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Lack of Association of Polymorphisms in *Elastin* With Pseudoexfoliation Syndrome and Glaucoma

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Abstract

Purpose: To evaluate the elastin gene (ELN) as a secondary risk factor for pseudoexfoliation syndrome (PXFS) and the associated glaucoma pseudoexfoliation glaucoma (PXFG).

Methods: One hundred seventy-eight unrelated patients with PXFS, including 132 patients with PXFG, and 113 unrelated controls were recruited from the Massachusetts Eye and Ear Infirmary. All the patients and controls were white of European ancestry. Three tag SNPs (rs2071307, rs3823879, and rs3757587) that capture the majority of alleles in *ELN* were genotyped. Single-SNP association was analyzed using Fisher exact test. Haplotype analysis and the set-based test were used to assess the association for the whole gene. Interaction analysis was done between the *ELN* SNP rs2071307 and *LOXL1* SNP rs2165241 using logistic regression. Multiple comparisons were corrected using the Bonferroni method.

Results: All 3 *ELN* tag SNPs were not significantly associated with PXFS and PXFG ($P > 0.20$). The minor allele frequencies in PXFS, PXFG, and controls were 40.7%, 39.8%, and 45.6%, respectively for rs2071307, 6.7%, 6.3%, and 5.4% for rs3823879, and 14.8%, 16.2%, and 13.6% for rs3757587. Haplotype analysis and the set-based test did not find significant association of *ELN* with PXFS ($P = 0.94$ and 0.99, respectively). No significant interaction effects on PXFS were identified between the *ELN* and *LOXL1* SNPs ($P = 0.55$).

Conclusions: Our results suggest that common polymorphisms of *ELN* are not associated with PXFS and PXFG in white populations. Further studies are required to identify secondary genetic factors that contribute to PXFS.

Keywords

pseudoexfoliation glaucoma; elastin; polymorphisms

Pseudoexfoliation syndrome (PXFS) is a generalized disease of the extracellular matrix that results in deposition of microfibrillar material throughout the eye. The composition of the

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PXFS-related material, although not completely defined, seems to be a complex glycoprotein structure containing elements of basement membranes and the elastic fiber system.[1] The biologic processes that cause this material to accumulate in ocular structures are not yet known. The accumulation of the fibrillar material in the trabecular outflow pathways can influence the egress of aqueous humor causing an elevation of intraocular pressure and subsequent degeneration of the optic nerve. The optic nerve in individuals with PXFS may also be more susceptible to degeneration caused by elevated intraocular pressure.[2]

PXFS and the associated glaucoma pseudoexfoliation glaucoma (PXFG) are inherited as a complex genetic trait. Earlier studies have identified familial aggregation and significant heritability, that is consistent with complex or multifactorial inheritance.[3–5] A genome-wide scan using a large Finnish family indicated potential linkage to multiple chromosome regions including 18q, 2q, 17q, and 19q.[6] A significant association between pseudoexfoliation and 3 SNPs (rs1048661, rs3825942, and rs2165241) in the *lysyl oxidase-like 1* (*LOXL1*) gene was initially observed in patients from Iceland and Sweden,[7] and the consistently significant association of rs3825942 has been subsequently replicated in our US clinic-based population with broad ethnic diversity[8] and in a number of other populations including white,[9–15] Indian,[16] and Japanese.[17–21] These results show that *LOXL1* is a major gene associated with PXFG.

Two of the highly associated *LOXL1* SNPs are missense changes in exon 1 (rs3825942, G153D, and rs1048661, R141L), however, it is not yet known if these variants are biologically causative or are in linkage disequilibrium with other gene variants that are biologically active. The G153D risk allele (G) frequency is very high in PXFG patients in most of the populations studied (92% to 99%), but is also prevalent in control samples, with a frequency of 74% to 88% in the studied populations.[8–21] The prevalence of PXFS is variable in different populations, with as high as 4.7% to 23% in North Europeans, 1.8% to 3.2% in US whites, 0.98% in Australians, and 0.4% to 6.28% in Asians.[22–31] In the Australian population, the frequencies of the rs3825942 risk allele are similar to those in other populations (95% and 84%, respectively in PXFS and controls),[13] however, the disease prevalence is much lower than in other populations,[28] indicating a reduction in penetrance compared with other populations. In addition, in the Southern Chinese population PXFS is very rare with a prevalence of 0.4%,[31] however, the rs3825942 risk allele frequency is similar to those in other populations (87.6% in controls, no data available for PXFS),[32] further suggesting that the disease penetrance is reduced in some populations and that additional factors, both genetic and environmental, and potentially additive and protective could influence the development of this complex disorder.[33]

LOXL1 is a member of the lysyl oxidase family of proteins that catalyze the polymerization of tropoelastin to form the mature elastin polymer.[34] Elastin fibers are a major component of many structures in the eye, including those that could be involved in PXFG, such as the extracellular matrix of the trabecular meshwork and the lamina cribrosa of the optic nerve.[35,36] LOXL1 is also involved in elastin homeostasis and renewal, and participates in spatially organizing elastogenesis at sites of elastin deposition. Binding of LOXL1 to the elastin scaffold is required for this function.[37] These findings suggest that elastin might be

involved in the pathogenesis of PXFS. The purpose of this study is to evaluate *ELN* as secondary risk factor that could contribute to PXFS and PXFG.

PATIENTS AND METHODS

Patients and Controls

One hundred seventy-eight patients with PXFS were recruited from the Glaucoma Consultation Service at the Massachusetts Eye and Ear Infirmary. Patients with PXFS were identified by the presence of the characteristic fibrillar material on the lens capsule or pupillary margin. Patients with iris transillumination defects without the presence of the fibrillar material were not identified as pseudoexfoliation patients, or controls. Of the 178 patients with PXFS, 132 had glaucoma (PXFG) and 46 did not (pseudoexfoliation no glaucoma). Glaucoma was defined as: intraocular pressure more than 22 mm Hg in both eyes on 2 occasions or intraocular pressure more than 19 mm Hg in both eyes on treatment with 2 or more glaucoma medications; evidence of optic nerve damage in both eyes; and visual field defects consistent with optic nerve damage and characteristic for glaucoma in at least 1 eye. One hundred thirteen controls were recruited from the Comprehensive Ophthalmology Service at the Massachusetts Eye and Ear Infirmary. Controls had no evidence of pseudoexfoliation or glaucoma after clinical exam. The average age at diagnosis of the PXFS patients was 68. As of the age-dependence of the PXFS, only controls older than age 60 were used for this analysis with an average age at enrollment of 72. This study population (cases and controls) included only white participants of European ancestry. Sixty percent of the patients were female with 40% male, whereas 52% of the controls were female and 48% were male (Table 1).

This study adhered to the tenets of the Declaration of Helsinki and has been reviewed and approved by the Institutional Review Board of the Massachusetts Eye and Ear Infirmary. Informed consent was obtained from all patients and controls.

Gene Polymorphisms and Genotyping

Tag SNPs corresponding to *ELN* gene linkage disequilibrium (LD) blocks were selected using Haploview (version 4.1)[38] according to the HapMap data (release 22) from the CEU population (Fig. 1). The minimum minor allele frequency for checking markers was set to 0.01. Three tag SNPs (rs2071307, rs3823879, and rs3757587) were selected to capture the majority (88%) of alleles at r^2 greater than 0.8 across the whole gene including the 5′UTR and 3′UTR. Each LD block was captured by 1 or 2 SNPs. Genotyping was carried out by TaqMan assays [Applied Biosystems (ABI), Foster City, CA] and a random group of samples were confirmed by direct sequencing. For the TaqMan assays, oligonucleotide primers were ordered from ABI (assay by demand) and was carried out according to the manufacturer's instructions. The genotypes were extracted using ABI Prism 7000 Sequence Detection System Software. For direct sequencing, products from PCR amplification were purified and sequenced using BigDye chemistries (ABI) and an automated genetic analyzer (model 3100; ABI). Sequence data were analyzed using Vector NTI Suite (version 8).

Statistical Analysis

All statistical analyses were done using PLINK (version 1.05).[39] Hardy-Weinberg equilibrium was assessed by the χ^2 test. Linkage disequilibrium was measured using D' or r^2 Single-SNP association analysis was made using the Fisher exact test. Haplotype analysis and the set-based test were used to assess the association for the whole gene. Haplotype frequencies were estimated using the standard E-M algorithm and tested using the χ^2 test. The omnibus *P*-value for haplotype analysis was obtained from the omnibus test, whereas the *P*-values for individual haplotypes were obtained from the haplotype-specific tests. The set-based test selects the best set of SNPs whose mean of these single SNP statistics is significant after permutation.[40] The empirical *P*-values of the set-based test were obtained by a permutation of 10,000 times of phenotype labels. Interaction analysis was done between the *ELN* SNP rs2071307 and *LOXL1* SNP rs2165241 by including an interaction term in the logistic regression model. The additive effects model was applied to analysis of allele dosage in which the genotypes AA, AB, and BB were coded as 0, 1, and 2, respectively, in which, A represents the minor allele and B represents the common allele. Multiple comparisons were corrected using the Bonferroni method.

RESULTS

All 3 tag SNPs followed Hardy-Weinberg equilibrium in control samples ($P > 0.09$). The selected tag SNPs were not in LD ($r^2 < 0.01$), which is consistent with the HapMap data from the CEU population. All 3 SNPs were not significantly associated with PXFS and PXFG ($P > 0.20$). The minor allele frequencies in PXFS, PXFG, and controls were 40.7%, 39.8%, and 45.6% respectively for rs2071307, 6.7%, 6.3%, and 5.4% for rs3823879, and 14.8%, 16.2%, and 13.6% for rs3757587 (Table 2). Haplotype association analysis of all 3 tag SNPs revealed no association of *ELN* with PXFS (omnibus $P = 0.94$; Table 3). The set-based association test also did not identify significant association of *ELN* with PXFS (empirical $P = 0.99$). Logistic regression modeling showed that the interaction (additive) effects on PXFS between the *ELN* and *LOXL1* SNPs were not significant ($P = 0.55$; Fig. 2).

Direct genomic sequencing of the *ELN* gene in 8 unrelated individuals did not reveal any rare variants that could contribute to the condition.

DISCUSSION

Recent studies suggest that *LOXL1* is a major gene associated with PXFS/PXFG, contributing to the majority of cases in most populations.[7–21] However, the high prevalence of the rs3 825942 risk allele in control populations, and the apparent variable penetrance of the condition in some populations suggests that additional genetic factors and/or environmental exposures also contribute to this genetically complex disease. As elastin and LOXL1 are functionally interactive, we evaluated the *ELN* gene as a candidate for a secondary factor contributing to this disease.

We did not find significant association between single tag SNPs of the *ELN* gene and PXFS or PXFG in this study (Table 2). To increase the statistical power to identify a possible association, we further analyzed our data using haplotype analysis and the set-based test,

both of which are gene-based tests in which all selected SNPs in a gene are analyzed together. The set-based test is particularly suited to large-scale candidate gene studies. This method selects the best set of SNPs whose mean statistic is significant, leading to the inference that the entire set of SNPs might be interacting in some way to increase disease risk, or else that they are all contributing independently to disease risk.[40] In this study, both haplotype analysis and the set-based test did not find any significant association between the *ELN* gene and PXFS or PXFG (Table 3), in agreement with the association analysis of single SNPs in the *ELN* gene.

We estimated that this study had 87% of power to detect a moderate genetic effect (genotypic relative risk of 2.0 for Aa and 4.0 for AA, given an additive risk model).[41] However, this study had only 40% of power to detect a mild genetic effect (genotypic relative risk of 1.5 for Aa and 2.25 for AA, given an additive risk model). In addition, as we used tag SNPs to capture the majority of common variants in the *ELN* gene, it is possible that we might have missed rare variants in this gene associated with the disease. Further large-scale studies and resequencing of the whole gene are warranted to confirm our findings.

In summary, we have evaluated *ELN* as a secondary risk factor for PXFS and the associated glaucoma. Our results suggest that common variants in this gene are not major risk factors for the development of the PXFS. Further studies searching for secondary genetic and environmental factors that contribute to PXFS and PXFG are required to gain a better understanding of the complex etiology of this important ocular disease.

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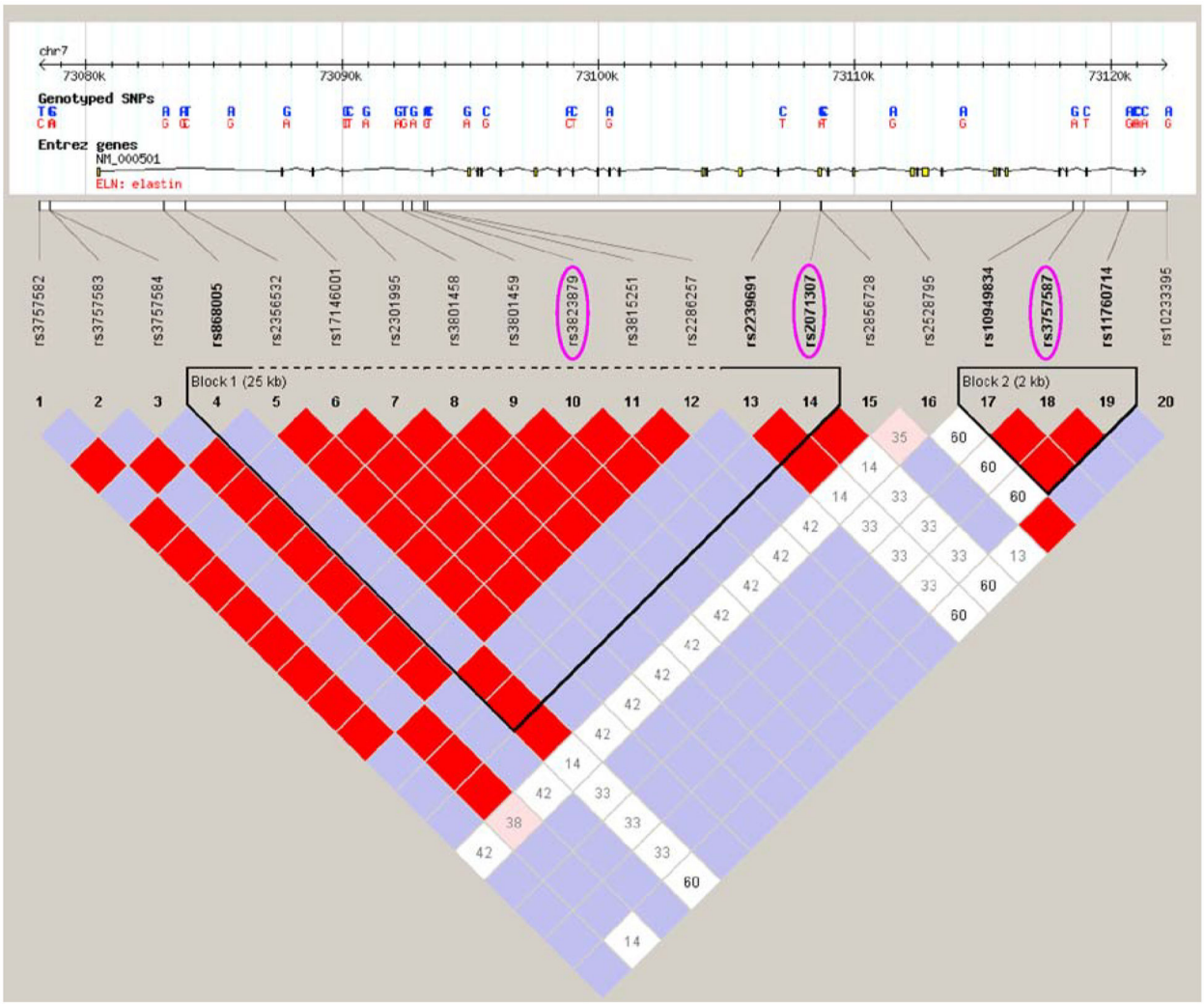

FIGURE 1.

Linkage disequilibrium (LD) plot of SNPs around elastin (ELN). The numbers in the diamond refer to D′. The LD block was defined according to the standard confidence intervals. The tag SNPs which are highlighted in circles were selected using Haploview (version 4.1).[38]

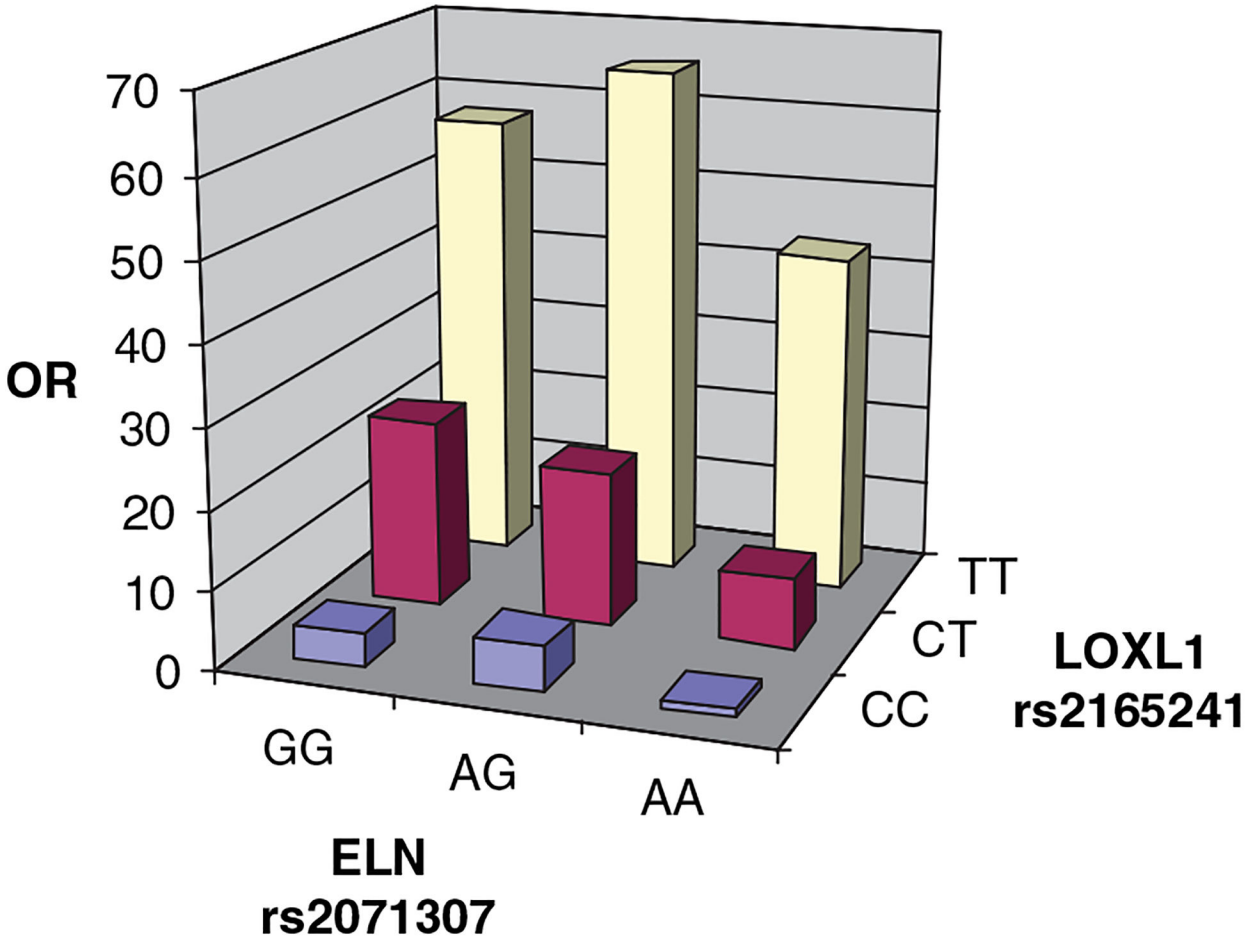

FIGURE 2.

Interaction analysis between elastin (ELN) and *LOXL1* SNPs in pseudoexfoliation syndrome (PXFS) patients and controls. Logistic regression modeling showed that the interaction (additive) effects on PXFS between the *ELN* and *LOXL1* SNPs are not significant (*P*=0.55).

TABLE 1.

Demographic Features of the Study Subjects

			Age at Diagnosis (y)	
Group	**N**	**Sex (M/F)**	**Range**	**Mean ± SD**
PXFS	178	71/107	46–97	67.8 ± 10.3
PXFG	132	58/74	48–97	67.6 ± 10.4
PXFNG	46	13/33	46–88	68.5 ± 10.1
Controls	113	54/59	61–89	72.0 ± 7.2

For controls, age at diagnosis refers to age at enrollment.

PXFG indicates pseudoexfoliation glaucoma; PXFNG, pseudoexfoliation no glaucoma; PXFS, pseudoexfoliation syndrome.

TABLE 2.

Single-SNP Association Analysis of ELN in PXFS Patients and Controls

		Genotype Frequency (%)				Allele Frequency (%)			
rs2071307 (S422G)	**N**	**GG**	**GA**	**AA**	***P***	**G**	**A**	***P***	**OR G/A (95%CI)**
PXFS	178	67 (37.6)	77 (43.3)	34 (19.1)	0.50	211 (59.3)	145 (40.7)	0.25	1.22 (0.87, 1.71)
PXFG	132	52 (39.4)	55 (41.7)	25 (18.9)	0.47	159 (60.2)	105 (39.8)	0.20	1.27 (0.89, 1.82)
PXFNG	46	15 (32.6)	22 (47.8)	9 (19.6)	0.71	52 (56.5)	40 (43.5)	0.73	1.09 (0.67, 1.77)
Controls	113	38 (33.6)	47 (41.6)	28 (24.8)		123 (54.4)	103 (45.6)		
rs3823879 (Intron)	N	AA	AG	GG	*P*	A	G	*P*	OR A/G (95%CI)
PXFS	90	1 (11)	10 (11.1)	79 (87.8)	0.81	12 (6.7)	168 (93.3)	0.62	1.24 (0.52, 2.95)
PXFG	64	0 (0.0)	8 (12.5)	56 (87.5)	0.76	8 (6.3)	120 (93.7)	0.76	1.16 (0.44, 3.02)
PXFNG	26	1 (3.8)	2 (7.7)	23 (88.5)	0.53	4 (7.7)	48 (92.3)	0.52	1.45 (0.44, 4.83)
Controls	92	1 (11)	8 (8.7)	83 (90.2)		10 (5.4)	174 (94.6)		
rs3757587 (Intron)	N	TT	TC	CC	*P*	T	C	*P*	OR T/C (95%CI)
PXFS	91	5 (5.5)	17 (18.7)	69 (75.8)	0.42	27 (14.8)	155 (85.2)	0.73	1.11 (0.62, 1.99)
PXFG	65	4 (6.2)	13 (20.0)	48 (73.8)	0.45	21 (16.2)	109 (83.8)	0.53	1.23 (0.65, 2.30)
PXFNG	26	1 (3.8)	4 (15.4)	21 (80.8)	0.49	6 (11.5)	46 (88.5)	0.70	0.83 (0.32, 2.14)
Controls	92	2 (2.2)	21 (22.8)	69 (75.0)		25 (13.6)	159 (86.4)		

P values were obtained from Fisher exact test when compared with controls. The Bonferroni corrected significance level is 0.017 (0.05/3).

PXFG indicates pseudoexfoliation glaucoma; PXFNG, pseudoexfoliation no glaucoma; PXFS, pseudoexfoliation syndrome.

TABLE 3.

Haplotype Analysis of rs3823879, rs2071307, and rs3757587 in PXFS Patients and Controls

	Estimated Haplotype Frequency (%)				
Haplotype	**PXFS**	**Controls**	**Combined**	***P***	**OR (95%CI)**
GGC	46.7	44.8	45.9	0.66	1.08 (0.77, 1.50)
GAC	32.8	36.1	34.1	0.41	0.86 (0.61, 1.22)
GGT	8.1	6.0	7.3	0.35	1.36 (0.71, 2.64)
GAT	6.0	7.5	6.6	0.47	0.79 (0.41, 1.51)
AGC	4.1	3.5	3.9	0.70	1.18 (0.50, 2.81)
AAC	1.9	1.8	1.9	0.93	1.06 (0.31, 3.58)
Total	99.6	99.7	99.7	0.94*	

*This *P* value was obtained from the omnibus test using PLINK (version 1.05),[39] while the other *P* values were obtained from the haplotype-specific test. OR was calculated for each of the individual haplotypes compared to all the other haplotypes. Only haplotypes with a frequency of more than 1% are shown.