



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

Gita Vita Soraya^{1,2} · Zulvikar Syambani Ulhaq^{3,4} · Syifaus Shodry⁵ · Muhammad A'raaf Sirojan Kusuma⁵ · Sarah Herawangsa⁵ · Maharani Oryza Sativa⁵ · Aridin Gustaf⁵ · Dzakky Avecienna Nur Faridwazdi⁵ · Shinta Wulandari Florentia⁶ · Neila Raisa⁶ · Andi Kurnia Bintang² · Muhammad Akbar²

Received: 20 June 2021 / Accepted: 14 December 2021
© Fondazione Società Italiana di Neurologia 2022

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 *SLC6A3/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

Gita Vita Soraya and Zulvikar Syambani Ulhaq have contributed equally to this work and share first authorship.

✉ Zulvikar Syambani Ulhaq
zulhaq@kedokteran.uin-malang.ac.id

Extended author information available on the last page of the article

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

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

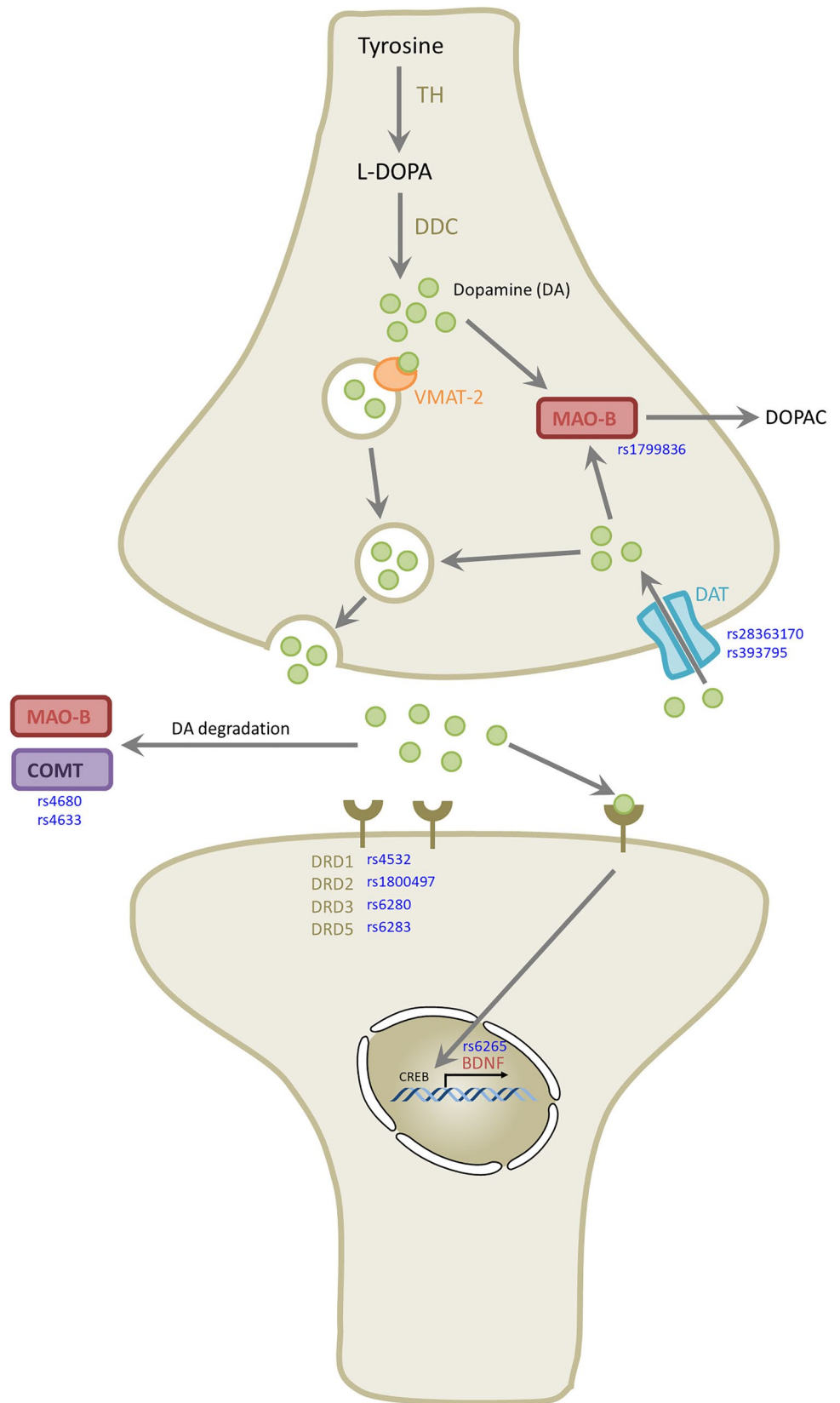
Literature search and data extraction

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-B 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.

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], Hao 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).

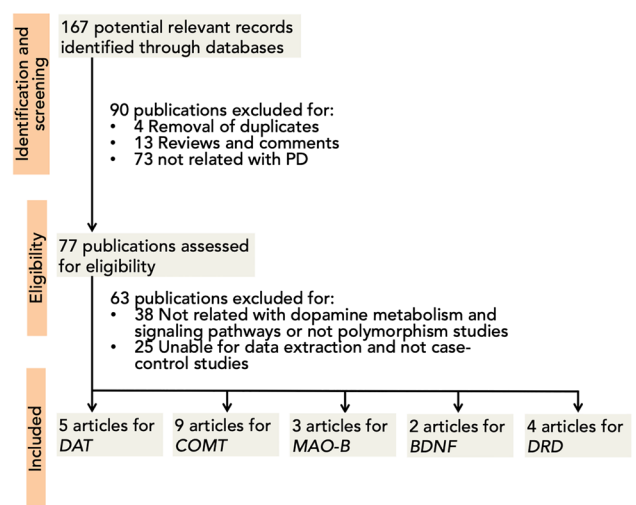


Fig. 2 Flow diagram of the selection process of studies on polymorphisms of dopamine metabolism and signaling pathways in relation to the occurrence of motor levodopa-induced complications (MLIC). The selection process is initiated with identification and screening of relevant studies, followed by eligibility 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

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
<i>SLC6A3/DAT</i>	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
		Purcaro, 2019 [a]	181	72.57	62.4	Retrospective	L-Dopa	NR	7.97	73/117/2	58/105/5	0.000
		Michalowska, 2020 [a + b]	76	65.7	52.6	Retrospective	Levodopa	Ropinirole, priribedil, ropinirole, entacapone, amantadine	8.6	18/22/2	20/14/0	0.130
<i>COMT</i>	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
		Michalowska, 2020 [a + b]	76	65.7	52.6	Retrospective	Levodopa	Ropinirole, priribedil, 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
<i>MAO-B</i>	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)

<i>BDNF</i>	rs6265 G>A	Michalowska, 2020 [a+b]	76	65.7	52.6	Retrospective	Levodopa	Ropinirole, priribedil, ropinirole, entacapone, amantadine	8.6	11/30/1	13/21/0	0.009
<i>DRD1</i>	rs4532 G>A	Cheshire, 2014 [a]	285	63	NR	Retrospective	L-Dopa	NR	≤5	95/48 GG/GA+AA	58/23 GG/GA+AA	ND
		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 inhibi- tor	6.71	3/16/33	18/72/86	0.612
<i>DRD2</i>	rs1800497 G>A	dos Santos, 2019 [b]	228	65	57.4	Retrospective	Levodopa	MAOB inhibitor, COMT inhibi- tor	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
		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 inhibi- tor	7.11	12/16/2	80/73/12	0.397
		dos Santos, 2018 [b]	195	55.81	58.5	Retrospective	Levodopa	MAOB inhibitor, COMT inhibi- tor	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
<i>DRD3</i>	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 inhibi- tor	6.71	12/37/3	31/125/20	0.000
		dos Santos, 2019 [b]	228	65	57.4	Retrospective	Levodopa	MAOB inhibitor, COMT inhibi- tor	6.71	25/87/15	18/75/8	0.000
<i>DRD5</i>	rs6283 T>C	Kakinuma et al., 2020 [a]	110	61	49	Retrospective	Levodopa	NR	11	21/16/0	38/34/1	0.030
		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), <i>p</i> value		
				OR	95% CI	<i>p</i> value	Model		<i>p</i> value	<i>I</i> ² (%)
<i>SLC6A3/DAT</i> rs28363170 10R > 9R**	9R vs. 10R	Overall	4	1.06	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
<i>SLC6A3/DAT</i> rs393795 A > G***	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
	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
<i>COMT</i> rs4680 G > A	AG vs. AA	Overall	2	1.71	0.39–7.40	0.472	Fixed	0.222	32.9	NA
	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
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

COMT rs4680 G > A [Caucasian]

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

Table 2 (continued)

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

Table 2 (continued)

<i>MAO-B</i> 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	0.691	
	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	
<i>BDNF</i> rs6265 G > A <i>DRD5</i> 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)

<i>DRD3</i> 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	
<i>DRD2</i> 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 = 1.96, 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; **C** LID subtype occurrence in the recessive (AA vs. GA + GG) model; **D** 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

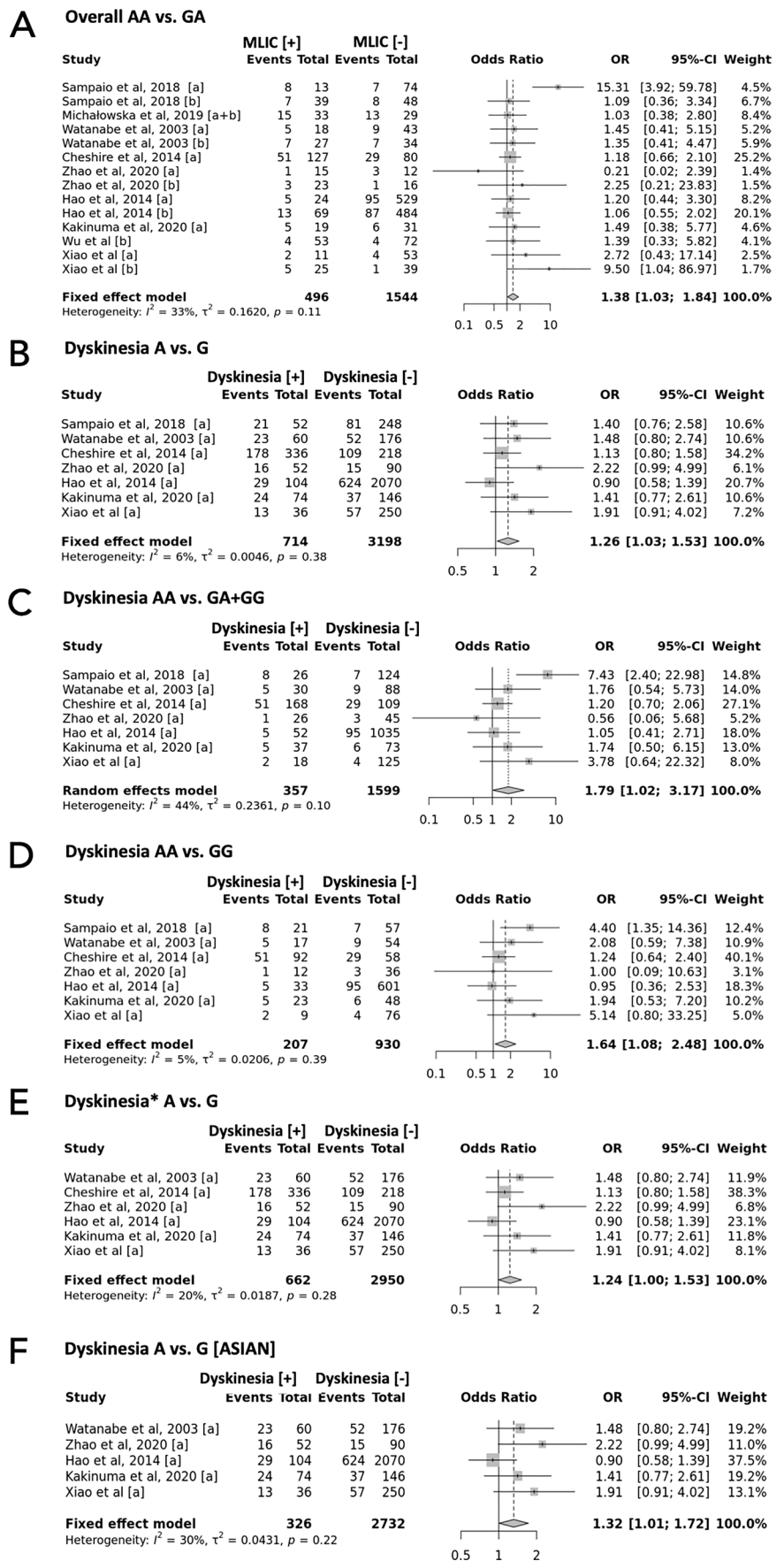


Fig. 5B), and heterozygous (GG vs. AG, OR = 0.62, 95% CI = 0.40–0.95, $p = 0.027$, Fig. 5C; AG vs. AA, OR = 1.78, 95% CI = 1.29–2.45, $p < 0.0001$, Fig. 5D) models. Subgroup analysis according to MLIC type revealed that both dyskinesia and motor fluctuation were significantly associated with overdominant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

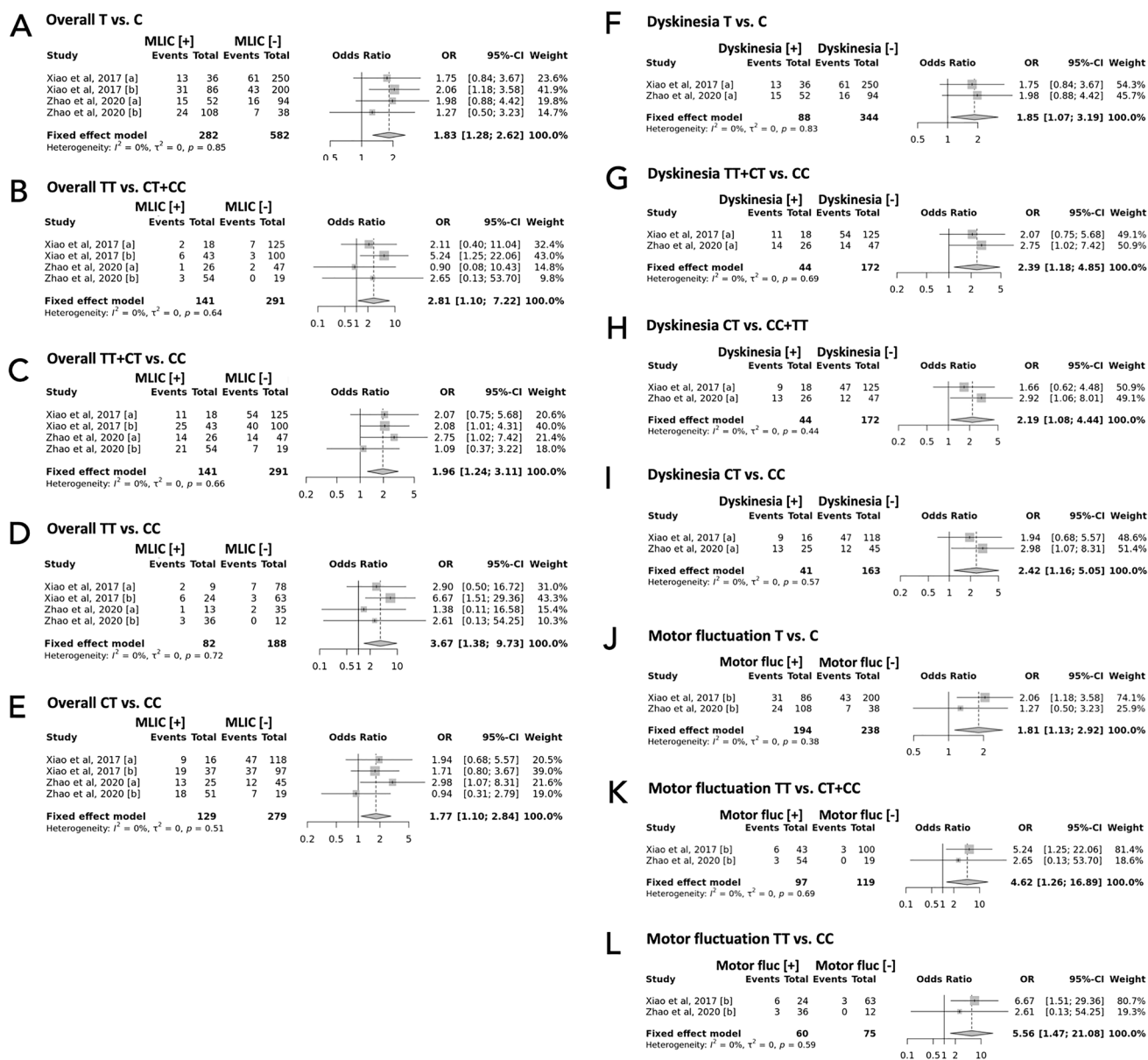


Fig. 4 Forest plot of associations between the *COMT* polymorphism rs4633 with **A** overall susceptibility towards motor levodopa-induced complications (MLIC) in the allelic model (T vs. C); **B** overall MLIC occurrence in the recessive (TT vs. CT+CC) model; **C** overall MLIC occurrence in the dominant (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

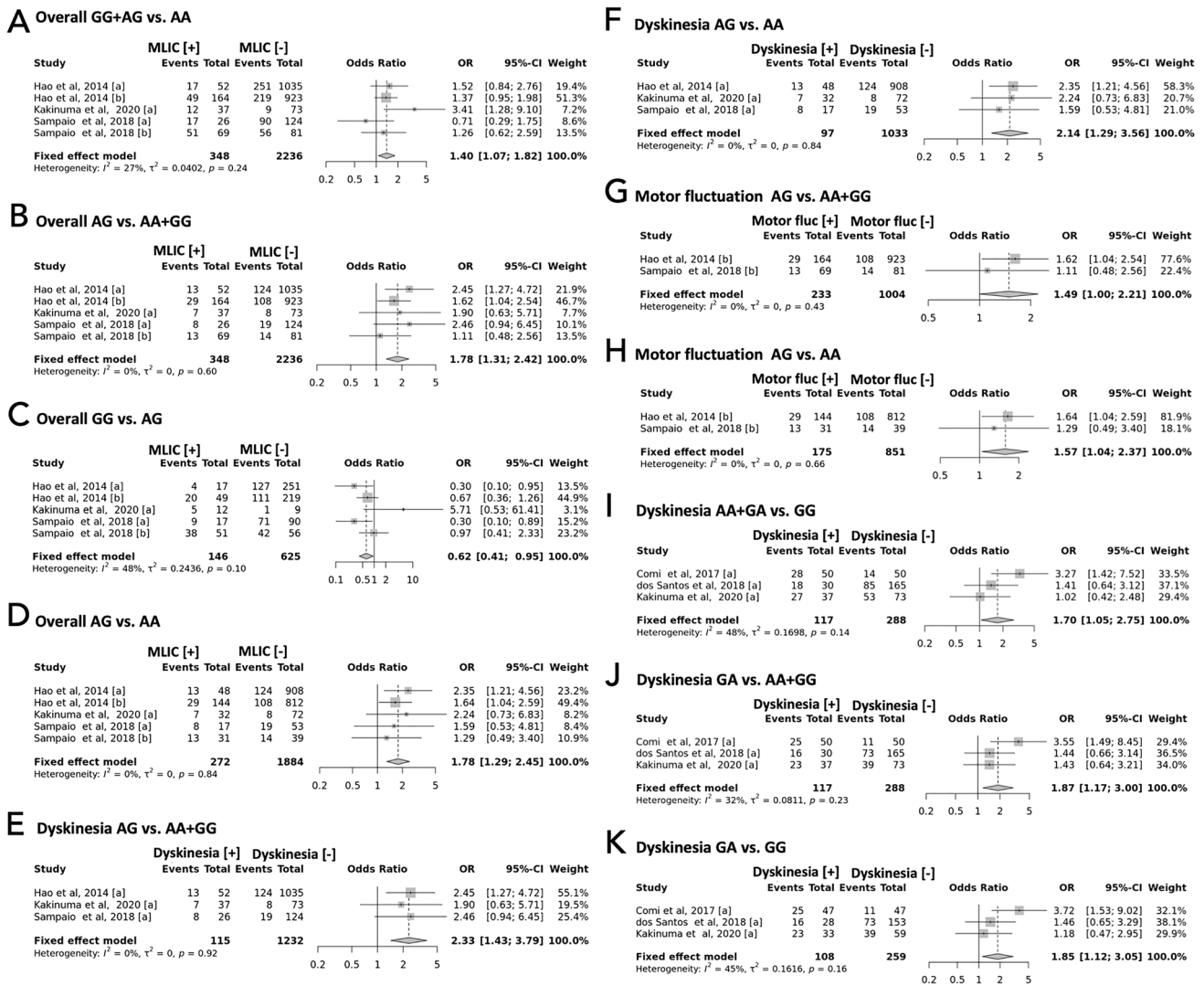


Fig. 5 Forest plot of associations between the *MAO-B* polymorphism rs1799836 and *DRD2* rs1800497 polymorphism with MLIC susceptibility. Association between the *MAO-B* rs1799836 polymorphism with the **A** overall susceptibility towards motor levodopa-induced complications (MLIC) in the dominant (GG+AG 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.

References

- Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J et al (2017) Parkinson disease. *Nat Rev Dis Primers* 3(1):1–21
- Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC et al (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 17(11):939–953
- Moore DJ, West AB, Dawson VL, Dawson TM (2005) Molecular pathophysiology of Parkinson's disease. *Annu Rev Neurosci* 28(1):57–87
- Schulz-Schaeffer WJ (2010) The synaptic pathology of α -synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol* 120(2):131–143
- Bergman H, Deuschl G (2002) Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. *Mov Disord* 17(S3):S28–40
- Lindenbach D, Bishop C (2013) Critical involvement of the motor cortex in the pathophysiology and treatment of Parkinson's disease. *Neurosci Biobehav Rev* 37(10):2737–2750
- Poewe W, Antonini A, Zijlmans JC, Burkhard PR, Vingerhoets F (2010) Levodopa in the treatment of Parkinson's disease: an old drug still going strong. *Clin Interv Aging* 5:229
- Ahlskog JE, Muentner MD (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 16(3):448–458
- Kalinderi K, Papaliagkas V, Fidani L (2019) Pharmacogenetics and levodopa induced motor complications. *Int J Neurosci* 129(4):384–392
- Kalinderi K, Fidani L, Katsarou Z, Bostantjopoulou S (2011) Pharmacological treatment and the prospect of pharmacogenetics in Parkinson's disease. *Int J Clin Pract* 65(12):1289–1294
- Hisahara S, Shimohama S (2011) Dopamine receptors and Parkinson's disease. *Int J Med Chem*: 403039
- Hyman C, Hofer M, Barde Y-A, Juhasz M, Yancopoulos GD, Squinto SP et al (1991) BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* 350(6315):230–232
- Falla M, Di Fonzo A, Hicks AA, Pramstaller PP, Fabbrini G (2021) Genetic variants in levodopa-induced dyskinesia (LID): a systematic review and meta-analysis. *Parkinsonism Relat Disord* 84:52–60
- Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7):e1000097
- Ulhaq ZS, Soraya GV, Milliana A, Tse WKF (2021) Association between GPER gene polymorphisms and GPER expression levels with cancer predisposition and progression. *Heliyon* 7(3):e06428
- Ulhaq ZS, Soraya GV, Budu Wulandari LR (2020) The role of IL-6–174 G/C polymorphism and intraocular IL-6 levels in the pathogenesis of ocular diseases: a systematic review and meta-analysis. *Sci Rep* 10(1):1–20
- Ulhaq ZS, Soraya GV (2020) Anti-IL-6 receptor antibody treatment for severe COVID-19 and the potential implication of IL-6 gene polymorphisms in novel coronavirus pneumonia. *Med Clin* 155(12):548
- Ulhaq Z, Soraya G (2020) Aqueous humor interleukin-6 levels in primary open-angle glaucoma (POAG): a systematic review and meta-analysis. *Arch Soc Esp Ophthalmol (Engl Ed)* 95(7):315–321
- Soraya GV, Ulhaq ZS (2020) Crucial laboratory parameters in COVID-19 diagnosis and prognosis: an updated meta-analysis. *Med Clin (Barc)* 155(4):143–151
- Ulhaq Z (2020) Chemokine IL-8 level in aqueous humor of open-angle glaucoma: a meta-analysis. *Arch Soc Esp Ophthalmol (Engl Ed)* 95(3):114–119
- Purcaro C, Vanacore N, Moret F, Di Battista ME, Rubino A, Pierandrei S et al (2019) DAT gene polymorphisms

- (rs28363170, rs393795) and levodopa-induced dyskinesias in Parkinson's disease. *Neurosci Lett* 690:83–88
22. Kakinuma S, Beppu M, Sawai S, Nakayama A, Hirano S, Yamanaka Y et al (2020) Monoamine oxidase B rs1799836 G allele polymorphism is a risk factor for early development of levodopa-induced dyskinesia in Parkinson's disease. *eNeurologicalSci* 19:100239
 23. Dos Santos EUD, Sampaio TF, Tenório dos Santos AD, Bezerra Leite FC, da Silva RC, Crovella S et al (2019) The influence of SLC 6A3 and DRD 2 polymorphisms on levodopa-therapy in patients with sporadic Parkinson's disease. *J Pharm Pharmacol* 71(2):206–12
 24. Michałowska M, Chalimoniuk M, Jówko E, Przybylska I, Langfort J, Toczyłowska B et al (2020) Gene polymorphisms and motor levodopa-induced complications in Parkinson's disease. *Brain Behav* 10(3):e01537
 25. Sampaio TF, Dos Santos EUD, de Lima GDC, Dos Anjos RSG, da Silva RC, Asano AGC et al (2018) MAO-B and COMT genetic variations associated with levodopa treatment response in patients with Parkinson's disease. *J Clin Pharmacol* 58(7):920–926
 26. Watanabe M, Harada S, Nakamura T, Ohkoshi N, Yoshizawa K, Hayashi A et al (2003) Association between catechol-O-methyltransferase gene polymorphisms and wearing-off and dyskinesia in Parkinson's disease. *Neuropsychobiology* 48(4):190–193
 27. Cheshire P, Bertram K, Ling H, O'sullivan SS, Halliday G, McLean C et al (2014) Influence of single nucleotide polymorphisms in COMT, MAO-A and BDNF genes on dyskinesias and levodopa use in Parkinson's disease. *Neurodegener Dis* 13(1):24–28
 28. Zhao C, Wang Y, Zhang B, Yue Y, Zhang J (2020) Genetic variations in catechol-o-methyltransferase gene are associated with levodopa response variability in Chinese patients with Parkinson's disease. *Sci Rep* 10(1):1–8
 29. Hao H, Shao M, An J, Chen C, Feng X, Xie S et al (2014) Association of catechol-O-methyltransferase and monoamine oxidase B gene polymorphisms with motor complications in Parkinson's disease in a Chinese population. *Parkinsonism Relat Disord* 20(10):1041–1045
 30. Wu H, Dong F, Wang Y, Xiao Q, Yang Q, Zhao J et al (2014) Catechol-O-methyltransferase Val158Met polymorphism: modulation of wearing-off susceptibility in a Chinese cohort of Parkinson's disease. *Parkinsonism Relat Disord* 20(10):1094–1096
 31. Qian Y, Liu J, Xu S, Yang X, Xiao Q (2017) Roles of functional catechol-O-methyltransferase genotypes in Chinese patients with Parkinson's disease. *Transl Neurodegener* 6(1):1–11
 32. Comi C, Ferrari M, Marino F, Magistrelli L, Cantello R, Riboldazzi G et al (2017) Polymorphisms of dopamine receptor genes and risk of l-dopa-induced dyskinesia in Parkinson's disease. *Int J Mol Sci* 18(2):242
 33. Dos Santos EUD, Duarte EBC, Miranda LMR, Asano AGC, Asano NMJ, Maia M de MD et al (2019) Influence of DRD1 and DRD3 polymorphisms in the occurrence of motor effects in patients with sporadic Parkinson's disease. *Neuromol Med* 21(3):295–302
 34. Wang J, Liu Z-L, Chen B (2001) Dopamine D5 receptor gene polymorphism and the risk of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Neurosci Lett* 308(1):21–24
 35. Perez-Lloret S, Negre-Page L, Damier P, Delval A, Derkinderen P, Destée A et al (2017) L-DOPA-induced dyskinesias, motor fluctuations and health-related quality of life: the COPARK survey. *Eur J Neurol* 24(12):1532–1538
 36. Thakkinstian A, McElduff P, D'Este C, Duffy D, Attia J (2005) A method for meta-analysis of molecular association studies. *Stat Med* 24(9):1291–1306
 37. Schrag A, Quinn N (2000) Dyskinesias and motor fluctuations in Parkinson's disease: a community-based study. *Brain* 123(11):2297–2305
 38. Lechun L, Yu S, Pengling H, Changqi H (2013) The COMT Val158Met polymorphism as an associated risk factor for Parkinson's disease in Asian rather than Caucasian populations. *Neurol India* 61(1):12
 39. Kaplan N, Vituri A, Korczyn AD, Cohen OS, Inzelberg R, Yahaalom G et al (2014) Sequence variants in SLC6A3, DRD2, and BDNF genes and time to levodopa-induced dyskinesias in Parkinson's disease. *J Mol Neurosci* 53(2):183–188
 40. Papapetropoulos S, Argyriou A, Ellul J, Chroni E (2004) Comparison of motor fluctuations and L-dopa-induced dyskinesias in patients with familial and sporadic Parkinson's disease. *Eur J Neurol* 11(2):115–119
 41. Nutt JG (2008) Pharmacokinetics and pharmacodynamics of levodopa. *Mov Disord* 23(S3):S580–S584
 42. Mones R, Elizan T, Siegel G (1971) Analysis of L-dopa induced dyskinesias in 51 patients with parkinsonism. *J Neurol Neurosurg Psychiatry* 34(6):668–673
 43. Zappia M, Annesi G, Nicoletti G, Arabia G, Annesi F, Messina D et al (2005) Sex differences in clinical and genetic determinants of levodopa peak-dose dyskinesias in Parkinson disease: an exploratory study. *Arch Neurol* 62(4):601–605

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Gita Vita Soraya^{1,2} · Zulvikar Syambani Ulhaq^{3,4}  · Syifaus Shodry⁵ · Muhammad A'raaf Sirojan Kusuma⁵ · Sarah Herawangsa⁵ · Maharani Oryza Sativa⁵ · Aridin Gustaf⁵ · Dzakky Avecienna Nur Faridwazdi⁵ · Shinta Wulandari Florentia⁶ · Neila Raisa⁶ · Andi Kurnia Bintang² · Muhammad Akbar²

¹ Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

² Department of Neurology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

³ Department of Biochemistry, Faculty of Medicine and Health Sciences, Maulana Malik Ibrahim State Islamic University of Malang, Malang, Indonesia

⁴ National Research and Innovation Agency (BRIN), Jakarta, Indonesia

⁵ Undergraduate Medical Program, Faculty of Medicine and Health Sciences, Maulana Malik Ibrahim State Islamic University of Malang, Malang, Indonesia

⁶ Department of Neurology, Faculty of Medicine, Brawijaya University, Malang, Indonesia