Genetic polymorphisms of lipid metabolism gene SAR1 homolog B and the risk of Alzheimer’s disease and vascular dementia

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KEYWORDS
Alzheimer’s disease; genetic polymorphism; lipid metabolism; SAR1 homolog B; vascular dementia

Background/purpose: Lipid metabolism is involved in beta amyloid generation, which has been related with the progression of Alzheimer’s disease (AD). No study has explored the association between polymorphisms of SAR1 homolog B (SAR1B) and the risk of dementia previously.

Methods: This is a case–control study. A total of 279 AD and 117 vascular dementia (VaD) patients were recruited from neurology clinics at three teaching hospitals in Taiwan from 2007 to 2010. Controls (n = 466) were recruited from the elderly health checkup program and volunteers in the hospital during the same time interval. Three common (frequency ≥ 5%) haplotype-tagging single nucleotide polymorphisms were selected from the lipid metabolism gene SAR1B to assess its association with AD and VaD.

Results: Homozygous variants of rs11948613 were associated with a decreased AD risk (CC vs. TT: adjusted odds ratio = 0.39, 95% confidence interval = 0.15–0.98) with a population attributable risk of 26.7%. This association decreased further in apolipoprotein E ε4 (ApoE ε4) noncarriers (adjusted odds ratio = 0.28, 95% confidence interval = 0.09–0.91). No association was found for VaD. Two common haplotypes (with a cumulative frequency of 95.7% in controls) were identified for SAR1B, and no association was found for AD or VaD.
Simultaneous screening using rs11948613 and ApoE ε4 significantly improved the sensitivity of ApoE ε4 alone (from 0.40 to 0.75).

Conclusion: SAR1B polymorphisms were associated with AD risk; results were not significant after correction for multiple tests. Simultaneous screening using SAR1B rs11948613 and ApoE ε4 status offered a better sensitivity for AD screening.

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Introduction

Dementia is characterized by a significant loss in cognitive function. In Taiwan, the age-adjusted prevalence of all-cause dementia was 8.04% based on a recent national survey in 2011–2013.1 In the United States, the incidence of Alzheimer’s disease (AD), the most common type of dementia in the elderly, was 1.4% in 1995 and estimated to reach 4.6% in 2050.2 AD was also the sixth leading cause of death among the elderly in 2007.3 In addition, dementia contributes to 17% of disability prevalence according to the report of World Health Organization in 2004. Therefore, dementia is an important health issue in the elderly.

The SAR1B gene was first cloned in 20024 and is located at chromosome 5q31.1. The protein encoded by SAR1B is a small GTPase, which can be activated by the guanine nucleotide exchange factor prolactin regulatory element binding. It is involved in protein transportation from the endoplasmic reticulum to the Golgi (http://www.ncbi.nlm.nih.gov/gene/51128). The updated study related to SAR1B supports the importance of this gene in organs (e.g., liver, intestine, skeletal muscle, and heart) involved in lipid transport and/or calcium trafficking in mice.5 The dysfunction of SAR1B has been related to chylomicron retention disease,6,7 an autosomal recessive disorder with severe fat malabsorption, deficiency of fat-soluble vitamins, low blood cholesterol levels, and a selective absence of blood chylomicrons.6,8,9 In addition, metabolic syndrome, dyslipidemia, and hypercholesterolemia have been related to cognitive impairment,10–12 and pathogenesis of AD13–15 and vascular dementia (VaD).16,17 Therefore, it is possible that the variations of SAR1B may affect lipid metabolism or facilitate the formation and aggregation of beta amyloid (Aβ) and tau protein,18,19 which then increase the risk of dementia.

The SAR1B gene plays a major role in lipid metabolism. However, previous genome-wide association studies failed to identify this gene probably because of (1) the high false negative rate as a result of insufficient statistical power and (2) the fact that study populations mainly consisted of white individuals. This study was aimed to explore the association between SAR1B polymorphisms and the risk of AD and VaD in a Taiwanese elderly population. Because apolipoprotein E (ApoE) ε420–25 and vascular risk factors (e.g., hypertension, type 2 diabetes, and hyperlipidemia)1,13,14,16,26–28 are important risk factors of AD, stratification analyses were performed to assess how these factors affect the association described above.

Materials and methods

Study population

This was a case–control study. A total of 279 AD and 117 small-vessel VaD patients were recruited from neurology clinics at three teaching hospitals in northern Taiwan from 2007 to 2010. Controls (n = 466) were recruited from the elderly health checkup program and volunteers of the hospitals during the same time interval. All study participants were aged ≥60 years. Participants were excluded if they had a history of depression, Parkinson’s disease, hemorrhagic stroke, cerebral infarction, or brain tumor, or had dementia subtypes other than AD or small-vessel VaD. This study was approved by the Institutional Review Boards of En Chu Kong Hospital, Cardinal Tien Hospital, and the National Taiwan University Hospital in Taipei, Taiwan. Written informed consent was obtained from each study participant. Consent from the legal guardian/next of kin/caregiver was obtained when the patient had a serious cognitive impairment. A self-reported questionnaire was administered to collect information on demography, dementia status, lifestyle (e.g., smoking status, alcohol consumption, and exercise), and comorbidity.

Dementia evaluation

At each hospital, one neurologist performed clinical examinations to screen potential dementia cases. Mini-mental State Examination29 and Clinical Dementia Rating30 were performed to assess the patients’ cognitive function. The diagnosis of dementia was evaluated based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.31 Head magnetic resonance imaging or computed tomography was taken to exclude participants with organic lesions. Diagnosis of probable (typical AD presentation) AD was based on the National Institute of Neurological and Communicative Disease and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria.32 Diagnosis of small-vessel VaD was made according to the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria.33 Because of the different etiologies between large- and small-vessel dementia, only VaD patients with small-vessel related stroke (e.g., lacunar infarction and leukoaraiosis) were included. The cognitive function of controls was assessed using the
Short Portable Mental Status Questionnaire to exclude participants with possible dementia and other mental disorders.

Single nucleotide polymorphism selection and genotyping assay

Three common (frequency  5%) single nucleotide polymorphisms (SNPs) in SAR1B gene were identified from Han Chinese in Beijing genotype data of the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/). Haploview (http://www.broadinstitute.org/haploview/haploview) was used to define haplotype block by applying the modified Gabriel algorithm. 35, 36 Three haplotype-tagging SNPs (htSNPs) (rs7728741, rs2305049, and rs11948613) were selected by the TagSNP program. 37

Blood samples were collected in tubes containing EDTA for genotyping. After centrifugation, genomic DNA was extracted from buffy coat by using QuickGene-Mini80 kit (Fujifilm, Tokyo, Japan) and then stored in a −80°C freezer. Genotypes were determined with TaqMan Genomic Assays using the ABI 7900 HT fast real-time PCR system (Applied Biosystems, Foster City, CA, USA). ApoE diplotypes (ε2/ε2, ε3/ε3, ε2/ε4, ε3/ε4, ε4/ε4) were determined by ApoE 112 (rs429358) and ApoE 158 (rs7412). 38 Genotypes of ApoE SNPs were determined using the assay developed by Chapman et al. 39 Genotyping success rate was > 95% for each SNPs except rs2305049 (93%). Quality control samples were replicates of 5% of study participants, and the concordance rate was 100%.

Statistical analysis

The Hardy–Weinberg equilibrium test was performed among controls for each SNP to examine possible genotyping error and selection bias. Haplotype frequencies were estimated using HAPSTAT (http://dlin.web.unc.edu/software/hapstat/). To control for the confounding effect of age, the study participants were stratified by an age interval of 5 years, and cases and controls were compared within each stratum in the multivariable analysis. We also adjusted for age in the multivariable regression model in order to control for residual confounding due to age within each age stratum. Conditional logistic regression models were used to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs) in participants carrying either one or two versus zero copies of minor allele of each SNP. Age, sex, education, and ApoE ε4 status were adjusted in the models as they are important covariates. The type I error rate was controlled by Bonferroni correction for the association between SAR1B SNPs and dementia risk.

This study further explored how ApoE ε4 status or vascular risk factors (hypertension, type 2 diabetes, and hypercholesterolemia) modified the association between SAR1B polymorphisms and the risk of AD or VaD by using the likelihood ratio test. Stratified analyses were performed by these vascular risk factors to assess the association between SAR1B polymorphisms and the risk of dementia (AD or VaD). SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for statistical analyses, and all statistical tests were two-sided.

### Table 1 Characteristics of the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>AD (n = 279)</th>
<th>VaD (n = 117)</th>
<th>Controls (n = 466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>79.1 ± 7.0*</td>
<td>79.1 ± 6.5*</td>
<td>72.8 ± 6.0</td>
</tr>
<tr>
<td>BMI at age 40s (kg/m²)</td>
<td>22.6 ± 3.1</td>
<td>24.4 ± 3.0*</td>
<td>22.3 ± 2.8</td>
</tr>
<tr>
<td>Female</td>
<td>180 (65)*</td>
<td>67 (57)</td>
<td>244 (52)</td>
</tr>
<tr>
<td>Education ≤6 y</td>
<td>140 (51)*</td>
<td>68 (58)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>6–12 y</td>
<td>96 (35)</td>
<td>36 (31)</td>
<td>185 (40)</td>
</tr>
<tr>
<td>&gt;12 y</td>
<td>40 (14)*</td>
<td>13 (11)</td>
<td>228 (49)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>64 (23)</td>
<td>32 (27)*</td>
<td>80 (17)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>35 (13)</td>
<td>20 (17)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>108 (39)*</td>
<td>79 (68)</td>
<td>247 (53)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>50 (18)*</td>
<td>27 (23)</td>
<td>140 (30)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>50 (18)</td>
<td>41 (35)*</td>
<td>63 (14)</td>
</tr>
<tr>
<td>ApoE ε4 carrier</td>
<td>111 (40)*</td>
<td>26 (22)*</td>
<td>69 (15)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD.

*p < 0.05 for comparing cases (AD or VaD) with controls. AD = Alzheimer’s disease; ApoE ε4 = apolipoprotein E ε4; BMI = body mass index; VaD = vascular dementia.

Simultaneous screening for AD using ApoE ε4 and SAR1B SNPs was performed. The population attributable risk (PAR) was estimated with the following equation:

\[
PAR = \frac{100 \times p(\text{odds ratio} – 1)}{1 + [p(\text{odds ratio} – 1)]}, (1)
\]

where \( p \) is the prevalence of genotypes associated with AD among controls. 41 Joint PAR was calculated to estimate the proportion reduction in AD if not carrying variant alleles using the following equation:

\[
1 – [\text{II}(1 – \text{PARi})], (2)
\]

where PARi is the individual PAR for each associated SNP calculated under the full model. 42

Results

Characteristics of the study population

This study included 279 AD, 117 VaD cases, and 466 controls (Table 1). As compared with controls, AD patients were older (age: 79.1 years vs. 72.8 years), included more females (65% vs. 52%), had a lower education (≥ 6 years of education: 51% vs. 11%), were less likely to have a history of hypertension (39% vs. 53%) and hypercholesterolemia (18% vs. 30%), and were more likely to be ApoE ε4 carriers (40% vs. 15%, Table 1). As compared with controls, VaD patients were older (79.1 years vs. 72.8 years), had a higher body mass index at age 40s (24.4 kg/m² vs. 22.3 kg/m²), and were more likely to be cigarette smokers (27% vs. 17%), to have a history of type 2 diabetes (35% vs. 14%), and to be ApoE ε4 carriers (22% vs. 15%, Table 1).
SAR1B polymorphisms and dementia risk

Three common htSNPs in the SAR1B gene were identified, and all of them were in Hardy–Weinberg equilibrium among controls (Table 2). Homozygous variants of SAR1B rs11948613 were associated with decreased AD risk (CC vs. TT: AOR = 0.39, 95% CI = 0.15–0.98; Table 3), which lost statistical significance after correction for multiple tests. By contrast, SAR1B polymorphisms were not associated with the VaD risk (Table 4). Three common htSNPs spanning SAR1B formed one haplotype block, which was determined using the modified Gabriel et al algorithm. Two common haplotypes with a cumulative frequency of 95.7% in controls were identified in SAR1B. None of the common haplotypes was associated with risk for AD (HAP1 TGTA: AOR = 1.40, 95% CI = 0.83–2.38; HAP2 CTCA: AOR = 0.86, 95% CI = 0.64–1.15).

Effect modification by ApoE ε4 status

After stratification by ApoE ε4 status, rs11948613 was associated with a reduced AD risk among ApoE ε4 noncarriers (CC vs. TT: AOR = 0.28, 95% CI = 0.09–0.91; Table 3), which did not reach statistical significance after correction for multiple tests. ApoE ε4 status did not significantly modify the association between SAR1B SNPs and risk of AD (Table 3) or VaD (Table 4).

Effect modification by vascular risk factors

After stratification by hypertension status, the heterozygosity of rs11948613 showed decreased AD risk among nonhypertensive participants (AOR = 0.52, 95% CI = 0.29–0.96), which did not reach statistical significance after correction for multiple tests. After stratification by type 2 diabetes or hypercholesterolemia, SAR1B SNPs were not associated with the risk of AD or VaD (data not shown). Hypertension, type 2 diabetes, and hypercholesterolemia did not significantly modify the association between SAR1B SNPs and risk of AD or VaD (data not shown).

Simultaneous screening and joint PAR of ApoE ε4 and SAR1B rs11948613

ApoE ε4 is a well-known risk factor of late-onset AD. However, the sensitivity for screening AD risk was low when ApoE ε4 and rs11948613 were used separately (0.40 and 0.59, respectively; Table 5). Simultaneous screening for AD using ApoE ε4 and SAR1B rs11948613 significantly increased the net sensitivity to 0.75.

Individual PAR is 28.3% and 26.7% for ApoE ε4 and SAR1B rs11948613, respectively, with a joint PAR of 47.4% (Table 5).

Discussion

No study has explored the association of sequence variants of SAR1B gene and the risk of dementia (AD and VaD). Homozygous variants of SAR1B rs11948613 was significantly associated with a decreased risk of AD (AOR = 0.39), and the association decreased further in ApoE ε4 noncarriers (AOR = 0.28). However, these associations did not remain significant after correction for multiple tests. Similarly, previous genome-wide association studies did not identify SAR1B as a marker for AD, probably because of the issue of nonindependent tests.

Table 2 Characteristics of SAR1B htSNPs.

<table>
<thead>
<tr>
<th>SNP name</th>
<th>rs no.</th>
<th>Nucleotide change</th>
<th>Location</th>
<th>HapMap CHB MAF</th>
<th>Controls MAF</th>
<th>HWE p</th>
<th>Cases MAF</th>
<th>HWE p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP1</td>
<td>rs7728741</td>
<td>T→C</td>
<td>3’-UTR</td>
<td>0.31</td>
<td>0.30</td>
<td>0.56</td>
<td>0.27</td>
<td>0.33</td>
</tr>
<tr>
<td>SNP2</td>
<td>rs2305049</td>
<td>G→T</td>
<td>Intron</td>
<td>0.31</td>
<td>0.30</td>
<td>0.60</td>
<td>0.28</td>
<td>0.38</td>
</tr>
<tr>
<td>SNP3</td>
<td>rs11948613</td>
<td>T→C</td>
<td>Intron</td>
<td>0.27</td>
<td>0.26</td>
<td>0.87</td>
<td>0.22</td>
<td>0.45</td>
</tr>
</tbody>
</table>

CHB = Han Chinese in Beijing, China; HWE = Hardy–Weinberg equilibrium; htSNP = haplotype-tagging single nucleotide polymorphisms; MAF = minor allele frequency; SNP = single nucleotide polymorphisms; UTR = untranslated region.

Table 3 Association between SAR1B htSNPs and the risk of Alzheimer’s disease by ApoE ε4 status.

<table>
<thead>
<tr>
<th>ApoE ε4 status</th>
<th>0 copies</th>
<th>1 copy (95% CI)</th>
<th>2 copies (95% CI)</th>
<th>PInteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case/control</td>
<td>AOR</td>
<td>Case/control</td>
<td>AOR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>rs7728741</td>
<td>143/226</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>98/194</td>
<td>94/162</td>
<td>0.94 (0.57–1.57)</td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>45/32</td>
<td>56/34</td>
<td>0.92 (0.41–2.08)</td>
<td></td>
</tr>
<tr>
<td>rs2305049</td>
<td>119/220</td>
<td>101/194</td>
<td>0.94 (0.61–1.46)</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>78/191</td>
<td>49/158</td>
<td>0.60 (0.31–1.51)</td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>41/29</td>
<td>52/34</td>
<td>0.80 (0.36–1.80)</td>
<td></td>
</tr>
<tr>
<td>rs11948613</td>
<td>168/254</td>
<td>99/181</td>
<td>0.74 (0.48–1.13)</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>111/216</td>
<td>51/150</td>
<td>0.78 (0.46–1.29)</td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>57/37</td>
<td>38/30</td>
<td>0.69 (0.31–1.51)</td>
<td></td>
</tr>
</tbody>
</table>

AOR = adjusted odds ratios; ApoE ε4 = apolipoprotein E ε4; CI = confidence interval; htSNP = haplotype-tagging single nucleotide polymorphism; NA = not applicable.

All models were adjusted for age, sex, and education.
false negative findings, reporting or publication bias, and the marginal association of \( \text{SAR1B} \) polymorphisms with AD. Despite the marginal association, we found that the addition of rs11948613 for simultaneous screening with \( \text{ApoE} \varepsilon 4 \) can significantly improve the sensitivity compared with using \( \text{ApoE} \varepsilon 4 \) alone (from 0.4 to 0.75). Previous studies showed that \( \text{ApoE} \varepsilon 4 \) has low sensitivity (about 0.40) when it was used alone for screening AD. This may have a beneficial impact on public health, especially when screening larger populations for AD risk at an early stage. Because these are germline polymorphisms, AD risk can be predicted at any point of a person’s life, and thus they become stable and reliable biomarkers. In simultaneous screening, “positive” indicates positive results in any one or more of the tests, whereas “negative” indicates negative results in all of the tests. This leads to a gain in net sensitivity but a loss in net specificity. Both \( \text{SAR1B} \) and \( \text{ApoE} \) genes are involved in lipid metabolism and the regulation of high-density lipoprotein, total cholesterol, low-density lipoprotein, and triglyceride. Dyslipidemia increases the accumulation of A\( \beta \) and is thus related to increased risk of AD, and VaD. Fewer noncarriers had dyslipidemia, as compared to \( \text{ApoE} \varepsilon 4 \) carriers, which may explain the interplay between \( \text{SAR1B} \) and \( \text{ApoE} \varepsilon 4 \), although it did not reach statistical significance. In addition, no protective effect was found for \( \text{SAR1B} \) SNPs among \( \text{ApoE} \varepsilon 4 \) carriers, probably because of the strong deleterious effect of \( \text{ApoE} \varepsilon 4 \), which cannot be counteracted by the protective effect of variant \( \text{SAR1B} \).

In this study, \( \text{ApoE} \varepsilon 4 \) status and vascular risk factors (e.g., hypertension, type 2 diabetes, and hypercholesterolemia) did not modify the association between \( \text{SAR1B} \) polymorphisms and dementia. Hypertension, hyperlipidemia, and type 2 diabetes may affect the pathogenesis of dementia. The nonsignificant findings may be attributable to medications for treating these diseases. This study also has several limitations. First, the information on vascular risk factors (e.g., hypertension, hypercholesterolemia, and type 2 diabetes) was obtained from a self-report questionnaire instead of medical charts. However, by a random sampling of 5% of all participants, a high concordance rate (> 95%) was found between self-reported and medical record-confirmed vascular diseases. In addition, previous studies showed that the participants’ awareness of these major health issues was high if their disease had been diagnosed by physicians. Therefore, information bias was not a concern. Second, the sample size of VaD is relatively small and may therefore overestimate OR/PAR owing to insufficient statistical power to assess the association between \( \text{SAR1B} \) genetic polymorphisms and the risk of VaD.

### Table 4 Association between \( \text{SAR1B} \) htSNPs and the risk of vascular dementia by \( \text{ApoE} \varepsilon 4 \) status.

<table>
<thead>
<tr>
<th>( \text{ApoE} \varepsilon 4 ) status</th>
<th>0 copies</th>
<th>1 copy</th>
<th>2 copies</th>
<th>Case/control AOR</th>
<th>AOR (95% CI)</th>
<th>Case/control AOR (95% CI)</th>
<th>Case/control AOR (95% CI)</th>
<th>( P ) interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs77278741</td>
<td>56/226</td>
<td>1.00</td>
<td>51/198</td>
<td>1.32 (0.75–2.31)</td>
<td>7/38</td>
<td>0.80 (0.26–2.48)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>40/194</td>
<td>1.00</td>
<td>42/162</td>
<td>1.88 (0.98–3.58)</td>
<td>5/35</td>
<td>0.81 (0.21–3.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>16/32</td>
<td>1.00</td>
<td>8/34</td>
<td>0.38 (0.10–1.45)</td>
<td>2/3</td>
<td>1.11 (0.09–14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2305049</td>
<td>56/220</td>
<td>1.00</td>
<td>47/194</td>
<td>1.18 (0.67–2.09)</td>
<td>7/38</td>
<td>0.80 (0.25–2.49)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>40/191</td>
<td>1.00</td>
<td>38/158</td>
<td>1.63 (0.85–3.14)</td>
<td>5/36</td>
<td>0.73 (0.20–2.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>16/29</td>
<td>1.00</td>
<td>8/34</td>
<td>0.37 (0.10–1.40)</td>
<td>2/2</td>
<td>1.71 (0.12–25.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs11948613</td>
<td>67/254</td>
<td>1.00</td>
<td>42/181</td>
<td>1.12 (0.64–1.97)</td>
<td>7/31</td>
<td>0.87 (0.27–2.80)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>50/216</td>
<td>1.00</td>
<td>34/150</td>
<td>1.52 (0.79–2.91)</td>
<td>5/29</td>
<td>0.87 (0.22–3.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carriers</td>
<td>17/37</td>
<td>1.00</td>
<td>7/30</td>
<td>0.36 (0.09–1.44)</td>
<td>2/2</td>
<td>1.37 (0.09–20.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AOR = adjusted odds ratios; \( \text{ApoE} \varepsilon 4 \) = apolipoprotein E \( \varepsilon 4 \); CI = confidence interval; NA = not applicable; htSNPs = haplotype-tagging single nucleotide polymorphism.

### Table 5 Simultaneous screening and joint PAR of \( \text{ApoE} \varepsilon 4 \) and \( \text{SAR1B} \) rs11948613 for Alzheimer’s disease.

<table>
<thead>
<tr>
<th>( \text{ApoE} \varepsilon 4 ) status</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11948613</td>
<td>0.59</td>
<td>0.45</td>
<td>26.7</td>
</tr>
<tr>
<td>Net specificity</td>
<td>0.75</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Joint PAR (%)</td>
<td>NA</td>
<td>0.38</td>
<td>NA</td>
</tr>
<tr>
<td>( \text{ApoE} \varepsilon 4 ) = apolipoprotein E ( \varepsilon 4 ); NA = not applicable; PAR = population attributable risk.</td>
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</table>

\( a \) Net sensitivity = sensitivity1 + sensitivity2 − sensitivity1 \times sensitivity2.

\( b \) Net specificity = specificity1 \times specificity2.
**SAR1B** polymorphisms may protect against AD via the facilitation of lipid metabolism. This study found that **SAR1B** rs11948613 was associated with a risk of AD; however, the results were not significant after correction for multiple tests. In addition, simultaneous screening using ApoE ε4 and the **SAR1B** rs11948613 may offer a potential screening tool for predicting AD risk at an early stage. Future large studies will be needed to confirm these findings.

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**References**


