Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer’s disease

A meta-analysis

Saeed Sadigh-Eteghad, PhD, Mahnaz Talebi, MD, Mehdi Farhoudi, MD.

ABSTRACT

Objective: To obtain a better insight into the effect of the epsilon (ε) 4 allele of the apolipoprotein E gene (APOE) on the risk of late onset Alzheimer’s disease (LOAD), and assess its heterogeneity in geographic regions.

Methods: We performed a systematic review and meta-analysis of available studies. An electronic and manual search of international and local databases was conducted to identify relevant studies between January 1991 and December 2011 in the Central Library of Tabriz University of Medical Sciences, Tabriz, Iran. All articles related to patients with LOAD that evaluated APOE genotype were included in our study. Two reviewers assessed the inclusion/exclusion criteria, summarized, and analyzed the extracted data. We assessed 21 separate studies overall involving 1480 subjects; the total sample size was 6777.

Results: According to the results, there was no heterogeneity among the included studies. The total APOE ε4 allele frequency was significantly higher in AD cases compared with control subjects (35% versus 11.43%, p<0.001). The odds ratio (OR) for APOE ε4 frequency in AD and control groups was 3.98 (95% confidence interval [CI]: 3.44-4.61). This factor in various geographic regions was different.

Conclusions: This meta-analysis is strongly supportive of the hypothesis that the APOE ε4 allele increases the risk of sporadic LOAD, and determination of the ε4 allele in populations may be a useful tool for monitoring demented patients and planning healthcare policies.

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Alzheimer's disease (AD) is the most common form of dementia, accounting for 50-60% of all cases, and affects the quality of life in the elderly. Late onset AD (LOAD), accounting for ~95% of AD, is thought to be a multi-factorial disease, probably caused by complicated interactions between genetic and environmental factors. From a genetic standpoint, AD is a heterogeneous disorder with both familial and sporadic forms. Nevertheless, the familial form of the disease is scarce (prevalence below 0.1%). To date, the apolipoprotein E gene (APOE) is universally recognized as a major disease susceptibility gene for sporadic LOAD in most populations. The 3 common isoforms of APOE are E2, E3, and E4 and they are encoded by the APOE epsilon (ε)2, ε3, and ε4 related genes. The ε4 allele of the APOE gene is a most important genetic risk factor for sporadic LOAD in multiple genetic backgrounds. The new treatment strategies have been promising for preventing or delaying the symptoms for individuals who are at risk for LOAD by virtue of their APOE genotype.

The odds ratios (OR) of sporadic LOAD within ε4 positive individuals in various populations and geographic areas are variable. Hence, we conducted a meta-analysis to assess the effect of ε4 APOE allele on risk of LOAD and define the effect of this risk in the various geographic regions, and to explore previous publications and evaluate the potential heterogeneity among studies.

**Methods. Search Strategy.** The following electronic databases were searched for studies conducted between January 1991 and December 2011: PubMed, Web of Science (ISI), the Cochrane Central Register of Controlled Trials (The Cochrane Library), Medline and Scientific Information Database (SID). This study was carried out in the Central Library of Tabriz University of Medical Sciences, Tabriz, Iran. The search strategy used the following keywords: 'Alzheimer' and 'APOE', 'Apolipoprotein E', 'epsilon 4', 'ε4', allele and polymorphism. Moreover, all the submitted scientific journals of Iranian medical universities published since 2011 were reviewed by hand searching. The references of selected articles were checked to maximize the sensitivity of our search.

**Inclusion criteria.** Two investigators attentively reviewed all distinguished studies independently, to determine whether a study qualified for inclusion in this meta-analysis. The authors were not blinded to the names of the study's authors, journals, and results. Any variations in ideas were discussed among the authors until a consensus was reached. All articles related to patients with LOAD that evaluated APOE genotype were included in our study. Studies on dementia, which was not limited to AD type were excluded. All subjects related to early onset AD or familial AD were excluded. Trials comparing different types of genotypes without APOE were excluded. No language restrictions were imposed.

**Data extraction.** Studies were evaluated for the main issues in descriptive studies such as the sampling method, and the validity of diagnostic tools. Two investigators extracted the raw data of each publication independently. The following information was extracted: publication date, population, name of first author, location, genotype or allele distributions, sample size, age of participants, and diagnosis criteria of AD.

**Analytic strategies.** The APOE genotypes were in Hardy-Weinberg equilibrium among cases, and controls were tested. The ORs and the 95% confidence intervals (CIs) for carriers of APOE ε4 alleles versus non-APOE ε4 carriers in AD and control groups were calculated using Review Manager (RevMan, The Nordic Cochrane Center, Copenhagen, Denmark) version 5.0, and Stata 11 (StataCorp LP, College Station, TX, USA). The Chi square test and the Higgins F test were used to assess heterogeneity. Homogeneous data sets were statistically pooled using a fixed effect model. In this study we had no heterogeneous data sets. Publication bias was assessed using the funnel plot.

**Results.** We retrieved 1480 studies dated between January 1991 and December 2011, including 1197 studies by searching electronic databases, and 283 studies by checking reference lists. The number of identified studies, and the stages of evaluation and exclusion are presented in Figure 1. All 21 eligible studies were of the case-control design. All patients had been diagnosed with AD according to the National Institute for Neurological and Communicative Disorders and Stroke AD and Related Disorder Association (NINDS-ADRDA) criteria. All AD cases and control subjects were older than 65 years old. The total sample size for all of the 21 included studies on APOE ε4 allele frequencies in LOAD was 6777. General characteristics and ε4 genotype distribution in the published articles included in this meta-analysis are shown in Table 1. Figure 2 shows percentages of allele frequencies in various main geographic regions.

There was no heterogeneity among the included studies, therefore, the results of Chi² test for heterogeneity were not significant (p=0.2). In addition, the F statistics confirmed this issue (Figure 3). The total APOE ε4 allele frequency (homozygous and heterozygous) was
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Figure 1 - Algorithm and flow chart of study selection.

Table 1 - Detailed characteristics of 21 articles included in the systematic review on the apolipoprotein E ε4 allele frequencies in Alzheimer’s disease (AD) patients and control groups.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Control/AD subjects (n)</th>
<th>Control ε4 allele frequency</th>
<th>AD ε4 allele frequency</th>
<th>Mean age (control)</th>
<th>Mean age (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebeck et al¹⁴</td>
<td>1993</td>
<td>USA</td>
<td>96/42</td>
<td>0.01</td>
<td>0.38</td>
<td>69±18</td>
<td>79±10</td>
</tr>
<tr>
<td>Ueki et al¹⁵</td>
<td>1993</td>
<td>Japan</td>
<td>35/39</td>
<td>0.05</td>
<td>0.31</td>
<td>72.1±9.9</td>
<td>75.6±7.8</td>
</tr>
<tr>
<td>Betard et al¹⁶</td>
<td>1994</td>
<td>Canada</td>
<td>97/258</td>
<td>0.12</td>
<td>0.41</td>
<td>69.5±2.9</td>
<td>71.3±6.6</td>
</tr>
<tr>
<td>Chartier-Harlin et al¹⁷</td>
<td>1994</td>
<td>France</td>
<td>36/34</td>
<td>0.05</td>
<td>0.24</td>
<td>80.8±4</td>
<td>79±9</td>
</tr>
<tr>
<td>Frisoni et al¹⁸</td>
<td>1994</td>
<td>Italy</td>
<td>51/93</td>
<td>0.19</td>
<td>0.45</td>
<td>69.2±3.6</td>
<td>73.6±8.2</td>
</tr>
<tr>
<td>Benjamin et al¹⁹</td>
<td>1995</td>
<td>UK</td>
<td>46/45</td>
<td>0.15</td>
<td>0.47</td>
<td>75.1±9.6</td>
<td>80.9±6.1</td>
</tr>
<tr>
<td>Benjamin et al²⁰</td>
<td>1996</td>
<td>Norway</td>
<td>16/52</td>
<td>0.07</td>
<td>0.34</td>
<td>84.1±7.9</td>
<td>85.5±5.9</td>
</tr>
<tr>
<td>Fallin et al²¹</td>
<td>1997</td>
<td>USA</td>
<td>228/117</td>
<td>0.14</td>
<td>0.32</td>
<td>72.7±6.9</td>
<td>74±7</td>
</tr>
<tr>
<td>Wang et al²²</td>
<td>2000</td>
<td>USA</td>
<td>274/235</td>
<td>0.11</td>
<td>0.30</td>
<td>&gt;65</td>
<td>&gt;65</td>
</tr>
<tr>
<td>Jacquier et al²³</td>
<td>2001</td>
<td>Colombia</td>
<td>1665/121</td>
<td>0.07</td>
<td>0.23</td>
<td>65.8±7.2</td>
<td>73.3±9.5</td>
</tr>
<tr>
<td>Molero et al²⁴</td>
<td>2001</td>
<td>Venezuela</td>
<td>44/83</td>
<td>0.11</td>
<td>0.17</td>
<td>&gt;65</td>
<td>&gt;65</td>
</tr>
<tr>
<td>Hoshino et al²⁵</td>
<td>2002</td>
<td>Japan</td>
<td>40/82</td>
<td>0.09</td>
<td>0.29</td>
<td>71.5±6.9</td>
<td>77±6.8</td>
</tr>
<tr>
<td>Souza et al²⁶</td>
<td>2003</td>
<td>Brazil</td>
<td>58/68</td>
<td>0.12</td>
<td>0.25</td>
<td>&gt;65</td>
<td>71.5±0.5</td>
</tr>
<tr>
<td>Raygani et al²⁷</td>
<td>2005</td>
<td>Iran</td>
<td>129/125</td>
<td>0.06</td>
<td>0.21</td>
<td>73±11.4</td>
<td>75.2±10.2</td>
</tr>
<tr>
<td>Gdovinova et al²⁸</td>
<td>2006</td>
<td>Slovak</td>
<td>111/94</td>
<td>0.02</td>
<td>0.12</td>
<td>75.0±9.11</td>
<td>74.2±9.94</td>
</tr>
<tr>
<td>Raygani et al²⁹</td>
<td>2006</td>
<td>Iran</td>
<td>166/61</td>
<td>0.06</td>
<td>0.22</td>
<td>72±11.4</td>
<td>74.2±10</td>
</tr>
<tr>
<td>Bahia et al³⁰</td>
<td>2008</td>
<td>Brazil</td>
<td>120/120</td>
<td>0.10</td>
<td>0.30</td>
<td>75.2±2.9</td>
<td>72.5±8.6</td>
</tr>
<tr>
<td>Smach et al³¹</td>
<td>2010</td>
<td>Tunisia</td>
<td>113/93</td>
<td>0.08</td>
<td>0.29</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Gozalpouri et al³²</td>
<td>2010</td>
<td>Iran</td>
<td>506/735</td>
<td>0.02</td>
<td>0.12</td>
<td>77.1±6.9</td>
<td>78±7.8</td>
</tr>
<tr>
<td>Lovati et al³³</td>
<td>2010</td>
<td>Italy</td>
<td>162/154</td>
<td>0.16</td>
<td>0.50</td>
<td>&gt;65</td>
<td>73.8±0.36</td>
</tr>
<tr>
<td>Rassas et al³⁴</td>
<td>2011</td>
<td>Tunisia</td>
<td>71/58</td>
<td>0.12</td>
<td>0.31</td>
<td>69±15.18</td>
<td>73±9.09</td>
</tr>
</tbody>
</table>
significantly higher in AD cases compared with control subjects (35% versus 11.43%, \( p < 0.001 \)). In addition, this rate was significantly different in various geographic regions (\( p < 0.01 \)). The OR of APOE \( \varepsilon 4 \) allele frequency in AD and control groups was 3.98. The funnel plot, a bivariate scatter plot of standard error against intervention effect, was reasonably symmetric, although the funnel plot asymmetry may raise the possibility of publication bias (Figure 4). The ORs of APOE \( \varepsilon 4 \) allele frequency in AD and control groups in various geographic regions are presented in Figure 5.

**Discussion.** A powerful approach to identify genetic factors that influence susceptibility to common disease is association studies.\(^{31}\) Systematic reviews and meta-analyses can collate evidence across all studied genetic variants for a phenotype. The notable examples of these studies are provided by 3 databases of genetic association evidence for AD, Parkinson disease, and schizophrenia.\(^{32,33}\) By attention to different distributions of the APOE \( \varepsilon 4 \) allele and ORs of disease in various populations and geographic areas, the differential studies to identify allele frequency, carrier-disease relations, and disease kinetics seem necessary. The first report of an association between the APOE \( \varepsilon 4 \) allele and AD was in 1993.\(^{34}\) Nowadays, the APOE \( \varepsilon 4 \) allele is the most frequently reported allele in association with LOAD.

Results of this evaluation show that the APOE \( \varepsilon 4 \) allele appears in LOAD patients 3.98 times more than controls. This factor is variable (2.45-4.97) according to their geographic localizations and ethnic considerations (Figures 3 & 5). The present systematic review and meta-analysis revealed an ORs of 4.9 for association of
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the APOE ε4 allele with LOAD in Asia, which is in the maximum range compared with other geographic regions. South America is the lowest, with a 2.45 OR.

The APOE ε4 allele prevalence varies among AD patients by region.35 The particulars of the ε4 allele association with AD in various geographic areas may result from complex gene-nutrient, gene-gene, and gene-environment interactions. For example, the dietary habits of children from Tunisia include a higher total caloric, monounsaturated fatty acid and fiber intake, and a lower saturated fatty acid and cholesterol intake.29 On the other hand, the ε4 allele has also been associated with familial hypercholesterolemia.34 In addition, cholesterol has been shown to affect amyloid production, and increased amyloid levels have been associated with an increased risk of AD.4,36 So LOAD is a complex and multi factorial disease, and the ε4 allele is a most important factor with different impact in various areas. Supernumerary research and meta-analyses are necessary to understanding other genetic and environmental risk factors impact.

In conclusion, genetic testing of this allele is not routinely considered in clinical practice, however, the determination of this allele in populations (especially in high OR geographic areas) may be a useful tool for monitoring demented patients and planning healthcare policies, especially for the elderly. Meta-analysis studies can be a useful procedure for this purpose. It must be pointed out that there were some limitations in access to some of the publications in our study. Thus, complementary studies are necessary to cover other publications, and future studies are required to clarify the effects of the other genetic variables on sporadic LOAD.

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References


