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Association of microtubule associated protein tau/Saitohin (MAPT/STH) MAPT_238bp/STH Q7R polymorphisms and Parkinson's disease: A meta-analysis

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ABSTRACT

Background: The association between the extended tau haplotype (H1) and susceptibility to Parkinson's disease (PD) was controversial in previous studies. Therefore, we performed this meta-analysis to determine whether the additional polymorphisms in MAPT_238bp and STH Q7R which both included in H1 are associated with PD.

Methods: 19 studies were identified by a search of PubMed, PDGENE, Elsevier, Springer Link, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese), and Wanfang (Chinese) databases, up to May 2014. Additionally, manual retrieval of the references of identified articles was performed. Odds ratios (ORs) with 95% confidence interval (CI) were calculated using random effects model or fixed effects model based on the between-study heterogeneity. The subgroup analyses were performed by the ethnicity. All the statistical tests were conducted using Stata 9.0.

Results: Both of MAPT_238bp/STH Q7R polymorphisms had a significant association with PD risk in all genetic models. Subgroup analyses by ethnicity showed that the association between MAPT_238bp polymorphism and PD existed in Caucasian populations.

Conclusions: The results of this meta-analysis suggested that MAPT_238bp/STH Q7R polymorphisms might modulate the risk of PD susceptibility. Certainly, additional well-designed studies are required to confirm these findings.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by progressive loss of dopamine neurons in the substantia nigra [1]. Besides, it is frequently associated with cognitive deficits, and dementia ultimately develops in a large number of patients [2]. The causes are likely due to both genetic and environmental influences [3]. Whatever the causes of PD, they all eventually lead to degeneration of the central nervous system through common mechanisms and pathogenesis of cell death, which include excitotoxic mechanisms, oxidative stress, growth factor deficiency, inflammatory responses and dysfunction of the protein degradation system [4,5].

Tau proteins are a group of microtubule-associated proteins that act as an important role in maintaining the structure of microtubules and promoting the assembly. They are expressed in neurons, being particularly plentiful in axons [6]. The extended Tau H1 haplotype comprises a certain of mutations, in complete linkage disequilibrium, localized along the entire length of the gene coding for the microtubule-associated protein tau (MAPT) [7]. This haplotype has been linked with neurogenerative diseases which characterized as tauopathies, such as corticobasal degeneration and progressive supranuclear palsy [7,8]. Moreover, these diseases share motor symptoms with PD [9,10]. MAPT_238bp polymorphism had been identified which involves 238bp's insertion (ins) or deletion (del) that discriminates H1/H2. Haplotype mutations within the microtubule-associated protein tau gene (MAPT) may bring PD susceptibility by H1-mediated gene overexpression [11].

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Saitohin (STH) is a 1-exon gene situated in intron 9 of MAPT, in which a coding variant Q7R was revealed to associate with risk of PD and progressive supranuclear gaze palsy (PSP) [12,13]. Although the function of STH is unknown it encodes a protein which is expressed and co-localizes with Tau in several tissues including the central nervous system implying they may function together in the same or overlapping biochemical pathways [14]. A single nucleotide polymorphic change (A to G) in the Saitohin gene (Q7R) has been identified [15] and is in complete linkage disequilibrium with the Tau haplotype H1 [31]. The corresponding protein reveals a similar tissue expression to tau, which is involved in many neurodegenerative disorders including Parkinson's disease (PD), Alzheimer's disease (AD) and frontotemporal dementia (FTD).

Previous case-control studies investigating the association between the MAPT/STH polymorphisms and PD have given controversial results. One reason may be attributed to limited sample size that any single study may be incapable to present the precise association. Moreover, characteristics among these studies are different, such as population and ethnicity. Hence, we performed the meta-analysis on the association between MAPT/STH polymorphisms and PD using eligible data acquired from the published case-control studies. In addition, the potential modifying effect of ethnicity was also taken into account in this meta-analysis.

2. Methods and materials

2.1. Search strategy and selection criteria

For electronic searches, eligible studies for this meta-analysis were found by using the comprehensive search strategy. Published studies were searched through PubMed, PDGENE, Elsevier, Springer Link, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese), and Wanfang (Chinese) databases. All researches were restricted to Chinese or English language articles published up to May 2014. We used the following search strategy ('Association of Microtubule associated protein tau' or 'MAPT' or 'Saitohin' or 'STH') and ('polymorphism' or 'mutation') and ('Parkinson's disease' or 'PD') or relevant Chinese technical terms for the Chinese Databases to search for published articles.

2.2. Inclusion and exclusion criteria

The eligible studies must satisfy the following inclusion criteria: (1) concerning the association between MAPT/STH genetic polymorphisms (including MAPT_238bp or STH Q7R or both) and PD; (2) case-control study design; (3) providing complete data on genotype frequencies of the MAPT_238bp and/or STH Q7R polymorphism(s) for calculating odd ratio (OR) with 95% confidence interval (CI); (4) not republished data; The exclusion criteria include: (1) a duplicated publication; (2) a review or a case report; (3) not reported the genotype frequencies.

2.3. Data extraction

According to the inclusion and exclusion criteria, data were extracted independently from each study by two authors (Lu and Gong) and the consensus was acquired for all data. The following information was extracted from each study included: the first author's last name, year of publication, the ethnicity of the population, the number of cases and controls, and number of cases and controls for each genotype.

2.4. Statistical analysis

The strength of association between MAPT_238bp/STH Q7R polymorphisms and PD was assessed by ORs with 95% CIs. The allele model (H2 vs H1), the dominant model (H2H2 + H1H2 vs H1H1), the homozygote model (H2H2 vs H1H1), and the recessive model (H2H2 vs H1H2 + H1H1) were used to evaluate the risk. Among the studies, I^2 statistics were used to assess between-study heterogeneity. The random effects model yields wider confidence intervals (CIs) if heterogeneity exists ($I^2 > 50\%$). Otherwise, the fixed effect model was used [16–18]. Subgroup analyses were mainly conducted by ethnicity, but due to the limitations of these studies that we could only perform subgroup analyses of MAPT_238bp in Caucasians. Sensitivity analyses were performed to evaluate the stability of the meta-analysis results by sequentially removing each study included in this meta-analysis. Furthermore, publication bias was analyzed by Begg's funnel plot and Egger's regression test [19]. All the above statistical analyses were conducted by using Stata 9.0 (StataCrop, College Station, Tex). A P value under 0.05 was supposed to be statistically significant.

3. Results

3.1. Characteristics of eligible studies

Based on our search criteria, 491 potentially eligible articles were identified in our primal search. Finally, a total of 19 studies from 15 articles were included in this meta-analysis, which contained 4230 cases and 5363 controls. Detailed process for selecting eligible studies was shown in Fig. 1. Among the 15 articles, we abstracted 11 studies and 8 studies about 238bp and Q7R polymorphisms, respectively by discriminating their studying populations. The main characteristics of these studies are summarized in Tables 1 and 2.

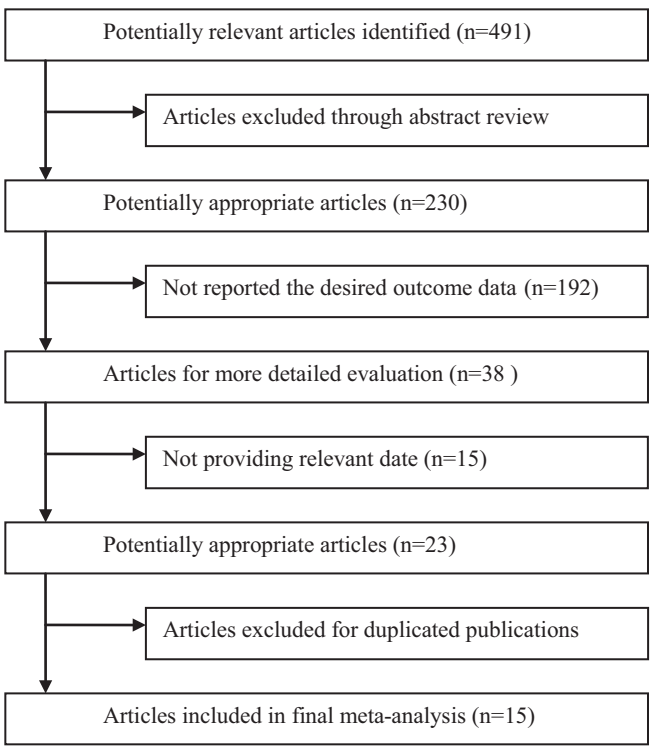


Fig. 1. Flow diagram of the study selection process.

Table 1
Characteristics of 11 MAPT_238bp case-control studies included in this meta-analysis.

First author	Yer	Population	Ethnicity	Cases	Controls	Cases			Controls		
						insins	insdel	deldel	insins	insdel	deldel
Kalindari et al. [20]	2009	Greece	Caucasian	196	163	131	55	10	89	55	19
Refenes et al. [21]	2009	Greece	Caucasian	122	123	84	34	4	63	56	4
Das et al. [22]	2009	India	Mixed	301	243	268	33	0	224	18	1
Camuzat et al. [23]	2008	Guadeloupe	African	40	132	38	2	0	129	3	0
Vandrovcova et al. [24]	2007	Norway	Caucasian	572	660	366	183	23	371	248	41
Winkler et al. [25]	2007	Germany	Caucasian	256	162	182	67	7	112	41	9
Winkler et al. [25]	2007	Serbia	Caucasian	191	156	141	42	8	91	55	10
Fung et al. [26]	2006	Finland	Caucasian	134	140	114	19	1	117	21	2
Fung et al. [26]	2006	Greece	Caucasian	224	215	128	83	13	134	73	8
Skipper et al. [27]	2004	Norway	Caucasian	296	441	227	62	7	282	143	16
Peplonska et al. [28]	2003	Poland	Caucasian	100	100	76	21	3	74	23	3

Table 2
Characteristics of 8 STH_Q7Rcase-control studies included in this meta-analysis.

First author	Year	Population	Ethnicity	Cases	Controls	Cases			Controls		
						AA	AG	GG	AA	AG	GG
Wider[29]	2011	Ireland	Caucasian	346	416	247	87	12	246	148	22
Wider[29]	2011	Norway	Caucasian	475	546	351	111	13	347	178	21
Wider[30]	2010	USA	Caucasian	361	405	234	111	16	233	144	28
Johansson[31]	2005	Sweden	Caucasian	105	160	82	21	2	112	43	5
Levecque[32]	2004	France	Caucasian	208	483	134	65	9	253	198	32
Peplonska[28]	2003	Poland	Caucasian	100	100	76	21	3	74	23	3
Clark[33]	2003	USA	Caucasian	47	129	29	15	3	73	45	11
Clark[33]	2003	USA	Mixed	37	329	25	12	0	259	64	6

3.2. Quantitative synthesis

3.2.1. Association between the MAPT_238bp polymorphism and PD

When we pooled the 11 studies (2551 cases and 2795 controls) about MAPT_238bp and PD into the meta-analysis, proof for significant association came under observation between the gene polymorphism and PD risk (Table 3, for del vs ins: OR = 0.779, 95% CI = 0.649–0.936; for deldel vs insins: OR = 0.600, 95% CI = 0.444–0.822; for deldel + insdel vs insins: OR = 0.763, 95% CI = 0.611–0.952; for deldel vs insdel + insins: OR = 0.662, 95% CI = 0.491–0.892. Forest plots were shown in Fig. 2). The association between the MAPT_238bp polymorphism and PD existed in Caucasian population was demonstrated by the subgroup analysis (2091 cases and 2160 controls) of ethnicity (Table 3, for del vs ins: OR = 0.741, 95% CI = 0.620–0.884; for deldel vs insins: OR = 0.605, 95% CI = 0.447–0.819; for deldel + insdel vs insins: OR = 0.710, 95% CI = 0.575–0.878; for deldel vs insdel + insins: OR = 0.668, 95% CI = 0.495–0.902). According to the heterogeneity (I^2 < 50% or I^2 > 50%) in these genetic models, the fixed or random effects model was used in this meta-analysis.

3.2.2. Association between the STH_Q7R polymorphism and PD

As for the STH Q7R polymorphism, a significant association was detected between the polymorphism and PD in all genetic models (Table 3, for G vs A: OR = 0.711, 95% CI = 0.633–0.789; for GG vs AA: for OR = 0.585, 95% CI = 0.422–0.809; for GG + AG vs AA: OR = 0.672, 95% CI = 0.587–0.770; for GG vs AG + AA: OR = 0.664, 95% CI = 0.481–0.916, forest plots were shown in Fig. 3). In the meta-analysis, the heterogeneity was not significant in these genetic models (I^2 < 50%) and the fixed effects model was employed.

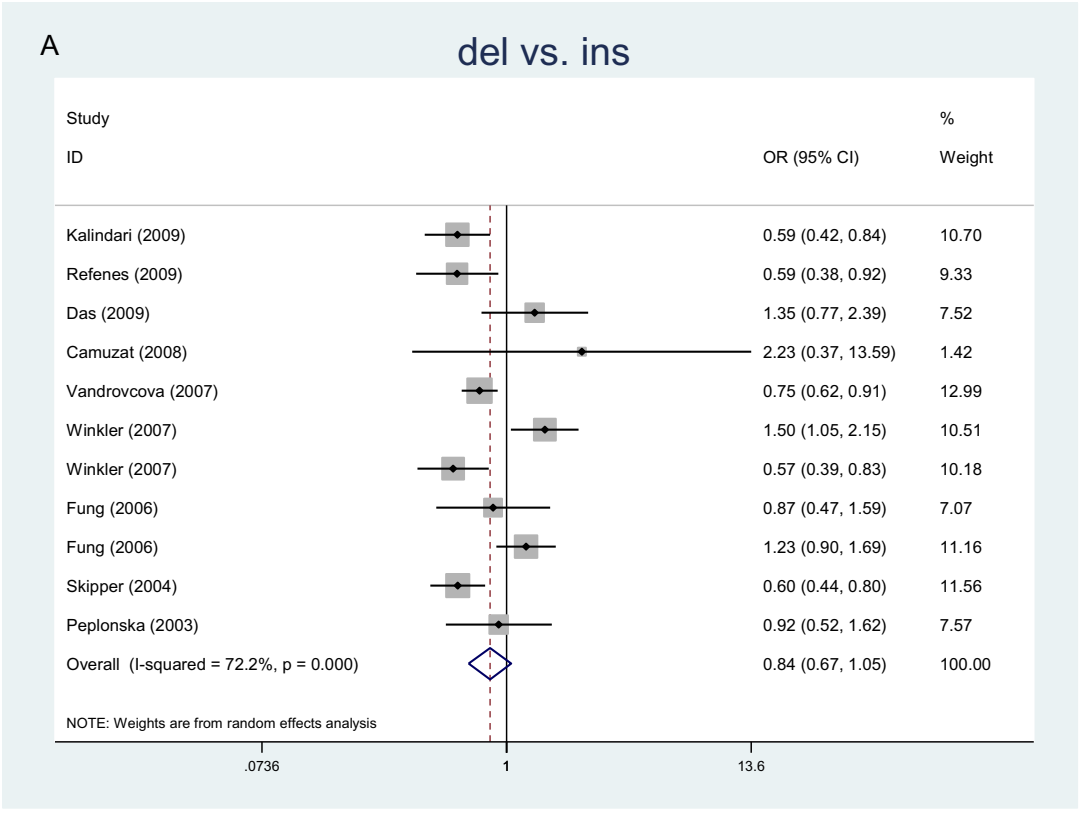
3.3. Sensitivity analyses

The results of this meta-analysis were stable on the whole since we found the sensitivity analysis did not adequately change the pooled ORs except the genetic model (deldel vs insdel + insins) in overall populations.

Table 3
Summary of pooled odds ratios (ORs) with confidence intervals (CIs) in the meta-analysis.

MAPT/STH genotype	Studies	Comparison model	Studies(cases/controls)	OR [95% CI]	P_{OR}	M*	I^2 (%)	P_{Begg}	P_{Egger}
238bp(H1H2)	All studies	del vs ins	12(2551/2795)	0.838(0.668–1.051)	0.000	R	72.20	0.213	0.377
		deldel vs insins	12(2551/2795)	0.600(0.444–0.811)	0.001	F	0.00	0.858	0.886
		deldel + insdel vs insins	12(2551/2795)	0.763(0.611–0.952)	0.017	R	60.40	0.436	0.379
		deldel vs insdel + insins	12(2551/2795)	0.662(0.491–0.892)	0.007	F	0.00	1.000	0.922
	Caucasian	del vs ins	9(2091/2160)	0.794(0.629–1.002)	0.000	R	74.40	0.602	0.957
		deldel vs insins	9(2091/2160)	0.605(0.447–0.819)	0.001	F	0.00	0.348	0.649
		deldel + insdel vs insins	9(2091/2160)	0.710(0.575–0.878)	0.002	R	56.60	0.917	9.944
		deldel vs insdel + insins	9(2091/2160)	0.668(0.495–0.902)	0.008	F	0.00	0.602	0.623
Q7R(H1H2)	All studies	G vs A	8(1679/2568)	0.711(0.633–0.789)	0.000	F	2.20	0.035	0.047
		GG vs AA	8(1679/2568)	0.585(0.422–0.809)	0.001	F	0.00	0.386	0.104
		GG + AG vs AA	8(1679/2568)	0.672(0.587–0.770)	0.000	F	28.40	0.063	0.052
		GG vs AG + AA	8(1679/2568)	0.664(0.481–0.916)	0.013	F	0.00	0.711	0.293

* Model of meta-analysis.



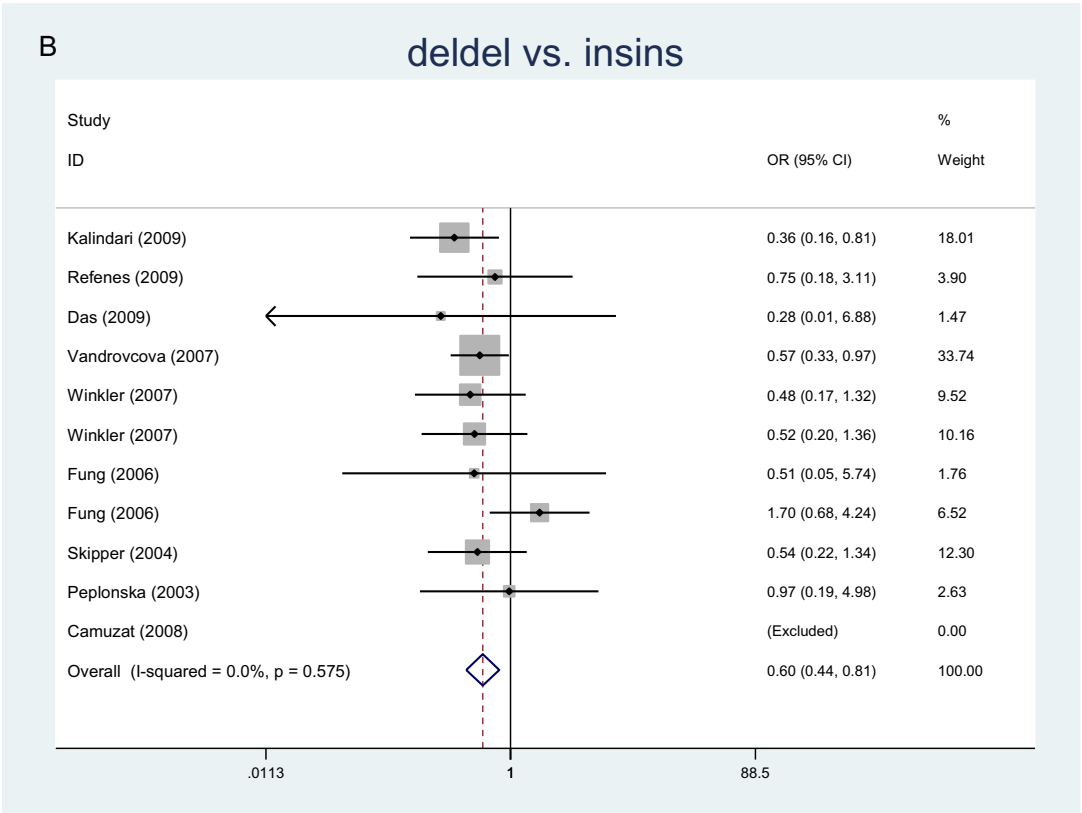
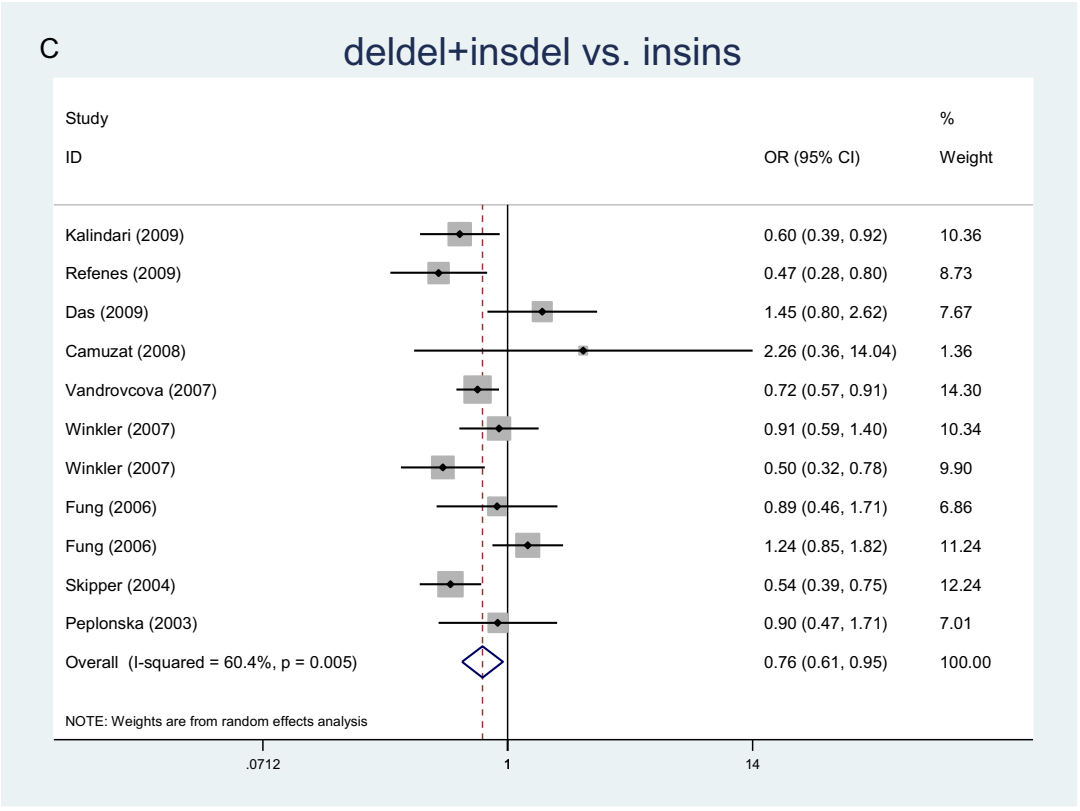
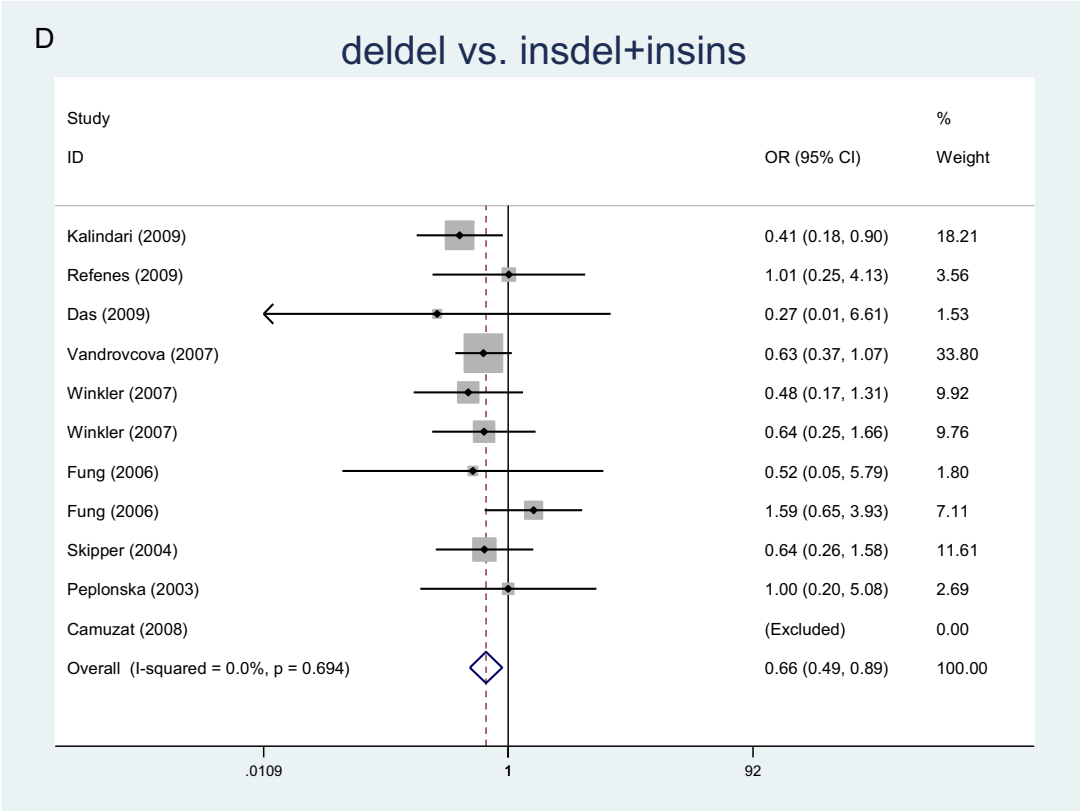


Fig. 2. Forest plot for the association between the MAPT_238bp polymorphism and PD in the whole population.





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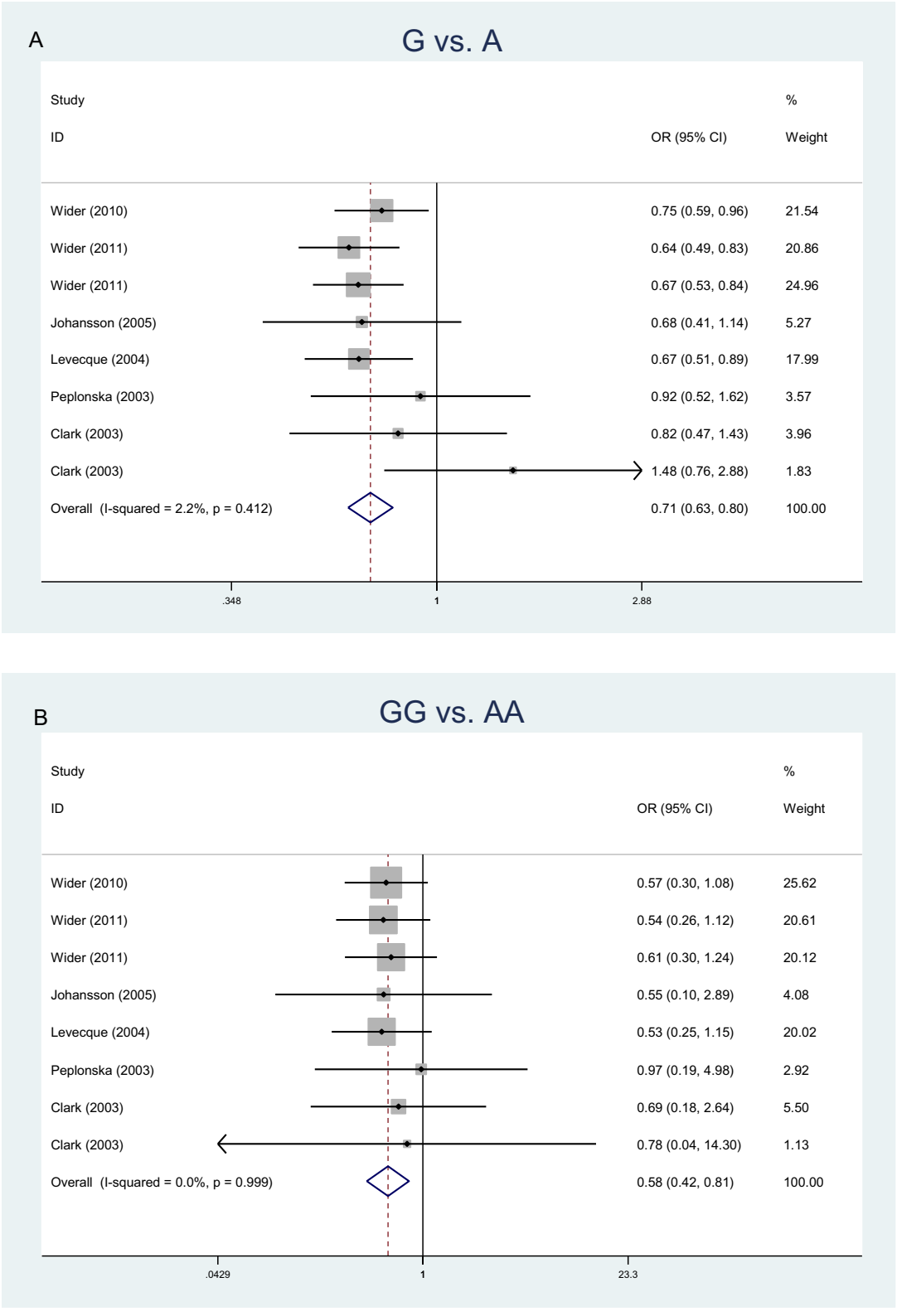
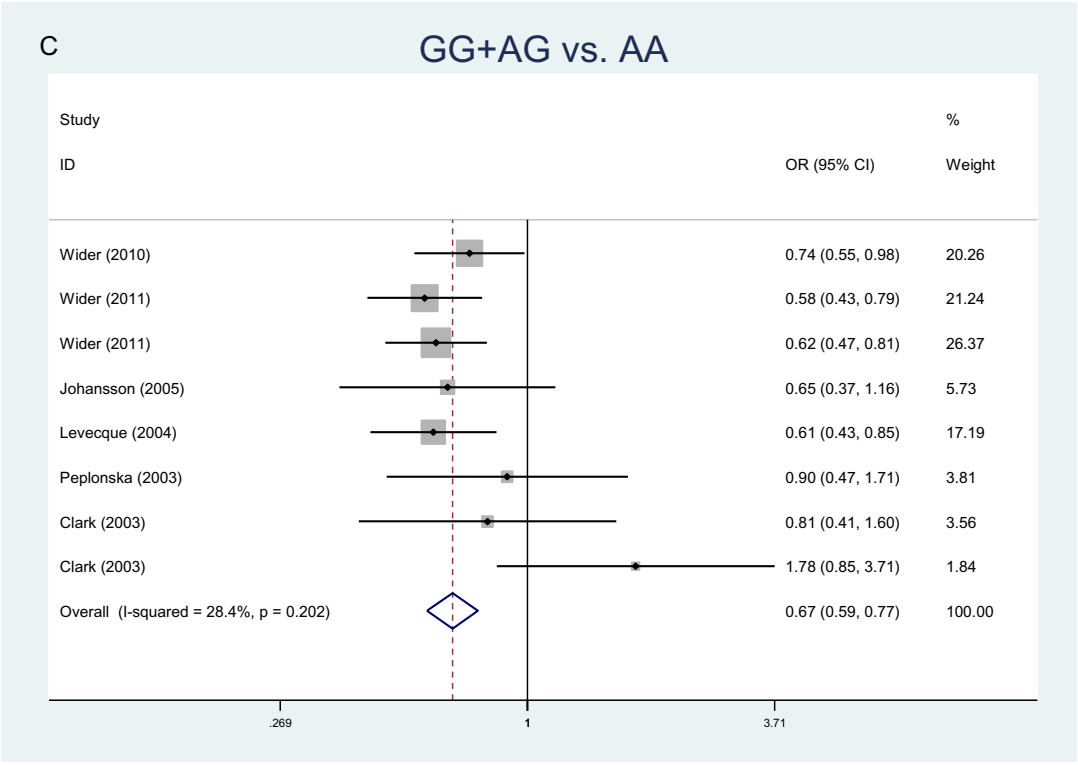


Fig. 3. Forest plot for the association between the STH Q7R polymorphism and PD in the whole population.



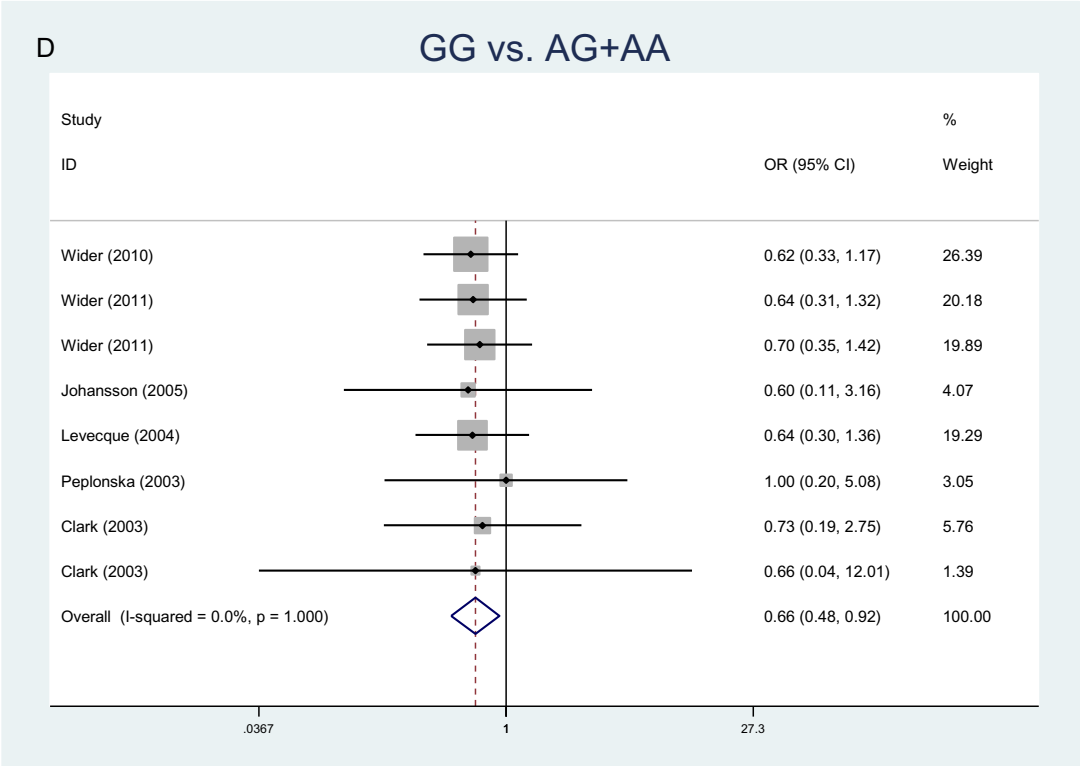


Fig. 3 (*continued*)

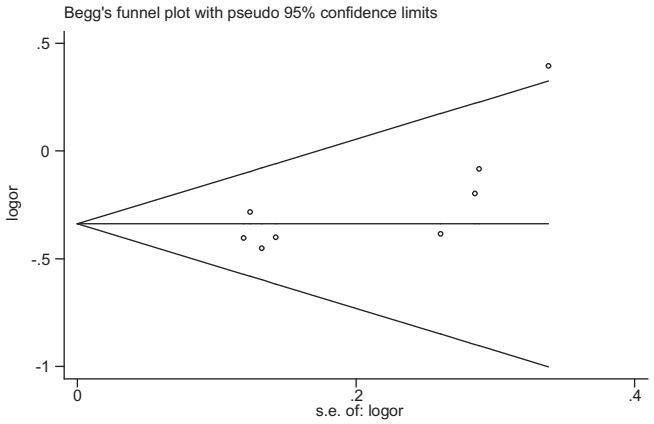


Fig. 4. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association. The Funnel plot for allele contrast (G vs A) of STH Q7R polymorphism.

3.4. Publication bias diagnostics

Both of the Begg's test and Egger's test results were significant in STH Q7R allele model (G vs A: $P_{Begg} = 0.035$, $P_{Egger} = 0.047$). Beyond that, no obvious evidence was indicated for the publication bias in other genetic models analyses by the Begg's tests or the Egger's tests. Funnel plots were showed in Fig. 4.

4. Discussion

PD is a complex disorder with multiple genetic and environmental factors which may influence disease risk [34]. However, the aetiology and pathogenesis of PD still remain largely unknown [35]. Up to now, many researchers have reported the association of PD with gene polymorphism, but no genetic factors is widely accepted as an important risk factor in PD [36]. The association between the extended tau haplotype (H1) polymorphisms and PD has been investigated for many years, but the results are controversial. Owing to too small sample size of the study populations, the credibility of results from a single study is questionable. At present, meta-analysis has been recognized as an important tool to more precisely define the link between selected genetic polymorphism and the risk of disease [37]. Consequently, hoping this meta-analysis will draw a stronger conclusion by increasing the sample size.

As for the MAPT_238bp polymorphism, the meta-analysis based on 12 case-control studies involving 2551 cases and 2795 controls revealed that the tau ins genotype (H1H1, H1H1 and H1H2) increased PD risk. In this meta-analysis, subgroup analyses in Caucasian populations also showed that the MAPT_238bp polymorphism could modulate the risk of PD in all genetic models despite the strengths were different. MAPT encodes microtubule-associated protein tau, which adjusts microtubule dynamics and assembles microtubules into parallel arrays within axons. Due to the proposed interactions of tau protein and α-synuclein and their abnormal intracellular aggregation in neurodegenerative diseases [38,39] the analysis of MAPT gene as a genetic susceptibility factor for PD has been of interest [40]. In addition, tau aggregation can take place in patients with parkin gene mutations, which enhances the possibility that tau dysfunction may also conduct independently of a synuclein to accelerate dopaminergic neuronal degeneration, meanwhile may be a necessary but insufficient factor in the pathogenesis of many PD cases [41]. And recent in vitro evidence illustrates that the H2 haplotype is linked with a reduction in transcriptional efficiency compared to the H1 haplotype [42]. Furthermore, a single common variant could enhance the hazard for both forms of parkinsonism, after which the interactions with other environmental and genetic factors would modify the final presentation of the disease [43]. Consequently, increased expression of H1 haplotype has been suggested as a mechanism of PD susceptibility. The sensitivity analysis did not substantially alter the results except the genetic model (deldel vs insdel + insins) in overall populations, which indicated the results of this meta-analysis were generally robust.

As for the STH Q7R polymorphism, its A and G alleles belong to the H1 and H2 tau haplotype respectively and the meta-analysis on the basis of 8 case-control studies involving 1679 cases and 2568 controls demonstrated that the STH A genotype (H1H1, H1H1 and H1H2) increased PD risk in all genetic models. Most of the populations are Caucasians, so we did not perform subgroup analysis by ethnicity. Sensitivity analysis revealed that the association between the STH Q7R polymorphism and PD was unaltered after an exclusion of the individual study, which also manifested that the results were robust. Nevertheless, the sample size was really small and the populations we used were too limited to obtain a strong conclusion about association between the STH Q7R polymorphism and PD. Therefore, a more accurate OR would have been estimated after further investigations with a larger sample size and greater statistical power.

For better explaining the results, some limitations of this meta-analysis should be acknowledged. First, if more detailed information such as marital status, degree of education, age had been available in the original studies, a more accurate OR would have been evaluated after further stratification. Second, meta-analysis is a type of retrospective study, and selection and recall bias might inescapable exist. Finally, there were only 8 studies on the Q7R polymorphism involved in this meta-analysis, and 7 studies among them were performed in Caucasian population. Hence, subgroup analysis was limited on this gene mutation. Considering these limitations, our findings should be interpreted with caution. In spite of these, our present meta-analysis also had some advantages. First, the meta-analysis had a much greater statistical power than the single case-control study. Secondly, Funnel plots suggested that publication bias was not evident except for the allele model (G vs A).

In conclusion, our meta-analysis supported the view that MAPT_238bp and STH Q7R polymorphisms could modulate the risk of PD. That is, the extended tau haplotype (H1) could increase the risk of PD susceptibility. However, more well-designed studies with a larger sample size are needed to further confirm our findings.

Competing interests

The authors declare that they have no competing interests.

Author contributions

SSL: participated in the design of the research and manuscript writing;
FFG: participated in the design of the research and data analysis;
FF: participated in the research and data analysis;
CYH: participated in the research and data analysis;
ZZQ: participated in the research and the analysis of results;
YLW: participated in the research and the analysis of results;
HYY: participated in the research and the analysis of results;
YHS: designed, interpreted results, and prepare the manuscript.

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