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The association of LOXL1 polymorphisms with exfoliation syndrome/glaucoma: Meta-analysis

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Abstract

• AIM: To investigate the association of lysyl oxidase-like 1 (LOXL1) single nucleotide polymorphisms (SNPs) with exfoliation syndrome (XFS)/exfoliation glaucoma (XFG).

• METHODS: Published manuscripts from PubMed and EMBASE were identified until May 2014. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for LOXL1 (rs1048661, rs2165241 and rs3825942) polymorphisms and the risk of XFS/XFG were estimated using random- or fixed- effect model.

• RESULTS: The three LOXL1 polymorphisms (rs1048661, rs3825942, and rs2165241) were associated with an increased risk for XFS/XFG among Caucasians, with OR 2.19 (1.96-2.45), 8.8 (6.05-12.79) and 3.41 (3.11-3.73), respectively. On the contrast, the rs1048661 and rs2165241, but not rs3825942 polymorphism, have a potential protective effect on XFS/XFG in Asians, with OR 0.06 (0.02-0.18), 0.15 (0.09-0.25), respectively.

• CONCLUSION: There is strong evidence that LOXL1 polymorphisms are associated with XFS/XFG risk. The strength of risk might be ethnicity-dependent.

• **KEYWORDS:** lysyl oxidase-like 1; polymorphism; exfoliation syndrome; glaucoma; Meta-analysis
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INTRODUCTION

Exfoliation syndrome (XFS) is an age-related systemic disorder of extracellular matrix characterized by progressive accumulation of an abnormal elastic microfibrillar material in various intra- and extra-ocular tissues [1]. This disorder may affect 10%-20% of people over age 60 in the worldwide distribution and is frequently associated with a severe and progressive form of chronic open-angle glaucoma [2]. Exfoliation glaucoma (XFG) occurs in the context of XFS, which is acknowledged as the most common identifiable cause of secondary open-angle glaucoma worldwide, causing rapid progression of glaucomatous optic neuropathy with a high resistance to medical treatments [3]. Several chromosomal loci have now been reported as linked to XFS/XFG, such as lysyl oxidase-like (LOXL1), clusterin, and contactin-associated protein-like 2 (CNTNAP2) genes[4].

LOXL1 was originally reported as a novel human gene with amino acid sequence homology to the COOH-terminus of lysyl oxidase (LOX) [5-7]. It was first discovered to be association with XFS in 2007[8]. Since then, a large number of studies have suggested that LOXL1 polymorphisms are associated with XFS in many different populations, including Caucasian (North America, Australia, Europe), South African, and Asian (China, Japan), but the results were inconclusive [9-13]. For example, the G allele of LOXL1 (rs1048661) and the T allele of LOXL1 (rs3825942) were risk factors for XFS/XFG among Caucasians, while the two alleles showed a protective effect on XFS/XFG in Japanese populations. Previously published Meta-analyses investigated the association of LOXL1 polymorphisms with XFS/XFG and POAG [14]. However, the Meta-analyses only contained published data from prior to 2010. In the present study, we carefully conducted a search and retrieved the possible

publications up to May 2014. Then, we performed an updated meta-analysis that increases statistical power to derive a more comprehensive and precise estimation of the relationship.

METHODS

Two investigators (Ji QS and Qi B) independently searched PubMed and EMBASE for eligible articles with the search strategy ("LOXL1" OR "Lysyl oxidase-like 1") and ("glaucoma" OR "exfoliation" OR "pseudoexfoliation"). We performed the final search on May 5, 2014.

We included only published manuscripts with English language restriction. All the studies have to fulfill the following criteria: 1) the studies reported on the association of three single nucleotide polymorphisms (SNPs) in LOXL1 (rs1048661, rs2165241, and/or rs3825942) polymorphisms with XFS/XFG using either case-control or cohort design; 2) the studies must offer the sample size, distribution of alleles, and/or genotype frequencies/counts in both patients and controls; 3) when multiple publications reported on the same or overlapping data, we used the most recent or largest population; and 4) if several different cohorts were reported in the same article, they were treated as independent studies. Exclusion criteria were: 1) studies with family-based designs; 2) studies on other gene polymorphism.

Two investigators (Ji QS and Qi B) independently extracted data and reached a consensus on all of the items. If there was disagreement in the retrieved information, a third reviewer (Liu L) would participate in the review. For each study, the following data were extracted: first author's surname, year of publication, ethnicity, sample size, allele, and/or genotype frequency/counts in both patients and controls.

The statistical analysis was performed by STATA statistical software (Version 12.0; STATA Corporation, College Station, TX, USA). We first examined whether the genotype distribution in controls of each study was consistent with Hardy-Weinberg equilibrium (HWE) by χ^2 test. The strength of the association between LOXL1 gene polymorphisms (rs1048661, rs2165241, and rs3825942) and susceptibility to XFS/XFG were estimated by ORs and 95% CIs. The pooled ORs were performed for allelic model, dominant model, recessive model, and additive model respectively. The significance of the pooled ORs was determined by Z test and P<0.05 was considered as statistically significant. Subgroup analysis was also performed by ethnicity. Heterogeneity among studies was assessed with the Q -test and I^2 statistics, P<0.10 and I^2 >50% indicated evidence of heterogeneity. Then, the random-effects model was used to calculate the pooled ORs. Otherwise, the fixed-effects model was applied. Sensitivity analysis was performed to examine the stability of the pooled effect after removing one study at a time. Publication bias was analyzed by performing funnel plots qualitatively, and estimated by Egger's test quantitatively. Two-sided P values <0.05 were considered statistically significant. In association analyses, the bonferroni correction was used to account for multiple testing [15]. Because four genetic models (allelic, dominant, recessive, and additive) were tested in three subgroups (Caucasians, Asians and Africans) for each SNP, a value of P<0.004 was considered statistically significant.

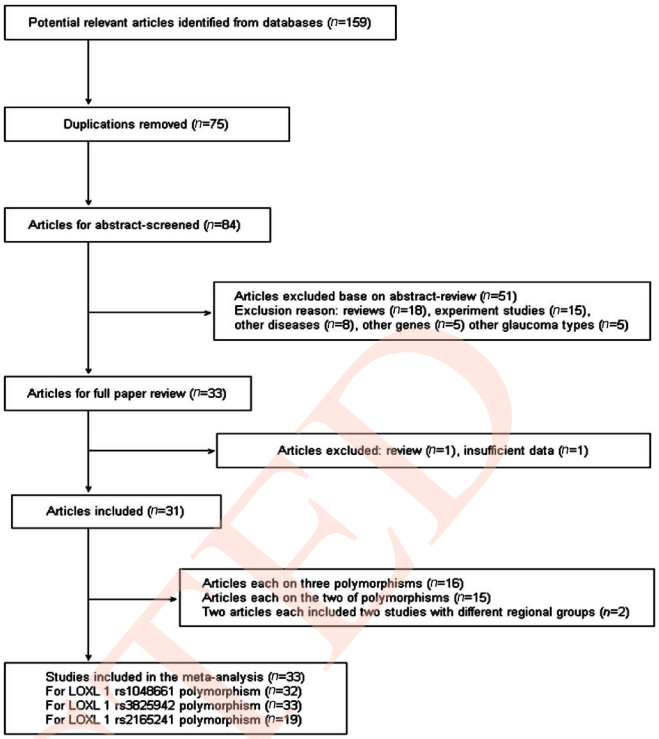

Figure 1 Flow diagram of the study selection for the Meta-analysis.

RESULTS

A number of 159 articles were preliminarily yielded from PubMed and EMBASE. After the abstract were screened and the full-text reviewed, a total of 33 studies were finally identified in 31 publications. The flow of study selection is shown in Figure 1, and the detailed study characteristics were summarized in Table 1. In the included studies, there were 21 groups of Caucasians, 10 groups of Asians, and 2 groups of Africans. The HWE of all three SNPs was calculated in the controls of all studies. No deviation from the HWE was identified. Combined analysis of the extracted datasets showed significant heterogeneity (P<0.00001, I^2>90%) among studies for three SNPs. However, no heterogeneity was observed in the subgroup analyses except studies of rs1048661 polymorphisms in Asians (P<0.0001, I^2=94%)

Table 1 Characteristics of publications included in meta-analysis of LOXL1 polymorphism and XFS/XFG

First Author	Year	Ethnicity	Country	Sample size		rs1048661G(%)		rs3825942G (%)		rs2165241T(%)	
				Case	Control	Case	Control	Case	Control	Case	Control
Thorleifsson *et al*[8]	2007	Caucasian	Iceland	130	14474	80.9	63.7	98.4	85.6	74.6	47.3
Thorleifsson *et al*[8]	2007	Caucasian	Sweden	199	198	83.4	68.2	99.5	87.8	81.3	53.5
Lemmela *et al*[9]	2009	Caucasian	Finland	141	404	82.5	68.3	96.8	82.3	73.2	46.8
Lee *et al*[10]	2009	Asian	China	62	171	52.4	44.4	99.2	91.8	NA	NA
Chen *et al*[11]	2009	Asian	China	50	124	11.0	48.4	100	89.6	2.0	10.0
Tanito *et al*[12]	2008	Asian	Japan	142	157	4.9	55.4	99.3	80.6	0.7	12.4
Ramprasad *et al*[13]	2008	Caucasian	India	52	97	72.1	63.4	92.3	74.2	NA	NA
Pasutto *et al*[16]	2008	Caucasian	Germany	517	348	81.8	63.9	95.1	83.5	75.2	47.9
Pasutto *et al*[16]	2008	Caucasian	Italy	209	70	82.5	69.3	100	82.1	79.8	50.7
Ozaki *et al*[17]	2008	Asian	Japan	209	172	5.3	49.7	98.6	86.3	1.7	10.2
Mossbock *et al*[18]	2008	Caucasian	Europe	167	170	84.1	67.1	99.4	81.8	NA	NA
Mori *et al*[19]	2008	Asian	Japan	95	190	0.5	47.4	99.5	85.3	NA	NA
Mabuchi *et al*[20]	2008	Asian	Japan	89	191	0.6	45.0	99.4	85.3	NA	NA
Hewitt *et al*[21]	2008	Caucasian	Australia	86	2087	77.9	66.0	94.8	84	NA	NA
Hayashi *et al*[22]	2008	Asian	Japan	59	190	0.8	46.0	100	85.7	NA	NA
Fuse *et al*[23]	2008	Asian	Japan	56	138	3.6	49.3	100	87.7	1.8	5.8
Fan *et al*[24]	2008	Caucasian	US	206	88	82.9	71.9	98.8	79.5	76.0	45.6
Challa *et al*[25]	2008	Caucasian	US	50	235	79.0	66.6	98.8	84.5	67.0	48.7
Aragon-Martin *et al*[26]	2008	Caucasian	Europe	287	333	84.3	70.3	96	79.8	73.4	44.8
Fingert *et al*[27]	2007	Caucasian	US	72	75	81.9	60.0	98.6	88	NA	NA
Wolf *et al*[28]	2010	Caucasian	Germany	128	280	84.4	66.0	99.2	85.6	78.2	49.1
Yang *et al*[29]	2008	Caucasian	US	62	170	NA	NA	100	85	83.1	52.1
Park do *et al*[30]	2013	Asian	Korean	110	127	2.7	29.5	91.1	89.8	1.0	6.5
Kasim *et al*[31]	2013	Caucasian	Turkey	200	100	87.5	71.0	100	84	NA	NA
Micheal *et al* l[32]	2012	Caucasian	Pakistani	128	180	85.2	65.8	97.3	83.9	NA	NA
Jaimes *et al*[33]	2012	Caucasian	Mexica	102	97	78.9	80.4	100	95.4	71.1	50.5
Sagong *et al*[34]	2011	Asian	Korean	89	146	7.3	35.6	98.3	89.4	1.7	9.2
Rautenbach *et al*[35]	2011	African	South Africa	43	47	100	88.3	14.3	61.7	NA	NA
Mayinu *et al*[36]	2011	Caucasian	Uygur	64	127	81.3	69.3	95.3	80.7	56.3	24.4
Malukiewicz *et al*[37]	2011	Caucasian	Poland	36	30	90.3	80.0	100	86.7	NA	NA
Fan *et al*[38]	2011	Caucasian	US	196	201	84.7	72.9	99.2	81.1	78.3	47.0
Williams *et al*[39]	2010	African	South africa	50	50	99.0	81.0	13	62	NA	NA
Abu-Amero *et al*[40]	2010	Caucasian	Saudi Arabia	93	101	87.6	76.2	96.8	81.7	NA	NA

NA: Not applicable.

and rs3825942 polymorphisms in Caucasians (P<0.0001, I^2=66%).

For rs1048661 polymorphism, a total of 4081 cases and 7838 controls were included in 32 studies. Overall, the results showed that no significant association between this polymorphism and XFS/XFG risk was observed in all genetic models (G *vs* T: OR=0.91, 95% CI=0.62-1.35, P=0.65; GG *vs* TT: OR= 1.29, 95% CI=0.57-2.92, P=0.54; GG/GT *vs* TT: OR= 0.81, 95% CI=0.32-2.06, P=0.56) and recessive model (GG *vs* GT/TT: OR= 1.54, 95% CI=1.14-2.10, P=0.006; Table 2). In subgroup analysis by ethnicity, the risk of developing XFS/XFG was remarkably increased in Caucasians (G *vs* T: OR= 2.19, 95% CI=1.96-2.45, P<0.00001) and Africans (G *vs* T: OR= 23.42, 95% CI=4.48-122.52, P=0.0002) and significantly decreased in Asians (G *vs* T: OR= 0.06, 95% CI=0.02-0.18, P<0.00001; Figure 2).

For rs3825942 polymorphism, 33 studies consisting of 4147 cases and 7488 controls were obtained. The overall data under any genetic models (G *vs* A: OR=9.21, 95% CI=5.12-16.54, P <0.00001; GG *vs* AA: OR= 5.81, 95% CI=2.67- 12.67, P <0.00001; GG/GA *vs* AA: OR= 4.13, 95% CI=1.92-1.76, P =8.88, P =0.0003; GG *vs* GA/AA: OR=11.42, 95% CI=7.23-18.04, P <0.00001) indicated that the G allele of rs3825942 had increased risk of XFS/XFG compared to the T allele (Table 2). In subgroup analyses, the G allele was found to confer an increase risk for XFS/XFG among Caucasians (OR=8.80, 95% CI=6.05-12.79, P<0.00001) and Asians (OR= 14.92, 95% CI=9.15-24.34, P<0.00001). However, the G allele of rs3825942 have been investigated as a protective factor for XFS/XFG among Africans (OR= 0.09, 95% CI=0.06-0.15, P=0.0002) (Figure 3).

For rs2165241 polymorphism, 19 studies including 2889 cases and 17762 controls were investigated. The overall results suggested that the rs3825942 polymorphisms was association with XFS/XFG risk (T *vs* C: OR=1.94, 95% CI=1.44-2.61, P <0.00001; TT *vs* CC: OR=9.85, 95% CI=6.72-14.43, P<0.00001; TT/TC *vs* CC: OR=2.12, 95% CI=1.09-4.12, P <0.03; TT *vs* TC/CC: OR=4.28, 95%

Table 2 Stratification analyses of XFS/XFG susceptibility associated with LOXL1 polymorphisms

SNP	Ethnicity	Study	Genetic contrast		Study	Genetic contrast		Genetic contrast		Genetic contrast	
rs1048661											
		n	G *vs* T		*n*	GG *vs* TT		GG/GT *vs* TT		GG *vs* GT/TT	
			OR (95% CI)	I^2 (%)		OR(95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)
	Total	32	0.91 (0.62,1.35)	95	27	1.29 (0.57,2.92)	90	0.81 (0.32, 2.06)	95	1.54 (1.14,2.10)	83
	Caucasian	20	2.19 (1.96,2.45)	32	17	5.36 (3.81,7.53)	24	3.90 (2.79, 5.45)	24	2.51 (2.15, 2.94)	43
	Asian	10	0.06 (0.02,0.18)	94	9	0.05 (0.01,0.23)	89	0.03 (0.01,0.11)	93	0.12 (0.03,0.49)	87
	African	2	23.42 (4.48,122.52)	0	1	3.48 (0.14,88.00)	NA	2.81 (0.11,70.75)	NA	24.36(1.38,429.83)	NA
rs3825942											
	Varibles	*n*	G *vs* A		*n*	GG *vs* AA		GG/GA *vs* AA		GG *vs* GA/AA	
			OR (95% CI)	I^2 (%)		OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)
	Total	33	9.21 (5.12,16.54)	90	27	5.81 (2.67,12.67)	59	4.13 (1.92,8.88)	67	11.42 (7.23,18.04)	74
	Caucasian	21	8.80 (6.05,12.79)	66	17	8.79 (5.04,15.33)	0	5.07 (3.29,7.82)	0	10.57 (6.96, 16.06)	63
	Asian	10	14.92 (9.15,24.34)	0	9	4.94 (1.60,15.24)	0	3.79 (1.23,11.68)	0	18.74 (10.26,34.24)	0
	African	2	0.09 (0.06,0.15)	NA	1	0.06 (0.02,0.20)	NA	0.04 (0.01,0.12)	NA	0.19 (0.06,0.58)	NA
rs2165241											
	Varibles	*n*	T *vs* C		*n*	TT *vs* CC		TT/TC *vs* CC		TT *vs* TC/CC	
			OR (95% CI)	I^2 (%)		OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)
	Total	19	1.94 (1.44,2.61)	89	15	9.85 (6.72,14.43)	57	2.12 (1.09,4.12)	90	4.28 (3.65,5.03)	19
	Caucasian	13	3.41 (3.11,3.73)	0	10	10.69 (8.50,13.4)	0	5.72 (4.56,7.18)	11	4.39 (3.83, 5.05)	0
	Asian	6	0.15 (0.09,0.25)	0	5	0.26 (0.04,1.56)	0	0.13 (0.07,0.25)	0	0.31 (0.05,1.85)	0

P value of Z-test for overall effect; NA: Not applicable; I^2 statistics for heterogeneity test.

CI=3.65-5.03, P <0.00001; Table 2). In stratification analyses by ethnicity, the T allele of rs3825942 have been showed as risk factors for XFS/XFG in Caucasians (OR=3.41, 95% CI=3.11-3.73, P<0.00001). On the contrary, the lower risk of XFS/XFG was found in Asians (OR=0.15, 95% CI=0.09-0.25, P<0.00001; Figure 4).

Sensitivity analyses were carried out to assess the influence of each individual study on the pooled ORs by omitting one single study each time. The results showed that no individual study remarkable affected the pooled ORs, thus indicating that the results of this meta-analysis are stable.

Publication bias was firstly examined by Begg's funnel plot and estimated by Egger's tests quantitatively. In the overall analyses, the results suggested obvious evidence of publication bias for rs1048661 and rs3825942 (t=3.2, P=0.003 and t=2.6, P=0.014, respectively), while for rs2165241, the funnel plots was symmetrical (t=0.69, P=0.503; Figure 5A-C). In the subgroup analyses, Neither Begg's funnel plot nor Egger's test detected obvious evidence of publication bias in Caucasians and Asians (All P >0.05), except for rs3825942 in Caucasians (t=5.17, P=0.000) (data did not show).

DISCUSSION

The present Meta-analysis, consisting of 33 studies, investigated the three polymorphisms (rs1048661, rs3825942, and rs2165241) in LOXL1 gene and their associations with XFS/XFG risk. On the whole, the results showed that significantly increased XFS/XFG risk were found in all subjects with two polymorphisms (rs3825942 and rs2165241) within the LOXL1 gene under any genetic models. No significant correlation was found between LOXL1 rs1048661 polymorphism and XFS/XFG risk. Because the allele frequencies and distribution of three polymorphisms (rs1048661, rs3825942, and rs2165241) were diverse in the different ethnicities, we carried out stratified analysis by ethnicity. The results pointed to an increased risk of XFS/XFG among Caucasians with rs1048661 G and rs2165241 T allele (OR=2.19 and 3.41, respectively). In contrast, the two alleles showed a protective factor for XFS/XFG among Asians, with an OR 0.06 and 0.15, respectively, while the G allele of rs3825942 play a risk role in Caucasians and Asians (OR=9.21, and OR=14.92, respectively). A protective effect of rs3825942 G allele and risk effect of rs1048661 G allele were found in Africans with

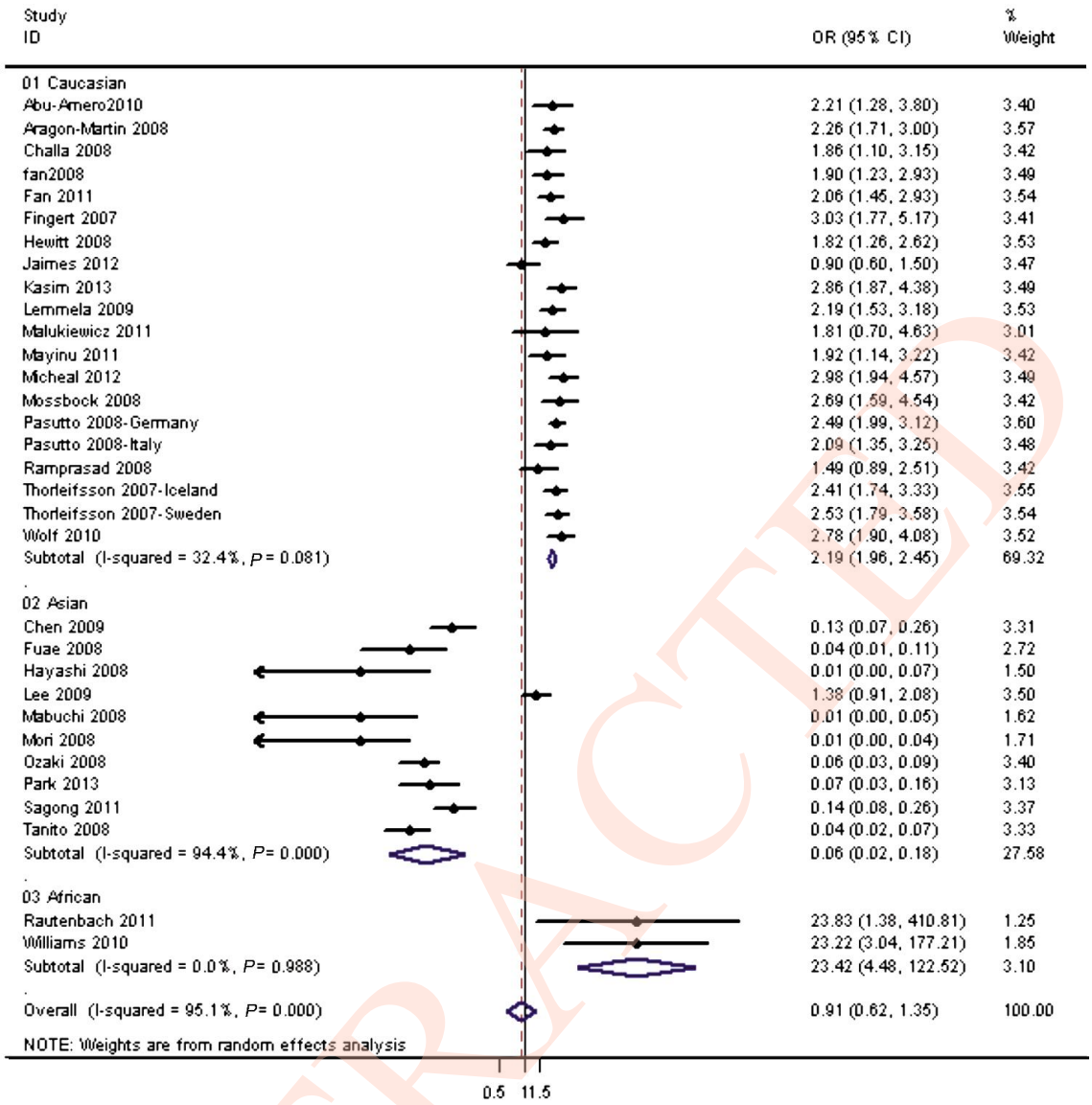

Figure 2 Forest plot from the meta-analysis of single nucleotide polymorphism (SNP) rs1048661 and risk of XFS/XFG in allelic risk model (G *vs* T) for different ethnicities.

two studies. Since limited Studies were from Africans, it is critical that larger studies based on Africans should be performed to re-evaluate the association.

Previous Meta-analysis showed that the genetic effect of rs3825942 is similar in different populations (Caucasian, Japanese, Chinese and Indian) [28]. However, there was inconsistence in the effect of rs1048661 and rs2165241 between Chinese and Japanese populations. Given the small size of subjects, we performed a combined analysis of Chinese, Japanese and Korean populations as Asians. The results indicated that the two polymorphisms (rs1048661 and rs3825942) of LOXL1 gene were correlated with XFS/XFG in Asians. The data may be more convincible due to the much larger number of the included studies. Nevertheless, considering the ethnicity-specific polymorphisms with XFS/XFG, more investigations with large sample sizes are required to detect the association among different groups.

The LOXL1 gene is a member of the lysyl oxidase family, which is necessary for the formation and maintenance of elastic tissue, playing an important role in the homeostasis of the extracellular matrix by inducing cross-linking in collagen and elastin molecules [41]. Thus, any alteration of LOXL1 activation, processing, and or substrate specificity may influence the function, synthesis, and subsequent deposition of the extracellular tissues. It has been reported in a recent study that reduced expression levels of LOXL1 and elastic proteins in the lamina cribrosa can increase the risk of pseudoexfoliation syndrome [42]. However, the causative functional role of LOXL1 polymorphisms played in the pathogenesis of XFS/XFG remains unclear. Neither rs1048661 nor rs3825942 polymorphism have been found to affect LOXL1 expression levels. In our Meta-analysis, we detected discrepancies in the effect of rs1048661 and rs2165241 polymorphisms between Caucasians and Asians.

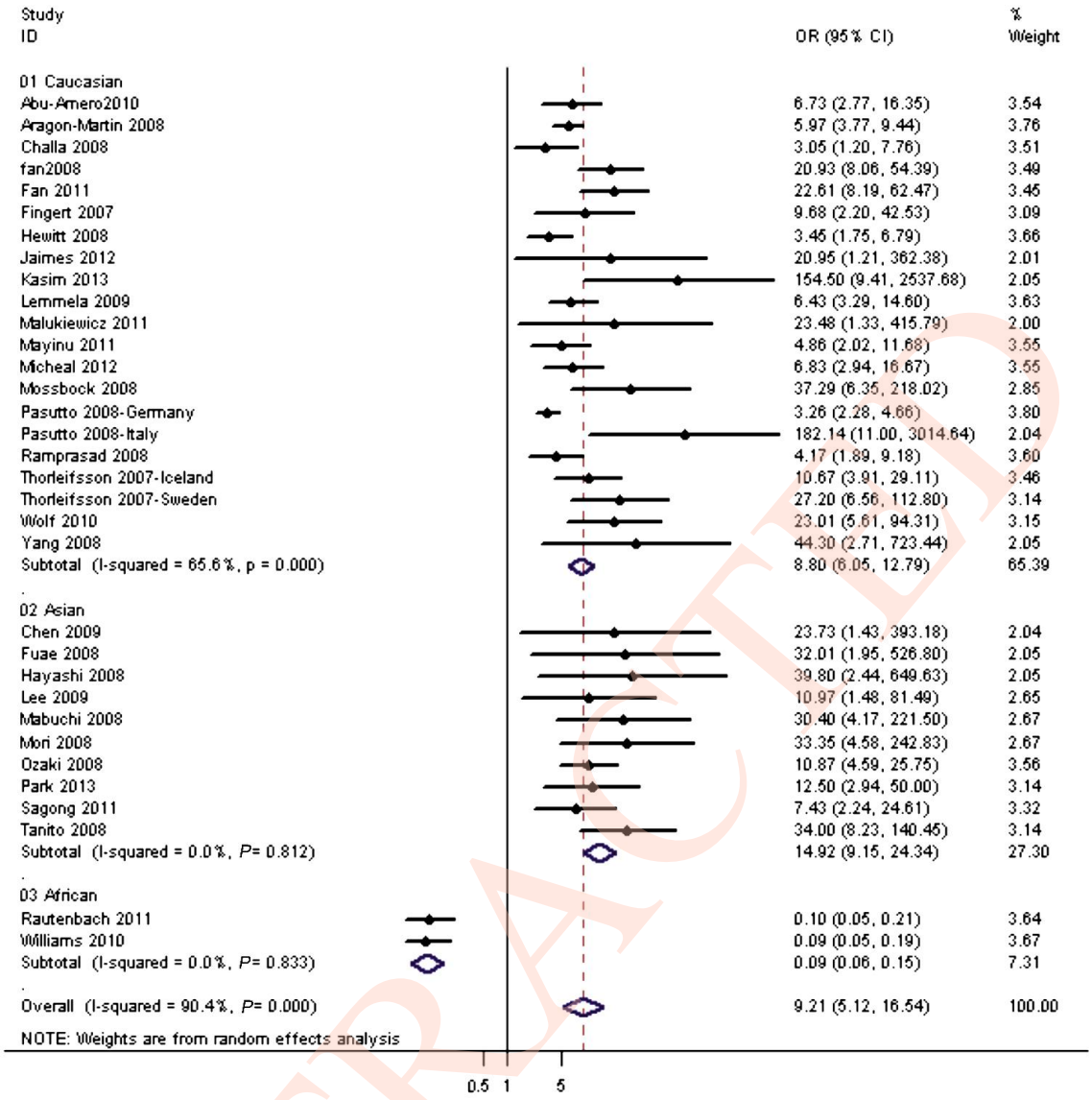

Figure 3 Forest plot from the Meta-analysis of single nucleotide polymorphism (SNP) rs3825942 and risk of XFS/XFG in allelic risk model (G *vs* A) for different ethnicities.

These inconsistencies in genetic findings among different ethnic groups suggest that missense changes in these SNPs of LOXL1 are not directly responsible for the development of XFS/XFG, while other unidentified genetic or environmental factors may affect LOXL1 gene expression or protein function, which needs further investigation.

Some limitations of this Meta-analysis should be addressed. First, only published studies were identified, while unpublished data and articles published in languages other than English were missed, which may have biased our results, although no obvious publication bias was apparent. Second, the controls were recruited in different ways and not uniformly defined, which may have distorted the Meta-analysis. Third, XFS/XFG is an age-related complex disease that results of combined effects of multifactor, including genetic and environmental factors. As none of the studies included in this meta-analysis considered the effect of gene-gene and environment interactions involved in the pathogenesis of XFS/XFG, this issue could not addressed in our Meta-analysis. Fourth, ethnicity was determined by populations' country due to inadequate available data. Furthermore, only Caucasians, Asians and Africans were concerned in the subgroup analysis. Thus, data regarding other ethnicity are desired. Fifth, adjustments over age, gender might help better detect the association between LOXL1 and XFS/XFG risk. Sixth, as is known, haplotype analysis might bring out bigger net effects. However, most studies did not perform haplotype analyses, which hampered our further analysis. Finally, all the studies were designed with retrospective studies. We cannot clearly determine the relationship between the LOXL1 polymorphisms and XFS/XFG risk.

In summary, our Meta-analyses suggested that the three LOXL1 polymorphisms (rs1048661, rs3825942, and

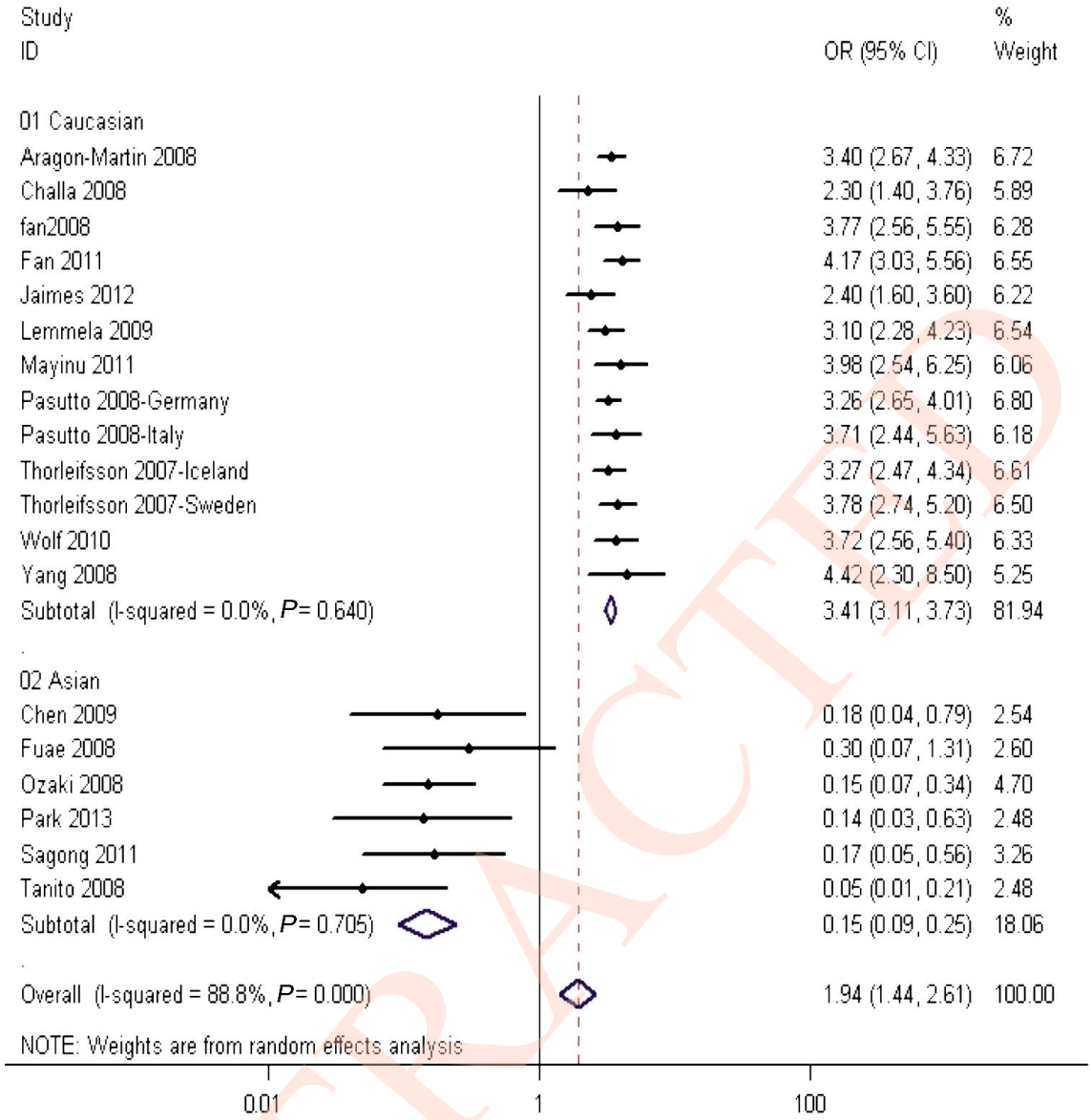

Figure 4 Forest plot from the Meta-analysis of single nucleotide polymorphism (SNP) rs2165241 and risk of XFS/XFG in allelic risk model (T *vs* C) for different ethnicities.

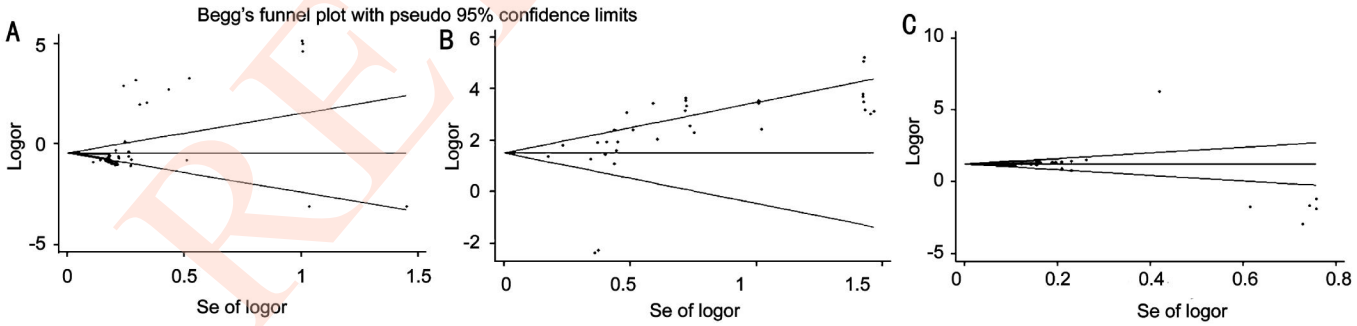

Figure 5 Begg´s funnel plot for publication bias test, each circle represents a separate study for the indicated association A: For rs1048661 polymorphism; B: For rs3825942 polymorphism; C: For rs2165241 polymorphism.

rs2165241) are associated with an increased risk for XFS/XFG in Caucasians, while rs1048661, rs2165241, but not rs3825942 polymorphisms have a potential protective effect on XFS/XFG in Asians. Furthermore, interaction between LOXL1 genes and other risk factors, such as age, sex, environmental factors, should also be considered in future studies, which should lead to a better understanding of the association between the LOXL1 polymorphisms and XFS/XFG risk.

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