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Lack of association between *lysyl oxidase-like 1* polymorphisms and primary open angle glaucoma: a meta-analysis

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Received: 2013-12-03 Revised: 2014-03-20

Abstract

• AIM: To study the associations between *lysyl oxidase-like 1* (*LOXL1*) polymorphisms and primary open angle glaucoma (POAG) remain inconsistent. In this study, we have performed a meta-analysis to investigate the association of *LOXL1* polymorphisms with POAG risk.

• METHODS: Published literature from PubMed and other databases were retrieved. All studies evaluating the association between *LOXL1* polymorphisms (rs2165241, rs1048661, rs3825942) and POAG risk were included. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using random- or fixed-effects model.

• RESULTS: Twelve studies were identified as eligible articles, with thirteen (2098 cases and 16 473 controls), thirteen (1795 cases and 2916 controls) and sixteen population cohorts (2456 cases and 2846 controls) for the association of rs2165241, rs1048661 and rs3825942 with POAG risk respectively. Overall analyses showed no association between each *LOXL1* polymorphism and POAG risk, and the negative associations were remained when the subjects were stratified as Caucasian and Asian. The heterozygote of rs2165241 was associated with reduced POAG risk in hospital-based populations (TC *vs* CC: OR, 0.79, 95%CI: 0.63-0.99), and rs1048661 was associated with increased POAG risk in hospital-based populations in a dominant model (TT *vs* CC+CT: OR, 1.23, 95%CI: 1.01-1.50); however, these associations were not found in population-based subjects.

• CONCLUSION: This meta-analysis suggests that *LOXL1* polymorphisms are not associated with POAG risk. Given the limited sample size, the associations of *LOXL1* polymorphisms with POAG risk in hospital-based populations await further investigation.

• KEYWORDS: glaucoma; gene polymorphism; meta-analysis; *lysyl oxidase-like 1*

DOI:10.3980/j.issn.2222-3959.2014.03.29

Sun W, Sheng Y, Weng Y, Xu CX, Williams SE, Liu YT, Hauser MA, Allingham RR, Jin MJ, Chen GD. Lack of association between *lysyl oxidase-like 1* polymorphisms and primary open angle glaucoma: a meta-analysis. *Int J Ophthalmol* 2014;7(3):550-556

INTRODUCTION

Glaucoma is a group of clinically and genetically heterogeneous optic neuropathies characterized by the progressive degeneration of the optic nerve and gradual loss of vision. It is considered to be the second most frequent cause of irreversible blindness globally and affects primarily the older population, estimated to affect about 80 million people worldwide by the year 2020 [1]. However, it remains unclear on the etiology of glaucoma. Risk factors for glaucoma include aging, elevated intraocular pressure (IOP), variable susceptibility of the optic nerve, vascular factors (ischemia), diabetes, myopia, cigarette smoking and positive family history [2]. Glaucoma can be inherited as a mendelian autosomal-dominant or autosomal-recessive trait, or as a complex multifactorial trait [3]. For instance, primary

openangle glaucoma (POAG), the most common form of glaucoma, is caused by multiple genetic and environmental factors, as well as their interactions. Recent studies have demonstrated that mutations, polymorphisms, and copy number variations (CNVs) could contribute to the pathogenesis of POAG, *e.g.* genetic approaches have defined the some genes in POAG pathogenesis for minority of patients, including *myocillin* (*MYOC*) and *optineurin* (*OPTN*)[4,5].

Lysyl oxidase-like 1 (LOXL1) is a member of the lysyl oxidase family that catalyzes the oxidative deamination of lysine residues of tropoelastin and is thought to be essential for elastogenesis [6]. It has been reported that LOXL1 is the major lysyl oxidase isoform in normal lamina cribrosa [7]. Dysregulated expression of LOXL1 and elastic proteins was associated with pronounced structural alterations of the elastic fiber network in the laminar beams of pseudoexfoliation syndrome eyes [7]. This suggests that a pseudoexfoliation-specific elastinopathy of the lamina cribrosa, which results from a primary disturbance in LOXL1 regulation and elastic fiber homeostasis, may render pseudoexfoliation syndrome eyes more vulnerable to pressure-induced optic nerve damage and glaucoma development[7].

The study by Thorleifsson *et al*[8] has established a strong association between single nucleotide polymorphisms (SNPs) in the *LOXL1* gene and exfoliation syndrome (XFS) or exfoliation glaucoma (XFG) in the Swedish and Icelandic populations using a genome-wide scan, including two nonsynonymous SNPs (rs1048661: Arg141Leu and rs3825942: Gly153Asp) in exon 1 and one intronic SNP (rs2165241) in *LOXL1*. This association was later independently replicated in other XFS/XFG patient cohorts[9,10]. XFS has been identified as the most common cause of open-angle glaucoma [11]. Both POAG and XFG are complex disorders that share a similar clinical phenotype, glaucomatous optic neuropathy. Similar to POAG, XFG is primarily an open-angle form of glaucoma frequently associated with elevated IOP. The glaucoma is a complex disease attributed to multiple gene variants with various magnitudes of effect. It remains unclear whether the *LOXL1* SNPs causing XFS and XFG may also be associated with primary glaucomas, which may vary between populations. Actually, the data based on stratified analysis from the first study also indicated an association between SNP in the *LOXL1* gene (rs2165241) and increased POAG risk in Iceland population[8]. However, the association was not found in Swedish population, and not confirmed in other patient cohorts [8,12]. To further investigate the association between *LOXL1* SNPs and POAG risk, we have systemically examined the association of *LOXL1* SNPs with POAG in different models by including recent published papers in this study.

SUBJECTS AND METHODS

Identification and Eligibility of Relevant Studies To identify all articles that examined the association of *LOXL1* polymorphism with glaucoma, we conducted a literature search through the PubMed databases up to February 2013 using the following MeSH terms and keywords: "*LOXL1*", "polymorphism" and "primary open angle glaucoma". Additional studies were identified by a manual search from other databases (*e.g.* Embase), references of original studies or review articles on this topic. Eligible studies included in this meta-analysis had to meet the following criteria: 1) evaluation of the association between *LOXL1* polymorphism and primary open angle glaucoma; 2) an unrelated case-control study, when the studies had partly overlapped subjects, only the one with a larger sample size was selected; 3) available genotype frequency, and 4) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data Extraction Three investigators (Sun W, Sheng Y and Weng Y) independently assessed the articles for inclusion/exclusion and extracted data, and reached a consensus on all of the items. For each study, the following information was extracted: name of the first author; publication year; ethnicity (country); number of cases and controls; sources of samples; genotyping methods.

Statistical Analysis The association between *LOXL1* polymorphism and glaucoma was estimated by calculating pooled odd ratios (ORs) and 95% CIs. For rs2165241, we first estimated the risks of the CT and TT genotypes on glaucoma, compared with the reference CC homozygote, and then evaluated the risks of (CT+TT *vs* CC) and (TT *vs* CC+CT) on glaucoma, assuming dominant and recessive effects of the variant T/T allele, respectively. In addition, the allele association of rs2165241 ([T] *vs* [C]) with POAG was also analyzed. Similar pooled analyses for rs1048661 and rs3825942 were carried out by using the reference GG homozygote respectively. The I^2-based Q statistic test was performed to evaluate variations due to heterogeneity rather than chance. A random-effects (DerSimonian-Laird method) or fixed-effects (Mantel-Haenszel method) model was used to calculate pooled effect estimates in the presence ($P \leqslant 0.10$) or absence ($P > 0.10$) of heterogeneity. Publication bias was detected by Egger's test [13] and Begg's [14] test for the

overall pooled analysis of different models of *LOXL1*. Additionally, Begg's funnel plot was drawn. Asymmetry of the funnel plot means a potential publication bias. Stratified analyses were also performed by ethnicities of study populations and the study design of controls. For the one-way sensitivity analysis, one single study was excluded each time, and the new pooled results could reflect the influence of that deleted study to the overall summary OR. All analyses were done with Stata software (version 11.0; StataCorp LP, College Station, TX, USA), using two-sided *P* values.

RESULTS

Characteristics of Studies Fourteen abstracts were retrieved through the search "LOXL1", "polymorphism" and "primary open angle glaucoma", and nine studies meeting the inclusion criteria were identified as eligible [15-23]. Among the fourteen studies, two were review articles, two articles were excluded due to evaluating the relationship between *LOXL1* polymorphisms and other glaucoma or syndromes and one was genome-wide association study to discover genetic markers associated with POAG but not provide *LOXL1* genotypes data [12,24-27]. We also included three eligible studies with manual searching [8,28,29]. As a result, a total of twelve studies met the inclusion criteria and were identified as eligible articles (Figure 1).

Thirteen population cohorts from nine studies were included in the meta-analysis of *LOXL1* polymorphism rs2165241 (2098 cases, 16 473 controls), thirteen population cohorts from eleven studies for *LOXL1* polymorphism rs1048661 (1795 cases, 2916 controls) and sixteen cohorts from twelve studies for *LOXL1* polymorphism rs3825942 (2456 cases, 2846 controls). For rs2165241, nine cohorts from Caucasian and four cohorts from Asian were included. As to rs1048661, eight cohorts from Caucasian and five cohorts from Asian were included. In addition, eleven and five cohorts were included on the association between the rs3825942 and POAG in Caucasian and Asian respectively. In addition to the genome-wide association study by Thoreleifsson *et al*[8], in which the three *LOXL1* polymorphisms were determined by Illumina Hap300 chip, the genotyping for rs2165241 was performed by polymerase chain reaction (PCR) based DNA sequencing[15,17-18,21-23] or TaqMan assays[16,19], for rs1048661 by PCR based DNA sequencing [15-18,21-23,28] or restriction fragment length polymorphism (RFLP) assays[20,29], and for rs3825942 by PCR based DNA sequencing [15,17-18,21-23,28], RFLP assays[20,29] or TaqMan assay [16,19]. The blood samples were used in all studies. Study characteristics included in the meta-analysis are presented in Table 1.

Quantitative Synthesis Table 2 presents in detail the results of the meta-analysis on the association between *LOXL1* polymorphisms and risk of POAG. By pooling all the studies, each *LOXL1* polymorphism was not associated with a glaucoma risk, and this negative association was remained in either Caucasian or Asian population (Table 2). Consistent with previous meta-analysis data[12], the T allele of rs2165241, T allele of rs1048661, or the G allele of rs3825942 was not associated with POAG risk (Figure 2). When the sources of controls were stratified as population-based or hospital-based, we found no association of each *LOXL1* polymorphism with POAG risk. However, compared with the reference CC homozygote, the CT heterozygote of rs2165241 was marginally significantly associated with decreased risk of POAG (OR: 0.79, 95% CI: 0.63-0.99, *P* =0.040) in hospital-based studies (Table 2). In addition, rs1048661 was marginally significantly associated with increased risk of POAG (OR: 1.23, 95% CI: 1.01-1.50, *P* =0.038) in a recessive model by pooling all hospital-based studies.

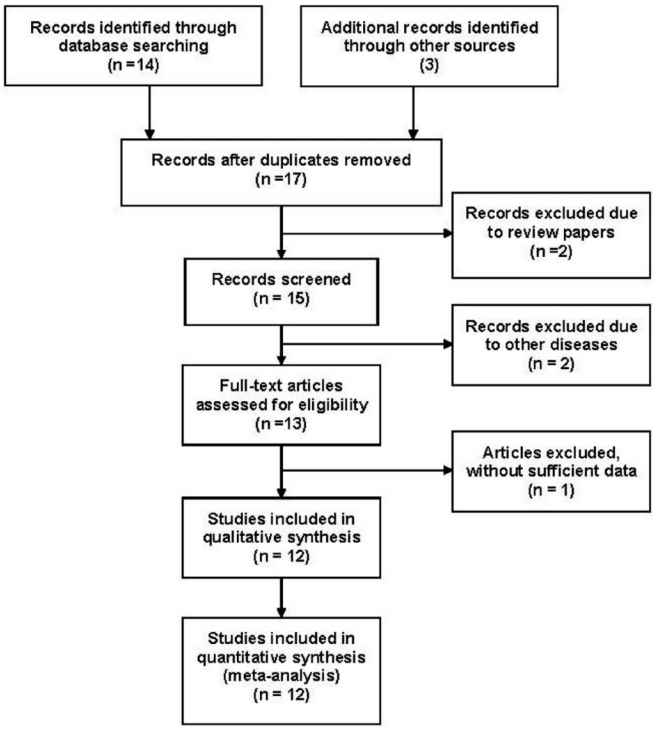

Figure 1 Flow diagram of studies identification.

Potential Publication Bias and Sensitivity Analysis All the *P* values of Begg's and Egger's tests were more than 0.05, and corresponding funnel plots showed symmetric distribution (Figure 3 and Data not shown). As a result, no evident publication bias was found in present study.

Sensitivity analysis was conducted by deleting each study in turn from the pooled analysis to examine the influence of the removed data set to the overall OR. We found that exclusion of each study did not influence the result in specific genotype comparison for *LOXL1* polymorphism, suggesting that the results of synthetic analysis were robust (Data not shown).

Table 1 Characteristics of literatures included in the meta-analysis

Author	Year	Origin	Ethnicity	*LOXL1* polymorphisms	Genotype	Study design[a]
Thoreleifsson	2007	Iceland Sweden	Caucasian Caucasian	rs2165241/rs1048661/rs3825942	GWAS Illumina Hap300 chip	Population-based
Fan	2008	USA	Caucasian	rs2165241/rs1048661/rs3825942	ABI TaqMan assays	Hospital-based
Fuse	2008	Japan	Asian	rs2165241/rs1048661/rs3825942	PCR Sequencing	Hospital-based
Tanito	2008	Japan	Asian	rs2165241/rs1048661/rs3825942	PCR Sequencing	Hospital-based
Mabuchi	2008	Japan	Asian	rs1048661/rs3825942	RFLP	Hospital-based
Liu	2008	USA USA Ghana	Caucasian Caucasian Caucasian	rs2165241/rs3825942	ABI TaqMan assays	Population-based
Gong	2008	North China South China	Asian Asian	rs2165241/rs1048661/rs3825942	PCR Sequencing	Hospital-based
Chakrabarti	2008	India	Asian	rs2165241/rs1048661/rs3825942	PCR Sequencing	Hospital-based
Lemmela	2009	Finland	Caucasian	rs2165241/rs1048661/rs3825942	PCR Sequencing	Population-based
Williams	2010	South Africa	Caucasian	rs1048661/rs3825942	PCR Sequencing	Hospital-based
Abu-Amero	2012	Saudi Arabia	Caucasian	rs2165241/rs1048661/rs3825942	PCR Sequencing	Hospital-based
Kasım	2013	Turkish	Caucasian	rs1048661/rs3825942	RFLP	Hospital-based

[a]The sources of controls were stratified as population-based or hospital-based. ABI: Applied biosystems incorporation; GWAS: Genome-wide association study; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism.

Table 2 Meta-analysis of the *LOXL1* polymorphisms on glaucoma risk

SNPs	*n*[a]	Heterozygote model		Homozygote model		Dominant model		Recessive model		Additive model	
		OR (95%CI)	*P*[b]	OR (95%CI)	*P*[b]	OR (95% CI)	*P*[b]	OR (95%CI)	*P*[b]	OR (95%CI)	*P*[b]
rs2165241[c]											
Pooled	13	0.92 (0.79-1.06)	0.323	1.03 (0.74-1.44)	0.080[d]	0.93 (0.80-1.07)	0.247	1.08 (0.79-1.48)	0.040[d]	0.98 (0.85-1.13)	0.060
Ethnics											
Caucasian	9	0.98 (0.82-1.16)	0.333	1.02 (0.72-1.46)	0.040	0.99 (0.84-1.16)	0.273	1.07 (0.77-1.49)	0.017	1.02 (0.87-1.19)	0.059
Asian	4	0.74 (0.54-1.01)	0.454	1.50 (0.36-6.19)	0.457[d]	0.75 (0.55-1.03)	0.338	1.66 (0.39-6.97)	0.491[d]	0.79 (0.59-1.06)	0.265
Study design											
PB	6	1.03 (0.84-1.26)	0.196	0.95 (0.61-1.47)	0.055	1.02 (0.78-1.34)	0.089	0.97 (0.69-1.37)	0.096	1.02 (0.83-1.25)	0.033
HB	7	0.79 (0.63-0.99)	0.715	1.17 (0.76-1.80)	0.273	0.83 (0.66-1.03)	0.683	1.40 (0.69-2.85)	0.078	0.93 (0.78-1.10)	0.230
rs1048661[c]											
Pooled	13	1.03 (0.89-1.20)	0.700	1.11 (0.90-1.37)	0.369	1.05 (0.91-1.21)	0.639	1.13 (0.91-1.35)	0.131	1.06 (0.96-1.17)	0.224
Ethnics											
Caucasian	8	1.07 (0.88-1.29)	0.376	0.94 (0.68-1.30)	0.310	1.04 (0.87-1.25)	0.264	0.89 (0.65-1.21)	0.458	1.00 (0.87-1.15)	0.216
Asian	5	0.98 (0.76-1.26)	0.878	1.25 (0.94-1.65)	0.457	1.07 (0.84-1.35)	0.930	1.31 (0.94-1.82)	0.087	1.13 (0.98-1.30)	0.352
Study design											
PB	3	1.06 (0.82-1.39)	0.303	0.78 (0.37-1.66)	0.095	1.01 (0.78-1.30)	0.136	0.76 (0.49-1.17)	0.185	0.94 (0.88-1.30)	0.072
HB	10	1.02 (0.85-1.22)	0.681	1.22 (0.96-1.55)	0.683	1.07 (0.90-1.27)	0.778	1.23 (1.01-1.50)	0.248	1.10 (0.99-1.24)	0.485
rs3825942[c]											
Pooled	16	0.98 (0.86-1.12)	0.139	0.83 (0.63-1.11)	0.986	0.96 (0.85-1.09)	0.280	0.87 (0.66-1.14)	0.936	0.95 (0.85-1.06)	0.608
Ethnics											
Caucasian	11	1.02 (0.82-1.28)	0.073	0.86 (0.63-1.18)	0.930	1.01 (0.86-1.18)	0.166	0.90 (0.67-1.21)	0.770	1.00 (0.87-1.15)	0.216
Asian	5	0.89 (0.70-1.13)	0.556	0.71 (0.36-1.42)	0.916	0.87 (0.69-1.10)	0.646	0.72 (0.36-1.43)	0.909	1.13 (0.98-1.30)	0.352
Study design											
PB	6	0.98 (0.80-1.19)	0.115	0.89 (0.59-1.33)	0.887	0.97 (0.80-1.18)	0.228	0.99 (0.68-1.43)	0.672	0.98 (0.84-1.15)	0.555
HB	10	0.99 (0.82-1.19)	0.209	0.78 (0.52-1.17)	0.932	0.95 (0.80-1.13)	0.294	0.75 (0.51-1.11)	0.936	0.92 (0.80-1.07)	0.469

[a]Number of comparisons; [b]*P* value of Q-test for heterogeneity test; [c]The heterozygote, homozygote, dominant, recessive and additive model for comparison of rs2165241 is TC *vs* CC, TT *vs* CC, TC + TT *vs* CC, TT *vs* CC + TC, and T allele *vs*. C allele respectively; of rs1048661 is TG *vs*. GG, TT *vs* GG, TG + TT *vs* GG, TT *vs* GG + TG, and T allele *vs* G allele respectively; of rs3825942 is AG *vs* GG, AA *vs* GG, AG + AA *vs* GG, AA *vs* GG + AG, and A allele *vs*. G respectively; [d]The study by Fuse *et al*[17] is excluded in the model analysis due to the limited case numbers.

DISCUSSION

In the present study, we systemically reviewed all available published studies and performed a meta-analysis to examine the association between the *LOXL1* polymorphisms and susceptibility to glaucoma. Our meta-analysis showed that no association between *LOXL1* polymorphisms and POAG risk in Caucasian or Asian populations. Although the rs2165241 was marginally significantly associated with decreased risk of POAG (CT *vs*CC, OR: 0.79, 95%CI: 0.63-0.99, *P*=0.040), and rs1048661 was marginally significantly associated with

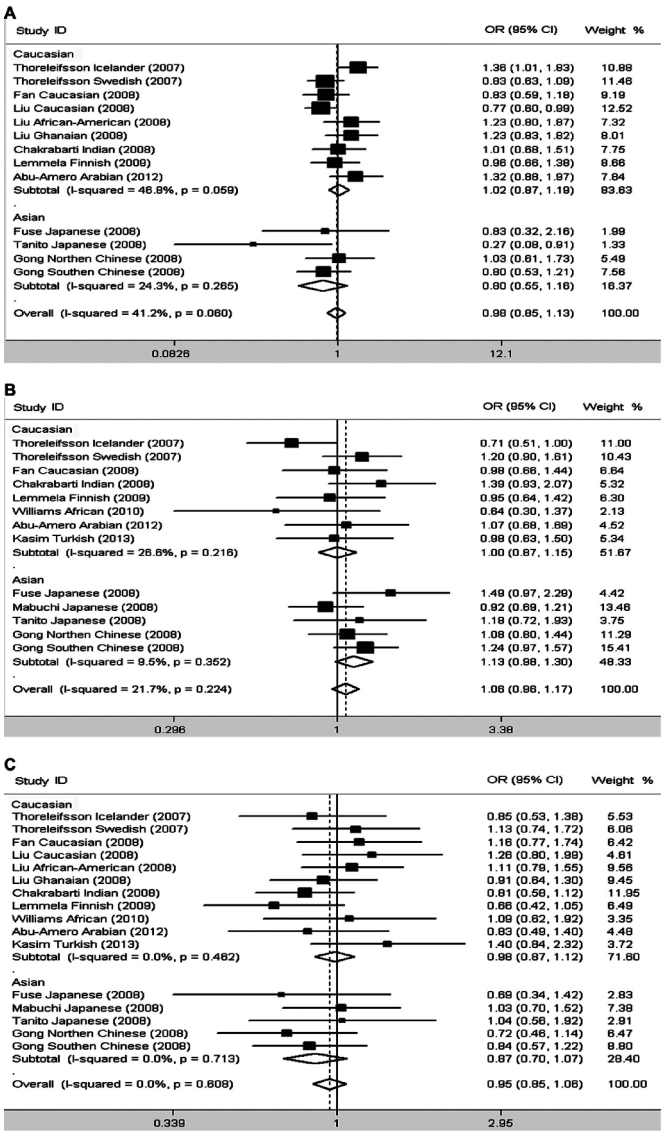

Figure 2 Forest plots of different models for ethnicity–based subgroup meta –analysis on the association of *LOXL1* polymorphisms with POAG risk The additive model for rs2165241 (A), rs1048661 (B) and rs3825942 (C) is presented. The squares and horizontal lines correspond to OR and 95% CI of specific study, and the area of squares reflects study weight (inverse of the variance). The diamond represents the pooled OR and its 95% CI.

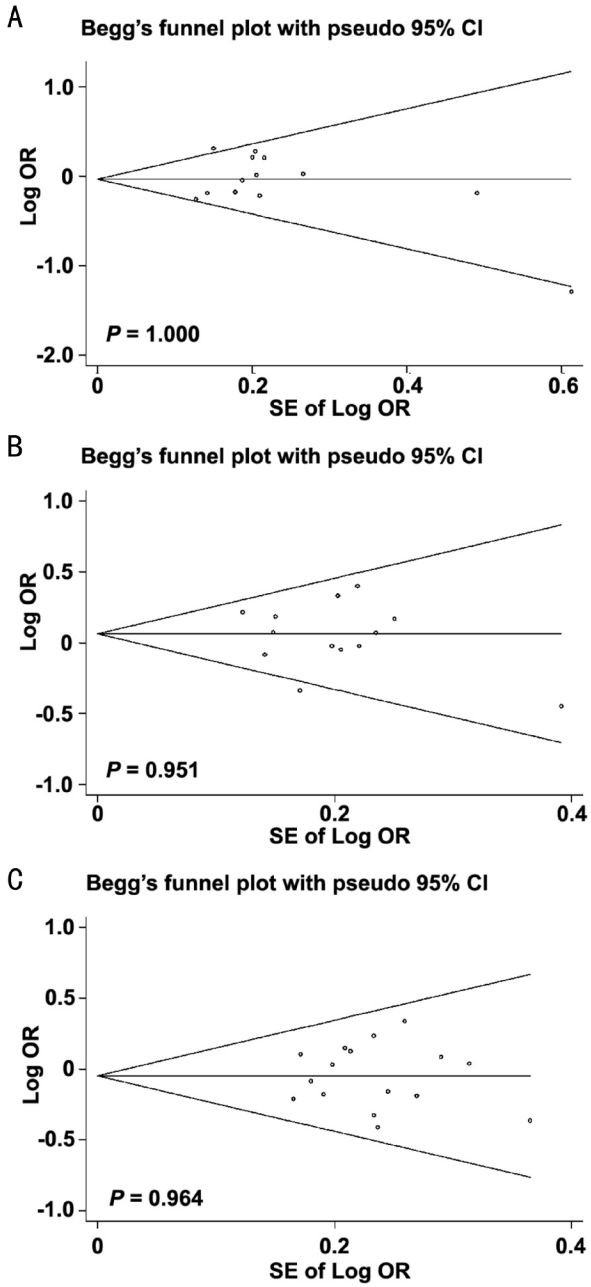

Figure 3 Funnel plots showed symmetric distribution Log OR is plotted against the standard error of log OR for studies on rs2165241 (A), rs1048661 (B) and rs3825942 (C). The dots represent specific studies for the indicated association.

increased risk of POAG (TT *vs*TG+GG, OR: 1.23, 95%CI: 1.01-1.50, *P*=0.038) in hospital-based studies, we did not find these significant associations in population-based studies or in all studies.

In the original study, *LOXL1* polymorphism (rs2165241) showed marginally significant association with increased POAG risk in the Icelandic population, but absence of association in the Swedish population [8]. The later studies found that this SNP in the *LOXL1* gene was not associated with an POAG risk in the African-American [19], Ghanaian (West-African)[19], Indian [15] and Chinese populations [18], or was associated with decreased POAG risk in Caucasian and Japanese populations [19,21] (Figure 2). However, previous meta-analysis showed that the overall OR of the 12 studies was 0.95 (95% CI 0.82-1.10, *P*=0.50) for the T allele of rs2165241[12]. By including one more study, we found that the T allele of rs2165241 was not associated with POAG risk. Similarly, we did not found association between rs2165241 and POAG risk in other models. As to rs1048661 and rs3825942, our data were consistent with previous pooled analysis results that no association was found between these two SNPs and POAG risk when including more studies (cohorts).

The subgroup analysis based on source of controls also suggested that rs2165241 was associated with decreased risk of POAG and rs1048661 was associated with increased risk

of POAG in hospital-based studies, however, we did not find these associations in population-based studies or in all studies. The reasons for this apparent difference in glaucoma risk are as yet unknown. This may be due to that the hospital-based case-control studies have some selection biases. It is conceivable that hospital-based controls may represent ill-defined reference population and may not be representative of the general population very well, especially when the genotypes under investigation were associated with the disease conditions that the hospital-based controls may have. The use of population-based other than hospital-based studies is, therefore, more appropriate to reduce biases in such genetic association studies. Thus, the marginally significant associations aforementioned between *LOXL1* polymorphisms and POAG risk should be interpreted with caution.

In the present study, we included one Japanese cohort, in which the genotype frequencies in the control group were inconsistent with Hardy-Weinberg equilibrium (HWE), for analysis on the association of rs1048661 with POAG risk[21]. Even excluding this cohort, we did not found the association between rs1048661 and POAG risk (Data not shown). For rs3825942, we included three cohorts, Japanese, Caucasian and African-American cohorts, with deviation from HWE [16,19,21]. Similarly, the pooled analysis showed no association of rs3825942 with POAG risk when excluding these three cohorts.

As a member of the lysyl oxidase family of proteins, LOXL1 catalyzes the oxidative deamination of lysine residues of tropoelastin and plays important roles in elastogenesis and elastic fiber homeostasis [30,31]. Thus, it is biologically reasonable that defects in *LOXL1* may cause features of XFS because of the aberrant production of elastin and accumulation of fibrillar material in the anterior segment of the eye. Recent study has showed that elimination of *LOXL1* in mice impairs the blood-aqueous humor barrier in the ocular anterior segment, but does not result in deposition of macromolecular material or glaucoma, suggesting that mice lacking *LOXL1* have some XFS features but that complete disease manifestation requires other factors, *e.g.*, genetic and/or environmental factors [32]. Actually, in addition to LOXL1, XFS fibrils also contain other proteins involved in elastic fiber synthesis and structure [33,34]. The data from the present study indicated that the three XFS/XFG-associated SNPs of *LOXL1* were not involved with POAG. Although POAG share clinical features in the disc and visual field with XFG, POAG is indeed more complex disease and its pathogenesis remains to be elucidated.

In conclusion, our meta-analysis data show that variants of *LOXL1* are not associated with POAG risk by pooling all populations, suggesting that *LOXL1* SNPs do not contribute the glaucomatous process of POAG.

ACKNOWLEDGEMENTS

Foundation: Supported by the Zhejiang Provincial Educational Bureau Foundation, China (Y201223905).

Conflicts of Interest: Sun W, None; **Sheng Y,** None; **Weng Y,** None; **Xu CX,** None; **Williams SE,** None; **Liu YT,** None; **Hauser MA,** None; **Allingham RR,** None; **Jin MJ,** None; **Chen GD,** None.

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