Molecular Vision 2014; 20:352-358 <http://www.molvis.org/molvis/v20/352>
Received 22 October 2013 | Accepted 19 March 2014 | Published 21 March 2014

Polymorphism in the 11q24.1 genomic region is associated with myopia: A comprehensive genetic study in Chinese and Japanese populations

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Purpose: To evaluate the association of polymorphisms in the 11q24.1 genomic region and the *CTNND2* gene with myopia.

Methods: We conducted a comprehensive meta-analysis included 6,954 cases and 9,346 controls. Odds ratios (ORs) were calculated using Carlin's method. Publication bias was assessed using Egger et al.'s approach. Sensitivity, heterogeneity, and trim and fill analyses were also conducted.

Results: For the 11q24.1 genomic region, the rs11218544 polymorphism showed significant association with myopia [OR and 95% confidence interval (CI): 1.167 (1.032–1.319), p=0.013], while rs577948 showed no association with the disease [OR and 95%CI: 0.988 (0.727–1.342), p=0.936]. For the *CTNND2* gene, neither rs6885224 nor rs12716080 was significantly associated with myopia {rs6885224: [OR and 95%CI: 1.051 (0.795–1.391), p=0.725], rs12716080: [OR and 95%CI: 1.173 (0.990–1.390), p=0.065]}.

Conclusions: Our study indicated that the 11q24.1 genomic region, and particularly the rs11218544 polymorphism, has a genetic association with the development of myopia.

Myopia (nearsightedness) is one of the most common visual disorders affecting both children and adults, with an average prevalence of 30% worldwide [1-3]. It is a refractive error of the eye in which parallel rays of light focus anterior of the retinal plane, resulting in blurred vision. The myopia rates among East Asians, especially in the Chinese and Japanese populations, are much higher than in Europeans [4,5].

The etiology of myopia is known to be knotted [6]. The environmental influences in the development of the disease have been indicated from many epidemiological studies [7,8]. However, a large body of research, especially that involving twin and familial studies, has shown that genetic factors play important roles in the pathogenesis of myopia [9,10]. Molecular genetic study provides a special tool to study the molecular basis of myopia. Genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) in different chromosomal regions that are significantly associated with myopia [11-13]. Linkage studies have mapped many myopia susceptibility loci. However, the exact genes in these loci that are responsible for the progression of myopia remain to be identified in further studies.

Chinese and Japanese populations exhibit a very high prevalence of myopia. In addition, the populations from these two countries are closely related [14]. Additionally, the LD structures of rs577948, rs11218544, rs12716080, and rs6885224 are very similar between the two populations. Given these considerations, we conducted the present comprehensive meta-analysis to evaluate whether these four polymorphisms of the *CTNND2* gene and the 11q24.1 genomic region are associated with myopia in Chinese and Japanese populations.

METHODS

Search strategy: To assess the total evidence of association between the *CTNND2* gene and myopia disease, and between 11q24.1 genomic region and myopia, we performed the present comprehensive meta-analysis of published studies. A total of 11 studies focusing either on the association between the *CTNND2* gene and myopia or between the 11q24.1 genomic region and myopia were identified according to our inclusion criteria; these publications comprised 6,954 cases and 9,346 controls [11,15-18]. The main characteristics of these studies are given in Table 1. We considered all studies that examined the association of the rs577948, rs11218544, rs12716080, and

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rs6885224 polymorphisms with myopia. Sources included MEDLINE and EMBASE (search last updated in Aug. 2012). The search strategy was based on combinations of the terms "CTNND2," "T-cell delta-catenin," "catenin delta-2," "11q24.1 genomic region," and "myopia." Reference lists in the retrieved articles were also screened.

Inclusion and exclusion criteria: All the studies included satisfied all the following criteria: (1) They were association studies either between the rs12716080 and rs6885224 polymorphisms in the *CTNND2* gene and myopia disease or between the rs577948 and rs11218544 polymorphisms and myopia; (2) they used myopia-free people as controls; (3) they provided genotype or allele distributions in both the case and control groups; and (4) they were independent studies and the subject groups investigated did not overlap with each other. Authors were contacted where clarification was required.

Only studies published in English were included. Studies presenting nonoriginal data were excluded, such as reviews, editorials, opinion papers, or letters to the editor. Studies using nonhuman subjects or specimens were excluded. Studies with no extractable numerical data were excluded. Only those articles that had some measure of diagnostic performance were included. Any duplicates that came up in the preliminary search were excluded.

Data extraction: The following information was independently extracted from the identified studies by two participants in the meta-analysis: first author, journal, year of publication, study design, ethnicity of the study population, gender, clinical characteristics, genotyping method, the number of cases and controls or odds ratio (OR) and 95 percent confidence interval (95%CI), country in which the study was conducted, and confirmation of diagnosis. The results were compared and any disagreement was discussed and resolved by consensus.

Statistical analysis: We used a comprehensive meta-analysis to analyze the ORs using Carlin's method [19]. To determine whether the results of the meta-analysis were unduly influenced by any one study, we recomputed the meta-analysis statistics after deleting each study one at a time. We assessed publication bias using Egger et al.'s approach [20]. This method is based on the fact that the precision of the OR increases with larger study groups. It regresses the standard normal deviation of the OR (the OR divided by its standard error) against the precision of the OR (the inverse of its standard error). In the absence of bias, Egger et al. [20] showed that the regression of the standard normal deviate on the precision of the OR should run through the origin (i.e., small study groups with low precision have large standard errors and therefore small standard normal deviates; large study groups have higher precision, smaller standard errors, and large standard normal deviates). The publication bias statistic of Egger et al. [20] is the intercept of the regression, which will be significantly greater than zero in the presence of publication bias.

The random effects model using the DerSimonian and Laird method was employed, and the estimate of heterogeneity was determined using the Mantel–Haenszel model [21]. Heterogeneity among studies was tested using the Q and I^2 statistics. The effect size was represented by an OR with 95%CI. Sensitivity analysis was conducted by removing each study and analyzing the others to ensure that no single study was totally responsible for overall results. Every time, each study was removed in turn from the total, and the remainder was reanalyzed. This procedure was used to ensure that no individual study was entirely responsible for a finding. Between-study heterogeneity was tested using Cochran's Q statistic, which is considered significant at $p<0.10$. The extent of inconsistency across studies was quantified with the I^2 statistic. The I^2 ranges between 0 and 100%. When there was very large or large (>50%) between-study heterogeneity, we used a simulation algorithm to evaluate how many studies had to be removed for the I^2 to reach <25%.

The significance level was set at 0.05, and all p values were two-tailed. The comprehensive meta-analysis was performed using Comprehensive Meta Analysis software (Version 2.2.046, BIOSTAT, Englewood, NJ) [22-24].

RESULTS

Eligible studies: The combined search yielded seven references. These were then filtered to ensure conformity with the inclusion criteria. One reference was discarded because it was a family-based study. Ultimately, six references met our criteria (Table 1, Figure 1).

Synthesis of quantitative data: The eligible studies for analysis included a total of 6,954 cases with myopia and 9,346 controls (Table 1). For the 11q24.1 genomic region, the rs11218544 polymorphism showed significantly association with myopia [OR and 95% CI: 1.167 (1.032–1.319), p=0.013], and rs577948 showed no association with the disease [OR and 95% CI: 0.988 (0.727–1.342), p=0.936]. For the *CTNND2* gene, neither the rs6885224 nor rs12716080 polymorphism was significantly associated with myopia {rs6885224: [OR and 95% CI: 1.051 (0.795–1.391), p=0.725], rs12716080: [OR and 95% CI: 1.173 (0.990–1.390), p=0.065; Figure 2A-D).

Publication bias and heterogeneity: The sensitivity analysis showed that when any one of the studies was removed, the heterogeneity of the population was not changed deeply;

Table 1. Characteristics of the studies included.

Study (reference number)	Year	Ethnicity	Region	Polymorphisms	Numbers		Mean age	
					Case (Female+Male)	Control (Female+Male)	Case (mean±SD)	Control (mean±SD)
Zhiqiang Yu [15]	2012	Chinese	CTNND2 gene	rs12716080, rs6885224	321 (163+158)	310 (142+168)	27.5±17.1	41.3±12.4
Boyu Lu-1 [16]	2011	Chinese	CTNND2 gene	rs12716080, rs6885224	1203 (610+593)	955 (397+558)	18.53±6.64	24.49±2.82
Boyu Lu-2 [16]	2011	Chinese	CTNND2 gene	rs12716080, rs6885224	615 (306+309)	955 (397+558)	20.70±1.59	24.49±2.82
Yi-Ju Li-1 [17]	2010	Chinese	CTNND2 gene	rs12716080, rs6885224	65 (/)	238 (/)	(/)	(/)
Yi-Ju Li-2 [17]	2010	Chinese	CTNND2 gene	rs12716080, rs6885224	222 (/)	435 (/)	(/)	(/)
Yi-Ju Li-3 [17]	2010	Japanese	CTNND2 gene	rs12716080, rs6885224	929 (481+448)	2008 (921+1087)	10.83±0.83	47.9±11.18
Zhiqiang Yu [15]	2012	Chinese	11q24.1 genomic region	rs577948, rs12118544	321 (163+158)	310 (142+168)	27.5±17.1	41.3±12.4
Qin Wang-1 [18]	2011	Chinese	11q24.1 genomic region	rs577948, rs12118544	1255 (641+614)	1052 (443+609)	20.70±1.59	20.91±1.78
Qin Wang-2 [18]	2011	Chinese	11q24.1 genomic region	rs577948, rs12118544	563 (274+289)	1052 (443+609)	20.06±14.01	20.91±1.78
Hideo Nakanishi-1 [11]	2009	Japanese	11q24.1 genomic region	rs577948, rs12118544	297 (204+93)	934 (/)	58.8±13.2	/
Hideo Nakanishi-2 [11]	2009	Japanese	11q24.1 genomic region	rs577948, rs12118544	533 (362+171)	977 (480+497)	59.0±14.3	48.3±16.3

"(/)" means the information is not available in the reference.

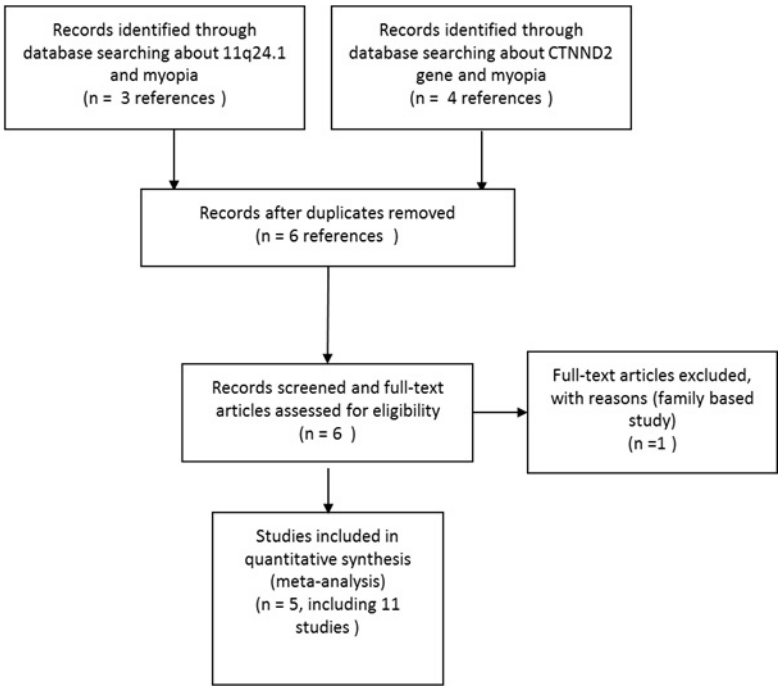

Figure 1. Process used to select published studies for a systematic review and genetic study between 2009 and Aug. 2012. MeSH: Medical Subject Headings.

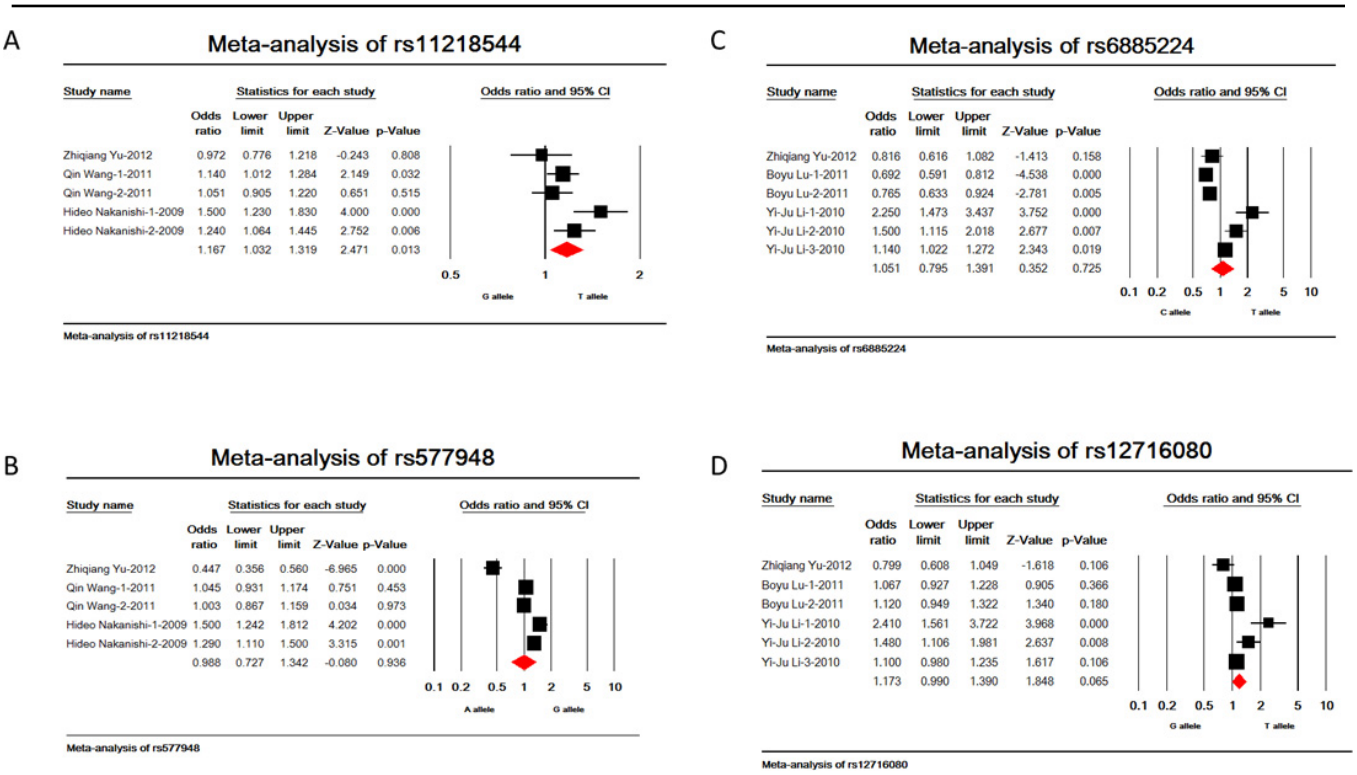

Figure 2. Meta-analysis of association studies of the polymorphisms and myopia. **A**: rs11218544, **B**: rs677948, **C**: rs6885224, **D**: rs12716080. Pooled overall OR is shown. The OR of each study is marked with a black square. Pooled OR is indicated by a red diamond.

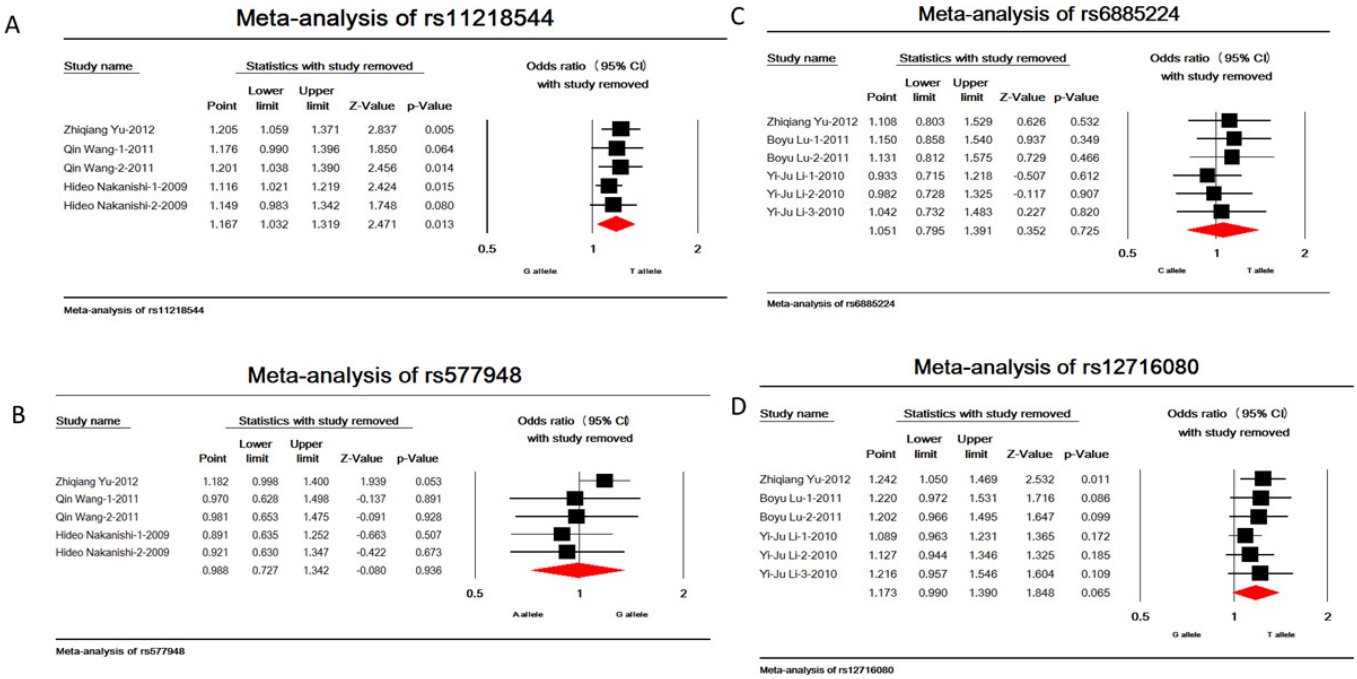

Figure 3. The sensitivity analysis of the polymorphisms. **A**: rs11218544, **B**: rs677948, **C**: rs6885224, **D**: rs12716080. When any one of the studies was removed, the heterogeneity of the population remained unchanged.

namely, when one study was removed, the result was still significant (Figure 3A-D). This indicated that no heterogeneity existed in the population. There was no evidence to suggest that the magnitude of the overall OR estimates changed in the same direction over time. Moreover, the Egger funnel plots of publication bias analysis for four polymorphisms were shown (Figure 4A-D).

DISCUSSION

This comprehensive meta-analysis was designed to further evaluate the importance of 11q24.1 loci and the *CTNND2* gene as potential susceptibility loci for myopia. Our results indicated that the 11q24.1 genomic region, and particularly the rs11218544 polymorphism, was significantly associated with myopia. On the other hand, the results for the *CTNND2* gene were not in the same direction as those reported by Lu et al. and Li et al. [16,17]. In Boyu Lu's study, the researchers found that rs6885224 was significantly associated with myopia, whereas rs12716080 was not. In Li et al.'s [17] study, it was reported that both the rs6885224 and rs12716080 polymorphisms were significantly associated with myopia.

In this study, we accessed as much of the literature as possible to achieve a complete and unbiased representation of the relevant research. Those studies with insufficient or ambiguous data were excluded. This effort to take a comprehensive and even-handed approach to the literature inclusion may have strengthened the robustness of the findings while avoiding publication bias and minimizing heterogeneity [25]. Compared with previous studies, this current meta-analysis pooled larger sample sizes, generated even more significant results with systematic design types and analysis approaches, and included tests of heterogeneity and sensitivity analyses. The current results demonstrate the robustness of the associations between the 11q24.1 genomic region and the disease, which was significant in some studies and not in others. As a polygenic disease, myopia is caused by the combined actions of many factors. For greater insight into its genetic component, more work is required to confirm the role of other genes that may have a small effect, and to identify new genetic risk factors. The large samples required will necessitate multisite projects and meta-analyses based on national and international collaboration.

In summary, this comprehensive meta-analysis supports the significant association of markers in the 11q24.1 genomic region with myopia, and no significant association of markers in the *CTNND2* gene with the disease. It remains unclear why the associated alleles vary across studies. Identification of functional variants will probably require biological and additional genetic assays.

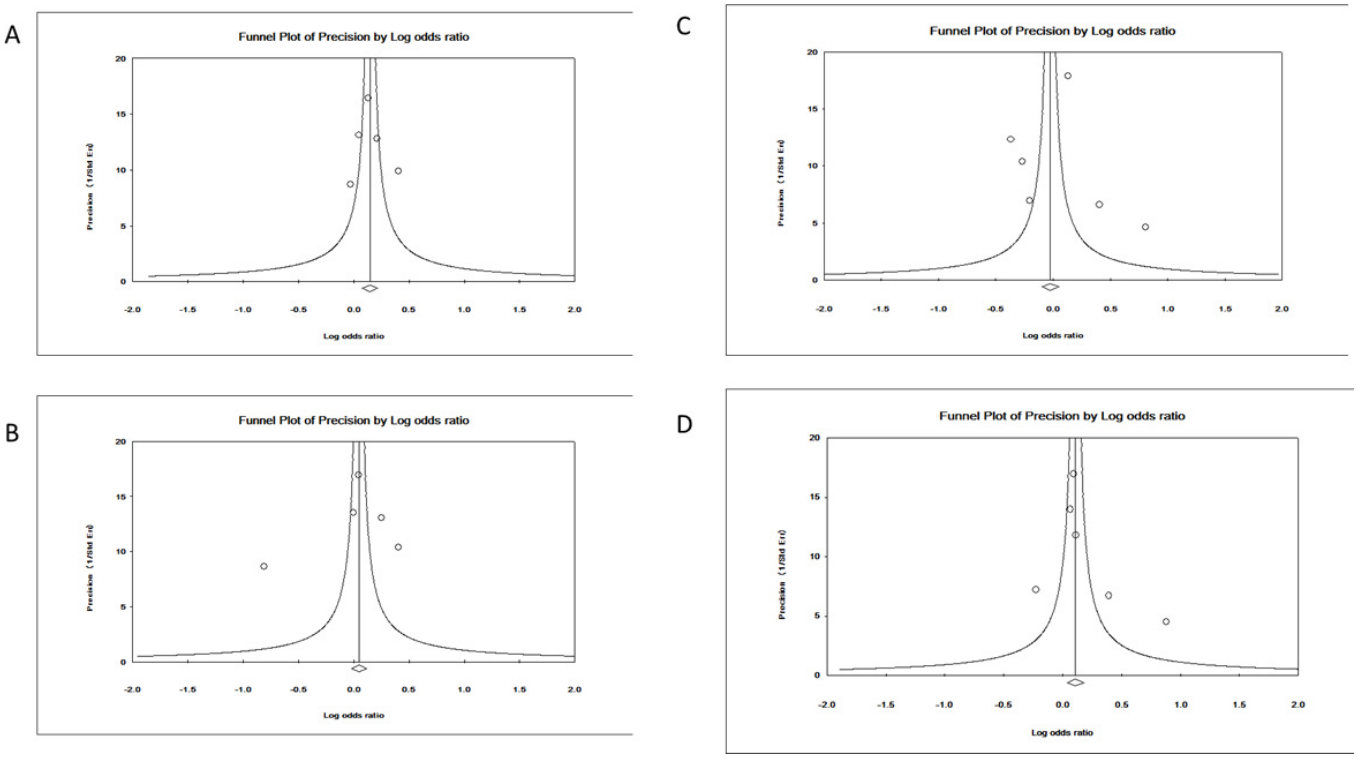

Figure 4. Egger's funnel plots of publication bias analysis for the polymorphisms. **A**: rs11218544, **B**: rs677948, **C**: rs6885224, **D**: rs12716080. The larger the deviation from the funnel curve of each study, the more pronounced the asymmetry. Results from small studies scatter widely at the bottom of the graph, with the spread narrowing among larger studies.

ACKNOWLEDGMENTS

J. Liu designed the study. J. Liu and HX. Zhang performed the statistical analysis and drafted the manuscript. All authors critically revised the manuscript and gave final approval of the article for submission. This work is supported by grants from the National Natural Science Foundation of China (31000408) and the Science and Technology Commission of Shanghai municipality (13ZR1461100). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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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 21 March 2014. 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.