Int J Clin Exp Med 2016;9(10):19709-19716
www.ijcem.com /ISSN:1940-5901/IJCEM0021613

Original Article

Correlations between single nucleotide polymorphisms in the lysyl oxidase-like 1 gene promoter region and exfoliation syndrome in the Uighur population

Yao Li, Ru-Xin Ding, Meng-Ying Guo, Xue-Yi Chen

Department of Ophthalmology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830054, China

Received December 10, 2015; Accepted August 10, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: The aim of this study was to investigate the correlations between single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (*LOXL1*) gene promoter region and exfoliation syndrome (XFS) in the Uighur population. This case-control study involved 152 unrelated XFS patients and 228 gender-matched volunteers with normal eye conditions. Five milliliters of peripheral blood was sampled from each subject for DNA extraction and genotyping for six SNPs in the *LOXL1* gene promoter region, using the polymerase chain reaction-ligase detection reaction. The χ^2 test was performed to analyze the allele and genotype frequency distributions, as well as the odds ratio and 95% confidence interval. The rs12914489 locus in the control group was shown to deviate from the Hardy-Weinberg equilibrium (HWE) (P = 0.033), whereas the other five SNP loci were all in line with the HWE. The frequencies of the rs4886467 G allele and GG genotype were statistically significantly lower in the XFS group than in the control group, implying that they had a protective effect against XFS onset. On the other hand, the frequencies of the rs4558370 G allele and GG genotype, rs4461027 C allele and CC genotype, rs4886761 T allele and TT genotype, and rs16958477 C allele and CC genotype were statistically significantly higher in the XFS group than in the control group, indicating that they were all risk factors for XFS. Taken together, these results indicate significant correlations between SNPs in the *LOXL1* gene promoter region and XFS in the Uighur population.

Keywords: Exfoliation syndrome, LOXL1 gene, promoter region, polymorphism, single nucleotide, susceptibility of disease gene

Introduction

Exfoliation syndrome (XFS) is an age-related disease that causes mainly pathological changes in the extracellular matrix. Its main clinical ocular manifestation is deposition of a fine, white, dust-like material in the anterior chamber tissues, commonly seen in the pupil margin, anterior lens capsule membrane, and anterior chamber. XFS can induce a variety of ocular complications, such as glaucoma, pigment dispersion syndrome, lens subluxation, insufficient mydriasis, blood-aqueous barrier dysfunction, posterior synechia, and corneal endothelial decompensation [1-3]. The intake of vitamins B_6 and B_{12} has been associated with the incidence of XFS [4]. In recent years, developments in the genetic research of XFS have laid a good foundation for revealing the molecular mechanisms underlying this disease. Studies have found that the single nucleotide polymorphism (SNP) loci rs1048661, rs2165241, and rs3825942, located in the first exon region of the lysyl oxidase-like 1 (*LOXL1*) gene, were closely related with the occurrence and development of XFS [5-9]. However, the results of these studies were not consistent in different races and populations, even among different regions or ethnic groups in the same country [10, 11]. Some studies also found that certain SNP loci in the *LOXL1* gene promoter region correlated with the incidence of XFS [12, 13]. This study investigated the correlations between six SNPs in the *LOXL1* gene promoter region and XFS pathogenesis in the Xinjiang Uighur population. This study was approved by the Ethics Committee of Xinjiang Medical University, and all the subjects understood the purpose and significance of this study, and signed the informed consent.

Methods

General information

This case-control study included a total of 152 Uighur patients who were treated for XFS between January and August 2014 at the First Affiliated Hospital of Xinjiang Medical University, the First People's Hospital of Kashgar, and the Kuqa County Hospital. The diagnosis of XFS was made according to criteria listed in the literature [5]. During the same period, 228 healthy volunteers were included into the control group, with the following inclusion criteria: 1) absence of XFS signs; 2) absence of characteristic glaucomatous changes in the optic disk; 3) normal vision field and intraocular pressure; 4) absence of family history of glaucoma; and 5) absence of other eye diseases, except for refractive errors or age-related cataracts. The exclusion criteria were as follows: 1) presence of other systemic diseases, such as cancer, rheumatoid and immunological diseases, kidney diseases, diabetes, and hypertension; 2) history of eye surgery; and 3) poor compliance, and inability to complete the appropriate inspections. All the subjects underwent detailed eye inspections, including visual acuity, slit lamp microscopy, tonometry, gonioscopy, indirect ophthalmoscopy, fundus photography, and visual field inspection.

Detection of SNP genotypes by polymerase chain reaction-ligase detection reaction

Five milliliters of peripheral blood was sampled from each subject, placed into an EDTA anticoagulant tube, and preserved at -80°C. A genomic DNA extraction kit (Qiagen Co., Germany) was used to extract the genomic DNA in accordance with the manufacturer's instructions. The polymerase chain reaction-ligase detection reaction (PCR-LDR) method was then performed for genotyping the SNPs (technical support provided by the Shanghai Tianhao Biotechnology Co., China). This study selected six SNP loci in the *LOXL1* gene promoter region; namely, rs12914489, rs4886467, rs4558370, rs4461027, rs4886761, and rs16958477. Fluorescence labeling with specific oligonucleotide probes for the different alleles of each SNP was performed, and the different SNP loci were marked by the different extension lengths at the 3' end.

DNA amplification and sequencing

The PCR volume was 10 μL, containing 1× GC-I buffer (Takara, Japan), 3.0 mmol/L Mg^{2+}, 0.3 mmol/L dNTP, 1 U (product unit) of HotStarTaq polymerase (Qiagen Co.), 1 μL of DNA sample, and 1 μL of multiplex PCR primers. The PCR amplification conditions were as follows: denaturation at 95°C for 2 min; 11 cycles of denaturation at 94°C for 20 s, annealing at 65°C for 40 s, and extension at 72°C for 1.5 min; 24 cycles of denaturation at 94°C for 20 s, annealing at 59°C for 30 s, and extension at 72°C for 1.5 min; and a final extension at 72°C for 2 min. The PCR products were stored at 4°C. For the LDR, 5 U of shrimp alkaline phosphatase and 2 U of Exonuclease I were added to 10 μL of the PCR product and the mixture was incubated in a water bath at 37°C for 1 h and then inactivated at 75°C for 15 min. Then, 1.00 μL of 10× LDR buffer, 0.25 μL of high-temperature ligase, 0.40 μL of 1 μmol/L 5' LDR primer mixture, 0.40 μL of 2 μmol/L 3' LDR primer mixture, 2.00 μL of purified multiplex PCR product, and 6.00 μL of ddH_2O were mixed uniformly and incubated at 94°C for 1 min, followed by 56°C for 4 min, for 38 cycles. The products were stored at 4°C. Finally, 0.5 μL of diluted LDR product (1:10) was mixed with 0.5 μL of LIZ 500 size standards and 9.0 μL of Hi-Di formamide, and denatured at 95°C for 5 min. Then, sequencing was performed with the ABI 3730XL sequencer. The raw data were collected and analyzed using GeneMapper 4.1 (Applied Biosystems, USA).

Statistical methods

SPSS19.0 statistical software (IBM, USA) was used for the statistical analysis, with Haploview 4.2 used for the linkage disequilibrium and haplotype analyses. The χ^2 test was performed to compare whether the genotypes of each SNP locus between the XFS group and the control group met Hardy-Weinberg equilibrium (HWE), and the data of allele and genotype frequency distribution of each gene locus were described using the frequency. The logistic regression equation was used to control for age and gender. The differences in the genotype and allele frequency distributions of each SNP locus between the two groups were compared using the χ^2 test with the bilateral probability test, at a test level of $\alpha = 0.05$. The dual logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) of the genotypes and alleles.

Table 1. Comparison of baseline demographic characteristics between the two groups

Group	Cases	Age ($\overline{x}$±s, years)[a]	Gender [*n* (%)][b]	
			M	F
XFS	152	70.81±8.37	102 (67.11)	50 (32.89)
Control	228	68.85±7.02	150 (65.79)	78 (34.21)
P		0.014	0.790	

NOTE: XFS: Exfoliation syndrome (a: independent sample t test; b: χ^2 test).

Table 2. HWE test results of the two groups

SNPs	Location	P of HWE *in each group*	
		Control	XFS
rs12914489	Promoter region	0.033	1.000
rs4886467	Promoter region	1.000	0.653
rs4558370	Promoter region	0.448	0.722
rs4461027	Promoter region	0.306	0.065
rs4886761	Promoter region	0.214	1.000
rs16958477	Promoter region	0.303	1.000
rs1048661	First exon region	1.000	1.000
rs3825942	First exon region	0.130	0.059
rs2165241	First exon region	0.494	0.988

NOTE: XFS: Exfoliation syndrome; HWE: Hardy-Weinberg equilibrium; SNPs: single nucleotide polymorphisms.

Results

Clinical data

Of the 380 subjects who received genotypic testing, 152 were XFS patients (XFS group) and 228 were healthy volunteers (control group). The two groups differed significantly in age (*P* = 0.014), but not in gender composition ratio (*P* = 0.790) (**Table 1**). Therefore, when analyzing the correlations between the SNPs and XFS, age was controlled as one confounding factor.

HWE test of SNP loci in the LOXL1 gene promoter region

The genotype distribution results of the SNP loci showed that rs12914489 in the control group deviated from HWE (*P* = 0.033), whereas the other loci were in line with HWE; thus, they all had group representativeness (**Table 2**).

Comparison of individual SNP allele and genotype frequencies

The genotyping graphs for the six SNPs are shown in **Figure 1**. The linkage disequilibrium correlations between these six SNP loci and XFS onset are shown in **Figure 2**.

Analysis of the allele and genotype frequencies in the six SNP loci showed that *LOXL1* polymorphisms were associated with the genetic susceptibility of the XFS patients. The frequencies of the G allele and GG genotype of the rs12914489 locus in the XFS group were not significantly different from those in the control group (*P* = 0.844 and *P* = 0.530, respectively), indicating that the G allele and GG genotype were not associated with XFS (OR = 0.94, *P* = 0.862; OR = 0.81, *P* = 0.552). However, the frequencies of the G allele and GG genotype of the rs4886467 locus were statistically significantly lower in the XFS group than in the control group (*P* = 0.000 and *P* = 0.001, respectively), indicating that the G allele and GG genotype had protective effects against XFS (OR = 0.54, 95% CI = 0.40-0.74, *P* = 0.000; OR = 0.51, 95% CI = 0.33-0.78, *P* = 0.001). The frequencies of the G allele and GG genotype of the rs4558370 locus were statistically significantly higher in the XFS group than in the control group (*P* = 0.004 and *P* = 0.002, respectively), indicating that the G allele and GG genotype were risk factors for XFS (OR = 1.96, 95% CI = 1.23-3.11, *P* = 0.004; OR = 2.18, 95% CI = 1.31-3.64, *P* = 0.002). The C allele and CC genotype frequencies of the rs4461027 locus were also statistically significantly higher in the XFS group (*P* = 0.000 and *P* = 0.000, respectively), indicating that the C allele and CC genotype were risk factors for XFS (OR = 2.25, 95% CI = 1.67-3.04, *P* = 0.000; OR = 3.06, 95% CI = 1.89-4.96, *P* = 0.000). In the case of the rs4886761 locus, the T allele and TT genotype frequencies were statistically significantly higher in the XFS group (*P* = 0.000 and *P* = 0.000), indicating that the allele and genotype were risk factors for XFS (OR = 2.44, 95% CI = 1.79-3.33, *P* = 0.000; OR = 3.02, 95% CI = 1.63-5.60, *P* = 0.000). Likewise, the C allele and CC genotype frequencies of the rs16958477 locus were statistically significantly higher in the XFS group (*P* = 0.000 and *P* = 0.004, respectively), indicating that both were risk factors for XFS (OR = 2.00, 95% CI = 1.47-2.71, *P* = 0.000; OR = 2.37, 95% CI = 1.31-4.27, *P* = 0.004). In other words, the emergence of the respective alleles and genotypes at the five SNP loci in HWE, as detected in the whole-blood DNA of Xinjiang Uighur individuals, was associated with XFS (**Table 3**).

Single nucleotide polymorphisms in LOXL1 gene promoter region

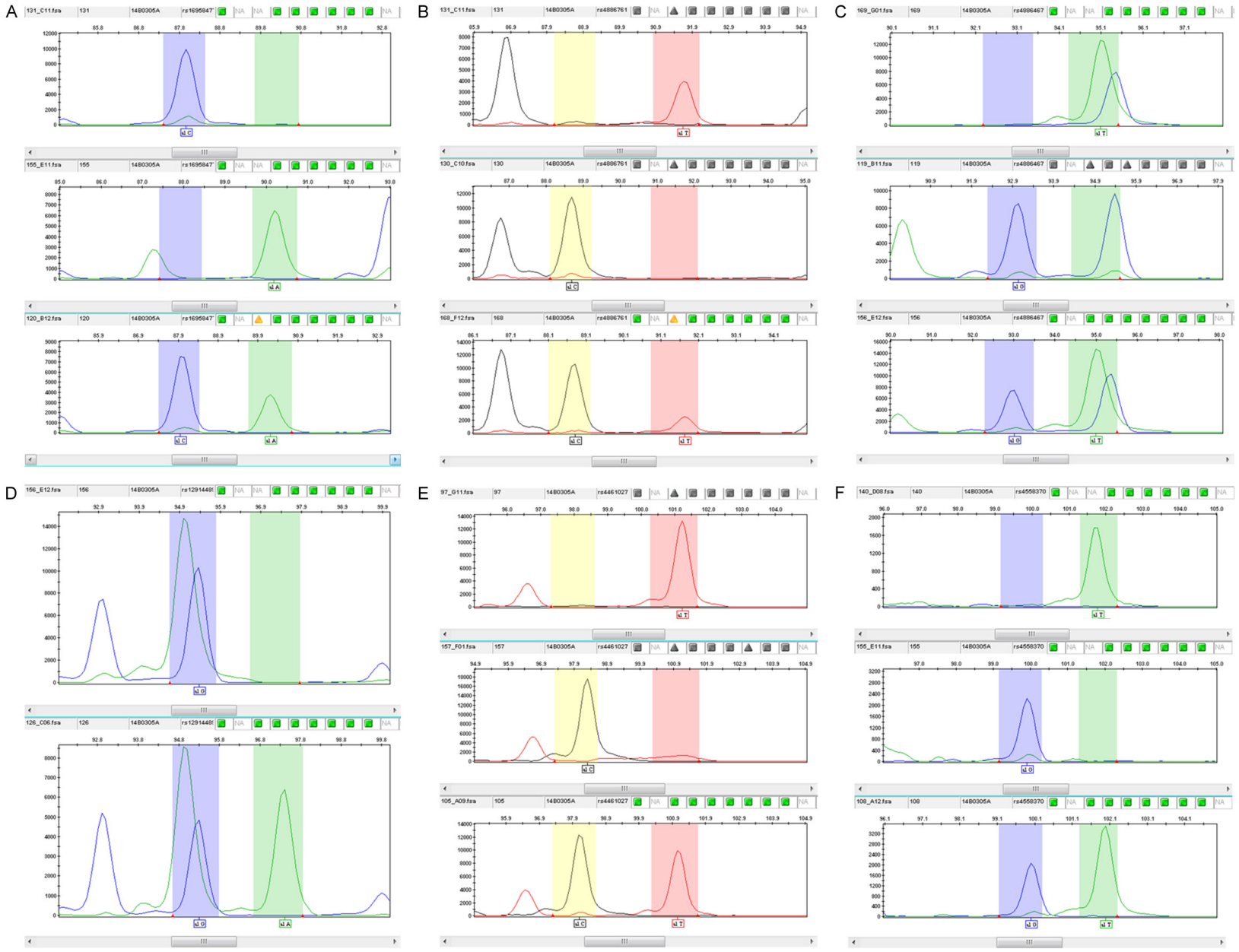

Figure 1. Genotyping graph for each of SNP. A: rs16958477; B: rs4886761; C: rs4886467; D: rs12914489; E: rs4461027; F: rs4558370.

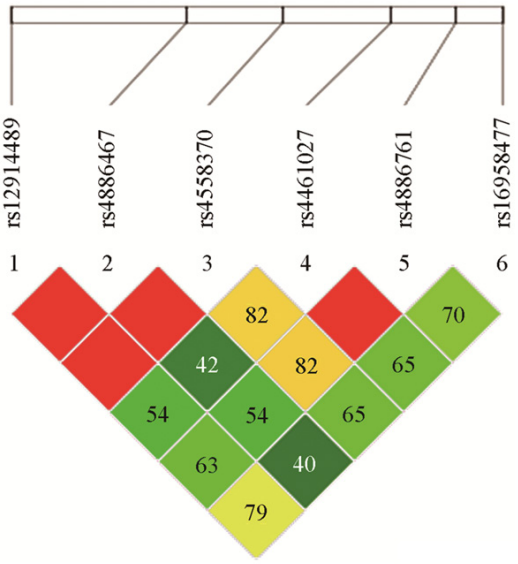

Figure 2. Linkage disequilibrium correlations of the six SNPs loci in the LOXL1 gene: the digitals inside the square represented the D value ×100, red represented D' = 1, blue represented D' = 0, the closer to 1 the D', the closer its color to red, the closer to 0 the D', the closer its color to blue.

Correlations between haplotypes in the promoter region and XFS

Haplotype GGGCTA, composed of the rs4461027 C allele and rs4886761 T allele, showed the strongest correlation with XFS onset, making it a risk factor for this disease in the Xinjiang Uighur population (OR = 4.15, 95% CI = 1.60-10.73, P = 0.003). On the other hand, haplotype GGGTCA, composed of the rs4461027 T allele and rs4886761 C allele, showed significant protective effects against XFS (OR = 0.53, 95% CI = 0.37-0.76, P = 0.001). Haplotype GTGCTC also had a definite correlation with XFS occurrence (OR = 2.07, 95% CI = 1.44-2.97, P = 0.000). Although haplotype GGTTCA was associated with XFS (OR = 1.73, 95% CI = 1.22-2.46, P = 0.001), the correlation was weaker than that of haplotype GGGCTA (**Table 4**).

Discussion

The *LOXL1* gene is a major risk factor for XFS in the global population. Although a number of studies on the correlations between *LOXL1* polymorphisms and XFS have been conducted in China and abroad, the results were inconsistent owing to differences in regions, races, etc. An epidemiological survey found that the incidence of XFS is high in the Xinjiang Uighur population. Since Xinjiang has the highest number of Uighurs, the analysis of the correlations between *LOXL1* SNPs and XFS within this population would have great significance for developing effective treatments in future, as well as preventing the occurrence and development of XFS and reducing its incidence.

In recent years, the research studies on SNPs of the *LOXL1* gene have been mainly focused on rs1048661, rs3825942, and rs2165241 in the first exon [5-9]. Moreover, using the full-genome sequencing method, Nakano *et al.* [14] revealed that the *LOXL1*, *TBC1D21*, and *PML* genes located on chromosome 15q24.1 could together increase the genetic susceptibility of Asian populations to XFS. Guadarrama-Vallejo *et al.* [15] found that the rs41435250 locus of the *LOXL1* gene was a new risk factor for XFS in Mexicans. Chen *et al.* [7] proved for the first time that *LOXL1* was the predisposing gene for XFS in the Han population. Likewise, Mayinu and Chen [16] confirmed for the first time that the rs2165241, rsl048661, and rs3825942 loci of *LOXL1* were associated with its genetic susceptibility in Uighur XFS patients in Xinjiang, with each SNP locus showing strong correlation with the disease.

The differences among the *LOXL1* gene family members are mainly in the first exon, exhibiting changes in length and sequence, and coding of the activation of the N-terminal propeptide enzymes. Mutations in the *LOXL1* gene can affect the catalytic activities or substrate binding capacities of enzymes, such as fiber protein 5 and tropoelastin. However, many recent studies have reported contrary results of risk loci such as rs1048661 and rs3825942 in different ethnic populations [8, 9, 17, 18]. Furthermore, these two variants had no impact on the amine oxidase activities of the LOXL1 protein. These genetic studies indicated that rs1048661 and rs3825942 might cause linkage disequilibrium of functional vari-

Table 3. Alleles and genotype frequencies of the six SNPs in each group

SNPs	Groups (cases)	Allele (cases/frequency)		*OR* (95% *CI*)	x^2	*P*	Genotype distribution (cases/frequency)			*OR* (95% *CI*)	x^2	$P_{corrected}$
		G	A	G vs. A			GG	GA	AA	GG vs. GA/AA		
rs12914489	XFS (152)	287/0.94	17/0.06	0.94 (0.50-1.80)	0.04	0.844	135/0.89	17/0.11	0/0.00	0.81 (0.41-1.61)	0.39	0.530
	Control (228)	432/0.95	24/0.05	--			207/0.91	18/0.08	3/0.01	--		
rs4886467	XFS (152)	180/0.59	124/0.41	0.54 (0.40-0.74)	15.34	0.000	55/0.36	70/0.46	27/0.18	0.51 (0.33-0.78)	10.46	0.001
	Control (228)	332/0.73	124/0.27	--			121/0.53	90/0.39	17/0.07	--		
rs4558370	XFS (152)	276/0.91	28/0.09	1.96 (1.23-3.11)	8.15	0.004	126/0.83	24/0.16	2/0.01	2.18 (1.31-3.64)	9.45	0.002
	Control (228)	381/0.84	75/0.16	--			157/0.69	67/0.29	4/0.02	--		
rs4461027	XFS (152)	126/0.41	178/0.51	2.25 (1.67-3.04)	29.19	0.000	32/0.21	62/0.41	58/0.38	3.06 (1.89-4.96)	22.31	0.000
	Control (228)	280/0.61	176/0.39	--			90/0.39	100/0.44	38/0.17	--		
rs4886761	XFS (152)	165/0.54	139/0.46	2.44 (1.79-3.33)	32.88	0.000	45/0.30	75/0.49	32/0.21	3.02 (1.63-5.60)	12.70	0.000
	Control (228)	339/0.74	117/0.26	--			130/0.57	79/0.35	19/0.08	--		
rs16958477	XFS (152)	167/0.55	137/0.45	2.00 (1.47-2.71)	20.13	0.000	46/0.30	75/0.49	31/0.20	2.37 (1.31-4.27)	7.95	0.004
	Control (228)	323/0.71	133/0.29	--			118/0.52	87/0.38	23/0.10	--		

Note: *P* was obtained by calculating the HWE equilibrium, $P_{corrected}$ was obtained after adjusting age with dual Logistic regression analysis; SNPs: Single nucleotide polymorphisms; XFS: Exfoliation syndrome; OR: Odds ratio; CI: Confidence interval.

Table 4. Correlations between the haplotypes in the LOXL1 gene promoter region and XFS

Haplotype	Haplotype frequency		χ^2	*P*	*OR* (95% *CI*)	$P_{corrected}$	*Beta*
	XFS	Control					
GGGTCA	0.178	0.289	12.34	0.000	0.53 (0.37-0.76)	0.001	-0.633
GGGCTA	0.053	0.013	10.11	0.001	4.15 (1.60-10.73)	0.003	1.422
GTGCTC	0.270	0.151	16.07	0.000	2.07 (1.44-2.97)	0.000	0.728
GGTTCA	0.076	0.154	10.29	0.001	0.45 (0.28-0.74)	0.002	-0.794

Note: *P* was obtained by calculating the HWE equilibrium, $P_{corrected}$ was obtained after adjusting age with dual Logistic regression analysis; LOXL1: Lysyl oxidase-like 1; XFS: Exfoliation syndrome; OR: Odds ratio; CI: Confidence interval.

ations instead of directly causing the disease. Several studies had shown that SNPs in the *LOXL1* gene promoter region were related to XFS onset, and confirmed that the correlation between the rs12914489 locus in the distal *LOXL1* gene promoter region and XFS was strong; that the rs16958477 locus would significantly affect the gene transcription; and that the haplotype formed by the rs12914489 and rs16958477 loci significantly affected the missense alleles rs1048661 and rs3825942, thus affecting the incidence of the disease [12, 13]. The latest research showed that both the regulation of long non-coding RNA activity and mutations in the *LOXL1* gene promoter region of XFS patients were associated with cell stress [19], prompting us to further investigate the correlations between the gene and XFS in the Uighur population. Environmental factors such as high latitude regions, solar radiation, climate, excessive coffee consumption, and low folate intake are also non-genetic factors that could increase the risk for XFS [20].

This study proposed and demonstrated for the first time that SNPs in the *LOXL1* promoter region were correlated with XFS in the Uighur population. Specifically, the T allele of rs4886467, G allele of rs4558370, C allele of rs4461027, T allele of rs4886761, and C allele of rs16958477 were the risk alleles in the studied population, among which the G allele of rs4558370 had the strongest correlation with the disease. The disease risk for individuals with genotypes TT, GG, CC, TT, and CC carried in these SNPs was increased by 2.74, 2.18, 3.06, 3.02, and 2.37 times, respectively. Haplotype GGGCTA in the promoter region was the highest risk haplotype for the Uighur XFS patients in Xinjiang, where the risk for individuals carrying this haplotype was increased by 4.15 times, whereas those carrying GTGCTC and GGTTCA had an increased risk of 2.07 times and 1.73 times, respectively. On the other hand, haplotype GGGTCA had significant protective effects, such as the T allele of rs4461027 and C allele of rs4886761. Foreign studies had shown that the rs12914489 locus in the distal *LOXL1* promoter region was independently associated with XFS; it could control the transcription binding sites, thus affecting the gene transcription activities, improving the overall risk of the haplotypes in the *LOXL1* promoter region [17]. In this study, the rs12914489 locus in the control group deviated slightly from the HWE, likely because of the insufficient sample size, or random or sampling errors; thus, there is a need to further expand the sample size to verify whether rs12914489 is correlated with the disease prevalence in the Uighur population.

In summary, SNPs in the *LOXL1* gene promoter region were correlated with the prevalence of XFS in the Uighur population. Based on the current findings, we need to increase the sample size in order to further validate the results as well as to investigate the correlations of SNPs in the *LOXL1* gene promoter region with the rs2165241, rs1048661, and rs3825942 loci in the first exon region in Uighur XFS patients living in Xinjiang, with the goal being to reveal the pathogenesis of XFS and provide a basis for its targeted treatment in this area of China.

Acknowledgements

This study was supported by National Natural Science Foundation of China (81360153).

Disclosure of conflict of interest

None.

Address corresponding to: Xue-Yi Chen, Department of Ophthalmology, The First Affiliated Hospital of Xinjiang Medical University, 137# Liyushan Road, Urumqi, Xinjiang Uygur Autonomous Region 830054, China. Tel: +86 991 4361200; Fax: +86 991 4361200; E-mail: xueyichendc@126.com

References

[1] Ritch R, Schlötzer-Schrehardt U, Konstas AG. Why is glaucoma associated with exfoliation syndrome? Prog Retin Eye Res 2003; 22: 253-275.

[2] Ritch R. Exfoliation syndrome-the most common identifiable cause of open-angle glaucoma. J Glaucoma 1994; 3: 176-177.

[3] Ritch R. Exfoliation syndrome. Curr Opin Ophthalmol 2001; 45: 124-130.

[4] Kang JH, Loomis SJ, Wiggs JL, Willett WC, Pasquale LR. A prospective study of folate, vitamin B6 and vitamin B12 in relation to exfoliation glaucoma or exfoliation glaucoma suspect. JAMA Ophthamol 2014; 132: 549-559.

[5] Thorleifsson G, Magnusson KP, Sulem P, Walters GB, Gudbjartsson DF, Stefansson H, Jonsson T, Jonasdottir A, Stefansdottir G, Masson G, Hardarson GA, Petursson H, Arnarsson A, Motallebipour M, Wallerman O, Wadelius C, Gulcher JR, Thorsteinsdottir U, Kong A, Jonasson F, Stefansson K. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science 2007; 317: 1397-1400.

[6] Kasim B, Irkec M, Alikasifoglu M, Orhan M, Mocan MC, Aktas D. Association of LOXL1 gene polymorphisms with exfoliation syndrome/glaucoma and primary open angle glaucoma in a Turkish population. Mol Vis 2013; 19: 114-120.

[7] Chen L, Jia L, Wang N, Tang G, Zhang C, Fan S, Liu W, Meng H, Zeng W, Liu N, Wang H, Jia H. Evaluation of LOXL1 polymorphisms in exfoliation syndrome in a Chinese population. Mol Vis 2009; 15: 2349-2357.

[8] Fuse N, Miyazawa A, Nakazawa T, Mengkegale M, Otomo T, Nishida K. Evaluation of LOXL1 polymorphisms in eyes with exfoliation glaucoma in Japanese. Mol Vis 2008; 14: 1338-1343.

[9] Ozaki M, Lee KY, Vithana EN, Yong VH, Thalamuthu A, Mizoguchi T, Venkatraman A, Aung T. Association of LOXL1 gene polymorphisms with pseudoexfoliation in the Japanese. Invest Ophthalmol Vis Sci 2008; 49: 3976-3980.

[10] Ji QS, Qi B, Wen YC, Liu L, Guo XL, Yu GC, Zhong JX. The association of LOXL1 polymorphisms with exfoliation syndrome/glaucoma: Meta-analysis. Int J Ophthalmol 2015; 8: 148-156.

[11] Tang JZ, Wang XQ, Ma FF, Wang B, Wang PF, Peng ZX, Zhou XY. Association between polymorphisms in lysyl oxidase-like 1 and susceptibility to pseudoexfoliation syndrome and pseudoexfoliation glaucoma. PLoS One 2014; 9: e90331.

[12] Dubey SK, Hejtmancik JF, Krishnadas SR, Sharmila R, Haripriya A, Sundaresan P. Lysyl oxidase-like 1 gene in the reversal of promoter risk allele in pseudoexfoliation syndrome. JAMA Ophthalmol 2014; 132: 949-955.

[13] Fan BJ, Pasquale LR, Rhee D, Li T, Haines JL, Wiggs LJ. LOXL1 Promoter Haplotypes Are Associated with Exfoliation Syndrome in a U.S. Caucasian Population. Invest Ophthalmol Vis Sci 2011; 52: 2372-2378.

[14] Nakano M, Ikeda Y, Tokuda Y, Fuwa M, Ueno M, Imai K, Sato R, Omi N, Adachi H, Kageyama M, Mori K, Kinoshita S, Tashiro K. Novel common variants and susceptible haplotype for exfoliation glaucoma specific to Asian population. Sci Rep 2014; 4: 5340.

[15] Guadarrama-Vallejo D, Miranda-Duarte A, Zenteno JC. The T allele of lysyl oxidase-like 1 rs41435250 is a novel risk factor for pseudoexfoliation syndrome and pseudoexfoliation glaucoma independently and through intragenic epistatic interaction. Mol Vis 2013; 19: 1937-1944.

[16] Ma Y, Xie T, Zhu G, Chen X. [Evaluation of LOXL1 polymorphisms in exfoliation syndrome in the Uygur population]. Mol Vis 2011; 17: 1734-1744.

[17] Williams SE, Whigham BT, Liu Y, Carmichael TR, Qin X, Schmidt S, Ramsay M, Hauser MA, Allingham RR. Major LOXL1 risk allele is reversed in exfoliation glaucoma in a black South African population. Mol Vis 2010; 16: 705-712.

[18] Rautenbach RM, Bardien S, Harvey J, Ziskind A. An investigation into LOXL1 variants in black South African individuals with exfoliation syndrome. Arch Ophthalmol 2011; 129: 206-210.

[19] Hauser MA, Aboobakar IF, Liu Y, Miura S, Whigham BT, Challa P, Wheeler J, Williams A, Santiagoturla C, Qin X, Rautenbach RM, Ziskind A, Ramsay M, Uebe S, Song L, Safi A, Vithana EN, Mizoguchi T, Nakano S, Kubota T, Hayashi K, Manabe S, Kazama S, Mori Y, Miyata K, Yoshimura N, Reis A, Crawford GE, Pasutto F, Carmichael TR, Williams SE, Ozaki M, Aung T, Khor CC, Stamer WD, Ashley-Koch AE, Allingham RR. Genetic Variants and Cellular Stressors Associated with Exfoliation Syndrome Modulate Promoter Activity of a lncRNA within the LOXL1 Locus. Hum Mol Genet 2015; 24: 6552-63.

[20] Dewundara S, Pasquale LR. Exfoliation syndrome: a disease with an environmental component. Curr Opin Ophthalmol 2015; 26: 78-81.