

## Research Article

# Polymorphisms in the Sortilin-Related Receptor 1 Gene Are Associated with Cognitive Impairment in Filipinos

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**Background/Aims.** Sortilin-related receptor 1 (SORL1) is involved in the neuronal transport processes and plays a role in the formation of amyloid plaques. This study investigated the association of 6 *SORL1* single nucleotide polymorphisms (SNPs 8, 9, 10, 13, 19, and 23) with cognitive impairment (CI) in Filipinos. **Methods.** DNA samples from 484 subjects (100 Alzheimer's Disease (AD) cases, 109 mild cognitive impairment (MCI) cases, 18 other types of CI, and 257 no dementia controls (NDC)) were genotyped using TaqMan SNP Genotyping Assays. **Data Analysis.** Our study showed strong linkage disequilibrium in the SNPs 8, 9, and 10 block. Our results showed that CI was significantly associated with SNPs 13 and 23. None of the *SORL1* SNPs studied was associated with AD while SNPs 8, 9, 10, and 23 were associated with MCI. **Conclusion.** The findings had provided evidence that *SORL1* may predispose individuals to CI. Further studies are needed to clarify the role of *SORL1* in Filipinos with AD.

## 1. Introduction

Sortilin-related receptor 1 (*SORL1*) is genetically linked to Alzheimer's disease (AD) [1–7]. Recent evidence indicates that it acts as a regulatory gatekeeper for determining the ultimate destination of amyloid precursor protein (APP) [8]. APP processing generates the  $\beta$ -amyloid (A $\beta$ ) peptides, which are deposited as the amyloid plaques in brains of individuals with AD [9].

AD was associated with the “C,” “G,” and “C” alleles at single nucleotide polymorphisms (SNP) 8, 9, and 10, in the 5'-end of *SORL1*, respectively and the “G” and “T” alleles at SNPs 19 and 23 in the 3'-end of *SORL1*, respectively [2]. Using frozen brain tissue from autopsy-confirmed AD cases, Lee et al. reported that some AD patients displayed low level of *SORL1* [1]. These data suggest that inherited or acquired changes in *SORL1* expression or function are mechanistically involved in causing AD.

Mild cognitive impairment (MCI) refers to individuals who exhibit cognitive deficit but not dementia [10]. It has an

incidence rate of 9.9/1000 person-years and an annual conversion rate of 10% to 12% to AD, in contrast to a conversion rate of 1% to 2% in the normal elderly population [11]. Sager et al. reported that MCI subjects with low *SORL1* expression levels were significantly more cognitively impaired than subjects with high levels of expressed *SORL1* [10].

Currently, there has been no published data on the genetic variation of *SORL1* in the Filipino population. In this study, we sought to investigate the role of *SORL1* (SNPs 8, 9, 10, 13, 19, and 23) in Filipinos with cognitive impairment (CI), MCI, and AD as well as its association with sex, age, and its interaction to *Apolipoprotein E-ε4* (APOE- $\epsilon$ 4).

## 2. Methodology

**2.1. Study Population.** The Institutional Ethics Review Committee of the St. Luke's Medical Center approved the study protocol, and subjects were selected based on inclusion and exclusion criteria. Informed, written consent was obtained

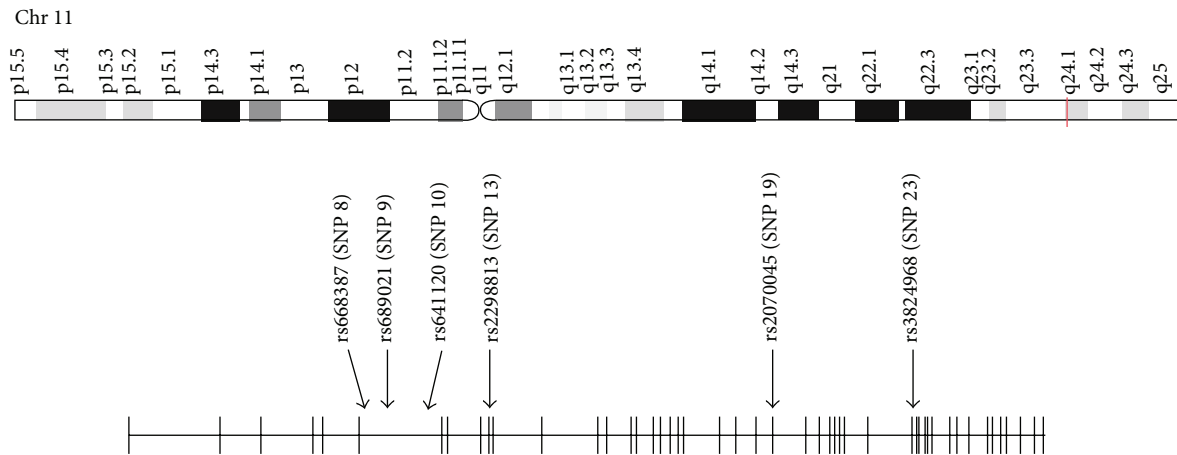


FIGURE 1: Chromosome location of *SORL1* and the 6 SNPs.

from each subject or from reliable collateral informants who are familiar with the subject's cognitive state.

The group who evaluated the subjects consisted of a neurologist, psychologists, and a nurse. Every data-gathering session began with briefing to include an intake interview for the demographic data and medical history using the Philippine Neurological Association (PNA) 10-item Questionnaire for Common Neurological Diseases. Clinical dementia rating (CDR), assessment of the presence or absence of AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's criteria, Montreal Cognitive Assessment (MOCA), Mini-Mental State Exam (MMSE-P), Disability Assessment for Dementia (DAD), Neuropsychiatric Inventory (NPI), and Geriatric Depression Scale (GDS) were individually administered to all the subjects.

**2.2. *SORL1* Genotyping.** Five milliliters of whole blood in BD Vacutainer tubes with EDTA was drawn from each subject. DNA was extracted from the buffy coat using Qiagen QIAamp DNA extraction kit. Polymorphisms (numbering relative to AP000977.4), rs668387 (51432C>T), rs689021 (54631G>A), rs641120 (64476G>A), rs2298813 (77195G>A), rs2070045 (131601T>G), and rs3824968 (159433T>A) in the *SORL1* gene, numbered as SNPs 8, 9, 10, 13, 19, and 23, respectively, were selected for testing (Figure 1). SNPs 8, 9, and 10 are located in the intron 6 of the gene while SNPs 13, 19, and 23 are located in exons 11, 25, and 34, respectively. Genotyping was performed using TaqMan SNP Genotyping Assays (Applied Biosystems).

**2.3. Data Analysis.** For each SNP, goodness-of-fit to Hardy-Weinberg equilibrium (HWE) was assessed using the Chi-Square test ( $\chi^2$ ). Haploview ver. 4.2 software developed by the Broad Institute was used to estimate the degree of linkage disequilibrium (LD), to detect single marker association, and to determine presence of haplotype blocks [12]. The default settings were used in these analyses, which create 95% confidence bounds on  $D'$  to delineate SNP pairs in strong LD.

SPSS ver. 16.0 software was used for the association analysis. Differences between the genotype and allele frequencies between the CI cases and no dementia controls (NDC) in Filipinos were determined by  $\chi^2$  test. Univariate logistic regression was performed to determine the association of the SNPs with the CI cases. The association of the *SORL1* SNPs with the CI cases was indicated in odds ratio (OR) with the corresponding 95% confidence intervals. Stratified analyses were performed to determine if associations differed between sex, age, and *Apolipoprotein E-ε4* (*APOE-ε4*) groups. All tests were two-tailed and considered significant at  $P < 0.05$ .

### 3. Results

**3.1. Study Subjects.** A total of 484 subjects including 227 (46.9%) CI cases (100 with AD, 109 with MCI, and 18 with other types CI) and 257 (53.1%) NDC were included in this study. There were 335 (69.2%) females and 149 (30.8%) males. The mean age was  $70.5 \pm 7.9$  years old (y/o), 253 (52.3%) were  $\leq 70$  y/o, 218 (45.0%) were  $< 70$  y/o, and 13 (2.7%) had no recorded age. *APOE* genotypes showed 391 (80.8%) were *APOE-ε4* noncarriers and 93 (19.2%) were *APOE-ε4* carriers.

**3.2. *SORL1* Genotypes.** The allele and genotype frequencies of the *SORL1* SNPs (Table 1) observed in this study population were in HWE, except for SNP 13 ( $\chi^2 = 7.2127$ ) which showed a significantly higher frequency for the G allele. When the  $\chi^2$  of SNP 13 was computed for the NDC only, the result was in HWE ( $\chi^2 = 0.4084$ ).

The alleles C, G, G, G, G, and A alleles of SNPs 8, 9, 10, 13, 19, and 23, respectively, were detected as the risk alleles for the cognitively impaired population (Table 2). Haplotype block 1 showed a strong LD in SNPs 8, 9, and 10 (Figure 2). This block formed a three-locus haplotype, C-G-G, and T-A-A. However, none of the haplotypes were associated with CI, MCI, and AD (data not shown).

**3.3. Genetic Association Analysis.** Individual SNPs were analyzed in the CI, MCI, and AD cases (Table 3). SNP 13 ( $P$  value

TABLE 1: Goodness-of-fit to HWE for the elderly Filipinos studied.

| SNP# | Observed |     |     | Total | $p$ obs | $q$ obs | $p^2$ exp | $2pq$ exp | $q^2$ exp | $P$ exp | $2PQ$ exp | $Q$ exp | $\chi^2$       |
|------|----------|-----|-----|-------|---------|---------|-----------|-----------|-----------|---------|-----------|---------|----------------|
| 8    | CC       | TC  | TT  |       |         |         |           |           |           |         |           |         |                |
|      | 56       | 204 | 224 | 484   | 0.3265  | 0.6735  | 0.1066    | 0.4398    | 0.4537    | 52      | 213       | 219     | <b>0.8355</b>  |
| 9    | AA       | GA  | GG  |       |         |         |           |           |           |         |           |         |                |
|      | 224      | 203 | 57  | 484   | 0.6725  | 0.3275  | 0.4523    | 0.4405    | 0.1072    | 219     | 213       | 52      | <b>1.1056</b>  |
| 10   | AA       | GA  | GG  |       |         |         |           |           |           |         |           |         |                |
|      | 224      | 203 | 57  | 484   | 0.6725  | 0.3275  | 0.4523    | 0.4405    | 0.1072    | 219     | 213       | 52      | <b>1.1056</b>  |
| 13   | AA       | GA  | GG  |       |         |         |           |           |           |         |           |         |                |
|      | 7        | 60  | 417 | 484   | 0.0764  | 0.9236  | 0.0058    | 0.1412    | 0.8530    | 3       | 68        | 413     | <b>7.2127*</b> |
| 19   | TT       | TG  | GG  |       |         |         |           |           |           |         |           |         |                |
|      | 75       | 218 | 191 | 484   | 0.3802  | 0.6198  | 0.1445    | 0.4713    | 0.3842    | 70      | 228       | 186     | <b>0.9488</b>  |
| 23   | TT       | TA  | AA  |       |         |         |           |           |           |         |           |         |                |
|      | 89       | 227 | 168 | 484   | 0.4184  | 0.5816  | 0.1750    | 0.4867    | 0.3383    | 85      | 235       | 164     | <b>0.6381</b>  |

Legend:

$\chi^2$  tabulated (dF = 1,  $P = 0.05$ ): 3.841.

$p$  obs: observed frequency of homozygous Allele 1.

$q$  obs: observed frequency of homozygous Allele 2.

$P$  exp: expected frequency of homozygous Allele 1.

$Q$  exp: expected frequency of homozygous Allele 2.

$2PQ$  exp: expected frequency of heterozygotes.

\* Genotypic and allelic frequencies are not in Hardy-Weinberg equilibrium.

If  $\chi^2$  calculated <  $\chi^2$  tabulated, do not reject null hypothesis.

If  $\chi^2$  calculated >  $\chi^2$  tabulated, reject null hypothesis.

TABLE 2: Single marker association of *SORL1* SNPs in elderly Filipinos using Haploview.

| SNP number | Single marker association |          |           |
|------------|---------------------------|----------|-----------|
|            | Risk allele               | $\chi^2$ | $P$ value |
| 8          | C                         | 0.871    | 0.350     |
| 9          | G                         | 1.01     | 0.315     |
| 10         | G                         | 1.01     | 0.315     |
| 13         | G                         | 3.49     | 0.062     |
| 19         | G                         | 1.015    | 0.314     |
| 23         | A                         | 1.687    | 0.192     |

= 0.041) and SNP 23 ( $P$  value<sub>AA</sub> = 0.016) were associated with CI. SNP 8 ( $P$  value<sub>TC</sub> = 0.028), SNP 9 ( $P$  value<sub>GA</sub> = 0.034), SNP 10 ( $P$  value<sub>GA</sub> = 0.034), and SNP 23 ( $P$  value<sub>AA</sub> = 0.026,  $P$  value<sub>TA</sub> = 0.007) showed association with MCI. The six (6) *SORL1* SNPs did not show association with AD.

Association of *SORL1* with sex and age was also evaluated (Table 4). The 6 *SORL1* SNPs were not associated with the CI, AD, and MCI cases in the male group. In the female group, SNPs 13 ( $P$  value = 0.045) and 23 ( $P$  value<sub>AA</sub> = 0.017;  $P$  value<sub>TA</sub> = 0.017) were associated with CI, SNP 23 was associated with MCI ( $P$  value = 0.033;  $P$  value<sub>AA</sub> = 0.011;  $P$  value<sub>TA</sub> = 0.013), and no *SORL1* SNP was associated with AD.

Based on the mean age, subjects were divided into two: the  $\leq 70$  y/o and the  $> 70$  y/o groups. In the  $\leq 70$  y/o group, SNPs 19 and 23 were associated with CI (SNP 19:  $P$  value<sub>GG</sub> = 0.021;  $P$  value<sub>TG</sub> = 0.029 and SNP 23:  $P$  value<sub>AA</sub> = 0.025;  $P$  value<sub>TA</sub> = 0.021) and MCI (SNP 19:  $P$  value<sub>GG</sub> = 0.038 and SNP 23:  $P$  value<sub>AA</sub> = 0.021;  $P$  value<sub>TA</sub> = 0.018), and no

association was observed for the AD cases. For the  $> 70$  y/o group, there was no association detected between the 6 SNPs and the CI, MCI, and AD cases.

*SORL1* showed no association with the *APOE-ε4* carriers. For the *APOE-ε4* noncarriers, *SORL1* was significantly associated with CI (SNP 23:  $P$  value = 0.008;  $P$  value<sub>AA</sub> = 0.020;  $P$  value<sub>TA</sub> = 0.002). SNP 8 ( $P$  value = 0.030;  $P$  value<sub>GA</sub> = 0.019), SNPs 9 and 10 ( $P$  value = 0.050;  $P$  value<sub>GA</sub> = 0.025), SNP 19 ( $P$  value<sub>GG</sub> = 0.046;  $P$  value<sub>TG</sub> = 0.031), and SNP 23 ( $P$  value<sub>AA</sub> = 0.017;  $P$  value<sub>TA</sub> = 0.002) were associated with MCI. All 6 *SORL1* SNPs were not significantly associated with AD (Table 3).

## 4. Discussion

When two or more alleles are in strong LD, it means that these alleles are inherited together. There are millions of polymorphisms in the human genome, many of which are in LD with each other; thus, it is not necessary to test all polymorphisms [12]. In this study, the block of SNPs 8, 9, and 10 was in strong equilibrium. However, none of the haplotypes were associated with CI, MCI, and AD. This result did not replicate the findings from the Caribbean-Hispanic, Israeli-Arab, and North European datasets [2], but a similar result was reported for the Han Chinese population [13].

Our data showed *SORL1* was associated with CI. But when restricted to AD and MCI, *SORL1* was associated with MCI but not with AD. *SORL1* has been reported to affect AD in different population but replication studies have given inconsistent results [3–7, 14]. The meta-analysis study by Reitz and colleagues suggested that negative findings were likely related to underpowered studies with small sample

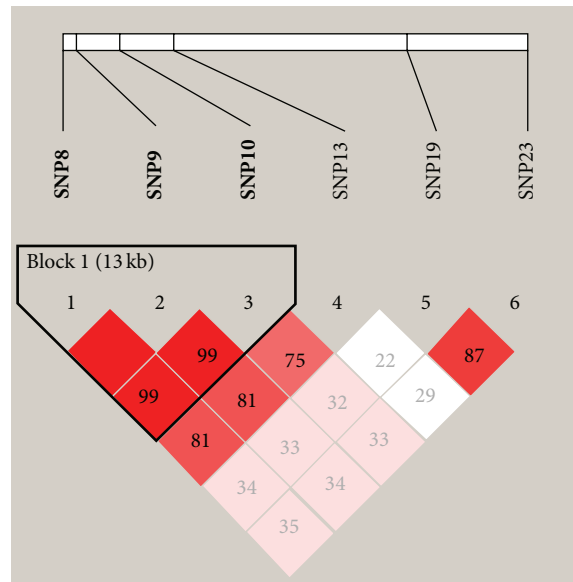


FIGURE 2: Linkage disequilibrium between the *SORL1* SNPs. The standard Linkage disequilibrium color scheme was ( $D'/LOD$ ) with white to red colors representing the increasing strength of Linkage disequilibrium. Block 1 (SNPs 8, 9, and 10) is in strong Linkage disequilibrium, resulting in haplotypes, T-A-A, and C-G-G with frequencies 0.673 and 0.323.

TABLE 3: Association analysis of the *SORL1* SNPs in Filipinos with CI, MCI, and AD.

| <i>SORL1</i> SNPs | <i>P</i> value | CI<br>OR (95% CI)          | <i>P</i> value | MCI<br>OR (95% CI)         | <i>P</i> value | AD<br>OR (95% CI)   |
|-------------------|----------------|----------------------------|----------------|----------------------------|----------------|---------------------|
| SNP 8             | 0.225          |                            | 0.076          |                            | 0.829          |                     |
| TT                |                |                            |                |                            |                |                     |
| TC                | 0.091          | 1.389 (0.949–2.033)        | <b>0.028</b>   | <b>1.710 (1.060–2.760)</b> | 0.586          | 1.146 (0.701–1.875) |
| CC                | 0.857          | 1.056 (0.586–1.904)        | 0.858          | 1.073 (0.498–2.320)        | 0.914          | 0.959 (0.446–2.060) |
| SNP 9             | 0.256          |                            | 0.101          |                            | 0.829          |                     |
| AA                |                |                            |                |                            |                |                     |
| GA                | 0.102          | 1.375 (0.939–2.014)        | <b>0.034</b>   | <b>1.680 (1.040–2.715)</b> | 0.586          | 1.146 (0.701–1.875) |
| GG                | 0.754          | 1.098 (0.612–1.970)        | 0.682          | 1.171 (0.552–2.483)        | 0.914          | 0.959 (0.446–2.060) |
| SNP 10            | 0.256          |                            | 0.101          |                            | 0.829          |                     |
| AA                |                |                            |                |                            |                |                     |
| GA                | 0.102          | 1.375 (0.939–2.014)        | <b>0.034</b>   | <b>1.680 (1.040–2.715)</b> | 0.586          | 1.146 (0.701–1.875) |
| GG                | 0.754          | 1.098 (0.612–1.970)        | 0.682          | 1.171 (0.552–2.483)        | 0.914          | 0.959 (0.446–2.060) |
| SNP 13            | <b>0.041</b>   |                            | 0.316          |                            | 0.085          |                     |
| AA                |                |                            |                |                            |                |                     |
| GA                | 0.667          | 0.348 (0.071–1.709)        | 0.350          | 0.402 (0.060–2.795)        | 0.173          | 0.256 (0.036–1.819) |
| GG                | 0.193          | 0.718 (0.159–3.249)        | 0.671          | 0.676 (0.111–0.4112)       | 0.629          | 0.641 (0.446–3.900) |
| SNP 19            | 0.289          |                            | 0.177          |                            | 0.596          |                     |
| TT                |                |                            |                |                            |                |                     |
| TG                | 0.120          | 1.529 (0.895–2.611)        | 0.075          | 1.921 (0.920–4.014)        | 0.317          | 1.421 (0.715–2.825) |
| GG                | 0.187          | 1.443 (0.837–2.488)        | 0.082          | 1.965 (0.934–4.134)        | 0.537          | 1.249 (0.617–2.528) |
| SNP 23            | 0.055          |                            | <b>0.025</b>   |                            | 0.309          |                     |
| TT                |                |                            |                |                            |                |                     |
| TA                | 0.089          | 1.861 (1.123–3.085)        | <b>0.007</b>   | <b>2.708 (1.319–5.559)</b> | 0.135          | 1.637 (0.858–3.123) |
| AA                | <b>0.016</b>   | <b>1.581 (0.931–2.682)</b> | <b>0.026</b>   | <b>2.329 (1.105–4.908)</b> | 0.425          | 1.321 (0.667–2.616) |

TABLE 4: *SORL1* SNPs analyses that showed significant association in Filipinos with CI and MCI according to sex and age groups and *APOE-ε4* carriage.

| <i>SORL1</i> SNPs          | <i>P</i> value | CI<br>OR (95% CI)          | <i>P</i> value | MCI<br>OR (95% CI)          | <i>P</i> value | AD<br>OR (95% CI)    |
|----------------------------|----------------|----------------------------|----------------|-----------------------------|----------------|----------------------|
| <i>Females</i>             |                |                            |                |                             |                |                      |
| SNP 13                     | <b>0.045</b>   |                            | 0.147          |                             | 0.169          |                      |
| AA                         |                |                            |                |                             |                |                      |
| GA                         | 0.464          | 0.344 (0.020–5.974)        | 0.214          | 0.156 (0.008–2.919)         |                |                      |
| GG                         | 0.915          | 0.859 (0.530–13.865)       | 0.509          | 0.391 (0.024–6.351)         |                |                      |
| SNP 23                     | 0.052          |                            | <b>0.033</b>   |                             | 0.359          |                      |
| TT                         |                |                            |                |                             |                |                      |
| TA                         | <b>0.017</b>   | <b>2.156 (1.144–4.063)</b> | <b>0.013</b>   | <b>3.566 (1.300–9.778)</b>  | 0.154          | 1.783 (0.804–3.951)  |
| AA                         | <b>0.037</b>   | <b>2.016 (1.043–3.895)</b> | <b>0.011</b>   | <b>3.762 (1.347–10.508)</b> | 0.261          | 1.612 (0.701–3.708)  |
| <i>≤70 years old</i>       |                |                            |                |                             |                |                      |
| SNP 19                     | 0.062          |                            | 0.113          |                             | 0.288          |                      |
| TT                         |                |                            |                |                             |                |                      |
| TG                         | <b>0.029</b>   | <b>2.742 (1.107–6.792)</b> | 0.059          | 2.985 (0.960–9.281)         | 0.125          | 5.118 (0.636–41.202) |
| GG                         | <b>0.021</b>   | <b>2.920 (1.172–7.277)</b> | <b>0.038</b>   | <b>3.328 (1.067–10.375)</b> | 0.122          | 5.230 (0.644–42.463) |
| SNP 23                     | 0.555          |                            | 0.052          |                             | 0.534          |                      |
| TT                         |                |                            |                |                             |                |                      |
| TA                         | <b>0.021</b>   | <b>2.576 (1.127–5.887)</b> | <b>0.018</b>   | <b>3.864 (1.258–11.869)</b> | 0.434          | 1.717 (0.443–6.653)  |
| AA                         | <b>0.025</b>   | <b>2.670 (1.157–6.164)</b> | <b>0.021</b>   | <b>3.810 (1.225–11.850)</b> | 0.265          | 2.149 (0.560–8.250)  |
| <i>APOE-ε4 noncarriers</i> |                |                            |                |                             |                |                      |
| SNP 8                      | 0.125          |                            | <b>0.030</b>   |                             | 0.778          |                      |
| TT                         |                |                            |                |                             |                |                      |
| TC                         | 0.088          | 1.446 (0.946–2.211)        | <b>0.019</b>   | <b>1.865 (1.106–3.146)</b>  | 0.789          | 1.081 (0.611–1.913)  |
| CC                         | 0.556          | 0.815 (0.412–1.612)        | 0.617          | 0.792 (0.318–1.973)         | 0.575          | 0.771 (0.310–1.917)  |
| SNP 9                      | 0.167          |                            | <b>0.050</b>   |                             | 0.778          |                      |
| AA                         |                |                            |                |                             |                |                      |
| GA                         | 0.100          | 1.429 (0.934–2.186)        | <b>0.025</b>   | <b>1.825 (1.080–3.084)</b>  | 0.789          | 1.081 (0.611–1.913)  |
| GG                         | 0.674          | 0.866 (0.422–1.695)        | 0.824          | 0.905 (0.378–2.170)         | 0.575          | 0.771 (0.310–1.917)  |
| SNP 10                     | 0.167          |                            | <b>0.050</b>   |                             | 0.778          |                      |
| AA                         |                |                            |                |                             |                |                      |
| GA                         | 0.100          | 1.429 (0.934–2.186)        | <b>0.025</b>   | <b>1.825 (1.080–3.084)</b>  | 0.789          | 1.081 (0.611–1.913)  |
| GG                         | 0.674          | 0.866 (0.422–1.695)        | 0.824          | 0.905 (0.378–2.170)         | 0.575          | 0.771 (0.310–1.917)  |
| SNP 19                     | 0.151          |                            | 0.091          |                             | 0.554          |                      |
| TT                         |                |                            |                |                             |                |                      |
| TG                         | 0.062          | 1.818 (0.970–3.409)        | <b>0.031</b>   | <b>2.653 (1.095–6.426)</b>  | 0.393          | 1.439 (0.624–3.322)  |
| GG                         | 0.075          | 1.773 (0.945–3.327)        | <b>0.046</b>   | <b>2.468 (1.015–6.000)</b>  | 0.278          | 1.583 (0.691–3.629)  |
| SNP 23                     | <b>0.008</b>   |                            | <b>0.007</b>   |                             | 0.162          |                      |
| TT                         |                |                            |                |                             |                |                      |
| TA                         | <b>0.002</b>   | <b>2.563 (1.410–4.657)</b> | <b>0.002</b>   | <b>4.023 (1.694–9.554)</b>  | 0.058          | 2.190 (0.973–4.933)  |
| AA                         | <b>0.020</b>   | <b>2.073 (1.121–3.834)</b> | <b>0.017</b>   | <b>2.962 (1.216–7.215)</b>  | 0.114          | 1.954 (0.851–4.490)  |

sizes, allelic heterogeneity, or both. Because AD is a complex disease, it is also likely that interaction between two or more genes contributes to disease's phenotype.

The relationship between *SORL1* and MCI remains unclear but may suggest that MCI can be modulated by *SORL1* like how it is modulated by *APOE*. Whitehair et al. reported the influence of *APOE-ε4* genotype on rates of cognitive decline in MCI. They found out that *APOE-ε4* carriers had significantly more rapid decline in cognitive

and functional performance [15]. On the other hand, *SORL1* expression in individuals with MCI was heterogeneous, such that some MCI cases had *SORL1* expression similar to healthy controls while it was reduced in others to levels similar to those seen in AD [10, 16]. These reports indicate that *SORL1* and *APOE* have similar effect on the cognition of individuals with MCI.

*SORL1* (SNP 23) was significantly associated with the female sex in this study. A previous report showed a similar



result wherein *SORL1* (SNP 4) was also associated with the female sex [6]. For individuals over the age of 80, women are at slightly higher risk of AD, while men may be at higher risk of vascular dementia [17]. Prevalence of MCI in males was higher than that in females; however, the transition in women from normal cognition to dementia is more abrupt in women [18]. The importance of estrogen receptor-mediated neuroprotection in females was cited as a plausible factor in cognition [19]. These reports suggest the possible sex-specific interplay of risk factors, disease course, and survival in this disease.

As we grow older, our cognitive abilities gradually decline. For AD, age is a major risk factor [2]. Around 50% of all people more than 85 years old suffer from AD [20]. Interestingly, no association was observed in the >70 y/o group with CI, MCI, and AD. Interestingly, the ≤70 y/o group was associated with *SORL1* in the CI and MCI cases. We hypothesized that the sample size, subject heterogeneity, and age range in our groupings may be the reasons why we were not able to replicate the positive results of Rogaeva et al.

The association of *SORL1* with CI, female sex, and ≤70 y/o group elucidated in this study may indicate the early effects of this gene in the development of CI leading to dementia.

It has been suggested that *SORL1* activity is influenced by APOE [20]. Alterations in the three-dimensional structure and binding properties of APOE in the *APOE-ε4* isoform may result in changes in the interaction between *SORL1* and APOE that could affect the capacity of *SORL1* to bind to APP. Thus, the *APOE* isoform may have a modifying effect on the association of *SORL1* and APOE; specifically, effects of distinct *SORL1* SNPs may be weakened by the *APOE-ε4* allele. Several studies showed association of *SORL1* SNPs with AD in *APOE-ε4* noncarriers [7, 21].

In this study, significant association of the *SORL1* SNPs was detected with MCI and CI in *APOE-ε4* noncarriers but not with AD. To determine possible interaction of *SORL1* and *APOE*, we also tested the association of *APOE-ε4* allele with CI, MCI, and AD. The result showed that *APOE-ε4* allele was associated with AD ( $P$  value = 0.017). *APOE-ε4* allele was not associated with CI ( $P$  value = 0.140) and MCI ( $P$  value = 0.870). Based on this result, it could be possible that the presence of *APOE-ε4* allele may have masked the effect of the *SORL1* in AD. These data support the role of *SORL1* in AD pathogenesis, contributing to an increased risk to CI even when the *APOE-ε4* allele is not present.

Because *SORL1* plays a crucial role in APP processing, it is a reliable gene that could help fill up missing links in the complex genetics of AD and other CIs. This study provides baseline information on the possible contribution of *SORL1* to increased risk of CI in Filipinos. Although no association was observed between the *SORL1* and AD, our findings provide evidence that *SORL1* may signal a predisposition to cognitive impairment in Filipinos.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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