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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

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these genes and their frequency. 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.

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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.

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.

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 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].

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 8,371 (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 1,045 patients with this mutation, motor symptoms and non-motor symptoms of *LRRK2* PD were more benign than those of a control group of patients, for example the risk for dementia was lower [45]. However, these findings remain uncertain [46] and need to be interpreted in light of the fact that that study's control group consisted of PD patients collected in a brain bank, which may not reflect the average idiopathic PD population. Penetrance is age-dependent and incomplete [45], illustrated by reports of healthy 91 and 95 year old mutation carriers [47, 48].

Clinical data regarding the other, rarer *LRRK2* mutations are available from descriptions of a limited number of cases and families per mutation. It appears probable that the mutations' biological effects are slightly different, as the clinical phenotype can be more or less severe and reported ages at onset vary between the mutations, albeit with a large overlap [49]. Seven

mutations in *LRRK2* are now considered definitively pathogenic for PD (Table 2) [44].Some patients had a distinct subtype of PD with additional features such as amyotrophy [26] or severe dystonia [35]. The role of *LRRK2* mutations in patients with PSP, FTLD-U or Alzheimer's disease [32, 50, 51] remains uncertain.

The neuropathology of patients with *LRRK2* mutation is highly variable, neuropathological findings from 49 patients with *LRRK2* mutation revealed a majority with alpha-synuclein positive pathology, but several other types of pathology also occurred [25, 35, 52].

VPS35

In 2011, the D620N (p.Asp620Asn, c.1858G>A) mutation in *vacuolar protein sorting 35 (VPS35)* was discovered in a previously described Swiss parkinsonism family [53, 54]. A report on three Austrian families with the identical mutation, immediately confirmed the finding [55]. The mutation was present in one family each from the United States and Tunisia, and in one family and one sporadic patient of Yemenite Jewish origin [53]. Analyses of the entire gene sequence revealed one family from the United States with a P316S (p.Pro316Ser, c.946C>T) mutation, but the pathogenicity of this mutation remains uncertain [53].

The presentation in the Swiss D620N kindred is that of tremor-dominant parkinsonism with a mean age at onset of 51 years. Learning disabilities requiring special schools, psychosis, and dementia have been described [54]. An incomplete neuropathological examination of only parts of the cortex and basal ganglia (but not the brainstem) did not reveal any alpha-synuclein immunoreactivity in these areas [54]. Penetrance was incomplete with the oldest reported unaffected carrier at 86 years [53]. Late-onset PD was reported in the Austrian family, one member had only developed depression and tremor with a pathological DATscan indicating incipient PD [55].

Meanwhile, other groups have been able to replicate the disease-association and familial co-segregation of the D620N mutation. It was found in 3 of 246 French patients with familial PD without cognitive deficits [56], in a large pedigree from the United Kingdom [57], where the clinical features included muscle spasms, depression, and cognitive decline, and an age at onset between 40 and 52 years of age, in seven PD patients in an international multicenter study [58], in four Japanese proband [59] and one German patient [60]. Given the prevalence of D620N of 0.14% among PD patients in the two initial studies and of 0.4% in the multicentre study [58], and the fact that replication studies in Belgium [61] or China [62] have not identified additional cases, this mutation is rare.

EIF4G1

Five mutations in this gene, encoding eukaryotic translation initiation factor 4-gamma 1, were described in PD patients in 2011 [63]. Co-segregation of a mutation with disease could only be demonstrated for the p.R1205H mutation, found initially in a French family and subsequently in patients from the USA, Canada, Ireland, Italy, and Tunisia [63]. The clinical phenotype was that of mild PD with a late age of onset (50-80, mean 64 years) and preserved cognition, but this is based on the few patients described. The initial report also found the mutations A502V (c.1505C>T, p.Ala502Val), G686C (c.2056G>T, p.Gly686Cys), S1164R (c.3490A>C, p.Ser1164Arg), R1197W (c.3589C>T, p.Arg1197Trp) in PD patients. Meanwhile, the G686C mutation was identified again in an isolated French PD patient, whereas the A502V, R1197W and the R1205H variants were found in unaffected control subject [56, 64, 65].

Neuropathology of patients with A502V, G686C, and R1197W mutations showed diffuse Lewy body disease [63]. Concomitant Alzheimer pathology was present in a family with dementia and parkinsonism who had both G686C and R1197W mutations [66]. Frequencies

of these mutations in populations of European or African descent are very low, between 0.2% for the R1205H mutation and 0.02% for A502V [63, 65]. It may be too early to decide which mutations in *EIF4G1* truly are disease-causing [56].

Other dominant and x-linked disorders that may present with parkinsonism

Trinucleotide expansions in *ATXN2* (*ataxin-2*) or *ATXN3* (*ataxin-3*) usually cause spinocerebellar ataxia that may include parkinsonian features. There are reports of families with expansions in these genes who had a pure parkinsonian phenotype, without other neurological signs, at least during the years following the initial presentation of the disease [67, 68]. A parkinsonian phenotype was also described with borderline *ATXN2* trinucleotide repeat lengths when the normal CAG repeat sequence was interrupted by CAA segments [68, 69].

Depending on their length, trinucleotide repeat expansions in the *FMR1* gene (*fragile X mental retardation protein, FMRP; FRAXA*) on the x-chromosome may cause different phenotypes. Premutations (55-200 CGG repeats) are relatively common and can be found in an estimated 1:800 males and 1:250 females; frequencies are higher in mediterranean populations. Men with premutations may develop the fragile X tremor/ataxia syndrome (FXTAS), typically characterized by adult-onset tremor, ataxia, neuropathy, autonomic dysfunction, cognitive decline, behavioral changes with apathy, disinhibition or irritability, and depression. Parkinsonism may form part of FXTAS, and the initial presentation may be levodopa-responsive parkinsonism indistinguishable from PD [70]. However, close examination frequently reveals signs of atypical parkinsonism [71].

Mutations in *microtubule-associated protein tau* (*MAPT*) cause frontotemporal dementia with or without parkinsonism and with tau pathology [72]. Some of the individuals with

pathogenic *MAPT* mutations present with parkinsonism; signs of frontotemporal dementia may occur years later [73]. Among the large number of known mutations in *MAPT*, predominantly the N279K mutation and intronic mutations may cause a parkinsonistic phenotype. This is usually an atypical parkinsonian syndrome, with the cardinal signs of PD (with or without tremor at rest), but often an unsatisfactory response to levodopa, corticospinal tract signs, vertical gaze palsy and disturbance of saccades, or unilateral dystonia and contractures [74].

Mutations in *granulin precursor* (*GRN*; *progranulin, PGRN*) cause frontotemporal lobar degeneration with tau-negative, ubiquitin- and TAR DNA-binding protein 43 (TDP43)-positive inclusions [75]. Parkinsonism occurs in many patients with *GRN* mutations, but usually late in the disease and only after the development of frontotemporal dementia [76]. In rare patients, parkinsonism has been the presenting or predominant clinical manifestation of *GRN* mutation [77], but mutations in *MAPT* or *GRN* are not considered a major cause of familial parkinsonism, especially in the absence of other clinical signs and symptoms. Recently, mutations in *TARDBP*, the gene for TDP-43, causing familial ALS or frontotemporal dementia, have also been identified in a few patients with late-onset PD [78, 79].

Similarly, dopa-responsive dystonia (DRD; dystonia-parkinsonism; DYT5) may sometimes present with parkinsonism only [80]. DRD can be caused by mutations in several genes involved in dopamine synthesis: *GCH1* (*guanosine triphosphate cyclohydrolase 1*), *TH* (*tyrosin hydroxylase*), *SPR* (*sepiapterin reductase*) or others. Classically described as a disease starting in childhood, the disease may also manifest in adulthood, with an adult-onset PD-like phenotype, especially when caused by *GCH1* mutations [81]. The phenotype may resemble PD but there are frequently signs of dystonia as well, such as dystonic tremor [81].

Two patients have been reported who had adult onset PD and *TH* mutations, but the association remains uncertain, although a pathophysiological connection appears reasonable [82]. The *PARK3* locus was initially linked to a genomic region that included the entire *SPR* gene [83], but a large study within the GEO-PD consortium failed to show any association of *SPR* mutations with PD [84].

Monogenic disorders with various manifestations that may include parkinsonism

Mutations in *mitochondrial DNA polymerase gamma* (*POLG*, *POLG1*) have been reported from patients with parkinsonism, with loss of dopaminergic cells evidenced in DATscans and at least partial response to dopaminergic medication [85, 86]. All these patients also had pronounced additional neurological signs such as progressive external ophthalmoplegia, ataxia, sensory neuropathy or sensorineural hearing loss, or muscle weakness with elevated creatine kinase and mitochondrial myopathy in muscle biopsy, and/or hypogonadism [85-88].

Most patients with hereditary leukoencephalopathy with spheroids, a disorder caused by mutations in the *CSF1R* gene, develop parkinsonism during the course of their disease, but parkinsonism is neither the initial nor the only symptom [89-91].

Parkinsonism has been described in some individuals with hexanucleotide expansions in *C9orf72*, that cause FTD/ALS linked to chromosome 9, but the overall clinical picture included pronounced additional neurological and neuropsychiatric features [92-94].

Recessive PD genes

Recessive inheritance is suggested in families where several members of one generation are affected, especially siblings, but not their parents or their children. In contrast to the dominant PD genes, for which between 1 and 7 mutations per gene are proven to be pathogenic, a large number of mutations in the recessive PD genes have been reported to be disease-causing (Table 1). Some of these have been published from several groups and have become well-established. Others have only been found in one or a few patients, and their significance is difficult to ascertain.

Parkin

In 1998, mutations in the *parkin* gene *(PARK2,* encoding parkinson protein 2, E3 ubiquitin protein ligase) were discovered in several siblings from consanguineous families in Japan and Turkey, who shared a peculiar clinical syndrome initially designated Early-Onset Parkinsonism with Diurnal Fluctuation (EPDF) [95, 96]. Soon, *parkin* mutations were considered a common cause of (very) early onset PD. In one study of 100 PD patients with an age at onset below 45 years, 77% of those with very young onset, below 20 years of age, carried at least one *parkin* mutation (homozygous or heterozygous). This percentage decreased sharply to 26% of those with a disease onset between 20 and 30 years, and only 2-7% of those where symptoms started between 30 and 45 years of age. Unfortunately, homozygous and heterozygous carriers were not reported separately, and about half of the PD patients with *parkin* mutations had only one mutation (heterozygote) [97]. Other studies found homozygous or compound heterozygous *parkin* mutations in a lower percentage of patients with early onset-PD (before 40 or 45 years), ranging from 8.2% in Italy, 2.7% in Korea, 2.5% in Poland, to 1.4% in Australia [8, 98-100]. More than 100 different *parkin* mutations have been reported from PD patients, including copy number variations (deletions, insertions, multiplications), missense and truncating mutations [101].

Features common to patients with *parkin* mutations and PD, aside from young or very young age at onset, are probably a good and lasting effect of levodopa, albeit with the occurrence of dyskinesias during the disease course, and a lower risk for non-motor symptoms such as cognitive decline and dysautonomia [102]. Rigidity, lower limb dystonia and hyperreflexia as well as psychiatric symptoms have been described [102, 103]. The initial patients with EPDF experienced marked alleviation of their parkinsonism after a night's sleep, at least during the first years of their illness [96]. The cardiac sympathetic nervous system is not usually affected although mild dysautonomia has been reported [104].

PINK1

Homozygous mutations in *phosphatase and tensin homolog-induced putative kinase1* (*PINK1, PARK6*) are associated with early-onset PD [105]. Over 40 point mutations and rarely, large deletions, have been detected [101]. The clinical phenotype seems to be similar to that of *parkin* mutations, but there are some indications that psychiatric symptoms may occur more commonly among patients with *PINK1* mutations [101, 106]. Mutations in *PINK1* are rarer than *parkin* mutations.

DJ1

Mutations in *oncogene DJ1* (*parkinson protein 7, PARK7*) are well-established but very rare causes for recessive PD [107]. Only a few patients homozygous for *DJ1* mutations have been described. Most had early-onset PD, but a family with early dementia, parkinsonism and amyotrophy has also been reported [108-111].

Aspects common to parkin, PINK1, DJ1

Mutations in these three genes are associated with a similar clinical phenotype, which is distinct from the average patient with idiopathic PD. Patients homozygous for pathogenic mutations in these genes share a disease presentation early or very early in life. The mean age at onset was 25.5 years in one of the larger studies [103]. Accompanying non-motor symptoms, if present, remain mild in most cases. Apart from the tendency to develop dyskinesias and dystonia common to all patients with early-onset PD irrespective of genetic background [112], no specific features reliably distinguish these forms. Furthermore, in almost all cases, the pathological changes in *parkin* and *PINK1* patients remain confined to the brainstem, in particular the substantia nigra, and do not include Lewy bodies [25, 102, 106]. No neuropathology of a patient with *DJ1* mutations has been described yet.

Although there is no doubt today that some of the mutations in *parkin*, *PINK1* or *DJ1* are associated with disease when present on both alleles [103, 113], the details are more difficult to examine. Part of this difficulty may be explained by the very nature of recessive inheritance in humans: An important criterion for the pathogenicity of a mutation is that of co-segregation within families, meaning that mutation carriers develop disease whereas their relatives without mutations remain unaffected. In families with recessive patterns of inheritance, co-segregation analysis is often limited to a few siblings, but siblings have a 25% chance probability to have inherited the identical allele. Stringent large-scale studies exploring the association of reported mutations with disease have not been performed, and the pathogenicity of a considerable number of mutations in these three genes remains unconfirmed. Some of the reported variants may be polymorphisms not causing PD.

Detailed information about clinical characteristics of carriers of certain mutations in *parkin, PINK1* and *DJ1* is also limited: Although a large number of different mutations are known, each one is comparatively rare. Grouping together patients with different mutations in the

same gene may overcome this problem but has limitations when different biological effects of the various mutations are assumed.

A pathogenic effect of certain heterozygous mutations in *parkin* and *PINK1* has been postulated but has been difficult to prove with certainty [98, 100, 113-115]. It has been suggested that certain mutations cause early-onset PD when they are present on both alleles, but cause late-onset PD in heterozygote carriers [115].

The overall frequency of mutations in these three genes is lower than previously estimated; a systematic review of publications covering more than 5,800 EOPD patients reported proportions of 8.6% with mutations in *parkin*, 3.7% in *PINK1* and 0.4% in *DJ1* [103].

Recessive disorders that may include parkinsonism

Mutations in *ATPase type 13A2* (*ATP13A2; PARK9*) were found to cause the rare Kufor-Rakeb syndrome in a Chilean family. The clinical features include early onset levodopa-responsive dystonia and parkinsonism, pyramidal signs, as well as eye movement abnormalities. There is generalized brain atrophy and dementia [116, 117], and iron accumulation on MRI [118, 119]. *ATP13A2* mutations appear to be exceedingly rare. There may be considerable inter-family phenotypic variability, including a pyramidal-parkinsonian syndrome, cognitive/psychiatric features, ataxia, and axonal neuropathy [119]. It has been debated whether heterozygous *ATP13A2* mutations may cause a milder form of this disease. Heterozygous carriers with parkinsonism as the only feature have been described [120, 121].

One patient with *SPG11* mutation presented with bilateral symmetric parkinsonism at 14 years of age. The patient rapidly deteriorated and developed spastic paraplegia and thinning of the corpus callosum on MRI, typical of spastic paraplegia 11 [122, 123].

Phospholipase A2, group VI (cytosolic, calcium-independent) (*PLA2G6; PARK14*) was identified in 2006 as the gene causing two types of a rare disorder called neurodegeneration with brain iron accumulation (NBIA), type 2A (also known as infantile neuroaxonal dystrophy) and type 2B [124]. Both are severe neuro-pediatric disorders that bear no resemblance to PD. Three years later, mutations in this gene were reported from patients who also developed what was called adult-onset levodopa-responsive dystonia-parkinsonism [125, 126]. However, age at onset was between 10 and 26 years in the six patients described, and they also had rapidly declining cognition, psychiatric symptoms and pyramidal signs. Motor function worsened quickly, and most lost independence within a few years. Thus, the clinical presentation of this disorder clearly differs from PD. MRI displayed severe generalized brain atrophy in more advanced patients, but no iron deposition [125, 126]. The few available pathology reports from patients with *PLA2G6* mutations have consistently shown a high load of alpha-synuclein pathology, both in patients with NBIA and with dystonia-parkinsonism [127, 128].

Mutations in *F-box protein 7* (*FBXO7*; *PARK15?*) cause a Parkinson-pyramidal syndrome which is also very different from PD [129]. Patients have pes equinovarus deformity since childhood, develop spasticity in the lower, and sometimes upper extremities, and levodopa-responsive parkinsonism occurs 5 to 20 years after the onset of spasticity [129].

Homozygous mutations in *DNAJC6* may cause very severe juvenile parkinsonism with an age at onset at 10-11 years and frequently associated with additional neurological features [130, 131].

Conclusions

The genetic causes of a considerable number of monogenic disorders with parkinsonism are known today. The phenotypes caused by mutations in *SNCA* or the recessive PD genes (*parkin*, *PINK1*, *DJ1*) represent characteristic subtypes of PD. LRRK2 mutations may cause PD, but with more variable clinical and pathological features; *LRRK2* PD cannot as readily be brought together with one particular PD subtype. Mutations in many of the other genes that have been proposed as causes for monogenic parkinsonism or PD are not associated with a clinical disease phenotype resembling PD.

In most populations, the known pathogenic mutations are exceptionally rare, and can only explain a very minor part [8, 24, 44, 103, 132] of the estimated 10% of PD patients with one or more affected first-degree relatives [133]. In general, the probability to find a pathogenic mutation in a given patient with parkinsonism remains low [44, 103, 132], but varies widely, depending on factors including the patient's age at onset, family history, origin, and clinical phenotype.

Genetic testing can today be offered to a subset of patients with unusually young onset, dominant inheritance, and/or a clinical phenotype suggesting a defined monogenic form of parkinsonism. Table 4 shows which genetic tests may be useful. Clinical genetic analysis should only be performed when adequate genetic counseling before, during and after testing can be provided. Interpretation of positive gene test results requires the understanding that the knowledge about a particular mutation's effect may still be limited.

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Table Captions

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. 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.

*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].

**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 6,378 PD patients [145].

***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.

Dom.: dominant; rec.: recessive.

Table 2: Established dominant and recessive PD genes

This table includes genes with mutations with proven pathogenicity for parkinsonism or PD [44, 101]. See text for details, full gene names, and further references.

DLBD, diffuse Lewy body disease. EOPD, early-onset PD. LOPD, late-onset PD.

*The number of truly pathogenic mutations in recessive PD-genes remains uncertain. See text for details.

** Estimations of frequencies for these mutations in the table are largely derived from publications reporting the discovery of pathogenic mutations in screened cohorts; due to reporting bias the true mutation frequency may be considerably lower than these figures.

Table 3: Pathogenic mutations in *LRRK2*

Summary of the *LRRK2* mutations that are considered definitively pathogenic, according to reference [44]. *The N1437H, R1441G, Y1699C and I2020T mutations were not found in a multicenter study with 8,611 PD patients [44] and must thus be considered rare. See text for further details and references.

Table 4: Considerations for genetic testing in a clinical setting

This table summarizes background information on which the choice of a genetic test may be based in patients with parkinsonism or PD. At present, indications for genetic testing on clinical grounds may exist when there is a suggestion of autosomal dominant inheritance, early or very early disease onset, or in patients with marked or characteristic additional clinical features beside parkinsonism. Details are provided in the text.

Table 1

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)**	*FBXO7 (PARK15)*
*HTRA2 (PARK13)***	*SPR (PARK3 locus)*
*UCHL1 (PARK5)****	

Table 2

Gene name	Year of original publication	Number of pathogenic mutations	Commonly associated clinical phenotype, neuropathology	Maximal frequency in population**
Autosomal dominant				
SNCA	1997	3, plus genomic duplications, triplications	Parkinsonism, cognitive, behavioral and autonomic symptoms, myoclonus Alpha-synuclein pathology, DLBD.	Point mutations: Very rare, two mutations only found in one family each. Duplications and triplications: Slightly more common.
LRRK2	2004	7	Parkinsonism, variable additional symptoms. Highly variable pathology.	Founder effects in specific populations. Rare or very rare internationally. See Table 3.
EIF4G1	2011	Uncertain, at least 1	Parkinsonism, long course and mild disease Cognition preserved Lewy body pathology.	Very rare: 0.02%-0.2%** [63, 65]. Newly described.
VPS35	2011	1 or more	Parkinsonism, possibly cognitive and behavioral changes. Pathology uncertain, probably not DLBD.	Very rare: 0.08%-0.14%** [53, 55, 58]. Newly described.
Autosomal recessive				
Parkin (PARK2)	1998	>100*	Young-onset parkinsonism. Low risk for cognitive symptoms. Cell loss in brain stem, usually no cortical pathology.	Relatively frequent among patients with very young onset. 1.4% to 8.2%** of EOPD patients [98, 100, 103]. Very rare in LOPD.
PINK1	2004	>40*	Young-onset parkinsonism, Cognitive and psychiatric symptoms described. Cell loss in brain stem / substantia nigra.	Rarer than *parkin* mutations. Rare in EOPD (3.7% [103]) Very rare in LOPD.
DJ1 (PARK7)	2003	>10*	Young-onset parkinsonism, Low risk for cognitive symptoms. Pathology not described.	Rarer than *parkin* and *PINK1* mutations. Very rare, even in EOPD (0,4% [103]).

Table 3

LRRK2 mutation	First description [ref.]	Comments
N1437H	2010 [34]	Very rare*
R1441C	2004 [26]	Rare, found in 10 of 8,611 PD patients [44]
R1441G	2004 [27]	Founder effect among Basques, very rare in other populations*
R1441H	2005 [30, 31]	Very rare
Y1699C	2004 [26, 27]	Very rare*
G2019S	2005 [39]	Most common PD-associated mutation, frequent in some Mediterranean populations, but rare in other populations (0.58% in ref.[44])
I2020T	2004 [26]	Very rare*

Table 4

Autosomal dominant or x-linked inheritance		
(affected members in at least two generations)		
Consider testing in	**Gene**	**Comment**
PD/ parkinsonism	*LRRK2*	Most common in general, especially patients with Ashkenazi Jewish or Mediterranean origin
	SNCA	If phenotype includes cognitive or autonomic symptoms or myoclonus
	VPS35	Probably rare
	EIF4G1	Probably rare
Parkinsonism, usually with additional features (few cases presented with parkinsonism only)	*ATXN2, ATXN3*	Parkinsonism and ataxia
	FMR1	Parkinsonism and ataxia, male patients, may develop characteristic MRI signs in cerebellar peduncle
	MAPT, GRN	Parkinsonism and signs of frontotemporal dementia
	GCH1	Parkinsonism and dystonia
Parkinsonism with additional features	*C9orf72*	Parkinsonism and signs of frontotemporal dementia and/or motor neuron disease
	POLG	Parkinsonism with ophthalmoplegia, ataxia, neuropathy, hearing loss, muscle weakness and/or hypogonadism
	CSF1R	Parkinsonism with cognitive dysfunction, seizures, white matter changes on MRI

Early onset parkinsonism		
(EOPD, before 40-45 years)		
Consider testing in	**Gene**	**Comment**
EOPD	*Parkin*	Consider testing the genes in this order.
	PINK1	Mean age at onset for carriers of homozygous or compound heterozygous mutations in these genes is around 25 years [103].
	DJ1	Lower age at onset, affected family members in the same generation or consanguineous parents increase likelihood for mutations in these genes.
EOPD with additional features	*POLG*	Parkinsonism with ophthalmoplegia, ataxia, neuropathy, hearing loss, muscle weakness and/or hypogonadism.
	ATP13A2	Homozygous mutation carriers: Parkinsonism with pyramidal-parkinsonian syndrome, cognitive/psychiatric features, ataxia, and axonal neuropathy. Single heterozygous mutation carriers with only parkinsonism have been described. Exceedingly rare.