Published in final edited form as:
Int Ophthalmol Clin. 2014 ; 54(4): 43–56. doi:10.1097/IIO.0000000000000042.

Genetics of Exfoliation Syndrome and Glaucoma

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Abstract

Exfoliation glaucoma (XFG) is the most common identifiable secondary form of open-angle glaucoma in the world. It is an ocular manifestation of exfoliation syndrome (XFS), an age-related systemic disease characterized by deposition of extracellular fibrillar material in various tissues and organs. XFS/XFG has been studied in populations around the world, which has led to identification of genetic factors that play a significant role in disease pathogenesis. Here, we summarize current knowledge of the genetics of XFS/XFG and identify areas for future research.

Keywords

Glaucoma; exfoliation; pseudoexfoliation; *LOXL1*; lysyl oxidase; ocular genetics

Introduction

Glaucoma refers to a heterogeneous group of disorders that are characterized by progressive loss of retinal ganglion cells and visual field loss[1]. It is the leading cause of irreversible blindness in the world[1]. Exfoliation glaucoma (XFG) is the most common identifiable form of open-angle glaucoma, accounting for up to 25% of glaucoma cases worldwide[2]. XFG is characterized by deposition of white, flaky material in all anterior segment structures, including the lens capsule, iris, ciliary body, zonules and trabecular meshwork[2]. Compared to primary open-angle glaucoma (POAG), XFG is associated with greater mean intraocular pressure (IOP), more advanced visual field loss at diagnosis, and poorer treatment response[3].

XFG is an ocular manifestation of exfoliation syndrome (XFS), an age-related systemic disorder that leads to accumulation of extracellular fibrillar material throughout the body[2]. Other ocular manifestations of XFS include angle-closure glaucoma, cataract formation and retinal vein occlusion[3,4]. XFS is also associated with numerous systemic conditions, including Alzheimer's-like dementia, sensorineural hearing loss, cerebrovascular disease, and cardiovascular disease[5].

Epidemiologic studies have found significant variability in prevalence of XFS/XFG among different ethnic groups, suggesting that genetic factors may play a role in disease pathogenesis. For instance, prevalence rates as high as 38% have been reported in Native American Navajo populations, whereas XFS and XFG were undetected in Greenland's Inuit

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population[6,7]. Pedigree-based and twin studies have also supported familial aggregation of XFS/XFG[8]. These findings fueled interest in identification of genes that may be involved in this common ocular disorder.

This review summarizes the progress that has been made in our understanding of the genetic basis of XFS/XFG in recent years, including a brief discussion of environmental factors that likely modify disease risk in genetically susceptible individuals.

LOXL1 Variants and XFS/XFG

A landmark genome-wide association study (GWAS) performed in a Scandinavian population identified single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (*LOXL1*) gene on chromosome 15 that were strongly associated with risk for XFS/XFG[9]. Three SNPs reached genome-wide significance levels ($p<1.6 \times 10^{-7}$) in this study. Two of the SNPs, rs1048661 and rs3825942, are protein-coding variants located in exon 1 of *LOXL1*. These lead to amino acid changes Arg141Leu and Gly153Asp, respectively. Homozygotes for the two risk alleles (approximately 25% of individuals in the Icelandic region) were estimated to have 700 times higher risk of XFG compared to individuals with the low-risk haplotype. The third SNP, rs2165241, was located in intron 1 of *LOXL1*.

LOXL1 is a member of a family that contains 5 related proteins, lysyl oxidase (*LOX*) and lysyl oxidase-like 1–4 (*LOXL1-4*). The *LOX* and *LOXL* proteins play a critical role in creation and repair of the extracellular matrix (ECM) by catalyzing formation of covalent crossbridges that stabilize collagen and elastin[10]. Notably, elastin fibers are a major component of XFS/XFG material, which is compatible with the potential role of *LOXL1* in this disorder[9]. Interestingly, variants in the *LOXL1* gene are not associated with primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), or pigmentary glaucoma, suggesting that XFG is genetically distinct[11–15].

The two coding variants in *LOXL1* (rs1048661 and rs3825942) were initially hypothesized to be functional variants. They have now been examined in many populations around the world (Table 1). rs3825942 (Gly153Asp) is strongly associated with risk for XFG in all populations studied to date, including Swedish/Icelandic, U.S. Caucasian, Mexican, Australian, central European, German, Italian, Saudi Arabian, Indian, Chinese, Japanese, Korean, and South African[16–40]. However, the risk allele for this SNP is reversed in South Africans[17,36]. Similarly, the risk allele for rs1048661 (Arg141Leu) is reversed in Japanese, Chinese and Korean populations[18,19,21,23,25,27,28,33,37]. rs1048661 is not associated with XFG risk in Greek, Indian, Mexican, and Polish populations[16,20,24,39]. These data suggest that although these *LOXL1* coding variants alter the protein structure, this change does not contribute functionally to the XFS/XFG disease process. Additionally, the intronic SNP identified in the initial GWAS, rs2165241, is reversed in Japanese, Chinese and Korean cohorts[18,19,21,28,33]. Therefore, to date, there are no reported DNA variants that are shared among all studied populations.

Given the conflicting genetic associations observed in different study populations, meta-analyses have been performed to further investigate the association of *LOXL1* polymorphisms with XFS/XFG risk. An ethnicity-based subgroup meta-analysis found that

rs3825942 (Gly153Asp) is associated with XFS/XFG risk in different ethnic populations, but rs1048661 (Arg141Leu) and rs2165241 are not[41]. Another meta-analysis found that the rs1048661 TT, rs3825942 AA and rs2165241 CC genotypes are associated with reduced risk of XFS/XFG[42].

Recent studies have sought to find other variants in *LOXL1* that may have functional roles in disease pathogenesis. One study identified a novel variant, rs41435250, that was strongly associated with XFS/XFG risk in a Mexican population[43]. This SNP is located in exon 1 of *LOXL1* and results in a synonymous mutation (p.A310A). The strength of association was modified by the patient's genotype at the intronic SNP rs2165241, suggesting possible intragenic epistasis. This variant has yet to be studied in other populations. The possibility that functional variants lie in regulatory, non-coding regions of *LOXL1* has also been explored. In a Caucasian dataset, *LOXL1* promoter region haplotypes consisting of risk alleles for SNPs rs12914489 and rs1694877 were associated with XFS/XFG[44]. Notably, SNP rs16958477 has previously been shown to alter *LOXL1* gene expression *in vitro*[45]. The role of *LOXL1* copy number variants in XFG has also been examined, though no significant association has been found[46].

Studies have also explored potential functional roles for *LOXL1* in the pathogenesis of XFS/XFG. LOXL1 null mice ($LOXL1^{-/-}$) have a distinct phenotype, which includes enlarged lung airspaces, increased skin laxity, intestinal diverticula, vascular abnormalities, and pelvic organ prolapse in females[47]. These findings support a role for *LOXL1* in elastic fiber homeostasis. $LOXL1^{-/-}$ mice also have ocular abnormalities, including an impaired blood-aqueous barrier and lens abnormalities consistent with cataract formation[48]. However, no IOP elevation or deposition of exfoliative material was observed in this model.

Importantly, the *LOXL1* protein is found in exfoliative material isolated from the anterior lens capsule of XFG patients during surgery, along with apolipoprotein E (ApoE), latent TGF-β binding protein 2 (Ltbp2), complement 3 and clusterin[49]. Mass spectrometric imaging analysis has shown that the *LOXL1* protein is more abundant in the iris region of the lens capsule, whereas ApoE is more abundant in the pupillary region[50].

Gene expression studies have found that *LOXL1* levels are increased during early stages of XFS but decrease in advanced stages, irrespective of whether glaucoma is present[51]. In lens capsules obtained from patients with XFG, *LOXL1* expression levels are decreased, compared to normal expression levels in patients who have XFS but not XFG[52]. Downregulation of *LOXL1* has been shown to interfere with elastic fiber assembly by optic nerve astrocytes *in vitro*, providing a possible mechanism whereby altered *LOXL1* expression may contribute to XFG[53].

Studies also suggest that *LOXL1* functions in cellular signaling pathways that mediate glaucomatous changes. For instance, *LOXL1* expression in human trabecular meshwork cells is induced by TGF-β via both canonical Smad and non-Smad signaling pathways[54]. Similarly, in human Tenon's capsule fibroblasts, TGF-β1, oxidative stress, UV light and hypoxia have all been found to increase *LOXL1* expression levels[55]. These findings suggest

that *LOXL1* and TGF-β may cooperative in cellular processes that lead to buildup of exfoliative material, IOP elevation and impaired trabecular meshwork outflow[54,55].

Another recent study utilized a reporter system controlled by the *LOXL1* promoter to screen for drugs that exert effects on this promoter[56]. Emodin was found to have strong enhancer effects on the *LOXL1* promoter in this drug screen. Treatment with emodin in an animal model also enhanced extracellular matrix (ECM) homeostasis, suggesting that alteration of *LOXL1* promoter activity can serve as a therapeutic strategy for ECM disorders, including XFS/XFG.

Other Genes Associated with XFS/XFG

In addition to *LOXL1*, several other loci have been investigated and found to confer susceptibility to XFS/XFG. Recently, two loci that confer susceptibility to normal-tension glaucoma, a subgroup of POAG, were also found to be associated with exfoliation glaucoma in a Caucasian dataset[57]. These include 9p21 containing the *CDKN2BAS* gene (rs2157719) and a probable regulatory region on 8q22 (rs284489). Interestingly, both loci influence TGF-beta signaling, suggesting that this pathway may be a viable drug target for multiple forms of glaucoma. These variants have yet to be studied in other XFG cohorts. Polymorphisms in the Toll-like receptor 4 gene (*TLR4*), which functions in innate and adaptive immunity, were also recently shown to be associated with XFG risk in a Japanese cohort[58]. Replication studies in other populations have yet to be performed, however.

Other genes that have been found to be associated with XFS/XFG risk include contactin-associated protein-like 2 (*CNTNAP2*), clusterin (*CLU*), apolipoprotein E (*APOE*), glutathione-S-transferase genes (*GST*s), *TNF*-α, methylenetetrahydrofolate reductase (*MTHFR*), matrix metalloproteinases (*MMP*s), and latent TGF-β binding protein 2 (*LTBP2*). However, unlike the case with *LOXL1* variants, which are strongly associated with XFS/XFG risk in all populations studied to date, variants in these genes demonstrate association in a limited number of populations, suggesting that these associations are either weak or are confined to specific ethnic groups (Table 2).

Environmental Factors Involved in the Pathogenesis of XFS/XFG

While the role of genetic factors in XFS/XFG is well established, identified variants have low penetrance. For instance, known *LOXL1* SNPs are found in high frequency among healthy individuals without XFS/XFG. This suggests that other genetic and/or environmental factors are also involved. To explore the contribution of environmental factors to XFS, studies have assessed disease risk based on geographic latitude in the continental United States[59,60]. Individuals living in northern regions of the United States had increased risk of XFS compared to those living in middle and southern regions. Moreover, risk increased as the number of sunny days annually increased. These data suggest that geographic factors such as altitude and UV exposure may contribute to XFS. Further studies are needed to determine whether these factors play a role in XFS/XFG risk in populations outside of the U.S.

The relationship between caffeinated beverage consumption and XFS/XFG risk has also been explored. In a prospective study, individuals who drank ≥3 cups of caffeinated coffee daily had increased risk of developing XFS/XFG[61]. No association was found with consumption of other caffeinated products, such as tea and soda. Although the exact mechanism is unclear, increased homocysteine levels from coffee consumption may contribute to formation of exfoliative material via vascular damage, oxidative stress and extracellular matrix alterations[61]. Higher levels of folate intake were recently reported to be associated with reduced risk of XFG, which further supports a role for homocysteine in XFG/XFS pathogenesis[62].

Trauma to the anterior segment of the eye may also contribute to the development of XFS/XFG, as evidenced by case reports of disease onset at a relatively young age following surgery to the anterior aspect of the affected eye[63].

Conclusions

Significant progress has been made in our understanding of the genetics of XFS/XFG over the last decade. It is clear that variants in the *LOXL1* gene contribute the dominant risk for XFS/XFG in populations around the world. However, there is no single DNA variant that is consistently shared across all populations, suggesting that these SNPs are either markers for disease or may play different roles depending on the genetic background of specific populations. Regardless, it is likely that functional variants are regulatory in nature. Identification of functional SNPs in *LOXL1* and characterization of their role in disease pathogenesis may enable development of effective gene-directed therapies to treat XFS/XFG. Although it is likely that additional genetic loci are involved, none have been found that are widely shared at the time of this report. However, as XFS/XFG datasets become individually and collectively larger and more powerful, additional genetic influences will likely be found. Identification of these genetic participants and possible environmental influences will greatly enhance our understanding of the pathobiology of this prevalent and fascinating disorder, ultimately providing the framework for risk assessment, treatment, and a cure.

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Table 1

XFS/XFG Risk Alleles for *LOXL1* Polymorphisms in Different Study Populations

Population	rs3825942 (Gly153Asp)	rs1048661 (Arg141Leu)	rs2165241 (Intron 1 of *LOXL1*)	Reference(s)
Iceland/Sweden (Initial GWAS)	G	G	T	9
Australian	G	G	-	34
U.S. Caucasian	G	G	T	29
Central European	G	G	-	22
Finish	G	G	T	31
German/Italian	G	G	T	32
Saudi Arabian	G	G	-	40
Turkish	G	G	-	26
Greek	G	**No association**	T	24
Indian	G	**No association**	-	20
Mexican	G	**No association**	T	16
Polish	G	**No association**	T	39
Chinese	G	**T**	**C**	13,28
Japanese	G	**T**	**C**	18,23,25,27,33,37
Korean	G	**T**	**C**	19,21
South African	**A**	G	-	17,36

LOXL1 polymorphisms are strongly associated with risk for XFS/XFG in all populations studied to date. However, the risk alleles for all SNPs are reversed in some study populations. The rs3825942 risk allele is reversed in South Africans. The rs1048661 SNP is not strongly associated with XFS/XFG risk in four populations and is reversed in Chinese, Japanese and Korean populations. The risk allele for the intronic SNP rs2165241 is also reversed in Chinese, Japanese and Korean study cohorts. ("-" denotes that this SNP has not been genotyped in the population).

Table 2

Other Genes Associated with XFS/XFG Disease Risk

Gene	Gene Function	Chromosomal Location	Study Design	Population	Number of Cases/ Number of Controls	Significant Association?	Reference(s)
Contactin-associated protein-like 2 (*CNTNAP*	Potassium channel trafficking and membrane stabilization	7q35-q36	GWAS	German Italian	160 / 80, 610 / 364 (2 independent cohorts) 249 / 190	Yes No	64
			Replication study	Japanese	108 / 199	Yes	65
			Replication study	Polish	48 / 30	No	66
Clusterin (*CLU*)	Apoptosis, inhibition of stress-induced protein aggregation	8p21	Candidate gene study	Australian	86 / 2422	Yes (though not significant after controlling for age)	67
			Candidate gene study	German Italian	333 / 342, 328 / 342 (2 cohorts) 209 / 190	Yes No	68
Apolipoprotein E (*APOE*)	Amyloid deposition and fibril formation	19q13.2	Candidate gene study	Turkish	76 / 74	Yes	69
			Candidate gene study	German Italian	661 / 342 209/190	No No	70
			Candidate gene study	Greek	151 / 107	No	71
Glutathione-S-transferase genes (*GST*s)	Protect cells from oxidative stress	Multiple chromosomal loci	Candidate gene study	Swedish	188 / 200	No	72
			Candidate gene study	Turkish	60 / 65	No	73
			Candidate gene study	Pakistani	165 / 162	Yes (association only seen in female patients, not males)	74
TNF-α	Pro-inflammatory cytokine	6p21.3	Candidate gene study	Pakistani	122 / 126	Yes	75
			Candidate gene study	Iranian	223 / 202	Yes	76
			Candidate gene study	Caucasian	204 / 204	No	77
			Candidate gene study	Turkish	110 / 110	No	78
			Meta-analysis	Multiple (14 studies included)	1182 / 3003	No	79

Gene	Gene Function	Chromosomal Location	Study Design	Population	Number of Cases/ Number of Controls	Significant Association?	Reference(s)
Methylene-tetrahydrofolate reductase (*MTHFR*)	Folate and amino acid metabolism	1p36.3	Candidate gene study	Turkish	76 / 34	No	[80]
			Candidate gene study	Greek	151 / 107	No	[71]
			Candidate gene study	U.S. Caucasian	140 / 127	No	[81]
			Candidate gene study	Central European	138 / 211	No	[82]
			Candidate gene study	German	71 / 71	No	[83]
			Candidate gene study	Iranian	85 / 90[8382828281]	No	[84]
Matrix metalloproteinases (*MMP*s)	Extracellular matrix turnover	Multiple chromosomal loci	Candidate gene study	Greek	182 / 214	Yes (though not significant after adjusting for multiple comparisons)	[85]
			Candidate gene study	Caucasian	202 / 248	No	[86]
Latent TGF-β binding protein 2 (*LTBP2*)	Structural component of microfibrils	14q24.3	Candidate gene study	Iranian	48 / None	Yes	[87]
			Candidate gene study	German	333 / 342	No	[68]

In addition to *LOXL1*, several other genes have been found to be associated with XFS/XFG risk. However, variants in these genes demonstrate association in only a limited number of populations, suggesting that these associations are either weak or are confined to specific ethnic groups.