Chapter 3

Effects of Genetic Variability in Dopaminergic Pathway on Treatment Response in Parkinson's Disease

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Additional information is available at the end of the chapter

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Abstract

Parkinson's disease (PD) is a chronic progressive neurodegenerative brain disorder presenting with motor signs and symptoms, such as akinesia, rest tremor, rigidity, and later in disease progression postural instability. However, nonmotor symptoms may harm patients' quality of life even more than the motor ones. The etiopathogenesis is not clear yet. PD may develop due to a combination of genetic and environmental factors. It is treated symptomatically with dopaminergic drugs. The gold standard of PD management is L-Dopa, however also other drugs are frequently used, such as dopamine agonists, MAOB inhibitors, COMT inhibitors, and occasionally amantadine and anticholinergic drugs. Many patients experience several adverse events of L-Dopa treatment, such as different motor complications. Furthermore, nonmotor adverse events of dopaminergic treatment may occur. The efficacy of drugs varies between patients as well. Several polymorphic genes have already been associated with treatment outcome in PD, such as metabolic enzymes, transport and receptor genes, and might serve as treatment outcome prediction factors. As gene-environment interactions were also shown to contribute to PD development, they might also be able to predict treatment response. Such genetic biomarkers could be helpful in personalized care of PD patients to prevent adverse events and inefficacy of a certain drug.

Keywords: Parkinson's disease, pharmacogenetics, genetic polymorphisms, personalized medicine, L-Dopa, dopaminergic treatment

1. Introduction

Parkinson's disease (PD) is a chronic progressive brain disorder. It is the second most common neurodegenerative disorder after Alzheimer's disease [1]. The exact etiopathogenesis is not clear yet, although it may develop due to various genetic and environmental factors. Two main

pathological hallmarks are indicative of PD: intraneuronal inclusions containing α-synuclein aggregates and neurodegeneration of dopaminergic neurons projecting from substantia nigra (SN) to striatum. Several motor symptoms occur as a result of striatal dopaminergic deficiency: akinesia, rest tremor, rigidity, and in later stages also postural instability with gait disorder [2, 3]. Other motor symptoms encompass hypomimia, micrographia, dysarthria, dysphagia, and others [4]. Furthermore, patients are also affected by nonmotor symptoms. The most common are depression, anxiety, cognitive decline, REM-sleep behavior disorders, constipation, sialorrhoea, and hyposmia. Few of them are present already in the prodromal phase, which may last up to 20 years before the clinical diagnosis is made [2, 3, 5–7].

The underlying molecular pathogenesis of PD encompasses defects in different cellular pathways, such as protein aggregation, protein and membrane trafficking, lysosomal autophagy, immune response, neurodevelopment, neuron cell differentiation and survival, mitochondrial homeostasis, and others [8]. Genetic defects in key genes of these pathways may contribute to the molecular pathogenesis of PD [9].

Clinical diagnosis is normally established by a clinical examination, when motor symptoms are already present. At that time, nearly 80% of dopaminergic neurons in the nigrostriatal pathway are irreversibly lost and only symptomatic treatment is available to alleviate the symptoms. PD management is based on the replacement of dopamine. Some symptoms can also be managed by concomitant supportive therapy, depending on the symptom [2–4].

1.1. Dopaminergic pathway

Dopamine is an organic compound of the catecholamine family. It plays several roles especially in the brain and also in the periphery. It acts as a neurotransmitter and is thus responsible for the transmission of either inhibitory or excitatory stimuli to the postsynaptic neuron depending on the type of the binding receptor. Dopaminergic neurons projecting from substantia nigra pars compacta, part of basal ganglia, to the striatum, which constitutes the nigrostriatal pathway, are responsible for motor functions [10, 11].

Dopamine synthesis and degradation, along with dopamine function in the nigrostriatal pathway, is schematically displayed in **Figure 1**. Tyrosine hydroxylase (TH) converts tyrosine to levodopa (L-Dopa), which is then converted to dopamine by dopa decarboxylase (DDC). Dopamine is then transported to a synaptic vesicle via the vesicular monoamine transporter 2 (VMAT2). It is excreted from the presynaptic neuron to the synaptic cleft via exocytosis. Dopamine then binds to dopamine receptors, either on the membrane of postsynaptic or presynaptic neuron. The downstream effect depends on the receptor it binds to. D1-like receptors (DRD1 and DRD5) are excitatory, whereas D2-like receptors are inhibitory (DRD2, DRD3, and DRD4), which depends on the type of secondary messengers. Binding to the presynaptic receptor inhibits dopamine synthesis and continuous release of dopamine to the synaptic cleft. Once dopamine is released from the receptor, it is reuptaken to the presynaptic neuron via the dopamine transporter (DAT), where it gets deactivated or repackaged into the vesicles by VMAT2 for future release. Metabolism of dopamine is managed by two main enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Furthermore, aldehyde dehydrogenase (AD) also participates in dopamine

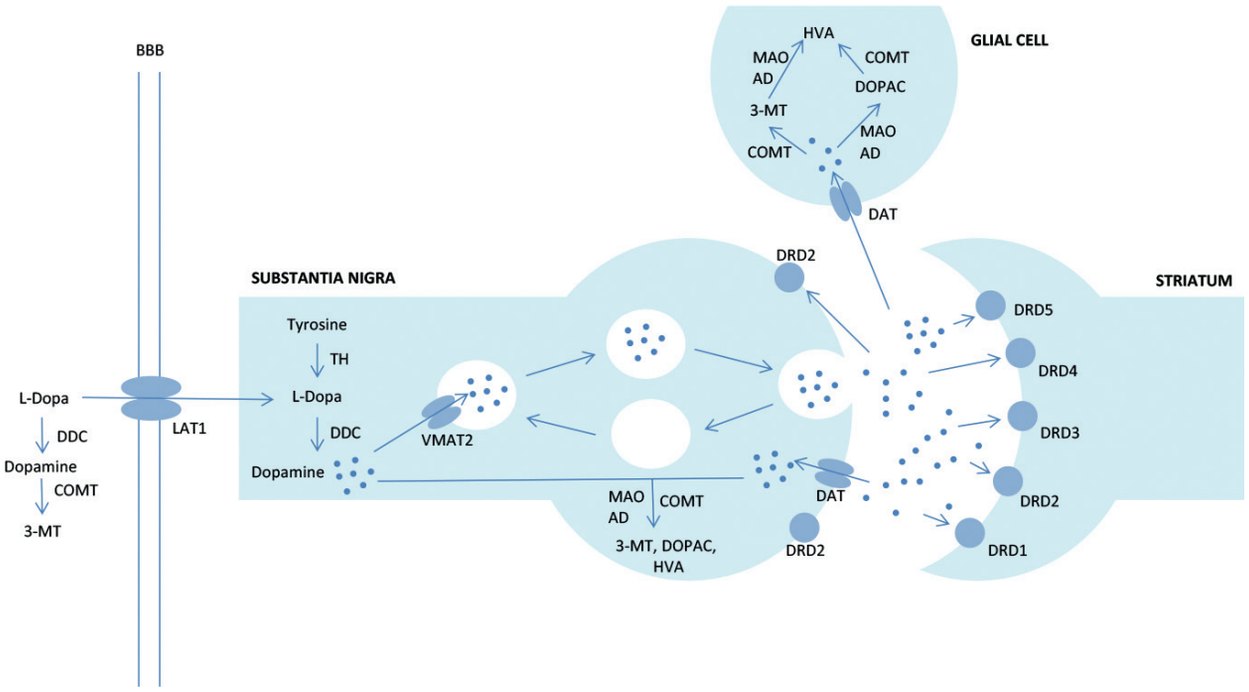

Figure 1. Dopamine synthesis, function, and degradation in the nigrostriatal pathway.

metabolism. COMT introduces a methyl group to the dopamine, whereas MAO catalyzes oxidative deamination. There are two types of the MAO enzyme, MAOA and MAOB. MAOB is more specific for the breakdown of dopamine, whereas MAOA also degrades other catecholamines. Furthermore, AD catalyzes oxidation of aldehydes. As a result of degradation reactions, several different metabolites are produced, such as 3-methoxythyramine (3-MT), 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) as the end metabolite, which gets eliminated in the urine. Degradation of dopamine can either be carried out in the presynaptic neuron after reuptake via DAT or in the glial cells. COMT is predominantly expressed in the glial cells, MAOB in the astrocytes, and MAOA in the catecholaminergic neurons like dopaminergic neurons of SN [12–14].

L-Dopa, which is also the gold standard treatment option in PD, is transported to the brain through the blood-brain barrier (BBB) via large neutral amino acid transporter (LAT1) [15]. L-Dopa can be broken down in the peripheral tissues by COMT and DDC, which might be the source of peripheral adverse events occurring during the treatment. Thus, DDC inhibitors and sometimes also COMT inhibitors are concomitantly administered to shield L-Dopa from degradation. Dopamine itself is not suitable for oral treatment, because it cannot be transported to the brain through the BBB due to its high polarity. Moreover, it is also not an amino acid compound and is thus not a transporter substrate [13].

1.2. Treatment of Parkinson's disease

PD is an incurable disease. Management of PD is based on dopamine replacement and endogenous dopamine enrichment or activation of dopamine receptors. All dopaminergic drugs,

such as MAOB inhibitors, dopamine agonists (DA), L-Dopa, COMT inhibitors, and amantadine, aim to enhance or replenish the dopamine function in the striatum [3].

The least potent drug compounds are MAOB inhibitors, rasagiline, and selegiline. Rasagiline is more broadly used. MAOB inhibitors increase the concentration of dopamine in the synapse and prolong its action by the inhibition of MAOB enzyme. They can either be used as a monotherapy as one of the first prescribed drugs in the early stages of PD or concomitantly with L-Dopa to prolong its action. MAOB inhibitors demonstrate a very small symptomatic benefit, although they might according to some studies have a slight neuroprotective effect. MAOB inhibitors are taken once a day [3, 16–18].

Next line of PD treatment represents DA. DA mimic the dopamine action as they bind to postsynaptic dopamine receptors. Two main types of DA, ergoline and nonergoline derivatives, are available, but usually nonergoline DA are used in clinical practice, such as pramipexole, ropinirole, and rotigotine. They can be used either as monotherapy or in combination with L-Dopa and/or MAOB inhibitors. As their half-life is longer compared to L-Dopa's and the prolonged release forms are available, they can be administered once a day. Rotigotine is available as a transdermal patch. Furthermore, their action is believed to be less pulsatile compared to L-Dopa's, which might be the reason for less motor complications after years of treatment. Nevertheless, their overall symptomatic effect is less pronounced, which means that usually L-Dopa has to be added to therapy in few years after diagnosis. Moreover, apomorphine is a very potent DA, which can be applied subcutaneously, intermittently or as a continuous infusion in advanced disease stages to reduce motor fluctuations [3, 16, 17].

L-Dopa is the gold standard of PD management. L-Dopa crosses the BBB and gets converted to dopamine by DDC in the brain. L-Dopa is always administered in combination with DDC inhibitors, either carbidopa or benserazide. DDC inhibitor is added to prevent L-Dopa conversion to dopamine in the periphery, which could cause several adverse events. L-Dopa alleviates most motor symptoms very effectively, although it poses a high risk for motor complication development. Consequently, many physicians are postponing the L-Dopa prescription to avoid motor complications. Particularly in PD patients younger than 65 years, DA or rasagiline is the common first treatment with L-Dopa being added when the symptomatic effect of DA is not sufficient. However, since the continuous dopaminergic treatment options for advanced PD became available (subcutaneous apomorphine infusion, levodopa/carbidopa intrajejunal gel infusion, and deep brain stimulation), physicians are less hesitant to prescribe L-Dopa early in the disease course. L-Dopa is usually administered in the form of tablets, which are taken a few times daily (3–6 times) to deliver L-Dopa as continuously as possible [3, 13, 16, 17]. Furthermore, COMT inhibitors, especially entacapone, are commonly used concomitantly with L-Dopa when early motor fluctuations (wearing-off phenomena) occur. On the other hand, amantadine may be used to alleviate L-Dopa-induced dyskinesia [16].

Management of PD should be individualized in the scope of options available. Patient's age, symptoms' severity, and cognitive status are considered in the process of choosing the most suitable drug [2, 17].

1.3. Adverse events of dopaminergic treatment

Dopaminergic therapy can cause several adverse events (AEs), which can be classified as motor and nonmotor ones.

Several peripheral AEs can occur during PD treatment. The common peripheral AEs are nausea and vomiting, which occur in approximately 15% of PD patients treated with dopaminergic drugs. Nausea and vomiting can be avoided by a very slow titration of a drug dose or by concomitant administration of domperidone at the initiation of treatment. Furthermore, orthostatic hypotension is also common in PD patients as 34% of patients experience this AE after the first dose of a DA. Peripheral edema usually limited to ankles is mostly occurring in DA treatment rather than L-Dopa treatment. It affects 6.4% of patients treated with ropinirole and 15% of patients treated with pramipexole. Risk factors for the development of edema are female sex and cardiovascular comorbidities [19–21].

Central AEs are excessive daytime sleepiness and sleep attacks, hallucinations, and impulse control disorders (ICD). Excessive daytime sleepiness and sleep attacks affect approximately 30% of patients taking dopaminergic medications, especially DA. Sleep attacks are defined as a sudden, irresistible, and overwhelming sleepiness without awareness of falling asleep. Good sleep hygiene is very important in PD patients to prevent daytime sleepiness, so some nonpharmacological interventions can be undertaken to achieve as many hours of sleep during night as possible to avoid this AE. It is important to warn the patients about this possible AE and advise them not to drive a vehicle during DA titration phase. Furthermore, hallucinations in PD are mostly visual. Patients usually see simple and not threatening images of silent animals and people. Although all dopaminergic drugs are associated with this AE, patients taking DA are more likely to be affected. Longer duration of the disease and cognitive impairment are risk factors for the development of visual hallucinations [19–21]. They affect from 25 to 39.8% of PD patients [19]. ICD prevalence rates reports are quite variable and range from 6 to 39%. This AE presents as pathological gambling, hypersexuality, compulsive buying, and binge eating. The AE should be recognized early due to possible severe personal, financial, and socio-familial consequences when it remains unrecognized [19–21].

Motor AEs occur after few months to few years of treatment with L-Dopa and affect almost every PD patient chronically treated with L-Dopa. The time and severity of motor complications vary among patients and cannot be predicted yet. The most common motor complications are motor fluctuations, which first manifest as *wearing-off* of the drug effect before the next dose is administered. Consequently, patient fluctuates between *on* and *off* periods. During the *on* period, motor symptoms are least pronounced, whereas in the *off* period, symptoms re-emerge. Motor fluctuations may occur because of long-lasting pulsatile stimulation of striatal dopamine receptors, and as the disease advances, the ability to store dopamine is diminished and finally lost. Consequently, the patients' clinical picture parallels the blood L-Dopa level. The fluctuations may be managed either by increasing the number of smaller L-Dopa doses and/or by adding the COMT inhibitors, MAOB inhibitors or DA, which may prolong L-Dopa action. Dyskinesia is another type of motor complications. It is usually defined as involuntary and choreatic movements most

often related to the peak dopamine levels (peak-dose dyskinesia). This type of dyskinesia is usually managed by reducing the single L-Dopa doses or by discontinuation of COMT or MAOB inhibitors, but this intervention may prolong the *off* periods. Furthermore, diphasic dyskinesia may occur as plasma L-Dopa levels are rising or falling. It is more bothersome for the patient, with dystonic features and difficult to treat. The same strategies may be used as for the treatment of peak-dose dyskinesia. The third type of dyskinesia occurs in the *off* state, and is usually presented as painful early morning leg dystonia, when the blood L-Dopa level falls low due to long time since the last L-Dopa dose. It can be managed by taking the prolonged release L-Dopa at night or by adding COMT inhibitors, MAOB inhibitors or DA [2, 14, 17, 19–21]. Botulinum toxin injection in the affected muscle is effective too [22]. L-Dopa-induced dyskinesia can also be treated by adding amantadine to the therapy scheme [2, 14, 17, 19–21].

1.4. Treatment efficacy evaluation with the MDS-unified Parkinson's disease rating scale (MDS-UPDRS)

MDS-UPDRS is a four part scale for the evaluation of PD severity and treatment efficacy. Part I evaluates nonmotor aspects of experiences of daily living, Part II motor aspects of experiences of daily living, Part III motor examination, and Part IV motor complications. The first part of Part I and Parts III and IV are evaluated by physicians, whereas the second part of Part I and the whole Part II are self-administered by patients. MDS-UPDRS can be used for different applications, but in some pharmacogenetic studies, where the efficacy of dopaminergic drugs is evaluated in association with genetic factors, the main efficacy criterion is a difference in MDS-UPDRS score over a particular period of time [16, 23–26].

1.5. Genetic factors and treatment response in PD

Genetic characteristics of each person are encoded in the genome. Interindividual differences occur due to changes in DNA in only 1% of the whole sequence. Different variants of the same gene or locus are called alleles. Furthermore, a variant is called a polymorphism when at least two different alleles are present in the population and the less frequent allele is carried by at least 1% of population. The most common type of genetic variation are single nucleotide polymorphisms (SNPs), where one nucleotide is substituted with the other. Furthermore, many other types of polymorphisms can change the DNA sequence, such as deletions, insertions, duplications of nucleotides or longer sequences, microsatellites, changes in variable number of tandem nucleotide repeats (VNTR), and others. These genetic polymorphisms may lead to changes in transcription, translation, and/or function of proteins [27, 28]. These polymorphisms may also influence expression and function of proteins involved in metabolism, transport and effector pathways of drugs, and also structure and function of drug targets. Consequently, polymorphisms may have an effect on drug response in terms of efficacy and occurrence of AEs. Also in PD, this effect has already been shown in several pharmacogenetic studies [29, 30].

The aim of this chapter is to summarize the current knowledge on the effect of different polymorphisms, mostly SNPs, on dopaminergic treatment outcome, especially the occurrence of AEs. The chapter focuses on the polymorphisms within the dopaminergic pathway, but also includes polymorphisms from other pathways, that have already been associated with

treatment response. The rationale behind investigating polymorphisms is that they may serve as the possible predictive biomarkers of treatment response in PD patients and could therefore support personalized treatment approaches. Furthermore, this chapter also discusses gene-environment interactions already investigated in PD.

2. Genetic variability in dopaminergic receptor genes affecting response to PD treatment

Dopaminergic receptors reside in the membrane of postsynaptic neurons in striatum. There are five types of dopaminergic receptors, divided into two groups—type-1 and type-2. Dopaminergic receptors are coded by *DRD1–5* genes [14]. At least 11 pharmacogenetic studies (**Table 1**) have already been performed searching for associations between different *DRD* gene variants and AEs or efficacy and have found positive results [23, 31–40].

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
DRD1	rs4867798 c.*863A>G	0.0054	91	Impulse control disorder	[31]
	rs4532 c.-48G>A	0.0024			
DRD2/ANKK1	rs1800497 c.2170G>A p.Glu724Lys	0.0009	274	Sleep attacks	[32]
		0.0044	91	Impulse control disorder	[31]
	-141CIns/Del	0.007	199	Dyskinesia	[33]
	rs2283265 c.724-353G>T				
	rs1076560 c.811-83G>T				
	rs6277 c.957C>T p.Pro319=				
	rs1800497 c.2170G>A p.Glu724Lys				
	rs2734849 c.1469A>G p.His490Pro				
DRD2	(CA)n-STR	0.005	215	Dyskinesia	[34]
		0.04 (14 allele) 0.003 (14/15 genotype)	92	Dyskinesia	[35]
	rs1799732 c.-486_-485insC	0.027	217	Nausea and vomiting	[36]
DRD3		0.0094	404	Impulse control disorder	[37]

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
	rs6280 c.25G>A p.Gly9Ser	0.024	30	Therapeutic efficacy	[23]
		0.041	170	Impulse control disorder	[38]
		0.022	217	Nausea and vomiting	[36]
		0.001	168	Dose of dopamine agonist	[39]
DRD4	48-bp VNTR	<0.0001	204	Sleep attacks	[40]

Table 1. Genetic polymorphisms in dopaminergic receptor genes associated with dopaminergic treatment outcome in patients with PD.

DRD1 was reported to be associated with L-Dopa-induced dyskinesia. Carriers of the rs4867798 C allele and rs4532 T allele were more prone to develop this AE [31]. Association of *DRD2* variants with drug response was shown in at least six studies [31–36]. *DRD2* (CA)n-STR (intronic short tandem repeat with four common alleles—13, 14, 15, and 16 CA repeats) was checked for association with dyskinesia after L-Dopa treatment. Results showed association of allele with 14 repeats and 14 repeats/15 repeats genotype as associated with earlier development of dyskinesia [35]. The same variant was also evaluated in the study performed by Zappia et al. Male carriers of the 13 and/or 14 repeat alleles had a decreased risk for developing dyskinesia, whereas in females the association was not confirmed [34]. Furthermore, *DRD2* haplotype of six variants (-141CIns/Del, rs2283265, rs1076560, rs6277, rs1800497, and rs2734849) was checked for association with dyskinesia. Carriers of the TTCTA haplotype were more likely to develop L-Dopa-induced dyskinesia [33]. Association of *DRD2* rs1800497 with ICDs was found in a study performed by Zainal Abidin et al. T allele significantly increased risk for ICD [31]. This SNP was also associated with sleep attacks, namely G allele increased chances of this AE [32]. Moreover, *DRD2* rs1799732 Ins/Ins genotype was associated with gastrointestinal AEs (nausea and vomiting) after L-Dopa therapy [36]. Association of *DRD3* variants with drug outcome in PD was shown in at least five pharmacogenetic studies [23, 36–39]. *DRD3* rs6280 AA genotype (Ser/Ser) was shown to be associated with increased risk for developing ICDs and gastrointestinal AE [36, 37]. Furthermore, the same genotype was also associated with higher response rate in treatment with pramipexole [23]. Another study showed that heterozygous genotype carriers of this were more prone to develop ICDs [38]. Lastly, Gly/Gly genotype of rs6280 was associated with higher doses of DA needed to manage PD [39]. *DRD4* was also already reported to be associated with AE in dopaminergic treatment. Sleep attacks were more likely to develop in carriers of the short allele of the 48-bp VNTR in exon 3 of the gene [40].

3. Genetic variability in transporter genes affecting response to PD treatment

Most frequently studied transporter gene in pharmacogenetic of PD is *SLC6A3* encoding DAT. DAT is located in the membrane of presynaptic dopaminergic neurons and of glial cells almost exclusively in striatum. It pumps dopamine from the synaptic cleft back to the presynaptic neuron or into the glial cell. Consequently, it ends the action of dopamine in

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
SLC6A3	rs28363170 3′-UTR 40 bp VNTR	0.006	183	Psychosis and dyskinesia	[41]
	rs2652511 c.-972T>C	0.02	196	Visual hallucinations and levodopa equivalent dose	[42]
	rs28363170 3′-UTR 40 bp VNTR	0.01			
	rs393795 c.653+4065C>A	4.1E−5	352	Dyskinesia	[43]
	rs3836790 (VNTR in intron 8–5/6 repeat)	<0.0001	61	Motor response to acute L-Dopa challenge	[44]
SLC22A1	rs622342 c.1386-2964C>A	0.017	99	Levodopa dose	[45]

Table 2. Genetic polymorphisms in dopaminergic transporter genes associated with dopaminergic treatment outcome in patients with PD.

the synaptic cleft. At least four studies (**Table 2**) have already shown association of polymorphisms in *SLC6A3* with response to dopaminergic treatment [41–44]. First, a study by Kaiser et al. showed association of the nine copy allele 40-bp VNTR of the DAT with the occurrence of dyskinesia and psychosis after L-Dopa treatment [41]. Furthermore, this variant showed association with L-Dopa equivalent dose (LED) needed for proper disease management, where nine repeat allele of the DAT 3′-UTR VNTR was associated with lower LED [42]. In the same study, *SLC6A3* rs2652511 C allele was shown to be associated with visual hallucinations [42]. Moreover, C allele of the rs393795 in *SLC6A3* was recognized as one of the factors that extend the time to dyskinesia occurrence in L-Dopa treatment [43]. After an acute L-Dopa challenge, patients with six repeat/six repeat genotype of the VNTR in intron 8 responded better [44].

Organic cation transporters (OCT) are involved in the absorption, distribution, and elimination of a wide variety of compounds. Pramipexole and amantadine are substrates for OCT1 and OCT2. L-Dopa is also transported by one of the OCTs, but the subtype has not been determined yet. Becker et al. evaluated the association between the rs622342 and the dose of dopaminergic drugs needed for proper disease management (**Table 2**). Between the first and fifth L-Dopa prescription, for each minor rs622342 C allele, the prescribed doses were 0.34 defined daily dose higher (DDD), where DDD is a standardized dosing measure representing the recommended daily dose for the main indication in an adult [45].

4. Genetic variability in dopamine metabolic pathway genes affecting response to PD treatment

Three enzymes in the metabolic pathway of dopamine, COMT, MAO-B, and DDC, have already been associated with the response to dopaminergic treatment in PD (**Table 3**).

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
COMT	rs4680 c.472G>A p.Val158Met	0.047	121	Wearing-*off* phenomenon	[46]
		0.045		Dyskinesia	
		0.18 (NS)	95	L-Dopa dose	[49]
		0.004	219	Dyskinesia	[50]
		0.049 (GG) 0.031 (G allele)	1087	Wearing-*off* phenomenon	[47]
		<0.001	259	Wearing-*off* phenomenon	[48]
	rs6269 c.-98A>G	<0.05	322	L-Dopa dose and dyskinesia	[51]
	rs4633 c.186C>T p.His62=				
	rs4818 c.408C>G p.Leu136=				
	rs4680 c.472G>A p.Val158Met				
MAO-B	rs1799836 c.1300-36A>G	0.018	1087	Dyskinesia	[47]
DDC	rs921451 c.-29+9697A>G	0.0097	33	Motor response to acute L-Dopa challenge	[26]
	rs3837091 c.-61_-58delAGAG				

NS, not significant.

Table 3. Genetic polymorphisms in dopamine metabolic genes associated with dopaminergic treatment outcome in patients with PD.

Polymorphism rs4680 has been the most studied SNP in the *COMT* gene in association with treatment outcome by now. The substitution of nucleotides in the SNP results in the switch of valine to methionine (p.Val158Met). This substitution causes lower activity of the enzyme. In the majority of the studies, this switch was associated with motor complications of L-Dopa treatment. Watanabe et al. showed that homozygosity for the low-activity allele (AA genotype) increased chances for wearing-*off* phenomenon ($p = 0.047$) and dyskinesia ($p = 0.045$) [46]. On the contrary, a later study found association of the GG genotype with wearing-*off* phenomenon ($p = 0.049$ for the GG genotype and 0.031 for the G allele) [47]. The same results were also found in the study by Wu et al. [48]. In another study, the same SNP was checked for association with the dose of L-Dopa after the first 5 years of treatment. The association was not significant, but the frequency of homozygotes for the AA genotype was higher in a group with lower doses of L-Dopa (500 mg/24 h) [49]. The same genotype was also associated with the development of dyskinesia with evidence of a dose-response effect [50]. One of the studies

also checked the association between the most common COMT haplotypes of four SNPs—rs6269, rs4633, rs4818, and rs4680. The enzyme activity differs between haplotypes: low activity—ACCG, medium activity—ATCA, and high activity—GCGG. The L-Dopa dose increased with the activity of the enzyme (low < medium < high). Doses prescribed to low-activity haplotype carriers were significantly higher in comparison to noncarriers. No association was found for dyskinesia [51].

Devos et al. investigated *DDC* variants for the association with response after acute L-Dopa challenge. Response to L-Dopa was evaluated by the area under the curve for the change in the UPDRS Part III score ($AUC_{\Delta UPDRS}$) 4 h after L-Dopa administration relative to baseline. The $AUC_{\Delta UPDRS}$ was significantly lower in rs921451 CC or CT genotypes than in TT genotype. Furthermore, $AUC_{\Delta UPDRS}$ was also significantly lower in rs3837091 Del/Del or AGAG/Del genotypes than in the AGAG/AGAG genotype [26].

MAO-B is also important in dopamine metabolism and its variants affect drug response. Carriers of the heterozygous genotype at the *MAO-B* rs3837091 were found to be more prone to develop dyskinesia [47].

5. Genetic variability in other genes affecting response to PD treatment

Genetic variability in several other pathways and its influence on drug response in PD was also investigated in several studies and some statistically significant associations have been found (**Table 4**).

At least four pharmacogenetic studies pointed out association of nondopaminergic genes with the occurrence of dyskinesia [35, 52–54]. Higher chance for developing L-Dopa-induced dyskinesia was described in carriers of the following genotypes or alleles within different systems: opioid system—*OPRM1* rs1799971 G allele; neuroprotection system—*BDNF* rs6265 A allele; glutamate system—*GRIN2A* rs7192557 GG genotype, rs8057394 CC genotype; adenosine pathway—*ADORA2A* rs2298383 TT and CT genotypes, rs3761422 CC, and CT genotypes [35, 52–54]. Psychosis as an AE of DA or L-Dopa was already associated with *APOE*, *ACE*, *HOMER1*. APOE ε4 allele increased risk for the earlier development of psychosis [55]. *ACE* deletion/insertion (D/I) of a 287-base pair Alu repeat sequence in the intron 16 was associated with psychosis after L-Dopa treatment, namely I/I genotype increased risk for development of the AE [56]. Furthermore, allele A of the *HOMER1* rs4704559 increased risk for development of psychosis, especially hallucinations [57]. Another AE occurring in dopaminergic treatment are sleep attacks. According to Rissling et al. *HCRT* rs760282 T allele increased risk for developing this AE, where TT genotype carriers were even more susceptible to it [58]. *GRIN2B* and ICDs are another association of the glutamate system with AE of dopaminergic treatment. *GRIN2B* rs7301328 CC genotype increased risk for at least one of the types of ICDs [37]. The same finding was reported by Zainal Abidin et al. [31]. Also, *HTR2A* receptor in the serotonin system was according to Lee et al. associated with ICD. The T allele, which is presumably associated with higher expression of the receptor, increased risk for developing ICDs in the lower-L-Dopa-equivalent dose group [59]. *SV2C,* which participates in the process of

Gene	Variants	p-Value	No. of PD patients	Outcome	Reference
HCRT	rs760282 c.-909T>C	0.024 (TC) 0.018 (TT)	264	Sleep attacks	[58]
APOE	*e4* allele	<0.05	87	Psychosis	[55]
OPRM1	rs1799971 c.118A>G p.Asn40Asp	0.05	92	Dyskinesia	[35]
ACE	A deletion/insertion (I/D) of a 287-base pair Alu repeat sequence in the intron 16	0.012	251	Psychosis	[56]
HOMER1	rs4704559 g.78812909A>G	0.004	131	Psychosis	[57]
BDNF	rs6265 c.196G>A p.Val66Met	0.001	315	Dyskinesia	[52]
GRIN2B	rs7301328 c.366C>G p.Pro122=	0.0087	404	Impulse control disorders	[37]
		0.0097	91	Impulse control disorders	[31]
GRIN2A	rs7192557 c.415-91061C>T	0.0062	101	Dyskinesia	[53]
	rs8057394 c.415-83080G>C	0.0033			
ADORA2A	rs2298383 c.-275+1797C>T	0.023 (TT) 0.039 (CT)	208	Dyskinesia	[54]
	rs3761422 c.-274-2427T>C	0.017 (CC) 0.012 (CT)			
HTR2A	rs6313 c.102C>T p.Ser34=	0.011	404	Impulse control disorders	[59]
SV2C	rs30196 c.-1888G>T	0.024	224	L-Dopa dose	[60]

Table 4. Genetic polymorphisms in other genes associated with dopaminergic treatment outcome in patients with PD.

dopamine storage in vesicles, was associated with L-Dopa dose. The presence of each rs30196 C allele reduced the average dose of L-Dopa for approximately 76 mg per day [60].

6. The role of gene-environment interactions in PD

So far, mostly genetic factors have been investigated as potential modifiers of drug response. However, drug response can also be influenced either directly or indirectly by environmental factors. Several environmental factors have already been associated with PD risk, among them: coffee and alcohol consumption and cigarette smoking are reducing and pesticide

exposure and well water drinking are increasing the risk. Several single locus and genome wide studies evaluating gene-environment interactions have already been performed in PD and these interactions should also be assessed in association with the treatment outcome (**Table 5**) [2, 61, 62].

A genome-wide gene-environment study found association between *GRIN2A* rs4998386 in combination with coffee consumption and PD risk. Light-coffee drinkers were defined as people with ccy (cups per day multiplied by the number of years of coffee consumption) less than median ccy (three datasets with different medians: 67.5, 70.0, and 74.0) and heavy-coffee drinkers as people with ccy more than median ccy. The *GRIN2A* association was present in heavy-coffee drinkers, but not in light-coffee drinkers. T allele decreased risk for PD in comparison to CC genotype in heavy-coffee drinkers. Compared to light-coffee drinkers CC genotype carriers, heavy-coffee drinkers with CC and CT genotype had lower risk for PD [63]. Furthermore, Gao et al. investigated interaction of both smoking and coffee drinking with genetic factors and their combined effect on risk for PD. *SLC2A13* rs2896905 was recognized as an important risk modifier. Each A allele was associated with a 35% higher PD risk among never smokers with low caffeine intake, but with a 32% lower risk among smokers with high caffeine intake [64]. *SV2C*, which was

Gene	Variants	p-Value	Number of participants	Outcome	Reference
SV2C	rs30196 c.-1888G>T rs10214163 c.-101-133065C>T	1E-10	1600 cases 1506 controls	PD risk and smoking	[65]
SLC12A3	rs2896905 c.556+5639C>T	0.0008	584 cases 1571 controls	PD risk and smoking and coffee drinking	[64]
ERCC6L2	rs67383717 g.98626548C>A	2.4E-6	443 cases 443 sibling controls	PD risk and pesticide exposure	[68]
BST1	rs11724635 c.852-575C>A	0.024 (AC) 0.008 (CC)	468 cases 487 controls	PD risk and well water drinking	[66]
SNCA	rs3775423 c.307-7063G>A	<0.05	1098 cases 1098 controls	PD risk in combination with pesticide exposure and coffee and alcohol consumption	[67]
MAPT	rs4792891 c.-18+1448T>G H1/H2 haplotype rs16940806 c.*2289G>A rs2435211 c.1127-1162C>T				
GRIN2A	rs4998386 c.415-38137G>A	6E−7	Initial phase: 1458 cases 931 controls Replication phase: 1014 cases 1917 controls	PD risk and coffee drinking	[63]

Table 5. Results of studies on gene–environment interactions in PD.

already associated with drug response in one of the pharmacogenetic studies, showed association with PD risk in combination with smoking. Two SNPs rs30196 and rs10214163 protected from PD risk, when people carried both wild type alleles (CC and TT, respectively). The risk increased with number of polymorphic alleles [65]. A single locus study aimed to look for association between the combined effect of well water drinking and *BST1* rs11724635 and PD. The results show that polymorphic rs11724635 AC and CC genotypes combined with well water drinking increase risk for PD [66]. Another study investigated gene-environment interactions for *SNCA* and *MAPT* with multiple environmental factors. Five interactions were associated with PD risk: pesticides × *SNCA* rs3775423 or *MAPT* rs4792891, coffee drinking × *MAPT* H1/H2 haplotype or *MAPT* rs16940806, and alcohol drinking × *MAPT* rs2435211. Unfortunately, no interaction remained significant after Bonferroni correction [67]. Lately, a genome-wide gene-interaction study of pesticide exposure and PD risk was performed. No results remained significant after genome-wide correction for multiple testing. Top signal of the *ERCC6L2* gene suggested that this gene may modify the effect of pesticide exposure on PD risk [68].

7. Future perspectives

PD is a complex and heterogeneous syndrome, which presents with different signs and symptoms in different patients and progresses with different rates. The current treatment approach to individual patients varies depending on the patient's age, disease duration, disease severity, and cognitive state. The treatment regime is then adjusted according to treatment's efficacy, the disease progression and in regard to AEs. We have searched the current literature to compile a comprehensive review of today's knowledge on genetic variants that may influence the outcome of dopaminergic treatment in PD. At least 35 pharmacogenetic studies have already been published in PD. Several genetic factors potentially predictive of treatment outcome have already been found, although some of the studies show conflicting results regarding the same genetic factors. This may be largely due to the small size of the study cohorts, since many studies included less than 100 patients. The largest study was performed on a cohort of 1087 patients.

Pharmacogenetic studies in PD mostly look at the treatment outcome of dopaminergic drugs in general, rarely they focus on a particular drug as patients are usually treated with the combination of treatments. Furthermore, most of the cohorts included patients with different symptomatology, which may also reflect differences in pathogenesis of PD in these patients, consistent with reports that different cellular defects contribute to development of PD or are even causative of PD [8]. As cohorts in pharmacogenetic studies are so heterogeneous, significant factors that may predict treatment outcome may be overlooked, because they might be relevant only for one particular subgroup of PD patients but not for the others. If we could stratify PD patients according to cellular pathways that may be defective in each subgroup, predictive genetic factors could be found more easily.

The future studies should also expand the range of polymorphisms investigated as potential predictive biomarkers. So far, researchers have mostly focused on dopamine receptor genes, transporter genes, dopamine metabolic genes, and few genes in other pathways, but there

are plenty of genes that warrant further analysis. For example, genes involved in the pathways of inflammation (*IL-1*, *IL-6*, *TNFα*, and *IFNϒ*), oxidative stress (*CAT*, *SOD*, and *GPX*), neurodevelopment (*BDNF*, *GDNF*, and *NOTCH*), mitochondrial and lysosomal function, and also genes significant in gene-environment interaction studies (*SLC12A3*, *ERCC6L2*, *BST1*, *SNCA*, and *MAPT*). Furthermore, some of the genes that increased PD risk in genome-wide association studies could also influence treatment outcome (*GBA*, *SYT11*, *INPP5F*, *SNCA*, *MAPT*, *TMEM175*, *GAK*, *DGKQ*, *STK39*, and *HLA-DQB*).

The validated pharmacogenetic biomarkers would enable physicians to stratify PD patients according to their genetic characteristics and not only by their phenotype. Stratification would allow a more targeted pharmacotherapy and a more individualized approach to treatment. Pharmacogenetic factors could also be supported with clinical data. Algorithms encompassing both aspects, clinical and genetic, could be constructed to enable physicians to choose the most suitable treatment strategy for each patient at the particular stage of the disease. If such algorithms are constructed, AE and treatment inefficacy could be at least minimized if not avoided. As PD pharmacotherapy is usually very complex and drugs are taken many times daily patients' compliance may be expected to improve with better treatment outcome, as well as their quality of life.

8. Conclusions

Personalized medicine has been evolving rapidly in the recent years, but the reliable biomarkers of treatment outcome are not validated yet. The ultimate goal of personalized medicine is to approach every patient individually and provide the best care possible for each individual patient. In this chapter, we summarized the current knowledge on genetic predictors of response to dopaminergic treatment in PD patients. Additionally, we looked into gene-environment interaction studies to find potential biomarkers that should be further evaluated in pharmacogenetic studies. Many studies have already been performed, but the cohorts were small and heterogeneous. To be able to validate and translate these findings into clinical practice, more targeted studies with larger cohorts and better characterized patients should be conducted. However, some promising candidates have already been identified and could be used in clinical practice after validation in independent cohorts.

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