• Basic Research •

Association of *LOXL1* gene common sequence variants in Jordanian patients with exfoliation syndrome and exfoliative glaucoma

Wisam Shihadeh[1,2], Omar Khabour[3,4], Mohammed Bilal Khalil[5], Alaa Al-Dabbagh[1], Mustafa Al-Hashimi[1]

[1]Department of Ophthalmology/Special Surgery, Faculty of Medicine, Jordan University of Science & Technology, Irbid 22110, Jordan
[2]Department of Ophthalmology/Clinical Medical Sciences, Faculty of Medicine, Yarmouk University, Irbid 21163, Jordan
[3]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, Jordan University of Science & Technology, Irbid 22110, Jordan
[4]Faculty of Applied Medical Sciences, Taibah University, Al-Medina 42353, Saudi Arabia
[5]Department of Ophthalmology, Islami Hospital, Amman 11190, Jordan
Correspondence to: Wisam Shihadeh. Faculty of Medicine, Yarmouk University, PO Box 150474, Irbid 21141, Jordan. wshihadeh@yu.edu.jo
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Abstract

• AIM: To investigate the association between single nucleotide polymorphisms (SNPs) in the *LOXL1* gene with exfoliation syndrome/glaucoma (XFS/XFG) among Jordanians.

• METHODS: Sixty-one patients with XFS/XFG and 59 healthy control individuals were recruited in the study. Patients were diagnosed with XFS/XFG using standard clinical examination techniques. The exonic rs1048661 SNP and the intronic rs2165241 SNP in *LOXL1* gene were genotyped using sequencing technique. Allele and genotype frequencies were compared between cases and controls using Chi-square analysis.

• RESULTS: The G allele of the rs1048661 SNP and the T allele of the rs2165241 SNP were common in the sample with frequencies of 86.4% and 81.4%, respectively. In addition, there were no significant differences in the genotypic and allelic distributions between patients and controls for rs1048661 SNP (*P*=0.770, OR=1.21, 95%CI: 0.56-2.60) and for rs2165241 SNP (*P*=0.605, OR=1.12, 95%CI: 0.59-2.09). In addition, no significant associations were found between haplotypes of the examined SNPs and XFS/XFG in the sample (*P*>0.05).

• CONCLUSION: Variations in *LOXL1* gene may not be associated with XFS/XFG in the Jordanian population. More studies are required to confirm the current findings.

• KEYWORDS: *LOXL1*; polymorphism; exfoliation syndrome; Jordan; glaucoma

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INTRODUCTION

Exfoliation syndrome (XFS) is a late onset fibrillopathic disease that involves formation and progressive accumulation of exfoliation material (XFM) in various ocular and extraocular tissues[1]. It is considered as the most global common cause of exfoliative glaucoma (XFG)[2-3] and it is associated with raised intraocular pressure (IOP) and increased aqueous humor outflow resistance[4]. On an ultrastructural level, XFM is a complex glycoprotein/proteoglycan structure composed of a protein core surrounded by abundant glycoconjugates[5-6]. The protein core comprises three components: 1) basement membrane component that contains laminin, nidogen, and fibronectin proteins; 2) components of the elastic fiber system that contains structures such as fibrillin-1 and elastin; 3) components with enzymatic activity such as matrix metallo-proteinases, clusterin chaperone, and the lysyl oxidase-like 1 (LOXL1)[7-8]. LOXL1 belongs to lysyl oxidase family of proteins that are involved in the biogenesis of connective tissue. LOXL1 has Cu-dependent amine oxidase activity that mediates the formation of the crosslinks in collagen and elastin[9]. In the ocular tissues, LOXL1 plays an essential role in homeostasis of elastic fiber networks[9-10].

In humans, LOXL1 is encoded by *LOXL1* gene that is located at 15q24.1[11]. In 2007, Thorleifsson *et al*[12] published the results of a genome-wide association study on Icelandic and Swedish populations and established a significant association between two exonic (rs3825942 and rs1048661) as well as one intronic (rs2165241) single nucleotide polymorphisms (SNPs) of the *LOXL1* gene with XFS/XFG. Both exonic SNPs, rs1048661 (R141L) and rs3825942 (G153D), are located in the chromosomal region 15q24.1, specifically in exon 1 of *LOXL1* gene. This exon encodes the unique N-terminal domain that is

required for proper LOXL1 enzyme activation and for substrate recognition and binding[13]. Several lines of evidence suggest that a reduction in *LOXL1* gene expression contributes to XFS/XFG development. In one study, using ocular tissue samples from the iris, lens and ciliary body, *LOXL1* expression was reduced by approximately 20% per risk allele of rs1048661[14]. However, the association between the *LOXL1* SNPs and XFS/XFG has been examined in different populations worldwide, with contradictory results[15]. For example, rs1048661 G allele has been reported to increase the risk of XFG in Caucasian populations, whereas it has been shown to protect against the disease in Asian populations[16]. Therefore, in this study, we aimed to investigate the association of *LOXL1* gene SNPs with XFS/XFG in Jordanian patients and to compare our data with the results from worldwide populations.

SUBJECTS AND METHODS

Subjects This cross-sectional analysis is part of an ongoing prospective study on XFS/XFG in Jordan. Sixty-one unrelated Jordanian patients with XFS/XFG and 59 age and gender matched unrelated controls from the same geographical area were included in the study. All patients were recruited from King Abdullah University Hospital, the major hospital that serves the northern municipalities of Jordan. XFS diagnosis was based on the presence of the characteristic XFM on the anterior lens surface on dilated ophthalmic examination by slit lamp biomicroscopy, regardless of IOP or glaucoma status. Exclusion criteria include patients presented with other related pathologies such as retinopathies, or maculopathies or other conditions causing secondary glaucoma[15,17]. Ethical approval on carrying out the study was obtained from the Institutional Review Board at Jordan University of Science and Technology. Informed consents were signed by all subjects enrolled in this study.

Demographics that include age, gender, time since diagnosis of the disease were obtained using a questionnaire. Informed consent was obtained from all XFS cases and normal subjects after the objectives and procedures of the study had been fully explained.

***LOXL1* Gene Analysis** A total of 5 mL of whole blood in EDTA-tube was collected from each participant and stored at -20.0℃. Genomic DNA was extracted from the blood samples using commercially DNA extraction kit (Promega, Madison, WI, USA) following the manufacturer's instructions. For the rs2165241 SNP, DNA fragments were amplified using forward primer 5'-cgcattatagccatgcatca-3' and reverse primer 5'-gtggccagaggtctgctaag-3'. For the rs1048661 SNP, DNA was amplified using forward primer 5'-gctcaactcgggctcaga-3' and reverse primer 5'-ttctcgtactggctgacgaa-3'. Polymerase chain reaction (PCR) was carried out in a total of 25 μL volume containing ready-to-use master mix (Promega, Madison, WI, USA), 1 pmol of each primer, and 50 ng of genomic DNA. For both SNPs, the PCR conditions were 95℃ for 5min followed by 35 cycles of 95℃ for 60s, 60℃ for 35s and 72℃ for 45s, and the final extension at 72℃ for 10min. PCR products were then purified using quick-spin TM Kit (iNtRON Biotechnology Inc., Korea). The purified PCR products were sequenced using the Big Dye Terminator Cycle Sequencing Kit (version 3.1, Qiaquick, Germany). DNA sequencing was carried out in one direction in all exons using either the forward or the reverse primer. The DNA sequencing reaction was cleaned from the excess Dye Deoxy terminator using the DyeEx 2.0 spin purification kit (Qiagen, USA). The amplified DNA fragments were then sequenced using ABI 310 DNA sequencer (Applied Biosystems, Foster city, USA). Sequencing results were analyzed using chromasPro software (Technelysium, Australia). Reference sequences of *LOXL* were obtained from Ensembl Genome Browser (httb://www.ensembl.org/index.html).

Table 1 Demographic data of studied participants

Variable	Control group	XFS/XFG group
Age, y		
Mean	70.24	70.08
Range	59-90	58-90
Gender		
Male	29	28
Female	30	33

XFS/XFG: Exfoliation syndrome/glaucoma.

Statistical Analysis Chi-square test, using SPSS software version 19 (SPSS Inc., Chicago, IL, USA), was carried out to evaluate genotype distribution and allele frequencies of the 2 studied polymorphisms for XFS cases and normal subjects. Haplotype frequencies were calculated using the SHEsis program (http://analysis.bio-x.cn/myAnalysis.php). A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 61 patients with XFS/XFG and 59 healthy control subjects participated in the study. The average age in the exfoliation group was 70.08y (range 58-90) while the average age in the control group was 70.24y (range 59-90). Male to female ratio was 1:1.18 in the XFS/XFG group and 1:1.03 in the normal subject group (Table 1).

The G allele in the rs1048661 SNP and the T allele in the rs2165241 SNP were the most common alleles in the Jordanian population with frequencies of 86.4% and 81.4%, respectively. The abundance of these alleles is similar to that observed in other populations from other countries in the world (Table 2).

Table 3 showed the allelic and genotypic distributions of the rs1048661 and rs2165241 SNPs of the *LOXL1* gene in both cases and controls. All examined SNPs are in Hardy-Weinberg equilibrium. There were no significant differences in the allelic distributions between patients and controls for rs1048661 SNP (*P*=0.770, OR=1.21, 95%CI: 0.56-2.60). In addition, no significant difference was obtained when genotypic distribution

Table 2 Summary of the distribution of *LOXL1* polymorphisms among various populations

Variable	rs1048661		rs2165241	
	G	T	T	C
Jordanian (this study)	0.86	0.14	0.81	0.19
Spanish[18]	0.72	0.28	0.48	0.52
Italian[19]	0.64	0.36	0.48	0.52
Greek[20-21]	0.80	0.20	0.53	0.47
Mexican[22]	0.80	0.20	0.50	0.50
Saudi Arabian[23]	0.76	0.24	NA	NA
American[24]	0.67	0.33	0.49	0.51

Table 3 Genotypic and allelic frequencies of rs1048661 and rs2165241 SNPs of *LOXL1* in cases and controls *n* (%)

Genotypes & alleles	Control group	XFS/XFG group	*P*	OR (95%CI)
rs1048661				
GG	44 (74.6)	46 (75.4)		
GT	14 (23.7)	15 (24.6)		
TT	1 (1.7)	0 (0.0)	0.592	
Allele G	102 (86.4)	107 (87.7)		
Allele T	16 (13.6)	15 (12.3)	0.77	1.21 (0.56-2.60)
rs2165241				
TT	42 (71.2)	38 (62.3)		
TC	12 (20.3)	20 (32.8)		
CC	5 (8.5)	3 (4.9)	0.263	
Allele T	96 (81.4)	96 (78.7)		
Allele C	22 (18.6)	26 (21.3)	0.605	1.12 (0.59-2.09)

of the rs1048661 was considered (*P*=0.592). Similar findings were obtained with allelic distribution (*P*=0.605, OR=1.12, 95%CI: 0.59-2.09) and genotypic distribution (*P*=0.263) of the rs2165241 SNP.

Haplotype analysis of the rs1048661 and rs2165241 SNPs was shown in Table 4. The most common haplotype in the population was GT (74%) followed by GC (12.4%), TC (7.1%) and TT (6.5%). The results showed no significant association between any of the examined haplotypes and the disease (GT: *P*=0.735, OR=1.106, 95%CI=0.62-1.98; GC: *P*=0.963, OR=1.018, 95%CI=0.47-2.19; TC: *P*=0.641, OR=1.252, 95%CI=0.49-3.22; TT: *P*=0.171, OR=0.413, 95%CI=0.11-1.52). Thus, it appears that none of the examined SNPs are associated with XFS/XFG among Jordanians.

Table 4 Haplotype analyses of rs1048661 and rs2165241 SNPs of *LOXL1* in cases and controls *n* (%)

Haplotypes	Control group	Cases group	*P*	OR (95%CI)
GC	14.67 (12.4)	15.41 (12.6)	0.963	1.018 (0.47-2.19)
GT	87.33 (74.0)	92.59 (75.9)	0.735	1.106 (0.62-1.98)
TC	8.33 (7.1)	10.59 (8.7)	0.641	1.252 (0.49-3.22)
TT	7.67 (6.5)	3.14 (2.8)	0.171	0.413 (0.11-1.52)

DISCUSSION

The *LOXL1* gene belongs to the lysyl oxidase gene family which is involved in the biogenesis of connective tissue by formation of crosslinking in collagens and elastin[1]. Several studies have investigated the association between variations in *LOXL1* gene (particularly the rs1048661 and rs2165241 SNPs) and XFS/XFG, a condition where the extracellular spaces accumulate large amounts of cross-linked, amyloid-like fibrillar material and glycoproteins[15]. In this report, we compared distributions of genotypes, alleles and haplotypes of rs1048661 and rs2165241 SNPs of *LOXL1* gene in XFS/XFG patients as well as normal subjects in Jordanians. The results showed absence of association between examined SNPs and the disease.

The rs1048661 is a nonsynonymous coding SNP located in the first exon of the *LOXL1* gene on chromosomal region 15q24.1[11]. The data showed no statistically significant difference between the XFS/XFG patients and control groups when comparing genotypic distributions and allelic frequencies of rs1048661. This finding is in agreement with previous reports conducted on Spanish[18], Italian[19], Greek[20-21], Mexican[22], Saudi[23], Amerian[24], Turkish[25-26] and Indian[27], Polish[28] and Chinese[29] populations. However, the G allele of rs1048661 SNP has been shown to be associated with XFS/XFG in Icelandic[12], Finnish[30] and Austrian[31] populations.

On the other hand, the G allele of rs1048661 SNP was found to be protective against the disease among Japanese[32-33] and Korean[34-35] populations. With respect to the intronic rs1048661 SNP, the results showed lack of association between rs2165241 SNP of *LOXL1* gene and XFS/XFG among Jordanians. This result is in agreement with a previous report from Japan[32]. However, the T allele was found to be associated with XFS/XFG in Caucasian populations such as Spanish[18], Polish[28], Icelandic[12], Finnish[30], German[19] and Austrian[31], while it was found to be protective against the disease among Chinese[36], Japanese[37] and Korean[34-35] populations. Thus, the relationship between rs1048661 and rs2165241 SNPs and XFS/XFG seems to be complex and might have a population specific component, being affected by the population specific gene pool as well as by gene-environment interactions. In support of this, allelic and genotypic distributions of the examined SNPs were found to be significantly different among different ethnicities. The allelic distribution of East Asian populations including Japanese and Chinese are reversed for rs1048661 and rs2165241 when compared with that of European populations (Table 2). In addition, *in vitro* assay has provided evidence that the rs1048661 SNP does not affect LOXL1 enzymatic activity[38]. This means there are other regions in the *LOXL1* gene regulating the expression of the gene itself and/or that there are other genes or environmental factors contributing to the development of the disease[39]. Alternatively, combinations of SNPs (haplotypes) in the *LOXL1* gene might be more important in the determination of susceptibility to XFS/

XFG rather than individual SNPs. In our study, none of the examined haplotypes were found associated with the disease. More studies at the molecular level are required to understand the role of different SNPs of *LOXL1* gene in the pathogenesis of XFS/XFG.

In conclusion, we have performed an analysis of two SNPs in *LOXL1* gene and XFS/XFG in Jordanian population and have not found any association with the disease. More studies are required to confirm these findings.

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