

META-ANALYSIS

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# Inflammation-related gene polymorphisms associated with Parkinson's disease: an updated meta-analysis



Zulvikar Syambani Ulhaq<sup>1\*</sup>  and Cristian Peinado Garcia<sup>2</sup>

## Abstract

**Background:** Strong evidence supports the involvement of inflammation processes in the development and progression of Parkinson's disease (PD), where increasingly correlations have been identified between genetic variations in inflammation-related genes and PD. However, data varies between studies. Therefore, we conducted a meta-analysis to clarify associations between inflammation-related gene polymorphisms and PD risk.

**Methods:** All studies were identified through online databases. Pooled and stratified groups based on racial descent were assembled to evaluate associations between polymorphisms and PD.

**Results:** The pooled results showed that protective effects for PD were observed for (1) IL-1 $\alpha$  -889 C/T in Asian populations (T vs. C, OR = 0.831,  $P$  = 0.031; TT + CT vs. CC, OR = 0.827,  $P$  = 0.049); (2) IL-6 -176 G/C in Caucasian populations (CC + GC vs. GG, OR = 0.656,  $P$  = 0.000; GC vs. GG, OR = 0.673,  $P$  = 0.000); (3) IL-8 -251 A/T (T vs. A, OR = 0.812,  $P$  = 0.041; TT vs. AT + AA, OR = 0.663,  $P$  = 0.012), particularly in Caucasian populations (TT vs. AT + AA, OR = 0.639,  $P$  = 0.010); (4) IL-10 -819 T/C (C vs. T, OR = 0.742,  $P$  = 0.034); (5) IL-18 -607 C/A (AA + CA vs. CC, OR = 0.597,  $P$  = 0.015; CA vs. CC, OR = 0.534,  $P$  = 0.005), and (6) CCR2 +190 G/A (AA vs. GA + GG, OR = 0.552,  $P$  = 0.018; AA vs. GG, OR = 0.554; 95% CI 0.336–0.914,  $P$  = 0.005). An increased risk of PD was associated with IL-10 -1082 G/A in Asian populations (A vs. G, OR = 1.731,  $P$  = 0.000; AA + GA vs. GG, OR = 1.910,  $P$  = 0.000). No significant associations with PD were observed for polymorphisms in IL-1 $\beta$  -511 C/T, IL-10 -592 C/A, IL-18 -137 G/C, TNF $\alpha$  -863 C/A, TNF $\alpha$  -857 C/T, TNF $\alpha$  -308 G/A, IFN $\gamma$  +874 T/A, and MCP1/CCL2 +2518 A/G.

**Conclusions:** We suggest that IL-1 $\alpha$  -889, IL-6 -176, IL-8 -251, IL-10 -1082, IL-10 -819, IL-18 -607, and CCR2 +190 polymorphisms may be associated with PD risk; however, further studies must verify these conclusions.

**Keywords:** Inflammation, Cytokines, Chemokines, Polymorphism, Parkinson's disease

## Background

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the slow and progressive degeneration of dopaminergic (DA) neurons in the substantia nigra [1–4]. DA is a neurotransmitter synthesized by tyrosine hydroxylase (TH), which functions in movement control [5]. Thus, the primary motor symptoms of PD include

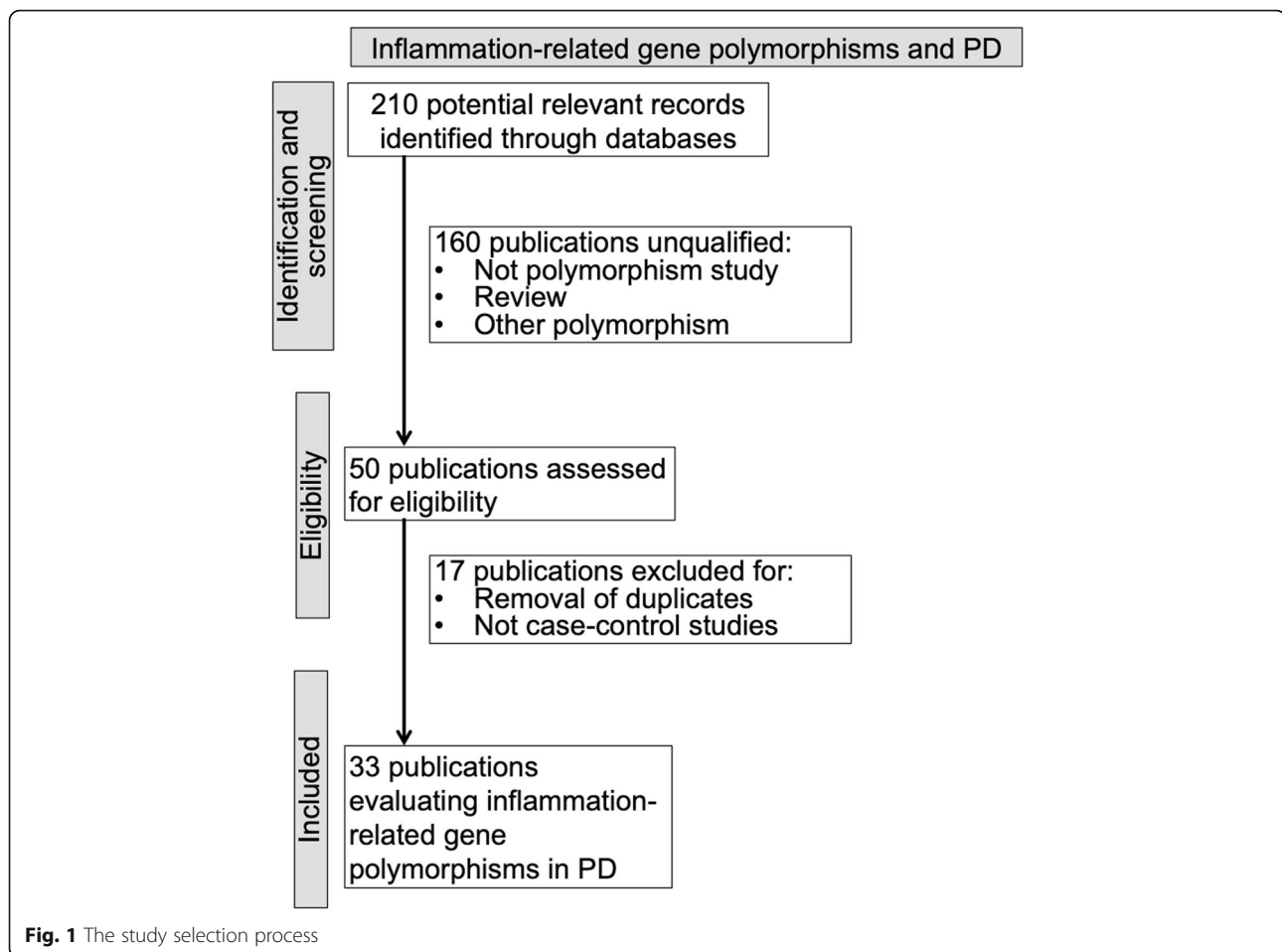
bradykinesia, rest tremors, rigidity, and postural instability [6–9]. Although PD pathogenesis appears to be multifactorial in nature, growing evidence strongly suggests that a chronic inflammatory mechanistic process is associated with DA neuronal death [10–13]. Indeed, elevated levels of pro-inflammatory mediators such as TNF $\alpha$ , IL-1 $\beta$ , IL-3, IL-2, and IL-6 have been detected in the substantia nigra, striatum, and cerebrospinal fluid (CSF) of PD patients [6, 11, 12, 14–16].

DA neuron degeneration has been linked with microglial cell activation [4, 7, 17], leading to the promotion of inflammatory processes in PD. Microglia are resident immune

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cells in the central nervous system (CNS) that play important roles in a majority of brain disorders. Leukocyte infiltration promoted by degenerated neurons also stimulates microglia activation [18] and is modulated by chemokines. Among these molecules, MCP-1 (monocyte chemoattractant protein-1; CCL2), IL-8 (C-X-C Motif Chemokine Ligand 8, CXCL8), and its receptor CCR2/5 (C-C chemokine receptor type 2/5) are reported to be involved in PD etiology [19–21].

It is believed that genetic variations (polymorphisms) in cytokines and chemokines as well as their corresponding receptors are associated with the mechanism of PD. To date, it is unclear whether these polymorphisms correlate with PD development and progression, as several studies are equivocal in this regard. Previous meta-analyses have been investigated associations between inflammation and PD risk [1, 22, 23]; however, these studies focused on cytokine polymorphisms, rather than chemokines and their receptors. Therefore, we provide an updated comprehensive meta-analysis, summarizing the latest studies evaluating associations between inflammation-related gene polymorphisms and PD.

## Methods

### Literature search

A literature search was conducted using PubMed, Google Scholar, Scopus, and Web of Science. Keywords including “cytokine,” “chemokine,” “inflammatory,” “tumor necrosis factor (TNF),” and “Parkinson’s disease (PD)” were used singularly and in combination. The literature search was conducted up to the September 30 2019. Inclusion criteria were (1) studies evaluating associations between inflammation-related gene polymorphisms and PD risk, and (2) case-control designed studies.

### Data extraction

The following data were extracted: (1) name of the first author, (2) year of publication, (3) country of origin, (4) number of cases and controls, and (5) number of genotypes in cases and controls.

### Statistical analyses

Meta-analyses for each gene polymorphism were performed for two or more studies. The genotype frequency of the inflammation-related gene polymorphism was tested for deviation from Hardy–Weinberg equilibrium

(HWE), against control subjects. Genetic associations were assessed using different genetic models, including allelic (mutant type (M) vs. wild type (W)), recessive (MM vs. WM + WW), dominant (MM + WM vs. WW), homozygous (MM vs. WW), and heterozygous (WM vs. WW). Associations between inflammation-related gene polymorphisms and PD risk were calculated by the pooled odds ratio (OR) and 95% confidence intervals (CI). Z tests were used to evaluate the significance of the pooled effect size.

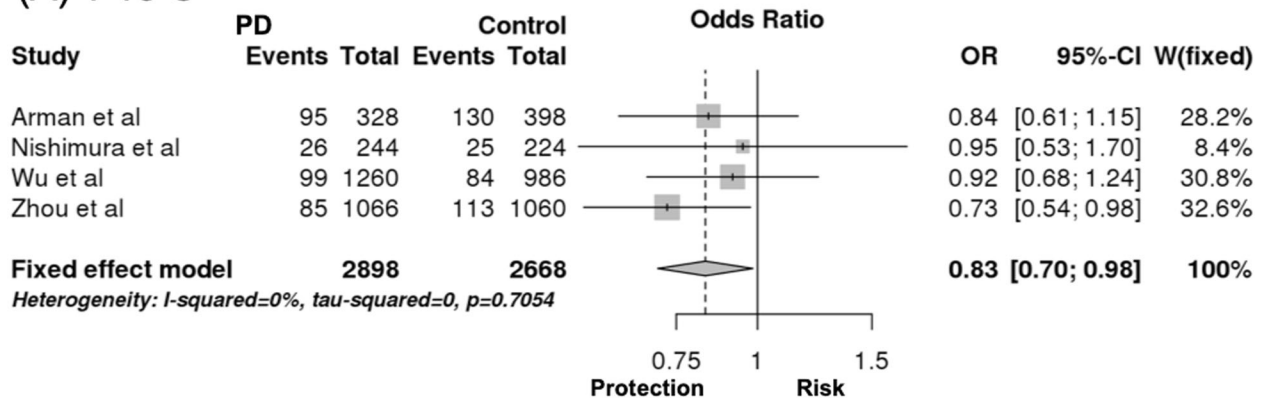
Heterogeneity among studies was evaluated using the Q test and  $I^2$  statistic [24]. A significant Q test ( $P < 0.10$ ) indicated heterogeneity across studies. The  $I^2$  statistic indicated no (0–24.9%), low (25–49.9%), moderate (50–74.9%), or high (75–100%) study heterogeneity. The random-effect model (REM) was used if heterogeneity existed; otherwise, the fixed-effect model (FEM) was used. Subgroup analysis was stratified by the racial descent of subjects. Begg's funnel plots and Egger's regression tests were performed to assess potential publication bias [25]. A sensitivity analysis was conducted if two or more studies were included in a meta-analysis. However,

the associations did not change (data not shown). A  $P < 0.05$  value indicated statistical significance.

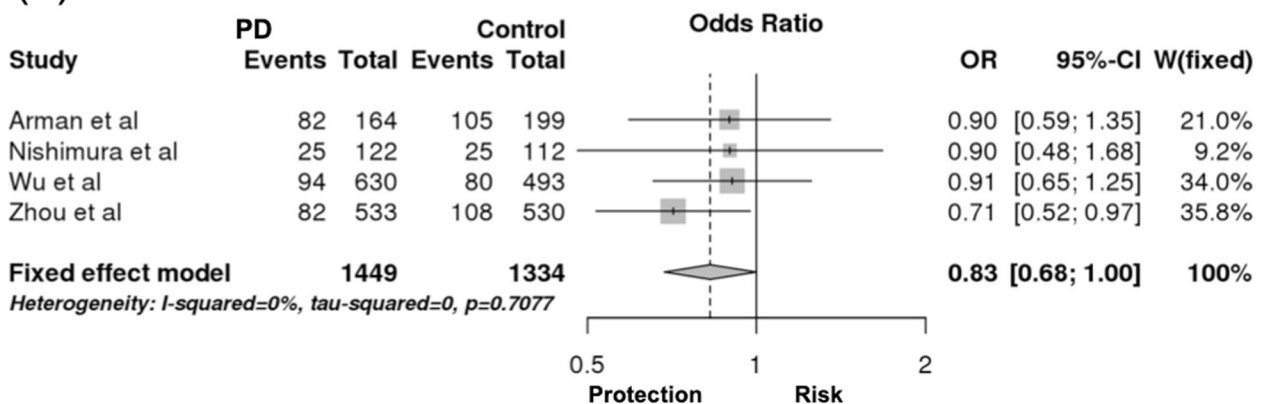
## Results

Thirty-three studies were retrieved (Supplemental Table 1). The study selection process is described (Fig. 1). Ten studies evaluated PD associations with IL-1 $\alpha$  -889 C/T (rs1800587) [6, 8, 13, 15, 26–31]. Only two out of the ten studies [15, 27] did not comply with the HWE ( $P < 0.05$ ) (Supplemental Table 1). No associations were found for all genetic models, which is in line with previous reports [1, 22]. After excluding the non-compliant HWE studies, the associations remain unchanged (Supplemental Table 2). However, the results showed that significant associations were observed for allelic (T vs. C, OR = 0.831; 95% CI 0.702–0.983,  $P = 0.031$ ,  $I^2 = 0\%$ , Fig. 2a) and dominant (TT + CT vs. CC, OR = 0.827; 95% CI 0.684–0.999,  $P = 0.049$ ;  $I^2 = 0\%$ , Fig. 2b) models in Asian populations. For assessment of the IL-1 $\beta$  -511 C/T (rs16944) polymorphism, all eligible studies were included (Supplemental Table 1) [2, 8, 11, 15, 26, 28, 30–32], which differed slightly from a previous study [22]. Similarly,

### (A) T vs C



### (B) TT+CT vs CC



**Fig. 2** Association of IL-1 $\alpha$  -889 C/T polymorphism with PD in Asian populations. **a** The allelic model. **b** The dominant model

no associations were observed, neither in Caucasian nor Asian populations (Supplemental Table 2).

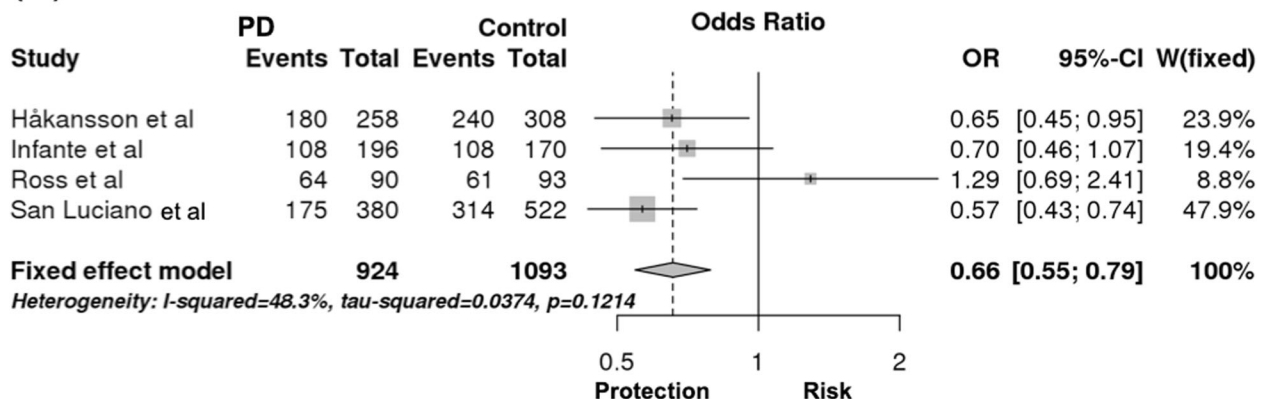
Previously, the C allele of IL-6 -176 G/C (rs1800795) showed protective effects for PD in Caucasian populations [13, 14, 17]. In this meta-analysis, two additional studies [7, 33] were also included. Significant associations were found for the dominant (CC + GC vs. GG, OR = 0.656; 95% CI 0.545–0.790,  $P = 0.000$ ,  $I^2 = 48.33\%$ , Fig. 3a) and heterozygous (GC vs. GG, OR = 0.673; 95% CI 0.553–0.818,  $P = 0.000$ ,  $I^2 = 0\%$ , Fig. 3b) models of IL-6 -176 G/C clusters in four Caucasian population studies. Hence, these results strengthen the fact that the C allele in the IL-6 -176 G/C polymorphism was associated with a lower risk of PD, particularly in Caucasian populations.

While previous studies have analyzed associations between the IL-10-1082 G/A (rs1800896) polymorphism with PD [2, 12, 13, 17, 34], none have been established with IL-10 -819 T/C (rs1800871) and IL-10 -592 C/A (rs1800872) polymorphisms [4, 12, 34, 35]. In this meta-analysis, three additional studies [33, 36, 37] were included

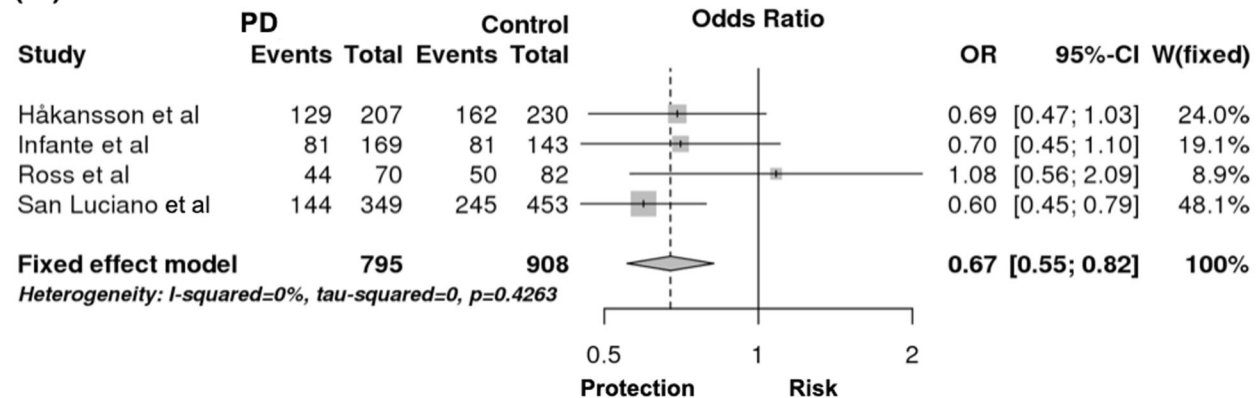
for the analysis of IL-10 -1082 G/A polymorphisms. Our analyses showed that the A allele (A vs. G, OR = 1.731; 95% CI 1.338–2.239,  $P = 0.000$ ,  $I^2 = 0\%$ , Fig. 4a), and the dominant model (AA + GA vs. GG, OR = 1.910; 95% CI 1.106–3.297,  $P = 0.000$ ,  $I^2 = 65.20\%$ , Fig. 4b) from Asian populations were associated with PD risk. This observation was in contrast with a previous report indicating a lack of association between the IL-10 -1082 G/A polymorphism and PD [22]. Moreover, it showed that the C allele of IL-10 -819 T/C had a lower risk of developing PD (C vs. T, OR = 0.742; 95% CI 0.628–0.878,  $P = 0.034$ ,  $I^2 = 58.30\%$ , Fig. 4c), though this does not apply for IL-10-592 C/A (Supplemental Table 2).

The role of TNF $\alpha$  -1031 T/C and -308 G/A (rs1800629) in PD was previously evaluated [22, 23]. Here, we evaluated two additional TNF $\alpha$  polymorphisms; (TNF $\alpha$  -863 C/A and TNF $\alpha$  -857 C/T) [8, 38]. In total, eight studies were used for the TNF $\alpha$  -308 G/A meta-analysis [2, 8, 9, 11, 14, 16, 33, 34]. One study relating to TNF $\alpha$  -308 G/A [34] did not comply with HWE (Supplemental Table 1); however, when excluded,

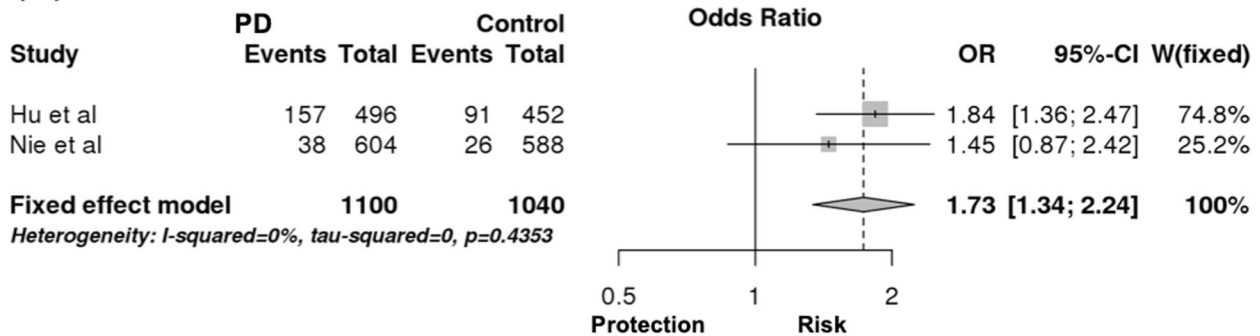
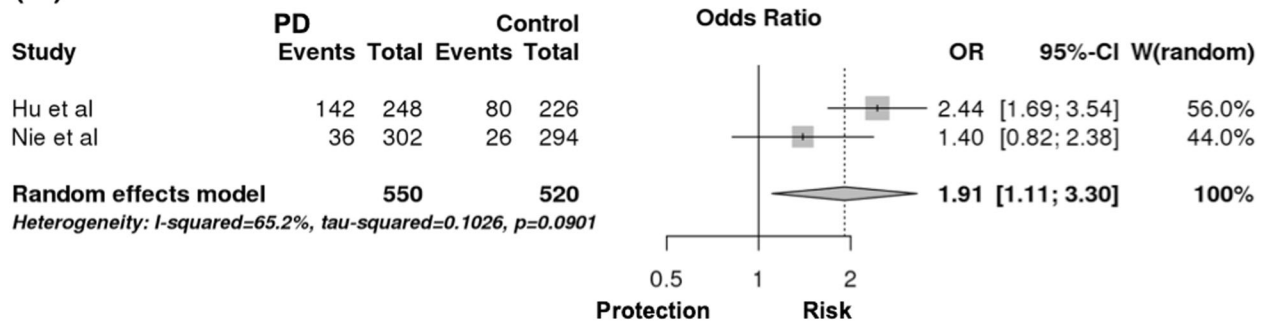
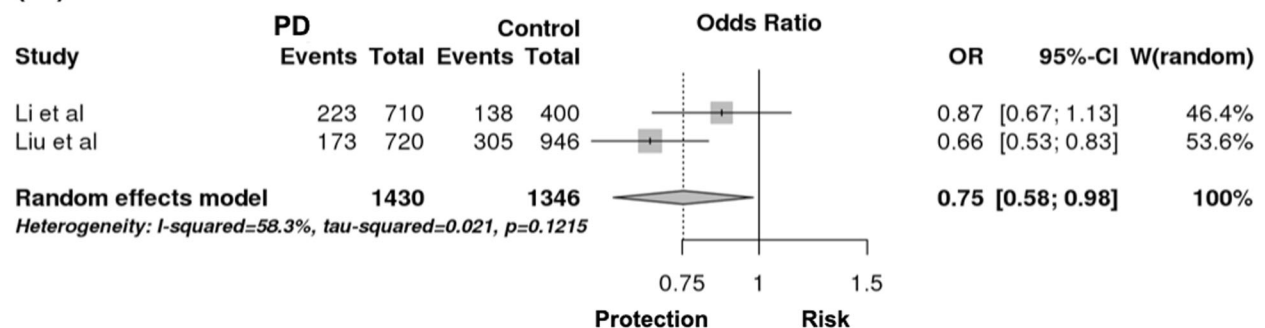
### (A) CC+GC vs GG



### (B) GC vs GG



**Fig. 3** Association of IL-6 -176 G/C polymorphism with PD. **a** The dominant model. **b** The heterozygous model

**(A) A vs G****(B) AA+GA vs GG****(C) C vs T**

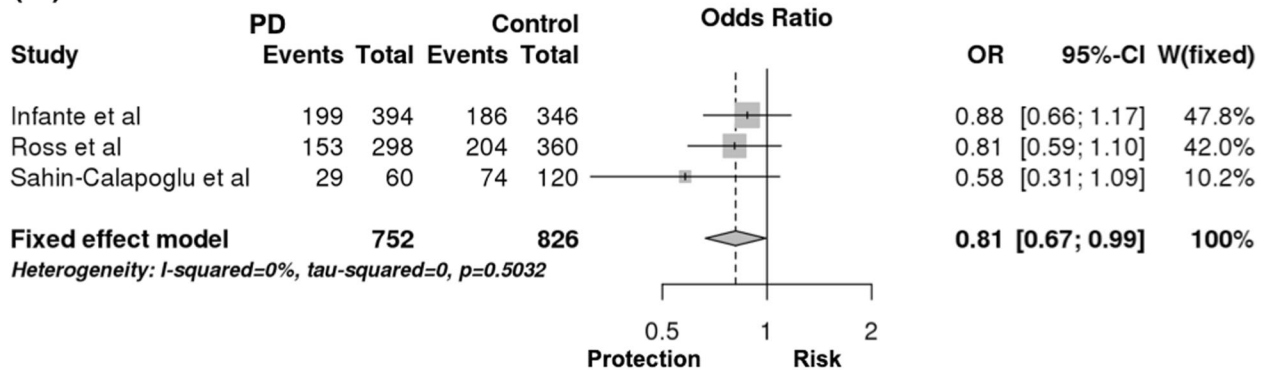
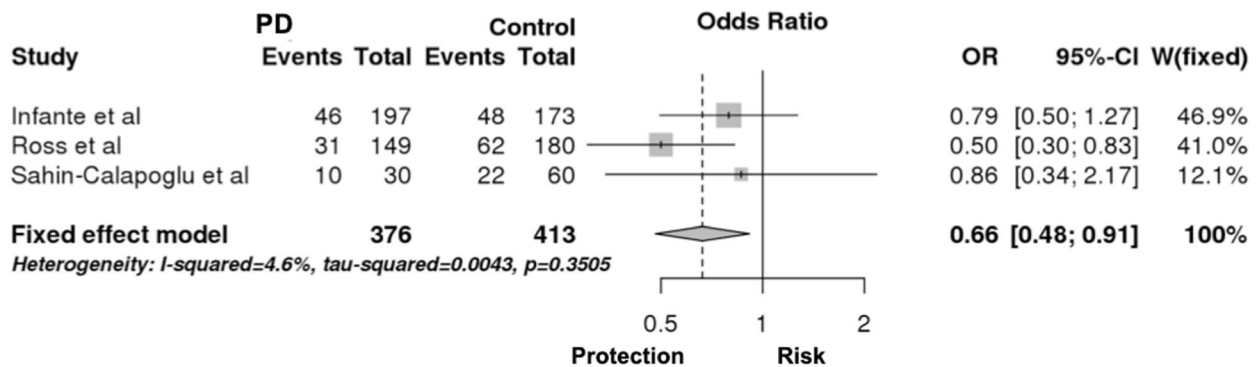
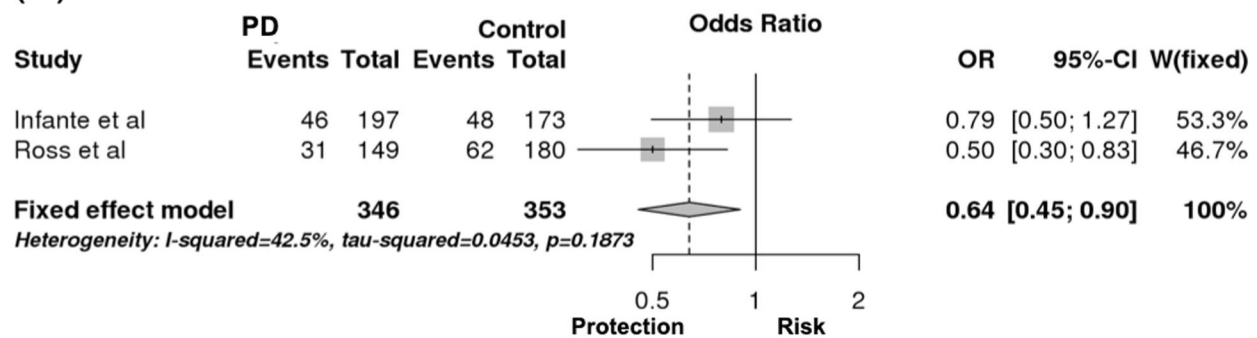
**Fig. 4** Association of IL-10 -1082 G/A and IL-10 -819 T/C polymorphisms with PD. **a** The allelic model in IL-10 -1082 G/A. **b** The dominant model in IL-10 -1082 G/A. **c** The allelic model in IL-10 -819 T/C

this study did not change the results (data not shown). No associations with PD were found for all TNF $\alpha$  polymorphism types (Supplemental Table 2).

In addition to the aforementioned genes, polymorphisms for IL-8 -251 A/T (rs4073) [13, 14, 20], IL-18 -607 C/A (rs1946518) [3, 39], IL-18 -137 G/C (rs187238) [3, 35], IFN $\gamma$  +874 T/A (rs2430561) [17, 36], MCP1/CCCL2 + 2518A/G (rs1064211) [19–21, 40, 41], and CCR2 + 190 G/A (V64I; rs1799864) [19, 20, 40, 41] were also evaluated. No associations were detected between IL-18 -137 G/C, IFN $\gamma$ +874T/A, and MCP1/CCCL2 +2518A/G and PD risk (Supplemental Table 2).

Meanwhile, the IL-8 -251 A/T polymorphism showed that the allelic (T vs. A, OR = 0.812; 95% CI 0.665–0.992,  $P = 0.041$ ,  $I^2 = 0\%$ , Fig. 5a) and recessive (TT vs. AT + AA, OR = 0.663; 95% CI 0.481–0.914,  $P = 0.012$ ,  $I^2 = 4.62\%$ , Fig. 5b) models had lower PD risks, especially in Caucasian populations (TT vs. AT + AA, OR = 0.639; 95% CI 0.454–0.900,  $P = 0.010$ ,  $I^2 = 42.50\%$ , Fig. 5c). Significant associations with PD were also observed for IL-18 -607 C/A and CCR2 +190 G/A. The dominant and heterozygous models of the IL-18 -607 C/A polymorphism were significantly reduced for PD risk (OR = 0.597; 95% CI 0.394–0.905,  $P = 0.015$ ,  $I^2 = 0\%$  and OR = 0.534;



**(A) T vs A****(B) TT vs AT+AA****(C) TT vs AT+AA**

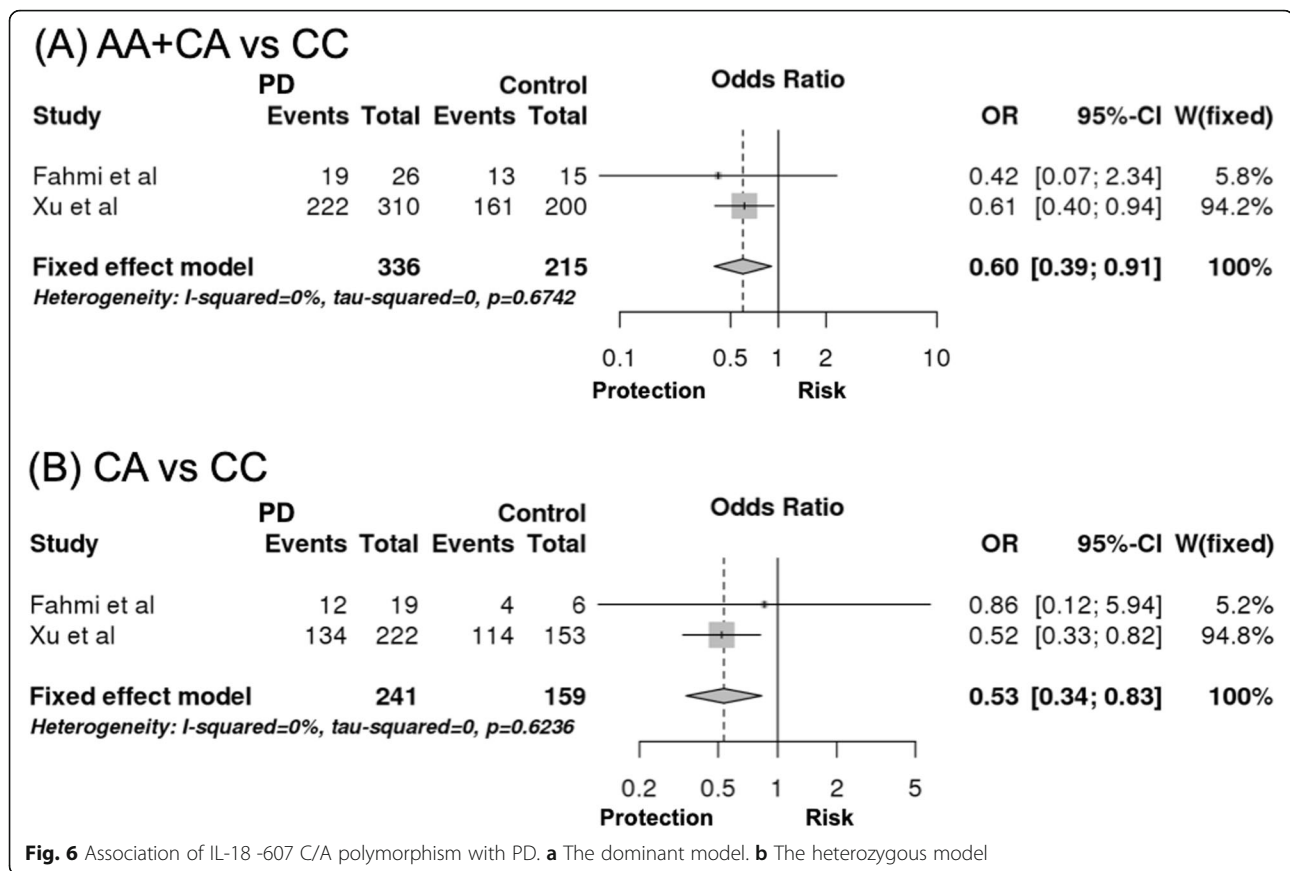
**Fig. 5** Association of IL-8 -251 A/T polymorphism with PD. **a** The allelic model. **b** The recessive model. **c** The recessive model in Caucasian populations

95% CI 0.344–0.830,  $P = 0.005$ ,  $I^2 = 0\%$ ), respectively (Fig. 6a, b). In parallel, recessive and homozygous models of CCR2 +190 G/A also decreased the risk of developing PD (OR = 0.552; 95% CI 0.338–0.903,  $P = 0.018$ ,  $I^2 = 0\%$  and OR = 0.554; 95% CI 0.336–0.914,  $P = 0.005$ ,  $I^2 = 0\%$ ), respectively (Fig. 7a, b). For CCR2 analyses, studies deviating from HWE [3, 19, 39] (Supplemental Table 1) were not excluded from the evaluation, because of the highly limited study numbers. Begg's funnel plot (data not shown) and the Egger's test were applied,

but no publication bias was identified ( $P_{\text{Egger's test}} > 0.05$ ) (Supplemental Table 2).

### Discussion

In this meta-analysis, a comprehensive investigation of associations between inflammation-related gene polymorphisms and PD risk was performed. Our findings suggest a negative association between IL-1 $\alpha$  -889 C/T and PD in Asian populations; the T allele, as well as the TT and CT genotype conveyed a lower risk for PD, which differed



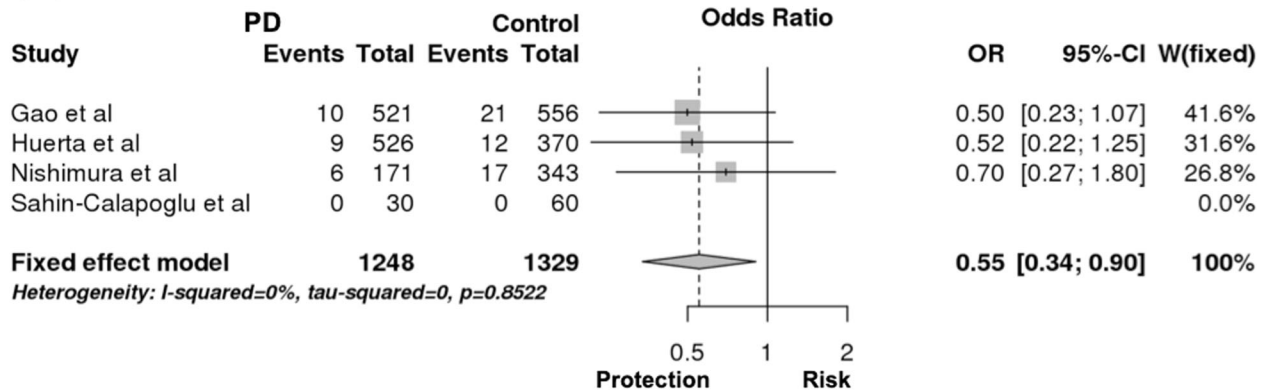
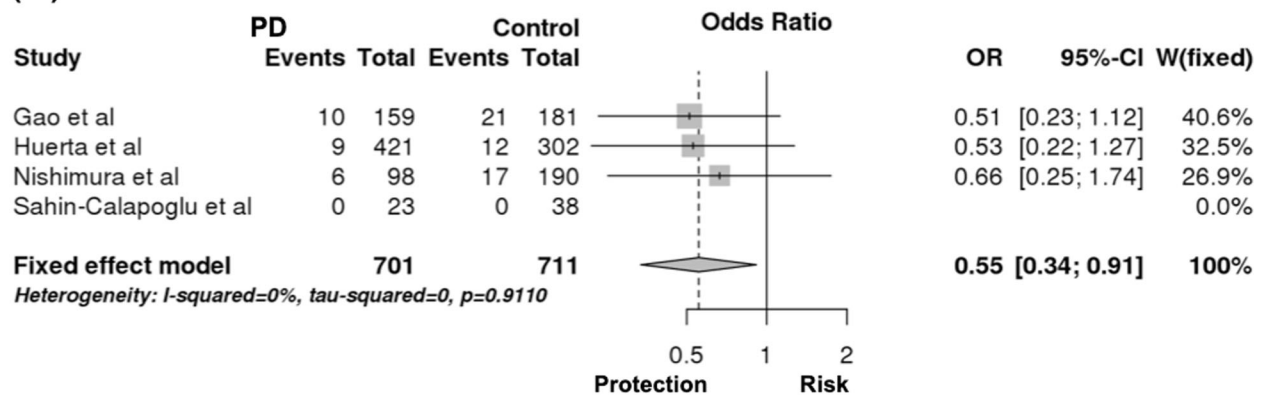
with previous reports [1, 22]. Furthermore, a previous study also demonstrated that the T allele of IL-1 $\alpha$  (+889 C/T) was associated with better cognitive function in the elderly [42]. Interestingly, a previous study also reported that the TT genotype of IL-1 $\alpha$  (+889 C/T) had significantly increased promoter activity, and that its mRNA levels compared well with the CC genotype [43]. Thus, further studies evaluating IL-1 $\alpha$  levels and the TT genotype are required to investigate relationships between these molecular phenomenon and PD risk.

This study also reinforces a previous finding that carriers of the C allele in IL-6 -176 G/C showed a lower risk for PD, particularly in Caucasian populations [13, 14, 17]. A strong association was also observed in this study between PD and IL-10-1082 G/A, in which risk increased for Asian individuals carrying the A allele and decreased in the C allele. These findings contrast with the pooled results from previously reported studies that show lack of association between the IL-10-1082 G/A with PD risk. Production of the anti-inflammatory cytokine IL-10 is crucial to prevent damage driven by excessive inflammation [44]. This neuroprotective role of IL-10 has been extensively studied in PD, an example of which is a study showing that administration of a recombinant human IL-10 in the PD model improves

forelimb akinesia [45]. However, definitive IL-10 levels in PD are equivocal [46–48]. Larsson et al. demonstrated that IL-10 mRNA expression was higher in the GG, rather than the AA genotype [49], suggesting that A allele carriers with the IL-10 -1082 G/A genotype, may express low IL-10 levels. In contrast, the C allele of the IL-10 -819 T/C genotype tends to generate higher IL-10 mRNA expression levels [50]. Together, these results support the oppositional effect of IL-10 -1082 G/A and IL-10 -819 T/C polymorphisms on the expression levels of IL-10, which was also observed in this current study. Nevertheless, studies with larger sample sizes are required to validate the effects of IL-10 -1082 G/A and IL-10 -819 T/C polymorphisms on PD progression.

The pooled results indicated a decreased risk for PD in IL-18 -607A carriers. IL-18 exerts pleiotropic affects and is believed to mediate neuroinflammation and neurodegeneration [3, 39]. And although it is known that IL-18 expression is regulated by polymorphism of IL-18-607C/A [39], to date no reports exist regarding the level of IL-18 in serum or CSF of PD subjects.

Lastly, we also showed a protective role for T and A alleles in the chemokines, IL-8 -251 A/T and CCR2 +190 G/A polymorphisms, respectively. Elevated IL-8 mRNA expression and IL-8 serum levels were correlated

**(A) AA+GA vs GG****(A) AA vs GG**

**Fig. 7** Association of CCR2 +190 G/A polymorphism with PD. **a** The recessive model. **b** The homozygous model

with an IL-8 -251A carrier [51], while the AA genotype of CCR2 +190 G/A was reported to exert protective effects against Alzheimer's disease (AD) progression [52], though another study in the same population showed insignificant results [53]. Together, these results suggest that chemokine/chemokine receptor interactions are essential in directing inflammatory response in injured or degenerated neuronal tissues.

## Conclusions

Despite the strengths of this study, there were some limitations, such as the limited number of studies available. Thus, gene effect estimates on PD may not be precise. Notwithstanding this issue, PD etiology is multifactorial; therefore, the interplay of genetic, hormonal, and environmental factors must be investigated and verified in larger cohort studies.

In conclusion, we observed that IL-1 $\alpha$  -889, IL-6 -176, IL-8 -251, IL-10 -1082, IL-10 -819, IL-18 -607, and CCR2 +190 polymorphisms were associated with PD susceptibility; however, more studies will be required to definitively verify these conclusions.

## Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s43042-020-00056-6>.

**Additional file 1: Supplemental Table 1.** Characteristic of individual studies for the association between inflammation-related gene polymorphisms and PD. **Supplemental Table 2.** Meta-analysis for the association between inflammation-related gene polymorphisms and PD.

## Abbreviations

A: Adenine; AD: Alzheimer disease; C: Cytosine; CCL2: C-C Motif Chemokine Ligand 2; CCR2: C-C chemokine receptor type 2; CCR5: C-C chemokine receptor type 5; CI: Confidence interval; CNS: Central nervous system; CSF: Cerebrospinal fluid; CXCL8: C-X-C Motif Chemokine Ligand 8; DA: Dopaminergic; FEM: Fixed-effect model; G: Guanine; HWE: Hardy-Weinberg equilibrium; IFN $\gamma$ : Interferon gamma; IL-1 $\alpha$ : Interleukin-1 alpha; IL-1 $\beta$ : Interleukin-1 beta; IL-2: Interleukin-2; IL-3: Interleukin-3; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; IL-18: Interleukin-18; M: Mutant type; MCP1: Monocyte chemoattractant protein 1; mRNA: Messenger ribonucleic acid; OR: Odds ratio; PD: Parkinson's disease; REM: Random-effect model; T: Thymine; TH: Tyrosine hydroxylase; TNF $\alpha$ : Tumor necrosis factor alpha; W: Wild type

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**Authors' contributions**

ZU designed, performed, analyzed, and wrote the manuscript. CG analyzed and wrote the manuscript. All authors have read and approved the final manuscript.

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**Availability of data and materials**

All data and supplementary materials are available in the manuscript.

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

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**Competing interests**

The authors declare that they have no competing interests.

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