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# Prevalence of risk alleles in the lysyl oxidase-like 1 gene in pseudoexfoliation glaucoma patients in India

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**Purpose:** The purpose of this study was to genotype two previously identified SNPs (rs1048661:R141L, and rs3825942:G153D) in the lysyl oxidase-like 1 (*LOXL1*) gene and determine their association with pseudoexfoliation glaucoma (XFG) in patients from Pune, India. **Methods:** All subjects underwent detailed phenotyping, and DNA extraction was performed on blood samples by using standardized techniques. Exon 1 of the *LOXL1* gene containing the SNPs (rs3825942:G153D; rs1048661:R141L) were Sanger sequenced, and the results were analyzed using sequence analysis software SeqScape 2.1.1. **Results:** Data were analyzed from 71 patients with XFG and 81 disease-negative, age-matched controls. There was a strong association between the G allele of rs3825942 and XFG with an odds ratio of 10.2 (CI: 3.92–26.6; $P < 0.001$). The G allele of rs1048661 also showed an increase in risk relative to the T allele (OR = 1.49; CI: 0.88–2.51; $P = 0.13$), but this was not significant. Haplotype combination frequencies were estimated for rs1048661 and rs3825942; the GG haplotype was associated with a significant increase in risk (OR = 3.91; CI: 2.27–6.73; $P < 0.001$). Both the GA and TG haplotypes were associated with decreased XFG risk, although the latter was not significant (GA: OR = 0.08; CI: 0.03–0.21; $P < 0.001$; TG: OR = 0.67; CI: 0.40–1.13; $P = 0.13$). **Conclusion:** The risk G allele in rs3852942 (G153D) is strongly associated with the development of XFG in the Western Indian population. Genetic screening strategies to identify *LOXL1* risk alleles in the population can assist in case definition and early diagnosis, targeting precious resources to high-risk patients.

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Pseudo-exfoliation syndrome (XFS) is a systemic condition associated with open-angle glaucoma that affects over 60 million people worldwide.[1] Pseudoexfoliation glaucoma (XFG) is the most common secondary cause of open-angle glaucoma worldwide.[2,3] XFS is characterized by the deposition of pathological grayish-white extracellular fibrillar protein components (PEX material) in multiple ocular tissues that are composed of constituents of the basement membrane and elastic fiber components.[4] Deposition of this PEX material in the trabecular meshwork obstructs aqueous outflow, and almost 50% of XFS patients will ultimately develop XFG in their lifetime.[3] The ocular phenotype of XFG is more aggressive than primary open-angle glaucoma and is associated with greater elevations in intraocular pressure (IOP) and poorer treatment response.[5]

The prevalence of XFS varies with age and ethnicity,[6,7] with much higher prevalence reported in certain populations, for example, Scandinavian countries and Ireland.[8,9] The role of genetics in the pathogenesis of XFS was confirmed when a genome-wide association study in the Scandinavian population identified three single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (*LOXL1*) gene that strongly associated with risk for developing XFS and XFG.[10] *LOXL1* is a member of the lysyl oxidase group of enzymes involved in the cross-linking of collagen fibrils and elastin in the extracellular matrix. In the Nordic population, individuals homozygous for the high-risk *LOXL1* haplotype in three SNPs (rs1048661, rs3825942, and rs2165241) had an estimated 700-fold increased risk for developing XFG compared to individuals with the

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low-risk haplotype. Although the two non-synonymous SNPs rs1048661 (G>T; Arginine 141 Leucine; R141L) and rs3825942 (G>A; Glycine 153 Aspartate; G153D) in the first exon of the *LOXL1* gene confer a higher than 99% population attributable risk for PXS and PXG in the Nordic population, they are associated with different risks in other populations;[10,11] for example, the A allele of rs3825942 (G153D) in a South-African population showed a stronger association with an increased risk of XFG than the well-reported opposite G allele.[11]

Given that the *LOXL1* risk alleles are reversed in the South-African[11,12] and Asian populations,[13,14] understanding the ethnic distributions of *LOXL1* alleles is relevant to understand the genetic epidemiology of XFS/XFG. Furthermore, while the proportion of cases and controls harboring *LOXL1* risk alleles is relatively consistent across geographic regions, the prevalence of XFG appears to increase with latitude.[15] There have only been three studies to date examining the prevalence of SNPs in *LOXL1* in individuals with XFS or XFG from the Indian population.[16–18] Two of these studies were based in the Tamil population of South India.[16,17] The third study was from northern India, based in Chandigarh, Punjab but was underpowered to detect significant genetic associations.[18] Therefore, the purpose of this study was to sequence two previously identified SNPs (rs1048661; R141L and rs3825942; G153D) in *LOXL1* [Fig. 1] and to determine their association with XFG among patients from a population on the Indian subcontinent of higher latitude (Pune, Maharashtra in the Western part of India) and ethnically different from the Tamil population of southern India.

## Methods

### Patients

Patients with XFG were recruited following careful phenotyping (by CS) from clinics in Pune, Maharashtra, in western India. The study was approved by the (BLINDED FOR THE PURPOSES OF PAPER REVIEW) and the Indian Medical Research Council (http://www.icmr.nic.in/). Written, informed consent was obtained from all subjects, and the study was performed according to the tenets of the Declaration of Helsinki. All subjects and controls underwent a comprehensive ocular examination, including visual acuity, slit-lamp examination, Goldmann applanation tonometry, and optic disc examination. All subjects underwent a standardized ophthalmic examination, and XFS was identified when the presence of exfoliation material was noted on the lens capsule, iris, or corneal endothelium. Pseudoexfoliation glaucoma was diagnosed if the patient fulfilled the criteria for XFS and the presence of the following: (1) a presenting intraocular pressure (IOP) of >21 mm Hg in at least one eye by Goldmann applanation tonometry; (2) glaucomatous optic nerve head damage on stereoscopic optic disc examination (notching or thinning of the neuroretinal rim and/or increased cup/disc ratio in relation to the optic disc size); (3) an open anterior chamber angle on gonioscopy; (4) reproducible and characteristic glaucomatous visual field defect with the Humphrey 24-2 full-threshold strategy (Carl Zeiss Meditec, Oberkochen, Germany). Ethnic and age-matched control subjects were also recruited from the study population.

### Polymerase chain reaction amplification and DNA sequencing

Genomic DNA was extracted from all the subjects by using a Wizard Genomic DNA Purification Kit (Promega, Southampton, U.K.**)** according to the manufacturer's instructions. In XFG patients and controls, the region of the *LOXL1* gene harboring the SNPs, rs1048661 (R141L) and rs3825942 (G153D), was amplified using the primers, 5-ATTCGGCTTTGGCCAGGT-3′ and 5-GAACTGCTGCGGGTAGGA-3. Bidirectional cycle sequencing was performed using BigDye Terminator

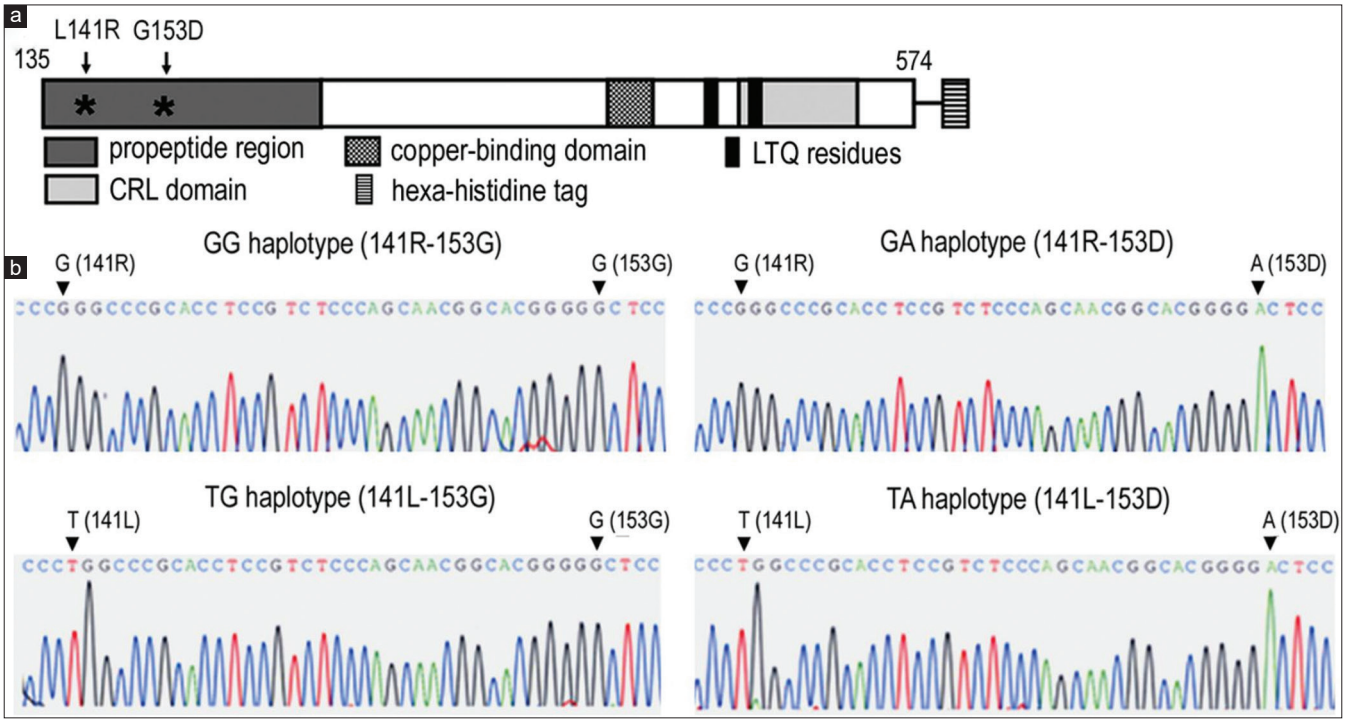


**Figure 1:** Showing LOXL1 gene with SNPs L141R and G153D (a) and the at-risk haplotypes (b)[19]

**Table 1: Genotype and allele frequencies, odds ratios, 95% confidence intervals, and *P* values for rs1048661 (R141L) and rs3825942 (G153D) in 71 cases of pseudoexfoliation glaucoma and 81 controls**

| SNP | Genotype | Cases *n* (%) | Controls *n* (%) | Odds Ratio (95% CI) | *P* |
|---|---|---|---|---|---|
| rs1048661 | GG | 43 (60.6) | 39 (48.1) | 1.93 (0.52-7.01) | 0.32 |
| R141L | GT | 24 (33.8) | 35 (43.2 | 1.61 (0.82-3.16) | 0.17 |
| | TT | 4 (5.6) | 7 (8.6) | 1.00 (reference) | |
| | G allele | 110 (77.5) | 113 (69.7) | 1.49 (0.88-2.51) | 0.13 |
| | T allele | 32 (22.5) | 49 (30.3) | 1.00 (reference) | |
| rs3825942 | GG | 66 (93.0) | 40 (49.4) | 12.5 (4.56-34.5) | <0.001 |
| G153D | GA | 5 (7.0) | 38 (46.9) | 1.00 (reference) | |
| | AA | 0 (0.0) | 3 (3.7) | -[a] | - |
| | G allele | 137 (96.5) | 118 (72.8) | 10.2 (3.92-26.6) | <0.001 |
| | A allele | 5 (3.5) | 44 (27.2) | 1.00 (reference) | |

[a]It was not possible to estimate the odds ratio for the AA genotype for G153D as no cases were detected

**Table 2: Estimated haplotype frequency and analysis of missense variants R141L and G153D**

| Haplotype | Case *n* (%) | Control *n* (%) | Combined *n* (%) | Odds ratio (95% CI) | *P* |
|---|---|---|---|---|---|
| GG | 105 (74) | 69 (43) | 174 (57) | 3.91 (2.27-6.73) | <0.001 |
| TG | 32 (22) | 49 (30) | 81 (27) | 0.67 (0.40-1.13) | 0.13 |
| GA | 5 (4) | 44 (27) | 49 (16) | 0.08 (0.03-0.21) | <0.001 |

95% CI: 95% confidence interval

v3.1 cycle sequencing kit (Applied Biosystems, Warrington, UK) and electrophoresed on an ABI PRISM 3730 DNA sequencer (Applied Biosystems, Foster City, CA, USA) (conditions available on request). Sequencing results were analyzed manually using the sequence analysis software SeqScape version 2.1.1 (Applied Biosystems, Foster City, CA, USA).

Statistical analysis was performed using Pearson's $X^2$ test (adjusted by Yates correction where necessary) to compare patient and control groups for possible associations between SNP alleles, genotype, and haplotype frequencies with the disease state. Odds ratios (ORs) were calculated using binary logistic regression, taking a 95% confidence interval (95% CI) into account. $P < 0.05$ was considered as statistically significant. ORs, and 95% CIs were calculated for each haplotype compared to all the other haplotypes. Hardy–Weinberg equilibrium was assessed using $\chi 2$ test.

## Results

Mutational analysis for both SNPs was performed on 71 patients with XFG and 81 ethnically matched controls from Maharashtra, India. The distribution of genotype and allele frequencies of rs1048661 (R141L) and rs3825942 (G153D) in *LOXL1* are reported in Table 1. There was a strong association between the G allele of rs3825942 and XFG with an odds ratio of 10.2 (CI: 3.92–26.6; $P < 0.001$). The G allele of rs1048661 also showed an increase in risk relative to the T allele (OR = 1.49; CI: 0.88–2.51; $P = 0.13$), but this was not significant. Haplotype combination frequencies were estimated for rs1048661 and rs3825942 [Table 2]. The GG haplotype was associated with a significant increase in risk (OR = 3.91; CI: 2.27–6.73; $P < 0.001$). Both the GA and TG haplotypes were associated with decreased XFG risk, although the latter was not significant (GA: OR = 0.08; CI: 0.03–0.21; $P < 0.001$; TG: OR = 0.67; CI: 0.40–1.13; $P = 0.13$).

## Discussion

Glaucoma is the second leading cause of blindness in the adult population in India,[20] affecting 12 million people and is responsible for 12.8% of the total blindness in India.[21] The prevalence of XFS in India has been reported to be between 3% and 6% in those aged 40 years and above.[22–24] SNPs in *LOXL1* have been associated with the development of XFG across multiple populations,[10,11,14,16,25] but studies have been limited in the Indian population.[16–18] The results of our study in XFG patients from Maharashtra in western India indicate a strong association between the G allele of rs3825942 (G153D) and XFG, which was statistically significant (OR = 10.2; $P < 0.001$). However, an association between rs1048661 (R141L) and XFG in our study population was not significant (OR = 1.49; $P = 0.13$). This is in contrast with the data from original genome-wide association study (GWAS) in XFG in the Scandinavian population in which the "at-risk" allele produced an odds ratio of 2.46 ($P = 2.3 \times 10^{-12}$).[10] Meta-analyses of published studies in multiple populations implicated rs3825942 (G153D) as the main disease associated SNP in XFG,[26,27] and this is represented in our genotype data. Furthermore, single-variant analysis in GWAS of XFS cases and controls from 24 countries showed that of all common variants polymorphic across all collections studied, rs3825942 (G >A) remained the most significantly associated (fixed-effects $P = 4.14 \times 10^{-62}$) but showed very high heterogeneity across the study groups (random-effects $P = 0.0039$).[28]

Three previous genetic association studies have investigated *LOXL1* SNPs and XFS/XFG risk in India. Two of these were based in the Tamil populations from Chennai[16] and Madurai[17] in southern India and the third was from north India.[18] The study from northern India was underpowered (30 XFG cases and 61 controls) and no significant genetic association was detected for rs3825942 or rs1048661). In 52 individuals with XFS (some

with or without glaucoma) in Chennai, Tamil Nadu, southern India, the G allele of rs3825942 (G153D) showed a significant association ($P$ = 0.0001, OR = 4.17, CI: 1.89–9.18)[16] in keeping with our findings. In 150 XFG cases from Madurai, Tamil Nadu, southern India, there was a strong association of the "at risk" G allele in rs3852942 and XFG (OR = 6.40; $P = 2.47 \times 10^{-13}$). The data for the effect of the risk allele in rs1048661 (R141L) and XFG is conflicting in the Indian population and less strongly associated with XFG. No significant association between rs1048661 and XFG was detected in our data which reflects the findings of the Chennai study (($P$ = 0.156 for allele G; OR = 1.49)[16] and is in contrast to the data from Madurai (OR = 2.03; $P = 6.77 \times 10^{-5}$).[17] Based on our study and these published studies,[16,17] the risk G allele in rs3852942 (G153D) is strongly associated with the development of XFG in the Indian population. A consideration that needs to be accounted for while interpreting the results of this study is that the significance of the smaller effect sizes observed may be as a result of the smaller sample size used in this study in comparison to others.

Most previous studies have identified the G allele in rs3852942 (G153D) as the risk allele in the development of XFG.[29] However, the A allele of rs3825942 (G153D) showed a stronger association with an increased risk of XFG in black individuals from the South-African population in contrast to the well-reported opposite G allele.[11] Similarly, other SNPs in *LOXL1* show variations in the direction of effect between different populations. The risk-associated allele for rs16958477 (promoter SNP) varied between the South Indian population[17] and the Caucasian population of the United States.[30] The A allele of rs16958477 was associated with an increased risk in Caucasian individuals, whereas in Indian subjects, this allele showed a protective effect.[30] The reversal of the *LOXL1* risk alleles in ethnically different populations [13,14] suggest that while specific *LOXL1* alleles are associated with XFG risk, they are not causative.[31] In addition, a large international GWAS study found no common variant in *LOXL1* consistently associated across all cohorts, and no common variant in this gene surpassed genome-wide significance in random-effects analysis.[28] This GWAS also identified five new XFS-associated loci that may be implicated in novel biological pathways for disease pathogenesis.[28] Such stark allele reversals and the results from GWAS imply that the genetic architecture underlying XFG disease biology is complex and worthy of further study.[28]

The biological mechanism associated with the risk of allelic variation in the *LOXL1* gene and XFG is poorly understood.[32] The *LOXL1* SNPs rs1048661 and rs3825942 alter the coding sequence of LOXL1 resulting in amino acid substitutions: R141L (rs1048661; arginine to leucine) and G153D (rs3825942; glycine to aspartate). Overexpression of these mutant LOXL1 proteins (R141L and G153D) in a fibroblastic cell line demonstrated altered LOXL1 processing.[33] However other studies have suggested that the missense changes are not biologically significant[11,13,32,34] and do not affect enzymatic activity.[19] The dysregulation of LOXL1 in XFG may simply be a contributing factor to development of the disease in addition to other factors: raised transforming growth factor beta-1 (TGFβ1), oxidative stress, UV light,[35] and hypoxia.[31,36] There is some emerging evidence that latitude plays a role in the pathogenesis of XFG, but the mechanism of this effect is unknown.[35] In our study, patients from a more northern latitude than the south India studies who carried the risk allele in rs3825942 (G153D) had an OR of 9.90 for XFG compared to 6.40[16] and 4.17[17] in patients from southern India.

## Conclusion

The findings of this study contribute to the genetic epidemiology of XFG and the role of SNPs in *LOXL1* and disease risk. The study has demonstrated that in the Indian population, the G allele in rs3825942 (G153D) confers a significantly increased risk for the development of XFG. Many glaucoma patients already have advanced disease at the time of diagnosis with irreversible visual loss and this is particularly seen in XFG, even in western populations.[5] In the developing world, a major element of any glaucoma strategy must be "case detection."[37] Genetic screening strategies to identify *LOXL1* risk alleles in the population can assist in case definition and early diagnosis, targeting precious resources to high-risk patients.

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### Conflicts of interest

There are no conflicts of interest.

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