



GENETICS OF PARKINSON'S DISEASE : HOW CLOSE AND HOW FAR WE ARE? Rajan Kumar¹, Rakesh Kumar¹, Neha Sharma^{1,*}, Manish Vyas¹, Sanchit Mahajan², Saurabh Satija¹, Sachin Kumar Singh¹, Meenu Mehta¹ and Navneet Khurana¹

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Abstract

Parkinson's disease (PD) is one of the neuronal disorder in which there is continuous degeneration of the neurons occur. It is an age related disorder, so the most effected peoples are those who are 60 or above 60years of age. The main neurons involved in PD are the dopaminergic neurons, specifically present in the substantia nigra pars compacta. It is known that, at the time of diagnosis of PD or appearance of its symptoms, 80% of the dopaminergic neurons got deteriorated. The major symptoms of PD are tremors, rigidity, akinesia and postural instability. There are various etiological factors which are responsible for the development of the PD and among them, genetic factor considered to be one of main factor involved in this condition. The major genes which are involved in PD are SNCA, PARK1, PARK 2 and DJ-1. Whenever, any mutation occurs in these genes, it alters the protein expression which ultimately leads to the dysfunction of the neuronal cell organelles. There is aggregation of the α -synuclein protein occurs due to the mutation of these genes. In the present review, we reviewed the available information regarding the genetic of the PD and try to conclude about its present status.

Keywords: Parkinson's disease, Genetics, Dopamine, Neurodegeneration, α - synuclein, Substantia nigra.

Introduction

Parkinson's disease (PD) was founded by James Parkinson (Jefferson, 1973). PD is a neurological disorder acknowledged by ameliorative loss of neuron in temporal lobe region of brain. Symptoms are more common and predominant such as slowness in locomotion, rigidity, shaking, bradykinesia, motor neuron dysfunction, gait disturbance and rest tremor (Batla *et al.*, 2016; De Medeiros *et al.*, 2011). Lewy bodies in substantia nigra were first described by Frederick Lewy in 1912 (Gomperts, 2016). Decrease of dopaminergic neuronal cells occurred in nigrostriatal system. It is characterized by α -synuclein protein deposition in cortical Lewy bodies and Lewy neuritis in the brain. Dementia Lewy Bodies and Parkinson's disease dementia are basic and important dementia syndromes (Gomperts, 2016; Weil *et al.*, 2017).

As per the clinical symptoms of PD which is described as motor and non motor progression disease. Probably the etiology of PD is multifactorial. There is no treatment available except the symptomatic treatment by using the dopaminergic drugs such as Levodopa a prodrug to dopamine is offer the most effective therapy correcting the motor disturbances (Capriotti and Terzakis, 2016; Court *et al.*, 1971; Sveinbjornsdottir, 2016). White matter disease, cognition and modifiable vascular risk are the factor in initial level of PD. Greater temporal white matter hyperintensity burden was related with over time in verbal memory. In PD, White matter hyperintensities can act as a surrogate marker for the effect of vascular risk factors on cognitive capabilities (Chahine *et al.*, 2018).

Viral vector i.e. adeno-associated virus is a non infectious virus gene therapy to shuttle genetic substances into a region of the brain. The formation of enzyme is occurred by use of the gene which aid to manage PD and serve of brain from further damage (Feng and Maguire-Zeiss, 2010; Obeso *et al.*, 2010).

The Genetic factors are also involved in the progression of the PD. Mutations in certain gene are responsible for

development of PD. Till now 18 genes are mapped which are shown in table 1. But, major identified genes such as α -synuclein (PARK1), PARKIN (PARK2), LRRK2 (PARK8), PINK 1(PARK6), ATP13A2 (PARK9) and DJ-1 (PARK7) gene as shown in figure 1. Identification of the protein generated during the mutation of these gene help in the understanding the mechanism that may be responsible for PD and other NDDs. A point mutation and duplication, triplication of the SNCA gene leads to the onset of PD and development of the symptoms in the later age respectively (Cookson *et al.*, 2005; Reeve *et al.*, 2014). Common cause of the familial or sporadic PD is the mutations in the LRRK 2 gene (Gilks *et al.*, 2005).

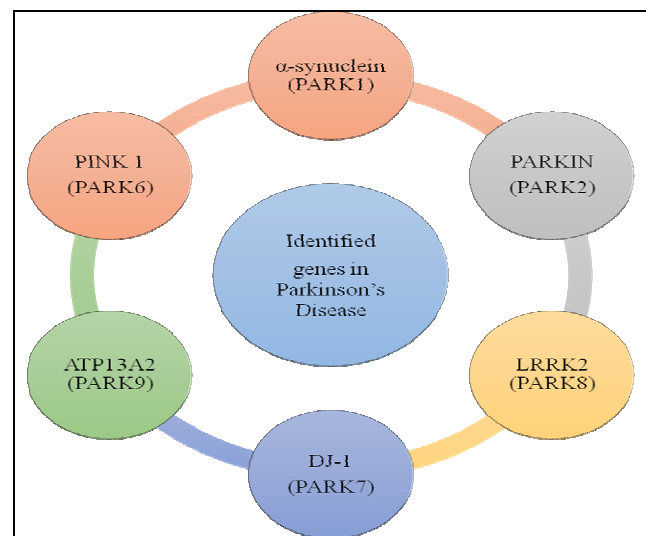


Fig. 1: Genes identified in Parkinson's disease

Method

The literature research of articles was carried out in PubMed and Google Scholar by using terms: "Parkinson's disease", "Genetics", "Symptoms", "Lewy Bodies", "Levodopa", "Parkinson's disease etiology", "Parkinson's disease therapy", "Neurodegeneration", " α -synuclein" and "Substantia nigra". We focused particularly on the studies

that considered the genetics of the PD. Through many research articles, gene and gene mutation based studies closeness to PD and gap of genetics in PD was extracted to clarify the closeness and farness of genetics in PD.

α -synuclein(PARK1)

α -synuclein is small protein mostly expressed in temporal lobe of the brain at presynaptic nerve terminals. α -synuclein is also a non-amyloid component of the plaques. Pathologically, mutation in gene for α -synuclein developed PD and nigral degeneration with Lewy bodies inherited α -synuclein protein gene (PARKIN1) (Gasser, 2005; Klein and Westenberger, 2012). Mutation in gene (PARKIN1) transparently appears to be very rare etiology of the disorder. α -synuclein changes the vesicle binding properties of the protein. Chromosome 4 linked PD is PARKIN1 with dominant inherited PD linked with the polymorphic DNA markers on chromosome 4q21 (Klein and Westenberger, 2012).

PARKIN (PARK2)

In PD, Parkin is observed as the second largest gene codes for 465 amino acid protein. In onset in childhood and homozygous mutation in PARK2 is responsible for juvenile (Klein and Westenberger, 2012). In presence of ubiquitination, ubiquitin ligase develops of posttranslational modification that conjugate ubiquitin to lysine residues of target protein as function of the Parkin. The Parkin amino terminal ubiquitin like domain play a beneficial role in stabilizing the structure and control the expression levels of PARK2 (Klein and Westenberger, 2012).

PINK 1(PARK6)

PINK1 is identified as the sixth gene in PD. Average onset age of the PARKIN1 is 41 years. In some studies, it has been reported that PARK6 don't have a typical autosomal recessive juvenile Parkinson phenotype. Dyspnea at onset could be a marker for Parkin as compare to PINK1 disorders and sleep benefits were found as lacking features. As per etiology of PD, it will be an important gene than DJ-1 (Morris, 2005).

Two Italian families were considered as mutation in PINK1. PINK1 mutation was reported either missense or nonsense mutation. It has been reported that only three families with whole exon deletions and one heterozygous all gene deletion. 581 amino acid ubiquitiously expressed protein kinase occurred in PINK1. It is consisting N-terminal 34 amino acid mitochondrial targeting motif. It conserved serine threonine kinase domain with 156-509 amino acids and C-terminal autoregulatory domain. Kinase domain is mostly affected by the PINK1 mutation (Kumar, 2011).

DJ-1 (PARK7)

DJ-1 (PARK7) is seventh gene in PD, multirole protein that protect of cells from oxidative stress. DJ-1 declined the locomotor activity in null mice, decrease in release of dopamine in striatum without loss of dopaminergic neuron (Goldberg *et al.*, 2005; Yokota *et al.*, 2003). PARK7 and mitochondrial function were kept in doubt for long time, but PARK7 null mice showed no apparent mitochondrial defects (Goldberg *et al.*, 2005). In PARK7 null cultured dopaminergic neurons were reported higher of ROS production, mitochondrial damage and complex-I deficit.

PARK7 mutation in PD patients have higher echogenicity rather than in healthy control. Enhanced iron contents cause hyperechogenicity that was observed PARK7 mutation can cause iron aggregation (Kurosawa *et al.*, 1990; Schweitzer, 2007).

LRRK2 (PARK8)

LRRK2 is PARK8 gene in PD that is a cytosolic serine threonine protein kinase. It is associated with the outer mitochondrial membrane. PARK8 animal model display no functional disruption of dopaminergic neurons in substantia nigra (IN Rudenko and MR Cookson, 2014). PARK8 consists 51 exons considered as large gene encodes 2527 amino acid cytoplasmic protein Leucine rich repeat kinase 2 (LRRK2) which is a terminus of the protein a kinase domain toward carboxyl terminus. More than 50 various missense and nonsense mutations were reported in PARK8. As per the pathological alteration were accumulated in 10 exons encoding carboxyl terminal region of the protein. These all proofs support the notion in which PD consequence from differentiation in enhanced oxidative damage to evaluate this speculation for further analysis (Nuytemans *et al.*, 2010).

ATP13A2 (PARK9)

ATP13A2 is PARK9 gene in PD that is homozygous and heterozygous mutations in ATP13A2. PARK9 has been found to have an autosomal recessive form of PD called as Kufor Rakeb syndrome. Kufor Rakeb syndrome has juvenile onset with fast disorder progression that is accompanied by dementia, supranuclear gaze palsy and pyramidal (Ramirez *et al.*, 2006). PARK9 is considered as 29 exons encoding for 118 amino acid protein. ATP13A2 protein is located in lysosomal membrane which has 10 transmembrane domains and an ATPase domain. As per 10 various the pathogenic mutations, it has been reported that homozygous or heterozygous state directly or indirectly affecting transmembrane domains. Truncated proteins are unstable and produced by the most of the mutations that are retained in endoplasmic reticulum and degraded by proteasome. Till date, there is no exonic deletion of entire gene occur. The most of single heterozygous missense mutations are well known. However, its role in pathogenicity of PD is unclear (Ramirez *et al.*, 2006).

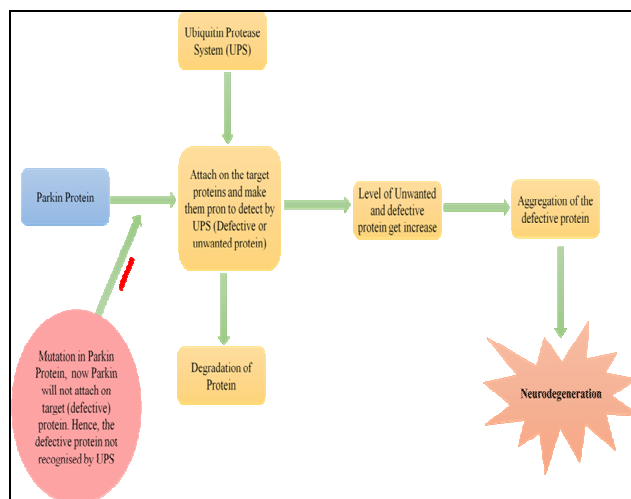


Fig. 2: Role of genes in Parkinson's disease

Table 1: Mapped genes of Parkinson's disease

Locus	Inheritance	Chromosome position	Gene	Phenotype	References
PARK1	AD	4q21	SNCA	EOPD	(Kumar, 2011; Polymeropoulos <i>et al.</i> , 1997).
PARK2	AR	6q25.2	PARKIN	EOPD & Juvenile	(Klein and Westenberger, 2012; Kitada, <i>et al.</i> , 1998)
PARK3	AD	2p13	Unknown	LOPD	(Gasser <i>et al.</i> , 1998)
PARK4	AD	4q21	SNCA	EOPD	(Singleton <i>et al.</i> , 2003)
PARK5	AD	4p14	UCH-L1	LOPD	(Leroy <i>et al.</i> , 1998)
PARK6	AR	1p35	PINK1	EOPD	(Valente <i>et al.</i> , 2002)
PARK7	AR	1p36	DJ-1	EOPD	(Bonifati <i>et al.</i> , 2003)
PARK8	AD	12q12	LRRK2	LOPD	(Funayama <i>et al.</i> , 2002)
PARK9	AR	1q32	ATP13A2	KRS	(Ramirez <i>et al.</i> , 2006).
PARK10	Unknown	1p32	Unknown	Unclear	(Hicks <i>et al.</i> , 2002)
PARK11	AD	2q36	GIGYF2	LOPD	(Pankratz <i>et al.</i> , 2003)
PARK12	X-Linked	Xq	Unknown	Unclear	(Klein and Westenberger, 2012)
PARK13	AD	2p13	HTRA2	Unclear	(Kumar, 2011).
PARK14	AR	22q13.1	PLA2G6	PWAF	(Klein and Westenberger, 2012)
PARK15	AR	22q12	FBXO7	EOPD	(Kumar, 2011).
PARK16	SL	1q32	Unknown	LOPD	(Klein and Westenberger, 2012)
PARK17	SL	4p16	GAK	LOPD	(Kumar, 2011).
PARK18	SL	6p21.3	HLA-DRA	LOPD	(Klein and Westenberger, 2012)

Note: AD: Autosomal dominant, AR: Autosomal recessive, EOPD: Early-onset Parkinson's disease, LOPD: Late-onset Parkinson's disease, KRS: Kufor Rakeb syndrome, PWAF: Parkinsonism with additional features

Conclusion

We know that 18 genes are mapped till dates in PD among these genes some have indentified genes in PD. Medicine given in PD provide only symptomatic relief but not etiopathologic relief. That is why, identified genes play major role in PD and these genes are close to PD. It can be treated by using suitable medicine. Any mutation occurs in these genes that change the protein expression which ultimately lead to the dysfunction of the neuronal cell organelles. Mutation of genes is responsible for aggregation of the α -synuclein protein in substantia nigra region of the brain. In the present review, we reviewed the available information regarding the genetic of the PD and try to conclude about its present status of further going research on identification of the genes other than identified genes responsible for PD.

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