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Review Article

Parkinson's Disease Treatment and the Role of Genetic Polymorphisms in the Efficacy and Adverse Effects

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Abstract

Parkinson's disease (PD) is a relentlessly growing neurodegenerative disorder clinically manifested by rigidity, tremors and dyskinesia ascribed to loss of nigrostriatal dopaminergic innervation. Conventional therapies focus on alleviating disease symptoms as far as possible, yet lack the ability to halt progression of neurodegenerative process. A major historic turning point in PD therapy came through inception of levodopa (l-dopa), however, its prolong use is associated with complications and decline in response. Some alternate modalities to treat PD are also available as dopamine agonists, catechol-o-methyl transferase inhibitors (COMTIs) and non-dopaminergic drugs that could be used as either supportive therapy with or alone. Nonetheless, these drugs are less effective than l-dopa in regulating motor symptoms. On the other hand, substantial inter individual variations are observed in response to l-dopa. Although many factors can influence individual's response to therapy, patient's genetic makeup could be a starting point in creating precision medicine with greater safety and efficacy. Precision medicine that incorporates pharmacogenomics data can optimize patient's response to PD drugs and facilitate treatment. In this review we aim to present PD pathogenesis, challenges of current therapy and pharmacogenetics aspects of l-dopa.

Keywords: Parkinson's disease, pharmacogenetics, genetic polymorphism, precision medicine, efficacy, adverse effects

Introduction

Parkinson's disease (PD) is the world's second fastest emerging neurodegenerative illness, after Alzheimer's disease, affecting people predominantly in late years of life (Dorsey et al. 2018). PD is a well distinguished clinical syndrome with multiple clinical presentations and etiologies. Currently PD is characterized by the presence of bradykinesia accompanied by rigidity or resting tremors or both as well as postural instability. Nonetheless, the multifaceted clinical presentation of PD includes several non-motor features too (Bloem, Okun, and Klein 2021) as olfactory dysfunction, sleep disturbance, pain, depression and cognitive impairment contributing largely to disability of afflicted people. The exact causes of PD remain elusive in most patients however, many genetic risk factors have been identified now in almost 5-10% of cases (Balestrino and Schapira 2020). PD associated neurodegeneration probably starts several decades before the onset of conspicuous motor symptoms. Risk factors for developing PD include genomic defects, environmental poisons, pesticides, focal cerebrovascular damage; traumatic brain injury and drugs (Cacabelos 2017). The pre-eminent neurological features of PD include loss of dopaminergic neurons in substantia nigra pars compacta (SNc) and presence of Lewy bodies (LB). The diagnostic hallmark LB are spherical, eosinophilic, intraneuronal inclusions consist of more than 90 proteins mainly ubiquitin and α-synuclein (aSYN). aSYN has propensity to misfold and form insoluble β sheet rich aggregates that accumulate intracellularly (Poewe et al. 2017, Balestrino and Schapira 2020).

PD has been a rare illness in human history; however, industrial development and demographic changes have led to a PD pandemic that demands rigorous measures to stem (Dorsey et al. 2018). From 1990 to 2015, the number of individuals affected with PD disease increased 118% to 6.2 million patients globally (Feigin et al. 2017). The prevalence of PD is fueled by increasing longevity, aging population, and by-products of industrialization. The risk of developing PD increases with age and rises exponentially after 65 years (Van Den Eeden et al. 2003). However the disease does not affects older population only, as nearly 25% of individuals affected by PD are younger than 65 years and 5-10% younger than 50years (Bloem, Okun, and Klein 2021). By 2040, the number of individuals affected by PD are estimated to exceed 12 million globally (Dorsey and Bloem 2018).

Dopamine replacement forms the basis of current pharmacological therapy for PD , while in late stages of disease, deep brain stimulation is an alternative approach (Balestrino and Schapira 2020). Available therapies provide symptomatic relief for motor symptoms however the goal of ongoing research on PD is to find agents that can retard or arrest disease progression (Bloem, Okun, and Klein 2021). Moreover, the dopamine replacement therapy (DRT) ameliorates motor function in selective patients while many patients develop complications after prolong use of these drugs. Inconsistent response to PD treatment is multifactorial and relies on environmental, clinical and genetic variations (Ciccacci and Borgiani 2019). This pronounced variation in drug response along with adverse effects associated to PD treatment has led the researchers to identify genetic markers corresponding to these features. This review of literature focuses on pathophysiology of PD, current therapies, their limitations and challenges and implication of pharmacogenomics in PD and recommendations for future research.

Epidemiology

The incidence of PD ranges from 1 to 2 per 1000 in general populations and increases 1% with increase in age above 60 years. Prevalence of PD before 50 is very low but reaches to 4% in people older than 80 years (Tysnes and Storstein 2017). As compared to Asian, African and Arabic countries, the occurrence of PD is higher in North America, Europe and South America (Kalia and Lang 2015). Moreover, a gender bias is observed in the prevalence of PD symptoms, as males have twice higher risk of developing the disease than females. Contrarily, females having PD have higher mortality rate than male patients (Khan et al. 2021b). The possible explanation put forward for less frequent occurrence of disease in women than men is higher estrogen activity, which produces higher dopamine levels in striatum (Hidalgo-Lopez and Pletzer 2017, Hirsch et al. 2016). History of trauma, especially head injury, exposure to chemical intoxicants, life style and family history are the other risk factors attributed to PD development.

Pathophysiology

PD affects peripheral, central and enteric nervous systems of patients. The basic pathological process develops slowly yet persistently while the clinical symptoms of disease are manifested very late until the disease has progressed to relatively advanced stage (Braak and Braak 2000). It is crucial to understand the underlying mechanism involved in coordinated movements of our body in order to comprehend the pathology of PD. A considerable part of striatal neurons consist of GABAergic neurons knowns as spiny projection neuron or medium spiny neurons (MSNs) that are responsible for regulation of body movements. One of the most important functions of dopamine is to potentiate transmission occurring between the cortex, striatum and thalamus through these MSNs (figure 1). The two types of MSNs in brain are direct MSNs that facilitate appropriate locomotive activity and the indirect MSNs that inhibit inappropriate activity. In order to facilitate the coordinated movement, these two pathways need to be in state of equilibrium (Tanimura et al. 2019) . Direct MSNs activity is stimulated by binding of dopamine to D1 receptors while indirect MSNs activity is favored through binding of dopamine to D2 receptors (Lee and Gilbert 2016). Moreover, acetyl choline binds to M4 muscarinic receptors to inhibit direct MSNs whereas when it binds to M1 muscarinic receptors, it promotes activation of indirect MSNs (Ztaou and Amalric 2019b). Cholinergic interneurons have projections that surround striatum and are the primary source of acetyl choline in striatum as well as responsible for cholinergic transmission mediated by striatal nicotinic and muscarinic receptors of basal ganglia. To establish proper coordinated movements, balance

between dopamine and acetylcholine is critical, to maintain equilibrium between direct and indirect transmission pathways of the striatum (Khan et al. 2021a).

In PD, a remarkable instability in the balance between acetyl choline and dopamine has been observed (Ztaou and Amalric 2019a). Loss of dopaminergic neurons innervating striatum result in loss of balance between dopaminergic inputs and cholinergic interneurons in the striatum thus exhibiting classic motor symptoms of disease (Ztaou and Amalric 2019a). The two widely accepted theories explain the rationale behind loss of dopaminergic neurons in striatum during PD. One is based on Lewy body that are proteinaceous cytoplasmic inclusions rich in fibrillary forms of aSYN commonly present in SNc of PD patients (Surmeier 2018). The intracerebral development of aberrant toxic Lewy neurites and Lewy body occur at specific induction sites and progresses topographically. As the disease advances, the damage encompasses components of limbic, autonomic and somatomotor systems as well. In pre-symptomatic phase, the Lewy body pathology is restricted to medulla oblongata and olfactory bulb. However later on, initially subtle and then severe pathological changes may involve substantia nigra and nuclear grays of forebrain and mid brain consequently instigate symptomatic phase of PD. During final phase of illness, pathological changes affect neocortex and all the clinical symptoms of disease are fully manifested(Braak et al. 2004).The reason behind specific vulnerability of DA neurons in SNc to aSYN aggregation is still unexplained (Brundin and Melki 2017).

The other theory implicates mitochondrial dysfunction as reason for loss of SNc DA neurons in PD (Dauer and Przedborski 2003). This hypothesis is substantially supported by the studies on familial cases of PD. Loss of function mutation in PINK1 (PARK6), parkin (PARK 2) and DJ-1 (PARK 7) are associated with early onset, recessive forms of PD. The products of these three genes are critically involved in mitochondrial biology thus affecting functions as oxidant defenses, quality control and oxidative phosphorylation. Mutation in genes linked to dominant form of PD include LRRK2 (PARK 8), SNCA (PARK 1) and CHCHD2, are also been associated to mitochondrial dysfunction (Haelterman et al. 2014). Other studies that implicate mitochondria in PD were carried out on environmental toxins as rotenone, that inhibits mitochondrial electron transport chain particularly mitochondrial complex (Greenamyre et al. 2010). The increase in oxidative stress due to diminished levels of complex I and mitochondrial DNA (mtDNA) deletion is observed in SNc of PD patients. Although the levels of functional complex I are diminished in the SNc of PD patients, mtDNA deletions, which can be caused by reactive oxygen species (ROS), are elevated in the SNc of PD patients. These observation signify that mitochondrial dysfunction and elevated oxidative stress in PD induce bioenergetics crisis and consequently loss of SNc DA neurons (Surmeier 2018).

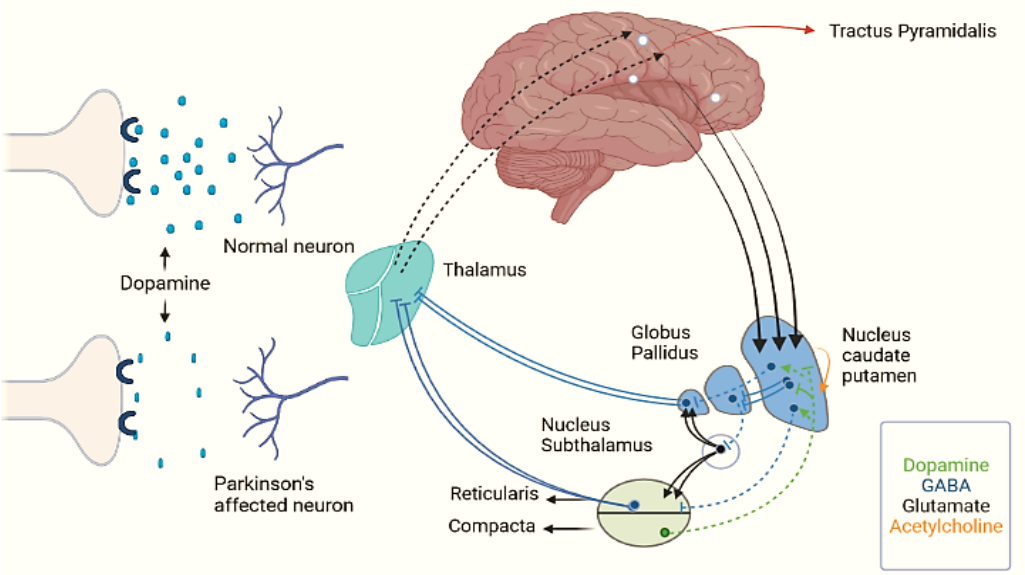

Figure 1 Pathophysiology of Parkinson's disease.

Pharmacological Treatment of PD

Currently available PD therapy provides symptomatic relief and targets dopaminergic pathway only, so there are no disease modifying agents available for PD at present. There are several druggable targets for the treatment of PD (figure 2).

Levodopa (l-DOPA)

Loss of dopaminergic neurons in SNc causes dopamine deficiency in PD patients' brain. Administration of exogenous l-dopa that replaces dopamine insufficiency is the most effective approach to treat motor symptoms of PD and is considered gold standard therapy (Balestrino and Schapira 2020). Since dopamine cannot cross blood brain barrier it is administered as its precursor l-dopa. L-dopa after crossing blood brain barrier is decarboxylated to give dopamine by aromatic amino acid decarboxylase (AADC) in presynaptic terminal. However pre-systemic metabolism of l-dopa in gut due to enzyme AADC generates dopamine in periphery (Papavasiliou et al. 1972) thus only 1-5% dopamine enters brain and leads to peripheral dopaminergic side effects. To prevent peripheral metabolism, it is administered in combination with AADC inhibitor carbidopa, even then 56% drug fails to reach the brain (Rekdal et al. 2019). The common side effects associated with l-dopa includes confusion, narcolepsy, impulse control and hallucinations. However, its major limitation is development of disabling motor complications, which commence after five to ten years of favorable response to dopamine therapy and manifest as dyskinesia, fluctuations, wearing off and dystonia (Münchau and Bhatia 2000). These complications are thought to be a consequence of intermittent phasic stimulation of striatal dopaminergic receptors, unlike the natural continuous supply of dopamine (Olanow, Obeso, and Stocchi 2006).

Dopamine Agonists

Dopamine agonist drugs mimic endogenous neurotransmitter and directly acts on dopamine receptors. These drugs can be either ergot derivative such as bromocriptine, cabergoline, pergolide or lisuride or non-ergot derivatives as pramipexole, apomorphine and ropinirole (Münchau and Bhatia 2000). Theoretically there are certain benefits of dopamine agonists over l-dopa, as long duration of action that helps to decrease or prevent motor fluctuations more similar to natural dopamine released from nigral neurons (Chase, Engber, and Mouradian 1996). However, depending on agonists as well as individual patients, their half-life may vary (Goetz et al. 1985). Moreover, they do not require metabolic conversion like l-dopa and directly act on dopamine receptors. They do not undergo oxidative metabolism thus do not increase oxidative stress and additionally have l-dopa sparing effects (Yoshikawa et al. 1994).

Clinically their effectiveness is well established in PD, either used as monotherapy before starting l-dopa especially in younger patients or frequently in combination with l-dopa after onset of motor complications. Motor fluctuations are not manifested in dopamine agonist monotherapy unless dopamine is added to regimen. Nonetheless dopamine agonists alone take longer time to show desired therapeutic effect than l-dopa and require co-administration of l-dopa after certain time. As dopamine agonists stimulates region of medulla that is outside the blood brain barrier, they commonly cause nausea. Other psychiatric side effects such as hallucinations are identical to those observed with l-dopa (Münchau and Bhatia 2000).

Monoamine Oxidase Inhibitors (MAOIs)

Even though MAOI as rasalgiline and selegiline are commonly used in mild early stage of PD, they are not less effective in patients having moderately advanced PD with l-dopa associated motor complications. Safinamide is another MAOI, administered once daily has been found to improve mean on time without dyskinesia and decrease morning and daily off times (Schapira et al. 2017). Safinamide lowers neuronal dopamine reuptake and inhibits MAO reversibly. It also reduces release of neuronal glutamate by blocking voltage dependent activated sodium channel and entry of intracellular calcium (Jankovic and Tan 2020).

Catechol-o-Methyl Transferase Inhibitors (COMTIs)

Entacapone, tolcapone and opicapone limit the peripheral degradation of l-dopa. Moreover, tolcapone additionally inhibits central degradation of dopamine and l-dopa thus elevate the levels of central l-dopa and dopamine. However, tolcapone is hepatotoxic that limits its use. Since the

main role of COMTIs is to extend the effectiveness of l-dopa, they are prescribed as adjunct drugs with l-dopa in patients who sustain motor fluctuation associated with l-dopa. Although generally well tolerated, nausea, diarrhea, postural hypotension and orange coloration of urine are the common side effects of COMTIs (Jankovic and Tan 2020).

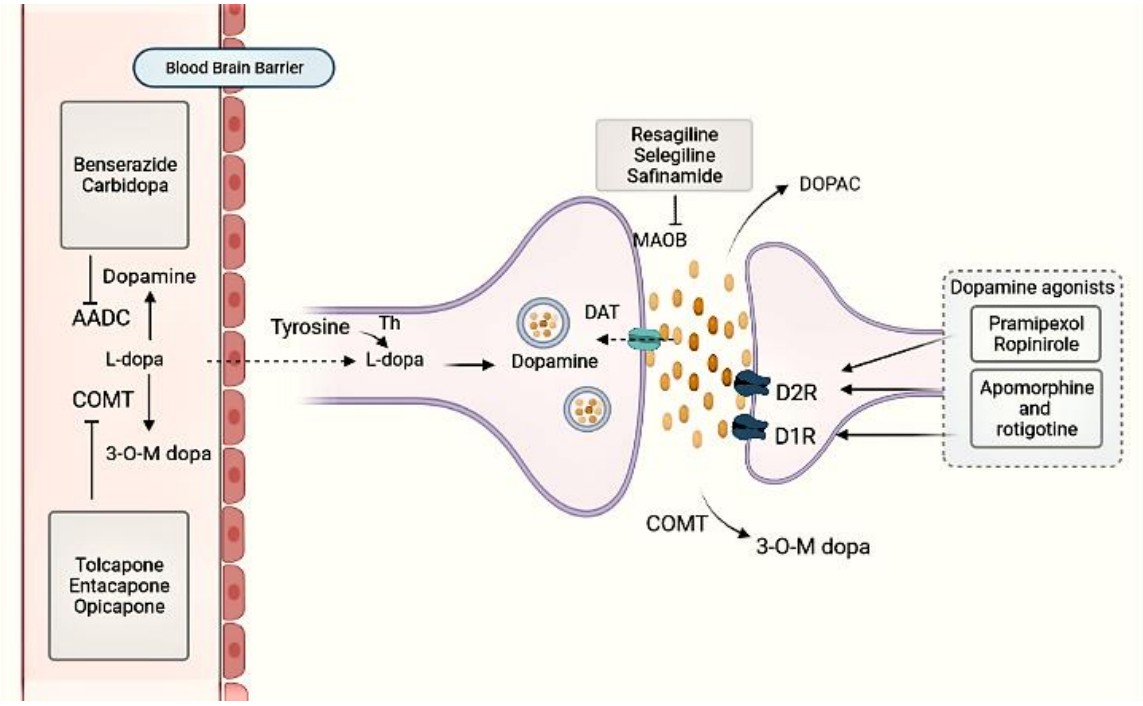

Figure 2 Therapeutic drug targets against Parkinson's disease.

Symptomatic Treatment of Non-motor Symptoms

Beside the classic motor features of PD, patients may experience some non-motor symptoms as well such as cognitive impairment, anxiety, hallucinations, apathy and depression either due to the illness itself or the medications used to treat it (Seppi et al. 2019). These non-motor symptoms amplify overall load of illness, especially in late stage of disease. The most frequently occurring psychiatric disturbance in PD is depression. Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) is most commonly prescribed in patients with PD because of lesser possibility of adverse effects with them. To treat the psychotic symptoms such as delusions or hallucinations in additions to dose adjustment for anti PD drugs, anti-psychotic drugs as pimavanserin, clozapine and quetiapine are used if necessary. For sialorrhea in PD patient, botulinum injection in salivary glands is proved to be effective in about five percent patients (Seppi et al. 2011).

Challenges with Current Therapy

PD is the second amongst the most frequently occurring neurodegenerative diseases with numerous evidences supporting involvement of genetic factor in its etiology (Billingsley et al. 2018, Foltynie et al. 2002, Pang et al. 2019). Availability of effective therapy discriminates PD from other neurodegenerative illnesses. These available pharmacological therapies mostly target nigrostriatal dopaminergic pathway (Factor 2008). DRT to replace dopamine deficiency or by dopamine agonists that stimulate dopamine receptors provides symptomatic relief. L-dopa and dopamine agonists are the drugs of choice, however, some

less potent therapeutic options are also available such as COMTI and MAOI (Redenšek and Dolžan 2020). A large number of patients gain symptomatic relief via dopaminergic treatments but impact of these treatments on frequently occurring non motor symptoms are negligible (Payami and Factor 2014). Moreover, a large inter-individual deviation in response to anti-PD drugs is experienced. While in some patients l-dopa shows favorable response for several years, many others do not get the anticipated benefits (R D Sweet 1975). Correspondingly some patients tolerate higher doses while others develop troublesome side effects even to low dose (Fahn et al. 2004). A meta-analysis reports that almost 40% individuals experience motor related complications within 4 to 6 years after initiating l-dopa therapy (Ahlskog and Muenter 2001). The pronounced variation in adverse effect and therapeutic response profile among PD patients prompted us to search the scientific literature for polymorphism and genetic markers linked to drug response that might allow us to prognosticate individual's response to therapy in terms of toxicity and effectiveness (R and Bashir 2016)

Pharmacogenomics and PD

An important accomplishment in PD drug development was made through advent of l-dopa to ameliorate the disease symptoms nearly 60 years back. After that, the efforts to establish disease modifying agents increased but are yet to bear any worthwhile fruit (Payami and Factor 2014). Many promising agents are being investigated for PD treatment but none has gained approval for general use in PD, usually the reason being inadequate efficacy. Furthermore, substantial inter individual dissimilarity is observed in PD patients not just in response to l-dopa therapy, but even in time and frequency to develop drug induced motor complications (A A Tappakhov 2020). Many extrinsic (drug interactions related) and intrinsic (gene, sex) factors contribute to fluctuation in drug response among the individuals. However, in clinical trials, drug interactions and medical history are critically monitored while the role of genetics is ignored in most of the cases (Burt and Dhillon 2013). Consider a clinical trial consisting of people belonging to different ethnicities, some people have genotypes that is favorable to get benefit from drugs while others possess genotype that make drugs less or ineffective or even toxic. When genetics is ignored, efficacy is measured on average which may not be statistically significant, thus the trials terminate and the drugs that might have proved effective for some of the patients are rejected. Same is true for approved drugs for PD. As the response to therapy is unpredictable, the right combination and appropriate dose of drugs for each individual prescribed is determined through trial and error which takes longer time and even then may not prove to be effective and safe (Payami and Factor 2014). Pharmacogenomics brings hope to reform the way novel drugs are evolved and the manner drugs are prescribed. By exploiting genetic finger prints the individual drug response in terms of effectiveness, pharmacokinetics and safety can be estimated (R and Bashir 2016). In this section we tried to summarize the pharmacogenomic studies done in PD and their outcomes.

Levodopa

L-dopa, a precursor to dopamine, is the mainstay of therapy for PD and is often used concomitantly with COMTIs, DAs and MAO inhibitors that potentiate and/or synergize its effect. However, the biggest challenge associated with PD treatment is not only heterogeneity in response to these drugs but also related adverse effects that may vary from person to person. Since the main drug used for treatment of PD is l-dopa, most of the pharmacogenomics investigations have focused on the effect of genetic variants implicated in response to its treatment (Table 1). The genes selected for these studies are mainly

are entailed in transport; metabolism and excretion of l-dopa (Ciccacci and Borgiani 2019). These studies indicate that onset of adverse effects after prolong use of l-dopa or other dopaminergic drugs may be associated with polymorphism in gene involved in reuptake and degradation of dopamine.

Table 1: Pharmacogenetics studies on PD involving various genes.

Gene	Sample Size	Location	SNP ID	Main Findings	References
ADORA2A	208	Brazil	rs2298383 and rs3761422	Associated with LID	(Rieck et al. 2015)
BDNF	315	UK	rs6265	Associated with higher dyskinesia	(Foltynie et al. 2009)
DDC	33	Caucasian	rs921451 and rs3837091	Associated with l-dopa response	(Devos et al. 2014)
DDC	51	China	rs921451 and rs3837091	Associated with l-dopa response	(Li et al. 2020)
GRIN2A	101	Russia	rs7192557 and rs8057394	Associated with LID	(Ivanova et al. 2012)
GRIN2B	91	Kuala Lumpur	rs7301328	Associated with ICB development	(Zainal Abidin et al. 2015)
OPRM1	92	Ohio	rs1799971	Associated with dyskinesia	(Strong et al. 2006)
SV2C	224	Brazil	rs30196 and rs10214163	Associated with l-dopa dose	(Altmann et al. 2016)

Adenosine A2A Receptor (*ADORA2A)*

$A_{2A}R$ antagonists recently showed potential affect in relieving PD related motor symptoms during preclinical studies. *ADORA2A* gene encodes $A_{2A}R$ receptor and is located on chromosome 22q11.23. $A_{2A}R$ receptor belongs to guanine nucleotide-binding protein (G protein)-coupled receptor superfamily. The receptor is vastly expressed in striatum and negatively regulates dopamine D2 receptor (DRD2) activity which is the critical site for dopamine action in the nigrostriatal pathway (Morelli et al. 2007).

Rieck and colleagues investigated any possible association between *ADORA2A* gene polymorphism and l-dopa related adverse effects in a study comprising of 285 PD patients on l-dopa therapy (table 1). In this study conducted in Brazil, *ADORA2A* gene polymorphisms, rs2298383 and rs3761422 were genotyped by allelic discrimination assays. A higher incidence of l-dopa induced dyskinesia (LID) was observed among carriers of rs3761422 C allele, rs2298383 T allele and diplotypes acquired from both polymorphisms. Their results suggest that these two alleles as risk factor for development of l-dopa related adverse effects (Rieck et al. 2015).

Brain derived neurotrophic factor (*BDNF*)

BDNF is critically involved in neuronal differentiation (Binder and Scharfman 2004), maturation and their survival and provide neuroprotection under adverse states such as hypoglycemia, cerebral ischemia, glutamatergic hyper stimulation,

and neurotoxicity. BDNF also stimulates and regulates growth of new neurons from stem cells (Bathina and Das 2015). A growing body of evidence supports involvement of aberrant synaptic plasticity in l-dopa related dyskinesia (LID), which in turn depends on release of BDNF (Wang and Zhang 2016).

The impact of functional polymorphism of BDNF gene on probability of evolving LID was investigated through a cohort study including 315 patients diagnosed with PD receiving l-dopa and other dopaminergic agents for treatment. Carriers of the mutant allele of BDNF (dbSNP rs6265) that is linked to reduced activity dependent secretion of BDNF, were reported to develop dyskinesia earlier during course of treatment with dopaminergic agents, than non-carriers (Foltynie et al. 2009).

Table 2 Pharmacogenetics studies on PD involving *COMT*.

Gene	Sample Size	Location	SNP ID	Main Findings	References
COMT	121	Japan	rs4680	Associated with dyskinesia and neurodegeneration	(Watanabe et al., 2003)
COMT	95	Poland	rs4680	Associated with efficacy & safety of l-dopa	(Białecka et al. 2004)
COMT	679	Poland	rs6269, rs4633, rs4818 and rs4680	Associated with higher doses of l-dopa	(Bialecka et al. 2008)
COMT	133	Iran	rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, rs174696	No association with dyskinesia	(Torkaman-Boutorabi et al. 2012)
COMT	79	Korea	rs4680	No association	(Lee, Lyoo, Ulmanen, Syvänen, and Rinne 2001)
COMT	232	Russia	rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, rs174696	No association	(Ivanova et al. 2018)

Catechol-o-Methyl Transferase (*COMT*)

COMT is an enzyme that mediates biodegradation of hormones, dopamine, toxic metabolites and xenobiotics having a catechol moiety via enzymatic methylation (Lee, Lyoo, Ulmanen, Syvänen, and O Rinne 2001). This enzyme is encoded by COMT gene located on chromosome 22q11. The activity level of COMT may differ in various COMT gene polymorphic variants (Ivanova et al. 2018). Due to critical involvement of COMT enzyme in l-dopa metabolism, many pharmacogenetics studies on PD emphasized on polymorphism of COMT gene, however these studies generated inconsistent conclusions that might be due to variable recruiting criteria and difference of populations (Redenšek and Dolžan 2020).

A change in amino acid (Val-108-Met) has been detected to alter the activity of enzyme from high to low. An investigation conducted in Japan verified the frequency of COMT genotypes in 121 patients diagnosed with PD and in healthy control and studied whether a variant COMT allele is correlated with susceptibility to develop l-

dopa associated adverse effects after long term therapy (table 2). The inferences drawn from this study expounded that patient with homozygosity for low-activity allele (rs4680) was more susceptible to LID and 'wearing-off' when compared to controls. Moreover, increased concentration load of l-dopa in plasma may augment neurodegenerative process (Watanabe et al. 2003).

Ninety-five (95) patients diagnosed with sporadic PD in Poland enrolled in a study were allocated to 2 groups on the basis of dose of l-dopa administered, Group 1- consisted of patients having dose of l-dopa below 500mg during first five years, Group 2- patients received l-dopa dose greater than 500mg/day during first 5 years of treatment. The aim of this retrospective study was to identify potential effect of COMT genetic polymorphism on effective daily dose of l-dopa administered during the first 5 years of treatment. The conclusions drawn from the study indicated that patients with low activity allele COMT (L/L) (rs4680) may show better response to the treatment with less complication (Białecka et al. 2004). However, the study had low statistical power due to small sample size. Moreover, impact of pharmacokinetics parameters on efficacy of l-dopa daily dose was not monitored.

Another case-control study investigated the influence of functional COMT haplotypes on PD risk and response to l-dopa treatment as well as complications associated with it. A total of 679 participants (322 PD and 357 controls) were inducted for the study in Poland. All of these participants were genotyped for four SNPs in COMT gene rs6269: A>G; rs4633C>T; rs4818: C>G; and rs4680: A>G located in common haploblock that has been shown to govern the enzymatic activity of COMT. The incidence of high activity haplotype was found to be greater in late onset PD when compared to control and required comparatively higher doses of l-dopa (Bialecka et al. 2008).

However, a conflicting result was observed in PD patients of Korean origin. The genotype frequencies of the COMT gene in 73 patients with PD and 49 controls were investigated. Moreover, the association between effectiveness of single dose of l-dopa and COMT genotypes in PD patients was studied. Motor response to l-dopa was estimated by the motor part of the unified PD's disease rating scale (UPDRS), and by walking and tapping tests. No association was ascertained between response to l-dopa and rs4680 polymorphism. Also, no significant dissimilarity was seen between PD patients and normal individuals for distribution of COMT genotypes (Lee, Lyoo, Ulmanen, Syvänen, and Rinne 2001).

In Iran, 133 patients diagnosed with idiopathic PD were recruited for a study. This study was designed to investigate any possible impact of COMT genetic polymorphism on effective daily dose of l-dopa in the fifth year of treatment. Patients receiving l-dopa concomitantly with dopa decarboxylase inhibitors were considered eligible for this study and were divided into 2 groups, Group1 patients receiving l-dopa less than 500mg daily in the fifth year of treatment, Group 2 patients receiving more than 500 mg daily dose of l-dopa in the fifth year of treatment. Motor fluctuations were more frequent in second group with higher l-dopa dose; however, no significant relationship was confirmed between COMT genotype and LID (Torkaman-Boutorabi et al. 2012).

In a separate study, 232 patients diagnosed with PD were investigated in Russia to unravel connection between seven reported SNPs of COMT gene (rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, rs174696) and LID in these patients. Dyskinesia was assessed through Abnormal Involuntary Movement Scale (AIMS). Four SNPs, rs4680, rs4818, rs4633, rs165774 were identified to be associated with LID. When the duration of disease was added as a covariate in regression analysis, the results did not reach statistical sig-

nificance and failed to provide evidence for contribution of the studied polymorphisms in development of LID (Ivanova et al. 2018).

Table 3 Pharmacogenetics studies on PD involving *DRD* genes.

Gene	Size	Location	SNP ID	Main Findings	References
DRD1	91	Kuala Lumpur	rs4532 and rs4867798	*Associated with* ICB development	(Zainal Abidin et al. 2015)
DRD1	360	Italy	rs4532, rs4867798, rs265981	*No association*	(Oliveri et al. 1999)
DRD2	274	Germany	rs1800497	Significant association	(Rissling et al. 2004)
DRD2	91	Kuala Lumpur	rs1800497	Significant association	(Zainal Abidin et al. 2015)
DRD2	195	Brazil	rs1800497	No association with dyskinesias	(dos Santos et al. 2018)
DRD2	360	Italy	rs1800497	Significant association was observed	(Oliveri et al. 1999)
DRD3	1062	Korea	rs6280	Associated with dyskinesias	(Lee et al. 2011)
DRD4	177	Germany	rs1800955	Associated with sleep attacks	(Paus et al. 2004)

DOPA Decarboxylase (DDC)

Aromatic l-amino acid decarboxylase (AAAD) a key enzyme implicated in conversion of l-dopa to dopamine is encoded by *DDC* gene. As AAAD is critical for metabolism of l-dopa, polymorphisms in DDC gene have been deemed to modify the expression of AAAD and consequently promote inter individual variations in treatment response and clinical heterogeneity (Bertoldi 2014).

Devos et al., conducted a study to investigate the motor response to l-dopa in PD patients as a function of the DDC gene promoter polymorphisms (rs921451 T > C polymorphism (DDC (T/C)) and rs3837091 AGAG del (DDC (AGAG/-))). A total of 33 Caucasian PD patients went through acute l-dopa challenge while benserazide was administered concomitantly to inhibit AAAD peripherally. The rs921451 and rs3837091 polymorphisms of the DDC gene promoter affected the motor response to l-dopa although peripheral pharmacokinetic parameters of l-dopa and dopamine remained unchanged. These conclusions support *DDC* as a genetic modifier of response to l-dopa in PD (Devos et al. 2014).

The aforementioned conclusion was corroborated by another study in 51 Chinese patients diagnosed with PD. Patients went through acute l-dopa challenge and were analyzed by Unified PD Disease Rating Scale (UPDRS)-III after receiving l-dopa. Participants were genotyped in the *DDC* loci for polymorphisms: rs3837091 and rs921451. The obtained data suggested that individuals carrying *DDC* TT or CT genotype showed more favorable motor response to l-dopa than those with the *DDC* CC genotype which was obvious from lower UPDRS-III sub scores, including axial symptoms and bradykinesia in patients with the *DDC* CC genotype. The *DDC* SNP rs921451 modified the motor response to l-dopa in Chinese PD patients and thus substantiate that *DDC* may be a modifier gene for the l-dopa therapy response in PD (Li et al. 2020).

Dopamine receptor 1(*DRD1*)

Although extensive data is available regarding genetic diversity of dopaminergic receptors, only a few studies addressed them as potential influencer of heterogenic response to PD treatment. PD patients on dopaminergic medications

specifically l-dopa and dopamine agonist frequently develop impulse control behavior (ICB) and impulse control disorder (ICD).

In Kuala Lumpur, 91 PD patients were selected to find association of polymorphism within *DRD1* gene and development of ICD and ICB in patients receiving l-dopa and dopamine agonist (table 3). These patients were genotyped using high resolution melt analysis for the selected SNPs in *DRD1* gene (rs4532, rs4867798 and rs265981). The studies concluded that genetic variations in *DRD1 gene* (rs4532 and rs4867798) pose greater risk to develop ICB in PD patients (Zainal Abidin et al. 2015).

On the other hand, a study carried out in Italy recruited 136 subjects and analyzed affiliation between DRD1 receptor genetic variants and risk to develop peak dose associated dyskinesia in PD patients. The study declared lack of any association between DRD1 gene polymorphism and risk of developing dyskinesia at the highest dose (Oliveri et al. 1999).

Dopamine receptor 2 (DRD2)

The *DRD2* gene located on chromosome 11q23 is implicated in the dopaminergic response to exogenously administered l-dopa in PD patients. It is therefore, speculated that any variation in gene coding DRD2 could be a risk factor for development of complications associated with prolong use of l-dopa (Wang, Liu, and Chen 2001). However, the data obtained so far is inconclusive. According to Dos Santos et al., no significant relationship was verified between *DRD2*(rs1800497) gene polymorphism and the l-dopa induced complications as dyskinesia in 195 Brazilian patients diagnosed with idiopathic PD.(dos Santos et al. 2018). Another study in Italy, investigated the effect of polymorphisms in the genes for DRD2 on risk of developing LID. The results showed that certain alleles of the *DRD2* gene decreased the risk of developing peak-dose dyskinesia and could impart variable susceptibility to establish peak-dose dyskinesia following l-dopa therapy(Oliveri et al. 1999).

Narcolepsy-like symptoms as excessive day time sleepiness are frequent among PD patients receiving anti PD agents. Therefore, Rissling et al., devised a study consisting of 274 German patients diagnosed with PD, receiving l-dopa concomitantly with DA and other PD treatments. The purpose of the study was to clarify any interdependence among variation in the *DRD2* gene (rs1800497) and sleep attacks linked to PD treatment. Results showed significant association between the DRD2 allele A2 and sleep disorders resulting from use of anti-PD drugs, thus suggested that presence of A2 confers greater risk to develop sleep problems in PD patients (Rissling et al. 2004). Moreover, *DRD2* rs1800497 was also found to be associated with increased risk of ICB development among PD patients who previously used dopaminergic medications, particularly l-dopa and dopamine agonists (Zainal Abidin et al. 2015).

DRD3

To investigate whether gene polymorphism alters the susceptibility to induce peak dose and diphasic forms of dyskinesia after prolong use of l-dopa in PD patients, a study was carried out in Korea. The cohort study included 503 PD patients and 559 healthy controls who received l-dopa and their duration of disease was no less than 5 years. Genotyping was done to search for polymorphisms of DRD3 p.S9G (rs6280). The presence of diphasic dyskinesia (DDSK) was associated with the DRD3 p.S9G variant and duration of l-dopa treatment. However, no such association was observed among peak dose dyskinesia and genetic variability of DRD3 (Lee et al. 2011).

DRD4

Sudden onset sleep (SOS) occurs frequently in PD patients particularly in those having dopaminergic drugs. To find correlation between polymorphism of *DRD4* gene with SOS in PD patients receiving dopaminergic drugs, a study was conducted on 177 German PD patients. The

results indicated that carriers of DRD4*2 allele on dopaminergic therapy, are more susceptible to SOS than non-carriers (Paus et al. 2004) .

N-methyl-D-aspartate 2A (*GRIN2A)*

NMDA glutamate receptors belongs to class of excitatory amino acid receptors that have crucial role in regulating the motor circuits of the basal ganglia (PD)(Hallett and Standaert 2004). In order to test the role of the NMDA receptor ***GRIN2A*** variants, rs7192557 and rs8057394 in LID, 101 Caucasian PD patients in Russia were investigated. Patients were evaluated for the absence or presence of l-dopa induced complications as dyskinesia, in accordance with the abnormal involuntary movement scale (AIMS) (Loonen and van Praag 2007). Blood sample of participants were collected for DNA extraction and genotyping. ***GRIN2A*** SNPs rs7192557 and rs8057394 were found to be associated with susceptibility to develop LID (Ivanova et al. 2012).

N-methyl-D-aspartate 2B (*GRIN2B)*

The *GRIN2B* gene encodes a protein called N-methyl D-aspartate receptor sub type 2B (GluN2B) located on chromosome 12p13. 1. The encoded protein is distinct component of NMDA receptor complexes that make the ion channel, and acts as agonist binding site for glutamate. Numerous studies affirmed correlation between polymorphisms in the *GRIN2B* gene with the development of ICB among PD patients(Lee et al. 2009) . Based on previous findings 91 PD patients were screened for ICB using the QUIP questionnaire in Kuala Lumpur. The data obtained suggested that positive association existed between glutamate receptor gene polymorph (*GRIN2B* rs7301328) and increased risk of ICB development among PD patients (Zainal Abidin et al. 2015).

mu Opioid Receptor (OPRM1)

Several pharmacological studies have determined that clinically effective opiates and morphine act through stimulating mu-opioid receptor (MOR). MOR is encoded by *OPRM1* gene located on chromosome 6q24-q25. Besides inducing analgesia, MOR has salient role in addiction to other drugs of abuse, through modulation of mesolimbic dopamine system (Ravindranathan et al. 2009, LaForge, Yuferov, and Kreek 2000). Opioids act as co-transmitters in both the direct and the indirect basal ganglia pathways. Some preclinical studies have shown involvement of dysfunctional striatal opioid transmission in PD models. The changes produced are pharmacologically, anatomically and transiently linked to development of dyskinesia (Henry and Brotchie 1996). Moreover, PET scan confirmed lower binding of opioid in thalamus and striatum in PD patients having dyskinesia (Piccini, Weeks, and Brooks 1997)

A study carried out in USA on 92 Caucasian subjects investigated possible associations between the mu opioid receptor A118G (rs1799971**)** genetic variant and the development of dyskinesia in PD patients on l-dopa therapy for at least five years. The study concluded that common DNA polymorphism in the mu opioid receptor coding region A118G are associated with earlier onset of dyskinesia during l-dopa treatment (Strong et al. 2006).

Table 4 Pharmacogenetics studies on PD involving *SLC* genes.

Gene	Size	Location	SNP ID	Main Findings	References
SLC6A3	81	France	rs28363170, rs3836790	Associated with l-dopa efficacy	(Moreau et al. 2015a)
SLC6A3	195	Brazil	rs28363170	Inversely associated with dyskinesias	(dos Santos et al. 2019)
SLC6A3	196	Brazil	rs28363170	Associated with complications after l-dopa	(Schumacher-Schuh et al. 2013)

SLC22A1	231	Slovenia	rs628031	Associated with orthostatic hypertension, peripheral edema and ICDs	(Redenšek et al. 2019)
SLC22A1	99	Netherland	rs622342	Associated with increased mortality ratio after l-dopa therapy	(Becker et al. 2011)

Solute carrier family 6 member 3*(SLC6A3)*

The *SLC6A3* gene mapped at chromosome 5p15 encodes the protein dopamine transporter (DAT)(Robertson et al. 2018). The dopamine transporter type 1, also known as solute carrier family 6 (neurotransmitter transporter), member 3 (SLC6A3) is the most dominant factor for neurotransmission of dopamine and might regulate the therapeutic response (Moreau et al. 2015b).

Extensive inter individual variation is observed among PD patients in response to l-dopa therapy. To investigate the possible contribution of genetic variation to this variation in therapeutic response, 81 patients were enrolled in France for a study (table 4). The study was designed to seek association between SLC6A3 gene polymorphs and effectiveness to l-dopa in treating gait disorders and motor symptoms. Patients were genotyped for polymorphisms in *SLC6A3* gene; rs28363170 and rs3836790. The results acknowledged that SLC6A3 variants are significantly correlated to better efficacy of l-dopa in treating motor symptoms and suggests *SLC6A3* gene variants as genetic modifiers of l-dopa treatment response (Moreau et al. 2015a).

In another study in Brazil (dos Santos et al. 2019), aimed to evaluate a possible relationship between *SLC6A3* (rs28363170) gene polymorphisms with the response to l-dopa therapy in patients with PD, 195 PD patients diagnosed with PD according to criteria of the British Association of PD (UK) were recruited. Patients were genotyped for rs28363170 polymorphism using PCR-RFLP. In this study, a shielding effect against developing dyskinesia was observed among individuals carrying the genotype *DAT1 9/9* of VNTR (rs28363170).

According to another study attempted to explore *DAT1* gene polymorphisms impact on l-dopa equivalent dose and prevalence of visual hallucination in 196 Brazilian PD patients. Only those PD patients treated with at least 200 mg l-dopa equivalent dose for at least 1 year were included in the study. These patients were genotyped for the −839 C > T and 3′ VNTR *DAT1* (rs28363170) polymorphism. Visual hallucinations occurred in 25.5% of the sample. The results supported positive association of *DAT1* polymorphisms on complications of anti-PD treatment and in l-dopa equivalent dose usage (Schumacher-Schuh et al. 2013).

Solute carrier family 22 member 1*(SLC22A1)*

SLC22A1 gene located on chromosome 6q25.3 encodes organic cation transporter (OCT1). Heterospecific OCT1 is predominantly found in liver and to a lesser extent in kidney, intestine and other organs. These transporters are crucial for elimination of small organic cations, environmental toxins, xenobiotics as well as many drugs including PD drugs as l-dopa, (Goswami et al. 2014).

Several *SLC22A1 gene* polymorphisms have been related with functional modification in protein activity, as well as drug response, elimination and toxicity. A population-based cohort study (Becker et al. 2011) was conducted to find association between prescribed doses of l-dopa and other anti PD drugs and polymorphism rs622342 A > C in the *SLC22A1* gene and also investigated the difference in mortality rate after start of l-dopa therapy. This study corroborated that the minor C allele at rs622342 in the *SLC22A1* gene, that encodes OCT1, was correlated with higher prescribed doses of anti-PD drugs and a shorter survival after commencing l-dopa therapy. The study showed that rs622342 variant C allele is responsible for decreased response to l-dopa treatment due to its decreased transportation to brain by OCT1 and therefore higher dose of other PD

drugs are prescribed to compensate this effect. Moreover, AC or CC genotype carriers experienced more severe symptoms and less response to PD treatment thus increased the mortality ratio.

Redenšek et al. comprehensively ascertained the effect of SNP of primary dopaminergic pathway gene *SLC22A1* rs628031 on development of motor and non-motor complications ensued by dopaminergic treatment in PD. *SLC22A1* rs628031 AA carriers showed greater propensity to develop complications such as orthostatic hypertension, ICD and peripheral edema. Contrarily *SLC22A1* rs628031 heterozygotes showed less susceptibility to cause dyskinesia and motor fluctuations. Additionally, under dominant model carriers of at least one *SLC22A1* rs628031 A allele had less susceptibility to develop dyskinesia (Redenšek et al. 2019).

Synaptic vesicle glycoprotein 2C (*SV2C*)

SV2C gene located on chromosome 5q13.3 encodes SV2C proteins implicated in regulation of synaptic functions in the brain particularly in substantia nigra, pallidum, brainstem, midbrain and olfactory bulb. SV2C is substantially expressed on the vesicles of neurons producing dopamine (Rai et al. 2018). Therefore, genetic deletion of SV2C reduces dopamine release and thus reduces motor activity associated with it (Dunn et al. 2017).

To investigate a possible role of *SV2C* gene polymorphisms in l-dopa dose fluctuation among PD patients, 224 subjects were enrolled and assessed at the Movement Disorder Clinics at Hospital de Clínicas de Porto Alegre, Brazil, from 2006–2013. The patients diagnosed with PD as stated in UK Brain Bank criteria, receiving l-dopa for at least one year and showed positive response after initial dose were included in the study. *SV2C* gene variants; rs30196 and rs10214163 were genotyped. Univariate analyses showed association of l-dopa dose with *SV2C* rs30196 genotypes. The presence of each C allele reduced the average daily dose (Altmann et al. 2016).

Future Perspectives

Conventional treatments available for PD provide symptomatic relief attained through replenishing cerebral dopamine levels or by stimulation of dopamine receptors. The effectual options include l-dopa and dopamine agonists while less potent therapeutic alternatives such as COMTIs and MAOBIs are also accessible. Despite of substantial effectiveness of l-dopa in PD, the anticipated therapeutic outcomes are not always accomplished in all patients and many of them experience adverse effects. So far there is no reliable way to predict treatment response in patients; hence pharmaceutical companies are restricted to 'one size fits all' approach while developing therapeutic agents. However, this perspective for drug development in PD does not benefit all patients. Moreover, the studies stated above show that this approach may lead to detrimental effects in many others PD patients. Despite many environmental and pharmacokinetic factors fostering this heterogeneity, a major contributor 'genetic variation' is often ignored. In order to reduce risk of such adverse events, incorporation of pharmacogenomics into clinical practice would be a prudent choice. The main goal of pharmacogenomics is to identify the genetic factors accountable for variable drug efficacy among the individuals, consequently predict drug response and facilitate personalized medicine. This approach ultimately lowers the cost of health care, patient's treatment duration as well as drug induced complications, thus enhances treatment safety. Besides it can also lower the risk of failures and cost in clinical trials by selecting only those patients who are eligible to respond drug therapy.

In this manuscript, we reviewed important studies conducted to identify influence of genetic variations on variable response to PD treatments. However, the data obtained so far

are mostly erratic and the functional role of genetic variants is generally ambiguous as these were underpowered and small-scale studies. There is need to upgrade these researches in order to reap benefit from them by adding in clinical practice. Furthermore, novel disease modifying drugs for treatment of PD are also needed, so as to have more treatment options for personalized medicines based on pharmacogenomic signature of individuals.

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