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Pharmacogenetics of Parkinson's Disease – Through Mechanisms of Drug Actions

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Abstract: In the last years due to development of molecular methods a substantial progress in understanding of genetic associations with drug effects in many clinical disciplines has been observed. The efforts to define the role of genetic polymorphisms in optimizing pharmacotherapy of Parkinson's disease (PD) were also undertaken. So far, some promising genetic loci for PD treatment were determined. In the review pharmacogenetic aspects of levodopa, dopamine agonists and COMT inhibitors are discussed.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder originating from interplay between genetic and environmental factors, and results in selective loss of dopamine neurons in substantia nigra. However, the relative role of genes and environmental agents in the etiology of PD has not been entirely elucidated. Studies on familial forms of PD identified numerous susceptibility loci, i.e. *SNCA (PARK1)*, *LRRK2*, *PRKN (PARK2)*, *PINK1 (PARK6)*, *DJ-1* (*PARK7)*, and recently *ATP13A2* (*PARK9*), *PLA2G6* (*PARK14*), and *FBXO7* (*PARK15*) have been detected to cause familial atypical parkinsonism [1-5]. However, the aforementioned associations refer to familial cases of PD. Much less is known about genetic background of sporadic cases of PD, usually developing at later life stages. Many common genetic variants were postulated to be associated with sporadic PD [N-acetyltransferase 2 (*NAT2*), monoamine oxidase B (*MAOB*), glutathione transferase (*GST*), mitochondrial tRNA, S18Y variant of ubiquitin carboxy-terminal hydrolase L1 (*UCHL1*), Rep 1 variant of alpha-synuclein (*SNCA*) and tau (*MAPT*) H1 haplotype and leucine-rich repeat kinase-2 (*LRRK2*)] [6]. Recently more risk loci have been identified in genome-wide association studies (GWAS; *BST1*, *GAK*, *HLA-DR*, *ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11*, *PAKR16*, *FGF20*, and *GPNMB*) [5]. However, the associations are rather week, and currently are not applied in clinical medicine.

Over the last decades, it has become clear that genetic differences between individuals may be responsible, among other factors, for observed variation in patients' responses to medications. Pharmacogenetics aimes at identification of patients at higher, genetically determined, risk of drug adverse effects or ineffective medication, to modify dosage or switch to alternative therapy, i.e. to individualize therapy. Thus, it leads to improvement in efficacy and safety of pharmacotherapy. Influence of genetic factors on drug action primarily was extensively studied in relation to genes encoding enzymes involved in drug metabolism, that defective variants, associated with complete absence of enzymatic activity were common in some populations. Numerous single nucleotide polymorphisms (SNPs) were identified in genes encoding cytochrome P450 izoenzymes, and in some phase II enzymes (i.e. thiopurine S-methyltransferase, N-acetyltransferase 2), underlying the observed variations in response to drugs principally metabolized by those enzymes [7-9]. More recently, in the case of some polymorphic enzymes, pharmacogenetically-guided protocols of treatment have been designed, providing recommended modifications of therapy based on genetic testing results [10]. The Food and Drug Administration (FDA) has approved genetic information in labeling of over 80 drugs, and even though genetic testing is only 'suggested' (not recommended) in the case of most drug listed, that status may change to 'required' based on results of ongoing prospective studies [11]. Although no antiparkinsonian drugs are among those with pharmacogenetic labels, many efforts have been made to define role of genetic variations in treatment outcome among PD patients.

Apart from the search for useful genetic diagnostic tools of PD there is a great interest in identification of genetic markers of drug response for agents applied in the disease treatment. A broad range of responses is seen in patients medicated with antiparkinsonian drugs, both in terms of efficacy and side effects. Available data shows that about 80% of patients medicated with levodopa respond well to initial therapy as evidenced by improvement in rigidity and hypokinesia, and 45% of them develop levodopa induced dyskinesias within 5 years of treatment [12]. Likewise, rate of side effects produced by dopaminergic drugs ranges to about 25% [13]. Therefore, there is a need to define factors underlying the observed differences in antiparkinsonian drug efficacy and toxicity.

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Mechanisms of action of drugs tailored for PD involve their interference with patholophysiological processes triggered during the disease development, mainly influence dopaminergic system, and much less cholinergic system functions. Motor symptoms of the disease, i.e. bradykinesia and rigidity, can be controlled by drugs enhancing dopaminergic transmission, i.e. levodopa, dopamine receptor agonists, COMT inhibitors as well as MAOA and MAOB inhibitors. Anticholinergic agents are not frequently used, and are applied for the control of tremor and rigidity. Efforts of pharmacogenetic studies are thus directed on targets associated with mechanisms of antiparkinsonian drug actions, and the review summarizes available knowledge in this field.

DIRECT TARGETS OF ANTIPARKINSONIAN DRUGS

Natural targets for dopamine agonists constitute dopaminergic receptors of several types: from D1 to D5, with D1 and D2 being the most important for PD pathology and drug response. They are not homogenously distributed within central nervous system, and some of them show defined functional genetic polymorphisms.

Dopamine Receptors (DRD)

The *DRD1* gene is located on chromosome 5, and shows several polymorphic *loci* that may modulate its function [14]. Polymorphic *loci* in *DRD1* gene most frequently studied involve: -48A>G (D1.1; B1/B2) and 1403T>C (D1.7; C1/C2) [15]. There are also data suggesting modulatory effects of genetic polymorphism in DRD2 functions. The *DRD2* gene located on chromosome 11 encodes two isoforms with distinct functions. i.e. long (D2L) and short (D2S). Several polymorphisms in *DRD2* gene were identified. The *TaqIA* polymorphism is associated with reduced number of striatal DRD2 receptor density in A1 allele carriers [16]. Later it was documented that the *TaqIA* polymorphism is located in a kinase gene - ankyrin repeat and kinase domain containing 1 (*ANKK1*), located downstream of *DRD2* gene [17]. Another known polymorphism in *DRD2* gene constitutes of repeat CA, *DRD2* $(CA)_n$, and is located in a non-coding region of the gene. The functional consequences of this polymorphism are not established [18].

The *DRD3* gene is located on chromosome 3 [19]. Most frequently investigated polymorphisms include Ser9Gly (or *MscI* or *BalI*), which may affect DRD3 receptor membrane insertion, and its intracellular response. *In vitro* expression studies revealed that receptors encoded by allele A2 demonstrated significantly higher affinity to dopamine [20-22]. Another polymorphic loci is defined by *Msp*I cleavage, located in an intron with its functional role remaining to be defined [18].

The *DRD4* gene is located on chromosome 11, and demonstrate VNTR polymorphism within third exon of 2- to 11 repeats of 48 bp, probably modulating G-protein binding [23, 24]. Long forms have different binding properties with spiperone analogues as opposed to the shorter forms [23]. The *DRD5* gene is located on chromosome 4, and its polymorphism may, due to its similar structure and function to *DRD1*, mediate antiparkinsonian drug actions.

Dopamine Transporter (DAT)

DAT gene (*SLC6A3*) is located on chromosome 5. A 40 bp variable number tandem repeats (VNTR) polymorphism in the 3'UTR was identified, and may affect gene expression, thus dopamine uptake from synaptic cleft [25].

Catechol-O-methyltransferase (COMT)

The gene coding for COMT is located on chromosome 22. The enzyme metabolizes, i.e. degrades dopamine and levodopa, and exists in two distinct forms: soluble (S-COMT) and membrane bound (MB-COMT). The G to A transition at codon 158 [Val158Met; (rs4680)] is the most commonly studied *COMT* polymorphism, results in substitution of methionine for valine, and was initially linked to low enzyme activity (COMT-L) due to its termoliability, opposite to H (high activity) allele [26]. Later findings documented that *COMT* haplotypes better describe enzymatic activity. The three most common haplotypes are composed of four *COMT* SNPs combinations: one in the *S-COM*T promoter region (rs6269:A>G, in boundary region of 3 intron in *MB-COMT* gene) and in the S- and *MB-COMT* - two synonymous changes (rs4633:C>T, His62His) and (rs4818: C>G, Leu136Leu) as well as one nonsynonymous change (rs4680:A>G, Val158Met). Three most common haplotypes derived from the above four SNPs determine enzyme activity: A_C_C_G - low, A_T_C_A – intermediate and G_C_G_G - high. The major *COMT* haplotypes vary in terms of mRNA local stem-loop structures, such that the most stable structure was associated with the lowest protein levels and enzymatic activity [27, 28].

Monoamine Oxydase B

Monoamine oxidase B gene (*MAOB*) is located on chromosome X. *MAOB Tsp*45I polymorphism is located in intron 13, and associates with different enzymatic activity in the brain. It is postulated that a *cis*-regulatory element being in linkage disequilibrium with intron 13 SNP may alter the enzyme activity [29].

PHARMACOGENETIC ISSUES OF THE TREATMENT

Levodopa

L-dopa is the most effective drug in alleviation of motor impairments in PD, and its effectiveness and tolerability significantly improved after an introduction of its combination with a dopa-decarboxylase inhibitor, either benserazide or carbidopa. The majority of patients respond well to l-dopa, but approximately 20% of treated patients may not respond to the medication. In the group of good responders, l-dopa improves quality of life, especially in the early stage of the disease. However, with disease progression the response declines, and becomes more unpredictable and inadequate, named as motor fluctuation and dyskinesia. Approximately 50% of PD patients treated with l-dopa develop motor complications within 5 years after therapy initiation, and the risk yields 90% with treatment longer than 10 years. However, a large inter-individual variability has been observed in PD patients treated with l-dopa, both with respect to drug efficacy and toxicity, with potential contribution of genetic fac-

tors, mainly in genes encoding drug receptors, metabolizing enzymes and intracellular signaling proteins.

Genetic evidence has implicated *DRD1* and *DRD2* polymorphisms as strong candidates determining efficacy and safety of l-dopa treatment. The dopamine D2 receptor (DRD2) gene polymorphism has been found to be associated with increased risk of motor fluctuations in response to l-dopa [16]. Higher frequency of *DRD2 Taq*IA A1 in PD carriers with motor fluctuations in comparison to patients without fluctuations (33 % vs. 10%) was observed. Low striatal DRD2 receptor density, as a result of *DRD2 Taq*IA A1 variant, predisposed to l-dopa induced fluctuations. Associations between *DRD3* (Ser9Gly, *Msp*I) and *DRD5 (*978*T>C)* with motor fluctuations were not documented. However, the study of Paus *et al.* did not confirm the impact of *DRD2 Taq*IA polymorphism on inter-individual variability of dopaminergic requirement in PD [30]. Another *DRD2* polymorphism (CAn-STR – CA, dinucleotyde short tandem repeat) has been investigated for possible associations with l-dopa-induced dyskinesias. The anty-dyskinetic effects of *DRD2* 13 and 14 allele was shown for the first time by Oliveri *et al.* [31], and then was confirmed by Zappia *et al.* [32], who reported significant differences in *DRD2* CAn-STR distribution between patients with and without dyskinesias. Carriers of 13 or 14 copy allele had lower risk for development of peak-dose dyskinesias. However, further analysis of the data pointed out a gender effect, i.e. only men carrying the 13, 14 genotype were characterized by a decreased risk for dyskinesias, whereas in women the genetic effect was negligible. In contrast, Strong *et al.* [33] did not replicate the previous results. Moreover, the authors found that *DRD2* 14 allele and 14/15 genotype was significantly associated with earlier onset of dyskinesias (OR for 14 allele: 3.4; 95% CI: 1.1-10.4; p=0.003). Further data came from a large study of Kaiser *et al.* [25], who investigated SNPs within various genes: nine polymorphisms of *DRD2* gene (*Taq*IA, *Taq*IB, *Taq*ID, Val96Ala, Leu141Leu, Pro310Ser, Ser311Cys, A>G231, -141C ins/del), two in *DRD3* (Ser9Gly, *Msp*I), three in *DRD4* (48-bp VNTR, 13-bp repeat, 13-bp deletion), and *DAT* gene (40-bp VNTR) in l-dopa induced dyskinesias. It was shown that genetic variations in *DRD2*, *DRD3* and *DRD4* did not influence the occurrence of l-dopa induced complications. However, in patients with dyskinesias the prevalence of 40-bp VNTR nine copy allele in *DAT* was observed. The risk of dyskinesias development in PD patients carrying 40-bp VNTR was 2.5 higher (95% CI: 1.3-4.7) than in non-carriers.

The results of Lee *et al.* [34] indicate, that a development of diphasic dyskinesias in PD patients on chronic, over 5 years, l-dopa therapy, may by genetically determined. The risk of diphasic dyskinesias occurrence significantly increased with the duration of l-dopa therapy in patients carrying *DRD3* rs6280 AA genotype, even after adjustment for gender, age at PD onset, HY stage, and duration of l-dopa treatment. The *DRD3* polymorphism was not associated with the risk of peak-dose dyskinesia development.

The genetic differences in COMT activity may influence not only individual response to l-dopa therapy but also the risk of developing motor complications. However, available data still remains conflicting. Lee *et al.* [35] as well as Watanabe *et al.* [36] failed to show any correlation between *COMT* Val158Met (rs4680:G>A) genotypes and motor complications in PD patients during l-dopa treatment.

Similarly, *COMT* Val158Met genotypes did not influence main l-dopa pharmacokinetic-pharmacodynamic variables and dyskinesias [37]. Our first study demonstrated slightly higher frequency of *COMT* Met/Met homozygotes in PD patients treated with low doses of l-dopa, thus suggesting that carriers of *COMT* Met/Met genotype may benefit from more efficient and safer l-dopa treatment [38]. Recent findings on the role of *COMT* haplotypes changed the attitude to genetic *COMT* investigations. Haplotype structure formed by all four SNPs characterizes COMT enzymatic activity better than a single SNP rs4680: G>A, previously studied as the major COMT activity determinant. The effects of *COMT* haplotypes on clinical response to l-dopa PD therapy was examined in our later study [39]. It was revealed that the mean l-dopa dose paralleled *COMT* activity determined by functional haplotypes (low<medium<high). Doses prescribed for G_C_G_G (high activity) haplotype carriers (mean 604.2±261.9 mg) were significantly higher than those for the non-carriers (mean 512.2±133.5 mg, $p<0.05$) at the fifth year of l-dopa therapy. However we failed to show any relationship between *COMT* haplotypes and development of l-dopa induced dyskinesias. Better clinical response to lower l-dopa doses administered in patients with low and medium activity *COMT* haplotypes when compared with doses used in high activity haplotype carriers, may be explained by slower catabolism of the drug, more stable serum and central nervous system drug concentrations, and lower levels of 3-0MD. Recently, results of a prospective cohort study in PD patients without dyskinesia at baseline have been published [40], and a relationship between allele A *COMT* Val158Met polymorphism and increased risk of developing dyskinesias during l-dopa therapy was revealed. The carriers of *COMT* AA genotype in comparison to GG, were significantly more prone to develop dyskinesia. The results remained significant after additional adjustments for duration and dosage of l-dopa, and dopamine agonists (AG and AA vs. GG: 2.09 (95% CI: 1.07-4.06) and 2.81 (95%CI: 1.43-5.54), respectively. Nevertheless, *COMT* gene polymorphism seems to be a very attractive target for pharmacogenetic studies, but conflicting results from different populations indicate the need for more expanded investigations.

Monoamine oxidase B (MAOB) is involved in the metabolism of biogenic amines such as tyramine and dopamine, and may be potentially involved in the PD pathogenesis, because of its role in reactive oxygen species generation as well as in activating exogenous neurotoxins, such as MPTP. Our study showed that *MAOB Tsp*45I polymorphism was not a determinant of l-dopa dose in PD patients during the first 5 years of the treatment [38]. Even though no significant differences were observed, some trends related to distribution of *MAOB* and *COMT* combined genotype suggested that *MAOB* might be a determinant of l-dopa medication efficacy, but those findings should be further replicated.

The literature data provide also an insight into the role of other genes, not directly implicated in l-dopa mechanism of action, that may modulate response to the drug. Brain-derived neurotrophic factor (BDNF) belongs to the

Table 1. Summary of the Pharmacogenetic Studies in Parkinson's Disease

Gene	Polymorphism	No pts	Comments	Significant Association	Reference
Levodopa					
DRD2, DRD3	rs1800497 (*Taq*IA) rs6280 (*Bal*I), rs4646996 (*Msp*I)	80	*DRD2* A1A1 (TT) genotype significantly more frequent among fluctuators vs. nonfluctuators	OR=4.33 p= 0.01	[16]
DRD2	rs1800497 (*Taq*IA)	503	No association with requirement of dopaminergic medication		[30]
DRD2 *DRD1*	(CA)n STR in intron 2	98	Protective effect of *DRD2* alleles 13 and 14 on the risk of peak-dose dyskinesias. The risk reduction of developing peak-dose dyskinesias for PD subjects carrying at least 1 of the 13 or 14 alleles - 72%	OR=0.23 p=0.002	[31]
DRD2	(CA)n STR	215	Protective effect of *DRD2* alleles 13 and 14 on the risk of peak-dose dyskinesias in men, not an independent factor in women	OR=0.339, p=0.02 (multivariate in men)	[32]
DRD2	(CA)n STR	92	Allele 14 carrier status and 14/15 genotype significantly associated with early dyskinesia	OR for 14 allele carriers: 3.4, p=0.04; OR for the 14/15 genotype: 27.2, p=0.003	[33]
DRD2 *DRD3* *GRIN2B* *SLC6A4*	rs1800497 (*Taq*IA) rs6280 (Ser9Gly) rs1806201 rs7301328 rs1019385 VNTR	503	Association of *DRD3* rs6280 AA variant genotype with diphasic dyskinesia (DDSK), significant after adjusting for gender, age at PD onset, Hoehn & Yahr stage, and duration of levodopa treatment. No association between peak-dose dyskinesia and any of the variants studied.	OR for DDSK: 3.1, p=0.002	[34]
DRD2 *DRD3* *DRD4*	various (9) various (2) various (3)	183	No association with adverse effects of l-dopa treatment (i.e. dyskinesia, psychosis, or "on–off"/wearing-off phenomena)		[25]
DAT	40-bp VNTR	165	Higher risk of developing dyskinesias or psychotic episodes in allele 9 carriers vs. others (l-dopa treated PD patients).	OR for dyskinesias: 2.5; p=0.006; OR for psychosis: 2.6; p=0.008;	[25]
OPRM1	rs1799971 (118A>G, Asn40Asp)	90	G allele carrier status (AG or GG genotype) was independently associated with increased risk of earlier onset of dyskinesia	OR=2.8; p=0.05	[33]
COMT	rs4680 (Val158Met)	73	No differences between different genotype groups in motor response after single oral levodopa challenge test		[35]
COMT	rs4680 (Val158Met)	118	Higher frequency of AA (Met/Met) homozygotes among patients with dyskinesias or showing the 'wearing-off' phenomenon compared to healthy controls	p=0.0302 for dyskinesia; p=0.0445 for 'wearing-off'; not significant after correction for multiple testing	[36]
COMT	rs4680 (Val158Met)	104	No influence on l-dopa pharmacokinetic nor pharmacodynamic variables and dyskinesias		[37]
COMT	rs4680 (Val158Met)	95	Not significantly higher frequency of Met/Met low-activity genotype among patients treated with lower doses of l-dopa		[38]

(Table 1) contd….

Gene	Polymorphism	No pts	Comments	Significant Association	Reference
Levodopa					
COMT	haplotype based on rs6269:A>G rs4633:C>T rs4818:C>G rs4680:A>G	159	L-dopa doses administered to G_C_G_G (high activity) haplotype carriers significantly higher than those for the non-carriers, during fifth year of treatment.	p<0.05	[39]
COMT	rs4680 (Val158Met)	219	Association of low activity A (Met) allele with higher risk of dyskinesias.	Adjusted HR: 2.09 (1.07–4.06) for AG and 2.81 (1.43–5.54) for AA genotype	[40]
MAOB	rs1799836 intron 13	95	No association with l-dopa dosage.		[38]
BDNF	rs6265 (Val66Met)	315	Met (A) allele associated with significantly higher risk of developing dyskinesias earlier in the course of treatment with dopaminergic agents.	HR: 2.12, p = 0.001, for each additional A allele	[41]
GBA	various mutations	278	GBA mutation carriers more likely to report the presence of dyskinesias; however, the dose of levodopa was significantly higher among carriers than among noncarriers;	p=0.02	[43]
GBA	various mutations	1391	Dyskinesias more frequent among GBA mutation carriers, independently of gender, dose of levodopa, disease and treatment duration;	p=0.037	[44]
ACE	rs4646994 (I/D – ins/del)	91	No association with the occurrence of l-dopa-induced adverse effects in long-term treatment		[45]
ACE	rs4646994 (I/D – ins/del)	251	ACE-II genotype associated with l-dopa-induced psychosis; no association with the risk to develop dyskinesia or motor fluctuation induced by l-dopa.	Unadjusted OR: 1.435, p = 0.012 Adjusted OR: 2.542, p = 0.012	[46]
APOE	rs429358 rs7412 (e2, e3, e4)	155	No association with l-dopa-induced dyskinesias		[47]
CCK CCKAR CCKBR	rs1799923 (-45C>T) rs1800857 (779T>C) rs1805002 (1550G>A)	96	CCK -45T allele associated with halucinations (not significantly)	p=0.06	[48]
CCK CCKAR CCKBR	rs1799923 (-45C>T) rs1800857 (779T>C) rs1805002 (rs1550G>A)	174	No association with halucinations		[49]
SLC22A1 (OCT1)	rs622342	99	The rs622342 minor C variant allele was associated with higher prescribed doses of anti-Parkinsonian drugs and shorter survival time after start of levodopa therapy.	Defined daily dose raised for 0.34 for each C allele; p=0.017; mortality for each C allele: HR 1.47, p=0.045;	[52]
Dopamine agonists					
DRD2	rs1800497 (*Taq*IA)	30	Not significantly associated with therapeutic efficacy of pramipexole		[58]
DRD3	rs6280 (Ser9Gly)	30	Significantly associated with therapeutic efficacy of pramipexole		[58]
DRD2	rs1799732 (141C Ins/Del)	38	No significant association with non-ergoline DA discontinuation		[18]

(Table 1) contd….

Gene	Polymorphism	No pts	Comments	Significant Association	Reference
Dopamine agonists					
DRD2	(CA)n STR	38	The absence of a 15 CA repeat allele was significantly related with a decreased discontinuation of non-ergoline treatment (pramipexole, ropinirole).	[HR 0.23; 95%CI: 0.07–0.81]	[18]
DRD2	rs1800497 (*Taq*IA)	38	No significant association with non-ergoline DA discontinuation		[18]
DRD3	rs6280 (*Msc*I),	38	No significant association with non-ergoline DA discontinuation		[18]
DRD3	rs4646996 (*Msp*I)	38	No significant association with non-ergoline DA discontinuation		[18]
COMT inhibitors					
UGT1A	see text	135	*UGT1A SNPs* were significantly associated with tolcapone-associated elevated liver transaminase level	for marker UGT1A6-A-528G [OR 2.76 (95%CI: 1.5-5.06]	[56]
COMT	rs4680 (Val158Met)	24	No significant association between tolcapone efficacy and drug induced diarrhea and *COMT* genotype.		[55]
COMT	rs4680 (Val158Met)	65	No significant association between entacapone efficacy and *COMT* genotype.		[54]
COMT	rs4680 (Val158Met)	34	The gain in the best ON time was higher in *COMT*-H than in *COMT*-L patients. AUC of levodopa higher after entacapone in *COMT*-H than in *COMT*-L patients. COMT inhibition by entacapone higher in *COMT*-H than in *COMT*-L patients.		[53]
Pyridoxine					
COMT	rs4680 (Val158Met)	39	Significant association between *COMT* polymorphism and response to pyridoxine		[59]

OR - odds ratio; HR - hazard ratio.

neurotrophin family of growth factors, which contribute to the survival, differentiation, and maintenance of neurons in the peripheral and central nervous system. BDNF has been shown to play an important role in the survival of dopaminergic neurons in substantia nigra and its genetic polymorphism was associated with an increased risk for late onset PD. However, the studies provide inconsistent results. The most explored polymorphism in the *BDNF* gene is G to A change resulting in valine to methionine substitution at codon 66 (Val66Met) in the terminal exon of the gene (rs6265). The functional consequence of *BDNF* Val66Met polymorphism is decreased protein secretion in carriers of allelic variants of the gene. The study conducted by Foltynie *et al.* [41] indicated that the genetic variation in *BDNF* could possibly influence some aspects of PD therapy, such as the time of development l-dopa induced dyskenesias. Patients with the Met allele of *BDNF* were at significantly higher risk of early dyskinesias in the course of treatment with dopaminergic agents, including l-dopa (hazard ratio for each additional Met allele 2.12, p = 0.001) in comparison to the Val allele carriers, and after adjustment for other potential confounding variables for example age at diagnosis, gender, total UPDRS score at baseline.

Mutations in glucorebrosidase gene (*GBA*) are recently being considered as one of the genetic factors predisposing to PD, particularly early-onset type of disease. GBA mutations cause Gaucher's disease (GD), a recessive glycolipid storage disorder. Although there is no significant overlap between GD and PD phenotypes, the indication for a relationship between the two conditions came with the observation of the occurrence of parkinsonism and Lewy body pathologies in patients with GD and their relatives, as well as the identification of *GBA* mutations in patients with PD [42]. Apart from predisposition to PD, subsequent genotyping studies have shown increased frequency of dyskinesias in a group of PD patients carrying *GBA* mutations [43]. That observation was confirmed by a large French study, where the carriers demonstrated l-dopa-induced dyskinesias more frequently (62%) than non-carriers (50%; p=0.037), independently of gender, dose of l-dopa, disease and treatment duration [44].

The importance of the renin–angiotensin system (RAS) as targets for developing new treatment strategies in PD is a new concept. It is known that the brain RAS may be involved in lesion of dopaminergic neurons and probably the PD progression. Nevertheless, the role of angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism in modifying the response to dopaminergic treatment in PD is controversial. ACE gene is located on chromosome 17q23 and consists of 26 exons and 25 introns. The most studied *ACE* polymorphism is characterized by an insertion (I) or a deletion (D) of a 287 noncoding base pairs of Alu repeat sequence (rs4646994). The functional consequences of three genotypes (DD, ID and II) result in changes in ACE circulating and intracellular activity. Pascale *et al.* [45] investigated a *ACE* D/I polymorphism in PD, and failed to observe any significant association with the occurrence of l-dopa-induced adverse effects in long-term treatment. Contrary, Lin *et al.* [46] revealed that the *ACE* polymorphism affected effects of l-dopa treatment outcome, i.e. predisposition for l-dopa-induced psychosis was significantly higher in homozygotes of ACE-II genotype (OR=1.435, 95%CI= 1.105-1.864). The authors, likewise in the previous study, failed to confirm associations between *ACE* polymorphism and the risk to develop l-dopa induced dyskinesias or motor fluctuation.

Apolipoprotein E – *APOE* gene polymorphism has been reported as a risk factor for Alzheimer disease (AD) and PD, but PD data is less consistent. The *APOE* gene is located on the long arm of chromosome 19 at position 13.2. There are at least three alleles of the *APOE* gene, called e2, e3, and e4. Molchadski *et al.* [47] determined the relationship between *APOE* polymorphisms and time to l-dopa-induced dyskinesia in PD patients, and reported no significant associations between the genetic factors and clinical findings.

Cholecystokinin (CCK) is a neuropeptide, which was found in the gut and central nervous system, and in the latter it takes part in dopaminergic regulation by cholecystokinin A receptor (CCKAR) and cholecystokinin B receptor (CCK BR). Some studies indicated that polymorphism of *CCK* gene -45C/T may be positively associated with hallucinations in PD patients under l-dopa treatment. Goldman *et al.* [48] have shown more frequent representation of *CCK* T allele in hallucinating PD subjects in comparison to non-hallucinating patients. However, this finding was not supported by their own further observation in a larger cohort of PD [49]. *CCK* polymorphisms appear to differentially affect hallucination risk in different racial groups, since CCK and CCK receptor gene polymorphisms were shown to increase hallucination risk in Asian PD patients, whereas in white PD patients the effect was not revealed. That example points to the importance of ethnicity in the case of genetic studies, as frequencies of SNPs associated with certain outcomes in one population may fail to be replicated in ethnically different cohorts. That is also observed in gene-environment interaction studies, e.g. investigation of *ABCB1/MDR1* (coding for P-glycoprotein) SNPs reported to influence various toxicants entry into the brain; *ABCB1* polymorphism was reported to modify PD risk only in Asians, while no influence was observed in Caucasian population [50, 51]. That issue may be of particular significance for SNPs not directly affecting protein expression/activity, that can be used as useful markers only in some ethnic groups, as certain linkage between different *loci* can differ between populations.

Organic cation transporters (OCT) play a major role in the carriage of dopamine, and some antiparkinsonian drugs including l-dopa, and demonstrate polymorphisms in genes coding OCT1 (*SLC22A1*), OCT2 (*SLC22A2*), and OCT3 (*SLC22A3*). Becker *et al.* [52] showed a significant association between *SLC22A1* rs622342 A>C polymorphism (minor C allele is most likely associated with lower activity OCT1 transporter) and higher prescribed doses of antiparkinsonian drugs, as well as a shorter survival after l-dopa therapy initiation. The authors revealed that for each minor rs622342 C allele, the prescribed doses were 0.34 defined daily dose higher (95% CI 0.064, 0.62; p= 0.017) between the first and fifth l-dopa prescriptions. Moreover, the mortality ratio after start of l-dopa therapy was 1.47 times higher (95% CI 1.01, 2.13; p=0.045).

COMT Inhibitors

The association between efficacy of entacapone and *COMT* polymorphism in PD patients was evaluated by Corvol *et al.* [53]. In a randomized, double-blind crossover trial higher COMT inhibition by entacapone in *COMT*-H (Val158Val) than in *COMT*-L (Met158Met) patients was reported. Moreover, the study revealed that the exposure to levodopa was higher in *COMT*-H subjects, as area under the concentration over time curve (AUC) of levodopa increased more after entacapone in *COMT*-H than in *COMT*-L patients. These findings were paralleled by a clinical observation that the gain in the best ON time was significantly higher in *COMT*-H than in *COMT*-L patients. However, clinical observations by Lee *et al.* [54] in Korean PD patients medicated with entacapone for 2 months did not reveal any significant relationship between *COMT* (Val158Met) genotype and measures of the disease activity: increase in ON time, a reduction in OFF time, and a reduction in the total UPDRS score. The patients were given daily dose of l-dopa over 6 months, and experienced at least two periods of "wearing off" that lasted longer than 2 hours with Hoehn and Yahr stage 2 to 4 for longer than 3 months.

Similar observations were also reported from North American PD subjects presenting fluctuations and medicated with l-dopa receiving tolcapone for 6 months [55]. Chong *et al.* did not found any significant association between *COMT* (Val158Met) genotype and extent of improvement in UPDRS score. Likewise, there was no significant association between *COMT* genotype and tolcapone side-effect of diarrhea. Also, individuals who had different genotypes showed no significant changes in the amount of daily l-dopa dosage. In a retrospective study Acuña *et al.* [56] identified genetic markers (30 polymorphic loci in 12 candidate genes implicated in the drug metabolism) for tolcapone administration associated hepatic toxicity, defined as elevation of liver transaminase levels ≥1.5 times above the upper normal limit. The results of the study revealed a SNPs located within the UDP-glucuronosyl transferase 1A gene complex (*UGT1A*), coding for the enzymes involved in the main elimination pathway of the drug, were found to be significantly associated with the occurrence of tolcapone-associated elevated liver transaminase level, for G allele at marker *UGT1A6* loci

A528G (OR=2.76, 95% CI=1.5–5.06; p<0.001) as well as nine other markers in the UDP-glucuronosyltransferase gene complex, which are in significant linkage disequilibrium with *UGT1A6* A528G.

Anticholinergics

No data available

MAO Inhibitors

No data available

Dopamine Agonists (DA)

Bromocriptine, Cabergoline, Pergolide

Rissling *et al.* [57] revealed in an association study on dopamine D2, D3, and D4 receptor gene polymorphisms and sudden onset of sleep in PD, a significant relationship between dopamine D2 receptor gene polymorphism *Taq*IA, with predisposing role of *DRD2* allele A2, and sudden onset of sleep. The association between *DRD2* allele A2 and sudden onset of sleep was most pronounced in patients taking bromocriptine, pergolide or cabergoline. No significant association between *DRD3* (*Msc*I polymorphism) and *DRD4* (120-bp tandem duplication polymorphism in the promoter region) polymorphisms and the phenomenon of "sleep attacks" was shown.

Non-ergoline DA

The main targets of non-ergoline DA are DRD2 and DRD3 receptors, with preferential affinity for the DRD3. An association of *Taq*1A *DRD2* and Ser9Gly *DRD3* polymorphisms with response to pramipexole administered for 2 months in PD patients of Chinese origin was reported by Liu *et al.* [58]. The study revealed that PD patients carrying Ser/Ser genotype were characterized by a significantly higher response rates, using improvement in UPDRS by at least of 20% as responsiveness indication, to pramipexole (60%) than Gly allele subjects (13%). No significant relationship between *DRD2 Taq*1A polymorphism and pramipexole efficacy was observed. Genetic determinants, i.e. polymorphisms of: *DRD2* 141C Ins/Del, *DRD2* (CA)n STR, *DRD2 Taq*IA, *DRD3 Msc*I and *DRD3 Msp*I underlying non-ergoline dopamine agonists discontinuation were evaluated by Arbouw *et al.* [18], in PD patients medicated for the first time with ropinirole and pramipexole. The study revealed that the absence of a *DRD2* 15×CA repeat allele was significantly associated with a decreased discontinuation of non-ergoline treatment (HR 0.23; 95% CI 0.07–0.81). In case of the *DRD3 Msp*I polymorphism, a correlation was observed between the number of G alleles and risk of treatment discontinuation (increasing hazard ratio: AA<AG<GG), but the differences were not significant, possibly due to a limited number of patients.

Pyridoxine

Tan *et al.* [59] examined the effect of COMT Val158Met polymorphism on clinical response, using UPDRS, to pyridoxine in PD patients with stable and optimized dose of l-dopa. In a multivariate model applied in the study, the presence of *COMT*-L allele was found to predict response to pyridoxine, with the best outcome observed in *COMT*-LL homozygotes. The authors concluded that status of functional *COMT*-L variant might be potentially useful to select PD patients for high (400 mg/day) dose pyridoxine therapy.

CONCLUSION AND FUTURE PERSPECTIVE

Large variation in response to the administered drug medication is observed in PD patients. Some polymorphic genes, important for antiparkinsonian drugs' metabolism and action were identified, and those findings may have potential implications for disease management. The results of the genetic studies support the role of interindividual variation in the activity of COMT and dopamine receptors, providing important data complementing the knowledge on molecular mechanisms of drug actions. However, despite many efforts to identify genetic factors affecting the risk of adverse effects or therapy ineffectiveness, the role of pharmacogenetics in the treatment of Parkinson's disease is still relatively unexplored and lacks unequivocal conclusions that could be translated into clinical recommendations. Recently, several *loci* have been identified as sporadic PD risk factors in genome-wide association studies [5]. Those SNPs could be also investigated in relation to safety and efficacy of disease treatment, as some of them can possibly influence the course of therapy or increase disease risk only in a presence of additional environmental factors. Gene-environment interactions in PD were previously identified in case of exposure to pesticides and genes related to xenobiotic transport and metabolism (*PON1*, CYP2D6, *SOD2*, *NQO1*) [60], whereas *DAT* polymorphism was associated with both disease risk and dyskinesias or psychotic episodes in patients treated with levodopa [25]. Similarly, *loci* identified in GWAS could also modify outcome of therapy with antiparkinsonian drugs. On the other hand, with the rapid development of high-throughput genotyping platforms, pharmacogenetic GWAS might be performed, analyzing therapy outcome in hypothesis-free study for identification of SNPs associated with treatment inefficacy or toxicity. Hence, a lot of progress is still to be made to put forward the idea of individualized therapy of PD, guided by genetic testing.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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