

## LOXL1 Mutations Are Associated with Exfoliation Syndrome in Patients from the Midwestern United States

EDITOR:

BOTH POPULATION-BASED AND PEDIGREE-BASED STUDIES have shown that genetic factors contribute to the pathogenesis of exfoliation syndrome.<sup>1,2</sup> However until recently, the genetic basis of exfoliation syndrome was unknown. Thorleifsson and associates conducted a large association study in search of the specific genes that cause glaucoma in patients from Iceland and Sweden.<sup>3</sup> In this study, 594 patients and 14,672 control subjects were typed at more than 300,000 single nucleotide polymorphism (SNP) genetic markers that are distributed across the genome. As part of the glaucoma study, a strong association was discovered between exfoliation syndrome and two nonsynonymous SNPs (rs1048661, R141L; rs3825942, G153D) in the lysyl oxidase-like protein 1 gene (*LOXL1*). These *LOXL1* SNPs are highly associated with exfoliation syndrome and account for the vast majority of disease in the study populations from Iceland and Sweden (99% population attributable risk).<sup>3</sup> The *LOXL1* gene is a member of a gene family that has important roles in elastogenesis. Thus, it is biologically plausible that defects in the *LOXL1* gene may cause features of exfoliation syndrome resulting from aberrant production of elastin and accumulation of fibrillar material in the eye.

Thorleifsson and associates established a strong association between SNPs in the *LOXL1* gene and exfoliation syndrome in Scandinavian populations. We set out to confirm and extend this association by testing a cohort of patients and controls from Iowa, where a smaller fraction (9%) of open-angle glaucoma is caused by exfoliation syndrome.<sup>4</sup> An ethnically matched cohort of 72 patients with exfoliation syndrome and 75 control subjects was recruited from the eye clinics at the University of Iowa using standard diagnostic criteria.<sup>5</sup> All patients and control subjects were genotyped at the *LOXL1* SNPs rs1048661 (R141L) and rs3825942 (G153D) using a standard bidirectional deoxyribonucleic acid sequencing protocol.<sup>6</sup> Allele and genotype frequencies were compared with two-tailed *P* values using Chi-square analysis.

The allele frequencies, genotypes, and haplotypes of the *LOXL1* SNPs were determined in the cohort of subjects from Iowa (Table 1). The G allele of SNP rs1048661 was detected at a statistically higher frequency in patients with exfoliation syndrome than in control subjects (*P* = .000036). Similarly, the G allele of SNP rs3825942 also was strongly associated with exfoliation syndrome (*P* =

**TABLE 1.** *LOXL1* Allele Frequencies in Patients with Exfoliation Syndrome and in Controls

SNP	Allele	Exfoliation Syndrome (n = 72)	Control Subjects (n = 75)	<i>P</i> value (Chi-Square Test)
R141L (rs1048661)	G	118 (81.9%)	90 (60.0%)	.000036
	T	26 (18.1%)	60 (40.0%)	
G153D (rs3825942)	G	142 (98.6%)	132 (88.0%)	.0003
	A	2 (1.4%)	18 (12.0%)	

SNP = single nucleotide polymorphism.

**TABLE 2.** *LOXL1* Haplotypes in Patients with Exfoliation Syndrome and in Controls

rs1048661 - rs3825942 Haplotype	Exfoliation Syndrome (n = 72)	Control Subjects (n = 75)	<i>P</i> value (Chi-Square Test)
GG	116 (80.6%)	72 (48.0%)	$1.2 \times 10^{-8}$
TG	26 (18.1%)	60 (40.0%)	
GA	2 (1.4%)	18 (12.0%)	

.00030). The genotype frequencies for each of the two *LOXL1* SNPs were compared between exfoliation syndrome patients and control subjects, and statistically significant differences were detected (see Supplemental Table at [AJO.com](http://AJO.com)). These two SNPs are in strong linkage disequilibrium ( $D' = 0.996$ ). Haplotypes composed of the two *LOXL1* SNPs were determined by inspection of the genotypes of the Iowa cohort using the PLINK software package (Table 2).<sup>7</sup> The frequencies of the two-SNP haplotypes in patients with exfoliation syndrome were statistically different than those of control subjects (*P* =  $1.2 \times 10^{-8}$ ). The GG and TG haplotypes were associated with the highest risk for exfoliation syndrome, whereas the GA haplotype was associated with the lowest risk and the TA haplotype was not detected by our haplotype analysis. Using the PLINK software package,<sup>7</sup> the odds ratio (OR) for the GG and TG haplotypes were calculated relative to the GA haplotype. The TG haplotype had an OR of 3.9 (*P* = .12), whereas the GG haplotype had an OR of 14.5 (*P* =  $2.7 \times 10^{-5}$ ). The GG and TG haplotypes were associated with an 88% population attributable risk for exfoliation syndrome in the Iowa cohort.

Overall, the frequencies of *LOXL1* SNP alleles, genotypes, and haplotypes detected in the Iowa cohort were remarkably similar to those reported in Scandinavian

populations.<sup>3</sup> The G allele of each of the *LOXLI* SNPs was highly associated with exfoliation syndrome, and the risk for disease in the Iowa population was associated most strongly with the GG haplotype. These results confirm the previously detected association between the *LOXLI* and exfoliation syndrome. Furthermore, our study demonstrated a strong association between *LOXLI* and exfoliation syndrome in patients derived from a population with a lower prevalence of disease than those in Scandinavia. In both the current study and that of Thorleifsson and associates, high-risk *LOXLI* haplotypes account for a significant fraction of exfoliation syndrome (population attributable risk of 99% in Scandinavian cohorts<sup>3</sup> and 88% in the Iowa cohort), indicating that the *LOXLI* gene is the principal genetic risk factor for this condition. The discovery of a powerful genetic risk factor for exfoliation syndrome represents a major advancement in research of this condition. However, because many patients that carry *LOXLI* risk alleles do not have exfoliation syndrome, there may be limited usefulness in genetic testing for these alleles at present.

JOHN H. FINGERT  
WALLACE L. M. ALWARD  
YOUNG H. KWON  
KAI WANG  
LUAN M. STREB

VAL C. SHEFFIELD  
EDWIN M. STONE  
Iowa City, Iowa



Supplemental Material available at AJO.com.

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**SUPPLEMENTAL TABLE. *LOX1* Genotypes in Patients with Exfoliation Syndrome and in Controls**

SNP	Genotype	Exfoliation Syndrome (n = 72)	Control Subjects (n = 75)	P value (Chi-Square Test)
R141L (rs1048661)	GG	48 (66.7%)	26 (34.7%)	.00021
	GT	22 (30.6%)	38 (50.7%)	
	TT	2 (2.8%)	11 (14.7%)	
G153D (rs3825942)	GG	70 (97.2%)	59 (78.7%)	.0026
	GA	2 (2.8%)	14 (18.7%)	
	AA	0	2 (2.7%)	

SNP = single nucleotide polymorphism.