Research article

APOE rs405509 polymorphism and Parkinson’s disease risk in the Chinese population

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A B S T R A C T

Parkinson’s disease (PD) is the second most common progressive neurodegenerative disorder with complex etiology involving both genetic and environmental factors. Apolipoprotein E (ApoE) rs405509 (−219 T/G), a promoter SNP, controls the expression of APOE gene, and plays a modifier effect of APOE ε4 on the susceptibility of Alzheimer’s disease. In this study, we investigate the association between APOE rs405509 polymorphism and the susceptibility of PD in a Chinese population. A total of 1020 subjects were collected including 510 sporadic PD patients (mean age: 63.11 ± 9.28 years) and 510 healthy control subjects (mean age: 62.97 ± 9.09 years). APOE rs405509 polymorphism was genotyped using a TaqMan genotyping method. The Hardy-Weinberg Equilibrium (HWE) was calculated for the control group by Chi-square (χ²) test. The strength of this association between the APOE rs405509 polymorphism and PD risk was evaluated with crude odds ratios (ORs) and 95 % confidence intervals (CIs) using a logistic regression analysis. The T allele frequency was 0.84 and 0.70 in the PD and control groups, respectively. T allele carriers of rs405509 were associated with an increased overall risk of PD and in male subjects in the allele, recessive, and additive genetic models. Similar results in female subjects were found in the allele and recessive genetic models. In conclusion, our study suggests that the APOE rs405509 T allele is correlated with increased susceptibility of PD in a Chinese population.

1. Introduction

Parkinson’s disease (PD) is the second most common progressive neurodegenerative disorder after Alzheimer’s disease (AD) with complex etiology involving both genetic and environmental factors. To date, the etiology of PD still remains unclear [1]. The genetic factor is complicated, including Mendelian inherited genes and non-Mendelian factors, and the environmental factors include aging, caffeine, tobacco, black tea, and pesticides [2–4]. The prevalence of PD will be 8.7 ~ 9.3 million by the year 2030 [5]. Mendelian inherited genes linked to PD include SNCA, LRRK2, VPS35, Parkin, PINK1, DJ1, etc. Non-Mendelian factors include single nucleotide polymorphisms of numerous genes, such as APOE, CCDC62, BDNF [6–8].

ApoE plays essential roles in the regulation of cholesterol transport, neuronal signaling, and synaptic plasticity. APOE ε4 is associated with numerous neurodegenerative conditions such as AD and PD [6]. In addition, the promoter single nucleotide polymorphism (SNP), rs405509 (−219 T/G), has been found to control the APOE gene expression, and plays a modifier effect of APOE ε4 on the susceptibility of AD or as an independent risk factor [9]. Pal P et al., reported that the haplotype of two APOE promoter SNPs (rs449647-A, rs405509-G) was over represented among female PD patients posing risk in Eastern India [10]. In Chinese population, the relationship between APOE rs405509 polymorphism and PD risk has not been studied.

In this study, we studied the correlation between APOE rs405509 polymorphism and PD risk in a Chinese population involving 1020 subjects.

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2. Materials and methods

2.1. Subjects

A total of 1020 Chinese subjects comprising 510 sporadic PD patients (mean age: 63.11 ± 9.28 years) and 510 healthy control subjects (mean age: 62.97 ± 9.09 years) were collected in this study. The PD patients were recruited from Tongji hospital, between Nov 2015 and Dec 2019. PD was diagnosed according to the 2015 MDS Clinical Diagnostic Criteria [11]. Unrelated healthy volunteers with matched ethnicity, gender, and age were enrolled as the control group. This study was approved by the ethics committee of Tongji Hospital. We obtained written informed consent from all participants.

2.2. DNA extraction and genotyping

2 mL peripheral blood samples were collected for genomic DNA extraction using NP698-C system (TIANLONG, Xi’an, China). APOE rs405509 polymorphism was genotyped using a TaqMan genotyping method (Nanjing BioSteel BioTechnologies Co. Ltd, Nanjing, China). The 5 μL reaction solution included 2 μL TaqMan SNP Genotyping Master Mix (2X), 0.8 μL H2O, 0.125 μL 10 μM probe (two probes), 0.225 μL 20 μM Primer (Forward and Reverse), and 1 μL DNA. The Genotyping was performed on the LightCycler480 using 384 well plate (Roche, Switzerland). The following PCR primers were used: Forward: 5′-GTGGGCAATGAGGTCCTTGA-3′, Reverse: 5′-GTCAGGAAAGGACTCTGG-3′, Probe for rs405509-T: VIC-CAGTAATCCAGACCC-MGB, Probe for rs405509-G: FAM-CAGTAATCCAGACCC-MGB. The PCR was performed as following: 95 °C 10 min, followed by 40 cycles of 95 °C 15 s and 60 °C 30 s.

2.3. Statistical analyses

Data were shown as the mean ± SD. All data were analyzed using SPSS 16.0 (SPSS, IL, USA). Hardy-Weinberg Equilibrium (HWE) was calculated for control group with Chi-square (χ²) test. The strength of this association between the APOE rs405509 polymorphism and PD risk was evaluated with crude odds ratios (ORs) and 95% confidence intervals (CIs) using a logistic regression analysis. P < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of the subjects

1020 subjects were collected in this study composing 510 sporadic PD patients (mean age: 63.11 ± 9.28 years) and 510 healthy control subjects (mean age: 62.97 ± 9.09 years). Male subjects accounted for 56.9% of both groups. No significant difference was observed in age between the two groups. More detailed data can be found in Table 1.

3.2. APOE rs405509 polymorphism

There was a significant correlation between APOE rs405509 polymorphism and PD risk in the allele (T vs G, OR = 2.179, 95% CI = 1.759–2.699, P = 0.000), recessive (TT vs GG + GT, OR = 2.950, 95% CI = 2.264–3.843, P = 0.000), and additive (TT vs GG, OR = 1.963, 95% CI = 1.230–3.133, P = 0.005) genetic models (Table 2). The control group followed the HWE principle (P = 0.784).

Stratification was performed by gender. There was a significant correlation between APOE rs405509 polymorphism and PD risk in the allele (T vs G, OR = 2.463, 95% CI = 1.843–3.921, P = 0.000), recessive (TT vs GG + GT, OR = 3.178, 95% CI = 2.226–4.538, P = 0.000), and additive (TT vs GG, OR = 2.602, 95% CI = 1.404–4.824, P = 0.002) genetic models in male subjects (Table 3). Within the female population, significant association was found in the allele (T vs G, OR = 1.866, 95% CI = 1.356–2.567, P = 0.000), recessive (TT vs GG + GT, OR = 2.683, 95% CI = 1.806–3.984, P = 0.000) genetic model (Table 4).

Taken together, significant correlation between APOE rs405509 polymorphism and PD risk was found in allele, recessive, and additive genetic models in the overall population and male subgroup. Significant association was found in allele and recessive genetic models in female subgroups.

4. Discussion

ApoE is an essential component of several lipoproteins playing vital role in lipid metabolism, consisted of 299 amino acids and widely expressed in the brain by neurons, glia, and macrophages [12]. The genotype of APOE is determined by two SNPs (rs429358 and rs7412) resulting in six genotypes (ɛ3/ɛ3, ɛ3/ɛ4, ɛ4/ɛ4, ɛ3/ɛ2, ɛ2/ɛ2, and ɛ2/ɛ4) and three protein isoforms (E2, E3 and E4), among which ApoE4 (caused by ɛ3/ɛ4 or ɛ4/ɛ4) is a confirmed risk factor for AD [13]. APOE ɛ4 increases the PD risk and decreases the onset age of PD [14]. Iwaki H et al., found that APOE ɛ4 was correlated with greater cognitive deficits in PD patients in 12 longitudinal patients’ cohorts [15]. However, Mengel D et al., reported that APOE ɛ4 did not affect cognitive performance in PD patients [16].

APOE rs405509 is one of the two promoter SNPs of APOE gene. The rs405509-T showed only 60% promoter activity compared with rs405509-G [9]. Dysregulated expression of ApoE has been found in PD [17]. The association between APOE rs405509 polymorphism and PD risk is seldomly investigated [10].

In this study, we found that the APOE rs405509 T allele was associated with increased PD risk in a Chinese population. Pal P et al., showed no correlation between APOE rs405509 polymorphism and PD risk in Eastern India, however, they found that the haplotype of rs449647-A and rs405509-G was over represented among female PD patients posing risk [10]. This difference may be caused by genetic background. The frequencies of T allele of rs405509 were 0.57 and 0.70 in the study by Pal P et al., and the current study, respectively. Choi KY et al., also found that the genotype frequency of APOE rs405509 varied among East Asian, European ancestry, and African ancestry [9]. In our study the T allele of rs405509 was higher than previously reported studies [9,10], indicating the genetic difference in different ethnic groups.

In the current study, PD group had higher male patients as compared with females (56.9% vs 43.1%), which is consistent with that fact that the incidence of PD largely affects the males [18]. The association between APOE rs405509 and the susceptibility of PD varied slightly in male and female subjects. Significant association between APOE rs405509 polymorphism and PD risk were found in allele, recessive, and additive genetic models in males, while this association was observed in allele and recessive genetic models in females.

Some limitations exist here. Serum ApoE level was not measured. APOE ɛ4 status was unclear. The statistics was only adjusted by gender and age. The stratification was only performed by gender. The stratification by stage was not performed. Early onset PD (EOPD) was commonly defined by the cutoff of age < 50 years [19]. In this study,
only 30 and 32 subjects were aged < 50 years in PD and control groups, respectively.

5. Conclusion

In conclusion, our study suggests that the \textit{APOE} rs405509 T allele is correlated with increased susceptibility of PD in a Chinese population. Further studies with larger sample sizes considering ApoE level, \textit{APOE} \(\varepsilon4\) status are needed to further investigate the role of \textit{APOE} in the pathogenesis of PD.

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CRediT authorship contribution statement

Ming Huang: Data curation. Yu Wang: Resources. Lu Wang: Data curation. Bo Chen: Resources. Xiong Wang: Conceptualization, Funding acquisition. Yu Hu: Supervision.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Table 2

| Model      | Genotype | Case (n = 510) | Control (n = 510) | OR (95 %CI)* | P value* |
|------------|----------|---------------|------------------|-------------|----------|
| Co-dominant| GG       | 35 (6.9 %)    | 46 (9.0 %)       | 1           |          |
|            | GT       | 95 (18.6 %)   | 210 (41.2 %)     | 0.592 (0.358, 0.979) | 0.041    |
|            | TT       | 380 (74.5 %)  | 254 (49.8 %)     | 1.963 (1.230, 3.133) | 0.005    |
| Allele     | G        | 165 (32.6 %)  | 302 (59.6 %)     | 1           |          |
|            | T        | 855 (83.8 %)  | 718 (70.4 %)     | 2.179 (1.759, 2.699) | 0.000    |
| Dominant   | GG       | 35 (6.9 %)    | 46 (9.0 %)       | 1           |          |
|            | TT + GT  | 475 (93.1 %)  | 464 (91.0 %)     | 1.344 (0.850, 2.125) | 0.206    |
| Recessive  | GG + GT  | 130 (25.5 %)  | 256 (50.2 %)     | 1           |          |
|            | TT       | 380 (74.5 %)  | 254 (49.8 %)     | 2.950 (2.264, 3.843) | 0.000    |

* P value was adjusted by gender and age.

Table 3

| Model      | Genotype | Case (n = 290) | Control (n = 290) | OR (95 %CI)* | P value* |
|------------|----------|---------------|------------------|-------------|----------|
| Co-dominant| GG       | 18 (6.2 %)    | 31 (10.7 %)      | 1           |          |
|            | GT       | 50 (17.2 %)   | 112 (38.6 %)     | 0.769 (0.393, 1.501) | 0.441    |
|            | TT       | 222 (76.6 %)  | 147 (50.7 %)     | 2.602 (1.404, 4.824) | 0.002    |
| Allele     | G        | 86 (14.8 %)   | 174 (30.0 %)     | 1           |          |
|            | T        | 494 (85.2 %)  | 406 (70.0 %)     | 2.463 (1.843, 3.921) | 0.000    |
| Dominant   | GG       | 18 (6.2 %)    | 31 (10.7 %)      | 1           |          |
|            | TT + GT  | 272 (93.8 %)  | 259 (89.3 %)     | 1.809 (0.988, 3.313) | 0.055    |
| Recessive  | GG + GT  | 68 (23.4 %)   | 143 (49.3 %)     | 1           |          |
|            | TT       | 222 (76.6 %)  | 147 (50.7 %)     | 3.178 (2.226, 4.538) | 0.000    |

* P value was adjusted by age.

Table 4

| Model      | Genotype | Case (n = 220) | Control (n = 220) | OR (95 %CI)* | P value* |
|------------|----------|---------------|------------------|-------------|----------|
| Co-dominant| GG       | 17 (7.7 %)    | 15 (6.8 %)       | 1           |          |
|            | GT       | 45 (20.5 %)   | 98 (44.5 %)      | 0.399 (0.183, 0.872) | 0.021    |
|            | TT       | 158 (71.8 %)  | 107 (48.6 %)     | 1.283 (0.613, 2.684) | 0.508    |
| Allele     | G        | 79 (18.0 %)   | 128 (29.1 %)     | 1           |          |
|            | T        | 361 (82.0 %)  | 312 (70.9 %)     | 1.866 (1.356, 2.567) | 0.000    |
| Dominant   | GG       | 17 (7.7 %)    | 15 (6.8 %)       | 1           |          |
|            | TT + GT  | 203 (92.3 %)  | 205 (93.2 %)     | 0.860 (0.417, 1.771) | 0.682    |
| Recessive  | GG + GT  | 62 (28.2 %)   | 113 (51.4 %)     | 1           |          |
|            | TT       | 158 (71.8 %)  | 107 (48.6 %)     | 2.683 (1.806, 3.984) | 0.000    |

* P value was adjusted by age.
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