

# Association between *SNCA* Intron and genetic predisposition to sporadic Parkinson's disease: a meta-analysis based on 49576 individuals

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## Systematic Review

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# Abstract

## Background

The aetiology of Parkinson's disease (PD) is indistinct, but previous studies of different ethnicities have shown that genetic variations in synuclein alpha (SNCA) have an essential character in the risk of PD. The relation between SNCA intronic single nucleotide polymorphisms (SNPs) and the risk of PD is unclear. Based on the general population and five ethnic groups, this article managed a meta-analysis about the connection of SNCA intronic SNPs with the PD genetic predisposition.

## Methods

This study was implemented according to the 24-step guideline, with strict criteria. The analysis was performed using Stata 16.0 software. Five genetic models were used to analyze the strength of the association, which was quantified by OR value and 95% CI.

## Results

We included 15433 cases and 34143 controls from 31 articles. 6 SNPs in the intron region were screened, and 5 SNPs were statistically significant. Three variants augmented the PD susceptibility (rs2736990, rs3822086, and rs3857059), and two SNPs decreased the risk (rs356186 and rs7684318). Subgroup analysis showed that rs2736990 and rs3822086 carriers added the PD genetic predisposition in the East Asian group. European and Latin group carrying rs3857059 and rs2736990 is the high-risk populations of PD.

## Conclusions

This study finally found 5 SNCA intronic SNPs related to the risk of PD. And racial factors should not be ignored.

## 1. Introduction

Parkinson's disease (PD) is one of the progressive neurodegeneration disorders characterized by motor and non-motor dysfunction [1]. As we all know, the SNCA gene predisposes individuals to develop PD. The progressive loss of dopaminergic neurons in the substantia nigra of the midbrain and the accumulation of Lewy bodies are thought to trigger the clinical symptoms of PD[2]. The SNCA gene encodes the  $\alpha$ -synuclein protein modulating neurotransmitter release and vesicular transport, which is the hallmark of PD [3]. The aetiology of PD remains unclear, while a recent genome-wide association study (GWAS) shows that single nucleotide polymorphisms (SNPs) of the SNCA have an essential function in the genetic predisposition to PD.

A recent review about the genetic architecture of PD showed that most variants were identified in the European ancestry, while little is known about the genetics of other populations[4]. SNPs in the promoter and 3' region of SNCA make for the  $\alpha$ -synuclein overexpression and confers PD predisposition. However, the genetic architecture of PD still needs to be investigated. In 1977, the intron was discovered. However, the significance of its existence remains unclear. Scientists think introns may regulate gene expression by delaying the time required for DNA to encode proteins; others suggest that introns can also perform selective splicing, allowing ribosomes to assemble multiple proteins from a single gene [5]. Introns are generally considered “junk DNA”, however two recent independent studies on the function of introns suggest that introns are associated with survival under stress in eukaryotic cells, at least in yeast [6–7]. It is believed that introns may be closely related to the risk and progression of the disease. For a clinical example, CpG methylation in the intron region of the IL10 gene is positively correlated to the risk of asthma[8]. The function of introns in the pathogenic mechanism of PD has not been reported. Based on it, we systematically reviewed the relationship between the SNCA intronic SNPs and disease susceptibility.

More and more studies have been concerned with the association between gene non-coding SNPs and disease incidence. A PD-risk associated SNP review[9] showed that 25/39 positive SNPs were located at the SNCA intronic region, with the largest number and unknown function. The most studied SNP in SNCA intron is rs2736990 of intron 4. A meta-analysis published in 2017[10] suggested that the carrier rs2736990(TT/TC) may reduce PD susceptibility, and the results of previous studies are still inconsistent. Above all, it is necessary for us to conduct an in-depth meta-analysis about the association between SNCA intron and PD genetic predisposition involving a large sample.

## 2. Methods

We carried out this study according to the 24-step guideline for systematic review and meta-analysis in the medical research [11].

### 2.1. Search strategy

We searched the relevant researches from PubMed, Web of Science, Embase, Google Scholar, Wanfang, and Chinese national knowledge infrastructure(CNKI) databases up to Oct 31th, 2021, using the keywords: (“Parkinson’s disease” or “Parkinson disease” or “PD”) and (“ $\alpha$ -synuclein” or “Alpha-synuclein” or “SNCA”) and (“single nucleotide polymorphism” or “polymorphism” or “SNP” or “mutation” or “variant” or “locus”). References in the searched papers were also identified to be added studies. Articles associated with the relationship between SNPs of SNCA intron and PD predisposition were further chosen and reviewed to ascertain the qualification. Papers published in Chinese and English were included in our study.

### 2.2. Inclusion and exclusion standard

The inclusion standards was as below: (1) Case-control studies; (2) Patient and compared populations were strictly defined. We employed the UK Parkinson's Disease Society Brain Bank clinical diagnostic standard to diagnose PD patients. The control group came from a healthy community that matches gender and age. Compared subjects are fit without psychiatric history; (3) We obtain the genotypic data for PD and controls. (4) All or part of the research data is about SNCA SNPs and disease risk; (5) The polymorphic site is in the SNCA intron; (6) The genotype periodicity of the control group accord with Hardy-Weinberg equilibrium (HWE). The exclusion standard was: (1) Review, case report, meta-analysis, systematic review, or meeting abstract; (2) Family-based studies; (3) Incomplete genotypic data ; (4) Repetitive publications; (5) Genotype distribution of controls are not consistent with Hardy-Weinberg equilibrium (HWE); (6) Variations in regions other than SNCA intron.

## 2.3. Quality evaluation

On the ground of 3 components: comparability, choice, and reveal of patients and controls, the Newcastle-Ottawa Scale (NOS) was utilized by reviewers(P Li, ZQ Fu) in assessing the quality of the studies. The NOS score varied from 0 to 9. It is considered high quality if an article has a NOS score of 6 or greater [12].

## 2.4. Data extraction

P Li and ZQ Fu carefully fetched information from eligible research, and the third investigator (WG Liu) reached a consensus. For every research, data were included: the first author's name, published year, population and race, sum and features of patients and controls, genotype frequency, genotyping platform, and proof of HWE in controls. The whole population groups were divided into five ethnic subgroups: East Asian, West Asian, European, Latino, and mixed [13].

## 2.5. Statistical analysis

We counted odds ratios (ORs) and 95% confidence interval (CI) to assess the relationship between SNCA intronic SNPs (M: wild type gene, N: mutant type gene) and PD in 5 genetic models, including allele model (N vs M), heterozygote model (MN vs MM), homozygote model (NN vs MM), dominant model (MN+NN vs MM), and recessive model (MM+MN vs NN). Regarding the method published in the paper by Zhang et al. [14], the total population is also divided into five races for subgroup analysis. We directed the sensitivity analysis to detect proveniences of heterogeneity by precluding one research at a time and recalculating the risk-effect.

We used  $I^2$  statistics and  $I^2$  metric values for the heterogeneity test.  $P < 0.10$  and  $I^2 > 50\%$ , which showed that heterogeneity occurred, and we have used a random effect model to pool ORs. Elsewise, we used a fixed-effect model. An evaluation of publication bias was conducted based on a funnel plot. We performed the meta-analysis by software Stata version 16.0 (Stata Corp. College Station, TX, USA).  $P < 0.05$  is statistically significant.

## 3. Results

## 3.1. Characteristics of studies

In the flowchart, we found a total of 385 articles by searching the database. After removing 236 duplicate studies, there remain 149 valid studies. We reviewed the titles and abstracts, then excluded 12 articles. In the end, the meta-analysis included 31 articles involving 15433 cases and 34143 controls. In Table 1, we carefully described the main characteristics of the eligible studies.

## 3.2. Overall and subgroup analysis

A meta-analysis of 6 SNPs was performed, as can be seen in Table 2. Apart from rs894278, remaining 5 SNPs were statistically significant (rs356186, rs2736990, rs3822086, rs7684318, and rs3857059). Of these five SNPs, three added the risk of PD (rs2736990, rs3822086, and rs3857059), and two reduced the susceptibility to PD (rs356186 and rs7684318) in the total populations. Regarding the six SNCA SNPs, we investigated the contributions of allele, dominant, recessive, heterozygote and homozygote concerning each variant using five models. In the whole population, rs2736990 polymorphism augmented the PD susceptibility by five models (OR=1.28-1.64,  $P=0.000$ ), while rs7684318 polymorphism decreased the risk of PD under all genetic models (OR=0.47-0.70,  $P=0.000$ ). Rs3857059 aggrandized the risk of PD under allelic (OR=1.28, 95% CI: 1.01–1.63,  $P=0.044$ ) and recessive model (OR=1.49, 95% CI: 1.11–2.00,  $P=0.008$ ).

A cross-ethnic analysis was further conducted. In the East Asian group, the carrier rs3822086 was significantly related with PD under the allelic (OR=1.25, 95% CI :1.11–1.41,  $P=0.000$ ), homozygous (OR=1.50, 95% CI: 1.18–1.89,  $P=0.001$ ), heterozygous (OR=1.30, 95% CI: 1.06–1.59,  $P=0.012$ ), dominant (OR=1.36, 95% CI: 1.12–1.65,  $P=0.002$ ) and recessive model (OR=1.42, 95% CI: 1.03–1.97,  $P=0.032$ ). Rs2736990 was significantly related with the high-risk PD under allelic (OR=1.22, 95% CI: 1.11–1.35,  $P=0.000$ ) and homozygous models (OR=1.54, 95% CI: 1.25–1.89,  $P=0.000$ ), while weak correlation with PD susceptibility under the recessive (OR=1.25, 95% CI: 1.09–1.43,  $P=0.001$ ), dominant (OR=1.41, 95% CI: 1.21–1.63,  $P=0.001$ ) and heterozygous model (OR=1.30, 95% CI: 1.06–1.60,  $P=0.012$ ). In the East Asian group, there was no relationship between rs3857059 and PD susceptibility under all models ( $P>0.05$ ). European carrying rs356186 reduced risk of PD under the allelic (OR=0.78, 95% CI :0.71–0.86,  $P=0.000$ ), homozygous (OR=0.66, 95% CI: 0.49–0.88,  $P=0.006$ ), heterozygous (OR=0.78, 95% CI: 0.64–0.95,  $P=0.012$ ), dominant (OR=0.76, 95% CI: 0.67–0.85,  $P=0.000$ ) and recessive model (OR=0.71, 95% CI: 0.53–0.96,  $P=0.025$ ). Rs3857059 was significantly relevant with the greater risk under allelic, dominant and heterozygous models (OR=1.47-1.50,  $P=0.000$ ), while weak correlation with PD susceptibility under the recessive (OR=2.09, 95% CI: 1.08–4.03,  $P=0.028$ ) and homozygous model (OR=2.22, 95% CI: 1.15–4.28,  $P=0.018$ ). Rs2736990 was significantly associative with the larger PD susceptibility under five models (OR=1.27-1.66,  $P=0.000$ ). In the Latino group, rs2736990 augmented the risk of PD under allelic (OR=1.74, 95% CI: 1.17–2.60,  $P=0.007$ ), recessive (OR=2.54, 95% CI: 1.39–4.64,  $P=0.000$ ) and homozygous model (OR=2.66, 95% CI: 1.44–6.20,  $P=0.024$ ), while no correlation with PD susceptibility under dominant and heterozygous models ( $P>0.05$ ). Rs3857059 added the risk of PD under allelic (OR=1.52, 95% CI: 1.06–2.19,  $P=0.023$ ), dominant (OR=1.79, 95% CI: 1.01–3.16,  $P=0.046$ ) and homozygous model (OR=2.40, 95%

CI: 1.12–5.14,  $P=0.024$ ), while no interrelation with PD susceptibility under recessive and heterozygous models ( $P>0.05$ ).

### 3.1. Sensitivity analysis and publication bias

We directed the sensitivity analysis by dislodging one research every time. There was no significant difference in pooled OR and 95% CI values by five models, suggesting the highly stable results in this meta-analysis. The publication bias was assessed by funnel plots. The funnel plot's shape was approximately symmetrical, showing no observable publication bias.

## 4. Discussion

Our meta-analysis systematically analyzed the relationship between SNPs of SNCA intron and PD susceptibility in the whole population and grouped them by race. A GWAS meta-analysis of PD [15] revealed 90 independent key risk locus across 78 genomic regions. A large number of studies have shown that the SNCA was most significantly associated with sporadic PD. Many previous PD-risk associated meta-analyses[9–10] have focused on the single SNP of SNCA promoter, 5' and 3' end region. Meanwhile, there were few subgroup analyses of race and cross-ethnic research. The sample size was also too small to produce sufficient statistical power.

This meta-analysis showed five SNPs had statistically significant differences. Two SNPs (rs2736990, and rs3857059) were found in European, East Asian, and Latino groups, while the remaining four SNPs were only found in one population group. In the global population, three SNPs (rs2736990, rs3822086, and rs3857059) increased the risk of PD, and they should be detected during the early screening of PD. The other two SNPs (rs356186 and rs7684318) had protective effects. The ORs effectively represented the SNPs' contributions to PD. In the early clinical diagnosis of PD, the East Asian population carrying three SNPs (rs3822086, rs2736990, and rs3857059) is a high-risk group (with ORs of 1.25-1.28). The European and Latino population carrying two SNPs (rs3857059 and rs2736990) is a high-risk group (with ORs of 1.28, simultaneously). Our PD genetic architecture study showed that intron region rs2736990 is common to different ethnic populations. Rs3857059 is endemic to the Caucasian population (European and Latino). Rs3822086 could be the race-specific SNP that increases the risk of PD among East Asians. In contrast, Zhang et al.[14] also carried out a meta-analysis of the association between SNCA SNPs and PD risk under three genetic models. However, the results of the study indicated that rs2736990 was unique to the East Asian population. Two results verified that the SNCA intron might be a potential therapeutic target for PD intervention, especially in East Asia.

Although the ORs were relatively small, a previous study has revealed that functional non-coding SNCA variants can affect SNCA expression through epigenetic modification[16]. Introns afford the alternative splicing, which making multiple messenger RNAs from a single gene in a neuron[17]. This process increases variations in an organism and can be beneficial. Introns may regulate the dopamine neuron through RNA-mediation. The intron can regulate the alternative splicing of eukaryotic microRNA, and may regulate the expression of SNCA in splicing-mediated regulation of transcription [18]. This process

showed that SNCA intron might participate in the pathogenesis and disease progression of PD through epigenetic modification. Three SNCA intronic polymorphisms may also affect synaptic activity by regulating the release of synaptic vesicles, thereby disrupting the correct role of  $\alpha$ -synuclein and aggrandizing PD susceptibility[19]. It is necessary to investigate the mechanisms about SNCA intron (especially common rs2736990) in PD predisposition. All these results have revealed that intron could be the potential precise therapeutic target in the future. Rs3822086 carriers should especially be paid special attention to early genetic screening of diseases in East Asia.

This meta-analysis had some limitations. First, there may be some undiscovered biases in our research, such as selection bias and language bias. Second, too few studies on the West Asian and Latin races were included, which affected the power of the statistics. Third, the randomized clinical trials (RCT), follow-up and multi-centre studies still lacked. Finally, the occurrence of diseases was related to factors such as genes, environment, and epigenetics. It is still essential to consider how environmental factors (such as stress) mediate heredity (introns) to produce PD genetic predisposition in the future.

## 5. Conclusion

In short, five SNCA intronic SNPs carriers were PD risk-associated. Our PD genetic architecture study showed that intron region rs2736990 is common to different ethnic populations. Further studies on intron loci rs2736990 across ethnic groups were needed to clarify its functionally biological significance. Rs3822086 was endemic to East Asia, and rs3857059 was endemic to European and Latino. The SNCA intron may be a potential therapeutic target for PD intervention.

## Declarations

### Conflicts of Interest

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

P.L.: Study design and protocol, searches, title, abstract and full-text screening, data-abstraction, statistical analyses, interpretation of the data and drafting the article. Z.Q.F. and P.L.: Data verification, statistical analyses and interpretation of the data. Weiguo Liu and Mingyang Du contributed equally to this manuscript.

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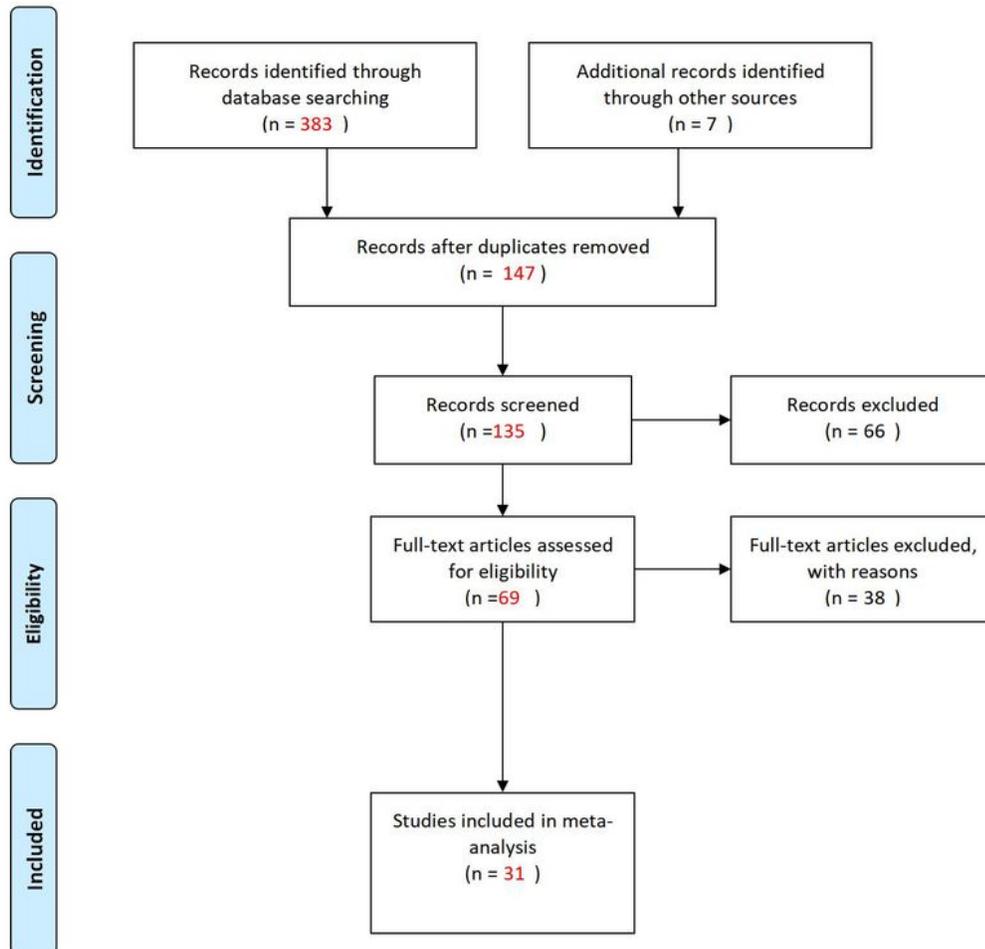
## Table 1

Table 1 is available in the Supplementary Files section.

## Figures



## PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Figure 1

Flowchart of studies selected in the meta-analysis

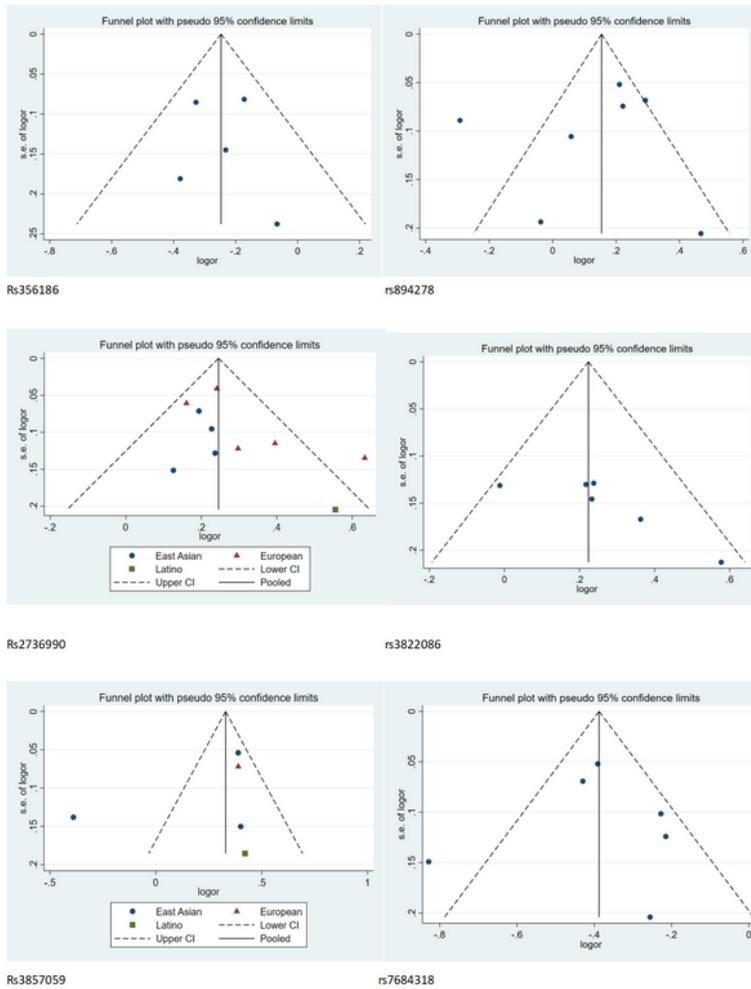


Figure: Funnel plot for publication bias in selection of studies on the SNCA intronic polymorphisms and PD. OR: odds ratio; logOR: the logarithm of the odds ratio value; se: standard error.

## Figure 2

Funnel plot for publication bias in the selection of studies on the SNCA intronic polymorphisms and PD. OR: odds ratio; logOR: the logarithm of the odds ratio value; se: standard error.

## Supplementary Files

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