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# Association between Genetic Variants in Sortilin-Related Receptor 1 (*SORL1*) and Alzheimer's Disease in Adults with Down syndrome

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## Abstract

Recent reports have suggested that variants in the sortilin-related receptor gene (*SORL1*) increase the risk of late onset Alzheimer's disease (AD) in Northern European, Hispanic, African-American and Isreali-Arab populations. *SORL1* directs trafficking of amyloid precursor protein (APP) and under-expression of *SORL1* may lead to over-expression of β amyloid peptides. Adults with Down syndrome (DS) over-express APP and have early onset and high risk for AD. We investigated the relation of seven variants in the gene for *SORL1* to age at onset and risk for AD among 208 adults with DS, 45–70 years of age at baseline. Participants were ascertained through the New York State developmental disability service system and followed at 18-month intervals. Information from cognitive assessments, caregiver interviews, medical record review and neurological examination was used to establish the diagnosis of dementia. Homozygosity for the minor T allele in rs556349 and for the minor C allele in rs536360 was associated with later age at onset and reduced risk of AD (HR= 0.26, 95% CI: 0.08–0.86; and HR= 0.40, 95% CI: 0.16–0.98, respectively). Mean age at onset was approximately four years later in individuals who were homozygous for those alleles compared with those who had at least one major allele. These findings indicate a modest association of variants in *SORL1* with AD. In addition, we did not observe the same alleles to be associated with AD compared with earlier studies, suggesting that these SNPs are in linkage disequilibrium (LD) with the putative functional variants or that expression of the *SORL1* gene and hence its interaction with APP might be modified by the extremely high levels of APP characteristic of Down syndrome. Thus, further studies are needed to identify functional variants that influence risk for AD in this uniquely vulnerable population.

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**Keywords**

*SORL1*; Down syndrome; Alzheimer's disease

Deposition of β amyloid peptides (Aβ) is a primary event in the pathogenesis of AD. Amyloid peptides Aβ40 and Aβ42, the two major species of amyloid β, are generated from a larger membrane bound protein, the amyloid precursor protein (APP), located on chromosome 21, by sequential proteolytic cleavage by β and γ secretases [6,8,19]. Several genes that are involved in Aβ generation have been identified [9,21]. Mutations in APP and in Presenilins 1 and 2 and the presence of the apolipoprotein E (APOE) ε4 allele are associated with increased accumulation of Aβ in the brain and increased risk for AD [10,12,16], yet the mechanisms through which the genetic variants act are still uncertain.

Recent reports have implicated the sortilin-related receptor gene (*SORL1*) as a susceptibility gene for AD [11,14]. *SORL1*, located on chromosome 11 (11q24.1), is a 250-kDa membrane protein expressed in neurons of the central and peripheral nervous system [1]. It is known to be involved with intracellular trafficking between the membrane, interacting with APP in endosomes and golgi in vitro and in living cells [5]. Several lines of evidence support the hypothesis that under-expression of *SORL1* leads to the over-expression of Aβ. Under-expression of *SORL1* has been observed in patients with AD [1,13]. In murine *SORL1* knockout models, Aβ levels were increased in the brain, suggesting that expression of *SORL1* has a protective effect on APP processing [1].

In previous studies investigating genetic variants within *SORL1*, allelic associations were found between AD and two clusters of single nucleotide polymorphisms (SNPs) in distinct regions of the *SORL1* gene: the cluster of rs668387, rs689021, and rs641120 in the intronic region (spanning 120,873,131 – 120,886,175 bp) and the cluster of rs1699102, rs3824968, rs2282649, and rs1010159 at the intron-exon boundary (spanning 120,962,172 – 120,988,611 bp) [11, 14]. Moreover, samples with putative homozygous haplotypes were associated with under-expression of *SORL1* and over-expression of Aβ levels [14]. However, the genetic variants associated with AD in the initial study by Rogaeva et al. [14] differed by ethnicity. In the subsequent study by Lee et al. [11], the same haplotype sets were associated with AD, but not all putative haplotypes were the same as those in the initial study by Rogaeva and colleagues. Taken together, there is likely to be a high degree of allelic heterogeneity, and the SNPs identified thus far are not likely to be the causative alleles but are in linkage disequilibrium (LD) with the causative alleles.

Triplication and over-expression of the gene for APP, located on chromosome 21, has been associated with early onset of dementia in adults with Down syndrome (DS) [4,15], although there is a wide range of age at onset which is associated with additional risk factors [17]. Since under-expression of *SORL1* leads to the over-expression of Aβ, we hypothesized that *SORL1* variants may contribute to variation in age at onset and risk for AD in adults with DS, in patterns consistent with that observed in the population without DS. To test this hypothesis, we examined the relation of AD to six SNPs along the *SORL1* gene that had been investigated in Caucasian samples. We also examined one additional SNP in the 5' end of *SORL1* that had not been examined in the previous papers but was close to a SNP previously associated with increased risk for AD. We found an association of two genetic variants in *SORL1* with AD. However, we did not observe the same alleles to be associated with AD compared with several other datasets.

A community-based sample of adults with DS, ascertained from the statewide service system and recruited with the help of state and voluntary service provider agencies was tracked in a

longitudinal study for a period of 5.5 years. Eligible participants were at least 45 years of age at enrollment and resided in New York State. Subjects were eligible to participate in the study if a family member or correspondent provided informed consent, and participants also signed a form acknowledging their assent and willingness to participate. The participation rate was 74.6%. Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of the New York State Institute for Basic Research in Developmental Disabilities and Columbia University Medical Center.

Because 93% of the cohort was Caucasian and ethnicity was associated with *SORL1* effects in earlier studies [11,14], we restricted the analysis to Caucasians. Since risk of AD in adults with DS is extremely high after age 70 and the effects of risk factors may become attenuated at older ages, we also restricted the analysis to those who were below 70 years of age at enrollment. There were 284 participants of whom 222 (78.2%) had *SORL1* genotype data. Five participants with mixed dementia, one participant with other dementia and eight participants who could not be diagnosed were excluded, leaving 208 participants for analysis, 53 with AD and 155 who remained nondemented throughout the course of the study.

Assessments included evaluations of cognition, functional and vocational abilities, behavioral/psychiatric conditions and health status. Assessments were repeated at 14–18 months over four cycles of data collection. Cognitive function was evaluated with a test battery used to assess cognitive functions that are typically affected in AD and designed for use with individuals varying widely in their levels of intellectual functioning. A complete description of the instrument battery and study procedures has been previously published [22]. Participants showing declines in cognition and in adaptive behavior and who were suspected of having dementia were evaluated by the study neurologist to confirm the presence of dementia and to determine the presence or absence of medical/psychiatric conditions other than AD that might result in or mimic dementia. Structured interviews were conducted with caregivers to collect information on changes in cognitive function, adaptive behavior and medical history. Past and current medical records were reviewed for all participants.

Classification of dementia and its cause was made in a consensus conference. Following the recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability [2] participants were considered demented if there was a history of progressive memory loss, decline in at least one other cognitive domain and functional decline over a period of one year or more. Participants were classified as demented if no other condition that might mimic dementia was present, such as untreated hypothyroidism or stroke, (n=59). Participants classified as demented showed substantial and consistent decline over the course of follow-up. Participants who were considered non-demented exhibited no cognitive or functional decline (n=137), or showed some cognitive and/or functional impairment, but not of sufficient severity to meet criteria (n=18). Among the participants who developed dementia, 90% of the cases were attributable to AD. Participants with evidence of vascular or other forms of dementia, detected during the neurological evaluations or from clinical histories, were excluded from the analysis (n=6).

SNPs in the *SORL1* gene were analyzed using MassARRAY Discovery RT (SNP Discovery). Use of laser desorption/ionization time-of-flight mass spectrometry analysis allows for the localization of SNPs via signal pattern differences. Samples underwent four base-specific cleavage reactions, yielding four sets of signal patterns for SNP analysis. The signals were compiled and analyzed in SNP Discovery Analysis, revealing substitutions at the sites of interest. Primer sets used in the genotyping were the same as described in an earlier publication (Supplementary Table 1 in [14]). 222 DNA samples were genotyped twice for every SNP marker. Genotypes on two experiments agreed >99% of the time. For genotypic analyses, participants were classified as carrying none, one or two copies of the alleles in each SNP.

Apolipoprotein E (APOE) genotyping was carried out as described in a previous study [18] by employing standard PCR-RFLP methods using Hha1 (CfoI) digestion of an APOE genomic PCR product spanning the polymorphic (cys/arg) sites at codons 112 and 158. Acrylamide gel electrophoresis was used to assess and document the restriction fragment sizes [7]. Participants were classified according to the presence or absence of an APOE ε4 allele.

Prior to association analysis, we tested all SNPs to see whether they conformed to Hardy-Weinberg Equilibrium (HWE). We observed that all SNPs were in HWE in non-demented individuals, but two SNPs (rs4935774 and rs536360) were out of HWE in demented individuals. Single point analysis and estimation of linkage disequilibrium (LD) structure and haplotype blocks were performed using the HAPLOVIEW program [3]. The default settings were used to estimate LD structure, creating 95% confidence bounds on the D' to define SNP pairs in LD.

In preliminary analyses, we used $\chi^2$ tests to analyze categorical variables and Student's t-test and analysis of variance for continuous variables to compare demographic characteristics of demented and nondemented participants. Because this study was designed to confirm previous investigations [11,14], a nominal p-value of 0.05 was set as the threshold for confirmation. We used Kaplan-Meier life table methods to estimate cumulative incidence, and used Cox proportional hazards models to estimate the hazard ratio (HR) of dementia by SNP genotype in a multivariable model, adjusting for sex, level of mental retardation and the presence of the APOE ε4 allele. Age at onset of AD or age at last visit was the time to event variable. After examining the relationship between the individual marker genotypes and dementia, we selected genotypes that were homozygous for the minor allele as the risk genotype and repeated the survival analysis, adjusting for covariates. All analyses were conducted using SPSS version 13.0 [20].

The mean age of the participants was 51.7 (± 5.9) years and 77.4% were female. There were 53 participants with dementia and 155 without dementia. Demented participants were older, more likely to be male and more likely to carry the APOE ε4 allele than non-demented participants (Table 1). The proportion of males among those with dementia was significantly greater than that among those who were non-demented (34.0% vs. 18.7%, p=0.02). However, demented males were, on average, seven years older than nondemented males (59.5 vs. 52.1), suggesting an effect of age rather than sex.

Allele frequencies for all SNPs were comparable to those reported for Caucasian populations (http://www.ncbi.nlm.nih.gov). All SNPs were in Hardy-Weinberg equilibrium when all individuals were examined. However, among demented participants, the frequency of the genotypes for rs4935774 and rs536360 deviated from Hardy-Weinberg equilibrium with p-values of 0.018 and 0.046, respectively. In multivariable Cox proportional hazards analyses, adjusting for sex, level of mental retardation and the presence of the APOE ε4 allele, individuals with the CC genotype in rs536360 and with the TT genotype in rs556349 had significantly lower risk of AD compared with those with at least one A allele or those with at least one G allele, respectively (HR for rs536360 = 0.40, 95% CI: 0.16–0.98; HR for rs556349=0.26, 95% CI: 0.08–0.86) (Table 2). The mean onset age was approximately four years later for those with the CC genotype in rs536360 (59.2 years) compared with those with at least one A allele (54.6 years). Similarly, those with the TT genotype in rs556349 (59.0 years) had onset four years later, compared with those with at least one G allele (54.9 years). In addition, individuals with the CC genotype in rs1699102 had a decreased risk for AD compared with those with at least one T allele that was of borderline significance (HR=0.33, 95% CI: 0.09–1.09).

In adults with DS, the observed association of genetic variants in *SORL1* was consistently protective for the minor alleles. Although these findings support an association of genetic

variants in *SORL1* with AD, we did not observe the same alleles to be associated with AD compared with other datasets from populations without DS, suggesting that these SNPs are in LD with the putative functional variants. In the current study, the TT genotype in rs556349 (SNP 17 in Rogaeva et al [14]) was *protective* for AD (HR=0.26). Similarly in the study by Rogaeva and colleagues [14], the T allele in rs556349 was also *protective* in the Israeli-Arab case-control set. However, it was associated with *increased risk* of AD in the North European case-control set in the same study by Rogaeva and colleagues [14]. The finding for this same SNP was equivocal in the study conducted in north Manhattan [11], where the T allele was marginally associated with an *increased risk* in non-Hispanic Whites, but was not significantly associated with AD in Caribbean Hispanics and in African-Americans [11]. Taken together, the most parsimonious explanation is that chromosomal locations near rs556349 may harbor one or more susceptibility variants for AD. As observed in the earlier studies of multi-ethnic cohorts, evidence of allelic heterogeneity is further corroborated in Caucasian individuals with DS where the associated alleles differed from those previously reported.

In the current study the CC genotype in rs536360 was also protective (HR=0.40). This SNP was not examined by Rogaeva and colleagues [14]. In addition, among adults with DS, rs1699102 showed a modest *protective* effect for AD in those with the CC genotype (HR=0.33), which failed to reach statistical significance. This finding has not been consistently replicated across previously studied samples. In the investigation by Rogaeva and colleagues [14], the authors observed that the C allele at rs1699102 was *protective* in the Israeli-Arab case-control set, as it was among adults with DS. However, in the North European families, the C allele was associated with *increased risk* of AD. In the north Manhattan study [11], the T allele was marginally associated with AD (p=0.09) among Caucasian samples.

Allelic association methods utilize LD to localize susceptibility genetic variants. Since LD is a function of population age, population size, population expansion, migration and admixture, LD patterns might be expected to differ across samples from different ethnic backgrounds. Depending on the relation between a chosen SNP marker and the putative functional variant (s), the direction of the association can vary in different populations. Genotype-phenotype relations can be further complicated by multiple genetic and environmental factors that alter expressivity of these genetic variants.

As in most human genetic association studies, multiple testing needs to be addressed, as it can lead to false positive findings. Perhaps the most reliable approach is to replicate the association in an independent sample. We attempted to replicate allelic associations with *SORL1* focusing on seven selected SNPS from a set of 29 examined in previous studies [11,14]. Based on a relatively small size of affected and unaffected individuals, we observed modest protective associations. These protective associations do not survive correction for multiple tests using the conservative Bonferroni approach. However, as shown in Supplementary Figure 1, SNPs 1 and 2, 4 and 5, plus 6 and 7 are in high LD. Therefore, these SNPs do not necessarily represent independent tests, and Bonferroni correction will be overly conservative. For these reasons, we present nominal p-value of 0.05 as the threshold for confirmation.

This is the first report to show associations between *SORL1* variants and AD in adults with DS. Because of triplication of the gene for APP in DS, adults with DS may provide particularly useful insights in understanding the genetic factors involved in the amyloid pathway. In adults with DS, expression of the *SORL1* gene and hence its interaction with APP in endosomes and golgi might be modified by the extremely high levels of APP characteristic of DS. Further work using related phenotypes, such as cognitive decline in nondemented participants and changes in amyloid beta are needed to determine how functional variants in *SORL1* influence AD risk in this uniquely vulnerable population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Demographic Characteristics by dementia status for individuals with Down syndrome

| Characteristic | Demented | Non-demented | Total[2] |
|---|---|---|---|
| **Sample Size (n)** | **53** | **155** | **208** |
| **Age at baseline (mean ± S.D.)** ** | 55.1 ± 6.1 | 50.5 ± 5.3 | 51.7 ± 5.9 |
| **Sex (n,%)** ** | | | |
| Male | 18 (34.0) | 29 (18.7) | 47 (22.6) |
| Female | 35 (66.0) | 126 (81.3) | 161 (77.4) |
| **Level of Function (n,%)** | | | |
| Mild/Moderate | 26 (49.1) | 81 (52.3) | 107 (51.4) |
| Severe/Profound | 27 (50.9) | 74 (47.7) | 101 (48.6) |
| **APOE ε4 Allele (n,%)** * | | | |
| No APOE ε4 Allele | 38 (71.7) | 124 (81.0) | 162 (78.6) |
| One or more APOE ε4 Allele | 15 (28.3) | 29 (19.0) | 44 (21.4) |

** $p < 0.05$

* Number is less than 208 because of missing data

**Table 2**

Cox Proportional Hazards Regression Analysis of SNPs in *SORL1*[1]

| | | | | Multivariable Analysis[3] | |
|---|---|---|---|---|---|
| ***SORL1* SNPs** | **Physical map location (bp)** | **Total[2]** | **Affected[2]** | **HR** | **95% C.I.** |
| rs4935774 | 120826964 | | | | |
| GG | | 15 | 6 | 1.15 | 0.48 – 2.8 |
| At least one A | | 188 | 48 | 1.0 | Reference |
| rs578506 | 120828687 | | | | |
| CC | | 49 | 14 | 0.96 | 0.53 – 1.7 |
| At least one G | | 154 | 40 | 1.0 | Reference |
| **rs536360** | 120833247 | | | | |
| **CC** | | 35 | 6 | **0.40** | **0.16 – 0.98** |
| At least one A | | 168 | 47 | 1.0 | Reference |
| rs668387 | 120873131 | | | | |
| TT | | 32 | 8 | 1.05 | 0.4 – 2.5 |
| At least one C | | 176 | 45 | 1.0 | Reference |
| rs2298813 | 120898894 | | | | |
| GA | | 16 | 4 | 0.78 | 0.36 – 1.1 |
| GG | | 189 | 50 | 1.0 | Reference |
| **rs556349** | 120931417 | | | | |
| **TT** | | 24 | 3 | **0.26** | **0.08 – 0.86** |
| At least one G | | 184 | 50 | 1.0. | reference |
| rs1699102 | 120962172 | | | | |
| CC | | 22 | 3 | 0.33 | 0.09 – 1.09 |
| At least one T | | 183 | 51 | 1.0 | reference |

[1] Cox Proportional Hazards Model

[2] Only the genotyped individuals are included in the analyses.

[3] Multivariable analysis includes sex, level of mental function and the presence of the APOE ε4 allele