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Determining Parkinson's Genes – Disease Causing and Risk Factors

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Abstract **: An estimated seven to 10 million people worldwide are living with Parkinson's disease. It is a progressive neurological disorder. Symptoms of the disease include trembling or inability to move; impaired balance and co-ordination. The patients may also develop dementia; depression and visual hallucinations. Mutations in ten genes causing the disease were investigated. Chromosome location of the change, normal function and the function after mutation were investigated. It was enquired how mutation in genes leads to dysfunctional protein and how other mutations may have no effect at all. It was observed that chromosome 1 is mostly affected in this genetic disorder. Changes in GBA, LRRK2, SNCA, and PARK11 (GIGYF2) genes were of uncertain significance or are just considered as 'risk factors'. Mutated genes localized on chromosome 1 such as PARK 7, PINK 1 and GBA results in production and accumulation of misfolded proteins leading to abnormal protein deposition in nerve cells thus leading to death of nerve cells together with affecting mitochondrial protein targeting motifs which in turn disables the nerve cells from preventing oxidative stress. A single change in the genes such as PARK1, PARK7 and PINK1 may lead to this disease.**

1. INTRODUCTION

Parkinson disease (PD) is a progressive neurological disorder. This disorder affects several regions of the brain, especially an area called substantia nigra that controls balance and movement. A mutation in one DNA nucleotide (SNP, single-nucleotide polymorphism) may cause the formation of a wrong amino acid and the resulting proteins may or may not be functional [1]. The reason for this is that different amino acids have different sizes and electric charges, mutation in these amino acids can lead to misfolding of the proteins, loss of ability to prevent nerve cells from oxidative stress, abnormal protein deposition in nerve cells and affects mitochondrial protein targeting motifs, thus leading to death of nerve cells. A further morphologic hallmark of PD is the presence of lewy bodies and lewy neuritis that arise from inappropriately folded versions of proteins and polypeptides present naturally in the body [2]. These misfolded structures alter their proper configuration such that they erroneously interact with one another or other cell components forming insoluble fibrils, including alpha-synuclein, synphilin-1, parkin and UCHL-1 [3]. Symptoms of the disease appear when dopamine-producing neurons become impaired or die. The loss of these cells weakens communication between the brain and muscles, and ultimately the brain becomes unable to control muscle movement. Parkinson's disease affects more than 4 million people worldwide. It occurs in approximately 13 per 100,000 people and 60,000 new cases are identified each year [1, 3].

2. METHODOLOGY

Genetics Home Reference (GHR), a national library of medicine's website for consumer information about genetic conditions was used. Pathogenic and non-pathogenic genes related to Parkinson's disease were noted [4]. NCBI Gene and SNP Tutorial, resource for knowing the gene sequences; gene alleles; mutations; amino acid sequences for proteins was used. The chromosome location; normal function of pathogenic and non-pathogenic genes causing Parkinson's disease; family name and the altered functions of the genes after mutation were investigated and recorded in the form of a table. SNP database of the National Center for Biotechnology Information, U.S. National Library of Medicine was used for extracting the rsID of the alleles of interest [5]. Variation and phenotype, i.e., whether the mutant variant is autosomal recessive or dominant; clinical significance and effect of the mutated genes on the amino acid sequence was recorded in the form of table1 and 2 [6].

3. RESULTS

Table 1. Gene Family, Location, Normal Function and Function after Mutation of genes, all belonging to PARK family

GENES	LOCATION	NORMAL FUNCTION IN CELL	FUNCTION AFTER MUTATION
LRRK2	CHROMOSOME 12 at position 12	Active in the brain, Provide instructions for protein dardarin which has kinase activity and GTPase activity	Kinase and GTPase activity gets affected ,It is responsible for the tremor in Parkinson disease
PARK2	LONG (q)ARM of CHROMOSOME 6 between positions 25.2 and 27	Provides instructions for protein parkin, breaks down unneeded proteins and act as tumor suppressor protein and also regulates the supply and release of synaptic vesicles	Disturbs the ubiquitin-proteasome system, disrupts supply and release of synaptic vesicles, shortage of parkin leads to uncontrolled growth of cells i.e. tumor
PARK7	SHORT(p) ARM OF CHROMOSOME 1 at position 36.23	Provides instructions for DJ-1 protein which protects brain cells from oxidative stress, also serves as chaperone molecule and also plays role in producing and processing RNA	Disrupts chaperone function and leads to toxic build up of misfolded or damaged protein and loses the ability to prevent nerve cells from destructive oxidative stress
PINK1	SHORT (q)ARM OF CHROMOSOME 1 at position 36	Provides instruction for protein PTEN induced putative kinase 1 which is present with highest level in heart, muscles and testes. It helps to protect mitochondria during cellular stress	Alter or eliminate the kinase domain, leading to loss of protein function, affects the mitochondrial targeting motif and disrupt delivery of protein to mitochondria, cause death of nerve cells
SNCA	CHROMOSOME 4 at position 21	Provides instruction for protein alpha-synuclein which is abundant in brain at the tip of nerve cells. It play important role in supply of synaptic vesicles ,regulate release of Dopamine	Mutation causes alpha-synuclein protein to take on an incorrect 3-dimensional shape. other mutation exceeds the amount of protein. misfolded or excess alpha-synuclein clusters and impair the function of neurons by disrupting the regulation of Dopamine
UCHL1	CHROMOSOME 4 at position 14	Found in nerve cells, provides instructions for an enzyme called ubiquitin carboxyl-terminal esterase L1.UCHL1 has hydrolase activity, removes and recycles ubiquitin molecules from degraded proteins and also has ligase activity,links together ubiquitin molecules for use in tagging proteins for disposal.	Polymorphism reduce ligase and hydrolase activity of ubiquitin and it results in accumulation of unneeded proteins to toxic levels that impair or kill nerve cells in the brain
PLA 2G6	CHROMOSOME 22 AT POSITION 13.1	Provides instructions for protein A2 phospholipase which is involved in breaking down phospholipids .it also regulate levels of phosphatidylcholine. ANKRD(ankyrin repeat	Adverse effect on the brain iron metabolism, responsible for slow movement(bradykinesia) and inability to hold the body upright

		domain containing)	and balanced
GBA	LONG(q) ARM OF CHROMOSOME 1 at position 21	Provides instructions for an enzyme called beta-glucocerebrosidase, it breaks down a large molecule called glucocerebroside into a sugar.	Contribute to faulty breakdown of toxic substances in nerve cells, increase the formation of abnormal protein deposits
ATP13A2	SHORT (q)ARM OF CHROMOSOME 1 at positions 36	Encodes a member of the P5 sub family of ATPases which transports inorganic cations	Cause Kufor-Rakeb syndrome ,impairment of nigrostriatal function,

Table 2. From DNA to Amino acid (only some of the data is presented)

GENE	VARIATION	CLINICAL SIGNIFANCE	rsID	EFFECT ON AMINO ACID
ATP13 A2	c.1510G>C (p.Gly504Arg)	Pathogenic	rs121918227	Non polar to positively charged
GBA	c.1444G>A (p.Asp482Asn)	Risk factor	rs75671029	Negatively charged to polar uncharged
LRRK2	c.7153G>A(p.Gly2385Arg)	Pathogenic	rs34778348	Non polar to positively charged
LRRK2	c.7067C>T (p.Thr2356Ile)	Uncertain significance	rs113511708	Polar uncharged to non polar
PINK1	c.650C>A (p.Ala217Asp)	Pathogenic	rs74315360	Non polar to negatively charged
PINK1	c.938C>T (p.Thr313Met)	Pathogenic	rs74315359	Polar uncharged to non polar
PINK1	c.813C>A (p.His271Gln)	pathogenic	rs28940284	Positively charged to polar uncharged
PINK1	c.926G>A (p.Gly10Asp)	Pathogenic	rs74315355	Non polar to negatively charged
SNCA	c.157G>A (p.Ala53Thr)	Pathogenic	rs104893877	Non polar to polar uncharged
VPS 35	c.1858G>A (p.Asp620Asn)	Pathogenic	rs188286943	Negatively charged to polar uncharged
PARK7	c.446A>C (p.Asp149Ala)	Pathogenic	rs74315352	Negatively charged to non polar
PARK7	c.487G>A (p.Glu168Lys)	Pathogenic	rs74315354	Negatively charged to positively charged
PARK7	c.115G>T (p.Ala39Ser)	Pathogenic	rs137853051	Non polar to polar uncharged

PARK2	c.1180G>A (p.Asp394Asn)	Pathogenic	rs1801334	Negatively charged to polar uncharged
PARK2	c.1096C>T (p.Arg366Trp)	Pathogenic	rs56092260	Positively charged to aromatic
PARK2	c.719C>T (p.Thr240Met)	Pathogenic	rs137853054	Polar uncharged to non polar
PARK2	c.633A>T (p.Lys211Asn)	Pathogenic	rs137863060	Positively charged to polar uncharged
PARK2	c.167T>A (p.Val56Glu)	Pathogenic	rs137853059	Non polar to negatively charged
PARK2	c.245C>A (p.Ala82Glu)	Pathogenic	rs55774500	Non polar to negatively charged
PARK2	c.1292G>T (p.Cys431Phe)	Pathogenic	rs397514694	Polar uncharged to aromatic
PARK2	c.635G>A (p.Cys212Tyr)	Pathogenic	rs137853058	Polar uncharged to aromatic
PARK2	c.483A>T (p.Lys161Asn)	Pathogenic	rs137853057	Positively charged to polar uncharged
PARK2	c.719C>G (p.Thr240Arg)	pathogenic	rs137853054	Polar uncharged to positively charged
PLA2G6	c.991G>T (p.Asp331Tyr)	Pathogenic	rs199935023	Negatively charged to aromatic
PLA2G6	c.1904G>A (p.Arg635Gln)	Pathogenic	rs387906863	Positively charged to polar uncharged
PLA2G6	c.2239C>T (p.Arg747Trp)	Pathogenic	rs121908687	Positively charged to aromatic
MAPT	c.1837_1839delAAT (p.Asn613del)	Risk factor	rs199422218	
SNCA1P	c.1861C>T (p.Arg621Cys)	Unknown significance	rs28937592	
LRRK2	c.7224G>A (p.Met2408Ile)	Uncertain significance	rs60545352	
LRRK2	c.7168G>A (p.val2390Met)	Uncertain significance	rs79546190	
PARK7	c.192G>C (p.Glu64Asp)	Uncertain significance	rs74315353	

4. DISCUSSION

There are 10 genes responsible for Parkinson's disease GBA, PARK2, PARK7, LRRK2, PINK1, SNCA, UCHL1, ATP13A2, VPS35, and PLA2G6. Some of these have been studied.

GBA: "glucosidase beta acid" provides instructions for making an enzyme called beta-glucocerebrosidase. Changes in this gene are associated with Parkinson disease. People who are carriers of a *GBA* gene mutation have an increased risk of developing Parkinson disease. Symptoms of the disease result from the loss of nerve cells that produce dopamine. Changes in this gene may contribute to the faulty breakdown of toxic substances in nerve cells by impairing the function of lysosomes. Alternatively, the changes may increase the formation of abnormal protein deposits. As a result, toxic substances or protein deposits could accumulate and kill dopamine-producing nerve cells, leading to abnormal movements and balance problems [5].

PARK2: "Parkin RBR E3 ubiquitin protein ligase" is one of the largest human genes encoding the protein Parkin. It has a role in ubiquitinated degradation of damaged proteins by tagging them with ubiquitin. It belongs to a group of proteins called E3 ubiquitin ligases. Parkin appears to be involved in the maintenance of mitochondria. More than 200 PARK2 gene mutations that cause parkinson disease have been identified. Mutations in these genes are associated with the juvenile form of parkinson disease. Some PARK2 gene mutations lead to an abnormally small parkin protein that is nonfunctional and is rapidly broken down (degraded) within cells. Other mutations insert, delete, or change DNA building blocks (nucleotides) in the PARK2 gene, leading to a defective version of the parkin protein or preventing the production of this protein. The loss of parkin activity probably disturbs the ubiquitin-proteasome system, which allows unneeded proteins to accumulate. A buildup of these proteins could disrupt normal cell activities such as the supply and release of synaptic vesicles, particularly those that contain a chemical messenger called dopamine. As parkin is normally abundant in the brain, its loss could lead to the impairment or death of nerve cells, including those that produce dopamine. Loss of dopamine-producing nerve cells is a characteristic feature of Parkinson's disease. It is speculated that mitochondrial dysfunction in dopamine-producing nerve cells may play an important role in causing the signs and symptoms of the disease [7].

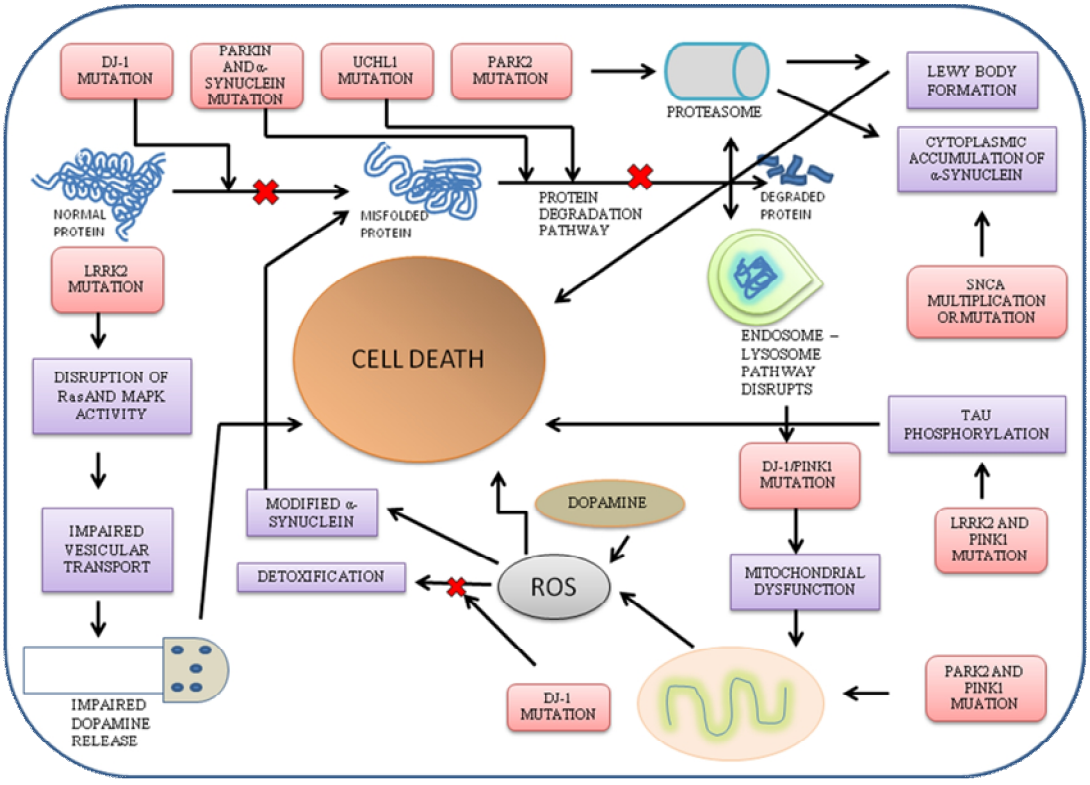

Figure 1- Overall pathway of mutated genes causing Parkinson's disease

PARK7: "Parkinson protein 7" encodes DJ-1 protein. This protein is found in many tissues and organs, including the brain. DJ-1 protein helps protect brain cells from oxidative stress. Oxidative stress occurs when unstable molecules called free radicals accumulate to levels that can damage or kill cells. Additionally, the DJ-1 protein may serve as a chaperone molecule that helps fold newly produced proteins into the proper 3-dimensional shape and helps refold damaged proteins. More than 25 PARK7 gene mutations that can cause Parkinson disease have been identified. Some PARK7 gene mutations lead to an abnormally small DJ-1 protein or change the building blocks (amino acids) used to make the protein. The altered protein is unstable and does not function properly, if at all. Other mutations delete a large portion of the PARK7 gene, preventing the production of any functional DJ-1 protein. It is reported that PARK7 gene mutations disrupt the protein's chaperone function, which leads to a toxic buildup of misfolded or damaged proteins and eventually to cell death. Another possibility is that PARK7 gene mutations impair the protein's ability to protect cells from destructive oxidative stress. Nerve cells that make the chemical messenger dopamine are particularly vulnerable to oxidative stress. With diminished protection, free radicals may cause enough damage to kill these nerve cells. The death of these cells weakens communication between the brain and muscles, and ultimately the brain becomes unable to control muscle movement [8].

LRRK2: "Leucine-rich repeat kinase 2" encodes a protein called dardarin. The LRRK2 gene is active in the brain and other tissues throughout the body. Dardarin has kinase activity and GTPase activities. More than 100 *LRRK2* gene mutations in families with late-onset Parkinson disease (the most common form of the disorder, which appears after age 50) have been identified [9].

PINK1: The product of the gene "PTEN induced putative kinase 1" helps protect mitochondria from malfunctioning during periods of cellular stress, such as unusually high energy demands. More than 70 mutations in the *PINK1* gene that can cause Parkinson disease have been identified. *PINK1* gene mutations are associated with the early-onset form of the disorder, which typically begins before age 50. Many *PINK1* gene mutations alter or eliminate the kinase domain, leading to a loss of protein function. With reduced or absent PTEN induced putative kinase 1 activity, mitochondria may malfunction, particularly when cells are stressed. Cells can die if energy is not provided for essential activities. It is unclear how *PINK1* gene mutations cause the selective death of nerve cells that characterizes Parkinson disease [10].

SNCA: "Synuclein alpha" encodes the protein alpha-synuclein. In the brain, alpha-synuclein is found mainly at the tips of nerve cells (neurons) in specialized structures called presynaptic terminals. Alpha-synuclein may help regulate the release of dopamine. At least 18 mutations in the *SNCA* gene have been found to cause Parkinson disease. *SNCA* gene mutations are associated with the early-onset form of the disorder. There are two types of alterations of the *SNCA* gene in people with Parkinson disease. One type includes SNP's. While in the other, one of the two *SNCA* genes in each cell is inappropriately duplicated or triplicated. The extra copies of the *SNCA* gene leads to an excess of alpha-synuclein. Misfolded alpha-synuclein is also a major component of Lewy bodies, abnormal deposits that appear in certain neurons in the brain in people with Parkinson disease. The presence of Lewy bodies in a region of the brain called the substantia nigra, which controls balance and movement, are a characteristic feature of Parkinson disease [11,12].

UCHL1: The product of the gene "Ubiquitin carboxyl-terminal esterase L1" is found in nerve cells throughout the brain. It has a function in the ubiquitin-proteasome system. A relatively common variation Ser18Tyr in the *UCHL1* gene may reduce the risk of developing Parkinson disease. It remains unclear how this amino acid variation might reduce the risk of developing Parkinson disease. A different mutation Ile93Met in the *UCHL1* gene may increase the risk of Parkinson disease. The mutation leads to a decreased hydrolase activity, which may disrupt the ubiquitin-proteasome system. Instead of being degraded, unneeded proteins could accumulate to toxic levels that impair or kill nerve cells in the brain [13].

5. CONCLUSION

Ten pathogenic genes were found responsible for Parkinson's disease. Most prominent ones include PARK2, LRRK2, PARK7 and PINK1. The disease is marked by the loss of ability of the brain cells/nerve cells to release the neurotransmitter, dopamine. Most of the mutations thrust the nerve cells towards destructive oxidative stress or to the accumulation of misfolded protein and impairment of lysosomal function. All of which culminate in the prevention of dopamine release. Majority of the mutations associated with the disease are clustered on chromosomes 1 and 4. Mutated genes located on chromosome 1 i.e. PARK 7, PINK 1 and GBA results in production of misfolded proteins, loss

of ability to prevent nerve cells from oxidative stress, abnormal protein deposition in nerve cells and affects mitochondrial protein targeting motifs, thus leading to death of nerve cells involved in dopamine release.

Misfolded protein deposits (such as lewy bodies in substantia nigra associated with balance and movement) could accumulate and kill dopamine-producing nerve cells, leading to abnormal movements and balance problems. Impairment in the chaperones function and ubiquitination and prevention of nerve cells from oxidative stress damage seems to be the prime cause of death of nerve cells associated with dopamine release. Some of the issues remain unresolved such as loss of kinase activity of PINK1 leading to mitochondrial malfunction during stress. Surprisingly, one amino acid mutation in UCHL1 lowers the risk of parkinson's while the other affecting it's hydrolase activity increases the risk. Clearly, hydrolase activity of this protein seems to play a key role in normal functioning and prevention of the disease.

The mutations result in substitution of amino acids from charged to uncharged; uncharged to charged or even negatively to positively charged. Such changes in charge and polarity of residues can have drastic consequences as an enzyme becomes dysfunctional. Apart from the pathogenic genes, non-pathogenic genes were also noted. Some gene mutations are silent, having no effect at all such as PARK11 (GIGYF2). Changes in these genes are of uncertain significance or some of them are only considered as 'risk factor'. Substitutions of methionine for isoleucine (Met2408Ile) or valine to methionine (val2390Met) in LRRK2 for example, is of uncertain significance as all the three largely contain non-reactive and flexible side chains that are ideally suited for packing in the protein interior; and all are hydrophobic. Glutamate to aspartate conversion in PARK7 at position 64 goes unaltered as both are negatively charged. Research on Parkinson's disease is still under way to reveal many other causes and cures.

6. ACKNOWLEDGEMENTS

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