Exfoliation syndrome and exfoliation glaucoma-associated *LOXL1* variations are not involved in pigment dispersion syndrome and pigmentary glaucoma

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**Purpose:** Single nucleotide polymorphisms (SNPs) in the *LOXL1* gene have been implicated in exfoliation syndrome (XFS) and exfoliation glaucoma (XFG). We have shown that these SNPs are not associated with the primary glaucomas such as primary open-angle (POAG) glaucoma and primary angle-closure glaucoma (PACG). To further establish the specificity of *LOXL1* SNPs for XFS and XFG, we determined whether these SNPs were involved in pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG).

**Methods:** Three SNPs of *LOXL1* (rs1048661, rs3825942, and rs2165241) were screened in a cohort of 78 unrelated and clinically well characterized glaucoma cases comprising of PG (n=44) and PDS (n=34) patients as well as 108 ethnically matched normal controls of Caucasian origin. The criteria for diagnosis of PDS/PG were Krukenberg spindle, hyperpigmentation of the trabecular meshwork, and wide open angle. Transillumination defects were detected by infrared pupillography, and the presence of a Zentmayer ring was considered as a confirmatory sign. All three SNPs were genotyped in cases and controls by resequencing the genomic region of *LOXL1* harboring these variants and were further confirmed by polymerase chain reaction (PCR)-based restriction digestions. Haplotypes were generated from the genotype data, and the linkage disequilibrium (LD) and haplotype analysis were done with Haploview software that uses the expectation maximization (EM) algorithm.

**Results:** The *LOXL1* SNPs showed no significant association with PDS or PG. There was no significant difference in the frequencies of the risk alleles of rs1048661 (‘G’ allele; p=0.309), rs3825942 (‘G’ allele’ p=0.461), and rs2165241 (‘T’ allele; p=0.432) between PG/PDS cases and controls. Similarly, there was no involvement of the XFS/XFG-associated haplotypes, ‘G-G’ (p=0.643; [OR=1.08, 95%CI, 0.59–1.97]) and ‘T-G’ (p=0.266; [OR=1.35, 95%CI, 0.70–2.60]), with the PDS/PG phenotypes. The risk haplotype ‘G-G’ was observed in ~55% of the normal controls.

**Conclusions:** There was no involvement of the *LOXL1* SNPs in patients with PDS and PG. The results further indicate that the associations of these SNPs are specific to XFS/XFG.

Glaucoma is a chronic, progressive neurodegenerative disorder characterized by a specific pattern of optic nerve head and visual field damage, which represents the final common pathway of a heterogeneous group of entities that affect the eye [1,2]. It is the second leading cause of irreversible blindness worldwide, and it has been estimated that it will affect approximately 80 million people by the year 2020 [3].

Exfoliation syndrome (XFS) is an age-related, generalized disorder of the extracellular matrix characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues and is the most common identifiable cause of open-angle glaucoma worldwide [4]. It plays an etiologic role in open-angle glaucoma, angle-closure glaucoma, cataract, and retinal vein occlusion and has been associated with an increasing number of systemic disorders including vascular disease, hearing loss, and Alzheimer disease [5-8]. Exfoliation syndrome appears to be a disease of elastic tissue microfibrils. Recently, single nucleotide polymorphisms (SNPs) in the *LOXL1* gene (OMIM 153456) at 15q24.1 have been implicated in exfoliation syndrome and exfoliation glaucoma (XFG) [9]. Two non-synonymous SNPs in exon 1 of *LOXL1* (rs1048661 [R141L] and rs3825942 [G135D]) were demonstrated to exhibit a strong association with XFS and XFG in an Icelandic and Swedish population [9] that was later replicated across multiple populations worldwide [10-19]. It was also shown that *LOXL1* SNPs are not associated with primary glaucomas [20,21].

Pigment dispersion syndrome (PDS; OMIM 600510) and pigmentary glaucoma (PG) are characterized by a disruption of the iris pigment epithelium (IPE) and deposition of the dispersed pigment granules throughout the anterior segment [22]. The classic diagnostic triad consists of corneal...
pigmentation (Krukenberg spindle); slit-like, radial, mid-
peripheral iris transillumination defects; and dense trabecular
pigmentation [23]. The iris insertion is typically posterior, and
the peripheral iris tends to bow posteriorly [24]. About 80%
of patients with PDS are myopes and 20% are emmetropes.
The basic abnormality in this hereditary disorder remains
unknown.

The frequency with which PDS converts to PG has
probably been greatly overestimated. The three studies that
have examined patients longitudinally suggest that up to 50%
will eventually develop glaucoma [25-27]. However, the true
rate of PDS in the general population may be an order of
magnitude greater than has previously been suspected [28]. In
a retrospective community-based study, 113 patients of whom
nine developed PG or elevated intraocular pressure (IOP) that
required therapy were newly diagnosed with PDS over 24
years [29]. The probability of converting to PG was 10% at
five years and 15% at 15 years.

PDS/PG is an autosomal dominant disorder and was
mapped to the 7q35-q36 locus by linkage analysis [30],
although the candidate gene is yet to be identified. While
POAG shares several clinical features with PDS, there was no
evidence of linkage to the POAG-associated 1q21-q31 locus
in PDS, indicating that there would be other candidate loci
that are yet uncharacterized [31,32].

XFS and PDS are two common disorders that can produce
secondary glaucoma through trabecular blockage [22,33]. To
further establish the specificity of this association, we studied
the involvement of the three XFS- and XFG-associated
LOXL1 SNPs in a cohort of Caucasian PDS and PG patients
from New York.

METHODS

Clinical details of the subjects: The study protocol adhered to
the tenets of the Declaration of Helsinki and was approved by
the Institutional Review Boards of the New York Eye and Ear
Infirmary (NYEE) and the L.V. Prasad Eye Institute. The
cohort comprised 78 unrelated patients with PG (n=44) and
PDS (n=34) seen at the NYEE between 1998 and 2003 along
with 108 normal controls. The diagnoses of PDS/PG were
independently confirmed by two surgeons based on the
inclusion and exclusion criteria mentioned earlier [33]. The
criteria for diagnosis of PDS required the presence of
Krukenberg spindles, a deep anterior chamber, wide open
angles on gonioscopy, and hyperpigmented trabecular
meshwork. Transillumination defects were detected by
infrared pupillography. A Zentmayer ring was considered to
be confirmatory. A pigment reversal sign was only considered as a soft sign and not categorized as PDS. A diagnosis of PG required PDS plus typical glaucomatous optic disc and visual field damage.

Normal adult individuals without any signs or symptoms of glaucoma and other systemic diseases served as controls. Their visual acuity ranged from 20/20 to 20/40, and their IOP was less than 21 mmHg. The stereodisc exam did not reveal any changes in the optic disc suggestive of glaucoma. All the subjects underwent visual field testing with the Humphreys visual field analyzer (Carl Zeiss Meditec, Dublin, CA). This was essentially a diagnosis of exclusion: normal pattern of neuroretinal rim, absence of notching or thinning of the rim, and disc hemorrhage or nerve fiber layer defects. The cup/disc ratio related to the disc size, the asymmetry of cup to disc ratio less than or equal to 0.2:1 (corrected for size), and the absence of a beta zone peripapillary atrophy were “soft” signs. All the patients and controls were matched with respect to their ethnicity.

**Molecular analysis:** Peripheral blood samples (5–10 ml) were collected from each subject by venipuncture with prior informed consent, and DNA was extracted by standard protocols [34]. The three SNPs in exon 1 (rs1048661 and rs3825942) and intron 1 (rs2165241) of *LOXL1* were amplified with pre-designed primers; the amplicons were purified and screened by re-sequencing using BigDye chemistry (version 3.1) on an ABI 3100 DNA Analyzer (Applied Biosystems, Foster City, CA) as described earlier [21]. The genotypes of a subset of patients and controls were further confirmed by restriction digestion of the amplicons at 37 °C overnight with appropriate restriction enzymes as detailed earlier [21]. The genotyping was repeated independently by investigators who were masked to the phenotypes. Representative chromatograms displaying all the genotype patterns for these three SNPs are provided in Figure 1 (rs1048661), Figure 2 (rs3825942), and Figure 3 (rs2165241).

**Statistical analysis:** The maximum likelihood estimates of allele frequencies, Hardy–Weinberg equilibrium, and haplotype frequencies were estimated from the genotype data at the three SNP loci using *Haploview* software that uses the expectation maximization (EM) algorithm [35]. Pairwise linkage disequilibrium (LD) between the individual SNPs was calculated using the LD-plot function of this software. χ² analysis was done to assess the significance between the allele frequencies. The odds ratios were calculated to assess the risk of the individual alleles of all three SNPs.
RESULTS

Distribution of the LOXL1 single nucleotide polymorphisms in pigment dispersion syndrome and pigmentary glaucoma:
The study cohort conformed to the Hardy–Weinberg equilibrium. The allele frequencies of the three SNPs and their corresponding allele counts are provided in Table 1. There was no significant difference in the frequencies of the XFS/XFG-associated alleles among the PG and PDS patients and controls. The allele frequencies were consistent even after categorizing the data set into PG and PDS phenotypes (Table 1). Similarly, there were no differences in the genotype frequencies of these alleles across these three LOXL1 SNPs in PG and PDS cohorts (data not shown).

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**Table 1. Allele frequency distributions across PG/PDS cases and controls for the three LOXL1 SNPs.**

| SNPs (Allele) | Phenotypes | Allele frequency (Counts) | p value |
|---------------|------------|---------------------------|---------|
| rs1048661     | PG+PDS     | Cases: 0.674 (97/47) | Controls: 0.724 (152/58) | 0.309 |
|               | PG         | Cases: 0.679 (57/27) | Controls: 0.734 (152/58) | 0.439 |
|               | PDS        | Cases: 0.667 (40/20) | Controls: 0.724 (152/58) | 0.389 |
| rs3825942     | PG+PDS     | Cases: 0.852 (121/21) | Controls: 0.822 (176/38) | 0.461 |
|               | PG         | Cases: 0.866 (71/11) | Controls: 0.822 (176/38) | 0.368 |
|               | PDS        | Cases: 0.833 (50/10) | Controls: 0.822 (176/38) | 0.844 |
| rs2165241     | PG+PDS     | Cases: 0.514 (74/70) | Controls: 0.471 (99/111) | 0.432 |
|               | PG         | Cases: 0.524 (44/40) | Controls: 0.471 (99/111) | 0.417 |
|               | PDS        | Cases: 0.500 (30/30) | Controls: 0.471 (99/111) | 0.91 |
Haplotype analysis of the LOXL1 single nucleotide polymorphisms: Haplotypes were generated with the three LOXL1 intragenic SNPs among PG/PDS cases and controls. There was a strong pairwise linkage disequilibrium (LD) between the rs1048661 and rs3825942 ($D'=0.89$, 95%CI, 0.57–0.97) SNPs and between the rs3825942 and rs2165241 ($D'=1.00$, 95%CI, 0.81–1.00) SNPs, similar to earlier studies [11-15,17-20].

Four different haplotypes could be generated (with frequency greater than 5%) with these three SNPs in PG/PDS patients and controls. There were no significant differences in the haplotype frequencies between the cases and controls. These results were consistent even after reanalysis of the haplotype data with respect to PG and PDS phenotypes and controls (Table 2).

**DISCUSSION**

XFS is the most common identifiable cause of open-angle glaucoma worldwide. It is also associated with extra-ocular abnormalities [36,37]. Recently, intragenic SNPs in LOXL1 were implicated in XFS and XFG in an Icelandic and Swedish population [9]. Several studies conducted on XFS and XFG worldwide were able to independently replicate these findings in geographically and ethnically diverse cohorts [10-19]. Since LOXL1 SNPs were implicated in a secondary glaucoma, we analyzed these variations in PDS/PG to establish the uniqueness of this association. To the best of our knowledge, this is the first report to screen for these SNPs in PG/PDS.

The data from the present study show that the three XFS/XFG-associated SNPs were not involved with PG or PDS. The significant associations of the rs1048661 (G allele) and the rs3825942 (G allele) SNPs have been consistent to XFS and XFG across multiple populations worldwide except in Japanese (Table 3). On the contrary, the “T” allele (rs1048661) has exhibited strong association with the Japanese XFS/XFG patients [16,19]. So far, these SNPs have not been involved with primary glaucomas [9,12,20,21]. However, the allele frequencies of the LOXL1 SNPs in PG/PDS patients were similar to that observed in primary glaucomas (Table 3).

There was no significant association with the LOXL1 haplotypes either with PG or PDS (Table 2). Since most studies had demonstrated a significant risk with haplotypes generated with the rs1048661 and rs3825942 SNPs [9-15,17-19], a similar exercise was conducted to draw a comparison of the haplotype structure in the present cohort with other studies. The frequency of the risk haplotype with these two SNPs (G-G) was observed in lower frequency among the PG/PDS patients compared to other studies; this risk haplotype was also present in ~55% of the control subjects (Table 4). Unlike previous studies on XFS and XFG, there was no risk associated with the G-G (OR=1.08, 95%CI, 0.59–1.97) and T-G (OR=1.35, 95%CI, 0.70–2.60) haplotypes in PG/PDS (Table 4).

While PG/PDS occurs relatively early in life, XFS/XFG occurs at a later stage. It has been suggested that certain PDS patients who do not achieve IOP control could later progress to develop XFS/XFG [38]. Based on this, the concept of an “overlap” syndrome has been suggested whereby the sequential appearance of two or more risk factors lead to glaucomatous damage [33].

In summary, we aimed to determine if the LOXL1 SNPs associated with XFS/XFG were involved in another secondary glaucoma. The high population attributable risks for the high-risk haplotype among the diverse XFS/XFG patients strongly suggest that these variants are exclusive to XFS and XFG [9,13]. The non-association of the LOXL1 SNPs in our PG/PDS cohort further supports the fact that these are XFS-specific and may not be involved with other secondary glaucomas. Although PG/PDS share certain discrete clinical features with XFS, their underlying molecular mechanisms remain to be elucidated.
| Type of glaucoma | Phenotypes            | Population [n cases] | rs1048661 (G) Freq | p value | OR (95% CI) | rs3825942 (G) Freq | p value | OR (95% CI) | rs2165241 (T) Freq | p value | OR (95% CI) | Reference |
|-----------------|-----------------------|----------------------|---------------------|---------|-------------|---------------------|---------|-------------|---------------------|---------|-------------|-----------|
| Primary         | POAG Iceland [n=90]   | 0.711                | 0.885               | 0.085   | 1.25        | 0.32                | 0.55    | 1.36        | 0.04                | 0.96    | 1.82        | [9]       |
|                | POAG Sweden [n=200]   | 0.638                | 0.863               | 0.19    | 0.87        | 0.49                | 0.488   | 0.83        | 0.18                | 0.63    | 1.09        | [9]       |
|                | POAG India [n=112]    | 0.616                | 0.83                | 0.112   | 1.33        | 0.105               | 0.321   | 0.95        | 0.426               | 0.54    | 1.67        | [20]      |
|                | PACG India [n=96]     | 0.667                | 0.755               | 0.332   | 0.94        | 0.456               | 0.296   | 0.82        | 0.262               | 0.45    | 1.50        | [20]      |
|                | POAG USA [n=331]      | 0.724                | 0.771               | 0.92    | 0.86        | 0.54                | 0.412   | 0.83        | 0.35                | 0.59    | 1.18        | [12]      |
|                | POAG Caucasians [n=279]| NA                   | NA                  | NA      | 0.829       | NA                  | NA      | 0.583       | NA                  | 0.066   | NA          | [21]      |
|                | POAG African-Americans [n=193]| NA | NA | NA | 0.617 | NA | 0.591 | 0.237 | NA | 0.408 | [21] |
|                | POAG Africans [n=170] | NA                   | NA                  | 0.622   | NA          | 0.217               | 0.226   | NA          | 0.472               | 0.056   | NA          | [21]      |
| Secondary      | XFS Iceland [n=55]    | 0.789                | 1.3x10^-3           | 0.982   | 10.1        | 8.5x10^-7          | 0.74    | 3.18        | 1.9x10^-8           | 0.32    | 1.2x10^-3   | [9]       |
|                | XFG Iceland [n=75]    | 0.827                | 1.8x10^-6           | 0.987   | 13.2        | 4.1x10^-9          | 0.753   | 3.40        | 4.3x10^-12          | 0.41    | 4.8x10^-1   | [9]       |
|                | XFS Sweden [n=199]    | 0.834                | 2.7x10^-7           | 0.995   | 27.3        | 9.1x10^-14         | 0.813   | 3.78        | 3.1x10^-17          | 0.27    | 7.7x10^-4   | [9]       |
|                | XFS USA [n=72]        | 0.819                | 9.68                | 0.0003  | 0.0003      | NA                  | NA      | NA          | NA                  | 0.011   | NA          | [10]      |
|                | XFG USA [n=50]        | 0.787                | 2.05                | 0.0222  | 0.0194      | 0.667               | 2.30    | 0.30        | 1.4x10^-3           | 0.14    | 3.7x10^-5   | [11]      |
|                | XFS/XFG USA [n=206]   | 0.829                | 20.9                | 0.005   | 1.6x10^-15  | 0.76                | 0.76    | 3.77        | 1.2x10^-11          | 0.26    | 5.5x10^-5   | [12]      |
|                | XFS/XFG American and European [n=287] | 0.843               | 8.06               | 0.959   | 3.1x10^-17  | 0.734               | 0.74    | 2.24        | 4.8x10^-24          | 1.76    | 2.86        | [13]      |
|                | XFS/XFG Germany and Italy [n=726] | 0.82               | 5.97                | 0.995   | 3.77        | 0.74                | 0.74    | 3.42        | 1.9x10^-4          | 2.85    | 4.11        | [14]      |
|                | XFG Europe [n=167]    | 0.841                | 8.2x10^-23          | 0.945   | 5.76x10^-15 | NA                  | NA      | NA          | NA                  | NA      | NA          | [18]      |
|                | XFS/XFG India [n=50]  | 0.72                 | 4.17                | 0.56    | 4.17        | 0.0001              | NA      | NA          | NA                  | NA      | NA          | [15]      |
|                | XFS/XFG Japan [n=59]  | 0.008                | 1                   | 10.87   | 1.30x10^-11 | NA                  | NA      | 0.017       | NA                  | 0.16    | NA          | [16]      |
|                | XFS/XFG Japan [n=209] | 0.055                | 2.63                | 1.084   | 1.30x10^-11 | NA                  | NA      | 0.017       | NA                  | 0.16    | NA          | [19]      |
|                | XFS Australia [n=86]  | 0.78                 | 8.5x10^-4           | 0.95    | 3.38        | 7.8x10^-5          | NA      | NA          | NA                  | 1.18    | 0.77        | [17]      |
|                | PG/PDS USA [n=78]     | 0.674                | 1.24                | 0.309   | 0.461       | 0.514               | 0.432   | 1.18        | 0.32                | 0.77    | 1.81        | Present study |

TABLE 3. WORLDWIDE DISTRIBUTION OF ALLELE FREQUENCIES AND THEIR ODDS RATIOS FOR THE THREE *LOXL1* SNPS ACROSS ALL GLAUCOMA PHENOTYPES INCLUDING THE PRESENT COHORT.
Table 4. The estimated haplotype frequencies and their odds ratios based on two SNPs (rs1048661 and rs3825942) across different secondary glaucoma phenotypes in the present cohort and other populations.

| Populations, [n (cases, controls)] | Phenotypes | G-G haplotype | T-G haplotype |
|-----------------------------------|------------|---------------|---------------|
|                                   |            | % Cases       | % Controls    | % Cases | % Controls | OR (95%CI)* | p value | OR (95%CI)* | p value | Reference |
| Sweden [399,198]                  | XFG        | 83.3          | 56.1          | 35.72#   | 2.2x10^-16 |             |         | 16.2        | 31.8      | 12.36#    | 1.6x10^-6 | [9]        |
| Iceland [195,14474]               | XFG        | 81.4          | 49.8          | 18.94#   | 3.3x10^-12 |             |         | 17.3        | 34.9      | 5.74#     | 0.0027    | [9]        |
| USA [72,75]                       | XFS        | 80.6          | 48            | 14.50    | 2.7x10^-5  |             |         | 18.1        | 40        | 3.90      | 0.12      | [10]       |
| American and European [566,658]   | XFS        | 80.2          | 50.3          | 3.40     | 1.5x10^-7  |             |         | 15.7        | 29.6      | 0.44      | 9.0x10^-9 | [13]       |
| Germany and Italy [726,418]       | XFS/XFG    | 78.6          | 50.7          | 3.43     | 5.2x10^-43 |             |         | 17.9        | 34.6      | NA        | NA        | [14]       |
| Europe [167,170]                  | XFG        | 83.5          | 48.8          | 52.1     | NA        |             |         | 15.9        | 32.9      | 14.67     | NA        | [18]       |
| India [52,97]                     | XFS/XFG    | 64            | 37            | 5.74     | 9.9x10^-6  |             |         | 27          | 36        | 2.55      | 0.129     | [15]       |
| Australia [86,2422]               | XFS        | 74            | 51            | 2.71     | 3.8x10^-9  |             |         | 22          | 34        | 0.54      | 7.8x10^-4 | [17]       |
| USA [78, 108]                     | PG/PDS     | 52.9          | 55.3          | 1.08     | 0.643     |             |         | 32.3        | 26.9      | 1.35      | 0.266     | Present study |

The asterisk indicates that the odds ratios were calculated with respect to the G-A haplotype. The sharp (hash mark) indicated that the 95%CI were not available in the reported studies.
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