

# New susceptibility locus for high myopia is linked to the uromodulin-like 1 (*UMODL1*) gene region on chromosome 21q22.3

R Nishizaki<sup>1,2</sup>, M Ota<sup>3</sup>, H Inoko<sup>4</sup>, A Meguro<sup>1</sup>, T Shiota<sup>3</sup>, E Okada<sup>2</sup>, J Mok<sup>4,5</sup>, A Oka<sup>4</sup>, S Ohno<sup>6</sup> and N Mizuki<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, Yokohama City University School of Medicine, Kanagawa, Japan

<sup>2</sup>Okada Eye Clinic, Kanagawa, Japan

<sup>3</sup>Department of Legal Medicine, Shinshu University School of Medicine, Nagano, Japan

<sup>4</sup>Department of Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Kanagawa, Japan

<sup>5</sup>Laboratory of Ophthalmology and Visual Science, Catholic Research Institutes of Medical Science College of Medicine, The Catholic University of Korea, Seoul, Korea

<sup>6</sup>Department of Ophthalmology, Hokkaido University School of Medicine, Hokkaido, Japan

Correspondence: M Ota, Department of Legal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi Matusmoto, 390-8621 Japan.  
 Tel: +81263373217;  
 Fax: +81263373084;  
 E-mail: otamasao@sch.md.shinshu-u.ac.jp

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## Abstract

**Purpose** To ascertain and define the position of a potential disease susceptibility gene around *D21S0083i* prioritized during our previous whole genome case-control association analysis with 27158 microsatellite markers, in Japanese high-myopia patients. **Methods** 520 high myopic patients and 520 healthy controls were genotyped using 39 SNPs distributed around *D21S0083i* on chromosome 21q22.3.

**Results** Only 1 SNP (rs2839471) of 39 SNPs was significant after correction for multiple testing (allele T:  $P = 0.00027$ ,  $P_c = 0.01$ , OR = 1.684). The SNP (rs2839471) did not reside in haplotype blocks constructed by the pairwise linkage disequilibrium between the SNPs. **Conclusions** The SNP (rs2839471) is suggested to be located in the frequent recombinant region within *UMODL1*. Together this region might play a critical role for susceptibility to high myopia, and warrants further confirming studies and investigations as to the mechanisms by which *UMODL1* may contribute to myopia.

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**Keywords:** high myopia; susceptibility; *UMODL1*

## Introduction

Myopia, diagnosed as a spherical refractive error of  $-0.50$  D or below, is the most common eye disorder in the modern world. High myopia ( $\leq -6.00$  D) is associated with the increased risk

of several ocular diseases, such as glaucoma, retinal detachment, visual impairment, and blindness.<sup>1,2</sup>

In a population of Japanese students three to 17 years old, the prevalence of myopia increased from 49.3 to 65.6%.<sup>3</sup> In other countries, the prevalence of myopia shows variable ratio (36.7–87.2% in a Chinese, 19.8–62.1% in a general Asian group, 5.2–40.5% in a Caucasian group aged 5–17 years, and 2.3–14.7% in Australian children aged 4–12 years).<sup>4–7</sup> These phenomena indicate a similar trend that the incidence of myopia is increasing from an early age in the general populations. Prevalence rates among different countries show considerable variability, but confirm that myopia affects a significant proportion of the population in many countries.

Myopia is a complex disease reflecting multiple interactions between genetic and environmental factors, and the aetiology of myopia has yet to be conclusively elucidated. However, several epidemiological studies have shown that several environmental factors, such as proximity to work, higher educational background, occupation, urban region, and socioeconomic status are important risk factors for myopia.<sup>8–14</sup>

On the other hand, determining the role of genetic factors in the development of nonsyndromic myopia has been hampered by the high prevalence, genetic heterogeneity, and clinical spectrum of this condition. Twin studies estimate a notable heritability value more than 0.5–0.87, indicating the proportion of the total phenotypic variance of genes. Furthermore, the importance of genetic factors in ocular

refraction has been implicated by the high heritability and strong familial effects observed in the previous twin studies, as well as parental and sibling studies.<sup>15–18</sup> Moreover, susceptibility genes for myopia have been recently identified in 14 genomic loci (MYP1 on Xq28, MYP2 on 18p, MYP3 on 12q, MYP4 on 7q, MYP5 on 17q, MYP6 on 22q12, MYP7 on 11p13, MYP8 on 3q26, MYP9 on 4q12, MYP10 on 8p23, MYP11 on 4q22–q27, MYP12 on 2q37.1, MYP13 on Xq23–q25, and MYP14 on 1p36).<sup>17,19–27</sup> Although several of the loci have not been replicated by experimental evidence as myopia and high-myopia candidate loci (MYP6–14), one study suggested the potential association of the MYP3 locus with autosomal dominant high myopia in approximately 25% of 51 UK families.<sup>28</sup> The polymorphisms of the transforming growth  $\beta$ -induced factor (*TGIF*) gene within the MYP2 locus were not associated with the high-myopia phenotype.<sup>29,30</sup>

Recently, we performed a whole-genome case–control association analysis of high myopia using 27 158 microsatellite markers and ultimately found significant association of 147 markers with high myopia (manuscript submitted). One of the 147 positive markers was located on chromosome 21q22.3 (microsatellite marker *D21S0083i*). Here, we dissected the position of the candidate susceptibility gene by SNP genotyping around the novel candidate region (*D21S0083i*).

## Materials and methods

### Subjects

A total of 520 high myopic individuals of Japanese ethnicity with a spherical equivalent of less than  $-9.25$  D at least in one eye and an abnormal axial elongation were recruited from the Okada Eye Clinic and Yokohama City University. Equal numbers of individuals of Japanese origin with normal vision were recruited from Tokai University as a control population group. The average ( $\pm$  SD) age in the high myopic group was  $39.7 \pm 12.07$  years (range: 3–77 years) and the male/female ratio was 1.0:1.3. The average age of the control group was  $41.2 \pm 11.67$  years (range: 25–75 years), and the male/female ratio was similar (1.0:1.2).

The high myopic participants underwent a non-cycloplegic refraction test with an autokeratometer (ARK-700K; NIDEK, Aichi, Japan/KR-8100P; Topcon, Tokyo, Japan). The patients had no known ocular disorders that could predispose them to high myopia, such as glaucoma, keratoconus, posterior staphyloma, or Marfan syndrome. The axial lengths of all affected subjects were measured with a pachymeter (AL-2000; TOMEY, Aichi, Japan). The average of axial length in the high myopic group was  $27.8 \pm 1.27$  mm

(range: 20.3–33.1 mm) for the right eye and  $27.8 \pm 1.29$  mm (range: 23.9–34.7 mm) for the left eye; in this group, the average keratometric value was  $43.9 \pm 1.56$  D (range: 39.5–50.3 D) for the right eye and  $43.9 \pm 1.58$  D (range: 39.–53.0 D) for the left eye. This study protocol adhered to the tenets of the Declaration of Helsinki.

These subjects are same cohort used in our previous whole-genome case–control association study.

### SNP genotyping

We selected one locus located on chromosome 21q22.3 (microsatellite marker *D21S0083i*) potentially associated with high myopia. The SNPs distributed around this candidate microsatellite marker were selected from the dbSNP database at the NCBI homepage (build 35), UCSC Genome Browser webpage, JSNP database,<sup>31</sup> and the SNP database of Applied Biosystems. The SNPs were selected for analysis based on the following criteria: (a) location within the 200 kb region around the candidate microsatellite marker (100 kb on either side); (b)  $>10\%$  minor allele frequency (MAF) in the Japanese population; (c)  $>0.3$  average heterozygosity; (d) marker density of at least one SNP per 5 kb; and (e) availability for validated assays. A total of 39 SNPs were selected for calculation of significant difference, linkage disequilibrium (LD), and haplotype analysis.

The SNP genotyping was performed using TaqMan<sup>®</sup> SNP Genotyping Assays, according to manufacturer's instructions. Reactions were performed with the ABI GeneAmp<sup>®</sup> PCR System 9700 thermal cycler, and the ABI PRISM<sup>®</sup> 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA), using a 384-well block module for measuring fluorescence. The SDS software version 2.0 was used for allelic discrimination analysis (Applied Biosystems). Two nanograms of genomic DNA were used as template in the PCR amplification reactions.

### Statistical analysis

To estimate statistical significance of comparisons between the high-myopic and control populations, we used the  $\chi^2$  test and Fisher's exact test for 2 by 2 and 2 by  $m$  contingency tables for SNPs and haplotypes (GDDBS: Genome Diversity Database System; <http://www.jbirc.aist.go.jp/gdbs/index.html>). For genotype frequency analysis, we employed the exact test, which was implemented using the Markov chain Monte Carlo simulation method for 2 by  $m$  contingency tables. We defined a  $P$ -value of less than 0.05 as statistically significant for all statistical analyses. The statistically

significant  $P$ -value was corrected by Bonferroni's correction ( $P_c$ ).

The pairwise relationship in SNPs or haplotypes was estimated by odds ratio (OR) and 95% confidence intervals (CIs) using the JavaStat Webpage. The SNPs genotyping in the control population was analysed for deviation of genotype frequencies from the Hardy–Weinberg equilibrium (HWE) using the procedure from the GDBS web page. The LD patterns, haplotype block structure, and haplotype frequency analysis for all SNPs with  $MAF > 10\%$  in both populations were identified using the block definition of Gabriel *et al*, and was based on 95% CI of  $D'$  with implementation of Haploview ver3.32 software.<sup>32,33</sup> LocusView was used to obtain generated images of candidate regions annotated with the haplotype analysis results.

## Results

Our previous study reporting a genome-wide association analysis with 27 158 microsatellite markers identified 21 markers as new candidate loci for high myopia (manuscript submitted). We characterized the novel candidate region around one microsatellite marker (*D21S0083i*; [AC]<sub>n</sub>; allele 4 in 15 alleles; Fisher's  $P = 0.016$ ,  $OR = 1.34$ ), and performed an association analysis using 39 SNPs and 10 constructed haplotypes located on chromosome 21q22.3 (Figure 1). The SNPs were principally located within four possible candidate genes: zinc-finger protein 295 (*ZNF295*, position: 42280009–42303519), chromosome 21 open reading frame 121 (*C21orf121*, position: 42315261–42318129), chromosome 21 open reading frame 128 (*C21orf128*, position: 42395313–42401627), and uromodulin-like 1 (*UMODL1*, position: 42356137–42436174). The allelic and genotype frequencies of 39 SNPs in the case and control groups are listed in Table 1. The SNP (rs220271: SNP A17) near the *D21S0083i* microsatellite showed a significant association with high myopia ( $P = 0.028$ ,  $OR = 1.219$ , 95% CI: 1.026–1.449). Two SNPs (rs2839430 and rs1628526; SNP A2 and A6) in the *ZNF295* gene and four SNPs (rs220271, rs220143, rs220148, and rs2839471; SNP A17, A25, A26, and A32) in the *UMODL1* and *C21orf128* genes showed statistical significance. Allele T-positive (rs 2839471; A32) phenotype was strongly associated with disease susceptibility ( $P = 0.00027$ ,  $P_c = 0.01$ ,  $OR = 1.684$ ). The alleles of two SNPs (rs915837 and rs150796: SNP A4 and A12) differed significantly from the expected Hardy–Weinberg values (probability test) in the control populations ( $P < 0.05$ ), therefore, these SNPs were excluded from the haplotype analysis. All SNPs, except SNP A32 (rs2839471), preliminarily showing statistical significance were later confirmed as not significant after Bonferroni's correction. The haplotype block structure

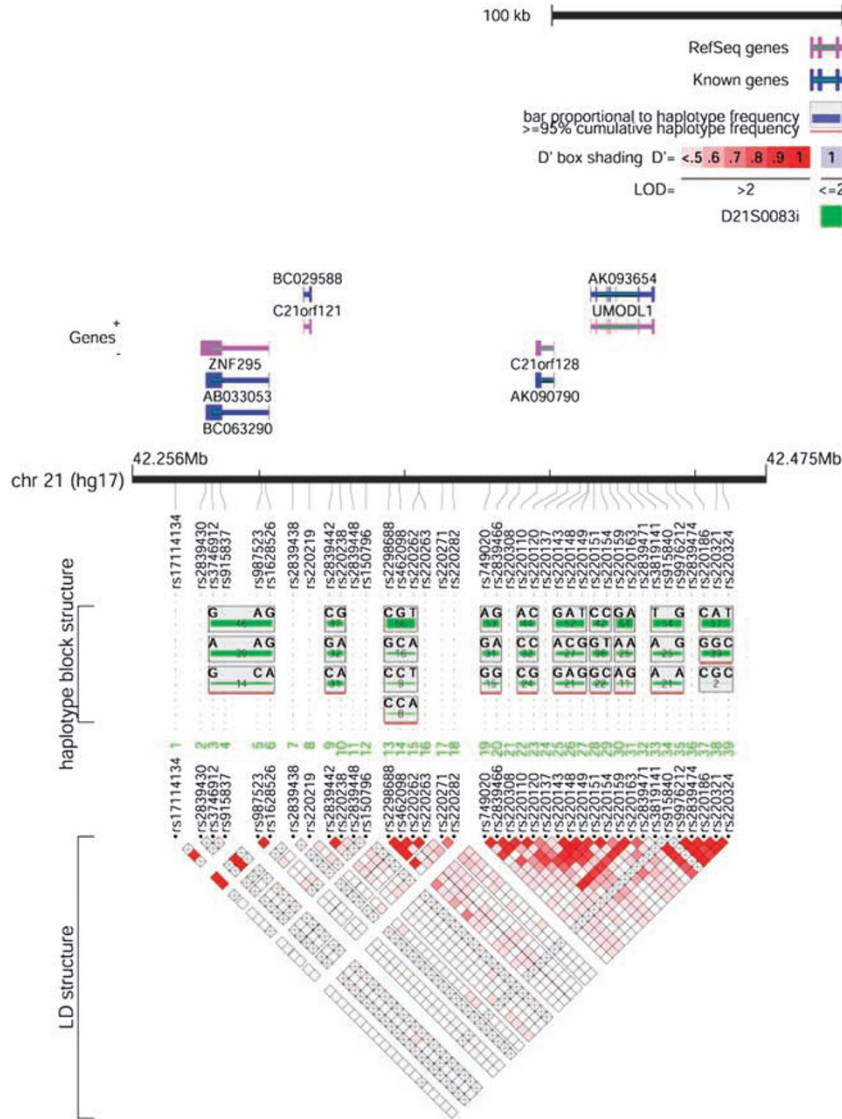
was analysed using SNPs with  $MAF > 10\%$ , and 10 haplotype blocks were found. Two haplotype blocks showed statistical significance between cases and controls: Block 1, GAG (SNP A3–A5–A6,  $P = 0.0493$ ,  $OR = 1.189$ , 95% CI: 1.000–1.414), including *ZNF295*, and Block 6, ACG (SNP A25–A26–A27,  $P = 0.0394$ ,  $OR = 1.228$ , 95% CI: 1.010–1.494), including *UMODL1* and *C21orf128* (Table 2, Figure 1). However, their significance disappeared after correction for multiple testing.

## Discussion

The aim of this study was to search for a candidate gene for high myopia around the microsatellite marker *D21S0083i*, which showed statistically significant association with high myopia by a previous genome-wide pooled DNA association mapping study (manuscript submitted). We used 39 SNPs located on chromosome 21q22.3 around the microsatellite marker (*D21S0083i*) to define critical regions influencing disease susceptibility.

Several SNPs within the *ZNF295*, *UMODL1*, and *C21orf128* genes showed statistically significant association with high myopia. The SNP rs2839430 (SNP A2) located in the 3'-UTR region of *ZNF295* showed a statistically strong association ( $P = 0.008$ ) with high myopia, although the  $MAF$  was low. As the sequence and structural motifs of the 3'-UTR often influence mRNA stability,<sup>34</sup> the SNP A2 may play a critical role in the regulatory process of *ZNF295* gene expression levels. The *ZNF295* gene, spanning approximately 24 kb, consists of five exons and encodes two protein isoforms: ZNF295L and ZNF295S. The ZNF295 protein belongs to the family of Pokemon (POK) proteins and contains a BTB (POZ) domain at its N-terminus and C2H2-type zinc-finger domain at its C-terminus. The ZNF295, ubiquitously expressed in human foetal and adult tissues, acts as a repressor of transcriptional activity and a cofactor of another POK protein ZFP161, being involved in the ZFP161-regulated pathway such as dopaminergic neurotransmission.<sup>35</sup>

The vast majority of individuals with high myopia are characterized by an increase in ocular axial length and scleral thinning. Although the exact mechanism underlying this axial length elongation has yet to be defined, it is presumed that a blurred image or light projected onto the retina induces the secretion of some substance from cells such as the visual, amacrine, horizontal, and bipolar cells, which evokes transfer of the signal to the sclera, thus leading to scleral remodelling and axial elongation. Stone *et al*<sup>36</sup> reported that retinal dopamine and its metabolite reduces form-deprivation myopia with axial length elongation in the chick model.



**Figure 1** Structures of LD and haplotype block from rs17114134 to rs220324 on chromosome 21q22.3. Pairwise LD between SNPs, as measured by  $D'$  in high-myopia patients and control individuals. Location of genes and the 39 SNPs are shown throughout the 219 Kb length lying D21S0083i on 21p22.3. Ten haplotype blocks are constructed by high LD between SNPs.

Deviation of this bidirectional interaction between *ZNF295* and *ZFP161* regulation might induce myopization following ocular axial elongation. In contrast, a mutation screening study by Scavello *et al*<sup>37</sup> reported that *ZFP161* was not associated with the myopia phenotypes.

The *UMODL1* gene spans approximately 80 kb, consists of 23 exons and encodes two major transcripts generated by alternative splicing. The two proteins, *UMODL1L* and *UMODL1S*, contain multiple domains typically found in extracellular matrix proteins, including an EMI (emilin) domain, WAP (whey acidic protein) domain, EGF\_CA (calcium-binding EGF-like) domain, FN3 (fibronectin type 3) domain, SEA (sea

urchin sperm protein, enterokinase, agrin) domain, ZP (zona pellucida) domain, and TRANS (transmembrane) domain. Altogether, this suggests that *UMODL1* proteins may be secreted and associated with extracellular matrix proteins involved in cell-to-cell and cell-to-extracellular matrix adhesion and in cell migration.<sup>38,39</sup> Consistent with this, results from a linkage study identified significant linkage for familial high myopia on chromosome 12q21–23, a region, which includes extracellular matrix genes such as *lumican*, *decorin*, and *DSPG3* (dermatan sulphate proteoglycan-3).<sup>21</sup> The synthesis and degradation of the extracellular matrix may influence the maintenance of scleral elasticity, strength, and thickness.<sup>40</sup>

**Table 1** Observed frequency of 39 SNPs in Japanese patients with high myopia and healthy individuals

SNP No.	SNP rs	Genes		Observed Allele (1/2)	Frequency (Allele 1)		Genotype distribution						P-value		exact2x2		OR	95% CI
		Name	Portion		Case	Control	Allele 1/1		Allele 1/2		Allele 2/2		Allele	Genotype (+/*1-/-)	P			
							Case	Control	Case	Control	Case	Control						
A1	rs17114134	ZNF295	Intergenic/unknown	A/G	0.602	0.603	200	192	221	232	95	87						
A2	rs2839430	ZNF295	3'UTR	T/A	0.943	0.912	457	426	59	82	0	4	0.008	0.008	2(A)	0.015	0.640	0.448–0.912
A3	rs3746912	ZNF295	3'UTR	G/A	0.619	0.609	203	197	232	231	80	85						
A4	rs915837	ZNF295	Silent mutation	T/C	0.515	0.556	128	171	275	228	113	114						
A5	rs987523	ZNF295	Intron	A/C	0.870	0.841	386	360	129	143	3	10						
A6	rs1628526	ZNF295	Intron	G/A	0.864	0.832	381	352	130	153	5	10	0.043					
A7	rs2839438	C21orf121, ZNF295	Intergenic/unknown	G/A	0.979	0.983	496	498	22	18	0	0						
A8	rs220219	C21orf121	Acceptor splice site	C/G	0.671	0.699	240	251	210	212	64	48						
A9	rs2839442	C21orf121	Intergenic/unknown	C/G	0.695	0.667	244	233	231	218	42	62			1(C)	0.039	1.555	1.029–2.348
A10	rs220238	C21orf121	Intergenic/unknown	A/G	0.621	0.630	192	207	259	235	67	73						
A11	rs2839448		Intergenic/unknown	C/A	0.628	0.624	196	195	260	254	63	67						
A12	rs150796		Intergenic/unknown	A/G	0.583	0.599	168	193	251	221	84	93						
A13	rs2298688		Intergenic/unknown	C/G	0.834	0.853	357	373	148	127	12	12						
A14	rs462098	UMODL1	Intergenic/unknown	G/C	0.654	0.684	213	246	248	211	54	57			2(C)	0.039	1.302	1.017–1.665
A15	rs220262	UMODL1	Intergenic/unknown	T/A	0.744	0.766	283	308	208	175	29	33						
A16	rs220263	UMODL1	Intergenic/unknown	A/G	0.526	0.556	135	158	274	254	108	101						
A17	rs220271	UMODL1	Intron	C/T	0.547	0.497	145	126	274	261	97	129	0.028	0.045	1(C)	0.020	1.440	1.069–1.939
A18	rs220282	UMODL1	Intron	G/A	0.576	0.611	161	194	274	241	82	80			2(A)	0.031	1.336	1.033–1.729
A19	rs749020	UMODL1	Intron	A/G	0.524	0.544	137	154	269	250	112	109						
A20	rs2839466	C21orf128, UMODL1	Intron	G/A	0.677	0.683	234	238	233	226	51	50						
A21	rs220308	C21orf128, UMODL1	Intron	T/G	0.590	0.608	184	191	243	245	91	80						
A22	rs220110	C21orf128, UMODL1	Intron, 3'UTR	C/A	0.566	0.552	165	157	256	256	97	103						
A23	rs220120	C21orf128, UMODL1	Intron	C/G	0.743	0.775	287	309	199	182	34	25						
A24	rs220137	C21orf128, UMODL1	Intron	G/A	0.819	0.842	347	365	156	139	16	12						
A25	rs220143	C21orf128, UMODL1	Intron	G/A	0.712	0.755	256	297	227	184	36	34	0.029	0.023	2(A)	0.0074	1.400	1.095–1.789
A26	rs220148	UMODL1	Intron	A/C	0.705	0.747	248	290	230	188	37	36	0.034	0.024	2(C)	0.0088	1.394	1.090–1.782
A27	rs220149	UMODL1	Intron	T/G	0.498	0.540	134	152	250	254	136	111						
A28	rs220151	UMODL1	Intron	G/C	0.592	0.563	182	162	250	258	87	97						
A29	rs220154	UMODL1	Intron	C/T	0.627	0.655	198	224	256	228	66	64						
A30	rs220159	UMODL1	Missense mutation	G/A	0.638	0.644	216	211	232	243	72	62						
A31	rs220163	UMODL1	Intron	A/G	0.870	0.894	394	409	117	103	9	3						
A32	rs2839471	UMODL1	Intron	C/T	0.490	0.554	114	166	282	241	124	110	0.004	0.001	2(T)	0.00027 <sup>a</sup>	1.684	1.276–2.224

**Table 1** (Continued)

SNP No.	SNP rs	Genes		Observed Allele (1/2)		Genotype distribution						P-value	exact2x2	OR	95% CI	
		Name	Portion	Allele (1/2)		Allele 1/1		Allele 1/2		Allele 2/2						Allele Genotype (+/* -/-)
				Case	Control	Case	Control	Case	Control	Case	Control					
A33	rs3819141	UMODL1	Silent mutation	T/A	0.543	0.538	159	140	247	273	114	101				
A34	rs915840	UMODL1	Intron	T/C	0.973	0.976	492	492	28	25	0	0				
A35	rs9976212	UMODL1	Intergenic/unknown	G/A	0.788	0.790	327	324	162	166	29	25				
A36	rs2839474	UMODL1	Intergenic/unknown	T/C	0.579	0.573	180	165	241	260	98	90				
A37	rs220186	UMODL1	Intergenic/unknown	C/G	0.607	0.591	196	182	239	247	85	88				
A38	rs220321	UMODL1	Intergenic/unknown	A/G	0.582	0.578	179	174	244	246	94	94				
A39	rs220324	UMODL1	Intergenic/unknown	T/C	0.582	0.580	181	176	243	245	96	94				

CI = confidence interval; OR = odds ratio SNP; rs = public reference SNP number from the dbSNP database.  
Only statistically significant P-values ( $P < 0.05$ ) are noted in table.  
<sup>a</sup> $P_c$  (corrected P-value) = 0.01.

Schiavi et al<sup>39</sup> demonstrated through *in situ* hybridization that mouse *UMODL1* was preferentially expressed in the olfactory and vomeronasal sensory neurons, starting at embryonic day 16.5, during embryonic development. Structure of *UMODL1* gene in mouse and human is very similar to each other in their sequence and domain organization. The olfactory system provides an excellent model for the development neurobiology of cell migration, axonal projections, and synaptic connections. Thus, we speculate that aberrations of *UMODL1* in cases of high myopia might be implicated in scleral thinning and neuronal disorder in postnatal eye development.

Eight SNPs were significantly associated with high myopia ( $P < 0.05$ ). Four statistically significant SNPs were involved in 10 haplotype blocks identified by LD analysis. However, four other SNPs (rs2839430, rs220271, rs220282, and rs2839471; SNP 2, 25, 26, and 32) were not in the haplotype blocks. Of these results, allele T-positivity of rs283971 (SNP No.32) indicated a strong association ( $P = 0.00027$ ; OR = 1.684) even after correction ( $P_c = 0.01$ ) for multiple testing. This result suggests that rs283971 is located in the frequent recombinant region on the *UMODL1*, and that this region might play a critical role in disease susceptibility to high myopia.

Our susceptibility gene mapping study in a Japanese population used SNP genotyping to identify the novel high-myopia candidate gene *UMODL1* around *D21S0083i*. However, further investigations (eg, replication studies) are required to confirm whether *UMODL1* is a high-myopia susceptibility gene, and functional investigations are also required to demonstrate the mechanisms by which aberrations in the *UMODL1* gene are related to and contribute to susceptibility for disease.

### Electronic database information

The following URLs were used in this study for the analysis of data.

dbSNP: <http://www.ncbi.nlm.nih.gov/SNP/index.html>

A database of Japanese single nucleotide polymorphisms (JSNP): <http://snp.ims.u-tokyo.ac.jp/index.html>

UCSC Genome Browser: <http://genome.ucsc.edu/cgi-bin/hgGateway>

Genome diversity database system (GDBS) Gene diversity DB: <http://www.jbirc.aist.go.jp/gdbs/index.html>

Genepop on the web: <http://wbiomed.curtin.edu.au/genepop/index.html> (statistical analysis)

JavaStat—2-way contingency table analysis: <http://statpages.org/ctab2x2.html> (OR calculation)

**Table 2** Estimated haplotype frequencies in Japanese high-myopia patients and healthy individuals

Locus	Haplotype block			Haplotype Frequency			P-value	OR (95% CI)
	Name	SNP No.	Haplotype	All	Case	Control		
21q22.3	Block 1	A3-A5-A6	GAG	0.462	0.483	0.440	0.0493*	1.189 (1.000–1.414)
			AAG	0.386	0.381	0.391	0.6193	
			GCA	0.145	0.130	0.160	0.0569	
	Block 2	A9-A10	CG	0.374	0.379	0.370	0.6448	
			GA	0.319	0.305	0.334	0.1478	
			CA	0.306	0.316	0.296	0.3271	
	Block 3	A13-A14-A15	CGT	0.66	0.642	0.678	0.0913	
			GCA	0.156	0.164	0.147	0.2925	
			CCT	0.094	0.100	0.088	0.3708	
	Block 4	A19-A20	CCA	0.081	0.081	0.081	0.9859	
			AG	0.527	0.520	0.535	0.4803	
			GA	0.313	0.317	0.308	0.6577	
	Block 5	A22-A23	GG	0.152	0.157	0.148	0.5558	
			AC	0.441	0.434	0.448	0.5341	
			CC	0.318	0.309	0.327	0.3688	
	Block 6	A25-A26-A27	CG	0.241	0.257	0.225	0.0890	
			GAT	0.519	0.498	0.540	0.0583	
			ACG	0.265	0.285	0.245	0.0394*	
	Block 7	A28-A29	GAG	0.206	0.204	0.208	0.8164	
			CC	0.419	0.404	0.434	0.1549	
			GT	0.356	0.370	0.342	0.1897	
	Block 8	A30-A31	GC	0.221	0.222	0.221	0.9460	
			GA	0.637	0.634	0.640	0.7617	
			AA	0.245	0.237	0.254	0.3689	
	Block 9	A33-A35	AG	0.113	0.124	0.102	0.1082	
			TG	0.536	0.537	0.534	0.8798	
			AG	0.253	0.250	0.256	0.7553	
	Block 10	A37-A38-A39	AA	0.206	0.206	0.205	0.9668	
			CAT	0.571	0.572	0.569	0.8904	
			GGC	0.392	0.383	0.400	0.4188	
			CGC	0.024	0.029	0.020	0.1576	

CI = confidence interval; OR = odds ratio. \*P < 0.05.

LocusView 2.0: <http://www.broad.mit.edu/mpg/locusview/> (generating images)

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