

Ethnicity-based subgroup meta-analysis of the association of *LOXL1* polymorphisms with glaucoma

Haoyu Chen,^{1,2} Li Jia Chen,² Mingzhi Zhang,¹ Weifeng Gong,¹ Pancy Oi Sin Tam,² Dennis Shun Chiu Lam,² Chi Pui Pang²

¹Joint Shantou International Eye Center, Shantou University & the Chinese University of Hong Kong, Shantou, China; ²Department of Ophthalmology and Visual Sciences, the Chinese University of Hong Kong, Hong Kong, China

Purpose: To investigate the association and ethnic heterogeneity of lysyl oxidase-like 1 (*LOXL1*) single nucleotide polymorphisms (SNPs) with exfoliation syndrome (XFS)/exfoliation glaucoma (XFG) and other types of glaucoma. **Methods:** We performed meta-analysis and ethnicity-based subgroup analyses according to published studies. Allele and genotype frequencies of SNPs rs1048661, rs2165241, and rs3825942 were extracted for analysis in Reviewer Manager: (1) comparison of the allelic distributions between XFS and XFG, (2) allelic association of *LOXL1* SNPs with XFS/XFG, (3) associations in homozygote, heterozygote, and dominant and recessive models, and (4) allelic association with primary open angle glaucoma (POAG).

Results: In total 24 reported articles were retrieved, including Caucasian, African, Japanese, Indian, and Chinese populations. There was no significant difference in the distributions of rs1048661, rs2165241, and rs3825942 between XFS and XFG. The G allele of rs3825942 was the common at-risk allele for XFS/XFG in all populations with a total odds ratio (OR) of 10.89. The total homozygote OR of rs3825942 was 9.06 for XFS/XFG combined, but the total heterozygote OR was not significant. We also found that in the recessive model, the total OR was 14.70. There was no association of the three SNPs with POAG.

Conclusions: The association of rs3825942, but not rs2165241 or rs1048661, with XFS/XFG is consistent in different ethnic populations in the recessive model. *LOXL1* is not associated with POAG in all study populations.

Glaucoma is one of the leading causes of irreversible blindness worldwide. It is a group of heterogeneous diseases characterized by progressive loss of retinal ganglion cells and degenerative optic neuropathy with or without elevated intraocular pressure (IOP) [1]. Open angle glaucoma is a major form of glaucoma and can be classified into primary open angle glaucoma (POAG) and secondary open angle glaucoma. Exfoliation glaucoma (XFG) is the most common form of secondary open angle glaucoma and is caused by obstruction of extracellular material in the anterior chamber angle in exfoliation syndrome (XFS), which is an age-related disease characterized by deposits of extracellular material in the anterior segment, including the cornea, lens, iris, and anterior chamber [2]. The prevalence of XFS varies widely across different ethnic populations. In people aged 60 or above, the prevalence of XFS is 0.4% in Hong Kong Chinese [3], 0.7% in Singapore Chinese [4], 4.4% in Japanese [5], and 10%–20% in the Caucasian population [6].

The etiology and pathogenesis of glaucoma are complex and involve multiple genetic and environmental factors. Myocilin (*MYOC*) is a causative gene for POAG and cytochrome P450, 1B1 (CYP1B1) for congenital glaucoma [7,8]. Mutations in optineurin (OPTN) and WD repeat domain 36 (WDR36) do not directly lead to POAG but increase the risk [9,10]. As for XFS and XFG, significant association with three single nucleotide polymorphisms (SNPs), rs1048661,rs2165241, and rs3825942, in the Lysyl oxidaselike 1 (LOXL1) gene was first discovered in 2007 in Icelandic and Swedish populations by a genome-wide association study [11]. SNP rs2165241 was marginally (p=0.04) associated with POAG in the Icelandic but not in the Swedish population, while rs3825942 and rs1048661 were not associated with POAG in either population [11].

Since then the association of *LOXL1* SNPs with XFS/ XFG has been reported in Caucasian populations in the USA [12-16], Australia [17], Austria [18], Germany [19,20], Italy [20], and Finland [21] and in other ethnic groups, including Japanese [22-27], Indian [28], and Chinese [29,30]. *LOXL1* SNPs in POAG have also been studied in Caucasian [14,21, 31], Japanese [22,24,27], Chinese [32], Indian [33], and African populations [31]. Other types of glaucoma, such as normal tension glaucoma and pigmentary glaucoma, have been investigated in India [33], Japan [27], Germany [19], and the USA [34]. Despite the large amount of information, the overall association of SNPs and the discrepancies between individual cohorts or subgroups remain to be characterized.

Meta-analysis is a very useful statistical tool not only to summarize data from individual studies concerning a specific

Correspondence to: Haoyu Chen, M.D., Joint Shantou International Eye Center, Shantou University & the Chinese University of Hong Kong, North Dongxia Road, Shantou, Guangdong, P.R.China 515041; Phone: +86-754-88393519 ; FAX: +86-754-88393501 ; email: drchenhaoyu@gmail.com

		Sam	ple size	Age (yea	rs ±SD)	Sex (]	Male %)	rs104	8661 G%	rs210	55241 T%	rs382	5942 G%	
First author	Cohorts	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Ref
Aragon-Martin	American	287	333	NA	NA	NA	NA	84.3	70.3	73.4	44.8	95.9	79.8	[12]
Challa*	American	50	235	74.0 ± 8.0	64.9±11.6	78.0	61.7	78.7	66.5	66.7	48.7	93.9	84.4	[13]
Fan	American	206	88	75	72	NA	43	82.9	71.9	76.0	45.6	98.8	79.5	[14]
Fingert	American	72	75	NA	NA	NA	NA	81.9	0.09	NA	NA	98.6	88.0	[15]
Yang	American	62	170	NA	74.2±8.8	38.7	52.9	NA	NA	83	53	100	85	[16]
Hewitt*	Australian	86	2087	76.4 ± 8.1	68.6 ± 10.0	37.2	44.8	78	99	NA	NA	95	84	[17]
Mossbock	Austrian	167	170	75.7	77.1	45.5	44.1	84.1	67.1	NA	NA	99.4	81.7	[18]
Wolf	Germany	128	280	71.9±9.7	66±13	44	41	84.4	66.0	78.2	49.1	99.2	85.6	[19]
Pasutto	Germany	517	348	76.6±8.5	73.9±6.4	44.5	43.4	81.8	64.4	75.2	48.2	95.1	85.7	[20]
Pasutto	Italian	209	70	78.3±7.7	75.2±7.4	39.2	35.7	82.5	69.3	79.8	51.5	100	82.1	[20]
Thorleifsson	Icelandian	130	14474	NA	NA	NA	NA	78.1	65.1	74.6	47.3	98.4	84.7	[11]
Thorleifsson	Swedish	199	198	NA	NA	NA	NA	83.4	68.2	81.3	53.5	99.5	87.9	[11]
Lemmela	Finnish	141	404	NA	NA	NA	NA	82.5	68.3	73.2	46.8	96.8	82.3	[21]
Ramprasad	Indian	52	97	68.9 ± 11.4	64.1±7.2	51.9	53.6	72.1	63.4	NA	NA	92.3	74.2	[28]
Lee	Chinese	62	171	74.7±7.7	67.4±5.6	48.4	46.8	54.2	44.4	NA	NA	99.2	91.8	[29]
Chen	Chinese	50	124	70.4±7.6	63.8 ± 5.1	62.0	57.6	11.0	48.0	2.0	10.0	100	90.0	[30]
Fuse	Japanese	56	138	74.8±6.2	68.0±7.7	55.4	55.1	3.6	49.3	1.8	5.8	100	87.7	[22]
Hayashi	Japanese	59	190	78.4±6.9	31.4 ± 1.5	37.3	50.0	0.8	46.0	NA	NA	100	85.7	[23]
Mabuchi	Japanese	89	191	76.5±6.6	65.7±11.4	NA	NA	0.6	45.0	NA	NA	99.4	85.3	[24]
Mori	Japanese	95	190	75.7±8.1	65.0 ± 6.8	NA	NA	0.5	47.4	NA	NA	99.5	85.0	[25]
Ozaki	Japanese	209	172	78.0±6.1	73.8±7.9	32.1	27.9	5.3	49.7	1.7	10.2	98.6	86.3	[26]
Tanito	Japanese	142	157	78.5±8.2	77.2±5.0	38.0	28.7	4.9	55.4	0.7	12.4	99.3	80.6	[27]

TABLE 1. CHARACTERS OF REPORTED COHORTS OF PSEUDOEXFOLIATION SYNDROME/EXFOLIATION GLAUCOMA ASSOCIATION WITH LOXLI SNNPS

The asterisk indicates the counting data was calculated from rate data. NA: data not available. Ref: references.

			TABLE 2. CH.	ARACTERS OF REPOR	TED COHORTS OF PI	RIMARY OPEN A	NGLE GLAUCOMA	. ASSOCIATION	I WITH LOXLI	SNPs				
		Sam	ple size	Age (yea	rs ±SD)	Sex (A	Male %)	rs1048	661 G%	rs216	5241 T%	rs3825	5942 G%	
First author	Cohorts	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Ref
Fan	American	331	88	75	72	NA	43.2	72.4	71.9	41.2	45.6	77.1	79.5	[14]
Thorleifsson	Icelandian	06	14474	NA	NA	NA	NA	71.1	65.1	55.0	47.3	87.2	84.7	Ξ
Thorleifsson	Swedish	200	198	NA	NA	NA	NA	63.8	68.2	48.8	53.3	86.3	87.9	Ξ
Lemmela	Finnish	71	404	NA	NA	NA	NA	69.4	68.3	45.7	46.8	78.7	82.3	[21]
Liu*	Caucasian	279	227	58.7±12.8	>55	NA	NA	NA	NA	42.4	48.6	82.9	84.4	[31]
Liu*	African	193	76	55.3 ± 13.3	>55	NA	NA	NA	NA	23.7	20.4	61.7	59.9	[31]
	American													
Liu*	Ghanaian	170	138	55.4 ± 13.8	>55	NA	NA	NA	NA	22.6	19.3	62.2	57.0	[31]
Chakrabarti*	Indian	112	105	NA	NA	NA	NA	61.6	69.5	32.1	32.0	83.0	75.0	[33]
Fuse	Japanese	62	138	NA	68.0±7.7	NA	55.1	39.5	49.3	4.8	5.8	91.1	87.7	[22]
Mabuchi	Japanese	213	191	62.9 ± 14.8	65.7±11.4	NA	NA	47.2	45.0	NA	NA	85.0	85.3	[25]
Tanito	Japanese	40	157	75.6±5.3	77.2±5.0	35.0	28.7	51.3	55.4	3.8	12.4	80.0	80.6	[27]
Gong	Southern	293	250	66.8±12.9	74.1±6.8	60.1	49.2	42.0	47.2	8.4	10.2	89.4	87.6	[32]
	Chinese													
Gong	Northern	169	197	39.1 ± 16.5	69.4 ± 6.0	78.1	49.2	47.9	49.7	8.6	8.4	89.9	86.5	[32]
	Chinese													

Molecular Vision 2010; 16:167-177 < http://www.molvis.org/molvis/v16/a21>

© 2010 Molecular Vision

The asterisk indicates the counting data was estimated from frequency data. NA: data not available. Ref: references

research question but also to identify and analyze the consistency and discrepancies of individual studies or population subgroups. The prevalence of XFS/XFG varies widely among different ethnic populations mainly due to variations in genetic background. Therefore, to ascertain effects due to ethnic differences, meta-analysis of the genetic association of LOXL1 SNPs with glaucoma could be performed based on subgrouping by ethnicity. In LOXL1, three SNPs (rs1048661, rs2165241, and rs3825942) were first found associated with XFS/XFG in Icelandic and Swedish populations. They appeared in most of the reported studies, despite some inconsistencies in their presence [16,24,29,31]. Several other SNPs at LOXL1 (rs12437465,rs2304719, and rs3522) have also been reported [13,17,31], but their associations were due to intermarker linkage disequilibrium (LD) and limited functional studies of these SNPs were reported, so they were not included in this meta-analysis. In this study, we perform a subgroup based meta-analysis using all of the reported studies on the association of LOXL1 SNPs (rs1048661, rs2165241, and rs3825942) with XFS, XFG, and POAG.

METHODS

An internet-based literature search was conducted on PubMed and Embase, using the search strategy ("LOXL1" OR "LOXL" OR "Lysyl oxidase-like") AND ("glaucoma" OR "exfoliation" OR "pseudoexfoliation"). The cut-off date was December 12, 2009. In total 41 articles were obtained from PubMed and 38 from Embase. Articles meeting the following criteria were included for further data analysis: (1) case-control study, cohort study, or population-based

	XEC		XES			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% C	M-H. Fixed, 95% Cl
1.1.1 Caucasian							
Aragon-Martin US+European	225	264	156	188	13.6%	1.18 [0.71, 1.97]	
Fan mostly American	237	282	93	116	10.6%	1.30 [0.75, 2.27]	
Lemmela Finnish	126	152	82	100	8.5%	1.06 [0.55, 2.06]	
Pasutto Germany	522	622	321	408	31.5%	1.41 [1.03, 1.95]	
Pasutto Italian	212	260	128	152	15.1%	0.83 [0.48, 1.42]	
Thorleifsson Iceland	124	150	83	106	8.5%	1.32 [0.71, 2.47]	
Subtotal (95% CI)		1730		1070	87.8%	1.22 [1.00, 1.49]	•
Total events	1446		863				
Heterogeneity: Chi2 = 3.12, df =	5 (P = 0.	68); l² =	0%				
Test for overall effect: Z = 1.97	(P = 0.05)						
1.1.2 Japanese							
Fuse Japanese	3	72	1	40	0.6%	1.70 [0.17, 16.86]	
Hayashi Japanese	0	54	1	64	0.7%	0.39 [0.02, 9.73]	· · · · ·
Ozaki Japanese	8	212	14	206	6.9%	0.54 [0.22, 1.31]	
Tanito Japanese	7	166	7	118	4.0%	0.70 [0.24, 2.05]	
Subtotal (95% CI)		504		428	12.2%	0.64 [0.34, 1.21]	-
Total events	18		23				
Heterogeneity: Chi2 = 0.96, df =	3 (P = 0.	B1); I ² =	0%				
Test for overall effect: Z = 1.38	(P = 0.17)						
Total (95% CI)		2234		1498	100.0%	1.15 [0.95, 1.39]	•
Total events	1464		886				
Heterogeneity: Chi2 = 7.67, df =	9 (P = 0.	57); l² =	0%				
Test for overall effect: Z = 1.45	(P = 0.15)						0.05 0.2 1 5 20
Tost for subgroup differences: h	lot applic	ablo				F	avours experimental Favours control

Figure 1. Meta-analysis of the distribution of single nucleotide polymorphism (SNP) rs1048661 between exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Meta-analysis indicated there is no statistical difference of distribution of the SNP rs1048661 G and T allele between XFS and XFG.

epidemiological survey; (2) reports on the association of three SNPs in *LOXL1*, i.e., rs1048661, rs2165241, and/or rs3825942, with XFS, XFG, POAG, or/and other types of glaucoma; (3) studies with reported and accessible sample size, allele, and/or genotype frequencies/counts in both patients and controls; and (4) original research articles, not reviews or comments. Repetitive publications, which were



Figure 2. Meta-analysis of the distribution of single nucleotide polymorphism (SNP) rs2165241 between exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). Squares indicate study-specific odds ration (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Meta-analysis indicated there is no statistical difference of distribution of the SNP rs2165241 T and C allele between XFS and XFG.

	XFG		XFS			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.3.1 Caucasian							
Aragon-Martin US+European	260	264	173	188	5.6%	0.06 [0.02, 0.11]	$ \longrightarrow$
Fan mostly American	289	292	118	120	10.5%	0.01 [-0.02, 0.03]	
Lemmela Finnish	150	152	94	100	4.2%	0.05 [-0.00, 0.10]	
Pasutto Germany	593	622	385	406	9.8%	0.01 [-0.02, 0.03]	_
Pasutto Italian	260	260	152	152	19.0%	0.00 [-0.01, 0.01]	+
Thorleifsson Iceland	148	150	106	108	8.3%	0.01 [-0.03, 0.04]	_
Yang Utah (US)	98	98	26	26	3.8%	0.00 [-0.05, 0.05]	
Subtotal (95% CI)		1838		1100	61.1%	0.01 [-0.01, 0.03]	-
Total events	1798		1054				
Heterogeneity: Tau ² = 0.00; Chi	² = 19.81,	df = 6	(P = 0.00	3); l² =	70%		
Test for overall effect: Z = 1.44	(P = 0.15)						
1.3.2 Japanese							
Fuse Japanese	72	72	40	40	6.2%	0.00 [-0.04, 0.04]	
Hayashi Japanese	54	54	64	64	7.8%	0.00 [-0.03, 0.03]	
Ozaki Japanese	209	212	203	206	11.8%	0.00 [-0.02, 0.02]	
Tanito Japanese	165	166	117	118	13.1%	0.00 [-0.02, 0.02]	
Subtotal (95% CI)		504		428	38.9%	0.00 [-0.01, 0.01]	•
Total events	500		424				
Heterogeneity: Tau ² = 0.00; Chi	² = 0.03, c	if = 3 (F	P = 1.00);	$ ^2 = 0$ %	6		
Test for overall effect: Z = 0.17	(P = 0.86)						
Total (95% CI)		2342		1528	100.0%	0.01 [-0.00, 0.02]	•
Total events	2298		1478				
Heterogeneity: Tau ² = 0.00; Chi	² = 18.62,	df = 10) (P = 0.0	5); l² =	46%		
Test for overall effect: Z = 1.31	(P = 0.19)					E	-0.1 -0.05 0 0.05 0.1
						F	avours experimental Favours control

Figure 3. Meta-analysis of the distribution of single nucleotide polymorphism (SNP) rs3825942 between exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). Squares indicate study-specific risk difference (RD); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary RD with its corresponding 95% CI. Meta-analysis indicated there is no statis tical difference of distribution of the SNP rs3825942 G and A allele between XFS and XFG.

ruled out through tracking references, were incorporated as the latest reports. If several different cohorts were reported in the same article, they were treated as independent studies.

The retrieved abstracts and full texts were separately reviewed by two investigators (H.Y.C. and W.F.G.) who also independently performed data extraction and quality evaluation. A third reviewer (L.J.C.) would participate in the review if there was disagreement in the retrieved information. Total consensus of the three reviewers needed to be obtained on all retrieved data. The ethnicity, sample size, age, sex, allele, and/or genotype frequency/counts in both patients and controls were recorded. For studies with no direct data of genotype or allele counts, we calculated the frequency according to the reported data, rounding to the closest integer. The allele counting was also calculated from genotype counting when needed.

The Review Manager (version 5.0.18; The Cochrane Collaboration, Copenhagen, Denmark and SPSS software (ver. 16.0; SPSS Inc., Chicago, IL) were used to perform the meta-analysis: (1) The Hardy–Weinberg equilibrium (HWE)

	Cas	e	Cont	rol		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Rando	om, 95% Cl
2.1.1 Caucasian								
Aragon-Martin US+European	477	566	464	660	5.1%	2.26 [1.71, 3.00]		+
Challa Duke (US)	79	100	313	470	5.0%	1.89 [1.12, 3.17]		
Fan mostly American	330	398	115	160	5.1%	1.90 [1.23, 2.93]	1	
Fingert Iowa (US)	118	144	90	150	5.0%	3.03 [1.77, 5.17]		
Hewitt Austrilian	134	172	2755	4174	5.1%	1.82 [1.26, 2.62]		-
Lemmela Finnish	208	252	444	650	5.1%	2.19 [1.52, 3.16]		-
Mossbock Austrian	281	334	228	340	5.1%	2.60 [1.80, 3.77]		+
Pasutto Germany	843	1030	437	684	5.2%	2.55 [2.04, 3.18]		+
Pasutto Italian	340	412	97	140	5.1%	2.09 [1.35, 3.25		
Thorleifsson Iceland	207	256	1305	2048	5.1%	2.41 [1.74. 3.33]		+
Thorleifsson Sweden	331	392	270	396	5.1%	2.53 [1.79, 3.58		+
Wolf Germany	216	256	351	532	5.1%	2,78 (1.90, 4.08		
Subtotal (95% CI)		4312		10404	61.1%	2.35 [2.12, 2.60]		•
Total events	3564		6869					
Heterogeneity: Tau ² = 0.00: Chi	2=6.61	df = 11	(P = 0.83)	$1^2 = 0.9$	6			
Test for overall effect Z = 16.51	(P < 0.00	0001)		,,				
2.1.2 Japanese								
Fuse Japanese	4	112	136	276	4.5%	0.04 [0.01, 0.11]		
Hayashi Japanese	1	118	174	378	3.2%	0.01 [0.00, 0.07]	, ←	
Mabuchi Japanese	1	178	172	382	3.2%	0.01 [0.00, 0.05]	i ←	
Mori Japanese	1	190	180	380	3.2%	0.01 [0.00, 0.04]	l ←	
Ozaki Japanese	22	418	171	344	5.0%	0.06 [0.03, 0.09]		
Tanito Japanese	14	284	174	314	4.9%	0.04 [0.02, 0.07		
Subtotal (95% CI)		1300		2074	24.0%	0.03 [0.01, 0.06]	•	
Total events	43		1007					
Heterogeneity: Tau ² = 0.40; Chi	² = 13.89	df = 5	(P = 0.02)); $l^2 = 64$	%			
Test for overall effect: Z = 10.04	(P < 0.00	0001)						
2.1.3 Chinese								
Chen Chinese	11	100	121	250	4.9%	0.13 [0.07, 0.26]		
Lee Singapore Chinese	65	124	152	342	5.1%	1.38 [0.91, 2.08]		+
Subtotal (95% CI)		224		592	9.9%	0.43 [0.04, 4.45]		
Total events	76		273					
Heterogeneity: Tau ² = 2.75; Chi	² = 34.87,	df = 1	(P < 0.00	001); l² =	= 97%			
Test for overall effect Z = 0.70 (P = 0.48)							
2.1.4 Indian								
Ramprasad Indian	75	104	123	194	5.0%	1.49 [0.89, 2.51]		÷
Subtotal (95% CI)		104		194	5.0%	1.49 [0.89, 2.51]		-
Total events	75		123					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.51 (P = 0.13)							
Total (05% CI)		6040		42264	100.0*	0 62 10 26 4 40		
Total (95% CI)	2750	0940	0070	13204	100.0%	0.05 [0.36, 1.10]	-	
I utar events	3/58	o	8212	000045	12 - 0.74			
Heterogeneity: Tau* = 1.60; Chi	-= 692.7	a' ai = ;	20 (P < 0.	00001);	1-= 81%		0.01 0.1 1	10 100
rescior overall effect: Z = 1.62 (r = 0.11)						Favours experimental	Favours control

Figure 4. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs1048661 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Subgroup meta-analysis indicated that the ORs of SNP rs1048661 G allele are reversed in Caucasian and Japanese.

of each SNP in the control group of each study was examined by using χ^2 analysis; (2) meta-analysis of the *LOXL1* SNPs rs1048661, rs2165241, and rs3825942 was performed to compare the allelic distributions between XFS and XFG; (3) if there were no statistical differences in allelic distributions between XFS and XFG, these two groups were combined. Meta-analyses of the allelic associations of rs1048661, rs2165241, and rs3825942 with overall XFS and XFG were performed; (4) if positive results were obtained from allelic association analysis, genotypic association analyses were performed using different genetic models, including multiplicative models estimating the homozygous odds ratio (OR) and heterozygous OR as well as the dominant model and recessive model; and (5) the allele association of rs1048661, rs2165241, and rs3825942 with POAG was analyzed. All the meta-analyses were performed in subgroupings by ethnicity. In all of the meta-analyses, the ORs were estimated by the fixed or random model according to the heterogeneity test. When the heterogeneity test α was <0.1, a random model was applied, and when the heterogeneity test α was >0.1, a fixed model was applied. Sensitivity tests were performed, but studies with counting data that were computed from frequencies data were excluded.

RESULTS

There were 20 articles reporting the association of *LOXL1* SNPs with XFS/XFG in a total of 3,068 cases and 20,363

	Cas	e 	Cont			Ouus Rauo	Ouus	Ratio
Study or Subgroup	Events	Total	Events	lotal	weight	M-H, Random, 95% C	M-H, Rand	om, 95% Cl
2.2.1 Caucasian								+
Aragon-Martin US+European	417	568	294	656	8.9%	3.40 [2.67, 4.33]	-
Challa Duke (US)	67	100	229	470	7.9%	2.14 [1.36, 3.37]	
Fan mostly American	304	400	73	160	8.3%	3.77 [2.56, 5.55]	-
Lemmela Finnish	205	280	296	632	8.6%	3.10 (2.28, 4.22]	
Pasutto Germany	770	1024	326	680	9.0%	3.29 [2.68, 4.05]	-
Pasutto Italian	327	410	69	136	8.1%	3.83 (2.53, 5.79]	
Thorleifsson Iceland	191	256	13691	28938	8.7%	3.27 [2.47, 4.34]	+
Thorleifsson Sweden	322	396	212	396	8.6%	3.78 (2.74, 5.20]	
/Volf Germany	158	202	275	560	8.3%	3.72 [2.56, 5.40]	-
Yang Utah (US)	103	124	177	340	7.6%	4.52 [2.70, 7.56]	
Subtotal (95% CI)		3760		32968	84.0%	3.39 [3.07, 3.74]	1	•
Total events	2864		15642					
Heterogeneity: Tau ^a = 0.00; Chi	² = 6.91, 0	df = 9 (F	P = 0.65);	I ² = 0%				
Test for overall effect: Z = 24.13	(P < 0.00	0001)						
2.2.2 Japanese								
Fuse Japanese	2	112	16	276	3.3%	0.30 (0.07, 1.31] —	-
Ozaki Japanese	7	418	35	344	5.9%	0.15 [0.07, 0.34	J	
Tanito Japanese	2	284	39	314	3.4%	0.05 [0.01, 0.21	·	
Subtotal (95% CI)		814		934	12.6%	0.13 [0.06, 0.32]	•	
Total events	11		90					
Heterogeneity: Tau ² = 0.22; Chi	² = 3.10, i	df = 2 (F	P = 0.21);	I ² = 35%	5			
Test for overall effect: Z = 4.57	P < 0.000	01)						
2.2.3 Chinese								
Chen Chinese	2	100	25	250	3.3%	0.18 [0.04, 0.79		
Subtotal (95% CI)		100		250	3.3%	0.18 [0.04, 0.79]		
Total events	2		25					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28	P = 0.02							
	,							
Total (95% CI)		4674		34152	100.0%	2.06 [1.48, 2.87	1	•
Total events	2877		15757					
Heterogeneity: Tau ² = 0.31: Chi	= 122.1	4. df = 1	3 (P < 0.	00001):	l ² = 89%		the state of the s	
Test for overall effect: Z = 4 25	P < 0.000	11)					0.01 0.1	1 10 100
		,					Favours experimental	Favours control

Figure 5. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs2165241 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Subgroup meta-analysis indicated that the ORs of SNP rs2165241 T allele are reversed in Caucasian and Japanese.

controls from 22 study cohorts (Table 1). Nine articles investigated the association between *LOXL1* SNPs and POAG in a total of 2,223 POAG patients and 16,664 controls from 13 cohorts (Table 2). The HWE of all three SNPs was tested in the control groups of all cohorts. No deviation from the HWE was identified.

There was no significant difference in allele frequencies between XFS and XFG for rs1048661 and rs2165241 in any cohort. The overall OR for the two SNPs was 1.15 (95% confidence interval [CI] 0.95–1.39, p=0.15, Figure 1) and 1.15 (95% CI 0.97–1.37, p=0.10, Figure 2), respectively. The OR due to rs3825942 could not be estimated in four out of the 11 cohorts due to 100% G allele frequencies occurring in both the XFS and XFG groups. Therefore, we calculated the risk difference instead of the OR. The risk difference between XFS and XFG was 0.01 (95% CI -0.00-0.02, p=0.20, Figure 3), and showed no statistically significant difference in the distributional profiles of the three SNPs between XFS and XFG. We thus combined the XFS and XFG groups in subsequent analyses.

Moreover, the association profiles of LOXL1 SNPs were examined by comparing the patients with XFS or XFG versus control subjects in different populations. The study cohorts were from four major ethnic groups: Caucasian, Japanese, Chinese, and Indian. In most individual studies, significant allelic association was found between XFS/XFG and the LOXL1 SNPs rs1048661, rs2165241, and rs3825942, regardless of ethnicity. In the association of rs3825942 with XFS/XFG, the ORs of the G allele in every study was significantly greater than 1 and the ORs lay on the same side of the y-axis. The OR was 9.30 (95% CI 5.70-15.16, p<0.00001) in Caucasian, 18.72 (95% CI 10.07-34.79, p<0.00001) in Japanese, 14.23 (95% CI 2.78–72.79, p=0.001) in Chinese, and 4.17 (95% CI 7.04-16.55, p=0.0004) in Indian populations. The overall OR was 10.89 (95% CI 7.20-16.45, p < 0.00001) for the four ethnic populations (Figure 6). Notably, however, the ORs of rs2165241 in Caucasian and Japanese populations were reversed. OR for the T allele was 3.39 (95% CI 3.07-3.74, p<0.00001) in Caucasian populations, suggesting that the T allele was the at-risk allele. The OR for the T allele was 0.13 (95% CI 0.06-0.32, p<0.00001) in Japanese populations, indicating that the T

	Cas	е	Cont	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.3.1 Caucasian							
Aragon-Martin US+European	543	566	530	664	7.9%	5.97 [3.77, 9.44]	
Challa Duke (US)	94	100	397	470	6.3%	2.88 [1.22, 6.82]	_
Fan mostly American	407	412	140	176	6.0%	20.93 [8.06, 54.39]	
Fingert Iowa (US)	142	144	132	150	4.1%	9.68 [2.20, 42.53]	
Hewitt Austrilian	163	172	3506	4174	7.1%	3.45 [1.75, 6,79]	
Lemmela Finnish	244	252	535	650	6.9%	6.56 [3.15, 13.64]	
Mossbock Austrian	332	334	278	340	4.3%	37.02 (8.97, 152,71)	
Pasutto Germany	978	1028	578	692	8.3%	3.86 (2.72, 5.46)	-
Pasutto Italian	412	412	115	140	1.7%	182 14 [11.00. 3014 64]	
Thorleifsson Iceland	254	258	839	980	5.8%	10.67 (3.91, 29,11)	
Thorleifsson Sweden	390	392	337	384	4.3%	27.20 (6.56, 112.80)	
Wolf Germany	252	254	460	544	4.3%	23.01 (5.61, 94.31)	
Yang Utah (US)	124	124	289	340	1.8%	44.30 [2.71, 723.44]	````````````````````````````````
Subtotal (95% CI)		4448		9704	68.8%	9.30 [5.70, 15.16]	•
Total events	4335		8136				
Heterogeneity: Tau ² = 0.48: Chi	$r^2 = 45.41$	df = 12	P < 0.0	0001) [.] P	= 74%		
Test for overall effect: 7 = 8.94 (P < 0.000	01)	- (i - 0.0	0001),1	-14%		
		,					
2.3.2 Japanese							
Fuse Japanese	112	112	242	276	1.7%	32.01 [1.95, 526.80]	│ ———→
Havashi Japanese	118	118	324	378	1.8%	39.80 [2.44, 649.63]	````````````````````````````````
Mabuchi Japanese	177	178	326	382	2.9%	30.40 [4.17, 221,50]	
Mori Japanese	189	190	323	380	2.9%	33.35 [4.58, 242.83]	
Ozaki Japanese	412	418	297	344	6.3%	10.87 [4.59, 25,75]	
Tanito Japanese	282	284	253	314	4.3%	34.00 (8.23, 140, 45)	\longrightarrow
Subtotal (95% CI)		1300		2074	19.9%	18,72 [10,07, 34,79]	•
Total events	1290		1765				
Heterogeneity: Tau ² = 0.00: Chi	= 3.58.	df = 5 (f)	= 0.61);	² = 0%			
Test for overall effect: Z = 9.27 (P < 0.000	01)					
		,					
2.3.3 Chinese							
Chen Chinese	100	100	224	250	1.7%	23.73 [1.43, 393.18]	→
Lee Singapore Chinese	123	124	314	342	2.9%	10.97 [1.48, 81, 49]	
Subtotal (95% CI)		224		592	4.6%	14.23 [2.78, 72.79]	
Total events	223		538				
Heterogeneity: Tau ² = 0.00; Chi	² = 0.20, 0	df = 1 (8	= 0.66);	$l^2 = 0\%$			
Test for overall effect: Z = 3.19 (P = 0.001)					
2.3.4 Indian							
Ramprasad Indian	96	104	144	194	6.6%	4.17 [1.89, 9.18]	
Subtotal (95% CI)		104		194	6.6%	4.17 [1.89, 9.18]	-
Total events	96		144				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.54 (P = 0.000	(4)					
Total (95% CI)		6076		12564	100.0%	10.89 [7.20, 16.45]	•
Total events	5944		10583				
Heterogeneity: Tau ² = 0.51: Chi	= 66.35	df = 2'	(P < 0.0	0001); P	= 68%		
Test for overall effect: Z = 11.33	(P < 0.00	0001)					0.01 0.1 1 10 100
						F	avours experimental Favours control

Figure 6. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs3825942 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Subgroup meta-analysis indicated that the ORs SNP rs3825942 G allele is consistent in Caucasian and Japanese.

	Cas	е	Cont	ol		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
3.1.1 Caucasian								
Aragon-Martin US+European	260	260	216	234	3.4%	44.52 [2.67, 743.02]		+
Fan mostly American	202	203	60	68	3.4%	26.93 [3.30, 219.66]		٠
Fingert Iowa (US)	70	70	59	61	3.5%	5.92 [0.28, 125.84]		٠
Lemmela Finnish	119	120	224	238	9.7%	7.44 [0.97, 57.25]	· · ·	
Mossbock Austrian	165	165	109	110	3.1%	4.53 [0.18, 112.32]		٠
Pasutto Germany	469	474	250	268	26.2%	6.75 [2.48, 18.41]		
Pasutto Italian	206	206	49	53	1.5%	37.55 [1.99, 708.90]		+
Thorleifsson Iceland	125	125	363	377	5.6%	10.01 [0.59, 169.07]		+
Thorleifsson Sweden	194	194	148	151	3.3%	9.17 [0.47, 178.87]		+
Wolf Germany	125	125	196	204	4.6%	10.86 [0.62, 189.77]		٠
Subtotal (95% CI)		1942		1764	64.4%	11.19 [5.72, 21.86]	•	
Total events	1935		1674					
Heterogeneity: Chi ² = 3.87, df =	9 (P = 0.9	32); I ² =	0%					
Test for overall effect: Z = 7.06	(P < 0.000	101)						
3.1.2 Japanese								
Fuse Japanese	56	56	108	112	5.0%	4.69 (0.25, 88.60)		-
Havashi Japanese	59	59	137	139	5.3%	2.16 (0.10, 45,76)	·	
Mabuchi Japanese	88	88	143	151	4.6%	10.48 [0.60, 183.89]		+
Mori Japanese	94	94	135	137	4.5%	3.49 (0.17, 73,46)		
Tanito Japanese	140	140	100	104	3.2%	12.58 (0.67, 236, 33)		٠
Subtotal (95% CI)		437		643	22.7%	6.14 [1.66, 22.70]	-	
Total events	437		623					
Heterogeneity: Chi ² = 0.98, df =	= 4 (P = 0.9	91); I ² =	0%					
Test for overall effect: Z = 2.72	(P = 0.008	0						
3.1.3 Chinese								
Chen Chinese	50	50	101	103	51%	2 49 10 12 52 801		
Lee Singanore Chinese	61	61	143	143	0.170	Not estimable		
Subtotal (95% CI)	0.	111	140	246	5.1%	2 49 [0 12 52 80]		
Total events	111		244			,,		
Heterogeneity: Not applicable			244					
Test for overall effect: Z = 0.58	(P = 0.56)							
2.4.4 Indian								
5.1.4 maian								
Ramprasad Indian Subtotal (95% CI)	45	46	52	57 57	7.9% 7.9%	4.33 [0.49, 38.42] 4.33 [0.49, 38.42]		
Total events	45		52					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.31	(P = 0.19)							
Total (95% CI)		2536		2710	100.0%	9.06 [5.16, 15.92]	•	
Total events	2528		2593					
Heterogeneity: Chi2 = 6.41, df =	= 16 (P = 0	.98); l²	= 0%					-
Test for overall effect: Z = 7.67	(P < 0.000	01)					0.01 0.1 1 10 10	U
							avours experimental Favours control	

Figure 7. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs3825942 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG) in additive models. Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Synthesized homozygous OR (GG versus AA) of SNP rs3825942 was 9.06 for XFS/XFG.

allele was a protective allele (Figure 5). Such discrepancy was also observed in rs1048661, with OR for the G allele being 2.35 (95% CI 2.12–2.60, p<0.00001) in Caucasian, and 0.03 (95% CI 0.01–0.06, p<0.00001) in Japanese populations but not significant in Chinese and Indian populations (Figure 4). Sensitivity tests were subsequently performed. Cohorts whose allele counting data were calculated from the frequencies data, Challa's Duke (US) cohort [13] and Hewitt's Austrian cohort [17], were removed. The OR for the rs3825942 G allele was 9.30 and 12.40 in Caucasians before and after removing the two cohorts, respectively. The OR for the rs1048661 G allele was 2.35 and 2.41 in Caucasians before and after removing the two cohorts, respectively. The OR for the rs2165241 T allele was 3.39 and 3.47 in Caucasians before and after removing the two cohorts, respectively.

Since the associations of rs1048661 and rs2165241 are inconsistently reported between Caucasian and Japanese populations, we performed genotype association analysis using different hereditary models only for rs3825942. When using a multiplicative/additive model, the total OR for the

			-				
Ct t C. t	Cas	e T-1-1	Contr	OI T-t-L		Odds Ratio	Odds Ratio
Study of Subgroup	Events	Total	Events	Total	weight	M-H, HXed, 95% CI	M-H, Fixed, 95% CI
3.2.1 Caucasian					1.00		
Aragon-Martin US+European	23	23	98	116	4.0%	8.83 [0.51, 151.82]	
Fan mostly American	3	4	20	28	1.2%	1.20 [0.11, 13.32]	
Fingert Iowa (US)	2	2	14	16	4.2%	0.86 [0.03, 23.84]	
Lemmela Finnish	б	1	87	101	9.2%	0.97 [0.11, 8.64]	
Mossbock Austrian	2	2	60	61	5.3%	0.12 [0.00, 3.87]	
Pasutto Germany	40	45	78	96	31.7%	1.85 [0.64, 5.34]	
Pasutto Italian	U	U	17	21		Not estimable	
Thorleifsson Iceland	4	4	113	127	4.9%	1.15 [0.06, 22.47]	
Thorleifsson Sweden	2	2	41	44	5.0%	0.42 [0.02, 10.62]	
Wolf Germany	2	2	68	76	4.9%	0.62 [0.03, 14.04]	
Subtotal (95% CI)	2.0	91		686	76.3%	1.66 [0.81, 3.37]	—
Total events	84		596				
Heterogeneity: Chi ² = 5.13, df =	8 (P = 0.)	74); l ² =	0%				
Test for overall effect: Z = 1.39 (P = 0.17						
222 Janangoo							
5.2.2 Japanese			20	20		blat a stimus bla	
Fuse Japanese	0	0	20	30		Notestimable	
Hayashi Japanese	0	0	50	52		NUL estimable	
Mabuchi Japanese	1	1	40	48	4.5%	0.63 [0.02, 16.82]	· · · · · ·
Mori Japanese	1	1	53	55	5.3%	0.14 [0.00, 4.38]	
Function (05% Ch	2	2	53	242	5.0%	0.42 [0.02, 10.16]	
Subtotal (95% CI)		4		242	14.9%	0.38 [0.06, 2.57]	
l otal events	4		222				
Heterogeneity: Chi* = 0.42, df =	2 (P = 0.)	31); 1*=	0%				
Test for overall effect: $Z = 0.99$ (P = 0.32						
3.2.3 Chinese							
Chen Chinese	0	0	22	24		Not estimable	
Lee Singanore Chinese	ĭ	1	28	28		Not estimable	
Subtotal (95% CI)		1		52		Not estimable	
Total events	1		50				
Heterogeneity: Not applicable	÷		00				
Test for overall effect Not appli	cable						
	Cabie						
3.2.4 Indian							
Ramprasad Indian	6	7	40	45	8.8%	0.75 [0.07, 7.57]	
Subtotal (95% CI)		7		45	8.8%	0.75 [0.07, 7.57]	
Total events	6		40				
Heterogeneity: Not applicable							
Test for overall effect Z = 0.24 (P = 0.81)						
Total (95% CI)		103		1025	100.0%	1.39 [0.73, 2.62]	+
Total events	95		908				
Heterogeneity: Chi2 = 7.52, df =	12(P = 0	.82); I²	= 0%				
Test for overall effect: Z = 1.01 (P = 0.31)					F	avours experimental Favours control

Figure 8. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs3825942 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG) in additive models. Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Meta-analysis indicated that the heterozygote genotype (GA) does have higher susceptibility to XFS/XFG compared to AA genotype. C: Synthesized OR of SNP rs3825942 was 7.05 for XFS/XFG with dominant model (GG+GA versus AA).

homozygous at-risk genotype (GG versus AA) was 9.06(95% CI 5.16-15.92, p<0.00001, Figure 7), whereas the total OR for the heterozygous genotype (GA versus AA) was not significantly different from 1 (total OR=1.39, 95% CI 0.73-2.62, p=0.31, Figure 8). On the other hand, the total OR was 7.05 (95% CI 4.03-12.34, p<0.00001, Figure 9) under the dominant model and 14.70 (95% CI 8.97-24.20, p<0.00001, Figure 10) under a recessive model. By subgroup-based meta-analysis, the ORs in different ethnic groups were comparable as the 95% CIs partially overlapped.

There was no single article reporting a significant difference in allele distributions of rs1048661 and rs3825942 between POAG patients and control subjects. Our meta-analysis also identified no significant association between SNP rs1048661 or rs3825942 and POAG in any subgroup or the entire study populations. The overall OR was 0.93 (95% CI 0.84–1.03, p=0.16) for the G allele of rs1048661 (Figure 11) and 1.06 (95% CI 0.94–1.19, p=0.34) for the G allele of rs3825942 (Figure 13). By contrast, two out of the 12 cohorts reported significant association between rs2165241 and POAG in Caucasian and Japanese populations. However, their ORs were in opposite directions, and the

	Cas	e	Contr	ol		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	ed, 95% Cl	
3.3.1 Caucasian									
Aragon-Martin US+European	283	283	314	332	3.5%	33.35 [2.00, 555.99]			
Fan mostly American	205	206	80	88	3.7%	20.50 [2.52, 166.55]			
Fingert Iowa (US)	72	72	73	75	3.4%	4.93 [0.23, 104.52]			
Lemmela Finnish	125	126	311	325	9.5%	5.63 [0.73, 43.25]		· · ·	
Mossbock Austrian	167	167	169	170	3.4%	2.96 [0.12, 73.29]			
Pasutto Germany	509	514	328	346	26.2%	5.59 [2.05, 15.19]			
Pasutto Italian	206	206	66	70	1.6%	27.95 [1.49, 525.90]			
Thorleifsson Iceland	129	129	476	490	5.3%	7.88 [0.47, 133.00]			\rightarrow
Thorleifsson Sweden	196	196	189	192	3.3%	7.26 [0.37, 141.47]	_		
Wolf Germany	127	127	264	272	4.5%	8.19 [0.47, 143.09]	_		\rightarrow
Subtotal (95% CI)		2026		2360	64.4%	8.82 [4.53, 17.15]		-	
Total events	2019		2270						
Heterogeneity: Chi ² = 3.67, df =	9 (P = 0.9	93); l ² =	0%						
Test for overall effect: Z = 6.41	(P < 0.000	001)							
3.3.2 Jananese									
Fuce Jananece	56	56	124	120	4 796	2 70 10 20 71 201			
Havachi Jananece	50	59	197	190	5 1 96	1 59 10 08 33 511			_
Mahuchi Japanese	00	00	102	101	4 696	0 20 10 47 146 271	_		
Manucin Japanese	05	95	100	100	4.5 %	2 52 10 12 52 201			_
Tanita Jananese	142	142	152	157	2.5%	9 26 10 45 156 571	_		,
Subtotal (95% Cl)	142	444	155	865	22 3%	4 64 [1 26 17 12]		-	
Total events	441	441	045	005	22.0 1	4.04[1.20, 17.12]			
Heterogeneity Chi2 - 0.96 df-	441	02)· 12-	040						
Tect for overall effect: 7 = 2.21	(P = 0.02)	52),1 =	0.0						
Testion overall ellect. Z = 2.51	(F = 0.02)								
3.3.3 Chinese									
Chen Chinese	50	50	123	125	4.8%	2.04 [0.10, 43.34]		· · · · · · · · · · · · · · · · · · ·	_
Lee Singapore Chinese	62	62	171	171		Not estimable			
Subtotal (95% CI)		112		296	4.8%	2.04 [0.10, 43.34]			
Total events	112		294						
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.46	(P = 0.65)								
3 3 4 Indian									
Devenues and Indian	54	50	00	07	0.50	2 77 10 22 24 201			_
Subtotal (95% CI)	51	52	92	97	8.5%	2.77 [0.32, 24.38]	-		-
Total events	51		92						
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.92	(P = 0.36)								
Total (95% Cl)		2631		3619	100.0%	7.05 [4.03, 12 34]		•	
Total events	2622	2001	3501	-510	1001014			-	
Heterogeneity Chi2 = 6.51 df=	16 (P = 0	0.00 · IZ	= 0%				H +		
Tact for overall effect: 7 = 6.94	/P < 0.000	1011	- 0.0				0.01 0.1	1 10	100
reactor overall effect. Z = 0.04	(~ 0.000	,01)				F	avours experimental	Favours con	trol

Figure 9. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs3825942 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG) in dominant models. Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Synthesized OR of SNP rs3825942 was 7.05 for XFS/XFG with dominant model (GG+GA versus AA).

overall OR of the 12 studies was 0.95 (95% CI 0.82–1.10, p=0.50) for the T allele of rs2165241 (Figure 12). Sensitivity tests were performed in that the cohorts whose allele counting data were calculated from frequency data, Liu's Caucasian and African cohorts [31] and Chakrabarti's Indian cohort [33], were removed; however, the results were similar. None of the overall ORs were significantly different from 1 without the two cohorts. Since there was no significant allelic association between the three SNPs and POAG, no further meta-analysis (e.g., genotypic association) was performed.

Apart from XFS/XFG and POAG, there was also one study reporting the *LOXL1* SNPs in primary angle closure glaucoma (PACG), two in normal tension glaucoma (NTG), and two in pigment dispersion syndrome and pigmentary glaucoma. However, none of these studies identified a significant association between the *LOXL1* SNPs and these subtypes of glaucoma (Table 3). In our meta-analysis to investigate the association of *LOXL1* SNPs with NTG and PG, no statistical significant association was found (all p>0.05).

DISCUSSION

Exfoliation glaucoma (XFG), a consequence of exfoliation syndrome (XFS), is the most common form of secondary open

	Cas	B	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.4.1 Caucasian							
Aragon-Martin US+European	260	283	216	332	9.8%	6.07 [3.75, 9.83]	
Fan mostly American	202	206	60	88	7.1%	23.57 [7.95, 69.85]	
Fingert Iowa (US)	70	72	59	75	5.4%	9.49 [2.10, 42.98]	
Lemmela Finnish	119	126	224	325	8.4%	7.67 [3.45, 17.02]	
Mossbock Austrian	165	167	109	170	5.7%	46.17 [11.06, 192.75]	
Pasutto Germany	469	514	250	346	10.1%	4.00 [2.72, 5.89]	+
Pasutto Italian	206	206	49	70	2.4%	179.38 [10.68, 3012.38]	
Thorleifsson Iceland	125	129	363	490	7.4%	10.93 [3.96, 30.19]	
Thorleifsson Sweden	194	196	148	192	5.6%	28.84 [6.88, 120.88]	
Wolf Germany	125	127	196	272	5.7%	24.23 [5.85, 100.45]	
Subtotal (95% CI)		2026		2360	67.5%	12.73 [7.03, 23.03]	•
Total events	1935		1674				
Heterogeneity: Tau ² = 0.57; Ch	i ² = 35.75,	df = 9	(P < 0.00	01); l ² =	= 75%		
Test for overall effect: Z = 8.40	(P < 0.000	01)					
3.4.2 Japanese							
Fuse Japanese	56	56	108	138	2.4%	31.76 [1.91, 529.13]	
Hayashi Japanese	59	59	137	189	2.4%	45.44 [2.76, 748.33]	
Mabuchi Japanese	88	89	143	191	3.9%	29.54 [4.01, 217.83]	
Mori Japanese	94	95	135	190	3.9%	38.30 [5.21, 281.60]	
Tanito Japanese	140	142	100	157	5.6%	39.90 [9.52, 167.26]	
Subtotal (95% CI)		441		865	18.3%	36.88 [15.04, 90.45]	-
Total events	437		623				
Heterogeneity: Tau ² = 0.00; Ch	i ² = 0.09, 0	if = 4 (I	P = 1.00);	I ² = 0%	6		
Test for overall effect: Z = 7.88	(P < 0.000	101)					
3.4.3 Chinese							
Chen Chinese	50	50	101	125	2.4%	24.38 [1.45, 409.10]	
Lee Singapore Chinese	61	62	143	171	3.9%	11.94 [1.59, 89.77]	
Subtotal (95% CI)		112		296	6.2%	15.21 [2.95, 78.44]	
Total events	111		244				
Heterogeneity: Tau ² = 0.00; Ch	i ² = 0.17, 0	if = 1 (i	P = 0.68);	$l^2 = 0\%$	6		
Test for overall effect: Z = 3.25	(P = 0.001)					
3.4.4 Indian							
Ramprasad Indian	45	52	52	97	8.0%	5.56 [2.28, 13.56]	
Subtotal (95% CI)		52		97	8.0%	5.56 [2.28, 13.56]	-
Total events	45		52				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.78	(P = 0.000)	12)					
Total (95% CI)		2631		3618	100.0%	14.70 [8.97, 24.10]	-
Total events	2528		2593				
Heterogeneity: Tau ² = 0.59; Ch	i ^z = 52.51,	df = 1	7 (P < 0.0	001); P	*= 68%		0.01 0.1 1 10 100
Test for overall effect: Z = 10.66	5 (P < 0.00	001)				Fa	wours experimental Favours control

Figure 10. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs3825942 with a combined group of exfoliation syndrome (XFS) and exfoliation glaucoma (XFG) in recessive models. Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Synthesized OR of SNP rs3825942 was 14.70 for XFS/XFG with recessive model (GG versus AA+GA).

angle glaucoma. Approximately 25% patients with XFS present with increased IOP, and one-third have developed glaucoma [19]. To date, association of SNPs in the *LOXL1* gene with XFS and/or XFG has been shown across different populations; however, there were several different phenotypes in these studies. Thus, it is necessary to test whether XFS and XFG are of genetic homogeneity. In the first part of this present meta-analysis, the distribution profiles of the *LOXL1* SNPs between XFS and XFG were evaluated. By reviewing all the reported association profiles with meta-analysis, no statistical difference in any population group or overall study subjects was identified for any of the three SNPs (rs1048661, rs2165241, and rs3825942). All the p values were >0.05.

Since *LOXL1* SNPs are not heterogenic in XFS and XFG, we combined these two phenotypes in our analysis. Our results also suggested that the *LOXL1* gene may contribute to disease onset of the exfoliation disease rather than just increased IOP. However, the current meta-analysis cannot prove this hypothesis because the data are from retrospective case-control studies. Further prospective longitudinal studies are warranted.

In most reported studies on *LOXL1* and XFS/XFG, the three SNPs (rs1048661, rs2165241, and rs3825942) have been investigated together [11-23,25-28]. They are in strong LD among different populations. The haplotype defined by

	Case	Contro	l		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tot	al Events	Total	Weight	M-H. Fixed. 95% C	M-H. Fixed. 95% CI
4.1.1 Caucasian						
Fan mostly American	440 60	08 115	160	6.8%	1.02 [0.70, 1.51]	_ _ _
Lemmela Finnish	93 13	444	650	6.3%	1.05 [0.70, 1.57]	
Thorleifsson Iceland	128 18	1305	2048	8.3%	1.40 [1.00, 1.96]	
Thorleifsson Sweden	255 39	8 270	396	13.2%	0.83 [0.62, 1.12]	
Subtotal (95% CI)	132	0	3254	34.7%	1.05 [0.88, 1.24]	•
Total events	916	2134				
Heterogeneity: Chi ² = 5.27	, df = 3 (P = 0	15); I ² = 43%	6			
Test for overall effect: Z =	0.52 (P = 0.61)				
4.1.2 Japanese						
Fuse Japanese	49 12	4 136	276	6.9%	0.67 [0.44, 1.03]	
Mabuchi Japanese	201 42	26 172	382	13.0%	1.09 [0.83, 1.44]	
Tanito Japanese	41 8	30 174	314	4.7%	0.85 [0.52, 1.38]	
Subtotal (95% CI)	63	0	972	24.6%	0.93 [0.75, 1.14]	-
Total events	291	482				
Heterogeneity: Chi ² = 3.59	, df = 2 (P = 0	17); l ² = 44%	5			
Test for overall effect: Z =	0.71 (P = 0.48)				
4.1.3 Chinese						
Gong Northern Chinese	162 33	38 196	394	12.8%	0.93 [0.70, 1.24]	
Gong Southern Chinese	246 58	36 236	500	20.1%	0.81 [0.64, 1.03]	
Subtotal (95% CI)	92	4	894	32.9%	0.86 [0.71, 1.03]	
Total events	408	432				
Heterogeneity: Chi ² = 0.52	, df = 1 (P = 0	47); $I^2 = 0\%$				
Test for overall effect: Z =	1.64 (P = 0.10)				
4.1.4 Indian						
Chakrabarti Indian	138 22	24 145	210	7.8%	0.72 [0.48, 1.07]	-
Subtotal (95% CI)	22	4	210	7.8%	0.72 [0.48, 1.07]	
Total events	138	145				
Heterogeneity: Not applica	ble					
l est for overall effect: Z =	1.62 (P = 0.10)				
Total (95% CI)	300	8	5330	100.0%	0 03 [0 84 4 03]	
Total (95% CI)	305	0400	5530	100.0%	0.93 [0.84, 1.03]	٦
Total events	1/53	3193	0/			
Heterogeneity: Chi* = 13.3	9, $ar = 9 (P = 1)$	J.15); (* = 33	70			0.2 0.5 1 2 5
i est for overall effect: Z =	1.39 (P = 0.16)				Destant Dist.

Figure 11. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs1048661 with primary open angle glaucoma (POAG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Meta-analysis indicated there is no statistical significant association of SNP rs1048661 with POAG.

		Ref	[33]	[27]	[19]	[19]	[34]	[34]	
TABLE 3. CHARACTERS OF REPORTED COHORTS OF OTHER OCULAR DISEASES ASSOCIATION WITH LOXLI SNPS.	942 G	Control	74.8	80.6	84.6	84.6	82.2	82.2	S. nimment
	rs3825	Case	76.6	79.6	85.3	88.1	86.6	83.3	oma DD6
	5241 T	Control	31.9	12.4	49.1	49.1	47.1	47.1	antary alam
	rs216	Case	30.2	13.9	48.9	48.8	52.4	50.0	- niam
	61 G	ontrol	0.69	55.4	66.0	66.0	72.4	72.4	DG .em
	rs10486	Case C	65.6	53.7	65.3	63.1	67.9	66.7	onela e
	Male %)	Control	NA	28.7	41	41	NA	NA	بيتمام فامق
	Sex (Case	NA	33.3	35	72	NA	NA	e memi
	s ±SD)	Control	NA	77.2±5.1	66 ± 13	66 ± 13	NA	NA	DACG- nr
	Age (year:	Case	NA	78.3 ± 4.8	63.9 ± 14.2	53.8 ± 13.5	NA	NA	emoniela no
	ole size	Control	105	157	280	280	108	108	normal tensi
	Samj	Case	96	54	273	88	44	34	NTG.
		Disease	PACG	NTG	NTG	PG	PG	PDS	references
		Cohort	Indian	Japanese	Germany	Germany	American	American	t available Ref
		First author	Chbakrabarti	Tanito	Wolf	Wolf	Rao	Rao	NA: data noi

	Case		Control		Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Random, 95% Cl				
4.2.1 Caucasian											
Fan mostly American	266	646	73	160	10.0%	0.83 [0.59, 1.18]					
Lemmela Finnish	64	140	296	632	9.4%	0.96 [0.66, 1.38]					
Liu Caucasian	237	558	221	454	14.0%	0.78 [0.61, 1.00]					
Thorleifsson Iceland	99	180	13691	28938	12.0%	1.36 [1.01, 1.83]					
Thorleifsson Sweden	196	402	212	396	12.7%	0.83 [0.63, 1.09]					
Subtotal (95% CI)		1926		30580	58.0%	0.93 [0.75, 1.14]	•				
Total events	862		14493								
Heterogeneity: Tau ² = 0.03; Chi ² = 9.45, df = 4 (P = 0.05); l ² = 58%											
Test for overall effect: Z = 0	0.71 (P =	0.47)									
4.2.2 Japanese											
Fuse Japanese	6	124	16	276	2.0%	0.83 [0.32, 2.16]					
Tanito Japanese	3	80	39	314	1.3%	0.27 [0.08, 0.91]					
Subtotal (95% CI)		204		590	3.4%	0.51 [0.17, 1.51]					
Total events	9		55								
Heterogeneity: Tau ² = 0.32	; $Chi^2 = 2$.03, df	= 1 (P =)	0.15); I ²	= 51%						
Test for overall effect: Z = '	1.23 (P =	0.22)									
4 2 3 Chinese											
Gong Northorn Chinoso	20	220	22	204	E 9%	1 02 [0 61 1 72]					
Gong Southorn Chinese	40	500	53	500	0.0%	0.90 (0.62, 1.23)					
Subtotal (95% CI)	45	924	51	894	13 9%	0.88 [0.64 1 22]	•				
Total events	78	024	84	004	10.070	0.00 [0.04, 1.22]	-				
Hotorogonoity: Tau2 = 0.00	- Chi2 - 0	52 df	- 1 /P - 1	171-12	- 0%						
Test for overall effect: 7 = 0	76 (P = 1)	0.45)	- 1 (+ - 1	0.47), 1	- 0 %						
	0.10 (1 -	0.40)									
4.2.4 Indian											
Chakrabarti Indian	72	224	67	210	8.3%	1.01 [0.68, 1.51]	+				
Subtotal (95% CI)		224		210	8.3%	1.01 [0.68, 1.51]	•				
Total events	72		67								
Heterogeneity: Not applical	ble										
Test for overall effect: Z = 0	0.05 (P =	0.96)									
4.2.5 African											
Liu African-American	91	386	40	194	7.9%	1.19 [0.78, 1.81]					
Liu Ghanaian	77	340	53	276	8.6%	1.23 [0.83, 1.82]					
Subtotal (95% CI)		726		470	16.5%	1.21 [0.91, 1.61]	-				
Total events	168		93								
Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 1 (P = 0.90); l ² = 0%											
Test for overall effect: Z = "	1.31 (P =	0.19)									
T-1-1 (05% CI)		4004		20744	400.0%	0.05 10.00 4.401	. .				
Total (95% CI)		4004	4 4700	32/44	100.0%	0.95 [0.82, 1.10]	Ť				
I otal events	1189		14792	0.001	070/						
Heterogeneity: Tau ² = 0.02	$Cn^2 = 1$	1.46, d	r = 11 (P	= 0.09);	r = 37%		0.1 0.2 0.5 1 2 5 10				
lest for overall effect: Z = 0	0.68 (P =	0.50)					Favours experimental Favours control				

Figure 12. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs2165241 with primary open angle glaucoma (POAG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Meta-analysis indicated there is no statistical significant association of SNP rs2165241 with POAG.

dispersion syndrome.

these SNPs was also significantly associated with the disease [11,13,20,26,28]. So far, however, there is no consolidated evidence to show which SNP plays a more major role in the molecular pathogenesis of XFS/XFG. On the other hand, the allelic and genotypic distributions of the three SNPs were found to be drastically different among different populations [11-23,25-28]. Genetic diversity occurs across different ethnicities [35,36]. Therefore, we resolved to find out which SNP plays a role across different populations. In the first part of our meta-analysis, we identified genetic homogeneity of the LOXL1 SNPs between XFS and XFG. Therefore, the two disease groups were combined in the second part of the metaanalysis of genetic association in subpopulations. We found that the distribution was similar within each individual ethnic group for all three SNPs, rs1048661, rs2165241, and rs3825942. However, the allelic distributions of Japanese and Caucasian populations are reversed for rs1048661 and rs2165241. The T allele of rs2165241 and the G allele of rs1048661 are the at-risk alleles in Caucasians, with an OR of 3.39 and 2.35, respectively. In contrast, the two alleles are protective in the Japanese population, with an OR of 0.13 and 0.03, respectively. All the ORs are statistically significant with p values < 0.00001. Therefore, it is more likely that SNPs rs1048661 and rs2165241 are not directly implicated in the pathogenesis of XFS/XFG. In contrast, the distribution of SNP rs3825942 followed a similar pattern in all three ethnic groups. The G allele was the at-risk allele, and the OR was 9.30, 18.72, 10.97, and 4.17 in Caucasian, Japanese, Chinese and Indian populations, respectively. The total OR was 10.75 (95% CI 7.08–16.31). Our finding suggests that rs3825942 is the common disease-associated polymorphism across different populations and may have functional impacts on the LOXL1 protein and contribute to the pathogenesis of XFS/ XFG. Moreover, in the third part of this meta-analysis, we found that the OR for the homozygous genotype of rs3825942 is 9.42, while the OR for the heterozygote is not statistically significant. Moreover, the OR in the recessive model was the highest among different genetic models (OR=14.55). Therefore, it could be inferred that rs3825942 plays a role in a recessive pattern; however, what functional role rs3825942 played in the pathogenesis of XFS/XFG remains unclear. LOXL1 is located in 15q22, encoding a member of the lysyl oxidase family. The LOXL family is an extracellular copper-dependent amine oxidase that involved in the first step of the formation of cross-links in collagen and elastin. Therefore, sequence variation in LOXL1 may influence the function, synthesis, and subsequent deposition of the extracellular tissues [37]. SNP rs3825942 is located in the first exon of LOXL1 and leads to a nonsynonymous amino acid change from glycine to asparagine at position 153 (G153D). However, functional prediction using in silico programs Polymorphism Phenotyping (PolyPhen) and Sorting Intolerant From Tolerant (SIFT) suggested that the amino acid substitution is benign and tolerated (data not

shown). The exact functional effects of this substitution remain to be further investigated.

The association of *LOXL1* SNPs with other types of glaucoma, including POAG, NTG, pigmentary glaucoma, and PACG, were reviewed in this meta-analysis. However, no significant association was found between POAG and *LXOL1* SNPs after merging the results from 13 cohorts. Therefore, it is likely that *LOXL1* is not implicated in the primary open angle glaucomatous mechanism. Associations between *LXOL1* SNPs and NTG, pigmentary glaucoma, or PACG were also negative, although the number of articles included in this meta-analysis was limited. The lack of association between *LOXL1* and primary glaucoma has provided evidence supporting that *LOXL1* is linked to the pathogenesis of the exfoliation syndrome but not the direct genetic cause of IOP elevation and subsequent glaucoma.

In summary, by using meta-analysis the genetic homogeneity of *LOXL1* between XFS and XFG has been confirmed. The genetic effect of rs3825942 is similar in different populations in a recessive genetic model. We detected inconsistencies in the effect of rs1048661 and rs2165241 between Caucasian and Japanese populations. Our results also revealed that the *LOXL1* gene is not a

						0.11- 0-11-	0.14- 8-4-			
	Case		Contr	ol		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	lotal	weight	M-H, Fixed, 95% C	I M-H. Fixed, 95% CI			
4.3.1 Caucasian	504	050		470	0.00/	0.00.00.07. 4.000				
Fan mostly American	501	650	140	1/6	9.0%	0.86 [0.57, 1.30]				
Lemmela Finnish	107	136	535	650	7.0%	0.79 [0.50, 1.25]				
Liu Caucasian	463	558	383	454	12.8%	0.90 [0.65, 1.26]				
I norieitsson iceland	154	1/6	839	980	5.7%	1.18 [0.73, 1.90]				
Subtetel (05% CI)	342	390	337	364	8.3%	0.88 [0.58, 1.34]	-			
Subtotal (95% CI)	4507	1910		2044	42.170	0.91 [0.76, 1.09]				
Total events	1567	- 0.00	2234							
Heterogeneity: Cni ² = 1.52,	df = 4 (P)	= 0.82); 1* = 0%							
Test for overall effect: $Z = 1$	1.02 (P =)	0.31)								
432 Jananese										
	112	124	242	276	2 49/	1 44 10 71 2 061				
Mahushi Japanese	262	426	242	200	0.0%	0.07 [0.66 1.43]				
Tapita language	302	420	320	244	3.270	0.97 [0.00, 1.43]				
Subtotal (95% CI)	04	620	255	072	3.7 70	1 04 [0.52, 1.76]	-			
Tatal augusts	500	030	004	512	13.270	1.04 [0.76, 1.40]	T			
Heteregeneity Chi2 = 0.09	539	- 0.64	821							
Heterogeneity: Chi* = 0.98,	df = 2 (P)	= 0.61); 1* = 0%							
Test for overall effect: $Z = 0$	J.20 (P =)	0.76)								
433 Chinese										
Gong Northorn Chinasa	204	220	244	204	E 60/	1 20 10 99 2 201				
Cong Southern Chinese	504	530	420	504	0.0%	1.39 [0.00, 2.20]				
Subtotal (95% CI)	524	924	400	894	14 5%	1 27 [0 95 1 70]	-			
Total quanta	000	524	770	004	14.070	1.27 [0.00, 1.70]	-			
Hotorogonoity Chi2 = 0.25	020	- 0.62	119							
Toot for overall effect: 7 = 1	1 62 (P - 1	- 0.02), 1 0 %							
Test for overall effect: Z =	1.03 (P =)	0.10)								
4.3.4 Indian										
Chakrabarti Indian	184	224	157	210	5 1%	1 55 10 08 2 471				
Subtotal (95% CI)	101	224	101	210	5.1%	1.55 [0.98, 2.47]				
Total events	184		157							
Heterogeneity: Not applical	hle		107							
Test for overall effect: 7 = 1	1 87 (P =)	(60.0								
		0.00)								
4.3.5 African										
Liu African-American	238	386	116	184	10.7%	0.94 [0.66, 1.36]				
Liu Ghanaian	211	340	157	276	11.7%	1.24 [0.90, 1.71]	+			
Subtotal (95% CI)		726		460	22.4%	1.10 [0.86, 1.40]	*			
Total events	449		273							
Heterogeneity: $Chi^2 = 1.22 df = 1 (P = 0.27)$; $l^2 = 18\%$										
Test for overall effect: Z = 0	0.76 (P =	0.45)								
Total (95% CI)		4420		5180	100.0%	1.06 [0.94, 1.19]	+			
Total events	3567		4264							
Heterogeneity: Chi ² = 10.94, df = 12 (P = 0.53); l ² = 0%										
Test for overall effect: Z = 0.95 (P = 0.34) U.2 U.5 1 2 5										
Test for subgroup differences: Not applicable Favours experimental Favours control										

Figure 13. Meta-analysis of the association of single nucleotide polymorphism (SNP) rs3825942 with primary open angle glaucoma (POAG). Squares indicate study-specific odds ratio (OR); the size of the box is proportional to the weight of the study; horizontal lines indicate 95% confidence interval (CI); diamond indicates summary OR with its corresponding 95% CI. Meta-analysis indicated there is no statistical significant association of SNP rs3825942 with POAG.

© 2010 Molecular Vision

susceptibility gene of other types of glaucoma other than XFG. Further genetic studies are required to unravel the discrepancy in LD patterns of the *LOXL1* gene among different populations.

ACKNOWLEDGMENTS

We thank the grant support to Haoyu Chen: National Natural Science Foundation of China (30901646), Science and Technology Project of Shantou City (2009–70). Portions of the data in this manuscript were presented at the 24th Asia Pacific Academy of Ophthalmology Association Congress (2009) in a poster presentation and at the 14th Congress of the Chinese Ophthalmological Society (2009) in a poster presentation.

REFERENCES

- Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary openangle glaucoma. N Engl J Med 2009; 360:1113-24. [PMID: 19279343]
- Ritch R. Exfoliation syndrome: beyond glaucoma. Arch Ophthalmol 2008; 126:859-61. [PMID: 18541854]
- Young AL, Tang WW, Lam DS. The prevalence of pseudoexfoliation syndrome in Chinese people. Br J Ophthalmol 2004; 88:193-5. [PMID: 14736771]
- Foster PJ, Seah SK. The prevalence of pseudoexfoliation syndrome in Chinese people: the Tanjong Pagar Survey. Br J Ophthalmol 2005; 89:239-40. [PMID: 15665360]
- Miyazaki M, Kubota T, Kubo M, Kiyohara Y, Iida M, Nose Y, Ishibashi T. The prevalence of pseudoexfoliation syndrome in a Japanese population: the Hisayama study. J Glaucoma 2005; 14:482-4. [PMID: 16276281]
- Ringvold A. Epidemiology of the pseudo-exfoliation syndrome. Acta Ophthalmol Scand 1999; 77:371-5. [PMID: 10463402]
- Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, Nishimura D, Clark AF, Nystuen A, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, Sheffield VC. Identification of a gene that causes primary open angle glaucoma. Science 1997; 275:668-70. [PMID: 9005853]
- Sheffield VC, Stone EM, Alward WL, Drack AV, Johnson AT, Streb LM, Nichols BE. Genetic linkage of familial open angle glaucoma to chromosome 1q21-q31. Nat Genet 1993; 4:47-50. [PMID: 8513321]
- Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, Heon E, Krupin T, Ritch R, Kreutzer D, Crick RP, Sarfarazi M. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science 2002; 295:1077-9. [PMID: 11834836]
- Kramer PL, Samples JR, Monemi S, Sykes R, Sarfarazi M, Wirtz MK. The role of the WDR36 gene on chromosome 5q22.1 in a large family with primary open-angle glaucoma mapped to this region. Arch Ophthalmol 2006; 124:1328-31. [PMID: 16966629]
- Thorleifsson G, Magnusson KP, Sulem P, Walters GB, Gudbjartsson DF, Stefansson H, Jonsson T, Jonasdottir A, Stefansdottir G, Masson G, Hardarson GA, Petursson H, Arnarsson A, Motallebipour M, Wallerman O, Wadelius C, Gulcher JR, Thorsteinsdottir U, Kong A, Jonasson F, Stefansson K. Common sequence variants in the LOXL1 gene

confer susceptibility to exfoliation glaucoma. Science 2007; 317:1397-400. [PMID: 17690259]

- Aragon-Martin JA, Ritch R, Liebmann J, O'Brien C, Blaaow K, Mercieca F, Spiteri A, Cobb CJ, Damji KF, Tarkkanen A, Rezaie T, Child AH, Sarfarazi M. Evaluation of LOXL1 gene polymorphisms in exfoliation syndrome and exfoliation glaucoma. Mol Vis 2008; 14:533-41. [PMID: 18385788]
- Challa P, Schmidt S, Liu Y, Qin X, Vann RR, Gonzalez P, Allingham RR, Hauser MA. Analysis of LOXL1 polymorphisms in a United States population with pseudoexfoliation glaucoma. Mol Vis 2008; 14:146-9. [PMID: 18334928]
- 14. Fan BJ, Pasquale L, Grosskreutz CL, Rhee D, Chen T, DeAngelis MM, Kim I, del Bono E, Miller JW, Li T, Haines JL, Wiggs JL. DNA sequence variants in the LOXL1 gene are associated with pseudoexfoliation glaucoma in a U.S. clinicbased population with broad ethnic diversity. BMC Med Genet 2008; 9:5. [PMID: 18254956]
- Fingert JH, Alward WL, Kwon YH, Wang K, Streb LM, Sheffield VC, Stone EM. LOXL1 mutations are associated with exfoliation syndrome in patients from the midwestern United States. Am J Ophthalmol 2007; 144:974-5. [PMID: 18036875]
- 16. Yang X, Zabriskie NA, Hau VS, Chen H, Tong Z, Gibbs D, Farhi P, Katz BJ, Luo L, Pearson E, Goldsmith J, Ma X, Kaminoh Y, Chen Y, Yu B, Zeng J, Zhang K, Yang Z. Genetic association of LOXL1 gene variants and exfoliation glaucoma in a Utah cohort. Cell Cycle 2008; 7:521-4. [PMID: 18287813]
- Hewitt AW, Sharma S, Burdon KP, Wang JJ, Baird PN, Dimasi DP, Mackey DA, Mitchell P, Craig JE. Ancestral LOXL1 variants are associated with pseudoexfoliation in Caucasian Australians but with markedly lower penetrance than in Nordic people. Hum Mol Genet 2008; 17:710-6. [PMID: 18037624]
- Mossbock G, Renner W, Faschinger C, Schmut O, Wedrich A, Weger M. Lysyl oxidase-like protein 1 (LOXL1) gene polymorphisms and exfoliation glaucoma in a Central European population. Mol Vis 2008; 14:857-61. [PMID: 18483563]
- Wolf C, Gramer E, Muller-Myhsok B, Pasutto F, Gramer G, Wissinger B, Weisschuh N. Lysyl Oxidase-like 1 gene polymorphisms in German patients with normal tension glaucoma, pigmentary glaucoma and exfoliation glaucoma. J Glaucoma 2009. [PubMed: 19373106]
- Pasutto F, Krumbiegel M, Mardin CY, Paoli D, Lammer R, Weber BH, Kruse FE, Schlotzer-Schrehardt U, Reis A. Association of LOXL1 common sequence variants in German and Italian patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Invest Ophthalmol Vis Sci 2008; 49:1459-63. [PMID: 18385063]
- Lemmela S, Forsman E, Onkamo P, Nurmi H, Laivuori H, Kivela T, Puska P, Heger M, Eriksson A, Forsius H, Jarvela I. Association of LOXL1 gene with Finnish exfoliation syndrome patients. J Hum Genet 2009; 54:289-97. [PMID: 19343041]
- Fuse N, Miyazawa A, Nakazawa T, Mengkegale M, Otomo T, Nishida K. Evaluation of LOXL1 polymorphisms in eyes with exfoliation glaucoma in Japanese. Mol Vis 2008; 14:1338-43. [PMID: 18648524]

- Hayashi H, Gotoh N, Ueda Y, Nakanishi H, Yoshimura N. Lysyl oxidase-like 1 polymorphisms and exfoliation syndrome in the Japanese population. Am J Ophthalmol 2008; 145:582-5. [PMID: 18201684]
- Mabuchi F, Sakurada Y, Kashiwagi K, Yamagata Z, Iijima H, Tsukahara S. Lysyl oxidase-like 1 gene polymorphisms in Japanese patients with primary open angle glaucoma and exfoliation syndrome. Mol Vis 2008; 14:1303-8. [PMID: 18636115]
- Mori K, Imai K, Matsuda A, Ikeda Y, Naruse S, Hitora-Takeshita H, Nakano M, Taniguchi T, Omi N, Tashiro K, Kinoshita S. LOXL1 genetic polymorphisms are associated with exfoliation glaucoma in the Japanese population. Mol Vis 2008; 14:1037-40. [PMID: 18552979]
- Ozaki M, Lee KY, Vithana EN, Yong VH, Thalamuthu A, Mizoguchi T, Venkatraman A, Aung T. Association of LOXL1 gene polymorphisms with pseudoexfoliation in the Japanese. Invest Ophthalmol Vis Sci 2008; 49:3976-80. [PMID: 18450598]
- Tanito M, Minami M, Akahori M, Kaidzu S, Takai Y, Ohira A, Iwata T. LOXL1 variants in elderly Japanese patients with exfoliation syndrome/glaucoma, primary open-angle glaucoma, normal tension glaucoma, and cataract. Mol Vis 2008; 14:1898-905. [PMID: 18958304]
- Ramprasad VL, George R, Soumittra N, Sharmila F, Vijaya L, Kumaramanickavel G. Association of non-synonymous single nucleotide polymorphisms in the LOXL1 gene with pseudoexfoliation syndrome in India. Mol Vis 2008; 14:318-22. [PMID: 18334947]
- 29. Lee KY, Ho SL, Thalamuthu A, Venkatraman A, Venkataraman D, Pek DC, Aung T, Vithana EN. Association of LOXL1 polymorphisms with pseudoexfoliation in the Chinese. Mol Vis 2009; 15:1120-6. [PMID: 19503743]
- Chen L, Jia L, Wang N, Tang G, Zhang C, Fan S, Liu W, Meng H, Zeng W, Liu N, Wang H, Jia H. Evaluation of LOXL1 polymorphisms in exfoliation syndrome in a Chinese population. Mol Vis 2009; 15:2349-57. [PMID: 19936304]

- Liu Y, Schmidt S, Qin X, Gibson J, Hutchins K, Santiago-Turla C, Wiggs JL, Budenz DL, Akafo S, Challa P, Herndon LW, Hauser MA, Allingham RR. Lack of association between LOXL1 variants and primary open-angle glaucoma in three different populations. Invest Ophthalmol Vis Sci 2008; 49:3465-8. [PMID: 18421074]
- 32. Gong WF, Chiang SW, Chen LJ, Tam PO, Jia LY, Leung DY, Geng YQ, Tham CC, Lam DS, Ritch R, Wang N, Pang CP. Evaluation of LOXL1 polymorphisms in primary open-angle glaucoma in southern and northern Chinese. Mol Vis 2008; 14:2381-9. [PMID: 19098994]
- Chakrabarti S, Rao KN, Kaur I, Parikh RS, Mandal AK, Chandrasekhar G, Thomas R. The LOXL1 gene variations are not associated with primary open-angle and primary angleclosure glaucomas. Invest Ophthalmol Vis Sci 2008; 49:2343-7. [PMID: 18223248]
- Rao KN, Ritch R, Dorairaj SK, Kaur I, Liebmann JM, Thomas R, Chakrabarti S. Exfoliation syndrome and exfoliation glaucoma-associated LOXL1 variations are not involved in pigment dispersion syndrome and pigmentary glaucoma. Mol Vis 2008; 14:1254-62. [PMID: 18618003]
- 35. Jakobsson M, Scholz SW, Scheet P, Gibbs JR, VanLiere JM, Fung HC, Szpiech ZA, Degnan JH, Wang K, Guerreiro R, Bras JM, Schymick JC, Hernandez DG, Traynor BJ, Simon-Sanchez J, Matarin M, Britton A, van de Leemput J, Rafferty I, Bucan M, Cann HM, Hardy JA, Rosenberg NA, Singleton AB. Genotype, haplotype and copy-number variation in worldwide human populations. Nature 2008; 451:998-1003. [PMID: 18288195]
- Li JZ, Absher DM, Tang H, Southwick AM, Casto AM, Ramachandran S, Cann HM, Barsh GS, Feldman M, Cavalli-Sforza LL, Myers RM. Worldwide human relationships inferred from genome-wide patterns of variation. Science 2008; 319:1100-4. [PMID: 18292342]
- Csiszar K. Lysyl oxidases: a novel multifunctional amine oxidase family. Prog Nucleic Acid Res Mol Biol 2001; 70:1-32. [PMID: 11642359]

The print version of this article was created on 4 February 2010. 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.