Movement Disorders
CLINICAL PRACTICE
REVIEW

Pharmacogenetics of Parkinson's Disease in Clinical Practice

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Abstract: **Background:** Pharmacogenetics aims to identify the genetic factors participating in the heterogeneity of drug response. The ultimate goal is to provide personalized treatment by identifying responders and non-responders, individuals at risk of developing drug adverse effects, and by adjusting dosage. Several studies have been performed in Parkinson's disease (PD), to investigate drug response variability according to genetic factors for dopamine replacement therapies.
Methods: We performed a systematic literature search of articles related to pharmacogenetic studies in PD, and found 47 studies.
Findings: Motor response and adverse reactions to dopaminergic drugs were associated with genes encoding enzymes of their metabolism as well as their receptors or targets. Despite some interesting results, considerable work remains to be done to replicate and validate their clinical relevance before translation into clinical practice.
Conclusions: There are currently no guidelines published for pharmacogenetic factors related to PD drugs. More research is need in this field in order to improve our knowledge in drug response variability in PD. Algorithms taking into account clinical, pharmacological, and genetic factors are probably the most promising way to help for a personalized medicine in PD.

Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically defined by its cardinal motor symptoms of bradykinesia, rigidity, and resting tremor, although most patients also suffer from a plethora of non-motor symptoms including autonomic, sleep, behavioral and cognitive disorders. Treatment of the motor symptoms of PD is essentially based on pharmacological dopamine replacement therapy (DRT), which includes levodopa, dopamine agonists, dopamine metabolism and/or inhibitors. While DRT is usually highly effective in improving motor symptoms it has no effect on disease progression, and little or no beneficial impact on non-motor symptoms. Progressive disability in the course of PD is driven both by ongoing neurodegeneration with increasing severity and a spectrum of motor and non-motor symptoms as well as by the occurrence of motor fluctuations and drug-induced dyskinesia in response to chronic levodopa therapy. Some of the adverse effects of DRT overlap with non-motor symptoms intrinsic to the disease, particularly those affecting sleep, autonomic function, cognition and behavior. The clinical presentation of PD is thus highly variable in terms of symptoms, motor response to treatment, and development of complications or adverse events, highlighting the need for 'personalized' treatment in order to ensure the best possible risk/benefit ratio in terms of motor response versus adverse effects and induction of motor complications.

The variability of the response to a drug is related to its pharmacokinetics (absorption, distribution, metabolism, and elimination) and/or its pharmacodynamics (target-level action) properties (Fig. 1). In neurological disease, the blood brain barrier (BBB) is also an important factor regulating the intracerebral concentration of the drug. These parameters may be influenced by environmental factors, drug interactions, or by

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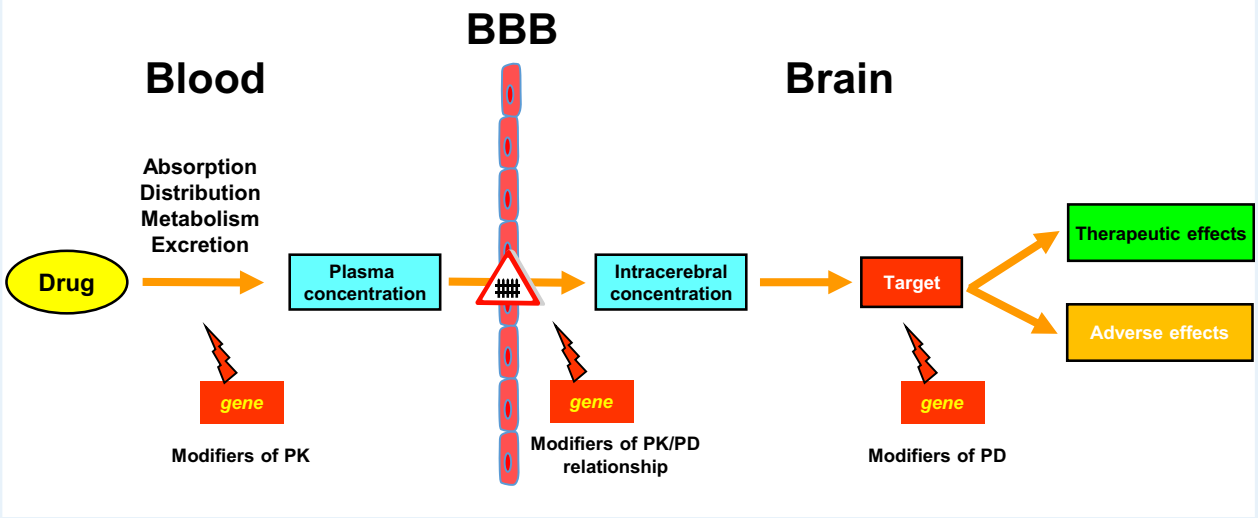

Figure 1 Pharmacogenetics in Neurology. The response to a drug in neurological disorders depends on its pharmacokinetics parameters including its absorption, distribution, metabolism and excretion, which determine its plasma concentration, but also on its capacity to cross the blood brain barrier (BBB) to finally access its targets. Variants of gene encoding metabolism enzymes, blood brain barrier transporters, and the target of the drug can modify the pharmacokinetic or pharmacodynamic parameters of the drug, and finally its therapeutic response or the risk of adverse reactions. BBB: blood brain barrier; PK: pharmacokinetic parameters; PD: pharmacodynamics parameters.

factors related to individual pathological or physiological conditions, including genetic variability. Pharmacogenetics aims to identify the genetic factors participating in the heterogeneity of drug response. Indeed, genetic variations at the DNA (polymorphisms, mutations, epigenetics) or at the RNA (differences in gene expression, micro-RNA) levels can directly or indirectly modify the expression or the activity of proteins involved in the mechanism of action of a drug or its metabolism. Genetic factors may also modify the disease itself, segregating patients into sub-populations with different responses to the same drug.

In PD, several studies have investigated genetic factors related to the response to DRT. The results of these studies provided important insights into the pharmacology of dopaminergic drugs, i.e. their mechanism of action and metabolism, and more generally into the mechanism of action of dopamine in the brain. The ultimate goal of pharmacogenetics is to personalize treatment to the individual by pre-identifying responders and non-responders, adjusting treatment dose, and identifying individuals at high risk for adverse drug reactions. This ambitious goal has not yet been achieved. However, recent advances in molecular genetics have paved the way to the transfer of pharmacogenetics into clinical practice.

Here, we review the most important advances that have been made into the pharmacogenetics of PD. We have deliberately chosen a clinical point of view, describing the results and their potential consequences for the management of patients in clinical practice. For a more detailed description of genetic variants and their molecular functional consequences we refer the reader to the original articles cited in this review and to other recent reviews on this topic.[1]

Methods

We performed a systematic literature search of articles related to pharmacogenetic studies in PD by using a strategy previously described for pharmacogenetic reviews.[2] We searched articles indexed in Medline—from its inception up to April 2016—using the Medical Subject Heading (MeSH) or full-text terms:

- Genetic Variation (MeSH)
- Genotype (MeSH)
- Genes (MeSH)
- Genotype
- Polymorphism
- Allele
- Mutation
- Treatment Outcome (MeSH)
- Therapeutics (MeSH)
- Adverse effects (Subheading)
- Pharmacogenetics
- Toxicogenetics (MeSH)
- Pharmacogenomic
- Pharmacogenetic
- Toxicogenetic
- Therapeutic
- Intervention
- Treatment
- Parkinson's disease (MeSH)
- English (language) not case report, not review

The search was filtered for articles on humans. The 628 articles found were then manually filtered to include only

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pharmacogenetic studies, i.e., a study in which the response to a drug treatment was examined in relation to genetic variation in PD patients, and to exclude pure genetic studies (without drug response), or gene-environment interaction studies on disease susceptibility. Studies on deep brain stimulation were not included in this review. We also searched for reviews on pharmacogenetic in PD.[1,3–9] No meta-analyses was found on this topic. The 47 remaining studies are detailed in Table S1.

Motor Response to DRT

Response to Levodopa

Levodopa remains the gold standard for DRT in PD. Dopamine is synthesized from levodopa by Aromatic L-Amino acid Dopa Decarboxylase (AADC) and subsequently metabolized by two major pathways, the Catechol-O-methyltransferase (COMT) and the monoamine oxidase B (MAOB) pathways.

Because levodopa is exclusively administered in conjunction with dopa-decarboxylase inhibitors (carbidopa or benserazide) levodopa metabolism is switched to the COMT pathway, which is also the target of COMT inhibitors. The *COMT* gene has a functional Val158Met polymorphism, which confers high (Val allele, or $COMT^{H}$) or low (Met allele, or $COMT^{L}$) enzymatic activity to the protein. This polymorphism is frequent (minor allele frequency = 0.5 in the Caucasian population), resulting in 25% of high metabolizers ($COMT^{HH}$), 50% intermediate ($COMT^{HL}$), and 25% of low metabolizers ($COMT^{LL}$). More complex haplotypes of the gene including non-coding or synonymous SNPs have also been described.[10] The COMT Val158Met polymorphism was not associated with differences in pharmacokinetic or pharmacodynamic parameters of levodopa during acute challenges.[11–13] However, daily doses of levodopa were higher in high metabolizers in some studies, suggesting a lower response to the drug when administered chronically.[10,14,15] The COMT Val158Met polymorphism was shown to modify the motor response to the COMT inhibitor entacapone during an acute challenge, the high metabolizers having a greater response as compared to the low metabolizers.[12] However, the clinical relevance of this finding remains to be clarified since no significant effect was found when COMT inhibitors were administered repeatedly, either with entacapone[16] or tolcapone,[17] another COMT inhibitor that crosses the blood brain barrier. No pharmacogenetic data has been published yet for the new COMT inhibitor opicapone.

In the central nervous system, tyrosine hydroxylase (TH) is the rate-limiting enzyme for dopamine synthesis in dopaminergic neurons. However, in PD, dopaminergic neurons degenerate, and dopamine is essentially generated from the metabolism of levodopa by AADC. One study has found an association between the motor response to levodopa and AADC activity.[18] In this study, the area under curve for the motor response during an acute challenge of levodopa was lower in subjects carrying a deletion in the promoter region of the *AADC* gene. The peak of the motor response was not different between genotypes (confirmed in another study).[13] This association is thought to be due to the effect of the polymorphism on dopamine concentrations in the brain rather than in the periphery because levodopa was co-administered with an AADC inhibitor. Indeed, levodopa and dopamine pharmacokinetics were not different between genotypes.[18] No study has examined the association between *AADC* genotype and the effects of benserazide or carbidopa on levodopa response characteristics in PD; nor have the effects of *AADC* polymorphisms on the response to chronic exposure to levodopa been addressed. However, a crossover study testing the administration of high doses of pyridoxine, a cofactor of AADC, found a greater motor response in PD patients which was associated with the *COMT*, but not the *AADC* gene.[19]

The solute carrier family 6 member 3 (*SLC6A3*) gene encodes the dopamine transporter, DAT. *SLC6A3* was not significantly associated with the motor response to levodopa in one study,[20] but there were associations with the peak of the motor response after an acute challenge of levodopa in a post-hoc pharmacogenetic analysis of a clinical trial in PD patients with deep brain stimulation.[13] This discrepancy might be related to the differences in disease duration between patients of the two studies, raising the possibility that pharmacogenetic effects might vary according to disease stage in PD.

The monoamine oxidase B gene (*MAOB*) was not associated with the motor response during an acute challenge of levodopa.[13] A possible association between the *MAOA* or the *MAOB* genes with the doses of levodopa used in PD was found in two studies, however this association was weak and remains to be confirmed.[14,15]

In conclusion, no major genetic effects on levodopa pharmacokinetics have been found so far. In terms of motor response, *SLC6A3* and the *AADC* polymorphisms have been linked to the acute effect of levodopa in some studies, whereas the *MAOB* and *COMT* genes had no effect on acute challenges but have been associated with chronic levodopa doses used in PD patients. The acute response to entacapone was influenced by the COMT Val158Met polymorphism but the response to chronic administration of COMT inhibitors did not differ in relation to this genotype. In clinical practice, there are currently no pharmacogenetic recommendations regarding the use of levodopa, COMT inhibitors, or MAO inhibitors in PD.

Response to Dopamine Agonists

Dopamine agonists are metabolized by different liver enzymes which have been previously reviewed.[1] Genes encoding cytochromes are subject to genetic variations and this is of clinical importance in other contexts, like for cancer therapies.[21] However, no pharmacogenetic study has been performed in relation to pharmacokinetic handling or clinical response to dopamine agonists in PD yet. The potential importance of cytochrome genetic variability on the pharmacokinetics of dopamine agonists can be estimated from results obtained when they were co-administered with cytochrome inhibitors. For example, co-administration of cytochrome P450 3A4 (CYP3A4) inhibitors increases the area under curve of bromocriptine[22,23] or

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cabergoline plasma levels.[24,25] When patients are treated with ropinirole and a cytochrome P450 1A2 (CYP1A2) inhibitor such as ciprofloxacin, an increase in the AUC for ropinirole is observed[26] and it has been suggested that dose adjustments of ropinirole may be necessary when introducing or discontinuing a potent CYP1A2 inhibitor.[27] Pharmacogenetic studies on dopamine agonists in PD would be needed to better assess these effects.

Transporters of dopaminergic drugs into the CNS across the blood brain barrier (BBB) might also potentially modify drug response. One study showed a correlation between a polymorphism of the organic cation transporter 1 gene (*OCT1*) and doses of anti-parkinsonian drugs,[28] but this result still awaits replication. Most dopamine agonists have been shown to cross the BBB using the multidrug resistance receptor 1 transporter (MDR1, or p-glycoprotein)[29] and one study in patients with prolactinomas suggested that polymorphisms in the gene coding this transporter predict side effects of their treatment with cabergoline.[30] However, no studies have examine the potential association between *MDR1* and the response to dopamine agonists in PD.

Regarding their targets, dopamine agonists are believed to exert most of their effects through the stimulation of D2 and D3 dopamine receptors. No association has been found between genes encoding these receptors (*DRD2* and *DRD3*) and the motor response or the daily dose of dopaminergic drugs.[31,32] Only one study found an association between the DRD3 Ser9Gly polymorphism and the motor response to pramipexole during an acute challenge in a population of Chinese origin.[33]

Motor Complications

Advanced PD is characterized by the presence of motor complications, i.e., motor fluctuations and levodopa-induced dyskinesia. The time to develop these motor complications during chronic treatment with levodopa is highly variable between patients, and the main factors associated with their early occurrence are: a young age of PD onset, high doses of levodopa, and disease duration.[34] Several genetic association studies have explored polymorphisms of genes affecting levodopa metabolism or dopamine receptors that may modify the progression of motor complications. Associations have been found between levodopa-induced dyskinesias or motor fluctuations and the *DRD2* gene,[35–39] however, these results have not been replicated by others.[40–42] This discrepancy may be due to the different polymorphisms tested or to differences in the clinical definition of dyskinesia. Interestingly, one study found a specific association between the D3 dopamine receptor (*DRD3*) Ser9Gly polymorphism and dystonic (biphasic) dyskinesia, but this polymorphism was not associated with peak-dose dyskinesia suggesting that the physiopathology of these two types of involuntary movements may be different.[42]

Two studies have suggested an association between the dopamine transporter gene *SLC6A3* and a shorter delay of dyskinesia onset.[40,41] Some studies have suggested that $COMT^{L}$ carriers are more at risk in developing motor complications, including dyskinesia,[43–45] but others have failed to confirm this result.[10,15,46] The monoamine oxidase genes (*MAOB* and *MAOA*) were not associated with the risk of dyskinesia in PD.[14,15,46]

Levodopa-induced dyskinesias are supposed to be due to non-physiological stimulation of striatal dopamine receptors but also involve aberrant signaling in other neurotransmitter systems leading to maladaptive neuronal plasticity in basal ganglia motor circuits.[47] Based on this hypothesis, genes regulating non-dopaminergic pathway activity were tested for their association to drug-induced dyskinesias in PD. Genetic studies found a significant association with the opioid receptor[37] and the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism.[48] However, the latter result was not replicated in two studies.[15,41] No significant association was found with the glutamate receptor 2B subunit (*GRIN2B*) or the serotonin receptor genes.[42]

In conclusion, current evidence suggests that motor complications in response to chronic levodopa exposure may differ among patients according to their genetic background. The susceptibility to develop early dyskinesias or motor complications probably involves several genes. Because results from available studies are inconsistent, replication and meta-analyses are needed to better understand the molecular mechanisms underlying these complications, and to propose a clinical-genetic model to predict their occurrence at the individual level.

Adverse Effects of DRT

Adverse effects of dopaminergic drugs include a large variety of symptoms related both to their peripheral and central actions, including dysautonomia; as well as cognitive, behavioral and sleep-wake dysfunction. There are a limited number of studies that have assessed pharmacokinetic determinants of DRT tolerability and safety.

A study of 90 PD patients who were first-time users of a non-ergoline dopamine agonist (50% ropinirole, 50% pramipexole) found that discontinuation of the drug due to side effects, or insufficient efficacy, was associated with DRD2 genetic determinants.[49] However, hallucinations in PD were not related to dopamine receptor genes *DRD1*, *DRD2*, *DRD3*, or *DRD4* in several studies,[40,50–52] while two reports suggested an association with cholecystokinine (*CCK*) and its cholecystokinin A receptor (*CCKAR*).[53,54] Inconsistent results were found for an effect on hallucinosis of polymorphisms of the *SLC6A3* gene, encoding the DAT,[40,52] or the Apolipoprotein E (*ApoE*),[50,55] while no association was found with polymorphisms of the serotonin transporter (*5HTT*), or the 2A serotonin receptor (*5HT2AR*) genes, although the latter was associated with delusions.[56,57]

An interaction effect was found between the executive functions, levodopa-therapy and *COMT* genotype in PD patients, consistent with the major role of COMT enzyme activity for the availability of dopamine in the prefrontal cortex.[58,59]

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Associations of daytime sleepiness or sleep attacks were found for *DRD4* and *COMT* genes but not for the *DRD2* or the serotonin transporting *5-HTT* genes.[32,60] However, another study in 240 patients with PD failed to confirm the association between *COMT* genotype and daytime sleepiness in PD,[61] but found an association with *DRD2*.[62] One study found a significant association of sudden-sleep onset and the gene encoding the hypocretin.[63]

Genetic association studies in the general population have shown a high heritability of impulse control disorders, related to a complex multigene heritability, involving multiple systems of neurotransmitters including the dopamine, norepinephrine, serotonin, glutamate, and opioid systems.[64] In PD, impulse control disorders affect 15 to 25% of PD patients treated with dopamine agonists, and genetic associations have been reported for the *DRD3* and the gene encoding the glutamate receptor 2B subunit, *GRIN2B* genes.[65] A dose-dependent association with the gene encoding *5HT2AR* has also been found in the same cohort of patients, suggesting an involvement of the serotoninergic system in the pathophysiology of this adverse effect due to dopamine agonists.[66] In accordance, a case-control study found that variants of the tryptophane hydroxylase type 2 gene (*TPH2*), the enzyme involved in the synthesis of serotonin, modulate severity and outcome of addictive behaviors in PD.[67] No association was found for *COMT*, *DAT*, or *5HTT*.[65,68] There are conflicting results about an association with the DRD2 gene.[65,68–70] A recent study performed in de novo PD patients, prospectively followed after DRT initiation, found heritability of ICD to be 57%.[69] In this study, a clinical genetic model including variants in 13 genes was able to predict ICD behavior occurrence with a high accuracy. Altogether, these results suggest that there is a strong heritability in ICD in PD. However, the effect of each individual gene is relatively small, the susceptibility to this adverse event is probably multigenic, and future predictive models should include both clinical and genetic factors. All these results remain to be replicated before being translated into clinical practice.

COMT inhibitors are extensively metabolized in the liver by glucuronidation. It has been shown that entacapone and tolcapone are metabolized by UDP-glucuronosyltransferase UGT1A enzymes.[71] There are several studies showing that polymorphisms of *UGT1A* genes could be related to tolcapone- or entacapone–induced liver toxicity and adverse reactions but no pharmacogenomic recommendations have been formulated from this yet.[1,72–74] The MAO inhibitor selegiline is metabolized by the cytochromes CYP2B6, CYP2C19, and to a lesser extent by CYP3A4 and CYP1A2.[1] CYP2B6 is a highly polymorphic gene with some variants affecting enzyme activity, particularly the *CYP2B6*18* variant, which is more frequent in subjects with African and Columbian genetic background.[1] However, to date, no clinical genetic association studies on selegiline pharmacokinetics and *CYP2B6* variant alleles have been performed, and no pharmacogenetic recommendations regarding *CYP2B6* pharmacogenetics and selegiline use have been formulated. It has been shown that common loss-of-function *CYP2C19* polymorphisms have little relevance for selegiline pharmacokinetics.[75] The MAOB inhibitor rasagiline is metabolized by CYP1A2 but no studies have addressed the potential role of functional CYP1A2 polymorphisms on rasagiline pharmacokinetics or its response in PD.

Future Directions: Perspectives

Genetic Forms of PD and Genetics-based Clinical Trials

Although PD is commonly sporadic, rare monogenic forms of the disease with autosomal dominant or recessive inheritance have been discovered. Treatment response may differ between these genetic forms of the disease as compared to sporadic PD. For example, autosomal recessive PD due *PARK2* mutations (Parkin) may respond dramatically to low doses of dopaminergic treatment[76,77] while levodopa response in autosomal dominant PD due to *LRRK2* mutations is similar to sporadic PD. There was suggestion of earlier development of motor complications in *LRRK2* patients[78] which was not replicated in a recent study.[79] Rare forms of PD with autosomal alpha-synuclein (*SNCA*) dominant mutation or duplication/triplication have usually a good although transient response to levodopa, and is accompanied with early psychosis and dementia.[80,81] Important case to case variability have been reported in relation to age at onset, levodopa responsiveness, motor fluctuations and non-motor symptoms. This variability is however probably more related to different neuropathological features rather than a direct effect of *SNCA* mutations on the pharmacology of levodopa.[82] PD associated with mutations in the glucocerebrosidase gene (*GBA*) appears to have earlier onset of hallucinations and cognitive decline as compared to sporadic cases without this mutation.[83–85] More importantly, mutations in PD genes may represent new targets for drug therapy and future trials may target genetically determined PD populations with specific interventions on defects caused by the underlying mutations, like kinase-inhibitors in *LRRK2* associated PD, or glucocerebrosidase enzyme activity in PD with GBA mutations.

The Next Steps Towards Transfer into Clinical Practice

It may be too early to design concrete next steps towards clinical practice implementation since many of the pharmacogentic associations still lack consistency. The pathway for pharmacogenetics associations from discovery to implementation in clinical practice has several stages including: discovery, replication, validation, translation, and finally implementation into clinical practice.[21] To date, several studies have screened many variants and phenotypes in relatively small sample size, and with generous statistical thresholds. The replication of top hits in independent cohorts are needed to assess reproducibility and robustness. Most of the published association studies are based on retrospective analyses and transversal cohorts.

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Only a few of them were case-control studies or clinical trials with pharmacogenetic outcomes as primary endpoints (see Table S1). Bias related to ethnic background, disease severity, doses of treatment, and drug association were rarely taken into account. For genetic effects to be replicated, the demonstration of their clinical validity will require adequately powered, a priori-defined clinical trials, and prospective confirmation before clinical implementation for gene-based treatment decisions can be proposed. Importantly, the amplitude of pharmacogenetic effects has been shown to be generally weak in PD. Multiple genes rather than a single variant may be involved in the response to treatment. Drug interaction and clinical factors such as disease duration, age, or gender also have an important effect on drug response in PD. Recent studies have shown that the combination of clinical and genetic factors dramatically increases the prediction of PD susceptibility in the general population.[86] Similarly, the ICD risk algorithm is a good example where pharmacogenetics might influence therapeutic decisions. The next steps should be to develop similar risk prediction models for motor complications and other dopaminergic side effects in longitudinal, prospective cohorts.

Conclusion

Despite many interesting studies showing an association between gene variants and drug response in PD, considerable work remains to be done to replicate these results and validate their clinical relevance before translation into clinical practice. So far, no gene-based recommendation can be made for the management of PD medication. The PharmGKB is an NIH-funded pharmacogenomics knowledge resource about the impact of human genetic variation on drug response (http://www.pharmgkb.org). It encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships. By contrast to other drugs or diseases, there are currently no guidelines published for PD drugs on this pharmacogenetic database. More studies are needed to better understand the variability of the pharmacokinetics and the clinical response to dopaminergic drugs in order to propose gene-based models to personalize the treatment in PD. Algorithms taking into account clinical, pharmacogical, and genetic factors are currently the most promising way to move towards a personalized medical treatment programme for PD. Future studies should be designed with pharmacogenetic primary endpoints, appropriate sample size allowing sufficient statistical power, and should take into account potential bias related to genetic factors, drugs dose and interaction, as well as disease stage and severity.

Authors' Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

J.C.C.: 1A, 1B, 1C, 3A, 3B
W.P.: 1A, 3B

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Pharmacogenetic studies in Parkinson's disease.

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