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UNDERSTANDING GENETIC BASIS OF PARKINSON'S DISEASE AND ITS PREVALENCE

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Abstract

Parkinson's disease (PD) is complex disease characterized by the neurodegeneration in mid brain and loss of activity of dopaminergic neurons. There are several factors responsible for the development of PD. Both the extrinsic and intrinsic factors potentiate disease progression and neuronal deterioration. Genetic predispositions along with the environmental cues can exacerbate PD in old age patients. There are number of genes such as the alpha synuclein (SNCA), leucine-rich repeat kinase 2 gene (LRRK2), PARK2 and DJ-1. Here we aim to describe the risks, prevalence and genetic factors responsible for PD and also shed light on their role in disease progression.

Key words: Parkinson Disease, therapeutics, genetic viability, prevalence

Introduction

Parkinson's disease (PD) is the most common neurodegenerative disease which is defined by the presence of Lewy bodies in the midbrain and there is loss of activity of dopaminergic neurons, mainly in the substantianigra. The first clinical description of PD was given by James Parkinson in 1817,He was a doctor in London who observed the symptoms of Parkinson's disease in his three patients that are common in patients now a days. The symptoms of PD can be muscle tremors and rigidity, bradykinesia and loss of balance is observed in some patients(Poewe et al., 2017).The most common feature of PD is the presence of intraneuronal protein inclusions that are called Lewy bodies or Lewy neurites. It is the most common disorder that has age dependent prevalence. It is considered as the second most prevalent disorder that is growing worldwide (E. R. Dorsey et al., 2018). Recent research indicates that 1% of the population is affected at the age of 65 that is increasing to 4-5% in 85 year old population(De Lau & Breteler, 2006). Although, the age of onset of disease is 70 years but some patients develop early-onset disease before the age of 50(Schrag & Schott, 2006).

As the cases of PD are increasing day by day globally, there are chances that it would get worse in future as it was seen in 2016, the calculated patients were greater than 6 million(Beghi et al., 2019).Recent studies predicted that in 2040 the expected cases will increase by 12 million (Dorsey, Sherer, Okun, & Bloem, 2018). Although age is the biggest risk factor but sex is also considered as the causative factor of PD(Willis, Evanoff, Lian, Criswell, & Racette, 2010).Vast number of studies have shown that some environmental factors can also cause PD. Environmental factors can be any kind of injury on head, depression, alcohol consumption, exposure to some chemicals and toxins can lead to PD(Noyce et al., 2012)(Li, Li, Liu, Shen, & Tang, 2015).

Scientific knowledge of PD has been increased in recent years. Although the genetic factors have been discovered but they describe only a small percentage of PD, as 90% cases of PD are sporadic. Current studies indicate that the major signs of PD are because of alpha-synuclein oligomers or fibrils that are spreading pathology in PD. When a person is diagnosed with PD the extensive proportion of nigrostriatal neurons have been lost at that time(Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004).So there is need of rapid treatments that can avert or stop the development of disease. There is a need that the patients who are at risk of PD should be diagnosed at early

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stages. Major outbreaks has been made by getting the knowledge of genetic factors that are responsible for causing PD. So, the continuous analysis of these genetic factors exposed the pathogenic activity of SNCA, PARK2 and PINK1 (Reed, Bandrés-Ciga, Blauwendraat, & Cookson, 2019).

Prevalence of Parkinson's disease

In major industrialized countries the estimated percentage of PD is 0.3% and this percentage is increasing day by day(Nussbaum & Ellis, 2003). Prevalence of PD which is considered as the most common neurodegenerative disorder increases with age. PD can cause severe motor and non-motor symptoms like severe morbidity, shocks, sensory symptoms, sleep-disturbances and weakness(Weikang, Jie, Likang, Weiwen, & Liping, 2016).Some studies have shown the cross-cultural variations in the prevalence of PD, these variations can be the result of differences in environmental or genetic factors(Van Den Eeden et al., 2003). There are only few methodological studies that describe the prevalence of PD related to ethnicity. Some studies suggest that PD has been observed less in black and Asian people. PD seems to be common in white people, however these observations are changing and different results are reported in terms of prevalence of PD across different ethnic groups(Mayeux et al., 1995).

Some studies suggest that PD is prevalent in men than in women(Benito-León et al., 2003). So the studies suggest that men are at greater risk of PD than women, these differences are because of neuroprotective effects of oestrogens in men. Some researchers confirmed the higher risk of PD in men than in women, the disease mostly start at the age of 50. These observations can be better explained with the help of environmental risk factors. The exposure to these risk factors is different in men than in women, for example the patterns of consumption of alcohol or smoking or any kind of head injury are different in both genders. The study of their prevalence is still under controversy(Savica, Grossardt, Bower, Ahlskog, & Rocca, 2013). Parkinson's disease is increasing at higher rate. The massive number of cases reported between 1990 and 2016. Some researchers predict that if the cases keep on increasing with this speed the result would me more than 20 million patients by the end of 2050 (Collaborators, 2018). Figure shows the global prevalence of PD by age and sex(Collaborators, 2018).

1.1. Presenting Features

The common signs and symptoms of Parkinson's disease include:

- **Motor symptoms** can be initiated when the brain is not able to maintain the dopamine production(Guest, 2016). The motor symptoms that are resulted because of these dopaminergic neurons can be:
  1. Bradykinesia
  2. Shocks
  3. Stiffness
  4. Postural instability
  5. Difficulty in walking
- The **non-motor symptoms** that are important in causing serious problems in patients with PD. Some recent studies suggest that non-motor symptoms can be:(Barrett, Blair, Sperling, Smolkin, & Druzgal, 2018; Hely, Reid, Adena, Halliday, & Morris, 2008)
  1. Decline in understanding
  2. Dementia
  3. Depression
  4. Psychosis
  5. Sleeplessness

1.2. Pathophysiology of Parkinson's Disease

The pathophysiological study of PD indicates that there is loss of dopaminergic neurons as well as depigmentation of substantianigra pars compacta(SNpc). When this loss in dopaminergic neurons takes place, the presence of LBs is also observed. LBs can be defined as circular, eosinophilic inclusions that consist of greater than 90 proteins(Wakabayashi et al., 2013). The main components that are responsible for causing PD are alpha-synuclein and ubiquitin(Spillantini et al., 1997). Several functions are performed by alpha-synuclein, it has ability to misfold. After misfolding itself it becomes insolouble and form b-sheet-rich amyloid aggregations. After aggregation it accumulates and form these inclusions. The intermediates that are responsible for causing aggregation are toxic oligomeric and proto-fibrill forms and cause neuronal degerenation. These forms also impair mitochondrial, lysosomal and proteasomal functions(Hsu et al., 2000)(Snyder et al., 2003). Studies suggest that when a person is diagnosed with PD 60% of dopaminergic neurons are lost. At that time alpha-synuclein continuously performs its functions by spreading itself in the neurons in prion like patterns(Brundin, Ma, & Kordower, 2016). Some researchers indicate that the aggregation takes place in plexi of gut (Klingelhoefer & Reichmann, 2015). This aggregation is influenced by the gut microbiome(Sampson et al., 2016).

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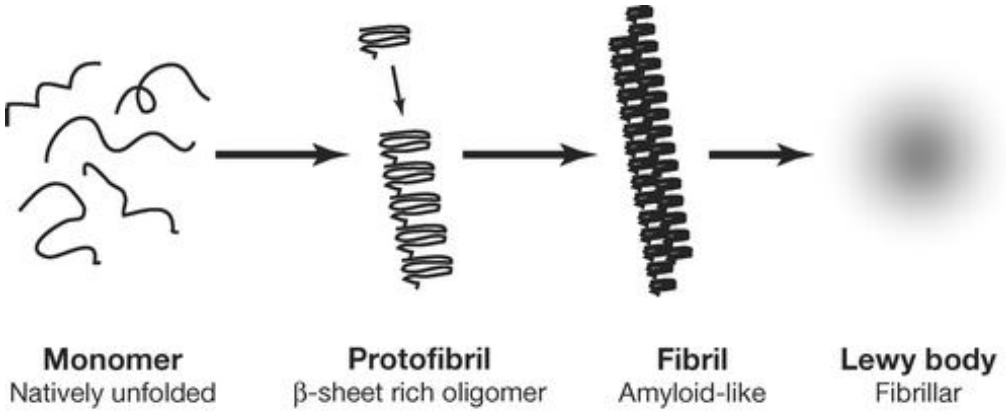

(Masliah et al., 2000; Moore, West, Dawson, & Dawson, 2005)

1.3. Genetic Factors in Parkinson's Disease

During the study of any disease, it is important to study the genes responsible for causing that disease. Although most of PD cases are sporadic but 10% of the patients report a family history. The genes responsible for causing PD are SNCA, LRRK2 (PARK8), Parkin (PARK2), PINK1 (PARK6), and DJ-1 which is also called PARK7. These genes show autosomal recessive mode of inheritance. In order to study the inheritance of any disorder it is important to study the family history i.e. how the disease is transmitted and from which person that disease is transmitted. This type of analysis require careful assembly of data among several generations. This also involves the collection of data from affected and unaffected individuals in order to study the individuals at risk of PD.

1.3.1. Role of SNCA in Parkinson's disease

The first gene that was considered responsible for causing PD was the gene encoding for alpha-synuclein named as SNCA and the first infectious SNCA mutation was caused by A53T(Polymeropoulos et al., 1997). These mutations provides the capability to alpha-synuclein to misfold and a result of this misfolding alpha-synuclein accumulates. Some other types of mutations in SNCA influence the amount of alpha-synuclein, this decrease or increase in the amount of alpha-synuclein occurs through duplications, changing its expressions or its removal. These mutations change the post-transcriptional modification and also change their collaboration with other organelles. Some recent studied emphasizes the role of alpha synuclein in immunological responses stimulation, they show that in order to clear alpha-synuclein the activated microglial cells consumes alpha-synuclein cells(Rocha, De Miranda, & Sanders, 2018). These changes in alpha-synuclein are also identified in pateints with idiopathic PD (Rocha et al., 2018) .

In humans, the study of their genome indicates that SNCA gene is present on 4^{th} chromosome. The patients with these mutations have early onset of the disease and at initial stages they show positive response to levodopa treatment. The mutations in SNCA gene are mainly associated with the pathways in PD. Studied identified that there is important association between SNCA levels and the chances of Parkinson's disease development, these SNCA levels are important in identification of Parkinson's disease. Studies in regards to study the association between SNCA gene and chances of Parkinson's disease development have been directed(Rahimi et al., 2017).Yet, PD has a hastydevelopment and frequently starts with cognitive decline and dementia, it also show the symptoms like myoclonus and hypoventilation. As the most common feature or PD is presence of lewy bodies, these lewy bodies spreads through cerebral cortex, hypothalamus and substantia (Polymeropoulos et al., 1996). Alterations in SNCA gene mainly occurs through duplications, triplications of the whole gene and different missense mutations, although many rare mutations have been reported(Klein & Schlossmacher, 2006). Among the three missense mutations the first and most common mutation identified was mutation in A53T, it was identified in 8 Greeks, 1 Italian, 2 Koreans and 1 Swedish family(Puschmann et al., 2009).

As it was mentioned earlier that SNCA gene has been related with the pathways of causing PD, simultaneously it encodes the presynaptic protein product. During the study of the causative agents of Parkinson's disease SNCA gene is the most widely studied gene (Bekris, Mata, & Zabetian, 2010). In familial PD it is considered as the first causative gene, as it encodes SNCA with main element of Lewy bodies. In familial PD, just after this encoding the Lewy bodies' aggregates in neural cells. This aggregation results due to excessive production of SNCA. Sporadic PD also occurs due to excessive production of (Lesage & Brice, 2009).

ISSN- 2394-5125 VOL 8, ISSUE 02, 2021

1.4.2. Role of LRRK2 in Parkinson's disease

The second gene that is responsible for causing PD is leucine-rich repeat kinase 2 gene (LRRK2). It is considered as the largest gene because it comprise of 51 exons.It is responsible for encoding the 2527-amino acid cytoplasmic protein leucine-rich repeat kinase 2 (LRRK2) which comprise of leucine-rich repeat towards the amino part of the protein and kinase domain towards the carboxyl terminus, they have some conserved domains. 50 different missense mutations and nonsense mutations have been reported in LRRK2 (Nuytemans, Theuns, Cruts, & Van Broeckhoven, 2010). Mutations in LRRK2 are associated with autophagy and they slow down the degradation of alpha-synuclein, hence results in accumulation of alpha-synuclein(Funayama et al., 2002)(Yue & Yang, 2013). In contrast with SNCA gene mutations that are responsible for early onset of disease, LRRK2 gene are responsible for late onset of disease and most commonly cause sporadic PD. The mutation frequency ranges from 2% to 40% in different studied (Brice, 2005). PD caused due to LRRK2 progresses slowly and results in late onset of disease. The patients show different features as compared to SNCA mutations, dementia is not common at this stage. Although, it shows the presence of Lewy body and pure nigral degeneration without Lewy bodies (Giasson et al., 2006).

The most common feature of LRRK2 gene is membrane trafficking because it slow down the degradation of alpha-synuclein and results in membrane traficking(Abeliovich & Gitler, 2016). Mutations in LRRK2 causes defects in the trafficking of endosomes, lysosomes, mitochondria etc. Mutant LRRK2 causes defects in the trafficking of endosomes, lysosomes, autophagosomes, and mitochondria.Additionally, RabGTPases, central regulators of membrane trafficking, are functional substrates of LRRK2(Steger et al., 2017). The PD mutations results in the phosphorylation of LRRK2's Rab substrates.

1.4.3. Role of PARK2 in Parkinson's disease

Another gene that is considered as the causative factor of PD is PARK2, It is situated on the 6q25.2-27 chromosome. It mainly interfere with early onset of PDand is responsible for development of a specific form of the disease mainly autosomal recessive PD. The frequency of mutations in PARK2 ranges with 15% of familial and 4% of sporadic PD cases. The patients usually develop the disease before the age of 40 years (Kilarski et al., 2012). The most common feature of PARK2 gene is that it encodes cytosolic ubiquitin-E3-ligase, which is called as Parkin protein. The most important function of this protein is the regulation of mitophagy, which is the removal of damaged part of of mitochondria through autophagy. It works along with PINK1 mitochondrial protein which is the product of recessive PD (Park et al., 2006). It works in a sequence of molecular pathways in the first step the dysfunctional mitochondrion is depolarized because of this depolarization PINK1 is stabilized, then they induct Parkin from cytosol and increase its activity at the time of delivery to mitochondria, by utilizing PINK1-kinase activity. The sequence of molecular events occurs as follows: the dysfunctional mitochondrion is depolarized, thereby stabilizing PINK1; the latter recruits Parkin from the cytosol and activates it during its delivery to the mitochondrion, using the PINK1-kinase activity; then, the activated Park initiates selective autophagy of the damaged organelle(Matsuda et al., 2010). There are number of mutations that result from parkin that may include deletions of a nucleotides that may range from hundreds to thousands of nucleotides, they also include genomic multiplications and missense mutations(West & Maidment, 2004). Hence the mutation in this gene led to early onset of PD.

1.4.4. Role of DJ 1 in Parkinson's Disease:

Another gene responsible for causing PD is DJ-1 which is also called PARK7, it is a causal gene of a familial form of PD(Bonifati et al., 2003). DJ-1 has important role in antioxidant defenses(Taira et al., 2004). When DJ-1 losses its ability to function properly it led to oxidative stress-induced cell death and cause PD. DJ-1 functions as a chaperone as it belongs to the superfamily DJ-1/Hsp31/PfpI. The loss of DJ-1 function increases sensitivity to oxidative stress-induced cell death. It is responsible for variety of physiological processes that involves transcriptional regulation, mitochondrial function, and signal transduction(Taira et al., 2004).

Conclusion

PD is extremely lethal disease that disturbs social life of patients to greater extent. Evaluating the genetic causes can enable us to foresee the disease progression as well as devising strategies to cope with PD. There are a number of genes that have been reported to trigger PD. Gene therapy can be hidden solution for the treatment of PD. In addition to this development of inhibitors of the above mentioned genes can aid in slowing the pace of disease and enhance survival of the patients. Recent cutting edge technologies have gained us advantage to unravel the complexities of PD and further research in this regard can surely bring us step closer towards development of efficient therapeutics that can hamper PD at early stage.

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ISSN- 2394-5125 VOL 8, ISSUE 02, 2021

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