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Short communication

The *SORL1* polymorphism rs985421 may confer the risk for amnestic mild cognitive impairment and Alzheimer's disease in the Han Chinese population

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HIGHLIGHTS

- The 'A' allele of rs985421 in the *SORL1* gene may increase the risk for SAD and aMCI in the Han Chinese population.
- The 'A' allele of rs985421 might be an *ApoE ε4*-independent risk factor for SAD.
- Future research should be performed to find other possible causative variants.

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ABSTRACT

Although the pathogenetic mechanisms driving Alzheimer's disease (AD) are unclear, genetic variations may play an important role. Previous studies have identified that single nucleotide polymorphisms (SNPs) in the sortilin-related receptor, L (DLR class) A repeats containing (*SORL1*) gene are associated with AD or amnestic mild cognitive impairment (aMCI) patients. However, the association of *SORL1* variants with AD or aMCI susceptibility in the Han Chinese population has not been adequately reported. Thus, we conducted a case-control study in 106 sporadic AD patients, 67 aMCI patients, and 179 healthy control Han Chinese subjects to determine whether *SORL1* genetic variations alter the risk for AD or aMCI. Using the LDR–PCR method to genotype five polymorphisms in *SORL1*, we found significant associations (for AD: OR = 1.968, 95% CI = 1.273–3.042; for aMCI: OR = 2.210, 95% CI = 1.353–3.610) between the 'A' allele of the *SORL1* SNP rs985421 and AD and aMCI, which may represent an *ApoE ε4*-independent risk factor for SAD. These findings suggest that the *SORL1* SNP rs985421 may alter the risk for sporadic AD and aMCI in the Han Chinese population.

1. Introduction

Alzheimer's disease (AD) is the most common polygenic multifactorial disease and is characterized by the interaction of both genetic and environmental factors [18]. Autosomal dominant mutations in the amyloid-β protein precursor (*AβPP*), presenilin 1 (*PSEN 1*), and presenilin 2 (*PSEN 2*) genes are involved in early-onset familial Alzheimer's disease (FAD) before 60 years of age. The ε4 allele of the apolipoprotein E gene (*ApoE ε4*) is the most important susceptibility gene for late-onset Alzheimer's disease (LOAD), but it is neither necessary nor sufficient for AD [3,15]. Thus, it is important to identify additional risk genes other than *ApoE ε4*. Previous genome-wide association studies (GWAS) have identified several genomic regions that are associated with the AD susceptibility, including the sortilin-related receptor, L (DLR class) A repeats containing (*SORL1*, also called *LR11* or *sorLA*) gene in European populations [14]. Moreover, the *SORL1* expression levels in the cerebrospinal fluid (CSF) and brain tissue of mild cognitive impairment (MCI) patients might be modulated by the SNPs within the *SORL1* gene [8,16]. It is well known that MCI is a transitional state between the cognition of normal aging and mild dementia including amnestic MCI (aMCI) and non-amnestic MCI. Most aMCI patients are considered to have a prodromal stage of AD that will progress to AD at a rate of 10–15% per year, which is higher than that in healthy controls, who develop AD at a rate of 1–2% per year [12].

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Table 1
Demographic characteristics of the study subjects.

	Control *n* (%)	SAD *n* (%)	aMCI *n* (%)
Total	179	106	67
Female	96 (53.6)	56 (52.8)	38 (56.7)
Male	83 (46.4)	50 (47.2)	29 (43.3)
Age	78.2 ± 8.7	76.4 ± 10.5	76.8 ± 8.5
MMSE	27.6 ± 3.1	16.1 ± 6.4	24.8 ± 3.5

Therefore, an aMCI genetic association study provides important information into the risks of developing dementia.

SORL1 is a member of the low-density lipoprotein receptor family that reduces amyloid-β (Aβ) production by regulating the intracellular transport and processing of APP [1,2,6]. Both genetic and biological evidence indicates that *SORL1* could have a role in AD susceptibility. Using meta-analysis methods, we further identified *SORL1* variants associated with sporadic Alzheimer' disease (SAD) [9]. Interestingly, Wen et al. found several *SORL1* variants associated with LOAD, which were not previously reported [19]. The current study was designed to evaluate the association of these SNPs with aMCI and SAD in the Han Chinese.

2. Materials and methods

2.1. Study population

The cohort used in this study included 106 SAD patients (56 women and 50 men aged 76.4 ± 10.5 years at recruitment), 67 aMCI patients (38 women and 29 men aged 76.8 ± 8.5 years at recruitment), and 179 unrelated healthy control subjects (96 women and 83 men aged 78.2 ± 8.7 years at recruitment) (Table 1), who were drawn from a Chinese population of Han descent.

In the patient sample, a clinical diagnosis of probable AD was established according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS–ADRDA). The following previously published criteria were used for proper diagnosis [12,13]: (1) memory complaint, preferably independently corroborated; (2) impaired memory function for age and education, such as a score of less than or equal to 1.5 standard deviations normalized for age and education; (3) preserved general cognitive function, measured using a mini-mental state examination (MMSE) with a score of 24 or higher; (4) a clinical dementia rating (CDR) score of 0.5; (5) intact daily living activities; and (6) not demented, or insufficient to meet the NINCDS–ADRDA criteria for AD. Participants with a family history of AD, other neurological or psychiatric illnesses or other with dementia were excluded. The control groups were selected from the Wuxi Mental Health Center, and these participants, who had no memory complaint or cognition dysfunctions, were confirmed to be healthy and neurologically normal according to their medical history, general examinations, and MMSE.

This study was approved by the ethics committees of the Wuxi Health Mental Center, and either the patients themselves or their guardians signed informed consents. We used the following criteria to evaluate whether the participants had the capacity to consent when this ability appeared to be compromised: (1) the patient had the ability to understand; (2) the patient had the ability to reason; and (3) the patient had the ability to make rational decisions. The patients' guardians were asked to complete the consent form on the patients' behalf, if the participants were asked to complete the consent form more than twice. Healthy subjects were recruited through advertisement. Based on the self-reporting of their paternal grandparents and their own place of birth, we excluded anyone who was not born in Jiangsu or whose family was not born in Jiangsu. Before being enrolled in the study, each healthy subject was required to sign a consent form.

2.2. DNA extraction

Blood samples were collected from all participants using K2EDTA tubes, and a Blood Genotyping DNA Extraction Kit (Tiangen Biotech., Beijing, China) was used to exact genomic DNA from 150 μl of peripheral blood. DNA samples were then stored at −80 °C for the purpose of genotype analysis.

2.3. SNP genotyping

The location of five genotyped SNPs within the *SORL1* gene is shown in Fig. 1. The genotype of each SNP was analyzed by the Shanghai Biowing Applied Biotechnology Co., Ltd. (www.biowing.com.cn) using the ligase detection reaction-polymerase chain reaction (LDR–PCR) method [10,17,20]. Genomic DNA extracted from clinical samples was first subjected to multiplex PCR to obtain a PCR product that included SNPs. This PCR product and the LDR probes were then subjected to a multiplex LDR reaction with a DNA sequencer to detect the products. To validate this procedure, approximately 10% of the samples were randomly selected and retested using the same process. The results in the retested samples were consistent with those obtained in the larger sample group.

2.4. Statistical analysis

Our statistical analyses were performed using the PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) and SPSS 17.0 software (IBM Corporation, California, USA) and included association studies, Hardy–Weinberg equilibrium (HWE) tests, and the calculation of genotype and allele frequencies in SAD, aMCI and healthy control subjects. Haplotype analysis was conducted using the

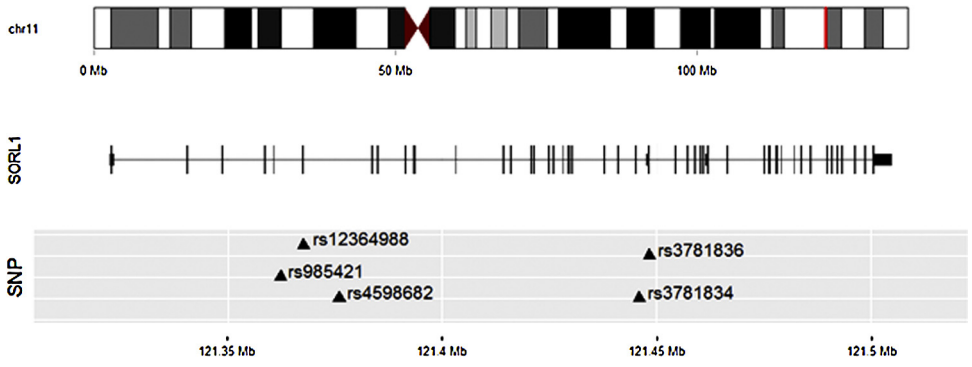

Fig. 1. Chromosome locations of the five genotyped SNPs.