Genes & Diseases (2019) 6, 120–128

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REVIEW ARTICLE

Impact of gene mutation in the development of Parkinson's disease

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Received 16 December 2018; accepted 31 January 2019
Available online 27 February 2019

KEYWORDS
Gene mutation;
Mitochondrial dysfunction;
Parkinson's disease;
Protein aggregation;
Susceptibility genes

Abstract Parkinson's disease (PD) is the second most common age related neurodegenerative disorder worldwide and presents as a progressive movement disorder. Globally seven million to 10 million people have Parkinson's disease. Parkinsonism is typically sporadic in nature. Loss of dopaminergic neurons from substantia nigra pars compacta (SNpc) and the neuronal intracellular Lewy body inclusions are the major cause of PD. Gene mutation and protein aggregation play a pivotal role in the degeneration of dopamine neurons. But the actual cause of dopamine degeneration remains unknown. However, several rare familial forms of PD are associated with genetic loci, and the recognition of causal mutations has provided insight into the disease process. Yet, the molecular pathways and gene transformation that trigger neuronal susceptibility are inadequately comprehended. The discovery of a mutation in new genes has provided a basis for much of the ongoing molecular work in the PD field and testing of targeted therapeutics. Single gene mutation in a dominantly or recessively inherited gene results a great impact in the development of Parkinson's disease. In this review, we summarize the molecular genetics of PD.

Introduction

Parkinson's disease is a neurodegenerative disorder that affects predominately dopamine producing neurons in a specific area of the brain called substantia nigra (SN). Symptoms generally develop slowly over years. People with Parkinson's disease may experience tremor, limb rigidity,

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Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2019.01.004

and gait, slowness of movements (bradykinesia), speech dysfunction, sleep disturbances, fatigue, behavioral changes, and sensory abnormalities.[1,2] Psychiatric manifestations can be an eminent feature of the disease and may have depression and visual hallucinations. Depression occurs in 25—50% of PD patients.[3,4] Later in disease progression, dementia eventually occurs in 20—40% of cases.[5,6] The occurrence of Parkinson's disease increases with age, but an estimated four percent of people with PD are diagnosed before age 50. Each year around 60,000 Americans are diagnosed with PD. Comparatively, men are 1.5 times more likely to have Parkinson's disease than women.[7] The root cause of PD is unknown.[8] Although there is no cure, treatments options vary include medications and surgery.[7]

Genetic researches in PD have led to the recognition of numerous monogenic forms of the disorder and of several genetic threat factors increasing the risk to develop the neuron degeneration.[9] In all cases, molecular testing is the most commonly recommended technique for individuals to diagnose the disease.[5] Pedigree and cohort studies identified numerous susceptibility genes and loci were related to dopamine deficiency. During the past decade, few genes have been identified that are important in autosomal dominant and autosomal recessive form of PD.[5] Whole genome linkage screening to distinguish chromosomal regions connected to the risk of PD or the time of PD beginning,[10—16] it has been recognized mutation at the locus PARK1 to PARK13 (13 chromosome loci) that show linkage to Parkinson Disease.[11,17—23]

Monogenic forms, caused by a single mutation in a dominantly or recessively inherited gene, are entrenched, although relatively account for about 30% of the familial cases.[9] Most of the gene mutations resulting in mitochondrial DNA (mtDNA) damage, increased reactive oxygen species (ROS) production, reduced mitochondrial membrane potential (MMP), decreased ATP levels and structural imperfection to the organelle and the mitochondrial network are associated with mitochondrial dysfunction, these various phases of mitochondrial dysfunction have been responsible for developing PD.[24—27] Autosomal dominant transformation associated with mutations in SNCA, UCHL1, GIGYF2 and LRRK2 genes and PRKN, DJ-1, PINK1, ATP13A2, PLA2G6, FBXO7 result in autosomal recessive Parkinsonism (Table 1).[28] Approximately, 27% of patients with early-onset PD (EOPD) bear a transformation in one of three genes: LRRK2, Parkin, and glucocerebrosidase (GBA).[29] Researchers have been identified a few susceptibility genes (A hereditary modification that expands a person's powerlessness or inclination to a specific disease or disorder) for PD. They are NR4A2 (Nurr1, nuclear receptor superfamily protein), SNCAIP (synphilin-1), APOE (apolipoprotein E), MAPT (tau protein), GBA (b-glucocerebrosidase) associated with an increased risk of developing PD.[5,9] This identification of new genes which associated with PD will increase the understanding of the underlying pathogenic mechanism of neurodegeneration.

Autosomal dominant PD

SNCA

SNCA (Alpha-synuclein) gene codes for the protein, that is enormously present in neurons. α-synuclein is a highly conserved protein, which controls the vesicular neurotransmission as well as the human α-synuclein regulate the dopamine neurotransmission.[30] A point mutation and missense mutation have been reported in the gene SNCA; the mutational transformation of A53T in exon 4,[2,30,31] A30P in exon 3[32] and E46K[33] results in the familial form of Parkinson's disease. Consequent sequence analyses in thousands of patients have revealed that point mutations in SNCA are an unusual cause of familial or simplex Parkinson's disease[34—40] as well as Multiple system atrophy. More recently two new point mutations (H50Q and G51D) have been identified from a British late-onset PD patient.[41,42] Further analyses have shown that other types of alterations in SNCA and Duplication of SNCA[43—45] and a triplication of a huge chromosomal region containing SNCA has been shown to cause autosomal dominant PD.[28,46] Triplication carriers show an extreme diffuse LB disease while duplication carriers include a phenotype difficult to discriminate from the disease[44] The difference in the promoter region of SNCA has been noted to increase susceptibility for a neurodegenerative disease,[47] and a meta-

Table 1 List of candidate genes and susceptibility genes involved in Parkinson's disease.

S.No	Gene Symbol	Locus Name	Protein product	Chromosome Location	Type of Mutation	Mode of Inheritance
1	SNCA	PARK1	Alpha-synuclein	4q21.3—22	Missense, Point	AD
2	LRRK2	PARK8	Leucine-rich repeat kinase 2	12q12	Missense	AD
3	PRKN	PARK2	Parkin	6q25.2—q27	Missense, Frameshift, splice site, point, nonsense	AR
4	PINK1	PARK6	PTEN-induced putative kinase 1	1p36.12	Missense, Frameshift, splice site, point, Truncating	AR
5	DJ-1	PARK7	Protein DJ-1	1p36.23	Point, Missense, frameshift, exon deletion and splice site	AR
6	ATP13A2	PARK9	ATPase 13A2	1p36	Frameshift	AR
7	PLA2G6	PARK14	Phospholipase A2 Group VI	22q13.1	missense	AR
8	*FBXO7*	PARK15	F-Box protein 7	*22q12-q13*	Missense, splice site	AR
9	GIGYF2	PARK11	GRB10 interacting GYF protein2	*2q36-37*	Missense	AD
10	UCHL1	PARK5	Ubiquitin C-Terminal Hydrolase L1	4p14	Missense	AD

analysis of 2692 cases and 2652 controls has advance sustain evidence that this marker, known as Rep1, is linked with a slight, but significant, increase in the risk of PD.[48] Rep1 is a dinucleotide replicate sequence that has three prominent allele sizes. Analysis of the nearby DNA recommends that two domains flanking the Rep1 repeat interact to increase expression of SNCA whereas the repeat acts as a negative modulator. In addition, various alleles can differ the expression levels of SNCA in SH-SY5Y cells by up to threefold.[49] It is possible that even a subtle increase in expression could, over the course of many decades, predispose an individual to develop neuronal loss. Although mutations in SNCA have been known to cause PD for nearly a decade, the mechanism by which these mutations lead to disease is poorly understood. It is thought that abnormal aggregation of the protein leads to cell damage and ultimately neuronal death. However, further research is essential to understand how mutations in SNCA or multiplication of SNCA result in Parkinsonism.[5,128]

LRRK2

The LRRK2 (Leucine-rich repeat kinase 2) gene gives directions to making a 2527-amino acid cytoplasmic protein known as Dardarin. LRRK2 is active in the brain and consists of 51exons; it. Dardarin consists of five functional domains in the C terminal[50,51]; a part of this protein is called leucine-rich region because it contains a large quantity of Leucine amino acid (building block of protein). This protein may also have an enzyme function such as kinase activity (assist the transfer of phosphate group) as well as GTPase activity (ROC domain function). It helps to maintain the cytoskeletal dynamics (cell's structural framework) vesicular transport, autophagy and also involved in protein-protein interaction.[30,52] More than 100 types of missense and nonsense mutations reported in a LRRK2 gene found in families with Late-onset Parkinson's disease and appear to result in typical idiopathic PD[1,51–53] and a possibility to cause Crohn disease. This mutation replaces single amino acid in the dardarin protein, which changes the structure and function of a protein. Most commonly, the mutation replaces the amino acid arginine and glycine at the protein position leads to the population to get Parkinsonism.[52] About twelve distinct mutational transformations have been accounted for; the most widely recognized, G2019S, has been found in around 1–2% of sporadic[54] and 5–7% of familial, autosomal dominant cases.[55–57] These evaluations have been gotten from the Northern European and North American populations; the G2019S mutation seems to be extremely uncommon in East Asia.[58,59] Heterozygotes and homozygotes for the G2019S mutation have the same clinical features and these two genotypes show reduced penetrance.[60] In some PD patients with LRRK2 gene transformation identified with unique neuropathology, which had included diffuse Lewy bodies, Lewy bodies confined to the brain stem, front temporal lobar degeneration with ubiquitinated neuronal intranuclear incorporations and abnormal aggregation of tau protein in neurofibrillary tangles.[53,60–64] Moreover, LRRK2 gene was extremely expressed in immune cells. Recent research shows that, in early life, the expanded LRRK2 action may ensure against opportunistic pathogenic infection however then later enhance the possibility of promoting PD, this perception called antagonistic pleiotropy.[65]

Autosomal recessive PD

PINK1

Early onset of an autosomal recessive form of PD caused by a mutation in phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1). This mutational transformation was found inside a huge Italian family pedigree on chromosome 1(PARK 6 locus) in 2001.[66,67] Mutation in the PINK1 gene has been responsible for 1–7% of early-onset PD in white patients,[68–70] and 9% of autosomal recessive PD in Japanese patients.[71] PARK 6 contains 8 exons that encode the 581 amino acid protein PINK1,[68] a highly conserved serine/threonine kinase domain, and a C-terminal auto-regulatory domain.[72] It maintains the regulation and health quality of entire mitochondria by removal of dysfunctional mitochondria.[73] PINK1 encodes a mitochondrial protein[68] and have been hypothesized to have a proteasomally induced apoptosis and a neuroprotective role against mitochondrial dysfunction. Truncating mutations, point mutations and frameshift mutations reported throughout the gene. Mutation in PINK1 is hypothesized that may result in enhancing the susceptibility to cellular stressors and other reactive oxygen species and subsequently may result in PD.[74] PINK1 mutation in a heterozygous state may enhance the chance of developing PD.[75–78] A solitary PINK1 mutation that exclusively aims fractional decrease in enzymatic action could likewise bring about a milder phenotype or contribute to disease vulnerability later in life.[72]

PRKN

PRKN (Parkin) contains 12 exons that encode the 465 amino acid protein[22]; it belongs to the group of E3 Ubiquitin ligase composed of an amino-terminal ubiquitin-like (Ubl) domain and a carboxyl-terminal ubiquitin ligase domain with two ring finger motifs.[23] Parkin plays a vital role in the cell's quality control system with the help of Ubiquitin proteasome system (breaks down unwanted protein by tagging harmed and remaining proteins with Ubiquitin) and maintains the healthy mitochondrial network via the destruction of mitochondria which are not having the proper function in the cellular system. A mutational change in PRKN at the sixth chromosome was the common cause of Autosomal Recessive Juvenile Parkinsonism (AR-JP) and early onset of Parkinsonism.[30] Up to date more than hundred different autosomal recessive mutational transformations of PRKN gene have been recognized involving the insertion and deletion of one or more exons. In addition, when the reading frame has been changed by point mutation cause premature termination of translation or amino acid substitutions and half of the depicted gene transformations are nonsense/missense type.[79–82] Heterozygous Parkin mutation is an evidently dominant phase of the transmission, suggesting that carriers of a solitary parkin mutation might be at the risk of developing PD manifestation.[66,67]

PINK1/parkin pathway

When mitochondria are harmed, PINK1 initiates phosphorylate parkin at the outer membrane of mitochondria (OMM).[55] Parkin starts to tag pro-fusion mitochondrial proteins including Mitofusion 1 and 2 with ubiquitin, lead to their gradual reduction through the ubiquitin-proteasome framework.[56] This drive a move from high mitochondrial organize network towards diminished fusion and expanded fission, and thus remove the affected mitochondria from a network of healthy mitochondria. These dysfunctional organelles engulfed by autophagosomes and they are processed by lysosomal enzymes through the procedure of mitophagy. This helps to take into account a consistent turnover of healthy mitochondria and prevents the mitochondrial dysfunctions such as the damage of mtDNA, increased ROS, decreased MMP and ATP level, morphological defects, and respiratory dysfunction of complex I (Fig. 1).[57,83–85]

ATP13A2

ATP13A2 (ATPase 13A2) is a substantial gene contained 29 exons codes for 1180 amino acid protein. The ATP13A2 protein is ordinarily situated in the layer of lysosome with an ATPase domain and ten transmembrane domains.[9]The encoded protein associated with the prevention of alpha-synuclein aggregation, abnormal mitochondrial/lysosomal function and neurodegeneration. Mutations in ATP13A2 have been found among patients with juvenile-onset PD (12–16 years). At first, a Chilean family found with EOPD.[86] Around ten distinctive pathogenic gene transformations have been found in the compound heterozygous and homozygous state, which influence the function of transmembrane domains directly/indirectly. The vast majority of the genetic changes deliver unstable truncated proteins, which are retained in the endoplasmic reticulum and are consequently degraded by the proteasome. Yet, there is no amino acid aberrations (deletion, exonic deletion, multiplication) are found in the whole gene. The role of heterozygous missense mutations in PD pathogenicity is known, but the exact mechanism is still not clear.[9] In addition, ATP13A2 gene mutations have been responsible for the other type of neurodegenerative disorders called neuronal ceroid lipofuscinoses (NCLs)[86,87] and Kufor-Rakeb syndrome (KRS).

DJ-1

DJ-1(protein DJ-1) gene has seven coding exons, which code for 189 amino acid long protein known as Parkinson protein 7. DJ-1 proteins expressed ubiquitously and function as a cellular sensor of oxidative stress.[88,89] One of the major functions of DJ-1 is protecting the brain cells from oxidative stress. DJ-1 has acted as a chaperon particle, while protein folding. It assists the newly produced protein to fold into a correct possible three dimensional shape and aides refold damaged protein, deliver the selected proteins to proteasomes and also take a part in the process of production and regulate the RNA. Mutation in the DJ-1 gene is associated with 1%–2% of autosomal recessive Early Onset Parkinson

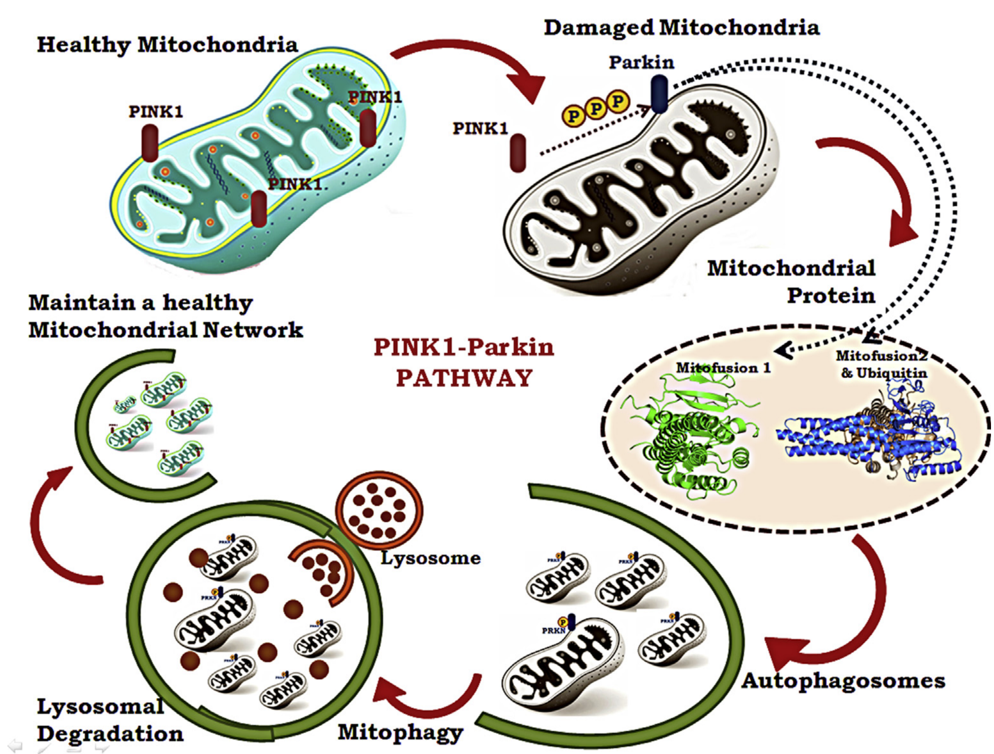

Figure 1 PINK1-PARKIN Pathway. Healthy mitochondria (blue color), Damaged mitochondria (grey color); Parkin and PINK1 function together in pathways relevant to PD pathogenesis. Parkin ubiquitinates outer membrane proteins preferentially on the mitochondrion on which PINK1 has accumulated. Ubiquitination of OMM proteins by Parkin leads either to their degradation by the proteasome or to the recruitment of ubiquitin-binding adaptor proteins to effect the removal of the damaged mitochondrion by autophagy.

disease.[90] In homozygous and compound heterozygous state, ten different gene transformations (exonic deletion and point mutation) have been described in this gene.[9] Under physiological condition, it forms a dimeric structure.[91] The dimeric structure of DJ-1 protein appears that have many diseases causing mutants (p.D149A, p.L166P, p.M26I, and p.E64D).[92] After the mutation, the transformed proteins are not regulating their function properly. It starts to collapse the protein folding, stability and rapidly tainted by the proteasome. Along these lines, their antioxidant activity and neuroprotective capability have been ruined.[93,94] DJ-1 protein levels are hoisted in the CSF (cerebrospinal fluid) of people with idiopathic PD, especially for those in the prior phases of the disease, recommending that DJ-1 may be helpful as a biomarker for neurodegenerative disease.[95] Comparatively DJ-1 related PD seems to be very rare, there are not enough reports to say about the patients have been affected with PD due to the heterozygous mutation of the DJ-1 gene.[9]

FBXO7

FBXO7 (F- box protein 7) gene encodes the FBX7 protein, which consist of approximately forty amino acid motif (N-terminal ubiquitin-like domain) and a C-terminal proline-rich region (PRR).[96–98] It constitutes a ubiquitin protein ligase (subunit) complex termed SKP1-cullin-F-box (SCFs). Substrate recognition component of SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase intervenes ubiquitination and consequent proteasomal deprivation of target proteins.[99] Nevertheless, FBXO7 might also be implicated in non-proteasomal pathways, Ubiquitin-mediated and SCF-independent activity. FBPs serve as molecular scaffolds in the construction of protein complexes and have been involved in various functions such as cell cycle, genome stability, development, circadian rhythms and synapse formation.[96] Homozygous truncating/missense mutation in the FBXO7 gene cause an autosomal recessive form of Juvenile Parkinsonism.[99–101] Splice site mutation affects only the FBXO7 isoforms having exon 1A. A cDNA analysis revealed mutational changes in the FBXO7 transcripts expressed by alternative combinations of exons like 1A/1B or 2A/2B. The splice site mutation evaluates the perpetual splice donor of intron7, and possible to disturb the mRNA splicing of FBXO7.[129] The missense mutation replaces the ubiquitin-like domain from N-terminal of FBXO7 protein, which is just communicated in the two longer FBXO7 isoforms. This circumstance predicts that some unaltered isoforms compatible with a few residual FBXO7 functional activities in the PD patients.[99]

PLA2G6

PLA2G6 (A2 phospholipase group VI) gene involves in the production of an enzyme called cytosolic, calcium-independent phospholipase A2. This enzymatic protein helps to regulate the amount of phosphatidylcholine in the cell membrane, and break down the phospholipid to maintain the integrity of the cell membrane.[102] Mutations in PLA2G6 cause an aggressive and complex autosomal recessive early-onset dystonia Parkinson disease[103,104] as well as additional neurodegenerative diseases such as Infantile neuroaxonal dystrophy and Karak syndrome.[105,106] The potential role of this mutation repeatedly shows brain-iron aggregation, which is an element of neurodegeneration related to brain—iron accumulation.[107] The revealed clinical highlights of neurodegeneration related to the genetic transformation in the PLA2G6 gene are dystonia, axonal dystrophy, brain dystrophy, cerebellar signs and dementia with or without iron accumulation.[106,108,109] Homozygous and heterozygous mutation in the PLA2G6 gene plays a significant role in the enhancement of PD in various populations. A novel heterozygous mutation shows C-to-G substitution in exon 17 resulting in a proline (nonpolar: hydrophobic amino acid) to arginine (polar: hydrophilic amino acid) change. This aminoacid substitution could affect the interaction of PLA2G6 with other proteins.[110] This might influence the enhancement of EOPD.

Autosomal dominant susceptibility genes

GIGYF2

The missense mutation in the GIGYF2 gene at the second chromosome leads to late-onset Parkinson disease (LOPD). GIGYF2 (Grb-10 Interacting GYF protein-2) gene consists of 27 exons encodes 1299 amino acid protein called Trinucleotide Repeat Containing 15 (TNRC15). The encoded protein may be associated with the regulation of tyrosine kinase receptor signaling and have potential involvement in insulin growth factor (IGF) and insulin signaling in the central nervous system.[111–115] Seven different type of missense mutation in GIGYF2 gene found in the heterozygous state compatible with the autosomal dominant mode of transmission, resulting in amino acid substitution like insertion or deletion. Initially Italian and French families (4.8%) were identified with familial PD due to the transformation in GIGYF2.[116] The GIGYF2 p.Arg610Gly mutation occurs in the GYF domain of the encoded protein was anticipated be pathogenic and interrupt the ligand-binding function. The mutation results in aberration in GIGYF2, which leads insulin dysregulation and abnormal signaling pathway of insulin/IGF-1 receptor (IGF-1R: a homeostatic modulator for brain function) shows the causative mechanism for LOPD.[117,118]

UCHL1

The UCHL1 (Ubiquitin carboxyl-terminal esterase L1) gene encodes an enzymatic protein, called ubiquitin thiolesterase. UCHL1 protein is abundantly present in nerve cells throughout the brain.[119] This protein takes part in the Ubiquitin-proteasome system, act as a cell's quality control system by removing misfolded proteins and abnormal proteins, including produce free ubiquitin monomers.[120] UCHL1 and alpha-synuclein colocalize with synaptic vesicles and can be coimmunoprecipitated from human brain.[19] Mutation in the UCHL1 gene causes autosomal dominant Parkinson's disease.[120] When the missense mutation, which replaces the amino acid isoleucine with methionine at the position 93 (Ile93Met/I93M). This mutation results to decreases catalytic hydrolase activity, which may interrupt the normal function of the ubiquitin-proteasome pathway.[121,122] Later, another missense mutation variant has been identified that the amino acid serine replaces with tyrosine (Ser18Tyr or S18Y) in UCHL1. This mutation reduces the ligase activity and increasing the hydrolase activity. These are the two common mutant variants considered as a pathological hallmark of Parkinson's disease.[19,123] Sequencing of the UCHL1 gene in French families with PD consequently recognized an uncommon A371C polymorphism in exon 5, driving to an M124L amino acid change.[124,125] This variant did not segregate with PD and its role in disease development remains questionable.[126]

Summary

Genes PRKN and LRRK2, all mutations are not equally penetrated, yet the accurate penetrances of both the genes are not known. Therefore, the molecular technique is not recommended for presymptomatic individuals. In 50% of early-onset PD patients (onset age before 40) have a mutation in DJ-1, PRKN or PINK1. In such a state of illness, prioritizing the diagnosis of mutational changes in PRKN gene would seem to be the effect. If the PRKN mutation found to be negative, it may be appropriate to consider screening DJ-1 and PINK1. The implication of a gene transformation in just a single of the two PRKN alleles isn't yet known.[5] The clinical and comparability of the disorder caused by PLA2G6 deficiency to those caused by ATP13A2 and PANK2 deficiencies recommended that each of the three genes and their encoded proteins may lie on a single biochemical pathway.[103] PLA2G6 and FBXO7 generate clinically similar phenotype in that they develop a rapid Parkinsonism at first receptive to Levodopa treatment but later established some new features including loss of Levodopa responsiveness and cognitive decline.[127] The function of FBXO7 in the human brain remains inadequately described, and its expression in PD pathology and many neurodegenerative diseases has not been explored.[100] The continuous research of candidate genes has prompted the finding of a few susceptibility genes. However, most have neglected to reliably repeat in different populations.[61] UCHL1 and GIGYF2 are the autosomal dominant susceptibility genes, it remains unclear how this amino acid variation might reduce the risk of developing Parkinson's disease.[126]

This is not an exhaustive review of all gene examined as a candidate gene/biomarker of PD. Rather, we have recapitulated the genes that have been the topic of the most concentrated in recent years. The smallest genetic change in a gene causes a large degree of disease to the population. Every newly discovered gene and updated information of already existing genes is the stepping stone of researchers in PD. Thus genetic researches in PD results across the world are expected to discover a new treatment for the permanent cure.

Conflict of interest

The author declares that there is no conflict of interest.

Acknowledgement

Nil.

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