to be male, had a lower level of education, and were more likely to have nuclear cataract than the entire Beaver Dam Eye Study cohort.[30] No data were obtained from family members who did not reside in Beaver Dam.

Although no genes for refraction, myopia, and hyperopia have been identified, linkage has been reported to regions on chromosomes 12, 17, and 18 in studies of families with extremely high values of refraction (i.e., high myopia), on chromosome 22 in families in which there is a large degree of aggregation of moderate myopia, and on chromosomes 3, 4, 8, and 11 for refractive error as a quantitative trait in a cohort of dizygotic twins. In addition to the possibility that multiple

genes act to influence overall refraction, these results may suggest that some of the genes that influence myopia are distinct from the genes that influence hyperopia. Linkage and association studies of the entire Beaver Dam Eye Study family resource, designed to localize the genes involved in refractive error, myopia, and hyperopia, are currently under way.

## *References*


1. 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.
2. 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.
3. 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.
4. Stambolian D, Ibay G, Reider L, et al. Genome-wide 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.
5. 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.
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.
7. 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.
8. Hammond CJ, Andrew T, Mak YT, Spector T. 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.
9. Sorsby A, Sheridan M, Leary GA. *Refraction and Its Components in Twins* . London, UK: Her Majesty's Stationary Office. Medical Research Counsel Special Report Series 303; 1962.
10. Ashton GC. Segregation analysis of ocular refraction and myopia. *Hum Hered*. 1985;35:232–239.
11. Lee KE, Klein BE, Klein R. Changes in refractive error over a 5-year interval in the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci*. 1999;40:1645–1649.
12. Lee KE, Klein BE, Klein R, Wong TY. Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. *Invest Ophthalmol Vis Sci*. 2002;43:2566–2571.
13. Grosvenor T, Scott R. Three-year changes in refraction and its components in youth-onset and early adult-onset myopia. *Optom Vis Sci*. 1993;70:677–683.
14. McBrien NA, Adams DW. A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group: refractive and biometric findings. *Invest Ophthalmol Vis Sci*. 1997; 38:321–333.
15. The Framingham Offspring Eye Study Group. Familial aggregation and prevalence of myopia in the Framingham Offspring Eye Study. *Arch Ophthalmol*. 1996;114:326–332.
16. Wang Q, Klein BE, Klein R, Moss SE. Refractive status in the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci*. 1994;35:4344–4347.
17. Sperduto RD, Seigel D, Roberts J, Rowland M. Prevalence of myopia in the United States. *Arch Ophthalmol*. 1983;101:405–407.
18. Midelfart A, Aamo B, Sjohaug KA, Dysthe BE. Myopia among medical students in Norway. *Acta Ophthalmol* (*Copenh*). 1992; 70:317–322.
19. Klein R, Klein BEK, Linton KLP, DeMets DL. The Beaver Dam Eye Study. Visual acuity. *Ophthalmology*. 1991;98:1310–1315.
20. Campbell J, Palit C. Total digit dialing for a small area census by phone. *Proc Am Stat Soc.* 1988;1249–1251.
21. *S.A.G.E. Statistical Analysis for Genetic Epidemiology.* Cork, Ireland, UK: Statistical Solutions Ltd.; 2002.
22. Atwood LD, Kammerer CM, Mitchell BD. Exploring the HDL Likelihood surface. *Genet Epidemiol*. 1993;10:641–645.
23. *S.A.G.E. Statistical Analysis for Genetic Epidemiology*. Release 2.1. Cork, Ireland, UK: Statistical Solutions Ltd.; 1984.
24. Box GED, Cox DR. An analysis of transformations. *J R Stat Soc Series B*. 1964;26:211–252.
25. Bonney G. On the statistical determination of major gene mechanism in continuous human traits: regressive models. *Am J Med Genet*. 1984;18:731–749.
26. Bonney G. Regressive logistic models of familial disease and other binary traits. *Biometrics*. 1986;42:611–625.
27. Go RC, Elston RC, Kaplan EB. Efficiency and robustness of pedigree segregation analysis. *Am J Hum Genet*. 1978;30:28–37.
28. Self SG, Liang KY. Large sample properties of the maximum likelihood estimator and the likelihood ratio test on the boundary of parameter space. *J Am Stat Assoc*. 1987;82:605–610.
29. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Con*. 1974;19:716–723.
30. 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.
31. Mutti DO, Zadnik K. Age-related decreases in the prevalence of myopia: longitudinal change or cohort effect? *Invest Ophthalmol Vis Sci*. 2000;41:2103–2107.