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ORIGINAL PAPER

SORL1 genetic variants and cerebrospinal fluid biomarkers of Alzheimer's disease

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Abstract The neuronal sortilin-related receptor with A-type repeats (SORL1, also called LR11 or sorLA) is involved in amyloidogenesis, and the *SORL1* gene is a major risk factor for Alzheimer's disease (AD). We investigated AD-related CSF biomarkers for associations with *SORL1* genetic variants in 105 German patients with mild cognitive impairment (MCI) and AD. The homozygous CC-allele of single nucleotide polymorphism (SNP) 4 was associated with increased Tau concentrations in AD, and the minor alleles of SNP8, SNP9, and SNP10 and the haplotype CGT of these SNPs were associated with increased SORL1 concentrations in MCI. SNP22 and SNP23, and the haplotypes TCT of SNP19-21-23, and TTC of SNP22-23-24 were correlated with decreased Aβ42 levels in AD. These results strengthen the functional role of *SORL1* in AD.

Keywords Amyloid cascade · Biomarker · Mild cognitive impairment · Dementia · Genetic risk

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Introduction

The neuronal sortilin-related receptor with A-type repeats (SORL1, also called LR11 or sorLA) has been linked to protective effects against amyloidogenesis in Alzheimer's disease (AD) [1]. SORL1 seems to be capable of regulating the intracellular trafficking and processing of amyloid precursor protein (APP) by impairing the cleavage of APP through α-secretase, β-secretase (β-site APP-cleaving-enzyme-1, BACE1), and γ-secretase in a way that leads to reduced levels of soluble APP (sAPP) and amyloid beta protein (Aβ), the major component of amyloid plaques [2]. In line with this theory, reduced SORL1 expression has been demonstrated in human brains with amyloid pathology [3]. *SORL1* gene variants can reduce SORL1 expression or function and thereby increase Aβ production as well as AD risk [4]. Recently, multiple single nucleotide polymorphisms (SNP) within the *SORL1* gene have emerged as risk factors for sporadic AD in a variety of populations. Although replications are inconsistent, implicating influences of multi-ethnicity and allelic heterogeneity [4, 5], several independent studies have observed that significant associations were located in 2 distinct regions: the 5′ end and the 3′ end of the *SORL1* gene [4]. So far, only few studies have reported associations of *SORL1* variants with cerebrospinal fluid (CSF) endophenotypes in

AD [6–8]. In the present study, we have investigated eleven AD risk SNPs in a German sample to evaluate the effect of *SORL1* variants on the CSF levels of Aβ42, total TAU, sAPPα, sAPPβ, and SORL1 protein as well as on the CSF activity of BACE1.

Methods

The study population consisted of 44 Caucasian patients with probable AD according to NINCDS-ADRDA criteria and 61 patients with mild cognitive impairment (MCI) according to the revised International Working Group on MCI consensus criteria recruited from a university-based memory clinic in compliance with standardized guidelines [9, 10]. Written informed consent was obtained according to the 1975 Helsinki Declaration and the study protocol was approved by the ethics committee of the medical faculty at Technische Universität München.

The CSF concentrations of Aβ42, Tau (Innogenetics, Zwijndrecht, Belgium) as well as sAPPα and sAPPβ (Immuno-Biological Laboratories Co. Ltd., Gunma, Japan) were measured by enzyme-linked immunosorbent assay (ELISA) as described previously [11]. BACE1 activity in CSF was determined as the fluorescence signal of europium, which is proportional to the activity of BACE1, by a commercial BACE1 assay kit (Perkin Elmer Inc., Turku, Finland) according to a standard protocol [12, 13]. SORL1 concentration in CSF was quantified by ELISA in the laboratories of Sekisui Medical Co Ltd. (Ryugasaki, Japan) according to published procedures [14]. Genomic DNA was extracted from whole blood, and the apolipoprotein E *(APOE)* genotype was determined by a polymerase chain reaction and restriction enzyme digestion, simultaneously utilizing two distinct restriction enzymes, according to standard procedures.

Five marker SNPs at the 5′ end of the *SORL1* gene, rs661057 (SNP4), rs11600875, rs668387 (SNP8), rs689021 (SNP9), and rs641120 (SNP10), as well as 6 markers at the 3′ end, rs2070045 (SNP19), 21rs18ex26 (SNP21), rs1699102 (SNP22), rs3824968 (SNP23), rs2282649 (SNP24), and rs1010159 (SNP25), were selected from the published data based on their significant association with AD risk in Caucasian populations [4, 5, 7]. The genotypes were determined using TaqMan assays (SNP assays-on-demand) on a StepOne analyzer with StepOne software v2.1 (all assays, machine, and software from Applied Biosystems, Carlsbad, CA, USA).

Deviations from the Hardy–Weinberg equilibrium to exclude population stratification were tested for all 11 *SORL1* SNPs (http://www.oege.org/software/hwe-mr-calc.shtml) [15]. The sample size required to detect a significant difference between carriers and non-carriers with 90% power and a type I error rate of 0.05 was estimated in G-Power v3.1.3 [16] at $N = 14$ per group according to previous results [7] (mean Aβ42 concentration difference between carriers and non-carriers of the *SORL1* SNP23 T-allele of 56.60 ng/L with a shared standard deviation of 41.59 ng/L).

Patient characteristics were compared between the AD and the MCI groups using parametric tests for normally distributed data in the Predictive Analytics Software package (PASW) v18 (The SPSS Inc., Chicago, IL, USA). Analysis of covariance (ANCOVA) in PASW was used to test for the genotypic or allelic effect of all 11 SNPs of interest on CSF biomarker concentrations, adjusting for age, gender, and *APOE*, which was coded as a dichotomous variable for carriers and non-carriers of the ε4 allele. In addition, three-marker haplotypes of SNP8/SNP9/SNP10, SNP19-21-23, SNP22-23-24, and SNP23-24-25, again selected from the literature according to their linkage disequilibrium (LD) and the significant association with AD risk, were reconstructed and assessed with the Haplo.stats package in R software v2.1 (http://www.r-project.org/). The associations between *SORL1* haplotypic variants and CSF biomarker concentrations were examined in multivariate linear models after adjustment for age, gender, and *APOE* ε4 carrier status. Only genetic frequency higher than 5% was considered. Significance was set at $p < 0.05$. The study was driven by a priori hypotheses; therefore, no correction for multiple comparisons was applied [17] in accordance with similar previous studies [18].

Results

The demographic and clinical characteristics are summarized in Table 1; genotype and allele frequencies are provided in the Supplementary Tables 1 and 2. None of the 11 SNPs showed significant deviation from the Hardy–Weinberg equilibrium in the AD group; in the MCI group, deviation was only observed for SNP21 (Supplementary Table 1). The APOE ε4 allele was associated with lower Aβ42 levels in the MCI group ($p < 0.001$, $N = 61$). The single-marker analysis revealed significant associations between Aβ42 concentrations and the synonymous coding SNP22 and SNP23 at the 5′ end of the gene in the AD group. Carriers of the SNP22 C-allele ($p = 0.04$, $N = 22$) and SNP23 A-allele ($p = 0.04$, $N = 23$) had lower levels of Aβ42 than non-carriers (Supplementary Table 3). In the haplotype analyses, we observed associations of haplotype TCT (frequency 36.9%) of SNP19-21-23 ($p = 0.04$, $N = 38$) and TTC (frequency 24.7%) of SNP22-23-24 ($p = 0.04$, $N = 38$) with decreased CSF Aβ42 levels in the AD group (Fig. 1a). At the 3′ end of the gene, a significant association between the homozygous minor allele CC of

Table 1 Characteristics of the study sample

	AD (N = 44)	MCI (N = 61)	p value
Age at lumbar puncture*	66 (9.6)	65 (8.7)	0.44
Age at onset of symptoms*	6 (8.8)	63 (8.8)	0.62
Men:women	23:21	35:26	0.81
Schooling, years*	13 (2.9)	1 (2.7)	0.91
MMSE score*	23 (3.1)	27 (1.9)	<0.001**
ApoE4 carrier, n (%)	26 (59.1%)	27 (44.3%)	0.55
Aβ42 (ng/L)*	551.8 (233.52)	771.1 (350.84)	<0.001**
TAU (ng/L)*	627.8 (384.24)	383.9 (255.87)	<0.001**
sAPPα (ng/mL)*	287.1 (159.21)	332.2 (166.75)	0.17
sAPPβ (ng/mL)*	897.0 (402.65)	1047.2 (493.75)	0.10
BACE1 (FU/μL)*	8333.06 (2585.76)	9381.67 (3239.94)	0.08
SORL1 (μg/L)*	11.9 (4.69)	11.9 (4.28)	0.95

SNP single nucleotide polymorphism, *CSF* cerebrospinal fluid, *Aβ42* amyloid beta 42, *sAPPα, sAPPβ* alpha- and beta-soluble amyloid precursor protein, *BACE1* β-site APP-cleaving-enzyme-1, *SORL1* sortilin-related receptor with A-type repeats, *AD* Alzheimer's disease, *MCI* mild cognitive impairment, *FU* fluorescence units

* Mean (SD), ** significant at $p < 0.05$

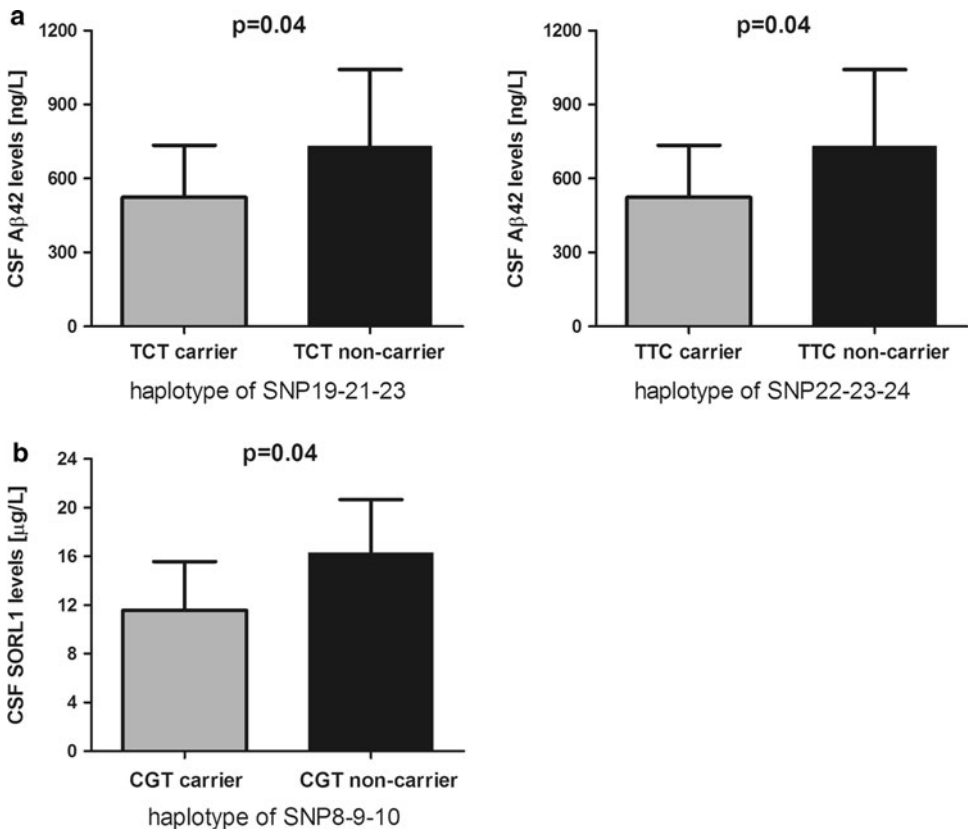

Fig. 1 **a** Effects of SORL1 haplotypes on CSF Aβ42 levels in the AD group; and **b** effects of SORL1 haplotypes on CSF SORL1 levels in the MCI group

SNP4 and increased Tau levels was observed (p = 0.03, N = 7) in the AD group. No association was found in heterozygous carriers, which points to a strong gene dosage effect (Supplementary Table 4). In the MCI group, at the 3′ end of the gene, SNP8, SNP9, and SNP10 showed significant associations with CSF SORL1 levels in a way that minor allele carriers had increased SORL1 concentrations (SNP8 TT: p = 0.04; SNP9 AA: p = 0.04; SNP10 CC: p = 0.04) (Supplementary Table 5). Again, these associations were driven by the homozygous carriers of the minor alleles of each of the three SNPs. In the haplotype analyses, a significant association between reduced CSF SORL1

levels was found with haplotype CGT (frequency 22.5%) of SNP8-9-10 in the MCI group ($p = 0.04$, $N = 55$) (Fig. 1b). There were no associations between sAPP levels and BACE1 activity with any of the SNPs or haplotypes.

Discussion

SORL1 regulates the intracellular sorting of APP and hinders APP cleavage and thereby Aβ production [1, 2]. The *SORL1* gene has been identified as a major risk factor for sporadic AD [4]. In the present study, associations between *SORL1* genetic variants and CSF levels of Aβ42, Tau, and SORL1 were observed at two distinct gene regions in patients with MCI and probable AD. Associations between *SORL1* genetic variants and CSF sAPPα and sAPPβ concentrations as well as BACE1 activity were not observed.

In the AD group, lower CSF Aβ42 levels were found in carriers of the exonic SNP22 (C-allele) and SNP23 (A-allele), and haplotypes TCT of SNP19-21-23 and TTC of SNP22-23-24 at the 3′ gene end. It has been demonstrated that SNP19 is in strong linkage disequilibrium with SNP22 and SNP23 in various Caucasian cohorts [19]. SNP21, on the other hand, has been reported as AD-related *SORL1* polymorphism in a German cohort [3] and the haplotype TGA of SNP19-21-22 correlated with lower CSF Aβ42 in AD before [7]. This finding was not replicated in our work, probably due to the low frequency of these markers in our sample (Supplemental Tables 1 and 2). In the initial genetic association study [4], the SNP22 C-allele, SNP23 T-allele, and haplotype CTT of SNP22-23-24 were associated with an increased risk for AD. In contrast, in our study, reduced Aβ42 levels were correlated with genotypes and haplotypes consisting of the alternative alleles. This inconsistency suggests that *SORL1* allelic heterogeneity and ethnic variants may also play a role [20]. Since exonic SNPs of the *SORL1* gene are present in the mature mRNA, they could directly alter translation and thus protein levels [21]. Therefore, the 3′ end SNPs, in particular the synonymous coding SNPs, might directly influence the function of the SORL1 protein and thereby alter the CSF levels of Aβ42.

We also found that Tau levels were associated with CC homozygotes of SNP4 in the AD group. The C-allele of SNP4 has been associated with AD among Caucasian populations in multiple independent cohorts and genome-wide association studies before [4, 5, 20, 22–25]. Although the present work is a case-only study that precludes a statement on the association of *SORL1* SNPs with AD risk per se, our data still confirm that the SNP4 C-allele is significantly associated with upregulated CSF Tau levels, which in turn are correlated to neurodegenerative pathology.

SORL1 protein is considered an important regulator of amyloidogenesis since reduced SORL1 levels may lead to dysfunctional retromer trafficking and upregulated cerebral Aβ production [1]. It remains inconclusive how reduced SORL1 protein expression in AD brain is related to alterations of SORL1 in CSF. It has been reported that the expression of SORL1 protein is reduced in brain tissue from patients with sporadic AD [3]. The two published CSF studies are inconsistent in this regard, reporting both decreased [26] and increased [27] SORL1 levels in AD compared with healthy controls. We identified associations between CSF SORL1 concentrations and three AD risk marker SNPs in the MCI group; the homozygous minor allele carriers of the intronic SNP8 (T-allele), SNP9 (A-allele), and SNP10 (A-allele) had increased SORL1 concentrations in CSF. Moreover, the haplotype analysis confirmed that a three-marker haplotype CGT (a combination of the major alleles) of SNP8/SNP9/SNP10 was associated with reduced CSF SORL1 levels in the MCI group. These three SNPs have been confirmed as the most significant AD risk markers within the *SORL1* gene in Caucasian samples in a recent meta-analysis including 11,592 cases and 17,048 controls [28]. The association of three 5′ end SNPs in our study with CSF SORL1 concentrations is consistent with the allelic disease association in this meta-analysis. Since MCI often represents pre-dementia AD, our data may suggest that the influence of *SORL1* genetic variants is particularly relevant in early clinical AD stages.

Our current study extends the existing literature on associations between SORL1 genetic variants and AD biomarkers, thereby supporting the role of SORL1 as an important influence factor on AD pathogenesis. Limitations include the rather small study sample and the lack of longitudinal data as well as neuropathological verification of the diagnoses. Therefore, replication studies with independent larger samples are warranted. We did not aim to replicate the results from previous genetic association studies; neither did we aim to identify new risk SNPs, and no control group was included because of this study design choice. Lack of consistent replication of genetic findings is a common occurrence in the study of complex phenotypes and may be indicative of inadequate power resulting from small sample size and genetic or environmental heterogeneity. The use of CSF biomarkers for genetic studies of AD may provide increased statistical power and important insight into the biological mechanisms by which these variants modulate disease risk. In any study attempting to associate genetic information with pathology, the exact effect of genetic variants on phenotypic variation often remains unclear. On the one hand, the genetic variants may have a direct effect on markers of pathology; on the other hand, neighboring SNPs in LD with the variant tested or other downstream factors may also have an influence.

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Conflict of interest The authors declare that they have no conflict of interest.

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