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The Association Between Genetic Variants in *SORL1* and Autopsy-Confirmed Alzheimer's Disease

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Keywords

SORL1; Alzheimer's disease; sporadic; autopsy confirmed

Genetic variants within two distinct regions of *SORL1* have recently been associated with both familial and sporadic Alzheimer's disease (AD) in multiple cohorts composed of more than 6,000 individuals (1). The original report was subsequently confirmed in an independent cohort of unrelated patients with probable AD and healthy elderly controls from a prospective study in multiethnic communities in northern Manhattan (2). To extend these results, we investigated a series of autopsy confirmed cases with AD (n=103) of white, non-Hispanic origin, and compared them to controls (n = 93) from similar ethnic origins. These analyses revealed that the same alleles in a haplotype in the 5' region of the gene and a haplotype in the same 3' region are associated with autopsy proven AD.

Frozen brain tissue was obtained from 103 autopsy confirmed cases of AD, and from 17 elderly controls with a normal postmortem examination, and without a history of dementia or another neurological disorder. . To augment the number of controls from the same ethnic background, we included 76 non-demented elderly participants who have been followed prospectively at approximately 18-month intervals as part of a study of aging and dementia among Medicare recipients residing in northern Manhattan since 1999 (3-5). The average age of onset for the patients was 80.5 and 52.4% were women. The mean age of the combined group of controls was 79.7 years and 48.4% were women. The Institutional Review Boards of Columbia University Medical Center and the New York Psychiatric Institute approved recruitment, informed consent and study procedures.

Genotyping was performed using matrix assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (Sequenom). Detailed information on genotyping was

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previously described (1), and is available upon request. The numbering system for the SNPs 1 to 29 reflects their relative order on the physical map of *SORL1*, and was the same system used in the previous publication (1). We restricted the work to include only 12 of the previously genotyped SNPs to focus on 5' (SNPs 1, 2 and 7−10) and 3' (SNPs 13, 17 and 22−25) regions highlighted in the previous report. SNP marker data were assessed for deviations from Hardy-Weinberg equilibrium using the HAPLOVIEW program (6), and none deviated. The χ^2 test (or the Fisher's exact test) was used to for analysis of genotypic and allelic associations between AD and each of the SNP markers. The HAPLOVIEW program was used to perform single point analysis, estimates of linkage disequilibrium (LD) structure and haplotype blocks. 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 (1). The objective of this study was to confirm associations in the previous two studies (1,2), therefore a nominal p-value of 0.05 wass considered sufficient evidence of confirmation (7). Consequently, nominal p-values are presented in the table for single point and haplotype analyses.

The single SNP analyses revealed that the C and G alleles in SNPs 8 and 9 were significantly associated with AD ($0.015 \leq p \leq 0.017$, table 1a). Haplotype analysis confirmed this result, showing that the CGC haplotype in SNPs 8−9−10 was also significantly associated with AD (nominal p=0.0047, global p = 0.02, table 1b). Importantly, these were the same alleles within the same haplotype that was associated with AD in Caribbean Hispanic families, the Israeli Arabs and the northern European case-control series in the initial report(1). Haplotypes in the 3' region involving SNPs 23−24−25 previously found to be associated with AD were also statistically significant (nominal p=0.015, global p =0.012, table 1b), but the alleles differed; ATC in the current report contrasted with TTC in the original report (1).

These results provide yet further independent confirmation of the observation that inherited variants in *SORL1* are associated with AD. Our findings in this series of white, non-Hispanic autopsy confirmed patients with AD and controls of European and North American ancestry are nearly identical to those in the original case control series of northern Europeans. As was apparent in the original and follow-up studies (1,2), the significant association in two regions of the gene, and the discovery of different alleles within the AD-associated haplotypes in different datasets indicates that there may be a high degree of allelic heterogeneity, with disease-associated variants occurring on multiple different haplotype backgrounds. While the exact identity of the genetic effectors in *SORL1* remains to be determined, it has been shown that *SORL1* interacts with the amyloid precursor protein (APP), directs trafficking of APP into recycling pathways, and that when *SORL1* is under-expressed, APP is sorted into Aβ-generating compartments (1,8-11). Furthermore, neurons of in some patients with AD display low levels of *SORL1*, and knockout of *SORL1* in mice has been associated with increased brain Aβ levels. The results reported here provide additional support for the association between genetic variants in *SORL1* and AD in an independent series confirmed by postmortem examination.

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Table 1a and 1b

Results of genotyping of the 12 SNPs in *SORL1* by single point and haplotype analysis. The SNP order refers to original order of the SNPs in our previous publication (1). The single SNPs and haplotypes in boldface were statistically significant. The associated alleles for SNPs 8 and 9 were identical to those in the original manuscript as was the haplotype CGC from SNPs 8–9–10 (1).

1a. *SORL1* SNP Order (1)	SNP Name	Associated Allele	Frequency Cases : Controls	X^2	P-value
1	rs4935774	A	0.789 : 0.703	2.793	0.0947
2	rs578506	C	0.531 : 0.451	1.843	0.1746
7	rs12364988	G	0.588 : 0.506	2.106	0.1467
8	**rs668387**	**C**	**0.665 : 0.534**	**5.885**	**0.0153**
9	**rs689021**	**G**	**0.654 : 0.518**	**5.655**	**0.0174**
10	rs641120	C	0.654 : 0.588	1.401	0.2365
13	rs2298813	A	0.047 : 0.034	0.319	0.572
17	rs556349	T	0.338 : 0.330	0.025	0.8733
22	rs1699102	C	0.354 : 0.335	0.136	0.7123
23	rs3824968	A	0.316 : 0.259	1.198	0.2736
24	rs2282649	T	0.301 : 0.212	3.229	0.0724
25	rs1010159	T	0.662 : 0.625	0.451	0.502

1b. Haplotype Location	Haplotype			Frequency Cases : Controls	Z score	Haplotype P-value	Global P-value
8–9–10	T	A	T	0.334 : 0.432	−1.8875	0.0591	**0.02863**
	C	A	C	0.001 : 0.024	−1.79354	0.0729	
	T	G	C	0.001 : 0.012	−1.31871	0.1873	
	T	A	C	0.002 : 0.023	−1.28693	0.1981	
	C	**G**	**C**	**0.662 : 0.509**	**2.82608**	**0.0047**	
23–24–25	**T**	**C**	**C**	**0.029 : 0.103**	**−2.42463**	**0.0153**	**0.01255**
	A	**C**	**C**	**0.007 : 0.052**	**−2.11649**	**0.0343**	
	T	T	C	0.009 : 0.013	−1.37823	0.1681	
	T	C	T	0.654 : 0.628	0.49746	0.6189	
	A	**T**	**C**	**0.301 : 0.204**	**2.00448**	**0.0450**	