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ORIGINAL RESEARCH

Analysis of the association between the *LUM* rs3759223 variant and high myopia in a Japanese population

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Purpose: Many studies have investigated the relationship of the lumican gene (*LUM*) rs3759223 variant with the risk of high myopia, but the results have been inconsistent and inconclusive. In this study, we investigated whether *LUM* rs3759223 is associated with high myopia in a Japanese population.

Methods: We recruited 1,585 Japanese patients with high myopia (spherical equivalent [SE] <−9.00 diopters [D]) and 1,011 Japanese healthy controls (SE ≥−1.00 D). The rs3759223 variant was genotyped using the TaqMan assay, and the allelic and genotypic diversity among cases and controls was analyzed according to the SE level.

Results: In the allelic tests, the odds ratio (OR) for the T allele of rs3759223 tended to increase with the progression of SE, and the highest OR (1.56) was found in patients with SE <−15 D in both eyes. The OR of the T allele tended to increase with the progression of SE in the additive, dominant, and recessive inheritance models. However, we found no significant associations for any of the alleles or genotype models.

Conclusion: These data support the possibility that the *LUM* rs3759223 T allele accelerates the progression of SE in the Japanese population, although no significant associations were observed in this study. Additional genetic studies with larger samples that take into account the degree of SE are needed to clarify the contribution of rs3759223 to the risk of high myopia.

Keywords: high myopia, lumican, association study, polymorphism

Introduction

Myopia is a type of refractive error and is one of the most common eye disorders in the modern world. High myopia, which is generally defined by a spherical equivalent (SE) refractive error <−6 diopters (D) or an axial length (AL) >26 mm, is associated with an increased risk of various ocular diseases, including retinal detachment, glaucoma, and cataracts.[1] The prevalence of myopia in East Asian and Southeast Asian countries is higher than the global average.[2] Therefore, myopia, especially high myopia, is considered an important public health problem in Asian countries.

The etiology of myopia remains uncertain, but it is thought that certain environmental factors, such as near work (reading, studying, and computer use), can trigger the symptoms of myopia in individuals with a particular genetic background.[3–6] Familial linkage studies have reported 19 genetic loci for myopia to date (MYP1–MYP19),[7,8] and recent genome-wide association studies have identified many important candidate loci/genes that are implicated in myopia, refractive error, and/or AL elongation in several ethnic populations.[9–12]

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The lumican (*LUM*) gene is located on chromosome 12q21.33 within the MYP3 locus (12q21–q23). *LUM* is a member of the small leucine-rich proteoglycan family, which regulates collagen fibril assembly[13] and contributes to the maintenance of tissue-structural homeostasis and the regulation of cell proliferation, migration, and adhesion.[14] An animal study found that the eyes of lumican–fibromodulin double-deficient ($Lum^{-/-}$ $Fmod^{-/-}$) mice show some of the key features of high myopia, such as increased AL, scleral thinning, and retinal detachment.[15] In 2006, Wang et al[16] showed that the *LUM* promoter variant rs3759223 was significantly associated with high myopia in a Taiwanese population of Han Chinese origin. Subsequently, many studies in Taiwanese, Chinese, or Korean populations have investigated the association of *LUM* variants, especially rs3759223, with the risk of high myopia, but the results have been inconsistent and inconclusive.[17–22] Accordingly, the aim of the present study was to investigate whether *LUM* rs3759223 is associated with high myopia in Japanese patients.

Methods

Subjects

We recruited 1,585 unrelated Japanese patients with high myopia (SE <−9.00 D in at least one eye) and 1,011 unrelated healthy Japanese controls (SE ≥−1.00 D in both eyes) at Yokohama City University, Okada Eye Clinic, and Aoto Eye Clinic in Japan. The participants were the same as in our previous study,[23] and they had similar social backgrounds and resided in the same urban area. All participants were diagnosed by comprehensive ophthalmologic tests, including AL measurement, fundus examination, SE determination, and corneal curvature determination (autorefractor; NIDEK, Gamagori, Japan; ARK-730A, ARK-700A; TOPCON, Tokyo, Japan; KP-8100P, Biometer/Pachymeter AL-2000; Tomey Corporation, Nagoya, Japan). We excluded individuals in the patient cohort who had any genetic diseases that were known to be associated with myopia and/or high myopia, including glaucoma, keratoconus, or Marfan syndrome. We recruited individuals aged 20 years and older for the control cohort to exclude potential myopia patients. Written informed consent was obtained from all participants. The study methodology adhered to the tenets of the Declaration of Helsinki and was approved by the relevant ethics committees at Yokohama City University, the Okada Eye Clinic, and the Aoto Eye Clinic.

DNA extraction and *LUM* rs3759223 genotyping

Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Procedures were performed using standardized protocols to ensure uniform DNA quality.

LUM rs3759223 genotyping was performed using the TaqMan 5′ exonuclease assay and a predesigned primer–probe set supplied by Applied Biosystems (Foster City, CA, USA). Polymerase chain reaction (PCR) was performed using a reaction mixture with a total volume of 10 µL containing 1× TaqMan Universal PCR Master Mix (Applied Biosystems), 24 nM of each primer–probe set, and 3 ng of genomic DNA. The PCR conditions were as follows: 95°C for 10 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds, and annealing/extension at 60°C for 1 minute. The probe fluorescence signal was detected using the StepOnePlus Real-Time PCR System (Applied Biosystems) following the manufacturer's instructions.

Statistical analysis

The SNP & Variation Suite 8.4.0 software (Golden Helix, Inc., Bozeman, MT, USA, http://www.goldenhelix.com) was used to test for Hardy–Weinberg equilibrium (HWE) and to perform allelic and genotypic association analyses. Multiple inheritance models were used in the analysis of genotype data to assess each risk allele. Specifically, assuming that R is the risk allele and nR is the nonrisk allele, we assessed additive (R/R versus R/nR versus nR/nR), dominant (R/R + R/nR versus nR/nR), and recessive (R/R versus R/nR + nR/nR) models. *P*-values and odds ratios (ORs) in genotypic models were adjusted for age and sex (P_{adj} and OR_{adj}, respectively). The *P*- and P_{adj}-values were determined using the chi-square test and logistic regression, respectively. The meta-analyses of various populations in previous studies were performed using the Mantel–Haenszel method. The possibility of publication bias was assessed by Egger's regression test using the CMA v3 software (Biostat, Englewood, NJ, USA, https://www.meta-analysis.com/index.php).

Results

The clinical characteristics of the study populations are shown in Table 1. A total of 44.2% of patients and 41.6% of controls were male, and the mean ages of the patients and controls were 38.8±12.2 years (range: 12–78) and 58.2±12.3 years (range: 20–87), respectively. The average SEs of the patients were −10.94±2.06 D (range: −4.50 to −22.75 D) in the right eye and −10.82±2.07 D (range: −4.50 to −24.50 D) in the left eye. The average ALs of the patients were 27.55±1.22 mm (range: 23.92–33.85 mm) for the right eye and 27.51±1.24 mm (range: 23.99–34.74 mm) for the left eye. For the controls, the average SEs were 0.48±0.64 D (range: −1.00 to 3.50 D) in the right eye and 0.48±0.63 D

Table 1 Clinical characteristics of the study population

Parameters	High myopia cases,[a] n=1,585	Control subjects,[b] n=1,011
Sex, male, %	44.2	41.6
Mean age,[c] years	38.8±12.2 [12, 78]	58.2±12.3 [20, 87]
Mean SE,[c] diopter (D)		
Right eyes	−10.94±2.06 [−4.50, −22.75]	0.48±0.64 [−1.00, 3.50]
Left eyes	−10.82±2.07 [−4.50, −24.50]	0.48±0.63 [−1.00, 3.00]
Mean AL,[c] mm		
Right eyes	27.55±1.22 [23.92, 33.85]	23.22±0.80 [18.76, 25.96]
Left eyes	27.51±1.24 [23.99, 34.74]	23.20±0.79 [18.99, 26.05]

Notes: [a]High myopia cases were defined as SE <−9.0 D in at least one eye. [b]Controls were defined as SE ≥−1.0 D in both eyes. [c]Data are presented as means ± standard deviations [minimum value, maximum value].
Abbreviations: AL, axial length; SE, spherical equivalent.

(range: −1.00 to 3.00 D) in the left eye. The average ALs were 23.22±0.80 mm (range: 18.76–25.96 mm) for the right eye and 23.20±0.79 mm (range: 18.99–26.05 mm) for the left eye.

The genotype frequency of rs3759223 was in HWE in both cases and controls ($P>0.05$). Table 2 shows the allelic association results for rs3759223 after stratification according to SE in high myopia cases: <−9.0 D in at least one eye; <−9.0 D in both eyes; <−11.0 D in both eyes; <−13.0 D in both eyes; and <−15.0 D in both eyes. The OR for the T allele of rs3759223 increased according to the progression of SE, and the highest OR was found in patients with SE <−15 D in both eyes (OR =1.56, 95% confidence interval [CI]=0.79–3.06). However, in the allele test, we did not find any significant association in any of the patients who were stratified according to the level of SE ($P>0.05$).

Table 3 shows the genotypic association results after stratification according to SE in high myopia cases. The OR for the T allele of rs3759223 tended to increase according to the progression of SE in all of the tested inheritance models, that is, in the additive, dominant, and recessive models. The dominant model of the T allele showed higher ORs than the additive and recessive models in all of the patient groups that were stratified by the level of SE. The highest OR was found in patients with SE <−13 D in both eyes in the dominant model (OR_{adj} =1.77, 95% CI =0.53–5.83), while the OR was not calculated in patients with SE <−15 D in both eyes in the dominant model because of the absence of the CC genotype in the patient group. Note, however, that the OR before adjustment for age and sex was estimated to be 3.20 (95% CI =0.19–53.03) in patients with SE <−15 D in both eyes in the dominant model when a continuity correction[24,25] for sparse data is applied by adding 0.5 to each cell of the 2×2 table. However, no significant associations were found in any of genotypic models for any of the patient groups ($P_{adj}>0.05$).

Discussion

The aim of this study was to assess whether the *LUM* promoter rs3759223 variant is associated with the risk of high myopia in a Japanese population. To address this question, we genotyped rs3759223 and assessed the allelic and genotypic diversity in cases and controls according to the level of SE. Because a higher degree of myopia suggests that genetic factors may be involved, this study only included patients with SE <−9.00 D in at least one eye. Here, we report that the OR for the T allele of rs3759223 tended to increase with the progression of SE in both allelic and genotypic association tests, although the results did not reach statistical significance. Our findings suggest the possibility that *LUM* rs3759223 contributes to the risk of very high myopia.

Table 4 summarizes previous studies that investigated the association between *LUM* rs3759223 and high myopia. In 2006, Wang et al[16] reported that there was a statistically significant difference in the genotypic distribution between cases (SE <−10.0 D in both eyes) and controls in Taiwanese subjects of Han Chinese origin. Subsequently, Zhang et al[17] reported significant associations with high myopia (SE <−6.0 D in both eyes) for rs3759223 in a Northern Han Chinese population in both genotypic and allelic tests.[16] However,

Table 2 Allelic association results for *LUM* rs3759223 after stratification according to spherical equivalent refractive error

SNP	Position on Chr.12 (GRCh37)	Alleles (1>2)	Risk allele	Phenotype			n	Risk allele (T) frequency, %	*P*-value[a]	OR (95% CI)
					Criteria of SE (diopter)	Eye meeting criteria				
rs3759223	91,506,783	T > C	T	Controls	≥−1	Both	1,011	79.9		
				Cases	<−9	At least one	1,585	80.7	0.512	1.05 (0.91–1.21)
					<−9	Both	1,252	80.8	0.485	1.05 (0.91–1.22)
					<−11	Both	394	81.5	0.353	1.10 (0.90–1.36)
					<−13	Both	130	83.8	0.134	1.30 (0.92–1.85)
					<−15	Both	36	86.1	0.196	1.56 (0.79–3.06)

Note: [a]The *P*-values were determined using the chi-square test.
Abbreviations: CI, confidence interval; OR, odds ratio; SE, spherical equivalent; 1, major allele; 2, minor allele; SNP, single nucleotide polymorphism; Chr., chromosome.

Table 3 Genotypic association results for *LUM* rs3759223 after stratification according to spherical equivalent refractive error

Phenotype			n	Genotype (TT/CT/CC)[a] frequency, %	HWE *P*	Genetic models[b]					
						Additive model		Dominant model		Recessive model	
	Criteria of SE (diopter)	Eye meeting criteria				P_{adj}	OR_{adj} (95% CI)	P_{adj}	OR_{adj} (95% CI)	P_{adj}	OR_{adj} (95% CI)
Controls	≥−1	Both	1,011	64.0/31.8/4.2	0.808						
Cases	<−9	At least one	1,585	65.1/31.1/3.8	0.906	0.296	1.10 (0.92–1.32)	0.225	1.28 (0.86–1.90)	0.495	1.08 (0.87–1.33)
	<−9	Both	1,252	65.4/30.7/3.9	0.635	0.419	1.08 (0.89–1.31)	0.400	1.27 (0.73–2.19)	0.542	1.07 (0.85–1.35)
	<−11	Both	394	66.2/30.5/3.3	0.861	0.474	1.10 (0.85–1.42)	0.523	1.28 (0.59–2.77)	0.558	1.09 (0.81–1.48)
	<−13	Both	130	70.8/26.2/3.1	0.694	0.123	1.34 (0.92–1.96)	0.327	1.77 (0.53–5.83)	0.155	1.37 (0.88–2.13)
	<−15	Both	36	72.2/27.8/0.0	0.333	0.146	1.63 (0.82–3.27)	nd	nd	0.291	1.50 (0.69–3.26)

Notes: [a]T is a risk allele. [b]Multiple inheritance models were applied in analysis of genotype data to assess risk allele: additive (TT versus CT versus CC), dominant (TT + CT versus CC), and recessive (TT versus CT + CC) models were assessed. The P_{adj}-values were determined using logistic regression.

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; nd, not detected; OR_{adj}, OR adjusted for age and sex; P_{adj}, *P* value adjusted for age and sex; SE, spherical equivalent; SNP, single nucleotide polymorphism.

other studies have reported a lack of association between rs3759223 and high myopia in Taiwanese, Chinese, and Korean populations.[18–22]

Recent meta-analyses of the genotype results for rs3759223 that were reported in previous studies suggest that rs3759223 is associated with an increased risk of high myopia in a recessive model of the T allele.[26–28] Table 4 shows the results of genotypic association tests that used the genotype results reported by each study; the T allele was associated with an increased risk of high myopia in a recessive model in all of the studies. Our meta-analysis of the results of previous studies also suggested a significant association between rs3759223 and high myopia in a recessive model of the T allele (meta-P=1.0×10^{-9}, meta-OR =1.47; Table 4). Egger's regression test showed that there was no significant publication bias in this meta-analysis (P=0.184). On the other hand, in our Japanese population, the genotype tests showed that the T allele had a stronger association with high myopia in a dominant model than in a recessive model, regardless of the SE level of the patients (Table 3). This finding is not in line with previous studies.[26–28]

Previous studies that investigated the association of rs3759223 with high myopia have three limitations. The first is the relatively small sample size: all of the studies involved fewer than 300 cases and fewer than 300 controls (Table 4), making them underpowered to detect susceptibility variants, especially modest or small effect variants. This can lead to false-positive or false-negative results in an association study. To overcome this issue, larger sample sizes are required.

The second weakness is that some of the previous studies showed deviations from HWE in controls, and these deviations may be the result of genotyping errors (Table 4). Significant deviations from HWE in controls were found in the two studies by Lin et al[19,20] that reported that the rs3759223 T allele is associated with a 1.53-fold or a 1.95-fold increased risk of high myopia, respectively, in a recessive model. In addition, there was a marginal deviation from HWE in the controls in the study by Zhang et al,[17] who found strong associations in all of the allele and genotype models that they tested. All three of these studies of individuals of Chinese origin used very small sample sizes for the controls (<100 subjects), and the frequency of the T allele was ~30% in controls (Table 4). However, the 1000 Genomes Project East Asian database shows that the frequency is between 65% and 75% in populations of Chinese origin, and 79.8% and 71.7% in Japanese and Vietnamese Kinh populations (Table 5). This disparity may result from complex factors in the three studies, including small sample size and possible genotyping errors. Further analyses need to be performed in these populations. Accordingly, we performed a new meta-analysis of previous studies that excluded these three studies. This analysis still showed that there was only a significant association between rs3759223 and high myopia in a recessive model of the T allele (meta-P=2.0×10^{-4}, meta-OR =1.27; Table 4), although the association level was lower than that in the meta-analysis that included all previous studies.

The third weakness of previous studies was that they did not assess associations between rs3759223 and high myopia according to the progression of SE. The present study found that the OR for the T allele tended to increase with the progression of SE in the Japanese population and suggested that the T allele has the potential to contribute to the risk of very high myopia. Therefore, an association between rs3759223 and very high myopia should be assessed in other populations.

Conclusion

In summary, we found that it is possible that the *LUM* rs3759223 T allele accelerates the progression of SE in the Japanese population, although no significant associations were

Table 4 Summary of previous studies investigating the association between *LUM* rs3759223 and high myopia

Study	Population		Criteria[a] of SE (diopter)	n	Genotype distribution, n (frequency, %)				Allele frequency, %		Genetic models[b]				
											2×3 table	Dominant model		Recessive model	
					TT	CT	CC	HWE *P*	T	C	*P*-value	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)
Wang et al[16]	Taiwanese (Han Chinese origin)	Cases	<−10.0	120	61 (50.8)	32 (26.7)	27 (22.5)	4.2E-06	64.2	35.8	2.8E–04	0.0073	0.39 (0.19–0.79)	0.086	1.54 (0.94–2.53)
		Controls	−1.5 to 0.5	137	55 (40.1)	68 (49.6)	14 (10.2)	0.290	65.0	35.0					
Zhang et al[17]	Northern Han Chinese	Cases	<−6.0	94[c]	57 (60.6)	31 (33.0)	6 (6.4)	0.527	77.1	22.9	3.4E–13	3.9E–11	14.67 (5.82–36.97)	1.1E–10	9.12 (4.45–18.72)
		Controls	−0.25 to 0.25	90	13 (14.4)	32 (35.6)	45 (50.0)	0.078	32.2	67.8					
Wang et al[18]	Southeastern Chinese	Cases	≤−6.0	288	155 (53.8)	112 (38.9)	21 (7.3)	0.901	73.3	26.7	0.048[d]	0.034[d]	1.90 (1.04–3.46)	0.058	1.41 (0.99–2.02)
		Controls	−0.5 to 1.0	208	94 (45.2)	87 (41.8)	27 (13.0)	0.337	66.1	33.9					
Lin et al[19,e]	Taiwanese (Chinese origin)	Cases	≤−6.0	201	14 (7.0)	83 (41.3)	104 (51.7)	0.640	27.6	72.4	0.213	0.176	0.70 (0.42–1.17)	0.459	1.53 (0.49–4.80)
		Controls	−0.5 to 0.5	86	4 (4.7)	45 (52.3)	37 (43.0)	0.035	30.8	69.2					
Lin et al[20,e]	Taiwanese (Han Chinese origin)	Cases	<−6.5	182	13 (7.1)	74 (40.7)	95 (52.2)	0.784	27.5	72.5	0.195	0.241	0.73 (0.43–2.33)	0.301	1.95 (0.54–7.04)
		Controls	−0.5 to 1.0	78	3 (3.8)	41 (52.6)	35 (44.9)	0.032	29.7	69.9					
Dai et al[21]	Northeastern Han Chinese	Cases	≤−10.0	220	125 (56.8)	74 (33.6)	21 (9.5)	0.047	73.6	26.4	0.746	0.637	0.82 (0.35–1.91)	0.692	1.10 (0.69–1.77)
		Controls	−0.75 to 0.75	101	55 (54.5)	38 (37.6)	8 (7.9)	0.691	73.3	26.7					
Park et al[22]	Korean	Cases	≤−9.25[f]	128	86 (67.2)	34 (26.6)	8 (6.3)	0.080	80.5	19.5	0.625	0.521	0.74 (0.29–1.88)	0.631	1.12 (0.71–1.76)
		Controls	≥−1.5	235	152 (64.7)	72 (30.6)	11 (4.7)	0.514	80.0	20.0					
									Meta-analysis using all previous studies			0.573	1.05 (0.83–1.34)	1.0E–09	1.47 (1.20–1.79)
									Meta-analysis using four previous studies[16,18,21,22]			0.589	0.89 (0.62–1.28)	2.0E–04	1.27 (1.02–1.58)

Notes: [a]We confirmed that the SE criteria were applied to both eyes in all studies except for the study by Zhang et al,[17] which did not have this information. [b]We calculated the *P*-values and ORs using the genotype results reported in each study. The *P*-values of 2×3 contingency table, dominant (TT + CT versus CC) and recessive (TT versus CT + CC) models in each study were determined using the chi-square test. The meta-analyses were performed using the Mantel–Haenszel method. [c]The 94 cases include 12 familial and 82 sporadic cases. [d]Statistical difference did not exist after Bonferroni correction. [e]Based on their methods' descriptions, most of the cases and controls overlap in the two studies. [f]The myopia cases also had an AL of ≥26.55 mm in both eyes.

Abbreviations: AL, axial length; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SE, spherical equivalent.

Table 5 Genotype and allele frequencies of the *LUM* rs3759223 variant in East Asian populations (Phase 3) of the 1000 Genomes Project[a]

Population	Genotype frequency, n (%)			Allele frequency, %	
	TT	CT	CC	T	C
Chinese Dai in Xishuangbanna, People's Republic of China (CDX), n=93	41 (44.1)	42 (45.2)	10 (10.8)	66.7	33.3
Han Chinese in Beijing, People's Republic of China (CHB), n=103	57 (55.3)	39 (37.9)	7 (6.8)	74.3	25.7
Southern Han Chinese, People's Republic of China (CHS), n=105	50 (47.6)	45 (42.9)	10 (9.5)	69.0	31.0
Japanese in Tokyo, Japan (JPT), n=104	68 (65.4)	30 (28.8)	6 (5.8)	79.8	20.2
Kinh in Ho Chi Minh City, Vietnam (KHV), n=99	48 (48.5)	46 (46.5)	5 (5.1)	71.7	28.3

Note: [a]Data reprinted with permission from Macmillan Publishers Ltd: Nature[29] copyright 2015. Available from: http://www.1000genomes.org/

observed in this study. This was probably due to small sample sizes after stratification by SE. To clarify the contribution of rs3759223 to the risk of high myopia, additional larger genetic studies are needed that take into account the degree of SE.

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Disclosure

The authors report no conflicts of interest in this work.

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