Linkage Replication of the *MYP12* Locus in Common Myopia

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Purpose. Myopia is a common disorder with a large public health impact. Although 12 myopia loci have been reported and heterogeneity for high myopia loci have been demonstrated, replication of high-myopia loci with a common myopia phenotype has not been successful. This study reports the successful replication of MYP12 in three large, multigenerational families with autosomal dominant (AD) common myopia (spherical equivalent [SphE] ≤ −0.50 D).

Methods. These families contained 49 participants (35 affected). The average spherical equivalent was −2.76 D (range, −0.50 to −10.25 D), average axial length was 24.52 mm (range, 23.05–27.11 mm), and average keratometry was 43.21 D (range, 39.12–47.31 D). Only five individuals in the three families presented with myopia of SphE ≤ −6.00 D. Glaucoma, keratoconus, lenticonus, and dislocated lens were not present in any study participants. A genomewide scan was performed using a mapping set with 400 markers at ~10 cM coverage. Merlin software was used for multipoint linkage analysis based on an AD model with a penetrance of 0.9 and disease allele frequency of 0.013.

Results. Significant linkage with a multipoint parametric LOD score of 3.428 ($P = 0.000035$) and a multipoint nonparametric (Kong and Cox) LOD score of 2.37 (empiric $P < 0.001$) was obtained on 2q37.1, with a 1-LOD support interval that overlapped the previously reported MYP12 locus for high myopia.

Conclusions. This study provided evidence that some high-myopia loci may contribute to all degrees of myopia and indicated the likely location of a myopia gene for the low/moderate as well as the high form of myopia. (*Invest Ophthalmol Vis Sci.* 2007;48:4433–4439) DOI:10.1167/iovs.06-1188

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Myopia is the most common ocular condition in the world and is one of the leading causes of correctable visual impairment and blindness.[1] It is broadly defined as an optical condition wherein intersecting light rays focus before the retina and result in a blurred image. The optical properties of the eye are determined by four major components: the corneal curvature, the anterior chamber depth, the crystalline lens, and the ocular axial length.[2] The development of myopia has been strongly associated with structural changes of the eye—in particular, ocular axial length elongation.[3] The diagnosis of myopia is commonly made when individuals have a spherical equivalent (SphE) of −0.50 D or worse in both eyes.[2] The prevalence of myopia is increasing around the world. In particular, the increase has been most rapid in Southeast Asian nations.[4,5] In the United States, correction of refractive error, including the cost of glasses, contact lenses, and refractive surgery, amounted to over 12 billion dollars in 1990.[6] The human and economic costs of myopia therefore make it a public health research priority.

It is now well established that both environmental and genetic factors play a role in the etiology of myopia. A large quantity of literature is available on the environmental aspects of myopia, and excessive near work such as reading is the most commonly cited environmental risk factor in myopia.[7–9] Twin studies have indicated that there is a substantial genetic component to disease, with heritability estimates for refraction raging from 0.58 to 0.94.[10–13] Family studies in both Asian[14–17] and Caucasian populations[14,18–22] have also demonstrated that parental refractive status plays an important role in the refractive status of their offspring.

As myopia is a complex disease, identifying the gene(s) involved in the development and progression of myopia has been hampered by challenges inherent in mapping genes for complex disease, such as the high prevalence, genetic heterogeneity, and wide clinical spectrum of this condition. Nevertheless, several genetic loci (MYP1 to 12) have been linked with myopia. These include the loci at 2q37.1 (MYP12),[23] 4q22-27 (MYP11),[24] 7q36 (MYP4),[25] 12q23-24 (MYP3),[26] 17q21-22 (MYP5),[27] 18p11.31 (MYP2),[26] and Xq28 (MYP1),[28] which are linked to high myopia (SphE ≤ −6.00 D). In addition, low/moderate (common) myopia (SphE ≤ 0.50 to ≤ −5.99 D) has been linked to 22q12 (MYP6),[29] 11p13 (MYP7), 3q36 (MYP8), 4q12 (MYP9), and 8q23 (MYP10).[30] There is now evidence to show that the high-myopia loci are heterogeneous.[23,27,31] Further, it has been speculated that some high-myopia loci may contribute to all degrees of myopia.[32,33] However, two studies that have attempted to achieve this have so far failed to replicate high-myopia loci (MYP2 and MYP3) when using the phenotype of common myopia (−1.00 or −0.75 D in each meridian).[32,33]

Common (low/moderate) myopia accounts for most of the disease prevalence in the United States, Western Europe, and Australia.[4] Approximately five in six persons with myopia in the general United States and Western European population have common myopia.[4] Compared with high myopia, common myopia is associated with lower rates of

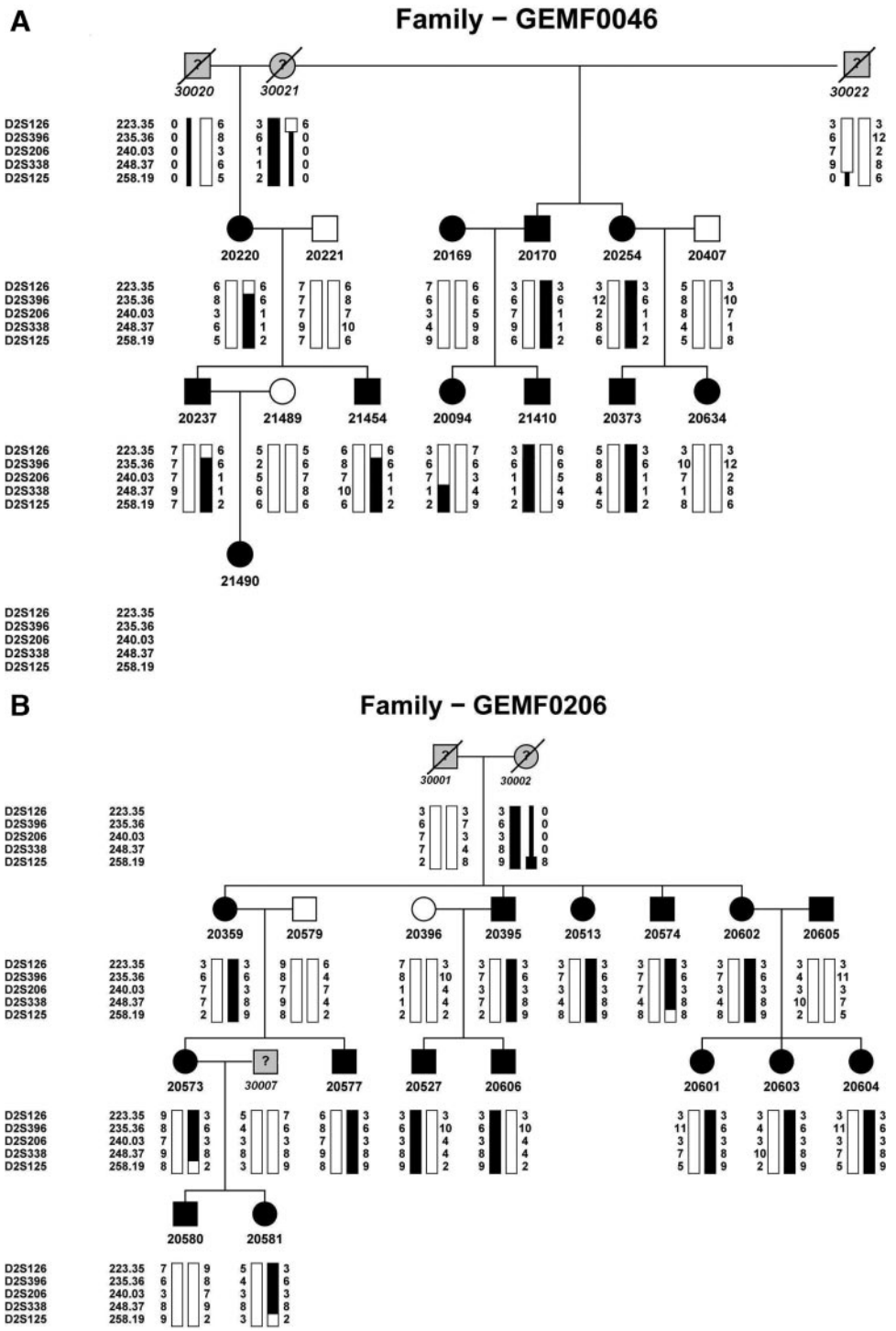

FIGURE 1. Haplotypes of the three GEM families (GEMF0046, -0206, -0251) with familial myopia. *Circles*: females; *squares*: males; *filled symbols*: affected individuals; *slashed symbols*: deceased individuals. The alleles for *D2S126*, *D2S396*, *D2S206*, *D2S338*, and *D2S125* are shown for each of the studied individuals. Haplotypes were constructed by using an algorithm in Merlin that minimizes the number of recombinations and were plotted using Haplopainter.[41] Italics denote inferred haplotypes for individuals who were not genotyped. (■)The haplotype assumed to carry the disease allele.

ocular diseases that may lead to vision loss, such as retinal detachment. However, given the high prevalence of common myopia, the absolute number of individuals who have uncorrectable vision loss due to complications of refractive error treatment such as contact lens–associated eye infection is substantial.[4] Another reason for studying common myopia is that it may provide further insight into the pathogenesis of high myopia. Hence, to investigate further the genetic basis of common myopia, we performed a linkage analysis on three large myopia families identified from the Genes in Myopia (GEM) study.

SUBJECTS AND METHODS

The GEM family study recruited index cases (probands) through the Melbourne Excimer Laser Group (MELG) in Victoria, Australia. Inclusion criteria for the GEM family study are (1) index case with refraction of SphE −0.50 D or worse in both eyes; (2) positive family history of myopia (at least one sibling or parent affected); and (3) index case and family residing within Australia. The detailed recruitment protocol of the GEM family study is described elsewhere.[34] Individuals with greater than a 2.0-D difference between both eyes or a history of systemic or ocular diseases that may predispose to myopia, including

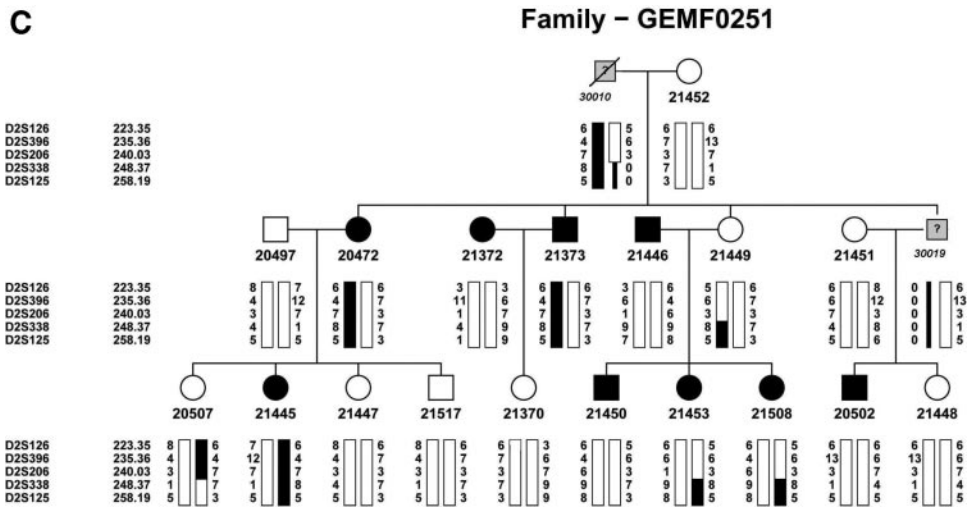

FIGURE 1. (*continued*).

premature birth, were excluded from the study. The GEM family study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Royal Victorian Eye and Ear Hospital (02/511H).

Each participant signed a consent form and privacy statement, completed a questionnaire, underwent an ophthalmic examination, and donated a blood or saliva sample for DNA analysis. The questionnaire included demographic information, ethnicity, level of education, medical and ocular histories, refractive error–associated information such as age of diagnosis, type of correction, current prescription if known, and detailed family history. The eye examination for each participant included tests for presenting visual acuity, objective refraction, subjective refraction for best corrected visual acuity, ocular biometric measurements based on partial coherence inferometry readings using optical biometer (IOLMaster; Carl Zeiss Meditec, GmbH, Oberkochen, Germany) and corneal topography if indicated. Automated refraction was performed with an autorefractor (model RM-8800; Topcon American Corp., Paramus, NJ). Distance acuity was tested using the Early Treatment of Diabetic Retinopathy Study protocol with the logMAR chart at 3 m, illuminated at 130 cd/m^2.[35] All probands and family members under the age of 21 years underwent a noncycloplegic autorefraction and subjective refraction as well as cycloplegic autorefraction. For family members over 21 years of age, noncycloplegic autorefraction and subjective refraction were performed. For participants who had undergone refractive surgery, preoperative refraction was used. The preoperative refraction was measured using the GEM family study protocol by optometrists and orthoptists in MELG.[34]

DNA was isolated from peripheral blood lymphocytes by use of standard techniques, and genotyping was performed at the Australian Genome Research Facility (AGRF; model 377 automated DNA sequencer; Applied Biosystems, Inc. [ABI] Foster City, CA) with linkage mapping (400 markers, average spacing 10 cM; Prism ver. 2 MD 10; ABI).

Genotype error checking was performed using PedManager version 0.9 (developed by M. P. Reeve-Daly and M. J. Daly; The Whitehead Institute, Massachusetts Institute of Technology, Cambridge, MA. http://www.genome.wi.mit.edu/ftp/distribution/software/pedmanager/) to identify Mendelian inconsistencies and probable incorrect genotypes on the basis of estimation of the probability of double-crossover events.[36] A total of 23 genotype errors were detected in the cases. These genotypes were set to "missing" to minimize the possible impact of misspecified genotypes. No pedigree errors were detected.

Allele frequencies were estimated from 42 control subjects who were recruited from a similar but unrelated population from Victoria. Inclusion criteria for control subjects were: (1) 25 to 45 years of age; (2) SphE 0.50 to −0.50 D (normal refraction); (3) no reported family history of myopia; and (4) axial length of 22.5 to 23.5 mm. Individuals with a history of systemic or ocular disease that may predispose to myopia, including premature birth, were excluded from the control group. The control subjects were representative of the Victorian population as a whole, that is, predominantly of Anglo-Celtic ancestry, but with sizeable minorities from Italy and elsewhere in southern Europe.

There are several options in Merlin (ver 0.10.1; http://www.sph.umich.edu/csg/abecasis/merlin/index.html; provided in the public domain by the Center for Statistical Genetics, School of Public Health, University of Michigan, Ann Arbor, MI) to estimate allele frequencies from families being analyzed.[37] However, there were only 19 founders in the three GEM family study pedigrees involved in this analysis. This number was considered insufficient for estimating allele frequencies; hence, we used a separate control population. Further, the controls were recruited from a similar but unrelated population from Victoria with stringent inclusion criteria to ensure that the controls were truly unaffected, hence provided a more closely matched and appropriate allele frequency dataset than most publicly available databases such as the CEPH database (Centre d'Etude du Polymorphisme Humain).

Multipoint nonparametric (Kong and Cox) linkage analysis and multipoint and single-point parametric linkage analyses were performed with the Merlin program.[37] There were very high correlations between the right and left ocular refractions (Pearson coefficient = 0.96), and therefore only right eyes were considered in all analyses. In terms of linkage definitions, affected was defined as SphE = −0.50 D or worse, unaffected as SphE better than −0.50 D, and unknown as all nonexamined individuals. In the nonparametric analysis, the Kong and Cox allele-sharing LOD score was calculated from IBD (identity by descent)-sharing probabilities inferred for affected individuals,[38] and an empiric probability was determined from analysis of 1000 datasets simulated under the null hypothesis of no linkage. Three autosomal dominant penetrance models were tested in the multipoint parametric analyses, using probabilities of being affected for noncarriers (phenocopy rates) of 0.1 (Model 1) and 0.2 (Model 2) with a penetrance of 0.9 and a disease allele frequency of 0.0133.[26] The two models were chosen to reflect the previous models used to identify candidate regions linked with common myopia (Model 1)[29] and the prevalence of myopia in the local population (Model 2).[39] Genetic distances were based on a deCode high-resolution genetic map,[40] and graphic representation of haplotypes was constructed using Haplopainter.[41]

RESULTS

The GEM family study recruited 916 participants from 290 different pedigrees. The size of the pedigrees varied from 2 to 38 individuals. Because of budgetary constraints, it was not possible to genotype all collected families in the GEM database. As a consequence we genotyped the three largest multigenera-

Table 1. Ocular Biometric Parameters Contributing to Refractive Error in the Participants in the Three Pedigrees

			SphE (D)		Axial Length (mm)		Keratometry (D)	
Subject ID	**Sex**	**Age**	**OD**	**OS**	**OD**	**OS**	**OD**	**OS**
GEMF0046								
20094	F	36	−5.75	−6.125	24.98	25.08	39.9	39.81
20169	F	61	−0.75	−1	23.23	23.07	46.08	46.68
20170	F	64	−4.5	−3	26.53	26.11	39.57	40.49
20220	M	68	−6.375	−6.75	26.55	26.26	43.53	43.72
20221	M	72	0.125	1	24.56	24.48	42.39	42.5
20237	F	43	−2.375	−2	25.92	26.13	42.24	41.7
20254	M	62	−8.125	−10.25	26.08	27.11	44.82	44.77
20373	F	35	−5.375	−5.125	25.65	25.9	44.04	44.3
20407	F	65	0	0.75	23.13	23.06	47.31	46.82
20634	M	33	−3.75	−1.75	23.81	23.22	46.06	46.02
21410	F	38	−0.625	−0.625	23.41	23.3	44.3	44.47
21454	M	46	−6.5	−6.25	26.2	26.09	42.97	43.05
21489	M	44	−1.625	0.125	25.18	24.17	41.85	42.09
21490	F	14	−4.25	−3.75	25.46	25.05	41.21	41.62
GEMF0206								
20359	F	62	0	−0.5	23.06	23.05	45.83	45.93
20395	M	61	−3.875	−4.25	25.88	26.09	42.51	42.24
20396	F	57	0.625	0.875	22.63	22.45	44.77	45.08
20513	F	52	−6	−7.625	24.74	25.15	44.36	44.33
20527	M	31	−0.75	−0.75	24.34	24.48	42.22	41.73
20573	F	38	−8	−6.5	25.48	25.2	39.12	39.87
20574	M	64	−4.5	−5	24.66	25.03	45.74	45.56
20577	M	39	−3.625	−3.625	25.06	25.12	43.42	43.49
20579	M	61	0	0	24.08	24.09	42.57	42.92
20580	M	8	−1	−0.75	23.25	23.25	42.56	42.3
20581	F	14	−1.5	−1.625	23.48	23.41	44.21	44.56
20601	F	34	−1.5	−1.25	23.3	23.31	44.48	44.47
20602	F	58	−3.125	−3	24.22	24.02	43.67	43.92
20603	F	32	−1.75	−1.5	24.18	24.11	44.1	44.15
20604	F	29	−2.5	−2.75	23.68	23.86	44.91	44.71
20605	M	59	−2	−1.5	24.16	23.77	44.01	44.01
20606	M	32	−2.5	−2.5	25.81	25.76	41.19	41.19
GEMF0251								
20472	F	50	−5.75	−6	25.73	25.58	40.23	39.46
20497	M	53	3.5	3.5	22.55	22.72	42.01	42.04
20502	M	38	−5.625	−6.125	25.71	25.55	43.85	44.11
20507	F	21	0.25	−0.125	22.75	22.77	44.06	44.21
21370	F	31	0	0	23.34	23.27	42.9	42.87
21372	F	57	−0.5	−0.5	23.42	23.45	41.37	41.34
21373	M	55	−1.875	0	26.06	25.95	40.28	39.28
21445	F	25	−2.25	−2.5	24.17	23.96	44.1	44.22
21446	M	57	−6.5	−5.75	24.41	25.76	44.9	45.35
21447	F	15	0	0	22.88	22.78	44.86	45.22
21448	F	41	0	0	22.92	22.94	45.71	45.96
21449	F	59	0.625	1.125	23.72	23.68	43.98	43.92
21450	M	30	−2	−2	23.76	23.87	42.62	42.7
21451	F	62	1.25	1	22.71	22.57	45.26	45.55
21452	F	90	−1	0.75	23.81	23.61	43.8	43.91
21453	F	25	−1.125	−1.25	23.13	23.17	43.68	43.74
21508	F	28	−0.5	−0.5	23.97	23.77	42.75	43.08
21517	M	19	0.25	0	23.65	23.59	42.39	42.84

tional families that had the most complete recruitment of family members as well as the largest number of affected individuals, to maximize the power to detect linkage. Figure 1 shows the structure of the three families (GEMF0046, -0206, and -0251). The largest family (GEMF0206) was of Italian decent, and the other two families (GEMF0046 and -0251) were of Anglo-Celtic origin. Of the genotyped individuals, the average age was 40 years (range, 8–90 years). There were 35 affected individuals in total, with an average age at first glasses prescription of 15.4 years (range, 6–28 years), average SphE = −2.76 D (range, −0.50 to −10.25 D), average axial length = 24.52 mm (range, 23.05–27.11 mm), and average keratometry of 43.21 D (39.12–47.31 D). Only five individuals in the three families presented with myopia of SphE ≤ −6.00 D. Glaucoma, keratoconus, lenticonus, and dislocated lens were not present in any study participants. Table 1 summarizes the ophthalmic examination results for the participants.

A multipoint nonparametric analysis was conducted using all three families and revealed a maximum LOD score of 2.37 at *D2S338* (empiric $P < 0.001$). This region fell within 5 cM of a previously identified candidate locus for high myopia, MYP12.[23] Furthermore, the 1-LOD support interval in our study includes the entire MYP12 region (Fig. 2). The maximum parametric multipoint LOD scores for Models 1 and 2 were 4.002 and 3.428, respectively, and again all three families showed linkage support to a myopia locus at *D2S338* (Ta-

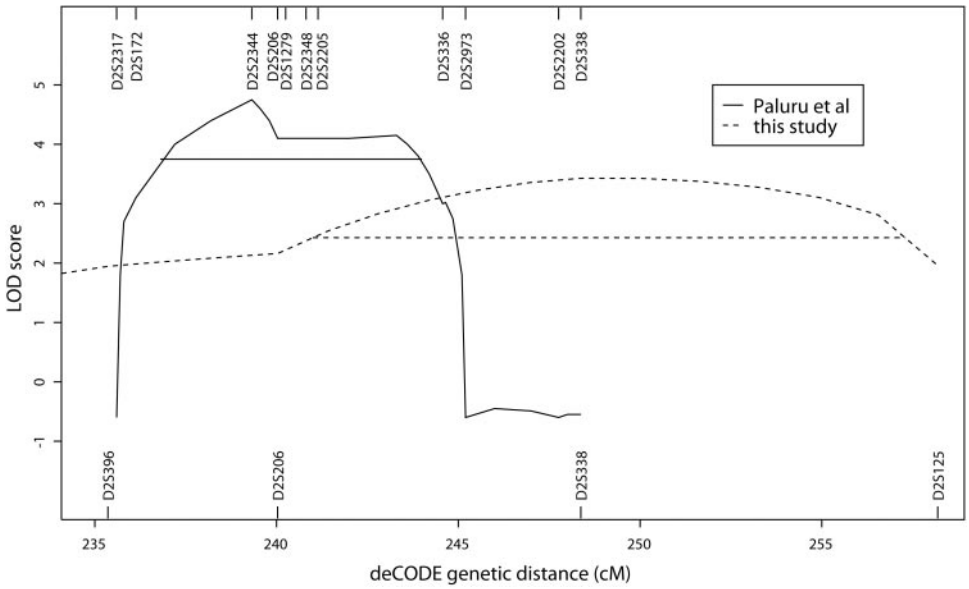

FIGURE 2. A comparison of multipoint parametric LOD scores obtained in this study (*dashed line*) and in the study by Paluru et al.[23] (*solid line*). *Horizontal lines*: overlapping 1-LOD support intervals from the two studies. Markers genotyped by Paluru et al. are shown along the *top* of the graph, and markers genotyped in the present study are shown along the *bottom* of the graph.

ble 2). In both models, no evidence for heterogeneity was detected at *D2S338* with $\alpha = 1$. As genotyping errors can cause true linkage signals to be missed in multipoint analysis, we ran a single point parametric analysis using Model 2. However, the highest LOD score in this analysis was only 1.77.

Haplotypes of family members in this region supported the linkage results (Fig. 1). All myopic individuals in the three families shared haplotypes between markers *D2S396* and *D2S125*, except for individuals 20634 (GEMF0046), 20580 (GEMF0206), and 20502 and (GEMF0251). In GEMF0206, haplotype analysis showed recombination events at *D2S396* and *D2S338*, suggesting that the critical region is located between 235.36 and 248.37 cM on chromosome 2.

Multipoint nonparametric (Kong and Cox) and parametric linkage analyses with a more stringent phenotype definition (−1.00 D or worse in each meridian) were performed with the corresponding model used by Stambolian et al.[29] in the identification of MYP6 (AD with 0.9 penetrance, allele frequency of 0.0133, and phenocopy rate of 0.10). The maximum multipoint parametric LOD score was 2.745 at *D2S338* ($P = 0.0002$). This result remains a significant replication.

We did not find any evidence suggesting linkage to any other region of the genome including the previously reported loci for mild, moderate, or high myopia on 3q26, 4q12, 4q22-27, 7q36, 8p23, 11p13, 12q21-23, 17q21-22, 18p11.31, and 22q12 (Figs. 3, 4).

DISCUSSION

The present study provided evidence of significant linkage for low/moderate myopia to marker *D2S338* (LOD = 3.4–4.002) at 2q37.1. The region described in this article has reached an LOD score of genome-wide significance as well as providing replication to the region previously linked to high myopia (MYP12).[23] The present study, although providing successful replication to this locus, was of the common myopia phenotype, and we used a different model in an independent population.

In our analysis using either multipoint nonparametric or parametric linkage analysis, the strongest linkage signal was localized to 2q37.1 (nonparametric LOD = 2.37; parametric LOD = 3.415–4.002). Linkage to the MYP12 region was demonstrated in a large family of northern European descent with 31 participants, of whom 14 were affected with high myopia (SphE ≤ −6.00 D).[23] Paluru et al.[23] obtained a maximum multipoint LOD score of 4.75 and maximum two-point LOD score of 5.67 at marker *D2S2344* and reported a minimum critical disease region spanning 9.1 cM (238.7–247.8 cM on 2q37.1). The region described in the present study lies 5 cM distal to the max LOD reported in the study by Paluru et al.[23] However, the 1-LOD support interval for the currently described region includes all of the MYP12 critical region. As no myopia disease gene has so far been identified from the MYP12 region, the results suggest replication of the region in the two studies. However, it is also possible that the locus described in the present study represents a novel locus that is actually distal to MYP12. Only further fine mapping and eventual disease gene identification will allow us to determine which of these scenarios is valid.

Two other MYP loci that have been successfully replicated are those of MYP2[42,43] and MYP6.[44] MYP2 was first identified in eight multigenerational pedigrees with high myopia and of

TABLE 2. Multipoint LOD Scores for the GEMF0046, −0206, and −0251 Families for 2q37 Microsatellite Markers for Model 2 (Combined Results Plus Family Breakdowns)

Marker	*D2S126* (221.13 cM)	*D2S396* (232.9 cM)	*D2S206* (240.79 cM)	*D2S338* (250.54 cM)	*D2S125* (260.63 cM)
Combined	0.099	1.945	2.161	**3.428**	1.959
GEMF0046	−0.8289	0.3833	0.4287	**0.9550**	0.9526
GEMF0206	0.6099	1.5610	1.6192	**1.8200**	0.3015
GEMF0251	0.3176	0.0010	0.1131	**0.6527**	0.7048

Model 2: AD, allele frequency 0.0133, phenocopy rate 0.20, penetrance 0.9.

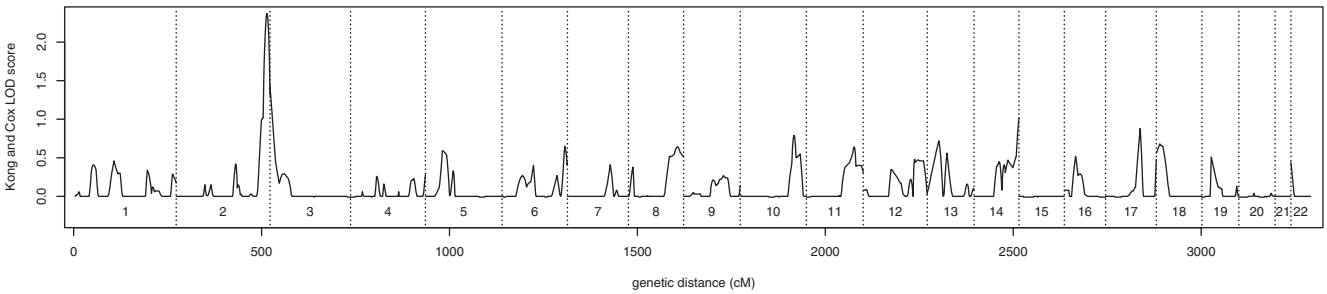

FIGURE 3. Results of the combined genomewide multipoint nonparametric (Kong and Cox) LOD score of the three families (GEMF0046, -0206, and -0251). Genetic distances based on the deCODE high-resolution genetic map.

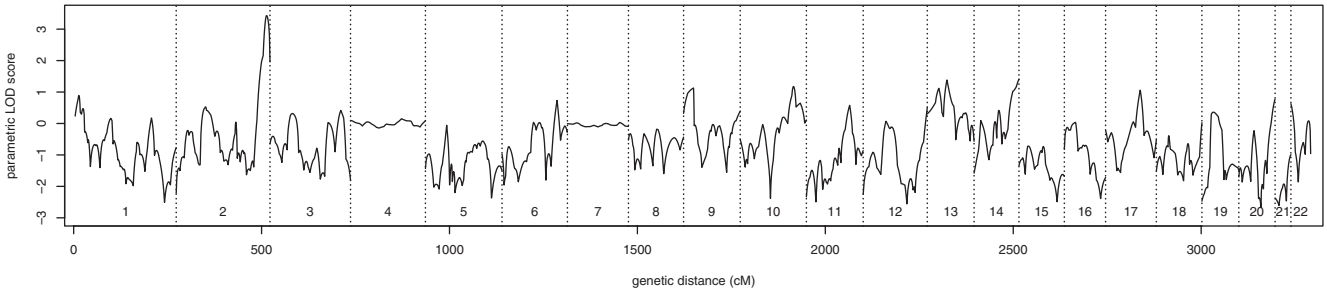

FIGURE 4. Results of the combined genomewide multipoint parametric LOD score (Model 2) of the three families (GEMF0046, -0206, and -0251). Model 2: AD, allele frequency 0.0133, phenocopy rate 0.20, penetrance 0.9. Genetic distances based on the deCODE high-resolution genetic map.

mixed ethnicity (Asian and Caucasian). Replication of this region has also been obtained in myopia families from these populations but only in those exhibiting high myopia.[42,43] Although myopia is a common disease in which heterogeneity is likely to play a large role, there remains the possibility that some of the currently described MYP loci are false positives. Thus, replicated loci are likely to provide the most fruitful results in identifying the disease genes. The importance of cross-validation of results obtained by different groups in different populations cannot therefore be overstated.

In summary, we have observed a strong linkage signal for myopia to 2q37.1, a region that has been linked to high myopia. This suggests that gene(s) in this region may influence disease susceptibility to all degrees of myopia. The identification of susceptibility loci for low/moderate myopia will be of major public health importance, and provide insights into the pathogenesis of low/moderate as well as high myopia. It will give us a better understanding of the causes of this common eye disorder and eventually will lead to methods of preventing or slowing progression of this disease.

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