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ARTICLE

PARK16 rs708730 Polymorphism Decreases Parkinson's Disease Risk in European Ancestry Population: A Meta-analysis

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ABSTRACT

Parkinson's disease (PD) is a complex fatal chronic neurodegenerative disease most common in elderly people. The early genome-wide association studies (GWAS) found that the minor allele variant of PARK16 rs708730 polymorphism is a significant protective factor for PD in Caucasian populations. However, these results cannot be repeated by the following studies in Caucasian populations and other populations. We considered that the inconsistency of the findings may be caused by the small-scale samples or the heterogeneity among di□erent populations. Therefore, in this study, we synthesized the previous related GWAS studies through three authoritative sources, and used the large-scale samples (10,645 PD cases and 30,499 controls) to reevaluate the association between rs708730 polymorphism and PD. The results showed that there is no association between them in Asian ancestry population. While, in European ancestry population, we found that the minor allele variant (G) of rs708730 polymorphism is significantly associated with a decreased risk of PD. Collectively, our findings further verified the association of rs708730 with PD and show its genetic heterogeneity among different populations, which can help to develop a better understanding of the PD's pathogenesis.

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1. Introduction

Parkinson's disease (PD) is a chronic progressive complex neurodegenerative disorder, and it is common in elderly people [1,2]. Particularly, the prevalence of PD in the people aged above 60 years is more than three times that in entire population [2]. Another study further showed a rising popularizing rate of PD with age (425 per 100,000 in individuals aged 60-69 years, 1087 in 70-79 years, and 1903 in aged above 80 years) [3]. PD is characterized by the dopaminergic neurons prominent death in substantia nigra and Lewy body formation [4,5]. A previous study predicted that the newly diagnosed PD patients are expected to reach as many as 8.7-9.3 million by 2030 from 4.1-4.6 million in 2005 around the 15 most populous nations [6].

The variants in a specific gene region, which is designated as PARK16 (1q32), are considered to play an important role in pathogenesis of PD [7-9]. In this region, the single nucleotide polymorphism (SNP) rs708730 (G < A) was identified significantly associated with PD in Caucasian populations by a large-scale genome-wide association studies (GWAS) [10]. Particularly, Sanchez et al. collected and analyzed 14,075 Caucasian individuals (including 5,272 PD patients and 8,803 controls) from USA, Germany and UK by GWAS. They found that the rs708730 polymorphism minor allele variant (G) can reduce the risks of PD (odds ratio (*OR*)=0.90, $P=1.59\times10^{-3}$) [10].

However, the consistent and inconsistent results for the effect of rs708730 variant on PD in USA, UK, China, Japan and Korea populations have been reported by the subsequent studies. For example, by analyzing 2,000 PD and 1986 control Caucasian subjects from USA, Hamza et al. also found that the rs708730 polymorphism minor allele variant is a protective factor for PD (*OR*=0.87, *P*=0.03) [11]. While according to the results of two independent studies, the rs708730 is found not associated with PD in UK (*OR*=0.98, *P*=0.82) [12] and China populations (*OR*=0.81, *P*=0.19) [13], respectively. Further, Satake et al. and Chung et al. selected 20,392 (including 2,011 PD patients and 18,381 controls) and 2,244 (including 1,036 PD patients and 1,208 controls) individuals from Japan and Korea, respectively, and they found that the minor allele of rs708730 are associated with an increased risk of PD (*OR*=1.33 and $P=2.43\times10^{-8}$ for Japan population [14]; *OR*=1.22 and *P*=0.008 for Korea population [15]).

We considered that the inconsistency of the findings may be caused by the small-scale samples or the heterogeneity among dierent populations. To overcome these defects and enhance reliability of the results, we selected a more complete sample set by searching the PubMed, ClinicalKey and Google Scholar databases. The large-scale samples include 10,645 PD patients and 30,499 controls from nine related GWAS studies, which are involved in European and Asian ancestry populations. Then, according to the method used in the previous studies [16-24], we conducted a meta-analysis to reevaluated the association between rs708730 polymorphism and PD. Further, we explored the heterogeneity among different populations and assessed the association between rs708730 and PD in Asian and European ancestry populations, respectively.

2. Methods

2.1 Literatures Acquisition and Studies Selection

We selected all the possible studies by searching PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and ClinicalKey (https://www.clinicalkey.com/) databases, respectively, using the keywords: "Parkinson's disease" and "rs708730", or "Parkinson's disease" and "PARK16". We collected all these literatures from the two databases before the last update on September 25 2018. And then, the Google Scholar (http://scholar.google.com/) was further used to query all the references of the studies and the articles citing these studies identified from PubMed and ClinicalKey databases.

After that, the appropriate studies were identified according to the following criteria: (1) The study is designed according to the case-control strategy. (2) The study evaluates the association of rs708730 polymorphism and PD. (3) The study provides the number of cases and controls. (4) The ethnicity of each individual in the study was presented clearly. (5) The number of rs708730 genotypes both in cases and controls are provided by the study or it provides enough data to calculate these. (6) The *OR* value with 95% confidence interval (*CI*) and the *P* value are provided by the study or it provides enough data to calculate these.

2.2 Data Extraction

The following information from each of the selected studies was extracted: (1) The publication year and the first author of these studies. (2) The ethnicity and population of the participants in these studies. (3) The number of PD patients and healthy controls in these studies. (4) The genotype information of rs708730 both in the PD patients and healthy controls. (5) The association analysis results (*OR* value with 95%*CI* and *P* value) in these studies. (6) The genotyping platforms. For the genotypes, *OR* value

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and the 95%*CI* as well as the corresponding *P* value, we worked them out using R program (http://www.r-project.org/) if these informations didn't be provided directly.

2.3 Genetic Model Choice

Among the two alleles G and A of the rs708730 polymorphism, G was the minor allele. According to the previous studies [25-29], the allele model (A allele versus G allele), the dominant model (AG+GG versus AA), the recessive model (GG versus AA+AG), and the additive model (AA versus GG) are the common genetic model for the association analysis. Given that only the genotyping data of A allele versus G allele are provided from the selected studies (shown in Table 1), the allele model was used to analyze the association between rs708730 polymorphism and PD in this study.

2.4 Heterogeneity Test

We chose the two common quantities, Cochran's Q and I^2, to measure the heterogeneity among the di erent ethnic groups in this study. Cochran's Q approximately follows a chi-squared distribution whose degrees of freedom is k-1 (where k is the number of studies), and the I^2 value is calculated through Cochran's $Q\left(I^2 = \frac{Q-(k-1)}{Q}\times 100\%\right)$, which ranges from 0 to 100%. Usually, the low, moderate, high and extreme heterogeneity are tentatively assigned to the I^2 value of <25%, 25-50%, 50-75% and >75%, respectively. According to previous studies, when the I^2>50% and P<0.01, the heterogeneity among different ethnic groups is deemed significant in this study [25-29].

2.5 Meta-analysis and Subgroup Analysis

Usually, there are two models (fixed e ect model and random e ect model) used for meta-analysis. According to the results of heterogeneity test, we used the random and the fixed e ect model in the meta-analysis when heterogeneity is significant or not, respectively [30]. In meta-analysis, we calculated the pooled *OR* value and its 95%*CI* as well as the corresponding *P* value to measure the association between the rs708730 polymorphism and PD based on the Z test. The meta-analysis was performed by the R package 'meta' (http://cran.r-project.org/web/packages/meta/index.html). By most criteria, the threshold of significant association was set as 95%*CI* of *OR* value do not include 1 and. And then, we further split the original samples into European and Asian ancestry populations, and performed the meta-analyses in each subgroup, respectively.

2.6 The Sensitivity and Publication Bias Analysis

By most criteria, we used the two methods, Begg's test [60] and Egger's test [61], to evaluate the publication bias in this allele model. When the *P* values are less than 0.05, we deemed the publication bias is significant. Then, the funnel plot was drawn to show the results of the publication bias analysis based on its asymmetry. Finally, we performed the sensitivity analyses. For this purpose, each of the selected studies was excluded from the whole sample orderly to assess the influence of these studies one by one.

3. Results

3.1 Study Collection and Data Acquisition

Through the keyword search in PubMed and ClinicalKey databases and the filtration according to these criteria (see Methods for details), we identified a total 5 articles and corresponding 9 studies in them which include 10,645 PD cases and 30,499 controls from European and Asian ancestry populations. Moreover, another related study involved in Asian ancestry population was further obtained by checking the citation using Google Scholar. The workflow was shown in Figure 1. Then, we extracted the characteristics of these 9 studies, and the main contents were exhibited in Table 1. Finally, we counted the rs708730 polymorphism genotype data of each study for the following meta-analysis (Table 2).

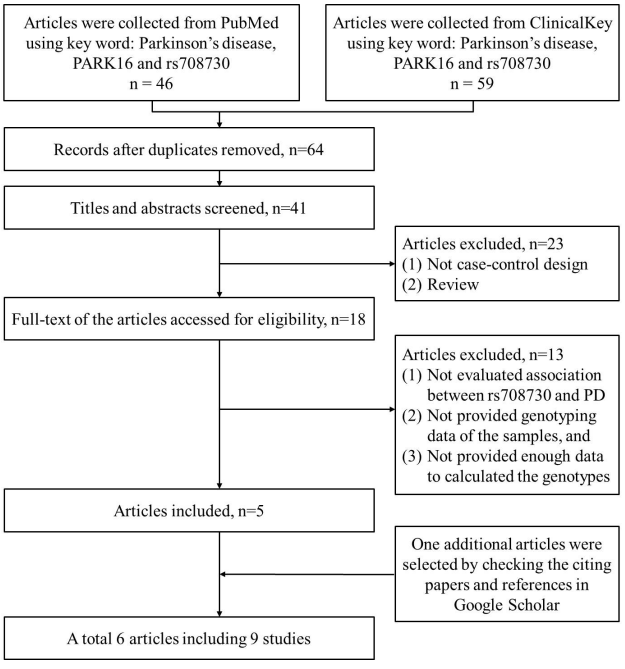

Figure 1. The flow chart of studies selection for re-evaluating the association of SNP rs708730 with PD

Table 1. The main contents in the selected studies for this meta-analysis

Study	Year	Country	Ethnicity	No. of cases	No. of controls	Genotyping platform	Kind of genotype
Sanchez *et al.*(Stage I)	2009	USA and Germany	European	1,063	3,071	HumanHap550	G/A
Sanchez *et al.*(Stage II)	2009	USA, UK and Germany	European	3,452	4,756	Illumina	G/A
Pankratz *et al.*	2009	UK	European	857	867	Illumina	G/A
Hamza *et al.*	2010	USA	European	2,000	1,986	Illumina	G/A
Yan *et al.*	2011	China	Asian	226	230	ABI 3100 automated sequencer	G/A
Satake *et al.*(Stage I)	2009	Japan	Asian	1,078	2,628	Illumina	G/A
Satake *et al.*(Stage II)	2009	Japan	Asian	612	14,139	VeraCode	G/A
Satake *et al.*(Stage III)	2009	Japan	Asian	321	1,614	TaqMan	G/A
Chung *et al.*	2013	Korea	Asian	1,036	1,208	Sequenom MassARRAY system	G/A
All				10,645	30,499		

Note: "G/A" means that the data of genotypes G and A are provided by the study both in cases and controls.

Table 2. the genotype information of the selected studies

Study	Year	Ethnicity	Minor allele	MAF in case/control	PD.G	TOTAL.G	PD.A	TOTAL.A
Sanchez *et al.*(Stage I)	2009	European	G	0.15/0.17	319	1363	1807	6905
Sanchez *et al.*(Stage II)	2009	European	G	0.16/0.17	1105	2722	5799	13694
Pankratz *et al.*	2009	European	G	0.17/0.17	291	586	1423	2862
Hamza *et al.*	2010	European	G	0.16/0.17	640	1315	3360	6657
Yan *et al.*	2011	Asian	G	0.19/0.23	87	192	365	720
Satake *et al.*(Stage I)	2009	Asian	G	0.14/0.18	302	1248	1854	6164
Satake *et al.*(Stage II)	2009	Asian	G	0.15/0.17	1040	25077	184	4991
Satake *et al.*(Stage III)	2009	Asian	G	0.12/0.18	565	3212	77	658
Chung *et al.*	2013	Asian	G	0.19/0.22	1678	3563	394	925

Note: MAF: Minor allele frequency

3.2 Heterogeneity Test

Given that only the genotyping data of G and A allele are provided from the 9 studies, we first tested the heterogeneity of all these samples based on the allele model. We found a significant genetic heterogeneity of rs708730 polymorphism among these selected samples (I^2=83% and P<0.01). Therefore, according to the ethnicity of these samples, we further tested the rs708730 polymorphism heterogeneity in European and Asian ancestry populations, respectively. We also found a significant genetic heterogeneity of rs708730 polymorphism among Asian ancestry populations using the allele model (I^2=90% and P<0.01). However, we did not identify the significant genetic heterogeneity among the European ancestry populations (I^2=0 and P=0.63).

3.3 Meta-analysis and Subgroup Analysis

Because we observed a significant heterogeneity for all these samples, we performed a meta-analysis to assess the association between rs708730 polymorphism and PD using the random e ect model. We have not found a significant association for the comprehensive population based on the allele model (*OR*=0.989, 95% *CI*=0.878-1.115, *P*=0.875). The corresponding forest plot was described in Figure 2. Given that the genetic heterogeneity of rs708730 polymorphism in the comprehensive population is significant, we further divided these samples into Asian and European ethnicity subgroups. According to the results of heterogeneity, we performed the meta-analyses using the fixed e ect and random e ect model for the European and Asian ancestry populations, respectively. Still, we have not observed a significant association between rs708730 polymorphism and PD in the Asian ancestry population (*OR*=1.055, 95% *CI*=0.811−1.372, *P*=0.689) (Figure 3a). However, the significant association was identified in the European ethnicity subgroups. Particularly, we found that the minor allele G of rs708730 polymorphism is significantly associated with a reduced risk of PD in European ancestry population

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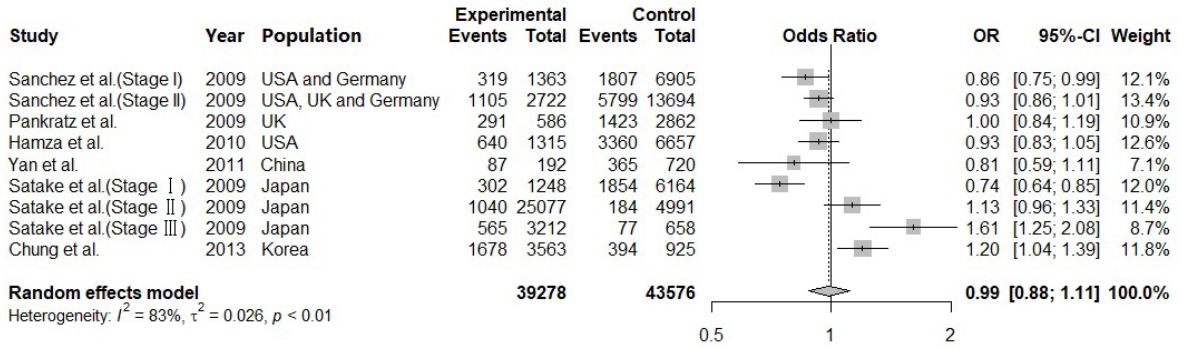

Figure 2. The forest plot showing the results of the meta-analysis in allele model.

Note: Because the genetic heterogeneity of rs708730 polymorphism in the comprehensive population is significant, we used the random effect model to perform the meta-analysis of all 9 selected studies in the allele contrast (G versus A)

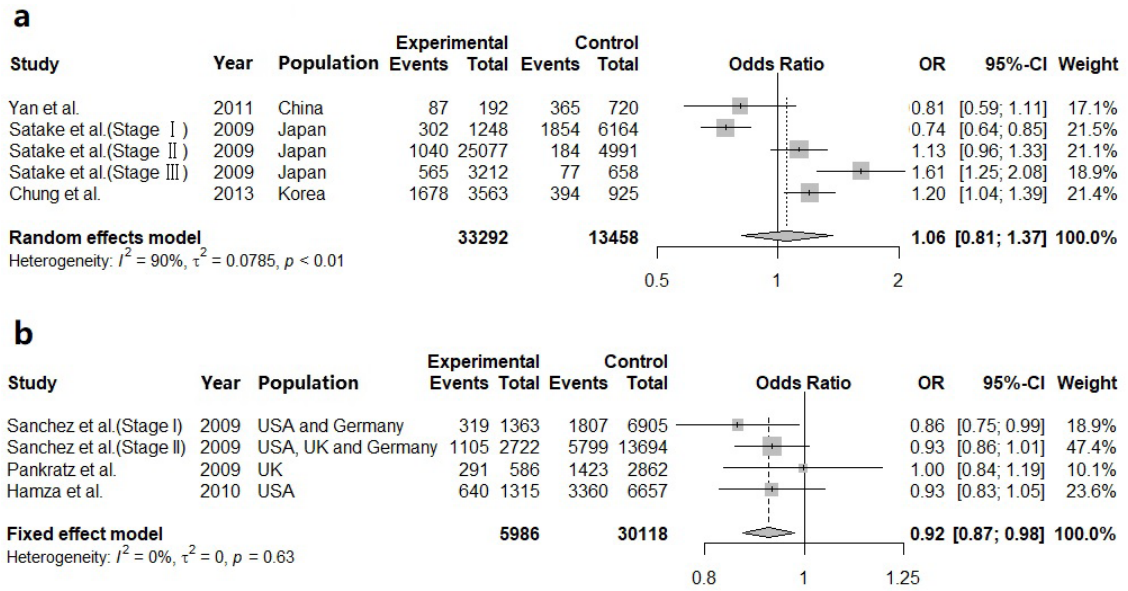

Figure 3. The forest plot showing the results of the meta-analysis in subgroups.

Note: (a) In Asian ancestry population, the significant association between rs708730 polymorphism and PD is not observed. While, (b) the minor allele variant (G) of rs708730 polymorphism is significantly associated with a reduced risk of PD in European ancestry population.

(*OR*=0.924, 95% *CI*=0.872−0.979, *P*=0.007) (Figure 3b).

3.4 The Sensitivity and Publication Bias Analysis

After the Egger's test and Begg's test, we found no significant publication bias in all these studies based on the allele model (Egger's test, *P*=0.393, and Begg's test, *P*=0.404). The results were described in a funnel plot (Figure 4). Moreover, we further excluded each study orderly to perform the sensitivity analysis. The results showed that the heterogeneity and the association between rs708730 polymorphism and PD have not changed significantly when excluding any of the studies from the whole. The detailed information was shown in the Table 3.

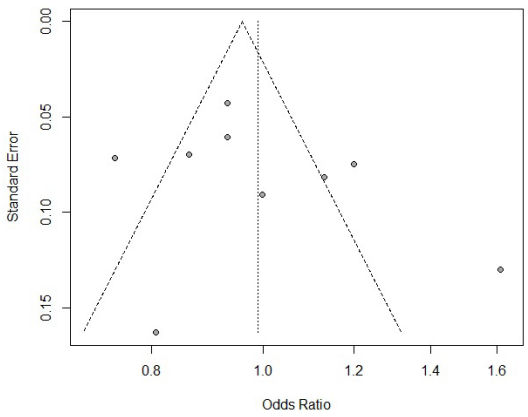

Figure 4. The funnel plot showing the results of the publication bias analysis.

Note: The allele genetic model is used for the association assessment between rs708730 polymorphism and PD.

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Table 3. The result of Sensitivity Analysis in allele model

The omitted study	Year	OR	95% CI	p-value	tau^2	I^2
Sanchez *et al.*(Stage I)	2009	1.0087	[0.8824; 1.1531]	0.8989	0.0292	84.00%
Sanchez *et al.*(Stage II)	2009	1.0005	[0.8624; 1.1608]	0.9945	0.0373	84.70%
Pankratz *et al.*	2009	0.9889	[0.8659; 1.1294]	0.8688	0.0292	84.80%
Hamza *et al.*	2010	0.9993	[0.8685; 1.1497]	0.9921	0.0326	84.80%
Yan *et al.*	2011	1.005	[0.8865; 1.1393]	0.9384	0.0267	84.50%
Satake *et al.*(Stage I)	2009	1.0266	[0.9152; 1.1515]	0.6546	0.0198	78.20%
Satake *et al.*(Stage II)	2009	0.9723	[0.8553; 1.1053]	0.6679	0.0265	83.20%
Satake *et al.*(Stage III)	2009	0.9449	[0.8516; 1.0484]	0.2852	0.0161	76.40%
Chung *et al.*	2013	0.9626	[0.8530; 1.0863]	0.5367	0.0227	80.60%

4. Discussion

PD is characterized by the Lewy body formation and dopaminergic neurons death in substantia nigra, and is most seen in elderly people [1-5]. The previous studies reported that a specific gene region, PARK16 (1q32), plays a key role in PD's pathogenesis [7-9]. And then, the subsequent GWAS studies found that the SNP rs708730 is in PARK16 and its minor allele variant (G) is a protective factor for PD in Caucasian populations [11,10]. However, these results cannot be repeated in China (*OR*=0.81, *P*=0.19) [13], Japan (*OR*=1.33, *P*=2.43×10^{-8}) [14], Korea (*OR*=1.22, *P*=0.008) [15] and another Caucasian population (*OR*=0.98, *P*=0.82) [12]. We considered that the inconsistency of the findings may be caused by the small-scale samples or the heterogeneity among di erent populations. Therefore, after selecting and summarizing the related studies, the larger scale samples and more comprehensive population were used to explore the association between rs708730 polymorphism and PD.

In this study, 9 related GWAS studies (involving in a total 10,645 PD cases and 30,499 controls from USA, UK, Germany, China, Japan and Korea) were selected through three authoritative public databases. Then, we re-evaluated the association between rs708730 polymorphism and PD in European and Asian ancestry ethnicity, respectively. The results showed that there is no association between rs708730 polymorphism and PD in Asian ancestry population (*OR*=1.005, 95% *CI*=0.811−1.372 *P*=0.689). While, in European ancestry population, we found that the minor allele variant (G) of rs708730 polymorphism is significantly associated with a reduced risk of PD (*OR*=0.924, 95% *CI*=0.872−0.979 *P*=0.007). Moreover, we found that genetic heterogeneity of rs708730 polymorphism is significant on the whole (I^2=83% and *P*<0.01). When we split the original samples into European and Asian ancestry populations, the genetic heterogeneity is still significant in Asian (I^2=90% and *P*<0.01) but not European ancestry populations (I^2=0 and *P*=0.63). So, the more similar association studies should be performed in more subgroups of Asian ancestry population.

To our knowledge, this meta-analysis selected the most comprehensive samples by far to explore the association between the PARK16 rs708730 polymorphism and PD. Our findings reveal a significant protective function of rs708730 minor allele variant for PD in European but not Asian ancestry populations, which have further verified the association between rs708730 and PD and also show its genetic heterogeneity among different populations. In summary, the findings of this study would help deepen cognition about pathogenesis of PD.

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