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 β-amyloid (Aβ) 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-ε4).

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.
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rs668387 (SNP 8)
rs689021 (SNP 9)
rs641120 (SNP 10)
rs2298813 (SNP 13)
rs2070045 (SNP 19)

Individual SNPs were analyzed in the CI, MCI, and AD cases (Table 3). SNP 13 (𝑃 value was in HWE, except for SNP 13 (𝜒² = 7.2127) which showed a significantly higher frequency for the G allele. When the 𝜒² of SNP 13 was computed for the NDC only, the result was in HWE (𝜒² = 0.4084).

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

Legend:
χ^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 χ^2 calculated < χ^2 tabulated, do not reject null hypothesis.
If χ^2 calculated > χ^2 tabulated, reject null hypothesis.

Table 2: Single marker association of SORL1 SNPs in elderly Filipinos using Haplovew.

| SNP number | Single marker association | Risk allele | χ^2 | P value |
|------------|---------------------------|-------------|-----|---------|
| 8          | G                         | 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_AA = 0.016) were associated with CI. SNP 8 (P value_TC = 0.028), SNP 9 (P value_GA = 0.034), SNP 10 (P value_GA = 0.034), and SNP 23 (P value_AA = 0.026, P value_TA = 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_AA = 0.017; P value_TA = 0.017) were associated with CI, SNP 23 was associated with MCI (P value = 0.033; P value_AA = 0.011; P value_TA = 0.013), and no SORL1 SNP was associated with AD.

Based on the mean age, subjects were divided into two: the ≤70 y/o and the >70 y/o groups. In the ≤70 y/o group, SNPs 19 and 23 were associated with CI (SNP 19: P value_GG = 0.021; P value_TG = 0.029 and SNP 23: P value_AA = 0.025; P value_TA = 0.021) and MCI (SNP 19: P value_GG = 0.038 and SNP 23: P value_AA = 0.021; P value_TA = 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_AA = 0.020; P value_TA = 0.002). SNP 8 (P value = 0.030; P value_GA = 0.019), SNPs 9 and 10 (P value = 0.050; P value_GA = 0.025), SNP 19 (P value_GG = 0.046; P value_TG = 0.031), and SNP 23 (P value_AA = 0.017; P value_TA = 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.

| SORL1 SNPs | CI P value | OR (95% CI) | MCI P value | OR (95% CI) | AD P value | OR (95% CI) |
|------------|------------|-------------|-------------|-------------|------------|-------------|
| SNP 8      | 0.225      | 0.076       | 0.829       |
| TT         | 0.091      | 1.389 (0.949–2.033) | **0.028** | **1.710 (1.060–2.760)** | 0.586 | 1.146 (0.701–1.875) |
| TC         | 0.857      | 1.056 (0.586–1.904) | 0.858 | 1.073 (0.498–2.320) | 0.914 | 0.959 (0.446–2.060) |
| CC         | 0.256      | 0.101       | 0.829       |
| SNP 9      |            |             |             |             |            |             |
| AA         | 0.102      | 1.375 (0.939–2.014) | **0.034** | **1.680 (1.040–2.715)** | 0.586 | 1.146 (0.701–1.875) |
| GA         | 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) | **0.034** | **1.680 (1.040–2.715)** | 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     | **0.041**  | 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 (0.111–0.411) | 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**  | **0.025**   | 0.309       |
| TT         |            |             |             |             |            |             |
| TA         | 0.089      | 1.861 (1.123–3.085) | **0.007** | **2.708 (1.319–5.559)** | 0.135 | 1.637 (0.858–3.123) |
| AA         | **0.016**  | **1.581 (0.931–2.682)** | **0.026** | **2.329 (1.105–4.908)** | 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.

| SORL1 SNPs | CI P value | CI OR (95% CI) | MCI P value | MCI OR (95% CI) | AD P value | AD OR (95% CI) |
|------------|------------|---------------|-------------|----------------|------------|----------------|
| **Females** |           |               |             |                 |            |                |
| SNP 13     | 0.045      | 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      | 0.033         | 0.359       |                 |            |                |
| TT         |            |               |             |                 |            |                |
| TA         | 0.017      | 2.156 (1.144–4.063) | 0.013 | 3.566 (1.300–9.778) | 0.154 | 1.783 (0.804–3.951) |
| AA         | 0.037      | 2.016 (1.043–3.895) | 0.011 | 3.762 (1.347–10.508) | 0.261 | 1.612 (0.701–3.708) |
| ≤70 years old |       |               |             |                 |            |                |
| SNP 19     | 0.062      | 0.113         | 0.288       |                 |            |                |
| TT         |            |               |             |                 |            |                |
| TG         | 0.029      | 2.742 (1.107–6.792) | 0.059 | 2.985 (0.960–9.281) | 0.125 | 5.118 (0.636–41.202) |
| GG         | 0.021      | 2.920 (1.172–7.277) | 0.038 | 3.328 (1.067–10.375) | 0.122 | 5.230 (0.644–42.463) |
| SNP 23     | 0.555      | 0.052         | 0.534       |                 |            |                |
| TT         |            |               |             |                 |            |                |
| TA         | 0.021      | 2.576 (1.127–5.887) | 0.018 | 3.864 (1.258–11.869) | 0.434 | 1.717 (0.443–6.563) |
| AA         | 0.025      | 2.670 (1.157–6.164) | 0.021 | 3.810 (1.225–11.850) | 0.265 | 2.149 (0.560–8.250) |
| **APOE-ε4 noncarriers** |           |               |             |                 |            |                |
| SNP 8      | 0.125      | 0.030         | 0.778       |                 |            |                |
| TT         |            |               |             |                 |            |                |
| TC         | 0.088      | 1.446 (0.946–2.211) | 0.019 | 1.865 (1.106–3.146) | 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      | 0.050         | 0.778       |                 |            |                |
| AA         |            |               |             |                 |            |                |
| GA         | 0.100      | 1.429 (0.934–2.186) | 0.025 | 1.825 (1.080–3.084) | 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      | 0.050         | 0.778       |                 |            |                |
| AA         |            |               |             |                 |            |                |
| GA         | 0.100      | 1.429 (0.934–2.186) | 0.025 | 1.825 (1.080–3.084) | 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) | 0.031 | 2.653 (1.095–6.426) | 0.393 | 1.439 (0.624–3.322) |
| GG         | 0.075      | 1.773 (0.945–3.327) | 0.046 | 2.468 (1.015–6.000) | 0.278 | 1.583 (0.691–3.629) |
| SNP 23     | **0.008** | **0.007**     | 0.162       |                 |            |                |
| TT         |            |               |             |                 |            |                |
| TA         | **0.002** | **2.563 (1.141–4.657)** | **0.002** | **4.023 (1.694–9.554)** | 0.058 | 2.190 (0.973–4.933) |
| AA         | **0.020** | **2.073 (1.121–3.834)** | **0.017** | **2.962 (1.216–7.215)** | 0.114 | 1.954 (0.851–4.940) |

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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