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ORIGINAL ARTICLE

Polymorphisms of the dopamine metabolic and signaling pathways are associated with susceptibility to motor levodopa-induced complications (MLIC) in Parkinson's disease: a systematic review and meta-analysis

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Abstract

Background Dopamine replacement therapy remains the gold standard for symptomatic management of Parkinson's disease worldwide. However, most patients will develop debilitating motor levodopa-induced complications (MLIC) in the form of levodopa-induced dyskinesia (LID) and/or motor fluctuations (MF). This study aimed to conduct a systematic review and meta-analysis on the pharmacogenetic association between LID and MF with common genetic variants of the dopamine metabolic and signaling pathways.

Methods A meta-analysis was conducted according to the PRISMA guidelines. Extracted studies include case–control studies evaluating the association between *SLC6A3/DAT* rs28363170 and rs393795; *COMT* rs4680 and rs4633; *MAO-B* rs1799836, *BDNF* rs6265, *DRD1* rs4532, *DRD2* rs1800497, *DRD3* rs6280, and *DRD5* rs6283 polymorphisms; and the overall risk of MLIC and its subtypes LID or MF. Genotypic frequency were tested for deviation from the Hardy–Weinberg equilibrium (HWE), and the genetic association was examined using the allelic (a vs. A), recessive (aa vs. Aa + AA), dominant (aa + Aa vs. AA), overdominant (Aa vs. aa + AA), homozygous (aa vs. AA), and heterozygous (Aa vs. AA and aa vs. aA) models.

Results Fourteen studies were included in the meta-analysis. A significant association was found between *COMT* rs46809 polymorphisms with LID but not MF, with the association observable in Asians but not Caucasians. In Asians, the *COMT* rs4633 was significantly associated with the occurrence of both LID and MF. The *MAO-B* rs1799836 was associated with both MF and LID. Among all the dopamine receptor genes analyzed, only *DRD2* exhibited an association with LID. No association was observed between the *SLC6AT/DAT* and *BDNF* genes with either LID or MF.

Conclusion Strong associations were observed between polymorphisms of genes regulating dopamine metabolism with the occurrence of LID and/or MF. The *MAO-B* rs1799836 may be potential for use as a general pharmacogenetic marker of MLIC, while the *COMT* rs4680 and rs4633 may be used as markers of LID in Asian ethnicities.

Keywords Dopamine metabolic and signaling pathways · Polymorphism · Motor levodopa-induced complications (MLIC) · Parkinson's disease

Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder affecting 2–3% of the population ≥ 65 years of age [1] and currently exhibits one of the fastest growths in prevalence, disability rates, and death, relative to other neurological disorders [2]. The central pathologic feature of PD includes the formation of Lewy bodies and accumulation of α-synuclein protein, leading to the degeneration

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of dopaminergic neurons, particularly within the substantia nigra [3, 4]. Ultimately, reduced activation of the motor cortex results in hallmark manifestations of PD such as resting tremor, bradykinesia, muscle rigidity, gait dysfunction, and postural instability [5, 6].

Clinical manifestations of PD dramatically affect the quality of life of sufferers, and since no cure is available, treatment is provided with the goal of symptomatic relief and improved functionality for daily activities [7]. The dopamine precursor, L-dopamine (L-dopa/levodopa), is one of the most frequently utilized first-line treatments for PD and remains the treatment of choice in elderly subjects due to its lower side effect potential [1, 7].

However, approximately 40% of patients on levodopa will develop adverse effects of motor levodopa-induced complications (MLIC) which manifests as levodopa-induced dyskinesia (LID) and/or motor fluctuations (MF), within the first 4–6 years of treatment [8]. The occurrences of these disabling complications are multi-factorial, as a result of disease progression, cumulative treatment effect, and the reorganization of neural circuitry or imbalance within the basal ganglia pathways [9].

Certain genetic predispositions have been implicated in the occurrence of both LID and MF, due to the marked heterogeneity of patient responses towards levodopa [10]. The most notable polymorphisms include genes involved in dopamine metabolism and signaling function. The most commonly studied genes are illustrated in Fig. 1. In terms of metabolic function, the first is the catechol-O-methyltransferase (*COMT*) enzyme, with soluble (*S-COMT*) and membrane-bound (*MB-COMT*) subunits that are responsible for catecholamine degradation, including dopamine. The rs4680 variant results in the substitution of valine with methionine in position 158, which has been linked to the reduced COMT activity and higher dopamine levels. Additionally, another group of metabolic enzymes, the monoamine oxidase (*MAO*) enzymes, encompasses subtypes *MAO-A* and *MAO-B* and plays a crucial role in the oxidative deamination of monoamines.

Meanwhile, pharmacogenetically relevant genes that are involved in dopamine signaling function (Fig. 1) and have been implicated in MLIC development include those that encode the dopamine transporter/solute carrier-6 (*DAT/SLC6*) genes responsible for dopamine transport across the plasma membrane and genes encoding the dopamine receptor families D1 (*DRD1*, *DRD5*) and D2 (*DRD2*, *DRD3*, *DRD4*) through which dopamine can exert its physiological functions [11]. Additionally, other pathways can also impact dopamine effectivity, and one of the most notable genes that have been implicated in MLIC development is the brain-derived neurotrophic factor (*BDNF*) which may play a crucial role in enhancing the survival of dopaminergic neurons that reside within the substantia nigra [9, 12].

In this study, we aimed to systematically review the relevant single nucleotide polymorphisms (SNPs) that have been identified in levodopa-induced complications. A recent systematic review has been performed to assess the role of certain genes in the occurrence of levodopa-induced dyskinesia [13], but did not distinguish between the MF and LID phenotype. In this meta-analysis, we assessed the associations between the genes with susceptibility towards MLIC in general, followed by a subanalysis of the association between polymorphisms with either the dyskinesia (LID) or MF phenotype using the genotypic frequency in each individual study. Additionally, all the meta-analyses were performed using multiple genetic models to determine the associations between polymorphic genes of the dopamine pathway with susceptibility of either LID or MF.

Methods

Literature search and data extraction

A systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [14]. A literature search was conducted in PubMed and Scopus using keywords related to dopamine metabolic and signaling pathways such as "dopamine transporter/*DAT*/solute carrier-6 member 3 (*SLC6A3*)," "catechol-o-methyltransferase/*COMT*," "monoamine oxidase/*MAO*," "dopamine receptor/*DR*," "brain-derived neurotrophic factor/*BDNF*," "polymorphism," "polymorphismneurotrophic factorne me (MLIC)," "levodopa," "dyskinesia," "motor fluctuation," and "Parkinson's disease (PD)" singularly and in combination. The literature search was updated until January 2021. The inclusion criteria of studies were as follows: (1) evaluating the association between *SLC6A3/DAT* rs28363170 and rs393795; *COMT* rs4680 and rs4633; *MAO-B* rs1799836, *BDNF* rs6265, *DRD1* rs4532, *DRD2* rs1800497, *DRD3* rs6280, and *DRD5* rs6283 polymorphisms; and the risk of MLIC (including dyskinesia and/or motor fluctuation) and (2) conducted with a case–control design. Data were extracted as follows: (1) name of the first author, (2) year of publication, (3) type of single nucleotide polymorphism (SNP), (4) age, (5) sex, (6) type of study, (7) therapy, (8) duration of L-dopa or levodopa treatment, (9) sample size, and (10) number of genotypes in patients with and without MLIC.

Statistical analysis

Meta-analysis for each gene polymorphism was performed for two or more studies, as previously described [15–17]. Genotypic frequency of the selected genes were tested for

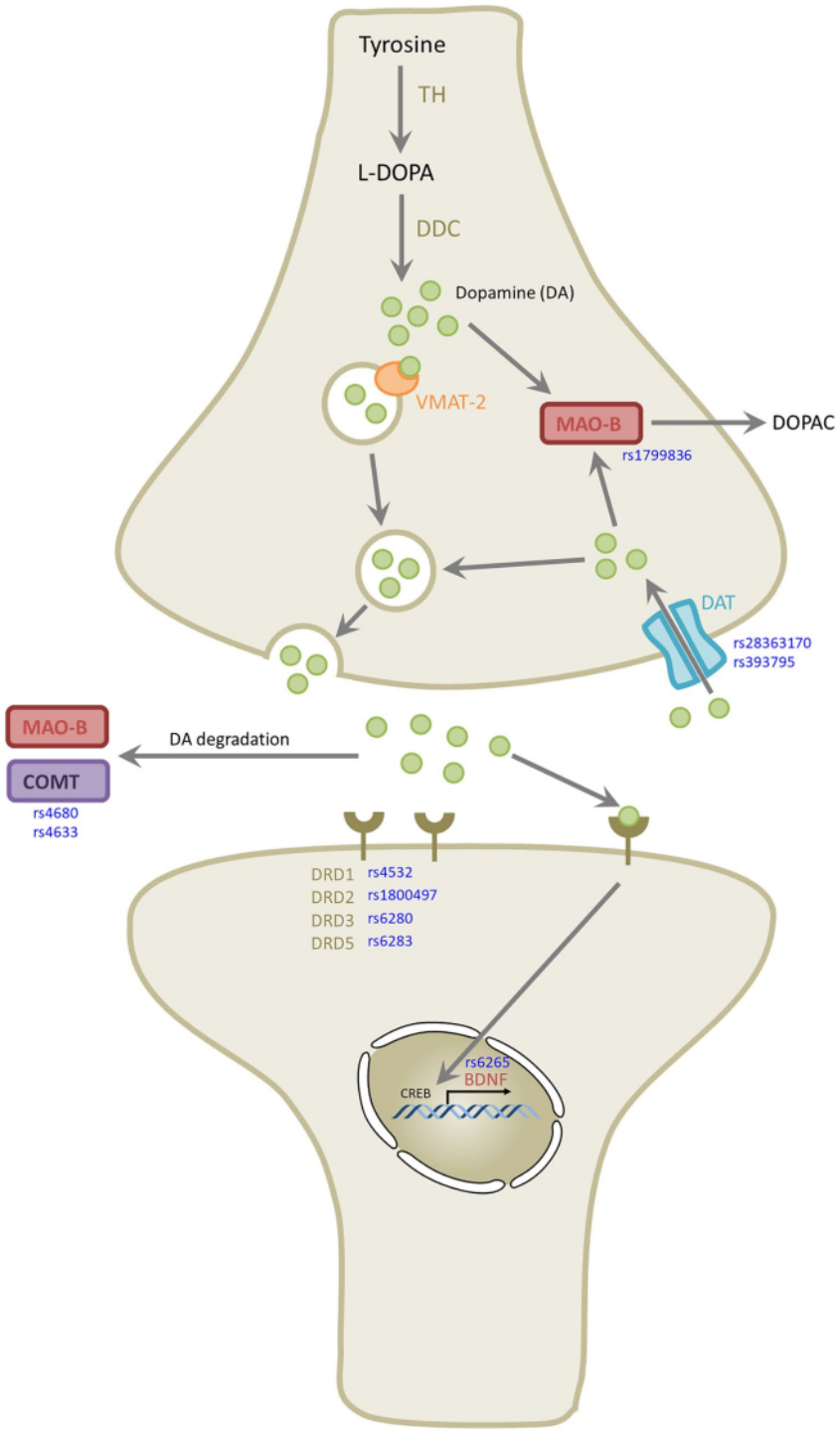

Fig. 1 Summary of genes involved in the dopamine metabolism and signaling pathways. TH tyrosine hydroxylase, DDC dopa decarboxylase, VMAT vesicular monoamine transporter, MAO monoamine oxidase-B, DOPAC 3,4-dihydroxyphenylacetic acid, DAT dopamine transporter, COMT catechol-O-methyltransferase, DRD1-5 dopamine receptors 1–5, BDNF brain-derived neurotrophic factor

deviation from the Hardy–Weinberg equilibrium (HWE) in the control subjects if HWE was not reported in the original study. The genetic association was examined using different genetic models, including allelic (a vs. A), recessive (aa vs. Aa + AA), dominant (aa + Aa vs. AA), overdominant (Aa vs. aa + AA), homozygous (aa vs. AA), and heterozygous (Aa vs. AA and aa vs. aA) models [15–17]. The associations between selected gene polymorphisms with MLIC predisposition were calculated by the pooled odds ratio (OR) and 95% confidence interval (CI). Heterogeneity among studies was evaluated using Q test and I^2 statistic. The random-effect model (REM) was used if heterogeneity existed; otherwise, the fixed-effect model (FEM) was used [18–20]. Subgroup analysis was conducted by stratifying based on ethnicity and type of MLIC. Potential publication bias was assessed by Begg's funnel plots and Egger's regression test. Begg's funnel plot was applied if the pooled effect size consisted of 10 or more studies. A quantified result of $p < 0.05$ was indicative of statistical significance. A sensitivity test was performed by sequentially omitting one study each time to evaluate the stability of the results. All the meta-analysis was performed using Review Manager 5.4.

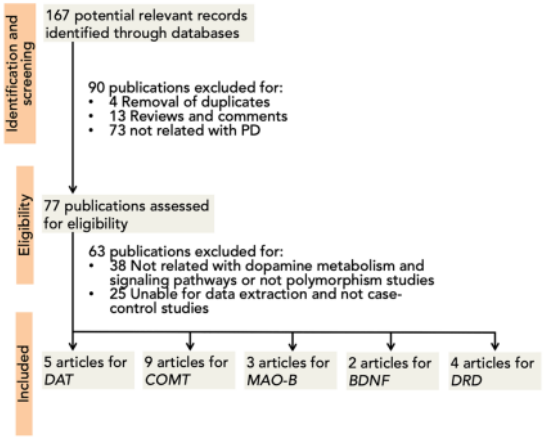

Fig. 2 Flow diagram of the selection process of studies on polymorphisms of dopamine metabolism and signaling pathways in relation to the occurrence of motor levodopa-induced complications (MLIC). The selection process is initiated with identification and screening of relevant studies, followed by eligibility assessment, and determination of included studies. MAO-B monoamine oxidase-B, DAT dopamine transporter, COMT catechol-O-methyltransferase, DRD dopamine receptors, BDNF brain-derived neurotrophic factor

Results

Dataset description

Using our inclusion criteria (Fig. 2), a total of 167 potential relevant records were identified, among which 77 were reviewed. Sixty-three studies were then excluded due to the following: (1) not relating to dopamine metabolism and signaling pathways and its polymorphism; (2) conducted other than case–control design; and (3) failed to extract the data. Fourteen studies were then included in this meta-analysis [21–34]. A total of 562, 2316, 1359, 361, 328, 405, 328, and 200 subjects for *SLC6A3/DAT* [21–24], *COMT* [22, 24–31], *MAO-B* [22, 25, 29], *BDNF* [24, 27], *DRD1* [22, 32, 33], *DRD2* [22, 32, 33], *DRD3* [22, 32, 33], and *DRD5* [32, 34] polymorphisms, respectively, were further analyzed.

All the included studies were comparable in terms of age and sex. Duration of levodopa treatment varies between studies, ranging from 3 to 11 years. Several anti-PD co-therapies were reported in some studies, including MAO inhibitor, COMT inhibitor, non-ergoline dopamine agonist, and decarboxylase inhibitor. All studies complied with the HWE except for the study from Purcaro et al. [21], Kakinuma et al. [22], Wu et al. [30], Hast et al. [29], Sampaio et al. [25], and dos Santos et al. [23]. Details of the retrieved studies are depicted in Table 1. As a supplementary, we also list other genes that have been implicated in Parkinson's MLIC, but were not eligible for our analysis because they did not suit our study's inclusion criteria (Supplementary Table 1).

Analysis of genes related to dopamine metabolism and signaling

SLC6A3/DAT

Two *SLC6A3/DAT* polymorphisms, rs28363170 and rs393795, were analyzed (Table 2). Overall, there was no significant association between *SLC6A3/DAT* rs28363170 and rs393795 polymorphisms with MLIC susceptibility in all inheritance models. Due to limited studies on motor fluctuations, subgroup analysis was only performed for dyskinesia, yielding similar findings of no significant association with rs28363170. Moreover, Mineli et al. [21] described that there is no advantage in excluding studies that appear not to be in HWE, unless there are other reasons for doubting the quality of the study.

COMT

Two *COMT* polymorphisms rs4680 and rs4633, were analyzed (Table 2). Generally, we did not find any significant association between rs4680 and MLIC predisposition in all inheritance models, except patients with the AA genotype exhibited higher susceptibility to the overall development of MLIC (AA vs. GA, OR = 1.38, 95% CI = 1.03–1.84, $p = 0.029$, Fig. 3A). Interestingly, however, subgroup analyses stratified by MLIC type revealed a significant association between rs4680 with dyskinesia predisposition in

Table 1 Characteristic of included studies

Gene	SNP	First author, year	*N*	Mean/median age	Male (%)	Type of study	Therapy	Anti-PD co-therapy	Mean duration of treatment (years)	MLIC (+) (wtwt/wtmt/mtmt)	MLIC (−) (wtwt/wtmt/mtmt)	*p*, HWE
SLC6A3/DAT	rs28363170 10R > 9R	Purcaro, 2019 [a]	181	72.57	62.4	Retrospective	L-Dopa	NR	7.97	31/141/16	35/121/10	0.000
		Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	60/6/7	31/3/3	0.000
		dos Santos, 2018 [a]	195	55.81	58.5	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	7.11	14/11/2	75/51/21	0.016
		dos Santos, 2018 [b]	195	55.81	58.5	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	7.11	31/20/8	58/42/15	0.105
	rs393795 A > G	Purcaro, 2019 [a]	181	72.57	62.4	Retrospective	L-Dopa	NR	7.97	73/117/2	58/105/5	0.000
		Michałowska, 2020 [a + b]	76	65.7	52.6	Retrospective	Levodopa	Ropinirole, piribedil, ropinirole, entacapone, amantadine	8.6	18/22/2	20/14/0	0.130
COMT	rs4680 G > A	Sampaio, 2018 [a]	162	64.0	56.7	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor, amantadine	7.2	13/5/8	50/67/7	0.010
		Sampaio, 2018 [b]	162	64.0	56.7	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor, amantadine	7.2	30/32/7	33/40/8	0.409
		Michałowska, 2020 [a + b]	76	65.7	52.6	Retrospective	Levodopa	Ropinirole, piribedil, ropinirole, entacapone, amantadine	8.6	9/18/15	5/16/13	0.982
		Watanabe, 2003 [a]	121	68.2	NR	Retrospective	Levodopa	Decarboxylase inhibitor, selegiline	NR	12/13/5	45/34/9	0.499
		Watanabe, 2003 [b]	121	68.2	NR	Retrospective	Levodopa	Decarboxylase inhibitor, selegiline	NR	24/20/7	33/27/7	0.675
		Cheshire, 2014 [a]	285	63	NR	Retrospective	L-Dopa	NR	≤5	41/76/51	29/51/29	0.502
		Zhao et al., 2020 [a]	73	63.95	38.3	Retrospective	Levodopa	NR	7.21	11/14/1	33/9/3	0.060
		Zhao et al., 2020 [b]	73	63.95	38.3	Retrospective	Levodopa	NR	7.21	31/20/3	13/5/1	0.587

Table 1 (continued)

Gene	SNP	First author, year	*N*	Mean/median age	Male (%)	Type of study	Therapy	Anti-PD co-therapy	Mean duration of treatment (years)	MLIC (+) (wtwt/wtmt/mtmt)	MLIC (−) (wtwt/wtmt/mtmt)	*p*, HWE
		Hao et al., 2014 [a]	1087	63	58	Retrospective	Levodopa	Decarboxylase inhibitor	3	28/19/5	506/434/95	0.889
		Hao et al., 2014 [b]	1087	63	58	Retrospective	Levodopa	Decarboxylase inhibitor	3	95/56/13	439/397/87	0.840
		Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	18/14/5	42/25/6	0.417
		Wu et al., 2014 [b]	259	57.30	NR	Retrospective	Levodopa	NR	4.82	116/49/4	18/68/4	0.000
		Xiao et al., 2017 [a]	143	65.1	55	Retrospective	Levodopa	NR	6.0	7/9/2	72/49/4	0.204
		Xiao et al., 2017 [b]	143	65.1	55	Retrospective	Levodopa	NR	6.0	18/20/5	61/38/1	0.060
	rs4633 C > T	Xiao et al., 2017 [a]	143	65.1	55	Retrospective	Levodopa	NR	6.0	7/9/2	71/47/7	0.830
		Xiao et al., 2017 [b]	143	65.1	55	Retrospective	Levodopa	NR	6.0	18/19/6	60/37/3	0.336
		Zhao et al., 2020 [a]	73	63.95	38.3	Retrospective	Levodopa	NR	7.21	12/13/1	33/12/2	0.509
		Zhao et al., 2020 [b]	73	63.95	38.3	Retrospective	Levodopa	NR	7.21	33/18/3	12/7/0	0.324
MAO-B	rs1799836 A > G	Hao et al., 2014 [a]	1087	63	58	Retrospective	Levodopa	Decarboxylase inhibitor	3	35/13/4	784/124/127	0.000
		Hao et al., 2014 [b]	1087	63	58	Retrospective	Levodopa	Decarboxylase inhibitor	3	115/29/20	704/108/111	0.000
		Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	25/7/5	64/8/1	0.227
		Sampaio, 2018 [a]	162	64.0	56.7	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor, amantadine	7.2	9/8/9	34/19/71	0.000
		Sampaio, 2018 [b]	162	64.0	56.7	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor, amantadine	7.2	18/13/38	25/14/42	0.000

Table 1 (continued)

BDNF	rs6265 G > A	Michałowska, 2020 [a + b]	76	65.7	52.6	Retrospective	Levodopa	Ropinirole, piribedil, ropinirole, entacapone, amantadine	8.6	11/30/1	13/21/0	0.009
		Cheshire, 2014 [a]	285	63	NR	Retrospective	L-Dopa	NR	≤5	95/48 GG/GA + AA	58/23 GG/GA + AA	ND
DRD1	rs4532 G > A	Comi, 2017 [a]	100	64.2	56	Retrospective	Levodopa	NR	9.25	19/29/11	18/21/11	0.311
		dos Santos, 2019 [a]	228	65	57.4	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	6.71	3/16/33	18/72/86	0.612
		dos Santos, 2019 [b]	228	65	57.4	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	6.71	13/45/69	8/43/50	0.767
		Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	29/7/1	55/16/2	0.532
DRD2	rs1800497 G > A	Comi, 2017 [a]	100	64.2	56	Retrospective	Levodopa	NR	9.25	22/25/3	36/11/3	0.119
		dos Santos, 2018 [a]	195	55.81	58.5	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	7.11	12/16/2	80/73/12	0.397
		dos Santos, 2018 [b]	195	55.81	58.5	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	7.11	34/28/4	58/61/10	0.267
		Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	10/23/4	20/39/14	0.517
DRD3	rs6280 G > A	Comi, 2017 [a]	100	64.2	56	Retrospective	Levodopa	NR	9.25	9/21/20	26/18/6	0.312
		dos Santos, 2019 [a]	228	65	57.4	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	6.71	12/37/3	31/125/20	0.000
		dos Santos, 2019 [b]	228	65	57.4	Retrospective	Levodopa	MAOB inhibitor, COMT inhibitor	6.71	25/87/15	18/75/8	0.000
		Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	21/16/0	38/34/1	0.030
DRD5	rs6283 T > C	Comi, 2017 [a]	100	64.2	56	Retrospective	Levodopa	NR	9.25	35/15/0	33/13/4	0.126
		Wang, 2001 [b]	120	63.8	25	Retrospective	Levodopa	NR	5.41	12/28/10	12/29/9	0.245

[a] Dyskinesias; [b] motor fluctuations; (1) dose < 500 mg/day; (2) dose > 500 mg/day; inclusion: min 3 years, with minimum dose of levodopa 300 mg daily

Table 2 Meta-analysis of the associations between selected gene polymorphisms and motor levodopa-induced complications

SNP	Model	MLIC type	Number of studies	Test of association				Test of heterogeneity		Publication bias (Egger's test), *p* value
				OR	95% CI	*p* value	Model	*p* value	I^2 (%)	
SLC6A3/DAT rs28363170 10R > 9R**	9R vs. 10R	Overall	4	106	0.84–1.33	0.591	Fixed	0.790	0	0.415
		Dyskinesia	3	1.09	0.84–1.41	0.490	Fixed	0.659	0	0.614
	9R9R vs. 10R9R + 10R10R	Overall	4	1.11	0.65–1.88	0.696	Fixed	0.655	0	0.274
		Dyskinesia	3	1.14	0.60–2.17	0.682	Fixed	0.451	0	0.421
	9R9R + 10R9R vs. 10R10R	Overall	4	1.11	0.78–1.57	0.547	Fixed	0.806	0	0.592
		Dyskinesia	3	1.21	0.79–1.82	0.371	Fixed	0.789	0	0.443
	10R9R vs. 9R9R + 10R10R	Overall	4	1.07	0.76–1.50	0.692	Fixed	0.913	0	0.980
		Dyskinesia	3	1.15	0.76–1.70	0.504	Fixed	0.942	0	0.964
	9R9R vs. 10R10R	Overall	4	1.17	0.66–2.05	0.579	Fixed	0.564	0	0.325
		Dyskinesia	3	1.28	0.63–2.55	0.492	Fixed	0.391	0	0.293
	9R9R vs. 10R9R	Overall	4	1.10	0.62–1.93	0.745	Fixed	0.672	0	0.365
		Dyskinesia	3	1.09	0.54–2.16	0.807	Fixed	0.462	0	0.561
	10R9R vs. 10R10R	Overall	4	1.13	0.78–1.63	0.514	Fixed	0.855	0	0.632
		Dyskinesia	3	1.25	0.80–1.92	0.326	Fixed	0.936	0	0.142
SLC6A3/DAT rs393795 A > G**	G vs. A	Overall	2	1.02	0.76–1.36	0.871	Fixed	0.105	62	NA
	GG vs. AG + AA	Overall	2	1.01	0.68–1.48	0.972	Fixed	0.124	57.8	NA
	GG + AG vs. AA	Overall	2	1.65	0.38–7.09	0.498	Fixed	0.157	50.1	NA
	AG vs. AA + GG	Overall	2	1.03	0.69–1.51	0.893	Fixed	0.313	1.6	NA
	GG vs. AA	Overall	2	1.65	0.37–7.20	0.506	Fixed	0.112	60.4	NA
	GG vs. AG	Overall	2	1.00	0.67–1.47	0.997	Fixed	0.192	41.2	NA
	AG vs. AA	Overall	2	1.71	0.39–7.40	0.472	Fixed	0.222	32.9	NA
COMT rs4680 G > A	A vs. G	Overall	14	1.06	0.79–1.41	0.702	Random	0.000	78.46	0.081
		Dyskinesia	7	1.26	1.03–1.53	0.026	Fixed	0.385	5.61	0.019
		Motor fluctuation	6	0.83	0.49–1.40	0.488	Random	0.000	87.16	0.542
		Overall*	12	1.14	0.91–1.41	0.233	Random	0.020	51.33	0.026
		Dyskinesia*	6	1.24	1.00–1.53	0.046	Fixed	0.285	1.97	0.038
		Motor fluctuation*	5	1.03	0.71–1.50	0.862	Random	0.018	66.32	0.294

Table 2 (continued)

AA vs. GA+GG	Overall	14	1.38	0.94–2.01	0.092	Random	0.081	36.94	0.176
	Dyskinesia	7	1.79	1.02–3.17	0.044	Random	0.099	43.77	0.472
	Motor fluctuation	6	1.01	0.65–1.56	0.954	Fixed	0.221	28.55	0.206
	Overall*	12	1.18	0.88–1.56	0.256	Fixed	0.583	0	0.066
	Dyskinesia*	6	1.32	0.88–1.95	0.173	Fixed	0.758	0	0.535
	Motor fluctuation*	5	1.09	0.68–1.71	0.723	Fixed	0.195	33.94	0.094
AA+GA vs. GG	Overall	14	0.94	0.61–1.43	0.779	Random	0.000	80.73	0.230
	Dyskinesia	7	1.21	0.91–1.59	0.186	Fixed	0.116	41.24	0.099
	Motor fluctuation	6	0.67	0.31–1.41	0.293	Random	0.000	88.79	0.843
	Overall*	12	1.13	0.83–1.51	0.428	Random	0.016	52.89	0.031
	Dyskinesia*	6	1.30	0.96–1.74	0.086	Fixed	0.146	38.99	0.012
	Motor fluctuation*	5	0.94	0.60–1.45	0.782	Random	0.048	58.39	0.326
GA vs. GG+AA	Overall	14	0.81	0.54–1.21	0.304	Random	0.000	78.74	0.438
	Dyskinesia	7	1.04	0.61–1.76	0.875	Random	0.004	68.31	0.680
	Motor fluctuation	6	0.62	0.31–1.19	0.155	Random	0.000	85.61	0.926
	Overall*	12	0.92	0.76–1.11	0.391	Fixed	0.127	32.93	0.028
	Dyskinesia*	6	1.12	0.84–1.49	0.439	Fixed	0.100	45.84	0.057
	Motor fluctuation*	5	0.80	0.61–1.02	0.081	Fixed	0.390	2.88	0.457
AA vs. GG	Overall	14	1.28	0.80–2.02	0.293	Random	0.021	48.81	0.227
	Dyskinesia	7	1.64	1.08–2.48	0.021	Fixed	0.385	5.48	0.278
	Motor fluctuation	6	0.97	0.40–2.30	0.944	Random	0.020	62.59	0.467
	Overall*	12	1.15	0.83–1.57	0.393	Fixed	0.271	17.63	0.044
	Dyskinesia*	6	1.42	0.90–2.21	0.122	Fixed	0.656	0	0.280
	Motor fluctuation*	5	1.27	0.57–2.83	0.554	Random	0.093	49.76	0.113

Table 2 (continued)

	AA vs. GA	Overall	14	1.38	1.03–1.84	0.029	Fixed	0.111	33.02	0.219
		Dyskinesia	7	1.74	0.83–3.63	0.140	Random	0.021	59.78	0.678
		Motor fluctuation	6	1.28	0.81–2.02	0.288	Fixed	0.580	0	0.064
		Overall*	12	1.22	0.90–1.65	0.190	Fixed	0.814	0	0.275
		Dyskinesia*	6	1.23	0.80–1.87	0.338	Fixed	0.716	0	0.824
		Motor fluctuation*	5	1.27	0.78–2.06	0.332	Fixed	0.437	0	0.099
	GA vs. GG	Overall	14	0.85	0.54–1.33	0.489	Random	0.000	80.06	0.331
		Dyskinesia	7	1.18	0.71–1.96	0.519	Random	0.018	60.92	0.511
		Motor fluctuation	6	0.63	0.29–1.30	0.212	Random	0.000	87.39	0.860
		Overall*	12	1.06	0.79–1.42	0.693	Random	0.039	46.28	0.037
		Dyskinesia*	6	1.25	0.90–1.70	0.174	Fixed	0.110	44.32	0.025
		Motor fluctuation*	5	0.80	0.61–1.03	0.094	Fixed	0.158	39.49	0.363
COMT rs4680 G > A [Caucasian]	A vs. G	Overall	4	1.07	0.84–1.35	0.572	Fixed	0.643	0	0.792
		Overall*	3	1.02	0.79–1.32	0.867	Fixed	0.663	0	0.084
		Dyskinesia	2	1.19	0.87–1.59	0.264	Fixed	0.549	0	NA
	AA vs. GA + GG	Overall	4	1.60	0.71–3.56	0.255	Random	0.020	69.64	0.577
		Overall*	3	1.10	0.72–1.69	0.650	Fixed	0.860	0	0.340
		Dyskinesia	2	2.79	0.47–16.50	0.259	Random	0.004	87.72	NA
	AA + GA vs. GG	Overall	4	0.91	0.63–1.30	0.598	Fixed	0.709	0	0.097
		Overall*	3	0.97	0.65–1.44	0.875	Fixed	0.664	0	0.243
		Dyskinesia	2	0.97	0.60–1.53	0.882	Fixed	0.325	0	NA
	GA vs. GG + AA	Overall	4	0.69	0.39–1.21	0.195	Random	0.065	58.55	0.255
		Overall*	3	0.91	0.63–1.29	0.594	Fixed	0.976	0	0.128
		Dyskinesia	2	0.47	0.10–2.09	0.321	Random	0.009	85.52	NA
	AA vs. GG	Overall	4	1.34	0.82–2.15	0.232	Fixed	0.142	44.89	0.935
		Overall*	3	1.06	0.62–1.78	0.823	Fixed	0.667	0	0.203
		Dyskinesia	2	2.12	0.62–7.17	0.229	Random	0.068	70.02	NA
	AA vs. GA	Overall	4	1.90	0.70–5.16	0.206	Random	0.005	76.37	0.411
		Overall*	3	1.13	0.71–1.78	0.595	Fixed	0.970	0	0.316
		Dyskinesia	2	3.94	0.32–48.29	0.284	Random	0.001	91.33	NA
	GA vs. GG	Overall	4	0.80	0.53–1.18	0.262	Fixed	0.220	32.08	0.196
		Overall*	3	0.93	0.60–1.41	0.733	Fixed	0.754	0	0.226
		Dyskinesia	2	0.60	0.16–2.11	0.426	Random	0.041	76.15	NA

Table 2 (continued)

COMT rs4680 G > A [Asian]	A vs. G	Overall	10	1.08	0.71–1.62	0.726	Random	0.000	84.14	0.085
		Dyskinesia	5	1.32	1.01–1.72	0.045	Fixed	0.219	30.29	0.000
		Motor fluctuation	5	0.81	0.42–1.53	0.520	Random	0	89.42	0.635
		Overall*	9	1.24	0.91–1.67	0.165	Random	0.005	63.19	0.013
		Motor fluctuation*	4	1.07	0.65–1.75	0.793	Random	0.008	74.72	0.401
	AA vs. GA + GG	Overall	10	1.17	0.81–1.69	0.400	Fixed	0.325	12.77	0.114
		Dyskinesia	5	1.46	0.81–2.61	0.201	Fixed	0.664	0	0.819
		Motor fluctuation	5	1.01	0.62–1.62	0.969	Fixed	0.136	42.83	0.281
		Overall*	9	1.24	0.84–1.82	0.264	Fixed	0.346	10.7	0.053
		Motor fluctuation*	4	1.10	0.66–1.82	0.714	Fixed	0.110	50.36	0.168
	AA + GA vs. GG	Overall	10	1.00	0.55–1.79	0.996	Random	0.000	86.28	0.209
		Dyskinesia	5	1.55	0.92–2.58	0.095	Random	0.097	48.93	0.009
		Motor fluctuation	5	0.63	0.25–1.56	0.321	Random	0	90.76	0.913
		Overall*	9	1.24	0.83–1.84	0.291	Random	0.004	64.47	0.014
		Motor fluctuation*	4	0.97	0.54–1.71	0.905	Random	0.023	68.63	0.437
	GA vs. GG + AA	Overall	10	0.89	0.52–1.52	0.678	Random	0.000	83.28	0.234
		Dyskinesia	5	1.38	0.80–2.37	0.241	Random	0.076	52.63	0.054
		Motor fluctuation	5	0.58	0.26–1.27	0.173	Random	0	87.92	0.997
		Overall*	9	1.06	0.75–1.49	0.730	Random	0.038	51.05	0.037
		Motor fluctuation*	4	0.78	0.59–1.03	0.081	Fixed	0.262	24.94	0.582
	AA vs. GG	Overall	10	1.27	0.67–2.38	0.453	Random	0.023	53.43	0.172
		Dyskinesia	5	1.59	0.86–2.91	0.133	Fixed	0.558	0	0.409
		Motor fluctuation	5	1.02	0.33–3.10	0.975	Random	0.010	69.86	0.544
		Overall*	9	1.20	0.80–1.78	0.367	Fixed	0.134	35.54	0.020
		Motor fluctuation*	4	1.56	0.50–4.82	0.436	Random	0.047	62.32	0.197
	AA vs. GA	Overall	10	1.31	0.88–1.93	0.175	Fixed	0.683	0	0.301
		Dyskinesia	5	1.29	0.69–2.38	0.423	Fixed	0.582	0	0.529
		Motor fluctuation	5	1.32	0.80–2.18	0.274	Fixed	0.448	0	0.094
		Overall*	9	1.30	0.86–1.95	0.200	Fixed	0.586	0	0.335
		Motor fluctuation*	4	1.32	0.76–2.24	0.317	Fixed	0.296	18.79	0.153
	GA vs. GG	Overall	10	0.95	0.52–1.70	0.853	Random	0.000	85.17	0.201
		Dyskinesia	5	1.52	0.85–2.68	0.152	Random	0.073	53.25	0.033
		Motor fluctuation	5	0.59	0.24–1.41	0.236	Random	0	89.51	0.936
		Overall*	9	1.16	0.78–1.71	0.465	Random	0.011	59.8	0.020
		Motor fluctuation*	4	0.88	0.53–1.43	0.603	Random	0.089	53.99	0.484

Table 2 (continued)

COMT rs4633 C > T [Asian]	T vs. C	Overall	4	1.83	1.28–2.62	0.001	Fixed	0.846	0	0.191
		Dyskinesia	2	1.85	1.07–3.19	0.027	Fixed	0.828	0	NA
		Motor fluctuation	2	1.81	1.13–2.92	0.014	Fixed	0.381	0	NA
	TT vs. CT + CC	Overall	4	2.81	1.10–7.22	0.031	Fixed	0.643	0	0.378
		Dyskinesia	2	1.61	0.40–6.36	0.494	Fixed	0.573	0	NA
		Motor fluctuation	2	4.62	1.26–16.89	0.021	Fixed	0.688	0	NA
	TT + CT vs. CC	Overall	4	1.96	1.24–3.11	0.004	Fixed	0.656	0	0.653
		Dyskinesia	2	2.39	1.17–4.85	0.016	Fixed	0.693	0	NA
		Motor fluctuation	2	1.70	0.93–3.11	0.083	Fixed	0.330	0	NA
	CT vs. CC + TT	Overall	4	1.53	0.96–2.41	0.072	Fixed	0.425	0	0.906
		Dyskinesia	2	2.19	1.07–4.44	0.030	Fixed	0.435	0	NA
		Motor fluctuation	2	1.17	0.64–2.14	0.605	Fixed	0.498	0	NA
	TT vs. CC	Overall	4	3.67	1.38–9.73	0.009	Fixed	0.720	0	0.242
		Dyskinesia	2	2.26	0.53–9.48	0.264	Fixed	0.631	0	NA
		Motor fluctuation	2	5.56	1.47–21.08	0.012	Fixed	0.587	0	NA
	TT vs. CT	Overall	4	2.02	0.75–5.35	0.160	Fixed	0.528	0	0.502
		Dyskinesia	2	1.03	0.24–4.26	0.971	Fixed	0.452	0	NA
		Motor fluctuation	2	3.67	0.95–14.04	0.058	Fixed	0.856	0	NA
	CT vs. CC	Overall	4	1.77	1.10–2.84	0.019	Fixed	0.507	0	0.914
		Dyskinesia	2	2.42	1.16–5.05	0.018	Fixed	0.569	0	NA
		Motor fluctuation	2	1.40	0.75–2.62	0.288	Fixed	0.375	0	NA

Table 2 (continued)

MAO-B rs1799836 A > G**	G vs. A	Overall	5	1.21	0.79–1.86	0.378	Random	0.005	73	0.765
		Dyskinesia	3	1.30	0.48–3.46	0.604	Random	0.001	86.3	0.585
		Motor fluctuation	2	1.21	0.94–1.55	0.126	Fixed	0.912	0	NA
	GG vs. AG + AA	Overall	5	0.91	0.50–1.65	0.761	Random	0.044	59.2	0.69
		Dyskinesia	3	0.97	0.23–3.98	0.967	Random	0.021	74.2	0.005
		Motor fluctuation	2	1.06	0.71–1.58	0.770	Fixed	0.786	0	NA
	GG + AG vs. AA	Overall	5	1.40	1.07–1.82	0.013	Fixed	0.240	27.2	0.848
		Dyskinesia	3	1.52	0.70–3.26	0.289	Random	0.070	62.5	0.923
		Motor fluctuation	2	1.35	0.97–1.86	0.074	Fixed	0.846	0	NA
	AG vs. AA + GG	Overall	5	1.78	1.31–2.42	0.000	Fixed	0.602	0	0.783
		Dyskinesia	3	2.33	1.43–3.79	0.001	Fixed	0.920	0	0.486
		Motor fluctuations	2	1.49	1.00–2.21	0.048	Fixed	0.434	0	NA
	GG vs. AA	Overall	5	1.04	0.58–1.87	0.885	Random	0.088	50.6	0.615
		Dyskinesia	3	1.17	0.27–4.88	0.831	Random	0.028	71	0.089
		Motor fluctuation	2	1.15	0.75–1.75	0.518	Fixed	0.779	0	NA
	GG vs. AG	Overall	5	0.62	0.40–0.95	0.027	Fixed	0.103	48.1	0.708
		Dyskinesia	3	0.54	0.14–2.04	0.367	Random	0.070	62.4	0.056
		Motor fluctuation	2	0.76	0.45–1.26	0.296	Fixed	0.497	0	NA
	AG vs. AA	Overall	5	1.78	1.29–2.45	0.000	Fixed	0.842	0	0.950
		Dyskinesia	3	2.14	1.29–3.55	0.003	Fixed	0.836	0	0.515
		Motor fluctuation	2	1.57	1.04–2.37	0.031	Fixed	0.657	0	NA
BDNF rs6265 G > A *DRD5* rs6283 T > C	GG vs. AG + AA	Overall	2	0.72	0.43–1.20	0.206	Fixed	0.509	0	NA
	C vs. T	Overall	2	0.88	0.56–1.37	0.580	Fixed	0.336	0	NA
	CC vs. TC + TT	Overall	2	0.89	0.34–2.29	0.806	Fixed	0.129	56.54	NA
	CC + TC vs. TT	Overall	2	0.90	0.48–1.68	0.752	Fixed	0.772	0	NA
	TC vs. CC + TT	Overall	2	1.05	0.58–1.88	0.882	Fixed	0.642	0	NA
	CC vs. TT	Overall	2	0.79	0.26–2.42	0.686	Fixed	0.148	52.3	NA
	CC vs. TC	Overall	2	0.88	0.33–2.36	0.806	Fixed	0.128	56.9	NA
	TC vs. TT	Overall	2	1.03	0.53–1.96	0.929	Fixed	0.857	0	NA

Table 2 (continued)

DRD3 rs6280 G > A**	A vs. G	Overall	4	1.25	0.67–2.32	0.482	Random	0.000	83.9	0.621
		Dyskinesia	3	1.34	0.50–3.55	0.552	Random	0.000	88.9	0.747
	AA vs. GA + GG	Overall	4	1.49	0.50–4.41	0.475	Random	0.038	64.3	0.639
		Dyskinesia	3	1.33	0.21–8.34	0.759	Random	0.015	76	0.715
	AA + GA vs. GG	Overall	4	1.22	0.55–2.71	0.619	Random	0.006	76.2	0.224
		Dyskinesia	3	1.39	0.44–4.41	0.572	Random	0.003	83.2	0.141
	GA vs. AA + GG	Overall	4	0.92	0.65–1.31	0.661	Fixed	0.753	0	0.251
		Dyskinesia	3	1.04	0.67–1.60	0.871	Fixed	0.794	0	0.858
	AA vs. GG	Overall	4	1.52	0.32–7.03	0.593	Random	0.004	77.2	0.717
		Dyskinesia	3	1.48	0.12–17.43	0.756	Random	0.002	84.2	0.734
	AA vs. GA	Overall	4	1.43	0.78–2.61	0.248	Fixed	0.228	30.7	0.629
		Dyskinesia	3	1.30	0.57–2.90	0.529	Fixed	0.122	52.4	0.783
	GA vs. GG	Overall	4	1.09	0.59–1.97	0.781	Random	0.081	55.4	0.118
		Dyskinesia	3	1.24	0.52–2.91	0.628	Random	0.045	67.9	0.068
DRD2 rs1800497 G > A	A vs. G	Overall	4	1.12	0.73–1.68	0.603	Random	0.092	53.4	0.129
		Dyskinesia	3	1.24	0.87–1.75	0.229	Fixed	0.106	55.5	0.121
	AA vs. GA + GG	Overall	4	0.73	0.36–1.42	0.355	Fixed	0.903	0	0.208
		Dyskinesia	3	0.71	0.31–1.60	0.410	Fixed	0.756	0	0.044
	AA + GA vs. GG	Overall	4	1.34	0.71–2.50	0.364	Random	0.046	62.5	0.358
		Dyskinesia	3	1.70	1.05–2.75	0.031	Fixed	0.145	48.2	0.805
	GA vs. AA + GG	Overall	4	1.49	0.82–2.69	0.190	Random	0.059	59.7	0.094
		Dyskinesia	3	1.87	1.17–3.00	0.009	Fixed	0.231	31.8	0.212
	AA vs. GG	Overall	4	0.84	0.40–1.71	0.626	Fixed	0.768	0	0.105
		Dyskinesia	3	0.93	0.38–2.24	0.869	Fixed	0.612	0	0.101
	AA vs. GA	Overall	4	0.63	0.31–1.26	0.193	Fixed	0.884	0	0.764
		Dyskinesia	3	0.54	0.23–1.25	0.153	Fixed	0.878	0	0.858
	GA vs. GG	Overall	4	1.44	0.74–2.77	0.279	Random	0.043	63.1	0.266
		Dyskinesia	3	1.85	1.12–3.05	0.016	Fixed	0.162	45	0.935

Table 2 (continued)

DRD1 rs4532 G > A	A vs. G	Overall	4	1.15	0.88–1.49	0.294	Fixed	0.455	0	0.798
		Dyskinesia	3	1.22	0.86–1.71	0.261	Fixed	0.306	15.7	0.589
	AA vs. GA + GG	Overall	4	1.30	0.89–1.87	0.163	Fixed	0.543	0	0.652
		Dyskinesia	3	1.39	0.82–2.32	0.213	Fixed	0.364	1	0.639
	AA + GA vs. GG	Overall	4	1.03	0.64–1.65	0.901	Fixed	0.666	0	0.539
		Dyskinesia	3	1.15	0.66–1.99	0.617	Fixed	0.614	0	0.623
	GA vs. AA + GG	Overall	4	0.81	0.57–1.14	0.241	Fixed	0.522	0	0.595
		Dyskinesia	3	0.87	0.55–1.35	0.541	Fixed	0.360	2.1	0.818

*Excluding study deviated from HWE

**Without excluding study deviated from HWE

allelic (A vs. G, OR = 1.26, 95% CI = 1.03–1.53, $p = 0.026$, Fig. 3B), recessive (AA vs. GA + GG, OR = 1.79, 95% CI = 1.02–3.17, $p = 0.044$, Fig. 3C), and homozygous (AA vs. GG, OR = 1.64, 95% CI = 1.08–2.48, $p = 0.021$, Fig. 3D) models. Excluding studies deviating from HWE, our data indicated that patients harboring the A allele exhibited higher susceptibility to the development of dyskinesia (A vs. G, OR = 1.24, 95% CI = 1.00–1.53, $p = 0.046$, Fig. 3E).

Subgroup analysis was also performed according to ethnicity, and we found that in Asians, the rs4680 A allele was associated with the development of dyskinesia (A vs. G, OR = 1.32, 95% CI = 1.01–1.72, $p = 0.045$, Fig. 3F), based on the pooled analysis without excluding studies that deviated from HWE. However, this finding did not stand when the deviating study was excluded. No association was observed between rs4680 polymorphism with MLIC predisposition in Caucasians.

For rs4633, all included studies were Asians (Table 2). Overall, a significant association between rs4633 polymorphism with MLIC susceptibility was observed in the allelic (T vs. C, OR = 1.83, 95% CI = 1.28–2.62, $p = 0.001$, Fig. 4A), recessive (TT vs. CT + CC, OR = 2.81, 95% CI = 1.10–7.22, $p = 0.031$, Fig. 4B), dominant (TT + CT vs. CC, OR = 1.98, 95% CI = 1.24–3.11, $p = 0.004$, Fig. 4C), homozygous (TT vs. CC, OR = 3.67, 95% CI = 1.38–9.73, $p = 0.009$, Fig. 4D), and heterozygous (CT vs. CC, OR = 1.77, 95% CI = 1.10–2.84, $p = 0.019$, Fig. 4E) models. When subgroup analysis based on MLIC type was introduced, dyskinesia was significantly associated with allelic (T vs. C, OR = 1.85, 95% CI = 1.07–3.19, $p = 0.027$, Fig. 4F), dominant (TT + CT vs. CC, OR = 2.39, 95% CI = 1.18–4.85, $p = 0.016$, Fig. 4G), overdominant (CT vs. CC + TT, OR = 2.19, 95% CI = 1.08–4.44, $p = 0.030$, Fig. 4H), and heterozygous (CT vs. CC, OR = 2.42, 95% CI = 1.16–5.05, $p = 0.018$, Fig. 4I) models, while motor fluctuation was significantly associated with allelic (T vs. C, OR = 1.81, 95% CI = 1.13–2.92, $p = 0.014$, Fig. 4J), recessive (TT vs. CT + CC, OR = 4.62, 95% CI = 1.26–16.89, $p = 0.021$, Fig. 4K), and homozygous models (TT vs. CC, OR = 5.56, 95% CI = 1.47–21.08, $p = 0.012$, Fig. 4L). Marginal association between the occurrences of motor fluctuation was detected in the heterozygous model (TT vs. CT, OR = 3.67, 95% CI = 0.95–14.04, $p = 0.058$, see Table 2).

MAO-B

Only a single *MAO-B* polymorphism, rs1799836, was examined. Similar with *SLC6A3/DAT*, we did not exclude studies that deviated from the HWE. Our data indicated significant associations between rs1799836 with MLIC predisposition in the dominant (GG + AG vs. AA, OR = 1.40, 95% CI = 1.07–1.82, $p = 0.013$, Fig. 5A), overdominant (AG vs. AA + GG, OR = 1.78, 95% CI = 1.31–2.41, $p < 0.0001$,

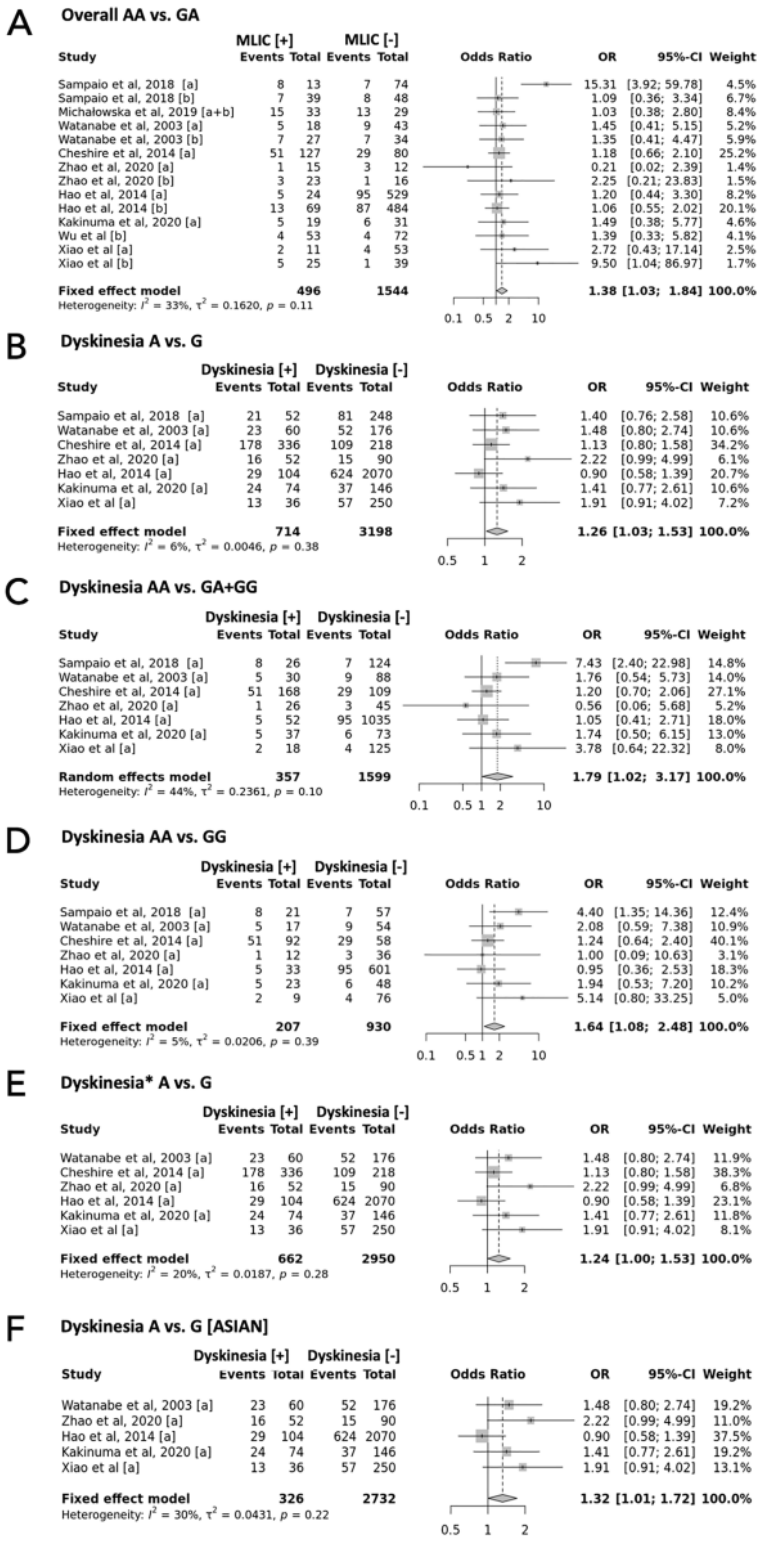

Fig. 3 Forest plot of associations between the *COMT* polymorphism rs4680 with **A** overall susceptibility towards motor levodopa-induced complications (MLIC) in the heterozygous (AA vs. GA) model; **B** levodopa induced-dyskinesia (LID) subtype occurrence in the allelic (A vs. G) model; [47] LID subtype occurrence in the recessive (AA vs. GA + GG) model [47] LID subtype occurrence in the homozygous (AA vs. GG) model; **E** LID subtype occurrence in the allelic (A vs. G) model after exclusion of studies deviating from the Hardy–Weinberg equilibrium; and **F** LID subtype occurrence in the allelic (A vs. G) model in Asians

Fig. 5B), and heterozygous (GG vs. AG, OR = 0.62, 95% CI = 0.40–0.95, $p = 0.027$, Fig. 5C; AG vs. AA, OR = 1.78, 95% CI = 1.29–2.45, $p < 0.0001$, Fig. 5D) models. Subgroup analysis according to MLIC type revealed that both dyskinesia and motor fluctuation were significantly associated with overdominant and heterozygous models (Fig. 5E–H, see Table 2).

DR

Four types of DR polymorphisms (*DRD1* rs4532, *DRD2* rs1800497, *DRD3* rs6280, and *DRD5* rs6283) were examined. Among them, only the *DRD2* of rs1800497 polymorphism was significantly associated with dyskinesia susceptibility (dominant model, AA + GA vs. GG, OR = 1.70, 95% CI = 1.05–2.75, $p = 0.031$, Fig. 5I; overdominant model, GA vs. AA + GG, OR = 1.87, 95% CI = 1.17–3.00, $p = 0.009$, Fig. 5J; and heterozygous model, GA vs. GG, OR = 1.85, 95% CI = 1.12–3.05, $p = 0.016$, Fig. 5K).

Analysis of genes influenced by dopaminergic transmission

BDNF

Only a single BDNF polymorphism, rs6265, was evaluated. And because we are unable to extract a complete number of genotypes from the study by Cheshire et al. [27], analysis was performed only on the dominant model, yielding no significant association between the BDNF rs6265 polymorphisms with MLIC predisposition.

Publication bias and sensitivity analysis

Publication bias was assessed with the Begg's funnel plot (Supplementary Fig. 1) and Egger's regression tests. Publication biases were observed in several analytical models (see Egger's regression tests column in Table 2), which is possibly due to the high variability among different studies. Sensitivity analyses were performed in a group (consisting minimal of 3 studies) with significant results, yet associations detected in pooled analyses remained unchanged, suggesting robustness of the findings (Supplementary Fig. 2–3).

Discussion

Motor levodopa-induced complications (MLIC) both in the forms of LID and MF are common complications of dopamine replacement therapy and significantly impact the quality of life of PD patients [35]. This study aimed to systematically review and meta-analyze the associations between LID and MF with notable polymorphisms of the dopaminergic metabolism and signaling pathways. A recent meta-analysis has shown inconclusive findings in determining the association between genetic variants with LID [13]. In this study, we utilized multiple genetic models to reflect the biology and population genetics of the disorders [36]. Furthermore, this is also the first study that analyzes not just the overall association between the polymorphisms and MLIC, but also the association between variants with either the LID or MF subtypes of MLIC, as previous epidemiologic studies have demonstrated differences between the occurrence patterns of the two MLIC subtypes [37].

The *MAO-B* and *COMT* enzymes have been implicated in dopamine metabolism and bioavailability, and this study confirms that *COMT* and *MAO-B* polymorphisms potentially increase MLIC susceptibility. The *MAO-B* rs1799836 polymorphism was found to be significantly associated with overall MLIC occurrence, with a stronger association for the occurrence of dyskinesia relative to motor fluctuations. Meanwhile, the *COMT* polymorphism rs4680 was significantly associated with the dyskinesia subtype only, but not with motor fluctuation subtype or overall MLIC, with maintained associations in the Asian subgroup on ethnicity analysis. The predominance of the rs4680 association in Asians have been demonstrated in a previous meta-analysis showing increased PD susceptibility in Asians with the rs4680 polymorphism [38]. The rs4633 studies analyzed in this study were all on Asian subjects, wherein we found a disparingly higher risk among Asians with certain models displaying a higher risk for the occurrence of MF. We also found a strong association between the *MAO-B* rs1799836 polymorphism with overall MLIC occurrence, with a stronger association for the occurrence of LID relative to MF.

Dopaminergic receptors, from D1 to D5, play an important role as the natural targets of dopamine agonist in dopamine replacement therapies, with most studies stating D1 and D2 as most important in PD drug response [24, 25]. Interestingly, none of the DR gene polymorphisms analyzed in this study exhibited any meaningful associations with MLIC, except for *DRD2* rs1800497 which was significantly associated with LID susceptibility only. The *DRD2* receptor plays a major role in dopaminergic response to levodopa in PD patients, and the rs1800497 polymorphism is the main variant of the DRD2 gene [23]. However, most association studies have yielded conflicting results, and this study confirms the presence of an association between the *DRD2* rs1800497 with LID susceptibility.

No association was observed between *DAT/SLC6A3* polymorphisms with MLIC susceptibility in this study. In previous studies, the *DAT* rs393795 polymorphism has been associated with time to LID, possibly due to the altered reuptake of dopamine in the synapse [39]. However, more studies are needed to confirm this finding, since the number of studies

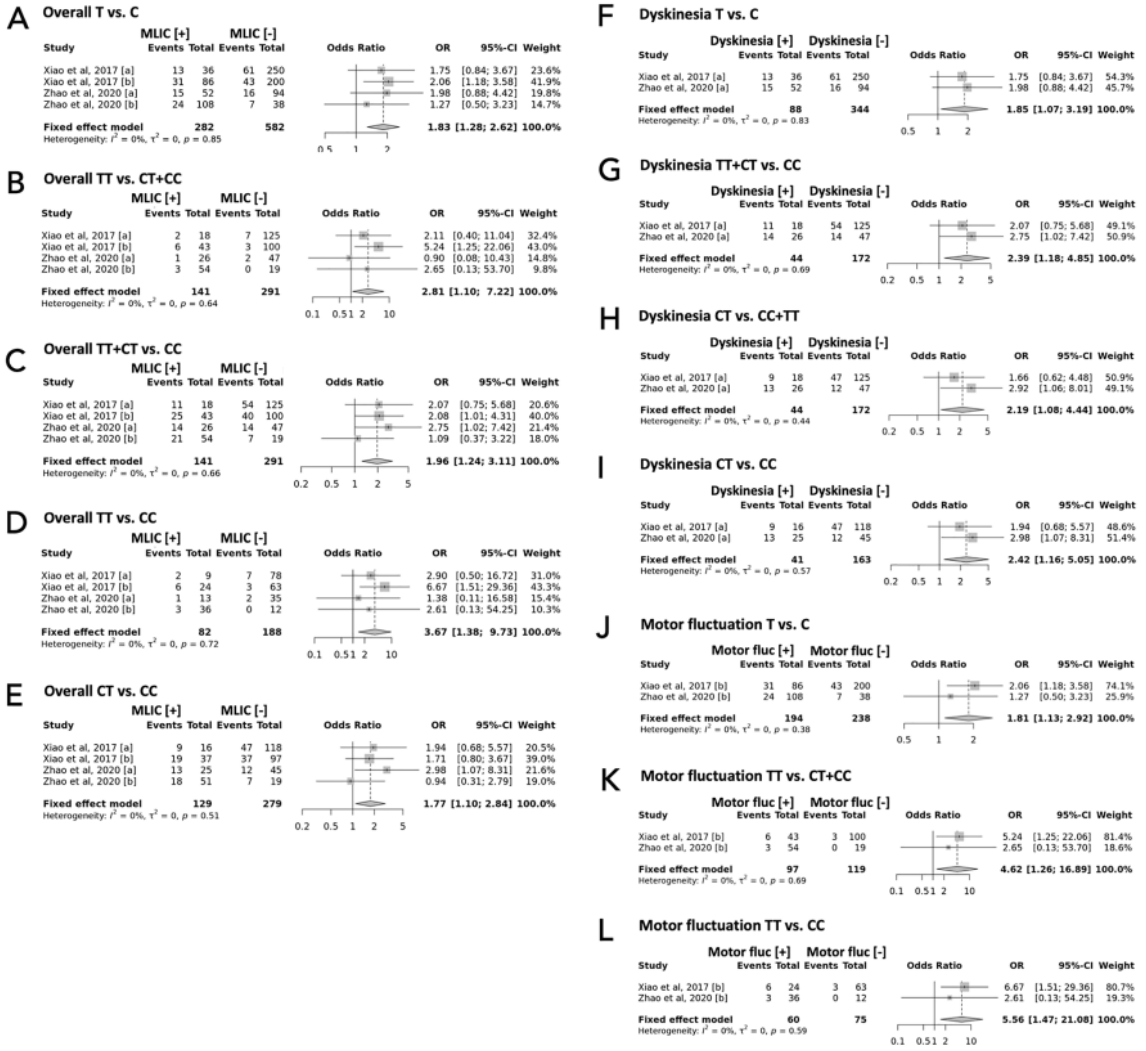

Fig. 4 Forest plot of associations between the *COMT* polymorphism rs4633 with **A** overall susceptibility towards motor levodopa-induced complications (MLIC) in the allelic model (T vs. C); **B** overall MLIC occurrence in the recessive (TT vs. CT + CC) model; **C** overall MLIC occurrence in the dominant (TT + CT vs. CC) model; **D** overall MLIC occurrence in the homozygous (TT vs. CC) model; **E** overall MLIC occurrence in the heterozygous (CT vs. CC) model; **F** levodopa-induced dyskinesia (LID) subtype occurrence in the allelic (T vs. C) model; **G** LID subtype occurrence in the dominant (TT + CT vs. CC) model; **H** LID subtype occurrence in the overdominant (CT vs. CC + TT) model; **I** LID subtype occurrence in the heterozygous (CT vs. CC) model; **J** motor fluctuation (MF) subtype occurrence in the allelic (T vs. C) model; **K** MF subtype occurrence in the recessive (TT vs. CT + CC) model; and **L** MF subtype occurrence in the homozygous model (TT vs. CC). All studies were performed in the Asian population

and patient data extracted for the *DAT/SLC6A3* and *BDNF* polymorphisms were small.

It is interesting to note the difference between the strength of association between genetic variants with either the LID or MF subtypes. This highlights the importance of our approach, wherein subgroup analysis of the LID and MF subtypes needs to be performed in order to acquire a complete understanding of the associations. Overall, the polymorphisms examined in this meta-analysis showed a stronger likelihood of association with LID specifically, although certain genetic models of *COMT* rs4633 showed a remarkably higher risk for MF. There may be several reasons contributing to the differences in the strength of association across subtypes. While the onset of LID and motor

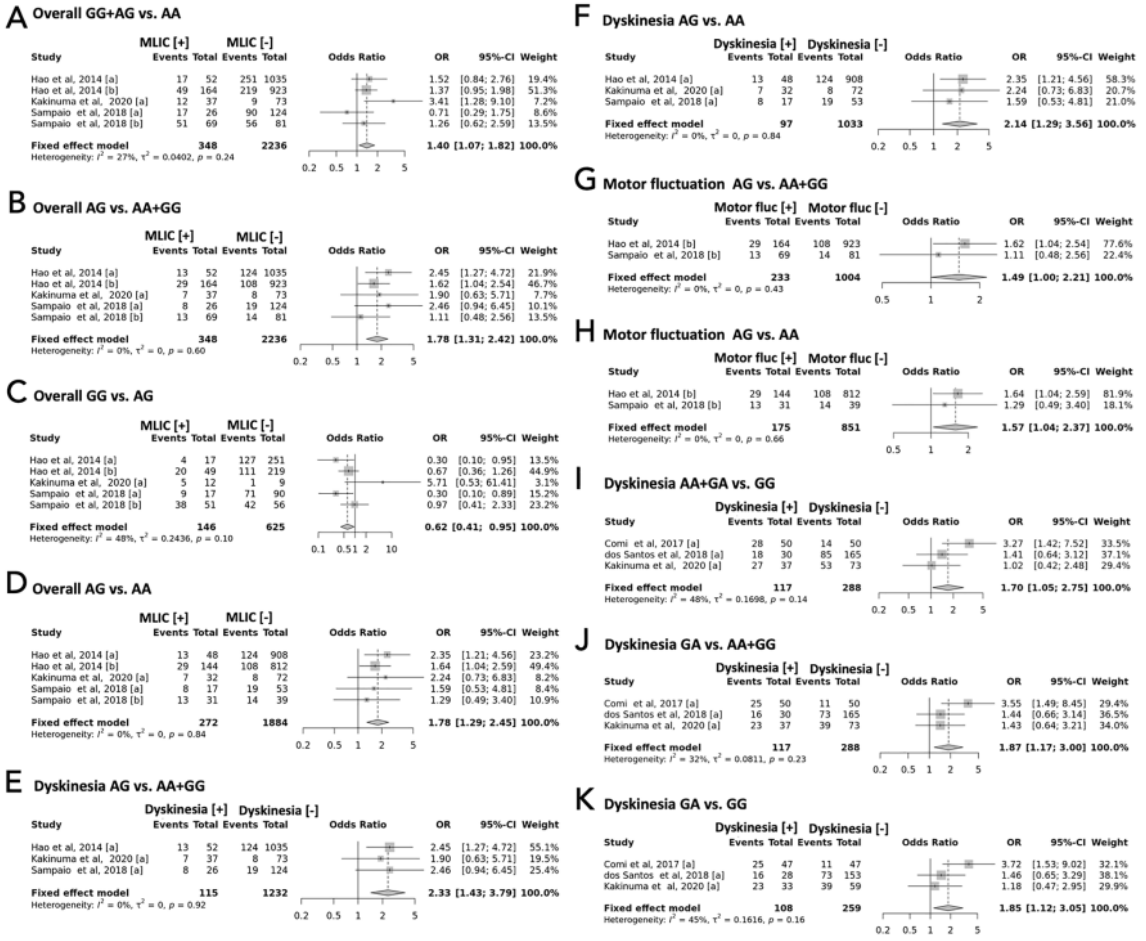

Fig. 5 Forest plot of associations between the *MAO-B* polymorphism rs1799836 and *DRD2* rs1800497 polymorphism with MLIC susceptibility. Association between the *MAO-B* rs1799836 polymorphism with the **A** overall susceptibility towards motor levodopa-induced complications (MLIC) in the dominant (GG + AG vs. AA) model; **B** overall MLIC occurrence in the overdominant (AG vs. AA + GG) model; **C** overall MLIC occurrence in the heterozygous (GG vs. AG) model; **D** overall MLIC occurrence in the heterozygous (AG vs. AA) model; **E** levodopa-induced dyskinesia (LID) subtype occurrence in the overdominant (AG vs. AA + GG) model; **F** LID subtype occurrence in the heterozygous (AG vs. AA) model; **G** motor fluctuation (MF) subtype occurrence in the overdominant (AG vs. AA + GG) model; and **H** MF subtype occurrence in the heterozygous model (AG vs. AA). Association between the *DRD2* rs1800497 polymorphism with **I** LID subtype occurrence in the dominant (AA + GA vs. GG) model; **J** LID subtype occurrence in the overdominant (GA vs. AA + GG) model; and **K** LID subtype occurrence in the heterozygous model (GA vs. GG) model

fluctuations both average between 4 and 6 years, studies have shown that MF is slightly more prevalent relative to LID with a quicker average onset, and that both MF and LID had a quicker onset in familial PD relative to sporadic PD [40]. Secondly, it has been noted that the occurrence of LID is highly influenced by disease severity [41], with a tendency to appear earlier in severe PD and in the more severely affected limbs of asymmetrical parkinsonism [8, 42].

This study has several limitations. Firstly, our analysis did not adjust for the potential variables that can impact the rates of motor fluctuations in dyskinesias. These variables include age, levodopa dosage, prior or concomitant use of other medications such as peripheral decarboxylase inhibitors and dopamine agonists, and duration of disease or treatment [37]. We also did not stratify based on gender, which could have a potential impact on the associations, as previous studies have observed sexual dimorphism in PD pharmacogenetics, wherein male individuals carrying the *MAO-B* G allele treated with higher levodopa doses had an increased risk of MLIC [25], and in studies of *DRD2* polymorphism

that indicate a strong protective effect towards motor complications in males relative to females [43]. And finally, due to the substantial heterogeneity and publication bias found in the analysis, the results should be interpreted with caution as more studies are needed to confirm these findings.

Overall, this study provides significant insight into the role of pharmacogenetics in the manifestation of MLIC and highlights the potential differences in the impact of these polymorphisms across the LID and MF subtypes. And while more studies are required to confirm these findings, it is postulated that early identification of genetic markers of MF of LID susceptibility can be possible, and the exploration of alternative therapeutic approaches can be initiated earlier.

Conclusion

Strong associations were observed between polymorphisms of genes regulating dopamine metabolism with the occurrence of LID and/or MF. The *MAO-B* rs1799836 may be potential for use as a general pharmacogenetic marker of MLIC, while the *COMT* rs4680 and rs4633 may be used as markers of dyskinesia in Asian ethnicities.

Abbreviations BDNF: Brain-derived neurotrophic factor; CI: Confidence interval; COMT: Catechol-O-methyltransferase; DAT: Dopamine transporter; DRD: Dopamine receptor; HWE: Hardy-Weinberg equilibrium; L-Dopa: L-dopamine; LID: Levodopa-induced dyskinesia; MAO: Monoamine oxidase; MF: Motor fluctuations; MLIC: Motor levodopa-induced complications; OR: Odds ratio; PD: Parkinson's disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SLC6: Solute carrier 6; SNP: Single nucleotide polymorphism

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-021-05829-4.

Author contribution GS and ZU conceived, designed, and performed the study. GS, ZU, SF, NR, AKB, and MA analyzed and interpreted the data. GS, ZU, SS, MK, SH, MS, AG, and DF aided data collection and extraction. GS and ZU wrote the main draft and revise the manuscript. NR, AKB, and MA critically reviewed the manuscript. All authors reviewed and finally approved the manuscript.

Declarations

Ethical approval and informed consent None.

Conflict of interest The authors declare no competing interests.

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