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Genetics of Parkinson Disease

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Abstract

Parkinson disease is a common neurodegenerative disorder, characterized by bradykinesia, tremor, rigidity and difficulty in initiating movement. It is caused due to loss of dopaminergic neurons in the substantia nigra in the midbrain. Sporadic forms account for 90% of cases and manifest by 60 years of age. Both environmental and genetic factors have been implicated in sporadic forms. Various genes with autosomal dominant, recessive and X linked inheritance have been identified for monogenic forms of Parkinsonism. This brief review is about the latest advances in the understanding of the genetics of Parkinsonism and some of the novel therapeutic approaches that are being tried.

Introduction

Parkinsonism refers to a constellation of symptoms like bradykinesia, rigidity, resting tremor and postural instability. Parkinsonism can occur as a side effect to drugs like neuroleptics, as a complication of stroke or as a manifestation of other autosomal dominant genetic disorders like Huntington disease, Spinocerebellar ataxias and Frontotemporal dementias with Parkinsonism. Parkinson disease is the second most common neurodegenerative disease, preceded by Alzheimer disease and is the most common primary cause for Parkinsonism (Pankratz et al., 2004). The most important pathology that defines Parkinson disease is the loss of dopaminergic neurons in the substantia nigra in the midbrain with Lewy body inclusions (Pankratz et al.,2004). In the population above 60 years of age, the estimated worldwide prevalence is 1% and in the population above 80 years, the prevalence is as high as 4% (de Lau et al., 2006). Even though the median age of onset is 70 years, around 4% of individuals manifest symptoms before 50 years of age (Lin et al., 2014)

Classification based on the age of onset of symptoms

Based on the age of onset, Parkinson disease can be classified as:

1. Juvenile: Onset before 20 years
2. Early onset: Onset before 50 years
3. Late onset: Onset after 50 years

Causes of Parkinson disease

Environmental, genetic and epigenetic mechanisms have been implicated in Parkinson disease.

- Non-genetic/ environmental causes which have been shown to be associated with Parkinson disease include:

1. Occupational exposure to herbicides, pesticides, heavy metals
2. Head trauma
3. Smoking, which has an inverse association with Parkinson disease (de Lau et al., 2006)
4. Coffee and alcohol consumption
5. Dietary factors and physical activity

- Heritable or genetic factors: Monogenic forms account for 5-10% of cases of Parkinson disease. Following the identification of a missense variant in the *SNCA* gene in an Italian family with autosomal dominant Parkinson disease, several other genes and loci have been implicated in Mendelian forms of Parkinson disease. The loci were named as PARK followed by a number, in the order of their discovery. These genes are thought to be involved in various cellular processes like synaptic transmission, lysosome mediated autophagy and mitochondrial quality control (Trinh et al., 2013). Mendelian forms of Parkinson disease can be inherited in autosomal dominant, autosomal recessive or X linked manner. Table 1 summarizes the genes implicated in Parkinson disease.

Table 1 Genes associated with Mendelian forms of Parkinson disease.

Loci	Gene	Mode of inheritance	Clinical phenotype
PARK1 (4q21-22)	*SNCA*	AD	EOPD
PARK2 (6q25.2–q27)	*PRKN*	AR	Juvenile onset Parkinson disease
PARK3 (2p13)	Unknown	AD	Classical PD
PARK4 (4q21-22)	*SNCA*	AD	EOPD due to heterozygous triplication in *SNCA* gene.
PARK5 (4p13)	*UCHL1*	AD	Single family with late onset PD
PARK6 (1p36.12)	*PINK1*	AR	EOPD
PARK7 (1p36.23)	*DJ1*	AR	EOPD
PARK8 (12q12)	*LRRK2*	AD	Classical PD
PARK9 (1p36)	*ATP13A2*	AR	Juvenile onset atypical Parkinson disease (Kufor-Rakeb syndrome)
PARK10 (1p32)	*Unknown*	AD	Classical PD
PARK11 (2q37.1)	*?GIGYF2*	AD	Late onset PD; unconfirmed
PARK12 (Xq21-25)	*Unknown*	X linked	Classical PD
PARK13 (2q13.1)	*HTRA2*	AD	Classical PD; unconfirmed
PARK14 (22q13.1)	*PLA2G6*	AR	Adult onset dystonia-Parkinsonism
PARK15 (22q12.3)	*FBX07*	AR	Early onset Parkinsonian pyramidal syndrome
PARK16 (1q32)	*Unknown*	Not known	Susceptibility to Classical PD
PARK17 (16q11.2)	*VPS35*	AD	Classical PD
PARK18 (3q27.1)	*EIF4G1*	AD	Classical PD
PARK19 (1p31.3)	*DNAJC6*	AR	Early onset and juvenile PD
PARK20 (21q22.11)	*SYNJ1*	AR	EOPD
PARK21 (3q22)	*Unclear*	AD	Classical PD
PARK22 (7p11.2)	*CHCHD2*	AD	Classical PD
PARK23 (15q22.2)	*VPS13C*	AR	EOPD

AD: Autosomal dominant
AR: Autosomal Recessive
PD: Parkinson disease
EOPD: Early onset Parkinson Disease

Autosomal dominant PD: Heterozygous variants in the *SNCA, LRRK2, VPS35, CHCHD2* and *EIF4G1* genes cause autosomal dominant forms of Parkinson disease. Generally autosomal dominant forms tend to manifest at a later age compared to autosomal recessive forms. *SNCA* is the first gene in which a mutation was identified in Parkinson disease and this gene codes for alpha- synuclein, which is the primary protein found in Lewy bodies. Disease causing variants in *SNCA* could be single nucleotide variants or gene duplications and triplications. The p.Gly2019Ser variant in *LRRK2* accounts for 5-7% of autosomal dominant forms (Nichols et al.,2005).

Autosomal recessive PD: Autosomal recessive forms have an earlier onset of disease, mild non-motor symptoms and a slow progression. They are caused due to biallelic variations in *PRKN* which codes for Parkin, *PINK1, ATP13A2, DNAJC6, SYNJ1* etc.

X-linked PD: PARK 12 is the only locus that has been shown to demonstrate X-linked transmission. *ATP6AP2* is the gene that has been implicated in X-linked Parkinsonism (Korvatska et al., 2013).

Pathogenesis of Parkinson disease

The genes identified as causing idiopathic Parkinsonism are shown to affect four different processes: synaptic transmission, endosomal trafficking, lysosomal autophagy and energy metabolism.

- Synaptic transmission: Alpha- synuclein, which is found in presynaptic terminals in the central and autonomous nervous system, is involved in exocytosis and synaptic release of neurotransmitters and it is the main component of Lewy bodies. Triplications of the *SCNA* gene which codes for alpha synuclein lead to earlier onset of symptoms compared to duplications, implicating a dosage effect in the pathogenesis. The exact mechanism by which alpha synuclein leads to neuronal death and spreads throughout the CNS still remains unexplained. There are various theories regarding the spread of alpha synuclein pathology in the brain, like 'selective vulnerability hypothesis' and 'pathogenic spread hypothesis' (Lill, 2016).

LRRK2 codes for a protein kinase, which regulates glutamate transmission and striatal signal transduction (Lin et al., 2014). *DNAJ6,* a biallelic mutation of which causes autosomal recessive forms of Parkinsonism, encodes a protein auxilin, which aids in clathrin mediated synaptic vesicle recycling. Synaptojamin, a protein coded by *SYNJ1,* forms complexes with auxilin and has been implicated in autosomal recessive Parkinsonism.

- Endosomal trafficking: This is a complex process by which the receptors or vesicles are internalized and then recycled in the Golgi complex or degraded in the lysosomes. *VPS35* and *DNAJC13* are implicated in endosomal trafficking causing Parkinsonism.

- Lysosomal autophagy: Alpha synuclein, which gets accumulated in cells in Parkinsonism, is not degraded by lysosomes and it is not clear whether this is the cause or effect of dysfunction in that pathway. Accumulation of intracellular alpha synuclein is found in many disorders like neuronal ceroid lipofuscinosis, Gaucher disease and Neimann-Pick type C. Heterozygous carriers of mutations in *GBA*, which in the homozygous state cause Gaucher disease, have an increased prevalence of Parkinsonism and Lewy body-associated dementia. It is postulated that accumulation of glucosylceramide due to decreased GBA enzyme activity, results in decreased lysosomal degradation of alpha synuclein (Mazzulli et al.,2011). *ATP6AP2* which is implicated in X-linked Parkinsonism and *ATP13A2* code for lysosomal proteins and when mutated cause impairment in lysosomal autophagy.

- Energy metabolism in mitochondria: Mitochondrial dysfunction has been implicated in the pathogenesis of Parkinsonism and several mutations in genes in the common pathway in mitophagy in mitochondria cause Parkinsonism. The most important among them are *PARK2, PINK1, FBXO7* and *DJ1*.

Genetic testing for Parkinsonism

Three-generation pedigree, detailed family history and evaluation need to be done in every family to determine whether the cases are simplex or familial. Age of presentation of affected individuals and their relevant medical records should be collected and noted in detail. No formal guidelines have been formulated to regulate genetic testing in Parkinson disease (Klein et al., 2012).

- Whom to test?

1. Early onset PD with atypical features and/ or family history
2. Any patient with juvenile onset of Parkinson disease irrespective of family history
3. Late onset disease with a strong family history

- Which genes to test? Testing strategy can be stepwise single gene testing or multigene panel testing. In families with autosomal dominant inheritance, the European Federation of Neurological Sciences recommends screening for mutations in *LRRK2*. In specific populations with familial and sporadic PD, the same federation recommends screening for the *LRRK2* mutation - p.G2019S. Testing for Parkin, *PINK1* and *DJ1* is indicated in families with autosomal recessive PD.

- Ethical concerns regarding molecular testing: Without appropriate pretest counseling by a trained Medical Geneticist and/ or genetic counselor, molecular testing for Parkinson disease should not be attempted. Direct- to- consumer testing is available and is being used by patients and healthy at-risk individuals. With many susceptible loci being identified without ample evidence to prove causality, genetic counseling is crucial before molecular testing is ordered. Susceptibility testing should be strongly discouraged, especially in healthy individuals. Providing prenatal diagnostic testing for an adult onset disease is still debatable.

Genetic counseling

A family with an affected individual should be counseled regarding the environmental, epigenetic and genetic factors, which can cause Parkinson disease. Since Parkinson disease is a common neurodegenerative condition, the lifetime risk of developing this condition is 1-2% (Elbaz et al., 2002). The empiric risk of recurrence in a family with a sporadic case of late onset classical PD is 3-7%. (Elbaz et al., 2002). In monogenic forms, depending on the pattern of inheritance, the risk of recurrence will vary.

Therapeutic strategies

The treatment strategies being tried for Parkinson disease include pharmacologic therapy, therapies based on molecular mechanisms of disease, cell-based therapy and gene therapy.

a. Pharmacological therapy: The main intention of pharmacological methods is to achieve symptom control by normalizing dopamine levels. This includes monotherapy with dopaminergic drugs like levodopa, combination of levodopa-carbidopa, monoamine oxidase B inhibitors (MAO B inhibitors) and Catechol-o-methyl transferase inhibitors, which increase the levels of dopamine. Dopamine agonists like pramipexole and ropinirole can also be tried in early stages of disease. Non-dopaminergic drugs, which are useful, include anticholinergic compounds, antiviral drugs like amantadine, norepinephrine and serotonergic receptor and muscarinic related compounds. The main drawbacks of these pharmacological agents are that they cannot alleviate non-motor symptoms like dementia and mood disorders and they do not correct the abnormalities in cholinergic and serotonergic pathways.

b. Therapeutic strategies based on molecular mechanism of disease:

1. Small molecular therapy: Table 2 shows the various small molecules that have been tried in Parkinson disease.

2. Cell based therapy: Attempts to improve dopamine levels in the brain by transplanting fetal midbrain tissues and adrenal medullary tissues to mice models started as early as 1980s (Parmer, 2018). These transplants were later shown to induce transplant related side effects (Barker et al., 2015). Moreover due to limited supply of human fetal ventral mesencephalic tissue and related ethical concerns, grafting to human brain had limited clinical utility. With the discovery of human embryonic stem (hESC) cells in 1998, attempts to use them for producing dopaminergic neurons began. Several stem cell sources for grafting were considered and these were pluripotent embryonic stem cells, induced pluripotent stem cells (iPSCs), mesenchymal stem cells and induced neurons obtained by reprograming somatic cells (Barker et al., 2015). Many research groups have completed preclinical trials with GMP (Good Manufacturing Practice) level cell manufacturing and now clinical trials are on their way (Barker et al., 2017).

3. Gene therapy-based approach: Viral vector mediated approach using lenti virus, adeno virus and recombinant adeno virus has been tried in animal models. (Maiti et al., 2017). Triple gene therapy by delivering the genes required for the three enzymes to produce dopamine from L Dopa has also been tried. RNA interference to silence *SNCA*, Parkin and *PINK* is another approach. CRISPR-cas9 mediated genome editing has been used to develop a stable cell line, which expresses *SNCA*. More studies in animal and cellular models are required before gene-based therapy can be tried on human beings.

c. Surgical therapy: The two surgical approaches that are used for Parkinsonism include deep brain stimulation and pallidotomy or thalamotomy.

Conclusion

Parkinson disease is a common neurodegenerative condition, which occurs due to interplay between environmental, epigenetic and genetic factors. Only 5-10% of Parkinson disease is due to monogenic causes. Genetic testing for Parkinson disease should be attempted with utmost care only after appropriate pretest counseling. Newer modalities of treatment for Parkinsonism like cell-based therapy are on the horizon with clinical trials being conducted now.

References

1. Barker RA, et al. Cell-based therapies for Parkinson disease – past insights and future potential. Nat Rev Neurol 2015;11: 492-503.

Table 2 Small molecule therapy being tried for Parkinson disease.

Small molecule	Targeted protein	Model	Effect	Reference
BIOD303	SCNA *(Synuclein)*	Neuronal cell culture	Synuclein accumulation decreased	Moore et al., 2015
ELN484228 and ELN484217	SCNA *(Synuclein)*	Cortical neuron from embryonic rat	Rescue of synuclein-induced disruption of vesicle trafficking and dopaminergic neuronal loss and neurite retraction	Toth et al., 2014
Flavonoid epigallocatechin gallate (EGCG)	SCNA *(Synuclein)*	OLN-93 oligodendrocyte cell line	Neuroprotective effect by decreasing cytotoxicity	Lorenzen et al., 2014
Oligomer modulator anle138b	SCNA *(Synuclein)*	PD mouse model	Improved survival 50 weeks after onset of symptoms	Levin et al., 2014
PREP inhibitor, KYP-2047.	SCNA *(Synuclein)*	Homozygous A03P mice	Increases clearance of protein by increasing autophagy	Savolainen et al., 2014
NOS inhibitor, NG -nitro-L-arginine methyl ester (L-NAME)	Parkin	Mice model	Protection against dopamine neurotoxicity	Singh et al., 2013
STI 571	Parkin	Cell model (SH-SY5Y)	Neuroprotective	Ko et al., 2010
K 560	LRRK2	Cellular and mice models	Prevented neuronal death by inhibiting HDAC1 and HDAC2 (Histone deacetylase)	Choong et al., 2016
Nurr1 agonists (Amodiaquine and chloroquine)	Nurr1	Mice	Neuroprotective	Kim et al., 2015

2. Barker RA, et al. Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era. Cell Stem Cell 2017; 21: 569-573.
3. Choong CJ, et al. A novel histone deacetylase 1 and 2 isoform-specific inhibitor alleviates experimental Parkinson's disease. Neurobiol Aging 2016; 37:103-116.
4. de Lau LM, et al. Epidemiology of Parkinson's disease. Lancet Neurol 2006; 5: 525-535.
5. Elbaz A, et al. Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol 2002; 55: 25-31.
6. Klein C, Westenberger A. Genetics of Parkinson's Disease. Cold Spring Harb Perspect Med 2012; 2: a008888.
7. Kim CH, et al. Nuclear receptor Nurr1 agonists enhance its dual functions and improve behavioral deficits in an animal model of Parkinson's disease. Proc Natl Acad Sci USA 2015; 112: 8756-8761.
8. Ko HS, et al. Phosphorylation by the c-Abl protein tyrosine kinase inhibits parkin's ubiquitination and protective function. Proc Natl Acad Sci USA 2010; 107: 16691-16696.
9. Korvatska O, et al. Altered splicing of ATP6AP2 causes X-linked parkinsonism with spasticity (XPDS). Hum Mol Genet 2013; 22: 3259-3268.
10. Levin J, et al. The oligomer modulator anle138b inhibits disease progression in a Parkinson

mouse model even with treatment started after disease onset. Acta Neuropathol 2014; 127: 779-780.
11. Lill CM. Genetics of Parkinson's disease. Mol Cell Probes 2016; 6: 386-396.
12. Lin MK, Farrer MJ. Genetics and genomics of Parkinson's disease. Genome Med 2014; 6: 48.
13. Lorenzen N, et al. How Epigallocatechin Gallate Can Inhibit alpha-Synuclein Oligomer Toxicity in Vitro. J Biol Chem 2014; 289: 21299-21310.
14. Maiti P, et al. Current understanding of the molecular mechanisms in Parkinson's disease: Targets for potential treatments. Transl Neurodegener 2017; 6: 28.
15. Mazzulli JR, et al. Gaucher disease glucocerebrosidase and alphasynuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 2011; 146: 37-52.
16. Moree B, et al. Small molecules detected by second-harmonic generation modulate the conformation of monomeric alpha-synuclein and reduce its aggregation in cells. J Biol Chem 2015; 290: 27582-27593.
17. Nichols WC, et al. Genetic screening for a single common LRRK2 mutation in familial Parkinson's disease. Lancet 2005; 365: 410-412.
18. Pankratz N, Foroud T. Genetics of Parkinson disease. NeuroRx 2004; 1: 235-242.
19. Parmar M. Towards stem cell based therapies for Parkinson's disease. Development 2018; 145(1). pii: dev156117. doi: 10.1242/dev.156117.
20. Toth G, et al. Targeting the Intrinsically Disordered Structural Ensemble of alpha-Synuclein by Small Molecules as a Potential Therapeutic Strategy for Parkinson's Disease. PLoS One 2014; 9: .
21. Trinh J, et al. Advances in the genetics of Parkinson disease. Nat Rev Neurol 2013; 9: 445-454.
22. Savolainen MH, et al. The beneficial effect of a prolyl oligopeptidase inhibitor, KYP-2047, alpha-synuclein clearance and autophagy in A30P transgenic mouse. Neurobiol Dis 2014; 68:1-15.
23. Singh S, et al. Involvement of nitric oxide in neurodegeneration: a study on the experimental models of Parkinson's disease. Redox Rep 2005; 10:103-109.
24. Wagner J, et al. Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease. Acta Neuropathol 2013; 125:795-813.