Association of TOMM40, CHAT and SORLI Polymorphisms with the Alzheimer’s Disease in the Turkish-speaking Azeri population in Northwest of Iran

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Abstract

Recent genome-wide association studies have introduced several genetic variants which contribute to the late-onset Alzheimer’s disease (LOAD). Polymorphisms of CHAT, TOMM40, and SORLI genes have been reported to be associated with the LOAD phenotype. This study was endeavored to evaluate the association of the CHAT rs3810950, TOMM40 rs1160985 and SORLI rs11218304 polymorphisms with the LOAD in the Turkish-speaking Azeri population of northwest Iran. In a case-control study, we included 174 cases: 88 cases with LOAD diagnosis and 86 healthy individuals. Peripheral blood samples were collected and the genomic DNA of all participants were extracted. Genotyping was carried out by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. We did not observe any significant association between the CHAT rs3810950 and SORLI rs11218304 alleles with the LOAD. However, both the TOMM40 rs1160985 minor allele T and TT genotype showed significant negative associations with the LOAD. Hence, the TOMM40 rs1160985 polymorphism could be considered as a protective genetic factor against the LOAD in the Turkish-speaking Azeri population of northwest Iran.

Keywords: Alzheimer’s disease, SORLI, CHAT, TOMM40, Genome-wide association study

Introduction

Dementia syndrome due to the Alzheimer’s disease (AD) is one of the most expensive chronic diseases with powerful threat (Belmonte et al., 2015). According to the 2019 Alzheimer’s Disease Facts and Figures, of 5.6 million persons aged 65 and older with Alzheimer’s in the United States, 3.5 million are women and 2.1 million are men (Association, 2019). Considering the ever-increasing feature of the disease, it is estimated that the number of individuals with AD will be more than 15 million in 2060 (Brookmeyer et al., 2018). These warns highlighted the urgent need for the development of new diagnostics and therapeutics; ranging from biomarker discovery (Fotuhi et al., 2019; Yanfang Zhao, 2019) to in vivo reprogramming of the terminally differentiated cells (Yavarpour-Bali et al., 2020). AD occurs in familial and non-familial forms (early vs. late age-onset, respectively). Both genes and environment are responsible for the appearance of the non-familial sporadic late-onset AD (LOAD), as a complex disorder (Bertram et al., 2010). Genetic factors are estimated to play a role at least in 80% of AD cases (Gatz et al., 2006; Tanzi, 2012). In addition, at least up to age of 80, having a family history of AD increases the risk of developing disease up to 4 to 10 folds (Honea et al., 2012). Recent case-control and genome-wide association studies (GWAS) have partly revealed the genetic origin of the LOAD and highlighted its complex nature (Liu et al., 2016; Ortega-Rojas et al., 2016; Talebi et al., 2020; Yuan et al., 2016). Based on these reports, CHAT, SORLI, and TOMM40 are important genes in the LOAD pathogenesis. The gene encoding for TOMM40 (Translocase of outer mitochondrial membrane 40 homolog) is located on the chromosome19, closely next to the gene which is encode for Apolipoprotein E (ApoE). So, it has a strong linkage disequilibrium (LD) with it (Lyall et al., 2014). TOMM40, the central and key subunit of the translocase of the outer mitochondrial membrane, is essential for protein import into the mitochondria. Genetic variations in or close to the TOMM40 gene affect the role of the TOMM40,

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thereby, causing mitochondrial dysfunction (Petschner et al., 2018). Involvement of TOMM40 in the LOAD pathogenesis has been proposed by several researchers (Petschner et al., 2018; Willette et al., 2017), however, its role in LOAD pathogenesis was controversial (Yu et al., 2007). Yu et al. reported a significant LD between TOMM40 and APOE in the Caucasians. The involvement of TOMM40 in LOAD was further supported by some later studies (Jiao et al., 2015; Omoumi et al., 2014; Ortega-Rojas et al., 2016; Roses et al., 2016). Interestingly, two studies on the Chinese and Columbian populations reported that TOMM40 rs1160985 might be useful for early diagnosis of the LOAD (Jiao et al., 2015; Ortega-Rojas et al., 2016). CHAT (Choline O-acetyltransferase) encodes an enzyme which is crucial for the synthesis of acetylcholine, one of the main neurotransmitters in the brain. The choline acetyltransferase (ChAT) activity seems to be associated with the severity of dementia (Gao et al., 2016), and its polymorphisms are known to be also related with the LOAD (Thangnipon et al., 2016; Yu et al., 2015). Conversely, others did not find any significant association between CHAT polymorphisms and LOAD (Cook et al., 2005).

Sortilin related receptor 1 (SORL1) functions as a neural sorting factor (Felisky et al., 2014). It transfers the amyloid precursor protein (APP) to the recycling pathway and hinders the beta amyloid formation in the brain (Rogaeva et al., 2007). Some studies have reported the association of SORL1 with the LOAD (Rosenberg et al., 2016); but, others didn’t approve this association (Rogaeva et al., 2007) or reported inconsistent findings (Reynolds et al., 2013). Controversial findings also were recorded for SORL1 rs11218304. Rogaeva et al. reported no relationship between this variant with the LOAD (Rogaeva et al., 2007), while others indicated significant associations between rs11218304 and LOAD (Louwersheimer et al., 2015; Shao et al., 2017).

This study aimed to investigate genotypes and alleles frequencies of the polymorphisms rs3810950 (CHAT), rs11218304 (SORL1), and rs1160985 (TOMM40) in a population from northwest of Iran and evaluate their associations with the late-onset Alzheimer's disease.

Materials and Methods

Participants
In the present case-control study, 88 patients with LOAD (53 women, 35 men) and 86 healthy voluntaries (53 women, 33 men) from the Turkish-speaking Azeri population of northwest Iran were included. All subjects were older than 65 years. The case and control groups, as far as possible, were matched for different parameters such as age and sex. All of the subjects were evaluated by a neuroscience specialist in the Clinic of the Imam Reza Medical Research Center, Tabriz, Iran. Subjects were diagnosed based on the National Institute of Neurological and Communicative Disorders (NINCDS) and Stroke and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (Dubois et al., 2007). All cases were assessed using physical examinations and neuropsychological tests. Furthermore, the Mini-Mental State Examination (MMSE) was carried out to evaluate any cognitive deficit in both groups. The study protocol was approved by the Clinical Research Ethics Committee of Tabriz University of Medical Sciences and written informed consent was obtained from all individuals in accordance with the approved guidelines from the Neurology Department at Imam Reza Hospital. Participants with a family history of AD and other neurological illnesses such as hypothyroidism, alcoholism, hepatic lesions, spasticity, subdural hematoma, traumatic brain injury, encephalitis, frontal lobe dementia, and Lewy body dementia were excluded from the study. Participants with no memory complaint or cognitive dysfunctions and MMSE score more than 27 were defined as normal cases.

DNA preparation and genotyping
Genomic DNA were extracted from peripheral blood lymphocytes using the salting out DNA extraction method (Miller et al., 1988). The Single-nucleotide polymorphisms (SNPs) in TOMM40 (rs1160985), CHAT (rs3810950), and SORL1 (rs11218304) genes were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. Primer sequences and size of their ampiclons are shown in the Table 1. The PCR reactions were done in a final volume of 20 μl (1 μl genomic DNA, 0.75 μl dNTPs 10 mM (Fermentas, Life Sciences), 1 μl of each of the forward and reverse primers (Metabion), 2 μl of 10× buffer, 0.5 μl MgCl2 50 mM and 1U of Taq polymerase (Sinacolon)). The optimized PCR condition was as follows: initial denaturation (95°C, 5 min), followed by 35 cycles of 95°C for 30s, 60°C for 30s, and 72°C for 40s. It was followed by a final extension (72 °C, 5 min). Then, PCR products were digested by specific restriction enzymes. In addition, 10% of the total volume of PCR products were randomly sequenced to confirm the results of RFLP.
analysis.

Table 1. Primer sequences applied during PCR experiments in addition to their amplicons size.

<table>
<thead>
<tr>
<th>Gene (SNP)</th>
<th>Length (bp)</th>
<th>Primer sequence</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOMM40 (rs1160985)</td>
<td>345 bp</td>
<td>5'-CAAAGTGAATCCATCTCCATCC-3'</td>
<td>Forward</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5'-CAAAGGCAGATCCAAGC-3'</td>
<td>Reverse</td>
</tr>
<tr>
<td>CHAT (rs3810950)</td>
<td>483 bp</td>
<td>5'-GTGATGCTTTCCCCACTTCTTG-3'</td>
<td>Forward</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5'-GTAGGAATTCGCCGCCACC-3'</td>
<td>Reverse</td>
</tr>
<tr>
<td>SORL1 (rs11218304)</td>
<td>386 bp</td>
<td>5'-TCCCTCTGTCCCCAGACTTC-3'</td>
<td>Forward</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5'-GCATACAAGCAGCGATAAAG-3'</td>
<td>Reverse</td>
</tr>
</tbody>
</table>

SNP: Single-nucleotide polymorphism; bp: base pair

Genotyping of CHAT rs3810950
The resulting 483 bp PCR products of CHAT were digested with 1U of ApeK1 (Ferments, Life Sciences) for 16h at 37°C. Final preparations were electrophoresed on agarose gel (2%) in order to identify the genotypes of each person. Samples prepared from homozygous (GG) and heterozygous (GA) genotypes were contained 2 (100 and 383 bp) and 3 (483, 100, and 383 bp) fragments, respectively, whereas a single band with 483 bp length was obtained for genotype AA.

Genotyping of TOMM40 rs1160985
The resulting 345 bp PCR product of TOMM40 gene was digested with 1U of AccI (Ferments, Life Sciences) at 37°C for 16h. Following digestion, genotypes of the people were determined using 2% agarose gel electrophoresis. The homozygote TT and heterozygous CT genotypes contained 2 fragments (100 and 245 bp) and 3 fragments (345, 100, and 245 bp), respectively; whereas CC genotype showed a band of 345 bp.

Genotyping of SORL1 rs11218304
The resulting 386 bp PCR product of SORL1 gene was digested with 1U of ApeK1 (Ferments, Life Sciences) for 16h at 37°C. Digestion products were electrophoresed on 2% agarose gel and genotypes of the people were determined. The homozygote AA and heterozygous AG contained 2 fragments (142 and 244 bp) and 3 fragments (386, 142, and 244 bp), respectively; while GG genotype showed a band of 386 bp.

Statistical analyses
The SPSS software version 21.0 (IBM SPSS, Armonk, NY, USA) was utilized for statistical analyses. The Hardy-Weinberg equilibrium (HWE) was assessed using a goodness-of-fit χ² test. Allelic and genotypic frequencies were compared among examined groups using the Student’s t-test and Odds ratio (OR) of each genotype was assessed with confidence interval (CI) 95%. P value ≤0.05 was considered as statistically significant.

Results
In this case-control study, 88 LOAD patients and 86 healthy individuals were enrolled. Table 2 represents demographic data of the LOAD and healthy subjects. There were no significant differences between LOAD and control groups regarding age, sex, and educational levels (p>0.05). Moreover, allele and genotype frequencies were calculated for CHAT rs3810950, TOMM40 rs1160985, and SORL1 rs11218304 gene polymorphisms in LOAD and control cases. The Chi-square Test revealed that the study population was in Hardy-Weinberg equilibrium for these loci.

Allele and genotype distributions of rs3810950 (CHAT) polymorphism
The frequency of minor allele A of CHAT rs3810950 polymorphism was 36% in the LOAD group and 46% in the control group; while the frequency of allele G was 64% in the LOAD and 54% in the control group. The frequencies of AA, AG, and GG genotypes were calculated as 9%, 53%, and 38% in the LOAD group, respectively. However, the frequencies of these genotypes were equal to 10%, 70%, and 19% in the control group. Statistical analysis (Table 3) revealed that the frequencies of genotype GG were significantly different between the LOAD and control groups (p= 0.002, OR=2.49, 95% CI=1.25-5.03).

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Table 2. Sociodemographic characteristics of LOAD patients and healthy controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>LOAD (n=88) (%)</th>
<th>Control (n=86) (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53 (60.2)</td>
<td>53 (61.6)</td>
<td>0.85</td>
</tr>
<tr>
<td>Male</td>
<td>35 (39.8)</td>
<td>33 (38.4)</td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>71.84±6.51</td>
<td>71.22±5092</td>
<td>0.57</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate (%)</td>
<td>54 (61.33)</td>
<td>50 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Primary (%)</td>
<td>26 (29.54)</td>
<td>31 (36.05)</td>
<td></td>
</tr>
<tr>
<td>Diploma (%)</td>
<td>3 (3.40)</td>
<td>4 (4.6)</td>
<td></td>
</tr>
<tr>
<td>College (%)</td>
<td>1 (1.13)</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>MMSE (mean±SD)</td>
<td>19.33±5.0002</td>
<td>27.30±0.543</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; MMSE: mini-mental status score; AD: Alzheimer’s disease; n: number.

Table 3. Allele and genotype distributions of the CHAT rs3810950, TOMM40 rs1160985 and SORL1 rs11218304 polymorphisms in the LOAD and healthy control groups.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Alleles/ Genotypes</th>
<th>LOAD (n=88) (%)</th>
<th>Control (n=86) (%)</th>
<th>Total population (n=174) (%)</th>
<th>HWE</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAT rs3810950</td>
<td>A</td>
<td>63 (36)</td>
<td>79 (46)</td>
<td>142 (41)</td>
<td></td>
<td>0.660 (0.375-1.164)</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>113 (64)</td>
<td>93 (54)</td>
<td>206 (59)</td>
<td></td>
<td>1.514 (0.859-2.670)</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>8 (9)</td>
<td>9 (10)</td>
<td>17 (9.8)</td>
<td>0.00017</td>
<td>0.890 (0.345-2.294)</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>47 (53)</td>
<td>61 (71)</td>
<td>108 (62.06)</td>
<td></td>
<td>0.461 (0.257-0.826)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>33 (38)</td>
<td>16 (19)</td>
<td>49 (28.16)</td>
<td></td>
<td>2.49 (1.25-5.03)</td>
<td>0.002</td>
</tr>
<tr>
<td>TOMM40 rs1160985</td>
<td>T</td>
<td>49 (28)</td>
<td>98 (57)</td>
<td>147 (42)</td>
<td></td>
<td>0.292 (0.163-0.529)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>127 (72)</td>
<td>74 (43)</td>
<td>201 (58)</td>
<td></td>
<td>3.409 (1.891-6.145)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>8 (9)</td>
<td>33 (38)</td>
<td>41 (23.56)</td>
<td>0.0019</td>
<td>0.161 (0.073-0.357)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>33 (38)</td>
<td>32 (37)</td>
<td>65 (37.36)</td>
<td></td>
<td>1.044 (0.589-1.850)</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>47 (53)</td>
<td>21 (24)</td>
<td>68 (39.08)</td>
<td></td>
<td>3.571 (1.952-6.533)</td>
<td>0.000</td>
</tr>
<tr>
<td>SORL1 rs11218304</td>
<td>A</td>
<td>126 (72)</td>
<td>129 (75)</td>
<td>255 (73)</td>
<td>0.00084</td>
<td>0.857 (.457-1.607)</td>
<td>0.374</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>50 (28)</td>
<td>43 (25)</td>
<td>93 (27)</td>
<td></td>
<td>1.167 (.422-2.188)</td>
<td>0.374</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>43 (49)</td>
<td>43 (50)</td>
<td>86 (49.42)</td>
<td></td>
<td>.961 (.552-1.673)</td>
<td>0.500</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>40 (45)</td>
<td>43 (50)</td>
<td>83 (47.70)</td>
<td></td>
<td>.818 (.469-1.426)</td>
<td>0.286</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>5 (6)</td>
<td>0</td>
<td>5 (2.87)</td>
<td></td>
<td>2.053 (.935-2.053)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

LOAD: late-onset Alzheimer’s disease; SORL1: Sortilin related receptor 1; CHAT: choline O-acetyltransferase; TOMM40: translocase of outer mitochondrial membrane 40 homolog; HWE: Hardy-Weinberg equilibrium; n: number; CI: confidence interval.

Allele and genotype distributions of rs1160985 (TOMM40) polymorphism
The frequency of minor allele T of rs1160985 polymorphism was 28% in the LOAD group and 57% in the control group while the allele C frequency was 72% in the LOAD group and 43% in the control group. Distribution of TT, TC, and CC genotypes (Table 3) for this polymorphism in the case group was 9%, 38%, and 53%, and in healthy individuals was 38%, 37%, and 24%, respectively. Statistical analysis revealed significant differences for allele C (p=0.000, OR=3.429, 95% CI=1.83-6.47) and CC genotype (p=0.000, OR=3.550, 95% CI=1.865-6.795) frequencies in case and control groups.

Allele and genotype distributions of rs11218304 (SORL1) polymorphism
The frequency of minor allele G of rs11218304 polymorphism was 28% in the LOAD group and 25% in the control group, while the allele A frequency was calculated as 72% and 75% in the
LOAD and control groups, respectively (Table 3). Genotype frequencies of AA, AG, and GG for rs11218304 were calculated as 49\%, 45\%, and 6\% in the LOAD group, respectively. They were equal to 50\%, 50\%, and 0\% in the control group. There was a significant difference between the frequencies of genotype GG in the case and control groups \((p=0.030, \text{OR}=2.053, \text{95\% CI}=0.935-2.053)\).

**Discussion**

Recent meta-analyses, reviews, and genome-wide association studies have reported that the genetic variants in TOMM40, CHAT, and SORL1 are in association with the LOAD (Campion et al., 2019; Grupe et al., 2007). In the present study, we evaluated the association of CHAT rs3810950, TOMM40 rs1160985 and SORL1 rs11218304 polymorphisms with the LOAD in the Turkish-speaking Azeri population of northwest Iran. In the case of CHAT rs3810950 polymorphism, the minor allele A frequency was 0.41 which is higher than all minor allele frequencies (MAFs) reported in the dbSNP (https://www.ncbi.nlm.nih.gov/snp/). However, its frequency was not significantly different between LOAD and control groups \((p=0.891)\), which demonstrated the lack of association between the allele A and LOAD in the study population. It was while, the comparison of the genotype frequencies between the LOAD and control groups revealed a significant difference for the GG genotype \((p=0.002, \text{OR}=2.49, \text{95\% CI}=1.25-5.03)\). These results are consistent with the results from a previous study which reported the lack of relationship between the rs3810950 (CHAT) polymorphism and the LOAD risk in Caucasian cohort (UK) (Cook et al., 2005). In contrast, another study performed on the Korean population by Lee et al. showed that individuals carrying the AA genotype had a significantly earlier onset of the LOAD (Lee et al., 2011). Furthermore, a meta-analysis showed that rs3810950 of CHAT is associated with the LOAD susceptibility (Gao et al., 2016; Yuan et al., 2016).

Moreover, we evaluated the association of TOMM40 rs1160985 with the LOAD condition. The frequency of minor allele T in the whole study population was calculated as 0.42 which was higher than the Vietnamese people and lower than all other populations which were reported in the dbSNP (https://www.ncbi.nlm.nih.gov/snp/). Differences between minor allele T frequencies among the LOAD \((0.28)\) and control \((0.57)\) groups were statistically significant \((p=0.000; \text{OR}=0.292; \text{CI}: 0.163-0.529)\); implying its negative association with the LOAD in the examined population. Furthermore, the frequencies of people with TT genotype in the LOAD \((0.09)\) and control \((0.38)\) groups were significantly different \((p=0.000; \text{OR}=0.157; \text{CI}: 0.07-0.37)\). The frequency of heterozygote TC genotype did not show any significant difference between the two investigated groups \((p=0.471)\). These findings suggested that the minor allele T and the genotype TT of the TOMM40 rs1160985 strongly protect people against the LOAD in the northwestern Iran. These findings are consistent with the reports obtained for the populations of European descent (Roses, 2010), mainland China (Jiao et al., 2015), and the Japanese people (Takei et al., 2009). However, these are inconsistent with the results reported by the studies focused on the Northern-Han Chinese population (Ma et al., 2013). It should be mentioned that the Alzheimer-associated C allele of rs1160985 (TOMM40) was reported as the LOAD risk allele by Jiao et al. (Jiao et al., 2015). Unlike the TOMM40 rs1160985 with protective role against the LOAD, several SNPs of TOMM40 are served as the LOAD genetic risk factors (Prendecki et al., 2018; Zeitlow et al., 2017).

A high-quality meta-analysis performed on more than 30000 individuals showed that different SNPs in SORL1 gene are in relationship with the LOAD status (Reitz et al., 2011). We examined the association of an intronic polymorphism of the SORL1 gene, designated with rs11218304, with the LOAD. Results demonstrated that the frequency of minor allele G is equal to 0.27 in the study population. Comparative studies indicated non-significant differences in the frequency of the allele G in LOAD and control groups \((p=0.374)\). Reversely, the frequency of risk genotype GG was significantly different between the LOAD and control groups \((p=0.03; \text{OR}=2.053; \text{CI}: 0.935-2.053)\). In fact, although we had 5 patients with GG genotype, we did not observe any individual with the same genotype among the controls. These data, at least to some extent, support similar data from other studies introduced allele G and GG genotype as key genetic risk factors for the appearance of LOAD phenotype in other populations. For example, Rogaeva et al. reported that rs11218304 (SORL1) is significantly associated with LOAD (Rogaeva et al., 2007). Moreover, its association with the poor cognitive efficiency in the LOAD was reported previously (Cruz-Sanabria et al., 2018). However, Ortega-Rojas et al. did not find any significant association between the rs11218304 variant and cognitive decline in the LOAD patients in the Colombians (Ortega-Rojas et al., 2016).

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Conclusion

In conclusion, the frequency of rs3810950 (CHAT) allele was not significantly different between LOAD and control subjects, while the GG genotype showed a significant association with LOAD in the examined population. Moreover, we observed that the minor allele T of rs1160985 (TOMM40) and TT genotype can strongly serve as protective genetic factors against the LOAD. Furthermore, although rs11218304 (SORL1) alleles frequencies were not significantly different between the LOAD and control groups, the GG genotype frequency showed a significant difference between the investigated groups. This implies the potential association of GG genotype with the LOAD phenotype in the Azeri population of Northwest Iran.

Acknowledgments

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