Review Article
Relationship between apolipoprotein E gene polymorphism and Parkinson’s disease: a meta-analysis

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Abstract: The Apolipoprotein E (APOE) gene, with its 3 common isoforms (E2, E3 and E4), was such a candidate risk gene in Parkinson’s disease explored by many case-control studies, but the conclusion still remains contradictory and inconclusive. To identify the association between APOE gene polymorphism and the risk of PD, we performed this meta-analysis. A total of 63 eligible published studies including 8546 PD cases and 10403 health controls were searched up to 5th, 2015 in the final analysis. All literature was searched in PUBMED, EMBASE, Web of science, Wanfang Data and China National Knowledge Infrastructure. Overall, no significant association was found between APOE gene polymorphism and Parkinson’s disease risk under four genetic models (E2 allele vs. E3 allele: OR = 1.16, 95% = 0.967-1.398, P = 0.11; E4 allele vs. E3 allele: OR = 1.10, 95% = 0.9998-1.2179, P = 0.0507; E2 carriers vs. E3 carriers: OR = 1.07, 95% CI = 0.873-1.305, P = 0.52; E4 carriers vs. E3E3: OR = 1.12, 95% CI = 0.992-1.264, P = 0.066). The results of subgroup analysis by ethnicity showed no significant association was observed in both Caucasians and Asians. No potential publication bias was detected in any genetic model in our meta-analysis which suggested the stability of our results. In conclusion, our study suggests that APOE gene polymorphism were not associated with PD risk.

Keywords: APOE, polymorphism, Parkinson’s disease, meta-analysis

Introduction
Parkinson’s disease (PD) is the 2nd most common neurodegenerative disorder among the elderly population, which affects about 2% of the population older than 65 years of age, although it has been observed in younger people [1, 2]. It is clinically characterized by parkinsonism (resting tremors, rigidity, slowness of movement, postural imbalance) [3] and pathologically by the loss of neurons in the substantia nigra and in association with the presence of ubiquitinated protein deposits in the cytoplasm of neurons [4]. After English doctor James Parkinson describe this disorder for the first time, people argue whether hereditary or environmental factor is the main factor of PD. With the discovering of disease-causing gene α-synuclein and Parkin, the role of hereditary factor has been recognized gradually [5, 6]. Significant researches have been conducted to establish the relationship between the functional variants of genes and the risk of PD in different ethnic groups across the world, including UCHL1 (ubiquitin carboxy-terminal hydrolase L1), NURR1 (nuclear receptor-related 1), DJ-1, PINK1 genes and so on [7, 8].

Apolipoprotein E (APOE), located on chromosome 19, with 3 common isoforms (E2, E3 and E4) and 6 genotypes (E2E2, E2E3, E2E4, E3E3, E3E4 and E4E4), encodes a major lipid-binding protein, which serves as a cholesterol carrier [9]. These isoforms are defined by amino acid changes at positions 112 (rs.429358) and 158 (rs.7412) and alleles (E2, E3 and E4) are defined. E3 is the most common isoform, with a frequency of approximately 70-80% [10]. APOE is highly polymorphic and plays an imperative role in endogenous lipoprotein metabolism and tissue distribution. It has been discovered that the presence of the APOE E4 allele is associated with higher levels of total and LDL serum cholesterol while APOE E2 is associated with the lower effect with reference to cholesterol effects from E3 allele [11]. Huang et al [12]
reported the association of lower serum low-density lipoprotein cholesterol level with PD patients which suggested that abnormality in gene of lipid metabolic pathway may contribute to PD.

Numerous case-control studies investigating a role for APOE in PD, however, results in these studies are conflicting. The results of previous meta-analysis have suggested APOE-E2 was a risk factor for susceptibility to Parkinson’s disease [13, 14]. Even so, there are still no consistent perspective about the role of APOE and PD. Therefore, this comprehensive meta-analysis were designed to overcome the limitations of independent studies, resolve inconsistence, reduce the likelihood that random errors were responsible for false association and reveal the real association between APOE polymorphism and the development of PD.

Materials and methods

Literature search

Relevant studies evaluating the APOE gene polymorphism and PD were searched by the following electronic database: Pubmed, Web of Science, Embase, China national Knowledge Infrastructure (CNKI), Wanfang Data, with the last updated search conducted before April 2015. We used various combinations of keywords as search terms, including “apolipoprotein E or APOE”, “Parkinson disease or Parkinson’s disease or PD” without language restriction.

Inclusion and exclusion criteria

The criteria used to include studies in this meta-analysis were as follows: (1) providing information evaluating the association of APOE gene polymorphism with PD; (2) using a case-control or nest case-control design; (3) containing genotype frequency information for calculating an odds ratio (OR) and its 95% confidence interval (CI). If one article was published for more than one time, the one with more comprehensive data would be selected. Reasons for exclusion of studies were: (1) lack of control group; (2) overlapping study populations. A total of 1000 relevant studies were searched, and 900 were excluded, only 63 met all inclusion criteria.

Data extraction

Two reviewers independently viewed all the papers searched from the electronic data and standard protocol was used for data extraction. A third reviewer as served as an arbiter when different opinion occurred. The information extracted from each eligible study: The last name of the first author, publication year, ethnicity of the population studied, number of cases and controls, baseline characteristics of population in each studies, genotype information and frequencies of alleles, Hardy-Weinberg equilibrium (HWE) in controls. It should be noticed that the genotype information were not reported in some papers. Therefore, the frequency of each allele was extracted from each paper or calculated manually if not reported explicitly.

Statistical analysis

Pooled OR (odds ratio) and CI (corresponding 95% confidence intervals) were estimated for the association between APOE gene polymorphism and PD risk. HWE for the controls was assessed in each study by the Chi-square test or Fisher exact test goodness of fit. Genotype E3E3, well accepted as the ‘wild-type’ genotype, is the most common genotype between the healthy population and PD cases with the frequency about 67% [15]. Therefore, genotype E3E3 and allele E3 are designated as reference category. Risk of E2 carriers (E2E2, E2E3 and E2E4 genotypes), E4 carriers (E4E4, E3E4 and E2E4 genotypes) allele E2 and allele E4 are compared with E3E3 and allele E3 respectively. Heterogeneity among studies was measured by Q statistic (P<0.10 was considered statistically significant heterogeneity) and I² statistic. I² values of 25%, 50% and 75% were defined as low, moderate and high heterogeneity respectively. Association of APOE gene polymorphism and PD risk were measured using random or fixed effect models according to the heterogeneity of the study. Begg’s funnel plot and egger’s test [16] was used for assessment of publication bias.

Results

Study characteristics

1864 published papers were relevant to the initial literature search. Finally, 63 eligible stud-
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A
Relevant case-control studies were retrieved from databases (n=1864)

Studies retrieved from other source (n=0)

Delete the reduplicate papers (n=1184)

Studies excluded (not relevant to the analysis) (n=821)

Relevant studies retrieved for more detailed evaluation (n=363)

Excluded (n=300)
- no controls (n=24)
- meeting paper and only has abstract (n=5)
- review paper (n=192)
- not human studies (n=33)
- not sufficient data (n=45)
- republication (n=1)

Studies included in the meta-analysis (n=63)

D
Begg's funnel plot with pseudo 95% confidence limits

logor

s.e. of logor
Meta-analysis of APOE polymorphism with PD
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ies, including 8546 PD cases and 10403 health controls, which reported APOE polymorphism and the risk of PD, were included in this meta-analysis [14, 17-77]. The flow chart of the literature selection was provided in Figure 1. Of the 63 studies, 34 studies conducted in Caucasian, 22 conducted in Asian and 6 studies conducted in mixed population. 55 studies

Figure 1. A. Flow chart of the literature selection; B. Forest plot of the meta-analysis of E2 versus E3; C. Forest plot of the meta-analysis of E4 versus E3; D. Funnel plot of the meta-analysis of E2 versus E3; E. Funnel plot of the meta-analysis of E4 versus E3.
## Meta-analysis of APOE polymorphism with PD

### Table 1. Characteristic of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Numbers</th>
<th>Characteristics of included studies</th>
<th>Genotyping method</th>
<th>HWE in controls</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy</td>
<td>1994</td>
<td>USA/UK</td>
<td>24/35</td>
<td>Age = 75±7</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>Harrington</td>
<td>1994</td>
<td>UK</td>
<td>51/58</td>
<td>Male: 26 age = 77.7 (7.1) Male: 28 age = 78.1 (7.7)</td>
<td>PCR-RFLP</td>
<td>0.233</td>
<td>6</td>
</tr>
<tr>
<td>Marder</td>
<td>1994</td>
<td>US</td>
<td>59/44</td>
<td>Age = 71.2</td>
<td>PCR-RFLP</td>
<td>0.101</td>
<td>7</td>
</tr>
<tr>
<td>Han</td>
<td>1994</td>
<td>US</td>
<td>5/6</td>
<td>Age = 82±6 male: 5 Age = 70±10 male: 3</td>
<td>PCR-RFLP</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Rubinsztein</td>
<td>1994</td>
<td>UK</td>
<td>34/34</td>
<td>Male: 26 age = 57 Age and sex matched</td>
<td>PCR-RFLP</td>
<td>0.416</td>
<td>5</td>
</tr>
<tr>
<td>Podusle</td>
<td>1995</td>
<td>USA</td>
<td>54/77</td>
<td>Age = 74.1±7.5 Age = 71.9±7.4</td>
<td>PCR-RFLP</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Koller</td>
<td>1995</td>
<td>USA</td>
<td>61/78</td>
<td>Male: 38 age = 67.4±7.9 Male: 37 age = 69.0±6.5</td>
<td>PCR</td>
<td>0.063</td>
<td>6</td>
</tr>
<tr>
<td>Martinoli</td>
<td>1995</td>
<td>Canada</td>
<td>10/243</td>
<td>Age = 24-86 Age = NA</td>
<td>PCR-RFLP</td>
<td>0.147</td>
<td>5</td>
</tr>
<tr>
<td>Morris</td>
<td>1996</td>
<td>UK</td>
<td>11/99</td>
<td>NA</td>
<td>PCR-RFLP</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Egensperger</td>
<td>1996</td>
<td>Germany/Austria</td>
<td>20/54</td>
<td>Age = 76±6.2 Age = 71.2±9.5</td>
<td>PCR-RFLP</td>
<td>0.462</td>
<td>5</td>
</tr>
<tr>
<td>Helisalmi</td>
<td>1996</td>
<td>Finland</td>
<td>15/60</td>
<td>Male: 8 age = 71±6 Male: 28 age = 69±8</td>
<td>PCR-RFLP</td>
<td>0.016</td>
<td>5</td>
</tr>
<tr>
<td>Whitehead</td>
<td>1996</td>
<td>Ireland</td>
<td>189/162</td>
<td>Male: 123 age = 56.9 (6.6) Male: 101 age = 58 (7.1)</td>
<td>PCR-RFLP</td>
<td>0.242</td>
<td>8</td>
</tr>
<tr>
<td>Durr</td>
<td>1997</td>
<td>France</td>
<td>103/387</td>
<td>Male: 56 age = 56.6 Male: 215 age = 67</td>
<td>PCR</td>
<td>0.426</td>
<td>6</td>
</tr>
<tr>
<td>Ballering</td>
<td>1997</td>
<td>The netherland</td>
<td>50/107</td>
<td>NA</td>
<td>Semi-nested PCR</td>
<td>0.959</td>
<td>5</td>
</tr>
<tr>
<td>Yamamoto</td>
<td>1997</td>
<td>Japan</td>
<td>163/576</td>
<td>Male: 65 age = 59.3 Aged 32-86 years</td>
<td>PCR-RFLP</td>
<td>0.259</td>
<td>5</td>
</tr>
<tr>
<td>Qin B</td>
<td>1998</td>
<td>China</td>
<td>36/60</td>
<td>Male: 24 age = 66.6±10.3 Male: 55 age = 68.1±9.2</td>
<td>PCR-RFLP</td>
<td>0.014</td>
<td>5</td>
</tr>
<tr>
<td>Li JR</td>
<td>1998</td>
<td>China</td>
<td>52/438</td>
<td>Male: 31 age = 58.8±12.6 Male: 228 age = 53.16±13.3</td>
<td>PCR-RFLP</td>
<td>0.003</td>
<td>4</td>
</tr>
<tr>
<td>Grassbon-Frodl</td>
<td>1999</td>
<td>Germany</td>
<td>62/53</td>
<td>Male: 29 age = 70 Male: 22 age = 71</td>
<td>PCR-RFLP</td>
<td>0.459</td>
<td>6</td>
</tr>
<tr>
<td>Bon</td>
<td>1999</td>
<td>The Netherland</td>
<td>50/96</td>
<td>NA</td>
<td>Semi-nested PCR</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Kruger</td>
<td>1999</td>
<td>Germany</td>
<td>193/177</td>
<td>Male: 108 age = 66.53 (11.08) Resemble age and sex of PD group</td>
<td>PCR-RFLP</td>
<td>0.186</td>
<td>6</td>
</tr>
<tr>
<td>Oliveri</td>
<td>1999</td>
<td>Italy</td>
<td>126/119</td>
<td>Male: 72 age = 65.8 (9.01) Male: 57 age = 66.3 (8.5)</td>
<td>PCR-RFLP</td>
<td>&lt;0.001</td>
<td>6</td>
</tr>
<tr>
<td>Lu XL</td>
<td>1999</td>
<td>China</td>
<td>72/66</td>
<td>Male: 46 age = 60.7±11.8 Male: 39 age = 77±7.5</td>
<td>PCR-RFLP</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>Zhang JW</td>
<td>1999</td>
<td>China</td>
<td>72/438</td>
<td>Age = 60.67±11.68 Age = 65.88±9.5</td>
<td>PCR-RFLP</td>
<td>0.003</td>
<td>5</td>
</tr>
<tr>
<td>Maraganore</td>
<td>2000</td>
<td>USA</td>
<td>139/113</td>
<td>Male: 90 age = 69 (39-91) Male: 39 age = 62 (31-82)</td>
<td>PCR</td>
<td>0.325</td>
<td>7</td>
</tr>
<tr>
<td>Zeng XY</td>
<td>2000</td>
<td>China</td>
<td>54/234</td>
<td>Male: 37 age = 68±6.1 Male: 158 age = 59.2±16.3</td>
<td>PCR-RFLP</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>Higuchi</td>
<td>2000</td>
<td>Japan</td>
<td>140/382</td>
<td>Male: 61 age = 56.5±9.5 Male: 117 age = 74.0±5.6</td>
<td>PCR</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Goetz</td>
<td>2001</td>
<td>US</td>
<td>44/44</td>
<td>NA</td>
<td>PCR-RFLP</td>
<td>0.811</td>
<td>5</td>
</tr>
<tr>
<td>Qin B</td>
<td>2001</td>
<td>China</td>
<td>54/234</td>
<td>Male: 37 age = 68.2±6.1 Male: 158 age = 59.2±16.3</td>
<td>PCR-RFLP</td>
<td>&lt;0.001</td>
<td>6</td>
</tr>
<tr>
<td>Wang F</td>
<td>2001</td>
<td>China</td>
<td>40/52</td>
<td>Male: 28 age = 66.13±7.32 Male: 30 age = 65.50±8.07</td>
<td>PCR-RFLP</td>
<td>0.745</td>
<td>6</td>
</tr>
<tr>
<td>Hao YX</td>
<td>2001</td>
<td>China</td>
<td>64/101</td>
<td>Male: 37 age = 63±11 Male: 53 age = 62±11</td>
<td>PCR-RFLP</td>
<td>&lt;0.001</td>
<td>7</td>
</tr>
<tr>
<td>Eerola</td>
<td>2002</td>
<td>Finland</td>
<td>147/137</td>
<td>Male: 87 age = 65.8 Male: 50 age = 67.2</td>
<td>PCR-RFLP</td>
<td>0.516</td>
<td>7</td>
</tr>
<tr>
<td>Tang GM</td>
<td>2002</td>
<td>China</td>
<td>68/160</td>
<td>Male: 35 age = 65.61±5.42 Male: 84 age = 55.81±15.46</td>
<td>PCR-RFLP</td>
<td>&lt;0.001</td>
<td>7</td>
</tr>
<tr>
<td>Schulte</td>
<td>2003</td>
<td>Germany</td>
<td>382/306</td>
<td>Male: 206 age = 67.5 (10.5) Male: 159 age = 72 (4.3)</td>
<td>PCR-RFLP</td>
<td>0.544</td>
<td>6</td>
</tr>
</tbody>
</table>

## Meta-analysis of APOE polymorphism with PD

Zhao XP 2003  China  68  110  Male: 40 age = 63±11  Male: 59 age = 75±9  PCR-RFLP  0.080  7  
Zhou CW 2004  China  36  52  Age = 67.4±10.2  Male: 33 age = 69.4±11.4  PCR-RFLP  0.024  5  
Martinez 2005  Mixed  387  257  NA  NA  PCR-RFLP  0.488  6  
Ghebremedhin 2006  The Netherland  108  108  Male: 62 age = 75.1±6.9  Male: 62 age = 75.1±6.9  PCR  0.008  6  
Troster 2006  USA  62  146  NA  NA  PCR  0.135  5  
Blazquez 2006  Spain  276  212  Male: 162 age = 71.1±10.2  Male: 110 age = 70.9±8  PCR-RFLP  0.104  6  
Papapertropoulos 2007  USA  118  91  Male: 85 age = 77±7.9  Male: 43 age = 79.1±12.8  PCR  0.619  5  
Buchanan 2007  USA  422  387  Male: 239 age = 66.95±9.8  Male: 114 age = 64.16±10.83  PCR  0.505  7  
Lopez 2007  Mexico  229  229  Male: 138 age = 62.28±12.85  Male: 138 age = 63.97±11.23  PCR-RFLP  0.681  6  
Ma AJ 2007  China  133  105  Male: 73 age = 68.38±9.18  Male: 62 age = 68.26±9.18  PCR-RFLP  0.362  6  
Mi DH 2007  China  68  56  Male: 41 age = 67±7.09  Male: 30 age = 68.26±9.18  PCR-RFLP  0.558  6  
McCulloch 2008  USA  932  664  Male: 636 age = 67.3  Male: 73 age = 67.3  PCR-RFLP  \  6  
Mario 2008  Spain  138  91  Male: 80 age = 56±8.4  Male: 40 age = 67±9.2  PCR-RFLP  0.087  5  
Chen T 2008  China  26  49  Age = 73.38±9.68  Male: 40 age = 70.1±8.4  PCR-RFLP  0.729  6  
Gallegos-Arreola 2009  Mexico  105  107  Male: 63 age = 63±9  Male: 47 age = 50±14  PCR-RFLP <0.001  4  
Williams-Gray 2009  UK  505  478  Male: 303 age = 62.5±11.8  Male: 229  Taqman  0.304  6  
Kurz 2009  Norway  95  73  NA  NA  PCR-RFLP  0.000  5  
Ryu 2010  Korea  234  192  Male: 68 age = 71.1±8.2  Male: 97 age = 72.2±4.4  PCR  0.404  7  
Wang Y 2010  China  150  100  Male: 88 age = 68.38±9.18  Male: 55 age = 68.26±9.18  PCR  0.389  6  
Vefring 2010  Norway  203  187  Male: 120 age = 68.2±9.1  Male: 99 age = 66.2±9.6  LightCycler  \  6  
Kiyohara 2011  Japan  238  296  Male: 91 age = 68.5±8.68  Male: 114 age = 69.7±5.63  Taqman  0.086  5  
Pulkes 2011  Thailand  155  158  Male: 88 age = 61.2±9.8  Age: older than 65  PCR-RFLP  0.423  5  
van den Berge 2012  The Netherland  9  10  Male: 7 age = 79  Male: 7 age = 82  NA  0.050  4  
Maarouf 2012  USA  43  49  Male: 30 age = 79 (64-90)  Male: 31 age = 83 (68-97)  NA  \  5  
Gregorio 2013  Brazil  232  137  Male: 143 age = 69.2±11.1  Male: 66 age = 71.7±8.5  PCR-RFLP  0.515  6  
Peplonska 2013  Poland  407  305  Male: 223 age = 64.2±11.6  Male: 85 age = 70.36±5.9  Taqman  0.195  7  
Dong X 2013  China  50  50  Male: 34 age = 65.93±11.28  Male: 30 age = 65.02±9.19  PCR-RFLP  0.734  6  
Singh 2014  India  70  100  Male: 38 age = 58.01±8.62  Male: 61 age = 59.71±8.11  PCR-RFLP  0.588  5  
Wang YQ 2014  China  85  280  Male: 50 age = 65.53±6.54  Male: 141 age = 66.74±7.25  PCR  0.343  5  

NA: Not available; HWE: Hardy-Weinberg equilibrium; PCR-RFLP: Polymerase chain reaction with restriction fragment length polymorphism; NOS: Newcastle-ottawa quality assessment scale case control studies; PD: Parkinson’s disease.
Meta-analysis of APOE polymorphism with PD

Table 2. Main result of meta-analysis

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Group</th>
<th>No. of studies</th>
<th>Test of association</th>
<th>Test of heterogeneity</th>
<th>Test of association</th>
<th>Test of heterogeneity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>z</td>
<td>P*</td>
<td>Model</td>
</tr>
<tr>
<td>E2 allele vs. E3 allele</td>
<td>ALL</td>
<td>62</td>
<td>1.16</td>
<td>0.97-1.40</td>
<td>0.110</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>ALL in HWE</td>
<td>40</td>
<td>1.03</td>
<td>0.91-1.17</td>
<td>0.646</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasians</td>
<td>39</td>
<td>1.12</td>
<td>1.01-1.24</td>
<td>0.029</td>
<td>F</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Asians</td>
<td>23</td>
<td>1.00</td>
<td>0.60-1.65</td>
<td>0.989</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>High quality</td>
<td>56</td>
<td>1.06</td>
<td>0.91-1.24</td>
<td>0.430</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td>E4 allele vs. E3 allele</td>
<td>ALL</td>
<td>63</td>
<td>1.10</td>
<td>0.99983-1.22</td>
<td>0.0507</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>ALL in HWE</td>
<td>40</td>
<td>1.01</td>
<td>0.93-1.11</td>
<td>0.813</td>
<td>F</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Caucasians</td>
<td>40</td>
<td>1.05</td>
<td>0.94-1.16</td>
<td>0.392</td>
<td>R</td>
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<td>Asians</td>
<td>23</td>
<td>1.23</td>
<td>0.99-1.52</td>
<td>0.058</td>
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<td></td>
<td>High quality</td>
<td>56</td>
<td>1.06</td>
<td>0.99-1.13</td>
<td>0.516</td>
<td>F</td>
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<td>E2 carriers vs. E3E3</td>
<td>ALL</td>
<td>54</td>
<td>1.17</td>
<td>0.94-1.45</td>
<td>0.165</td>
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<td>0.90-1.18</td>
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<td>32</td>
<td>1.10</td>
<td>0.97-1.24</td>
<td>0.132</td>
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<td>Asians</td>
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<td>E4 carriers vs. E3E3</td>
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<td>1.05</td>
<td>0.95-1.15</td>
<td>0.361</td>
<td>R</td>
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- Z test was used to determine the significance of overall OR. P<0.05 was considered to be significant; **b. Model**: F: Fixed-effects model; R: Random-effects model; Q test was used to determine heterogeneity. P>0.1 & I² ≤40%, Fixed-effects model was used, P≤0.1 & I² >40%, Random-effects model was used; OR: Odds ratio; CI: Confidence interval; PD: Parkinson’s disease; APOE: Apolipoprotein.

provided the data of genotypes while 8 studies only provide the alleles frequencies. Of these 55 studies, the genotype frequencies in 40 are in line with HWE among the controls, and other 15 deviated from HWE. According to the Newcastle-ottawa quality assessment scale case control studies, 56 studies were rated as high quality and 7 were rated as low quality. The characteristics of studies were presented in Table 1.

**Main results of meta-analysis**

The main results of meta-analysis regarding the relationship between E2, E4 and PD were showed in Table 2.

No significant association was found between APOE-E2 allele and PD risk under two genetic models (E2 allele vs. E3 allele: OR = 1.16, 95% CI = 0.967-1.398, P = 0.11; E2 carriers vs. E3E3: OR = 1.07, 95% CI = 0.873-1.305, P = 0.52). In the subgroup analyses according to ethnicity, no significant association was observed in Asians but a significantly increased risk for APOE-E2 allele and PD risk in Caucasians population (E2 allele vs. E3 allele: OR = 1.12, 95% CI = 1.012-1.237, P = 0.029). No significant association were found in the stratified analysis by studies conformed to HWE and quality of studies.

The similar results were obtained in APOE-E4 allele and PD risk under two genetic models (E4 allele vs. E3 allele: OR = 1.104, 95% CI = 0.9998-1.2197, P = 0.051; E4 carriers vs. E3E3: OR = 1.12, 95% CI = 0.992-1.264, P = 0.066). When stratified by ethnicity, conformed to HWE and quality of studies, no significant association...
was observed. The stratified analysis by ethnicity conformed to HWE and quality of studies.

Comparison of prevalence of E2 vs. E3 alleles, under a random-effect model, among cases and controls showed no significant association (E2 allele vs. E3 allele: OR = 1.16).

Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of single study on the pooled results by omitting individual studies in turn. After excluding the studies deviating from HWE, we obtained almost the same results, suggesting that our results were statistically robust.

Public bias

Begg’s test and Egger’s test were examined to assess publication bias. The shape of the funnel plots showed no evidence of obvious asymmetry in any genetic models. (E2 allele vs. E3 allele: P = 0.619; E4 allele vs. E3 allele: P = 0.889; E2 carriers vs. E3E3: P = 0.975; E4 carriers vs. E3E3: P = 0.864).

The results of Egger’s test also indicated a lack of publication bias for all genetic models (E2 allele vs. E3 allele: t = -0.22, P = 0.829; E4 allele vs. E3 allele: t = 0.415; E2 carriers vs. E3E3: t = -0.08, P = 0.937; E4 carriers vs. E3E3: t = 1.01, P = 0.317).

Discussion

The roles of genetic polymorphisms of APOE in susceptibility to PD had been well investigated by many case-control studies but the results still remain contradictory. Kiyohara [72] suggested that the APOE polymorphism might play an important role in PD susceptibility in Japanese population, while Gregorio [75] found that the APOE polymorphism did not distinguish PD patients from controls. Estimation of the correlation might be conducted on small sample size, and the confused results were concluded unsurprisingly. To summarize the published literature and clarify the relationship between APOE polymorphism and PD. Therefore, a meta-analysis of all studies available is imperative to estimate this relationship and provide a reliable evidence on statistical power.

In this meta-analysis, systematic literature search in different databases were carried out and included 63 independent studies of 8546 PD cases and 10403 health controls. The present meta-analysis suggested that there was no significant association of APOE gene polymorphism and PD risk in overall comparisons and subgroup analyses by studies conformed to HWE and quality of studies. Therefore the polymorphism of APOE gene may not play a vital role in the risk of PD, which conflicted with the conclusion of previous meta-analysis [14, 21, 22].

Subgroup analysis was performed by ethnicity. In Asians, pooled estimates showed that the association between APOE-E2, APOE-E4 and PD were not significant in contrast of genetic mode of E2 allele vs. E3 allele, E2 carriers vs. E3E3, E4 allele vs. E3 allele and E4 carriers vs. E3E3. However the analyses by ethnicity found that APOE gene polymorphism was significant associated with an increased risk for PD under genetic mode of E2 allele vs. E3 allele in Caucasians, which suggested that the association of APOE gene polymorphism and PD might be different in Asians and Caucasians. The differences may be explained by genetic diversity and gene-gene, gene-environment interactions varied greatly by different ethnic background.

APOE E4 allele has been associated with high levels of serum cholesterol and low-density lipoprotein cholesterol (LDL cholesterol) while E2 allele has been associated with low levels of serum cholesterol and LDL cholesterol [69]. Huang [12] found the association of lower serum LDL cholesterol level with PD patients which suggest that altered lipid metabolism and abnormalities in genes/proteins of the lipid metabolic pathway may contribute to PD risk.

It is noteworthy that only 40 of 63 studies conformed to HWE in our meta-analysis, 8 literatures did not have genotype information and other 15 studies deviated from HWE in controls. Deviation from HWE may induce genotyping error, ethnic heterogeneity, publication bias or other factors. The results, including all studies in agreement with HWE, showed that the association between E2 and PD were not significant, different with the results that including all studies. The difference of the results may be explained by heterogeneity of studies.

In our meta-analysis, we observed heterogeneity in overall comparisons of E2 allele vs. E3 allele, E2 carriers vs. E3E3, E4 allele vs. E3
Meta-analysis of APOE polymorphism with PD

allele and E4 carriers vs. E3E3, which may affect the stability of this study. When stratified by ethnicity, severe heterogeneity was observed among Asians only in E4 allele vs. E3 allele model. Hence, the ethnicity may contribute to the heterogeneity. When significant heterogeneity was detected in any genetic models, random effects model was adopted for the analysis. Publication bias is a potential factor that may influence the results of our study. In this meta-analysis no obvious publication bias were identified in any genetic models, which strengthening this conclusion.

Although quite a few studies were included in our meta-analysis, some limitations should be taken into account. Firstly, due to the lack of genotypes information, the data which could be used for genotype models were less than that of allele models. Secondly, the controls of each eligible study came from different population while others were based on hospital population, therefore, the controls may not be representative of the underlying source population. Thirdly, the controls of several studies were not accord with Hardy-Weinberg equilibrium expectations. Fourthly, our results were based on unadjusted evaluate due to the insufficient of original data. Furthermore, for the sufficient of original data, such as individual gender and age information, it was hard for us to perform further subgroup analysis which would help to detect heterogeneity of this study. Finally, we only searched the literature in English or Chinese in published. It is possible that several unpublished articles with negative results or studies in other languages were missed.

In conclusion, our meta-analysis demonstrates that APOE polymorphism was not associated with altered risk for Parkinson’s disease. Considering the limitation of this meta-analysis, further well-designed and large sample sizes regarding the association of APOE polymorphism and PD should be conducted in the future.

Disclosure of conflict of interest

None.

Abbreviations

APOE, Apolipoprotein E; PD, Parkinson’s disease; OR, odds ratio; CI, confidential interval.

References

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