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Update on Genetics of Parkinsonism

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Key Words
Genetics · Parkinsonism · *SNCA* · *PRKN* · *LRRK2* · *GBA* · *eIF4G1* · *VPS35*

Abstract
Background: Major progress in genetic studies of Parkinson's disease (PD) and parkinsonism has been achieved in the last two decades. ***Objective:*** We provide a brief review of the current status of PARK and non-PARK loci/genes, and discuss two new genes: *eIF4G1* and *VPS35*. ***Methods:*** The literature on PARK and non-PARK loci/genes was reviewed and some novel information on two new genes is provided. ***Results:*** There are 18 PARK loci. The symptomatic carriers of these genes usually present with parkinsonism, although additional clinical features can be seen during the course of the disease. Carriers of non-PARK loci/genes frequently present with a mixed phenotype that includes parkinsonism and additional clinical features. Carriers of the *eIF4G1* and *VPS35* genes present with a parkinsonian phenotype. The pathology of *eIF4G1* is of the α-synuclein type; the pathology of *VPS35* is unknown. ***Conclusion:*** The current genetic classification of PD/parkinsonism genes is not ideal. The pathological classification based on the accumulation of particular proteins/inclusions is also misleading since there are kindred with a single mutation but pleomorphic pathology. A better classification of neurodegenerative conditions is needed. It is hoped that the genetic studies will lead to better therapies.

A number of loci/genes associated with Parkinson's disease (PD) and parkinsonism have been discovered. They can be artificially grouped into two broad categories: PARK and non-PARK. We will discuss these, as well as newly discovered PD genes.

PARK Loci/Genes

There are 18 PARK loci currently described (table 1), with 5 confirmed pathogenic PD genes, i.e. *SNCA*, *PRKN*, *LRRK2*, *PINK1*, and *DJ1* associated with a more or less typical parkinsonian phenotype in the majority of affected gene carriers [1, 2]. *SNCA* and *LRRK2* are autosomal dominant and *PRKN*, *PINK1*, and *DJ1* are autosomal recessive [3]. The other 13 PARK loci/genes are either provi-

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Table 1. PARK loci/genes

	Gene	Locus	Inheritance
PARK1/4	*SNCA*	4q22.1	AD
PARK2	*PRKN*	6q26	AR
PARK3	–[a]	2p13	AD
PARK5	*UCHL1*[a]	4p13	AD
PARK6	*PINK1*	1p36.12	AR
PARK7	*DJ1*	1p36.23	AR
PARK8	*LRRK2*	12q12	AD
PARK9	*ATP13A2*	1p36.13	AR
PARK10	–[a]	1p32	AD
PARK11	*GIGYF2*[a]	2q37.1	AD
PARK12	–[a]	Xq21-q25	X-linked
PARK13	*Omi/HtrA2*[a]	2p13.1	AD
PARK14	*PLA2G6*[a]	22q13.1	AR
PARK15	*FBXO7*[a]	22q12.3	AR
PARK16	–[a]	1q32	–
PARK17	*GAK*[b]	4p16	–
PARK18	*HLA-DRA*[b]	6p21.3	–

SNCA = α-Synuclein; *PRKN* = parkin; *UCHL1* = ubiquitin carboxyl-terminal esterase L1; *PINK1* = PTEN-induced putative kinase 1; *LRRK2* = leucine-rich repeat kinase 2; *ATP13A2* = ATPase type 13A2; *GIGYF2* = Grb10-interacting GYF protein 2; *HtrA2* = HtrA serine peptidase 2; *PLA2G6* = phospholipase A2, group 6; *FBXO7* = F-box protein 7; *GAK* = cyclin G-associated kinase; *HLA-DRA* = major histocompatibility complex, class II, DR α; AD = autosomal dominant; AR = autosomal recessive.

[a] Provisional loci/genes awaiting further confirmation. [b] Provisional loci/genes identified through the recent genome-wide association studies also awaiting further confirmation.

sional or clinically associated with atypical parkinsonism. The *LRRK2* and *PRKN* mutations are the most prevalent [4, 5]. The *SNCA* and *LRRK2* mutations are pathologically characterized by α-synuclein deposition, albeit in some *LRRK2* cases, tau and TDP-43 pathologies were identified [6]. The knowledge about the pathology of *PRKN, PINK1,* and *DJ1* is limited due to a small number of examined gene carriers, and therefore awaits further detailed assessments.

Non-PARK Loci/Genes

Table 2 summarizes the current status of non-PARK loci/genes associated with the parkinsonian phenotype in some affected cases. However, it should be emphasized that in the majority of these cases, the clinical phenotype is usually dominated by other signs such as ataxia, chorea, dystonia, and/or dementia. The mode of inheritance varies and can be autosomal dominant, autosomal recessive, X-linked, or mitochondrial. Parkinsonism is most consistently seen in spinocerebellar ataxia type 3, spinocerebellar ataxia type 12, frontotemporal dementia with parkinsonism linked to chromosome 17 with tau pathology and in Perry syndrome [7–9]. The pathology varies depending on the specific gene.

Newly Identified PD Genes

Recently, several genes associated with PD (some are listed in table 3) have been identified; among them, *GBA* mutations are the most prevalent, particularly in the Ashkenazi Jewish population [10]. Very little is known about the prevalence of the *eIF4G1* and *VPS35* genes but inheritance is autosomal dominant [11, 12]. Both genes, *eIF4G1* and *VPS35,* have been identified only in few families, but these families are from different European and North American countries [11–13]. The phenotype is consistent with levodopa-responsive PD, but in some cases dementia is present. The pathology of *eIF4G1* is of the α-synuclein type. To date, the pathology of *VPS35* is relatively unknown.

Table 2. Non-PARK loci/genes

Disease/syndrome	Gene	Locus	Inheritance
SCA2	*SCA 2*	12q24.12	AD
SCA3	*SCA 3*	14q32.12	AD
SCA12	*PPP2R2B*	5q32	AD
SCA17	*TBP*	6q27	AD
SCA21	–	7p21.3-p15.1	AD
DYT5/DYT14	*GCH1*	14q22.2	AD
DYT12	*ATP1A3*	19q13.2	AD
FTDP-17T	*MAPT*	17q21.31	AD
FTDP-17U	*PGRN*	17q21.31	AD
FTD-3	*CHMP2B*	3p11.2	AD
FTD	*FUS*	16p11.2	AD
9p-linked FTD/ALS	*C9ORF72*	9p21.2	AD
Perry syndrome	*DCTN1*	2p13.1	AD
Neuroferritinopathy	*FTL*	19q13.33	AD
Huntington disease	*HTT*	4p16.3	AD
DYT5	*TH*	11p15.5	AR
DYT16	*PRKRA*	2q31.2	AR
SPG11	*Spatacsin*	15q21.1	AR
Wilson's disease	*ATP7B*	13q14.3	AR
Niemann-Pick disease	*NPC1*	18q11.2	AR
PKAN	*PANK2*	20p13	AR
DYT3	*TAF1, TAF1/DYT3*	Xq13.1	X-linked
Fragile X tremor ataxia syndrome	*FMR1*	Xq27.3	X-linked
Complex 1	*ND4*	–	mitochondrial

SCA = Spinocerebellar ataxia; DYT = dystonia; FTDP-17T = frontotemporal dementia with parkinsonism linked to chromosome 17 with tau pathology; FTDP-17U = frontotemporal dementia with parkinsonism linked to chromosome 17 with ubiquitin pathology; FTD-3 = frontotemporal dementia linked to chromosome 3; FTD = frontotemporal dementia; 9p-linked FTD/ALS = chromosome 9p-linked frontotemporal dementia/amyotrophic lateral sclerosis; SPG = spastic paraplegia; PKAN = pantothenate kinase-associated neurodegeneration; *PPP2R2B* = protein phosphatase 2, regulatory subunit B, β; *TBP* = TATA box-binding protein; *MAPT* = microtubule-associated protein tau; *PGRN* = progranulin; *CHMP2B* = chromatin modifying protein 2B; *FUS* = fused in sarcoma; *DCTN1* = dynactin 1; *FTL* = ferritin light chain; *HTT* = huntingtin; *TH* = tyrosine hydroxylase; *PRKRA* = protein kinase, interferon-inducible double-stranded RNA-dependent activator; *ATP7B* = ATPase, Cu^{2+} transporting, β-polypeptide; *NPC1* = Niemann-Pick disease type C1; *PANK2* = pantothenate kinase 2; *TAF1* = TATA box-binding protein-associated factor 1; *FMR1* = fragile X mental retardation 1; *ND4* = NADH dehydrogenase, subunit 4; AD = autosomal dominant; AR = autosomal recessive.

Table 3 . Newly discovered genes associated with PD

Disease	Gene	Locus	Inheritance
PD	*GBA*	1q21	AD
PD	*eIF4G1*	3q27	AD
PD	*VPS35*	16q12	AD

GBA = Glucosidase, β, acid; *eIF4G1* = eukaryotic translation initiation factor 4-γ protein 1; *VPS35* = vacuolar protein sorting 35; AD = autosomal dominant.

Conclusion

The field of the genetics of PD/parkinsonism is evolving at a high speed. There will be many more genes identified as studies progress. For example, the Mayo Clinic Florida collection of PD/parkinsonism families contains more than 800 kindred, but the genetic defect for the majority of them is unknown. The current classification of PD loci and genes based on PARK and non-PARK categories is misleading and imprecise. It does not reflect the clinical presentation of certain gene carriers (for example, carriers of the PARK9/*ATP13A2* gene present at a very early age and with a mixed phenotype consistent with atypical parkinsonism). The current pathological classifications based on protein product/inclusion accumulation in the brain are also imprecise since there are cases from the same family, carriers of the same genetic mutation (for example, *LRRK2,* R1441C or I2020T), that have pleomorphic pathology. Therefore, better classifications of the neurodegenerative conditions associated with a parkinsonian phenotype need to be devised. We hope that therapeutic interventions will be forthcoming based on the identification of these genes.

Note Added in Proof

C9ORF72 gene mutation has recently been identified for 9p-linked FTD/ALS. Dejesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R: Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 2011;72:245–256.

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