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Genetics of Pseudoexfoliation Syndrome

Pratap Challa, MD
Department of Ophthalmology, Duke University Medical Center, Durham, NC

Abstract

Purpose of Review—Pseudoexfoliation syndrome (XFS) is a late onset and complex disorder that is strongly associated with the development of glaucoma. The purpose of this review is to discuss the inheritance patterns and recent genetic advances in the study of this disorder.

Recent Findings—XFS has a strong familial association and recently, the lysyl oxidase-like 1 gene (*LOXL1*) has been strongly associated with this disorder. This gene is involved in the synthesis and maintenance of elastic fibers and therefore has a strong biological rationale for being involved in this disorder. However, the exact relationship between *LOXL1* polymorphisms and the development of XFS has not been elucidated. Also, the value of genetic testing for this disorder has not been validated.

Summary—Pseudoexfoliation syndrome is an important risk factor for glaucoma and *LOXL1* polymorphisms are strongly associated with XFS. The mechanisms behind glaucoma development and the value of genetic testing are not clear and further study is needed.

Keywords

Pseudoexfoliation; Exfoliation; Glaucoma; *LOXL1*; Genetics

Introduction

Pseudoexfoliation syndrome (XFS) is one of the most common causes of secondary open angle glaucoma worldwide. XFS was initially described by Lindberg in 1917[1] and further characterized by Vogt in 1925[2], it is a systemic disorder in which an unidentified, fibrillar substance is produced in abnormally high concentrations within ocular tissues. The incidence of XFS varies among ethnic groups[3] with incidences that vary from no known reports in Greenland Eskimos[4] to a prevalence of 20–25% in the Scandinavian countries of Iceland and Finland[5].

XFS is clinically visualized as white, flaky deposits on intraocular tissues. The lens epithelium, the trabecular meshwork, iris, ciliary processes, conjunctiva, and peri-ocular tissues have all been shown by pathologic study to be sources of the XFS protein[6, 7]. In addition, it is a systemic disorder since multiple tissues such as skin, aorta, brain, heart, and kidney have been shown to contain the typical deposits. Electron microscopic studies suggest localized production by these cells and extracellular accumulation and deposition of the material.

Corresponding Author: Pratap Challa, MD, DUMC Box 3802 Erwin Road, Durham, NC 27710, Phone: 919-684-3283, Email: E-mail: Chall001@mc.duke.edu.

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Glaucoma Association

Both Lindberg and Vogt noted XFS's association with glaucoma and increasing age[1, 2]. XFS is associated with 20–60% of open angle glaucoma cases in many regions of the world including several scandinavian countries, Russia, Iran, Ethiopia, and the South African Bantu tribe[3, 8, 9]. High incidences are also reported from Ireland[10] and Sweden[11] where Pseudoexfoliation glaucoma (XFG) is present in up to two-thirds of individuals with open-angle glaucoma.

The association of glaucoma with XFS may be due to either accumulation of XFS material in the trabecular meshwork (TM) or production by trabecular or Schlemm's canal endothelium[6, 12]. Glaucoma development in these patients is likely due to accumulation of the abnormal extracellular material in the juxtacanalicular tissue (JCT) leading to disorganization and degeneration of the JCT and Schlemm's canal[6]. XFS material can also be seen *en masse* by transmission electron microscopy (TEM) to lie within the JCT. The material also aggregates along the periphery of Schlemm's canal and leads to bulging of its endothelial lining into the canal lumen. Focal collapse of the canal occurs that can then lead to decreased outflow and hence increased IOP[12]. Based on these observations, XFG can be considered a secondary form of OAG that is due to an obstruction and collapse of the outflow pathway of the eye. Therefore, it is not surprising that XFG is relatively resistive to medical therapy and that many patients eventually require glaucoma surgery.

Moreover, XFG appears to be distinct from primary open angle glaucoma (POAG). One distinction is that XFG patients tend to present with higher pressures that are more resistive to medical treatment. Moreover, although both types of glaucoma are relatively responsive to argon laser trabeculoplasty (ALT), XFG has a more rapid elevation in intraocular pressure (IOP) upon ALT failure[13]. Another distinguishing feature of XFS not found in POAG patients is the relatively high fraction of narrow anterior chamber angles. More than one-fifth of XFS patients have associated narrow angles[14, 15]. Finally, greater than 90% of POAG patients are steroid responders whereas XFS patients have a similar steroid response to the general population[16, 17]. Therefore, XFG and POAG are distinct diseases rather than spectrum disorders and therefore they would be expected to have different genetic associations.

Inheritance

XFS and XFG have been shown to demonstrate strong familial aggregation that is consistent with inherited disorders. Further evidence for inheritance is supported by increased relative risk of XFS in first degree relatives[18], twin studies[19], loss of heterozygosity[20], and documented transmission through two generation pedigrees. Multiple inheritance patterns have been suggested for XFS including autosomal dominant[18, 21], autosomal recessive[22], X-linked[23], and even maternal[24]. Therefore, a clear inheritance pattern is not evident implying that theses are complex disorders that likely involve multiple genes and/or environmental influences. Furthermore, XFS appears to be a late-onset disorder with incidences that increase with age. The Framingham eye study showed that incidences increase from 0.6% for ages 52–64 to 5.0% for ages 75–85[25]. Therefore, a diagnosis is usually made late in life and pedigrees with two or more affected generations are difficult to identify. This leads to difficulties in distinguishing normal young individuals from those who will eventually develop the disorder. Therefore, traditional linkage analysis and association studies are difficult to perform.

Genetic Association

One frequently used method to identify genes that may cause a disorder is to look at genetic markers throughout the genome and identify ones that occur more frequently in affected individuals. Genes near these markers can then be scrutinized further to see if they segregate with the disease. Thorleifsson *et.al*. performed such a genome-wide association study on

pseudoexfoliation individuals from Iceland and Sweden. After genotyping 594 affected and 14,672 control individuals, they demonstrated a strong association (>99% population attributable risk) of XFS and XFG conferred by three single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (*LOXL1*) gene[26]. Two SNPs were identified in the first coding exon and one within the first intron of this gene. Since introns are not transcribed into proteins, the effect of this intronic variant is unknown while both exonic variants are theorized to affect the function of the *LOXL1* enzyme and contribute to the development of XFS and XFG. *LOXL1* belongs to the lysyl oxidase or "LOX" family of extracellular enzymes that have multiple functions including the oxidative deamination of lysine residues to allow the proper orientation and crosslinking of elastin polymers from tropoelastin. *LOXL1* and elastin are expressed in the cornea, iris, ciliary body, lens capsule, and optic nerve[27]. Elastin has also been identified in the trabecular meshwork[28] and has been associated with zonular fibers[29]. In addition to the association study, *LOXL1* has a strong biochemical rationale for being associated with XFS and XFG.

The *LOXL1* association with XFS/XFG has been replicated in several other populations including the Unites States[30–32], Australia[27], India[33], and Japan[34–37]. No association has been shown with POAG[38], pigmentary glaucoma[39], or angle closure glaucoma[40]. Of the two exonic variants, the rs3825942 variant (Gly1153Asp) appears to be the most prevalent occurring in 94 to 100 % of XFG, 95 to 100% of XFS, and 57 to 88% of control individuals (see table). What these numbers basically suggest is that the rs3825942 variant is strongly associated with XFS and XFG. Interestingly, the second variant, rs1048661 (Arg141Leu) has not been replicated to the same degree as the previously mentioned one. Association has been replicated in an Australian[27] and two United States cohorts[30, 31] but a third United States[32] and an Indian cohort[33] do not demonstrate an association. Furthermore, this variant's effect appears to be inversely related to XFS/XFG development in all Japanese cohorts reported to date. In most groups, the "G" allele confers increased risk but it is the opposite "T" allele that confers increased risk in the Japanese. In the populations in which association has been proven, the "G" risk allele occurs in 78 to 84% of XFG, 78 to 83% of XFS, and 60 to 68% of control individuals. In the Japanese cohorts, the "T' risk allele occurs in 96 to 100% of XFG, 98 to 100% of XFS, and 51 to 54% of control individuals. This inverse relationship in Japanese subjects is particularly interesting and suggests that the rs1048661 has an unclear association with XFS/XFG. It is possible that this variant's effect is modified by other genes or the environment to produce an XFS/XFG phenotype. It is also possible that it may not play a role in the development of this disorder and underscores the need for further studies into the role of the rs1048661 SNP in the development of XFS/XFG.

The most striking feature of the *LOXL1* association is the very high prevalence of the SNPs in affected individuals. This shows that this gene is a major genetic risk factor for this disease conferring an approximately 80 to 99% population attributable risk in various cohorts. However, there is also a relatively high prevalence among control groups with reported prevalences up to 88%. One group has analyzed the rs3825942 and rs1048661 SNPs' ability to predict affection status in a genetic test for this disorder[30]. Although both SNPs have very high sensitivity (proportion of people who have the disorder and test positive), they also have a very low specificity (proportion of people who do not have the disorder and test negative). For rs3825942, the sensitivity of the "G" allele is 100% and specificity 3.1%. For rs1048661, the sensitivity of the "G" allele is 95.7% and the specificity is 13%. This means that although almost all patients who will eventually develop XFS or XFG can be identified by genetic testing, it would very difficult to exclude individuals who would not develop this disorder and thus straightforward allelic testing would have limited usefulness. Furthermore, the prevalence of the *LOXL1* SNPs is very similar between individuals with XFS and XFG. Therefore, allelic screening also wouldn't be able to isolate those individuals who would eventually develop glaucoma.

Moreover, the exact mechanism by which these two genetic variants lead to the development of XFS/XFG has not been identified. It is not clear if these *LOXL1* variants can significantly affect *LOXL1* expression. For instance, adipose tissue from individuals with the strongest risk allele of rs3825942 does not result in any detectable change in *LOXL1* expression. Furthermore, the smaller risk allele, rs1048661, results in only an 8% decrease in expression. This amount of change is generally considered negligible and would not be expected to cause a systemic disease such as XFS. Therefore, there are likely other genes or environmental influences that would lead to the development of XFS and XFG. However, one shouldn't discount the possibility that these variants are important. Tissue-specific expression of the *LOXL1* variants in ocular tissues has not been studied and expression in these tissues may be very different from that in adipose tissue. Moreover, rodent studies suggest that *LOXL1* expression decreases considerably with age[41] and therefore even small changes in *LOXL1* expression may become more significant with increased age. More studies in the expression of *LOXL1* in the trabecular meshwork, lens capsules, and optic nerve are needed. Some of these questions may be answered in the near future since a *LOXL1* knockout mouse is now being used to study the ocular phenotype of this disorder[42].

The similar and high prevalence of *LOXL1* variants in XFS and XFG suggest that these variants confer nearly equal risk to developing either of these disease states. Also, given the high prevalence in control samples, one would suspect that there must be other factors influencing the development of both XFS and XFG. Studies are currently underway to identify other genes associated with XFS/XFG. Evidence for this is suggested by a second genome-wide association study that has been performed on a Finnish family and demonstrates linkage to18q12.1–21.33, 2q, 17p, and 19q[43]. Although a major gene for XFS/XFG has been identified in *LOXL1*, this linkage study suggests that there must be other genes involved with this complex and late-onset disorder. Furthermore, the high prevalence of *LOXL1* variants in control individuals raises the possibility that there are protective genes or environmental factors that retard the development of XFS or XFG. Therefore, future studies will be aimed at identifying such genes or factors. This line of research may eventually help elucidate some of the basic mechanisms behind glaucoma development in general.

Conclusion

Pseudoexfoliation syndrome is a major cause of glaucoma that has a strong familial association. Recent studies have confirmed that *LOXL1* is a major gene associated with both XFS and XFG. Based on the high prevalence of LOXL1 variants in normal individuals and the relative similarity of prevalences in individuals with XFS and XFG, genetic testing for this disorder is problematic. Further study is needed to distinguish how the LOXL1 gene leads to XFS and XFG development.

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Table

List of the allelic frequencies of *LOXL1* variants reported in different populations

Summary of representative studies reporting on the allelic frequencies of SNPs rs3825942 and rs1048661 in the *LOXL1* gene related to pseudoexfoliation syndrome and glaucoma.

Population	Affection status	rs3825942 (%)	rs1048661 (%)	Reference
Iceland	Control	85	65	26
	XFG	99	83	26
	XFS	98	79	26
Sweden	Control	88	68	26
	XFG	100	83	26
	XFS	n/a	n/a	26
United States	Control	84	67	30
	XFG	94	79	30
	XFS	n/a	n/a	30
United States	Control	99	60	31
	XFG	n/a	n/a	31
	XFS	88	82	31
India	Control	74	63	33
	XFS/XFG combined	92	72	33
Japan*	Control	86	54	35
	XFG	100	100	35
	XFS	100	100	35

The asterick (*) denotes that the reported frequencies in the Japanese are for the “T” allele of rs1048661. All other allelic frequencies are for the respective “G” allele.