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REVIEW ARTICLE **OPEN ACCESS**

Genetic and Phenotypic Variations of Parkinson Disease

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ABSTRACT
Parkinson's is a complex neurodegenerative disease of the mid brain, primarily affecting the substantia nigra.Substantia nigrais densely populated with dopaminergic neuron and the death of these neurons result in the loss of smooth and coordinated skeletal muscle movement. The severity of the disease depends on the degree of death of the dopaminergic neurons. The symptoms and the clinical features of the patients are highly variable. The motor and non- motor symptoms varies in severity among the patients. Parkinson is a complex and multifactorial disease ranges from mono-genic to multi-genic Mendelian form of genetics. More than 11 genes and 16 loci have been identified for Parkinson's disease. Genetic factors contribute significantly to causing Parkinson's disease (PD). Variation in the frequency of phenotypes of Parkinson's is also due to the complexity of the disease. In this review we will explain familial forms of Parkinson's disease, basic genetic principles of inheritance and their exceptions, and the genetic and phenotypic variability of Parkinson's.
Key Words: Dopaminergic Neuron Genes. Parkinson's disease

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INTRODUCTION

The first documented evidence of Parkinson's disease dates back to 1817 in publication by James Parkinson titled "An essay on the shaking palsy". Since then, it has emerged into the second most prevalent neurodegenerative disorder after Alzheimer, gaining significant scientific interest[1, 2]. Parkinson disease is a complex multi factorial disease. The underlying complexity involves Mendelian and non Mendelian inheritance pattern along with genetic and environmental risk factors. Although certain genes have been marked for familial Parkinson's disease; yet there are reports indicating no heritability [3, 4].Till 20th century Parkinson's disease was considered a sporadic disease with onset in old ages and the etiology incompletely understood. With advances in the sequencing technologies and molecular genetics, distinct genetic loci were marked for Parkinson disease [5]. Now-a-days Parkinson's disease is thought to be a multi-factorial disease which is caused by combination of genetic and environmental risk factors. Variations in the frequency age and gender among the different population indicates the involvement of environmental risks and complexity of the disease [6].

Genes causing monogenic form of the diseases are usually identified by linkage analysis and genetic risk factors are identified through association studies. Linkage studies have identified about 16 loci and 11 genes associated with Parkinson's disease[7].Genetic risk variants are much more common than high penetrance disease causing mutations in a population.

Phenotype:

Parkinson is a complex disease and the symptoms vary among the patients. Clinically Parkinson's disease is characterized by six cardinal feature i.e. rest tremors, rigidity, flexed posture, bradykinesia – hypokinesia, loss of postural reflexes and freezing phenomenon. Due to different contours and existence of the affected withPD, motor and non-motor impairments are required to evaluate the perspective of each patient's prerequisites and goals [8].Various measuring activities are used for the assessment of motor damage and debility in patients with PD, but various actions have not been entirely estimated for rationality and consistency[9, 10].The Hoehn and Yahr scale is generally used to associate sets of patients and to provide gross evaluation of disease headway, extending from stage 0 (no signs of disease) to stage 5 (wheelchair bound and/or bedridden unless assisted). The Unified Parkinson's Disease Rating scale (UPDRS) is very well-studied scale for evaluating infirmity and damage[10, 11, 12].Still the UPDRS have

some limitation; it gives accurate assessment at the later stages of the PD but at the earlier stage of the disease the score may obscure the severity of the PD [8, 13].

Variation by Age, Gender, and Race/Ethnicity:

There has been controversy for many decades about the frequencies based on race/ethnicity age, and gender of Parkinson diseases[14].Zhang and Roman (1993) reviewed the epidemiological and clinical data in different population to provide the true statistics, but only include the suspected and afflicted proportion of the population and does not show the true prevalence of the disease [15]. Overall, the lack of incidence data on Parkinson's disease has mainly been the consequence of the low frequency, difficulty in the differential diagnoses and lake of record keeping and inhabitants ground registries. Ultimately, rates were estimated based on relatively fewer epidemiological and clinical cases with imperfect accuracy, particularly in the oldest age groups. The few reports regarding frequency have revealed that the percentage of Parkinson's disease upsurges abruptly after the fifth decade. The average life also affect the prevalence statistics in the population having larger proportion of older population[16]. Gender alterations have been described in most studies, with men having higher rates [17]

Genetics:

Although PD was long considered a non-genetic disorder of 'sporadic' origin, 5–10% of patients are now known to have mono-genic forms of the disease. At least, 16 loci and 11 genes(Table 1) are associated with X linked, autosomal dominant, recessive and genetic risks based PD.

Autosomal Dominant Parkinson's Disease Genes:

Large families where PD occurred in many members spread over several generations have attracted the attention of medical professionals and researchers for a long time. The possibility of (dominant) inheritance is obvious in such families, and it is not surprising that the first gene mutations discovered in PD was dominant and found after careful clinical and genetic analyses of large kindred. In dominant inheritance, fully compatible to Mendel's laws, one mutation (on one allele, i.e. one gene copy inherited either from the father or mother, heterozygous) is sufficient to cause disease.

SNCA (Park1/Park4):

Alpha synuclein (SCNA) also known as PRAK1/4is the first identified autosomal dominantly inherited gene. The gene expressed in the brain and encoded alpha syncline protein which is the major component of lewy bodies[18]. The function of the protein is not fully understood except that it impasses to synaptic vesicle and alsoimplicated in plasticity of brain [19]. It has been found out that this gene lies on chromosome 4q21 and suffer from three mutations that are A53T, A30P and E40H. Apart from these mutation, duplication and triplication of the entire gene has also been identified [20].Although rare (<1%), SNCA mutations are the major cause of Parkinson'sdisease. The prevalence of the Mendelian familial SNCA mutations is extremely low [is not repeated], although an assessment of its exact prevalence as a percentage of familial or 'sporadic' PD cases is difficult[20,21].The mutation has been linked in certain Caucasian and Asian families along with certain sporadic patients.

SNCA forms the core of the prevailing pathogenic model of PD. In particular, its propensity to transform from its monomeric to an aggregated beta sheet-rich form is believed to be the key to its pathogenic properties with oligomeric and fibrillary intermediaries represent the source of its cellular toxicity[22, 23,24].In transgenic animals and cell lines with the mention mutations have elucidated the pathogenic mechanism of SNCA. Perhaps the most surprising finding is that the abnormally folded aggregated SNCA appears to spread its aberrant structure to adjacent cells in a manner analogous to prion disease[25,26,27,28].

However, in spite of SNCAs evident significance to the pathogenesis of PD, the pressing question of its physiological function remains unsolved. Detection of alpha synuclein in blood and cerebrospinal fluid is currently under evaluation as a biomarker for PD and in particular as a means to identify early or prodromal disease[29].Therapeutic vaccine which binds to aggregated alpha synuclein and clears it from the brain is currently under clinical trials (www.michaeljfox.org).

Leucine-rich repeat kinase 2 (LRRK2):

Earlier in 2004, the leucine-rich repeat kinase 2 (*LRRK2*) mutation was initially documented in an autosomal dominant Japanese family with Parkinsonism[30].Reports on the mutation in the *LRRK2* was followed in the latter years[29].Furthermore, some studies pointed out mutations in the *LRRK2*geneassociated with PD [31, 32].Numerous families reported mutations in *LRRK2* gene worldwide including Northern Germany, Denmark, Canada[33, 34],Japan[35,33], Spain and United Kingdom [34] as major cause of Parkinson's disease.Some common mutations in different ethnic groups includes (c.5096A>G; p.Tyr1699Cys), (c.4321C>G; p.Arg1441Gly), (c.4321C>T; p.Arg1441Cys) and (c.4662G>A; p.Arg1514Gln).Another mutation (c.6059T>C;p.Ile2020Thr,) is ordinarily described in large PD family from Japan [33, 36,37] while (c.4321C>G p.Arg1441Cys)rare variant documented only in three families

worldwide. Another rare variant is (c.4309A>C p.Asn1437His), revealed in two Norwegian families' analyzed with exome sequencing [38](c.4321C>T; p.Arg1441Gly)mutation is common in Basque population which accounts for 8% familial PD cases. The other common LRRK2 mutations are rarely the cause of Parkinson's disease in this population. A shared founder effect of this mutations was recognized[39,40]and it remains entirely infrequent, or absent in other populations.

c.6167G>A; p.Gly2019Seris the most frequently identified mutation associated with Parkinson's disease in most of the population but is nearly absent in Asian population. In previous studies, this mutation was estimated at about 41% in sporadic cases while around 37% of individuals with familial PD (although some percentage of healthy/normal controls) from the North African-Arab population [41], and about 18 % in PD patients of Ashkenazi Jewish group (about 1.3% of controls). In some population the c.6167G>A; p.Gly2019Ser mutation act as common founder [42]while in other population this mutation is rare or absent[43] proposing South-to-North gradient in Europe[44]. In Scandinavian population, it is considered very rare generally[45].

Interestingly, some important genealogical research linked the most of these to one common ancestor, and demonstrated identical haplotype to the common Mediterranean one, representing contact of several hundred years of ancient periods[42, 46, 47]. In recent years, a large multicenter study reported the common (c.6167G>A; p.Gly2019Ser) mutation of *LRRK2* in only 49 out of 8,371patients (<1% Parkinsonism) in European and Asian sources. While this mutation is more prevalent (30%) in patients from Arab origin [48].

Although found to be the most common mutation (c.6167G>A; p.Gly2019Ser) in PD among different population, the clinical characteristics associated with this mutation is not documented. Age of onset of disease, penetrance and the severity of the motor and non-motor symptoms associated with this mutation was evaluated in1,045 patients. Furthermore, they describe the risk of PD to be about 28%, 51%, and 74% at age 59, 69, and79 years, respectively. Themotor and non-motor features of PD due to this mutation were more severe as compared to the other LRRK2 mutation [49]. Incomplete penetrance has also been documented as a healthy 95 year old individual from Sweden was found to havec.6167G>A; p.Gly2019Ser mutation[47].

A very rare variant p.S1508G was found in a patient with the late onset PD affecting one of the most conserved functional domains of LRRK2. Although different bioinformatics analysis showed that mutation is deleterious, the patients also had a heterozygous N370S mutation in GBA gene. The disease is due to the heterozygous N370S or p.S1508G and still to be investigated through site directed mutagenesis and functional analysis[50].Overall, Sixteen mutations in *LRRK2* are now well-thought-out conclusively to be pathogenic [48].

The neuropathology of PD patients with *LRRK2* mutation is heterogeneous and adaptable. Wider *et al*(2010)studied the neuropathological findings in some patients with *LRRK2* mutation[51]. In majority of the patients it was found that LRRK2 protein interact with the alpha synuclein as well as other sub cellular protein [52].Due to this variability, the possible explanation for this diversity is that the *LRRK2* protein functions as a kinase taking part in multiple metabolic and cellular pathways. LRRK2 is also required for the synapse development and the cellular homeostasis. the post mortem changes due to LRRK2 was first studied in patient with c.4309A>C p.Asn1437His mutation from Sweden [53].

Eukaryotic translation initiation factor 4-gamma (*EIF4G1)*:

Mutation in the eukaryotic translation initiation factor 4-gamma 1*(EIF4G1*)causes PD in autosomal dominant pattern. The p.Arg1205His mutation was co-segregated with Parkinsonism in different families from France, Ireland, Italy and the US. Haplotype analysis in these families indicated the common founder effect of this mutation. In 2011, *EIF4G1* gene was anticipated to enclosethe mutations that cause autosomal-dominant Parkinson's disease (PD), often with dementia [54]. p. Arg1205His mutation was identified in a multi-incident autosomal-dominant late-onset Parkinsonism French family and subsequent screening of a cohort of PD patients identified withp.A502V, p.G686C, p.S1164R, and p.R1197W mutations in PD cases.

EIF4G1 mutation failed to show any significant association with PD[55-60].Most recent studies showed that the initially designated mutations are probably in frequent and benign.Variant p.Arg1205His verified in a large group of subjects showed that it is more frequent in controls as compared to PD patients. The high frequency of these mutation in controls proves that these mutations are non-pathogenic[61]. Hence the role of EIF4G1 mutations in PD remained unclear.

VPS35:

p.Asp620Asn mutations in the VPS35 gene was reported in one Swiss two Austrian autosomal dominant Parkinsonian families in 2011. The clinical feature of the families were similar and include late onset

tremor dominant parkinsonism, psychosis, dementia and learning disabilities.[62,63].Another mutation p.Pro316Ser was reported in a family from the United States, but the genetic indication for the pathogenicity of this mutation remained debatable due to the presence of the mutation in normal control. Moreover, the clinical features only include late onset tremors with no other symptoms [64]. The p.Asp620Asn mutation was screened and identified as a rare pathogenic mutation of VPS35. The mutation was also found in one 86 year old unaffected control subject. Finding the mutation in control makes the pathogenicity controversial [65]. A partial neuropathological evaluation of only few regions of the cerebral cortex and basal ganglia (excluding the brainstem) did not disclose any alpha-synucleinimmuno-reactivity in these areas.

Parkinsonism disease harboring recessive genes:

PD with recessive inheritance attributes in different families with heterozygous/carrier parents with single generation of affected siblings. In this pattern, two identical alleles one from each parents (inherited from both parents; heterozygous) are required to cause homozygous mutations that result in disease. Conferring to classical Mendelian genetics, the occurrence of such single mutation does not upshot disease, but this classical view has been challenged in the perspective of numerous recessive PD mutations[66].

Unlikely genes involved in autosomal dominant, very few genes are determined for the involvement in the autosomal recessive PD.Some of these genes are very common among autosomal recessive families while otherhave been reported in few families. Setting the basis of recessive inheritance pattern in human disease has some complications. In recessive patterns of inheritance, some family individuals are affected for specific phenotype, classically only siblings. In these patterns, far distant relatives are not generally affected, and thus co-segregation analysis is restricted to few members and generations of the core family. The probability for homozygous mutant and normal sibling are 25% and for the heterozygous carrier is 50%. This may elucidate why dominant genes/mutation are numerousas compared to less numbers of genes/mutations in recessive families.

PARK2/PARKIN:

PARKIN (Parkin RBR E3 Ubiquitin Protein Ligase) gene is one of earlier genetic contributor associated with PD[67]. The mutations in this gene were revealed in various families with several numbers of siblings from Japan and Turkey, who had an uncharacteristic clinical syndrome initially, originated as an early-onset Parkinsonism with diurnal fluctuation (EPDF) (68). After the characteristic identification of *PARKIN*, it was considered the most common causative of an early onset PD. Christoph *et al* (2000) studied 25 families with autosomal recessive PD and 100 independent sporadic cases, found homozygous mutation in parkin gene. They also studied the relationship of age of onset of disease and PARKIN mutation. They found that 77% of patients with PARKIN were below the age of 20 years, while 26% of the patients were between 20 and 30 years of age and only 2% where between 30-40 years of age [69]. Other studies determined homozygous or compound heterozygous *PARKIN* mutations among a lesser fraction of patients with early onset-PD (onset before 40 or 45 years), in the range between 8.2% in Italy [70], 2.7% in Korea [71], 2.5% in Poland [72], and 1.4% in Australia [73].

More than 100 different types of *PARKIN* mutations have been documented and consist of copy number variation, insertion, deletions, duplications and point mutations [74]. In a previous report by Hakansson *et al*., (2003) described cases with early-onset PD from Sweden without involvement of homozygous *PARKIN* mutation carrier [75].The clinical features associated with PD due to mutations in the PARKIN gene is early onset, levodopa responsive, dyskinesias, and additionally lesser risk for cognitive decline dysautonomiadystonia of lower limbs and hyperreflexia and psychiatric symptoms[76]. Early-onset Parkinsonism with diurnal fluctuation EPDF is also the clinically distinguishable and important symptom associated with PARKIN mutations [77]. Dysautonomia although has been reported with PARKIN mutation does not affect cardiac sympathetic nerve supply[78]. Gross Pathological changes in the brainrestrict to the brain stem and do not engross alpha-synuclein deposition, but enhance cell death in the brainstem, including locusceruleus and substantia nigra[79]. The PARKIN protein has been aptly called "A Top Level Manager in the Cell's Sanitation Department"[80].For various functions, it has E3 ubiquitin ligase activity, selectively marking definite proteins for degradation by the ubiquitin proteasome system. Pathogenic *PARKIN* mutations decline this activity, and proteins accumulate which should to be degraded [80].Re-establishment or boost of PARKIN ligase activity by gene therapy is one possible novel opportunity of PD treatment, is under clinical trials[81].

Phosphatase and tensin homolog-induced putative kinase1 (*PINK1)*:

Homozygous mutations in the gene phosphatase and tensin homolog-induced putative kinase1 (*PINK1* causative of PARK6) is connected with Parkinsonism of early age showing some homozygous mutations[82].In this gene various type of variants including point mutations and infrequently, some

large deletions are documented[83]. The characteristic phenotype appears to be comparable with that of *PARKIN* mutations, although few suggestions recommend that psychiatric symptoms may occur more frequently among patients with *PINK1* mutations [83].

***DJ1*:**

The oncogene *DJ1* (Parkinson protein 7, PARK7) is the third remarkably studied recessive PD gene[84]. It is uncommon and only very few patients with *DJ1* mutations have been explored. In this type of Parkinsonism, numbers of cases are affected with early age onset, but features of early dementia, amyotrophy and Parkinsonism have also been explained in a family[85,86]. Very little is known about the neuropathology of a patient with *DJ1* mutations.

Other dominant genes of uncertain significance:

Some additional mutations have been tested in PD families, but still remain inconclusive. The implication of these genes for PD looks indeterminate at present. Possible explanations are that the co-segregation of the mutations and disease in the early families may have ensued by chance and the segregation of mutation in the normal control, suggesting non pathological variations. They may denote particularly rare happenings, only noticeable in single families ("private mutations"), and the replication of the results in similar families or patients are inconclusive. Uncommonness by itself does not oppose the potential pathogenicity; as rare variants play a significant part in global PD occurrence in a population. Several of these genes have "PARK" designations.

In 1998, mutation in ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase, *UCHL1*, PARK5) was identified in a family with Parkinsonism from German source [87]. Numerous efforts to investigate the role of UCHL1 remain ineffective and brought no proof that *UCHL1* would upsurge PD susceptibility [88, 89]

Earlier, mutations in *GIGYF2*were reported in Parkinsonian families[90]. Subsequent investigation to elucidate the role of GIGYF2 remains inconclusive. Mutations in the *GIGYF2*remain controversial because these mutations were also found in the normal healthy controls and the replicate studies fails to reproduce the findings in similar PD families.[61,91].

Mutations in the HtrA serine peptidase 2 (HTRA2, Omi/HtrA2, PARK13) were identified in German family showing the characteristics of PD [92], however further analyses made these variations insignificant due to the fact that these mutations were found in the healthy controls[93]. A large study from multicenter coordination within the GEO-PD consortium remains unsuccessful to detect the mutation among 6,378 patients with Parkinsonism features, and also demonstrated that variants in this gene do not alter the risk for (sporadic) PD [94]

CONCLUSION

Parkinson's disease is a complex condition caused by the death of dopaminergic neurons in substantia nigra. The neurons in the brain send and receive messages through neurotransmitter and receptors. These neurotransmitters and receptors are encoded by genes. Mutation(s)inthese genes will result in the aberrant form of proteins, crucial for the signaling or integrity of the pathway. These mutations either occur spontaneously or run through inheritance. Parkinson's is complex and multifactorial disease and therefore, ranges from mono-genic Mendelian to multi-genic Mendelian.Non Mendelian forms of genetic and genetic risk loci are the underlying mechanism of Parkinson's disease. In summary, Parkinson's is a multifactorial and complex disease. The advances that have been made in understanding the etiology of PD have been remarkable and informative. Unfortunately, they have not yet translated into therapies as effective as L-dopa. However, unlike L-dopa, continued molecular research into the causes of PD offers the future promise of a personalized therapy that aims to prevent, halt or cure the underlying disease.

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