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Association between SORL1 and Alzheimer disease in a genome-wide study

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Abstract

Several studies [1–3] have reported an association of Alzheimer disease (AD) with polymorphic markers in *SORL1*. Data from a recently published genome wide association study in AD [4] have been made publically available. We tested the association of AD with *SORL1* in this dataset (TGEN), which included 31 *SORL1* SNPs, 8 of which overlapped the original study [1]. Six SNPs, near the 3′ region of *SORL1* containing SNPs which were strongly associated with AD in previous studies, showed significant association in the TGEN dataset. These results provide an independent replication of the association between AD and *SORL1*.

Keywords

Alzheimer disease; SORL1; association; genome-wide association study

Introduction

Rogaeva et al.[1] reported an association between Alzheimer disease (AD) and several SNPs in the gene encoding the sortilin-related receptor, low-density lipoprotein receptor class A repeat–containing protein - *SORL1* (11q23–q24) in four different ethnic groups (Caucasians, African Americans, Israeli-Arabs and Hispanics) analyzed separately. Although the precise identity of the genetic effectors in *SORL1* remains to be determined, this initial study pointed to two clusters of SNPs in distinct regions of the gene, implying the existence of multiple allelic variants associated with AD in different populations. Two positive replications have been

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reported [2,3]. Recently, results of a genome wide association study in AD was published [4] with a focus on a novel association of SNPs in the *GAB2* gene with AD. This report however did not mention any results for *SORL1*. We were therefore interested to test whether the association of AD with *SORL1* is replicated in this dataset (TGEN) which is publicly available.

Methods

Subjects

The TGEN dataset [4] was obtained from from the website http://www.tgen.org/neurogenomics/data. Although both the original study by Rogaeva et al [1] and the study by Reiman et al describing the TGEN dataset [4] included subjects ascertained at the Mayo Clinic in Rochester, Minnesota, the Mayo subjects in the TGEN data set and the Mayo subjects included in Rogaeva et al. study are independent. Consequently, we analyzed *SORL1* data for 1,408 subjects in the TGEN database which included 1,044 autopsied individuals (641 cases, 403 controls) and 364 clinically examined subjects from the Mayo Clinic (218 cases and 146 controls).

Statistical analyses

SNP marker data were assessed for deviations from Hardy-Weinberg equilibrium using Haploview [5] software. Single point allelic and genotypic tests were performed using PLINK [6]. Marker genotype distributions in cases and controls were compared in several ways: (1) a genotypic test with two degrees of freedom, models assuming (2) dominant and (3) recessive inheritance, and (4) the Cochran-Armitage trend test.

Linkage disequilibrium

The LD structure among the *SORL1* SNPs was examined using Haploview[5]. Haplotype blocks were defined using the confidence intervals algorithm. The default settings were used in these analyses, which create 95% confidence bounds on *D′* to delineate SNP pairs in strong LD.

Results

There were 31 *SORL1* SNPs in the TGEN database, and eight of those overlapped the 29 SNPs in the by Rogaeva et al study [1]. These 31 SNPs are referred to by their sequential order on the physical map in TGEN database, i.e. T.1, T.2, T.*n*, T.31. Therefore, a total of 52 unique SNPs were analyzed in these two studies (Table 1). All SNPs are in Hardy-Weinberg equlibrium in control samples. The LD structures of SNPs in the 5′ and 3′ regions are similar in the north European family data [1] and TGEN data [2] (Figure 1).

Six SNPs (T.17, T.19, T.20, T.21, T.26, T.27) showed nominally significant association ($0.01 \leq p < 0.05$) with AD under at least one model (Table 2). These six SNPs span a region of approximately 35 kb including SNPs 21–25 near the 3′ end of *SORL1* which were strongly associated with AD in the Rogaeva et al. study. TGEN SNPs T.17 and T.19 are located between SNPs 20 and 21, TGEN SNPs T.20 and T.21 are between SNPs 22 and 23, and TGEN SNPs T.26 and T.27 are between SNPs 24 and 25 (Table 2). Haplotype analysis strengthened the association signal in the region including the two SNPs between SNPs 22 and 23 (global p-value = 0.005, data not shown).

Discussion

The results from analysis of the TGEN data provide an independent replication of the association between AD and *SORL1*. We recognize that the magnitude of the significance of

these results would not survive correction for multiple testing in a hypothesis-generating study (e.g., genome-wide association study); however a p-value of less than 0.05 is sufficient to confirm a previously reported association between variants within a specific gene and disease. Furthermore, although the particular SNP associations in this study are novel, a Bonferroni or similar correction is not appropriate or justified because all of the associated SNPs are within the region of and in LD with SNPs implicated in previous investigations[1–3], and therefore these are not truly independent tests.

Conclusion

While the precise identity of genetic effectors in *SORL1* remains unknown, the TGEN data support the hypothesis that at least one disease risk enhancing allele is located near the 3′ end of *SORL1*.

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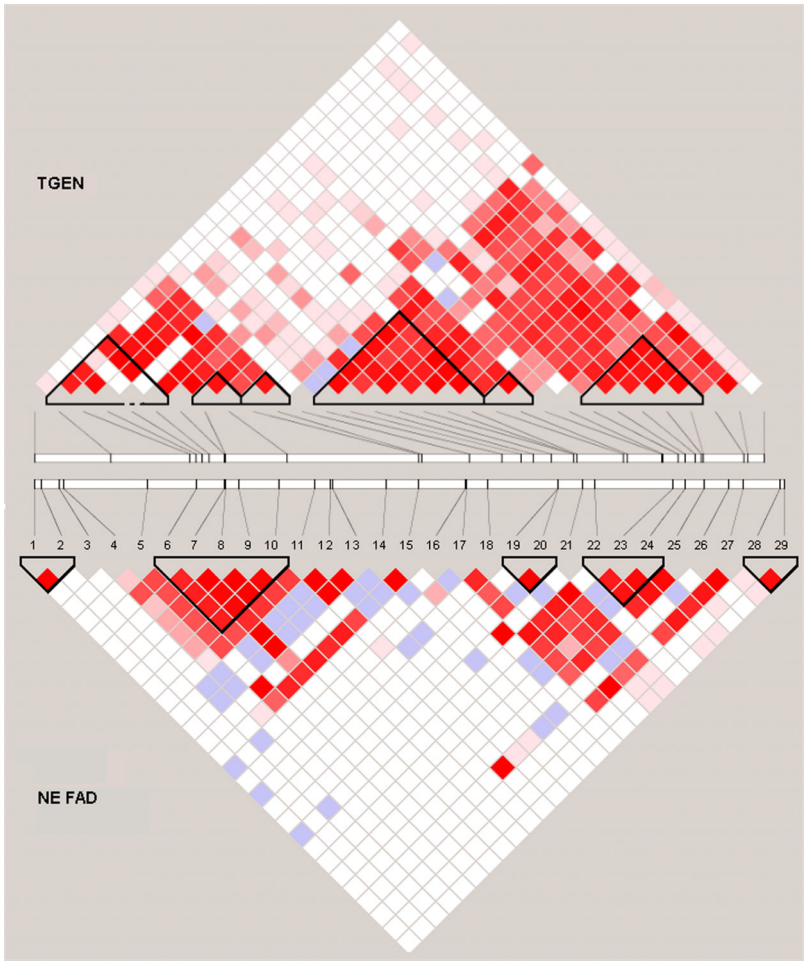

Figure 1.

Linkage disequilibrium (LD) structure of SORL1. Relative locations of SNPs included in each dataset are shown on two parallel stick diagrams, with LD maps for the TGEN dataset located above and the north European familial AD dataset studied by Rogaeva et al. [1] below the gene structure. The measure of LD (D′) among all possible pairs of SNPs is shown graphically according to the shade of red where white represents very low D′ and dark red represents very high D′. High D′ estimates associated with a large confidence interval (most likely due to one of the alleles being rare) are denoted by blue squares.

Table 1

SORL1 SNP information in the original study and in the TGEN dataset.

SNP order	dbSNP rs Number	Physical Map Location (bp)	Distance (bp) from Previous Marker	SNP Type	Orig order	TGEN order	NE FAD	Israeli Arab	TGEN
1	**rs4935774**	120,826,964		Upstream of 5′ UTR	1	T.1	0.20	0.18	0.39
2	rs578506	120,828,687	1,723	intron	2		0.07	ND	
3	rs582446	120,833,069	4,382	intron	3		0.32	0.08	
4	rs661057	120,834,164	1,095	intron	4		0.12	0.07	
5	rs676160	120,845,443	11,279	intron		T.2			0.49
6	rs11218304	120,854,321	8,878	intron	5		0.27	**0.046**	
7	rs676759	120,864,475	10,154	intron		T.3			0.57
8	**rs560573**	120,866,094	1,619	intron	6	T.4	0.64	0.29	0.55
9	rs985421	120,867,526	1,432	intron		T.5			0.28
10	rs593769	120,869,213	1,687	intron		T.6			0.57
11	**rs12364988**	120,872,836	3,623	H269H	7	T.7	0.15	**0.041**	0.33
12	**rs668387**	120,873,131	295	intron	8	T.8	0.52	**0.021**	0.32
13	rs689021	120,876,330	3,199	intron	9		0.71	**0.040**	
14	rs641120	120,886,175	9,845	intron	10		0.57	0.07	
15	rs11218313	120,888,081	1,906	intron		T.9			0.83
16	rs4935775	120,894,712	6,631	intron	11		0.22	**0.030**	
17	rs12285364	120,898,436	3,724	intron	12		**0.014**	0.56	
18	rs2298813	120,898,894	458	T528A	13		**0.012**	0.43	
19	rs11600231	120,911,918	13,024	intron	14		0.69	0.12	
20	**rs2276346**	120,919,686	7,768	intron	15	T.10	0.61	0.36	0.25
21	rs10502262	120,920,522	836	intron		T.11			0.17
22	SORL1-T833T	120,931,165	10,643	T833T	16		0.41	**0.0026**	
23	rs556349	120,931,417	252	intron	17		**0.0057**	0.20	
24	rs7131432	120,932,080	663	intron		T.12			0.14
25	rs11218340	120,936,564	4,484	intron	18		0.08	0.14	
26	rs10892756	120,939,766	3,202	intron		T.13			0.49
27	rs11218346	120,944,391	4,625	intron		T.14			0.48
28	rs1790213	120,947,399	3,008	intron		T.15			0.33
29	rs11218347	120,951,758	4,359	intron		T.16			0.78
30	rs2070045	120,953,300	1,542	S1187S	19		**0.031**	**0.00082**	
31	rs3824966	120,953,393	93	intron	20		0.15	0.15	
32	rs1699103	120,957,136	3,743	intron		T.17			**0.045**
33	rs7116734	120,957,150	14	intron		T.18			0.30
34	rs11218350	120,957,861	711	intron		T.19			**0.040**
35	SORL1-18ex26	120,959,359	1,498	(−18) 5′ of exon 26	21		0.41	**0.0091**	
36	rs1699102	120,962,172	2,813	N1246N	22		0.06	0.91	
37	rs10892759	120,969,298	7,126	intron		T.20			**0.021**
38	rs1792113	120,970,156	858	intron		T.21			0.20
39	rs11218360	120,978,601	8,445	intron		T.22			0.42
40	rs7128608	120,978,808	207	intron		T.23			0.44
41	rs3824968	120,981,132	2,324	A1584A	23		**0.0031**	**0.00073**	
42	rs1629493	120,982,306	1,174	intron		T.24			0.09
43	**rs2282649**	120,984,168	1,862	intron	24	T.25	**0.020**	0.64	0.26
44	rs726601	120,986,617	2,449	intron		T.26			0.07
45	rs1784931	120,988,148	1,531	intron		T.27			**0.049**
46	**rs1010159**	120,988,611	463	intron	25	T.28	0.09	0.91	0.14
47	rs1784933	120,994,626	6,015	intron	26		0.07	0.80	
48	**rs1614735**	120,998,211	3,585	intron	27	T.29	**0.010**	0.96	0.19
49	rs17125558	120,999,237	1,026	intron		T.30			0.70
50	rs10892761	121,003,094	3,857	intron		T.31			0.56
51	rs1133174	121,006,965	3,871	downstream of 3′UTR	28		0.07	0.09	
52	rs1131497	121,007,955	990	downstream of 3′UTR	29		0.20	0.06	

Notes: The nominal *P* values for allelic association with AD are shown for each dataset. NE FAD -- north European familial AD dataset; Israeli-Arab -- Israeli-Arab case-control dataset, and TGEN – TGEN dataset. Boldface rs number indicates that the SNP was genotyped in both Rogaeva et al. [1] and Reiman et al. [4] studies. Bold face p-value indicates that the SNP is nominally associated with AD in the original study. Bold face p-value with white font, black background refer to significant results from analyses of the TGEN data.

Table 2

Single-SNP association results in the TGEN dataset.

order	SNP	interval of SNPs in the original paper	Minor Allele	F_A	F_U	OR	Allele.P	Geno.P	DOM.P	REC.P	TREND.P
T.1	**rs4935774**	1	1	0.215	0.201	1.09	0.39	0.54	0.54	0.29	0.38
T.2	rs676160	4~5	2	0.100	0.092	1.10	0.49	0.78	0.50	0.73	0.48
T.3	rs676759	5~6	2	0.389	0.378	1.05	0.57	0.35	0.88	0.19	0.57
T.4	**rs560573**	6	2	0.386	0.374	1.05	0.55	0.40	0.95	0.21	0.55
T.5	rs985421	6~7	2	0.016	0.022	0.74	0.28	NA	NA	NA	0.27
T.6	rs593769	6~7	1	0.385	0.374	1.05	0.57	0.48	0.98	0.25	0.57
T.7	**rs12364988**	7	2	0.496	0.477	1.08	0.33	0.56	0.61	0.28	0.34
T.8	**rs668387**	8	2	0.430	0.411	1.08	0.32	0.57	0.52	0.31	0.32
T.9	rs11218313	10~11	2	0.088	0.086	1.03	0.83	0.92	0.78	0.82	0.83
T.10	**rs2276346**	15	1	0.351	0.372	0.91	0.25	0.22	0.10	0.95	0.24
T.11	rs10502262	15~16	1	0.288	0.312	0.89	0.17	0.33	0.14	0.60	0.17
T.12	rs7131432	17~18	2	0.016	0.024	0.67	0.14	NA	NA	NA	0.14
T.13	rs10892756	18~19	1	0.075	0.068	1.11	0.49	0.40	0.65	0.18	0.49
T.14	rs11218346	18~19	1	0.085	0.078	1.11	0.48	0.60	0.55	0.37	0.47
T.15	rs1790213	18~19	2	0.375	0.393	0.93	0.33	0.34	0.17	0.99	0.33
T.16	rs11218347	18~19	1	0.076	0.073	1.04	0.78	0.94	0.81	0.78	0.78
T.17	rs1699103	20~21	1	0.404	0.442	0.85	**0.045**	0.13	0.07	0.14	**0.043**
T.18	rs7116734	20~21	1	0.399	0.419	0.92	0.30	0.42	0.61	0.19	0.29
T.19	rs11218350	20~21	2	0.215	0.248	0.83	**0.040**	0.11	0.11	0.07	**0.045**
T.20	rs10892759	22~23	1	0.325	0.368	0.83	**0.021**	**0.040**	**0.011**	0.35	**0.020**
T.21	rs1792113	22~23	1	0.351	0.375	0.90	0.20	0.06	**0.041**	0.68	0.21
T.22	rs11218360	22~23	1	0.027	0.032	0.83	0.42	NA	NA	NA	0.41
T.23	rs7128608	22~23	1	0.044	0.038	1.17	0.44	0.75	0.45	0.84	0.45
T.24	**rs1629493**	23~24	2	0.356	0.388	0.87	0.09	0.20	0.15	0.14	0.08
T.25	rs2282649	24	2	0.289	0.309	0.91	0.26	0.52	0.31	0.43	0.26
T.26	rs726601	24~25	2	0.296	0.329	0.86	0.07	0.12	**0.038**	0.56	0.06
T.27	rs1784931	24~25	1	0.377	0.415	0.86	**0.049**	0.12	**0.049**	0.24	**0.046**
T.28	**rs1010159**	25	1	0.336	0.363	0.89	0.14	0.32	0.21	0.24	0.14
T.29	rs1614735	27	2	0.479	0.505	0.90	0.19	0.27	0.11	0.58	0.18
T.30	rs17125558	27~28	2	0.020	0.022	0.90	0.70	NA	NA	NA	0.70
T.31	rs10892761	27~28	2	0.411	0.422	0.96	0.56	0.07	0.10	0.32	0.56

Notes: F_A: Minor allele frequency in cases; F_U: Minor allele frequency in controls; OR: estimated odds ratio for AD of minor allele; Allele.P: p-value for allelic association; Geno.P: p-value for genotypic (2 df) test; DOM.P: p-value for genotypic (1 df) test with dominant model; REC.P: p-value for genotypic (1 df) test with recessive model; TREND.P: Cochran-Armitage trend test; NA: Not available (allelic, genotypic and dominant/recessive tests require that each cell has a frequency of 1 or greater). SNPs studied by both Rogaeva et al. [1] and Reiman et al. [4] are indicated in boldface.