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RESEARCH ARTICLE

LOXL1 gene polymorphisms are associated with exfoliation syndrome/exfoliation glaucoma risk: An updated meta-analysis

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Abstract

Background

Single nucleotide polymorphisms (SNPs) in the gene encoding LOXL1 are risk factors for exfoliation syndrome and exfoliation glaucoma. This meta-analysis comprehensively investigated the association between *LOXL1* gene polymorphisms (rs1048661, rs3825942, and rs2165241) and the risk of exfoliation syndrome/exfoliation glaucoma (XFS)/(XFG).

Methods

All eligible case-control studies, published before August 17, 2020, were searched on Medline (Ovid), PubMed, CNKI, EMBASE, and Wanfang databases.

Results

In total, 5022 cases and 8962 controls were included in this meta-analysis. Significant associations between *LOXL1* gene polymorphisms and XFS/XFG risk was observed in the disease types-based subgroups. In addition, in the subgroup analysis of ethnicity, positive associations between *LOXL1* gene polymorphisms (rs1048661, rs3825942, and rs2165241) and XFS/XFG risk were found in Caucasians. Furthermore, rs1048661 and rs3825942 polymorphisms were related to XFS/ XFG risk in Asians; however, no significant association was observed between the *LOXL1* gene rs2165241 polymorphism and XFS/ XFG risk in Asians. In addition, rs1048661 and rs3825942 correlated with XFS/XFG susceptibility in Africans.

Conclusions

Our results implicate *LOXL1* gene polymorphisms as XFS/XFG risk factors, especially in Caucasians.

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Introduction

Exfoliation syndrome (XFS) is an age-related, generalized disorder of the extracellular matrix characterized by progressive accumulation of abnormal fibrillar material in intra- and extraocular tissues $[\underline{1}, \underline{2}]$. It is estimated to affect around 80 million people worldwide, and 10–20% of people aged >60 years are severely affected by XFS $[\underline{3}, \underline{4}]$. This disorder is also associated with a progressive form of chronic open-angle glaucoma $[\underline{2}]$ and is the second most common cause of irreversible blindness globally.

Exfoliation glaucoma (XFG) is the most common form of secondary open-angle glaucoma and occurs in the context of XFS [4, 5]. Approximately 44% of XFS cases are estimated to progress to XFG [6]. XFG is characterized by deposition of exfoliation material in the anterior segment of the eyes, obstructing aqueous humor outflow, resulting in elevated intraocular pressure and secondary open-angle glaucoma [7]. Relative to primary open-angle glaucoma, XFS-associated secondary open-angle glaucoma is associated with a more severe prognosis, higher elevated intraocular pressure, and more severe optic nerve lesions at the time of diagnosis [8]. However, the mechanism of exfoliation material production is unclear.

XFS/XFG is a multifactorial disease involving a complex interaction between numerous risk factors, including genetic and environmental factors, myopia, cigarette smoking, and diabetes [9]. XFS/XFG prevalence varies widely across populations and geographical regions, ranging from <0.4% to >20% [10]. Thus, recent studies have increasingly focused on the relationship between gene polymorphisms and XFS/XFG susceptibility.

The lysyl oxidase-like 1 (LOXL1) gene has been extensively studied [11-14]. The LOXL family comprises five genes (LOXL, LOXL1, LOXL2, LOXL3 and LOXL4), which encode enzymes involved in fibrillin, elastin, and collagen cross-linking reactions (2). LOXL1, which catalyzes the oxidative deamination of tropoelastin lysine residues, is essential for elastogenesis [15]. A 2007 genome-wide association study of a Scandinavian population, found a significant association between XFS/XFG and the LOXL1 single nucleotide polymorphisms, rs1048661, rs3825942, and rs2165241, located on chromosome 15g24.1 [16]. Since then, numerous studies have affirmed that the LOX1 polymorphisms are associated with XFS/XFG in various populations, including Caucasians, Latin Americans, Africans and Asians. Dubey et al. [17] reported that LOXL1 G (rs1048661), G (rs3825942) and T (rs2165241) alleles are XFS/XFG risk factors in Asians, which were similar to the results found in the original study conducted by Thorleifsson et al (2007) in Caucasians (Scandinavian population), as well as in most studies carried out in Caucasians [13, 16]. However, in most studies in Asians, the alleles T and C of rs1048661 and rs2165241, respectively, are the risk alleles. Tanito et al. [18], Ozaki et al. [19], Fuse et al. [20] and Hayashi et al. [21] reported that the alleles T of rs1048661 as well as the alleles C of rs2165241 are associated with increased risk of XFS/XFG in the Japanese population. Park DY et al. [22] and Sagong et al. [11] also found a similar phenomenon in Koreans. Similar observations were made by Chen et al. in Chinese [23]. Moreover, De Juan-Marcos et al. [24] showed that the G allele of rs3825942 and the T allele of rs2165241 were XFS/XFG risk factors in a Spanish population. However, in contrast to what was observed in most Caucasian populations, no significant association between XFS/XFG and SNP rs1048661 was observed. In addition, Rautenbach et al. [25] and Williams et al. [26] indicated that the G allele of rs3825942 was protective in Black South Africans, and the G allele of rs1048661 was a risk allele for XFS/XFG. Therefore, the associations of LOXL1 gene polymorphisms (rs1048661, rs2165241, rs3825942) may differ across patients of different ethnicities.

Despite the existence of discrepancies between some studies related to the risk alleles of *LOXL1* SNPs, it is widely accepted that *LOXL1* gene is the most important genetic risk factor known so far for XFS/XFG. Additionally, a single study may be insufficient to explore the

small effect of *LOXL1* gene polymorphisms on XFS/XFG susceptibility, especially when the sample size is small. Given the associations between *LOXL1* gene polymorphisms and XFS/ XFG pathogenesis, we carried out an updated meta-analysis on the correlation between *LOXL1* gene polymorphisms (rs1048661, rs2165241, rs3825942) and XFS/XFG risk. To our knowledge, this is the most comprehensive and accurate meta-analysis of *LOXL1* gene polymorphisms in the context of XFS/XFG susceptibility.

Materials and methods

Search strategy and criteria

Medline (Ovid), PubMed, CNKI, EMBASE, and Wanfang database searches for articles published before August 17, 2020, were performed using the following terms: "Lysyl oxidase-like 1", "*LOXL1*", "Exfoliation syndrome", "XFS", "Exfoliation glaucoma", "XFG", and "Polymorphism". Articles were included if: 1) they examined the relationship between XFS/XFG susceptibility and *LOXL1* variations, 2) they were case-control studies, and 3) they had complete genotype frequency data. Articles were excluded if: 1) they lacked a control group, 2) the presented data was incomplete, 3) they were duplicate publications, and 4) controls failed to meet Hardy Weinberg Equilibrium (HWE) standards.

Quality score evaluation

The quality of the included studies was determined using the Newcastle-Ottawa Scale [27] which assesses quality based on selection, comparability, and exposure in the study. Quality scores ranged from 0 to 9. Studies scoring >6 were considered high quality. Furthermore, study quality was determined by consensus between authors.

Data extraction

Two independent investigators extracted tangible data from each study based on the inclusion criteria. In the case of divergent views, a third author examined the controversial articles. For each study, the first author, country, publication year, ethnicities, sample size, genotyping method, and genotype frequency in the case and control groups, were extracted.

Statistical analyses

All analyses were conducted using STATA 10.0 and RevMan 5.2. The Odds ratio (OR) and 95% confidence interval (CI) were used to estimate the association between the *LOXL1* gene polymorphisms and XFS/XFG susceptibility. Heterogeneity among studies was evaluated using the χ^2 -based Q statistic and a *p* value ≤ 0.1 was considered statistically significant. When the *p* value was >0.1, the pooled OR of each study was calculated using a fixed-effects model. Otherwise, a random-effects model was used. The significance of the pooled OR was demonstrated using the Z-test and a *p* value ≤ 0.05 was considered statistically significant. The association between *LOXL1* gene polymorphisms and XFS/XFG risk was evaluated in different genetic models. To assess the effects of ethnicity and disease type, we performed additional subgroup analyses based on ethnicity and disease type. Sensitivity analysis was carried out to assess the stability of the results. Hardy Weinberg equilibrium was evaluated using Pearson's χ^2 test, and $p \geq 0.05$ was considered statistically significant.

Publication bias

Publication bias was determined using asymmetry Begger's plots and Egger's tests [28, 29] and was carried out using STATA 10.0.

Results

Study characteristics

Our initial literature search returned 197 articles. Upon browsing the titles and abstracts, 111 articles were excluded, leaving 86 articles that underwent full-text review. Of the 86 articles, 41 articles were excluded because 32 articles involved other *LOXL1* gene polymorphisms (rs4461027, rs4886761, and rsl6958477), and six articles were excluded because they were not case-control studies, and three articles were excluded for meta-analyses. Then the remaining 45 full-text articles were assessed for eligibility, although five articles [10, 30–33] had been analyzed in a previous meta-analysis [34], we excluded them because three articles [10, 30, 31] did not achieve HWE in the control group, and two articles [32, 33] reported the relationship between *LOXL1* polymorphisms and primary open-angle glaucoma. This process yielded 40 case-control articles [9, 11–14, 16–26, 35–58] that were eligible for our study (Table 1). Of these, 38 articles [9, 11–14, 16–26, 35–56] studied rs1048661, 22 articles [11, 17–20, 22–24, 35, 38–42, 45–47, 49, 52, 55–57] involved rs2165241, and 38 articles [9, 11–14, 16–26, 35–37, 39–55, 57, 58] involved rs3825942 (Fig 1).

Quantitative synthesis of data

rs1048661 LOXL1 gene polymorphism. Thirty-eight articles that examined the relationship between the LOXL1 gene polymorphism, rs1048661, and XFS/XFG risk were included in this meta-analysis. Some studies recruited XFS and XFG patients as research subjects, but these subjects did not distinguish XFS patients from XFG patients when DNA samples were sequenced. Thus, in the subgroup analysis based on the type of disease, we only extracted data from studies in which disease types (XFS or XFG) are clearly illustrated. In the subgroup analysis based on ethnicity, we combined all types of studies (XFS, XFG, XFS/XFG) to conduct the meta-analysis. Because the reason that analysis of SNPs by ethnicity is more comprehensive, we choose its merger result as the overall result. Although negative associations were found in the total sample (G vs. T, OR:1.13,95%CI: 0.85–1.52, p:0.40), allelic contrast analysis revealed positive associations in the XFS (G vs. T, OR: 1.50,95%CI: 1.16–1.93, p<0.001) and XFG (G vs. T, OR: 1.97,95%CI: 1.45–2.66, *p*<0.001) subgroups. (Fig 2, Table 2). The rs1048661 G allele was significantly correlated with higher XFG and XFS risk relative to the T allele. In the subgroup analysis of ethnicity, the meta-analysis indicated a significant association between the LOXL1 polymorphism (rs1048661) and XFS/XFG risk in Africans (G vs. T, OR: 23.42, 95%CI: 4.48–122.47, p < 0.001) (Fig 3, Table 2). Notably, allelic contrast analysis showed that XFS/ XFG susceptibility markedly increased in Caucasians (G vs. T, OR:1.99, 95%CI: 1.70–2.33, p <0.001) and significantly decreased in Asians (G vs. T, OR: 0.52, 95%CI: 0.29–0.94, p:0.03) (Fig 3, Table 2). In Asians, the association between rs1048661 alleles and risk was opposite to that in Caucasians and Africans. A summary of the results from other comparative genetic models is shown in Table 2.

rs2165241 *LOXL1* gene polymorphism. Twenty-two case-control articles on the relationship between the *LOXL1* gene polymorphism, rs2165241, and XFS/XFG risk were included in the meta-analysis. Overall analyses revealed a significant association between XFS/XFG susceptibility and the rs2165241 (T vs. C, OR: 1.61, 95%CI: 1.18–2.19, p:0.002) polymorphism (<u>Table 2</u>). The results revealed that genetic polymorphism of *LOXL1*(rs2165241) was associated with susceptibility to XFS (T vs. C, OR: 2.14, 95%CI: 1.33–3.45, p:0.002) and XFG (T vs. C, OR: 2.00, 95%CI: 1.21–3.31, p:0.007) (Fig 4, Table 2), in the allelic contrast.

Subgroup analysis by ethnicity identified an increased risk in Caucasians (T vs. C, OR: 2.76, 95%CI: 1.99–3.84, p < 0.001) (Fig 5, Table 2). However, there was no significant association

First author	Year	Origin	Ethnicity	Туре	Case	Control		Case		C	ontro	1	NOS	Hardy-Weinberg equilibrium
Ref No rs1048661							GG	GT	ТТ	GG	GT	ТТ		
Lan [35]	2020	China	Asian	XFG	91	180	57	32	2	49	90	41	7	YES
Taghavi [36]	2019	Iran	Asian	XFS	60	40	48	12	0	24	16	0	7	YES
Pandav [37]	2018	India	Asian	XFG	30	61	17	10	3	41	16	4	6	YES
Pandav [37]	2018	India	Asian	XFS	27	61	15	10	2	41	16	4	6	YES
Shihadeh [38]	2018	Jordan	Asian	XFS/XFG	61	59	46	15	0	44	14	1	6	YES
Yaz [<u>39</u>]	2018	Turkey	Caucasian	XFG	58	171	46	12	0	87	64	20	6	YES
Yaz [39]	2018	Turkey	Caucasian	XFS	58	171	32	26	0	87	64	20	6	YES
Asfuroglu [40]	2017	Turkey	Caucasian	XFS	44	47	17	27	0	25	21	1	7	YES
Asfuroglu[40]	2017	Turkey	Caucasian	XFG	65	47	14	50	1	25	21	1	7	YES
De Juan-Marcos [24]	2016	Spain	Caucasian	XFS	60	90	33	25	2	47	35	8	6	YES
De Juan-Marcos [24]	2016	Spain	Caucasian	XFG	40	90	24	16	0	47	35	8	6	YES
Gayathri [13]	2016	Germany and Italy	Caucasian	XFS	48	40	26	20	2	15	20	5	8	YES
Alvarez [41]	2015	Spain	Caucasian	XFG	105	200	75	27	3	80	94	26	6	YES
Qiu [<u>42</u>]	2015	China	Asian	XFS	152	228	106	42	4	109	98	21	7	YES
Dubey [17]	2014	Indian	Asian	XFS	150	225	93	46	11	108	91	26	7	YES
Dubey [17]	2014	Indian	Asian	XFG	150	225	102	40	8	108	91	26	7	YES
Anastasopoulos [43]	2014	Greece	Caucasian	XFS	40	93	24	15	1	51	39	3	7	YES
Anastasopoulos [43]	2014	Greece	Caucasian	XFG	34	93	24	10	0	51	39	3	7	YES
Chiras [14]	2013	Greece	Caucasian	XFS	54	93	33	19	2	49	39	5	6	YES
Chiras [14]	2013	Greece	Caucasian	XFG	70	93	56	13	1	49	39	5	6	YES
Kasim [9]	2013	Turkey	Caucasian	XFS	100	100	77	22	1	52	38	10	6	YES
Kasim [9]	2013	Turkey	Caucasian	XFG	100	100	74	26	0	52	38	10	6	YES
Park [<u>22]</u>	2013	Korea	Asian	XFS/XFG	110	127	1	4	105	13	49	65	7	YES
Michael [44]	2012	Pakistan	Asian	XFG	128	180	91	36	1	78	81	21	6	YES
Rautenbach [25]	2011	South African	African	XFS	43	47	43	0	0	37	9	1	7	YES
Mayinu [<u>45]</u>	2011	China	Asian	XFS/XFG	64	127	42	20	2	60	56	11	7	YES
Malukiewicz [46]	2011	Poland	Caucasian	XFS	36	30	29	7	0	20	8	2	6	YES
Sagong [11]	2011	Korea	Asian	XFS	28	146	0	4	24	22	60	64	6	YES
Sagong [<u>11</u>]	2011	Korea	Asian	XFG	61	146	4	1	56	22	60	64	6	YES
Williams [26]	2010	South African	African	XFG	50	50	49	1	0	33	15	2	7	YES
Wolf [<u>47</u>]	2010	German	Caucasian	XFG	128	266	89	38	1	110	131	25	8	YES
Abu-Amero [<u>48</u>]	2010	Saudi Arabia	Asian	XFG	93	101	72	19	2	57	40	4	6	YES
Chen [<u>23</u>]	2009	China	Asian	XFS/XFG	50	125	4	3	43	23	75	27	5	YES
Lemmela [<u>49</u>]	2009	Finland	Caucasian	XFS/XFG	126	325	88	32	6	152	140	33	7	YES
Lee [<u>50</u>]	2009	China	Asian	XFS/XFG	62	171	20	25	17	29	94	48	6	YES
Ozaki [<u>19]</u>	2008	Japan	Asian	XFS/XFG	209	172	2	18	189	45	81	46	6	YES
Hewitt [<u>51</u>]	2008	America	Caucasian	XFS	86	2087	56	22	8	904	947	236	8	YES
Challa [<u>52]</u>	2008	America	Caucasian	XFG	47	215	29	16	2	99	88	28	7	YES
Fuse [<u>20</u>]	2008	Japan	Asian	XFS/XFG	56	138	1	2	53	28	80	30	7	YES
Mabuchi [<u>53]</u>	2008	Japan	Asian	XFS/XFG	302	191	47	108	147	40	92	59	6	YES
Mossbock [<u>54</u>]	2008	Australia	Caucasian	XFG	167	170	119	43	5	79	70	21	6	YES
Aragon-Martin [55]	2008	America	Caucasian	XFS/XFG	283	330	197	83	3	162	140	28	7	YES
Pasutto [<u>56</u>]	2008	Germany and Italy	Caucasian	XFS	280	412	179	91	10	170	194	48	7	YES
Pasutto [<u>56]</u>	2008	Germany and Italy	Caucasian	XFG	441	412	302	130	9	170	194	48	7	YES
Ramprasad [<u>12</u>]	2008	Indian	Asian	XFS/XFG	52	97	29	17	6	36	51	10	6	YES
Hayashi [<u>21</u>]	2008	Japan	Asian	XFS/XFG	59	189	0	1	58	37	100	52	7	YES

Table 1. Characteristics of case-control studies included in meta-analysis on LOXL1 gene polymorphism (rs1048661, rs2165241, rs3825942).

(Continued)

Table 1. (Continued)

Thorleifsson [16] rs2165241 Lan [35] Shihadeh [38] Yaz [39]	2008 2007	Japan	Asian	XFS/XFG	140	0.51	Case							Hardy-Weinberg equilibriun
rs2165241 Lan [<u>35</u>]	2007			AF5/AFG	142	251	2	10	130	65	143	43	6	YES
Lan [<u>35]</u> Shihadeh [<u>38]</u> Yaz [<u>39]</u>		Iceland	Caucasian	XFS/XFG	128	1024	86	35	7	414	477	133	8	YES
Shihadeh [38] Yaz [39]							ТТ	TC	CC	TT	TC	CC		
Yaz [<u>39]</u>	2020	China	Asian	XFG	91	180	43	34	14	90	70	20	7	YES
	2018	Jordan	Asian	XFS/XFG	61	59	38	20	3	42	12	5	7	YES
V. [00]	2018	Turkey	Caucasian	XFS	48	171	28	18	2	31	88	52	6	YES
Yaz [<u>39</u>]	2018	Turkey	Caucasian	XFG	58	171	37	18	3	31	88	52	6	YES
Asfuroglu [<u>40</u>]	2017	Turkey	Caucasian	XFS	44	47	21	23	0	9	31	7	7	YES
Asfuroglu [40]	2017	Turkey	Caucasian	XFG	64	47	39	25	0	9	31	7	7	YES
De Juan-Marcos [24]	2016	Spain	Caucasian	XFS	60	90	6	29	25	28	38	24	6	YES
De Juan-Marcos [24]	2016	Spain	Caucasian	XFG	40	90	2	14	24	28	38	24	6	YES
Alvarez [41]	2015	Spain	Caucasian	XFG	105	200	70	29	6	41	104	55	6	YES
Qiu [<u>42</u>]	2015	China	Asian	XFS	152	228	42	75	35	28	96	104	7	YES
Dubey [17]	2014	Indian	Asian	XFS	150	224	42	69	39	14	88	122	7	YES
Dubey [17]	2014	Indian	Asian	XFG	150	224	42	64	44	14	88	122	7	YES
	2013	Korea	Asian	XFS/XFG	101	115	0	2	99	1	13	101	7	YES
	2011	China	Asian	XFS/XFG	64	127	22	28	14	10	42	75	7	YES
Malukiewicz [46]	2011	Poland	Caucasian	XFS	36	30	28	7	1	14	11	5	6	YES
Sagong [11]	2011	Korea	Asian	XFS	28	146	0	0	28	3	21	122	6	YES
	2011	Korea	Asian	XFG	61	146	1	1	59	3	21	122	6	YES
	2010	German	Caucasian	XFG	101	280	60	38	3	70	135	75	8	YES
	2009	Finland	Caucasian	XFS/XFG	140	316	76	53	11	65	166	85	7	YES
	2009	China	Asian	XFS/XFG	50	125	0	2	48	0	25	100	5	YES
	2008	Japan	Asian	XFS/XFG	209	172	2	3	204	3	29	140	6	YES
Challa [52]	2008	America	Caucasian	XFG	50	235	29	17	4	76	114	45	7	YES
	2008	America	Caucasian	XFS/XFG	62	170	51	9	2	49	81	40	6	YES
	2008	Japan	Asian	XFS/XFG	142	251	0	2	140	5	47	199	6	YES
Fuse [20]	2008	Japan	Asian	XFS/XFG	56	138	0	2	54	0	16	122	7	YES
Aragon-Martin [55]	2008	America	Caucasian	XFS/XFG	284	328	149	119	16	60	174	94	7	YES
	2008	Germany and Italy	Caucasian	XFS	276	408	154	102	20	104	187	117	7	YES
Pasutto [56]	2008	Germany and Italy	Caucasian	XFG	441	408	272	143	26	104	187	117	7	YES
rs3825942							GG	GA	AA	GG	GA	AA		
	2020	China	Asian	XFG	91	176	76	15	0	150	23	3	7	YES
	2019	Georgia	Asian	XFS	132	194	99	28	5	102	62	30	7	YES
	2019	Iran	Asian	XFS	60	40	60	0	0	19	20	1	7	YES
	2018	India	Asian	XFG	30	61	26	4	0	41	16	4	6	YES
	2018	India	Asian	XFS	27	61	20	7	0	41	16	4	6	YES
	2018	Turkey	Caucasian	XFG	58	171	58	0	0	108	57	6	6	YES
	2018	Turkey	Caucasian	XFS	48	171	48	0	0	108	57	6	6	YES
	2017	Turkey	Caucasian	XFS	44	47	26	10	8	44	3	0	7	YES
	2017	Turkey	Caucasian	XFG	65	47	53	7	5	44	3	0	7	YES
	2017	Spain	Caucasian	XFS	60	90	58	1	1	66	21	3	6	YES
	2016	Spain	Caucasian	XFG	40	90	37	3	0	66	21	3	6	YES
,	2010	Germany	Caucasian	XFS	48	40	45	3	0	26	9	5	8	YES
	2010	Spain	Caucasian	XFG	105	200	103	2	0	144	50	6	6	YES
	2015	China	Asian	XFS	152	228	105	10	2	147	77	4	7	YES
	2013	Indian	Asian	XFS	152	228	140	6	1	147	100	4 18	7	YES

(Continued)

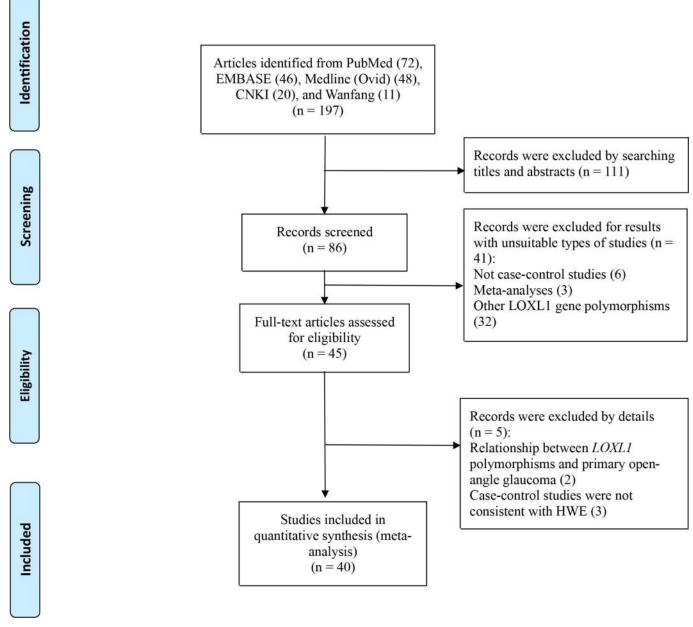
Table 1. (Continued)

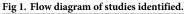
First author	Year	Origin	Ethnicity	Туре	Case	Control		Case		С	ontro	1	NOS	Hardy-Weinberg equilibrium
Dubey [<u>17]</u>	2014	Indian	Asian	XFG	150	225	138	5	7	107	100	18	7	YES
Anastasopoulos [43]	2014	Greece	Caucasian	XFS	40	93	39	1	0	61	31	1	7	YES
Anastasopoulos [43]	2014	Greece	Caucasian	XFG	34	93	33	1	0	61	31	1	7	YES
Chiras [<u>14</u>]	2013	Greece	Caucasian	XFS	53	97	36	17	0	48	45	4	6	YES
Chiras [14]	2013	Greece	Caucasian	XFG	71	97	52	19	0	48	45	4	6	YES
Kasim [<u>9</u>]	2013	Turkey	Caucasian	XFS	100	100	100	0	0	71	26	3	6	YES
Kasim [<u>9]</u>	2013	Turkey	Caucasian	XFG	100	100	100	0	0	71	26	3	6	YES
Park [<u>22]</u>	2013	Korea	Asian	XFS/XFG	110	127	108	2	0	101	26	0	7	YES
Micheal [44]	2012	Pakistan	Asian	XFG	128	180	121	7	0	130	42	8	6	YES
Rautenbach [25]	2011	South African	African	XFS	43	47	5	2	36	19	20	8	7	YES
Mayinu [<u>45</u>]	2011	China	Asian	XFS/XFG	64	127	58	6	0	80	45	2	7	YES
Malukiewicz [46]	2011	Poland	Caucasian	XFS	36	30	36	0	0	23	6	1	6	YES
Sagong [<u>11</u>]	2011	Korea	Asian	XFS	28	146	27	1	0	116	27	3	6	YES
Sagong [<u>11</u>]	2011	Korea	Asian	XFG	61	146	59	2	0	116	27	3	6	YES
Williams [<u>26</u>]	2010	South African	African	XFG	50	50	2	9	39	20	22	8	7	YES
Wolf [<u>47</u>]	2010	German	Caucasian	XFG	127	272	125	2	0	196	68	8	8	YES
Abu-Amero [<u>48</u>]	2010	Saudi Arabia	Asian	XFG	93	101	88	4	1	70	25	6	6	YES
Chen [23]	2009	China	Asian	XFS/XFG	50	125	50	0	0	101	22	2	5	YES
Lemmela [<u>49</u>]	2009	Finland	Caucasian	XFS/XFG	126	325	119	6	1	224	87	14	7	YES
Lee [<u>50</u>]	2009	China	Asian	XFS/XFG	62	171	61	1	0	143	28	0	6	YES
Ozaki [<u>19</u>]	2008	Japan	Asian	XFS/XFG	209	172	205	2	2	130	37	5	6	YES
Hewitt [<u>51</u>]	2008	America	Caucasian	XFS	86	2089	79	5	2	1479	552	58	8	YES
Challa [<u>52</u>]	2008	America	Caucasian	XFG	50	235	45	5	0	177	51	7	7	YES
Yang [57]	2008	America	Caucasian	XFS/XFG	62	170	62	0	0	124	41	5	6	YES
Fuse [<u>20</u>]	2008	Japan	Asian	XFS/XFG	56	138	56	0	0	108	26	4	7	YES
Mabuchi [<u>53</u>]	2008	Japan	Asian	XFS/XFG	302	191	243	53	6	143	40	8	6	YES
Mossbock [54]	2008	Australia	Caucasian	XFG	167	170	165	2	0	109	60	1	6	YES
Aragon-Martin [55]	2008	American	Caucasian	XFS/XFG	283	332	260	23	0	216	98	18	7	YES
Ramprasad [12]	2008	Indian	Asian	XFS/XFG	52	97	45	6	1	52	40	5	6	YES
Hayashi [<u>21]</u>	2008	Japan	Asian	XFS/XFG	59	189	59	0	0	137	50	2	7	YES
Tanito [<u>18]</u>	2008	Japan	Asian	XFS/XFG	142	251	140	2	0	158	87	6	6	YES
Thorleifsson [16]	2007	Iceland	Caucasian	XFS/XFG	129	490	125	4	0	363	113	14	8	YES

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between the *LOXL1* gene rs2165241 polymorphism and XFS/XFG risk in Asians (T vs. C, OR: 0.65, 95%CI: 0.36–1.17, *p*:0.15) (Fig 5, Table 2). A summary of the results from other comparative genetic models is also shown in Table 2.

rs3825942 *LOXL1* **gene polymorphism.** For the *LOXL1* gene polymorphism, rs3825942, 38 articles were included in our meta-analysis. Overall analyses revealed a positive *LOXL1* rs3825942 (G vs. A, OR: 5.33, 95%CI: 3.49–8.16, p < 0.001) association with XFS/XFG susceptibility (Table 2). In the subgroup analysis by disease type, the *LOXL1* rs3825942 gene polymorphism revealed a significant association with XFS (G vs. A, OR: 4.16, 95%CI: 1.86–9.30, p < 0.001) and XFG (G vs. A, OR: 4.72, 95%CI: 2.10–10.60, P < 0.001) (Fig 6, Table 2) susceptibility in a genetic model, G vs. A. In subgroup analysis by ethnicity, increased risks were identified among Caucasians (G vs. A, OR: 6.48, 95%CI: 3.67–11.44, P < 0.001) and Asians (G vs. A, OR: 5.89, 95%CI: 3.79–9.16, p < 0.001) (Fig 7, Table 2), suggesting that variant G allele carriers are at higher risk of XFS/XFG relative to A allele carriers. In contrast, the G allele indicates





protection from XFS/XFG in Africans (G vs. A, OR: 0.10, 95%CI: 0.06–0.16, p < 0.001). A summary of the results from other comparative genetic models is shown in Table 2.

Publication bias and sensitivity analyses

Funnel plot pictures were symmetrical inverted funnels. Egger's test was used to provide statistical evidence of the funnel plot (rs1048661: t = 1.62, p = 0.114; rs3825942: t = 1.26, p = 0.215; rs2165241: t = -2.10, p = 0.148) (Fig 8). To determine the potential source of heterogeneity, we performed a sensitivity analysis by sequentially excluding studies from the meta-analysis and assessing the effect of each article on the pooled results. This analysis did not reveal any significant alterations to the pooled ORs, indicating the stability of the three polymorphisms studied.

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Random, 95% CI		
1.1.1 XFS									
Anastasopoulos(XFS) 2014	63	80	141	186	2.9%	1.18 [0.63, 2.23]			
Asfuroglu(XFS) 2017	61	88	71	94	2.8%	0.73 [0.38, 1.41]			
Chiras(XFS) 2013	85	108	137	186	3.1%	1.32 [0.75, 2.32]			
De Juan-Marcos(XFS) 2016	91	120	129	180	3.2%	1.24 [0.73, 2.11]			
Dubey(XFS) 2014	232	300	307	450	3.6%	1.59 [1.14, 2.22]			
Gayathri 2016	72	96	50	80	2.9%	1.80 [0.94, 3.44]			
Hewitt 2008	134	172	2755	4174	3.6%	1.82 [1.26, 2.62]			
Kasim(XFS) 2013	176	200	142	200	3.2%	3.00 [1.77, 5.06]			
Malukiewicz 2011	65	72	48	60	2.0%	2.32 [0.85, 6.34]	· · · ·		
Pandav(XFS) 2018	40	54	98	122	2.6%	0.70 [0.33, 1.49]			
Pasutto(XFS) 2008	449	560	534	824	3.8%	2.20 [1.71, 2.83]			
Qiu 2015	254	304	316	456	3.6%	2.25 [1.57, 3.23]	Company of the second se		
Rautenbach 2011	86	86	83	94	0.5%	23.83 [1.38, 410.81]			
Sagong(XFS) 2011	4	56	104	292	2.0%	0.14 [0.05, 0.40]	•		
Taghavi 2019	108	120	64	80	2.5%	2.25 [1.00, 5.06]			
Yaz(XFS) 2018	90	116	238	342	3.3%	1.51 [0.92, 2.48]			
Subtotal (95% CI)		2532		7820	45.3%	1.50 [1.16, 1.93]	•		
Total events	2010		5217						
Heterogeneity: Tau ² = 0.17; Cl	$hi^2 = 52.67$	df = 15	(P < 0.00	001); l ²	= 72%				
Test for overall effect: Z = 3.11			0.0	000000000					
	1970 - 1973-1973								
1.1.2 XFG									
Abu-Amero 2010	163	186	154	202	3.1%	2.21 [1.28, 3.80]			
Alvarez 2015	177	210	254	400	3.4%	3.08 [2.02, 4.71]			
Anastasopoulos(XFG) 2014	58	68	141	186	2.6%	1.85 [0.87, 3.92]	-		
Asfuroglu(XFG) 2017	78	130	71	94	3.0%	0.49 [0.27, 0.87]			
Challa 2008	74	94	286	430	3.2%	1.86 [1.09, 3.17]	100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100		
Chiras(XFG) 2013	125	140	137	186	2.9%	2.98 [1.59, 5.58]			
De Juan-Marcos(XFG) 2016	64	80	129	180	2.9%	1.58 [0.84, 2.99]			
Dubey(XFG) 2014	244	300	307	450	3.6%	2.03 [1.43, 2.89]			
Kasim(XFG) 2013	174	200	142	200	3.2%	2.73 [1.64, 4.57]			
Lan 2020	146	182	188	360	3.4%	3.71 [2.44, 5.64]			
Micheal 2012	218	256	237	360	3.5%	2.98 [1.98, 4.48]			
Mossbock 2008	281	334	228	340	3.5%	2.60 [1.80, 3.77]			
Pandav(XFG) 2018	44	60	98	122	2.7%	0.67 [0.33, 1.39]			
Pasutto(XFG) 2008	734	882	534	824	3.8%	2.69 [2.15, 3.38]	· · · · · · · · · · · · · · · · · · ·		
Sagong(XFG) 2011	9	122	104	292	2.7%	0.14 [0.07, 0.30]	←		
Williams 2010	99	100	81	100	0.8%	23.22 [3.04, 177.21]	() () () () () () () () () ()		
Wolf 2010	216	256	351	532	3.5%	2.78 [1.90, 4.08]			
Yaz(XFG) 2018	104	116	238	342	2.9%	3.79 [2.00, 7.19]			
Subtotal (95% CI)		3716	200	5600	54.7%	1.97 [1.45, 2.66]	• • • •		
Total events	3008		3680			· · · · · · · · · · · · · · · · · · ·			
Heterogeneity: Tau ² = 0.34; Cl		6. df = 1		0001)-1	² = 86%				
Test for overall effect: Z = 4.38					00 10				
Total (95% CI)		6248		13420	100.0%	1.73 [1.41, 2.12]	•		
Total events	5018		8897						
Heterogeneity: Tau ² = 0.27; Cl		1 df = 2		0001)-	2 = 82%		1 T T T T T		
Test for overall effect: Z = 5.27			0 (1 - 0.0	0001), 1	02 /0		0.1 0.2 0.5 1 2 5		

Fig 2. Meta-analysis for the association between exfoliation syndrome/exfoliation glaucoma risks and LOXL1 gene polymorphism rs1048661 (G vs. T): Subgroup analysis by disease types (squares depict individual studies and diamonds depict summary effect size estimates (Odds Ratio, OR)).

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Discussion

XFS is associated with a high morbidity and blindness rate [5]. This systemic disease of the extracellular matrix, may cause pathological material accumulation in blood vessels, skin, heart, lung, liver, and cerebral meninges [59]. XFG, which results from XFS, is the most common identifiable cause of secondary open-angle glaucoma and is associated with cataracts [60–62]. Additionally, XFG increases the risk of potentially sight-threatening conditions and serious complications from cataract surgery [59]. Numerous studies indicate that XFS/XFG risk factors include inflammation, immune dysfunction, oxidative stress, unhealthy lifestyle, and various environmental factors [63]. Owing to clustering of XFS/XFG in families, concordance in monozygotic twins, and prevalence variability by ethnicity, genetic factors are regarded as

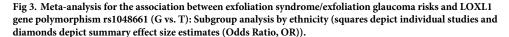
Variables/SNP	Studies	Case/Control	OR (95%CI) P	OR (95%CI) P	OR (95%CI) P	OR (95%CI) P	OR (95%CI) P
rs1048661			G vs. T	GT vs.TT	GG vs TT	GG+GT vs.TT	GG vs. GT+TT
Total	38	4828/10036	1.13(0.85-1.52) 0.40	0.98(0.57-1.67) 0.95	1.87(1.11-3.16) 0.019	1.4(0.78-2.54) 0.263	1.6(1.29–1.99) <0.001
Ethnicity							
Asian	19	2137/3240	0.52(0.29-0.94) 0.03	0.33(0.15-0.72) 0.005	0.54(0.23-1.27) 0.161	0.4(0.17-0.93) 0.033	0.87(0.55-1.37) 0.542
Caucasian	17	2598/6699	1.99(1.70-2.33) <0.001	2.22(1.69-2.92) <0.001	5(3.72-6.72) <0.001	3.59(2.73-4.71) <0.001	2.14(1.76-2.6) < 0.001
African	2	93/97	23.42(4.48–122.47) <0.001	0.48(0.02–15.52) 0.682	5.17(0.55-47.81) 0.148	3.89(0.42–35.81) 0.231	24.94(4.67–133.28) <0.001
Disease Category							
XFS	16	1266/3910	1.50(1.16–1.93) <0.001	1.44(1.06–1.95) 0.02	2.96(1.85-4.74) <0.001	2.1(1.18-3.73) 0.012	1.78(1.37-2.31) <0.001
XFG	18	1858/2800	1.97(1.45-2.66) < 0.001	2.19(1.19-4.03) 0.012	4.81(2.41-9.6) < 0.001	3.542(1.6-7.82) 0.002	2.26(1.69-3.02) < 0.001
rs2165241			T vs. C	TC vs.CC	TT vs.CC	TT+TC vs.CC	TT vs. TC+CC
Total	22	3124/5126	1.61(1.18-2.19) 0.002	1.31(0.86-1.99) 0.207	4.47(2.59-7.7) < 0.001	1.75(1.06-2.89) 0.028	2.98(.14-4.15) < 0.001
Ethnicity							
Asian	11	1315/2135	0.65(0.36-1.17) 0.15	0.55(0.26-1.15) 0.112	2.11(0.93-4.79) 0.074	0.6(0.27-1.31) 0.198	1.75(0.88-3.45) 0.108
Caucasian	11	1809/2991	2.76(1.99-3.84) <0.001	2.48(1.6-3.85) <0.001	7.52(3.69–15.33) <0.001	4.34(2.32-8.14) <0.001	3.89(2.75-5.5) <0.001
Disease Category							
XFS	8	794/1344	2.14(1.33-3.45) 0.002	2.12(1.27-3.54) 0.004	4.77(1.73-13.15) 0.003	2.74(1.33-5.67) 0.006	2.82(1.55-5.11) 0.001
XFG	10	1161/1981	2(1.21-3.31) 0.007	1.67(1.67-3.15) 0.109	4.71(1.72-12.88) 0.003	2.44(1.05-5.67) 0.037	3.15(1.8-5.49) < 0.001
rs3825942			G vs. A	GA vs. AA	GG vs. AA	GG+GA vs. AA	GG vs.GA+ AA
Total	38	4233/9017	5.33(3.49-8.16) <0.001	0.61(0.45-0.82) 0.001	2.35(1.84–2.99) <0.001	1.59(1.27-2) <0.001	6.16(4.15-9.14) < 0.001
Ethnicity							
Asian	19	2208/3371	5.89(3.79-9.16) <0.001	1.04(0.66-1.63) 0.866	4.71(3.15–7.06) <0.001	3.41(2.28–5.1) <0.001	7.09(4.23–11.91) <0.001
Caucasian	17	1932/5549	6.48(3.67–11.44) <0.001	1.(0.55–1.82) 0.989	3.46(2.27–5.29) <0.001	$\begin{array}{c} 2.88(1.87 - 4.43) \\ < 0.001 \end{array}$	7.38(4.26–12.81) <0.001
African	2	93/97	0.1(0.06-0.16) < 0.001	0.05(0.02-0.13) <0.001	0.04(0.01-0.1) < 0.001	0.05(0.02-0.1) <0.001	0.13(0.04-0.37) < 0.001
Disease Category							
XFS	17	1107/3698	4.16(1.86-9.30) < 0.001	0.51(0.18-1.45) 0.206	2.61(0.96-7.1) 0.061	1.96(0.69-5.57) 0.205	5.1(2.46-10.58) < 0.001
XFG	17	1420/2414	4.72(2.1-10.6) < 0.001	0.49(0.22-1.13) 0.093	2.92(1.05-8.09) 0.04	2.36(0.84-6.69) 0.105	5.23(2.51-10.88) < 0.001

Table 2. Summary of different comparative results on LOXL1 gene polym	morphism (rs1048661, rs2165241, rs3825942).
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XFS/XFG risk factors [64–68]. It is widely accepted that the *LOXL1* gene is the most important genetic risk factor known so far for XFS/XFG. Besides, a single study might lack sufficient power to detect the potential small *LOXL1* gene polymorphism effects associated with XFS/XFG, especially when the sample size is not adequate. Thus, a meta-analysis may effectively identify the association between genetic risk factors and XFS/XFG as such quantitative analyses integrate results from numerous studies on the topic of study, potentially drawing more objective and reliable conclusions. Here, we conducted a pooled analysis to evaluate the association between *LOXL1* gene polymorphisms and XFS/XFG susceptibility.

Three recent meta-analyses [<u>34</u>, <u>69</u>, <u>70</u>] investigated the association between the *LOXL1* gene polymorphisms and XFS/XFG risk. However, all of them covered papers published until to 2015, with the latest data unrepresented. Tang C et al. [<u>69</u>] and Chen H et al. [<u>70</u>] both

	Experim		Conti		101-1-1-1	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Random, 95% CI
		5223	1222				
Abu-Amero 2010	163	186	154	202	2.2%	2.21 [1.28, 3.80]	
Chen 2009	11	100	121	250	2.1%	0.13 [0.07, 0.26]	
Dubey(XFG) 2014	244	300	307	450	2.3%	2.03 [1.43, 2.89]	
Dubey(XFS) 2014	232	300	307	450	2.3%	1.59 [1.14, 2.22]	
Fuse 2008	4	112	136	276	1.8%	0.04 [0.01, 0.11]	
Hayashi 2008	1	118	174	378	1.1%	0.01 [0.00, 0.07]	
.an 2020	146	182	188	360	2.2%	3.71 [2.44, 5.64]	
.ee 2009	65	124	152	342	2.2%	1.38 [0.91, 2.08]	
Mabuchi 2008	202	604	172	382	2.3%	0.61 [0.47, 0.80]	
Mayinu 2011	104	128	176	254	2.2%	1.92 [1.14, 3.22]	
Micheal 2012	218	256	237	360	2.2%	2.98 [1.98, 4.48]	
Dzaki 2008	22	418	171	344	2.2%	0.06 [0.03, 0.09]	8
Pandav(XFG) 2018	44	60	98	122	2.1%	0.67 [0.33, 1.39]	
Pandav(XFS) 2018	40	54	98	122	2.0%	0.70 [0.33, 1.49]	
Park 2013	6	220	75	254	2.0%	0.07 [0.03, 0.16]	
Qiu 2015	254	304	316	456	2.3%	2.25 [1.57, 3.23]	
Ramprasad 2008	75	104	123	194	2.2%	1.49 [0.89, 2.51]	
Sagong(XFG) 2011	9	122	104	292	2.1%	0.14 [0.07, 0.30]	100 million (100 million)
Sagong(XFS) 2011	4	56	104	292	1.8%	0.14 [0.05, 0.40]	
Shihadeh 2018	107	122	102	118	2.0%	1.12 [0.53, 2.38]	
aghavi 2019	108	120	64	80	2.0%	2.25 [1.00, 5.06]	
Tanito 2008	14	284	273	502	2.2%	0.04 [0.02, 0.08]	
iubtotal (95% CI)		4274		6480	45.8%	0.52 [0.29, 0.94]	-
otai events	2073		3652				
leterogeneity: Tau ^a = 1.85; C			(P < 0.0	0001); I	² = 97%		
est for overall effect: Z = 2.18	3 (P = 0.03)						
.2.2 Caucasians							
Vvarez 2015	177	210	254	400	2.2%	3.08 [2.02, 4.71]	
nastasopoulos(XFG) 2014	58	68	141	186	2.0%	1.85 [0.87, 3.92]	
nastasopoulos(XFS) 2014	63	80	141	186	2.1%	1.18 [0.63, 2.23]	
Aragon-Martin 2008	477	566	464	660	2.3%	2.26 [1.71, 3.00]	-
Asfuroglu(XFG) 2017	78	130	71	94	2.1%	0.49 [0.27, 0.87]	
Asfuroglu(XFS) 2017	61	88	71	94	2.1%	0.73 [0.38, 1.41]	
halla 2008	74	94	286	430	2.2%	1.86 [1.09, 3.17]	
Chiras(XFG) 2013	125	140	137	186	2.1%	2.98 [1.59, 5.58]	
chiras(XFS) 2013	85	108	137	186	2.2%	1.32 [0.75, 2.32]	
De Juan-Marcos(XFG) 2016	64	80	129	180	2.1%	1.58 [0.84, 2.99]	
e Juan-Marcos(XFS) 2016	91	120	129	180	2.2%	1.24 [0.73, 2.11]	
Savathri 2016	72	96	50	80	2.1%	1.80 [0.94, 3.44]	
fewitt 2008	134	172	2755	4174	2.3%	1.82 [1.26, 2.62]	-
Kasim(XFG) 2013	174	200	142	200	2.2%	2.73 [1.64, 4.57]	
(asim(XFS) 2013	176	200	142	200	2.2%	3.00 [1.77, 5.06]	
emmela 2009	208	252	444	650	2.3%	2.19 [1.52, 3.16]	
Aalukiewicz 2011	206	72	444	60	1.8%	2.32 [0.85, 6.34]	
Aasabock 2008	281	334	228	340	2.3%	2.60 [1.80, 3.77]	
Pasutto(XFG) 2008	734	882	228 534	824	2.3%		-
	449	560	534	824	2.3%	2.69 [2.15, 3.38]	-
asutto(XFS) 2008 horleifsson 2007	449 207	256	534 1305	2048	2.3%	2.20 [1.71, 2.83]	-
Norleitsson 2007 Volf 2010	207	256	351	532	2.3%	2.41 [1.74, 3.33]	
	216	256	351 238	532	2.3%	2.78 [1.90, 4.08]	
'az(XFG) 2018		0.075				3.79 [2.00, 7.19]	
az(XFS) 2018	90	116	238	342	2.2%	1.51 [0.92, 2.48]	•
ubtotal (95% CI)	1000	5196	0000	13398	52.4%	1.99 [1.70, 2.33]	
fotal events	4263	40.000	8969	nnet in	- 0751		
leterogeneity: Tau ² = 0.09; C			P < 0.00	1001); P	= 65%		
est for overall effect: Z = 8.58	s (P < 0.00)	301)					
0.0.46							
.2.3 Africans	200	1228	101218	35/3	1 20223		
Rautenbach 2011	86	86	83	94	0.7%	23.83 [1.38, 410.81]	
Villiams 2010	99	100	81	100	1.1%	23.22 [3.04, 177.21]	
Subtotal (95% CI)		186		194	1.8%	23.42 [4.48, 122.47]	
otal events	185		164				
leterogeneity: Tau ^a = 0.00; C			= 0.99);	$ ^2 = 0\%$			
Fest for overall effect: Z = 3.74	(P = 0.000	02)					
Fotal (95% CI)		9656		20072	100.0%	1.13 [0.85, 1.52]	•
Total events	6521		12785				
A	$hi^2 = 839.44$	4. $df = 47$	(P<0.0	0001); [² = 94%		1 1 1
Heterogeneity: Tau ² = 0.96; C Test for overall effect: Z = 0.84							0.01 0.1 1 10 1



indicated that the allele G of rs1048661, the allele T of rs2165241 and the allele G of rs3825942 were associated with an increased risk for XFS/XFG among Caucasians, and that only the allele G of rs1048661 and the allele T of rs2165241 had a potential protective effect on XFS/XFG in Asians. Nevertheless, our study showed that there was no significant association between the LOXL1 gene rs2165241 polymorphism and XFS/XFG risk in Asians, and that rs3825942 ("G" allele) carriers are at higher risk of XFS/XFG relative to A allele carriers in Asians. On this point, our conclusion seems partially inconsistent with the previous two meta-analyses. Moreover, their study did not involve XFS/XFG in Africans, which is important and worthy of attention. Wang L et al. [34] reported that rs1048661("G" alleles) had a weak association with XFG/XGS; rs3825942 ("G" alleles) had a strong association with XFS/XFG; and rs2165241

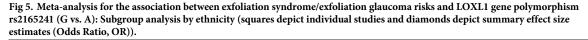
	Experim	ental	Contr	rol		Odds Ratio	Odds	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Rand	lom. 95% Cl		
3.2.1 XFS										
Asfuroglu(XFS) 2017	65	88	49	94	5.5%	2.60 [1.39, 4.85]				
De Juan-Marcos(XFS) 2016	41	120	94	180	5.9%	0.47 [0.29, 0.77]				
Dubey(XFS) 2014	153	300	116	448	6.4%	2.98 [2.19, 4.06]		-		
Malukiewicz 2011	63	72	39	60	4.6%	3.77 [1.57, 9.06]				
Pasutto(XFS) 2008	410	552	395	816	6.5%	3.08 [2.43, 3.89]		-		
Qiu 2015	159	304	152	456	6.4%	2.19 [1.63, 2.95]		-		
Sagong(XFS) 2011	0	56	27	292	1.2%	0.09 [0.01, 1.42]	<	-		
Yaz(XFS) 2018	74	96	150	342	5.8%	4.31 [2.56, 7.25]				
Subtotal (95% CI)		1588		2688	42.2%	2.14 [1.33, 3.45]		•		
Total events	965		1022							
Heterogeneity: Tau ² = 0.36; C	hi ² = 62.21,	df = 7 (P < 0.000	001); l ²	= 89%					
Test for overall effect: Z = 3.15	5 (P = 0.002	2)								
3.2.2 XFG										
Alvarez 2015	169	210	186	400	6.1%	4.74 [3.20, 7.03]				
Asfuroglu(XFG) 2017	103	128	49	94	5.5%	3.78 [2.09, 6.86]				
Challa 2008	75	100	266	470	5.9%	2.30 [1.41, 3.75]				
De Juan-Marcos(XFG) 2016	18	80	94	180	5.5%	0.27 [0.15, 0.48]				
Dubey(XFG) 2014	148	300	116	448	6.4%	2.79 [2.04, 3.80]		-		
Lan 2020	120	182	250	360	6.2%	0.85 [0.58, 1.25]		+		
Pasutto(XFG) 2008	687	882	395	816	6.5%	3.75 [3.04, 4.63]		-		
Sagong(XFG) 2011	3	122	27	292	3.6%	0.25 [0.07, 0.83]				
Wolf 2010	158	202	275	560	6.2%	3.72 [2.56, 5.40]				
Yaz(XFG) 2018	92	116	150	342	5.9%	4.91 [2.98, 8.07]				
Subtotal (95% CI)		2322		3962	57.8%	2.00 [1.21, 3.31]		•		
Total events	1573		1808							
Heterogeneity: Tau ² = 0.59; C		2. df = 9		0001): I	² = 93%					
Test for overall effect: $Z = 2.7$		영양 방송 입지 않는 것이 없다.	1813 - ANGU		(50503)					
Total (95% CI)		3910		6650	100.0%	2.07 [1.48, 2.90]		•		
Total events	2538		2830							
Heterogeneity: Tau ² = 0.44; C		6. df = 1		00001):	l² = 91%		+			
Test for overall effect: Z = 4.25		전송 시작 전 전 전 전 전 전 전 전 전 전 전 전 전 전 전 전 전 전			/ -		0.01 0.1	1 10 10		
Test for subgroup differences:		S. 1. 4. 5	(P = 0.84)	5) $l^2 = 0$	1%		Decreases risk	Increases risl		

Fig 4. Meta-analysis for the association between exfoliation syndrome/exfoliation glaucoma risks and LOXL1 gene polymorphism rs2165241 (T vs. C): Subgroup analysis by disease types (squares depict individual studies and diamonds depict summary effect size estimates (Odds Ratio, OR)).

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("T" alleles) had a significant risk with XFS/XFG in Caucasians. Our meta-analysis has corroborated their findings. However, three articles [10, 30, 31] included in Wang's meta-analysis [34], did not achieve HWE in the control group, while two articles [32, 33] examined the relationship between *LOXL1* gene polymorphisms and primary open-angle glaucoma. Here, we carried out an updated meta-analysis of the association between *LOXL1* gene polymorphisms and XFS/XFG susceptibility, involving 13984 participants. We identified three polymorphisms, rs1048661, rs3825942, and rs2165241, that met the inclusion criteria for meta-analysis. XFS/XFG analysis by ethnicity revealed a significantly high association between the G allele of rs1048661, the allele T of rs2165241 and the allele G of rs3825942, and XFS/XFG risk in Caucasians. We found that the G allele of rs1048661 may have potentially negative effects on XFS/ XFG in Africans, and the G allele of rs3825942 may protect from XFS/XFG in Africans. In Asians, a significantly increased XFS/XFG risk was associated with the G allele of rs3825942. However, we also found that the G allele of rs1048661 was associated with reduced XFS/XFG risk in Asians. In Asians, there was no significant association between the T allele of rs2165241 and XFS/XFG risk. Additionally, there was a significant association between the T allele of rs2165241

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	M-H. Random. 95% CI
3.1.1 Asians							
Chen 2009	2	100	25	250	2.2%	0.18 [0.04, 0.79]	
Dubey(XFG) 2014	153	300	116	448	4.2%	2.98 [2.19, 4.06]	
Dubey(XFS) 2014	148	300	116	448	4.2%	2.79 [2.04, 3.80]	
Fuse 2008	2	112	16	276	2.2%	0.30 [0.07, 1.31]	
Lan 2020	120	182	250	360	4.1%	0.85 [0.58, 1.25]	
Mayinu 2011	72	128	62	254	4.0%	3.98 [2.53, 6.25]	
Ozaki 2008	7	418	35	344	3.4%	0.15 [0.07, 0.34]	
Park 2013	2	202	15	230	2.2%	0.14 [0.03, 0.63]	
Qiu 2015	159	304	152	456	4.2%	2.19 [1.63, 2.95]	
Sagong(XFG) 2011	0	56	27	292	0.9%	0.09 [0.01, 1.42]	←
Sagong(XFS) 2011	3	122	27	292	2.6%	0.25 [0.07, 0.83]	
Shihadeh 2018	96	122	96	118	3.7%	0.85 [0.45, 1.60]	
Tanito 2008	2	284	57	502	2.3%	0.06 [0.01, 0.23]	
Subtotal (95% CI)	2	2630		4270	40.4%	0.65 [0.36, 1.17]	•
Total events	766	2000	994	1210	40.470	0.00 [0.00, 111]	
Heterogeneity: Tau ² = 0.91; C		7 df - 1'		0001)-1	2 - 0.20/		
Test for overall effect: Z = 1.43		CALCER 1	2 (F < 0.0	0001), 1	- 92 70		
Test for overall effect. 2 = 1.4.	5 (F = 0.15	,					
3.1.2 Caucasians							
Alvarez 2015	169	210	186	400	4.1%	4.74 [3.20, 7.03]	
Aragon-Martin 2008	417	568	294	656	4.3%	3.40 [2.67, 4.33]	-
Asfuroglu(XFG) 2017	65	88	49	94	3.7%	2.60 [1.39, 4.85]	10 B. B.
Asfuroglu(XFS) 2017	103	128	49	94	3.8%	3.78 [2.09, 6.86]	
Challa 2008	75	100	266	470	4.0%	2.30 [1.41, 3.75]	
De Juan-Marcos(XFG) 2016	41	120	94	180	4.0%	0.47 [0.29, 0.77]	
De Juan-Marcos(XFS) 2016	18	80	94	180	3.8%	0.27 [0.15, 0.48]	3
Lemmela 2009	205	280	296	632	4.2%	3.10 [2.28, 4.22]	
Malukiewicz 2011	63	72	39	60	3.3%	3.77 [1.57, 9.06]	
Pasutto(XFG) 2008	410	552	395	816	4.3%	3.08 [2.43, 3.89]	-
Pasutto(XFS) 2008	687	882	395	816	4.3%	3.75 [3.04, 4.63]	-
Wolf 2010	158	202	275	560	4.2%	3.72 [2.56, 5.40]	
Yang 2008	111	124	179	340	3.8%	7.68 [4.16, 14.17]	
Yaz(XFG) 2018	74	96	150	342	3.9%	4.31 [2.56, 7.25]	
Yaz(XFS) 2018	92	116	150	342	4.0%	4.91 [2.98, 8.07]	
Subtotal (95% CI)	92	3618	150	5982	59.6%	2.76 [1.99, 3.84]	•
Total events	2688	5010	2911	5502	33.078	2.70 [1.55, 5.64]	
		0 df = 1		00041-1	2 - 019/		
Heterogeneity: Tau ² = 0.36; C Test for overall effect: Z = 6.08			+ (F < 0.0	0001); 1	- 91%		
Total (95% CI)		6248		10252	100.0%	1.61 [1.18, 2.19]	•
Total events	3454		3905				
Heterogeneity: Tau ² = 0.56; C		2 df = 27		0001)-1	$^{2} = 92\%$		
Test for overall effect: Z = 3.03			1. 50.0		02/0		0.01 0.1 1 10 100
103110100001an effect. z = 3.00					= 94.3%		Decreases risk Increases risk



https://doi.org/10.1371/journal.pone.0250772.g005

polymorphisms and susceptibility to various disease types. These results affirmed the association between LOXL1 gene polymorphisms and XFS and XFG. Notably, we found a high frequency of risk alleles (rs1048661, rs2165241, and rs3825942) in non-XFG/XFS individuals, especially in Caucasians. Some studies have reported that these polymorphisms affect the proteolytic activity of LOXL1, and LOXL1 is an important matrix cross-linking enzyme that is required for elastic fiber formation and confer risk for the development of XFS/XFG [71]. However, the contribution of the risk alleles to XFS/XFG is complicated. Certain genetic variants of LOXL1, which has a prominent role in elastin fiber production, are not a single causative factor as many genetically affected individuals do not develop XFS or XFG [72]. It is likely that additional genetic or environmental factors modulate the penetrance of LOXL1 susceptibility alleles [52]. This meta-analysis found that LOXL1 gene polymorphisms may contribute to XFS/XFG susceptibility in different populations, and the differences in genetic susceptibility

Study croup Events Total Events Total Weight M-H. Random. 95% CI M-H. Random. 95% CI Anastasopoulos (XFS) 2014 79 80 153 186 2.5% 17.04 [2.29, 126.90] Anastasopoulos (XFS) 2013 89 194 3.2% 0.68 [0.20, 2.27]		Experim	ental	Cont	rol		Odds Ratio	Odds	Ratio
Anastasopoulos(XFS) 2014 79 80 153 186 2.5%, 17.04 [2.29, 126.90] Asturgul(XFS) 2017 62 88 91 94 3.2%, 0.08 [0.02, 0.27] Chiras(XFS) 2013 89 106 141 194 3.6%, 1.97 [1.07, 361] De Juan-Marcos(XFS) 2016 117 120 153 180 3.2%, 6.88 [2.04, 23.24] Dobey(XFS) 2014 222 300 314 450 3.5%, 158 [7.61, 32.83] Gayathr 2016 93 96 61 80 3.2%, 9.66 [2.74, 34.03] Hewlit 2008 163 172 3510 4178 3.6%, 3.45 [1.75, 678] Kasim(XFS) 2013 200 200 168 200 1.9%, 77.34 [4.70, 1272.60] Kabim(XFS) 2013 200 200 168 200 1.9%, 77.34 [8.10, 1272.61] Mukkiewiz 2011 226 264 266 388 3.7%, 2.73 [1.82, 4.09] Panday(XFS) 2018 47 54 98 122 3.4%, 1.64 [0.66, 4.09] Oui 2015 290 304 371 456 3.6%, 4.75 [2.44, 8.53] Rautenbach 2011 12 86 58 94 3.5%, 0.10 [0.05, 0.21] Sagong(XFS) 2018 96 96 273 342 1.9%, 49.04 [3.01, 799.62] Subtata (95% CI) 2.214 7396 47.2%, 4.16 [1.86, 9.30] Total events 2013 6026 Heterogeneity: Tau* = 2.11; C.Ir% = 166.30, df = 16 (P < 0.00001); P = 91% Test for overall effect: Z = 3.47 (P = 0.0005) 2.12 XFG Anastasopoulos(XFG) 2014 67 68 153 186 2.5% 14.45 [1.30, 7.78] Chiras(XFG) 2013 123 142 141 194 3.6%, 2.23 [1.30, 7.78] Chiras(XFG) 2013 123 142 141 194 3.2%, 0.22 [0.06, 0.77] Challe 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chiras(XFG) 2013 123 142 141 194 3.6% 2.23 [1.30, 6.77] Challe 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chiras(XFG) 2013 123 142 141 194 3.6% 0.22 [0.06, 0.77] Challe 2002 167 182 323 352 3.6% 1.00 [0.52, 1.92] Mossbock 2008 32 334 278 340 3.0% 37.02 [8.97, 152.71] Panday(XFG) 2011 120 122 259 292 3.0% 7.64 [1.80, 82.38] Mossbock 2008 332 334 278 340 3.0% 37.02 [8.97, 152.71] Panday(XFG) 2013 16 16 [7 0 0.00001); P = 91% Test for overall effect: Z = 3.75 (P = 0.0002) Total events 2649 3983 Heterogeneity: Tau* = 2.41; C.Ir% = 16 (P < 0.00001); P = 91% Test for overall effect: Z = 3.75 (P = 0.0002) Total (95% CI) 5054 1224 1000% 4.40 [2.53, 7.66] Total events 4662 10009	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Rand	om. 95% Cl
Asturoglu(XFS) 2017 62 88 91 94 32% 0.08 [0.02, 0.27] Dirag(XFS) 2013 89 106 141 194 36% 197 [107, 36] De Juan-Marcos(XFS) 2016 117 120 153 180 3.2% 6.88 [2.04, 23.24] Duby(XFS) 2014 292 300 314 450 3.5% 15.81 [7.61, 32.83] Sagarbin 2016 93 96 61 80 32% 9.6[2.74, 34.43] Hewiti 2008 163 172 3510 4178 3.6% 3.45[1.75, 6.78] Kasim(XFS) 2013 200 200 168 200 1.9% 77.34 [4.70, 127.260] Kobakhidze 2019 72 72 52 60 1.9% 23.48 [1.33, 415.79] Mulukiewicz 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandav(XFS) 2018 47 54 98 122 3.4% 164 [0.66, 4.09] Diu 2015 290 304 371 456 3.6% 4.75 [2.64, 8.53] Rautenbach 2011 12 86 55 94 3.5% 0.10 [0.05, 0.21] Sageng(XFS) 2011 55 56 299 292 2.5% 7.01 [0.94, 52.33] Faghavi 2019 120 120 58 80 1.9% 92 66 [5.53, 1554.75] Yaz(XFS) 2018 96 96 273 342 1.9% 49.04 [3.01, 799.62] Subtotal (95% CI) 2214 7398 47.2% 4.16 [1.86, 9.30] Total events 2013 6026 Heterogeneity: Tau" = 2.11; Ch ² = 166.30, df = 15 (P < 0.00001); P = 91% Test for overall effect: Z = 3.47 (P = 0.0005) 21.2 XFG Anastasopoulos(XFG) 2014 67 68 153 186 2.5% 14.45 [1.30, 1.78, 6] Anastasopoulos(XFG) 2014 67 86 153 186 2.5% 14.45 [1.30, 7.78] Chaia 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chaia 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chaia 2008 95 100 405 470 3.4% 3.05 [1.30, 7.43] Dubey(XFG) 2013 123 142 141 194 3.6% 2.43 [1.31, 7.4, 33] Dubey(XFG) 2011 120 122 295 922 3.0% 3.43 [1.31, 7.4, 33] Dubey(XFG) 2011 120 122 295 922 3.0% 3.43 [1.31, 7.4, 33] Dubey(XFG) 2011 120 122 295 922 3.0% 3.43 [1.31, 7.4, 33] Dubey(XFG) 2011 120 122 295 922 3.0% 3.43 [1.31, 7.4, 33] Dubey(XFG) 2011 120 122 295 922 3.0% 3.43 [1.31, 7.4, 33] Dubey(XFG) 2011 120 122 295 922 3.0% 3.44 [1.80, 32.38] Milams 2010 13 100 62 100 3.6% 0.09 [0.05, 0.19] Will zms 2010 13 100 62 100 3.6% 0.09 [0.05, 0.19] Will zms 2010 13 100 62 100 3.6% 0.09 [0.05, 0.19] Will zms 2010 13 100 62 100 3.6% 0.09 [0.05, 0.19] Will zms 2010 13 100 62 100 3.6% 0.09 [0.05, 0.19] Will zms 2011 13 100 62 100 3.6% 0.09 [0.05, 0.19] Will zms 201	2.1.1 XFS								
Chiras(XFS) 2013 89 106 141 194 3.6% 1.07 1.07 3.61 De Juan Marcos(XFS) 2016 117 120 153 180 3.2% 6.88 [2.04, 23.24] Duby(XFS) 2014 292 300 314 450 3.5% 6.88 [2.04, 23.24] Gayathr 2016 93 96 61 80 3.2% 9.66 [2.74, 34.03] Hewit 2008 163 172 510 4177 3.6% 3.45 [17.5, 6.78] Kasim(XFS) 2013 200 200 168 200 1.9% 77.34 [4.70, 1272.60] Kabakhidze 2019 72 72 52 60 1.9% 2.348 [1.33, 415.79] Malukiewicz 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandax(XFS) 2018 47 54 98 122 3.4% 1.64 [0.66, 4.09] Dara 2015 290 304 371 456 3.6% 0.10 [0.05, 0.21] Faquary 2019 120 120 56 269 22 2.5% 7.01 [0.94, 65.3] Taghav 2019 120 120 56 80 0.1.9% 92.69 [5.53, 1554.75] Yax(XFS) 2018 96 96 273 3.42 1.9% 4.04 [3.01, 79.62] Subtotal (95% CI) 2214 7396 47.2% 4.16 [1.86, 9.30] Total events 2013 6026 Heterogeneity: Tau ² = 2.11; Ch ² = 166.30, df = 15 (P < 0.00001); P = 91% Total events 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Anvarez 2015 208 210 338 400 3.0% 19.08 [4.62, 78.82] Anastasopulos(XFG) 2014 67 68 153 186 2.5% 1.4.45 [1.34, 107.86] Anvarez 2015 208 210 338 400 3.0% 19.08 [4.62, 78.82] Anastasopulos(XFG) 2014 77 80 153 180 3.2% 4.53 [1.33, 15.40] Debug/XFG) 2013 123 142 141 194 3.6% 2.43 [1.37, 4.33] De Juan Marcos(XFG) 2016 77 80 153 180 3.2% 4.53 [1.33, 15.40] Dubey/XFG) 2013 223 322 3.4% 7.73 [4.7,0, 127.260] Lan 2020 167 182 323 352 3.6% 1.00 [0.5, 2, 192] Mosbock 2008 332 334 278 340 3.0% 37.02 [8.97, 152, 71] Pandav(XFG) 2013 126 146 50 3.7% 6.48 [3.86, 16.23] Mosbock 2000 332 2334 278 340 3.0% 37.02 [8.97, 152, 71] Pandav(XFG) 2011 120 122 2.29 9.292 3.0% 7.64 [1.80, 32.38] Mosbock 2008 332 334 278 340 3.0% 37.02 [8.97, 152, 71] Mosbock 2008 332 334 278 340 3.0% 37.02 [8.97, 152, 71] Mosbock 2008 332 334 278 340 3.0% 37.02 [8.97, 152, 71] Mosbock 2008 322 2.54 460 544 3.0% 2.30 1[5.61, 9.4.31] Fat alf events 2649 3983 Heterogeneity: Tau ² = 2.17; Ch ² = 18.0%, Ch ² = 19.0% Total events 2649 3983 Heterogeneity: Tau ² = 2.11; Ch ² = 18.0, 0.00001; P = 91%	Anastasopoulos(XFS) 2014	79	80	153	186	2.5%	17.04 [2.29, 126.90]		· · · ·
De Juan-Marcos(XFS) 2016 117 120 153 180 3.2% 6.88 [2.04, 23.24] Dubey(XFS) 2014 292 300 314 450 3.5% 15.81 [7.61, 32.83] Sayathr 2016 93 96 61 80 3.2% 9.68 [2.74, 34.03] Hewti 2008 163 172 3510 4178 3.6% 3.45 [1.75, 6.78] Sayathr 2016 2019 72 72 52 60 1.9% 7.73 [4.70, 127.260] Cobakthdze 2019 72 72 52 60 1.9% 7.73 [4.70, 127.260] Pandav(XFS) 2011 226 264 266 388 3.7% 2.73 [18.2, 4.09] Pandav(XFS) 2011 226 264 266 388 3.7% 2.73 [18.2, 4.09] Pandav(XFS) 2011 226 526 9.292 2.5% 7.01 [0.94, 52.3] Bautenbach 2011 55 56 259 292 2.5% 7.01 [0.94, 52.3] Faghavi 2019 120 120 58 80 1.9% 25.68 [5.51, 155.475] Yaz(XFS) 2018 96 96 273 342 1.9% 49.04 [3.01, 799.62] Subtotal (95% CI) 2214 7396 47.2% 4.16 [1.86, 9.30] Total events 2013 6026 Heterogeneity: Tau ² = 2.11; Ch ² = 166.30, df = 15 (P < 0.00001); P = 91% Test for overall effect: Z = 3.47 (P = 0.0005) 2.1.2 XFG Anastasopuolos(XFG) 2016 180 186 165 202 3.4% 6.73 [2.77, 16.35] Avarez 2015 123 6026 Heterogeneity: Tau ² = 2.11; Ch ² = 166.30, df = 15 (P < 0.00001); P = 91% Test for overall effect: Z = 3.47 (P = 0.0005) 2.1.2 XFG Anastasopuolos(XFG) 2016 77 80 153 180 3.2% 4.53 [1.33, 15.40] Dubey(XFG) 2017 113 130 91 94 3.2% 0.22 [0.06, 0.77] Chala 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Anastasopuolos(XFG) 2016 77 80 153 180 3.2% 4.53 [1.33, 15.40] Dubey(XFG) 2013 200 200 168 200 1.9% 77.34 [4.70, 127.260] Mosabock 2008 332 334 278 340 3.0% 37.02 [8.97, 152.71] Mosabock 2008 332 334 278 340 3.0% 37.02 [8.97, 152.71] Mosabock 2008 332 334 278 340 3.0% 37.02 [8.97, 152.71] Mosabock 2008 332 334 278 340 3.0% 23.01 [6.61, 94.31] Mosabock 2008 332 334 278 340 3.0% 37.02 [8.97, 152.71] Mosabock 2008 332 334 278 340 3.0% 37.02 [8.97, 152.71] Mosabock 2008 332 334 278 340 3.0% 23.01 [6.61, 94.31] Mosabock 2008 332 334 278 340 3.0% 23.01 [6.61, 94.31] Mosabock 2008 332 344 278 340 3.0% 23.01 [6.61, 94.31] Mosabock 2008 332 344 278 340 3.0% 23.01 [6.61, 94.31] Mosabock 2008 332 344 278 340 3.0% 23.01 [6.61, 94.31] Mosabock 2008 392 326	Asfuroglu(XFS) 2017	62	88	91	94	3.2%	0.08 [0.02, 0.27]		
Dubey(XFS) 2014 292 300 314 450 35% 1581 [761, 32.83] Gayathri 2016 93 96 61 80 3.2% 9.66 [2.74, 34.03] Hewlt 2008 163 172 3510 4178 3.6% $3.45 [1.75, 6.76]$ Gasim(XFS) 2013 200 200 168 200 1.9% 77.34 [4.70, 1272.60] Malukiewicz 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandav(XFS) 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandav(XFS) 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandav(XFS) 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandav(XFS) 2011 226 526 292 2.5% 7.01 [0.94, 25.33] Gagong(XFS) 2011 12 86 58 94 3.5% 0.10 [0.05, 0.21] Sagong(XFS) 2011 55 56 259 292 2.5% 7.01 [0.94, 25.33] Taghavi 2019 120 120 58 80 1.9% 92.69 [5.53, 1554.75] Yaz(XFS) 2018 96 96 273 3.42 1.9% 94.04 [3.01, 79.62] Subtotal (95% CI) 2214 7396 47.2% 4.16 [1.86, 9.30] Total events 2013 6026 Heterogeneity: Tau ² = 2.11; Ch ² = 166.30, df = 15 (P < 0.00001); P = 91% Test for overall effect: Z = 3.47 (P = 0.0005) 2.1.2 XFG Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.73 [2.77, 16.35] Ahu-Amero 2010 180 186 165 202 3.4% 6.53 [1.30, 77] Challa 2008 95 100 405 477 3.4% 3.05 [1.20, 7.78] Challa 9005 2014 228 325 2.5% 4.453 [1.33, 15.40] Dubey(XFG) 2013 200 200 168 200 1.9% 77, 34 (4.70, 1272.60] Amatavity 2.92 (1.40, 1.22, 2.59 2.22, 3.0% 7.64 [1.80, 32.38] Molthenal 2012 249 226 302 3.5% 6.83 [3.06, 15.23] Mosbock 2006 332 334 278 340 3.0% 37.02 [8.97, 152,71] Pandavity 2.92 (1.11, 20, 122 2.259 292 2.3.0% 7.64 [1.80, 32.38] Molthenal 2010 13 100 62 100 3.6% 0.09 [0.05, 19] Molthenal 2010 252 254 460 544 3.0% 23.01 [Chiras(XFS) 2013	89	106	141	194	3.6%	1.97 [1.07, 3.61]	j	
Bayatim 2016 93 96 61 80 32% 966 [2.74, 34.03] Hewitt 2008 163 172 3510 4178 3.6% 3.45 [1.75, 6.78] SaminXFS) 2013 200 200 168 201 9% 77.34 [4.70, 1272.60] Sobathidze 2019 72 72 52 60 1.9% 23.48 [1.33, 415.79] PandavXFS) 2018 47 54 98 122 3.4% 1.64 [0.66, 4.09] PandavXFS) 2018 47 54 98 122 3.4% 1.64 [0.66, 4.09] PandavXFS) 2011 52 66 264 266 388 3.7% 0.10 [0.05, 0.21] Sagong(XFS) 2011 55 56 229 292 2.5% 7.01 [0.94, 52.33] Faghavi 2019 120 120 58 80 1.9% 92.69 [5.33, 1554.75] Yaz(XFS) 2018 96 96 273 342 1.9% 49.04 [3.01, 799.62] Subtotal (95% CI) 2214 7396 47.2% 4.16 [1.86, 9.0] Fost for overall effect: Z = 3.47 (P = 0.00005) 21.2 XFG PandavXFG) 2011 123 1626 Phaterageneity: Tau ² = 2.11; Ch ² = 166.30, df = 15 (P < 0.00001); P = 91% Test for overall effect: Z = 3.47 (P = 0.0005) 21.2 XFG Ansatasopoulos(XFG) 2014 67 68 153 188 2.5% 14.45 [1.94, 107.86] Asturoglu(XFG) 2017 113 130 91 94 3.2% 0.22 [0.06, 0.77] Chala 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chala 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chala 2008 395 100 405 470 3.4% 3.154.01 Dubey(XFG) 2017 113 130 91 94 3.2% 0.22 [0.06, 0.77] Chala 2008 95 100 405 470 3.4% 3.05 [1.20, 7.78] Chala 2020 167 182 323 352 3.6% 1.00 [0.52, 1.92] Michael 2012 249 256 302 360 3.5% 6.813 [1.33, 15.40] Dubey(XFG) 2013 123 142 141 194 3.6% 2.43 [1.33, 15.40] Dubey(XFG) 2014 281 300 314 450 3.7% 6.41 [3.06, 16.3] Casim(XFG) 2013 200 200 168 200 1.9% 77.34 [4.70, 1272.60] Lar 2020 167 182 323 352 3.6% 1.00 [0.52, 1.92] Michael 2012 249 256 302 360 3.5% 6.813 [3.06, 15.21] Mossbock 2008 332 344 278 340 3.0% 37.02 [8.97, 152.71] PandavXFG) 2018 56 60 98 122 3.3% 3.43 [1.31, 1.3, 0.39] Sagong(XFG) 2011 120 122 259 292 3.0% 7.64 I1.80, 32.38] Michael 2012 249 256 302 360 3.5% 6.813 [3.06, 15.21] Mossbock 2008 332 344 278 340 3.0% 37.02 [8.97, 152.71] PandavXFG) 2018 16 116 273 342 1.9% Mossbock 2008 332 344 278 340 3.0% 37.02 [8.97, 152.71] PandavXFG) 2018 166 116 273 342 1.9% Soci 164 events 264.99 3983 Heterageneity; Tau ² = 2.41	De Juan-Marcos(XFS) 2016	117	120	153	180	3.2%	6.88 [2.04, 23.24]		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Dubey(XFS) 2014	292	300	314	450	3.5%	15.81 [7.61, 32.83]		and the second second
Kasim(XFS) 2013 200 108 200 19% 77.34 [4.70, 1272.60] Kotakhidze 2019 72 72 52 60 1.9% 23.48 [1.33, 415.79] Aukidewicz 2011 226 264 266 388 3.7% 2.73 [1.82, 4.09] Pandav(XFS) 2018 47 54 98 122 3.4% 1.64 [0.66, 4.09] Sagong(XFS) 2011 55 56 259 292 2.5% 7.01 [0.94, 52.33] Rautenbach 2011 12 56 80 1.9% 49.04 [3.01, 799.62] Taghavi 2019 120 120 58 80 1.9% 49.04 [3.01, 799.62] Subtotal (95% CI) 2214 7396 47.2% 4.16 [1.86, 9.30] Tofial events Total events 2013 6026 6.73 [2.77, 16.35] Anastasopoulos(XFG) 2017 113 130 91 43.2% 0.22 [0.06, 0.77] The structure of	지수는 것은 것은 것은 것은 것은 것은 것이 같이 가지 않는 것이 같이 많이 많이 없다.	93	96	61	80	3.2%			
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Anastasopoulos(XFG) 2014	67	68	153	186	2.5%	14.45 [1.94, 107.86]	1.5	
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Heterogeneity: Tau ² = 2.11; Chi ² = 348.31, df = 32 (P < 0.00001); l ² = 91%			5054		12224	100.0%	4.40 [2.53, 7.66]		•
	Heterogeneity: Tau? = 2 11: C	hi ² = 348.3	1, df = 3	2 (P < 0.0	00001); I	² = 91%		0.01 0.1	10 1

Fig 6. Meta-analysis for the association between exfoliation syndrome/exfoliation glaucoma risks and LOXL1 gene polymorphism rs3825942 (G vs. A): Subgroup analysis by disease types (squares depict individual studies and diamonds depict summary effect size estimates (Odds Ratio, OR)).

https://doi.org/10.1371/journal.pone.0250772.g006

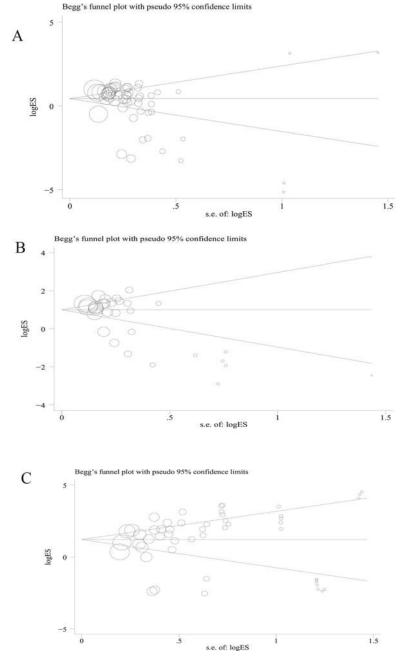
might be affected by ethnic factors, lifestyle factors and environmental exposures. Unfortunately, there are few studies concerning the association between *LOXL1* gene polymorphisms (rs3825942 and 1048661) and XFS/XFG in Africans, and no data were available for the SNP rs2165241 in Africans. This may lead to bias in the conclusion and generalization of the relationship between *LOXL1* gene polymorphisms and XFS/XFG in Africans. Thus, many such original studies are needed to confirm these findings as the currently included case-control studies are based on small sample sizes, especially for African populations.

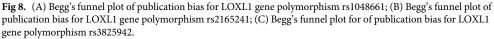
The mechanisms by which *LOXL1* gene polymorphisms affect XFS/XFG susceptibility remain unclear. Multiple studies [63, 73] have shown that LOXL1 mediates the formation and maintenance of elastic tissues, as well as maintenance of extracellular matrix homeostasis, by regulating cross-linking reactions between collagen and elastin. LOXL1 has also been reported

Study of Subserve	Experim		Cont		Malaki	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	M-H. Random, 95% Cl
2.2.1 Asians			00	400	2.3%	0 40 14 40 40 000	
Abu-Amero 2010 Chen 2009	56 47	60 54	98 98	122 122	2.3%	3.43 [1.13, 10.39] 1.64 [0.66, 4.09]	
Dubey(XFG) 2014	180	186	165	202	2.5%	6.73 [2.77, 16.35]	
Dubey(XFS) 2014	100	100	224	250	1.3%	23.73 [1.43, 393.18]	
Fuse 2008	292	300	314	450	2.6%	15.81 [7.61, 32.83]	
Hayashi 2008	281	300	314	450	2.7%	6.41 [3.86, 10.63]	-
Kobakhidze 2019	112	112	242	276	1.3%	32.01 [1.95, 526.80]	· · · · · · · · · · · · · · · · · · ·
Lan 2020	118	118	324	378	1.3%	39.80 [2.44, 649.63]	
Lee 2009	167	182	323	352	2.6%	1.00 [0.52, 1.92]	
Mabuchi 2008	123	124	314	342	1.7%	10.97 [1.48, 81.49]	
Mayinu 2011	539	604	326	382	2.7%	1.42 [0.97, 2.09]	
Micheal 2012	122	128	205	254	2.5%	4.86 [2.02, 11.68]	
Ozaki 2008	249	256	302	360	2.5%	6.83 [3.06, 15.23]	
Pandav(XFG) 2018	226 412	264 418	266 297	388 344	2.7% 2.5%	2.73 [1.82, 4.09]	
Pandav(XFS) 2018 Park 2013	218	220	297	254	2.5%	10.87 [4.59, 25.75] 12.43 [2.92, 53.00]	
Qiu 2015	290	304	371	456	2.1%	4.75 [2.64, 8.53]	
Ramprasad 2008	290	104	144	194	2.5%	4.17 [1.89, 9.18]	· · · · · · · · · · · · · · · · · · ·
Sagong(XFG) 2011	55	56	259	292	1.7%	7.01 [0.94, 52.33]	
Sagong(XFS) 2011	120	122	259	292	2.1%	7.64 [1.80, 32.38]	
Taghavi 2019	120	120	58	80	1.3%	92.69 [5.53, 1554.75]	
Tanito 2008	282	284	403	502	2.1%	34.64 [8.47, 141.60]	
Subtotal (95% CI)		4416	2010	6742	48.2%	5.89 [3.79, 9.16]	•
Total events	4205		5534				
Heterogeneity: Tau ² = 0.74; Cl			(P < 0.0	0001); I	² = 81%		
Test for overall effect: Z = 7.87	7 (P < 0.00	001)					
2.2.2 Caucasians							
	000	040	338	400	0.40/	10 00 14 00 70 001	
Alvarez 2015 Anastasopoulos(XFG) 2014	208 79	210 80	153	186	2.1% 1.7%	19.08 [4.62, 78.82] 17.04 [2.29, 126.90]	· · · · · · · · · · · · · · · · · · ·
Anastasopoulos(XFS) 2014 Anastasopoulos(XFS) 2014	67	68	153	186	1.7%	14.45 [1.94, 107.86]	
Aragon-Martin 2008	543	566	530	664	2.7%	5.97 [3.77, 9.44]	
Asfuroglu(XFG) 2017	62	88	91	94	2.3%	0.08 [0.02, 0.27]	
Asfuroglu(XFS) 2017	113	130	91	94	2.2%	0.22 [0.06, 0.77]	
Challa 2008	95	100	405	470	2.5%	3.05 [1.20, 7.78]	
Chiras(XFG) 2013	123	142	141	194	2.7%	2.43 [1.37, 4.33]	
Chiras(XFS) 2013	89	106	141	194	2.6%	1.97 [1.07, 3.61]	
De Juan-Marcos(XFG) 2016	117	120	153	180	2.3%	6.88 [2.04, 23.24]	
De Juan-Marcos(XFS) 2016	77	80	153	180	2.3%	4.53 [1.33, 15.40]	1
Gayathri 2016	93	96	61	80	2.2%	9.66 [2.74, 34.03]	
Hewitt 2008	163	172	3510	4178	2.6%	3.45 [1.75, 6.78]	
Kasim(XFG) 2013	200	200	168	200	1.3%	77.34 [4.70, 1272.60]	
Kasim(XFS) 2013	200	200	168	200	1.3%	77.34 [4.70, 1272.60]	
Lemmela 2009	244	252	535	650	2.6%	6.56 [3.15, 13.64]	
Malukiewicz 2011	72	72 334	52	60	1.2%	23.48 [1.33, 415.79]	
Mossbock 2008 Thorleifsson 2007	332	334 258	278 839	340 980	2.1% 2.4%	37.02 [8.97, 152.71]	
Volf 2010	254	258 254	460	980 544	2.4%	10.67 [3.91, 29.11]	
Yang 2008	124	124	289	340	1.3%	23.01 [5.61, 94.31]	
Yang 2008 Yaz(XFG) 2018	124	124	289	340	1.3%	44.30 [2.71, 723.44] 59.21 [3.64, 964.17]	
Yaz(XFS) 2018	96	96	273	342	1.3%	49.04 [3.01, 799.62]	
Subtotal (95% CI)	50	3864	213	11098	46.7%	6.48 [3.67, 11.44]	•
Total events	3719	00000	9255	0.00000			1110-140-1
Heterogeneity: Tau ² = 1.33; Cl		3, df = 22		0001); (2 = 83%		
Test for overall effect: Z = 6.45					2.5 - CH (92.50) (C		
2.2.3 Africans	122	227	325	32.9			
Rautenbach 2011	12	86	58	94	2.6%	0.10 [0.05, 0.21]	
Williams 2010	13	100	62	100	2.6%	0.09 [0.05, 0.19]	•
Subtotal (95% CI)	05	186	100	194	5.2%	0.10 [0.06, 0.16]	
Total events Heterogeneity: Tau ² = 0.00; Cl	25 bi² = 0.03	if = 1 /D	120	2 = 0.07			
Heterogeneity: Tau ^x = 0.00; CI Test for overall effect: Z = 8.99			- 0.86); 1	- = 0%			
100 10 0Vorall eneou. 2 = 0.95	1. 50.00						0255
Total (95% CI)		8466		18034	100.0%	5.33 [3.49, 8.16]	•
Total events	7949		14909				a 22 a
Heterogeneity: Tau ² = 1.68; Cl			(P < 0.0	0001); I	² = 89%	1	0.01 0.1 1 10 100
Test for overall effect: Z = 7.73							

Fig 7. Meta-analysis for the association between exfoliation syndrome/exfoliation glaucoma risks and LOXL1 gene polymorphism rs3825942 (G vs. A): Subgroup analysis by ethnicity (squares depict individual studies and diamonds depict summary effect size estimates (Odds Ratio, OR)).

to be involved in elastin renewal and XFS/XFG development [71, 74]. Sharma et al. [59] reported that the coding variants rs1048861 and rs3825942 may alter protein function and binding, wherein molecular modeling displayed that positions 141(rs1048661) and 153 (rs3825942) of the LOXL1 protein are likely surface residues and hence possible recognition sites for protein-protein interactions. Alterations at these residues might change the capacity





of LOXL1 to bind other proteins related to its cleavage as well as processing. Nevertheless, the difference in processing of the LOXL1 protein variants detected in their research does not completely interpret susceptibility to XFS/XFG among carriers of these variants as each of the variants confer the XFS/XFG risk in various ethnicities. The detailed mechanism whereby *LOXL1* gene polymorphisms lead to the XFS/XFG, remains poorly understood. Therefore, further studies are required to elucidate the mechanism on how the *LOXL1* gene polymorphisms

impact the occurrence and development of XFS/XFG. Moreover, the distinct genetic background of Caucasians from Asians may modify LOXL1-mediated genetic susceptibility; hence, the effects of rs2165241 and rs1048661 are opposite in Asians and Caucasians. Genetic and/or environmental factors may modify the effects of gene polymorphisms in different ethnic groups.

High heterogeneity was found in our study. For exploring the underlying source of heterogeneity, a subgroup analysis and sensitivity analysis were performed. Unfortunately, although subgroup and sensitivity analyses were performed, obvious heterogeneity still existed in certain genetic models, and it is difficult to explain the heterogeneity completely. Thus, we speculated that living environment and other complications might lead to heterogeneity. Publication bias was assessed using Begg's funnel plot and Egger's test; no significant publication bias was found in this meta-analysis. Moreover, all genotype distributions of controls were in -absolute accordance with the HWE, indicating that our results are stable and reliable.

We acknowledge several limitations of this study. First, in subgroup analysis by ethnicity and disease type, some subgroups consisted of less than three case-control studies, which may be too small to detect associations. Second, data were not stratified by other factors, such as gender, age, gene-environment/gene-gene interactions, and lifestyle, because sufficient information could not be extracted from primary publications. Third, we mainly focused on *LOXL1* gene polymorphisms, and did not take into consideration potential linkage disequilibrium with other mutations in this gene, or gene-gene and gene-environment interactions. Moreover, language bias may have occurred as only articles published in Chinese or English were included in the study. However, we minimized the likelihood of bias using a rigorous protocol, study identification, data selection, and statistical analysis.

Conclusion

In conclusion, our findings indicate that rs1048661, rs3825942, and rs2165241 *LOXL1* polymorphisms may contribute to XFS/XFG susceptibility, especially in Caucasians. Furthermore, well-designed studies with large sample sizes focusing on ethnicity or disease types are needed to confirm these findings.

Supporting information

S1 File. PRISMA 2009 checklist. (DOC)

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Author Contributions

Data curation: Jie He. Formal analysis: Xiaoyan Li. Methodology: Xiaoyan Li. Project administration: Jian Sun. Resources: Jie He. Supervision: Jian Sun. Validation: Jie He.

Writing – original draft: Xiaoyan Li.

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