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Impact of SORL1 Single Nucleotide Polymorphisms on Alzheimer's Disease Cerebrospinal Fluid Markers

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Key Words
Dementia · Mild cognitive impairment · Healthy aging · Amyloid cascade · Association

Abstract
Background: Recently, genetic variants of the neuronal sortilin-related receptor with A-type repeats (SORL1, also called LR11 or sorLA) have emerged as risk factors for the development of Alzheimer's disease (AD). ***Methods:*** In this study, *SORL1* gene polymorphisms, which have been shown to be related to AD, were analyzed for associations with cerebrospinal fluid (CSF) amyloid beta1–42 ($A\beta_{1-42}$), phosphorylated tau181, and total tau levels in a non-Hispanic Caucasian sample, which encompassed 100 cognitively healthy elderly individuals, 166 patients with mild cognitive impairment, and 87 patients with probable AD. The data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). Moreover, the impact of gene-gene interactions between *SORL1* single nucleotide polymorphisms (SNPs) and the apolipoprotein E *(APOE)* ε4 allele, the major genetic risk factor for sporadic AD, on $A\beta_{1-42}$ concentrations was investigated. ***Results:*** Significant associations between CSF $A\beta_{1-42}$ levels and the *SORL1* SNPs 23 (rs3824968) and 24 (rs2282649) were detected in the AD group. The latter association became marginally statistically insignificant after Bonferroni correction for multiple comparisons. Carriers of the *SORL1* SNP24 T allele and the SNP23 A allele both had lower CSF $A\beta_{1-42}$ concentrations than noncarriers of these alleles. The analysis of the impact of interactions between *APOE* ε4 allele and *SORL1* SNPs on CSF $A\beta_{1-42}$ levels unraveled significant influences of *APOE*. ***Conclusions:*** Our findings provide further support for the notion that *SORL1* genetic variants are related to AD pathology, probably by regulating the amyloid cascade.

P.A. and L.-H.G. contributed equally to this work.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/research/active-investigators.

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Introduction

The causes of late-onset Alzheimer's disease (AD) are multifactorial and complex [1]. Twin studies suggest that around 37–78% of the variance in age at onset of clinical AD can be explained by additive genetic effects [1]. In recent years, the gene encoding the neuronal sortilin-related receptor with A-type repeats (SORL1, also called LR11 or sorLA) has emerged among others as a candidate genetic risk factor for AD [2]. It is located on chromosome 11q23.2–q24.2 and encodes a membrane protein which is specifically expressed in neurons. Several studies have replicated the initial observation of the genetic association between *SORL1* and AD [3–13]. Nonetheless, no general consensus on the role of *SORL1* genetic variants as risk factors for AD exists, since other investigations only found weak or no associations between *SORL1* genetic variants and AD [14–19]. Furthermore, the detected allelic associations varied across studies and the impact on AD risk were only modest with odds ratios ranging from 1.4 to 2.2 [1]. However, a recent meta-analysis of all available data derived from studies including individuals of Caucasian or Asian origin confirmed that variants in the *SORL1* gene are related to risk for AD [20].

SORL1 is a member of the apolipoprotein E (APOE) and low-density lipoprotein receptor family; it is diffusely expressed throughout the brain and acts as an intracellular sorting receptor that engages in the Golgi apparatus-endosome transport [21]. SORL1 is thought to be crucially involved in the sorting of amyloid precursor protein (APP) and in its interactions with secretases [22, 23]. Low levels of SORL1 lead to overproduction of amyloid beta (Aβ) [2]. Interestingly, it has been reported that in patients with AD the expression of *SORL1* is decreased in neurons [24, 25]. Attempting to unravel possible associations between *SORL1* gene variants and biomarkers [26] of AD is a challenging task that may offer a meaningful contribution to our understanding of AD pathogenesis. Due to the role of SORL1 in the processing of APP, we explored possible associations between sequence variations within *SORL1* and established cerebrospinal fluid (CSF) markers of amyloid pathology ($A\beta_{1-42}$) and axonal degeneration (total tau, tTau; tau phosphorylated at threonine 181, $pTau_{181}$) in a large sample of patients with probable AD, mild cognitive impairment (MCI), and cognitively healthy control subjects. Additionally, the impact of sequence variations within SORL1 on $A\beta_{1-42}$ levels in CSF was investigated in association with the presence of an APOE ε4 allele, since APOE ε4 constitutes the major genetic predisposition factor for the development of late-onset AD [27] and since SORL1 levels in CSF are particularly increased in patients with AD carrying the APOE ε4 allele [28].

Materials and Methods

The data used in this study were obtained on September 9, 2010, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and non-profit organizations as a USD 60 million 5-year public-private partnership. The primary goal of ADNI has been to explore whether serial MRI, PET, other biological markers, and clinical and neuropsychological data can be combined to assess the progression of MCI and early AD. The determination of sensitive and specific markers of very early AD progression is intended to support researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and costs of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California San Francisco, USA. ADNI is the result of a broad collaboration of academic institutions and private corporations. Subjects have been recruited from over 50 sites across the USA and Canada. The initial goal of ADNI was to recruit 800 adults aged 55–90 years to participate in the research: approximately 200 cognitively normal older individuals to be followed for 3 years; 400 people with MCI to be followed for 3 years; and 200 people with early AD to be followed for 2 years. Detailed information on ADNI can be found in previous publications and at www.adni-info.org. The study was approved by the institutional review boards of all participating centers and written informed consent was obtained from all participants or authorized representatives after extensive description of ADNI.

Baseline CSF samples were obtained from 416 ADNI subjects and analyzed at the ADNI biomarker core laboratory at University of Pennsylvania; the detailed sampling methods have been described previously [29]. The CSF concentrations of $A\beta_{1-42}$, tTau, and $pTau_{181}$ were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, Tex., USA) with Innogenetics immunoassay kit-based reagents (INNO-BIA AlzBio 3; Ghent, Belgium; for research use-only reagents). From 416 samples, 410 passed quality control and an additional subject later failed ADNI screening, resulting in 409 valid CSF samples. This sub-sample is comparable to the entire ADNI cohort regarding demographic, clinical, and *APOE* genotyping results.

Single nucleotide polymorphism (SNP) genotyping for more than 620,000 target SNPs was performed on all ADNI participants according to published protocols [29]. Genomic DNA samples were analyzed using the Human 610-Quad BeadChip (Illumina Inc., San Diego, Calif., USA) according to the manufacturer's instructions (Infinium HD Assay; Super Protocol Guide; rev. A, May 2008). SNP genotypes were generated in Illumina BeadStudio software v3.2 from bead intensity data. The previously reported most significant *SORL1* SNPs for AD were selected from the literature [1, 20]. These markers included rs661057 (SNP4), rs668387 (SNP8), rs689021 (SNP9), rs641120 (SNP10), rs2070045 (SNP19),

Table 1. Characteristics of the study sample

	Control group	MCI group	AD group
Patients, n	100	166	87
Age, years	75.75 ± 5.32	74.98 ± 7.41	74.84 ± 7.52
Men:women	50:50	114:52	50:37
MMSE score	29.04 ± 1.06	26.93 ± 1.81	23.49 ± 1.93
APOE ε4 carriers, n	5	92	58
CSF $A\beta_{1-42}$, ng/l	205.46 ± 55.76	162.45 ± 54.38	144.34 ± 2.90
$pTau_{181}$, ng/l	25.27 ± 15.21	36.20 ± 18.19	42.46 ± 20.54
tTau, ng/l	69.82 ± 31.00	104.39 ± 59.78	123.01 ± 58.89
SNP4 (rs661057) TT/CT/CC	32/48/20	62/75/29	36/36/15
SNP8 (rs668389) CC/CT/TT	27/46/27	60/78/28	40/35/12
SNP9 (rs689021) GG/AG/AA	26/45/29	59/79/28	37/39/11
SNP10 (rs641120) TT/CT/CC	27/42/31	28/72/66	12/34/41
SNP19 (rs2070045) TT/GT/GG	61/34/5	110/48/8	59/26/2
SNP22 (rs1699102) TT/CT/CC	47/38/15	78/69/19	44/38/5
SNP23 (rs3824968) TT/AT/AA	49/42/9	83/70/13	48/34/5
SNP24 (rs22822649) CC/CT/TT	50/41/9	17/80/69	49/22/5
SNP25 (rs1010159) TT/CT/CC	43/43/14	69/80/17	43/39/5

Data are presented as means ± SD, unless otherwise indicated.

rs1699102 (SNP22) and rs3824968 (SNP23), rs2282649 (SNP24) and rs1010159 (SNP25). SNP23 and SNP24 are not available in the ADNI database. Therefore, they were genotyped at Washington University St. Louis as part of genome-wide association studies [30]. The present analysis was restricted to non-Hispanic Caucasians, who were identified in the clinical database and whose genotype data of *SORL1* SNPs were available. The final sample with genotype data for the present report included 353 individuals (100 controls, 166 patients with MCI, and 87 patients with AD).

Regarding the statistical analysis, a stepwise discriminant analysis, employing multiple linear regression models in PASW software v17 (SPSS Inc., Chicago, Ill., USA), was used to identify potential significant covariates for CSF tTau $pTau_{181}$ and $A\beta_{1-42}$ levels. The potential confounding variables that were tested were age, gender distribution, Mini Mental State Examination (MMSE) scores and the presence of the *APOE* ε4 allele (dichotomized into carriers and non-carriers of the allele). Subsequently, separate linear regression analysis models with the CSF parameters as dependent variables were built to assess the impact of *SORL1* SNPs on the neurodegeneration parameter concentrations after adjustment for the appropriate covariates. In order to unravel the influence of possible gene-gene interactions between the aforementioned *SORL1* SNPs and the *APOE* ε4 allele on $A\beta_{1-42}$ concentrations, the interaction parameter *SORL1 SNP genotype* × *APOE ε4 carriers/non-carriers* was fed as the independent factor together with the significant covariates detected in the first step of the analysis into a linear regression analysis model with $A\beta_{1-42}$ as the dependent factor. A Bonferroni correction for multiple comparisons was applied to the significance threshold of $p < 0.05$; this yielded a Bonferroni corrected $p < 0.006$. To compare the distributions of the dependent variables with the normal distribution, normal p-p plots of regression standardized residuals were generated, which plot the cumulative proportions of standardized residuals of the dependent variable against the cumulative proportions of the respective normal distribution. The normality assumption was supported by these plots (results not shown).

Results

Characteristics and SNP distributions of the sample are given in table 1. In the AD group, *APOE* ($p < 0.001$, n = 87), age ($p = 0.02$, n = 87), and gender ($p = 0.04$, n = 87) were associated with $A\beta_{1-42}$, and age with $pTau_{181}$ ($p < 0.01$, n = 87). In the MCI group, there was an association between *APOE* and $pTau_{181}$ ($p < 0.01$, n = 166), *APOE* and $A\beta_{1-42}$ ($p < 0.001$, n = 166), as well as *APOE* ($p < 0.01$, n = 166) and gender ($p = 0.02$, n = 166) with tTau. In the control group, *APOE* was correlated with $A\beta_{1-42}$ ($p < 0.001$, n = 100) and tTau ($p = 0.02$, n = 100), as well as *APOE* ($p < 0.01$, n = 100) and age ($p = 0.02$, n = 100) with $pTau_{181}$. The separate multivariate variance analyses yielded, after Bonferroni correction for multiple comparisons, a significant association between CSF $A\beta_{1-42}$ and the A allele of the *SORL1* SNP23 ($p = 0.003$, n = 87) in the AD group. *SORL1* SNP23 A allele carriers had lower CSF $A\beta_{1-42}$ concentrations than non-carriers (carriers vs. non-carriers: mean ± SD, 131.77 ± 35.65 vs. 154.56 ± 45.85 ng/l; fig. 1). Interestingly, the presence of

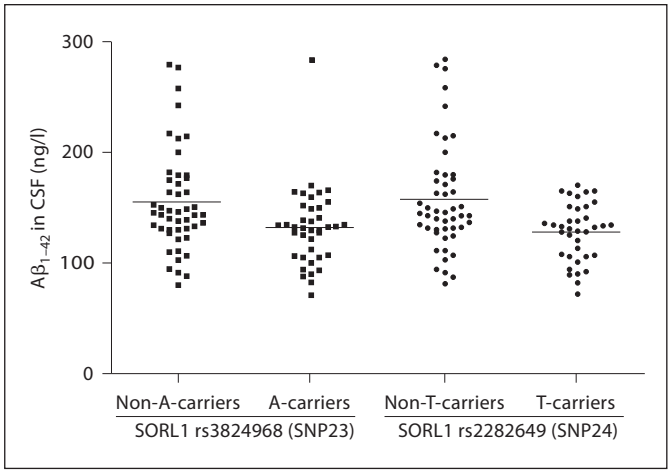

Fig. 1. CSF $A\beta_{1-42}$ concentrations in relation to *SORL1* SNPs 23 and 24 in the AS group (mean value indicated by horizontal line).

the *SORL1* SNP24 T allele was also significantly associated with CSF $A\beta_{1-42}$ levels in patients with AD ($p = 0.007$, $n = 87$). However, this association marginally failed to survive the Bonferroni correction. In carriers of the *SORL1* SNP24 T allele, lower CSF $A\beta_{1-42}$ concentrations were detected (carriers vs. non-carriers: 127.76 ± 25.74 vs. 157.20 ± 49.00 ng/l; fig. 1). Furthermore, *SORL1* SNP8 genotypes ($p = 0.04$, $n = 87$) and SNP25 genotypes ($p = 0.03$, $n = 87$) were associated with CSF $A\beta_{1-42}$ levels. Nonetheless, these associations did not remain statistically significant after Bonferroni correction. Unexpectedly, such a trend was also observed in the group of patients with MCI between $pTau_{181}$ and *SORL1* SNP24 genotypes ($p = 0.03$, $n = 166$), which did not reach statistical significance after Bonferroni correction. No further associations were detected between *SORL1* SNPs and CSF protein concentrations in any of the three study groups.

In line with the literature, the presence of the *APOE* ε4 allele was associated with lower CSF $A\beta_{1-42}$ concentrations in all three study groups ($p < 0.001$ for all groups). The interactions between the *APOE* ε4 allele and *SORL1* SNP23 genotypes ($p = 0.001$, $n = 87$), SNP24 genotypes ($p = 0.004$, $n = 84$), SNP25 genotypes ($p = 0.009$, $n = 87$), SNP8 genotypes ($p = 0.03$, $n = 87$), and SNP9 genotypes ($p = 0.04$, $n = 87$) were found to exert significant influences on CSF $A\beta_{1-42}$ concentrations in patients suffering from AD. The influence of the former two interaction factors on $A\beta_{1-42}$ remained statistically significant after Bonferroni correction. No further significant associations were observed.

Discussion

SORL1 is listed among the top 10 AD risk genes in the Alzgene.org database (accessed on February 6, 2011) [31]. In the present study, associations between variants of the *SORL1* gene and established CSF biomarkers of AD pathology were investigated in patients with probable AD and MCI, as well as healthy elderly controls. The main finding of our study is that patients with probable AD carrying the *SORL1* SNP23 A allele had lower levels of $A\beta_{1-42}$ compared with non-carriers. Moreover, a marginal association was also detected between the presence of the *SORL1* SNP24 T allele and $A\beta_{1-42}$ in patients with probable AD. Other studied *SORL1* SNPs tended to relate to altered levels of $A\beta_{1-42}$ or $pTau_{181}$. However, these associations did not survive Bonferroni correction.

A number of studies have tried to dig up biological evidence for a role of *SORL1* in AD, suggesting an influence of *SORL1* gene variants on AD endophenotypes. In contrast to our results, a study which derived its sample from the population-based Swedish Twin Registry [32] and an investigation partly using ADNI data [30, 33] both failed to detect associations between *SORL1* SNPs and CSF biomarkers of AD. Three possible reasons might be responsible for this inconsistence. Firstly, the former study significantly differed from our study in terms of gender distribution within the AD group (χ^2 test, $p < 0.001$). Our analysis revealed that gender influenced the levels of $A\beta_{1-42}$ in the AD group. This finding is in line with the previously reported association between *SORL1* gene variants and gender [13] and with reports from AD transgenic animal models indicating an impact of gender on amyloid pathology [34] Secondly, our study was restricted to individuals with a non-Hispanic Caucasian ancestry, whereas the Swedish Twin Registry Study comprised individuals drawn from the multiethnic Swedish society regardless of their origin. A recent meta-analysis on the association between variants in *SORL1* and AD showed clear deviations in the AD associated *SORL1* SNPs in the different ethnic groups [20] Thirdly, in the referenced ADNI study [30], patients with probable AD and MCI as well as healthy controls were treated as a single group, and no separate analyses were performed in each of the three groups. As a consequence it is possible that the effect of *SORL1* variants on $A\beta_{1-42}$ in the group of patients with AD was masked by the absence of such effects in the rest of the sample. A German multicenter study, which was not restricted to non-Hispanic Caucasians, identified an association between $A\beta_{1-42}$ and *SORL1* SNP21 in 153 pa-

tients with AD [35]. Such an association could not be replicated in our study sample. In addition, it should be underscored that linking gene variants with discrete variations in biological markers is a challenging task. It is possible that the investigated genetic variants exert a direct influence on the biomarker levels, but it is also plausible that the genetic variation mediates an effect through other downstream functional change or through the regulation of other genes [36]. These caveats must be borne in mind when the observed influence of *SORL1* genetic variants on $A\beta_{1-42}$ is considered or deviations in study observations are interpreted.

The detected significant influence of *SORL1* SNP23 A allele and SNP24 T allele on $A\beta_{1-42}$ was restricted to patients suffering from AD and no association between *SORL1* polymorphisms and CSF $A\beta_{1-42}$ concentrations was observed in patients with MCI. Although the clinical entity of MCI represents in many cases a prodromal phase of AD, it is not exclusively caused by AD and it has a variable prognosis [37–38]. Since the diagnosis of MCI in our study was based on clinical criteria, the MCI group probably did not exclusively encompass patients with incipient AD in whom an association between *SORL1* SNPs and $A\beta_{1-42}$ could be expected. As a consequence it can be reckoned that the presence of the aforementioned alleles may foster alterations, for instance in SORL1 shedding or intracellular concentrations [22, 28, 39], which exclusively occur in patients with AD pathology.

Decreased CSF $A\beta_{1-42}$ levels are generally found in AD and it has been reported that $A\beta_{1-42}$ concentrations decrease with disease progression [35, 40], although not in all published studies [41]. Thus, it might be argued that reduced levels of $A\beta_{1-42}$ in patients with AD possessing the *SORL1* SNP24 T allele or the *SORL1* SNP23 A allele are attributable to differences in the severity of amyloid pathology. However, in line with previous observations [35] no impact of MMSE scores, mirroring clinical disease severity, on CSF concentrations of $A\beta_{1-42}$ was observed in our sample.

The revealed impact of gene-gene interactions between *SORL1* genetic variants and the presence of the *APOE* ε4 allele on $A\beta_{1-42}$ provides further evidence for possible interactions between *APOE* and *SORL1*, which may affect the pathogenesis of AD. SORL1 binds multiple ligands including APOE and induces the endocytosis of APOE-containing lipoproteins [42]. Interactions between SORL1 and APOE might interfere with the formation of the APOE-Aβ complex, which has been detected in the CSF, and this process may foster the deposition of Aβ in brain by increasing unbound Aβ species [28].

The trend of *SORL1* SNP24 to affect the levels of $pTau_{181}$ in patients with MCI was unexpected since SORL1 has been shown to be implicated in the sorting of APP and in its interactions with the secretases [22] and not in the processes of hyperphosphorylation of tau. Though it cannot be ruled out with final certainty that this observation is due to a type I error, this finding is intriguing especially in the light of the absence of such an association in patients with AD. Further investigations are warranted, since *SORL1* SNP24 may be involved in the interrelation between the amyloid cascade and the hyperphopshorylation processes of tau [43] or hypothetically through gene-gene interactions in the molecular mechanisms inducing tau hyperphosphorylation in patients suffering from pathologies other than AD (e.g. frontotemporal lobar degeneration, Lewy-body pathology), which also lead to the clinical entity of MCI.

Though relatively large for a CSF investigation, it can be claimed that the present study sample is of limited size. However, our findings are in line with previous publications, which reported that *SORL1* exerts a relevant influence on amyloid metabolism and thus on AD risk and pathology [20–23]. Nonetheless, replication studies with independent larger samples are warranted.

To conclude, our findings show that *SORL1* variants have a significant influence on brain amyloid pathology within the framework of AD. Therefore, our results provide further in vivo validation of *SORL1* as a risk gene for AD and stress the need for subsequent studies to unveil its pathogenic and clinical relevance [44].

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