

Associations of polymorphisms of LOXL1 gene with primary openangle glaucoma: a meta-analysis based on 5,293 subjects

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Objective: Previous studies indicated that the relationship between lysyl oxidase-like 1 (LOXL1) gene polymorphisms and primary open-angle glaucoma (POAG) remains inconsistent. In the present study, we aimed to perform a metaanalysis to investigate the association of LOXL1 polymorphisms with POAG risk.

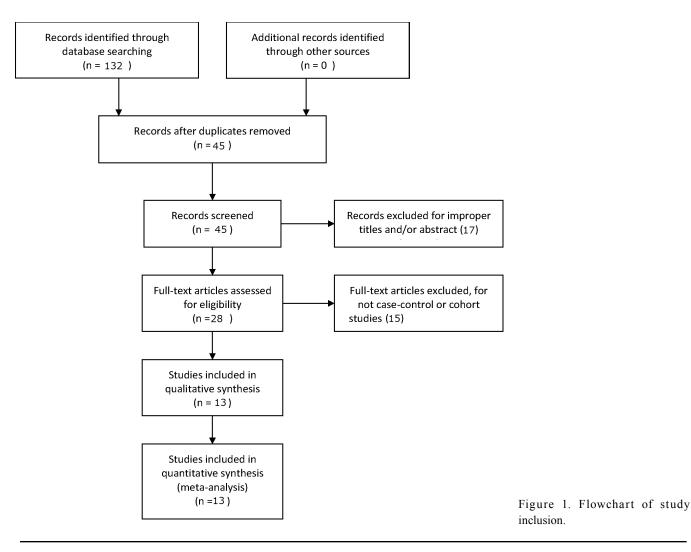
Methods: Literatures were electronically searched in the PubMed, EMBASE, CNKI, Wanfang, and VIP databases. The published literatures, which are case-control or cohort studies on the relationship between the polymorphisms (rs1048661, rs3825942, rs2165241) of the LOXL1 gene and POAG, were documented.

Results: We included 13 literatures including 5,293 subjects for the present study. A meta-analysis showed that the risk of POAG in individuals carrying the C allele of rs2165241 was 1.26 times higher compared with those carrying the T allele (odds ratio (OR) = 1.26, 95% confidence interval (CI): $1.09 \sim 1.46$) in the total population. In the Caucasian population, we also found that individuals carrying the C allele of rs2165241 have an increased risk for POAG compared to those subjects carrying the T allele (OR = 1.42, 95% CI: 1.19 ~1.69, p = 0.0001). In addition, we found that the rs1048661 polymorphism was associated with POAG in the Asian population (OR = 1.17, 95% CI: $1.02 \sim 1.35$, p = 0.03), and rs3825942 was associated with POAG in the Caucasian population (OR = 2.69, 95% CI: 1.61 ~4.47, p<0.001). **Conclusions:** The polymorphisms of the *LOXL1* gene were associated with the susceptibility of POAG.

Glaucoma is a common eye disease, and approximately 50% of glaucoma cases are primary open-angle glaucoma (POAG) [1-3]. In clinical practices, patients with POAG can experience glaucomatous optic neuropathy and visual field defects in the corresponding area for no obvious reasons. POAG can result in blindness if left untreated. The main clinical manifestations of POAG are optic neuropathy, including size increases of the optic disc, and the irregular loss of optic disc tissues. It is considered the second-most frequent cause of irreversible blindness globally, and it affects primarily the older population, estimated to affect about 80 million people worldwide by the year 2020 [1]. However, the etiology of glaucoma remains unclear. Epidemiological studies suggested that POAG is a complex multifactorial disease resulting from the interaction between genetic background and traditional risk factors, including diabetes, myopia, cigarette smoking, and a positive family history [4-6]. Recently, many genes were found to be associated with POAG, including the lysyl oxidase-like 1 (LOXL1; Gene ID: 4016) gene, which is a member of the lysyl oxidase family, which catalyzes the oxidative deamination of lysine residues of tropoelastin and is thought to be essential for elastogenesis [7,8]. Dysregulated expressions of LOXL1 and elastic proteins were associated with pronounced structural alterations to the elastic fiber network in the laminar beams of pseudoexfoliation syndrome eyes [7]. Theoretically, there was a relationship between LOXL1 gene polymorphisms and POAG. Recent studies suggested that there was an association between LOXL1 gene polymorphisms, such as rs2165241, rs1048661, and rs3825942, and POAG susceptibility [9-14]. As well, a previous study [15] suggested that these three single nucleotide polymorphisms (SNPs) demonstrated a strong linkage disequilibrium (rs1048661-rs3825942: D' = 1; rs1048661- rs2165241: D' = 0.8; rs3825942- rs2165241: D' = 0.8). Furthermore, rs1048661 and rs3825942 have been identified to be associated with POAG, and this association was later independently replicated in other patient cohorts [16,17]. Although an association between rs2165241 and increased POAG risk was found in the Icelandic population, the association was not found in other populations [16,18]. Liu et al. [19] reported that subjects carrying the C allele had a significantly lower risk of suffering from POAG. However, the findings by Fuse et al. [20] were contrary. Therefore, to clarify the relationship between LOXL1 gene polymorphisms and POAG further, we have systemically examined the association of these SNPs with POAG in the present study.

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Molecular Vision 2015; 21:165-172 < http://www.molvis.org/molvis/v21/165>



METHODS

Literature inclusion criteria and exclusion criteria: All the included studies must meet the following criteria: (1) Type of study: case-control or cohort studies; (2) content of study: *LOXL1* gene polymorphisms and POAG susceptibility; (3) data: studies providing genotype and allele frequencies. We excluded studies that 1) provided incomplete data and that cannot be used to extract genotype and allele frequencies; 2) presented unreliable genotyping methods; 3) published repeated data from the same study.

Identification and eligibility of relevant studies: To identify all articles that examined the association of *LOXL1* polymorphisms with POAG, we conducted a literature search of the PubMed, EMBASE, CNKI, Wanfang, and VIP databases

until February 2014 using the following MeSH terms and keywords: "LOXL1" of "lysyl oxidase-like 1"; and "polymorphism" or "SNP" or "mutation"; and "primary open angle glaucoma" or "POAG." Additional studies were identified by a manual search of references from original studies or review articles on this topic.

Statistical methods: Revman 5.2 statistical software was used to perform the meta-analysis. The odds ratios (OR) of the genetic *LOXL1* polymorphisms were combined and calculated, the 95% CIs were calculated, and the forest plots of the OR value distributions were drawn. Statistical heterogeneity was performed using an I² test analysis. If I² <50%, all the included studies had no significant statistical heterogeneity regarding OR quantity. The fixed effects model was adopted,

Huttors Publication from transmostant Ages realised (n) Huttor Hu						TABLE 1. T	TABLE 1. THE CHARACTERISTICS OF INCLUDED STUDIES.	TERISTICS OF	INCLUDED 5	TUDIES.					
Iton yard Patients Control Patien		Authors	Publica-	Country	Ages (years)	rs1048(661 (n)	H-W for	rs38259	942 (n)	H-W for	rs21652	241 (n)	H-W for
2009FinlandNANA714040.113714040.664714042008United States7572331880.227331880.112331882008United States55.4±13.8>550.3656424624624622008IndiaNANANA1121050.4556424624622008JapanNA68.0±7.0621380.556621380.2216424622008Japan75.4±5.377.2±5.04001570.0984624764764762008Japan75.4±5.377.2±5.04001570.0984624770.1981572008Japan75.4±5.377.2±5.04001980.1192001980.1274624472007EuropeNANANA2001980.1192001980.1274624472012Saudi Arabia 6.37 ± 14.7 6.93 ± 12.4 96101 0.876 9610190.212961012014SpainNANANANA2001980.1192001980.5572412014SpainNANANANANA20196969696962014SpainNANANANA201<			tion year	•	Patients	Control	Patients	Control	Control	Patients	Control	Control	Patients	Control	Control
2008 United States 75 72 331 88 0.227 331 88 0.112 331 88 2008 United States 55.4±13.8 >55 - - 0.365 642 462 462 462 462 2008 Japan NA NA 112 105 0.443 112 105 0.455 462 462 462 462 462 462 462 462 462 462 462 462 462 462 462 462 462 462 463 462 463 462 463 462 463 463 462 463 463 473 464 466 473 464 466 473 464 466 473 473 473 473 473 473 473 473 473 473 474 473 473 474 474 474 474 474 474 474 474 4		Lemmela et al.	2009	Finland	NA	NA	71	404	0.113	71	404	0.664	71	404	0.221
2008United States 55.4 ± 13.8 $>55-55 0.3656424626424624624622008JapanNANA112105044311210506651121052008Japan75.4\pm5.3772\pm5.0401570.212401570.476401572008Japan75.4\pm5.3772\pm5.0401570.212401570.476401572008Japan75.4\pm5.3772\pm5.0401570.212401570.476401572008Japan75.4\pm5.3772\pm5.0401570.202401570.476401572007EuropeNANANA2001980.1192001980.1274624472017EuropeNANA2001980.1192001980.5592001982014SpainNANANA201910.876961010.212961012015Souti Arabia637\pm14.7693\pm12.4961010.876961010.21296961012014SpainNANA -$		Fan et al.	2008	United States	75	72	331	88	0.227	331	88	0.112	331	88	0.327
2008IndiaNANA112105 0.443 112105 0.665 1121051052008JapanNA 68.0 ± 70 62 138 0.556 62 138 0.221 62 1382008Japan 75.4 ± 5.3 77.2 ± 5.0 40 157 0.212 40 157 0.476 40 157 2008Unina 39.1 ± 16.5 6.94 ± 6.0 462 447 0.022 40 157 0.476 40 157 2007EuropeNANA200198 0.19 200 198 0.659 200 198 2012Saudi Arabia 63.7 ± 14.7 69.3 ± 12.4 96 101 0.876 96 101 0.212 40 157 2012Saudi Arabia 63.7 ± 14.7 69.3 ± 12.4 96 101 0.876 96 101 0.212 96 101 2014SpainNANANA 200 198 0.199 0.659 200 198 2018JapanNANA 191 0.876 96 101 0.212 211 232 241 2010Japan >40 20 213 191 0.212 20 212 222 241 2011Japan >40 20 213 191 0.212 20 212 222 241 2012Japan >40 210 210 212 212 22		Liu et al.	2008	United States	55.4±13.8	>55	ı	ı	0.365	642	462	0.435	642	462	0.164
2008 Japan NA 680±70 62 138 0.556 62 138 0.221 62 138 2008 Japan 75.4±5.3 772±5.0 40 157 0.476 40 157 2008 China 39.1±16.5 69.4±6.0 462 447 0.098 462 447 0.127 462 447 2007 Europe NA NA 200 198 0.119 200 198 0.559 200 198 2017 Europe NA NA 200 198 0.119 200 198 0.659 200 198 2012 Saudi Arabia 63.7±14.7 69.3±12.4 96 101 0.876 96 101 0.212 96 101 2014 Spain NA NA NA 20 191 0.212 96 101 2018 Japan >40 213 191 0.213 213 214	0	Chakrabarti et al.	2008	India	NA	NA	112	105	0.443	112	105	0.665	112	105	0.143
2008Japan $75,4\pm5.3$ 77.2 ± 5.0 40 157 0.212 40 157 0.476 40 157 2008China 39.1 ± 16.5 69.4 ± 6.0 462 447 0.098 462 447 0.127 462 447 2007EuropeNANANA 200 198 0.119 200 198 0.659 200 198 2012Saudi Arabia 63.7 ± 14.7 69.3 ± 12.4 96 101 0.876 96 101 0.212 96 101 2014SpainNANA232 241 2014SpainNANA232 241 2014SpainNANA232 241 2013Japan>40>40 213 191 0.211 213 191 0.665 2010South AfricaNANA5050 0.332 50 50 0.443 2010South AfricaNANA50 50 0.332 50 50 0.443 2013Turkish 67.7 ± 9.3 66 ± 5.7 100 100 0.126 100 0.119 <td></td> <td>Fuse et al.</td> <td>2008</td> <td>Japan</td> <td>NA</td> <td>68.0±7.0</td> <td>62</td> <td>138</td> <td>0.556</td> <td>62</td> <td>138</td> <td>0.221</td> <td>62</td> <td>138</td> <td>0.779</td>		Fuse et al.	2008	Japan	NA	68.0±7.0	62	138	0.556	62	138	0.221	62	138	0.779
2008China 39.1 ± 16.5 69.4 ± 6.0 462 447 0.098 462 447 0.127 462 447 2007EuropeNANANA200198 0.119 200198 0.659 2001982012Saudi Arabia 63.7 ± 14.7 69.3 ± 12.4 96101 0.876 96101 0.212 961012014SpainNANA2322412014Japan>40213191 0.211 213191 0.665 2010South AfricaNANA2010South AfricaNANA5050 0.332 50 0.443 2013Turkish 67.7 ± 9.3 66 ± 5.7 1001000.1261001000.119	Γ	Tanito et al.	2008	Japan	75.4±5.3	77.2±5.0	40	157	0.212	40	157	0.476	40	157	0.088
2007 Europe NA NA 200 198 0.659 200 198 0.659 200 198 2012 Saudi Arabia 63.7±14.7 69.3±12.4 96 101 0.212 96 101 2014 Spain NA NA - - - 232 241 2014 Spain NA NA - - - 232 241 2014 Spain NA NA - - - 232 241 2018 Japan >40 >40 213 191 0.615 - - - - 232 241 2010 South Africa NA NA 50 0.332 50 50 -	-	Cong et al.	2008	China	39.1±16.5	69.4 ± 6.0	462	447	0.098	462	447	0.127	462	447	0.123
2012 Saudi Arabia 63.7±14.7 69.3±12.4 96 101 0.212 96 101 2014 Spain NA NA NA - - - 232 241 2018 Japan >40 213 191 0.211 213 191 0.665 - - 2008 Japan >40 213 191 0.211 213 191 0.665 - - - 2010 South Africa NA NA 50 50 50 50 50 - - - - - - - - - - 232 241 - - - 232 241 - <td>Τ</td> <td>'horleifsson et al.</td> <td>2007</td> <td>Europe</td> <td>NA</td> <td>NA</td> <td>200</td> <td>198</td> <td>0.119</td> <td>200</td> <td>198</td> <td>0.659</td> <td>200</td> <td>198</td> <td>0.943</td>	Τ	'horleifsson et al.	2007	Europe	NA	NA	200	198	0.119	200	198	0.659	200	198	0.943
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2008 Japan >40 >40 213 191 0.211 213 191 2010 South Africa NA NA 50 50 50 50 2013 Turkish 67.7±9.3 66±5.7 100 100 0.126 100 100	Σ	Zanon- loreno et al.	2014	Spain	NA	NA	·	·			ı	ı	232	241	0.332
2010 South Africa NA NA 50 50 50 2013 Turkish 67.7±9.3 66±5.7 100 100 0.126 100 100		Mabuchi et al.	2008	Japan	>40	>40	213	191	0.211	213	191	0.665	·	·	ı
2013 Turkish 67.7±9.3 66±5.7 100 100 0.126 100 100		Williams et al.	2010	South Africa	NA	NA	50	50	0.332	50	50	0.443	·	ı	ı
	K	Casım et al.	2013	Turkish	67.7±9.3	66±5.7	100	100	0.126	100	100	0.119	·	ı	

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				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Abu-Amero 2012	-0.28	0.2	13.9%	0.76 [0.51, 1.12]	
Chakrabarti 2008	0.01	0.29	6.6%	1.01 [0.57, 1.78]	_ + _
Cong 2008	0.11	0.23	10.5%	1.12 [0.71, 1.75]	
Fan 2008	0.26	0.24	9.6%	1.30 [0.81, 2.08]	+ - -
Fuse 2008	-0.22	0.71	1.1%	0.80 [0.20, 3.23]	
Lemmela 2009	0.08	0.26	8.2%	1.08 [0.65, 1.80]	
Liu 2008	0.49	0.14	28.3%	1.63 [1.24, 2.15]	+
Tanito 2008	0.97	0.77	0.9%	2.64 [0.58, 11.93]	
Thorleifsson 2009	0.2	0.2	13.9%	1.22 [0.83, 1.81]	
Zanon-Moreno et al. 2014	0.73	0.28	7.1%	2.08 [1.20, 3.59]	
Total (95% CI)			100.0%	1.26 [1.09, 1.46]	•
Heterogeneity: Chi ² = 15.68,	df = 9 (P = 0.07); f	² = 439	Ж		
Test for overall effect: Z = 3.0)8 (P = 0.002)				0.01 0.1 1 10 100 Favours [case] Favours [control]

Figure 2. Forest plot of association of POAG with rs2165241 in the total population; the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95% CI. In this analysis, a fixed-effects model was used.

Caucasian

Tanito 2008

Total (95% CI)

Caucasian				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Fan 2008	0.11	0.23	15.4%	1.12 [0.71, 1.75]	+
Lemmela 2009	0.08	0.26	12.1%	1.08 [0.65, 1.80]	+
Liu 2008	0.49	0.14	41.7%	1.63 [1.24, 2.15]	
Thorleifsson 2009	0.2	0.2	20.4%	1.22 [0.83, 1.81]	
Zanon-Moreno et al. 2014	0.73	0.28	10.4%	2.08 [1.20, 3.59]	
Total (95% CI)			100.0%	1.42 [1.19, 1.69]	•
Heterogeneity: Chi ² = 5.57	', df = 4 (P = 0.23); I ²	= 28%	5		
Test for overall effect: Z =	3.85 (P = 0.0001)				Favours [Case] Favours [control]
Asian					
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
0 h 0 m					
Abu-Amero 2012	-0.28	0.2	42.0%	0.76 [0.51, 1.12]	
Abu-Amero 2012 Chakrabarti 2008		0.2 0.29	42.0% 20.0%	0.76 [0.51, 1.12] 1.01 [0.57, 1.78]	
	0.01				* *

100.0%

2.8% 2.64 [0.58, 11.93]

0.94 [0.73, 1.21]

0.01

0.1

10

Favours [case] Favours [control]

100

0.97 0.77

Heterogeneity: $Chi^2 = 3.65$, df = 4 (P = 0.45); $l^2 = 0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

tion of POAG with rs2165241 in the Caucasian and Asian populations; the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95% CI. In this analysis, a fixed-effects model was used.

Figure 3. Forest plot of the associa-

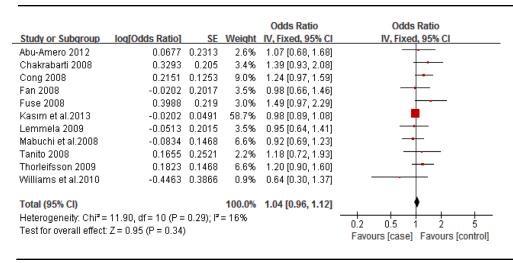


Figure 4. Forest plot of the association of POAG with rs1048661 in the total population; the horizontal lines correspond to the studyspecific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95%CI. In this analysis, a fixed-effects model was used.

Molecular Vision 2015; 21:165-172 <http://www.molvis.org/molvis/v21/165>

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Abu-Amero 2012	-0.1863	0.2689	6.2%	0.83 [0.49, 1.41]	
Chakrabarti 2008	-0.2107	0.1704	15.3%	0.81 [0.58, 1.13]	
Cong 2008	-0.1744	0.1978	11.4%	0.84 [0.57, 1.24]	
Fan 2008	0.1484	0.2091	10.2%	1.16 [0.77, 1.75]	- +
Fuse 2008	-0.3711	0.3611	3.4%	0.69 [0.34, 1.40]	
Kasım et al.2013	0.3365	0.2606	6.6%	1.40 [0.84, 2.33]	+
Lemmela 2009	-0.4155	0.2306	8.4%	0.66 [0.42, 1.04]	
Liu 2008	0.2469	0.2398	7.7%	1.28 [0.80, 2.05]	-+
Mabuchi et al.2008	0.0296	0.1971	11.5%	1.03 [0.70, 1.52]	-
Tanito 2008	0.0392	0.3158	4.5%	1.04 [0.56, 1.93]	
Thorleifsson 2009	0.1222	0.216	9.5%	1.13 [0.74, 1.73]	- -
Williams et al.2010	0.0862	0.2879	5.4%	1.09 [0.62, 1.92]	
Total (95% CI)			100.0%	0.97 [0.85, 1.10]	+
Heterogeneity: Chi ² =	10.52, df = 11 (P =	0.48); l²	= 0%		
Test for overall effect:	Z = 0.50 (P = 0.62)				Favours [case] Favours [control]

Figure 5. Forest plot of the association of POAG with rs3825942 in the total population; the horizontal lines correspond to the studyspecific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95%CI. In this analysis, a fixed-effects model was used.

and the random effects model analysis was used if the status was conversed.

RESULTS

Literature inclusion: As shown in Figure 1, the relevant databases were reviewed and 132 literatures were found to meet the inclusion criteria for the meta-analysis. Of the 132, 119 literatures were excluded due to duplicated publications, non-clinical-based research, or non-availabilities of full texts. In total, 13 literatures [12,19-30,] were included, all of which were case-control studies totaling 5,293 subjects. The characteristics of the included studies were shown in Table 1.

Caucasian

Meta-analysis: All the publications including these three SNPs showed no significant heterogeneity (rs2165241: $I^2 = 43\%$, p = 0.07; rs1048661: $I^2 = 16\%$, p = 0.29; rs3825942: $I^2 = 0\%$, p = 0.48), Therefore, the data were combined using the fixed effects model. For rs2165241, the meta-analysis results showed that the risk of POAG in individuals carrying the C allele was 1.26 times compared to those carrying the T allele (OR = 1.26, 95% confident interval (CI): 1.09 ~1.46, p = 0.002) in the total population (Figure 2). In the Caucasian population, we found that individuals carrying the C allele of rs2165241 have an increased risk for POAG compared to those subjects carrying the T allele (OR = 1.42, 95% CI: 1.19 ~1.69, 95%).

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ra	tio]	SE Weig	nt IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fan 2008	-0.02	202 0.20	17 4.8	% 0.98 [0.66, 1.46]	<u>+</u>
Kasım et al.2013	-0.02	202 0.04	91 80.2	% 0.98 [0.89, 1.08]	—
Lemmela 2009	-0.06	513 0.20	015 4.8	% 0.95 [0.64, 1.41]	
Thorleifsson 2009	0.18	323 0.14	68 9.0	% 1.20 [0.90, 1.60]	+ - -
Williams et al.2010	-0.44	463 0.38	366 1.3	% 0.64 [0.30, 1.37]	
Total (95% CI)			100.0	% 0.99 [0.91, 1.08]	•
Heterogeneity: Chi ² =	3.08, df = 4 (P = 0.55); I ^z = 0%			
Test for overall effect:	Z = 0.21 (P = 0.84)				0.05 0.2 1 5 20 Favours [case] Favours [control]
Asian				Odds Ratio	Odds Ratio
	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% Cl	Odds Ratio IV. Fixed, 95% Cl
Study or Subgroup	loq[Odds Ratio] 0.0677	<u>SE</u> 0.2313	Weight 9.9%	Odds Ratio IV, Fixed, 95% Cl 1.07 [0.68, 1.68]	Odds Ratio IV, Fixed, 95% Cl
Study or Subgroup Abu-Amero 2012				IV, Fixed, 95% Cl	
<u>Study or Subgroup</u> Abu-Amero 2012 Chakrabarti 2008	0.0677	0.2313	9.9%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68]	
Study or Subgroup Abu-Amero 2012 Chakrabarti 2008 Cong 2008	0.0677 0.3293	0.2313 0.205	9.9% 12.6%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08]	
Asian <u>Study or Subgroup</u> Abu-Amero 2012 Chakrabarti 2008 Cong 2008 Fuse 2008 Mabuchi et al.2008	0.0677 0.3293 0.2151 0.3988	0.2313 0.205 0.1253	9.9% 12.6% 33.7%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08] 1.24 [0.97, 1.59]	
Study or Subgroup Abu-Amero 2012 Chakrabarti 2008 Cong 2008 Fuse 2008	0.0677 0.3293 0.2151 0.3988	0.2313 0.205 0.1253 0.219 0.1468	9.9% 12.6% 33.7% 11.0%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08] 1.24 [0.97, 1.59] 1.49 [0.97, 2.29]	
Study or Subgroup Abu-Amero 2012 Chakrabarti 2008 Cong 2008 Fuse 2008 Mabuchi et al.2008 Tanito 2008	0.0677 0.3293 0.2151 0.3988 -0.0834	0.2313 0.205 0.1253 0.219 0.1468	9.9% 12.6% 33.7% 11.0% 24.5% 8.3%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08] 1.24 [0.97, 1.59] 1.49 [0.97, 2.29] 0.92 [0.69, 1.23] 1.18 [0.72, 1.93]	
Study or Subgroup Abu-Amero 2012 Chakrabarti 2008 Cong 2008 Fuse 2008 Mabuchi et al.2008 Tanito 2008 Total (95% CI)	0.0677 0.3293 0.2151 0.3988 -0.0834 0.1655	0.2313 0.205 0.1253 0.219 0.1468 0.2521	9.9% 12.6% 33.7% 11.0% 24.5% 8.3% 100.0%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08] 1.24 [0.97, 1.59] 1.49 [0.97, 2.29] 0.92 [0.69, 1.23]	
Study or Subgroup Abu-Amero 2012 Chakrabarti 2008 Cong 2008 Fuse 2008 Mabuchi et al 2008 Tanito 2008 Total (95% CI) Heterogeneity: Chi ^z =	0.0677 0.3293 0.2151 0.3988 -0.0834 0.1655 : 4.97, df= 5 (P = 0	0.2313 0.205 0.1253 0.219 0.1468 0.2521 42); I ^z = 0	9.9% 12.6% 33.7% 11.0% 24.5% 8.3% 100.0%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08] 1.24 [0.97, 1.59] 1.49 [0.97, 2.29] 0.92 [0.69, 1.23] 1.18 [0.72, 1.93]	
Study or Subgroup Abu-Amero 2012 Chakrabarti 2008 Cong 2008 Fuse 2008 Mabuchi et al.2008 Tanito 2008 Total (95% CI)	0.0677 0.3293 0.2151 0.3988 -0.0834 0.1655 : 4.97, df= 5 (P = 0	0.2313 0.205 0.1253 0.219 0.1468 0.2521 42); I ^z = 0	9.9% 12.6% 33.7% 11.0% 24.5% 8.3% 100.0%	IV, Fixed, 95% Cl 1.07 [0.68, 1.68] 1.39 [0.93, 2.08] 1.24 [0.97, 1.59] 1.49 [0.97, 2.29] 0.92 [0.69, 1.23] 1.18 [0.72, 1.93]	IV, Fixed, 95% Cl

Odds Ratio

Odds Ratio

Figure 6. Forest plot of the association of POAG with rs1048661 in the Caucasian and Asian populations; the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95%CI. In this analysis, a fixedeffects model was used.

Caucasian

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
Fan 2008	1.16	0.77	11.4%	3.19 [0.71, 14.43]	+
Kasım et al.2013	1.4	0.84	9.6%	4.06 [0.78, 21.04]	+
Lemmela 2009	0.66	0.42	38.4%	1.93 [0.85, 4.41]	+■
Liu 2008	1.28	0.8	10.6%	3.60 [0.75, 17.25]	+- -
Thorleifsson 2009	1.13	0.74	12.4%	3.10 [0.73, 13.20]	
Williams et al.2010	1.09	0.62	17.6%	2.97 [0.88, 10.03]	+- - -
Total (95% CI)			100.0%	2.69 [1.61, 4.47]	•
Heterogeneity: Chi ² = Test for overall effect:			= 0%		0.01 0.1 1 10 100 Favours [case] Favours [control]

Asian

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio	Odds Ratio
Study or Subgroup	logiodus Ratioj	3E	weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Abu-Amero 2012	-0.1863	0.2689	11.8%	0.83 [0.49, 1.41]	
Chakrabarti 2008	-0.2107	0.1704	29.4%	0.81 [0.58, 1.13]	
Cong 2008	-0.1744	0.1978	21.8%	0.84 [0.57, 1.24]	
Fuse 2008	-0.3711	0.3611	6.5%	0.69 [0.34, 1.40]	
Mabuchi et al.2008	0.0296	0.1971	22.0%	1.03 [0.70, 1.52]	_
Tanito 2008	0.0392	0.3158	8.6%	1.04 [0.56, 1.93]	
Total (95% CI)			100.0%	0.87 [0.73, 1.05]	•
Heterogeneity: Chi ² =	1.70, df = 5 (P = 0.	89); I ^z = 0)%		
Test for overall effect:	Z = 1.48 (P = 0.14)	I			0.0 0.1 1 1.0 L
	(,				Favours [case] Favours [control]

Figure 7. Forest plot of the association of POAG with rs3825942 in the Caucasian and Asian populations; the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and 95%CI. In this analysis, a fixedeffects model was used.

p = 0.0001). However, we found no association in the Asian population (p = 0.64, Figure 3).

For rs1048661 and rs3825942, we found no associations between the genotype or allele and POAG in the total population (Figure 4 and Figure 5). However, we found that the rs1048661 polymorphism was associated with POAG in the Asian population (OR = 1.17, 95% CI: 1.02 ~1.35, p = 0.03, Figure 6), and rs3825942 was associated with POAG in the Caucasian population (OR = 2.69, 95% CI: 1.61 ~4.47, p<0.001, Figure 7).

Publication bias analysis: We analyzed the publication bias using Revman 5.2 software; the funnel plot shows the points as evenly distributed and symmetric, and most of the points

are within the 95% CI. This indicates no publication bias, and the result of the study is credible (Figure 8).

DISCUSSION

In the present study, 13 literatures were included in a metaanalysis to investigate the relationship between the *LOXL1* gene polymorphisms and POAG. The results showed that the genetic polymorphisms of *LOXL1* were associated with a risk of POAG.

LOXL1 is located on human chromosome 15q22, and it is a member of the lysyl oxidase family [31], members of which can encode a kind of copper-dependent amino oxidase. This enzyme acted on the cell, and it catalyzes the first step of the

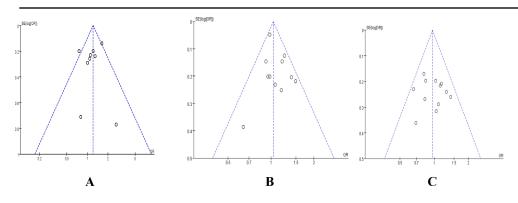


Figure 8. Begg's funnel plot to test for a publication bias. Each circle denotes an independent study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line stands for mean effect size. A: rs2165241; B: rs1048661; C: rs3825942. Molecular Vision 2015; 21:165-172 <http://www.molvis.org/molvis/v21/165>

cross-linking reaction between collagen and elastin [32]. The gene-encoded protein is a secreted protein; after that, it is synthesized in the form of a precursor, and it is glycosylated in the Golgi complex and secreted out of the cells in the plasminogen state. Under the action of the proteolytic enzymes, LOXL1 can convert to an active form and act on the elastic and collagen fibers in the extracellular matrix. LOXL1 expression upregulation and abnormally high levels of enzyme activity can cause excessive collagen accumulation and result in the occurrence and development of related diseases, such as POAG. The rs2165241 of the LOXL1 gene is located in the coding region of the gene. Thus, the polymorphism may be associated with the expressed products. The LOXL1 protein encoded by the C allele is different from the protein encoded by the T allele in the primary and spatial structures [12], which will result in changes to the biologic function of the protein, and it will eventually result in different incidences of POAG in individuals carrying different alleles. The other two SNPs (rs1048661 and rs3825942) are non-synonymous variants, which may affect protein function or expression. In the present study, we used meta-analysis methods to investigate the relationships between these three SNPs in the LOXL1 gene and POAG, which has certain advantages. We found that in the Caucasian population, individuals carrying the C allele of rs2165241 have an increased 1.42-fold risk for POAG compared to those subjects carrying the T allele. In addition, we found that the rs1048661 polymorphism was associated with POAG in the Asian population and rs3825942 was associated with POAG in the Caucasian population. We found neither heterogeneity nor a publication bias among the studies. In addition, the sensitivity analysis showed that the results were stable and reliable. In conclusion, the present study indicated that LOXL1 genetic polymorphisms are associated with susceptibility to POAG.

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