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Original Article

Association of MDR1 C3435T genetic polymorphism with Parkinson's disease: a meta-analysis

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Abstract: Parkinson's disease (PD) is the most common neurodegenerative disease. Several studies have identified the role of multidrug resistance 1 (MDR1) C3435T genetic polymorphism in PD susceptibility. However, the results still remain inconclusive. The objective of this study was to determine the effect of MDR1 C3435T variant on PD. Eligible case-control articles published between January 2000 and 2016 was searched in the electronic databases. The odds ratio (OR) with its 95% confidence interval (CI) was employed to calculate the strength of effect. A total of ten articles were retrieved, including 5408 participants (2349 PD patients and 3059 controls). No significant between-study heterogeneity was observed, and the fixed-effect model was used. Overall, our meta-analysis revealed that MDR1 C3435T was not associated with increased the risk of PD under each genetic models ($P<0.05$). Subgroup analysis by ethnicity showed no relevant association in either Asians or Caucasians as well. However, we detected that the mutation rate of TT+CT genotypes of MDR1 C3435T variant with pesticide exposure in PD patients was higher than those of non-exposure, and the statistical analysis detected a significant correlation with increased the risk of PD (TT+CT vs. CC: OR=2.85, 95% CI=1.66-4.90, P=0.0002). No publication bias was found in this meta-analysis. Our results suggested that MDR1 C3435T polymorphism might affect the risk of PD developing only in conjunction with exposure to pesticides. Future well-designed studies with more ethnicities are still needed to further evaluate the effect.

Keywords: Parkinson's disease, multidrug resistance 1, polymorphism, meta-analysis

Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder that is pathologically defined as degeneration of the dopaminergic neurons in the substantia nigra and development of Lewy bodies in the residual dopaminergic neurons [1]. It is the second common neurodegenerative disease after Alzheimer's disease (AD) [2]. The main clinical symptom of PD is movement disorders along with non-motor symptoms such as dementia, depression and autonomic dysfunction [3, 4]. The established risk factors for PD progression are age [5], sex [6], environmental factors [7, 8] as well as genetic variation [9]. According to the worldwide data, the prevalence of PD increases steadily with age, ranging from 41 to 1903 per 100000 [10], and the mortality ratios ranges from 0.9 to 3.8 per 100000 [11]. Demographic and clinical factors might impact PD survival, and the survival was reduced as compared to the general population [12]. Although several advances have made in the pharmacological treatment of PD [13], due to the mystery of its etiology, there is no cure at present, and the currently available drugs provide only symptomatic relief and cannot control or prevent disease progression [14]. Therefore, it is essential to detect some biomarkers to identify possible aetiological factors, plan health services and guide therapeutic strategies.

Epidemiologic studies have established a genetic contribution to PD risk, and approximately 10% of the cases carry the mutations that lead to rare Mendelian forms of this disease [15]. In addition, genetic variants were shown to drive the etiologic understanding and etiology-based therapeutic approaches in PD [16, 17]. Multidrug resistance 1 (MDR1), also known as ATP-binding cassette B1 (ABCB1), was one of the most studied genes. It is located on chromosome 7q21.1, and is one of the major

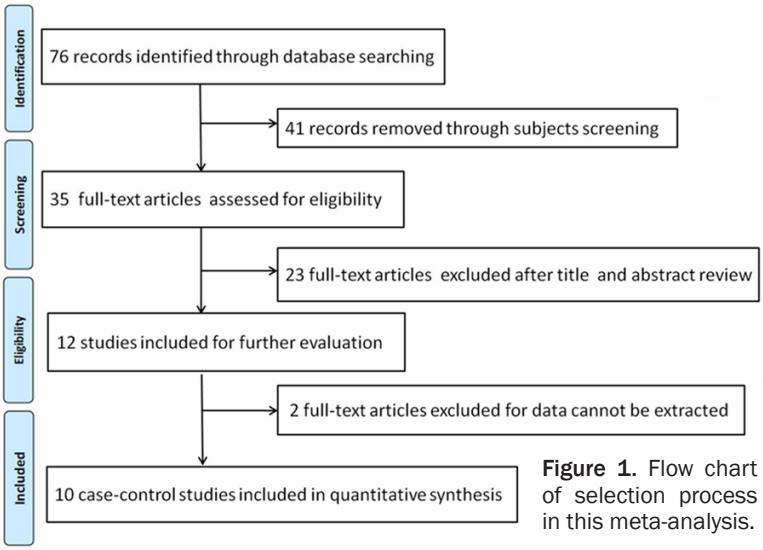

Figure 1. Flow chart of selection process in this meta-analysis.

drug transporters found in humans [18]. It has the ability to mediate drug resistance in cancer chemotherapy [19]. The encoding product of MDR1 is P-glycoprotein (P-gp), which is a major player in drug handling by mammals and plays an important role in bioavailability and cell-toxicity limitation of a wide range of drugs and xenobiotics [20, 21]. The MDR1 gene is highly polymorphic with at least 50 single-nucleotide polymorphisms (SNPs) which may not only influence P-gp level and function, but also contribute to inter-individual and ethnic differences in drug disposition, thus influencing the outcome and prognosis of certain diseases [22]. MDR1 C3435T (rs1045642), located in exon 26, is a synonymous SNP in the second ATP binding domain with no effect in amino acid change at position 1145 (Ile) [23]. The T allele of C3435T variant was shown to be associated with decreased P-gp expression by altering substrate specificity [24, 25]. This variant appeared to be a main factor in allelic variation of ABCB1 mRNA expression in the liver, by changing mRNA stability [26]. Studies have shown that C3435T polymorphism was associated with malignant tumor development [27] and neurodegenerative diseases risk [28].

Although several studies have identified the effect of MDR1 C3435T polymorphism in PD risk, the results remain inconclusive. For example, Lee et al. found that MDR1 C3435T polymorphism was associated with PD risk primarily among male ethnic Chinese >60 years of age [29]. While Kiyohara et al. showed that the C3435T variant might not play an important role in PD susceptibility [30]. Moreover, PD is a population-specific genetic heterogeneous disease [31, 32], and the frequency of MDR1 polymorphisms varies among different populations [33, 34]. Therefore, we conducted this meta-analysis to systematically review all the published articles and to reassess whether MDR1 variant was associated with PD risk.

Materials and methods

Search strategy

A comprehensive literature search for eligible studies published between January 2000 and 2016 was conducted in the following online database of Web of Science, PubMed, Embase, Medline and Cochrane Library. The MeSH terms: "Parkinson's disease", "multidrug resistance 1 or MDR1", "ABCB1 or P-glycoprotein", "polymorphism or mutation or variant" as well as their combinations were employed as the searching words. References of retrieved articles were manually searched to obtain more potential studies. Articles were only restricted in English language.

Inclusion and exclusion criteria

The retrieved articles must meet the following criteria: 1) case-control studies that focused on the association between MDR1 polymorphisms and PD risk; 2) patients underwent a detailed neurological examination, and should be in accord with the United Kingdom Parkinson's Disease BrainBank Criteria [35]; 3) the controls should be age-, gender- and race-matched participants without a previous diagnosis of a neurodegenerative or malignant disease; 4) the results were expressed as odds ratio (OR) with its 95% confidence interval (CI), and the frequencies of alleles and genotypes in each article were available to extract; 5) when the same authors or laboratories reported the same issue on the same populations, only the recent full-text article was included; and 6) genotype distribution of control for a certain polymor-

Table 1. Main characteristics of included studies in this meta-analysis

First author	Year	Country	Ethnicity	Mean age		Source of Control	Sample size		Sample	Genotyping method
				PD	Control		PD	Control		
Furuno T	2002	Italy	Caucasian	50.0±7.3	52.4±14.7	HB	95	106	Blood	DHPLC
Drozdzik M	2003	Poland	Caucasian	57.2±11.4	74.1±5.9	PB	107	103	Blood	PCR-RFLP
Tan EK-1	2004	Poland	Caucasian	63.3±9.1	73.1±5.9	PB	158	139	Blood	TaqMan
Tan EK	2005	China (Hong Kong)	Asian	68.9±10.9	70.3±10.5	PB	185	206	Blood	TaqMan
Funke C	2009	Germany	Caucasian	66.4±10.3	60.6±5.2	PB	300	302	Blood	SNaPshot
Westerlund M	2009	Sweden	Caucasian	67.8	57.9	PB	288	313	Blood	TaqMan
Zschiedrich K	2009	Germany	Caucasian	56.2±12.3	50.9±13.1	PB	415	184	Blood	TaqMan
Dutheil F	2010	France	Caucasian	69±9	69±9	PB	207	482	Blood	TaqMan
Kiyohara C	2013	Japan	Asian	68.5	66.6	HB	238	368	Bouche	TaqMan
Narayan S	2015	USA	Mixed	68.3±10.2	66.2±11.6	PB	356	856	Blood or saliva	AS-PCR

PD, Parkinson's disease; Mixed, White, Black, Latino, Asian, Native American; HB, hospital-based; PB, population-based healthy participants; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; AS-PCR, allele-specific PCR; DHPLC, denaturinghigh performance liquid chromatography assays.

Table 2. The alleles and genotypes distribution of MDR1 C3435T polymorphism in each included studies in this meta-analysis

First author	Parkinson's disease cases					Controls					
	CC	CT	TT	C	T	CC	CT	TT	C	T	HWE
Furuno T	20	50	25	90	100	28	58	20	114	98	0.584
Drozdzik M	26	66	15	118	96	24	58	21	106	100	0.434
Tan EK-1	35	78	45	148	168	30	73	36	133	145	0.826
Tan EK	81	77	27	239	131	87	95	24	269	143	0.969
Funke C	67	147	86	281	319	76	147	79	299	305	0.900
Westerlund M	53	141	83	247	307	56	140	96	252	332	0.927
Zschiedrich K	108	203	104	419	411	36	101	47	173	195	0.386
Dutheil F	45	112	50	202	212	120	231	131	471	493	0.667
Kiyohara C	75	114	49	264	212	138	166	64	442	294	0.518
Narayan S	82	162	111	326	384	217	438	188	872	814	0.503

HWE, Hardy-Weinberg equilibrium in controls.

phism must be in Hardy-Weinberg equilibrium (HWE).

The exclusion criteria were: 1) without control group; 2) data not available; 3) with duplicate data; and 4) review reports or conference papers.

Data extraction

Two experts independently estimated the quality of the included studies. Any disagreement was subsequently resolved by discussion with a third author to obtain a final consensus. The following information was extracted from each included article: the name of first author, published year, country, ethnicity, sample size, source of controls, genotyping method, frequencies of genotypes and alleles, and evidence of HWE in controls.

Statistical analysis

Statistical analyses were conducted in Review Manager (version 5.3, The Cochrane Collaboration). The strength of the correlation between MDR1 C3435T polymorphism and PD susceptibility was measured by ORs with 95% CI. The significance of the pooled ORs was determined by the Z test, with a *P* value less than 0.05 considered statistical significance. The allelic model (T vs. C), homologous model (TT vs. CC), heterogeneous model (CT vs. CC), dominant model (TT+CT vs. CC), and recessive effect (TT vs. CT+CC) were examined to evaluate the C3435T variant and the risk of PD. The I^2 test and the Q-statistic test were used to define the between-study heterogeneity. The fixed-effect model was used when the I^2 was less than 50% and the *p*-value for the Q-test was more than 0.10; otherwise, the random-

Table 3. Meta-analysis of MDR1 C3435T polymorphism on PD risk in total and subgroup analysis

Group	Comparisons	N	Test of association		Test of heterogeneity		
			OR (95% CI)	P	Ph	I^2	Model
Total	T vs. C	10	1.07 (0.99, 1.16)	0.08	0.29	17%	F
	TT vs. CC		1.16 (0.99, 1.36)	0.07	0.31	15%	F
	CT vs. CC		1.03 (0.90, 1.18)	0.67	0.61	0%	F
	TT+CT vs. CC		1.07 (0.94, 1.22)	0.29	0.60	0%	F
	TT vs. CT+CC		1.13 (0.99, 1.28)	0.07	0.12	36%	F
Asians	T vs. C	2	1.14 (0.95, 1.36)	0.17	0.41	0%	F
	TT vs. CC		1.33 (0.92, 1.94)	0.13	0.70	0%	F
	CT vs. CC		1.08 (0.82, 1.42)	0.60	0.20	40%	F
	TT+CT vs. CC		1.13 (0.87, 1.47)	0.34	0.22	33%	F
	TT vs. CT+CC		1.25 (0.89, 1.76)	0.19	0.89	0%	F
Caucasians	T vs. C	8	1.03 (0.94, 1.13)	0.49	0.46	0%	F
	TT vs. CC		1.06 (0.88, 1.28)	0.52	0.48	0%	F
	CT vs. CC		0.98 (0.84, 1.16)	0.84	0.48	0%	F
	TT+CT vs. CC		1.01 (0.87, 1.18)	0.90	0.64	0%	F
	TT vs. CT+CC		1.08 (0.93, 1.24)	0.32	0.14	37%	F

N, number of included studies; OR, odds ratio; 95% CI, 95% confidence interval; F, fixed-effect model.

effect model was used when the effect was heterogeneous. The evidence of publication bias was assessed by visual funnel plot inspection.

Results

Baseline characteristics of included studies

We firstly identified 76 articles, after applying the inclusion and exclusion criteria, ten relevant articles were finally screened out. **Figure 1** showed the flow diagram of selection process. Overall, a total of 5408 subjects were involved in this meta-analysis, including 2349 PD patients and 3059 controls. The ten studies were conducted in eight countries: Italy [36], Poland [37, 38], China (Hong Kong) [39], Germany [40, 41], Sweden [42], France [43], Japan [30] and USA [44]. All these articles were written in English, and MDR1 C3435T genetic polymorphism was measured by denaturing high performance liquid chromatography assays (DHPLC), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan, SNaPshot or allele-specific PCR (AS-PCR). The distribution information of genotypes in controls were all in accord with HWE (P>0.05). **Table 1** presented the main characteristics of included studies in this meta-analysis. **Table 2** listed the distribution of alleles and genotypes of MDR1 C3435T polymorphism in each study.

Correlation of MDR1 C3435T variant and PD susceptibility

The between-study heterogeneity was not observed in our study, and the fixed-effect model was employed to calculate the effect. **Table 3** provided the meta-analysis findings of the associations between MDR1 C3435T mutation and PD risk. Our result found that PD patients had a little higher T allele mutation rate than those of controls (50.1% versus 48.2%), however, no significant difference in the rate of allele mutation between PD cases and controls was detected (OR=1.07, 95% CI=0.99-1.16, P=0.08) as shown in **Figure 2**. This insignificant relationship was observed in other genetic models as well (P>0.05). Subgroup analysis by ethnicity showed that there was no positive association between MDR1 C3435T variant and PD susceptibility in either Asians or Caucasians as shown in **Figure 3**.

Interaction of MDR1 C3435T polymorphism and exposure to pesticides in PD risk

Five articles concerned the correlation of MDR1 C3435T variant and exposure to pesticides on PD risk. However, the data could be extracted only from four of them, including 508 PD patients (140 for pesticide exposed and 368 for non-exposed). Overall, our result found that interaction of T carrier (TT+CT) of C3435T polymorphism and pesticide use was significantly associated with increased risk of PD when compared with CC genotype (TT+CT vs. CC: OR=2.85, 95% CI=1.66-4.90, P=0.0002) in the fixed-effect model as shown in **Figure 4**.

Sensitivity analysis and publication bias

We conducted a sensitivity analysis to estimate whether our results were substantially affected by the presence of any individual study. We sys-

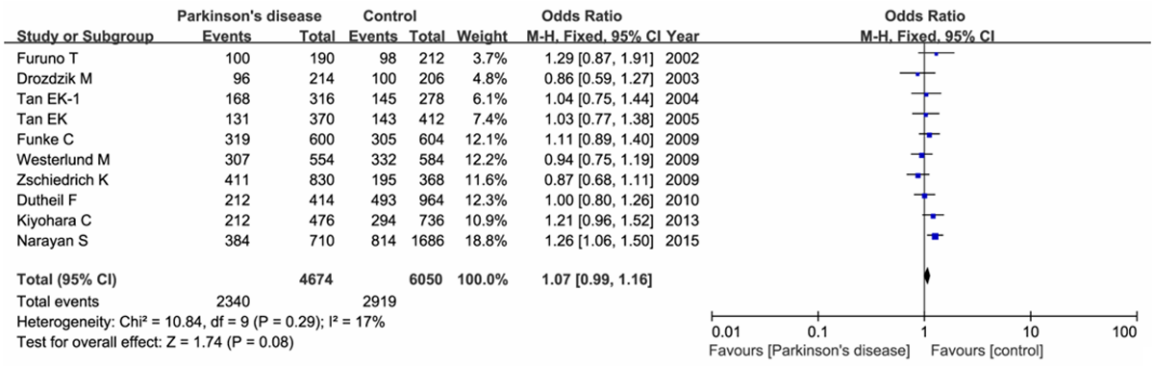

Figure 2. Meta-analysis of the relationship between the C3435T polymorphism of MDR1 gene and Parkinson's disease risk under the allelic model (T vs. C).

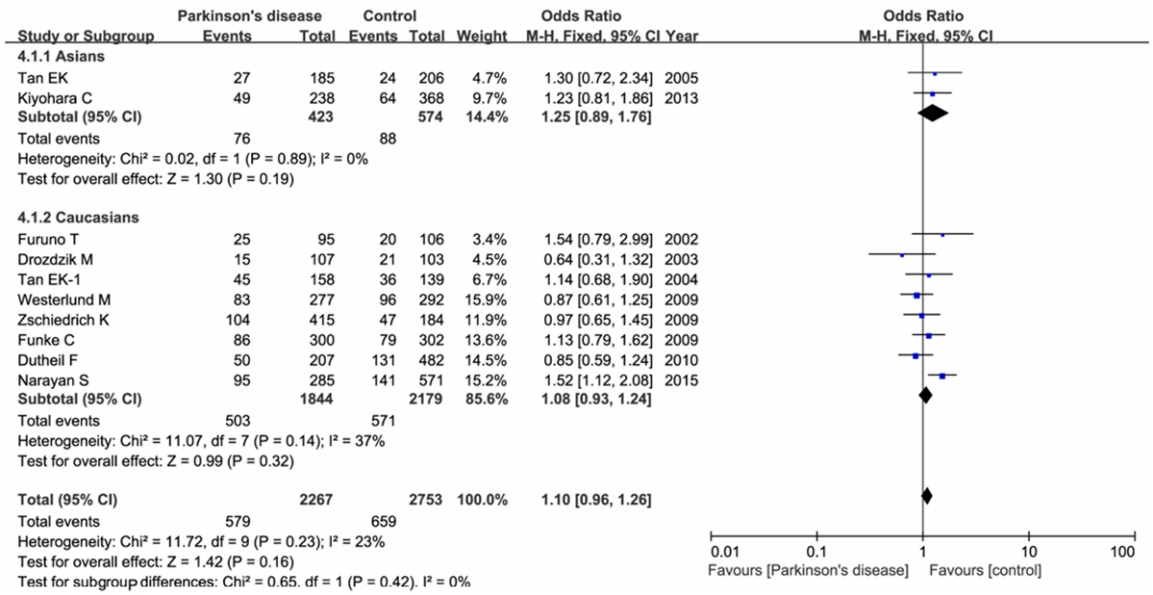

Figure 3. Forest plot of the relative strength of the association between MDR1 C3435T polymorphism and Parkinson's disease risk in subgroup analysis by ethnicity under the recessive model (TT vs. CT+CC).

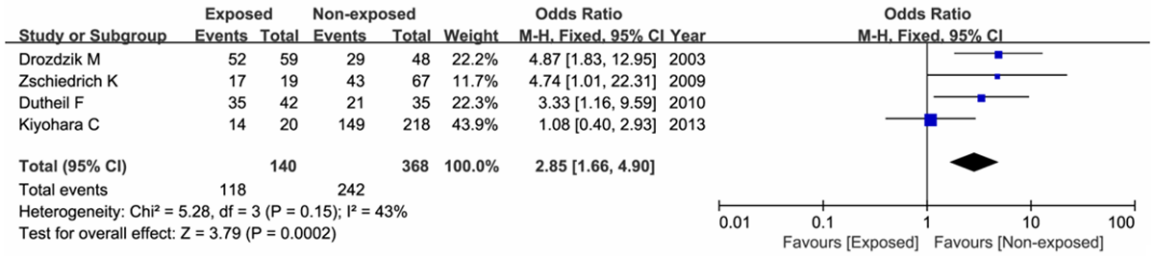

Figure 4. Meta-analysis of the combined effect of MDR1 C3435T variant and exposure to pesticides in Parkinson's disease risk under the dominant model (TT+CT vs. CC).

tematically removed each study and recalculated the significance of the pooled ORs, and our result showed that the ORs were not significantly changed. The funnel plots were used to assess the potential publication bias of included studies under each comparison model. The

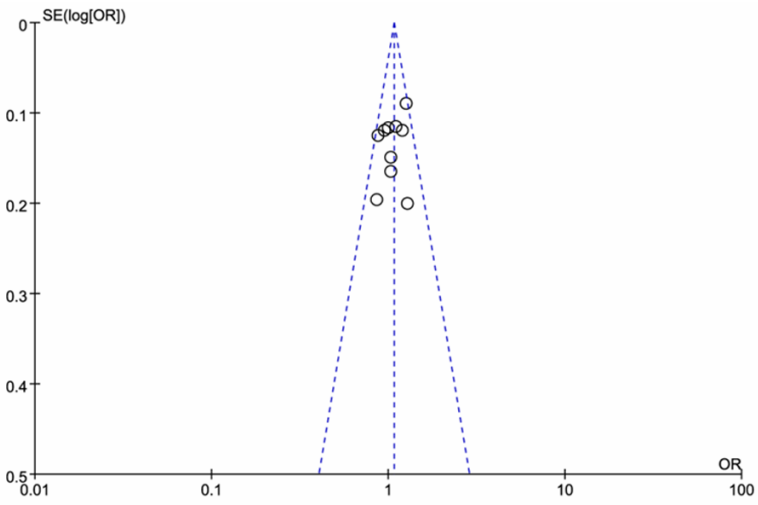

Figure 5. Funnel plot of MDR1 C3435T polymorphism in Parkinson's disease under the allelic model.

shape of the funnel plot did not reveal any obvious asymmetry as shown in **Figure 5**, indicating that there was no publication bias.

Discussion

In this meta-analysis, we totally screened out ten relevant articles. There was no significant association between MDR1 C3435T polymorphism and risk of PD. Subgroup analysis by ethnicity revealed no ethnic difference (Caucasians or Asians) as well. Our result suggested that MDR1 might not be a possible susceptibility gene in the pathogenesis of PD. However, interaction of C3435T variant and exposure to pesticides was shown to increase the risk of PD. Neither publication bias nor heterogeneity was found among the included studies.

PD is a neurological disorder with complex pathogenesis involving environmental and genetic factors. Studies have shown that genetics may improve diagnosis and can be used in identification of persons at risk. Drug transporters, which are important in drug resistance, disposition and response [45, 46], are increasingly recognized as possible therapeutic targets in the treatment of neurodegenerative disorders with brain pathology reduction or drug therapy improvement [47]. ABC transporters are the most studied and mediate the transport of a wide range of substrates important in normal physiology such as drugs, toxicants and endogenous compounds [48]. They may contribute to the blood-brain barrier, the maternal-fetal barrier, and the mucosal barrier [49]. Mutations in genes of ABC transporters have been associated with changes in drug disposition, sensitivity and toxicity [50]. ABCB1 encodes a full ABC transporter with drug-binding pockets and two nucleotide-binding ATPase domains [51]. P-gp, the encoded product of the human MDR1 (ABCB1) gene, is of particular clinical relevance in drug transporters with broad substrate specificity [52], associating with a number of neurodegenerative and malignant diseases [53, 54]. It can transport neurotoxic pesticides and function as a drug target [55, 56]. Decreased blood-brain barrier P-gp was found with aging, and effects of age on its function differed between men and women [57]. Genetic polymorphisms in MDR1 gene might alter drug levels and host susceptibility to diseases by significantly minimizing P-gp functionality, drug disposition and treatment outcome [58, 59]. Chen et al. showed that pesticide exposed individuals with susceptible MDR1 T129C (rs3213619) genotypes might experience increased risk of DNA damage [60]. MDR1 SNPs were linked to the susceptibility of carcinogenesis [61], refractory epilepsy [62, 63], leukemia [64] and so on. Thus, identifying MDR1 polymorphisms and haplotypes can help understand drug pharmacodynamics and pharmacokinetics, and predict drug responses, toxicity and side effects.

Studies have identified the effect of several MDR1 variants in PD risk. Westerlund et al. found a significant association of SNP 1236C/T with PD risk [42]. Dutheil et al. demonstrated an association between carrying 2 variant G2677 (A, T) alleles and organochlorines in PD risk [43]. Li et al. suggested that MDR1 gene promoter variants might contribute to PD development as a rare risk factor [65]. While Funke et al. detected no relevant association between ten MDR1SNPs and PD susceptibility in either the entire sample, or when separately investigating by ethnic origin or age at onset [40]. MDR1 haplotypes might protect against PD occurrence. Haplotypes containing SNPs 2677

and 3435, especially the 2677T-3435T haplotype, was strongly associated with a reduced risk of PD [39]. A significant association of the 1236C-2677G haplotype with PD and a trend towards association with disease of the 1236C-2677G-3435C haplotypes was revealed by haplotype analysis as well [42]. Moreover, the combined effect of commonly used pesticides and variant MDR1 genotypes might jointly increase risk of PD [44]. A meta-analysis conducted by Liu et al. indicated that pesticide-induced gene mutations especially in MDR1 might contribute to increasing susceptibility to PD [66].

In addition, genetic variations of MDR1 may cause inter-individual differences in pharmacokinetics and bioavailability of drugs. The MDR1 C3435T polymorphism was correlated with pharmacokinetics of tacrolimus [67]. The TT homozygotes of G2677T/A and C3435T variants required a higher tacrolimus dose than those with wild alleles or heterozygotes, which may be helpful in the prevention of tacrolimus nephrotoxicity early after transplantation [68]. G2677(A/T)-TT was considered as a positive predictor of tacrolimus-induced neurotoxicity after liver transplantation [69]. Patients with the TT genotype of C3435T variant required a lower dose of Cyclosporine A to achieve target therapeutic concentrations when compared with CC carriers especially in the Asian population during the early and middle time periods after kidney transplantation [70].

Several limitations were presented in this meta-analysis. Firstly, there were very limited included studies in the subgroup analysis for Asian population which might influence our results. Further studies are still needed to confirm the current results on Asians. Secondly, most of the relevant studies for the MDR1 variant in PD risk from different geographic regions. Our result would be affected for the prevalence of MDR1 variant and PD cases differs from variable origins [71]. Thirdly, some important effectors such as age, sex, occupational pesticide exposure, and smoking status for the association between MDR1 and PD could not be evaluated due to the limitation of the data. Because higher age, male sex, cognitive impairment and the presence of psychotic symptoms are independent predictors of decreased survival in PD [72], these factors should be considered in the future researches. Lastly, the interaction of gene-gene and gene-environment should be considered.

In conclusions, our result did not find a significant association between MDR1 C3435T polymorphism and PD risk. However, interaction of C3435T variant and exposure to occupational pesticide was shown to increase the risk of PD. Future well-designed, large-scale studies with more ethnicities are still required to further evaluate the relationship.

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Disclosure of conflict of interest

None.

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