LOXL1 variants in elderly Japanese patients with exfoliation syndrome/glaucoma, primary open-angle glaucoma, normal tension glaucoma, and cataract

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Purpose: To evaluate the association of lysyl oxidase like 1 (LOXL1) gene variants in Japanese patients with open-angle glaucoma.

Methods: We evaluated the association of three LOXL1 variants (rs1048661, rs3825942, and rs2165241) in 142 Japanese patients with exfoliation syndrome (EX; n=59) and exfoliation glaucoma (EG; n=83) as well as in 251 control patients aged 70 years or older with primary open-angle glaucoma (PG; n=40), normal tension glaucoma (NG; n=54), and cataract (CT; n=157).

Results: In comparison with the CT group, the single nucleotide polymorphisms (SNPs) showed significant association with EX, EG, and EX+EG. The odds ratio (OR)=19.71–28.23 and p=1.69x10^-23-3.00x10^-45 for allele T of rs1048661; OR=28.21–39.78 and p=1.77x10^-8-2.42x10^-22 for allele G of rs3825942; and OR=16.59–23.40 and p=4.79x10^-5-1.08x10^-9 for allele C of rs2165241. In comparison with the controls (CT+PG+NG), the haplotype rs1048661/rs3825942 (T/G) was significantly associated with EX+EG (p=8.27x10^-44), and haplotype G/A had a significant protective effect (p=2.25x10^-14). None of the three SNPs showed significant differences between the EX and EG groups or between the PG and NG groups.

Conclusions: These SNPs are associated with exfoliation syndrome/glaucoma in the Japanese population. The risk alleles in rs1048661 and rs2165241 are different from other populations. Additional genetic or environmental risk factors other than these LOXL1 SNPs could be associated with the development of exfoliation syndrome as well as exfoliation glaucoma among exfoliation syndrome patients.

Exfoliation syndrome is the most common identifiable cause of open-angle glaucoma worldwide. It is an age-related, generalized disorder of the extracellular matrix that is characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues [1]. A recent genome-wide association study demonstrated that one intronic single nucleotide polymorphism (SNP, rs2165241) and two exonic SNPs (rs1048661 [R141L] and rs3825942 [G153D]), which are located in the first exon of the lysyl oxidase like1 (LOXL1) gene on chromosome 15q24.1, are highly associated with exfoliation syndrome in Icelandic and Swedish populations while none of these SNPs were associated with primary open-angle glaucoma in either of the two populations [2].

Until now, several lines of studies have reported significant associations of these LOXL1 SNPs with exfoliation syndrome [3-16] or the lack of associations of these SNPs with primary open-angle glaucoma [16-18] in various populations. In these studies, subjects in their 40s and 50s are sometimes recruited as controls. The prevalence of clinical exfoliation syndrome increases with age, particularly after the age of 60 years [1]. However, preclinical exfoliation syndromes in younger generations are able to distinguish from normal subjects until patients become older. Accordingly, the level of statistical significance between exfoliation syndrome and controls could be underestimated in studies that include younger patients in the control group. To reduce the chance of misclassifying latent syndromes within the control group, only patients aged 70 years or older were recruited as primary open-angle glaucoma, normal tension glaucoma, and cataract. To the best of our knowledge, this is the first study reporting an association of...
LOXL1 SNPs with exfoliation syndrome/glaucoma using age-controlled subjects. This is also the first study reporting the association of LOXL1 SNPs with normal tension glaucoma.

**METHODS**

**Subjects:** Three hundred and ninety-three unrelated Japanese subjects presenting exfoliation syndrome without glaucoma (EX), exfoliation syndrome with glaucoma (EG), primary open-angle glaucoma (PG), normal tension glaucoma (NG), and cataract (CT) were recruited at the Shimane University Hospital and Iinan Hospital in Shimane, Japan. This study adhered to the tenets of the Declaration of Helsinki. The research was reviewed and approved by the Institutional Review Boards of both hospitals. Written informed consent was obtained from all of the subjects. All of the subjects underwent a dilated pupil examination of the anterior segments, ocular media, and fundus using a slit-lamp and a funduscope. The subjects with EX and EG exhibited the typical pattern of exfoliation material on the anterior lens surface and/or pupillary margin during slit-lamp examination. The subjects with EG and PG had a history of intraocular pressure (IOP) greater than or equal to 21 mmHg, and the subjects with EX, NG, and CT had a history of IOP never exceeding 20 mmHg. The subjects with PG, NG, and EG presented a typical glaucomatous optic disc cupping or rim thinning and visual field loss. The patients who had a history of IOP greater than or equal to 21 mmHg but no glaucomatous optic disc changes nor visual field loss were assigned as EG in this study. To avoid possible misclassification of latent exfoliation syndromes as PG, NG, or CT, patients younger than 70 years old were not recruited. The number of subjects, each gender, and the mean and range of ages in each group are summarized in Table 1.

**DNA genotyping:** Genomic DNA was extracted from the peripheral white blood cells of each subject. Polymerase chain reaction (PCR) was performed using primers designed to amplify the genomic region containing both rs1048661 and rs3825942 (forward primer: 5’-AGG TGT ACA GCT TGC TCA ACT C-3’ and reverse primer: 5’-TAG TAC ACG AAA CCC TGG TCG T-3’) or just rs2165241 (forward primer: 5’-AGA ATG CAA GAC CTC AGC ATG AG-3’ and reverse primer: 5’-TAG TGG CCA GAG GTC TGC TGC TAA G-3’). The sequence was determined based on the dideoxy terminator method using an ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA) according to the manufacturer’s protocol. We used SeqScape Software version 2.5 (Applied Biosystems) to analyze the sequence alignment.

**Statistical analysis:** The deviation of the genotype distributions from the Hardy–Weinberg equilibrium was assessed in the case and control samples using HAPLOVIEW version 4.0 [19]. Statistical analysis was performed using R version 2.6.2. Fisher’s exact test was used to compare the allele or genotype frequencies of each case group with the controls. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated by the logistic regression method. Individual haplotypes and their estimated population frequencies were inferred using HAPLOVIEW version 4.0 [19] with all of the parameters set at the default values.

**RESULTS**

The allelic and genotypic counts and frequencies of SNPs rs1048661, rs3825942, and rs2165241 within LOXL1 are shown in Table 2. The ORs and p values for the allelic and genotypic frequencies of the three SNPs in comparison between the cases (EX, EG, and EX+EG) and controls (CT, PG, NG, and PG+NG) are shown in Table 3. In comparison with the CT group, the SNPs showed a significant association with EX, EG, and EX+EG for the T allele of rs1048661 at OR=19.71–28.23 and p=1.69x10^{-22}, the G allele of rs3825942 at OR=28.21–39.78 and p=1.77x10^{-42}-2.42x10^{-22}, and the C allele of rs2165241 at OR=16.59–23.40 and p=4.79x10^{-5}-1.08x10^{-9} (Table 3). The genotypes, TT of rs1048661 (p=4.11x10^{-23}-3.78x10^{-43}), GG of rs3825942 (p=3.53x10^{-11}-2.10x10^{-33}), and CC of rs2165241 (p=1.95x10^{-4}-1.07x10^{-8}), also showed significant
| Allele | Count | Frequency | Count | Frequency | Count | Frequency | Count | Frequency | Count | Frequency | Count | Frequency |
|--------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|
| T      | 111    | 0.941     | 159    | 0.958     | 270    | 0.951     | 39     | 0.488     | 50     | 0.463     | 89     | 0.473     |
| G      | 7      | 0.059     | 7      | 0.042     | 14     | 0.049     | 41     | 0.513     | 58     | 0.537     | 99     | 0.527     |
| Genotype | | | | | | | | | | | | |
| TT     | 54     | 0.915     | 76     | 0.916     | 130    | 0.916     | 10     | 0.25      | 8      | 0.148     | 18     | 0.192     |
| TG     | 3      | 0.051     | 7      | 0.084     | 30     | 0.070     | 19     | 0.475     | 34     | 0.630     | 53     | 0.564     |
| GG     | 2      | 0.034     | 0      | 0         | 2      | 0.014     | 11     | 0.275     | 12     | 0.222     | 23     | 0.245     |
| Allele | | | | | | | | | | | | |
| G      | 117    | 0.992     | 165    | 0.994     | 282    | 0.993     | 64     | 0.800     | 86     | 0.796     | 150    | 0.798     |
| A      | 1      | 0.009     | 1      | 0.006     | 2      | 0.007     | 16     | 0.200     | 22     | 0.204     | 38     | 0.202     |
| Genotype | | | | | | | | | | | | |
| GG     | 58     | 0.983     | 82     | 0.988     | 140    | 0.986     | 25     | 0.625     | 33     | 0.611     | 58     | 0.617     |
| AG     | 1      | 0.017     | 1      | 0.012     | 2      | 0.014     | 14     | 0.350     | 20     | 0.370     | 34     | 0.362     |
| AA     | 0      | 0         | 0      | 0         | 0      | 0         | 1      | 0.025     | 1      | 0.019     | 2      | 0.021     |
| Allele | | | | | | | | | | | | |
| C      | 117    | 0.992     | 165    | 0.994     | 282    | 0.993     | 77     | 0.963     | 93     | 0.861     | 170    | 0.904     |
| T      | 1      | 0.009     | 1      | 0.006     | 2      | 0.007     | 3      | 0.038     | 15     | 0.139     | 18     | 0.096     |
| Genotype | | | | | | | | | | | | |
| CC     | 58     | 0.983     | 82     | 0.988     | 140    | 0.986     | 37     | 0.925     | 40     | 0.741     | 77     | 0.819     |
| CT     | 1      | 0.017     | 1      | 0.012     | 2      | 0.014     | 3      | 0.075     | 13     | 0.241     | 16     | 0.170     |
| TT     | 0      | 0         | 0      | 0         | 0      | 0         | 1      | 0.019     | 1      | 0.011     | 4      | 0.026     |

EX, exfoliation syndrome; EG, exfoliation glaucoma; PG, primary open angle glaucoma aged 70 years or older; NG, normal tension glaucoma aged 70 years or older; and CT, cataract aged 70 years or older.
| Parameter | rs1048661 | rs3825942 | rs2165241 |
|-----------|-----------|-----------|-----------|
| Allele    |           |           |           |
| p value   | 1.69x10−23 | 1.77x10−8  | 4.79x10−5  |
| OR        | 19.71     | 28.21     | 16.59     |
| 95% CI    | 8.90–43.67 | 38.6–205.97| 2.25–122.20|
| Genotype  |           |           |           |
| p value   | 4.11x10−25 | 3.86–205.97| 2.10x10−33|
| OR        | 4.41x10−8  | 3.53–219.07| 2.10x10−33|
| 95% CI    | 4.01–219.07| 3.96–226.36| 2.10x10−33|
| Allele    |           |           |           |
| p value   | 1.92x10−17 | 6.48x10−8  | 7.87x10−7  |
| OR        | 28.32     | 42.20     | 23.45     |
| 95% CI    | 9.96–57.27 | 42.12     | 24.54     |
| Genotype  |           |           |           |
| p value   | 4.80x10−32 | 5.46–289.78| 3.53x10−11|
| OR        | 4.87x10−6  | 5.36–317.49| 7.19x10−8  |
| 95% CI    | 4.01–219.07| 5.59–318.47| 2.88x10−9  |

OR, odds ratio; CI, confidence interval; NA, not applicable; EX, exfoliation syndrome; EG, exfoliation glaucoma; PG, primary open-angle glaucoma aged 70 years or older; NG, normal tension glaucoma aged 70 years or older; and CT, cataract aged 70 years or older. p values were obtained by Fisher's exact probability test.
associations with EX, EG, and EX+EG when they were compared to the CT group (Table 2 and Table 3). Significant associations with EX, EG, and EX+EG were detected in comparisons with the primary glaucoma groups (PG, NG, and PG+NG) for the alleles, T of rs1048661, G of rs3825942, and C of rs2165241, as well as the genotypes, TT of rs1048661, GG of rs3825942, and CC of rs2165241, with the exception of the comparisons between EX, EG, or EX+EG and the PG groups for allelic (OR=4.56–6.43 and p=0.3051–0.0729) and genotypic (p=0.3000–0.0715) frequencies in rs2165241 (Table 3).

None of the three SNPs showed a significant difference between the EX and EG groups in these allelic or genotypic frequencies (Table 4). In addition to this, none of the three SNPs showed significant differences in their allelic or genotypic frequencies in comparisons between the primary glaucoma (PG, NG, or PG+NG) and CT groups or between the PG and NG groups (data not shown), excepted for the allele C of rs2165241 (p=0.0233) and the genotype CC of rs2165241 (p=0.0294) in comparison between the PG and NG groups.

The two SNPs, rs1048661 and rs3825942, were in linkage disequilibrium (D’=1). In our study populations, only three of the four possible haplotypes in rs1048661/ rs3825942 were detected (Table 5 and Table 6). In the comparisons between cases (EX, EG, or EX+EG) and controls (CT+PG+NG), the T and G were significantly associated with EX, EG, and EX+EG, and the G and A had a significant protective effect (Table 5 and Table 6).

**DISCUSSION**

Based on this study among 393 elderly Japanese patients with exfoliation syndrome, exfoliation glaucoma, primary open-angle glaucoma, and cataract, we confirmed the findings of Thorleifsson and colleagues [2] that three SNPs within **LOXL1** are strongly associated with exfoliation syndrome and glaucoma. In addition to the original study in Icelandic and Swedish populations, allele G of rs3825942 has been consistently suggested as a risk–associated allele of exfoliation syndrome/glaucoma in five studies from the United States [3-7], two studies from Europe [8,9], one study from India [10], one study from Australia [11], and six studies including this one from Japan [12-16]. In this study, we found that allele T of rs1048661 is associated with exfoliation syndrome/glaucoma, which is consistent with other studies in the Japanese population [12-16], while allele G is reported to be risk-associated in studies from other countries [2-4,6-11]. We also found that allele C of rs2165241 is associated with exfoliation syndrome/glaucoma, which is consistent with one study from Japan [13], while allele T is risk-associated in other populations [2,4,5,7,8]. Allelic frequencies of the three SNPs reported in previous studies and the current study are summarized in Figure 1. These results suggest a possibility that the missense changes in **LOXL1** are not actually causative but mark a haplotype that carries variants that may indeed be causative.

This study revealed extremely high ORs and significant p values for the three SNPs in the comparisons between the exfoliation syndrome/glaucoma groups and cataract groups. Only patients aged 70 years or older were recruited as control subjects in this study, enabling us to reduce the chance of misclassifying latent or preclinical exfoliation syndromes into the control group. Accordingly, the inclusion criteria of the control group might contribute to the extremely significant association of the **LOXL1** SNPs with exfoliation syndrome in this study. In contrast, the significance of the association of the SNPs with exfoliation syndrome/glaucoma was relatively low when the PG group was used as a control comparison compared to when the NG or CT groups were used as control comparisons. Although the level of significance was relatively low, we found differences in frequencies between PG and NG for allele C of rs2165241 (p=0.0233) and the genotype CC of rs2165241 (p=0.0294). These may suggest the possible inclusion of late onset exfoliation syndrome in the PG group. Previously, a lack of association between **LOXL1** polymorphisms and primary open-angle glaucoma or primary angle-closure glaucoma were reported in Caucasian, African American, Ghanaian, and Indian populations [17,18]. We did
**Table 5. Counts and frequencies of haplotype rs1048661/rs3825942 in cases (EX, EG, and EX+EG) and controls (CT, NG, PG+NG, CT+NG, and CT+PG+NG).**

|        | Cases |          |        |          |        |          |        |          |
|--------|-------|----------|--------|----------|--------|----------|--------|----------|
|        | Count | EX       | Frequency | Count | EG       | Frequency | Count | EX+EG     | Frequency |
| TG     | 111   | 0.941    | 159     | 0.058   | 270     | 0.051    |
| GG     | 6     | 0.051    | 6       | 0.036   | 12      | 0.042    |
| GA     | 1     | 0.008    | 1       | 0.006   | 2       | 0.007    |

|        | Controls |          |        |          |        |          |        |          |        |
|--------|----------|----------|--------|----------|--------|----------|--------|----------|--------|
|        | Count | CT       | Frequency | Count | NG       | Frequency | Count | PG+NG     | Frequency | Count | CT+PG+NG | Frequency |
| TG     | 140   | 0.443    | 50     | 0.463   | 89     | 0.473    | 190    | 0.448    | 229     | 0.454 |
| GG     | 115   | 0.364    | 36     | 0.333   | 61     | 0.324    | 151    | 0.356    | 176     | 0.349 |
| GA     | 61    | 0.193    | 22     | 0.204   | 38     | 0.202    | 83     | 0.196    | 99      | 0.196 |

EX, exfoliation syndrome; EG, exfoliation glaucoma; PG, primary open angle glaucoma aged 70 years or older; NG, normal tension glaucoma aged 70 years or older; and CT, cataract aged 70 years or older.
not find any significant associations between any of the three SNPs with primary open-angle glaucoma, reconfirming the previous observations in our Japanese population. Most recently, one study from Japan reported a lack of association between \textit{LOXL1} polymorphisms and primary open-angle glaucoma in two of three SNPs (e.g., rs1048661 and rs3825942) \cite{16}. In addition to this, the current study suggests a lack of association between rs2165241 and primary open-angle glaucoma as well as a lack of association between any of the three SNPs with normal tension glaucoma.

In this study, none of the SNPs exhibited significant differences in their allelic and genotypic frequencies between exfoliation syndrome and glaucoma, suggesting that these SNPs are associated with exfoliation glaucoma through their association with exfoliation syndrome as reported previously \cite{2}. Accordingly, our data suggest that additional genetic or environmental risk factors are associated with the development of exfoliation glaucoma among exfoliation syndrome patients. Further study is required to clarify these risks.

In summary, we have demonstrated significant associations of \textit{LOXL1} variants with Japanese patients who have exfoliation syndrome/glaucoma. Compared to other populations, the risk alleles in rs1048661 and rs2165241 are unique in this population. The \textit{LOXL1} association of exfoliation glaucoma is through the association of exfoliation syndrome. \textit{LOXL1} lacked any association with primary open-angle glaucoma or normal tension glaucoma in this population. Additional genetic or environmental risk factors

TABLE 6. \textit{P} values for haplotype rs1048661/rs3825942 in comparisons between cases (EX, EG, and EX+EG) and controls (CT, NG, PG+NG, CT+NG, and CT+PG+NG).

|       | Versus | Versus | Versus | Versus | Versus |
|-------|--------|--------|--------|--------|--------|
|       | EX     | CT     | EG     | CT     | CT     |
|       |        | Versus | Versus | Versus | Versus |
|       |        | NG     | PG+NG  | CT+NG  | CT+PG+NG |
| TG    | 9.36x10^-21 | NA    | 9.56x10^-21 | 6.19x10^-17 | 1.27x10^-21 |
| GG    | 9.69x10^-11 | NA    | 9.69x10^-11 | 1.76x10^-10 | 1.43x10^-10 |
| GA    | 1.01x10^-6 | NA    | 1.01x10^-6 | 5.63x10^-7 | 5.63x10^-7 |

Significant association was found between cases and controls. EX, exfoliation syndrome; EG, exfoliation glaucoma; PG, primary open angle glaucoma aged 70 years or older; NG, normal tension glaucoma aged 70 years or older; and CT, cataract aged 70 years or older. NA, not available due to a small number of samples.

Figure 1. Allelic frequencies of the three SNPs reported in previous studies and the current study. Allelic frequencies of three SNPs in cases (exfoliation syndrome and exfoliation glaucoma) and controls (cataract or normal population) that have been reported in literatures are summarized.
other than LOXL1 are likely to be associated with an increase in exfoliation glaucoma among exfoliation syndrome patients.

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