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Basics of pharmacogenetics and pharmacogenomics in Parkinson's disease

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ABSTRACT: Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra pars -compacta (SNPC). PD is the second most common neurodegenerative disorder. There are different types of drugs used in PD treatment such as dopamine agonists, MAO inhibitors and COMT inhibitors, etc. Pharmacogenetics is the study of the effects of genetic differences between individuals in their response to medicine and pharmacogenomics is the study of the influence of genetic variation on pharmacological response in patients by correlating gene expression or single-nucleotide polymorphisms with efficacy or toxicity. The different biomarkers and genotyping methods or geno-editing methods are used in exploring the pharmacogenetics and pharmacogenomics role in particular disease. Pharmacogenetics and pharmacogenomics have a wide range of applications and benefits which contributes in determining the dosage regimen. The current review is focusing on the involvement of pharmacogenetics and pharmacogenomics in Parkinson's disease.

KEYWORDS: Parkinson's disease, Pharmacogenetics, Pharmacogenomics, Biomarkers, Genes

I. INTRODUCTION

Parkinson's disease (PD) occurs due to dopamine deficiency, which is caused by the death of dopaminergic neurons in the nigrostriatal pathway and the deposition of specific cytoplasmic protein aggregates known as Lewy bodies. PD is an age-related disorder that is more frequent in males than in females, with a mean prevalence of 1680 per 100,000 in people older than 65yrs of age(1). PD is a neurodegenerative disorder that mainly occurs due to the interaction of multiple environmental and genetic factors. PD is characterized by the motor and non-motor symptoms present in this disease. Dopamine agonists are the most widely prescribed medications for Parkinson's disease. Drugs designed for PD work by interfering with pathophysiological processes triggered during disease progression which primarily affect dopaminergic system functions and less cholinergic system functions. Drugs that enhance dopaminergic transmissions, such as levodopa, dopamine receptor agonists, COMT inhibitors, and MAO-A and MAO-B inhibitors, can control the disease's motor symptoms, including bradykinesia and stiffness (2). Pharmacogenetics is the study of the effects of genetic differences between individuals in their response to the medicine. The aim of pharmacogenetics is the improvement of the safety and efficacy of the medicine. The pharmacogenetic test can be done to detect the presence or absence of or any change in particular genes/chromosomes. This can be done by analyzing the chromosomes /DNA of an individual. There are three objectives of pharmacogenetic testing are such as to identify individuals who are likely or unlikely to react to an intended medicine (i.e. indication), testing to identify patients who are likely to develop harm from a drug (i.e. contraindication/harm), and testing to guide drug dosing (3) SNPs (single nucleotide polymorphisms) are single base changes in DNA. Pair substitutions are the most common form of substitution and account for many well-studied human traits. A type of spontaneously occurring variationfound in the human genome. Only a few studies have been done to investigate the genetic influence on levodopa dose-response, and most of them have been focused on (catechol-O-methyltransferase) (COMT) Polymorphisms. Dopamine precursor L-3, 4-dihydroxyphenylalanine (L-DOPA) was discovered about 50 years ago, treatmentwith this drug remains the gold standard regarding symptomatic efficacy in PDtherapy. This drugimproves the motor symptoms of PD by pharmacologically and increasing dopaminergic neurotransmission. L-DOPA is taken by dopaminergic neuronal terminals and converted into dopamine by the DOPA-decarboxylase enzyme.

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Dopamine agonists stimulate directly the postsynaptic dopamine receptors acting selectively upon the D2-receptors (DRD2, DRD3, or DRD4) and the D1-like receptors (DRD1/DRD5). Compared with other available dopaminergic therapy, dopamine replacement with L-DOPA gives the best improvement in motor function. L-dopa is the most effective therapy for PD, but the long-term treatment of levodopa can cause adverse effects such as dyskinesia and motor fluctuations (3). According to investigation the role of genetic variation in person-to-person differences is associated with drug response and adverse effects, which may clear the mechanism of the interindividual variability observed in symptomatic benefit to antiparkinsonian agents in PD. There are mainly two types of genetic testing first one is disease-gene-specific tests and the second is the study of the pharmacogenetic profile. The disease-gene-specific test is mainly for mutations in single genes which are highly predictive for disease susceptibility gene polymorphisms that provide information about the risk of disease. And a **s**tudy of the pharmacogenetic profiles is used for gene polymorphisms, drug-metabolism enzymes, and drug target genes or abbreviated SNP profiling.(4) Mechanism of PD Parkinson's disease in which α-synucleinopathy with Lewy bodies are deposited in the midbrain. Here the neuropathological phenotype includes the following points: (i) genomic factors (ii) epigenetic changes (iii) toxic factors (iv) oxidative stress anomalies (v) neuroimmune/neuroinflammatory reactions (vi) hypoxic-ischemic conditions (vii) metabolic deficiencies and (viii) ubiquitin-proteasome system dysfunction. All these conditions tend to protein misfolding and aggregation and premature neuronal death. Mutations in several primary genes are known to cause autosomal dominant and recessive PD variants. Mutations were found in some genes, including -Synuclein (SNCA), Parkin 2 (PARK2), PTEN-induced putative kinase 1 (PINK1), PARK7, Leucine-rich repeat kinase 2 (LRRK2), and Bone narrow protein (BNP). The reasons could be microtubule-associated protein tau (MAPT) and stromal cell antigen 1 (BST1). Familial forms of Parkinson's disease, whereas genetic abnormalities in other areas may indicate risk. In the absence of family history, several loci have been related to sporadic PD. Mendelian frequency variants are those that have a high frequency of occurrence. Penetrance accounts for less than 10% of familial Parkinson's disease (e.g., SNCA, LRRK2, PINK1, PARK7 genes). By oxidizing RNA and promoting mitochondrial DNA (mtDNA) mutation, oxidative stress has an impact on nucleic acid stability. ATP-sensitive potassium channels (KATP), and oxidative stress disrupt protein homeostasis by accelerating -Synuclein formation and regulating dopamine release via aggregation, parkin aggregation, and proteasome dissociation. Raising cytoprotective receptors (nAChRs) and enhancing cytoprotective receptors while increasing the oncogene DJ1 (DJ-1), and the phosphatase and tensin homolog PINK1 dysregulation impact cellular self-defenses.

Pharmacogenomics is a branch of pharmacology that deals with the study of the influence of genetic variation on pharmacological response in patients by correlating gene expression or single-nucleotide polymorphisms to a treatment's efficacy or toxicity(5). Pharmacogenomics implies that we may be able to custom-make pharmaceuticals for individuals based on their genetic makeup in the future. Its goal is to provide pharmacological therapy that is tailored to the genotype of the patient for maximum efficacy and minimal adverse effects. Such techniques anticipate the onset of personalized medicine in which drugs and treatment combinations are customized to each individual's genetic profile. Pharmacogenomics is a branch of pharmacogenetics that studies single gene interactions with drugs all across the genome. Single nucleotide variants are the most common variations in the human genome. There are around 11 million SNPs in the human population, with one every 1,300 base pairs on average. Fred Sanger invented genomics when he sequenced the whole genomes of a virus and a mitochondrion. Pharmacogenomics is the most effective treatment for adverse drug reactions. Pharmacogenomics may eventually lead to a reduction in overall healthcare costs. (5)There are five types of genes involved in the pharmacogenomics of CNS drugs genes involved in CNS pathogenesis; (ii) genes involved in drug mechanism of action; (iii) genes involved in drug metabolism; (iv) genes related to drug transporters (v) pleiotropic genes implicated in multiple cascades and metabolism processes Pharmacogenomics is responsible for 30–90% of pharmacokinetic and pharmacodynamics variability**.** The cytochrome P450 (CYP) is a family of liver enzymes it is responsible for the break down the different classes of drugs it can break more than 30 different classes of drugs. The DNA variations in which genes code for those enzymes can influence their ability to metabolize certain drugs. Many pharmaceutical companies screen their chemical compounds to determine how efficiently they are broken down by different forms of CYP enzymes, and researchers perform genetic testing for variants in cytochrome

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P450 genes to screen and monitor patients in clinical trials. Metabolizers are responsible for the genetic mutation and variation the flow of genomic study is that many researchers follow the following procedures as they first selected the SNPs. DNA Isolation Genotyping was performed by PCR technique and they were resolved by electrophoresis in denaturing polyacrylamide gels and detected by silver staining (6). Another method is polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay and statistical analysis. And some other new techniques are recently added (genotype techniques) named clustered Regularly Interspaced Short Palindromic Repeats (CRISPER), somatic cell editing, Retron Library Recombinerring (RLR).

Relation of pharmacogenetics and pharmacogenomics with biomarkers in PD – Parkinson's disease mainly occurs due to genetic and environmental causes. Based on genes different forms of PD such as familial PD, hereditary PD etc.

Familial PD – familial PD occurs due to a monogenic defect with clinical and neuropathological variability(7) . This variability has been associated to genetic variants in the Alpha-synuclein gene (SNCA), including point mutationsalanine 53 to threonine (A53T). (A53T, A30P, and E46K) and multiplications(8). The familial PD is also affected by variability of parkin gene. In this have two A53T heterozygotes had markedly different neuropathology and different parkin genotypes such as A N167 and A S167. A N167 had early onset rapidly progressive neurological disease. A SN167 had late onset slowly progressive neurological disease. LRRK2 and GBA have been associated with familial PD(7).

Hereditary PD – Parkinson's disease is inherited in some cases, it is not in the majority of cases. Only about 15% of Parkinson's disease patients have a family history of the disease(9). Genetic changes, like environmental factors such as exposure to toxins and the use of certain drugs, and other cause is due to traumatic brain injury may also increase the PD risk. But sometimes disease occurs without a clear reason(10). There are different genes affect to influence Parkinsons disease such as COMT, DRD, LRRK2, SNCA, DJ-1, MAO-A, MAO-B, GBA, etc. in the pharmacogenetics and pharmacogenomics the disease progression is diagnosed by the different biomarkers. The certain biomarkers are helps to identify the disease and its etiology. There are different types of biomarkers are used in PD diagnosis. The biomarkers are as follows.

Biomarkers Used In Pd - Biomarkers -

The term 'biomarker,' a portmanteau of 'biological marker,' is the large subclass of medical signs, objective indications of a patient's medical state that can be evaluated reliably from outside the patient and with consistency(11). There are two main reasons for the diagnosis of biomarkers firstly to intervene at the onset of disease and to follow the progress of therapeutic interventions that may reduce or stop the progression of the disease. PD is frequently diagnosed only after a significant number of SN neurons have degenerated; PD biomarkers are needed. These include prodromal, preclinical, or premotor stage biomarkers, risk or susceptibility biomarkers, and motor stage biomarkers (12). There are different types of biomarkers are involved in PD biochemical markers, Neuroimaging biomarkers, and genetic biomarkers.

1. **Biochemical marker** -(13)

Biochemical biomarkers are being used to measure how much exposure organisms have to chemicals in the environment. Biochemical markers are found in body fluids like serum, blood, cerebrospinal fluid (CSF), and saliva. CSF is used mostly used in targeted body fluid while searching for biomarkers because it has the advantage that it projects the neurological and pathological state of the CNS. The development of the omics technologies, such as proteomics and metabolomics allows the identification of several genes and proteins that can be correlated with PD. There are different biochemical markers like alpha-Synuclein, DJ-1, a-beta, Tau, and Uric acid.

a. **Alpha-Synuclein** – (14)

Alpha-Synuclein is a physiological biomarker. It is used for Confirming PD. Alpha-Synuclein is a key protein in Lewy bodies it is a pathological hallmark for PD and the mutations of genes are known to cause PD. it was reported to be decreased CSF levels in PD patients compared with controls and well-controlled studies. Alpha-Synuclein genome-wide association studies have found gene encoding tau (MAPT) and PD.

b. **Protein deglycase (DJ-1)** - (14)

DJ-1 is a protein form in a dimeric structure. It is also known as deglycase encoded by the PARK7 gene. The DJ-1 gene has seven coding exons code for a 189-amino-acid-long protein that is widely expressed and functions as a cellular sensor of oxidative stress. Under physiological conditions, the DJ-1 protein forms a dimeric structure and it appears that most disease-causing mutations are dimeric. It is present in CSF fluid. There is a new

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technology for DJ- quantitation. The method is a bead-based flow cytometric assay commonly known as Luminex.

2. Neuroimaging biomarker –(15)

Neuroimaging biomarkers are mostly used for the diagnosis and progress of Parkinson's disease. There are three approaches to the large range of imaging modalities that have been investigated first is the target the basal ganglia's dopaminergic function the second is to scan the substantia nigra directly and the third one is to assess disease-related brain network abnormalities. There are different types of neuroimaging biomarkers such as DAT, 18F-dopa/FDG, TCS, MRI (DWI, iron deposit.

a. Dopamine transport (DAT) –(14)

DAT imaging biomarker is used as an in-vivo biomarker it helps to reflect integrity and the number of DA neurons. It reported that it reduces striatal DAT in more than 95% of Parkinsonism patients including at early stages. Several tracers including 11C-CFT, 18F-FP-CIT, 11C-RTI-32, and 11C-methylphenidate, can be used to assess the dopamine transporter (DAT), a protein present on the membrane of presynaptic DA terminals and involved in DA reuptake. Single-photon emission computed tomography (SPECT), is a technology used commonly in clinical practice for DAT.

b. [18F]fluoro-2-deoxy-2-D-glucose (FDG) - (16)

It plays an important role in 18F-FDG PET for diagnostic and risk stratification in cognitive impairment in PD. Neurology Level of Evidence suggests that 18F-FDG- PET is used as a test of APS differential diagnosis. It is also associated with a specific metabolism network in the brain. It shows Sensitivity and specificity for PD diagnosis is 95% and 94%. (APS, atypical parkinsonian syndrome)

c. Transcranial sonography (TCS) - (17)

TCS is known as Transcranial sonography (TCS). It is a non-dopamine imaging method. It is used for prodromal diagnosis in Pd. It includes important information on brain structure and function in Parkinson's disease that can be used for clinical testing. These non-invasive methods can assess the integrity of the DA system regularly and offer morphological profiles (e.g., asymmetry of uptake, etc.) as well as information on the period of neuron loss. In some cases, they are related to the severity of the disease (18). It helps in the diagnosis of Prodromal-PD4 (8). Prodromal-PD4 refers to the stage at which individuals do not fulfill diagnostic criteria for PD (i.e., bradykinesia and at least 1 other motor sign) but do exhibit signs and symptoms that indicate a higher than average risk of developing motor symptoms and a diagnosis of PD in the future.

d. **Magnetic resonance imaging (MRI)** – (19)

The MRI consists of potential markers of underlying neurodegeneration including regional changes in tissue volume, signal alterations on cMRI, and increased iron deposition and it reflects Astroglial activation, cell loss, and microglial proliferation. MRI helps in the quantitative evaluation of brain abnormalities and different features of neurodegeneration. In the high-field MRI, the signal-noise ratio is increased so that it increases field strength and spatial resolution also. Increasing spatial resolution, it increased provided by high-definition scanning may improve sensitivity to smaller lesions of the brain. The high-field MRI gives better grey-to-white-matter contrast and it shows sharp images and smooth transitions between the different brain structures.

3. Genetic biomarker –

Genetic biomarker consists of mutations that cause monogenetic forms of PD so the clinical researchers have been able to determine the etiology of the disease. The SNCA is the first dominating gene in causing PD. The well-known cause of autosomal dominantly inherited PD has been discovered as point mutations, duplications, and triplications. The alpha-Synuclein gene (SNCA) and the mutation of the SNCA gene confer a high probability of developing the disease. The second most common autosomal dominant gene causing PD is the gene for LRRK2. Mutations in the LRRK2 gene are more common than the SNCA gene (20). A-syn (SNCA), Parkin, PTEN-induced kinase1 (PINK1), DJ-1, and Leucine-rich repeats all have genetic variants that cause family types of PD. leucine-rich repeat kinase 2 (LRRK2), and they account for 2-3% of all cases of Classic Parkinsonism. According to genetic, clinical, pathological research, the autosomal dominant and recessive mutation shows that the identification of genetic risk loci for PD is mainly focused on LRRK2 and GBA (glucocerebrosidase) because mostly 5-10% of people with PD have GBA mutations are the most significant danger in terms of numbers and a risk factor for the disease (9).Gene polymorphisms possibly associated with PD risk include various gene to the specific location and

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there physiology. The detailed potential genes are enlisted in Table number 1

Table Number 1:Potential genes for polymorphism in PD

SL. NO	Class of gene	Location of gene	Receptor of gene	Name of genes	SNPs	Associated with	PD risk
1	Metabolizing enzyme	Neuronal microglial cells	COMT Receptor	COMT(21)	rs4680	Wearing of phenomenon	Increased risk
					rs165815	Visual hallucination	Decreased risk
		Glial cells	MAO-A	MAO-A(22)	rs1137070	Dyskinesia	Increased risk of PD
			MAO-B	MAO-B (22)	rs1799836		
		Lysosomal enzyme membrane	GBA (Glucosylceramidase Beta)	GBA(23)	rs2230288	Carrying GBA gene mutations	Increased risk
2	Dopamine transport	SNPC	G-protein coupled receptor	DDC(24)	rs921451	Motor response to acute L-dopa challenge.	Increased risk
					rs3837091		
					rs921451		
					rs3837091		
			D1	DRD1 (25)	rs4867798	Impulse control disorders	
		Postsynaptic dopaminergic neurons.	D2 (G-protein coupled receptor)	DRD2(26)	rs1800497	Sleep attacks and Motor fluctuation	
			D3	DRD3(27)	rs6280	Dose of dopamine agonist	
			D4	DRD4(25)	48-bp VNTR	Sleep Attacks	
2B	Vesicular monoamie transporter	SNPC	Dopamine	SLC18A	rs363371	Levodopa dose	
2C	Organic Cation Transporter	SNPC (intron region)	Dopamine	SLC22A1(20)	rs622342	Levodopa dose	
2D	Dopamine transporter	Synaptic vesicle glycop	Dopamine	SVC2(28)	rs30196	L-Dopa dose	Decreased risk

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		rotein					
3.	Glutamate Regulator	SNPC	NMDA Receptor	GRIN2A(29)	rs7192557 rs8057394	Dyskinesia	Increased risk
3A	Dopamine regulator	Adenosine A2A	dopamine	Adora2A(29)	rs2298383	Dyskinesia	Increased risk
3B	BNDF	BNDF	SNPC	BDNF Gene(21)	rs6265	Increase survival of dopaminergic neurons in snpc	Expression is found decreased PD.
3C	Hereditary PD	Chromosome 12q12	SNPC	LRRK2 (29)	rs11776238	Hereditary PD	Decreased risk
4	Genes involved in oxidative stress	SNPC	SNPC	Transferrin (TF) gene TFR2 gene(23)(30)	rs188066A rs1024796G	early-onset PD	Decreased risk
5	Cotransmitters	Basal ganglia	mu 1	OPRM1 Gene(24)	rs1799971	Dyskinesia	Increased risk
6	Neurotran smitters release	Located on human chromosome 4	Alpha-Synuclein	SNCA(31)	rs2572324 rs7684318	hereditary PD	Increase risk
7	Genes involved in the activation or detoxification of drugs, xenobiotic and exogenous toxins	SNPC	SNPC	ALDH2	rs4767944	Levodopa dose	Increase risk for PD

II. CONCLUSION

The Pharmacogenetics and pharma cogenomics are the best tools for assessing and identify the genetic basis for pharmacological response variability in terms of safety, efficacy, and pharmacokinetics. In this review we have explored the promising role of pharmacogenetics and pharmacogenomics in PD. Thus the involvement of particular class of genes, genetic makeup and understanding the defective gene can be made applicable in treating the patient more efficiently. Individualize treatment based on the patient's unique genetic profile by matching the appropriate medicine to the relevant patient at the appropriate time is one of the best scheme to reflect the use of pharmacogenetics and pharmacogenomics

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Benefits of Pharmacogenetics and Pharma cogenomics –

Pharmacogenetics and pharmacogenomics have a wide range of applications and benefits like they produce the more powerful medicine and better safer drugs the first time. It gives more accurate methods of determining appropriate drug dosages and advanced screening for the disease it also helps to Improvement in the drug discovery and approval process and Decreases the overall cost of health care (32). The application of pharmacogenetics in which it has a great potential to reduce and prevent ADRs and to improve therapeutic drug efficacy.Pharmacogenetics provides clinicians an attractive way to improve drug therapy, reduce side effects, and reduce prices. Avoiding medications that may or may not work, as well as those that may cause unwanted side effects. Prescriptions are safer because a doctor may be able to forecast which drugs and dosages a patient would respond to, resulting in fewer side effects. For conditions such as pain, nausea, and heart disease, new and more effective medications are being developed(33).

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