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

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

Design: We used a nested case-control analysis in a population-based, prospective study of aging and dementia in Medicare recipients, 65 years and older.

Setting: Northern Manhattan, NY.

Participants: There were 296 patients with probable AD and 428 healthy, elderly controls. The participants were African American (34%), Caribbean Hispanic (51%), or non-Hispanic white (15%).

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 apolipoprotein E 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 AD. Single nucleotide polymorphism 12, near the 5′ region, was associated with AD in African American and Hispanic individuals. Two SNPs in the 3′ region were also associated with AD in African American (SNP 26) and non-Hispanic white (SNP 20) individuals. A single haplotype in the 3′ region was associated with AD in Hispanic individuals. However, several different haplotypes were associated with AD in African American and white individuals, including the TTC haplotypes at SNPs 23 through 25 (*P*=.035), which was significantly associated with AD in the North European white individuals in our previous report.

Conclusions: This study confirms the association between genetic variants in *SORL1* and AD. While the associations observed in these data sets overlap with those previously reported, the finding of novel SNP and haplotype associations suggests 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.

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I N A PREVIOUS STUDY, WE FOUND that genetic variants within the *SORL1* gene were associated with an increased risk of Alzheimer disease (AD).[1] To ensure the validity of that study, we investigated the association using a variety of specialized data sets, including multiplex family samples and clinic-based case-control cohorts from genetically and culturally distinct populations. This strategy allowed the discovery and replication of individual single nucleotide polymorphism (SNP) and haplotypic associations in 2 distinct regions of *SORL1* in multiple independent cohorts. To explore the observation further, we have reinvestigated 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, NY. 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 normal status are highly secure and are relatively unaffected by referral bias inherent in clinic-based series (eg, enrichment of patients from centers with known interests in genetics). However, sampling from commu-

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Table 1. Characteristics of Genotyped Cases vs Controls in 3 Ethnic Groups Residing in Northern Manhattan, NY*

	Caribbean Hispanic†		African American†		White Non-Hispanic European†	
	Case	Control	Case	Control	Case	Control
Sample size (N = 724)	178	194	88	158	30	76
Age at onset, y, mean (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, y, mean (SD)	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

Abbreviation: *APOE*, apolipoprotein E.

*Demographic characteristics of the cases and controls from the prospective, longitudinal, multiethnic, community-based study of aging and dementia in northern Manhattan, who met diagnostic criteria for either probable Alzheimer disease or for normal aging on at least 2 occasions separated by 18 months.

†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.

nity-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

The patients with AD and elderly controls without dementia assessed herein were participants 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 originally consisted of a stratified random sample of 50% of all persons older than 65 years that was obtained from the Health Care Finance Administration. Individuals were sent a letter from the Health Care Finance Administration 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 to be white, black, or other and then asked if they were Hispanic. Participants were recruited at 2 points (1992-1994 and 1999-2002). They have been followed up 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, 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 later, on at least 2 occasions (**Table 1**). Similarly, the healthy, elderly controls included subjects who were also followed up on at least 2 occasions sepa-

rated 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 data sets with different ancestries, we collated cases and controls in the present study into 3 nested subsets: Caribbean Hispanic (178 cases, 194 controls); African American (88 cases, 158 controls); and white non-Hispanic European (30 case, 76 controls). While these cohorts are small, statistical power estimates, assuming the parameters from our initial study (eg, SNP 8, allele frequency of 0.39 in cases; odds ratio of 1.5), reveal that the current study had 98% power to detect significant allelic association between genetic variants in *SORL1* and AD at an α of .05 for Caribbean Hispanic individuals; 90% power for African American individuals; and 53% power for white individuals, based on the model by Gordon and colleagues.[9] For rarer SNPs (eg, SNP 23, allele frequency of 0.125; odds ratio of 2), the current study had 84% power for Caribbean Hispanic individuals, 66% for African American individuals, and 32% for white individuals.

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 and Related Disorders Association criteria for probable AD.[10,11] The diagnosis of dementia required evidence of cognitive decline, including memory impairment on the neuropsychological test battery as well as evidence of impairment in social or occupational function (Clinical Dementia Rating >1.0).[8]

GENOTYPING

Genotyping was performed using the GenomeLab SNPstream System and primer sets as previously described.[1] One hundred DNA samples were genotyped twice for every SNP marker (concordance rate >99%). Apolipoprotein E (*APOE*) was genotyped as

Table 2. Allelic Association Between SNPs in _SORL1_ and AD*

		Caribbean Hispanic				African American				Non-Hispanic White			
SNP	Name	Minor Allele	Cases, %	Controls, %	χ^2	P Value	Minor Allele	Cases, %	Controls, %	χ^2	P Value	Minor Allele	Cases, %	Controls, %	χ^2	P Value
1	rs4935774	G	0.353	0.380	0.55	.4595	A	0.422	0.484	1.67	.1960	G	0.315	0.288	0.14	.7083
2	rs578506	C	0.334	0.317	0.24	.6271	C	0.107	0.068	2.14	.1436	C	0.431	0.457	0.11	.7436
3	rs582446	G	0.279	0.285	0.03	.8695	G (A)	0.413	0.402	0.05	.8196	G	0.125	0.118	0.02	.8933
4	rs661057	C	0.353	0.394	1.27	.2592	C	0.274	0.291	0.15	.6976	C	0.276	0.382	2.04	.1531
5	rs11218304	C	0.272	0.251	0.40	.5271	C	0.187	0.226	0.98	.3227	C	0.431	0.393	0.25	.6185
6	rs560573	A	0.334	0.351	0.22	.6375	A	0.341	0.291	1.30	.2548	A	0.310	0.396	1.29	.2553
7	rs12364988	A, G (A)†	0.488	0.492	0.28	.5987	A (G)	0.494	0.471	0.24	.6228	G (A)	0.500	0.493	0.01	.9333
8	rs668387	T	0.384	0.395	0.09	.7680	T	0.366	0.314	1.37	.2418	T	0.362	0.459	1.59	.2078
9	rs689021	A	0.397	0.430	0.72	.3975	A	0.391	0.323	1.98	.1595	A	0.420	0.493	0.78	.3774
10	rs641120	T	0.348	0.379	0.74	.3890	T	0.311	0.257	1.53	.2169	T	0.407	0.410	0	.9748
11	rs4935775	C	0.249	0.254	0.03	.8671	C	0.178	0.173	0.02	.8933	C	0.379	0.382	0	.9748
12‡	rs12285364‡	T‡	0.215‡	0.146‡	4.74‡	.0294‡	T‡	0.083‡	0.173‡	5.77‡	.0163‡	T	0.120	0.062	1.64	.2003
13	rs2298813	A	0.101	0.071	2.03	.1540	A	0.057	0.084	1.24	.2657	A	0.056	0.033	0.52	.4708
14	rs11600231	C	0.104	0.104	0	>.99	C	0.100	0.096	0.02	.8848	C	0.077	0.096	0.17	.6828
15	rs2276346	T	0.202	0.171	1.12	.2893	T	0.145	0.102	2.03	.1547	T	0.350	0.289	0.74	.3893
16	_SORL1_-T833T	T	0.062	0.057	0.07	.7899	T	0.041	0.042	0.01	.9244	T	0.037	0.116	2.89	.0891
17	rs556349	G (T)	0.474	0.484	0.07	.7884	G	0.343	0.382	0.70	.4021	T	0.433	0.313	2.72	.0990
18	rs11218340	T	0.074	0.072	0.01	.9333	T	0.066	0.045	1.00	.3173	T	0.067	0.140	2.14	.1431
19	rs2070045	G	0.231	0.237	0.04	.8495	G	0.098	0.132	1.17	.2786	G	0.300	0.194	2.40	.1216
20‡	rs3824966‡	G	0.232	0.261	0.77	.3802	G	0.116	0.127	0.13	.7216	G‡	0.345‡	0.197‡	5.03‡	.0249‡
21	_SORL1_-ex26c-g	A	0.170	0.155	0.26	.6115	A	0.282	0.274	0.03	.8580	G	0.083	0.123	0.68	.4082
22	rs1699102	C	0.471	0.476	0.01	.9058	C (T)	0.466	0.487	0.20	.6572	C	0.446	0.329	2.43	.1192
23	rs3824968	T	0.283	0.303	0.34	.5616	T	0.140	0.155	0.22	.6429	T	0.385	0.264	2.63	.1049
24	rs2282649	T	0.281	0.276	0.02	.8821	T	0.110	0.166	2.68	.1019	T	0.321	0.208	2.83	.0927
25	rs1010159	C	0.483	0.460	0.38	.5392	T	0.405	0.444	0.70	.4038	C	0.426	0.380	0.35	.5535
26‡	rs1784933‡	G	0.178	0.164	0.23	.6315	G	0.262‡	0.371‡	5.53‡	.0187‡	G	0.069	0.088	0.20	.6580
27	rs1614735	C	0.299	0.322	0.42	.5174	C	0.157	0.117	1.50	.2207	C, A (A)	0.431	0.486	1.14	.2863
28	rs1133174	G	0.438	0.500	2.78	.0957	G	0.287	0.332	1.04	.3081	G, A (A)	0.450	0.411	3.32	.0684
29	rs1131497	G	0.287	0.289	0	.9563	G	0.151	0.190	1.12	.2899	G	0.431	0.414	0.05	.8284

Abbreviations: AD, Alzheimer disease; SNP, single nucleotide polymorphism.

*Allelic association between individual _SORL1_ SNPs and AD was evident in at least 1 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 and non-Hispanic white individuals was obtained from previously published data from these ethnic groups.[1]

†The minor allele differed by ethnic group.

‡Significant values.

previously described.[12,13] We numbered the SNPs 1 to 29 reflecting their relative order on the physical map of _SORL1_ and using the same nomenclature as in our previous publication (**Table 2**).[1]

STATISTICAL ANALYSES

Single nucleotide polymorphism marker data were assessed for deviations from Hardy-Weinberg equilibrium using the Haploview program.[14] The χ^2 test (or the Fisher 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 structure and haplotype blocks. For linkage disequilibrium structure estimation, the default settings were used, which created 95% confidence bounds on D' to define SNP pairs in strong linkage disequilibrium. Haplotype analyses were performed with Haplo.Stats version 1.1.1 for case-control data using the same sliding window of 3 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 .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 of 724 participants in the study, which included 296 individuals (41%) with probable AD. The mean (SD) age of the cohort was 81.1 (6.6) years and the mean (SD) age at onset for the patients was 82.0 (7.2) years. Hispanic individuals 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 individual SNP analyses revealed that 3 SNPs (SNPs 12, 20, and 26) were significantly associated with probable AD in at least 1 of the 3 case-control series (Table 2)

$(.029 \leq P \leq .016)$. Single nucleotide polymorphism 12, which is located 12.2 kilobases (kb) from the SNP 8 through 10 cluster associated with AD in multiple data sets in our initial article,[1] was significantly associated with AD in African American and Caribbean Hispanic individuals. The T allele at SNP 12 was significantly associated with AD in Caribbean Hispanic individuals ($P=.029$). In non-Hispanic white individuals, the T allele was associated with AD but was not significant ($P=.20$). The T allele was also associated with AD in both the Mayo Clinic autopsy cohort ($P=.003$) and in the overall Mayo Clinic case-control cohort ($P=.046$) in our initial report of an association between SORL1 and AD (Table 4[1]). In African American individuals, however, the C allele at SNP 12 was associated with AD ($P=.016$). Single nucleotide polymorphism 20 was significantly associated with AD in the non-Hispanic white individuals ($P=.025$, G allele). Single nucleotide polymorphism 20 is closely flanked by both SNP 19 (-93 base pairs [bp]), which was associated with AD in several data sets in our report, and by SNP 21 ($+5966$ bp), which was associated with AD in the North European case-control data set.[1] Single nucleotide polymorphism 26 was associated with AD in the African American cohort ($P=.019$, G allele) and is located $+6015$ bp from the SNP 23 through 25 cluster that had previously shown a haplotypic association with AD in the MIRAGE African American sibships and in 3 different white data sets.[1]

SORL1 HAPLOTYPE ASSOCIATION

Haplotype analyses using a sliding window size of 3 contiguous SNPs demonstrated several haplotypic associations in all 3 ethnic group data sets (**Table 3**). Although these haplotypes were distributed across the SORL1 gene and varied in frequency (0.01-0.037), several of them clustered. The common TTC haplotype at SNPs 23, 24, and 25 was associated with AD in non-Hispanic white individuals ($P=.035$). This same haplotype had previously been shown to be associated with AD in the North European familial AD (FAD) data set and the Israeli Arab, North European, and Mayo Clinic–Jacksonville case-control data sets in our initial report.[1] In this same region of the SORL1 gene, the frequent CCA haplotype at SNPs 24, 25, and 26 was robustly associated with AD in African American individuals (haplotype $P=.0006$, empirical $P=.0005$, and global $P=.01$), while the common CTG haplotype at these same SNPs had a borderline protective effect ($P=.06$). 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, in the MIRAGE African American cohort, the CCA haplotype was protective while the CTG haplotype was deleterious.[1] We interpret these opposite allelic associations to mean that 1 or more risk alleles nearby are in linkage disequilibrium with these haplotypes in this region in African American individuals.

In the central region of SORL1, several frequent, overlapping haplotypes at SNPs 16 through 22 were also associated with AD. Thus, the haplotypes ATA at SNPs 16 through 18, TAG at SNPs 17 through 19, AGG at SNPs 18 through 20, GGC at SNPs 19 through 21, and GCC at SNPs 20 through 22 were significantly associated with AD ($<.001 \leq$ haplotype $P \leq .032$). The ATA haplotype at SNPs at 16 through 18 was also associated with risk for AD in the North European FAD data set in the initial report (haplotype frequency, 0.218; $z=2.794$; haplotype $P=.005$; global $P=.057$; Supplementary Table 5[1]).

At the 5′ end of the gene, several low-frequency haplotypes at SNPs 1 through 6 and SNPs 8 through 13 were also associated with AD in all 3 cohorts. The CGC haplotype at SNPs 8 through 10, which was previously associated with AD in the Caribbean Hispanic FAD, Israeli Arab, and North European case-control data sets in the initial report,[1] was not replicated in the sporadic Caribbean Hispanic case-control samples herein. Nevertheless, at SNPs 8 through 10, both the CAT haplotype in white non-Hispanic individuals (haplotype $P=.014$) and the CGT haplotype in African American individuals (haplotype $P=.016$) were associated with AD.

COMMENT

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, and 25 and the ATA haplotype at SNPs 16 through 18 among white individuals in the present and the previous report.[1] We have also shown that SNPs 26 through 28 display haplotypic association with AD in African American individuals in both the present data set and in the previously studied MIRAGE African American cohort,[1] although the same haplotypes had opposite effects on risk for AD in African American individuals from these 2 data sets. A similar situation exists at SNPs 8 through 10 where different haplotypes were associated with AD in the present study and the previous study (CAT in white non-Hispanic individuals and CGT in African American individuals herein and CGC in data sets from our previous study[1]). The failure to detect an association at SNPs 8 through 10 in the sporadic Caribbean Hispanic AD cases from this population-based cohort in Washington Heights does not contradict the findings from the earlier study of the Caribbean Hispanic FAD pedigrees. Indeed, weak allelic associations at SNP 12 ($+11.7$ kb from SNPs 8-10) and weak haplotypic associations at SNPs 4 through 6 (-7037 bp from SNPs 8-10) were observed in the 5′ region of the SORL1 gene in this data set. There are several possible explanations for the disparity in location of the association. First, there may be further allelic heterogeneity within the Caribbean Hispanic population. Second, it is conceivable that genetic factors such as SORL1 play a relatively smaller role in community-based sporadic AD in Caribbean Hispanic individuals and are observable only with larger sample sizes or when investigated in sibships multiply affected with AD.

Taken together, the current results suggest 2 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

Table 3. Haplotype Frequencies Among Patients and Controls by Ethnic Group*

	SNPs			Haplotype		Caribbean Hispanic Haplotype Frequency*	z Score	P Value	Permutation Empirical P Value	Permutation Global P Value	African American Haplotype Frequency*	z Score	P Value	Permutation Empirical P Value	Permutation Global P Value
1	2	3	C	C	G						0.01	2.35	.0186†	.0140†	.183
2	3	4	C	G	C	0.04	−1.46	.1455	.1520	.541	0.01	2.08	.0380†	.0280†	.530
4	5	6	C	C	A	0.01	2.09	.0367†	.0380†	.416					
8	9	10	C	G	T	0.01	−0.09	.9264	.8950		0.01	2.40	.0164†	.0250†	
8	9	10	C	A	T	0.01	0.74	.4596	.4630	.576	0.01	−0.49	.6243	.6310	.530
10	11	12	C	C	T	0.03	0.34	.7344	.7550		0.01	−1.11	.2653	.2520†	
10	11	12	C	A	T	0.11	1.54	.1227	.1330	.461	0.10	−2.01	.0447†	.0470†	.307
11	12	13	C	T	G	0.03	0.40	.6927	.7110	.717	0.01	−1.16	.2464	.2420	.374
16	17	18	A	T	A	0.44	0.09	.9318	.9370	.957	0.58	0.39	.6935	.6940	.674
16	17	18	T	G	A	0.06	0.15	.8821	.8710		0.04	−0.10	.9186	.8640	
17	18	19	T	A	G	0.22	−0.57	.5716	.5670	.544	0.11	−0.83	.4040	.4210	.602
18	19	20	A	G	G	0.23	−0.62	.5375	.5500	.640	0.12	−0.58	.5650	.5890	.828
19	20	21	G	G	C	0.23	−0.66	.5072	.5150	.606	0.12	−0.50	.6192	.6340	.898
20	21	22	G	C	C	0.24	−0.87	.3827	.3710		0.12	−0.56	.5748	.5840	
20	21	22	G	G	C					.953	0.01	2.19	.0287†	.0230†	.183
22	23	24	C	T	T	0.24	−0.18	.8596	.8580	.630	0.09	−1.22	.2227	.2130	.242
23	24	25	T	T	C	0.25	0.02	.9857	.9860	.571	0.12	−1.54	.1246	.1240	.143
24	25	26	C	T	A	0.43	−0.87	.3821	.3870		0.26	0.64	.5195	.5274	
24	25	26	C	T	G	0.09	0.71	.4792	.4690		0.17	−1.82	.0683	.0626	
24	25	26	C	C	A	0.13	0.62	.5357	.5590	.862	0.27	3.43	.0006†	.0005†	.010†
26	27	28	A	A	A	0.35	1.68	.0922	.0830	.247	0.38	2.09	.0362†	.0330†	.081
27	28	29	C	A	C	0.01	0.32	.7495	.8040		0.02	1.60	.1104	.1350	
27	28	29	A	A	C	0.26	1.75	.0802	.1010		0.53	0.99	.3205	.3180	
27	28	29	A	G	G	0.02	−0.67	.5034	.5270	.203	0.03	−1.91	.0566	.0500†	.428

	SNPs			Haplotype		European White Non-Hispanic Haplotype Frequency*	z Score	P Value	Permutation Empirical P Value	Permutation Global P Value
1	2	3	C	C	G					
2	3	4	C	G	C					
4	5	6	C	C	A					
8	9	10	C	G	T	0.01	0.32	.7463	.7807	
8	9	10	C	A	T	0.01	2.46	.0138†	.0304†	.003†
10	11	12	C	C	T	0.03	2.15	.0315†	.0300†	
10	11	12	C	A	T	0.04	0.64	.5205	.5550	.363
11	12	13	C	T	G	0.02	2.16	.0305†	.0250†	.200
16	17	18	A	T	A	0.23	2.75	.0060†	.0050†	.032†
16	17	18	T	G	A	0.09	−1.54	.1231	.1340	
17	18	19	T	A	G	0.20	2.30	.0214†	.0200†	.202
18	19	20	A	G	G	0.23	2.13	.0328†	.0250†	.195
19	20	21	G	G	C	0.22	2.25	.0242†	.0180†	.267
20	21	22	G	C	C	0.19	2.28	.0225†	.0230†	
20	21	22	G	G	C	0.01	−0.42	.6771	.7350	.333
22	23	24	C	T	T	0.20	2.00	.0451†	.0420†	.430
23	24	25	T	T	C	0.23	2.11	.0348†	.0350†	.113
24	25	26	C	T	A	0.61	−0.91	.3614	.3220	.310
24	25	26	C	T	G					
24	25	26	C	C	A	0.09	−0.78	.4370	.4680	.420
26	27	28	A	A	A	0.31	1.81	.0700	.0700	.310
27	28	29	C	A	C	0.02	2.31	.0207†	.0230†	
27	28	29	A	A	C	0.03	2.10	.0356†	.0300†	
27	28	29	A	G	G					.048†

Abbreviations: See Table 2.

*Haplotype frequency was estimated using both cases and controls. Haplotypic associations between *SORL1* SNPs and AD were investigated using a sliding window of 3 contiguous SNPs and the Haploview program, as described previously.[1] Only those haplotypes generating a significant result in at least 1 data set are shown. The entire set of 3 SNP haplotypes is available on request. Rows without data indicate that the specific haplotype was not present in that cohort.

†Significant values.

and the discovery of different AD-associated haplotypes in different data sets support 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 be needed 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 through 10 and 22 through 25.

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