COL1A1 and *COL2A1* Genes and Myopia Susceptibility: Evidence of Association and Suggestive Linkage to the *COL2A1* Locus

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Purpose. Collagen involvement in myopia development via scleral remodeling is well-known. Recently, *COL1A1* and *COL2A1* gene polymorphisms were reported to be associated with high-grade and common myopia, respectively. This study was conducted to investigate whether these collagen genes are associated and/or genetically linked with myopia in large Caucasian family datasets.

Methods. High-grade myopia was defined as ≤−5.00 D. Two independent datasets comprising 146 (Duke) and 130 (Cardiff) families with high-grade myopia participated in the association study. Allelic discrimination assays were performed on tagging SNPs for *COL1A1* and *COL2A1*. The pedigree disequilibrium test (PDT) and the association test in the presence of linkage (APL) were used for association analyses. Linkage analyses for *COL2A1* locus markers were performed with the Fastlink and Merlin programs in conjunction with data obtained from our collaborative whole-genome linkage study (254 families).

Results. Significant association was identified between five SNPs (rs1034762, rs1635529, rs1793933, rs3803183, and rs17122571) of the *COL2A1* locus and high-grade myopia ($P < 0.045$, minimum (min) $P = 0.008$) and with myopia status set at ≤−0.50 or −0.75 D (min $P = 0.004$) in the Duke dataset. The SNP rs1635529 also showed significant association in the Cardiff dataset (≤−5.00 D, min $P = 0.004$; ≤−0.50 D, min $P = 0.007$). Linkage analyses showed suggestive linkage to the *COL2A1* locus on 12q. No association was found between *COL1A1* SNPs and any degree of myopia.

Conclusions. The *COL2A1* gene was associated with high-grade myopia in two independent Caucasian family datasets. *COL1A1* gene polymorphisms were not associated with myopia in our dataset, indicating possible heterogeneity across different ethnicities. (*Invest Ophthalmol Vis Sci.* 2009;50:4080–4086) DOI:10.1167/iovs.08-3346

Genetic involvement in susceptibility to myopia is well recognized.[1,2] Identifying causative genes will lead to enhanced understanding of the disease process and may aid in prevention. Pathologic myopia is associated with molecular changes in the sclera that result in significant scleral thinning, altered scleral architecture, and ocular axial elongation.[3] The sclera is composed of approximately 85% to 90% collagen, with type I collagen the most prevalent.[4] Collagen involvement in myopia development by scleral extracellular matrix remodeling leading to ocular elongation has been well characterized.[5] Studies of human donor and tree shrew eyes have shown that 19 subtypes of collagen are expressed in the sclera.[6,7]

Mutations in the collagen type I (*COL1A1*) gene have been reported in clinical conditions associated with myopia, such as type I osteogenesis imperfecta, the Ehlers-Danlos and Marfan syndromes, and osteoporosis.[8] The cytogenetic location of the *COL1A1* gene is adjacent to a previously identified locus for myopia (MYP5, OMIM 608474; Online Mendelian Inheritance in Man; http://www.ncbi.nlm.nih.gov/Omim/ provided in the public domain by the National Center for Biotechnology Information, Bethesda, MD) on 17q.[9] An association of *COL1A1* polymorphisms with high-grade myopia was found in a Japanese case–control cohort,[10] but was not seen in another independent Japanese case–control cohort[11] and a Taiwanese case–control cohort.[12]

Collagen type-II (*COL2A1*) mutations are associated with Stickler syndrome, a condition that has severe myopia as a consistent phenotype.[13–15] To date, no myopia studies have determined linkage to the *COL2A1* locus. A family-based association study of *COL2A1* polymorphisms in a Hong Kong Chinese population did not reveal any association with myopia (Tang W, et al. *IOVS* 2004;45:ARVO E-Abstract 3724). However, a recent association analysis in a predominantly Caucasian family-based dataset suggested involvement of *COL2A1* in common, low degrees of myopia.[16]

Myopia is a common, complex, and multifactorial disorder. The likelihood that multiple genes and environmental factors influence myopia development warrants determination or replication of potential candidate gene involvement in independent and/or diverse datasets. Hence, we investigated the association of *COL1A1* and *COL2A1* polymorphisms with myopia in two independent, large, Caucasian multiplex high-grade myopia family datasets. Evidence of suggestive linkage to the *COL2A1* locus on chromosome 12 from a subset analysis of a genome-wide linkage scan is also presented.

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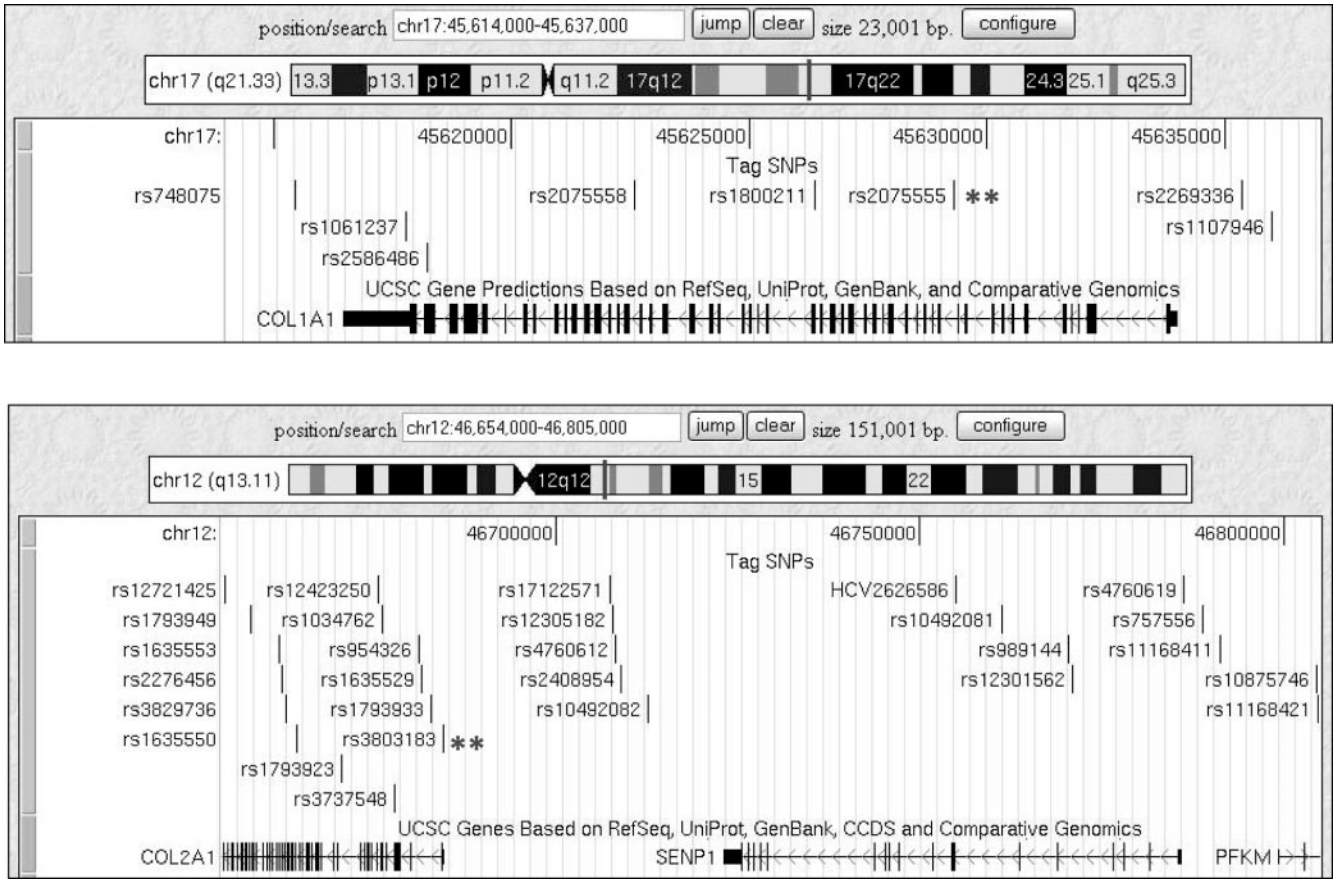

FIGURE 1. Schematic representation of the SNPs selected for the *COL1A1* and *COL2A1* genes (source, Human Genome Browser, http://genome.ucsc.edu/ provided in the public domain by UCSC Genome Bioinformatics, University of California at Santa Cruz, Santa Cruz, CA). A total of 8 SNPs were selected for *COL1A1* and 14 SNPs for *COL2A1*. **SNPs associated with high myopia and reported by Inamori et al.[10] for *COL1A1* and Mutti et al.[16] for *COL2A1*.

MATERIALS AND METHODS

Subject Selection

Informed consent was obtained from all participants. The protocol complied with the principles of the Declaration of Helsinki and received the approval of local ethics committees and institutional review boards. All subjects underwent a complete ophthalmic examination, and individuals with syndromic disorders and systemic conditions that could predispose to myopia were excluded from participation. Two large family-based datasets from Duke University and Cardiff University participated in the association study. The Duke dataset comprised 146 multiplex families with 649 total subjects, and both *COL1A1* and *COL2A1* polymorphisms were tested. The Cardiff dataset comprised 130 families with 582 individuals and served as an independent study of *COL2A1* gene association. In a parallel study in our research program, a total of 254 families from five international centers including the above 146 Duke families (total 1457 subjects) participated in a genome-wide single nucleotide polymorphism (SNP) scan for linkage analyses.[17]

Marker Selection and Genotyping

The SNPSelector program[18] was used to select tagging SNPs that met the following two criteria: (1) a squared Pearson correlation (r^2) of at least 0.67 in the linkage disequilibrium (LD) bins; and (2) a minor allele frequency of at least 5% in a Caucasian population. For *COL1A1*, eight SNPs were chosen and included the SNPs that showed significant association with high myopia identified by Inamori et al.[10] For *COL2A1*, 14 SNPs were selected, and included the SNP marker of significance reported by Mutti et al.[16] A diagram of positions of the selected SNPs relative to the *COL1A1* and *COL2A1* genes is presented in Figure 1. To screen the region downstream of the *COL2A1* gene, we selected13 additional markers based on LD structure in Caucasians, covering 50 kb (rs12305182, rs4760612, rs2408954, rs10492082, HCV2626586, rs10492081, rs989144, rs12301562, rs4760619, rs757556, rs11168411, rs10875746, and rs11168421).

For the Duke dataset, total genomic DNA was extracted from venous blood collected from patients (AutoPure LS DNA Extractor and Puregene reagents; Gentra Systems Inc., Minneapolis, MN). Custom allelic discrimination assays (*Taq*Man; Applied Biosystems, Inc. [ABI], Foster City, CA) consisting of a mixture of unlabeled polymerase chain reaction (PCR) primers and the minor groove binding group (MGB; *Taq*Man; ABI) probe (FAM and VIC dye-labeled; ABI) were used. Each assay comprised two unlabeled PCR primers and two allele-specific probes. PCR reactions were performed with PCR master mix and genetic analyzers (Taqman Universal PCR Master Mix on the GeneAmp PCR System 9700 and the 7900HT Fast PCR System; ABI) were used for reading allelic discrimination calls. CEPH (Centre d'Etude du Polymorphisme Humain, Paris, France) DNA standards and known duplicate DNA samples were included for quality control. A threshold of 95% genotyping efficiency was required for submission to the analysis database. For the Cardiff replication dataset, DNA was extracted from saline mouthwashes, as previously reported[19] and genotyping was performed by KBiosciences, Ltd. (Herts, UK), on three *COL2A1* SNPs (rs1034762, rs1635529, and rs1793933).

TABLE 1. Descriptive Statistics of the Number of Affected and Unaffected Individuals in Each Group for the Association Analyses: Duke Dataset

Group	Definition Based on Myopia Severity	Affected (A)	Unaffected (N)	Unknown (U)	Total
High-grade myopia	SE data: A ≤ −5.00 D, N ≥ −0.49 D, U others	285	155	209	649
Mild to moderate myopia	SE data: −4.99 D ≤ A ≤ −0.50 D, N ≥ −0.49 D, U others	204	155	290	649
Any myopia	SE data: A ≤ −0.50 D, N ≥ 0 D, −0.50 D < U < 0 D	489	131	29	649
−0.75 D (Threshold used in Mutti et al.[16])	SE data: A ≤ −0.75 D, N ≥ 0 D, −0.75 D < U < 0 D	476	131	42	649
−9.25 D (Threshold used in Inamori et al.[10])	SE data: A ≤ −9.25 D, N ≥ −0.49 D, U others	126	155	368	649

Classification of the dataset was based on myopia severity using spherical equivalent refractive data. D, diopters; SE, spherical equivalent refractive data; A, affected; N, unaffected, U, unknown.

Statistical Analyses

All markers were tested for Hardy-Weinberg equilibrium (HWE) with the Genetic Data Analysis (GDA) program.[20] LD between markers was computed for all pairs with the Graphical Overview of Linkage Disequilibrium (GOLD) program.[21] For association analyses, the family-based pedigree disequilibrium test (PDT) and the association in the presence of linkage (APL) test were used to determine the association of the markers with myopia.[22–24] The dataset was classified into groups based on the degree of myopia for both spherical (SPH) and spherical equivalent (SE) values. The high-grade myopia group was defined as ≤−5.00 D, the mild-to-moderate myopia group, between −0.50 D and −5.00 D, and the any-myopia group, ≤ −0.50 D. Analyses were also performed with the threshold set at ≤−9.25 D for *COL1A1* to mirror the phenotypic threshold criterion established by Inamori et al.,[10] and at ≤−0.75 D for *COL2A1* to simulate threshold in Mutti et al.[16]

The number of affected and unaffected subjects for each classification in Duke and Cardiff datasets is described in detail in Tables 1 and 2, respectively. The dataset was stratified to investigate the effect of genetic background on lower degrees of myopia within this cohort. Approximately 83% of the Duke and 98% of the Cardiff cohorts were over age 20 (an age by which refractive state becomes stable).The clinical information regarding age, sex, and refractive error for various groups in both the datasets is provided in Supplementary Tables S1 and S2, online at http://www.iovs.org/cgi/content/full/50/9/4080/CD1. For multiple testing correction, we obtained *q*-values for all markers by using the *Q*-Value program (http://faculty.washington.edu/jstorey/qvalue/; provided in the public domain by the University of Washington, Seattle).[25] Markers were declared to be significantly associated at $q < 20\%$.

To examine whether any linkage signal existed in the *COL2A1* region, linkage analysis on a set of SNPs in the *COL2A1* gene and its nearby region (57.69–70.80 cM) was performed. In addition to the SNPs from the association study, the SNPs from the linkage study by Li et al.[17] within the *COL2A1* region were used in the analysis. The dataset in the linkage study was also predominantly Caucasian (91.2%) with Asian- and African-American families contributing 4.8% and 5%, respectively. High myopia was defined as −5.00 D or more, and analyses for the overall dataset and Caucasian subgroup were performed for both the SPH and SE phenotypes. The Merlin program was used to perform parametric multipoint (http://www.sph.umich.edu/statgen/abecasis/Merlin/ provided in the public domain by the Center for Statistical Genetics, School of Public Health, University of Michigan, Ann Arbor) and nonparametric (two-point and multipoint) linkage analyses.[26] Affected-only, two-point linkage analysis was performed with the FastLink program (http://linkage.rockefeller.edu/ provided in the public domain by Rockefeller University, New York, NY) assuming autosomal dominant inheritance. HLOD (heterogeneity logarithm of odds) scores for each marker were generated.

RESULTS

Association Analyses

All results are presented for the SE phenotype only. The SPH analyses were generally in agreement and not substantially different from the SE analyses. For the *COL1A1* gene, there was no significant association of any of the eight markers with the myopia affection status. This lack of association was consistent for all thresholds set for defining myopia and across all the association tests performed. Figure 2 depicts the results of APL and PDT analyses for *COL1A1* markers. For the moderate myopia group, rs2586486 showed moderate significance ($P = 0.03$) with spherical data in the APL analysis. Other tests did not support this finding and, when corrected for multiple testing, there was no significant association. The SNP rs1800211 showed moderate significant values in the any-myopia and −9.25 D groups with the APL test; however, the PDT analysis did not support this finding. The SNP rs1061237 showed moderate significance in the −9.25 D group with the APL analysis but was not significant after correcting for multiple testing.

For the *COL2A1* gene, both PDT and APL analyses identified significant association between five SNPs (rs1034762,

TABLE 2. Descriptive Statistics of the Number of Affected and Unaffected Individuals in Each Group for the Association Analyses: Cardiff Dataset

Group	Definition Based on Myopia Severity	Affected (A)	Unaffected (N)	Unknown (U)	Total
High-grade myopia	SE data: A ≤ −5.00 D, N ≥ −0.49 D, U others	327	56	199	582
Mild to moderate myopia	SE data: −4.99 D ≤ A ≤ −0.50 D, N ≥ −0.49 D, U others	130	56	396	582
Any myopia	SE data: A ≤ −0.50 D, N ≥ 0 D, −0.50 D < U < 0 D	457	44	81	582
−0.75 D (Threshold used in Mutti et al.[16])	SE data: A ≤ −0.75 D, N ≥ 0 D, −0.75 D < U < 0 D	448	44	90	582

Classification of the dataset was based on myopia severity using spherical equivalent refractive data. D, diopters; SE, spherical equivalent refractive data; A, affected; N, unaffected; U, unknown.

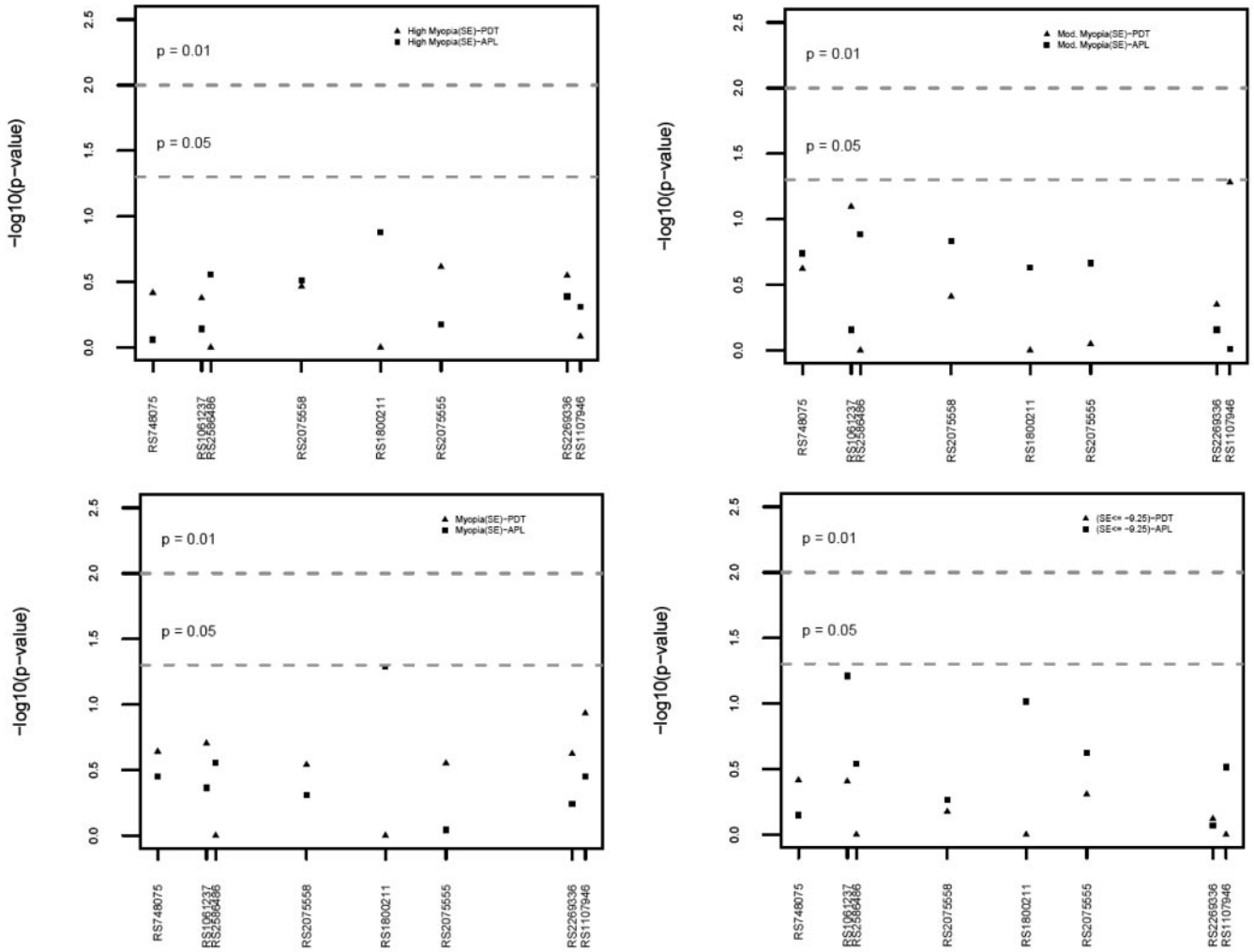

FIGURE 2. APL and PDT analyses of the *COL1A1* gene-tagging polymorphisms. Analyses were performed for high, moderate, and any-myopia states (SE data presented). The threshold used by Inamori et al.[10] (−9.25 D) was also considered for analysis.

rs1635529, rs1793933, rs3803183, and rs17122571) of the *COL2A1* locus and high-grade myopia status with $P < 0.045$ (min $P = 0.008$) in the Duke dataset (Fig. 3). Analysis of the *COL2A1* SNPs with the mild-to-moderate myopia group revealed no significant association, with the exception of the marker rs17122571, but this was not significant after correcting for multiple testing. However, analysis with myopia status set at ≤−0.50 D or ≤−0.75 D (mild, moderate, and high-grade myopia groups combined) revealed significant association of the same five SNPs (min $P = 0.004$). The APL and PDT analyses results for *COL2A1* polymorphisms for the Duke dataset are depicted in Figure 3 along with the 13 markers that covered the 50-kb region downstream of *COL2A1*. The SNP rs1635529 also showed significant association in the Cardiff dataset in high-grade myopia and any-myopia groups (≤−5.00 D, min $P = 0.004$; ≤−0.50 D and −0.75 D, min $P = 0.007$). The APL and PDT results for markers tested in the Cardiff dataset are shown in Table 3 based on each criterion tested. The positive association of all significant *COL2A1* markers was confirmed after correcting for multiple testing (*Q*-Value program).

Linkage Analyses

Figure 4 shows the linkage results for chromosome 12 from a recent study by Li et al.[17] A 36.59-cM region on chromosome 12 (89.57–126.16 cM, 12q21.2-22) with a peak marker at rs337663 (HLOD = 3.48, 101.97 cM) was found to have significant linkage using the SPH phenotype. This region included four markers (rs2063239, rs20508, rs1849929, and rs4213) with two-point HLOD scores ≥2. In addition, the nonparametric multipoint analysis of the initial genome-wide linkage scan revealed suggestive linkage peaks that encompassed 53.89 to 57.69 cM (peak marker at rs956066, 12q12, 56.41 cM, HLOD = 1.35) and 70.8 to 74.32 cM (peak marker at rs1504464, 12q14.1, 73.95 cM, HLOD = 1.22; Fig. 4). The *COL2A1* gene maps to 12q13.11 (62.5 cM) and lies between these two suggestive linkage peaks. After the inclusion of *COL2A1* SNPs (genotyped in the association phase) in this region (57.69–70.80 cM), analysis revealed HLOD scores (>1.5) for the *COL2A1* locus indicating suggestive linkage. The two-point nonparametric analysis revealed suggestive HLOD scores of 1.69 for marker rs855272 (62.14 cM) and 1.52 for marker rs894734 (69.11 cM; Table 4). The multipoint nonparametric analysis revealed several suggestive HLOD scores for the entire region tested between 60.07 and 70.80 cM (peak HLOD = 2.14 at rs1793949, 62.49 cM; Table 5). The parametric analyses assuming autosomal dominant inheritance on the *COL2A1* locus also revealed similar suggestive HLOD scores (data not shown). The *COL1A1* locus did not show linkage to any myopia disease state in this cohort.

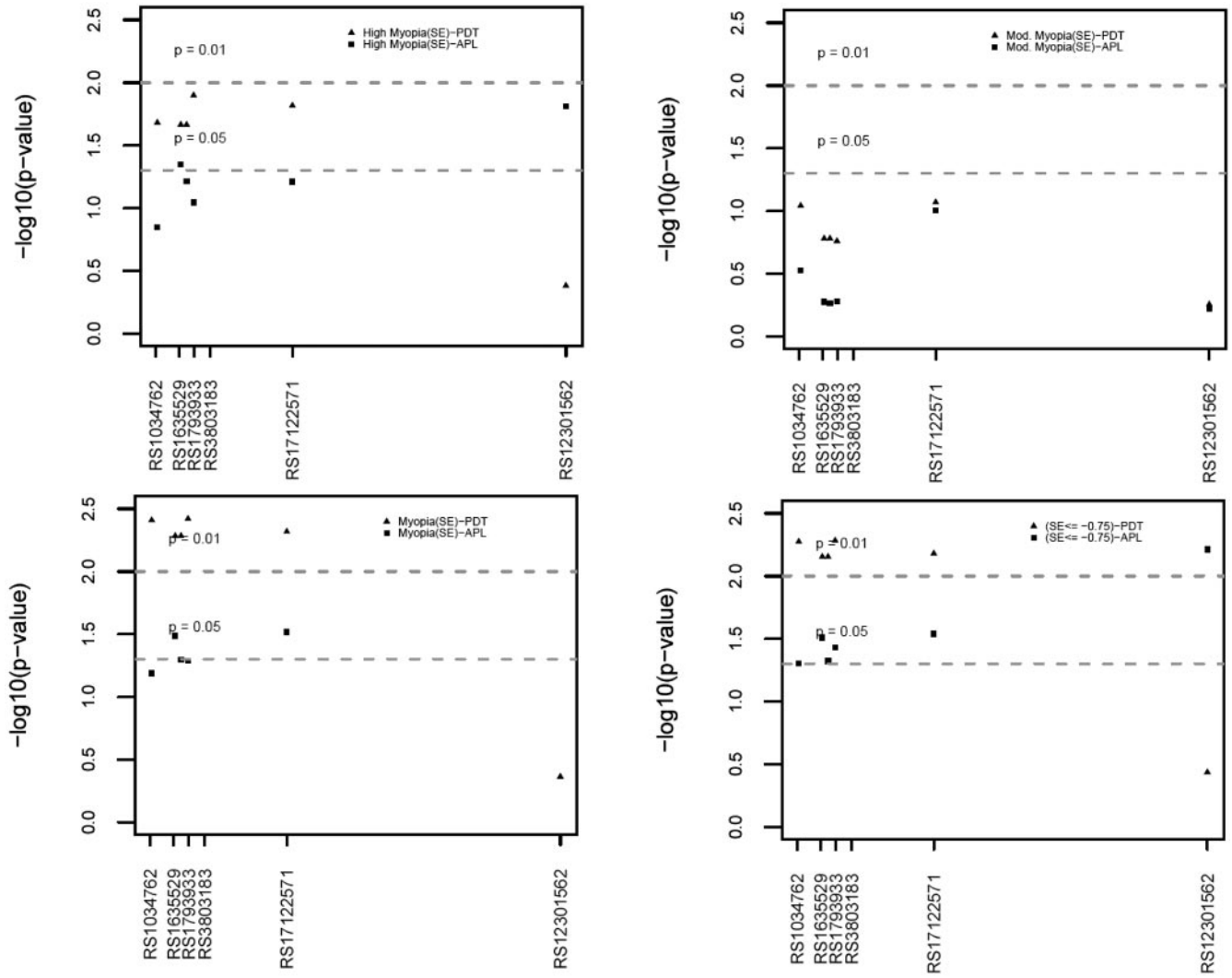

Figure 3. APL and PDT analyses of the *COL2A1* gene-tagging polymorphisms. Analyses were performed for high, moderate, and any-myopia states (SE analyses and significant SNPs presented). The threshold used by Mutti et al.[16] (−0.75 D) was also considered for analysis. A 50-kb region downstream of *COL2A1* was also screened.

Discussion

Ocular axial elongation in myopia is facilitated by collagen remodeling in the sclera during the development of myopia. We investigated the potential association of the collagen genes *COL1A1* and *COL2A1* with predisposition to myopia. In large Caucasian family-based cohorts, we examined this relationship by using a complementary genetic association and linkage analyses. We report that *COL2A1* alleles are associated with and linked to high-grade myopia in Caucasians.

The high-grade myopia and any-myopia groups showed significant association with *COL2A1* polymorphisms in the two independent family datasets tested, whereas the mild-to-moderate myopia group was not associated, thus indicating major contribution from the high-grade myopia group. The lack of association in the mild-to-moderate myopia group indicates that *COL2A1* may not have an effect on lower degrees of myopia in this cohort. The results of this study are consistent with the *COL2A1* association with myopia reported by Mutti et al.[16] in a predominantly Caucasian family-based cohort. It is

Table 3. Association Analyses of the *COL2A3* Gene Polymorphisms: Cardiff Dataset

	High-Grade Myopia SE		Mild to Moderate Myopia SE		Any Myopia SE		−0.75 D SE	
Marker	**APL**	**PDT**	**APL**	**PDT**	**APL**	**PDT**	**APL**	**PDT**
rs1034762	0.1516	0.0629	0.6597	0.4795	0.1314	0.1221	0.1529	0.1221
rs1635529	**0.0242**	**0.0044**	0.6803	0.7389	**0.0154**	**0.0073**	**0.0165**	**0.0073**
rs1793933	0.1471	0.1175	0.3584	0.7815	0.1121	0.1118	0.1054	0.1118

Analyses were performed for high, moderate, and any myopia states. The threshold used by Mutti et al.[16] (−0.75 D) was also considered for analysis. All probabilities are uncorrected; significant associations are in bold.

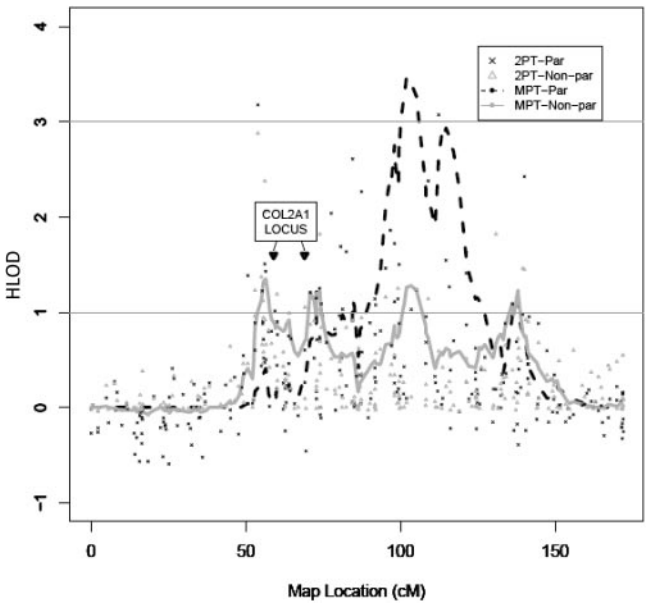

FIGURE 4. Linkage analysis results for chromosome 12 from the whole-genome linkage scan (Li et al.[17]). The MERLIN program was used to perform both two-point and multipoint parametric and nonparametric linkage analyses. Graph depicts the results from parametric analyses using a dominant model, and nonparametric linkage analyses for the overall dataset for chromosome 12.

notable that their analyses were not stratified based on the severity of myopia and therefore reflects the outcome of the any-myopia groups examined in our study. Since association analyses do not necessarily identify the causative gene, based on the linkage disequilibrium structure in Caucasians, further analysis of a 50-kb region downstream of the *COL2A1* gene was performed. The analysis did not reveal a stronger association signal than what was observed with the *COL2A1* gene polymorphisms. The overall linkage analyses on chromosome 12 from Li et al.,[17] in addition to the replication of the previously reported MYP3 locus,[9] revealed suggestive LOD scores near the *COL2A1* locus. Substantiating this finding, the subset analysis involving the markers in the *COL2A1* locus also revealed significant linkage. Taken together, our findings suggest that the *COL2A1* gene could be involved in susceptibility to high-grade myopia in Caucasians. In a recent genome-wide scan performed in dizygotic twin pairs in a U.K. cohort,[27] the *COL2A1* locus did not show positive linkage, further supporting the idea of involvement of multiple genes in the development of myopia.

TABLE 5. Multipoint Linkage Analysis of SNPs in the *COL2A1* Gene and the Surrounding Region

SNP	Map Location (cM)	HLOD (SE)
RS2061192	57.69183	1.27
RS871880	58.31127	1.24
RS1224438	59.41061	1.18
RS965125	59.63653	1.18
RS1012642	60.0763	1.31
RS1444588	60.15375	1.33
RS1492891	60.23427	1.38
RS739856	62.10426	***1.82***
RS855272	62.14832	***1.82***
RS1793949	62.4935	***2.14***
RS4760612	62.54197	***2.11***
RS1565933	63.06102	***1.79***
RS296736	63.82122	***1.69***
RS7532	63.94475	***1.69***
RS868884	64.57	***1.62***
RS2641530	65.75965	***1.74***
RS644524	66.9268	***1.99***
RS894734	69.10619	***1.87***
RS2279400	69.47388	***1.70***
RS3935215	70.80392	***1.82***

SNPs within the *COL2A1* locus from the association study and the whole genome linkage scan were combined for this analysis. LOD scores > 1.5 are in bold italic.

TABLE 4. Two-point Linkage Analysis of SNPs in the *COL2A1* Gene and the Surrounding Region

Marker	Map Location (cM)	HLOD (SE)	Marker	Map Location (cM)	HLOD (SE)
RS2061192	57.691833	0.83	RS12305182	62.54154	0.00
RS871880	58.311269	0.00	RS4760612	62.541973	0.67
RS1224438	59.410607	0.49	RS2408954	62.542583	0.47
RS965125	59.636525	1.08	RS10492082	62.546254	0.68
RS1012642	60.076303	0.3	RS1978161	62.586208	0.87
RS1444588	60.153754	0.09	HCV2626586	62.587106	0.26
RS1492891	60.234269	0.73	RS10492081	62.593087	0.68
RS739856	62.104263	1.26	RS989144	62.601883	0.18
RS855272	62.148323	***1.69***	RS12301562	62.602503	0.02
RS1793949	62.493497	0.81	RS4760619	62.617274	0.03
RS1635553	62.497329	1.09	RS757556	62.619745	0.00
RS2276456	62.497722	1.12	RS11168411	62.622166	0.26
RS3829736	62.498231	0.57	RS10875746	62.634956	0.11
RS1635550	62.499646	−0.02	RS11168421	62.635022	0.08
RS1793923	62.505579	0.89	RS1565933	63.061015	0.27
RS12423250	62.51052	0.15	RS296736	63.821215	0.50
RS1034762	62.510904	0.00	RS7532	63.944748	0.87
RS3737548	62.512614	0.48	RS868884	64.570001	0.50
RS954326	62.5159	0.39	RS2641530	65.759645	0.04
RS1635529	62.516169	0.00	RS644524	66.926797	0.11
RS1793933	62.517469	0.00	RS894734	69.10619	***1.52***
RS3803183	62.519041	−0.01	RS2279400	69.473882	0.00
RS17122571	62.54118	0.00	RS3935215	70.80392	0.62

SNPs within the *COL2A1* locus from the association study and the whole-genome linkage scan were combined for this analysis. LOD scores > 1.5 are in bold italic.

As described earlier, mutations in the *COL2A1* gene have been associated with Stickler syndrome,[12–14] a condition associated with severe myopia. Furthermore, *COL2A1* mutations have also been reported in autosomal dominant rhegmatogenous retinal detachment (RRD),[28] a phenotype that is clinically different from Stickler syndrome and is associated with high-grade myopia. It is interesting to note that high-grade myopia associated with the RRD phenotype is due to ocular elongation without the vitreous body abnormalities generally seen in Stickler syndrome. It is not clear how the *COL2A1* gene plays a role in the development of myopia; however, the expression data of *COL2A1* in relevant ocular tissues suggest that it could be a potential candidate for future studies on myopia. The *COL2A1* gene is expressed in the sclera,[7,29,30] the combined retinal pigment epithelium and choroid[29,31] and the retina.[28]

The finding that the *COL1A1* gene polymorphisms were not associated with myopia is surprising, given that the sclera is predominantly composed of type-I collagen. However, it is possible that *COL1A1* may not be associated with myopia in these Caucasian datasets indicating heterogeneity in disease development across different ethnicities. A recent study reported the absence of *COL1A1* involvement in a Taiwanese cohort.[12] More recently, a study on Japanese population failed to replicate the association of *COL1A1* gene polymorphisms (that was previously reported by Inamori et al.[10]) in an independent dataset.[11] Another reason for the lack of detection of *COL1A1* association could be because of overriding effects of other genes involved in myopia development in our cohorts.

In conclusion, we report genetic association along with suggestive linkage to the *COL2A1* locus for nonsyndromic, high-grade myopia in ethnically homogenous, family-based cohorts. The involvement of *COL2A1* sequence variants in myopia causation has only been coupled with syndromic disorders in the past. It is important that this locus be investigated in other cohorts with nonsyndromic, high-grade myopia.

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