



# Pharmacogenetics of antiparkinsonian drug treatment: a systematic review

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Pharmacotherapy is the mainstay in the treatment of Parkinson's disease and the armamentarium of drugs available for the therapy of this disease is still expanding. Anti-Parkinson's disease drugs are effective in reducing the physical symptoms, such as hypokinesia, bradykinesia, rigidity and tremor. However, there is a large interindividual variability in response to anti-Parkinson's disease drugs with respect to both drug efficacy and toxicity. It is thought that genetic variability in genes encoding drug-metabolizing enzymes, drug receptors and proteins involved in pathway signaling is an important factor in determining interindividual variability in drug response. Pharmacogenetics aims at identifying genetic markers associated with drug response. Ideally, knowledge of these genetic markers will enable us to predict an individual's drug response in terms of both efficacy and toxicity. The role of pharmacogenetics in the treatment of Parkinson's disease is relatively unexplored. Therefore, we aim to present a systematic review of the published pharmacogenetic studies in Parkinson's disease and to describe polymorphic genes of interest for future research.

Parkinson's disease (PD) is characterized by bradykinesia, rigidity and tremor, and is the result of degeneration of dopaminergic neurones in the substantia nigra pars compacta. Despite knowledge of genetics in familial PD, the knowledge of the common, late-onset form of PD remains limited. The ultimate goal, prevention of the disease, is still far away. The pharmacological and the nonpharmacological symptomatic treatment is therefore still the only choice.

The motor symptoms of PD can be controlled pharmacologically by increasing dopaminergic neurotransmission. This is achieved by treatment with levodopa, which is taken up by dopaminergic terminals and converted into dopamine by 3,4-dihydroxyphenylalanine (DOPA) decarboxylase. Alternatively, dopamine agonists are employed that directly stimulate the postsynaptic dopamine receptors acting relatively selectively upon the dopamine D2-like receptors (D2, D3 or D4) over the D1-like receptors (D1 or D5).

Use of both levodopa and the direct-acting dopamine agonists are associated with the development of motor complications such as fluctuations in response to medication. Psychotic side-effects, such as hallucinations, and excessive daytime sleepiness also occur. However, there is a large interindividual variability in response to anti-PD drugs both with respect to drug efficacy and toxicity. It is thought that genetic variability in genes encoding drug-metabolizing enzymes, drug receptors and

proteins involved in pathway signaling is an important factor in determining interindividual variability in drug response.

Indeed, several investigators have studied genetic variability with regard to drug response in PD. Until now, one review on pharmacogenetics of PD has been published, but this provides only a concise summary on drug-related response and complications in PD [1]. Therefore, we conducted a systematic literature search and summarized published studies that are reported in the current review.

## Search criteria

We used the following methodology. PubMed was searched with the MeSH® headings 'Parkinson disease/drug therapy/\*genetics' [101]. Also the combination of the keywords 'Parkinson's disease' and 'pharmacogenetics', 'alleles', 'genotype', 'polymorphism', 'dyskinesia', 'psychosis', 'hallucinations', 'sleep attacks', 'drug response', or 'wearing off' was used. For identification of articles not indexed in PubMed, a search in Embase was performed with the keywords 'pharmacogenetics' combined with 'Parkinson' [102]. Articles collected until July 2006, published in English, that described an association study in humans on anti-PD drug effect or side-effect and a genetic polymorphism were included. All references in selected articles were screened and included when of interest. A cited reference search in Web of Science [103] was done in order to identify missing

articles. Finally, we have checked two genetics databases for additional published articles [104,105]. We did not include criteria for the quality of the selected articles, as the total number of articles published on the subject is relatively low. Case-reports were not included.

#### Search results

We identified 29 articles studying pharmacogenetics in PD, of which two articles were excluded. One was excluded because cases were only compared with healthy controls [2]; the other study was excluded because the different genotypes were not statistically compared [3]. We include one article that was published as a letter [4]. Of the remaining 27 studies, most studies used a case-control design ( $n = 18$ ; 67%), others ( $n = 4$ ; 15%) used data from randomized clinical trials or applied a levodopa challenge test ( $n = 4$ ; 15%). One study was a prospective crossover trial (4%). The characteristics of these studies are summarized in Table 1.

#### Candidate genes

The candidate genes under study might be classified in different ways. First, a classification based on pharmacokinetic and pharmacodynamic principles might be made, that is, polymorphisms in drug-metabolizing enzymes versus polymorphisms in receptors and in proteins involved in drug response. However, until now no pharmacokinetic polymorphism (e.g., a cytochrome P450 polymorphism) has been studied in patients with PD in relation to drug response. Another way to classify candidate genes might be to distinguish direct and indirect genes, based on the degree with which the protein product of the gene actually interacts with the drug in question. For example, the catechol-*O*-methyl transferase (*COMT*) gene would be considered direct for levodopa and COMT inhibitor response. In contrast, apolipoprotein E (*APOE*) and cholecystokinin (*CCK*) genes would be considered indirect for levodopa response. Selecting direct candidate genes over indirect ones will minimize false-positive results and increase the likelihood of identifying a true association. We have used this concept, introduced by Masellis and colleagues, in the selection of candidate genes under study [5].

#### Dopamine receptor polymorphisms

##### Dopamine receptor D1

Dopamine receptor (*DRD1*) is involved in the dopaminergic response to exogenous levodopa in patients with PD. Messenger RNA for

*DRD1* is most abundant in caudate, nucleus accumbens with little or no messenger (m)RNA detectable in substantia nigra [6]. Polymorphism of the genes coding for this receptor, located on chromosome 5, could therefore be implicated in the genetic susceptibility to variability in efficacy and adverse effects of anti-PD treatment. Furthermore, *DRD1* modulates dopamine receptor D2-mediated events [7]. Of interest are the -48A>G (D1.1; B1/B2) polymorphism in the 5' untranslated region (UTR), the 1403T>C (D1.7; C1/C2) polymorphism in the 3' UTR and the Ser421Ser polymorphism [8]. The gene coding for *DRD1* is considered to be a direct gene for levodopa therapy (actually for dopamine) and for some dopamine agonists.

##### Dopamine receptor D2

The *DRD2* gene is located on chromosome 11 and encodes a long (D2L) and short (D2S) isoform with distinct functions. D2L acts mainly at postsynaptic sites and D2S serves presynaptic autoreceptor functions. The *DRD2* gene is mainly expressed in the dorsal regions of the striatum (both the putamen and the caudate nucleus) and also in the ventral striatum and the globus pallidus [9,10]. Signaling through *DRD2* receptors governs physiologic functions related to locomotion and drug abuse [11]. Several polymorphisms in the *DRD2* gene are known. It has been shown that individuals carrying the A1 allele of the TaqIA polymorphism have a low striatal *DRD2* receptor density [12] and may affect substrate binding specificity [13]. Recently, it has been shown that the TaqIA restriction fragment length polymorphism, a C>T base change, is located in a novel kinase gene, named ankyrin repeat and kinase domain containing 1 (*ANKK1*), which is located downstream of the *DRD2* gene. This polymorphism may affect substrate binding specificity [13]. The TaqIA polymorphism was implicated in smoking behavior and alcoholism, but this association remains controversial.

Furthermore, the *DRD2* gene has a -141C insertion (ins)/deletion (del) polymorphism in the promoter region resulting in an increased mRNA expression for the -141C ins-allele [14], and a higher striatal *DRD2* density [15]. An intronic CA dinucleotide short tandem repeat (CASTR) polymorphism in a noncoding region has been studied in relation to response to anti-PD drugs [16].

The gene coding for *DRD2* is considered to be a direct gene for levodopa therapy and dopamine agonists.

Table 1. Pharmacogenetic studies in Parkinson's disease.

First author	Year published	Race	Study design	Number of patients	(Adverse) effect studied	Gene under study	Polymorphism (allele frequency in controls)	Significant association?	Ref.
De la Fuente-Fernández	1999	NS (Spanish)	Case-control, not matched	33 cases, 72 controls	Hallucinations	APOE	E4 allele (?)	Yes, OR: 8.57 (95%CI: 2.25–32.59)	[58]
Fujii	1999	Japanese (Mongoloid)	Case-control	23 cases, 93 controls	Hallucinations	CCK	-196G>A (?), -45C>T (T: 27%), 1270C>G (?), 6662C>T (?)	No	[56]
Oliveri	1999	NS (Italian)	Case-control, matched	49 each group	Levodopa-induced dyskinesias	DRD1	-48G>A (G:36%); 1403T>C (T: 34%); Ser421Ser (G: 7.1%)	No	[49]
						DRD2	CAn-STR (13: 20%; 14: 11%; 15: 55%; 16: 14%)	Yes, OR: 0.28 for patient carrying at least 1 of 13 or 14 allele	
Chong	2000	Caucasian (Canadian and American)	Retrospective cohort	24 patients	Tolcapone respons (UPDRS in time)	COMT	Val158Met (?)	No	[48]
Inzelberg	2000	NS (Israeli)	Case-control, not matched	29 cases, 37 controls	Hallucinations	APOE	E4 (E4: 33%)	No	[4]
Makoff	2000	Caucasian (English)	Case-control, matched	84 cases, 71 controls	Hallucinations	DRD2	-141C ins/del (del: 13%), TaqIA (T: 17%)	Yes, late hallucinators have OR: 3.15 (95%CI: 1.10–9.15) for TaqIA C/C genotype	[53]
Goetz	2001	Caucasian (American)	Case-control, matched	44 each group	Chronic visual hallucinations	DRD3	Ser9Gly (Gly: 35%)	No	[51]
						DRD1	-48A>G (G: 35%)	No	
						DRD2	Ser311Cys (2.3%)	No	

5-HTT: Serotonin Transporter; APOE: Apolipoprotein E; bp: Base pair; CAn-STR: CA dinucleotide short tandem repeat; CCK: Cholecystokinin; CCKAR: Cholecystokinin receptor A; CCKBR: Cholecystokinin receptor B; CI: Confidence interval; COMT: Catechol-O-methyltransferase; DAT: Dopamine transporter; del: Deletion; DRD: Dopamine receptor; HH: High level of activity; HL: Intermediate level of activity; HR: Hazard ratio; ins: Insertion; LL: Low level of activity; MAOB: Mono-amine oxidase B; NS: Not stated; OPRM1: Opioid receptor  $\mu$ -1; OR: Odds ratio; p: P-value; UPDRS: Unified Parkinson's Disease Rating Scale; VNTR: Variable number of tandem repeats.

Table 1. Pharmacogenetic studies in Parkinson's disease (cont.).

First author	Year published	Race	Study design	Number of patients	(Adverse) effect studied	Gene under study	Polymorphism (allele frequency in controls)	Significant association?	Ref.
Goetz (cont.)									
						DRD3	Ser9Gly (2:30%)	Yes, significant difference in allele frequency (p = 0.047)	
						DRD4	48-bp VNTR (2+3+4+5: 77%; 6+7+8: 23%)	No	
						APOE	E4 allele (E4: 15%)	No	
Lee	2001	Korean	Levodopa challenge test	73 patients	Response (time to peak response; duration and magnitude of response)	COMT	1947A>G (A: 27% = low)	No	[44]
Wang	2001	NS (Chinese)	Case-control, matched	50 each group	Levodopa motor fluctuations	DRD5	978T>C (C: 47%)	No	[25]
Wang	2001	NS (Chinese)	Case-control, matched	40 each group	Motor fluctuations	DRD2	TaqIA (A1: 30%)	Yes, OR: 4.33 (95%CI: 1.27–14.78) in patients carrying A1/A1 genotype	[12]
						DRD3	Ser9Gly (2: 27%), MspI (2: 37%)	No	
Kaiser	2003	Caucasian (German)	Case-control and retrospective cohort	Dyskinesia: 79 cases, 93 controls; psychosis: 48 cases, 126 controls; on-off 93 cases; 80 controls. Overall 183 patients	Dyskinesia, psychosis, on-off/wearing-off (case-control). Time to adverse event (cohort)	DRD2	TaqIA, TaqIB, TaqID, Val96Ala (0%), Pro310Ser, Ser311Cys (3.6%), -241A>G, -141Cins/del	No	[26]

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Table 1. Pharmacogenetic studies in Parkinson's disease (cont.).

First author	Year published	Race	Study design	Number of patients	(Adverse) effect studied	Gene under study	Polymorphism (allele frequency in controls)	Significant association?	Ref.
Kaiser (cont.)						DRD3	Ser9Gly, MspI	No	
						DRD4	48-bp VNTR, 12-bp VNTR, 13-bp del	No	
						DAT	40-bp VNTR	Yes, OR: 2.6 (95% CI: 1.3–5.3) for developing psychosis and OR: 2.5 (95% CI: 1.3–4.7) for developing dyskinesia in patients carrying 9-copy 40-bp allele	
Wang	2003	NS (Chinese)	Case-control, matched	45 each group	Visual hallucinations	CCK	-45C>T (T: 19%)	Yes, OR: 4.4 (95%CI: 1.7–11.9) for TT/TC genotype	[55]
Bialecka	2004	Polish	Case-control	Group 1: 53 patients, Group 2: 42 patients	Daily levodopa dose during first 5 years	CCKAR	779T>C (C: 25%)	No	
						CCKBR	1550G>A (A: 3%)	No	
						MAOB	A>G Tsp45I (G: 44%)	No	[46]
Contini	2004	Italian	Levodopa challenge test	36 patients	Latency, duration, magnitude of motor effect; presence of dyskinesias	COMT	Val158Met (L: 44%)	No	
						DAT	40-bp VNTR (9:36%; 10:64%)	No	[43]

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Table 1. Pharmacogenetic studies in Parkinson's disease (cont.).

First author	Year published	Race	Study design	Number of patients	(Adverse) effect studied	Gene under study	Polymorphism (allele frequency in controls)	Significant association?	Ref.
Goldman	2004	White	Case-control, matched	44 each group	Hallucinations	CCK	-45C>T (T: 9%)	No	[57]
Paus	2004	Caucasian (German)	Case-control, matched	102 each group	Sleep attacks	CCKAR	779T>C (C: 13%)	No	[60]
						CCKBR	1550G>A (A: 7%)	No	
						DRD2	-141C ins/del (del: 12%), TaqIA (?)	No	
						DRD3	Ser9Gly (Gly: 32%)	No	
Rissling	2004	NS (German)	Case-control, matched	137 each group	Sleep attacks	DRD4	48-bp VNTR (2+3+4: 78%; 5+6+7: 22%)	Yes, sleep attacks without warnings signs and *2 allele (p < 0.0001)	[61]
						5-HTT	5-HTTLPR (44-bp del/ins) (del: 42%)	No	
						DRD2	TaqIA (1: 34%)	Yes, OR: 5.24 (95%CI: 1.65–16.59) for homozygous carriers of allele 2	
Frauscher	2004	Caucasian	Case-control	11 cases, 35 controls	Daytime sleepiness	DRD3	Ser9Gly (1: 29%)	No	[62]
						DRD4	120-bp tandem (429-bp: 84%; 549-bp: 16%)	No	
						COMT	Val158Met (L: 53%)	Yes, LL+LH 40% vs HH 9.1% (p = 0.039)	
Wang	2004	NS (Chinese)	Case-control, matched	45 each group	Hallucinations	DRD2	TaqIA (1: 4.7%)	No	[52]

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Table 1. Pharmacogenetic studies in Parkinson's disease (cont.).

First author	Year published	Race	Study design	Number of patients	(Adverse) effect studied	Gene under study	Polymorphism (allele frequency in controls)	Significant association?	Ref.
Wang (cont.)									
						DRD3	Ser9Gly (2: 27%), Mspl (2: 37%)	No	
						DRD5	978T>C (C: 48%)	No	
						DAT	40-bp VNTR (9:4%; 10:93%; 11:2%)	No	
Camicioli	2005	NS (Canadian)	Retrospective cohort	47 patients	Time to onset of hallucinations	COMT	Val158Met (L: 50%)	No	[54]
Contini	2005	Italian	Levodopa challenge test	104 patients	Latency, duration, magnitude of motor effect and dyskinesias	APOE	E4 (E4: 26%)	No	[45]
						COMT	Val158Met (A: 49%)	No	
Rissling	2005	Caucasian (German)	Case-control	132 each group	Sleep attacks	HCRT	-909T>C, -22C>T, -20C>A	Yes, OR: for homozygous -909T allele carriers was 2.81 (95%CI: 1.09–7.25)	[64]
Tan	2005	NS (Singapore)	Prospective cohort	39 patients	UPDRS	COMT	Val158Met (L: 33%)	Yes, improvement in motor score with COMT L allele (p = 0.004)	[47]

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Table 1. Pharmacogenetic studies in Parkinson's disease (cont.).

First author	Year published	Race	Study design	Number of patients	(Adverse) effect studied	Gene under study	Polymorphism (allele frequency in controls)	Significant association?	Ref.
Zappia	2005	Caucasian (Italian)	Case-control after Levodopa challenge test	105 cases, 110 controls	Peak-dose dyskinesias	DRD2	CAn-STR (13, 14+: 48%; 13, 14-: 52%)	Yes, OR: 0.45 (95%CI: 0.26–0.79) for carriers of 13, 14+ genotype, but only in men	[16]
Feldman	2006	NS (Israeli)	Retrospective cohort	87 patients	Time to onset of psychosis	APOE	E4 allele (24%)	Yes, HR: 3.24 (95%CI: 1.62–6.46) for carriers of E4 allele	[59]
Strong	2006	Most caucasian	Case-control and retrospective cohort	29 cases, 29 controls; 30 cases, 62 controls (smoking subset).	Early dyskinesias (cases) versus late onset dyskinesias (controls)	OPRM1	A118G (G:11%)	Yes, OR: 2.8 (95%CI: 0.97–4.0) for carriers of G allele	[37]
Rissling	2006	NS	Case-control	121 cases, 119 controls	Sudden onset of sleep	DRD2	CAn-STR (13, 14+: 12%; 13, 14-: 88%).	Yes, OR: 3.4 (95%CI: 1.1–10.4) for carriers of 14 allele	[63]

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*Dopamine receptor D3*

The *DRD3* gene is located on chromosome 3 and differs from the *DRD1* and *DRD2* in representing both an autoreceptor and postsynaptic receptor [17]. The *DRD3* gene is mainly expressed in the ventral striatum and the globus pallidus [10]. Most frequently studied is the Ser9Gly polymorphism (also known as MscI or Balli [18]). The Ser9Gly mutation of the *DRD3* gene affects the N-terminal extracellular part of DRD3, which could disturb membrane insertion. Lately, it was demonstrated that with the Gly-9 variant, the dopamine-mediated cyclic (c)AMP response was increased, and the mitogen-associated protein kinase (MAPK) signal was prolonged, as compared with the Ser-9 variant [19].

Also studied is a polymorphism in intron 5, which alters the restriction site for MspI [20].

The gene coding for DRD3 is considered to be a direct gene for levodopa therapy and dopamine agonists.

*Dopamine receptor D4*

Several polymorphic sites have been described in the *DRD4* gene, which is located on chromosome 11. The *DRD4* gene is widely expressed in the CNS, particularly the frontal cortex, hippocampus, amygdala and hypothalamus, and is polymorphic with respect to a 48 base pair (bp) sequence occurring in 2- to 11-fold repeat in the third exon of DRD4 [21,22]. This segment codes for a 16 amino acid repeated sequence in the third intracellular loop of DRD4 probably involved in G-protein binding. In cultured cells the sevenfold repeat has a blunted response to dopamine inhibition of cAMP formation [23]. It is shown that the long form has different binding properties with spiperone analogues as contrasted with the shorter forms [22].

The gene coding for DRD4 is considered to be a direct gene for levodopa therapy and some dopamine agonists.

*Dopamine receptor D5*

The *DRD5* gene, located on chromosome 4, is mainly expressed in the lateral mammillary nuclei, in the anterior pretectal nuclei in several layers of the hippocampus [24]. Due to the similarity in structure and function to *DRD1*, it may also be involved in the pharmacological treatment of PD. Polymorphisms in this gene could be implicated in the susceptibility to complications of long-term levodopa use [25]. The gene coding for DRD5 is considered to be a direct gene for levodopa therapy.

*Dopamine transporter*

The dopamine transporter (DAT) gene (*SLC6A3*) is located on chromosome 5. DAT takes released dopamine back up into presynaptic terminals. Interindividual genetic differences in DAT that controls the presynaptic uptake of dopamine in the dopaminergic neurons of the nigrostriatal system may also play a role in the therapeutic outcome of PD [26]. A 40-bp variable number of tandem repeats (VNTR) in the 3' UTR is identified and possibly affects gene expression [26]. The gene coding for DAT is considered to be a direct gene for levodopa therapy.

*Catechol-O-methyltransferase*

The gene coding for COMT is located on chromosome 22. The COMT protein occurs as two distinct forms: a soluble form found in cell cytoplasm (S-COMT) and a longer, membrane-bound form (MB-COMT). The MB-COMT is the more prevalent form in the brain [27]. COMT metabolizes and inactivates compounds including dopamine and levodopa. The level of COMT activity is polymorphic with a trimodal distribution of low (LL), intermediate (HL) and high levels of activity (HH). The high activity is coded for by a valine residue and the low activity by a methionine protein located at protein position 158 for the MB-COMT form and located at protein position 108 for the S-COMT form [28,29]. A decreased COMT activity may result in prolonged dopamine levels. The gene coding for COMT is considered to be a direct gene for levodopa therapy and COMT inhibitor therapy.

*Monoamine oxidase B*

Monoamine oxidase (MAO) is a mitochondrial enzyme involved in the degradation of biogenic amines, such as dopamine. MAO is classified as A or B on the basis of differential substrate specificities and differential sensitivity to inhibitors. MAOA and MAOB are encoded by X chromosome-linked genes [30]. A genetic polymorphism in *MAOB* is known in intron 13 (Tsp45I) that is associated with different levels of MAOB enzyme activity in the human brain. It is postulated that there may be a *cis*-regulatory element in linkage disequilibrium with the intron 13 single nucleotide polymorphism (SNP) that alters MAOB enzyme activity [31]. The gene coding for MAOB is considered to be a direct gene for levodopa therapy and MAOB inhibitors.

*Cholecystokinin gene, cholecystokinin A receptor & cholecystokinin B receptor*  
CCK, a neuropeptide found in the gut and CNS, has been implicated in dopaminergic regulation. The gene coding for CCK is located on chromosome 3. CCK receptors are divided into two types: cholecystokinin A receptor (CCKAR), located on chromosome 4, and cholecystokinin B receptor (CCKBR), located on chromosome 11. CCKAR mediates the action of CCK on contraction of the gallbladder, secretion of pancreatic amylase and gastric emptying. CCKBR activity is associated with increased neuronal firing, anxiety and nociception. In addition, CCK modulates the release of dopamine and dopamine-related behaviors in the mesolimbic pathway, where CCK and dopamine coexist [32]. The genes coding for CCK, CCKAR and CCKBR are considered to be an indirect gene for dopaminergic therapy.

#### *Apolipoprotein E*

APOE, with its gene located on chromosome 19, binds the amyloid- $\beta$  peptide. The major isoforms of human APOE are coded for by three alleles (E2, E3 and E4). The E2, E3 and E4 isoforms differ in amino acid sequence at two sites, residue 112 (called site A) and residue 158 (called site B). At sites A/B, APOE2, -E3 and -E4 contain cysteine/cysteine, cysteine/arginine and arginine/arginine, respectively [33,34]. An increased frequency of the E4 allele has been associated with a higher frequency of Alzheimer's disease [35]. The gene coding for APOE is considered to be an indirect gene for dopaminergic therapy.

#### *$\mu$ 1 opioid receptor*

The  $\mu$ 1 opioid receptor (*OPRM1*) gene is located on chromosome 6. The most common genetic variant is the A118G polymorphism, coding for an AsnN40Asp change, which is carried by 20% of Caucasians. This polymorphism has been shown to increase binding affinity and functional potency of the endogenous opioid peptide  $\beta$ -endorphin [36]. It is hypothesized that *OPRM1* could have a role in developing dyskinesias, as opioids are cotransmitters in both the direct and the indirect basal ganglia pathways [37]. The gene coding for *OPRM1* is considered to be an indirect gene for dopaminergic therapy.

#### *Serotonin transporter*

Serotonin (5-HT) is a neurotransmitter in the central and peripheral nervous systems, with its coding gene located on chromosome 17. Following release, 5-HT is actively cleared from synaptic

spaces by 5-HT transporter (T). A few polymorphisms in 5-HTT have been detected. Experiments have demonstrated a long and a short variant of the *5-HTT* gene, with the long variant leading to higher *5-HTT* mRNA concentrations. This polymorphism consists of a 44-bp insertion or deletion involving repeat elements 6–8 and is referred to as *5-HTTLPR* [38,39]. The gene coding for 5-HTT is considered to be an indirect gene for dopaminergic therapy.

#### *Preprohypocretin*

The human preprohypocretin gene (*HCRT*; preprorexin) is located on chromosome 17 and encodes a hypothalamic neuropeptide precursor protein that could play a role in the pathophysiology of narcolepsy [40]. *HCRT* gene polymorphisms are located on position -909T, -22C>T and -20C>A in the 5' UTR, which have been studied in relation to the occurrence of sleep attacks in patients with PD [40–42]. The gene coding for *HCRT* is considered to be an indirect gene for dopaminergic therapy.

#### Polymorphisms associated with drug efficacy

##### *Levodopa*

All studies investigating the influence of polymorphisms on levodopa efficacy studied a relation with a mono-amine transporter system polymorphism (DAT) or a mono-amine degradation enzyme polymorphism (COMT and MAOB). Response to a single oral dose of levodopa, measured as response latency, duration and magnitude of the response and dyskinesias, did not differ between ninefold copy carriers and tenfold copy homozygotes of the 40-bp *VNTR* polymorphism in the *DAT* gene [43]. Similarly, no differences in levodopa response were found between groups with different *COMT* Val158Met gene polymorphism [44,45]. Bialecka and colleagues did not observe significant differences in *COMT* genotype and *MAOB* genotype between patients needing less than 500 mg levodopa/day and those needing more than 500 mg levodopa/day during the first 5 years of disease [46]. Separate evaluation of males and females, because of location of the *MAOB* gene on chromosome X, did not alter the results significantly. Tan and colleagues observed that low-activity COMT homozygotes had a better improvement on the motor score with high-dose pyridoxine adjunct therapy [47]. It is suggested that high-dose pyridoxine, which is a cofactor for DOPA decarboxylase, facilitates the conversion of levodopa to dopamine in the brain.

*Catechol-O-methyltransferase inhibitor*

The relation between the clinical efficacy of the COMT inhibitor tolcapone and the *COMT* Val158Met gene polymorphism in patients with PD was studied by Chong and colleagues [48]. Patients were divided into those who had a stable response to levodopa and those who were considered to be fluctuators. Furthermore, nine patients who had severe diarrhea as a side effect were enrolled to determine the possible relationship with *COMT* genotype. No significant association between genotype and improvement in Unified Parkinson's Disease Rating Scale (UPDRS) score at 1–2 weeks treatment until 6 months of treatment was found after adjustment for the severity of PD, the tolcapone dose and initial differences in baseline scores. No significant relation was seen in change in daily levodopa intake and *COMT* genotype. Furthermore, no relation was found between *COMT* genotype and diarrhea.

*Wearing off & 'on-off' phenomena*

Wearing-off effects are defined as reemergence of parkinsonian symptoms prior to intake of the next levodopa dose. 'On-off' phenomena are denoted as sudden, unpredictable fluctuations of motor symptoms. In the studies of Kaiser and colleagues [26] and Wang and colleagues [12,25], these two symptoms were recorded as one item, and are denoted as motor fluctuations by Wang and colleagues. Patients who experienced on-off/wearing off and those who did not, showed no difference in frequencies of polymorphisms in the *DRD2* gene (TaqIA, TaqIB, TaqID, Pro310Ser, Ser311Cys, Val96Ala, -241A>G and -141C ins/del), the *DRD3* gene (Ser9Gly and the MspI), the *DRD4* gene (48-bp VNTR, 12-bp repeat and the 13-bp deletion variant) and *DAT* gene (40-bp VNTR) [26]. Wang and colleagues investigated whether polymorphisms in the *DRD2* gene (TaqIA), *DRD3* gene (Ser9Gly and MspI polymorphisms) and *DRD5* gene (978T>C) were associated with a higher risk of developing motor fluctuations in patients with PD using levodopa [12,25]. Patients with motor fluctuations and those without motor fluctuations were individually matched. The frequency of the *DRD2* TaqIA non-A2 carriers in patients with motor fluctuations was higher (33%) than in those without motor fluctuations (10%). The odds ratio (OR) for developing motor fluctuations for non-A2 carriers versus A2 carriers was 4.33 (95% confidence interval

[CI]: 1.27–14.78). The *DRD3* and *DRD5* genotypic frequencies did not differ between patients with or without motor fluctuations.

## Polymorphisms associated with drug tolerance

*Dyskinesias*

Peak-dose dyskinesias are common, disabling side effects of levodopa treatment and occur in approximately 30–80% of the patients with PD. Female gender, earlier age at onset of PD and a longer duration of levodopa therapy have been associated with a higher risk of developing peak-dose dyskinesias [49]. Genetic factors could also contribute to individual variability in the development of peak-dose dyskinesias.

Oliveri and colleagues [49], Zappia and colleagues [16] and Strong and colleagues [37] investigated whether the *DRD2* CAN-STR gene polymorphism is associated with the risk of levodopa induced peak-dose dyskinesias in PD. Due to the low frequencies of some genotypes, subjects were categorized as subjects carrying at least one of the 13 copy or 14 copy allele (13,14+) or as subjects carrying neither a 13 copy nor a 14 copy allele (13,14-). Oliveri and colleagues found that the gender-adjusted OR for developing peak-dose dyskinesias for the 13,14+ genotypes was 0.28 (95% CI: 0.11–0.77) [49]. This result is corroborated by Zappia and colleagues, who found an OR of 0.45 (95% CI: 0.26–0.79). However, when taking gender into account, Zappia and colleagues found out that only men carrying the 13,14+ genotype had a decreased risk for peak-dose dyskinesias, whereas in women the genotype status did not influence the risk [16]. In contrast, Strong and coworkers found that the 14 allele and the 14/15 genotype was a risk-factor for dyskinesias (crude OR for 14 allele: 3.4; 95% CI: 1.1–10.4) [37].

Furthermore, Oliveri and colleagues could not demonstrate that three polymorphisms of the *DRD1* gene (-48G>A, 1403T>C and Ser421Ser) were associated with the risk of levodopa-induced peak-dose dyskinesias.

Kaiser and colleagues assessed whether polymorphisms in the *DRD2* gene (TaqIA, TaqIB, TaqID, Pro310Ser, Ser311Cys, Val96Ala, A>G-241 and -141C ins/del polymorphisms), the *DRD3* gene (Ser9Gly and the MspI polymorphism), the *DRD4* gene (48-bp VNTR, 12-bp repeat and the 13-bp deletion variant) and the *DAT* gene (the 40-bp VNTR) are associated with dyskinesias in patients with PD on levodopa [26]. Patients with dyskinesias on

levodopa were more frequent carriers of the ninefold copy 40-bp *DAT* allele than all other patients (53.2 vs 34.8%). The OR for developing dyskinesias in patients with PD on levodopa carrying the ninefold copy 40-bp *DAT* allele was 2.5 (95% CI: 1.3–4.7). No significant genotype differences could be found between patients with or without dyskinesias for all other genes studied.

Strong and colleagues found a borderline significant association between *OPRM1* G-allele frequency and the risk of early dyskinesias versus late dyskinesias for PD patients on levodopa (crude OR: 2.8; 95% CI: 0.97–4.0) [37].

### Hallucinations

Hallucinations, mainly of a visual nature, affect approximately 25% of patients with PD. Independent risk factors for visual hallucinations are cognitive decline, daytime somnolence and a long duration of PD. Hallucinations are common side effects of dopaminergic treatment in PD, but dopaminergic treatment alone is not sufficient to explain the occurrence of all visual hallucinations [50]. A total of 12 studies have been performed investigating the relation between genetic variability and the occurrence of hallucinations on dopaminergic treatment. Goetz and colleagues determined the relation between *DRD1*, *DRD2*, *DRD3*, *DRD4* and *APOE* gene polymorphisms and hallucinations in patients with PD [51]. Included were patients with hallucinations and patients without hallucinations matched for age and dopaminergic medication. The frequency of the *DRD1* genotype (-48G>A) was not different between the patients with and without hallucinations. There were too few *DRD2* 311Cys alleles to compare *DRD2* allele genotypes or frequencies. There was no statistical difference in the distribution of the *DRD3* Ser9Gly genotype between the cases and controls. There was, however, a borderline significant difference in *DRD3* allele frequency ( $p = 0.047$ ). No statistical differences in the distribution of the *DRD4* 48-bp genotype (two- to eight-fold copy alleles) between cases and controls were determined, comparing those with any long allele (six- to eight-fold copy) with those with only short alleles. There was neither a significant difference between cases and controls for the *APOE* genotype distribution or the *APOE4* allele frequency.

Kaiser and colleagues observed that patients with psychotic episodes on levodopa were more frequent carriers of the *DAT* ninefold 40-bp allele than all other patients (60.0 vs 36.8%) [26]. The OR for developing psychosis on levodopa in

patients with PD carrying the ninefold copy 40-bp allele was 2.6 (95% CI: 1.3–5.3). No significant relationship with the occurrence of psychosis could be established for polymorphisms in the *DRD2* gene (TaqIA, TaqIB, TaqID, Pro310Ser, Ser311Cys, Val96Ala and the A>G241 and -141C ins/del polymorphisms), *DRD3* gene (Ser9Gly and the MspI polymorphism) and the *DRD4* gene (48-bp VNTR, 12-bp repeat and the 13-bp deletion variant).

Wang and colleagues could not show significant differences in genotype frequencies in the *DRD2* gene (TaqIA), *DRD3* gene (Ser9Gly and MspI), *DRD5* gene (978T>C) and *DAT* gene (40-bp VNTR) between PD patients on levodopa with and without hallucinations, individually matched for disease duration, age at disease onset, duration of dopaminergic therapy and gender [52].

Makoff and colleagues investigated the association of polymorphisms in the *DRD2* gene (-141C ins/del and the TaqIA) and *DRD3* gene (Ser9Gly) and hallucinations in patients with idiopathic PD [53]. Patients with and without hallucinations were matched for disease duration, age at disease onset, duration of dopaminergic therapy and gender. Corroborating the findings of Kaiser and Wang, the hallucinators did not differ from the nonhallucinators in the genotype frequencies of the polymorphisms in *DRD2* and *DRD3*, but in a subgroup analysis of late hallucinators compared with patients with a disease duration greater than 8 years who had never experienced hallucinations during treatment, the *DRD2* -141C/C genotype was more frequent in the hallucinators (OR: 3.15; 95% CI: 1.10–9.15).

No association was found between the *COMT* Val158Met gene polymorphism and hallucinations in autopsy-proven PD, but the etiology of the hallucinations was not recorded (e.g., relationship to medications) [54].

Interesting, albeit conflicting, results have been reported on the association between hallucinations in PD and polymorphisms in the *CCK* gene. Wang and colleagues found that the *CCK* -45C>T polymorphism was more frequent in PD patients with hallucinations than in those without [55]. The OR for hallucinations in patients with a T allele was 4.4 (95% CI: 1.7–11.9). Also, the presence of the combined *CCK* CT/TT genotypes and *CCKAR* TT/TC genotypes increased the risk of visual hallucinations in PD (OR: 5.9; 95% CI: 1.7–21.6). Fuji and colleagues corroborated



the relation between a *CCK* -45C>T polymorphism and hallucinations in PD [56], although no such relation was found by Goldman and colleagues [57]. Other polymorphisms in the *CCK* gene (196G>A, 1270C>G and 6662C>T) [56], the *CCKAR* gene (779T>C) or the *CCKBR* gene (1550G>A) were not associated with hallucinations [55,57].

Four studies have investigated the relationship between the *APOE4* allele and increased risk of drug-induced hallucinations in PD. De la Fuente-Fernández and colleagues included non-demented patients with PD on chronic levodopa treatment. They demonstrated a significant association between the presence of the *APOE4* allele and hallucinations. The OR for hallucinations in patients with the *APOE4* allele adjusted for age, severity of parkinsonism, duration of treatment and dose of levodopa was 8.57 (95% CI: 2.25–32.59) [58]. This finding was supported by the study of Feldman and colleagues who found that the hazard ratio for the development of psychosis if a patient carried the *APOE4* allele was 3.24 (95% CI: 1.62–6.46) [59]. In contrast, Inzelberg and colleagues and Camicioli and colleagues could not show an association of the *APOE* genotype on the development of hallucinations in patients with PD [4,54].

#### *Excessive daytime sleepiness*

Sleep disorders and daytime sleepiness are frequent in patients with PD. Sleep attacks or sudden onset of sleep (SOS) are defined as abrupt episodes of unplanned sleep during activities where they are not expected to occur. Although dopaminergic agents have been known for a long time to induce somnolence, the etiology of this side effect and particularly sleep attacks or SOS is still unknown. Five studies have been performed investigating the association between genetic variability and the occurrence of sleep attacks or day-time sleepiness on dopaminergic treatment.

Paus and colleagues studied the association between polymorphisms in the *DRD2* gene (141C del/ins and TaqIA), *DRD3* gene (Ser9Gly), *DRD4* gene (48-bp repeat) and *5-HTTLPR* and sleep attacks in patients with PD taking dopaminergic drugs [60]. PD patients with sleep attacks and without sleep attacks were matched for dopaminergic treatment, disease duration and age. There was a highly significant association between sleep attacks without warning signs and a *DRD4* 48-bp twofold copy (short) allele versus three- to seven-fold copy alleles (23.2 vs 7.4%;  $p < 0.0001$ ). There were

no significant differences between cases and controls for all other polymorphisms studied. In contrast with the findings of Paus and coworkers, Rissling and colleagues found a significant difference in the *DRD2* TaqIA genotype distribution between PD patients with SOS and a control group [61]. The OR for developing SOS for homozygous carriers of allele A2 was 5.24 (95% CI: 1.65–16.59). No significant difference could be demonstrated in the *DRD3* Ser9Gly gene polymorphism and the *DRD4* 120-bp *VNTR* genotype distribution between PD patients with SOS and the control group. Frauscher and colleagues demonstrated a significant association between the *COMT* Val158Met polymorphism and daytime sleepiness, which was defined by a score greater than 10 on the Epworth Sleepiness Scale ( $p = 0.039$ ) [62]. However, Rissling and colleagues were not able to confirm this finding in a larger study [63]. In another study, Rissling and colleagues demonstrated an association between the -909T polymorphism of the *HCRT* gene and SOS (OR = 2.81; 95% CI: 1.09–7.25) [64]. They found no association between a -22C>T or -20C>A *HCRT* gene polymorphism and SOS.

#### Discussion

Interindividual variability in anti-PD drug response is evident both from clinical experience and drug efficacy studies and may, at least in part, be explained by genetic variability in genes coding for drug-metabolizing enzymes, drug targets or proteins involved in signaling pathways. This systematic literature review shows that relatively few efforts have been made to investigate the role of pharmacogenetics in the individual response to anti-PD drugs. However, some interesting, albeit nonconsistent, associations have been found.

Summarizing the main results, positive associations have been found between the occurrence of levodopa-induced dyskinesias and polymorphisms in the *DRD2* gene (CAn-STR 13 and 14 copy alleles protective [16,49] and in contrary 14 copy allele as risk factor [37]), the *DAT* gene (ninefold copy) [26] and *OPRM1* G-allele [37]. Also, motor fluctuations have been associated with the *DRD2* TaqIA polymorphism [12], although others could not replicate this finding [26]. Conflicting results have been reported concerning the occurrence of hallucinations in PD and genetic polymorphisms. While some authors found significant associations between hallucinations and polymorphisms in the *DAT* gene [26], the *CCK* gene [55,56] or the *APOE*

gene [58,59], others failed to replicate these results [4,51–54,57]. Associations were found between sleep attacks without warning signs and a *DRD4* gene or a *HCRT* gene polymorphism [60,64]. Others found a positive association with a *DRD2* gene or a *COMT* gene polymorphism [61,62], although the latter could not be replicated [60,63].

Some remarks on the studies presented can be made, and many of these have been discussed previously in reviews of the pharmacogenetics of antipsychotic and antidepressant response [5,65–67]. Firstly, only a few replication studies have been performed, both with regard to studies with negative findings and those with positive findings. Obviously, it is important that replication studies are being performed for confirmation in order to establish the true association of the polymorphisms studied.

Moreover, the methodology of the replication studies that have been performed differ from the original studies with respect to design and factors such as case selection and race. Obviously, using case definitions and matching criteria of the controls different from the original study could influence the results. Also, differences in race distribution could influence the findings, as it is known that allele frequencies, as well as linkage disequilibria, may vary among races. For example, Asians and African-Americans have a lower frequency of the low activity allele of the *COMT* Val158Met gene polymorphism than Caucasians [68].

Furthermore, due to small sample sizes most of the pharmacogenetic studies in PD are likely to be underpowered. The sample size in the case-control studies as reviewed here was limited to 23–147 cases. A typical sample size of well-powered pharmacogenetic case-control studies is 300 cases and 600 controls to detect a true OR of 1.5 with 80% power and type I error probability ( $\alpha$ ) of 0.05 [69]. Moreover, the allele frequency is an important factor in the power of pharmacogenetic studies. If the variants are rare the necessary sample size steeply increases. In the reported studies some allele frequencies were below 10% in the control group (some *CCK* gene polymorphisms, one *CCKBR* gene polymorphism, one *DRD1* gene polymorphism and some *DRD2* gene polymorphisms). Thus, future pharmacogenetic studies with these alleles will probably require larger samples.

The emphasis in the studies published until now has been on SNPs and VNTR. Some of these are located in the coding or regulatory regions of genes that have an *a priori* relevance to

the drug response or adverse effect phenotype under study. However, some of the SNPs or VNTR are located in noncoding regions and the implications of these polymorphisms remain unclear. One explanation could be that the polymorphisms in noncoding regions are in linkage disequilibrium with other, possibly unknown, functional variants [70]. As in all association studies, a positive association between a gene polymorphism and drug response does not necessarily imply a causal relation.

PD is a complex trait, and so is its pharmacological treatment. It is therefore likely that several genes together are implicated in the response to anti-PD drugs and susceptibility to adverse effects. Therefore, future studies on pharmacogenetics of drug effects in PD require a polygenic approach. Indeed, relatively few examples (such as thiopurine drugs) of largely monogenic drug response are known [71].

A final remark is that the studies performed until now were all candidate-gene-driven. The findings are therefore easier to interpret, since only genes are studied in which the role of drug treatment in PD is more or less established. However, this approach may have limitations, as many regulatory processes in dopaminergic signaling are not known. In contrast, whole-genome screening does not have this limitation and may lead to finding novel genes of interest, but instead data-analysis and interpretation is much more complex.

#### Future perspective

To date, genetic associations with levodopa response, COMT inhibitor response and common drug side-effects, such as dyskinesias, hallucinations and excessive daytime sleepiness have been investigated. No pharmacogenetics studies have been performed on dopamine agonists response and side-effects. In the future it may be worth looking at variability in the suggested genetic background of the slower decline of imaged DAT by pramipexole [72,73]. Investigation of the role of genetic variability in susceptibility to side-effects, such as pathological gambling, punding and hypersexuality, may also be of interest [74–77]. These side effects are probably under-reported and socially disabling. Although disputed, some state that the newer dopamine agonists, pramipexole and ropinirole, have a higher incidence of these side-effects [74,77]. As these dopamine agonists have a higher affinity for DRD3, polymorphisms in the *DRD3* gene could be implicated. It would therefore be interesting to study the role of *DRD3* polymorphisms in PD, especially since such

polymorphisms have been implicated in other basal ganglia disorders as well, such as tardive dyskinesia [78] and essential tremor [19].

Another interesting side effect is the higher incidence of fibrotic reactions in lungs and hearts valves caused by ergolide dopamine agonists. It is suggested that the 5-HT<sub>2B</sub> receptor (HTR2B) plays a role in the development of these fibrotic reactions. The involvement of polymorphisms in the *HTR2B* gene, which is located on chromosome 2 may be relevant to study [79].

The role of polymorphisms in the cytochrome P450 (CYP) enzymes and transporter enzymes, such as P-glycoprotein in the response on anti-PD drug treatment have not been investigated [80]. Pergolide is partly metabolized by CYP2D6 [81], which is known to be highly polymorphic [82]. CYP2D6 poor metabolizers may experience a higher degree of adverse effects on pergolide. P-glycoprotein, encoded by the multidrug resistance 1 gene, is implicated in transport of substances, such as drugs, out of the brain and in the small intestine. The ergot-alkaloid bromocriptine is found to be an inhibitor

of P-glycoprotein [83]. Moreover, budipine is shown to be transported from the brain by P-glycoprotein in mice [84].

In conclusion, some studies point towards genetic variation in candidate genes being involved in interindividual drug response in the treatment of PD. However, replication of findings and additional research with larger patient numbers and a polygenic approach is needed to establish the role of pharmacogenetics in anti-PD drugs. To date, it seems not appropriate to investigate the mentioned polymorphisms routinely or exceptionally during the clinical management of PD.

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#### Executive summary

- Pharmacotherapy is the mainstay in the treatment of Parkinson's disease (PD) and the armamentarium of drugs available for the therapy of this disease is still expanding.
- Anti-PD drugs are effective in reducing symptoms such as hypokinesia, bradykinesia, rigidity and tremor.
- Interindividual variability in anti-PD drug response is evident both from clinical experience and pharmacological studies and may be explained by genetic variability in genes encoding drug-metabolizing enzymes, drug targets or proteins involved in signaling pathways.
- Some interesting associations between genetic variants and anti-PD drug response have been found, but these are conflicting. Positive associations have been found between the occurrence of levodopa-induced dyskinesias or motor fluctuations and polymorphisms in the dopamine receptor (*DRD2*) gene, between hallucinations and polymorphisms in the dopamine transporter gene, the cholecystikinin gene and the apolipoprotein E gene and between sleep attacks without warning signs and polymorphism in the *DRD2* and *DRD4* genes.
- Due to small sample sizes most of the pharmacogenetic studies in PD are likely to be underpowered.
- Our literature study reveals that relatively few efforts have been made to investigate the role of pharmacogenetics in the individual response to anti-PD drugs and only few replication studies have been performed.
- Replication of findings and additional research with larger patient numbers and a polygenic approach is needed to establish the role of pharmacogenetics for anti-PD drugs.

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• **Review with recommendations for future pharmacogenetic studies of clozapine response are done which also apply for pharmacogenetic studies in Parkinson's disease.**



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