

# Two SNPs (rs1801282 and -1279G/A) of PPAR $\gamma$ are associated with Parkinson's disease in a northern Chinese population

shanshan li

Affiliated hospital of Qingdao University <https://orcid.org/0000-0002-7448-6600>

Li Xue

Affiliated Hospital of Qingdao University

Huimin Wang

Affiliated Hospital of Qingdao University

Qingwu Tian

Affiliated Hospital of Qingdao University

Anmu Xie (✉ [xieanmu@163.com](mailto:xieanmu@163.com))

<https://orcid.org/0000-0003-2591-467X>

---

## Research article

**Keywords:** Parkinson's disease; PPAR $\gamma$ ; Gene polymorphism; Northern China

**Posted Date:** March 10th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-16498/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

## Abstract

**Background:** This study aimed to assess the association between PPAR $\gamma$  gene polymorphism and susceptibility to Parkinson's disease (PD) in a northern Chinese population. **Methods :** We conducted a case-control study which including 391 outpatients with PD and 391 healthy matched individuals. All subject genotypes on PPAR $\gamma$  gene in rs3856806, rs1801282, -1279G/A were determined by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) analysis. **Results :** Our results showed participants with AG and AG+AA (dominant model) genotypes of -1279G/A had a higher genetic risk of PD compared to those with GG (  $p = 0.024$ , OR = 1.781, 95% CI = 1.073-2.956;  $p = 0.024$ , OR = 1.768, 95% CI = 1.078-2.898). A allele of the -1279G/A polymorphism was presumably correlated with increased risk of PD (  $p = 0.037$ , OR = 1.639, 95% CI = 1.027-2.616) and male PD (  $p = 0.032$ , OR = 1.998, 95% CI = 1.051-3.798) as well as early-onset Parkinson's disease (EOPD)(  $p = 0.019$ , OR = 2.667, 95% CI = 1.263-5.629). Stratification analysis by age for rs1801282 indicated a significant genotype difference between EOPD and controls(  $p = 0.005$ ) as well as late-onset Parkinson's disease(LOPD) and controls(  $p = 0.008$ ). G allele frequency of rs1801282 in EOPD subjects was significantly higher than it in controls(  $p = 0.006$ , OR = 3.093, 95% CI = 1.446-6.615) and LOPD (  $p = 0.009$ , OR = 2.899, 95% CI = 1.344-6.253). **Conclusions :** The study showed that in a northern Chinese population, the A allele of -1279G/A might be a risk factor for PD and the G allele of rs1801282 might increase the susceptibility of EOPD.

## Introduction

Parkinson's disease(PD) is a vestigial illness that mainly occurs in elderly people. Dopamine deficiency in the substantia nigra causes a series of classical motor symptoms, such as static tremor, spasticity, bradykinesia, postural unsteadiness, and gait impairment[1].

Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is mainly located in the basal ganglia and other places where dopamine receptors are expressed, indicating a possible correlation between PD and PPAR $\gamma$ [2, 3]. PPAR $\gamma$  is a member of the steroid hormone receptor superfamily and a ligand-activated transcriptional factor [4]. In the last few years, animal model studies have shown an association between PPAR $\gamma$  and PD with a series of experiments demonstrating that PPAR $\gamma$  agonists could protect neurons from injury[2, 5]. The pathogenesis of PD remains unclear; however, the interaction between genetics and environment is considered to be involved in PD development[6]. Further, related studies have indicated an association between the susceptibility genes and PD development[7–9].

The chromosome site for the PPAR $\gamma$  gene is 3p-25[10] and many genetic variations of this gene have been found. Three gene loci sited in different functional region of PPAR $\gamma$ , with rs1801282 located in exon B of PPAR $\gamma$  which related with decreased PPAR $\gamma$  activity[11], and rs3856806 located in exon 6 [11] as well as -1279G/A located in the promoter area. Among these mutations, previous studies have revealed that the rs1801282 polymorphism might be related to PD or AD susceptibility[12–15]. One study found that type2 diabetes mellitus was associated with subsequent PD[16], and rs3856806 polymorphism was probably related with type2 diabetes in a Chinese Han population[17]. Moreover, -1279G/A within PPAR $\gamma$  gene as a novel polymorphism that has never been studied in patients with PD. We aimed to assess association between PPAR $\gamma$  genetic polymorphisms (rs1801282, rs3856806, and -1279G/A) and PD in a cohort of northern Chinese subjects. Additionally, we conducted stratification analyses by sex and age as well as haplotype analysis for the first time to better understand the association between PPAR $\gamma$  and PD risk .

## Methods

### Study subjects

In this case-control study, we enrolled 391 patients with PD (185 females and 206 males; age 62.42±9.32 years) who met the criteria of the UK PD Brain Bank and 391 gender, age, and ethnicity matched healthy individuals (178 females and 213 males; age: 61.08±10.16 years) without neurologic or psychiatric disorders, T2DM, or cardiopathy. All subjects in the PD group were enrolled from the Neurology clinic department of the Affiliated Hospital of Qingdao University while the controls were randomly recruited from the Health Examination center. As shown in Table 1, there was no significant between-group difference in the age ( $p = 0.056$ ) and sex ( $p = 0.616$ ).

Table 1  
Characteristics of the Study Participants

| Variable                         | Cases(N = 391)<br>N (%) | Controls(N = 391)<br>N (%) | P     |
|----------------------------------|-------------------------|----------------------------|-------|
| Gender                           |                         |                            |       |
| Female                           | 185(47.31)              | 178(45.52)                 | 0.616 |
| Male                             | 206(52.69)              | 213(54.48)                 |       |
| Age(Means±SD)                    | 62.42±9.32              | 61.08±10.16                | 0.056 |
| Hoehn and Yahrstage <sup>a</sup> | 2 (1–4)                 |                            |       |

### DNA extracting and SNPs genotyping

Using a DNA blood kit (Tiangen, Beijing, China), we isolated DNA from lymphocytes derived from the peripheral blood of each participant. The rs3856806, rs1801282, and -1279G/A genotypes for the PPAR $\gamma$  gene were detected through Polymorphism Chain Reaction and Restriction Fragment Length Polymorphism (PCR-RFLP) analysis. We used three restriction enzymes and three pairs of primers as previously described [18–20]. Table 2 shows the lengths of the PCR-amplified fragments, restriction fragments, primer sequences, and restriction enzymes. For accuracy, about 10% of the PCR-amplified DNA samples were selected for DNA sequencing.

The total PCR reaction volume for PPAR $\gamma$  was 25  $\mu$ l as follows: 2.5  $\mu$ l about 50–100 ng genomic DNA, 12.5  $\mu$ l 2  $\times$  Taq Master Mix, 0.5  $\mu$ l of each primer(10 pmol/ $\mu$ l), and 9  $\mu$ l double-distilled H<sub>2</sub>O. The conditions for rs3856806 were as follows: original denaturation at 94 °C for 5 min, 30 cycles each for 30 s at 94 °C, annealing at 57.3 °C for 30 s, and extension at 72 °C for 30 s with that a final extension step at 72 °C for 5 min. The PCR reaction conditions for rs1801282 were as follows: initial denaturation at 94 °C for 5 min, 30 30-s cycles at 94 °C, annealing at 64 °C for 30 s, and extension at 72 °C for 30 s with that a final extension step at 72 °C for 5 min. The PCR reaction conditions for -1279G/A were as follows: original denaturation at 94 °C for 5 min, 27 30-s cycles at 94 °C, annealing at 55 °C for 30 s, and extension at 72 °C for 30 s followed by a final extension step at 72 °C for 5 min. The obtained PCR amplification products for rs3856806 were digested by 1  $\mu$ l restriction enzyme BsaA $\square$  (New England BioLabs NEB, Beijing) overnight at 37 °C. We used 1  $\mu$ l BstU $\square$  (New England BioLabs NEB, Beijing) for rs1801282 PCR products at 60 °C overnight. In addition, PCR products of -1279G/A were digested by 0.5  $\mu$ l restriction enzyme NIA III at 37 °C overnight. Finally, all enzymic hydrolysates were detected by gel electrophoresis on 2.5% agarose gel and then visualized with an imaging analysis system.

# Statistical analysis

SPSS 21.0 was used to perform statistical analyses and statistical significance was set at  $P < 0.05$ . The genotype and allele frequencies were determined by counting. We used the Chi-square test to assess the agreement with Hardy-Weinberg equilibrium (HWE) for each locus. The Fisher's exact (two-tailed) or Chi-square test was used for between-group comparisons of categorical variables, while Student's t-test was used for continuous variables. To assess the strength of polymorphisms and PD susceptibility, the value of odds ratios (OR) and 95% confidence intervals (CI) were calculated. The Haploview 4.2 software was used to estimate the haplotype frequencies of three loci and the linkage disequilibrium (LD).

| SNP       | Primer sequence  | Product Size(bp) | Restriction enzyme | Restriction fragments of genotype(bp)         |
|-----------|--|------------------|--------------------|---|
| rs3856806 | F: AGGTTTGCTGAATGTGAAGC<br>R: GGTGAAGACTCATGTCTGT                      | 206              | BsaAI              | 206 = TT<br>206, 154, 52 = CT<br>154, 52 = CC |
| rs1801282 | F: GCCAATTCAAGCCCAGTC<br>R:GATATGTTTGCAGACAGTGTATCAGTGAAGGAATCGCTTTCCG | 270              | BstUI              | 270=CC<br>270,227,43= CG<br>227,43=GG         |
| -1279G/A  | F: TGCCATCGTGTCTGGATTAC<br>R: CCTGTCAATCATGGTGCAAG                     | 295              | NIAI               | 295 =GG<br>295,238,57= AG<br>238,57 =AA       |

Table 2

Primary information on genotyping assays for three SNPs of PPAR $\gamma$  gene

## Results

The characteristics of all the study subjects are summarized in Table 1. The Hardy-Weinberg equilibrium analysis of the three SNPs were  $> 0.05$ , which indicated there was no sample bias. Table 3 shows the results of the between-group analysis of dominant, and recessive genetic models as well as genotype and allele frequency for rs3856806 and - 1279G/A. We just detected two genotypes in all samples for rs1801282, so only genotype and allele frequency about rs1801282 are presented in the Table 3.

Table 3

Allelic and genotypic frequency of PPAR $\gamma$  polymorphisms in PD patient and each healthy-matched control subgroup

|                            | Cases (N = 391) | Controls(N = 391) | P     | OR(95% CI)         |
|----------------------------|-----------------|-------------------|-------|--------------------|
| rs 3856806                 |                 |                   |       |                    |
| CC, n (%)                  | 229(58.57)      | 242(61.89)        |       |                    |
| CT, n (%)                  | 145(37.08)      | 137(35.04)        | 0.457 | 1.118(0.833–1.503) |
| TT, n (%)                  | 17(4.31)        | 12(3.07)          | 0.296 | 1.497(0.700-3.204) |
| Dominant(CC vs. CT + TT)   |                 |                   | 0.309 | 1.161(0.871–1.548) |
| Recessive(TT vs. CT + CC)) |                 |                   | 0.350 | 1.432(0.674–3.046) |
| C, n(%)                    | 603(77.11)      | 621(79.41)        |       |                    |
| T, n(%)                    | 179(22.89)      | 161(20.59)        | 0.270 | 1.145(0.900-1.456) |
| -1279G/A                   |                 |                   |       |                    |
| GG, n (%)                  | 345(88.24)      | 363(92.84)        |       |                    |
| AG, n (%)                  | 44(11.25)       | 26 (6.65)         | 0.024 | 1.781(1.073–2.956) |
| AA, n (%)                  | 2(0.51)         | 2(0.51)           | 0.960 | 1.052(0.147–7.511) |
| Dominant(AG + AA vs.GG)    |                 |                   | 0.024 | 1.768(1.078–2.898) |
| Recessive(AG + GG vs.AA)   |                 |                   | 0.905 | 0.887(0.123–6.398) |
| G, n (%)                   | 734(93.86)      | 752(96.16)        |       |                    |
| A, n (%)                   | 48(6.14)        | 30(3.84)          | 0.037 | 1.639(1.027–2.616) |
| rs1801282                  |                 |                   |       |                    |
| CC, n (%)                  | 357(91.30)      | 365(93.35)        |       |                    |
| CG, n (%)                  | 34(8.70)        | 26(6.65)          | 0.347 | 1.337(0.786–2.274) |
| GG, n (%)                  | 0               | 0                 |       |                    |
| C, n (%)                   | 748(95.65)      | 756(96.68)        |       |                    |
| G, n (%)                   | 34(4.35)        | 26(3.32)          | 0.292 | 1.322(0.785–2.224) |

Regarding rs1801282 polymorphisms, subgroup analysis in terms of age indicated statistical differences between the early-onset PD (EOPD) (age of diagnosis < 50) and healthy group ( $p = 0.005$ ). Compared to the healthy group, the EOPD subgroup had a higher G allele frequency (OR = 3.093, 95% CI = 1.446–6.615,  $p = 0.006$  in Table 4). Further, significant difference was found between the EOPD and late-onset PD (LOPD) (age of diagnosis > 50) ( $p = 0.008$ ). Compared with the LOPD subgroup, the EOPD subgroup had a higher frequency of the G allele of rs1801282 ( $p = 0.009$ , OR = 2.899, 95% CI = 1.344–6.253). Furthermore, no significant difference was found among other subgroups in the allele frequencies and genotype distribution ( $p > 0.05$ ) in Table 4.

Table 4

Distribution of PPAR $\gamma$  polymorphisms observed in every PD patient and each healthy-matched control subgroup.

| rs3856806     | Genotype |             |            |          | Allele |             |            |       |
|---------------|----------|-------------|------------|----------|--------|-------------|------------|-------|
|               | N        | CC (%)      | CT (%)     | TT (%)   | P      | C (%)       | T (%)      | P     |
| Male PD       | 206      | 123(59.71)  | 74 (35.92) | 9 (4.37) | 0.880  | 320(77.67)  | 92(22.33)  | 0.694 |
| FemalePD      | 185      | 106(57.30)  | 71(38.38)  | 8(4.32)  |        |             |            |       |
| FemalePD      | 185      | 106(57.30)  | 71(38.38)  | 8(4.32)  | 0.476  | 283(76.49)  | 87 (23.51) | 0.244 |
| Female health | 178      | 113(63.48)  | 59 (33.15) | 6(3.37)  |        | 285(80.06)  | 71(19.94)  |       |
| Male PD       | 206      | 123(59.71)  | 74(35.92)  | 9(4.37)  | 0.694  | 320(77.67)  | 92(22.33)  | 0.673 |
| Male health   | 213      | 129(60.56)  | 78(36.62)  | 6(2.82)  |        |             |            |       |
| EOPD          | 52       | 31 (59.62)  | 18 (34.62) | 3 (5.77) | 0.598  | 80 (76.92)  | 24 (23.08) | 0.557 |
| Health        | 391      | 242(61.89)  | 137(35.04) | 12(3.07) |        |             |            |       |
| LOPD          | 339      | 198(58.41)  | 127(37.46) | 14(4.13) | 0.539  | 523(77.14)  | 155(22.86) | 0.293 |
| Health        | 391      | 242(61.89)  | 137(35.04) | 12(3.07) |        |             |            |       |
| EOPD          | 52       | 31(59.62)   | 18(34.62)  | 3(5.77)  | 0.823  | 80 (76.92)  | 24(23.08)  | 0.961 |
| LOPD          | 339      | 198(58.39)  | 127(37.46) | 14(4.13) |        |             |            |       |
| -1279G/A      | N        | GG (%)      | AG (%)     | AA (%)   | P      | G (%)       | A (%)      | P     |
| Male PD       | 206      | 179 (86.89) | 26 (12.62) | 1(0.49)  | 0.712  | 384(93.20)  | 28(6.80)   | 0.419 |
| FemalePD      | 185      | 166(89.73)  | 18(9.73)   | 1(0.54)  |        |             |            |       |
| FemalePD      | 185      | 166 (89.73) | 18(9.73)   | 1(0.54)  | 0.434  | 350 (94.59) | 20(5.41)   | 0.454 |
| Female health | 178      | 165 (92.70) | 11(6.18)   | 2(1.12)  |        | 341 (95.79) | 15(4.21)   |       |
| Male PD       | 206      | 179 (86.89) | 26(12.62)  | 1(0.49)  | 0.059  | 384 (93.20) | 28(6.80)   | 0.032 |
| Male health   | 213      | 198(92.96)  | 15(7.04)   | 0(0)     |        |             |            |       |
| EOPD          | 52       | 42 (80.77)  | 10(19.23)  | 0(0)     | 0.020  | 94(90.38)   | 10(9.62)   | 0.019 |
| Health        | 391      | 363(92.84)  | 26(6.65)   | 2(0.51)  |        |             |            |       |
| LOPD          | 339      | 303 (89.38) | 34(10.03)  | 2(0.59)  | 0.244  | 640(94.40)  | 38(5.60)   | 0.110 |
| Health        | 391      | 363 (92.84) | 26(6.65)   | 2(0.51)  |        |             |            |       |
| EOPD          | 52       | 42(80.77)   | 10(19.23)  | 0(0)     | 0.119  | 94 (90.38)  | 10(9.62)   | 0.113 |

| rs3856806     | Genotype |            |             |         | Allele |            |            |       |
|---------------|----------|------------|-------------|---------|--------|------------|------------|-------|
| LOPD          | 339      | 303(89.38) | 34(10.03)   | 2(0.51) |        | 640(94.40) | 38 (5.60)  |       |
| rs1801282     | N        | CG (%)     | CC (%)      | GG (%)  | P      | G (%)      | C (%)      | P     |
| Male PD       | 206      | 22 (10.68) | 184 (89.32) | -       | 0.154  | 22(5.34)   | 390(94.66) | 0.151 |
| FemalePD      | 185      | 12(6.49)   | 173(93.51)  | -       |        | 12 (3.24)  | 358(96.76) |       |
| FemalePD      | 185      | 12(6.49)   | 173(93.51)  | -       | 0.686  | 12(3.24)   | 358(96.76) | 0.617 |
| Female health | 178      | 14(7.87)   | 164 (92.13) | -       |        | 14(3.93)   | 342(96.07) |       |
| Male PD       | 206      | 22 (10.68) | 184(89.32)  | -       | 0.073  | 22 (5.34)  | 390(94.66) | 0.064 |
| Male health   | 213      | 12 (5.63)  | 201(94.37)  | -       |        | 12(2.82)   | 414(97.18) |       |
| EOPD          | 52       | 10(19.23)  | 42(80.77)   | -       | 0.005  | 10(9.62)   | 94(90.38)  | 0.006 |
| Health        | 391      | 26(6.65)   | 365(93.35)  | -       |        | 26(3.32)   | 756(96.68) |       |
| LOPD          | 339      | 24 (7.08)  | 315 (92.92) | -       | 0.884  | 24(3.54)   | 654(96.46) | 0.822 |
| Health        | 391      | 26 (6.65)  | 365(93.35)  | -       |        | 26(3.32)   | 756(96.68) |       |
| EOPD          | 52       | 10(19.23)  | 42(80.77)   | -       | 0.008  | 10(9.62)   | 94(90.38)  | 0.009 |
| LOPD          | 339      | 24(7.08)   | 315 (92.92) | -       |        | 24(3.54)   | 654(96.46) |       |

Regarding - 1279G/A polymorphisms, the PD group had a higher A allele frequency than the controls ( $p = 0.037$ , OR = 1.639, 95% CI = 1.027–2.616), which indicated that the allele A of -1279G/A was probably a risk factor for PD. Stratified analysis according to age indicated a significant discrepancy between the EOPD and healthy group ( $p = 0.020$ ). The patients with EOPD had a higher A allele frequency than the healthy group ( $p = 0.019$ , OR = 2.667, 95% CI = 1.263–5.629) (Table 4). Stratified analysis according to gender revealed the frequency of A allele for - 1279G/A was significantly higher in male PD than it in male health controls ( $p = 0.032$ , OR = 1.998, 95% CI = 1.051–3.798). A significantly higher PD risk was also found in allele A carriers in the dominant genotype model (AG + AA vs GG: OR = 1.768, 95% CI = 1.078–2.898,  $p = 0.024$ ). However, no significant between-group difference was found in the distribution of rs3856806 in the subgroup and genetic model analysis (Table 3 and Table 4).

According to Table 5, haplotype and LD analysis indicated a weak LD with PPAR $\gamma$  polymorphisms (-1279G/A and rs1801282:  $D' = 0.749$ ,  $r^2 = 0.427$ ; -1279G/A and rs3856806:  $D' = 0.678$ ,  $r^2 = 0.087$ ; rs1801282 and rs3856806,  $D' = 0.595$ ,  $r^2 = 0.051$ ) and there was no significant between-group difference in the haplotype analysis.

Table 5  
Frequency distribution of the PPAR $\gamma$  -1279G/A, rs1801282 and rs3856806  
haplotype alleles between cases and controls

| Genotype | Cases (frequency) | Controls (frequency) | Chi-square | P      |
|----------|-------------------|----------------------|------------|--------|
| GCC      | 586.8(0.750)      | 608.8(0.778)         | 1.717      | 0.1901 |
| GCT      | 143.0(0.183)      | 133.1(0.170)         | 0.431      | 0.5115 |
| AGT      | 21.1 (0.027)      | 13.6 (0.017)         | 1.643      | 0.1999 |
| ACT      | 13.8 (0.018)      | 9.8 (0.013)          | 0.676      | 0.4108 |

## Discussion

We found that the allele A of -1279G/A was significantly associated with PD risk in a northern Chinese population. Subgroup analysis showed that both - 1279G/A and rs1801282 were associated with EOPD and both A allele of -1279G/A polymorphism and G allele of rs1801282 polymorphism within PPAR $\gamma$  gene might be a risk factor for EOPD in a northern Chinese population. In addition, our finding showed that A allele of -1279G/A may increase the risk of male PD and AG + AA genotype may increase the susceptibility of PD in the dominant model. However, there was no mutual effect between the rs3856806 polymorphism and PD in the dominant and recessive model.

PPAR $\gamma$  has been reported to be associated with the development of numerous degenerative diseases. Additionally, an association of the rs1801282 genotype with early-onset AD has been reported in the Finnish population [13]. In the absence of the APOE $\epsilon$ 4 subgroup with PPAR $\gamma$  Pro12Ala polymorphism (rs1801282), the onset age of AD patients with the Pro/Ala genotype was found 4.6 years earlier than Pro/Pro genotype carriers in northeast China[15]. Another study on Italians reported that the risk of developing AD in Ala carriers was twice as high as that of octogenarian controls[21]. Interestingly, analysis after gender stratification showed that the G allele of rs1801282 played a protective role in females but had an opposite effect in male Caucasians from the UK[22]. Tanner CM et al demonstrated the effect of genetic factors was more obvious in the EOPD subgroup than it in the LOPD subgroup [23]. In a certain sense, above studies seems to tell us rs1801282 is more likely a age-related mutation after so many different racial analysis.

A previous association study on PPAR $\gamma$  gene polymorphism in Japanese patients with Parkinson's disease with dementia (PDD) (n = 171) and controls (n = 136) reported no significant between-group differences in the genotypic frequencies of the SNPs (rs3856806 and rs1801282) or the haplotype analysis for the 2 PPAR $\gamma$ - SNPs[24]. Yang investigated the PPAR $\gamma$  gene polymorphism (rs3856806 and rs1801282) in a Southern Chinese cohort comprising patients with PD (n = 206) and controls (n = 210) and reported no significant between-group difference in the genotype distribution [12]. Our results are clearly consistent with those of the aforementioned studies; however, we performed further subgroup analysis based on age and sex using a larger sample size from a different geographical area. This is the first study to provide evidence that the A allele of -1279G/A SNP may contribute to increasing PD risk in northern Chinese population. Our findings might contribute toward developing a novel therapy and a feasible means of predicting the risk for PD.

To date, the pathophysiology of PD remains elusive. A review reported that the most probable nosogenesis involves lesions of the ubiquitin-proteasome system (UPS), oxidative stress anomaly, and mitochondrial deficiency[25]. UPS dysfunction might result in excess or misfolded proteins in the brain, in turn resulting in PD development.

Rosiglitazone, a PPAR $\gamma$  agonist, not only reduces mHtt aggregates containing ubiquitin and heat shock factor1 (HSF1) but also enhance the function of the UPS, HSF1, and heat shock protein27/70 (HSP27/70) in N2A cells [26]. Moreover, in human neuroblastoma SH-SY5Y cells, rosiglitazone improves the expression of SOD, catalase, Bcl-2, and Bax, which might attribute to the prevention of mitochondrial impairment induced by the 1-methyl-4-phenylpyridinium ion (MPP+)[27]. In addition, ciglitazone, a PPAR $\gamma$  agonist, plays a role in protecting neurons from oxidative stress by regulating mitochondrial fusion and fission in hippocampal neurons [28]. Overall, PPAR $\gamma$  play a protective role in the development of PD.

To our knowledge, the rs1801282 G allele variation shows decreased transcriptional activity of PPAR $\gamma$  in vitro[29], suggesting potential association with PD. -1279G/A is located in the promoter region of PPAR $\gamma$  and the polymorphism of the promoter region tends to affect gene expression and contribute to the occurrence of disease[30]. The ENCODE project and bioinformatics approaches identified the - 1279G/A(rs7647481) as the cis-regulatory variant which exerts the effect of regulating transcriptional activity, and ultimately contributes to different sensitivity of insulin in primary adipose cells[31]. In addition, Yin Yang 1(YY1) has been confirmed as an allele-specific transcription factor for - 1279G/A (rs7647481) A allele, which may affects the level of PPAR $\gamma$ [31]. Taken together, the - 1279G/A polymorphism is a cis-regulatory variant[31], which may play a role in decreasing transcriptional activity of PPAR $\gamma$ , leading to the low expression level of PPAR $\gamma$  which confers to susceptibility for the development of PD. In fact, the precise molecular mechanism is more complicated than we expect, and hence, further research is required to elucidate the underlying mechanism between variants and disease risk.

Our study had several limitations, such as limited sample size, race, and mutational sites. Therefore, there is a need for more studies with more ethnicities and larger cohorts to assess the association of PPAR $\gamma$  polymorphism with PD susceptibility.

## Conclusion

This is the first study to demonstrate that the A allele of -1279G/A and the G allele of rs1801282 might be a risk factor for EOPD in the Han population of northern China. Moreover, carriers with A allele of -1279G/A have a higher risk for PD and male PD. Further, genetic polymorphism of PPAR $\gamma$  may be a promising biomarker for PD susceptibility.

## Abbreviations

PD

Parkinson's disease

PCR-RFLP

Polymerase chain reaction and restriction fragment length polymorphism

EOPD

Early-onset Parkinson's disease

LOPD

late-onset Parkinson's disease

PPAR $\gamma$

Peroxisome proliferator-activated receptor

HWE

Hardy-Weinberg equilibrium

OR  
Odds ratio  
CI  
Confidence interval  
LD  
linkage disequilibrium  
PDD  
Parkinson's disease with dementia  
UPS  
Ubiquitin-proteasome system  
HSF1  
Heat shock factor1  
HSP27/70  
Heat shock protein27/70  
MPP+  
1-methyl-4-phenylpyridinium ion

## **Declarations**

### **Acknowledgments**

We appreciate all subjects for participating this study and we would like to acknowledge the investigators for their helpful comments regarding this paper.

### **Funding**

This work was supported by grants from Natural Science Foundation of China(81571225). The study design and the collection of the PD data were supported by the funding.

### **Availability of data and materials**

The data used and analyzed in the current study are available from the corresponding author on reasonable request.

### **Authors' Contributions**

SSL and AMX designed experiments; SSL and LX and HMW collected the samples; SSL carried out the experiments; SSL, AMX and QWT analyzed experimental results; SSL wrote the manuscript. All authors read and approved the final manuscript.

### **Ethics approval and consent to participate**

These participants or their legal guardians provided written informed consent and the study was approved by the Ethical Committee of the Affiliated Hospital of Qingdao University(QYFYWZLL25594).

### **Consent for Publication**

Not applicable.

## Competing interests

The authors declare that they have no conflicts of interest. Anmu Xie is the member of the Editorial Board of BMC Neurology and declares no conflict of interest.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Author information

### Affiliations

Department of Neurology, Affiliated Hospital of Qingdao University, Qingdao, 266003, China

Shanshan Li, Huimin Wang, Qingwu Tian, Anmu Xie

Medical Record Room, Affiliated Hospital of Qingdao University, Qingdao, China

Li Xue

## References

1. Opara, J., et al., *Motor assessment in Parkinson's disease*. Ann Agric Environ Med, 2017. **24**(3): p. 411-415.
2. Corona, J.C. and M.R. Duchon, *PPARGgamma and PGC-1alpha as therapeutic targets in Parkinson's*. Neurochem Res, 2015. **40**(2): p. 308-16.
3. Helisalmi, S., et al., *Lack of genetic association between PPARG gene polymorphisms and Finnish late-onset Alzheimer's disease*. Neurosci Lett, 2008. **441**(2): p. 233-6.
4. Yang, L., et al., *Association of SNPs in the PPARGgamma gene and hypertension in a Mongolian population*. Genet Mol Res, 2015. **14**(4): p. 19295-308.
5. Carta, A.R., et al., *Rosiglitazone decreases peroxisome proliferator receptor-gamma levels in microglia and inhibits TNF-alpha production: new evidences on neuroprotection in a progressive Parkinson's disease model*. Neuroscience, 2011. **194**: p. 250-61.
6. Emamalizadeh, B., et al., *RIT2, a susceptibility gene for Parkinson's disease in Iranian population*. Neurobiol Aging, 2014. **35**(12): p. e27-e28.
7. Zhao, C.C., et al., *Role of ADH2 and ALDH2 gene polymorphisms in the development of Parkinson's disease in a Chinese population*. Genet Mol Res, 2016. **15**(3).
8. Li, C., et al., *Vitamin D receptor gene polymorphisms and the risk of Parkinson's disease*. Neurol Sci, 2015. **36**(2): p. 247-55.
9. Yang, X., et al., *SNP rs1805874 of the Calbindin1 Gene Is Associated with Parkinson's Disease in Han Chinese*. Genet Test Mol Biomarkers, 2016. **20**(12): p. 753-757.
10. Wang, Y., et al., *PPARGgamma gene polymorphism, C-reactive protein level, BMI and periodontitis in postmenopausal Japanese women*. Gerodontology, 2016. **33**(1): p. 44-51.
11. Meirhaeghe, A., et al., *Study of a new PPARGgamma2 promoter polymorphism and haplotype analysis in a French population*. Mol Genet Metab, 2005. **85**(2): p. 140-8.

12. Yang, X.D., et al., *Expression of the gene coding for PGC-1alpha in peripheral blood leukocytes and related gene variants in patients with Parkinson's disease*. Parkinsonism Relat Disord, 2018. **51**: p. 30-35.
13. Koivisto, A.M., et al., *Association analysis of peroxisome proliferator-activated receptor gamma polymorphisms and late onset Alzheimer's disease in the Finnish population*. Dement Geriatr Cogn Disord, 2006. **22**(5-6): p. 449-53.
14. Sauder, S., et al., *Influence of peroxisome proliferator-activated receptor gamma gene polymorphism on 24S-hydroxycholesterol levels in Alzheimer's patients*. J Neural Transm (Vienna), 2005. **112**(10): p. 1381-9.
15. Yao, L., et al., *Influence of the Pro12Ala polymorphism of PPAR-gamma on age at onset and sRAGE levels in Alzheimer's disease*. Brain Res, 2009. **1291**: p. 133-9.
16. De Pablo-Fernandez, E., et al., *Association between diabetes and subsequent Parkinson disease: A record-linkage cohort study*. Neurology, 2018. **91**(2): p. e139-e142.
17. Lv, X., et al., *Interaction between peroxisome proliferator-activated receptor gamma polymorphism and obesity on type 2 diabetes in a Chinese Han population*. Diabetol Metab Syndr, 2017. **9**: p. 7.
18. Cheng, S., et al., *Association of polymorphisms in the peroxisome proliferator-activated receptor gamma gene and osteoarthritis of the knee*. Ann Rheum Dis, 2006. **65**(10): p. 1394-7.
19. Cui, X., et al., *Genetic Variations in Inflammatory Response Genes and Their Association with the Risk of Prostate Cancer*. Biomed Res Int, 2015. **2015**: p. 674039.
20. Vimalaswaran, K.S., et al., *Evidence for an association with type 2 diabetes mellitus at the PPARG locus in a South Indian population*. Metabolism, 2010. **59**(4): p. 457-62.
21. Scacchi, R., et al., *The peroxisome proliferator-activated receptor gamma (PPAR-gamma2) Pro12Ala polymorphism is associated with higher risk for Alzheimer's disease in octogenarians*. Brain Res, 2007. **1139**: p. 1-5.
22. Hamilton, G., et al., *Candidate gene association study of insulin signaling genes and Alzheimer's disease: evidence for SOS2, PCK1, and PPARgamma as susceptibility loci*. Am J Med Genet B Neuropsychiatr Genet, 2007. **144b**(4): p. 508-16.
23. Tanner, C.M., et al., *Parkinson disease in twins: an etiologic study*. Jama, 1999. **281**(4): p. 341-6.
24. Shibata, N., et al., *Lack of Genetic Associations of PPAR-gamma and PGC-1alpha with Alzheimer's Disease and Parkinson's Disease with Dementia*. Dement Geriatr Cogn Dis Extra, 2013. **3**(1): p. 161-7.
25. Bartels, A.L. and K.L. Leenders, *Parkinson's disease: the syndrome, the pathogenesis and pathophysiology*. Cortex, 2009. **45**(8): p. 915-21.
26. Chiang, M.C., et al., *Rosiglitazone activation of PPARgamma-dependent signaling is neuroprotective in mutant huntingtin expressing cells*. Exp Cell Res, 2015. **338**(2): p. 183-93.
27. Jung, T.W., et al., *Rosiglitazone protects human neuroblastoma SH-SY5Y cells against MPP+ induced cytotoxicity via inhibition of mitochondrial dysfunction and ROS production*. J Neurol Sci, 2007. **253**(1-2): p. 53-60.
28. Zolezzi, J.M., et al., *Peroxisome proliferator-activated receptor (PPAR) gamma and PPARalpha agonists modulate mitochondrial fusion-fission dynamics: relevance to reactive oxygen species (ROS)-related neurodegenerative disorders?* PLoS One, 2013. **8**(5): p. e64019.
29. Deeb, S.S., et al., *A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity*. Nat Genet, 1998. **20**(3): p. 284-7.

30. Ye, D., et al., *A novel SNP in promoter region of RP11-3N2.1 is associated with reduced risk of colorectal cancer.* J Hum Genet, 2018. **63**(1): p. 47-54.
31. Lee, H., et al., *Allele-specific quantitative proteomics unravels molecular mechanisms modulated by cis-regulatory PPARG locus variation.* Nucleic Acids Res, 2017. **45**(6): p. 3266-3279.