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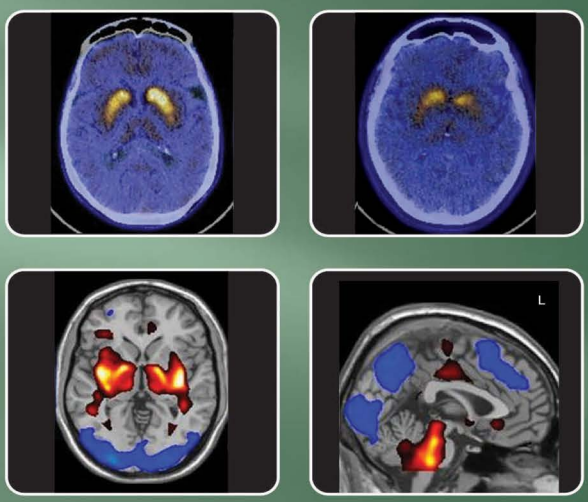
UNDERSTANDING PARKINSONISM

The Clinical Perspective



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CHAPTER 4

Pathophysiology and Genetics of Parkinson's Disease

Tatiana J Orme, Jose Tomas Bras

CASE STUDY

A 43-year-old woman, who worked in an office in the United Kingdom, presented with a 6-month history of slowness, rigidity, and tremor of the left hand. She had been otherwise healthy but was caring for her father who lived in France and had poorly controlled Parkinson's disease. He had recently been started on Duodopa infusion and was being shifted to a care home as he required increased level of care. She came in the clinic dreading to hear the news. She had been the main carer for her father and she suspected the signs in her suggested Parkinson's disease but had been telling her friend that she would die rather than have a life with Parkinson's disease as she had seen her father transform from a very independent and authoritative personality to being incontinent and bed bound.

She received counseling and was treated with a dopamine agonist and antidepressant (citalopram). A year after the diagnosis she was better and agreed to get a genetic test. She carried the *G2019S LRRK2* mutation. She has one child, a daughter who is 20 years old and is asymptomatic.

INTRODUCTION

The analysis of rare familial forms of Parkinson's disease has been fundamental in the discovery of genes implicated in the disease etiology. This has historically been achieved by linkage analysis in large pedigrees, which found genomic regions, *PARK* loci (Table 1), segregating with Parkinson's disease that were later refined to specific genes. More recently, disease-causing mutations have been discovered by the application of novel technological approaches such as next generation sequencing. In addition to Mendelian causes of disease, the use of genome-wide association studies (GWAS) has enabled us to identify risk loci. Nevertheless, hereditary Parkinson's disease only accounts for 5–10% of all Parkinson's disease cases, strongly suggesting that the majority of cases are sporadic in nature and likely caused by a combination of low-impact genetic factors and, perhaps,

TABLE 1: Genes known to harbor mutations that cause Mendelian forms of Parkinson's disease

Locus	Location	Gene	Inheritance	Onset	Protein name and function	Type of mutation
PARK 1/4	4q22.1	*SNCA*	Dominant	30–70	Alpha synuclein- presynaptic protein involved in vesicle fusion	Missense, copy number variation
PARK 2	6q26	Parkin	Recessive	Juvenile	Parkin - E3 ubiquitin ligase involved in protein turnover and mitophagy	Missense, loss of function, copy number variation
PARK 3	2p13	Unknown	Dominant	~60 years	–	N/A
PARK 6	1p36.12	*PINK1*	Recessive	Juvenile	PTEN-induced putative kinase 1–kinase involved in mitophagy	Missense
PARK 7	1p36.23	*PARK7*	Recessive	Juvenile	DJ-1 -many: Tumor formation, chaperone protein oxidative stress sensor, mitochondrial function	Missense
PARK 8	12q12	*LRRK2*	Dominant	50–70	Leucine rich repeat kinase 2- Putative kinase-autophagy control	Missense
PARK 9	1p36.13	*ATP13A2*	Dominant	Juvenile	P type ATPase, lysosome function	Missense
PARK 10	1p32	Unknown	–	–	–	N/A
PARK 12	Xq21-q25	Unknown	–	–	–	N/A
PARK 14	22q13.1	*PLA2G6*	Recessive	Juvenile	Calcium dependent phospholipase -ceramide metabolism	Missense, loss of function
PARK 15	22q12.3	*FBXO7*	Recessive	Juvenile	F box only protein 7 – component of SCF E3 ubiquitin protein ligase	Missense, loss of function
PARK 17	16q12	*VPS35*	Dominant	50–70	Vacuolar protein sorting 35, yeast homolog – part of retromer complex	Missense
PARK 18	3q27.1	*EIF4G1*	Dominant	50–80	Eukaryotic translation initiation factor 4G – initiation of protein synthesis	missense

Continued

Continued

Locus	Location	Gene	Inheritance	Onset	Protein name and function	Type of mutation
PARK 19	1p31.3	*DNAJC6*	Recessive	Juvenile	DNAJ/HSP40 homolog, subfamily C, member 6 – clathrin-mediated endocytosis	Loss of function
PARK 20	21q22.11	*SYNJ1*	Recessive	Juvenile to adult	Synaptojanin 1 – Synaptic vesicle recycling	Missense
PARK 21	3q22	*DNAJC13*	Dominant	30–70	DNAJ/HSP40 homolog, subfamily C, member 13 –endosomal transport	Missense

environmental influences. The identification of genes associated with monogenic forms of Parkinson's disease and of those that confer susceptibility to the disease has resulted in the discovery of biological pathways involved in disease pathogenesis. For example, *PINK1* and *PARK2* mutations, identified in early onset recessive Parkinson's disease, suggest that mitochondrial dysfunction contributes to disease. Although the exact cause of dopaminergic neuron loss in the substantia nigra pars compacta remains unclear, aberrant protein homeostasis (the ubiquitin-proteasome system, the lysosome and autophagic pathways), aberrant mitochondrial quality control, dopamine metabolism, and potentially the immune system are mechanisms that have been implicated in Parkinson's disease.

AUTOSOMAL DOMINANT PARKINSON'S DISEASE GENES

SNCA (PARK1/4)

SNCA was the first gene to be implicated in the pathogenesis of Parkinson's disease through genetic analysis of the Contursi kindred; a large Italian family with autosomal dominant Parkinson's disease presenting with an earlier age of onset and a more rapid disease progression than its sporadic counterpart.[1] A point mutation, *p.A53T*, segregated with the disease in this family as well as in three Greek kindreds.[2] In the following years, subsequent point mutations were found in *SNCA*, in addition to gene duplications and triplications[3] that augment a dose-dependent effect on disease severity. The *SNCA* gene encodes α-synuclein, a synaptic terminal protein thought to play a central role in Parkinson's disease. Indeed, the hallmark of Parkinson's disease—the Lewy body (LB), primarily consists of aggregated fibrillar α-synuclein.[4] Nonetheless, LBs are not exclusive to Parkinson's disease, as α-synuclein positive lesions are present in other neurodegenerative disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies LBs (DLB). The location and

morphology of the inclusions vary within the diseases. Parkinson's disease typically displays brainstem LBs, whereas the LBs seen in DLB exhibit a widespread, cortical distribution. *SNCA* variants have been shown to act as a predisposing factor for DLB. Despite α-synuclein inclusions acting as a characteristic feature of the disease, it is not known if LBs are toxic to neurons, have a protective effect, or arise during disease progression and do not contribute to pathology.

LRRK2 (PARK 8)

In 2004, independent investigations in German, Basque, and Nebraskan families with *PARK-8* linked Parkinson's disease were found to have mutations in the *LRRK2* gene, a gene comprising of 51 exons and 144 kb.[5,6] *LRRK2* encodes the leucine-rich repeat kinase 2 protein and is the gene most commonly implicated in familial Parkinson's disease. There are numerous confirmed disease-associated mutations in *LRRK2*. Some of these mutations are almost population specific, for instance the *p.G2385R* variant is a common risk factor for Parkinson's disease only in the Asian population. The *p.G2019S* mutation is by far the most predominant, having a frequency of 1% in apparently sporadic Parkinson's disease and 4% in familial Parkinson's disease worldwide, with the highest frequency reported in North African, Arabs, and the Ashkenazi Jewish population.[7] The *p.G2019S* mutation is estimated to cause a wide range of penetrance in an age-dependent manner, with estimates ranging for 21–51% at age 69–70 years and 32–74% at 79–80 years.[7,8] Interestingly, patients with *LRRK2* mutations show pleomorphic pathology that ranges from fairly typical LBs, diffuse LB disease to absence of LBs and tau pathology.[5,9]

VPS35 (PARK 17)

Previous methods of finding causative genes relied on analyzing large pedigrees by linkage analysis; however, next generation sequencing of Swiss and Austrian families with autosomal dominant Parkinson's disease identified a rare mutation (*p.D620N*) in the *VPS35* gene.[10] *VPS35* is 29.6 kb, consists of 17 exons and encodes a subunit of the retromer complex involved in endosomal-lysosomal trafficking. Mutations in *VPS35* are a rare cause of Parkinson's disease; a recent multicenter report of 15,000 individuals identified five familial and two apparently sporadic Parkinson's disease cases with the p.D620N mutation.[11] From a clinical perspective, *VPS35* mutation carriers have a high incidence of bradykinesia and a good response to levodopa.[12]

AUTOSOMAL RECESSIVE PARKINSON'S DISEASE GENES

Parkin (PARK2)

In 1997, deletions in a gene on chromosome 6 were linked to autosomal recessive, juvenile onset (onset at age 20 years or younger) Parkinson's disease.[13] The encoded protein, named parkin, is an e3 ubiquitin ligase. In addition to deletions,

there are a large number of recognized pathogenic mutations in *PARK2*, making it the most commonly mutated gene in early-onset, recessive Parkinson's disease to date. Pathological studies in individuals with pathogenic *PARK2* mutations have shown degeneration of the substantia nigra (SN) but, of interest, LBs are largely absent, which suggest LB pathology is unlikely to have a primary role in *PARK2* related Parkinson's disease. When present, the α-synuclein inclusions display a basophilic morphology that is distinct from the classical brainstem LB seen in idiopathic Parkinson's disease.[14] This may suggest that functional parkin may be required for LB formation or that LBs may only occur when another mechanism (other than the UPS) is impaired, such as the lysosomal pathway.

PINK1 (PARK6)

Early onset Parkinson's disease manifests before the age of 55 years. Analysis of early onset, recessive Parkinson's disease in PARK6 associated consanguineous families implicated the *PINK1* gene.[15] *PINK1* is the second most common cause of early onset recessive Parkinson's with a mutation frequency of 1–8%.[16] *PINK1* consists of 1.8 kb, 8 exons and encodes phosphatase and tensin homolog (PTEN)-induced kinase 1 of 581 amino acids, which encompass a kinase domain and a mitochondrial target sequence.[15] As such, *PINK1* is suggested to play a protective role in mitochondrial function, and is involved in mitophagy where it acts upstream from parkin. The majority of disease-causing mutations exist in or around the kinase domain, and lead to loss of function of the protein. *PINK1*-linked Parkinson's disease exhibits a slow disease progression, presence of LBs and neurites and occasionally psychiatric symptoms.[17]

DJ-1 (*PARK7*)

Families presenting with autosomal recessive, early onset Parkinson's disease were shown to harbor deletions and homozygous point mutations in the *PARK7* gene,[18] which consists of eight exons and is 24 kb. The encoded protein, DJ-1, is highly conserved across multiple species and has several putative and diverse functions. Mutations in *PARK7* appear to be an extremely rare cause of familial Parkinson's disease. Moreover, homozygous mutations in this gene have been seen in a family with Parkinsonism, dementia, and amyotrophic lateral sclerosis (ALS)[19] potentially expanding the spectra for DJ-1 pathology. Clinical analysis in the initial kindred suggests a slow disease progression with a variable severity. The first and only paper so far to define brain pathology in a case with a *PARK7* mutation described a patient who had early onset Parkinson's with dementia and pyramidal signs. Immunohistochemistry revealed severe and diffuse LB pathology.[20]

Atypical Parkinson's Disease Genes

PARK 14 (also known as Kufor-Rakeb syndrome) is a rare disease that manifests with Parkinsonism, pyramidal degeneration and dementia. Mutations in the *ATP13A2* gene encoding a lysosomal P-type ATPase have shown to segregate with the disease.[21]

Mutations in *PLA2G6*, a gene encoding a phospholipase A2 enzyme, have been shown to cause dystonia-parkinsonism, a rare disease in which the prominent features are Parkinsonism, dystonia, and cognitive features. Those affected are initially levodopa responsive but development of dyskinesia often occurs early.[22] *ATP13A2* and *PLA2G6* are also implicated in neurodegeneration with brain iron accumulation.[23]

FBXO7 on chromosome 22q12.3 has been shown to be responsible for early onset, autosomal recessive, Parkinsonian pyramidal syndrome.[24]

GENETIC RISK AND SUSCEPTIBILITY TO PARKINSON'S DISEASE

The advances in genotyping technologies have resulted in the identification of common variants that increase the risk of developing Parkinson's disease. In particular, there have been multiple GWAS over the past decade, which have successfully uncovered risk loci associated with the common form of the disorder. One such study conducted by the International Parkinson's Disease Genomics Consortium in 119,894 samples identified and replicated 28 independent variants for Parkinson's disease across 24 loci[25] that impart risk for the development of the disease (Table 2). One important point is that there is heterogeneity in the

TABLE 2: Loci and closest gene associated with Parkinson's disease genome-wide association studies

Locus	Top hit*	Nearest gene	Function/pathway#
2q21.3	rs6430538	*ACMSD*	Tryptophan metabolism, metal ion binding, metabolic pathways
16p11.2	rs14235	*STX1B*	Synaptic function, SNAP receptor activity, protein domain-specific binding
		BCKDK	Kinase activity
4p15	rs11724635	*BST1*	Immune system
12q24.31	rs11060180	*CCDC62*	Nuclear receptor coactivator, cancer pathways
20p13	rs8118008	*DDRGK1*	Protein binding
4q21.1	rs6812193	*FAM47E*	Autophagy-lysosomal degradation
		SCARB2	Autophagy-lysosomal degradation, receptor activity (lysosomal receptor for *GBA* targeting)
8p22	rs591323	*FGF20*	Growth factor activity, FGF receptor binding
1q21.2	rs35749011	*GBA*	Autophagy-lysosomal degradation
		SYT11	Synaptic function, metal ion binding, substrate for *PARK2*
14q22.1-q22.2	rs11158026	*GCH1*	GTP binding, calcium ion binding, BH4 metabolism, metabolic pathways
7p15	rs199347	*GPNMB*	Integrin binding, heparin binding, cancer pathways

Continued

Continued

Locus	Top hit*	Nearest gene	Function/pathway#
6p21.3	rs9275326a	*HLA-DQB1*	Inflammation/immune system
10q26.11	rs117896735	*INPP5F*	Phosphoric ester hydrolase activity
12q12	rs76904798	*LRRK2*	Kinase activity, protein kinase A binding
17q21.1	rs17649553	*MAPT*	Microtubule stabilization and axonal transport
3q27	rs12637471	*MCCC1*	Biotin carboxylase activity, methylcrotonoyl-CoA carboxylase activity, metabolic pathways
11q25	rs329648	*MIR4697*	–
1q32	rs823118	*RAB7L1*	Autophagy-lysosomal degradation
18q12.3	rs12456492	*RIT2*	Synaptic function, calmodulin binding, GTP binding
1q42.2	rs10797576	*SIPA1L2*	GTPase activator activity
4q22.1	rs356182	*SNCA*	Synaptic function
17p11.2	rs11868035	*SREBF1*	Chromatin binding, cholesterol and steroid metabolic processes
		RAI1	Protein binding
2q24.3	rs1474055	*STK39*	Inflammation/immune system, protein kinase binding, cellular stress response
4p16	rs34311866	*GAK*	Autophagy-lysosomal degradation, synaptic function, endocytosis
15q22.2	rs2414739	*VPS13C*	Endocytosis

SNAP, synaptosomal-associated protein; FGF, fibroblast growth factor; GTPase, guanosine triphosphatase.

Note: The top hits and nearest gene(s) identified by the most recent GWAS* for susceptibility to Parkinson's disease.

*Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet. 2014;46(9):989-93.

#Bras J, Guerreiro R, Hardy J. SnapShot: Genetics of Parkinson's disease. Cell. 2015;160(3):570- e1.

genes that confer risk between populations. The first large-scale GWA studies in the European population identified common variants associated with disease in *SNCA*, *MAPT*, *PARK16, LRRK2, GAK,* and interestingly, at the *HLA* locus,[26,27] possibly implicating the immune system in the etiology of the disease. However, in the Asian population, risk variants have been identified in *PARK16, LRRK2,* and *SNCA* but not in *MAPT*.[28] Overall each variant contributes a small effect on risk; however, multiple variants have a cumulative effect and thus a polygenic risk score can be calculated; increased scores have been associated with an earlier age of onset[29] and faster disease progression.[30]

GBA

The association between *GBA* and Parkinson's disease originated from the observation that patients with type 1 Gaucher disease displayed Parkinsonism[31] and that Gaucher disease carriers (harboring heterozygous variants that when bi-allelic

cause Gaucher disease) had a higher frequency of Parkinson's disease. Gaucher disease is the most prevalent autosomal recessive lysosomal storage disorder and is caused by homozygous or compound heterozygous mutations in the *GBA* gene, which encodes an essential lysosomal enzyme for glycolipid hydrolysis. Subsequently, a large number of studies have reported the association of variants in the *GBA* gene with Parkinson's disease patients making it the most significant genetic risk factor for the development of the disease seen to date. The frequency of heterozygous *GBA* mutations in Parkinson's disease patients of European populations (non-Ashkenazi Jewish descent) is between 2.3 and 9.8%, whereas in European Ashkenazi Jews it can be as high as 16.9–31.3%.[32] The most common *GBA* variants associated with Parkinson's disease are *p.L444P* and *p.N370S*; and the presence of a single mutation in *GBA* is estimated to increase the risk of the development of Parkinson's disease by more than fivefold.[33] *GBA* consists of 11 exons and is located on chromosome 1q21. Parkinson disease patients with *GBA* mutations are clinically indistinguishable from idiopathic Parkinson's disease cases; however, they present a slightly earlier age of onset and increased frequency of cognitive decline.

MAPT

Common genetic variability in the *MAPT* gene, encoding microtubule associated-protein tau, has been associated with susceptibility to Parkinson's disease. Tau protein is an abundant neuronal protein critical for microtubule stabilization which has long been implicated in neurodegenerative diseases such as Alzheimer's, PSP, and frontotemporal dementia (FTD). Remarkably, Parkinson's disease does not exhibit tau pathology and yet *MAPT* variability confers disease risk, whereas Alzheimer's disease commonly displays tau pathology but variability in *MAPT* is not a strong modulator of risk.

GCH1

Mutations in *GCH1* have been shown to cause young onset, dopa-responsive dystonia, and in some cases, adult-onset Parkinsonism. Through whole exome sequencing analysis in 1,318 Parkinson's disease cases, variants in *GCH1* were identified as a risk factor for Parkinson's disease.[34] *GCH1* plays a role in dopamine metabolism, and mutations in this gene are thought to result in severe impairment of dopamine production.

PATHOPHYSIOLOGY

The principal features of Parkinson's disease are the presence of LBs and the loss of dopaminergic neurons in the substantia nigra pars compacta. The Parkinson's disease brain has a 66% reduction[35] in the pigmented neurons of the SN, as demonstrated by the depigmentation of this region that is characteristic of Parkinson's disease pathology at autopsy. Dopaminergic neurons from the substantia nigra pars compacta innervate the striatum through the indirect and

direct pathways. In Parkinson's disease, the disruption of the nigrostriatal pathway due to death of dopaminergic neurons culminates in an excess of inhibitory input to the thalamus and results in reduced excitatory output to the cortex, leading to the classic symptoms of Parkinson's disease such as bradykinesia and rigidity.[36]

Aberrant Protein Homeostasis and Protein Aggregation

In order to maintain protein homeostasis and prevent the toxic build-up of proteins, systems such as the ubiquitin-proteasome system, autophagy, and chaperone-mediated autophagy pathways allow the cell to clear misfolded, damaged, or aggregated proteins. Aberrant protein aggregation is a common theme of neurodegenerative disorders and in the case of Parkinson's disease, intracellular aggregates of α-synuclein are present in LBs, suggesting that one or more of the mechanisms of protein turnover are dysfunctional in this disease.[37]

Indeed, α-synuclein has been shown to be degraded by all three mechanisms.[38] Furthermore, parkin, implicated in familial Parkinson's disease, is responsible for the ubiquitination of a variety of substrates destined for degradation by the proteasome and lysosome, hence dysfunctional parkin may lead to accumulation of its soluble or aggregated protein substrates and again implicates these systems in the pathogenesis of Parkinson's disease.

Ubiquitin-Proteasome System

The ubiquitin-proteasome system (UPS) was first implicated in Parkinson's disease pathophysiology through identification of genes such as *PARK2* that were involved in the UPS and were mutated in familial Parkinson's disease. Sporadic Parkinson's disease brains were shown to have SN proteasomes with an altered structure and reduced function[39] and a mouse model with SN-specific depletion of proteasomes showed SN degeneration with α-synuclein positive Lewy-like inclusions.[40] In addition, *LRRK2* and *SNCA* have been associated with proteasome inhibition—aggregated α-synuclein can inhibit proteasome activity by selectively binding a proteasomal protein[41] and *LRRK2* affects the ability of the proteasome to clear substrates.[42]

Chaperone-mediated Autophagy

Alpha-synuclein contains a chaperone-mediated autophagy (CMA) recognition motif and can be degraded by CMA. This is only the case for WT protein however, as the pathogenic *SNCA* mutants *p.A53T* and *p.A30P* appear to not only avoid degradation but also hinder proteolysis of other CMA substrates.[43]

Autophagy-Lysosome Pathway

Loss of autophagy in dopaminergic neurons results in degeneration, presynaptic accumulation of α-synuclein and *LRRK2,* and leads to locomotor dysfunction in

mice.[44] The overexpression of WT α-synuclein culminates in inhibition of autophagy and seems to occur early in autophagosome inhibition and could potentially demonstrate a pathological mechanism for gene dosage mutations in *SNCA*.[45]

The discovery of genetic variability in Parkinson's disease genes involved in lysosomal ceramide metabolism such as *GBA* and *PLA2G6* has provided a potential role for this pathway in LB diseases.[46] *GBA* encodes a lysosomal enzyme glucocerebrosidase (GCase) and mutations in this gene are hypothesized to predispose to Parkinson's disease by either impairing lysosome function, or by contributing to the accumulation of α-synuclein. Parkinson's disease patients with heterozygous *GBA* mutations were shown to have a 58% decrease in GCase activity in the SN and, interestingly, sporadic cases without *GBA* mutations also had a 33% decrease in GCase activity in this area.[47] *GBA* and α-synuclein exhibit an inverse relationship: lower GCase activity correlates with increased levels of α-synculein, and conversely, an increased load of α-synuclein results in reduced GCase activity.[48] It has been proposed that reduced Gcase activity may promote α-synuclein accumulation through impairment of the lysosome or ER stress. As such, GCase is currently being investigated as a potential therapeutic target for Parkinson's disease. It is believed that some GCase mutants are trapped in the endoplasmic reticulum, therefore, unable to be transported to the lysosome. Ambroxol, a drug used to treat respiratory infections, can act as a *GBA* chaperone to relieve this effect, and a recent study demonstrated ambroxol was able to increase GCase activity in *GBA*-mutant patient derived fibroblasts and reduce the amount of α-synuclein in an overexpressing cell line.[49]

Furthermore, the *SCARB2* gene, which has been recognized as a risk factor for Parkinson's disease by GWAS, encodes a lysosomal membrane protein involved in the transport of GCase to the lysosome. *SCARB2*-deficient mice had decreased GBA protein activity, α-synuclein accumulation and corresponding neurotoxicity to dopaminergic cells.[50] *GBA* and *SCARB2* are also risk factors for the development of DLB, suggesting these genes may play a considerable role in synucleinopathies. *ATP13A2* and *ATP6AP2*, genes causing autosomal and X-linked recessive parkinsonism are lysosomal enzymes, again implicating the lysosome in Parkinson's disease pathology. Loss-of-function mutations in *ATP13A2* result in impaired lysosomal function and increased levels of endogenous α-synuclein.[51] Mutations in *ATP13A2* also cause neuronal ceroid lipofuscinosis (NCL) that presents with mood disturbance, dysarthria, Parkinsonism, and displays lysosome dysfunction[52] further showing that the lysosome plays an important role in Parkinson's disease.

Mitochondrial Dysfunction

Complex 1 Inhibition

The first clue for mitochondrial dysfunction in Parkinson's disease came from the observation that mitochondrial complex 1 inhibitors can cause Parkinson's symptoms, albeit with the absence of LBs. 1-Methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), a contaminant of a synthetic opioid drug, is converted to MPP+,

which has a high affinity for DA transporters. Once in the dopaminergic neurons, MPP+ can inhibit complex 1 mediating neuronal cell death.[53] Rotenone causes parkinsonism in rats, and although it does not accumulate in dopaminergic neurons, it causes selective death of these neurons implying that they are particularly sensitive to this type of damage.[54] Further, complex 1 deficiency has been noted in some Parkinson's disease brains.[55]

Mitophagy

The mitochondria are turned over by mitophagy and dysfunction in this process had been linked to Parkinson's disease pathogenesis.[56] Damaged mitochondria generate oxygen radicals, the accumulation of which can cause further mitochondrial damage leading to cell death. Normal clearance of damaged mitochondria can protect cells. Evidence suggests that *PINK1, PARKIN*, and *DJ-1* interact to maintain mitochondrial quality control in the presence of oxidative stress.[57] These proteins are implicated in recessively inherited Parkinson's and as such, the pathological effects are suspected to arise from loss of function mutations, however, unexpectedly, the simultaneous knock out of all three genes did not lead to nigral degeneration in mice.[58] Upon mitochondrial depolarization, *PINK1* is stabilized and accumulates on the mitochondrial outer membrane. Here it recruits parkin[59] which ubiquitinates outer membrane proteins facilitating degradation by the proteasome to initiate mitophagy. It is not clear how DJ-1 is involved in mitophagy, but DJ-1 knockout flies have dysfunctional mitochondria and are able to rescue PINK1 loss of function, perhaps suggesting DJ-1 works in a parallel pathway.[60] The mutations in *PINK1* found in Parkinson's disease impair the recruitment of *PARKIN* and *PARKIN* mutants cannot support the clearance of impaired mitochondria.[61] *FBXO7* interacts directly with *PINK1* and *PARKIN* during mitophagy and *FBX07* deficiency abrogates *PARKIN* translocation to the mitochondria and impairs mitophagy.[62]

Recently, analysis of recessive early-onset Parkinson's disease families identified truncating mutations in the *VPS13C* gene, a member of the vacuolar sorting proteins involved in vesicle transport. The protein localizes to the mitochondrial surface, and *siRNA* silencing resulted in mitochondrial dysfunction. In addition, loss of *VPS13C* augmented *PINK1* and *PARKIN*-dependent mitophagy.[63] Cases with the truncating *VPS13C* mutations presented clinically with an early onset, severe disease progression, and diffuse LB pathology.[63] Interestingly, common variability in *VPS13C* has also been shown to modulate risk for disease by GWAS.

Prion Hypothesis

Prion proteins are infectious protein particles able to transform the conformation of normal α helical protein (Prpc) into an infectious structure rich in β-pleated sheets (PrPsc) with the ability to spread from cell-to-cell. In its native state, α-synuclein is monomeric and intrinsically unfolded. Alpha-synuclein can form pathological oligomer and fibrillar aggregates and within the LB, α-synuclein is hyperphosphorylated and forms fibrils rich in beta-pleated sheets. Recent evidence

showing that fibrillar α-synuclein injected both *in vitro* and *in vivo* can spread to unaffected areas of the brain have led to the protein being described as "prion-like".[64] It is postulated that these pathogenic fibrils act as seeds to convert monomeric α-synuclein to a "pathogenic" form.[64] Intrastriatal injection of synthetic α-synuclein fibrils into mice results in deposition of hyperphosphorylated α-synuclein in Lewy-like bodies and neuritis, and spread of the pathogenic α-synuclein to connecting neurons. The Lewy pathology mediates dopaminergic neuron loss in the SN leading to motor deficits.[65] Furthermore, LBs purified from postmortem of Parkinson's disease brains were injected into mouse and monkey SN and striatum where they elicited the conversion of intrinsic α-synuclein and caused nigrostriatal degeneration.[66]

DEMENTIA AND PARKINSON'S DISEASE

Parkinson's disease and Alzheimer's disease do not overlap in terms of genetic risk, which is interesting given the fact that a large proportion of Parkinson's disease cases go on to develop dementia (Parkinson's disease dementia, Parkinson's disease-D). Additionally, the existence of a third condition, dementia with LBs, a disease that shares clinical and pathological characteristics with both Parkinson's disease and AD, further suggests that these diseases may share some etiology.

It is well known that the clinical presentation of Parkinson's disease is heterogeneous. A significant amount of families with *SNCA* mutations display clinical features of dementia (incidence ranging from 39 to 80%, depending on the mutation), and in particular, all cases with *SNCA* triplications show cognitive decline.[67] Similarly, in a study analyzing Parkinson's disease patients for *GBA* mutations, 15/31 *GBA* mutant positive patients were reported to have dementia or cognitive decline,[68] and *GBA* mutations are associated with an increased risk of dementia in those with Parkinson's disease. Interestingly both genes have a strong lysosomal link suggesting that the occurrence of dementia in Parkinson's disease may be mediated by that pathway. This is even more evident when the results at *ATP13A2* and *SCARB2* are considered; both are lysosomal encoded proteins and both have been associated with dementia and Parkinsonism. There is now a strong body of evidence suggesting that lysosomal dysfunction may be pivotal for the development of dementia in parkinsonism.

FUTURE PERSPECTIVES

So far, the use of GWAS to identify loci and next generation sequencing and linkage to identify causal genes in sporadic and familial Parkinson's disease has resulted in a large amount of genes being implicated in Parkinson's disease pathogenesis. These methods have allowed us to gain a more robust overview of the genetic architecture of Parkinson's disease. From this, biological pathways and mechanisms hypothesized to contribute to pathophysiology have been uncovered, potentially allowing for therapeutic targets such as the lysosome to be investigated.

In addition, these genetic data have also been crucial in allowing us to more accurately diagnose neurological disease, for example in disparate diseases with similar or overlapping clinical features.

- Data suggest that there is missing genetic heritability in Parkinson's disease, and thus far we have only been able to account for approximately 30% of heritability, suggesting that there are still a considerable amount of Parkinson's disease related genes to be uncovered.[69] However, large-scale studies of common variability now face a law of diminishing returns, whereby significant increases in sample size only provide variants with minute effect sizes on disease. This, however, should not discourage these types of study; the identification of a weak effect on a novel pathway, or a novel member of a pathway can be of tremendous importance in providing us with novel therapeutic approaches. In addition, even in cases where no familial history is present, it is possible that *de novo* mutations are underlying these diseases,[70] suggesting that even in such cases, genetic analyses should be performed. Although there is currently no cure for Parkinson's disease, understanding the genes, and thus the mechanisms, involved in disease etiology is bringing us closer than ever before to developing a therapeutic approach to halt or even prevent this devastating disease.

KEY POINTS

- Hereditary Parkinson's disease only accounts for 5–10% of all Parkinson's disease cases and the majority of cases are sporadic, likely caused by a combination of genetic factors and environmental influences
- The principal features of Parkinson's disease are the presence of LBs and the loss of dopaminergic neurons in the substantia nigra pars compacta
- Although the exact cause of dopaminergic neuron loss in the substantia nigra pars compacta remains unclear, aberrant protein homeostasis (the ubiquitin-proteasome system, the lysosome and autophagic pathways), aberrant mitochondrial quality control, dopamine metabolism, and potentially the immune system are mechanisms that have been implicated in Parkinson's disease
- There is experimental support for the "prion hypothesis" as fibrillar a-synuclein injected both *in vitro* and *in vivo* can spread to unaffected areas of the brain have led to the protein being described as "prion-like".

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