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The Association Between Genetic Variants in *SORL1* and Alzheimer's Disease in an Urban, Multiethnic, Community-Based Cohort

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Abstract

Context—Variants in 3′ and 5′ regions of *SORL1*, the neuronal sorting protein-related receptor, were recently found to be associated with late onset familial and sporadic Alzheimer's disease in several datasets that were selected for familial aggregation or were ethnically diverse or clinic-based selected series.

Objective—To investigate the association between Alzheimer's disease and variant alleles in SORL1 using a series of single nucleotide polymorphisms (SNPs) in an urban, multiethnic community-based population.

Design & Setting—We used a nested case-control analysis in a population-based, prospective study of aging and dementia in Medicare recipients, 65 years and older, residing in northern Manhattan.

Participants—There were 296 patients with probable Alzheimer's disease and 428 healthy elderly controls. The participants were of African American (34%), Caribbean Hispanic (51%) or non-Hispanic whites (15%).

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Main Outcome Measures—We genotyped all 29 SNPs in *SORL1* that were examined in the earlier report. We assessed allelic association with AD using standard case-control methods which included APOE genotype as a covariate.

Results—Several individual SNPs and SNP haplotypes were significantly associated with AD in this prospectively collected community-based cohort, confirming the previously reported positive association of SORL1 with Alzheimer's disease. SNP 12 near the 5′ region was associated with AD in African-Americans and Hispanics. Two SNPs in the 3′ region were also associated with AD in African-Americans (SNP 26) and Whites (SNP 20). A single haplotype in the 3′ region was associated with AD in Hispanics. However, several different haplotypes were associated with AD in the African-Americans and Whites, including the "TTC" haplotypes at SNPs 23–25 (p=0.035) that was significantly associated with AD in the North European Whites in the previous report.

Conclusions—This study confirms the association between genetic variants in *SORL1* and AD. While the associations observed in these datasets overlap with those previously reported, the finding of novel SNP and haplotype associations suggest that there may be extensive allelic heterogeneity in SORL1. Broad regions of the SORL1 gene will therefore need to be scrutinized for functional pathogenic variants.

Keywords

SORL1; Alzheimer's disease; sporadic; African American; Caribbean Hispanic

Introduction

In a previous study we found that genetic variants within the *SORL1* gene were associated with an increase risk of Alzheimer's disease (AD)[1]. To ensure the validity of that study, the association had been investigated using a variety of specialized datasets including multiplex family samples and clinic-based, case-control cohorts from genetically and culturally distinct populations. This strategy allowed the discovery and replication of single SNP and haplotypic associations in two distinct regions of the *SORL1* in multiple independent cohorts. To explore the observation further, we investigated the association between *SORL1* and AD in an independent collection of patients with probable AD and healthy elderly controls from a longitudinal prospective study of aging and dementia in multiethnic communities in northern Manhattan. The investigation of a randomly sampled, prospectively studied, community-based cohort has advantages and disadvantages in replicating genetic association studies. The diagnoses for both affected and for normal status are highly secure, and are relatively unaffected by referral bias inherent in clinic-based series (e.g. enrichment of patients from centers with known interests in genetics). However, sampling from community-based series ablates the ability to collate patients and controls according to their true genetic backgrounds. Nevertheless, we reasoned that, on balance, the investigation of samples from this study would serve as a credible source of independent replication, and might provide valuable initial insights from which to formulate future questions about population and relative risks from *SORL1* variants, and the degree of allelic heterogeneity in the *SORL1* AD locus.

Methods

Subjects and Setting

Patients with AD and non-demented elderly were participating in a prospective study of aging and dementia in Medicare recipients, 65 years and older, residing in northern Manhattan (Washington Heights, Hamilton Heights and Inwood). This epidemiological study consisted of a stratified random sample of 50% of all persons older than 65 years was obtained from the Health Care Finance Administration (HCFA). All persons were sent a letter from HFCA

explaining that they had been selected to participate in a study of aging by investigators at Columbia University. The sampling procedures have been described in detail elsewhere[2, 3]. Each participant underwent an in-person interview of general health and functional ability at the time of entry into the study followed by a standardized assessment, including medical history, physical and neurological examination and a neuropsychological battery especially developed for this community[4–6]. Ethnic group was classified by participant's self-report using the format of the 1990 US Census[7]. Participants were asked if they considered themselves white, black or other, and then asked if they were Hispanic. Participants were recruited at two time points (1992–1994 and 1999–2002). They have been followed at approximately 18-month intervals with similar assessments at each interval. The Institutional Review Boards of Columbia University Medical Center and the New York Psychiatric Institute approved recruitment, informed consent and study procedures.

In the present study, in order to maximize diagnostic accuracy, we included all patients with probable AD who had a clinical dementia rating scale score[8] of 1 or higher and who had been followed-up, using the criteria described below, on at least two occasions (Table 1). Similarly, the healthy elderly controls included subjects who were also followed-up on at least two occasions separated by approximately 18 months, and who had had no evidence of AD or mild cognitive impairment on either assessment (Table 1). Because our prior study revealed evidence for allelic heterogeneity, with different SNPs and haplotypes showing association with AD in datasets with different ancestries, we collated cases and controls in the present study into three nested subsets: Caribbean Hispanic (178 cases, 194 controls); African American (88 cases, 158 controls) and White, non-Hispanic Europeans (30 case, 76 controls). While these cohorts are small, statistical power estimates, assuming the parameters from our initial study (e.g., SNP 8, allele frequency of 0.39 in cases; OR of 1.5), reveal that the current study had 98% power to detect significant allelic association between genetic variants in SORL1 and AD at a of 0.05 for Caribbean Hispanics; 90% power for African Americans; and 53% power for Caucasians based on the model by Gordon and colleagues [9]. For rarer SNPs (e.g., SNP 23; allele frequency of 0.125 and OR of 2), the current study has 84% power for Caribbean Hispanics, 66% for African Americans, and 32% for Caucasians.

Clinical Assessment and Neurological Diagnosis

All participants received structured neurological and functional assessments by physicians, and underwent a standardized neuropsychological battery that included measures of memory, orientation, language, abstract reasoning, and visuospatial ability[5, 6]. The diagnosis of dementia was established at a consensus conference that included neurologists, neuropsychologists and psychiatrists and based on all available information gathered from the initial and follow-up assessments and medical records. The diagnosis was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease Related Disorders Association (NINCDS-ADRDA) criteria for probable AD[10, 11]. The diagnosis of dementia required evidence of cognitive decline, including memory impairment, the neuropsychological test battery as well as evidence of impairment in social or occupational function (clinical dementia rating, CDR >1.0)[8].

Genotyping

Genotyping was performed using the GenomeLab SNPstream System and primer sets were as previously described [1]. 100 DNA samples were genotyped twice for every SNP marker (concordance rate >99%). APOE was genotyped as previously described[12, 13]. We numbered the SNPs 1 to 29 reflecting there relative order on the physical map of *SORL1*, and is the same nomenclature used in our previous publication (Table 2) [1].

Statistical Analyses

SNP marker data were assessed for deviations from Hardy-Weinberg equilibrium using the HAPLOVIEW program [14]. The χ^2 test (or the Fisher's exact test) was used to assess genotypic and allelic associations between AD and each of the SNP markers. The HAPLOVIEW program was used to perform single point analysis as well as estimation of linkage disequilibrium (LD) structure and haplotype blocks. For LD structure estimation, the default settings were used, which created 95% confidence bounds on *D*′ to define SNP pairs in strong LD. Haplotype analyses were performed with HAPLO.STATS v1.1.1 for case-control data using the same sliding window of three contiguous SNPs as described in our previous publication.

We designed this study to confirm an earlier investigation[1]. Under these circumstances, a nominal p-value of 0.05 is widely considered to be sufficient for confirmation [15]. Consequently, nominal p-values are presented in Table 2 for single point analysis. However, to minimize the risk of a false positive finding from rare haplotypes, we computed empirical p-values by generating the null distribution based on 10,000 replicates of the haplotype analyses.

Results

Demographics

There were a total 724 participants in the study which included 296 (41%) individuals with probable AD. The mean age of the cohort was 81.1 years (s.d.=6.6) and the mean age of onset for the patients was 82.0 years (s.d.=7.2). As noted, Hispanics from the Dominican Republic were the most frequently represented ethnic group, and there were more women than men in the analysis cohort. The other demographic characteristics are included in Table 1.

SORL1 Association

The single SNP analyses revealed that three SNPs (SNPs 12, 20 and 26), were significantly associated with probable AD in at least one of the three case-control series (Table 2) ($0.029 \leq p \leq 0.016$). SNP12, which is located 12.2 kb from the SNP 8–10 cluster associated with AD in multiple datasets in our initial paper[1], was significantly associated with AD in the African-Americans and Caribbean Hispanics. The "T" allele at SNP 12 was significantly associated with AD in Caribbean Hispanics (p=0.029). In the non-Hispanic Whites, the T allele was associated with AD, but was not significant (p=0.20). These findings are consistent with the findings from the Mayo Clinic autopsy cohort (p = 0.003) and in the overall Mayo Clinic case-control cohort (p =0.046) in the initial report of an association between *SORL1* and AD (Table 4 [1]). In the African Americans, however, the C allele at SNP 12 was associated with AD (p=0.016). SNP 20 was significantly associated with AD in the non-Hispanic white cases (p = 0.025, G allele). SNP 20 was not significantly associated with AD in our previous study, but is closely flanked by both SNP 19 (−93 b.p.), which was associated with AD in several datasets, and by SNP 20 (+5966 b.p.), which was associated with AD in the N. European case control dataset in the initial report [1]. In both datasets, the same G allele was associated with AD. SNP 26 was associated with AD in the African American cohort (p = 0.019 G allele), and is located 6015 b.p. from the SNP23–25 cluster that had previously show a haplotypic association with AD in the MIRAGE African American sibships as well as in three different Caucasian datasets [1].

SORL1 haplotype association

Haplotype analyses using a sliding window size of three contiguous SNPs demonstrated several haplotypic associations in all three ethnic group datasets (Table 3). Although these haplotypes were distributed across the *SORL1* gene and varied in frequency (0.01 to 0.037) several of them

clustered. The common "TTC" haplotype at SNPs 23, 24, 25 was associated with AD in non-Hispanic Whites (p=0.035). This haplotype was also associated with AD in the North European FAD dataset and the Israeli Arab, North European and Mayo Clinic - Jacksonville case-control datasets in our initial report[1]. In this same region of the *SORL1* gene, the frequent "CCA" haplotype at SNPs 24, 25, 26 was robustly associated with AD in African-Americans (haplotype p=0.0006, empirical p=0.0005 and global p value p=0.01), while the common CTG haplotype at these same SNPs had a borderline protective effect (p = 0.06). Intriguingly, these same haplotypes were also previously shown to be associated with AD in the MIRAGE African American cohort in the previous study [1]. However, the CCA haplotype was protective while the CTG haplotype was deleterious in the MIRAGE African American cohort [1]. We interpret this to mean that one or more risk alleles are in LD with these haplotypes in this region in African Americans.

In the central region of *SORL1*, several frequent, overlapping haplotypes at SNPs 16–22 were associated with AD. Thus the haplotypes "ATA" at SNPs 16–18, "TAG" at SNPs 17–19, "AGG" at SNPs 18–20, "GGC" at SNPs 19–21, and "GCC" at SNPs 20–22 were significantly associated with AD ($0.0006 \leq$ haplotype $p \leq 0.032$). The "ATA" haplotype was also associated with risk for AD in the N. European FAD dataset in the initial report (haplotype frequency 0.218, Z =2.794, haplotype p = 0.005; global p = 0.057; Supplementary Table 5 [1])

At the 5′ end of the gene, several low frequency haplotypes at SNPs 1–6 and SNPs 8–13 were also associated with AD in all three cohorts. The "CGC" haplotype at SNPs 8–10, which was previously associated with AD in the Caribbean Hispanic FAD, the Israeli Arab, and North European case-control datasets in the initial report [1], was not replicated in the sporadic Caribbean Hispanic case-control samples here. Nevertheless, at SNPs 8-10, both the "CAT" haplotype in White non-Hispanics (haplotype p=0.014) and the "CGT" haplotype in African-Americans (haplotype p=0.016) were associated with AD.

Discussion

Our results independently confirm the previous conclusion that multiple genetic variants in *SORL1* are associated with AD. We have directly replicated the previously reported association between AD and both the "TTC" haplotype at SNPs 23, 24, 25 and the "ATA" haplotype at SNPs 16–18 among Whites in the present and in the previous report [1]. We have also shown that SNPs 26–28 display haplotypic association with AD in African Americans in both the present dataset and in the previously studied MIIRAGE African Americans [1], although the exact haplotypes had opposite effects on risk for AD in African Americans from these two datasets. A similar situation exists at SNPs 8–10 where different haplotypes were associated with AD in the present study and in the previous study ("CAT" in white non-Hispanics, and "CGT" in African Americans in the present study, and "CGC" in several datasets in the previous study including the Caribbean Hispanic FAD, Israeli Arab and some North European datasets [1]). The failure to detect an association at SNPs 8 –10 in the sporadic Caribbean Hispanic AD cases from this population based cohort at the Hispanic dataset in Washington Heights does not contradict the findings from the earlier study of the Caribbean Hispanics FAD pedigrees. Indeed, weak allelic associations at SNP 12 (+11.7 kb from SNPs 8–10) and weak haplotypic associations at SNPs 4–6 (−7037 b.p. from SNPs 8–10) were observed in this dataset. Other explanations for the disparity in location of the association include the existence of further allelic heterogeneity within the Caribbean Hispanic. It is also conceivable that genetic factors such as *SORL1* play a relatively smaller role in community-based sporadic AD in Caribbean Hispanics, and are observable only with larger sample sizes or when investigated in sibships multiply affected with AD. Nevertheless, when taken together, the current results suggest two conclusions. First, the association between AD and variants in the *SORL1* gene is likely to be correct. Second, the discovery of significant association in multiple regions of the

gene, and the discovery of different AD-associated haplotypes in different datasets supports the notion that there may be a high degree of allelic heterogeneity, with disease-associated variants occurring on multiple different haplotypic backgrounds. This situation differs markedly from the circumstances observed with APOE *ε4*[16].

Two practical considerations arise from these conclusions. Further replication studies will need to assess cohorts with as few founders as possible. Second attempts to identify the pathogenic variants in *SORL1* will likely have to investigate larger regions of the *SORL1* gene than simply just between SNPs 8–10 and 22–25.

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Table 1

Demographic characteristics of the cases and controls from the prospective, longitudinal, multi-ethnic community-based study of aging and dementia in northern Manhattan, who met diagnostic criteria for either probable AD or for normal aging on at least two occassions separated by 18 months in time.

	Caribbean Hispanic*		African-American		White, non-Hispanic European	
	Case	**Control**	**Case**	**Control**	**Case**	**Control**
N (724 total)	178	194	88	158	30	76
Age at onset† (±SD)	80.9 (±6.8)	79.1 (±5.1)	83.3 (±7.3)	81.1 (±6.1)	84.4 (±8.0)	82.7 (±7.2)
Education (in years)	4.8 (±4.0)	7.6 (±4.5)	8.5 (±3.7)	11.7 (±3.7)	10.0 (±3.7)	13.0 (±3.0)
Women (%)	73.0	73.7	78.4	73.4	80.0	75.0
APOE ε4 (%)	21.1	11.3	18.8	17.1	13.3	11.8

*Ethnicity based on self-report.

†For prevalent cases, we used the age at which the first complaint was reported, if available; otherwise, age at first evaluation was used to conservatively approximate age at onset.

Table 2

Allelic association between individual SORL1 SNPs and AD was evident in at least one of the nested cohorts at SNPs 12, 20 and 26. Nominal p-values are reported because this is a replication study. The minor allele is depicted using the same nomenclature as in reference [1]. The minor allele for the African-American was obtained from the MIRAGE samples, and that for the non-Hispanic Whites was obtained from the North European case-control samples.

		Caribbean Hispanic					African-American					Non-Hispanic Whites				
SNP	**Name**	**Minor Allele**	**Cases**	**Controls**	**Chi Sq**	**p**	**Minor Allele**	**Cases**	**Controls**	**Chi Sq**	**p**	**Minor Allele**	**Cases**	**Controls**	**Chi Sq**	**p**
1	rs4935774	G	0.353	0.380	0.55	0.4595	A	0.422	0.484	1.67	0.1960	G	0.315	0.288	0.14	0.7083
2	rs578506	C	0.334	0.317	0.24	0.6271	C	0.107	0.068	2.14	0.1436	C	0.431	0.457	0.11	0.7436
3	rs582446	G	0.279	0.285	0.03	0.8695	G(A)	0.413	0.402	0.05	0.8196	G	0.125	0.118	0.02	0.8933
4	rs661057	C	0.353	0.394	1.27	0.2592	C	0.274	0.291	0.15	0.6976	C	0.276	0.382	2.04	0.1531
5	rs11218304	C	0.272	0.251	0.40	0.5271	C	0.187	0.226	0.98	0.3227	C	0.431	0.393	0.25	0.6185
6	rs560573	A	0.334	0.351	0.22	0.6375	A	0.341	0.291	1.30	0.2548	A	0.310	0.396	1.29	0.2553
7	rs12364988	A,G(A)*	0.488	0.492	0.28	0.5987	A(G)	0.494	0.471	0.24	0.6228	G(A)	0.500	0.493	0.01	0.9333
8	rs668387	T	0.384	0.395	0.09	0.7680	T	0.366	0.314	1.37	0.2418	T	0.362	0.459	1.59	0.2078
9	rs689021	A	0.397	0.430	0.72	0.3975	A	0.391	0.323	1.98	0.1595	A	0.420	0.493	0.78	0.3774
10	rs641120	T	0.348	0.379	0.74	0.3890	T	0.311	0.257	1.53	0.2169	T	0.407	0.410	0.00	0.9748
11	rs4935775	C	0.249	0.254	0.03	0.8671	C	0.178	0.173	0.02	0.8933	C	0.379	0.382	0.00	0.9748
12	**rs12285364**	**T**	**0.215**	**0.146**	**4.74**	**0.0294**	**T**	**0.083**	**0.173**	**5.77**	**0.0163**	T	0.120	0.062	1.64	0.2003
13	rs2298813	A	0.101	0.071	2.03	0.1540	A	0.057	0.084	1.24	0.2657	A	0.056	0.033	0.52	0.4708
14	rs11600231	C	0.104	0.104	0.00	1.0000	C	0.100	0.096	0.02	0.8848	C	0.077	0.096	0.17	0.6828
15	rs2276346	T	0.202	0.171	1.12	0.2893	T	0.145	0.102	2.03	0.1547	T	0.350	0.289	0.74	0.3893
16	SORL1-T833T	T	0.062	0.057	0.07	0.7899	T	0.041	0.042	0.01	0.9244	*T*	*0.037*	*0.116*	*2.89*	*0.0891*
17	rs556349	*G(T)*	0.474	0.484	0.07	0.7884	G	0.343	0.382	0.70	0.4021	*T*	*0.433*	*0.313*	*2.72*	*0.0990*
18	rs11218340	T	0.074	0.072	0.01	0.9333	T	0.066	0.045	1.00	0.3173	T	0.067	0.140	2.14	0.1431
19	rs2070045	G	0.231	0.237	0.04	0.8495	G	0.098	0.132	1.17	0.2786	G	0.300	0.194	2.40	0.1216
20	**rs3824966**	G	0.232	0.261	0.77	0.3802	G	0.116	0.127	0.13	0.7216	**G**	**0.345**	**0.197**	**5.03**	**0.0249**
21	SORL1-ex26c-g	G	0.170	0.155	0.26	0.6115	G	0.282	0.274	0.03	0.8580	G	0.083	0.123	0.68	0.4082
22	rs1699102	C	0.471	0.476	0.01	0.9058	C(T)	0.466	0.487	0.20	0.6572	C	0.446	0.329	2.43	0.1192
23	rs3824968	T	0.283	0.303	0.34	0.5616	T	0.140	0.155	0.22	0.6429	T	0.385	0.264	2.63	0.1049
24	rs2282649	T	0.281	0.276	0.02	0.8821	T	0.110	0.166	2.68	0.1019	*T*	*0.321*	*0.208*	*2.83*	*0.0927*
25	rs1010159	C	0.483	0.460	0.38	0.5392	T	0.405	0.444	0.70	0.4038	C	0.426	0.380	0.35	0.5535
26	**rs1784933**	G	0.178	0.164	0.23	0.6315	G	**0.262**	**0.371**	**5.53**	**0.0187**	G	0.069	0.088	0.20	0.6580
27	rs1614735	C	0.299	0.322	0.42	0.5174	C	0.157	0.117	1.50	0.2207	C,A(A)	0.431	0.486	1.14	0.2863

SNP	Name	Caribbean Hispanic					African-American					Non-Hispanic Whites				
		Minor Allele	Cases	Controls	Chi Sq	p	Minor Allele	Cases	Controls	Chi Sq	p	Minor Allele	Cases	Controls	Chi Sq	p
28	rs1133174	*G*	*0.438*	*0.500*	*2.78*	*0.0957*	*G*	0.287	0.332	1.04	0.3081	*G,A(A)*	*0.450*	*0.411*	3.32	*0.0684*
29	rs1131497	G	0.287	0.289	0.00	0.9563	G	0.151	0.190	1.12	0.2899	G	0.431	0.414	0.05	0.8284

Table 3

Haplotypic associations between SORL1 SNPs and AD were investigated using a sliding window of three contiguous SNPs and the HAPLOVIEW program as described previously [1]. Only those haplotypes generating a significant result in at least one dataset. Significant results are in bold typeface.

						Caribbean Hispanics					African American					European White, Non-Hispanic				
SNPs			Haplotype			Hap Freq*	Z	P	Permutation		Hap Freq*	Z	P	Permutation		Hap Freq*	Z	P	Permutation	
									Empirical P	Global P				Empirical P	Global P				Empirical P	Global P
1	2	3	C	C	G	.	.	.	.	.	0.01	2.35	**0.0186**	**0.0140**	0.183	.	.	.	.	.
2	3	4	C	G	C	0.04	−1.46	0.1455	0.1520	0.541	0.01	2.08	**0.0380**	**0.0280**	0.530	.	.	.	.	.
4	5	6	C	C	A	0.01	2.09	**0.0367**	**0.0380**	0.416	.		.	.	.	.	.	.	.	.
8	9	10	C	G	T	0.01	−0.09	0.9264	0.8950		0.01	2.40	**0.0164**	**0.0250**		0.01	0.32	0.7463	0.7807	
8	9	10	C	A	T	0.01	0.74	0.4596	0.4630	0.576	0.01	−0.49	0.6243	0.6310	0.530	0.01	2.46	**0.0138**	**0.0304**	**0.003**
10	11	12	C	C	T	0.03	0.34	0.7344	0.7550		0.01	−1.11	0.2653	**0.2520**		0.03	2.15	**0.0315**	**0.0300**	
10	11	12	C	A	T	0.11	1.54	0.1227	0.1330	0.461	0.10	−2.01	**0.0447**	**0.0470**	0.307	0.04	0.64	0.5205	0.5550	0.363
11	12	13	C	T	G	0.03	0.40	0.6927	0.7110	0.717	0.01	−1.16	0.2464	0.2420	0.374	0.02	2.16	**0.0305**	**0.0250**	0.200
16	17	18	A	T	A	0.44	0.09	0.9318	0.9370	0.957	0.58	0.39	0.6935	0.6940	0.674	0.23	2.75	**0.0060**	**0.0050**	**0.032**
16	17	18	T	G	A	0.06	0.15	0.8821	0.8710		0.04	−0.10	0.9186	0.8640		0.09	−1.54	0.1231	0.1340	
17	18	19	T	A	G	0.22	−0.57	0.5716	0.5670	0.544	0.11	−0.83	0.4040	0.4210	0.602	0.20	2.30	**0.0214**	**0.0200**	0.202
18	19	20	A	G	G	0.23	−0.62	0.5375	0.5500	0.640	0.12	−0.58	0.5650	0.5890	0.828	0.23	2.13	**0.0328**	**0.0250**	0.195
19	20	21	G	G	C	0.23	−0.66	0.5072	0.5150	0.606	0.12	−0.50	0.6192	0.6340	0.898	0.22	2.25	**0.0242**	**0.0180**	0.267
20	21	22	G	C	C	0.24	−0.87	0.3827	0.3710		0.12	−0.56	0.5748	0.5840		0.19	2.28	**0.0225**	**0.0230**	
20	21	22	G	G	C	.		.	.	0.953	0.01	2.19	**0.0287**	**0.0230**	0.183	0.01	−0.42	0.6771	0.7350	0.333
22	23	24	C	T	T	0.24	−0.18	0.8596	0.8580	0.630	0.09	−1.22	0.2227	0.2130	0.242	0.20	2.00	**0.0451**	**0.0420**	0.430
23	24	25	T	T	C	0.25	0.02	0.9857	0.9860	0.571	0.12	−1.54	0.1246	0.1240	0.143	0.23	2.11	**0.0348**	**0.0350**	0.113
24	25	26	C	T	A	0.43	−0.87	0.3821	0.3870		0.26	0.64	0.5195	0.5274		0.61	−0.91	0.3614	0.3220	0.310
24	25	26	C	T	G	0.09	0.71	0.4792	0.4690		0.17	−1.82	0.0683	0.0626		.	.	.	.	
24	25	26	C	C	A	0.13	0.62	0.5357	0.5590	0.862	0.27	3.43	**0.0006**	**0.0005**	**0.010**	0.09	−0.78	0.4370	0.4680	0.420
26	27	28	A	A	A	0.35	1.68	0.0922	0.0830	0.247	0.38	2.09	**0.0362**	**0.0330**	0.081	0.31	1.81	0.0700	0.0700	0.310
27	28	29	C	A	C	0.01	0.32	0.7495	0.8040		0.02	1.60	0.1104	0.1350		0.02	2.31	**0.0207**	**0.0230**	
27	28	29	A	A	C	0.26	1.75	0.0802	0.1010		0.53	0.99	0.3205	0.3180		0.03	2.10	**0.0356**	**0.0300**	
27	28	29	A	G	G	0.02	−0.67	0.5034	0.5270	0.203	0.03	−1.91	0.0566	**0.0500**	0.428	.	.	.	.	**0.048**

*Haplotype frequency was estimated using both cases and controls.