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ROLE OF GENETIC VARIATIONS AND ITS CONTRIBUTION TOWARDS THE PATHOLOGICAL DEVELOPMENT OF PARKINSONISM

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ABSTRACT

Parkinson's accounts for the second most common neurodegenerative disease with about 10 million cases affected by it, out of which most cases are familial. Eighteen years of genetic research in Parkinsonism has led to the identification of several genetic risk factors that have contributed to this disease. Hence, targeting such genes for therapeutic intervention can be a good strategy in Parkinson's treatment. Mutations in such dominantly or recessively inherited genes have led to its conversion into monogenic forms that conclusively have been shown to cause hereditary-based parkinsonism. Four such genes like SNCA, LRRK2, PRKN, and PINK 1 have been extensively discussed in this review since their contribution towards the pathology of Parkinson's is more clinically significant than the other genes. The onset of this disease usually starts after the age of 60, but in some cases, early symptoms of the disease can also be observed in patients. Thus, strategizing treatment plans is a major driving force behind Parkinson's

research. This review briefly summarizes the function of the genes and their role in the pathogenesis of the disease as well as the clinical manifestations and genetic components of Parkinson's disease. This article will help researchers on pursuing ground-breaking research towards the management of Parkinson's disease.

Keywords: LRRK2, Parkinson's disease, PINK1, PRKN, SNCA

INTRODUCTION:

Parkinson's disease outlines as one of the most common neurodegenerative diseases and it indicates a group of disorders that affects various regions of the brain such as the pigmented nuclei of the midbrain and the brainstem, olfactory tubercle, cerebral cortex, and elements of the cerebral nervous system **[1]**. It is characterized by hypokinesia, rigidity, tremors, bradykinesia, cognitive impairment **[2]**. This disease mostly affects the elderly where the patients walk with a characteristic gait movement **[2]**. As the degeneration process is not only confined to basal ganglia but also affects the other parts of the brain, Parkinson's patients may show both non-motor and motor symptoms **[3]**. The non-motor symptoms like dementia, depression, hallucinations, and autonomic dysfunction have always appeared earlier than the motor symptoms **[3]**.

Almost 60,000 people in the USA get affected with Parkinson's daily and the estimated count for the number of people affected reaches one million **[4]**. By the end of the year 2030, the approximate rise in Parkinson's cases reaches around 1.2 million **[4]**. The occurrence of the disease range from 41 per 10,000 in the age group below 40 to more than 1,900 people per 10,000 among the group of people who are more than 80 years of age **[4]**. There has been a study that proves that men are more prone to the disease compared to women **[4]**.

The major problem due to Parkinsonism is the degeneration of dopaminergic neurons in the midbrain that leads to a deficiency of dopamine in the brain **[4]**. The etiopathology of the disease suggests that several mechanisms may be responsible for the disease **[5]**. These mechanisms generally include exogenous toxins, inflammations, and genetic mutations **[5]**. The interactions between the genetic and environmental factors have been the main reason for Parkinson's disease **[5]**. This has resulted in mitochondrial respiratory failure and oxidative stress within the nigral neurons that leads to cell death **[5]**. This hypothesis is been proved by the fact that explains how the number of cases of Parkinson's increased in

areas that are more prone to environmental toxins like MPTP pesticides **[6]**. The main constituent responsible for the toxicity of MPTP is 1-methyl-phenyl-pyridine (MPP+) which gets collected in the dopaminergic neurons **[7]**. Complex 1 of the respiratory chain of the inner mitochondrial membrane gets constrained by MPP+ radical that reduces the neuronal energy and finally leads to cell death **[7]**. The link between the production of neuromelanin and neuronal cell death can be explained by the generation of free radicals during neuromelanin synthesis and their binding as MPP+ (a toxic metabolite of MPTP) **[8]**.

According to the oxygen hypothesis, patients suffering from Parkinson's have a deficiency of the antioxidant system. During Parkinson's disease, the level of glutathione in the brain decreases **[9]**. This glutathione is majorly responsible to clear out the toxic peroxides that are formed due to the oxidative metabolism of dopamine by the monoamine oxidase enzyme **[10]**. This leads to more release of these toxic oxygen radicals that on accumulation leads to dopaminergic cell death **[10]**.

Pedigree analysis of genes:

The design of inheritance of any gene that is contributing to some major disease is being scrutinized and this is been studied and understood by examining how any disease is being passed on to the family members **[11]**. A deep study of all disease-related documents over several generations is being done and the specimens of both the affected and unaffected members are been collected for the analysis **[11]**.

Monogenic Parkinson's disease can be either dominant or recessive **[11]**. They are connected with the regions of autosomes for which these diseases are autosomal **[11]**.

In the Autosomal-dominant type **(Figure 1)** of Parkinson's, only one of the mutated alleles of the gene would be responsible for causing the disease **[11]**. The star points observed in the family tree with this prototype of inheritance are that every child that is observed having the defective gene must have either of their parents carrying the same gene and in every age band, at least one affected family member would be present. Moreover, every member carrying the infected gene will be passing it on to half of his or her offspring **[11]**.

Any characteristic trait of disease would only be visible during autosomal recessive disorders **(Figure 2)** when two types of mutations would occur on any one of the homozygous or heterozygous gene copies **[11]**. If any individual is carrying the gene with a heterozygous mutation, then no traits

of the disease would be observed in the person **[11]**. The main feature observed in the family tree with an autosomal recessive type of disease is that both father and mother would be carrying the heterozygous genes and they have zero symptoms of the disease and also the offsprings of these parents won't be showing any characteristics traits and would be carrying the heterozygous gene **[11]**. This type of disorder is famous for its "generation-skipping" property as none of the children from the second generation would be showing characteristics of the mutated gene and only 25.0% of the third generation will show the presence of this disorder **[11]**.

An autosomal dominant trait **(Figure 3)** can be observed only when the mutation occurs in one allele, whereas the other allele remains normal **[11]**. Three types of situations often lead to these types of traits, that is haploinsufficiency where the required function of any allele is missing because of its inability to produce a desired amount of protein, the other one is the harmful effects caused due to the production of a mutant polypeptide with zero functions that hamper the normal functioning of the usual allele **[11]**. There are some conditions where mutations of the gene often produce unwanted functions and thus lead to these traits **[11]**. Any one of these characteristics might be observed in the allele that thus leads to phenotypes with autosomal dominant traits **[11]**.

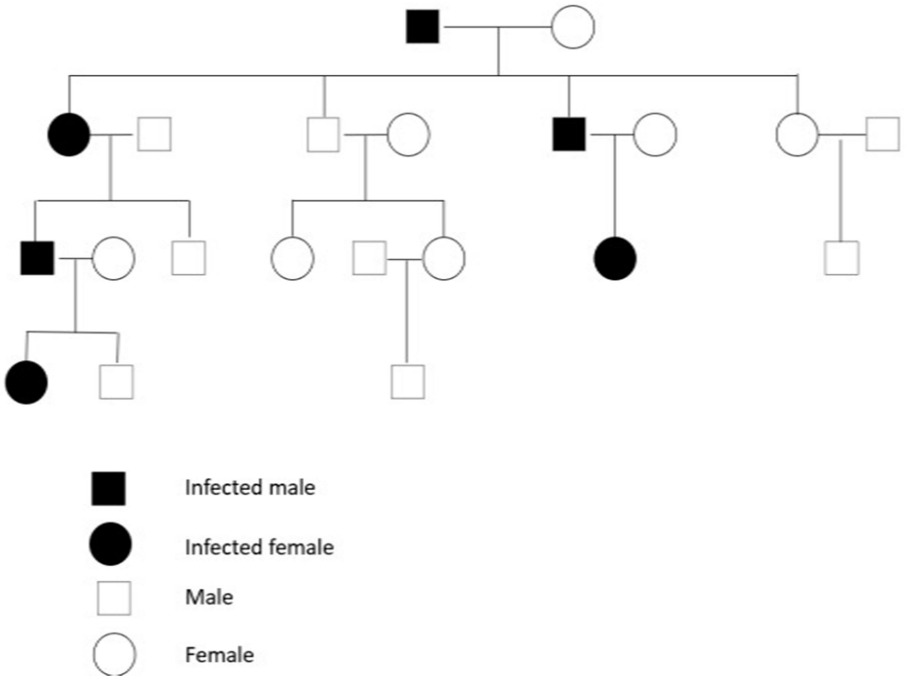

Figure 1: Autosomal dominant type of Parkinson's

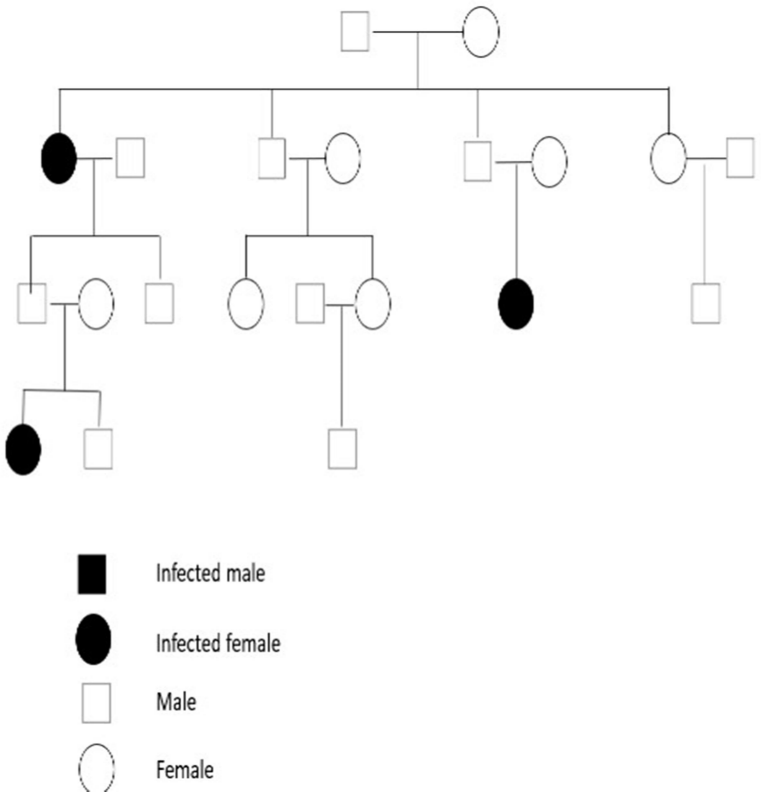

Figure 2: Autosomal recessive type of Parkinson's

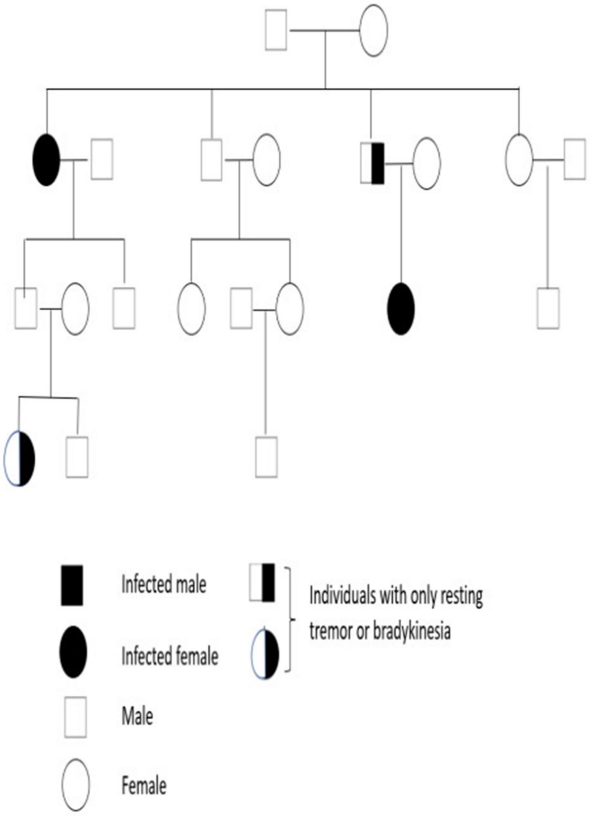

Figure 3: Haplo-insufficient Autosomal-dominant type of Parkinson's

Genes:

The main genes that are responsible for parkinsonism disease are α-synuclein (SNCA), glucocerebrosidase (GBA), parkin (PARK2), Pten-induced kinase 1 (PINK1), microtubule-associated protein tau (MAPT), and leucine-rich repeat kinase 2 (LRRK2) **[12]**. Mutations in these genes have been a major reason for the neurodegenerative disease, that is Parkinson's **[12]**. The description of these genes are as follows:

1. SNCA (PARK 1-4):

Figure 4: Structure of SNCA gene as shown in Discovery Studio

SNCA **(Figure 4)** originates from the synuclein family **[13]**. This family consists of three main members α-, β-, and ϒ-synucleins (AS, BS, and GS), and these are encoded by homologous genes **[13]**. The α-Synuclein protein was identified in the senile plaque and therefore was named the nonamyloid component of the plaque **[11]**. These proteins are present in the neural tissues and the tumour regions as small unorganized proteins and without any folded regions under physiological parts **[14, 15]**. A study was performed using α synuclein knockout mouse where the functioning of the synaptic region on aging was checked, where a significant decrease in its functioning on aging was observed, especially with triple knockout mice. **[16]** This resulted in a decrease in dopaminergic neurons in the substantia nigra pars compacta region of the brain **[17, 18**.] The main synuclein responsible for the pathogenesis of synucleinopathies is the α synuclein and as it accumulates in the glial cytoplasmic inclusions, it is included in

Parkinson's disease **[19]**. α synuclein is being encoded by the SNCA gene that is present on chromosome 4q21.3-q22 that consists of five coding exons and three additional 5' exons which are included in different SNCA transcripts **[20]**. An abundant level of Alpha-Synuclein is found in the presynaptic terminal **[21]**. They can be present either in a soluble unstructured form or in adjunction with phospholipid membranes along with synaptic vesicles **[21]**. Both of these forms have an important role in synucleinopathies **[21]**. Degeneration of Alpha-Synuclein usually includes the participation of the ubiquitin-proteasome system, lysosomal autophagy, or cytoplasmic proteases using capanin I **[22]**.

Lewy bodies are the circular or polymorphonuclear cellular inclusions that are present in the cytoplasm of the nerve cell **[23]**. The pathology of the Lewy body is rich in Alpha-synuclein **[23]**. During Parkinson's, the organization of Alpha-synuclein gets disorientated increases their level in the brain and leads to the formation of soluble oligomers thus forming indissoluble filaments and sediments in nerve cells **[24]**. These insoluble deposits lead to the making of Lewy bodies **[24]**.

Most neurodegenerative diseases like Parkinson's, Multiple Atrophy (MSA), or Dementia with Lewy bodies (DLB) includes problems with the functioning and the arrangement of alpha-synuclein. This is called as Alpha-Synucleinopathies **[25]**.

Role in normal body

Alpha-synuclein is located near the central region, therefore its role is mainly subjected to synaptic transport **[26]**. They are also responsible for axonal transport of the synaptic vesicles, modulation of the lipid metabolism, prevention of lipid hydrolysis to base and phosphatidic acid, binding and transporting of the fatty acids for regulating the activity of synaptic vesicles, inhibition of phospholipase D2 activity, differentiation and maintenance of the dopaminergic neuron cells and also it has anti-apoptotic activity **[27, 28]**. A study was performed by Benskey *et al*. who with his study had proved that alpha-synuclein has a major role in maintaining the nigrostriatal dopaminergic neuron viability **[29]**. For this, he had used adult wild-type rats and downregulation of the endogenous alpha-synuclein in the Substantia Nigra was done using Adeno-associated- virus short hairpin RNA that led to neuronal problems along with inflammation and nigral dopaminergic neuron loss **[29]**. No loss of viability was observed for glutaminergic neurons that proved the inclination of alpha-synuclein

towards dopaminergic neurons **[29]**. Alpha-synuclein goes and binds to the Kir6.2 subunit of the K-ATP channels, for which it also has a major role in inhibiting insulin production from pancreatic beta cells **[30]**. It can overcome the SNARE -complex assembly and regulate actin polymerization by promoting the collection of synaptic vesicles at the active site, corresponding to the heat shock proteins and prenylated Rab acceptor protein 1, and thus helps in facilitating cellular transport **[31-35]**.

It consists of 140 amino acids and has two junction forms that play a very important role in synucleinopathy.**[36]** This junction state protects the lumping up of proteins and when bonded to the negative charge carrying water-lipid interface, it gets converted into a particular arrangement that consists of 3 subitems: the N-Terminal of the protein which comprises the amphipathic alpha-helical domain that attaches the membrane collaterally; the mid part consisting of non-amyloid b component and the C-terminal end that is rich in glutamate and is acidic. This part protects the fibrillation and aggregation inhibition region **[37] (Figure 5)**.

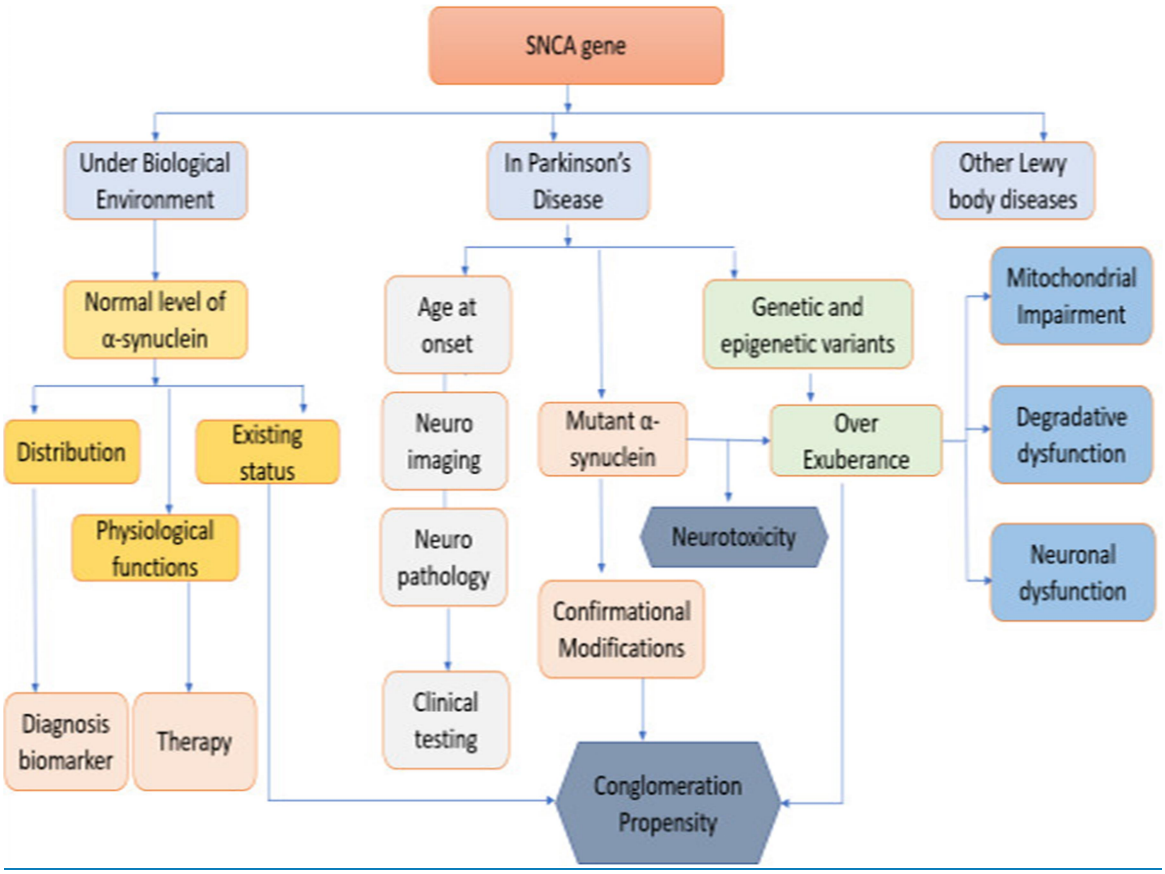

Figure 5: Role of SNCA in the body

Mutations in SNCA

SNCA gene is the one encoding for alpha-synuclein protein and it is present at the long arm of chromosome 4 **[11]**. In the year 1997, the missense mutation in A53T (c.157A>T) of SNCA was discovered in an Italian and Greek family **[38]**. This was the very first discovery that showed the relationship between mutations in the genes with parkinsonian activity **[38]**. After this, a single mutation in A30P (c.88G>C) was found in German family members who were suffering from typical Parkinson's disease **[39, 40]**. Similar mutation was observed in E46K (c.136G>A) of SNCA in the Spanish family who had traits with characteristics of dementia with Lewy bodies **[39, 40]**. In recent studies, a patient with a family history of Parkinson's disease and dementia, underwent a study where mutated H50Q (c.150T>G) was isolated from the SNCA gene **[41]**. A study was done on British family members who had cases of young-onset Parkinson's and it was found that a mutated G51D (c51G>A) allele was present in their gene **[42]**. Many cases of doubling or tripling of the gene were also major reasons for causing Parkinson's **[43]**. In total 13 Parkinson's cases where the whole coding area of SNCA showed 17 duplications thus contributing to the disease **[43]**. Similarly, 3 families were scrutinized for showing the presence of triplications of the genes in SNCA **[11]**.

In a cumulative study, it was probed that almost 812 single nucleotide proteins including 3' untranslated regions were identified. Amongst this, almost hundreds of mutated genes were responsible for the sporadic parkinsonian disease **[44]** .

Furthermore, epigenetic studies have proved that there is a direct relationship between the expression level of the gene with the methylation level of CpG present in intron 1 of the gene and finally also proved that overexpression of α-synuclein is directly related to the hypomethylation of CpG in intron-1, multiplication of the gene and UTR (464C>A) **[44]**.

2. LRRK2 (PARK8):

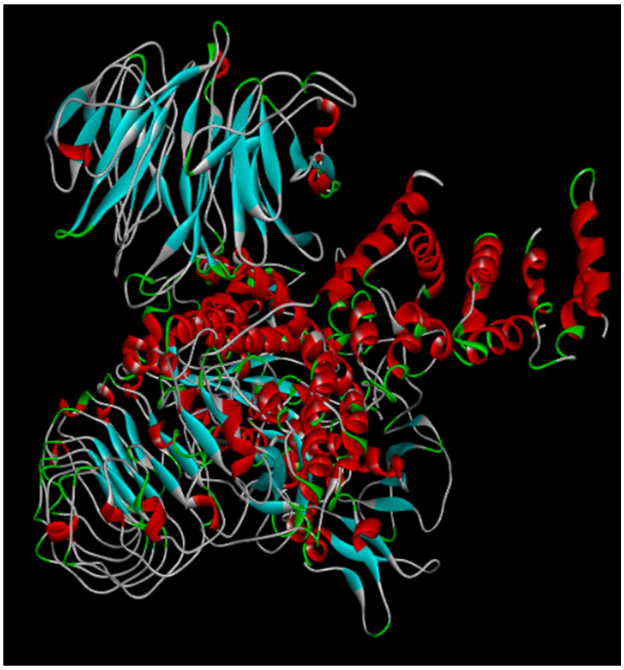

Figure 6: Structure of LRRK2 gene as shown in Discovery studio

LRRK2 **(Figure 6)** was discovered in the year 2004 and it belongs to the family of leucine-rich repeat kinase **[45, 46]**. The protein LRRK2 has a complicated structure that consists of many types of repeats and three considerable domains called Roc, COR, and kinase domains **[46]**. It is found in the cytoplasm region and is also associated with the outer region of the mitochondria **[47, 48, 49]**. This is a very large gene and it consists of 51 exons. **[50]** The protein comprises 2527- amino acid cytoplasmic protein LRRK2 and the long N-terminal region has 650 amino acids that are formed by repeats **[50]**. These repeats are rich in leucine that is carried to the amino-terminal of protein, and also there is a kinase domain present at the carboxy-terminal **[50]**. In between these terminals are the well-preserved domains that play a role in the gene-linked Parkinson's disease **[50]**. It codes for a complex protein that consists of kinase and GTPase activity that gets hampered because of mutations in this gene. **[51]** The other name of LRRK2 is Dardarin which means trembling **[50]**. Patients with LRRK2 linked Parkinson's usually show positive effects through levodopa therapy and no dementia is been observed in these kinds of patients **[50]**.

Mutations in LRRK2

The primary mechanism causing Parkinson's disease due to LRRK2 mutations is not known yet **[52, 53, 54]**. The main mutations in LRRK2 are majorly responsible for familial and sporadic Parkinsonism cases **[52, 53, 54]**. A large number of late-onset

autosomal dominant cases were observed with the percentage of mutations ranging between 2.0 to 40.0 % **[52, 53, 54]**.

Over 50 various types of missense and nonsense mutations were found in LRRK2 **[55]**. Amongst this, 16 mutations including p.R114C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S, and p.I2020T were infective and these are bunched in 10 exons especially in the carboxy-terminal of the protein **[55]**.

Mutation in c.6055G >A (p.G2019S) is a major causative agent of Parkinson's in 40% of Arabians, 20 % of Ashkenazi Jewish patients, and almost 7.0% of Europeans **[54, 56]**. Twenty-nine patients with a mutation in p.G2019S have been known to have the mutated gene in a homozygous state due to incomplete penetrance **[57]**. The harmful effects of the LRRK2 G2019S mutated gene usually increase with the time of life, that is, the severity of the disease is 28.0% at 59 years of age, and at 69 years the severity has increased to 51.0% **[11]**. By the age of 79, the risk of disease is almost 74.0% **[11]** .

High penetrant mutation at P. R1441G allele of LRRK2 within the GTPase domain has led to parkinsonism in some regions of Basques between France and Spain and has mainly affected the patients at the age of 75 **[58, 59]**. In this type of mutation, the amino acid arginine is replaced with glycine at 1441 position **[58, 59]**. It is therefore written as Arg1441Gly or R1441G **[58, 59]**.

Other mutations in P.I2020T of LRRK2 have been known to cause Parkinson's in Japan. **[60]**. In Asia, most of the patients with Parkinson's were known to have mutations in rs34778348 (G2385R, c.7153G>A) and rs33949390 (R1628P, c.4883G>C) alleles **[61]**. Similarly, a Single Nucleotide Protein in LRRK2, that is, rs1491942, could have been a reason for the disease in Caucasia **[61]**. A very in-depth study of the role of LRRK2 and the pathophysiology of its mutants were done in cultured cells and invertebrate models **[11]**. The in-vitro study has proved that there has been an increase in neuronal toxicity due to Parkinson-related mutations in LRRK2 **[11]**. The enhanced kinase activity due to these mutations has been a direct cause of this toxicity **[11]**. Along with this, studies were done using invertebrate models linked LRRK2 to cellular functions in vesicular trafficking, neuronal extension, cytoskeletal maintenance, etc. **[11]**.

3. PRKN (PARK 2)

Figure 7: Structure of PRKN gene as shown in Discovery studio

The PRKN **(Figure 7)** was the second gene that was identified to play a major role in Parkinson's disease **[61]**. It is been entitled as one of the largest genes in the human species that encodes for 465- amino acid proteins **[61]**. It is the only gene that is known to cause autosomal recessive juvenile Parkinson's disease **[11]**. This gene has a major role in the production of parkin protein **[61]**. Parkin protein is characterized under the E3 ubiquitin ligase system as these ubiquitin molecules are involved in the ubiquitin-proteasome system **[61]**. These ubiquitin particles in combination with Parkin play a very important part in cell technology where it destroys the unwanted protein molecules by tagging the damaged and extra proteins **[11]**. These proteins are degraded by specialized cells called proteasomes **[11]**. This system helps in maintaining the quality of the cell and helps to balance the number of proteins that are responsible for important cell events like cell division and maturation **[11]**. The gene has two domains; the amino-terminal consists of the ubiquitin-like domain of parkin which is confined towards structure stabilization and regulates the expression of the gene **[11]**. On the other hand, the carboxy-terminal domain has three RING (really interesting new gene) domains with RING0 having 145-215 amino acids, RING1 with 237-292, and RING3 with 237-292. Moreover, there is one in-between the ring domain that consists of 327-378 amino acids **[11]**.

This protein can be found as an evolutionary gene that is found in orthologs in *Caenorhabditis elegans*, *Drosophila melanogaster*, mouse, rats, and other species and is expressed in both neuronal and non-neuronal tissues. Inside the human brain, parkin protein is expressed in the cell body region of neurons, glial cells of the gray matter, and astrocyte-shaped cells of the white matter **[63]**. These proteins are also present in the Golgi apparatus, synaptic vesicles, and the nucleus. Parkin is found to travel from the mitochondria of the dividing cell to the extramitochondrial cytoplasm only under conditions when the cells are under dormant conditions **[63]**.

Role of Parkin

Parkin as a gene plays a crucial role in the maintenance of good mitochondria and destroying the ones that do not function properly. It also plays a vital role as a tumor suppressor protein, that is, it stops the cells from rapid and uncontrolled divisions plus it also controls the release of messages from one nerve cell to the other **[64]**.

This gene is being structured with an N-terminal consisting of a ubiquitin-like domain and the C-terminal that has two RING finger motifs. This structure helps in maintaining the regulatory function of the protein.

Parkin helps control the transcription and replication of mitochondrial DNA (mt-DNA) present in dividing cells. This protects the DNA from oxidative stress and helps in persuading the repair mechanisms **[11]**.

Mutations in PRKN

Between the years 2004 and 2009, 4841 patients having early-onset Parkinson's disease were studied for checking the role of the gene in Parkinsonism, and this study was performed on chromosome number 6. Almost 8.0% of the patients were showing positive results for mutations in PRKN gene that proved that mutations in the gene have a primary role in juvenile Parkinsonism (early-onset/symptoms of Parkinson's). It is been proven that these mutations are recessive and this has led to Juvenile parkinsonism in a certain percentage of Europeans **[65]** .

A cohort study was performed that concluded that there are various numbers of mutations including point mutations, exon reorganizations (deletion and duplications) that have linked the Parkin gene with parkinsonism **[66]**. The point mutations in the gene were studied using a direct sequencing pattern **[67]**. Maximum numbers of mutations were found on exon numbers 2, 4,7, 8, 10, and 11. About 50.0% of mutations in the gene are due to single or multiple exon deletion and duplication and this is only

because this gene is present inside a common fragile site, that is, FRA6E **[65]**.

Until now, a total of 887 exonic mutations have been discovered that consist of approximately 147 new variations **[65]**. Amongst all, 293 mutations were showing variations in single nucleotides, 119 mutations had small deletions in the alleles, and about 475 mutations included deletions or duplication of one or a large number of exons **[62]**. Around 459 out of the 887 mutations occur in the region spanning exons 2-4. (Codes for Ubiquitin linked domain, linker site, and starting of RING0 domain) **[11]**. Exon 3 is counted for the highest total number of mutations and exon 1 for the maximum mutation density with 2.4 mutations per base pair **[62]**. The highest variety of that is, 27 different types of mutations are seen in exon 2. Most numbers of Parkinson's patients have been found with the absence of exon 3 in the gene, this number is followed by an alteration in the single nucleotide c.924C>T of exon 7 **[65]**.

4. Pink1

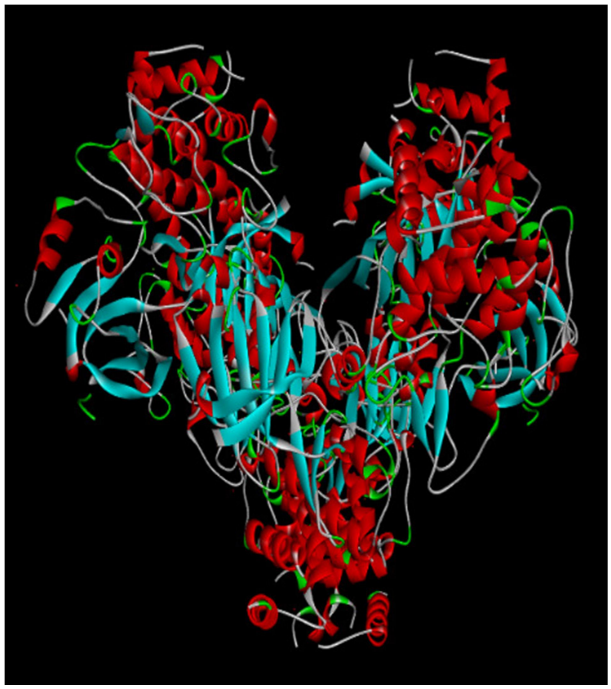

Figure 8: Structure of PINK1 gene as shown in Discovery studio

PINK1 **(Figure 8)** gene can also call as BRPK, PARK6, PINK1, and PTEN induced putative kinase 1. It consists of 581 amino acids and gives direction for the production of a protein called PTEN induced putative kinase 1. The gene has an amino-terminal to a 34 amino acid mitochondrial targeting motif with a serine-threonine kinase domain and a carboxy-terminal self-regulatory domain. This protein is present all over the

body including the heart, muscles, and testes. Inside the cells, these proteins can be found in the mitochondria **[68]**.

The main function of PINK1 is to guard the mitochondria at the time of cellular stress, especially during high energy demands. Particularly, the presence of two main regions of the PINK1 gene is essential for the protein's proper functioning. The first region is called the mitochondrial targeting motif that acts as a delivery address. It is ensured by this motif that all proteins that are being prepared gets are sent to the mitochondria. The protective functioning of the protein is been carried out through the kinase domain **[11]**.

Most of the mutations lead to loss of function of the gene and this directly disturbs the kinase domain and thus shows Parkinsonism-like symptoms **[11]**. The phosphatase and tensin humalog PINK1 gene mutation have been a major reason for autosomal recessive early-onset Parkinson's disease **[11]**.

Most of the mutations in the PINK1 gene can be missense or nonsense mutations **[68]**. Till now, only 3 families have been discovered who had shown the presence of complete exon deletion (exon4-8, exon 6-8, exon 7) and in another study, one patient showed symptoms of Parkinson's as the heterozygous complete gene was absent in the gene **[68]**. More than 40.0% of patients with Parkinson's showed missense in three-fourths of the gene. **[68]** Major total number of mutations is seen in exon 7 of the gene and the highest everyday mutations were observed in p.Q456X **[68]**.

Other genes showing possible effects of Parkinson's disease

Besides these main genes, several other genes contribute to its role in Parkinson's disease. Some genes have also achieved PARK* title that includes DJ1 (PARK7), ATP13A2 (PARK9), UCHL1 (PARK5), GYGYF2 (PARK11), OMI/HTRA2 (PARK13), PLA2G6 (PARK14), and FBXO7 (PARK15). Apart from these, researchers have also identified other genes like VPS35, E1F4G1, RTC3, CHCHD2, NAJC13, TMEM230, SYNJ1, DNAJC6, VPS132, PTRHD1, AADC RAB39B and PODXL showing potent role in the disease **[11]**. Some of these are been listed in **Table 1**.

Table1: Major genes responsible for Parkinsonism, their location, disorders, proteins produced by them, and the mutations leading to that disorder

GENES	LOCATION	DISORDER	PROTEIN	MUTATION
SNCA	4q21-22	EOPD, Typical Parkinson's Disease	α-synuclein	p.A53T (c.157A>T) p.A30P (c.88G>L) p.E46K(c.136G>A)
LRRK2	12q12	Late-onset autosomal dominant parkinsonism, Sporadic Parkinson's disease and Classical Parkinson's disease	Leucine-rich repeat kinase	p.R114C, p.R1441H, p.Y1699C, p.G2019S, p.I2020T, rs34778348 (G2385R, c.7153G>A), rs33949390 (R1628P, c.4883G>c), rs1491942
PRKN	6q25.2-q27	Juvenile Parkinson's	Parkin	Mutations at Exon 2,4,7,8,10,11 Variation in Single nucleotide • Deletions of alleles Exon1: Maximum mutation density Exon2: 27 Types of mutations Exon3: Highest total number of mutations Exon7: Single Nucleotide alteration, c.924c>T
PINK 1	1p3-p36	Autosomal recessive EOPD	PTEN induced putative kinase	Missense and nonsense mutation in Phosphatase and tensin humalog PINK, Complete Exon deletion at Exon 4-8, 6-8 and 7
DJ-1	1p36	Autosomal recessive Parkinson's disease, EOPD	DJ-1 protein	p.L166P, p.E64D, p.M26I, and p.D149A
ATP3A2	1p36	Autosomal recessive atypical Parkinson's disease, Kufor-Rakeb syndrome, spasticity, supranuclear gaze palsy	$ATP3A2^{isoform-1}$ $ATP3A2^{isoform-2}$ $ATP3A2^{isoform-3}$	Deletion at cytosine residue 3057, a duplication at 1632–1653 in exon 16, and conversion of guanine-to-adenine at exon 13 leading to the skipping of exon 13, frameshift mutation
UCHL-1	4p13	Autosomal Dominant classical Parkinson's disease	UCHL-1 protein	Deletion of the whole gene
GYGYF2	2q36-27	Autosomal Dominant late-onset Parkinson's disease	Grb10 protein	Exon2-Asn56Ser, Exon4-Thr112A1a, Exon8-I1e278Val, Exon9-Ser335Thr, Exon11- Asn457Thr, Exon14-Asp606Glu, Exon25-InsQQ1217
HTRA2	2p12	Autosomal Dominant classical Parkinson's disease	HtrA serine peptidase 2	A141S and G399S

CONCLUSION

In recent years, Parkinsonism has affected around 10 million people amongst which 10% of the cases are due to genetic defects. Although the overall case of genetic-related parkinsonism is quite rare, it is essential to understand the pathophysiology of the disease. The genetic form of Parkinson's has been proved as a very important model for idiopathic studies and the main focus of the

researchers is confined to reducing the role of the proteins and reverting the causes leading to these defects. Apart from the main genes, there are a lot many new genes that have been identified and are being studied. As of now, there is no existing treatment for these defects, but with the advancements in technology and research, a better cellular model for therapeutic testing as well as better alternatives will be available shortly.

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None

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