

# Lysyl oxidase-like I polymorphisms in a southwestern Greek cataract population with pseudoexfoliation syndrome

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**Purpose:** The aim of this study was to determine the possible association of rs1048661 and rs3825942 single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (*LOXLI*) gene of cataract patients from southwestern Greece with pseudoexfoliation (PEX) syndrome.

**Patients and methods:** Ninety-three patients with PEX syndrome and 74 without PEX syndrome were recruited with the principal diagnosis being cataract. *LOXLI* SNPs, rs1048661 and rs3825942, were genotyped by using polymerase chain reaction.

**Results:** The G allele of rs1048661 was found in 96.7% in the PEX group as compared to 80.5% of non-PEX alleles ( $P=19\times 10^{-4}$ ; Odds ratio [OR] =5.37; 95% confidence interval [CI]=1.68–17.12). Similarly, the G allele of rs3825942 was found in 72.1% of the PEX group as compared to 41.8% of non-PEX alleles ( $P=4\times 10^{-5}$ ; OR =3.78; 95% CI =1.98–7.23). The T and A allele frequencies of rs1048661 and rs3825942, respectively, were underrepresented in the PEX group patients as compared to non-PEX group.

**Conclusion:** Our data confirm previously reported association between *LOXLI* polymorphisms and PEX syndrome in a southwestern Greek population. A significant association was found for the G allele of rs1048661 and rs3825942 demonstrating that the GG haplotype is a high-risk factor for the development of PEX syndrome.

**Keywords:** exfoliative syndrome, PEX syndrome, single nucleotide polymorphisms

## Introduction

Pseudoexfoliation (PEX) syndrome is an age-related systemic disease of the extracellular matrix characterized by the widespread deposition of an abnormal extracellular fibrillary material on many intra- and extraocular tissues. It is widely recognized that this syndrome is associated with severe chronic secondary open-angle glaucoma in up to 50% of the affected eyes and an increased risk of intraoperative and postoperative complications during cataract surgery.<sup>1</sup> Moreover, it is also associated with various other complications such as angle-closure glaucoma, blood–aqueous barrier dysfunction, or corneal endothelial decompensation.<sup>2</sup> Despite extensive research, the pathogenesis of PEX syndrome remains obscure. Similar pathological changes to those in the eye have been identified in many visceral organs such as lung, heart, gallbladder, brain, as well as in the skin.<sup>3–6</sup> Although the exact composition of the abnormal extracellular material and the mechanisms responsible for its excessive production and accumulation still remain unknown, the concept of an elastotic process has recently been established. Molecular, biological, and biochemical data support the pathogenetic concept of PEX syndrome as a type of stress-induced elastic fibrilopathy.<sup>7</sup> The etiopathogenesis involves genetic and nongenetic factors. Several genetic factors

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have been associated with development and heredity of PEX syndrome. The most important evidence for genetic causes is the identification of single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (*LOXL1*) gene on chromosome 15q24.1, the noncoding intronic rs2165241 SNP and two nonsynonymous coding SNPs (rs1048661 and rs3825942). They have been strongly correlated with PEX syndrome and PEX glaucoma in Icelandic and Swedish populations.<sup>8</sup> Moreover, the presence of certain apolipoprotein E gene variants,<sup>9</sup> fibrillin-1, MMP-2, TIMP-1 variants, and several region variations such as the 30 cM 18q12.1–21.33 locus on chromosome 18<sup>10</sup> showed an increased risk for developing PEX syndrome in certain populations. However, nongenetic factors including ultraviolet light exposure, dietary factors, infectious agents, trauma, as well as oxidative stress, hypoxia, and inflammation have also been suggested to act as comodulating external factors.<sup>11</sup>

Additionally, high oxidative stress and products of lipid peroxidation may promote abnormal extracellular matrix metabolism and cause disease progression.<sup>12,13</sup>

LOXL1 is a member of the lysyl oxidase family of enzymes that catalyze the covalent cross-linking of collagen and elastin in connective tissues through oxidative deamination of lysine or hydroxylysine side chains and is required for elastic fiber formation.<sup>7,14</sup> It is formed as a propeptide which accumulates in sites of elastogenesis, participating in the formation of a microfibril scaffold. There, it cleaves off to its active form and deaminates lysine residues of tropoelastin monomers. These are cross-linked to each other and lead to formation of elastin polymers in the extracellular matrix of several structures of the eye, such as iris, cornea, or zonules.<sup>14–16</sup> The two risk coding SNPs (rs1048661 and rs3825942) are located in the N-terminal part of pro-LOXL1 which was suggested to be critical in enzyme activation and substrate identification.<sup>15,17,18</sup> Our study was designed to investigate the incidence of the two nonsynonymous coding SNPs (rs1048661 and rs3825942) in *LOXL1* gene in a southwestern Greek cataract population with or without PEX syndrome.

## Material and methods

### Patient population and clinical diagnosis

A prospective study was designed. Patients with or without evidence of ocular PEX syndrome were selected from individuals admitted to the Ophthalmology Clinic of the University Hospital of Patras, Greece, with the principal diagnosis of cataract to be operated in a 24-month period. The hospital mainly admits patients from southwestern

Greece, consisting of about 50% urban and 50% rural areas, with a population of 780,000 inhabitants. Only patients with senile cataract and those belonging to the abovementioned geographic region were included. The study was approved by the ethics committee of the University Hospital of Patras, Greece, and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

All patients gave informed consent and full medical history before entering the study. They underwent detailed ophthalmologic examination that included slit-lamp biomicroscopic examination with dilated pupil, applanation tonometry, gonioscopy, and fundus examination. Moreover, they were examined independently by two medical doctors (ophthalmologists), with the same instruments, in a dark examination room. Patients with PEX syndrome were defined as those with clinical evidence of PEX material and intraocular pressure of less than 21 mmHg with no clinical evidence of glaucomatous optic neuropathy in either eye. Following examination, they were classified either in the PEX group or in the non-PEX group. Patients with aphakia or pseudophakia in the fellow eye were excluded because of difficulties in making a definite diagnosis of PEX syndrome. Patients and controls with diabetes mellitus or other malignant diseases were also excluded from the study.

### Sample collection and genotyping

Peripheral blood samples (2–5 mL) were collected in EDTA-containing tubes and immediately stored at  $-80^{\circ}\text{C}$  until further processing. Genomic DNA was extracted from peripheral blood nucleated cells using the QIAamp DNA blood mini kit (Cat. No 51104, Qiagen, Hilden, Germany), in accordance with the manufacturer's instructions, and stored in 50  $\mu\text{L}$  of elution buffer at  $-20^{\circ}\text{C}$  (240 ng/ $\mu\text{L}$ ). It was genotyped for two nonsynonymous SNPs located in exon 1 of *LOXL1*: rs1048661 (R141L) (c.758G>T; p.Arg141Leu) and rs3825942 (G153D) (c.794G>A; p.Gly153Asp) by polymerase chain reaction (PCR) using specific primers (forward: 5'-CAACGGGCAGGTGTACAGCTT-3', reverse: 5'-GCCGGGTCGTAGTTCTCGTAC-3'). The primers amplify a 441 bp product which spans both the polymorphic sites in exon 1 of *LOXL1*. The PCR mixture contained 20  $\mu\text{L}$  of genomic DNA, 2  $\mu\text{L}$  of each primer (10  $\mu\text{M}$ ), 0.5  $\mu\text{L}$  proofreading (Pfu) DNA polymerase (product M7741, Promega, Madison, WI, USA), 1  $\mu\text{L}$  PCR nucleotide mix (product C1141, Promega), and 3  $\mu\text{L}$  of ultrapure DMSO (Sigma-Aldrich, St Louis, MO, USA, compendia quality level product D2650) in a total volume of 50  $\mu\text{L}$  per reaction. PCR amplification was performed with an initial denaturation

at 94°C for 5 minutes, followed by 10 cycles of denaturation at 94°C for 30 seconds, primer annealing from 65°C to 60°C (touchdown PCR) for 1 minute with 0.5°C decrement, extension at 72°C for 45 seconds, followed by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C for 1 minute, extension at 72°C for 45 seconds, followed by a final extension at 72°C for 1 minute. PCR products were separated on a 2% low-melt agarose gel containing ethidium bromide and purified using the Wizard SV Gel and PCR Clean-Up System (product A9281, Promega), according to the manufacturer's protocol. Purified PCR products were analyzed by Sanger sequencing using an automated DNA sequencer (Big Dye Terminator chemistry, version 3 on a 3730XL capillary sequencer; Applied Biosystems, Inc., Foster City, CA, USA). Sequences were analyzed by using a sequencing analysis software BioEdit (BioEdit graphical sequence alignment editor, version 7.0.9.0).

## Statistical analysis

Data were analyzed using analytical statistical software (SPSS version 16.0; SPSS, Chicago, IL, USA). Hardy–Weinberg equilibrium and the significance between the allele and genotype frequencies were assessed using a standard chi-square ( $\chi^2$ ) test. Fisher's exact test was used to compare the PEX group with the non-PEX group. Odds ratios (ORs) for the allele and genotype frequencies of PEX group compared to non-PEX group were calculated using the  $\chi^2$  test, taking a 95% confidence interval (95% CI) into account. A *P*-value <0.05 was considered as statistically significant. All results were adjusted using the Yates correction.

## Results

A total of 93 patients with PEX syndrome (PEX group) and 74 patients without PEX syndrome (non-PEX group) were recruited for this study from among patients with the principal diagnosis of cataract to be operated in a 24-month period. All PEX group and non-PEX group patients originated from the southwestern province of Greece. The PEX group patients

had a mean age of 76.5±7.52 years (range, 47–94 years) and included 46 males and 47 females. The non-PEX group patients had a mean age of 73.1±8.2 years (range, 46–92 years) and included 36 males and 38 females. There were no significant differences in mean age and sex between the PEX and non-PEX groups (*P*>0.05). Unilateral involvement of PEX was found in 13 (14%) and bilateral involvement in 80 (86%) patients among those with PEX syndrome. The mean age 64.46±6.51 years (range, 47–69 years) of the unilateral PEX syndrome involvement was significantly different from that of 78.45±5.43 years (range, 70–94 years) of the bilateral involvement (*P*=0.000). The demographic characteristics of the study population are presented in Table 1. The distribution of the *LOXLI* allele and genotype frequencies of SNPs rs1048661 and rs3825942 was analyzed in patients with and without PEX syndrome. The genotype distribution of both SNPs in PEX and non-PEX group was consistent with the Hardy–Weinberg equilibrium. The detailed count of the allele and genotype frequencies of rs1048661 and rs3825942 polymorphisms of *LOXLI* are presented in Table 2. For both SNPs a significant association with PEX syndrome was identified for the allele and the genotype frequencies. The G allele of rs1048661 was found in 96.7% in PEX group alleles as compared to 80.5% of non-PEX group alleles (*P*=1.9×10<sup>-3</sup>; OR =5.37; 95% CI =1.68–17.12). In addition, the G allele of rs3825942 was significantly more frequent in PEX group, as it was found in 72.1% of PEX group alleles as compared to 41.8% of non-PEX group alleles (*P*=4×10<sup>-5</sup>; OR =3.78; 95% CI =1.98–7.23). Instead, the T allele of rs1048661 appeared at a significantly lower frequency, and the A allele of rs3825942 was underrepresented in the PEX group as compared to non-PEX group. The genotype GG of rs1048661 was found in 25.2% in PEX group as compared to 13.9% in non-PEX group (*P*=5×10<sup>-2</sup>; OR =2.23; 95% CI =0.99–5.02). The genotype GG of rs3825942 was found in 20.2% in the PEX group as compared to 10.8% in non-PEX group (*P*=3×10<sup>-2</sup>; OR =2.56; 95% CI =1.06–6.14). For rs1048661, the GT genotype was underrepresented,

**Table 1** Demographic and clinical characteristics of patients with and without PEX syndrome

Variables	PEX group		Non-PEX group (n=74)	P-value
	Unilateral (n=13)	Bilateral (n=80)		
Age, mean ± SD (years)	64.4±6.5	78.45±5.4	73.1±8.2	0.14
Age, range (years)	47–69	70–94	46–92	
Male/female (n)	8/5	38/42	36/38	

**Notes:** A total of 93 patients with pseudoexfoliation syndrome (PEX group) and 74 patients without pseudoexfoliation syndrome (non-PEX group) were recruited for this study. The mean age and age range of both groups, male/female distribution, as well as unilateral and bilateral involvement are shown in the table.

**Abbreviations:** SD, standard deviation; PEX, pseudoexfoliation.

**Table 2** Allele and genotype frequencies of rs1048661 and rs3825942 in the PEX and non-PEX groups

SNP	PEX group	Non-PEX group	OR (95% CI)	P-value
<b>rs1048661</b>				
Allele				
T	4 (3.3%)	14 (19.5%)	5.37 (1.68–17.12)	0.0019
G	89 (96.7%)	58 (80.5%)		
Genotype				
GT	69 (74.8%)	64 (86.1%)	2.23 (0.99–5.02)	0.05
GG	24 (25.2%)	10 (13.9%)		
<b>rs3825942</b>				
Allele				
A	26 (27.9%)	44 (58.2%)	3.78 (1.98–7.23)	0.00004
G	67 (72.1%)	30 (41.8%)		
Genotype				
GA	71 (79.8%)	66 (89.2%)	2.56 (1.06–6.14)	0.03
GG	22 (20.2%)	8 (10.8%)		

**Notes:** The allele and genotype association with PEX syndrome as well as their frequencies for both SNPs are shown in the table for the PEX group and for the non-PEX group separately. OR with 95% CI and P-values are mentioned for each allele and genotype compared.

**Abbreviations:** CI, confidence interval; OR, odds ratio; PEX, pseudoexfoliation; SNP, single nucleotide polymorphism.

whereas for rs3825942, the GA genotype was even more underrepresented in the PEX group as compared to non-PEX group. Haplotype association analysis identified four common haplotypes (GG, GA, TG, and TA) defined by the two SNPs (rs1048661–rs3825942). Accounted haplotype frequencies are presented in Table 3. The haplotypes were significantly associated with the PEX group either as a risk or as a protective haplotype. The high-risk haplotype GG was more frequent (69.9%) in the PEX group as compared to the non-PEX group (29.7%) ( $P=2.5 \times 10^{-7}$ ), while the haplotype GA was underrepresented in the PEX group (8.5%) than in non-PEX group (37.9%) ( $P=5 \times 10^{-6}$ ). Haplotypes TG and TA were present at lower levels in both groups without any statistical significance.

## Discussion

The potential roles of SNPs of *LOXLI* gene in PEX syndrome were suggested by Thorleifsson et al.<sup>8</sup> Their study

**Table 3** Haplotype analysis of rs1048661/rs3825942

Haplotype	PEX group (%)	Non-PEX group (%)	P-value
GG	69.9	29.7	0.00000025
GA	8.5	37.9	0.000005
TG	19.5	25.8	0.328
TA	2.2	6.6	0.140

**Notes:** Haplotype frequencies and P-values for PEX and non-PEX group are shown. The high-risk haplotype GG was more frequent (69.9%) in the PEX group as compared to the non-PEX group (29.7%), while the haplotype GA was underrepresented in the PEX group (8.5%) compared to the non-PEX group (37.9%). Haplotypes TG and TA were present at lower levels in both groups without any statistical significance.

**Abbreviation:** PEX, pseudoexfoliation.

established a strong association between three SNPs in the *LOXLI* gene on chromosome 15q24.1 with both PEX syndrome and PEX glaucoma in Swedish and Icelandic populations. *LOXLI* is a key enzyme involved in elastic fiber synthesis and homeostasis supporting a role of elastogenesis and elastosis in the pathophysiology of PEX syndrome.<sup>17</sup> Various studies in populations from the United States,<sup>19–23</sup> Europe,<sup>18,24</sup> and Australia<sup>25</sup> highlighted genetic susceptibility of *LOXLI* polymorphisms to PEX syndrome and showed that the *LOXLI* gene is the principal genetic risk factor for PEX syndrome. The risk for PEX disease in Caucasians was associated in a large number of cases with the G allele and GG genotype of rs1048661 and the G allele and GG genotype of rs3825942. A common haplotype (GG) formed by two nonsynonymous SNPs, rs1048661 and rs3825942 located in exon 1 of *LOXLI*, has been reported as a risk factor for the vast majority of PEX patients.

We studied 167 cataract patients, 93 with PEX syndrome (PEX group) and 74 without PEX syndrome (non-PEX group) from a southwestern Greek population. We confirmed a strong association with *LOXLI* variants in our PEX group patients. The frequency of allele G of SNPs rs1048661 and rs3825942 was higher in the PEX group than in the non-PEX group. Also, the frequencies of genotype GG at SNP rs1048661 and the same genotype at SNP rs3825942 were higher in the PEX group than in the non-PEX group. These findings indicate that the G allele and GG genotype of rs1048661 had an increased risk for PEX group, while the G allele and GG genotype of rs3825942 had an even stronger risk for PEX group. In accordance with our results, these frequencies are comparable to the rates observed in most Caucasians including Swedish, Icelandic, American, German, Italian, and Australian populations. Our results indicate that the prevalence of the G allele of SNP rs1048661 in PEX group (0.967) was higher than in the non-PEX group (0.79) and that this difference was statistically significant ( $P=19 \times 10^{-4}$ ). In addition, the prevalence of the G allele of SNP rs3825942 in PEX group (0.721) was higher than in the non-PEX group (0.418) and that this difference was statistically significant ( $P=4 \times 10^{-5}$ ). The association of the high-risk G alleles with PEX syndrome, for the two SNPs examined in the current study, seems to be largely consistent across most of the tested populations, with similar results. However, there are significant exceptions where G allele of rs1048661 is not statistically significant for the occurrence of PEX syndrome in Indian<sup>26</sup> or Chinese<sup>27</sup> populations. Moreover, the G allele of rs1048661 was found to be actually protective in one Chinese population<sup>27</sup> as in several Japanese populations.<sup>28–32</sup>



Finally, the A allele and not the G allele of rs3825942 seems to be the high-risk allele for PEX syndrome in South African populations.<sup>33,34</sup> These inconsistencies show that the connection between *LOXL1* and PEX syndrome may possibly involve another mechanism independent of the alleles of the abovementioned SNPs or could be associated with other SNPs in the *LOXL1* or other genes.<sup>35–37</sup>

Focusing on the results of the genotype frequencies, GG genotype of rs1048661 ( $P=5\times 10^{-2}$ ) and GG genotype of rs3825942 ( $P=3\times 10^{-2}$ ) show less significance than the equivalent statistics of G allele of rs1048661 ( $P=1.9\times 10^{-3}$ ) and rs3825942 ( $P=4\times 10^{-5}$ ). The high-risk haplotype GG formed by the two nonsynonymous coding SNPs, rs1048661 and rs3825942, was found in 69.9% in PEX group and 29.7% of the non-PEX group ( $P=2.5\times 10^{-7}$ ; OR =5.49; 95% CI =2.82–10.69), whereas the haplotype GA defined by rs1048661 and rs3825942 was found in 8.5% in the PEX group as compared to 37.9% in the non-PEX group ( $P=5\times 10^{-6}$ ; OR =6.47, 95% CI =2.73–15.34). In our study, the GA haplotype, defined by rs1048661 and rs3825942, was found to have a potential protective effect on developing PEX syndrome. However, many cataract patients carrying *LOXL1* risk alleles (and genotypes) do not have the PEX syndrome phenotype. Consequently, it must be assumed that additional genetic factors may influence the manifestation of the PEX syndrome. Additionally, a number of nongenetic factors have also been evaluated but not yet identified for the possible implication in the development of PEX syndrome. These include ultraviolet light, autoimmunity, slow virus infection, and trauma.<sup>38</sup>

## Conclusion

In summary, we showed that the G allele of *LOXL1* SNPs rs1048661 and rs3825942 is associated with the PEX syndrome population of this study in a similar manner to the Icelandic, Swedish, American, Australian, German, Italian, and Finnish populations. Finally, our results demonstrate that the SNP rs3825942 in the *LOXL1* gene constitutes a significant risk factor to development of PEX syndrome in the southwestern Greek population.

## Disclosure

The authors report no conflicts of interest in this work.

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