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REVIEW ARTICLE

Association between ubiquitin carboxy-terminal hydrolase-L1 S18Y variant and risk of Parkinson's disease: the impact of ethnicity and onset age

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Abstract The Ubiquitin carboxy-terminal hydrolase-L1 (UCHL1) is a candidate risk gene for Parkinson' disease (PD), and a function SNP (rs5030732) in the coding region of this gene has been studied for the association with the disease extensively among worldwide populations, but the results were inconsistent and controversial. Here, to estimate the association between UCHL1 S18Y polymorphism and risk of PD in general population, we conducted a systematic meta-analysis by combining all available case–control subjects in Asian, European, and American populations, with a total of 7742 PD cases and 8850 healthy controls, and the pooled odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for UCHL1 S18Y polymorphism and PD were calculated using the Mantel–Haenszel method with a fixed- or random-effects model. Subgroup analysis was also performed in different onset age-matched groups. Among high-quality studies, UCHL1 S18Y polymorphism was moderately associated with the risk of PD (allele contrasts, OR = 1.063, 95 % CI 1.008–1.122; $p = 0.024$; regressive genetic model, OR = 1.078, 95 % CI 1.005–1.157; $p = 0.035$). When stratifying for ethnicity, none association were observed in subgroups. Analysis of early-onset PD (EOPD) and late-onset PD (LOPD) revealed that the polymorphism was not associated with the risk of PD. In conclusion, our meta-analysis suggests that UCHL1 S18Y polymorphism is moderately associated with susceptibility to PD, and more studies are needed to confirm our conclusion.

Keywords Meta-analysis · Parkinson's disease · Polymorphism · UCHL1

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Introduction

Parkinson's Disease (PD; Online Mendelian Inheritance in Man, OMIM ID: #168600) is the second most common neurodegenerative disorder that affects more than 2 % of the population over age 65, and which is predicted to increase due to the aging of population [1–3]. Patients with PD show non-motor and motor symptoms, and the motor phenotype is characterized by variable severity of rigidity, bradykinesia, and tremor. The clinical diagnosis of the disease is according to the key features listed above and includes initial responsiveness to levodopa. PD serves a typical example of a complex disease, which may result from a interplay of neuroinflammation, environmental toxins, and genetic risk factors acting on a background of aging [4, 5]. Furthermore, the most important contribution to the comprehension of the etiology of PD may come from genetic investigations [6, 7]. Evidences showed that approximately 20 % of PD patients found a family history of the disease and monogenic forms correspond to nearly 20 % of EOPD and 3 % of LOPD [8, 9].

Over the past decade, genetic and molecular studies, especially the emergence of genome-wide association

study (GWAS) in familial PD, have identified pathogenic polymorphisms in several genes including FGF, TNF, GAK, MTHFR, LRRK2, and UCHL1 [10, 11]. The research of these causal genes has provided important insights into the etiology of PD. In addition, variant in UCHL1 accounts for the majority of familial and sporadic patients with a known genetic association [12, 13]. Leroy et al. [14] originally reported a missense I93M variant in the UCHL1 gene at chromosome locus 4p14 in some of 72 probands with familial PD. While sequencing the same gene in members of a family with chromosome 4p-associated parkinsonism and in additional autosomal dominant parkinsonism families, Lincoln et al. [15] discovered a new polymorphism variant, namely S18Y. The first case–control study reported that S18Y carriers had a significantly decreased risk of PD (OR = 0.53; $p = 0.03$), and the risk reduction was greater for early-onset patients [16]. However, to date, there have been many association researchers investigating the relationship between UCHL1 mutation and PD risk, the role of S18Y polymorphism in the pathogenesis of PD remains contradictory. Therefore, we performed this meta-analysis to further clarify the relationship between UCHL1 polymorphism and PD risk overcoming the limitation of individual studies, resolving inconsistencies and reducing the possibility that random errors are responsible for false-negative or false-positive associations.

Materials and methods

Search strategy

Studies which studied the association between UCHL1 S18Y polymorphism and PD risk were all searched in the databases of PubMed, EMBASE, Web of Science, the Chinese National Knowledge Infrastructure (CNKI) and the Chinese Biomedical Database (CBM) with the following terms: ubiquitin carboxy-terminal hydrolase L1, UCHL1, UCH, S18Y, rs5030732, Parkinson' disease, PD, variant, variants, mutation, polymorphism, and polymorphisms. There was no limit on languages. Besides, we reviewed references cited in identified additional articles and retrieved articles which may have been omitted by the search.

Inclusion criteria

Regarding PD susceptibility and the polymorphism, studies which met the following criteria were identified: (1) Investigations to study the association between the UCHL1 polymorphism and risk of PD. (2) All patients should meet the diagnosis criteria of PD (United Kingdom PD Society Brain Bank (UKPDBB)), or the criteria that cases had at least two of the four cardinal signs of Parkinsonism (rest tremor, rigidity, bradykinesia and postural instability). (3) Original studies must be case–control or cohort studies. (4) The clear numbers or genotype frequencies in case and control groups must be precisely showed in the articles. We excluded the following: (1) Studies in which family members were included, as these analyses are depended on linkage considerations. (2) Studies that contained overlapping data.

Data extraction

Two authors independently extracted following data from each included study according to the selection criteria: first author, year of publication, study design, ethnicity of the subjects, number of cases and controls, mean age of participants, and the frequencies or numbers of cases and controls for each genotype. We compared the results and made decision by consensus of all authors.

Quality assessment

The quality of those included studies was assessed mainly according to the confirmation of Hardy–Weinberg equilibrium (HWE) for the genotypes distribution of UCHL1 S18Y polymorphism in the controls. Studies with departures from HWE in the controls were defined as low-quality studies. On the opposite, studies with the genotype distribution of the polymorphisms in controls in agreement with HWE ($p > 0.05$) were defined as high-quality studies. Besides, the quality of included studies was also estimated by two authors independently with the Newcastle-Ottawa Scale (NOS) [17]. The NOS standard uses a "star" rating system to assess methodological quality, which depended on three aspects of the study, namely selection, comparability, and exposure. Scores ranged from nine stars (best) to zero stars (worst), with equal or higher than seven indicating that the quality was quite good. Disagreements were discussed through a comprehensive reassessment by all authors.

Statistical analysis

Crude ORs with their 95 % CIs were used to estimate the strength of association between the UCHL1 S18Y polymorphisms and PD susceptibility. The pooled ORs were calculated for the allele contrasts, dominant genetic model, recessive genetic model, and additive comparison. Stratified analyses were conducted to assess effect estimates in subgroups defined by ethnicity and onset age.

A random or fixed-effects model was employed based on the heterogeneity assumption [18, 19]. Heterogeneity

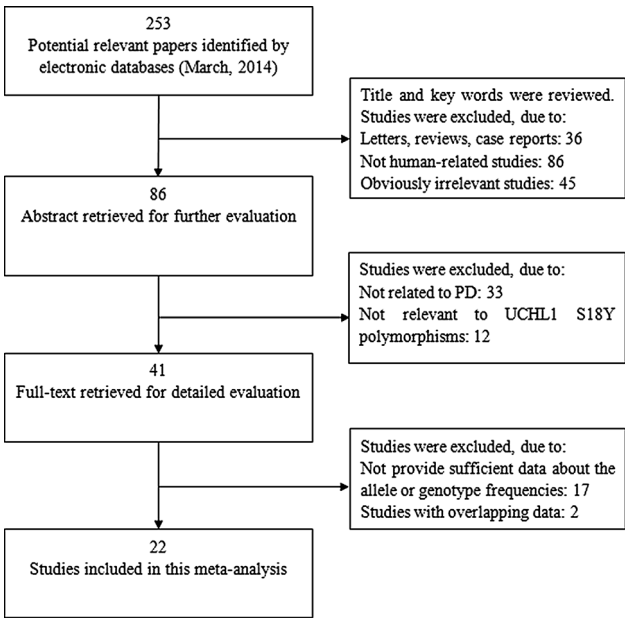

Fig. 1 Flow chart for inclusion procedure

assumption was examined by the Chi-square based Q test [20]. The random effect model was used as the pooling method in the presence of substantial heterogeneity ($p < 0.05$), otherwise, the fixed effect was performed to assess the pooled OR. The potential publication bias was assessed using Begg's test or Egger's linear regression test by visual examination of the funnel plot, and $p < 0.05$ was regarded as representative of statistically significant publication bias. To estimate the stability of the meta-analysis's results case definition influence on the pooled evaluation, one-way sensitivity analyses were performed: each study was excluded singly to determine the role of such exclusion on the overall results. To adjust for multiple comparisons, we used the Benjamini-Hochberg (BH) method and step-down Bonferroni method, which control for familywise error rate (FWE) and false discovery rate (FDR) [21, 22]. All statistical tests were used with STATA version 11.0 (Stata Corporation, College station, TX, USA). All p values tested were two-tailed.

Results

Initially, 253 articles were identified from PubMed, EMBASE, Web of science, CNKI,and CBM according to the search strategy. Of these articles, 167 papers were excluded after a review of their titles and keywords, then abstracts and full-texts were reviewed, and another 62 articles were excluded. Two studies came from the same department and involved the same subjects, so we excluded the overlapping study and chose the new data [23, 24]. Finally, 22 full-text publications on UCHL1 S18Y polymorphism with a total of 7,742 cases and 8,850 controls were finally identified and included into this meta-analysis (Fig. 1). One study included subjects from American and Asian, and divided into two case–control studies, respectively [25]. The qualities of the studies were considered abundantly for this meta-analysis. HWE were calculated for all the 23 samples and three showed deviation from HWE [26–28]. Studies had been carried out in America, UK, China, Japan, Germany, France, Italy, Australia, and Colombia. Eleven studies used samples of Asian ancestry [24–34], six studies used samples of European origin [35–40], and participants in six studies were of American origin [16, 25, 41–44]. Selected details of the individual studies are listed in Table 1. Genotype and allele frequencies between cases and controls are presented in Table 2. Four studies with a unified standard of onset age of PD were included in onset age-matched groups. The details were showed in Table 3.

Results of meta-analysis were showed in Table 4, and the combined results of overall analysis showed that UCHL1 S18Y polymorphism was not statistically associated with PD risk in all four genetic models (OR C vs. A = 1.068, 95 % CI 0.988–1.155, $p = 0.096$, FDR = 0.384 with $p = 0.384$ in stepdown Bonferroni testing, $I^2 = 46.3$ %; OR CC vs. AA = 1.122, 95 % CI 0.943–1.336, $p = 0.195$, FDR = 0.215 with $p = 0.390$ in stepdown Bonferroni testing, $I^2 = 36.2$ %; OR CC vs. CA + AA = 1.066, 95 % CI 0.968–1.175, $p = 0.195$, FDR = 0.390 with $p = 0.585$ in stepdown Bonferroni testing, $I^2 = 36.0$ %; OR CC + CA vs. AA = 1.104, 95 % CI 0.944–1.291, $p = 0.215$, FDR = 0.260 with $p = 0.390$ in stepdown Bonferroni testing, $I^2 = 39.1$ %) (Fig. 2). After omission of three low-quality studies, meta-analysis of high-quality studies showed a significant association of UCHL1 allele A and the risk of PD (OR = 1.063, 95 % CI 1.008–1.122; $p = 0.024$, FDR = 0.070 with $p = 0.096$ in stepdown Bonferroni testing) and under regressive genetic model (OR = 1.078, 95 % CI: 1.005–1.157; $p = 0.035$, FDR = 0.070 with $p = 0.105$ in stepdown Bonferroni testing). Additionally, there were no significant associations in other genetic models. The results were as followed: CC + CA vs. AA, OR = 1.082, 95 % CI 0.967–1.210, $p = 0.168$, FDR = 0.217 with $p = 0.326$ in stepdown Bonferroni testing; CC vs. AA, OR = 1.097, 95 % CI 0.963–1.248, $p = 0.168$, FDR = 0.168 with $p = 0.326$ in stepdown Bonferroni testing (Fig. 3). Furthermore, the subgroup analysis of UCHL1 polymorphism in Asians, Europeans, and Americans failed to show any ethnic-dependent association with PD risk (Fig. 4). To investigate the effect of the onset age of PD, we performed stratified analysis in EOPD and LOPD with age-matched groups. However, no significant associations were observed (Fig. 5).

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Ethnicity	Country	Mean age case/control	Diagnostic standard	Case/control	Genotype method	NOS score
Maraganore [16]	1999	American	America	70/72	Clinical	132/110	PCR	7
Wintermeyer [36]	2000	European	Germany	66.4/NR	UKPDBB	229/200	PCR-RFLP	8
Zhang [25]	2000	mixed	America	NR/NR	UKPDBB	313/302	PCR	8
Mellick [35]	2000	European	Australia	66/66	Clinical	142/142	PCR-RFLP	7
Satoh [26]	2001	Asian	Japan	69.0/66.4	Clinical	74/155	PCR-RFLP	7
Levecque [37]	2001	European	France	NR/NR	UKPDBB	114/93	PCR	8
Savettieri [38]	2001	European	Italy	67/73	Clinical	169/165	PCR	8
Wang [29]	2002	Asian	China	66.8/65.9	UKPDBB	160/160	PCR-RFLP	7
Toda [24]	2003	Asian	Japan	NR/NR	Clinical	230/248	PCR	7
Elbaz [39]	2003	European	France	68/68	Clinical	209/488	PCR	8
Facheris [41]	2005	American	America	66/65	Clinical	70/70	PCR	7
Healy [40]	2006	European	UK	NR/56.1	UKPDBB	1527/1482	TaqMan	9
Tan [31]	2006	Asian	China	65.0/61.0	UKPDBB	375/341	TaqMan	8
Mizuta [30]	2006	Asian	Japan	64.9/45.3	Clinical	613/736	PCR	7
Carmine [43]	2007	American	America	68/57	UKPDBB	296/285	PCR	9
Hutter [42]	2008	American	America	68.0/67.4	UKPDBB	1757/2016	TaqMan	8
Zhang [28]	2008	Asian	China	NR/NR	UKPDBB	334/600	PCR	7
Xiao [27]	2008	Asian	China	71.2/72.6	UKPDBB	75/100	TaqMan	9
Wu [32]	2010	Asian	China	62.7/59.0	UKPDBB	183/277	PCR	8
Benitez [44]	2010	American	Colombia	60.1/62.4	UKPDBB	103/125	PCR	7
Wang [33]	2011	Asian	China	54.3/50.5	UKPDBB	408/398	PCR	7
Miyake [34]	2012	Asian	Japan	68.4/66.6	UKPDBB	229/357	TaqMan	9

Clinical, at least three of the mandatory criteria (akinesia, rigidity, resting tremor, asymmetrical onset or >30 % improvement with levodopa), and the absence of exclusion criteria. And the diagnosis was made when at least two of these features were present with asymmetry in tremor, rigidity or akinesia

NR not report,*UKPDBB* United Kingdom PD Society Brain Bank

As shown in Fig. 6, the shape of the funnel plot did not reveal obvious evidence of asymmetry. Moreover, tests for potential publication bias (p value of the Egger's test was 0.534) showed no evidence of publication bias, also suggesting statistical evidence for funnel plot symmetry.

Discussion

PD is the second most severe adult-onset neurodegenerative disorder around world. A few genes have been identified with variants that result in Mendelian forms of the disease; however, variants have only been found in fewer than 5 % of patients with the disease, suggesting additional genes or factors contribute to PD susceptibility [2]. Several candidate gene association investigations and genome-wide association studies have been performed to identify the related risk factors [10, 11, 45]. However, the small size and modest power of individual study may lead to the lack in consistency of results from different studies. So, meta-analysis was used with the hopes that increasing the sample size and reducing the error will lead to stronger evidence.

UCHL1, also known as neuron-specific protein gene product 9.5 (PGP 9.5), is one of the most widespread proteins in the brain, with regionally high in situ hybridization signals within the substantia nigra pars compacta, and therefore used as a representative and sensitive neural marker [46]. It belongs to the family of de-ubiquitinating proteins (DUBs) and is an important component of the ubiquitin–proteasome system (UPS). UCHL1 plays a crucial role in ubiquitin-dependent proteolysis by transforming polymeric chains of ubiquitin to monomeric ubiquitin. Ubiquitin is actived, conjugated, and polymerized to damaged proteins for proteasomal degradation. Disruption of the ubiquitin proteasomal system has been considered as a causal pathway for Parkinson' disease [47]. Interestingly, as a dimer it alters its functions and becomes an ubiquitin-protein ligase resembling the E3 enzymes of the UPS [48]. The UCHL1 gene augmented special interest after it had been associated with a family with an autosomal dominant missense variant (p.I93M) causing PD [49]. This variant seems to be very rare, however, more frequent UCHL1 polymorphisms have been discovered in the course of a exploration for p.I93 M mutants. The p.S18Y variant

Table 2 Characteristics of case–control studies included in a meta-analysis of the link between the UCHL1 polymorphism and PD

First author	Year	Ethnicity	Case			Control		*P* for HWE
			CC	CA	AA	CC	CA	AA	
Maraganore [16]	1999	American	95	35	2	64	42	4	0.36
Wintermeyer [36]	2000	European	169	51	9	128	65	7	0.72
Zhang1 [25]	2000	American	108	40	5	105	36	1	0.26
Zhang2 [25]	2000	Asian	52	77	31	35	86	39	0.34
Mellick [35]	2000	European	100	33	9	101	38	3	0.79
Satoh [26]	2001	Asian	28	35	11	41	62	52	0.01
Levecque [37]	2001	European	76	33	5	64	24	5	0.19
Savettieri [38]	2001	European	118	46	5	115	45	5	0.82
Wang [29]	2002	Asian	40	82	38	45	80	35	0.96
Toda [24]	2003	Asian	71	119	40	69	114	65	0.21
Elbaz [39]	2003	European	139	67	3	323	145	20	0.47
Facheris [41]	2005	American	44	26	0	41	23	6	0.30
Healy [40]	2006	European	1,074	409	44	1,028	418	36	0.40
Tan [31]	2006	Asian	93	194	88	71	172	98	0.78
Mizuta [30]	2006	Asian	149	340	124	199	366	171	0.91
Carmine [43]	2007	American	218	74	4	191	89	5	0.14
Hutter [42]	2008	American	1,191	509	57	1,324	621	71	0.86
Zhang [28]	2008	Asian	76	197	61	152	336	112	<0.01
Xiao [27]	2008	Asian	55	19	1	88	10	2	0.02
Wu [32]	2010	Asian	38	87	58	66	130	81	0.33
Benitez [44]	2010	American	45	49	9	66	48	11	0.59
Wang [33]	2011	Asian	102	198	108	86	200	112	0.85
Miyake [34]	2012	Asian	61	98	70	96	183	78	0.60

Table 3 Characteristics of studies included in the meta-analysis of the association of the UCHL1 polymorphism with EOPD (<50 years) and LOPD (>50 years)

First author	Year	Ethnicity	Onset age	Case			Control		
				CC	CA	AA	CC	CA	AA
Healy [40]	2006	European	<50	180	63	8	1,028	418	36
Healy [40]	2006	European	>50	894	346	36	1,028	418	36
Zhang [28]	2008	Asian	<50	34	86	30	23	66	19
Zhang [28]	2008	Asian	>50	118	250	82	53	131	42
Hutter [42]	2008	American	<50	310	121	12	247	102	11
Hutter [42]	2008	American	>50	879	387	45	1,077	519	60
Wang [33]	2011	Asian	<50	34	51	41	44	89	46
Wang [33]	2011	Asian	>50	68	147	67	43	108	68

(C.53C>A, rs5030732) showed significantly diminished dimerization and ligase activity [50].

On the basis of 20 case–control studies providing data on UCHL1 polymorphism and PD involving 7,259 cases and 7,995 controls, we found a moderate association between UCHL1 polymorphism and PD risk in all populations but not in subgroup ethnicity, and the association was found only under regressive genetic model and allele contrasts. Further investigations with greater statistical power and a large sample size are necessary to confirm our findings. In addition, some studies have also examined potential impact modification by age [31, 32, 40, 43]. The major difficulty when comparing results between studies is the diversity in the age limitation used to define EOPD and LOPD, such as 50, 59, or 67 years. We found only four studies with a unified standard of onset age of PD. Further

Table 4 Summary ORs and 95 % CI for contrasts in *UCHL1* polymorphism

SNPs	Contrast	Odds ratio		Bon	FDR	Model	Heterogeneity	
		OR(95 % CI)	P_{OR}				I^2 (%)	P_H
Total	C vs. A	1.068 (0.988–1.155)	0.096	0.384	0.384	R	46.3	0.008
	CC vs. CA + AA	1.066 (0.968–1.175)	0.195	0.585	0.390	R	36.0	0.045
	CC + CA vs. AA	1.104 (0.944–1.291)	0.215	0.390	0.260	R	39.1	0.029
	CC vs. AA	1.122 (0.943–1.336)	0.195	0.390	0.215	R	36.2	0.044
High quality	C vs. A	1.063 (1.008–1.122)	0.024	0.096	0.070	F	30.5	0.097
	CC vs. CA + AA	1.078 (1.005–1.157)	0.035	0.105	0.070	F	19.4	0.213
	CC + CA vs. AA	1.082 (0.967–1.210)	0.168	0.326	0.217	F	34.2	0.068
	CC vs. AA	1.097 (0.963–1.248)	0.163	0.326	0.168	F	29.4	0.107
Asian	C vs. A	1.052 (0.973–1.138)	0.203	0.708	0.406	F	46.5	0.070
	CC vs. CA + AA	1.047 (0.921–1.190)	0.484	0.609	0.406	F	28.3	0.203
	CC + CA vs. AA	1.086 (0.890–1.326)	0.415	0.830	0.553	R	54.4	0.032
	CC vs. AA	1.115 (0.953–1.306)	0.177	0.830	0.484	F	47.0	0.067
European	C vs. A	1.043 (0.938–1.160)	0.437	1.192	0.874	F	0	0.577
	CC vs. CA + AA	1.067 (0.944–1.206)	0.298	1.311	0.874	F	0	0.525
	CC + CA vs. AA	0.934 (0.670–1.301)	0.685	1.370	0.913	F	20.8	0.277
	CC vs. AA	0.955 (0.684–1.334)	0.788	1.370	0.788	F	15.0	0.318
American	C vs. A	1.100 (0.996–1.214)	0.060	0.240	0.128	F	49.0	0.081
	CC vs. CA + AA	1.115 (0.994–1.251)	0.064	0.192	0.128	F	44.9	0.106
	CC + CA vs. AA	1.143 (0.844–1.547)	0.388	0.708	0.472	F	19.6	0.286
	CC vs. AA	1.156 (0.851–1.570)	0.354	0.708	0.388	F	28.4	0.222
EOPD	C vs. A	1.071 (0.985–1.164)	0.110	0.440	0.246	F	0	0.503
	CC vs. CA + AA	1.085 (0.978–1.204)	0.123	0.369	0.246	F	0	0.764
	CC + CA vs. AA	1.096 (0.891–1.348)	0.384	0.606	0.404	F	1.9	0.383
	CC vs. AA	1.129 (0.897–1.420)	0.303	0.606	0.384	F	1.5	0.384
LOPD	C vs. A	1.016 (0.878–1.175)	0.831	0.844	0.654	F	0	0.881
	CC vs. CA + AA	1.097 (0.911–1.322)	0.327	0.981	0.654	F	0	0.995
	CC + CA vs. AA	0.813 (0.588–1.124)	0.211	1.272	0.848	F	0	0.823
	CC vs. AA	0.914 (0.631–1.324)	0.636	1.272	0.831	F	0	0.927

OR odds ratio, 95 % *CI* confidence interval, *R* random-effects model, *F* fixed-effects model, *Bon p* value in stepdown Bonferroni testing

studies differ as to whether patients were stratified by age at diagnosis, age at onset, or age at study entry and whether controls were also divided by age. These inconsistencies limit our power to perform a strict meta-analysis stratified by age.

Parkinson's disease is a complex disease and multiple genes, environmental factors, and different genetic backgrounds contribute to the development of the disease. A number of studies have investigated gene—gene and/or gene-environment interplay involving Parkinson's disease and UCHL1 polymorphism, but the authors did not observe any evidence. Besides, the studies examined UCHL1 S18Y polymorphism in conjunction with other candidate gene polymorphisms, such as APOE or the environmental risk factors (smoking, pesticide use, and caffeinated coffee consumption) also showed no association [51, 52].

When interpreting the results, several limitations which may have affected the objectivity of the conclusions should be taken into account. Firstly, the clinical diagnostic accuracy of PD does not reach 80 %, caused by varying levels of expertise of researchers. Some PD patients recruited for the studies may be misclassified as cases of Parkinson-plus syndromes or Essential Tremor. This proportion of cases may alter the results of studies [53]. Secondly, different categories in different studies, such as ethnicity and onset age, may lead to the different conclusion. The participants in America were classified as the Americans, except the author clarified them as Europeans explicitly. As onset of PD is reported to associate with age, however, some studies included in this meta-analysis did not consider 'age-matching' for case–control, and the other studies classified by age had different definition on early onset or late onset of PD. Thirdly, a language bias may

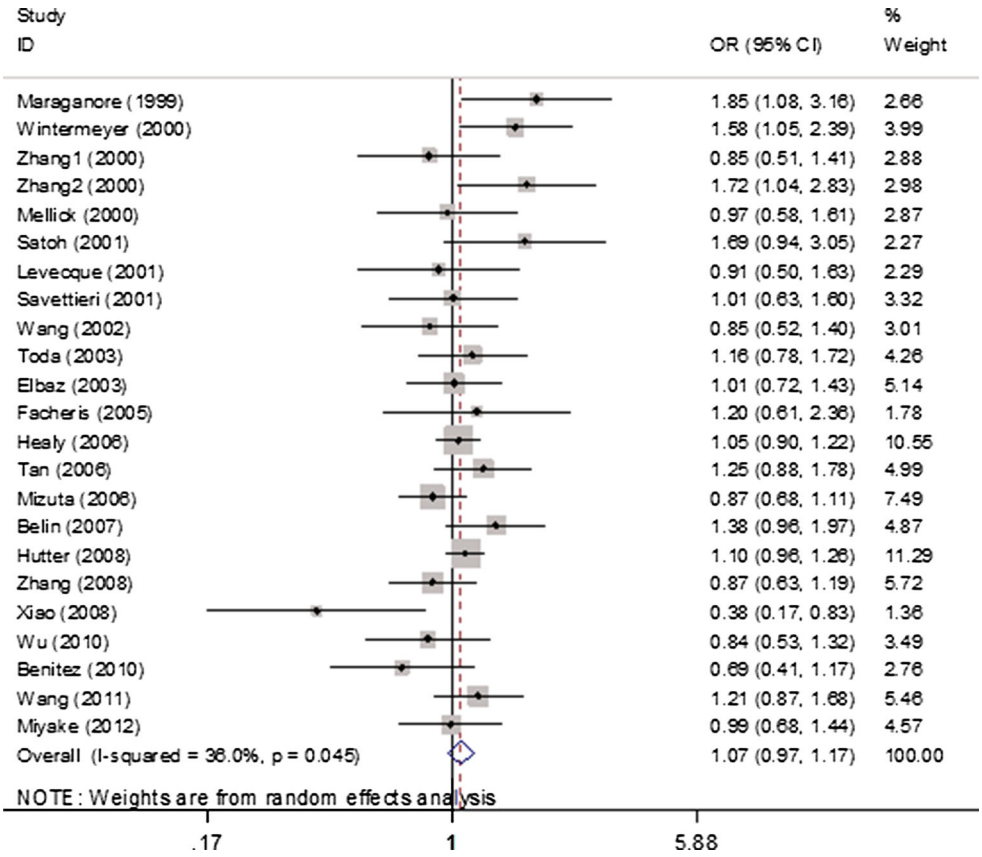

Fig. 2 The association of UCHL1 polymorphism and PD. Meta-analysis for the association between UCHL1 polymorphism and PD under regressive genetic model (CC vs. CA + AA) in the total populations using a random-effects model. The *squares* and *horizontal lines* correspond to the study-specific OR and 95 % CI. The area of the squares reflects the weight (inverse of the variance). The *diamond* represents the summary OR and 95 % CI

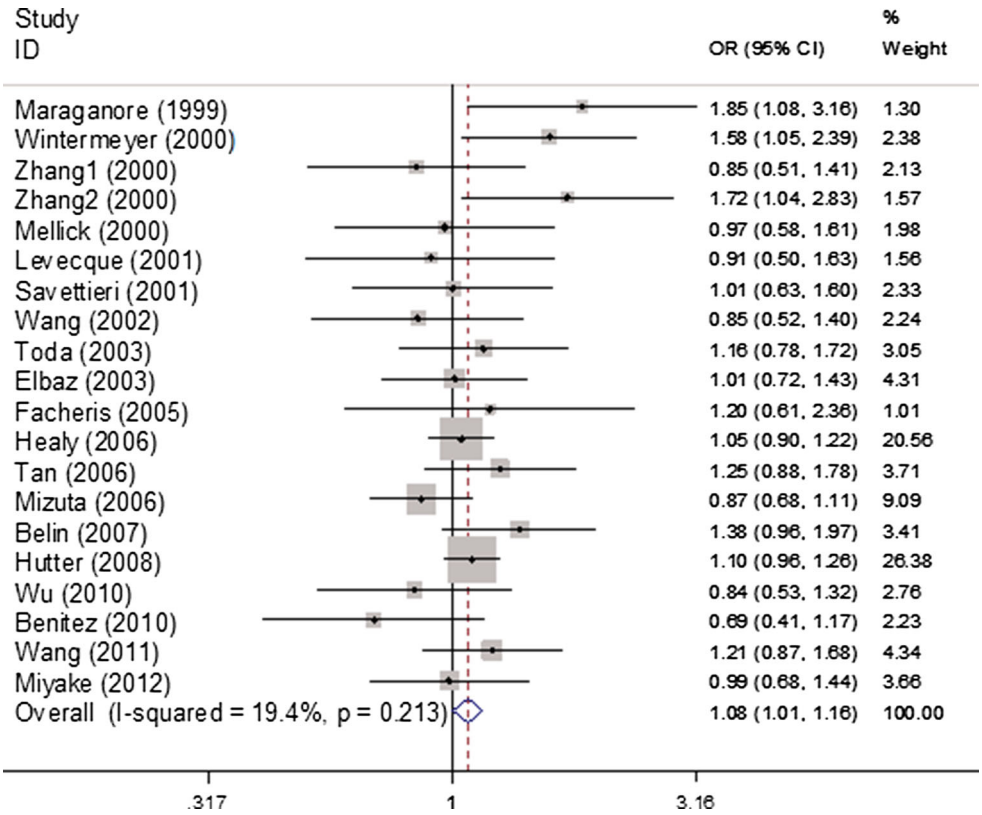

Fig. 3 The association of UCHL1 polymorphism and PD. Meta-analysis for the association between UCHL1 polymorphism and PD under regressive genetic model (CC vs. CA + AA) in the high-quality studies using a fixed-effects model. The *squares* and *horizontal lines* correspond to the study specific OR and 95 % CI. The area of the *squares* reflects the weight (inverse of the variance). The *diamond* represents the summary OR and 95 % CI

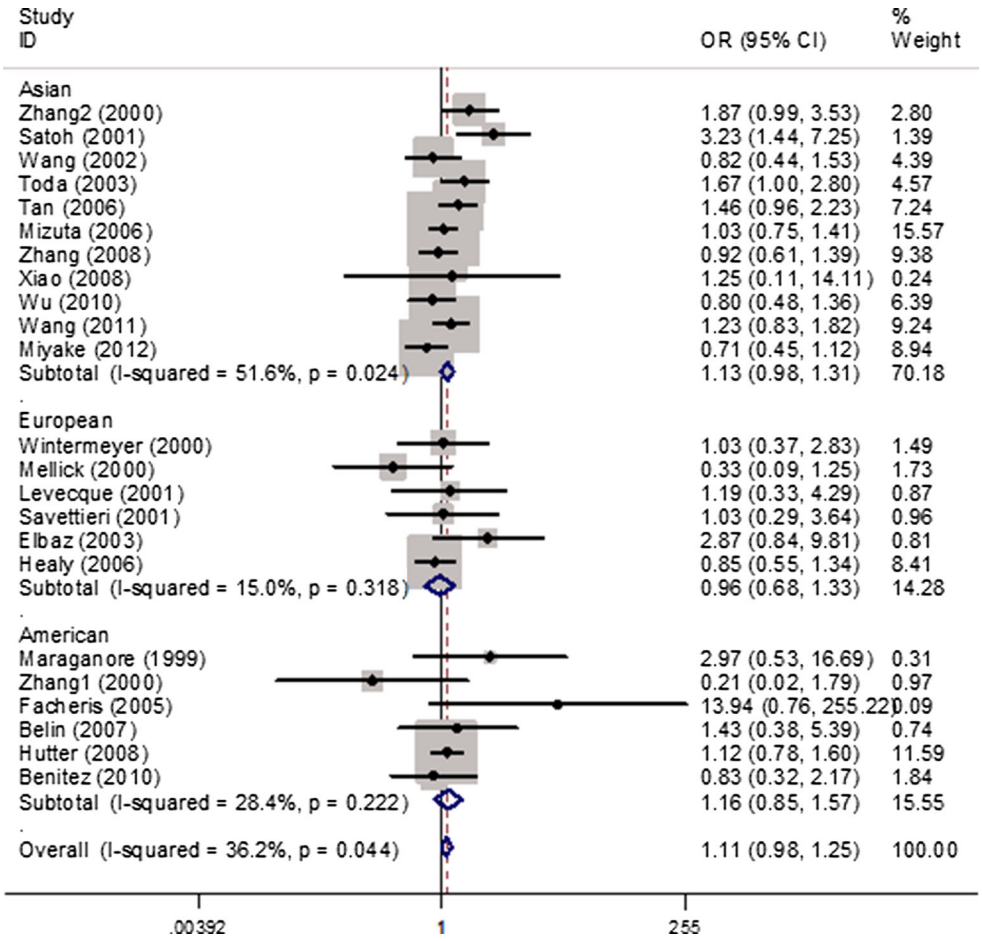

Fig. 4 The association of UCHL1 polymorphism and PD. Subgroup analysis of ethnicity for the association between UCHL1 polymorphism and PD under additive comparison (CC vs. AA) in the different populations using a fixed-effects model. The *squares* and *horizontal lines* correspond to the study specific OR and 95 % CI. The area of the squares reflects the weight (inverse of the variance). The *diamond* represents the summary OR and 95 % CI

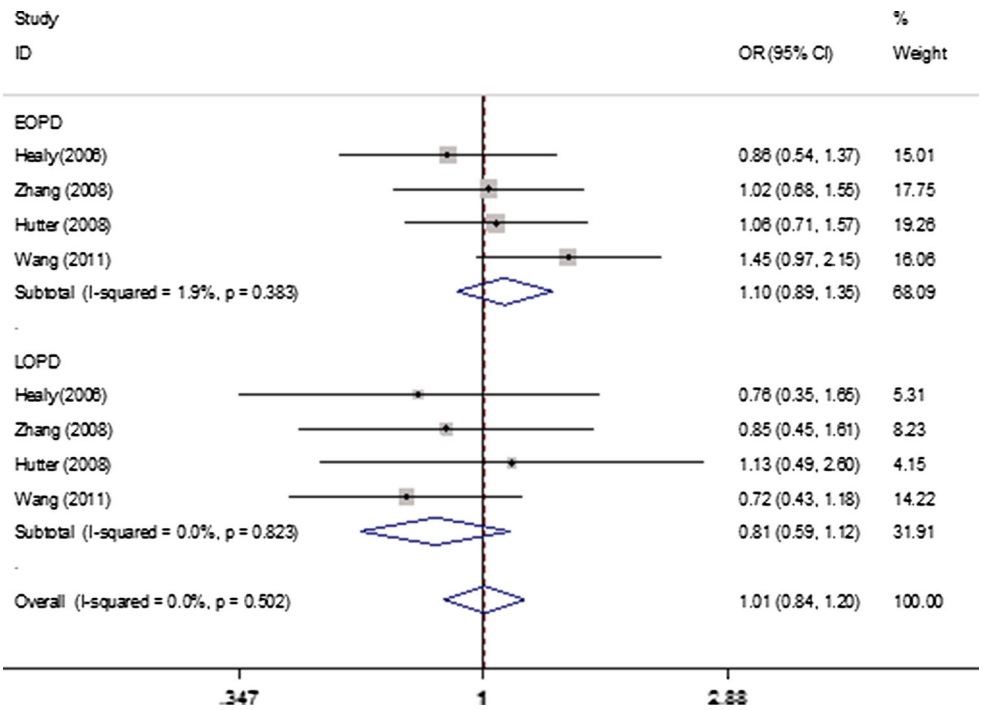

Fig. 5 The association of UCHL1 polymorphism and PD. Meta-analysis for the association between UCHL1 polymorphism and PD in EOPD and LOPD under dominant genetic model (CC + CA vs. AA) using a fixed-effects model. The *squares* and *horizontal lines* correspond to the study specific OR and 95 % CI. The area of the squares reflects the weight (inverse of the variance). The *diamond* represents the summary OR and 95 % CI

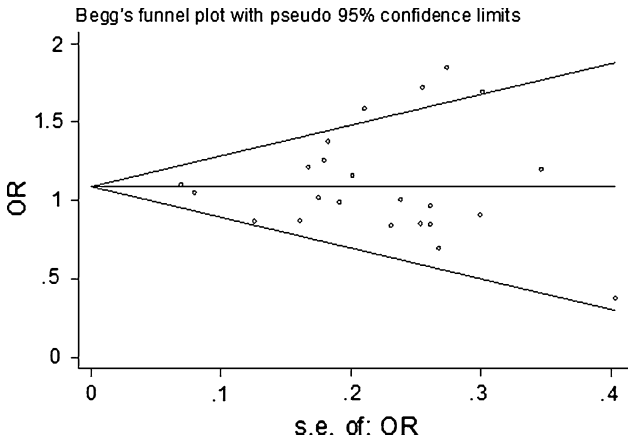

Fig. 6 Begg's funnel plot analysis was used to detect publication bias for the additive comparison (CC vs. CA + AA) of the UCHL1 polymorphism. No asymmetry was found as indicated by the *p* value of the Egger's test

have existed because this meta-analysis only contained English languages articles. Nevertheless, some studies in coincidence with the inclusion criteria in other languages published in specific journals could not be identified and included in this meta-analysis. Besides, all included articles were published studies, and unpublished studies that had null results were missed, which also might bias the results. Fourthly, given that only published articles were entered in this meta-analysis, a publication bias may have occurred, although it was not found when performing the statistical analysis.

Conclusion

Given the moderate level of evidence for UCHL1 as a PD susceptibility gene, and the insufficiency of effective prevention measures for PD, there is no valid public health application for this association. This adverse situation might change in the future if neuroprotective therapies are exploited that, if used early, could delay disease onset and reduce risk. It is also possible that interactions between genetic mutations and environmental agents will be identified such that polymorphism for UCHL1 or other susceptibility factors might prove useful in tailoring a patient's medication regimen.

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Conflict of interest The authors declare no conflict of interest.

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