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Genome-wide Scan of African-American and White Families for Linkage to Myopia

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Abstract

PURPOSE—To identify myopia susceptibility genes influencing common myopia in 94 African-American and 36 White families.

DESIGN—A prospective study of families with myopia consisting of a minimum of two individuals affected with myopia.

METHODS—Extended families consisting of at least two siblings affected with myopia were ascertained. A genome-wide linkage scan using 387 markers was conducted by the Center for Inherited Disease Research. Linkage analyses were conducted with parametric and nonparametric methods. Model-free linkage analysis was performed maximizing over penetrance and over dominance (that is, fitting a wide range of both dominant and recessive models).

RESULTS—Under the model-free analysis, the maximum two point heterogeneity logarithm of the odds score (MALOD) was 2.87 at D6S1009 in the White cohort and the maximum multipoint MALOD was 2.42 at D12S373-D12S1042 in the same cohort. The nonpara-metric linkage (NPL) maximum multipoint at D6S1035 had a *P* value of .005. An overall multipoint NPL score was obtained by combining NPL scores from both populations. The highest combined NPL score was observed at D20S478 with a significant *P* value of .008. Suggestive evidence of linkage in the White cohort mapped to a previously mapped locus on chromosome 11 at D11S1981 (NPL = 2.14; *P* = .02).

CONCLUSIONS—Suggestive evidence of linkage to myopia in both African Americans and Whites was seen on chromosome 20 and became more significant when the scores were combined for both groups. The locus on chromosome 11 independently confirms a report by Hammond and associates mapping a myopia quantitative trait locus to this region.

The prevalence of myopia has increased over the last several decades. Myopia is expected to affect 10% to 25% of adults in the United States, Europe, and Australia.[1–3] Prevalences of

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60% to 80% or more have been reported for Taiwan, Hong King and Singapore.[1–4] Worldwide, refractive errors are considered to be the leading cause of visual impairment and are a disease focus of VISION 2020 whose goal is to eliminate global blindness.[5]

Familial aggregation and twin studies have confirmed that myopia has a strong genetic component.[6] Genetic mapping studies have identified at least 17 loci[6] but no genes have been identified, possibly attributable to a lack of power and genetic heterogeneity. Family-based studies of common myopia have resulted in the discovery of significant loci. A large genome-wide scan (GWS) performed on Ashkenazi Jewish families found genome-wide significant linkage for common myopia to chromosome 22q12 (MYP6, OMIM 608908) and weaker linkage on chromosome 14q32.[7,8] Wojciechowski and associates[9] analyzed ocular refraction as a quantitative trait in the same Ashkenazi Jewish population and found genome-wide significance for linkage on chromo-some 1p36 (MYP14, OMIM 610320). One other previous study analyzed refraction in twins as a quantitative trait and found strong linkage to 11p13 (MYP7, OMIM 609256), 3q26 (MYP8, OMIM 609257), 8p23 (MYP9, OMIM 609258), and 4q12 (MYP10, OMIM 609259).[10] We reported confirmatory evidence of a linked locus for myopia on 8p23 (MYP9) in a set of Amish families as well as suggestive evidence on chromosome X.[11] Analyses of myopia and refractive error in the Beaver Dam Eye Study have shown confirmatory evidence of linkage of ocular refraction to chromosome 22q12 (MYP6) and provided suggestive evidence of linkage to chromo-some 1q.[12]

We have collected multiple, two or more generation families with aggregation of myopia from two racial groups: Whites and African Americans, and have performed genome-wide linkage studies using these data. A previous quantitative trait analysis of ocular refraction in these families showed significant linkage to chromo-some 7p15 in the African-American families.[13] Here, we present analyses of the data classified as the binary trait of myopia.

METHODS

FAMILY SCREENING

The identification of myopic families was accomplished through mailings, eye clinic interviews, and referrals from private optometrists and ophthalmologists. In order to be eligible to participate in the study, families had to satisfy the following criteria: 1) At least three participating family members; 2) only one myopic parent, and 3) at least two myopic siblings. Medical records were obtained for each consenting member of selected families and/or refractions were obtained when records were not current or available. Data were gathered for all eligible and consenting parents, cousins, grandparents, grandchildren, siblings, children, aunts, and uncles of each proband. Children had to be at least five years of age to participate. Determination of African-American or White ancestry was based on self-report.

The classification of myopia was based on the following criteria: 1) cycloplegic refraction of −1.00 in each meridian of both eyes (or previous evidence of myopia based on medical records or measurement of the prescription of an old pair of eyeglasses for persons who were not available for examination) and 2) no history of systemic or ocular disease that

might predispose to myopia including premature birth. This same classification scheme was used to determine affection status for all individuals in the pedigrees, and subjects who did not meet this standard for affection were considered unaffected, except in persons between the ages of 5 and 21 years as previously described.[13] If a subject was reported to have been myopic, but this diagnosis could not be confirmed with either medical records, measurement of the prescription of an old pair of eyeglasses, or current physical examination, this person was also treated as having an unknown phenotype.

DEOXYRIBONUCLEIC ACID EXTRACTION, GENOTYPING, AND LINKAGE ANALYSIS

Peripheral blood was collected from eligible, consenting family members. High molecular weight genomic deoxyribonucleic acid (DNA) was extracted from the blood samples with a commercial DNA purification kit (Puregene; Gentra Systems Inc; Minneapolis, Minnesota, USA). Samples were stored in a DNA repository under a unique code. Genome-wide genotyping was performed at the Center for Inherited Disease Research (CIDR) by use of automated fluorescent microsatellite analysis. Polymerase chain reaction (PCR) products were sized on an ABI 3700 sequencer. The marker set used was a modification of the Cooperative Human Linkage Center marker set, version 9 (387 markers; average spacing 9 cM; average heterozygosity 0.76). The error rate, which was based on paired genotypes from blind duplicate samples, was 0.06%. The overall missing-data rate was 3.6%. All genotyping was performed blind to clinical status.

Our genotyping data were subjected to several quality checks to ensure accuracy. Mendelian inconsistencies and potential relationship errors were evaluated and corrected prior to data analysis using SIBPAIR[14] and GAS.[15] The accuracy of putative relationships was checked using Rel-Check.[16,17] Individuals with Mendelian inconsistencies at multiple markers that could not be resolved were coded as having missing genotypes for the purpose of the analysis. Estimates of allele frequencies at marker loci were determined separately for each population, using all unrelated founders in the families using the SIBPAIR[14] and LINKMEND[18] programs. The Marshfield database was used to determine the inter-marker distances of the microsatellite markers.

Because the African-American and White families were not ascertained to strongly select for pedigrees exhibiting dominant inheritance of a susceptibility allele for myopia, no genetic model was the obvious choice for analysis. Therefore, we performed model-free linkage analyses for each population using the MFMAP utility of the MFLINK program, by allowing penetrance and dominance to maximize at the trait model.[19] The statistic MALOD is the maximum logarithm of the odds (LOD) score obtained in these analyses assuming admixture (genetic heterogeneity). The inheritance and penetrance models of the loci that yielded the most significant MALOD score were then used in multipoint, parametric linkage analyses for the two data sets. These multipoint, parametric linkage analyses assuming heterogeneity were performed with the GENEHUNTER program[20] and yielded heterogeneity LOD scores (HLODs) with an estimate of the proportion of linked families, α. The allele-sharing statistic, nonpara-metric linkage $(NPL)_{all}$, which estimates the statistical significance of alleles shared identical-by-descent (IBD) between all affected family members, was also calculated using GENEHUNTER.[20] This statistic uses hidden Markov

models in an optimized version of the Lander-Green algorithm[21] to calculate the multipoint inheritance distribution conditional on the genotypes at all marker loci. The NPL_{all} score statistic, a normalized version of the S_{all} statistic of Whittemore and Halpern,[22] is the average number of permutations that preserve a collection of marker alleles obtained by choosing one allele from each affected person. The size of the score increases sharply as the number of affected individuals sharing a particular founder allele IBD increases. We calculated the overall NPL score for the data set by use of equal weights for all pedigrees. The significance level for the NPL score is calculated by use of a perfect-data approximation on the basis of the exact approach.[20]

A nonparametric analysis combining the African-American and White families was also performed by calculating the sum of NPL scores for each family (obtained in the separate African-American and White analyses just described) divided by the square root of the total number of families (n = 130) to obtain an overall combined NPL score.[20]

RESULTS

A total of 94 african-american and 36 white families were analyzed for linkage to myopia (Table 1). The average family size for the African-American population was five, with five families having more than 10 members. The mean family size in the White group was 7.2, and seven families had more than 10 members each. The average refractive error (D) was similar in both populations.

Initial NPL analyses were performed for both the African-American and White data since the modes of inheritance for either population were difficult to ascertain. Table 2 shows the MALOD results for the model-free likelihood-based linkage using the MFMAP utility program in both populations.

In the African-American families, two-point linkage analysis resulted in a MALOD of 1.61 at marker D6S2436 and a similar multipoint MALOD was also found for the interval between D6S2436 and D6S1035, both observed under a dominant model. D7S1808 had a two-point MALOD = 1.33 and a higher multipoint MALOD = 1.87, also under dominant models. D4S2367, also maximizing with a dominant model, had the highest two-point MALOD = 1.95 but the multipoint MALOD in this region barely reached one. Supplemental Table 1 (available at AJO.com) gives full details of the models that yielded the MALOD scores at each of these loci.

In the White population, the nonparametric analyses using MFMAP showed three loci with some evidence of linkage (MALOD > 1). The two-point MALOD for D6S1009 was 2.87 while the multipoint maximum MALOD score for the interval between D6S1040 and D6S1009 was 2.19, both under recessive models. D12S373 had a two-point MALOD = 1.45 and the multipoint MALOD at the interval D12S373-D12S1042 increased to 2.42, under recessive models. A two-point MALOD = 2.46 was observed for D20S478 and the peak multipoint MALOD for the interval D20S477-D20S481 was 2.14, under recessive models. Supplemental Table 2 (available at AJO.com) gives full details of the models that yielded the maximum MALOD scores at each of these loci.

The data were also analyzed using parametric and nonparametric methods in the program GENEHUNTER. In the African-American families, a dominant model with penetrance in gene carriers of $f_1 = f_2 = 0.437$, a phenocopy rate of $f_0 = 0.038$, and an allele frequency of q = 0.031 was used for the multipoint parametric linkage analysis using GENEHUNTER. A linkage peak was observed at 164.9 Kosambi cM at D6S1035 with a parametric multipoint HLOD = 1.9. Another peak was found at 49.9 Kosambi cM near D7S817 with a multipoint parametric HLOD = 1.92. The NPL results are shown in Table 3. The most significant nonparametric results were at D6S1035 with a multipoint NPL score [NPL = 2.59 (*P* = .005)], D7S817 with a. multipoint NPL = 2.57 (*P* = .005), and D3S1259 (multipoint NPL = 2.11; *P* = .018). No other parametric LOD scores or NPLs were nominally significant (i.e., *P* < .05).

In the White families, a recessive model was used in multipoint parametric GENEHUNTER analyses, assuming an allele frequency q = 0.241, penetrance in susceptibility allele homozygotes f2 = 0.623, and penetrance in carriers and noncarriers of f0 = f1 = 0.023. The strongest evidence for linkage in these GENEHUNTER analyses was on chromosome 20. D20S481 had a multi-point HLOD of one and a multipoint NPL of 2.5 (*P* = .008). Several other regions showed multipoint nonpara-metric *P* values less than .05 (Table 3) but none of the other loci reached a *P* value of less than .01.

A combined analysis was performed using the 94 African-American families and 36 White families. Multipoint NPL scores from both genome screens were combined rather than combining the data into one joint analysis. This method allows calculation of an overall combined NPL score (Table 3) while still using ethnically appropriate allele frequencies when calculating the NPL scores in each population.

When the NPL scores were combined, four regions have nominally significant nonparametric scores (*P* < .05). The best evidence for linkage to myopia combining the two populations was observed at the 6.6-cM interval around D20S478 with a combined NPL of 2.48, and a significant *P* = .008. Both African-American and White families showed some evidence of linkage to this region. Three other markers also showed some evidence for linkage in the combined analysis: D3S1259 (*P* = .017), D6S1035 (*P* = .01), and D7S817 (*P* = .036). However, the linkage in these three regions seemed to be population-specific.

DISCUSSION

We observed several regions of suggestive evidence for linkage to myopia in these data. The most interesting of these regions is on chromosome 20, around 47 to 62 cM, where suggestive evidence for linkage was seen in both African-American and White families. The local linkage peaks in these subgroups were approximately 7 cM apart. Moreover, the combined analysis of the two populations resulted in nonparametric multipoint linkage scores with minimum *P* values between .007 and .008. Hence, the evidence for linkage to myopia in this region is seen in both populations, and becomes much more significant when the data are combined.

One of the regions with suggestive evidence of linkage in the White dataset mapped to the same loci that were significant in a previous study of refraction. D11S1981 (NPL = 2.14; *P* = .02 in the White families) is within the 3-LOD interval and 12 cM away from D11S904 where Hammond and associates[10] found significant evidence of linkage to refractive error (LOD = 6.1). All positions within Hammond 3-LOD drop interval had LOD scores ≥ 3, so this entire region gave strong evidence for linkage in the initial analysis. Thus, our observation of some evidence of linkage in this region in our White dataset is quite interesting. A larger sample of White families from the same population is needed to further confirm this region.

A previous quantitative trait analysis[13] of ocular refraction in the same African-American families studied here showed genome-wide significance (*P* = .00005) in the same region as the peak we observe at D7S817 for myopia (*P* = .005). It is interesting that both analyses show evidence of linkage to this region. This result is not unexpected since the derived binary trait, myopia, is based on ocular refraction. Nevertheless, quantitative and binary trait analyses of similar underlying phenotypes do not necessarily yield identical results, even when applied to the same sample. Refractive development is likely under the control of numerous genes and environmental influences. It is possible that some genes increase susceptibility to myopia while others influence the severity of refractive error within the myopic range. In addition, quantitative trait analyses can be more powerful when there is no clear threshold (on the continuous scale) separating affected and nonaffected individuals. Families in the current study were not selected based on extreme phenotypic values, so some misclassification in affection status may have occurred.

Ethnic differences in the prevalence of myopia have recently been reviewed.[23] Of particular interest is the difference in myopia prevalence between Africans and Whites. In Africa, myopia has been reported with a prevalence ranging from 1.4% to 7%.[24–29] The White and African-American myopia prevalence reported by the NHANES Study was 26% and 13%, respectively.[30] This myopia prevalence difference between African Americans and Whites was confirmed by the Baltimore Eye Study.[31] This prevalence difference suggests that myopia and its corresponding susceptibility alleles may be more common in Whites than Africans. The admixed population, African Americans, have a myopia prevalence intermediate between the two parental populations. This could mean that African Americans have inherited some myopia susceptibility genes from their White ancestors, thus increasing the risk of disease as compared with individuals with no White ancestry such as Africans. In chromosomal regions of the African-American genome that contain myopia susceptibility genes derived from European ancestors, White sequences will be over-represented. This enables the African Americans to be studied with admixture mapping, a whole genome association technique that is designed to study populations that have arisen from the recent mixing of two different ethnic groups. This technique has been used to successfully map genes for multiple sclerosis, prostate cancer and inflammatory markers in African Americans.[32–34]

Our study adds to the growing body of literature on the genetics of myopia and refractive error. It is apparent that human myopia is a complex disorder whose development is influenced by numerous genes and/or biological pathways. Moreover, a number of different

loci or polymorphisms may account for the varying degrees of myopia susceptibility between populations. Studying refractive development in various populations should help clarify the different epidemiology of myopia among these ethnic groups. Here, we found several areas of suggestive genetic linkage to myopia in African-American and White families. It should be noted, however, that our statistical power to detect linkage to loci of small effect was limited by our sample size (393 and 184 genotyped African-American and White individuals, respectively) and relatively small pedigree sizes. The combined analysis did, however, yield a greater sample size and, hence, an increase in statistical power to detect susceptibility loci that are common across the sampled populations. Further studies using additional families in both African-American and White populations are required to increase power to detect risk loci and to determine if the suggestive evidence of linkage detected here can be reproduced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of African-American and White Families Used in Linkage Analyses

Category	African-American	White
Families (individuals)	94 (467)	36 (260)
Total individuals genotyped (average per family)	393 (4.2)	184 (5.1)
Male: female	186:281	120:137
Affected: unaffected individuals genotyped	268:125	133:45
Mean no. of individuals per family (range)	5.0 (4 to 16)	7.2 (14)
Mean no. of affected individuals per family (range)	3.0 (2 to 9)	4.6 (2 to 8)
Mean spherical equivalent, D, in affected individuals	−4.39	−4
Mean spherical equivalent, D, in unaffected individuals	0.292	0.15
Mean age, in years, of examined individuals	40.4	24.31

D = diopters.

TABLE 2

Linkage Analysis Assuming Genetic Heterogeneity of the African-American and Whites Families

	African Americans							
	Two-point Analysis				Multipoint Analysis			
CHR.	Map[a]	Marker	MALOD	α	Marker Interval	Map	MALOD	α
4	78.4	D4S2367	1.95	0.30	D4S2367-D4S3243	70.5	1.03	0.20
6	152.6	D6S2436	1.61	0.60	D6S2436-D6S1035	156.7	1.65	0.60
	164.8	D6S1035	1.30	0.60	D6S1035-D6S1277	166.0	1.46	0.40
7	41.7	D7S1808	1.34	0.50	D7S1808-D7S817	46.0	1.87	0.60
	50.3	D7S817	1.30	0.40	D7S817-D7S2846	54.0	1.15	0.50

	Whites							
	Two-point Analysis				Multipoint Analysis			
CHR.	Map	Marker	MALOD	α	Marker Interval	MAP	MALOD	α
6	137.7	D6S1009	2.87	0.90	D6S1040-D6S1009	130.2	2.19	1
12	36.1	D12S373	1.45	0.40	D12S373-D12S1042	42.3	2.42	1
	48.7	D12S1042	1.29	0.90	D12S1042-GATA91H06	52.0	1.31	1
20	54.1	D20S478	2.46	1.00	D20S477-D20S478	48.7	2.14	0.7
	62.3	D20S481	132	0.90	D20S478-D20S481	56.1	2.09	1
	79.9	D20S480	1.50	0.60	D20S481-D20S480	69.1	1.76	0.6

CHR = ?; MALOD = maximum logarithm of the odds.

[a]Map location in cM of the marker in two-point linkage or the position on the chromosome at which linkage is evaluated in multipoint linkage analysis.

TABLE 3

Comparison of Multipoint NonParametric Logarithm of the Odds Scores for African-American and White Genome Scans

			African-American		White		Combined	
CHR.	**Marker**	**Genetic Map**	**NPL**	***P* value**[a]	**NPL**	***P* value**[a]	**NPL**	***P* value**[a]
3	D3S1259	36.7	**2.11**	**.018**	0.88	.183	**2.12**	**.017**
6	D6S1009	137.7	0.06	.475	**2.25**	**.015**	1.63	.052
	D6S1035	164.8	**2.59**	**.005**	0.68	.240	**2.31**	**.010**
7	D7S817	50.3	**2.57**	**.005**	−0.02	.496	**1.80**	**.036**
9	D9S1871	8.4	−0.76	.777	1.50	.068	0.52	.302
11	D11S1981	21.5	−0.28	.610	**2.14**	**.019**	1.31	.095
12	D12S1042	48.7	−1.04	.852	1.67	.050	0.44	.330
	D12S395	136.8	−1.56	.943	1.43	.078	−0.09	.464
13	D13S894	32.9	1.75	.204	0.83	.197	1.82	.464
17	D17S1299	62.0	0.12	.448	**2.03**	**.025**	1.52	.064
20	D20S477	47.5	**2.05**	**.022**	1.38	.084	**2.43**	**.008**
	D20S478	54.1	1.38	.083	**2.13**	**.020**	**2.48**	**.007**
	D20S481	62.3	0.27	.392	**2.52**	**.008**	**1.97**	**.024**

CHR = ?; NPL = nonparametric linkage.

NPL statistics with *P* values <.05 are shown in bold.

[a] *P* value = significance level of the corresponding NPL statistic.