Molecular Vision 2019; 25:843-850 <http://www.molvis.org/molvis/v25/843>
Received 25 April 2019 | Accepted 3 December 2019 | Published 5 December 2019

Common variants in the *COL2A1* gene are associated with lattice degeneration of the retina in a Japanese population

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Purpose: Lattice degeneration of the retina is a vitreoretinal disorder characterized by a visible fundus lesion that predisposes the patient to retinal detachment. It has been suggested that collagen type II alpha 1 (*COL2A1*) gene variants may contribute to the development of disorders associated with retinal detachment. Here we investigated whether *COL2A1* gene variants were associated with the risk of lattice degeneration of the retina.
Methods: We recruited 634 Japanese patients with lattice degeneration of the retina and 1694 Japanese healthy controls. We genotyped 13 tagging single-nucleotide polymorphisms (SNPs) in *COL2A1*. We also performed imputation analysis to evaluate the potential association of un-genotyped *COL2A1* SNPs, involving the imputation of 65 SNPs.
Results: Two intronic SNPs—rs1793954 and rs1635533—were significantly associated with lattice degeneration of the retina. The SNP rs1793954 showed the strongest association, with its C allele carrying an increased disease risk ($p = 0.0016$, corrected $p = 0.021$, OR = 1.25). The rs1793954 and rs1635533 SNPs were in strong linkage disequilibrium with each other ($r^2 = 0.99$), and conditional analysis revealed that rs1793954 could account for the association between rs1635533 and the disease.
Conclusions: Our results suggested that *COL2A1* gene variants may contribute to the development of lattice degeneration of the retina. Further genetic and functional analyses of COL2A1 variants are needed to clarify the present findings.

Lattice degeneration of the retina is a vitreoretinal disorder characterized by focal retinal thinning associated with liquefaction of the overlying vitreous gel and by firm vitreoretinal adherence to lesion margins [1,2]. After posterior vitreous detachment, vitreous traction at sites of substantial vitreoretinal adhesion often leads to retinal detachment [1,2]. Lattice degeneration is common in the general population, with reported prevalence rates of 6%–10.7% among Caucasians and Asians [1,3-5] and 1.8% among Africans [6]. In several ethnic populations, lattice degeneration is causally associated with 30%–60% of retinal detachment cases [7-11]. Lattice degeneration associated with retinal detachment is described in multiple hereditary disorders, including Stickler syndrome [12], Marfan syndrome [13], Ehlers-Danlos syndrome [14], and Wagner syndrome [15].

The exact pathophysiological mechanisms underlying lattice degeneration remain uncertain, but it is suggested that polygenic or multifactorial factors contribute to its etiology [16]. In 2012, we reported a genome-wide association study (GWAS) of lattice degeneration of the retina using 23,465 microsatellite markers in a Japanese population, in which we identified the collagen type IV alpha 4 (*COL4A4*) gene as a candidate susceptibility determinant [17]. Type IV collagen is the major structural component of the basement membranes that predominantly comprise the retinal structure; thus, we speculated that COL4A4 protein aberrations caused by genetic variants may promote retinal thinning in cases of retinal lattice degeneration. To date, our GWAS is the only genetic study to identify susceptibility genes for lattice degeneration.

Mutations in the collagen type II alpha 1 (*COL2A1*) gene are reportedly associated with rhegmatogenous retinal detachment (RRD), the most common type of retinal detachment [18,19]. Moreover, it is well known that *COL2A1* mutations are associated with Stickler syndrome type I, which carries a high risk of RRD [20-22]. These findings suggest that *COL2A1* variants may contribute to the development of inherited disorders associated with retinal detachment. However, our previous GWAS using microsatellite markers has not identified any significant association between *COL2A1* variants and lattice degeneration of the retina [17]. Given that the GWAS has a poorer mapping resolution and lower detection power compared to GWAS using single-nucleotide polymorphisms (SNPs), it could have failed to

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assess properly the association between *COL2A1* variants and lattice degeneration.

In the present study, we aimed to investigate the role of *COL2A1* gene variants in the development of lattice degeneration of the retina. We performed a candidate gene approach to evaluate the association between *COL2A1* SNPs and lattice degeneration in a Japanese population.

METHODS

Participants: For this study, we enrolled 634 unrelated patients with lattice degeneration of the retina and 1,694 unrelated healthy controls, all of Japanese descent, and these numbers included all patients and controls used in our previous GWAS [17]. The subjects were recruited from Yokohama City University, Ideta Eye Hospital, Yonemoto Eye Clinic, Nanbu Hospital, and Okada Eye Clinic. Blood samples were collected from patients who were scheduled for surgery for retinal detachment caused by lattice degeneration. The study details were explained to all patients and controls, and 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 each participating institute. Lattice degeneration was diagnosed by retina specialists using indirect ophthalmoscopy and scleral indentation. The criteria for a lattice degeneration diagnosis included one or more of the following observations: lattice-like white line changes in the crossing retinal vessels; snail-track variations; altered pigmentation; ovoid or linear reddish craters; localized round, oval, or linear retinal thinning; and attachment of condensed vitreous fibers to the lesion edges. Regardless of variations in pigmentation or other morphological features, a lesion was considered lattice degeneration if the examiner encountered an abrupt and discrete irregularity of an otherwise smooth retinal surface at the lesion border. The control subjects were all healthy volunteers, unrelated to each other or to the patients with lattice degeneration of the retina, and affected by neither lattice degeneration of the retina nor any local or systemic illnesses. All control subjects were confirmed as not having lattice degeneration through a dilated fundus examination, whereas whether their family members have lattice degeneration was not confirmed.

DNA and COL2A1 genotyping: From peripheral blood samples, we extracted genomic DNA using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Standardized conditions were used to maintain consistent DNA quality.

From the HapMap Phase III Japanese data (NCBI), we selected tagging SNPs that covered the *COL2A1* region, including 5 kb upstream and downstream from the gene, and SNPs that had a minor allele frequency of ≥5% and a pairwise r^2 value of ≥0.8. The chosen tagging SNPs were rs2071358, rs4760608, rs1793949, rs11168337, rs3829735, rs740024, rs2071437, rs12423250, rs1034762, rs1793958, rs1793953, rs12228854, and rs6580647. We performed SNP genotyping using the TaqMan 5′ exonuclease assay, with primers from Applied Biosystems (Foster City, CA). PCR was performed in a 10-µL reaction mixture containing 1× TaqMan Universal PCR Master Mix (Applied Biosystems), 24 nmol of each primer–probe set, and 3 ng genomic DNA. The PCR conditions included 95 °C for 10 min, followed by 40 cycles of denaturation at 92 °C for 15 s and annealing/extension at 60 °C for 1 min. The probe's fluorescence signal was detected using the StepOnePlus Real-Time PCR System (Applied Biosystems).

Imputation analysis of the COL2A1 gene region: We also performed imputation analysis to evaluate potential associations with un-genotyped SNPs within the region 5 kb upstream and downstream from *COL2A1*. We imputed the genotypes of 634 cases and 1,694 controls using MACH v1.0 [23,24]. As a reference panel, we used the 1000 Genomes Phase 3 data sets of 504 East Asian samples, which included a set of Japanese samples from Tokyo (JPT, n = 104), Han Chinese samples from Beijing (CHB, n = 103), Southern Han Chinese samples (CHS, n = 105), Chinese Dai samples from Xishuangbanna (CDX, n = 93), and Kinh samples from Ho Chi Minh City (KHV, n = 99; 1000Genomes) [25]. All imputed SNPs were filtered using the following quality controls: Hardy–Weinberg equilibrium (HWE) p>0.001, minor allele frequency >1%, and a squared correlation between imputed and true genotypes (Rsq) >0.70. MACH recommends an Rsq threshold of >0.30 that can remove 70% of poorly imputed SNPs while retaining 99.5% of well-imputed SNPs [24]. In the present study, we used an Rsq threshold of >0.70 to filter out even more poorly imputed SNPs and perform association analysis with SNPs imputed at high quality. After the quality control filtering, we included the 65 imputed SNPs in further analysis.

Online database analysis: We investigated the functional roles of candidate SNPs using HaploReg v4.1 [26] and RegulomeDB [27]. To assess associations between candidate SNPs and the *COL2A1* expression, we used the GTEx Portal online database [28].

Statistical analysis: Association analysis, stepwise regression analysis, and linkage disequilibrium (LD) estimation were performed using the SNP & Variation Suite software (version 8.6.0, Golden Helix, Inc., Bozeman, MT) and Haploview 4.2 software [29]. The obtained p values and odds ratios (ORs) were adjusted for spherical equivalent (SE; adj*P* and adjOR,

respectively). The *P* and adj*P* values were corrected for multiple testing using the Bonferroni method based on the number of tagging SNPs (n = 13). A corrected *P* (*Pc*) and adj*P* (adj*Pc*) values of <0.05 were considered significant. We generated a regional association plot for the *COL2A1* region using LocusZoom [30].

RESULTS

Among the control participants, the genotype frequencies of all 13 tagging SNPs were in HWE (p>0.05). Figure 1 shows the results of allelic association tests for the 13 tagging and 65 imputed SNPs in *COL2A1*. Of these 78 SNPs, the strongest significant associations were with two imputed intronic SNPs, rs1793954 (p = 0.0016, *Pc* = 0.021) and rs1635533 (p = 0.0017, *Pc* = 0.023). Specifically, increased disease risk was associated with the C allele of rs1793954 (OR = 1.25) and the G allele of rs1635533 (OR = 1.24; Table 1, Figure 1). We also observed associations with two tagging SNPs, but these associations were not significant after correction: rs3829735, p = 0.0050, *Pc* = 0.065, OR = 1.45; and rs1793953, p = 0.0040, *Pc* = 0.053, OR = 1.22 (Table 1, Figure 1; Appendix 1). Another six imputed SNPs showed moderate but not significant associations (p<0.05, *Pc* >0.05; Table 1). The remaining 68 SNPs showed no significant risk association.

Lattice degeneration is commonly found in patients with myopia [1,7]. In the present study, the average SEs of the patients were −3.81±3.94 diopters (D; range, −20.00 to +3.75 D) in the right eye and −3.79±3.94 D (range, −22.00 to +3.50 D) in the left eye and 53.4% of the patients had a SEM less than −3.00 D. For the controls, the average SEs were 0.48±0.66 D (range, −1.00 to 3.50 D) in the right eye and 0.48±0.64 D (range, −1.00 to 3.00 D) in the left eye. To adjust for differences in SEM between the patients and controls, we performed a logistic regression analysis for each SNP. After adjusting for SE, rs1793954 and rs1635533 still showed significant associations with lattice degeneration of the retina (rs1793954: adj*p* = 0.0036, adj*Pc* = 0.047, adjOR = 1.30; and rs1635533, adj*p* = 0.0038, adj*Pc* = 0.049, adjOR = 1.29).

Figure 1 and Figure 2 illustrate the LD between the strongly associated SNP rs1793954 and all other SNPs in *COL2A1*. The SNP rs1793954 showed strong LD with the other significantly associated SNP rs1635533 (r^2 = 0.99) and with the other four SNPs that showed p values of <0.05 (rs2023939, rs12308909, rs1635532, and rs1793953; r^2 ≥0.59). On the other hand, rs1793954 exhibited low LD with the remaining four SNPs having p values of <0.05 (rs12721423, rs34829929, rs28594309, and rs3829735; r^2 <0.10). Using the 10 SNPs showing p values <0.05, we performed stepwise regression analysis to test the independence of multiple

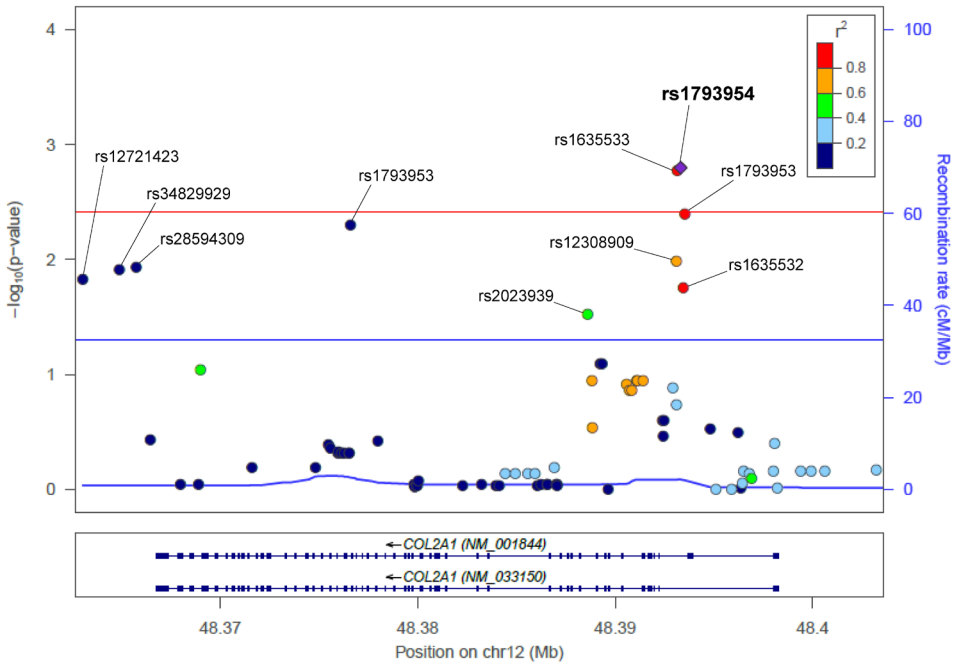

Figure 1. Allelic association results for the *COL2A1* gene region with lattice degeneration of the retina in the Japanese population. The SNP showing the strongest association (rs1793954) is depicted as a purple diamond. The color coding of the other SNPs indicates linkage disequilibrium (LE) with rs1793954: red, r^2 ≥0.8; yellow, 0.6 ≤ r^2 <0.8; green, 0.4 ≤ r^2 <0.6; cyan, 0.2 ≤ r^2 <0.4; blue, r^2 <0.2; and gray, r^2 is unknown. The left y-axis represents the −log10 p values for allelic association with lattice degeneration of the retina, and the right y-axis represents the estimated recombination rate. The horizontal blue and red lines indicate p = 0.05 and *Pc* = 0.05 (p = 0.00385 [0.05/13 SNPs]), respectively. Gene annotations are shown below the figure. The plot was created using LocusZoom.

Table 1. Allelic associations between 10 SNPs with p<0.05 and lattice degeneration of the retina in the Japanese population.

SNP	Position on Chr.12 (GRCh37)	Alleles	Risk Allele	Risk Allele Frequency Cases (n = 634)	Controls (n = 1694)	P	Pc	OR (95% CI)	adj*P**	adj*Pc*	adjOR (95% CI)*	Rsq Score**
rs12721423	48363024	C>A	A	0.478	0.438	0.015	0.19	1.17 (1.03–1.34)	0.1		1.14 (0.97–1.35)	0.739
rs34829929	48364881	C>T	T	0.478	0.437	0.012	0.16	1.18 (1.04–1.34)	0.094		1.15 (0.98–1.35)	0.757
rs28594309	48365733	A>G	G	0.478	0.437	0.011	0.15	1.18 (1.04–1.34)	0.091		1.15 (0.98–1.35)	0.765
rs3829735	48376599	G>A	G	0.94	0.915	0.005	0.065	1.45 (1.12–1.89)	0.062		1.36 (0.98–1.89)	Genotyped
rs2023939	48388612	A>G	A	0.774	0.744	0.03	0.38	1.18 (1.02–1.38)	0.016	0.21	1.27 (1.04–1.55)	0.969
rs12308909	48393098	G>A	G	0.764	0.727	0.01	0.13	1.22 (1.05–1.41)	0.0055	0.072	1.31 (1.08–1.60)	0.955
rs1635533	48393137	G>A	G	0.68	0.6305	0.0017	0.023	1.24 (1.09–1.43)	0.0038	0.049	1.29 (1.08–1.55)	0.977
rs1793954	48393320	C>T	C	0.68	0.6302	0.0016	0.021	1.25 (1.09–1.43)	0.0036	0.047	1.30 (1.09–1.55)	0.978
rs1635532	48393444	G>A	G	0.679	0.642	0.017	0.22	1.18 (1.03–1.36)	0.026	0.34	1.22 (1.02–1.46)	0.993
rs1793953	48393526	C>T	C	0.689	0.644	0.004	0.053	1.22 (1.07–1.41)	0.017	0.22	1.24 (1.04–1.47)	Genotyped

Chr., chromosome; OR, odds ratio; CI, confidence interval; adjP, p value adjusted for spherical equivalent; adjOR, OR adjusted for spherical equivalent. * The adjP values and adjORs were determined using logistic regression. **Rsq is an estimate of the squared correlation between imputed and true genotypes., minor allele frequency; LP, likely pathogenic; P, pathogenic; VUS, a variant of uncertain significance

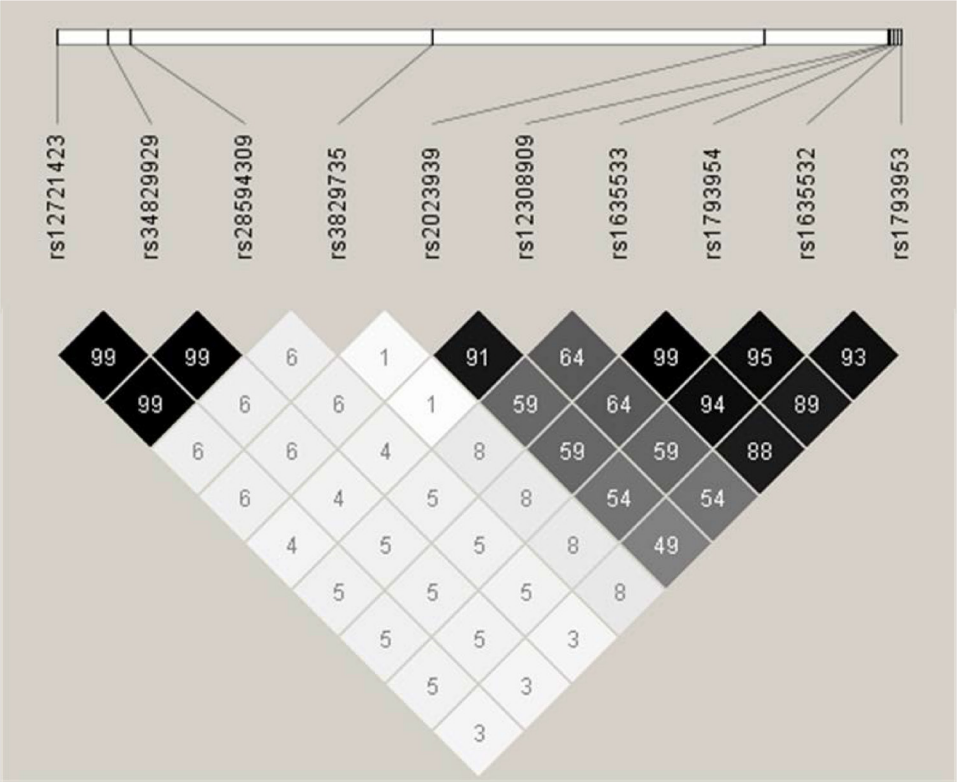

Figure 2. LE plot of 10 SNPs with p<0.05. For each SNP pair, the corresponding r^2 value is shown as a percentage within the respective square. Higher r^2 values are indicated by darker shading of the square's background.

possible associations in the *COL2A1* region. Conditioning by SNP rs1793954 completely eliminated the associations of the other five SNPs that were in strong LD with rs1793954 (rs1635533, rs2023939, rs12308909, rs1635532, and rs1793953; p>0.70). These findings suggested that rs1793954 might account for the associations of the other SNPs with lattice degeneration of the retina in the Japanese population.

The HaploReg v4.1 database predicts that the SNP rs1793954 within the intron of *COL2A1* is located in enhancer histone marks and alters the regulatory motif of an Evi-1 transcription factor. It also predicts that the rs1793954 C risk allele will show a much lower affinity to the transcription factor motif compared to its T allele, suggesting that rs1793954 has a potential role in regulating the *COL2A1* expression. However, the RegulomeDB database shows that rs1793954 has a score of 5 with minimal binding evidence (indicating that it is unlikely to affect transcription factor binding), and the GTEx Portal database includes no reported significant association between rs1793954 and the *COL2A1* expression.

DISCUSSION

The *COL2A1* gene encodes the alpha 1 chain of type II collagen, which is a major component of cartilage and the vitreous of the eye [31-33]. It spans about 33 kb, with 54 exons on chromosome 12q13.11, and *COL2A1* mutations are associated with RRD and Stickler syndrome type I [18-22]. Hoornaert et al. [21] demonstrated that *COL2A1* loss-of-function mutations are the predominant cause of Stickler syndrome type I and vitreoretinal abnormalities (including vitreous anomalies and retinal tear or detachment) are more common in Stickler syndrome type I patients with *COL2A1* mutation compared to those without a mutation. This evidence suggests that a *COL2A1* mutation can lead to vitreoretinal abnormalities that are associated with the development of retinal detachment.

In the present study, we aimed to assess whether *COL2A1* SNPs affected the development of lattice degeneration of the retina, which carries a high risk of RRD. We performed a comprehensive association analysis of SNPs in the *COL2A1* region among Japanese patients with lattice degeneration of the retina. To our knowledge, this study was the first attempt to investigate the possible association between *COL2A1* gene polymorphisms and lattice degeneration of the retina. Our findings demonstrated that the *COL2A1* intronic SNP rs1793954 had a significant impact on disease development, with the C allele of rs1793954 associated with elevated disease risk. Spickett et al. [34] recently reported that another common intronic SNP rs1635532 was significantly

associated with RRD in a white European population [34]. In our Japanese population, rs1635532 exhibited strong LD with rs1793954 (r^2 = 0.95, Figure 2) and showed a moderate non-significant association with lattice degeneration of the retina (p<0.05, *P*c >0.05). This suggested that the region showing strong LD and including rs1793954 may be an important locus for the development of RRD and RRD-associated disorders. Further validation studies in other ethnic populations are needed to clarify the association between the LD region and lattice degeneration of the retina.

Because non-coding variants can significantly affect gene expression [35], we assessed the functional role of rs1793954 in the *COL2A1* expression. The HaploReg v4.1 database predicts that rs1793954 has a potential role in regulating the *COL2A1* expression, with the risk allele C showing a much lower affinity to the transcription factor motif. Pathogenic features of lattice degeneration of the retina include vitreous humor liquefaction, loss of vitreoretinal attachments, loss of the internal limiting membrane over the lesions, and increased vitreoretinal attachment at the lesion margins. Therefore, the data from HaploReg v4.1 suggest that the vitreoretinal abnormalities in patients with lattice degeneration of the retina may arise from an altered *COL2A1* expression associated with the rs1793954 C allele. However, other public databases show little or no evidence that rs1793954 significantly affects the *COL2A1* expression. This inconsistent evidence highlights the necessity of further functional studies to clarify the contribution of *COL2A1* rs1793954 to the development of lattice degeneration of the retina.

In our present study, we targeted *COL2A1* SNPs with a minor allele frequency of >1% to investigate the contribution of *COL2A1* variants to the risk of lattice degeneration of the retina. However, most previous studies have reported rare *COL2A1* mutations, particularly mutations in the exon regions, as causative variants of RRD and Stickler syndrome type I [18-22]. This suggests that rare *COL2A1* mutations are also involved in the development of lattice degeneration of the retina. Therefore, there remains a need for mutation analyses of *COL2A1* in patients with lattice degeneration of the retina. Another limitation to be considered is that the present study was conducted in only Japanese population. An association observed in one population often fails to replicate in other populations. Thus, further genetic association studies with other ethnic populations are required to validate the findings observed in the present study.

In conclusion, our current results revealed a significant association between the *COL2A1* SNP rs1793954 and lattice degeneration of the retina in a Japanese population, suggesting that *COL2A1* variants play important roles in disease development. Moreover, the present results suggest the possibility that rs1793954 contributes to an altered *COL2A1* expression, which may be involved in the development of lattice degeneration of the retina. To validate these findings and to clarify the contribution of the *COL2A1* region to disease development, further genetic analyses and functional analyses of *COL2A1* variants should be performed.

APPENDIX 1. ALLELIC ASSOCIATION RESULTS FOR 13 TAG SNPS DIRECTLY GENOTYPED IN THIS STUDY.

To access the data, click or select the words "Appendix 1." Chr., chromosome; OR, odds ratio; CI, confidence interval; adjP, P value adjusted for spherical equivalent; adjOR, OR adjusted for spherical equivalent. * The adjP values and adjORs were determined using logistic regression. **Rsq is an estimate of the squared correlation between imputed and true genotypes.

ACKNOWLEDGMENTS

We sincerely thank all the participants for their participation in this study, and all the medical staff involved in sample collection and diagnosis. This study was supported by a grant from the Yokohama Foundation for Advancement of Medical Science (no grant number available).

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Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 5 December 2019. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.