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Review

Monogenic Parkinson's disease and parkinsonism: Clinical phenotypes and frequencies of known mutations

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ABSTRACT

Mutations in seven genes are robustly associated with autosomal dominant (*SNCA*, *LRRK2*, *EIF4G1*, *VPS35*) or recessive (*parkin*/*PARK2*, *PINK1*, *DJ1*/*PARK7*) Parkinson's disease (PD) or parkinsonism. Changes in a long list of additional genes have been suggested as causes for parkinsonism or PD, including genes for hereditary ataxias (*ATXN2*, *ATXN3*, *FMR1*), frontotemporal dementia (*C9ORF72*, *GRN*, *MAPT*, *TARDBP*), DYT5 (*GCH1*, *TH*, *SPR*), and others (*ATP13A2*, *CSF1R*, *DNAJC6*, *FBXO*, *GIGYF2*, *HTRA2*, *PLA2G6*, *POLG*, *SPG11*, *UCHL1*). This review summarizes the clinical features of diseases caused by mutations in these genes, and their frequencies. Point mutations and multiplications in *SNCA* cause cognitive or psychiatric symptoms, parkinsonism, dysautonomia and myoclonus with widespread alpha-synuclein pathology in the central and peripheral nervous system. *LRRK2* mutations may lead to a clinical phenotype closely resembling idiopathic PD with a puzzling variety in neuropathology. Mutations in *parkin*/*PARK2*, *PINK1* or *DJ1*/*PARK7* may cause early-onset parkinsonism with a low risk for cognitive decline and a pathological process usually restricted to the brainstem. Carriers of mutations in the other genes may develop parkinsonism with or without additional symptoms, but rarely a disease resembling PD. The pathogenicity of several mutations remains unconfirmed. Although some mutations occur with high frequency in specific populations, worldwide all are very rare. The genetic cause of the majority of patients with sporadic or hereditary PD remains unknown in most populations. Clinical genetic testing is useful for selected patients. Testing strategies need to be adapted individually based on clinical phenotype and estimated frequency of the mutation in the patient's population.

1. Introduction

The first mutation causing Parkinson's disease (PD) was discovered in the *SNCA* gene in 1997 [1]. Since then, intensive research efforts have established a total of seven genes containing causal mutations for parkinsonism clinically resembling PD, with autosomal dominant or recessive modes of inheritance. For mutations in at least 19 additional genes, a disease-causing role was postulated (Table 1), but subsequent studies either could not confirm that mutations in these genes are associated with parkinsonism or PD, or showed that they in most or all cases cause a clinical phenotype that is clearly distinguishable from PD. This article reviews the present knowledge on these monogenic disorders, with an emphasis on their clinical phenotype and their frequency.

2. Dominant PD genes

Today, there is good evidence that mutations in four dominant PD genes may cause parkinsonism. The first two, *SNCA* and *LRRK2*, have been studied in detail, whereas *EIF4G1* and *VPS35* have only been identified recently (Table 2).

2.1. SNCA

Three pathogenic point mutations as well as genomic duplications and triplications are known in the gene encoding alpha-synuclein (*SNCA*). The first point mutation, A53T (p.Ala53Thr, c.209G>A) was discovered in 1997 in members of the large Italian-American Contursi kindred [2] and in three families from Greece [1]. A very similar clinical phenotype had been described in the

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Table 1
Overview of genes containing causal mutations robustly associated with PD or parkinsonism, and those genes containing mutations whose common clinical phenotype is very different from PD or that were initially associated with PD but not confirmed.

Genes containing mutations robustly associated with PD/ parkinsonism:	
Autosomal dominant	Autosomal recessive
SNCA (*PARK1*, *PARK4*)	*PARKIN* (*PARK2*)
LRRK2 (*PARK8*)	*PINK1* (*PARK6*)
VPS35	*DJ1* (*PARK7*)
EIF4G1	

Genes containing mutations associated with non-PD disorders that may present with parkinsonism:		
Autosomal dominant	Autosomal recessive	X-linked
ATXN2	*ATP13A2* (*PARK9*)	*FMR1*
ATXN3	*DNAJC6*	
GCH1	*TH*	
GRN	*SPG11*	
MAPT		

Genes containing mutations associated with non-PD disorders that may include parkinsonism, but do not present with parkinsonism only:		
Autosomal dominant	Autosomal recessive	Dom. or rec.
C9ORF72	*PLA2G6* (*PARK14*)	*POLG*
CSF1R		

Genes containing mutations initially suggested to cause PD, but unconfirmed:	
Autosomal dominant	Autosomal recessive
GIGYF2 (*PARK11*)[a]	*FBXO7* (*PARK15*)
HTRA2 (*PARK13*)[b]	*SPR* (*PARK3 locus*)
UCHL1 (*PARK5*)[c]	

Gene names are given according to present day usage. Prior to the discovery of the genes, the genetic loci or postulated disease-associated genes within these loci were designated PARK-loci; PARK designations are provided in parentheses. Variants within several of these genes or loci modify the risk to develop PD or parkinsonism, but this property is outside the scope of this review article.
Dom.: dominant; rec.: recessive.
[a] Mutations in *GRB10-interacting GYF protein 2* (*GIGYF2*, *PARK11*) were found in PD families in 2008 [134], but subsequent studies found mutations in controls or not co-segregating with the PD phenotype in families [135–141].
[b] Mutations in *HtrA serine peptidase 2* (*HTRA2*, *Omi/HtrA2*, *PARK13*) were found in another German family [142], but mutations were subsequently also identified in healthy control subjects [143,144]. An extensive multicenter study from the GEO-PD consortium did not find any more cases among 6378 PD patients [145].
[c] A mutation in *ubiquitin carboxyl-terminal esterase L1* (*ubiquitin thiolesterase*, *UCHL1*, *PARK5*) was found in one German PD family in 1998 [146]. It has not been reported since in monogenic PD.

Greek-American Family H [3], which was soon found to harbor the same mutation [4]. Subsequently, the A53T mutation was identified in a number of families of Greek origin, with a regional common founder haplotype [5–7]. A Korean family with a different haplotype [8,9] was reported, as well as one sporadic case of Polish origin [10]. The mutation occurred *de novo* within a Swedish family [11].

In 1998, the A30P (p.Ala30Pro, c.88G>C) mutation was identified in one German family with three clearly affected members and two additional mutation carriers who only showed subtle neurological symptoms [12,13]. The E46K (p.Glu46Lys, c.188G>A) mutation was found in 2004 in one large kindred with 5 affected individuals spanning two generations [14]. The family originates from the Basque region in Northern Spain. The phenotype is characterized by fluctuating impairment of frontal lobe functions, memory dysfunction and parkinsonism as initial symptoms, and subsequent development of profound dementia [15]. The severity of the clinical symptoms and the response to levodopa were variable [14], and studies of mutation carriers without PD symptoms revealed sleep abnormalities [16] and cardiac sympathetic denervation [17]. Despite extensive efforts in many genetic screening studies, the A30P and E46K mutations have not been reported from any other family worldwide.

Triplications of the *SNCA* genomic locus in families with parkinsonism were reported in 2003 [18] and duplications in 2004 [19,20]. In contrast to the rare occurrence of A53T, A30P and E46K point mutations, these multiplications in *SNCA* have meanwhile been reported from 31 families worldwide [18,19,21–24].

The clinical phenotype of PD patients with *SNCA* mutations (including multiplications) has certain characteristics. Besides the cardinal signs of parkinsonism, most patients develop severe autonomic dysfunction, speech problems, behavioral changes, and cognitive decline. In the early stages, levodopa usually improves those PD symptoms that commonly respond. Advanced disease is often characterized by marked rigidity that cannot be alleviated with levodopa, dementia to the point of mutism, and cortical myoclonus. The neuropathology of patients with *SNCA* mutations is highly characteristic with widespread alpha-synuclein deposits not only in the brainstem but in the entire cerebrum, predominantly located in neurons but also found in glial cells [25].

2.2. LRRK2

In 2004, two groups simultaneously reported the discovery of mutations in the *leucine-rich repeat kinase 2* (*LRRK2*, *dardarin*) gene in PD [26,27]. The original families include Family A, from Northern Germany, Denmark and Canada, where a Y1699C (p.Tyr1699Cys, c.5096A>G) mutation was found [26], Family D from Western Nebraska with R1441C (p.Arg1441Cys, c.4321C>T) [26], 4 families from the Basque region of Spain with R1441G (p.Arg1441Gly, originally reported as R1396G, c.4321C>G) and 1 family from the United Kingdom also with Y1699C (originally reported as Y1654C) [27]. Other mutations include I2020T (p.Ile2020Thr, c.6059T>C) [26] that is responsible for familial PD a large kindred from Sagamihara in Japan [28,29], R1441H (p.Arg1441His, c.4322G>A) which was only found in a few families worldwide [30–33], and N1437H (p.Asn1437His, c.4309A>C) that was discovered in two Norwegian families [34] and in one patient from Sweden [35]. With the exception of R1441G, all the mutations mentioned above are rare. The R1441G mutation was found in more than 8% of patients with familial PD from the Basque population [36], where a common founder haplotype was identified [37]. Only one carrier with this mutation on a different haplotype is known [38].

By contrast, the LRRK2 G2019S mutation (p.Gly2019Ser, c.6055G>A) [39] is the most common PD-associated mutation known today. In two widely cited studies, LRRK2 G2019S was reported in 41% of sporadic and 37% of familial PD patients (and in 3% of healthy controls) from the North African Arab population [40], and in 18.3% of Ashkenazi Jewish PD patients (and 1.3% of controls) [41]. It soon became clear that a common founder haplotype explains the accumulation in these populations [42], and that G2019S is quite rare in other populations. About 0–2% of PD patients in other countries carry this mutation [43]; in Europe there is a clear South-to-North gradient. In a recently published international multicenter study, only 49 of 8371 (0.58%) PD patients of European and Asian origin carried a LRRK2 G2019S mutation [44].

Nevertheless, the large number of PD patients with the LRRK2 G2019S mutation allowed for a clear description of the clinical phenotype attributed to a single mutation in a PD gene, and for statistical analyses [45]. Based on data from 1045 patients with this mutation, motor symptoms and non-motor symptoms of *LRRK2* PD