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GLAUCOMA UPDATE

Review: The role of *LOXL1* in exfoliation syndrome/glaucoma

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Abstract Exfoliation syndrome is a common cause of open-angle glaucoma. It is characterized by microscopic flakes of protein-rich material being deposited in both ocular and non-ocular tissues. While its mechanism is poorly understood, family- and population-based studies have established that the disorder has a strong genetic component. A further understanding of the relevant gene variants might help reveal the molecular mechanism behind exfoliation. The most-strongly associated genetic variants are found in the *lysyl oxidase-like 1* (*LOXL1*) gene. However, two major risk alleles in the *LOXL1* coding region are reversed between ethnic groups. It now appears the strong association between *LOXL1* and XFS is due to non-coding variants that have not yet been identified. Such variants might alter *LOXL1* expression, which is decreased in the late stages of exfoliation syndrome/glaucoma. Here we discuss *LOXL1* as a risk gene for exfoliation syndrome and glaucoma.

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Contents

1. Introduction

Exfoliation syndrome (XFS) is the most common identifiable cause of open-angle glaucoma (Ritch, 1994). The resulting glaucoma, termed exfoliation glaucoma (XFG), is a blinding disorder characterized by whitish flakes in the anterior chamber of the eye, increased intraocular pressures, and optic nerve damage. The clinical presentation of XFG has been described in great detail in previous articles (Ritch and Schlotzer-Schrehardt, 2001; Vesti and Kivela, 2000). XFG currently carries a worse prognosis than primary open-angle glaucoma (POAG). XFG accounts for approximately 25% of open-angle glaucoma worldwide and is more concentrated in certain regions and ethnic groups (Ritch and Schlotzer-Schrehardt, 2001). The risk of developing glaucoma in patients with XFS is increased with longer duration. Approximately half of the eyes with XFS will develop glaucoma within 15 years of diagnosis (Jeng et al., 2007).

XFS is a systemic disorder that involves abnormal deposition of microscopic fibrils in numerous ocular and non-ocular tissues (Schlotzer-Schrehardt and Naumann, 2006). The etiology of XFS is not fully understood but appears to be related to the excessive production and abnormal crosslinking of elastic fibers (Schlotzer-Schrehardt, 2011). Deposition of these fibers is known to occur in the trabecular meshwork which likely contributes to reduced facility of aqueous outflow, elevated IOP, and can ultimately lead to the development of glaucoma (Ritch et al., 2003). While the etiology of XFS/XFG remains unknown, the disease appears to depend on risk genetic factors around the *lysyl oxidase-like 1* (*LOXL1*) gene. A full understanding of this association could be a powerful clue to the pathology of XFS and its associated glaucoma.

2. XFS has complex inheritance pattern

XFS has a strong hereditary component. Family studies have consistently supported a role for genetic factors XFS risk (Allingham et al., 2001; Damji et al., 1998; Forsman et al., 2007). The pattern of inheritance is not clear however, and may be due to late onset of disease and incomplete penetrance (Forsman et al., 2007). These factors make it difficult to identify segregation patterns in families. In addition to these factors there may be important environmental factors involved in the pathogenesis of XFG/XFS (Challa, 2009).

The prevalence of XFS/XFG is highly variable among different racial or ethnic groups. Rates in the Native American Navajo population have been reported at 38% (Friederich, 1982). The Nordic populations have rates of XFS above 15% in individuals over 60 years of age (Arnarsson et al., 2007). Some Arab and Greek populations have rates of XFS above 25% in people over 70 (Summanen and Tonjum, 1988; Topouzis et al., 2007). The reports in Arabs also found a significant burden of XFS in younger groups, nearing 8% in patients between ages 50 and 60 (Summanen and Tonjum, 1988). In contrast, XFS/XFG is rare among the West African and Eskimo populations (Forsius, 1988; Ntim-Amponsah et al., 2004). Although environmental factors may play a role in XFS or XFG, it is interesting to note that African Americans, largely descended from West African populations, also share the low prevalence of XFS/XFG despite living in a region where the prevalence is substantially higher (Cashwell and Shields, 1988).

3. Variants in *LOXL1* associate with XFS

The lysyl oxidase-like 1 (*LOXL1*) gene was first associated with XFS/XFG in a genome-wide association study (GWAS) (Thorleifsson et al., 2007). Three single-nucleotide polymorphisms (SNPs) were found to be highly associated with XFG and later with XFS. All three SNPs were located within the *LOXL1* gene. One SNP, rs2165241, was located in intron 1 of *LOXL1*. The other two SNPs, rs1048661 and rs3825942, were missense variants located in exon 1. For both coding SNPs, the 'G' allele was associated with a higher risk of XFS and XFG.

The relationship between the *LOXL1* SNPs and XFS has now been studied in numerous populations including Swedish (Thorleifsson et al., 2007), US Caucasian (Aragon-Martin et al., 2008; Challa et al., 2008; Fan et al., 2008; Fingert et al., 2007; Yang et al., 2008), Australian (Hewitt et al., 2008), German (Wolf et al., 2010), Italian (Pasutto et al., 2008), Central European (Mossbock et al., 2008), Finnish (Lemmela et al., 2009), Chinese (Chen et al., 2009; Lee et al., 2009), Japanese (Fuse et al., 2008; Hayashi et al., 2008; Mabuchi et al., 2008; Mori et al., 2008; Ozaki et al., 2008; Tanito et al., 2008), Indian (Ramprasad et al., 2008), South African (Rautenbach et al., 2011; Williams et al., 2010), and Saudi Arabian (Abu-Amero et al., 2010). Observed SNP frequencies for the two missense variants are shown in Table 1.

Table 1 Summary of the genetic association of two coding variants in *LOXL1* gene with XFS/XFG.

Studied population	rs1048661 'G' allele		Significant association	rs3825942 'G' allele		Significant association	References
	Case	Control		Case	Control		
Icelandic	0.781	0.651	Yes	0.984	0.847	Yes	Thorleifsson et al. (2007)
Swedish	0.834	0.682	Yes	0.995	0.879	Yes	Thorleifsson et al. (2007)
American	0.819	0.600	Yes	0.986	0.880	Yes	Fingert et al. (2007)
American	0.787	0.665	Yes	0.939	0.844	Yes	Challa et al. (2008)
American	NA	NA	NA	1.000	0.856	Yes	Yang et al. (2008)
American	0.843	0.703	Yes	0.959	0.798	Yes	Aragon-Martin et al. (2008)
American	0.829	0.719	No	0.988	0.795	Yes	Fan et al. (2008)
Australian	0.78	0.660	Yes	0.95	0.84	Yes	Hewitt et al. (2008)
Austrian	0.841	0.671	Yes	0.994	0.817	Yes	Mossbock et al. (2008)
Germany	0.844	0.660	Yes	0.992	0.856	Yes	Wolf et al. (2010)
Germany	0.818	0.644	Yes	0.951	0.857	Yes	Pasutto et al. (2008)
Finnish	0.825	0.683	Yes	0.968	0.823	Yes	Lemmela et al. (2009)
Italian	0.825	0.693	Yes	1.000	0.821	Yes	Pasutto et al. (2008)
Saudi Arabian	0.876	0.762	Yes	0.968	0.817	Yes	Abu-Amero et al. (2010)
Indian	0.721	0.634	No	0.923	0.742	Yes	Ramprasad et al. (2008)
Chinese	0.542	0.444	No	0.992	0.918	Yes	Lee et al. (2009)
Chinese	0.110	0.480	Yes	1.000	0.900	Yes	Chen et al. (2009)
Japanese	0.036	0.493	Yes	1.000	0.877	Yes	Fuse et al. (2008)
Japanese	0.008	0.460	Yes	1.000	0.857	Yes	Hayashi et al. (2008)
Japanese	0.006	0.450	Yes	0.994	0.853	Yes	Mabuchi et al. (2008)
Japanese	0.005	0.474	Yes	0.995	0.850	Yes	Mori et al. (2008)
Japanese	0.005	0.497	Yes	0.986	0.863	Yes	Ozaki et al. (2008)
Japanese	0.005	0.554	Yes	0.993	0.806	Yes	Tanito et al. (2008)
South African	0.990	0.810	Yes	0.130	0.620	Yes	Williams et al. (2010)
South African	1.000	0.883	Yes	0.140	0.617	Yes	Rautenbach et al. (2011)

NA: not available; *LOXL1*: lysyl oxidase-like 1; XFS: exfoliation syndrome; XFG: exfoliation glaucoma.

The association between the 'G' risk alleles and XFS has been largely consistent across all tested populations. However there have been important exceptions. For example, the 'G' allele for rs1048661 was not significantly associated with XFG in an Indian (Ramprasad et al., 2008) and Chinese (Lee et al., 2009) population. Furthermore, the 'G' allele of rs1048661 was found to actually be *protective* in another Chinese population (Chen et al., 2009) and several Japanese populations (Fuse et al., 2008; Hayashi et al., 2008; Mabuchi et al., 2008; Mori et al., 2008; Ozaki et al., 2008; Tanito et al., 2008). The inconsistent association between XFG and rs1048661 was also observed for the intronic SNP, rs2165241 (Chen et al., 2010). For this reason, it was concluded that this SNP is not a functional variant for XFS/XFG.

The inconsistencies with rs1048661 and rs2165241 left the third SNP, rs3825942, as the most promising functional candidates for XFS. The rs3825942 SNP appeared to contribute to XFS for two reasons. First, similar to rs1048661, the 'G' allele for rs3825942 causes a missense change, G153D, in the LOXL1 protein, a change that may have functional consequences for the LOXL1 protein (Abu-Amero et al., 2010). Second, the 'G' allele of rs3825942 was strongly, and consistently, associated with XFS in a diverse set of populations. However, recently two reports have found that the opposite 'A' allele for rs3825942 is the risk allele in the South African black population (Williams et al., 2010; Rautenbach et al., 2011). Given the South African result, it now appears that rs3825942 does not contribute to XFS. It now appears most likely that these SNPs are in association with the actual functional allele (Williams et al., 2010). The *LOXL1* coding sequence has now been completely sequenced in multiple populations with no consistent risk alleles emerging (Abu-Amero et al., 2010; Williams et al., 2010). Attention is now turning to non-coding, regulatory regions of *LOXL1*. These regions might contain functional variants that contribute to XFS/XFG.

4. Biochemical rationale for *LOXL1* in XFS

Efforts have begun to understand how the pathogenesis of XFS could be influenced by *LOXL1*. *LOXL1* is a member of the lysyl oxidase gene family, a group of enzymes involved in the synthesis and maintenance of elastic fibers (Csiszar, 2001; Kagan and Li, 2003). *LOXL1* appears to be particularly important in the renewal of elastic tissues. This is supported by LOXL1's strong colocalization with elastin in vivo and also by observations in *LOXL1*-knockout mice (Liu et al., 2004). These mice develop multiple abnormalities of elastic tissue that include lax skin, diverticula, enlarged airspaces, and prolapse of the rectum and pelvis. Female mice lacking *LOXL1* initially have normal appearing elastic tissue; however, they are unable to deposit new elastic tissues after pregnancy and birth. Collectively, these data suggest that LOXL1 is responsible for targeted renewal of elastic fibers (Liu et al., 2004).

On a molecular level, LOXL1 appears to polymerize tropoelastin monomers into growing elastin polymers (Kagan and Li, 2003; Liu et al., 2004). To accomplish this, LOXL1 is first targeted to sites of elastogenesis by a pro-region located near its N-terminus (Thomassin et al., 2005). LOXL1 is then activated by removal of the pro-region by a proteinase. This

cleavage activates a catalytic domain towards the C-terminus of LOXL1. Once activated, LOXL1 deaminates lysine residues in the tropoelastin molecule, allowing it to join the growing elastin polymer.

From the genetic studies cited above, it now appears that LOXL1 protein is involved in the pathogenesis of XFS, a disorder of elastic tissues (Schlotzer-Schrehardt, 2009). XFS fibrils also contain additional proteins involved in elastic fiber synthesis and structure (Ovodenko et al., 2007). In immunohistochemistry studies, XFS fibrils have been found to stain positively for the LOXL1 protein and its substrate tropoelastin (Schlotzer-Schrehardt et al., 2008). Interestingly, an important binding partner of LOXL1, fibulin-5, was absent in PEX deposits (Thomassin et al., 2005).

5. Altered *LOXL1* expression is a possible pathological mechanism

Altered *LOXL1* expression might contribute to the development of XFS. Current evidence suggests that *LOXL1* expression is altered in XFG. In cadaveric ocular tissues, the expression of *LOXL1* was found increased in early-stage XFS but decreased in late-stage XFS and in XFG (Schlotzer-Schrehardt et al., 2008). Subsequent studies regarding the expression of *LOXL1* in XFS/XFG have had mixed results (Khan et al., 2010; Mori et al., 2008).

Several SNPs have been investigated for their effects on *LOXL1* expression. Both coding SNPs identified in the initial GWAS were studied for effects on *LOXL1* expression. The coding SNP rs1048661 is associated with altered expression of *LOXL1*. Its 'G' allele was associated with a 7.7% decrease of *LOXL1* expression in adipose tissue (Thorleifsson et al., 2007) and approximately 20% in postmortem ocular tissue (Schlotzer-Schrehardt et al., 2008). In contrast, the most strongly associated SNP, rs3825942, was not associated with a net increase or decrease of *LOXL1* expression in adipose or ocular tissue (Schlotzer-Schrehardt et al., 2008; Thorleifsson et al., 2007).

Another SNP, rs16958477, was found to alter *LOXL1* expression *in vitro* (Ferrell et al., 2009). This SNP is located 659 base pairs upstream of *LOXL1*. It appears to influence the promoter activity of the one kilobase region upstream of *LOXL1*. Its 'C' allele was associated with increased promoter activity in a commercial plasmid. This SNP was originally investigated for a connection to pelvic organ prolapse but no significant correlation was observed (Ferrell et al., 2009). The SNP also did not associate with XFG in black South Africans (Williams et al., 2010). The 'A' allele did associate with XFS in a large Caucasian cohort with an OR 2.05 (1.54–2.72) (Jian Fan et al., 2011). However, this association was much weaker than rs3825942, which yielded an OR of 25 (8.3–50) in the same cohort.

Collectively, these data leave several questions about the role of expression in XFS and how to investigate it. First is the odd situation that there is no recognized correlation between the most-strongly associated variant, rs3825942, and *LOXL1* expression. One possible explanation is that rs3825942, and any variant in LD with rs3825942, might alter expression patterns of *LOXL1* without causing a net change of mRNA levels. Such a scenario could relate to the repeated observation that *LOXL1* expression does not decrease until late in the pathogenesis of XFS and might actually be increased in early stages of XFS (Schlotzer-Schrehardt et al., 2008).

6. Other possible mechanisms for *LOXL1* in XFS

The connection between *LOXL1* and XFS could also possibly result from another mechanism that does not center on expression. One possibility is that a variant in the *LOXL1* region could have an effect on *LOXL1* splicing. Evidence now supports that a non-coding SNP can influence mRNA splicing (Tazi et al., 2009). For example, the dopamine D2 receptor gene carries two intronic SNPs that decrease the expression of one splice product (Zhang et al., 2007). There is some evidence to suggest that many GWAS associations for human traits may be the result of splicing effects (Heinzen et al., 2008). In the case of *LOXL1*, an intronic SNP might alter *LOXL1* splicing. The *LOXL1* intronic sequence has not been studied in previous reports, but it does contain at least one SNP, rs2165241, that is strongly associated with XFS in some populations (Jian Fan et al., 2011; Thorleifsson et al., 2007).

7. Other genes associated with XFS

Other genes appear to have a role in XFS and XFG. While *LOXL1* variants associate strongly with XFS, the high-risk alleles are often found in older unaffected individuals (Table 1). This failure to develop XFS might partly result from other genes that influence XFS pathogenesis. Several other genes have been investigated. From these studies, a few possible population-specific risk factors have emerged (Schlotzer-Schrehardt, 2011).

A study in German patients looked at variants across six genes that appear to have a functional role in the pathogenesis of XFS (Krumbiegel et al., 2009). A total of 50 SNPs were genotyped across these genes. Of the 50, only one SNP was found to associate with XFS in the German cohort with an OR of 1.34. The SNP was located in the 8th intron of the *clusterin* (*CLU*) gene. This one variant was then tested in a second German cohort where it was still significant. However, in an Italian cohort, the SNP was not significant (Krumbiegel et al., 2009). It is possible that this allele has varying effects based on ethnic background. Other genes have been investigated because of a suspected role in the development of XFS or transition from XFS to XFG (Schlotzer-Schrehardt, 2011). To date, most investigations have found negative results. Significant associations have often been limited to studies in one population but not another (Schlotzer-Schrehardt, 2011).

A recent GWAS in German patients found an association with variants of the *CNTNAP2* gene with risk of exfoliation (Krumbiegel et al., 2011). *CNTNAP2* is a neuronal membrane protein that is expressed in numerous ocular tissues involved in XFS (Krumbiegel et al., 2011). This result was replicated in a second German cohort, with a combined odds ratio (OR) of about 1.4. However, *CNTNAP2* was not associated with XFS in an Italian cohort (Krumbiegel et al., 2011). Therefore, it appears that *CNTNAP2* may also be a population-specific risk factor.

8. Potential impact of *LOXL1* variants on XFS management

Genetic screens for XFS are currently impractical due to the low-specificity of known risk alleles (Challa, 2009). For instance, in Caucasians, the rs3825942 risk allele has an 88% frequency in controls (Fingert et al., 2007). Effective risk screening will require the identification of new risk variants, either in the *LOXL1* region or in other genes.

The *LOXL1* region might carry more genetic information to aid in risk stratification. To date, most studies have focused on the missense variants, which alone do not allow for meaningful risk stratification. However, it appears that the *LOXL1* region contains other SNPs that confer risk of XFS independently of the missense variants. For example, a promoter SNP identified in US Caucasians was found to increase of risk of XFS even when controlling for rs3825942 genotype (Jian Fan et al., 2011).

An understanding of all genetic contributions to XFS, both inside the *LOXL1* region and in other genes, might allow for improved risk stratification. However, the impact of environmental factors and the influence of random chance might limit the predictive value of XFS risk variants. Only with a better understanding of both genetic and environmental contributions could accurate risk stratification be achieved. Even then, a screen for risk-variants might only be cost-effective in certain ethnicities.

Genetic insights might also aid in the treatment of XFG. A mechanism to explain the *LOXL1*-XFG association could allow for new targets for intervention. For example, XFG patients might benefit from increased *LOXL1* expression since they tend to have reduced expression in the eye (Khan et al., 2010). More research might unveil additional targets for molecular interventions.

9. Conclusions

The *LOXL1* region contains variants that are strongly associated with XFS and XFG. Previous risk allele reversals observed in Asian and African populations suggest that the functional variants near *LOXL1* have not been identified. Identification of the functional variants near *LOXL1* will allow for a comprehensive study of the mechanisms that underlie XFS and XFG. Such knowledge might impact the diagnosis and management of these conditions.

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