

*Full Length Research Paper*

# Parkinson's disease: A perilous magic of nature

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**Parkinson's disease, a neurodegenerative disorder, has prominent symptoms like tremor, rigidity, akinesia and bradykinesia. Cases of Parkinson's disease are reported to be more in old age, mostly above the age of 60 years. Loss of dopaminergic neurons of the substantia nigra causes lack of motor functions. The dopaminergic neurons synthesizing dopamine from L-tyrosine degenerate. Both genetic and environmental factors are supposed to cause and enhance the disease. A number of genes (PARK1, Parkin, UCHL1, LRRK2, DJ1, PINK1) linked to Parkinson's disease had been identified. The entire mechanism of the gene action has not yet been revealed. Symptoms of Parkinson's disease are reported to be reduced by treatment at early stages of the disease onset. Complete cure for Parkinson's disease has not yet been worked out. Genetically engineered stem cells that form dopaminergic neurons are supposed to be an effective treatment for Parkinson's disease.**

**Key words:** Dopamine, neurodegenerative, levadopa, dopaminergic pathway, substantia nigra.

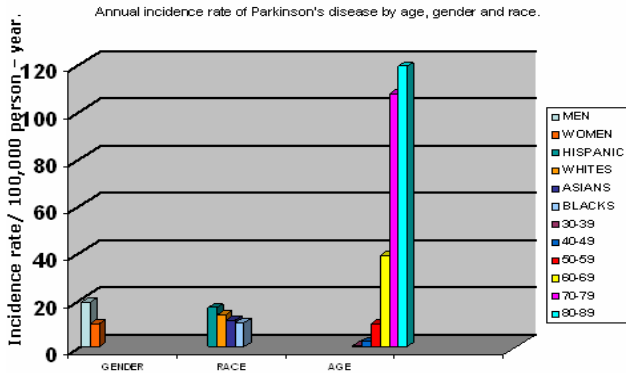
## INTRODUCTION

Parkinson's disease is the second most common progressive neurodegenerative disorder (after Alzheimer's) caused by loss of dopaminergic neurons mainly in the substantia nigra region of the brain (Monitjo, 2004). Parkinson's, Alzheimer's, Lou Gehrig's disease and other brain disorders are among those diseases which are ascribed to oxidative stress, ultimately the cell damage caused by more chemically reactive form of oxygen during the metabolism. But the precise connection between oxidation and neurodegenerative diseases has yet to be established. James Parkinson gave the first ever-clinical description of Parkinson's in the year 1817 in "An essay on the shaking palsy". Parkinson's is referred as an idiopathic disorder (i.e., the cause is unknown) but in some of the cases genetic factor may be involved in development of familial Parkinson's. Parkinson's not only affects the motor function of the body but also includes non-motor functions like cognitive disturbances, sleep and speech disturbances and other autonomic problems. Parkinson's can affect people of all age groups. It is more common in old age people. About 1 - 2% people above the age of 60 are affected by Parkinson's and its prevalence increases 4 - 5 % by the age of 85 (Burn, 2000).

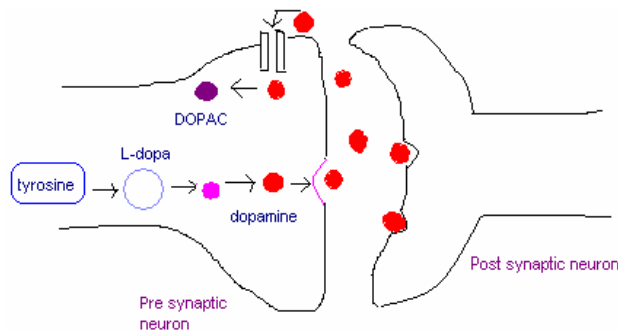
According to the study conducted by Kaiser Permanente Medical Care Program of Northern California, the incidence rate of Parkinson's disease was found to be 13.4 per 100,000 (Van Den Eeden et al., 2003). The data provided by this study suggested the incidence of Parkinson's by race/ethnicity, age and gender (Van Den Eeden et al., 2003). It was observed that the cases of Parkinson's are less in Asian population as compared to the Whites. Higher numbers of cases are reported in men. The incidence rate of Parkinson's was highest among Hispanics, followed by non-Hispanics, Whites, Asians and Blacks.

The Figure 1 depicts the comparative status of Parkinson's among different populations (Van Den Eeden et al., 2003). The most prominent and distinguishing symptom of Parkinson's is tremor, a slow rhythmic oscillation (5 - 8 Hz) of opposing muscles of the body at rest and abolished by movement. Tremor may start from hand and fingers but later on most of the body parts including lips, tongue, neck, chin and legs may be involved. Other symptoms of Parkinson's are rigidity and akinesia; both develop to hamper the movement of the body. Rigidity causes stiffness of muscles and akinesia leads to loss of movement. Thus, when the patient is about to move he experiences absence of movement. Another important and striking characteristic of Parkinson's is disturbed motor functions known as bradykinesia or slowness of movement. It includes irregular blinking of eyes, soft speech (hypophonia), drooling,

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**Figure 1.** Comparative status of Parkinson's among different populations



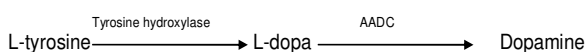
**Figure 2.** Formation and transmission of neurotransmitter dopamine.

slow swallowing, and slow thinking (bradyphrenia). 20 - 40% of Parkinson's patients suffer from depression (Lieberman, 2006). With progress of the disease, the patient is unable to move or walk without support.

## DISEASE PROGRESSION AND BIOCHEMICAL PATHWAY

Loss of dopaminergic neurons in the basal ganglia region of the brain causes Parkinson's. In order to understand the disease properly, let us first analyze the normal functioning of dopamine in the brain. Dopamine acts as a neurotransmitter in the substantia nigra (a part of basal ganglia) region of brain and plays an important role in controlling voluntary movements. Basal ganglia lead the signals from cortex to thalamus, which influences motor control center in the brain (Côté and Crutcher, 1991).

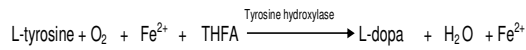
Dopaminergic neurons form dopamine from L-tyrosine. L-tyrosine is converted to L-dopa, which in turn forms dopamine by the action of the enzyme tyrosine hydroxylase and amino acid decarboxylase (AADC) respectively.



Steps involved in conversion;

### Step 1

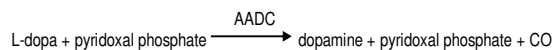
L-tyrosine to L-dopa



This reaction requires the presence of tetrahydrofolic acid (THFA), oxygen and ferrous ions.

### Step 2

L-dopa to dopamine



On stimulation, the synaptical vesicles (in the pre-synaptic neuron) release dopamine into the synaptic cleft. This released dopamine binds to the dopamine receptors present on the post-synaptic neurons. The remaining dopamine is transported back to the pre-synaptic neuron by transporters in the membrane or converted into DOPAC by the enzyme monoamine oxidase type B (MOA- B) (Vermeulen, 1994). Figure 2 shows the entire process.

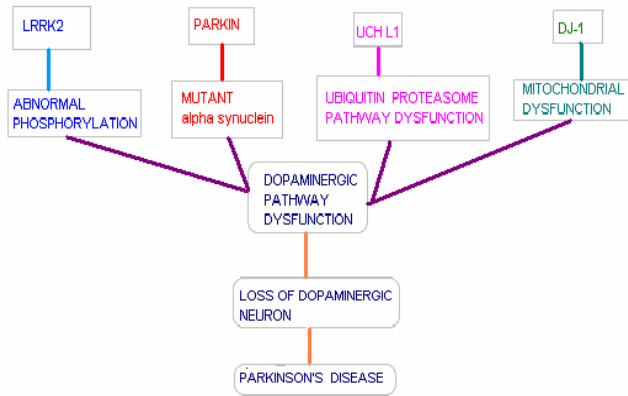
## Dopamine receptors

Based on the physiological and biochemical responses dopamine receptors are classified into D1 and D2 receptor subfamilies.

D1 receptor subfamily includes D1 and D5 receptor subtypes. The distribution of D1 receptors corresponds to the projection region of dopaminergic neurons (in striatum, nucleus accumbens, caudate nucleus, putamen, cardiovascular system and olfactory tubercles) (Strange, 2000). D2 receptor subfamily includes D2, D3 and D4 receptor subtypes. Post-synaptic D2 receptors are present in dopaminergic projection areas such as the striatum, limbic areas (nucleus accumbens, olfactory tubercles), hypothalamus and pituitary. Pre-synaptic D2 receptors are located in substantia nigra pars compacta, ventral tegmental area and striatum where they function to inhibit the release of dopamine (Crocker, 1994).

## Functioning of receptors

D1 type receptors cause activation of adenylylase, c-AMP dependent protein kinase and inhibition of protein phosphatase-1 by DARPP-32 (dopamine and c-AMP regulated phosphoprotein, 32 kDa) when it is phosphorylated by Protein kinase A (PKA) on Thr 34 (Neve et al., 2004). D2 type receptors inhibit c-AMP accumulation by inhibition of adenylylase and decreases phosphorylation of PKA substrate. The opposing effect of D1 and D2



**Figure 3.** Pathway representing role of different genes in Parkinson's disease

type receptors on DARPP-32 causes inhibition of  $\text{Na}^+\text{-K}^+$  ATPase in neostriatal neurons.

### Dopaminergic neuron degeneration

In Parkinson's, the dopaminergic pathway between the striatum and substantia nigra are degenerated causing depletion of dopamine. This results in over stimulation of the thalamus. Wide ranges of environmental and genetic factors cause Parkinson's.

### ENVIRONMENTAL FACTORS INVOLVED IN PARKINSON'S DISEASE

Environmental factors like herbicides, pesticides, exposure to chemicals and heavy metals, drugs are linked to Parkinson's. Majority of cases are related to environmental factors rather than genetic (Brown et al., 2005). Some chemical drugs are structurally similar to MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydro-pyridine) or form MPP<sup>+</sup> like compounds in their catabolism. These chemical compounds are believed to inhibit or alter dopamine metabolism and are supposed to cause damage to the mitochondrial respiratory chain (Burkhardt et al., 1993). MPP<sup>+</sup> is a potential inhibitor of Complex I (NADH Co Q1 reductase) (Nicklas et al., 1985; Schapira et al., 1989).

Calcium antagonists have a competitive action of blocking D2 receptors in the striatum, causing parkinsonian symptoms (Werneck et al., 1999). Occupational exposure to metals for a very long period increases the risk of Parkinson's (Gorell et al., 1997). Metal combinations like steel/copper, steel/iron and copper/iron have positive effect on Parkinson's. All these metals are supposed to favor the formation of free radicals in substantia nigra region of the brain. Increase in concentration of iron causes increase in concentration of ferritin, an iron storage protein in brain, which may increase the risk of free radical induced damage (Griffiths et al., 1999). Frequent exposure to pesticides especially by people working in farm enhances the

risk of Parkinson's. 40% increase in mortality from Parkinson's has been observed in Californian countries using restricted agricultural pesticides since early 1970's (Ritz and Yu, 2000). Paraquat, a quaternary ammonium herbicide structurally resembles MPTP and its metabolite MPP<sup>+</sup>, that are known to induce Parkinson's disease (Endo et al., 1988). Carbamate fungicides supposedly enhance the neurotoxicity of MPTP and methamphetamine (Bocchetta and Corsini, 1986; Irwin et al., 1996).

### GENETIC MUTATIONS INVOLVED IN PARKINSON'S (Figure 3)

**Park1:** Three missense mutations (A53T, A30P, E46K) in alpha synuclein coding gene (SNCA) causes autosomal dominant inherited Parkinson's disease (Kruger et al., 1998; Polymeropoulos et al., 1997). Alpha synuclein is a major component of lewy bodies that are abnormally expressed aggregates of cytoskeletal neurofilaments in the soma. Accumulations of these neurofilaments are toxic to the neurons (Forloni et al., 2000).

**Parkin:** Mutation in gene coding for parkin causes autosomal recessive Parkinson's disease. Lewy body formation is not seen in case of mutation in parkin gene. 465 amino acid parkin protein has ubiquitin protein ligase activity and is supposed to be involved in ubiquitination and protein processing (Shimura et al., 2000).

**UCHL1 gene:** Ubiquitin carboxyl terminal esterase L1 (ubiquitin thiol esterase). Cytogenic location 4p14, Molecular location on chromosome 4: base pairs 41,099,856 - 41,111,373 (<http://ghr.nlm.nih.gov/chromosome=4>). UCHL1 protein is believed to be involved in degradation of misfolded or unwanted protein via UPP (ubiquitin proteasome pathway). The exact function of this gene is yet to be discovered. However, it appears to have two enzyme activities, the 'hydrolase' activity that removes the bound ubiquitin molecules from degraded protein and the 'ligase' activity that is required to tag the protein to be degraded by ubiquitin.

Polymorphism (S18Y) of UCHL1 (Vila and Przedborski, 2004) reduces the risk of Parkinson's especially in Asian population (Vila and Przedborski, 2004; Maraganore et al., 1999). Single dominant mutation at position 93 (I93M) increases the risk of Parkinson's by reducing the hydrolase activity of the enzyme causing accumulation of unwanted protein resulting in neuronal death.

**LRRK2:** (Leucine rich repeat kinase 2) Cytogenic location 12q12, molecular location on chromosome 12: base pairs 38,905,079-39,049,353 <http://ghr.nlm.nih.gov/gene=lrrk2>). LRRK2 has a large N-terminus ending with leucine rich repeat and there is a WD40 repeat domain at the carboxylous domain (Ross and Farrer, 2005). LRRK2 gene is supposed to code for protein rich in amino acid leucine and appears to play a major role in protein-protein interactions

like signal transduction and in assembly of cytoskeleton (Mata et al., 2006). The kinase domain belongs to the MAPKKK (mitogen activated protein kinase) sub-family of kinases (Ross and Farrer, 2005). The mutation G2019S results in gain of function causing increased kinase activity of LRRK2 leading to autosomal dominant Parkinson's disease. Other mutations in LRRK2 protein are I1122V, I2020T, R1441C and Y1699C. Mutations in LRRK2 gene are most common cause of genetic, familial idiopathic and late onset Parkinson's disease to date (Ross and Farrer, 2005). G2019S mutation is most common and is found in 1-6% of U.S. and European patients, especially in Ashkenazi Jewish patients.

**DJ-1:** Mutations (E64D) in DJ-1 are associated with autosomal recessive early onset of Parkinson's (PARK 7) (Hering et al., 2004; Patrick et al., 2006). Cytogenetic location: 1p36.33-p36.12, Molecular Location on chromosome 1: base pairs 7,956,058 to 7,979,604 (<http://ghr.nlm.nih.gov/gene=park7>). The functional aspect of the gene is yet to be elucidated. It appears to be involved in cellular response against oxidative stress (Burn, 2000).

**Pink1:** Pink1 (PTEN-induced putative kinase1). Cytogenetic location: 1p36, Molecular Location on chromosome 1: base pairs 20,705,253 to 20,723,309 (<http://ghr.nlm.nih.gov/gene=pink1>). Pink1 protein is located in mitochondria. Its function is still not clear but it appears to protect mitochondria during cellular stress. Pink 1 protein has two regions, one that transports Pink 1 to mitochondria and kinase domain that carry out protective function. Mutation in Pink1 causes early onset of Parkinson's disease.

## TREATMENT

Parkinson's disease leads to the loss of dopaminergic neurons and thus dopamine. If the level of dopamine were restored to normal levels, it would possibly help the patients. Dopamine cannot be administered as a drug for the treatment because it cannot pass the blood brain barrier between the blood vessels and neurons. As L-dopa (precursor of dopamine) can cross this barrier it is widely used for the treatment, but it shows side effects like nausea, vomiting, blood pressure changes and dizziness. The side effects are because of the presence of the enzyme AADC in liver, kidney and many other body parts besides brain where the production of dopamine disturbs the chemical balance of the body (Côté and Crutcher, 1991; Vermeulen, 1994). Besides this, the exogenous uptake of dopamine via drug reduces the ability of the dopaminergic neurons to store dopamine (Conley, 1999). In order to reduce the effect of AADC except in CNS, AADC inhibitor was given along with L-dopa called carbidopa. Carbidopa decreases levodopa's peripheral conversion to dopamine and increases the amount of dopamine

entering the CNS (Conley, 1999).

Dopamine receptor agonists are chemically synthesized compounds that directly bind to the dopamine receptor thus decreasing the use of L-dopa as a drug (which in long run may aggravate the disease and result in formation of free radicals). Although agonists are less effective and have side effects like hallucinations and insomnia, yet better effects result from a combination of low doses of dopa with an agonist (Olanow and Koller, 1998).

In future, genetically engineered stem cells that transform into dopamine producing cells may become the most prominent cure for Parkinson's. The most exhaustive research is required in the field of transgenics.

## CONCLUSION

The insufficient scientific knowledge on genetic aspect of Parkinson disease has wedged the attention of neuroscientist and made it very important research topic for target specific drug designing in future. Though, many genes which are linked with Parkinson's disease have been revealed but the entire role of these genes is still not clear. In the same connection the mechanism of the dopaminergic neurons control and motor activity of the body has to be worked out. Even now the structures of many genes are not deciphered till date, so the interaction among various genes and their involvement is in the dubious state. Despite the availability of the various medical therapies, the complete cure for the disease is still not feasible and the drugs which are being used like levodopa have many side effects. Therefore, a lot of research is required to be done for understanding the gene-gene interaction, mechanism and their relationship with environment etc. In this arena the knowledge of advance biotechnology to the bioinformatics might be playing the futuristic role to uncover the hidden facts which will be helpful to view the better insight, hence better therapy.

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