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► **To cite this version:**

Suzanne Lesage, Alexis Brice. Role of mendelian genes in "sporadic" Parkinson's disease.. Parkinsonism and Related Disorders, Elsevier, 2012, 18 Suppl 1, pp.S66-70. 10.1016/S1353-8020(11)70022-0 . inserm-00807470

**HAL Id: inserm-00807470**

**<https://www.hal.inserm.fr/inserm-00807470>**

Submitted on 4 Apr 2013

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## Role of Mendelian genes in "sporadic" Parkinson's disease

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Number of references: 20

Number of figures: 1

Number of tables: 2

Number of words in the abstract: 182

Number of words in the main text: 1,975

## **ABSTRACT**

The molecular mechanisms underlying neuronal degeneration leading to Parkinson's disease (PD) remain unknown. However, it is becoming increasingly clear that genetic factors contribute to its complex pathogenesis. In the past 15 years, the genetic basis of rare forms of PD with Mendelian inheritance, which represent no more than 10% of the cases, has been investigated. More than 18 loci, identified through linkage analysis or genome wide association studies (GWAS), and eight validated genes have been identified so far [*parkin*, *PTEN-induced kinase 1 (PINK1)*, *DJ-1*, *ATP13A2*, *SNCA*, *Leucine-rich repeat kinase 2 (LRRK2)*, as well as two recently identified possibly causative genes, *VPS35* and *eukaryotic translation initiation factor 4G1 (EIF4G1)*]. Many studies have shed light on their implication not only in familial but also in sporadic forms of PD. Recent GWAS have provided convincing evidence that polymorphic variants in these genes also confer an increased risk for late-onset sporadic PD. In addition, heterozygous mutations in *GBA* have now been well-validated as susceptibility factors for PD. The role of the most relevant associated genes and risk factors in sporadic PD are discussed in this review.

## 1. Introduction

The pathology and physiopathology of Parkinson's disease (PD), a motor syndrome due to neurodegeneration of dopaminergic neurons in the *substantia nigra pars compacta*, are relatively well understood, but not the underlying cause. PD, thought to be mainly sporadic, caused by environmental factors, is now known to implicate genetic factors. Molecular genetics has identified genes linked to rare monogenic forms of PD with autosomal dominant (AD) or recessive (AR) inheritance. Although monogenic forms account for <10% of Mendelian cases, these genes also play a role in the much more common sporadic form of PD.

Much research, particularly during the last two years, has focused on genetic variability conferring susceptibility to sporadic PD. Variations in the same genes can be highly-penetrant mutations in Mendelian disease and risk factors for sporadic PD, linking the pathogenesis of familial and sporadic PD.

Since the first causal mutation was discovered in *SNCA*, 18 PD loci have been assigned through linkage analysis (PARK1-15) or genome-wide association studies (GWAS) (PARK16-18) (Tables 1&2). Two genes [*SNCA*/PARK1/4 and *Leucine-rich repeat kinase 2* (*LRRK2*)/PARK8] are conclusively associated with AD PD, and 4 [*parkin*/PARK2, *PTEN-induced kinase 1* (*PINK1*)/PARK6, *DJ-1*/PARK7, *ATP13A2*/PARK9] with early-onset AR PD [1]. Mutations in two other genes [*VPS35* and *eukaryotic translation initiation factor 4G1* (*EIF4G1*)], not yet assigned a PARK locus, segregate in large families with dominant late-onset PD [2-4]. Polymorphic variants in two PARK genes (*SNCA* and *LRRK2*) and in candidate genes such as microtubule-associated protein tau (*MAPT*), as well as rare mutations in the *glucocerebrosidase* gene (*GBA*) have also emerged as susceptibility factors in several populations. Genetic factors, therefore, confer a large proportion of the risk for rare Mendelian forms of PD and a modest proportion of risk in the vast majority of cases (Fig. 1).

## 2. Mendelian forms of PD

### 2.1. Dominant forms of PD

Although gain-of-function mutations in *SNCA*/PARK1/4 and *LRRK2*/PARK8 clearly cause AD PD, the effects of other dominant genes, such as *Ubiquitin-C terminal hydrolase L1* (*UCHL1*/PARK5), *GRB10-interacting GYF protein 2* (*GIGYF2*/PARK11), *Omi/Htra2* (PARK13), remain controversial; they have either not been replicated in other studies (*UCHL1*, *GIGYF2*) or appear to be risk factors (*HTRA2*).

After identification of *SNCA*,  $\alpha$ -synuclein was found to be the major fibrillar component of Lewy bodies, the pathological hallmark of familial and sporadic PD [5]. Two other *SNCA* point mutations, as well as whole gene duplications and triplications [6], have since been described, for an overall mutation frequency of ~1% in PD families compatible with AD inheritance. The phenotype of patients with *SNCA* mutations resembles sporadic PD, but with earlier onset and atypical features, including cognitive decline, psychiatric problems and autonomic dysfunction, in some cases. The same mutations have been found in “sporadic” PD patients, suggesting reduced penetrance or a significant frequency of *de novo* mutations.

The discovery of *LRRK2*, encoding a large 2,527 amino-acid multi-domain protein, was probably the most important step forward towards understanding the pathogenesis of PD since discovery of *SNCA*. *LRRK2* mutations are frequent in patients with typical, late-onset familial and sporadic PD. However, there are marked population-specific differences [7]: the *LRRK2* G2019S mutation, the most common, causes 4-5% of familial and 1-2% of sporadic PD in populations of European descent, 30-40% of both familial and sporadic PD in Arab patients from North Africa and 10-30% in Ashkenazi Jews, but is rare in Asians; two coding variants,

G2385R and R1628P, increase the risk of sporadic PD only in Asians; R1441G explains a large proportion of Basque cases; the last identified *LRRK2* mutation, R1437H, was found in two Norwegian families. Ethnicity may also affect penetrance; estimated lifetime penetrance of G2019S is ~30-60% by age 80 in Europeans, but as low as 14% in North Africans.

Reduced and age-related penetrance might explain the frequency of this mutation in “sporadic” cases and in some familial forms of PD with unclear patterns of inheritance, but also in rare controls including subjects over 80. Other genetic or environmental factors may, therefore, contribute to the phenotype in *LRRK2* carriers, which resembles sporadic PD with a good response to levodopa treatment, particularly in patients with the G2019S mutation.

## 2.2. Recessive forms of PD

One of the most important findings these last years was the high proportion of patients with early-onset parkinsonism caused by recessively inherited mutations. In addition to *parkin*/PARK2, *PINK1*/PARK6, and *DJ-1*/PARK7, *ATP13A2*/PARK9, initially associated with an atypical multisystemic phenotype, might also play a role in early-onset PD. Two other recessive genes (*PLA2G6*/PARK14, *FBXO7*/PARK15) were recently identified in a few patients with early-onset atypical parkinsonism. Since recessive inheritance manifests in offspring of unaffected parents with a frequency of 0.25, many cases appear to be “sporadic”, especially in small sibships. Most recessive alleles result in the absence of the encoded protein or an inactive protein, thus loss of function.

Mutations in *parkin* are the major cause of early-onset AR familial and sporadic PD in different ethnic groups. They account for ~50% of early-onset ( $\leq 40$  years) familial cases and ~20% of early-onset sporadic PD. More than 170 different mutations have since been

identified throughout the gene: large deletions or multiplications of one or more exons in more than 50% of the cases, small deletions/insertions, nonsense and missense mutations [8]. The frequency of *parkin* mutations decreases as age of onset increases, and are therefore uncommon in patients with late-onset PD. *Parkin* mutation carriers have a phenotype similar to that of “sporadic” patients, but also specific clinical features, including earlier and more symmetric onset, dystonia and hyperreflexia as the initial sign, a relatively benign disease course with slower disease progression, sleep benefit, better response to low doses of levodopa, but complicated signs with early motor fluctuations and development of dyskinesias [9].

Penetrance is generally complete in individuals with two disease-causing mutations in *parkin*, but the causative role of heterozygous mutations remains unclear since they are also detected in healthy individuals. *Parkin* heterozygotes might have an increased risk for PD [10]. <sup>18</sup>F-dopa PET showed striatal dopaminergic dysfunction in asymptomatic heterozygous mutation carriers; however, in the largest case-control study, mutation frequency was similar in both groups [11].

Homozygous and compound heterozygous mutations in ***PINK1*** are the second most frequent cause of AR early-onset parkinsonism (mutation frequency <1 to 15%). More than 50 *PINK1* mutations (point mutations, frameshifts, truncating and splice site mutations, deletion of the entire gene) have been reported [8]. In addition, *PINK1* mutations cause a significant percentage of sporadic early-onset parkinsonism (1-4%). *PINK1*-linked PD resembles idiopathic PD: good response to levodopa, frequently levodopa-induced dyskinesias, rarely dystonia. Many heterozygous putative pathogenic mutations were also

observed in familial and “sporadic” PD patients as well as in healthy controls. In a meta-analysis, heterozygous *PINK1* variants were equally common in controls and patients [12].

Recessively inherited *DJ-1* mutations are rare (<1% of early-onset parkinsonism). Both homozygous and heterozygous point mutations and exon deletions were found in different populations [8]. The associated phenotype, with early-onset and slow disease progression, seems comparable to that of *parkin* or *PINK1*. Although *DJ-1* is rare even in early-onset PD, it might play an important role in sporadic late-onset PD; the DJ-1 protein was oxidatively damaged and significantly increased in brains of “sporadic” PD patients [13].

### **3. Genetic risk factors for PD**

PD is rarely monogenic; the vast majority of cases may result from complex interactions among genes and/or environmental factors, stimulating the search for genetic susceptibility factors by allelic association analysis of candidate genes and, more recently, GWAS.

#### **3.1 Candidate gene approach**

Common polymorphisms are usually found by extensive screening of candidate genes in large series of patients. However, associations are not always replicated in follow-up studies, and few candidate genes have been confirmed in meta-analyses. Nevertheless, polymorphic variants in *SNCA*, *MAPT*, *LRRK2* and loss-of function mutations in *GBA* are emerging as susceptibility factors [14].



Haplotype analyses have found associations between sporadic PD and nucleotide polymorphisms in *SNCA* including the promoter, although much of the literature is equivocal. Meta-analyses including published studies and new data support an association of PD with variants in the promoter region and the 3' end of *SNCA*.

Common variability in *MAPT*, encoding the microtubule-associated protein tau, has been associated with progressive supranuclear palsy, Alzheimer's disease and, more recently, PD; the H1 haplotype, one of two common Caucasian haplotypes across the locus, confers risk with an odds ratio (OR) of ~1.5.

Beside *LRRK2* mutations that cause PD themselves, two common variants in *LRRK2* (G2385R and R1628P) appear to increase the risk of PD about two-fold, particularly in Asian populations.

Because of parkinsonism and Lewy body pathology in patients with the AR lysosomal storage disorder Gaucher's disease (GD) and their relatives, PD patients were screened for mutations in *GBA*, which, in the homozygous or compound heterozygous state, cause GD. Heterozygous *GBA* mutations have been found to increase the risk of PD in certain ethnic groups. However, the frequency of *GBA* mutations varies among populations; *GBA* mutations account for classical parkinsonism in ~30% of Jewish patients. These variants are more likely risk factors than highly penetrant causes. A recent large multi-centre study and the largest sequencing study of *GBA* in the French population definitely confirm that heterozygous *GBA* mutations increase of risk of PD >~5-fold [15,16].

### **3.2 Genome-wide association studies**

GWAS, an increasingly popular approach for identifying genetic factors influencing complex diseases, provide a powerful tool for finding low penetrance alleles undetectable by linkage.

Multiple GWAS in PD patients and controls have independently identified polymorphisms in the *SNCA*, *MAPT* and *LRRK2* regions as risk factors for idiopathic PD [17-19], confirming association with these genes. They also identified five new risk loci: a locus on 1q32 (PARK16); the *BST1* locus on 4p15 [17]; a locus on 12q24 [18]; the *GAK* (encoding cyclin G-associated kinase) locus on 4p16 (later designated PARK17) [19]; the *HLA* region on chromosome 6p (PARK18) [19]. A recent two-stage meta-analysis of over 12,000 cases and 21,000 controls from the United States and Europe and replication analyses of significantly associated loci in an independent series of more than 3,000 cases and 29,000 controls identified eight known (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK*, *LRRK2*, PARK16, and *FGF20*) and eight new loci (*ACMSD*, *STK39*, *MCCC1/LAMP3*, *SYT11*, *CCDC62/HIP1R*, *STX1B*, *STBD1* and *GPNMB*) [20]. The combined population-attributable risk across all identified loci was 60.3% and 25.6% for the *MAPT* and *SNCA* loci alone. Interestingly, the OR was 2.5 times higher in the highest quintile of disease risk than in the lowest.

#### **4. Conclusion**

Identification of the first causal missense mutation in AD PD triggered two decades of gene discovery and efforts to model parkinsonian neurodegeneration. Genetics now plays a much more important role in PD pathogenesis than previously thought. Studies of PD-linked genes have brought to light several pathways involved in neuronal death in the *substantia nigra* (protein aggregation, defects in the ubiquitin-proteasomal pathway, impaired defense against oxidative stress, abnormal protein phosphorylation, mitochondrial and lysosomal

dysfunction, apoptosis), thus improving our understanding of the more common sporadic form of the disease. “Sporadic” cases may, in fact, be monogenic as well, because a dominant mutation may have occurred *de novo* or has reduced penetrance, or because the mutation is recessive. This is important for genetic counseling; gene testing should be considered in “sporadic” patients, according to their age at onset and geographical/ethnic origin. Several dominant loci (common variants in *LRRK2*, *MAPT* and *SNCA*, and loss-of function mutations in *GBA*) have also been reliably identified as risk factors for sporadic PD.

Approximately 50% of recessive and probably more than 80% of dominant familial cases are caused by as yet unknown mutations, and only about half of the factors conferring risk of PD have been identified. The next challenge is to use new technological advances, such as high-throughput sequencing, to identify new genes that will enhance our knowledge of PD and orient future research.

**Table 1.** Genes/loci underlying monogenic parkinsonism

**Table 2.** Susceptibility genes/loci for PD

### **Figure legends**

Figure 1: Effect of genetic risk factors for PD as a function of their allele frequencies.

## **Conflict of interest**

The authors have no conflict of interest to declare.

## **Acknowledgements**

We thank Dr. Merle Ruberg for critical revision of the manuscript. Work in our laboratory was supported by the French National Agency of Research (<http://www.agence-nationale-recherche.fr>, ANR-08-MNP-012) and by the National Research Funding Agency (ANR-08-NEUR-004-01) in ERA-NET NEURON framework (<http://www.neuron-eranet.eu>)

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**Table 1.** Genes/loci underlying monogenic parkinsonism

PARK loci	Gene	Map position	Inheritance	Type of parkinsonism
<i>Well-validated</i>				
<i>loci/genes</i>				
PARK1/PARK4	<i>SNCA</i>	4q21	Dominant;  Rarely sporadic	EOPD
PARK2	<i>parkin</i>	6q25-q27	Recessive;  sporadic	Juvenile and EOPD
PARK6	<i>PINK1</i>	1p35-p36	Recessive	EOPD
PARK7	<i>DJ-1</i>	1p36	Recessive	EOPD
PARK8	<i>LRRK2</i>	12q12	Dominant;  sporadic	LOPD
PARK9	<i>ATP13A2</i>	1p36	Recessive	Kuffor-Rakeb syndrome
Not assigned	<i>VPS35</i>	16q11.2	Dominant;  sporadic	LOPD
Not assigned	<i>EIF4G1</i>	3q27.1	Dominant	LOPD

*Putative*

*loci/genes*

PARK3	Unknown	2p13	Dominant	LOPD
PARK5	<i>UCHL1</i>	4p14	Dominant	LOPD
PARK10	Unknown	1p32	Unclear	LOPD
PARK11	<i>GIGYF2</i>	2q36-q37	Dominant	LOPD
PARK12	Unknown	Xq21-q25	Unclear	Not clear
PARK13	<i>Omi/HTRA2</i>	2p12	Unclear	Not clear
PARK14	<i>PLA2G6</i>	22q12-q13	Recessive	Juvenile levodopa-responsive dystonia-parkinsonism
PARK15	<i>FBXO7</i>	22q12-q13	Recessive	Early-onset parkinsonian pyramidal syndrome

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*SNCA*,  $\alpha$ -synuclein; *PINK1*, PTEN-induced kinase 1; *LRRK2*, Leucine-Rich Repeat Kinase 2;

*UCHL1*, ubiquitin carboxyterminal hydrolase 1; *GIGYF2*, GRB10-interacting GYF protein 2;

*EIF4G1*, eukaryotic translation initiation factor 4G1.



**Table 2. Susceptibility genes/loci for PD**

PARK loci	Gene	Map position	Risk variants	Estimated odds ratio (OR)
<i>Well-validated</i>				
<i>loci/genes</i>				
PARK1/PARK4	<i>SNCA</i>	4q21	Promoter Rep1 5' and 3' variants	1.2-1.4
PARK8	<i>LRRK2</i>	12q12	G2385R, R1628P (Asians)	2-3
Not assigned	<i>MAPT-linked</i> <i>FTDP-17</i>	17q21.1	H1 haplotype (Europeans)	1.4
Not assigned	<i>GBA-linked</i> <i>GD</i>	1q21	>300 heterozygous mutations	>5
<i>Putative</i>				
<i>loci/genes</i>				
PARK16	Unknown	1q32	Multiple SNPs from GWAS	1.3-1.4
PARK17	<i>GAK</i>	4p16	Multiple SNPs from GWAS	1.1-1.5
PARK18	<i>HLA-DRA</i>	6p21.3	Multiple SNPs from	1.3

			GWAS	
Not assigned	<i>BST1</i>	4p15	Multiple SNPs from	0.9-1.2
			GWAS	
Not assigned	<i>FGF20</i>	8p22	Multiple SNPs from	0.9
			GWAS	
Not assigned	<i>ACMSD</i>	2q21	Multiple SNPs from	1.1
			GWAS	
Not assigned	<i>STK39</i>	2q24	Multiple SNPs from	1.1
			GWAS	
Not assigned	<i>MCCC1/</i>	3q27	Multiple SNPs from	0.9
	<i>LAMP3</i>		GWAS	
Not assigned	<i>SYT11</i>	1q22	Multiple SNPs from	1.2
			GWAS	
Not assigned	<i>CCDC62/</i>	12q24	Multiple SNPs from	1.1
	<i>HIP1R</i>		GWAS	
Not assigned	<i>STX1B</i>	16p11	Multiple SNPs from	1.1
			GWAS	
Not assigned	<i>STBD1</i>	4q21	Multiple SNPs from	0.9
			GWAS	
Not assigned	<i>GPNUMB</i>	7p15	Multiple SNPs from	0.9

## GWAS

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*LRRK2*, Leucine-Rich Repeat Kinase 2; *MAPT*, microtubule-associated protein tau; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; *GBA*, glucocerebrosidase; GD, Gaucher's disease; *GAK*, cyclin G-associated kinase.