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 table 1 and 2 [6].
### 3. RESULTS

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

<table>
<thead>
<tr>
<th>GENES</th>
<th>LOCATION</th>
<th>NORMAL FUNCTION IN CELL</th>
<th>FUNCTION AFTER MUTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRRK2</td>
<td>CHROMOSOME 12 at position 12</td>
<td>Active in the brain, Provide instructions for protein dardarin which has kinase activity and GTPase activity</td>
<td>Kinase and GTPase activity gets affected, It is responsible for the tremor in Parkinson disease</td>
</tr>
<tr>
<td>PARK2</td>
<td>LONG (q)ARM of CHROMOSOME 6 between positions 25.2 and 27</td>
<td>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</td>
<td>Disturbs the ubiquitin-proteasome system, disrupts supply and release of synaptic vesicles, shortage of parkin leads to uncontrolled growth of cells i.e. tumor</td>
</tr>
<tr>
<td>PARK7</td>
<td>SHORT(p) ARM OF CHROMOSOME 1 at position 36.23</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>PINK1</td>
<td>SHORT (q)ARM OF CHROMOSOME 1 at position 36</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>SNCA</td>
<td>CHROMOSOME 4 at position 21</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>UCHL1</td>
<td>CHROMOSOME 4 at position 14</td>
<td>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 ligation activity, links together ubiquitin molecules for use in tagging proteins for disposal.</td>
<td>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</td>
</tr>
<tr>
<td>PLA 2G6</td>
<td>CHROMOSOME 22 AT POSITION 13.1</td>
<td>Provides instructions for protein A2 phospholipase which is involved in breaking down phospholipids. It also regulate levels of phosphatidylcholine. ANKRD(ankyrin repeat</td>
<td>Adverse effect on the brain iron metabolism, responsible for slow movement(bradykinesia) and inability to hold the body upright</td>
</tr>
</tbody>
</table>
Determining Parkinson’s Genes – Disease Causing and Risk Factors

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIATION</th>
<th>CLINICAL SIGNIFICANCE</th>
<th>rsID</th>
<th>EFFECT ON AMINO ACID</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBA</td>
<td>LONG(q) ARM OF CHROMOSOME 1 at position 21</td>
<td>Provides instructions for an enzyme called beta-glucocerebrosidase, it breaks down a large molecule called glucocerebrosine into a sugar.</td>
<td>and balanced</td>
<td>Contribute to faulty breakdown of toxic substances in nerve cells, increase the formation of abnormal protein deposits</td>
</tr>
<tr>
<td>ATP13A2</td>
<td>SHORT (q) ARM OF CHROMOSOME 1 at positions 36</td>
<td>Encodes a member of the P5 sub family of ATPases which transports inorganic cations</td>
<td></td>
<td>Cause Kufor-Rakeb syndrome, impairment of nigrostriatal function,</td>
</tr>
</tbody>
</table>

Table 2. From DNA to Amino acid (only some of the data is presented)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Mutation Description</th>
<th>Type</th>
<th>rsID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK2</td>
<td>c.1180G&gt;A</td>
<td>(p.Asp394Asn)</td>
<td>Pathogenic</td>
<td>rs1801334</td>
<td>Negatively charged to polar uncharged</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.1096C&gt;T</td>
<td>(p.Arg366Trp)</td>
<td>Pathogenic</td>
<td>rs56092260</td>
<td>Positively charged to aromatic</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.719C&gt;T</td>
<td>(p.Thr240Met)</td>
<td>Pathogenic</td>
<td>rs137853054</td>
<td>Polar uncharged to non polar</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.633A&gt;T</td>
<td>(p.Lys211Asn)</td>
<td>Pathogenic</td>
<td>rs137863060</td>
<td>Positively charged to polar uncharged</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.167T&gt;A</td>
<td>(p.Val56Glu)</td>
<td>Pathogenic</td>
<td>rs137853059</td>
<td>Non polar to negatively charged</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.245C&gt;A</td>
<td>(p.Ala82Glu)</td>
<td>Pathogenic</td>
<td>rs55774500</td>
<td>Non polar to negatively charged</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.1292G&gt;T</td>
<td>(p.Cys431Phe)</td>
<td>Pathogenic</td>
<td>rs397514694</td>
<td>Polar uncharged to aromatic</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.635G&gt;A</td>
<td>(p.Cys212Tyr)</td>
<td>Pathogenic</td>
<td>rs137853058</td>
<td>Polar uncharged to aromatic</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.483A&gt;T</td>
<td>(p.Lys161Asn)</td>
<td>Pathogenic</td>
<td>rs137853057</td>
<td>Positively charged to polar uncharged</td>
</tr>
<tr>
<td>PARK2</td>
<td>c.719C&gt;G</td>
<td>(p.Thr240Arg)</td>
<td>Pathogenic</td>
<td>rs137853054</td>
<td>Polar uncharged to positively charged</td>
</tr>
<tr>
<td>PLA2G6</td>
<td>c.991G&gt;T</td>
<td>(p.Asp331Tyr)</td>
<td>Pathogenic</td>
<td>rs199935023</td>
<td>Negatively charged to aromatic</td>
</tr>
<tr>
<td>PLA2G6</td>
<td>c.1904G&gt;A</td>
<td>(p.Arg635Gln)</td>
<td>Pathogenic</td>
<td>rs387906863</td>
<td>Positively charged to polar uncharged</td>
</tr>
<tr>
<td>PLA2G6</td>
<td>c.2239C&gt;T</td>
<td>(p.Arg747Trp)</td>
<td>Pathogenic</td>
<td>rs121908687</td>
<td>Positively charged to aromatic</td>
</tr>
<tr>
<td>MAPT</td>
<td>c.1837_1839delAAT</td>
<td>(p.Asn613del)</td>
<td>Risk factor</td>
<td>rs199422218</td>
<td></td>
</tr>
<tr>
<td>SNCA</td>
<td>c.1861C&gt;T</td>
<td>(p.Arg621Cys)</td>
<td>Unknown significance</td>
<td>rs28937592</td>
<td></td>
</tr>
<tr>
<td>LRRK2</td>
<td>c.7224G&gt;A</td>
<td>(p.Met2408Ile)</td>
<td>Uncertain significance</td>
<td>rs60545352</td>
<td></td>
</tr>
<tr>
<td>LRRK2</td>
<td>c.7168G&gt;A</td>
<td>(p.val2390Met)</td>
<td>Uncertain significance</td>
<td>rs79546190</td>
<td></td>
</tr>
<tr>
<td>PARK7</td>
<td>c.192G&gt;C</td>
<td>(p.Glu64Asp)</td>
<td>Uncertain significance</td>
<td>rs74315353</td>
<td></td>
</tr>
</tbody>
</table>
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
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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5. REFERENCES

the causes and mechanisms of Parkinson's disease”,
Physiological Reviews, 91, October 2011, pp. 1161-1218.
[3]. Von Bohlen, H. O., Schober, A., Krieglstein, K., “Genes,
proteins, and neurotoxins involved in Parkinson's disease”,
Bethesda (MD): The Library; September 2013.
[5]. Leroy, E., Boyer, R., Auburger, G., Leube, B., Ulm, G.,
Mezey, E., Harta, G., Brownstein, M. J., Jonalalagada, S.,
Chernova, T., Dehejia, A., Lavedan, C., Gasser, T., Steinbach,
P. J., Wilkinson, K. D., Polymeropoulos, M. H. “The ubiquitin
pathway in Parkinson's disease”, Nature Publishing Group,
395, 6701, October 1998, pp. 451-452
[6]. Aharon-Peretz, J., Rosenbaum, H., Gershoni-Baruch, R.,
“Mutations in the glucocerebrosidase gene and Parkinson's
disease in Ashkenazi Jews”, New England Journal of
[7]. Abou-Sleiman, P. M., Muqit, M. M., Wood, N. W.,
“Expanding insights of mitochondrial dysfunction in
Parkinson's disease”, Nature Reviews Neuroscience, 7, 3,
[8]. Abou-Sleiman, P. M, Healy, D. G., Quinn, N., Lees, A. J.,
Wood, N. W., “The role of pathogenic DJ-1 mutations in
Parkinson’s disease,” Annals of Neurology, 54, 3, September
Stocco, F., Guedes, L., Fabrizio, E., Manfredi, M., Vanacore,
N., Goldwurm, S., Breedveld, G., Sampaio, C., Meco, G.,
Barbosa, E., Oostra, B. A., Bonifati, V., “A frequent LRRK2
gene mutation associated with autosomal dominant Parkinson's
[10]. Chu, C. T., “A pivotal role for PINK1 and autophagy in
mitochondrial quality control, implications for Parkinson
disease”, Human Molecular Genetics, 19, R1, April 2010, pp.
R28-R37.
normal function and role in neurodegenerative diseases”,
Current Topics in Developmental Biology, 60, May 2004, pp.
17-54.
[12]. Nuytemans, K., Theuns, J., Cruts, M., Van, Broeckhoven, C.,
“Genetic etiology of Parkinson disease associated with
mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2
gen:; a mutation update”, Human Mutation, 31, 7, July 2010,
pp.763-780.
[13]. Fachneris, M., Strain, K. J., Lesnick, T. G., de, Andrade, M.,
Bower, J. H., Ahlskog, J. E., Cunningham, J. M., Lincoln, S.,
Farrer, M. J., Rocca, W. A., Maraganore, D. M., “UCHL1 is
associated with Parkinson's disease: a case-unaffected sibling
and case-unrelated control study”, Neuroscience Letters, 381,
1-2., June 2005, pp. 131-134.