



HAL
open science

Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7 and LRRK2 genes: a mutation update

Karen Nuytemans, Jessie Theuns, Marc Cruts, Christine van Broeckhoven

► To cite this version:

Karen Nuytemans, Jessie Theuns, Marc Cruts, Christine van Broeckhoven. Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7 and LRRK2 genes: a mutation update. *Human Mutation*, 2010, 31 (7), pp.763. 10.1002/humu.21277 . hal-00552395

HAL Id: hal-00552395

<https://hal.science/hal-00552395>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7 and LRRK2 genes: a mutation update

Journal:	<i>Human Mutation</i>
Manuscript ID:	humu-2010-0075.R1
Wiley - Manuscript type:	Mutation Update
Date Submitted by the Author:	11-Apr-2010
Complete List of Authors:	Nuytemans, Karen; VIB, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics; University of Antwerp, Laboratory of Neurogenetics, Institute Born-Bunge Theuns, Jessie; VIB, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics; University of Antwerp, Laboratory of Neurogenetics, Institute Born-Bunge Cruts, Marc; VIB, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics; University of Antwerp, Laboratory of Neurogenetics, Institute Born-Bunge Van Broeckhoven, Christine; VIB, Neurodegenerative Brain Diseases Group, Department of Molecular Genetics; University of Antwerp, Laboratory of Neurogenetics, Institute Born-Bunge
Key Words:	Parkinson disease, Genetics, Mutations, Database



Humu-2010-0075

Mutation Update

Supporting Information for this preprint is available from the
Human Mutation editorial office upon request (humu@wiley.com)

**Genetic etiology of Parkinson disease associated with mutations in the *SNCA*, *PARK2*,
PINK1, *PARK7* and *LRRK2* genes: a mutation update**

Karen Nuytemans^{1,2}, Jessie Theuns^{1,2}, Marc Cruts^{1,2}, and Christine Van Broeckhoven^{1,2*}

¹Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Antwerpen,
Belgium

²Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerpen,
Belgium

***Correspondence to:**

Prof. Dr. Christine Van Broeckhoven PhD DSc

Neurodegenerative Brain Diseases Group

VIB - Department of Molecular Genetics

University of Antwerp - CDE, Universiteitsplein 1, B-2610 Antwerpen, Belgium

Phone +32 3 265 1001, Fax +32 3 265 1012

E-mail christine.vanbroeckhoven@molgen.vib-ua.be

ABSTRACT

To date, molecular genetic analyses have identified over 500 distinct DNA variants in five disease genes associated with familial Parkinson disease; *α-synuclein (SNCA)*, *parkin (PARK2)*, *PTEN-induced putative kinase 1 (PINK1)*, *DJ-1 (PARK7)*, *Leucine-rich repeat kinase 2 (LRRK2)*. These genetic variants include ~82% simple mutations and ~18% copy number variations. Some mutation subtypes are likely underestimated since only few studies reported extensive mutation analyses of all five genes, by both exonic sequencing and dosage analyses. Here we present an update of all mutations published to date in the literature, systematically organized in a novel mutation database (<http://www.molgen.ua.ac.be/PDmutDB>). In addition, we address the biological relevance of putative pathogenic mutations. This review emphasizes the need for comprehensive genetic screening of Parkinson patients followed by an insightful study of the functional relevance of observed genetic variants. Moreover, while capturing existing data from the literature it became apparent that several of the five Parkinson genes were also contributing to the genetic etiology of other Lewy Body Diseases and Parkinson-plus syndromes, indicating that mutation screening is recommendable in these patient groups.

Keywords: Parkinson disease, genetic etiology, database, *SNCA*, *PARK2*, *PINK1*, *PARK7*, *LRRK2*

INTRODUCTION

Parkinson disease (PD) is the second most common progressive neurodegenerative brain disorder. It affects 1 to 2 % of the population above 65 years and its prevalence increases to approximately 4 % in those above 85 years. As these demographic age groups are growing rapidly due to general aging of the population and increasing lifespans, neurodegenerative diseases will represent an ever growing social and economic burden for society. Through time, the scientific view on PD etiology has changed dramatically. Due to the observation that only 15 to 20% of PD patients have a clear positive family history of PD, researchers predicted that the majority of the PD patients have a complex etiology, including both a genetic and environmental component. During the last two decades, molecular genetic analyses in PD families provided important insights in disease mechanisms underlying PD pathology. Nine genes that contribute to the genetic etiology of familial PD were identified through positional cloning strategies in inherited PD patients and families [Bonifati et al., 2003; Di Fonzo et al., 2009; Kitada et al., 1998; Lautier et al., 2008; Paisan-Ruiz et al., 2004; Paisan-Ruiz et al., 2009; Polymeropoulos et al., 1997; Ramirez et al., 2006; Valente et al., 2004a; Zimprich et al., 2004a]. Two more PD genes, *UCH-L1* and *HTRA2*, were identified based on the functional relevance of their corresponding protein to PD pathogenesis [Leroy et al., 1998ba; Strauss et al., 2005]. Although follow-up genetic studies are inconsistent for some of these genes or conclusive data are still pending, ample evidence for a causal association was obtained for PD with five genes i.e. α -*synuclein* (*SNCA*; MIM# 163890), *parkin* (*PARK2*; MIM# 602544), *PTEN-induced putative kinase 1* (*PINK1*; MIM# 608309), *DJ-1* (*PARK7*; MIM# 602533) and *Leucine-rich repeat kinase 2* (*LRRK2*; MIM# 609007). Extensive mutation screening of these five causal genes revealed both simple mutations (missense, nonsense, silent, splice site and untranslated region (UTR)

1
2
3 mutations, small insertions and deletions (indels)) and copy number variations (CNVs) leading to
4
5 PD. Approximately 330 confirmed or possible pathogenic mutations in over 1900 families have
6
7 been identified so far (Supp. Tables S1 to S5; PDmutDB database:
8
9 <http://www.molgen.ua.ac.be/PDmutDB>). Possible pathogenic mutations include non-
10
11 synonymous variants, splice site variants or variants in UTRs that were not observed in control
12
13 individuals. In this mutation update we present the DNA variants identified so far and elaborate
14
15 on their clinical and biological relevance. We also discuss the importance of a new publicly
16
17 available and extensively curated database PDmutDB, and the implications of these analyses for
18
19 mutation analyses in a diagnostic setting.
20
21
22
23
24
25
26
27
28

29 MAJOR GENES AND PROTEINS

30 Autosomal dominant PD genes

31 *α - synuclein*

32
33
34 *SNCA* was the first causal PD gene identified segregating a pathogenic missense mutation –
35
36 p.Ala53Thr – in a large Italian family ('Contursi') (MIM# 163890) [Polymeropoulos et al., 1996;
37
38 Polymeropoulos et al., 1997] (Table 1 and Figure 1). The 144aa *SNCA* protein encoded by the
39
40 three different *SNCA* transcripts is typically found as a natively unfolded, soluble protein in the
41
42 cytoplasm or associated with lipid membranes [Davidson et al., 1998] (Table 2). The exact
43
44 biological function of *SNCA* in brain is still not fully understood, although there is evidence that
45
46 implicates *SNCA* in neurotransmitter release and vesicle turnover at the presynaptic terminals
47
48
49
50
51
52
53 [Abeliovich et al., 2000; Liu et al., 2004].
54
55
56
57
58
59
60

1
2
3 Mutations in *SNCA* are rather rare and explain disease in ~2.5% of known unrelated
4 affected carriers (see Supp. Tables S1-1 and S1-2 for mutations, PDmutDB for all references:
5 <http://www.molgen.ua.ac.be/PDmutDB>). Apart from the Italian Contursi family, p.Ala53Thr
6
7
8 was also identified in several families of Greek descent [Athanassiadou et al., 1999;
9
10 Papadimitriou et al., 1999; Polymeropoulos et al., 1996; Polymeropoulos et al., 1997; Spira et al.,
11
12 2001]. More recently, p.Ala53Thr was also detected in two other unrelated families from Asia
13
14 and Sweden [Choi et al., 2008; Ki et al., 2007; Puschmann et al., 2009] as well as in one
15
16 seemingly sporadic PD patient of Polish origin [Michell et al., 2005]. With only two other
17
18 missense mutations identified in *SNCA* – p.Ala30Pro [Kruger et al., 1998] and p.Glu46Lys
19
20 [Zarranz et al., 2004] (see Supp. Table S1-1), both also located in the N-terminus of the protein,
21
22 the missense mutation frequency of *SNCA* in different populations remains very low. In 2003, a
23
24 triplication of the wild-type *SNCA* locus was observed in a large multigenerational family
25
26 [Singleton et al., 2003] instigating the discovery of *SNCA* multiplications in several other
27
28 families with PD and related LBD disorders (see Supp. Table S1-2 for mutations, PDmutDB for
29
30 all references: <http://www.molgen.ua.ac.be/PDmutDB>) [Chartier-Harlin et al., 2004; Fuchs et al.,
31
32 2007; Ibanez et al., 2004; Ibanez et al., 2009; Ikeuchi et al., 2008; Nishioka et al., 2006; Nishioka
33
34 et al., 2009; Nuytemans et al., 2009]. Several of these dosage studies attempted to delineate the
35
36 boundaries of the multiplied genomic region identified in families or shared between
37
38 unrelated carriers. Most *SNCA* multiplied regions appeared in different genomic sizes (see
39
40 Supp. Table S1-2), suggestive of independent mutational events. Few studies however reported
41
42 equally sized duplicated or triplicated regions surrounding *SNCA* amongst different families or
43
44 within branches of the same family [Fuchs et al., 2007; Nishioka et al., 2009]. Of interest is that
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 *SNCA* duplications were also reported in four apparently sporadic PD patients [Ahn et al., 2008;
4
5 Nishioka et al., 2009; Nuytemans et al., 2009].
6
7
8
9

10 ***Leucine-rich repeat kinase 2 or dardarin***

11
12 The leucine-rich repeat kinase 2 gene (*LRRK2*) was the second causal gene linked to autosomal
13 dominant inherited PD (MIM# 609007) [Funayama et al., 2002] [Paisan-Ruiz et al., 2004;
14
15 Zimprich et al., 2004a; Zimprich et al., 2004b] (Table 1 and Figure 2). Its transcript contains 51
16
17 exons coding for the *LRRK2* protein [Paisan-Ruiz et al., 2004] (Table 2). *LRRK2* comprises
18
19 several functional domains suggestive of on the one hand a kinase activity dependent on the
20
21 GTPase function of the Roc domain and on the other hand a scaffold protein function implied by
22
23 the multiple protein-protein interaction regions (Figure 2). Of interest is that *LRRK2* was shown
24
25 to form dimers under physiological conditions [Greggio et al., 2008]. The exact biological
26
27 function of *LRRK2* remains largely unknown, since no physiological substrates have been
28
29 identified so far.
30
31
32
33
34
35

36 The first two publications of PD associated mutations in *LRRK2* described four different
37 pathogenic missense mutations segregating in families of European and North-American origin
38 [Paisan-Ruiz et al., 2004; Zimprich et al., 2004a]. Subsequent mutation analyses identified about
39
40 80 discrete missense mutations in over a 1000 families and sporadic patients worldwide (see
41
42 Supp. Table S2 for mutations, PDmutDB for all references:
43
44 <http://www.molgen.ua.ac.be/PDmutDB>). This corresponds to about 50% of all reported unrelated
45
46 carriers of mutations in the five major genes, making *LRRK2* the most frequently mutated PD
47
48 gene so far (Table 3 and PDmutDB: <http://www.molgen.ua.ac.be/PDmutDB>). The 80 missense
49
50 mutations are located over the entire *LRRK2* protein and affect all predicted functional domains.
51
52
53
54
55
56
57
58
59
60

1
2
3 Some mutations though have much higher frequencies than others, for example p.Gly2019Ser
4
5 and mutations altering codon Arg1441. Unfortunately, because of the large number of coding
6
7 exons, only a minority of studies performed mutation analyses of the complete coding region.
8
9 Most studies focused instead on those exons coding for functional relevant protein domains
10
11 namely Roc, COR and kinase domains (Figure 2). Only three studies included dosage analyses
12
13 aiming at detecting copy number variations (CNVs) but did not detect *LRRK2* multiplications or
14
15 deletions [Mata et al., 2005b; Nuytemans et al., 2009; Paisan-Ruiz et al., 2008]. Nonetheless,
16
17 rare CNVs of *LRRK2* or parts thereof cannot be excluded, before more dosage studies have been
18
19 performed for *LRRK2*.
20
21
22
23

24
25 An important observation is that the *LRRK2* mutation frequency is seemingly dependent
26
27 on the ethnicity of the population analysed. For example the most frequent mutation with a
28
29 strong founder effect – p.Gly2019Ser – was reported worldwide with an average frequency of
30
31 1% in PD patients [Paisan-Ruiz, 2009]. But, in Arab Berber and Ashkenazi Jewish populations
32
33 the p.Gly2019Ser frequency was significantly higher (20% and 40% respectively) [Lesage et al.,
34
35 2006; Ozelius et al., 2006], while in the first comprehensive screening of a Belgian population,
36
37 p.Gly2019Ser was apparently absent [Nuytemans et al., 2008]. Other codons in *LRRK2* are also
38
39 frequently mutated as a consequence of numerous independent mutational events. The
40
41 p.Arg1441 codon constitutes a mutation hotspot with three different codon substitutions –
42
43 p.Arg1441Cys, p.Arg1441Gly and p.Arg1441His. The relatively high mutation frequencies of
44
45 these mutations should be approached with some caution though, since underlying founder
46
47 effects have been reported. The most frequent mutation p.Gly2019Ser is observed on a limited
48
49 number of haplotypes. Also, p.Arg1441Gly was transmitted from a common founder in the
50
51 Basque population [Gaig et al., 2006; Gonzalez-Fernandez et al., 2007; Gorostidi et al., 2009;
52
53
54
55
56
57
58
59
60

1
2
3 Mata et al., 2005c; Paisan-Ruiz et al., 2004; Simon-Sanchez et al., 2006] while p.Arg1441Cys
4
5 was observed worldwide on several different founder haplotypes [Di Fonzo et al., 2006a; Gaig et
6
7 al., 2006; Goldwurm et al., 2005; Gosal et al., 2007; Haugarvoll et al., 2008; Hedrich et al.,
8
9 2006b; Nuytemans et al., 2008; Pankratz et al., 2006a; Tan et al., 2006a]. Additionally, several
10
11 missense mutations seemed to be (nearly) private mutations for Asian populations –
12
13 p.Arg1628Pro, p.Pro755Leu and p.Gly2385Arg [An et al., 2008; Di Fonzo et al., 2006b; Farrer
14
15 et al., 2007; Fung et al., 2006b; Ross et al., 2008; Tan et al., 2007; Tan et al., 2008; Tan et al.,
16
17 2009; Tomiyama et al., 2008].
18
19
20
21

22 In contrast to other PD genes, mutations in *LRRK2* have a relatively high frequency of up
23
24 to 2% in sporadic, late onset PD patients [Di Fonzo et al., 2005; Gilks et al., 2005; Nichols et al.,
25
26 2005; Tomiyama et al., 2006]. The high mutation frequency in both familial and sporadic
27
28 patients makes *LRRK2* the most frequently mutated gene of the five major PD genes. Some
29
30 prudence in interpreting data is warranted though. Some of the missense mutations have also
31
32 been reported in healthy control individuals, raising questions on the biological role of these rare
33
34 variants in disease [Meeus et al., 2010]. The highly variable onset ages associated with *LRRK2*
35
36 mutations [Hernandez et al., 2005; Kachergus et al., 2005; Paisan-Ruiz et al., 2005; Zimprich et
37
38 al., 2004a], the presence of *LRRK2* mutations in unaffected individuals [Carmine Belin et al.,
39
40 2006; Di Fonzo et al., 2006a; Gaig et al., 2006; Hernandez et al., 2005; Kay et al., 2005; Khan et
41
42 al., 2005b; Latourelle et al., 2008; Nichols et al., 2005; Zimprich et al., 2004a] and the high
43
44 frequency in sporadic patients render the assessment of pathogenicity of the identified variants
45
46 extremely difficult as these issues complicate segregation analyses. To date, pathogenicity
47
48 supported by segregation analyses has only been demonstrated for six *LRRK2* mutations
49
50 (p.Arg1441Cys, p.Arg1441Gly, p.Tyr1699Cys, p.Gly2019Ser and p.Ile2020Thr).
51
52
53
54
55
56
57
58
59
60

Autosomal recessive PD genes

PARK2 or parkin

The first of three recessive PD genes identified is *PARK2* (MIM# 602544), which was linked with disease in a nuclear Japanese consanguineous family [Kitada et al., 1998] (Table 1 and Figure 3). *PARK2* spans approximately 1.38 Mb and encodes the protein parkin. The 456 amino acid protein harbours four major functional domains corresponding to its function as an E3 ubiquitin ligase (Table 2) [Imai et al., 2000; Shimura et al., 2000; Zhang et al., 2000]. Its role in the ubiquitin proteasome system (UPS) comprises of tagging dysfunctional or excessive proteins for degradation. Further, it was shown that under physiological conditions parkin is involved in mitochondrial maintenance [Deng et al., 2008a; Exner et al., 2007; Park et al., 2009; Poole et al., 2008; Weihofen et al., 2009] and might induce subsequent autophagy of dysfunctional mitochondria [Narendra et al., 2008; Narendra et al., 2009].

The first mutation reports indicated a wide spectrum of loss-of-function mutations in *PARK2* including simple mutations like nonsense, missense and splice site mutations, indels as well as CNVs of the promoter region and single or multiple exons (Table 2) [Hattori et al., 1998a; Hattori et al., 1998b; Kitada et al., 1998]. *PARK2* mutations were identified spread across the entire gene in either homozygous, compound heterozygous or heterozygous state in familial and sporadic patients from different ethnicities (see Supp. Table S3-1 and S3-2 for mutations, PDmutDB for all references: <http://www.molgen.ua.ac.be/PDmutDB>). Heterozygous *PARK2* variants have also been observed in healthy control individuals, making assessment of pathogenicity for these variants quite complex. Approximately 40% of unrelated mutation carriers were reported to harbor a mutation in *PARK2* (Table 3 and PDmutDB:

1
2
3 http://www.molgen.ua.ac.be/PDmutDB). Of these, close to 8% carry both a simple mutation as a
4
5 CNV, while carriers of only simple mutations or CNVs are almost equally common (43,8%
6
7 versus 47,9%). Investigation of the haplotypes on which frequent *PARK2* mutations reside,
8
9 showed that most CNVs are independent events while point mutations were more commonly
10
11 transmitted from common founders [Periquet et al., 2001]. This suggests that the high mutation
12
13 frequency in *PARK2* is only partly due to small founder effects.
14
15
16
17
18
19

20 *P-TEN induced putative kinase 1*

21
22 Homozygosity mapping in *PARK2* negative European families led to the identification of the
23
24 second autosomal recessive gene, *P-TEN induced putative kinase 1* (*PINK1*; MIM# 608309)
25
26 [Valente et al., 2001; Valente et al., 2002; Valente et al., 2004a] (Table 1 and Figure 4). The
27
28 *PINK1* protein is a putative serine/threonine kinase involved in mitochondrial response to
29
30 cellular and oxidative stress [Valente et al., 2004a] (Table 2). This response is likely mediated by
31
32 regulation of the calcium efflux, influencing processes such as mitochondrial trafficking [Wang
33
34 et al., 2009; Weihofen et al., 2009], ROS formation, mitochondrial respiration efficacy [Liu et
35
36 al., 2009] and opening of the mitochondrial permeability transition pore [Gandhi et al., 2009] as
37
38 well as by interaction with cell death inhibitors and chaperones [Plun-Favreau et al., 2007;
39
40 Pridgeon et al., 2007; Wang et al., 2007]. In addition, *PINK1* is an important player in the
41
42 alleged *PINK1*/parkin pathway, regulating mitochondrial morphology and functionality in
43
44 response to stressors [Deng et al., 2008a; Exner et al., 2007; Park et al., 2009; Poole et al., 2008;
45
46 Weihofen et al., 2009].
47
48
49
50
51
52

53 The *PINK1* mutation spectrum involves nonsense and missense mutations, indels and
54
55 whole-gene or single/multiple exon CNVs (Table 2) located across the entire gene. Mutation
56
57
58
59
60

1
2
3 analyses in familial as well as sporadic patients identified homozygous and compound
4
5 heterozygous mutations (see Supp. Table S4-1 for mutations, PDMutDB for all references:
6
7 <http://www.molgen.ua.ac.be/PDMutDB>). Approximately 6.5% of known mutation carriers carry
8
9 a mutation in *PINK1* (Table 3). Again, many putative pathogenic mutations were also observed
10
11 in heterozygous state in familial and sporadic patients as well as in healthy control individuals
12
13 [Abou-Sleiman et al., 2006; Bonifati et al., 2005; Brooks et al., 2009; Choi et al., 2008; Djarmati
14
15 et al., 2006; Fung et al., 2006a; Healy et al., 2004; Klein et al., 2005; Kumazawa et al., 2008;
16
17 Mellick et al., 2009; Nuytemans et al., 2009; Rogaeva et al., 2004; Tan et al., 2005; Tan et al.,
18
19 2006b; Valente et al., 2004b; Weng et al., 2007]. With the current available mutation data, it
20
21 seems that CNVs in *PINK1* are less common than simple loss-of-function mutations (see Supp.
22
23 Table S4-2). But, at this stage we cannot exclude that this observation represents an
24
25 ascertainment bias since many studies did not perform *PINK1* dosage analyses and therefore
26
27 might have missed CNVs in their patient groups.
28
29
30
31
32
33
34
35

36 ***PARK7 or DJ-1***

37
38 The third autosomal recessive PD gene, *PARK7* (or *DJ-1*; MIM# 602533) was identified by
39
40 homozygosity mapping in an extended Dutch family with multiple consanguinity loops [Bonifati
41
42 et al., 2003; van Duijn et al., 2001] (Table 1 and Figure 5). The DJ-1 protein was found to be
43
44 H₂O₂ responsive suggesting that DJ-1 represents a sensor for oxidative stress e.g. dopamine
45
46 toxicity [Lev et al., 2009], and acts as an antioxidant [Mitumoto et al., 2001] (Table 2). It was
47
48 further hypothesized that DJ-1 could be part of a novel E3 ligase complex together with parkin
49
50 and PINK1 [Xiong et al., 2009].
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Mutation analyses identified homozygous, compound heterozygous as well as heterozygous [Bonifati et al., 2003; Clark et al., 2004; Hague et al., 2003; Hedrich et al., 2004ac; Nuytemans et al., 2009] missense mutations and CNVs in patients (see Supp. Table S5-1 and S5-2 for mutations, PDmutDB for all references: <http://www.molgen.ua.ac.be/PDmutDB>). Also for *PARK7*, heterozygous variants were observed in control individuals. Mutations in *PARK7* are reported near 1% of all known mutation carriers (Table 3). Current mutation data indicates that CNVs in *PARK7* are less frequent than simple mutations. But, because of the rarity of mutations in *PARK7*, most studies have not analysed their PD patient groups, making it highly likely that putative pathogenic mutations have been missed and that the current mutation frequency of *PARK7* is an underestimate.

30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

CLINICAL IMPLICATIONS

Clinical features of PD patients typically include tremor, bradykinesia, rigidity, good levodopa response and/or postural instability. Interestingly, PD is part of a wide Lewy Body Diseases (LBD) spectrum made up by closely related clinical phenotypes characterized by variable manifestation of parkinsonism and dementia (PD, PD with dementia (PDD), Dementia with LB (DLB), LB variant of Alzheimer's disease (AD) and AD). On the other hand, parkinsonism can be accompanied by additional atypical features defining the parkinson-plus syndromes, like multiple system atrophy (MSA; dysautonomia and/or cerebellar signs), progressive supranuclear palsy (PSP; impaired vertical eye movements and prominent postural instability) and corticobasal degeneration (CBD; apraxia). The clinical features reported in literature are mostly typical for disorders of the LBD spectrum. In some cases, however, more atypical features indicative of other related diseases, such as the Parkinson-plus syndromes were observed. This

1
2
3 indicates there is a high variability in phenotypes associated by mutations in *SNCA*, *LRRK2*,
4
5 *PARK2*, *PINK1* and *PARK7*.
6

7
8 Here we summarize typical and atypical presentations of specific mutation groups and discuss
9
10 some of its implications. This and more detailed information on familial, individual and clinical
11
12 data can be found in the newly constructed and publicly available PDmutDB database
13
14 (<http://www.molgen.ua.ac.be/PDmutDB>).
15
16
17

18
19
20 *SNCA* is the only one of the five genes in which an obvious correlation can be made between
21
22 distinct missense mutations or distinct CNVs and the resulting different phenotypes. The
23
24 majority of the familial PD patients carrying the *SNCA* missense mutations p.Ala53Thr or
25
26 p.Ala30Pro, typically present with bradykinesia and rigidity at an early onset age (< 55years)
27
28 [Bostantjopoulou et al., 2001; Ki et al., 2007; Kruger et al., 1998; Papapetropoulos et al., 2001;
29
30 Papapetropoulos et al., 2003; Puschmann et al., 2009; Spira et al., 2001]. The sporadic Polish
31
32 patient carrying p.Ala53Thr, however, showed typical PD features i.e. late onset at 74 years,
33
34 rigidity, progressive bradykinesia and mild tremor [Michell et al., 2005]. Also, clinical features
35
36 in carriers of the third *SNCA* missense mutation p.Glu46Lys are atypical in such that these
37
38 carriers present with symptoms at later age and suffer from dementia within several years after
39
40 PD onset [Zarranz et al., 2004]. Brain pathology in one p.Glu46Lys carrier showed diffuse LB
41
42 consistent with a diagnosis of DLB confirming the atypical clinical presentation [Zarranz et al.,
43
44 2004]. Also patients carrying *SNCA* multiplications present with atypical forms of the disease. A
45
46 direct correlation between phenotype and number of *SNCA* copies was consistently observed
47
48 among different studies. Most duplication carriers present with late-onset parkinsonism
49
50
51 [Chartier-Harlin et al., 2004; Fuchs et al., 2007; Ibanez et al., 2004; Ibanez et al., 2009; Nishioka
52
53
54
55
56
57
58
59
60

1
2
3 et al., 2006; Nishioka et al., 2009], which can be accompanied by a later onset cognitive decline
4
5 (PDD) [Nishioka et al., 2006; Nishioka et al., 2009; Nuytemans et al., 2009]. Triplication carriers
6
7 however seem to be more severely affected suffering from a more aggressive form of dementia
8
9 despite their shorter disease duration (DLB) [Farrer et al., 2004; Ibanez et al., 2009; Singleton et
10
11 al., 2003]. Also asymptomatic carriers have been reported in families of both seemingly sporadic
12
13 and familial PD patients [Ahn et al., 2008; Ibanez et al., 2009; Nishioka et al., 2006; Nishioka et
14
15 al., 2009]. Only few of these carriers have exceeded the onset age of the proband [Ibanez et al.,
16
17 2009; Nishioka et al., 2009], indicating variable onset ages or reduced penetrance for this
18
19 mutation. When considering all unaffected duplication carriers that are older than the average
20
21 onset age of the affected carriers as true asymptomatic individuals a crude estimate of 85%
22
23 penetrance could be obtained from the information in PDmutDB
24
25 (<http://www.molgen.ua.ac.be/PDmutDB>). Interestingly, one study describing both duplication
26
27 and triplication of *SNCA* in two separate branches of the same family, also reported clinical
28
29 features reminiscent of MSA (orthostatic hypotension and poor levodopa response) in both
30
31 branches [Fuchs et al., 2007].
32
33
34 Typically, patients carrying *LRRK2* missense mutations present with clinical features similar to
35
36 those of idiopathic PD i.e. asymmetrical late onset, bradykinesia, rigidity, tremor and good l-
37
38 dopa response. The incidence of tremor however seems to be elevated in *LRRK2* carriers
39
40 indicating that *LRRK2* mutations most likely lead to tremor-dominant disease [Haugarvoll et al.,
41
42 2008; Nuytemans et al., 2008; Paisan-Ruiz et al., 2004]. On the other hand isolated studies have
43
44 also reported *LRRK2* mutations in carriers with a clinical diagnosis of sporadic PD with late-
45
46 onset AD as well as CBD, PSP or frontotemporal dementia (FTD) [Chen-Plotkin et al., 2008;
47
48 Santos-Reboucas et al., 2008; Spanaki et al., 2006].
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Clinical features of *PARK2* homozygous mutation carriers are generally indistinguishable from
4 those of idiopathic PD patients with the exception of a clear drop in onset age. Typically *PARK2*
5 patients present with disease onset before the age of 50 years and a slow disease progression
6 [Abbas et al., 1999; Khan et al., 2005a; Lucking et al., 2000]. Although they respond well to
7 levodopa treatment they are more likely to develop treatment-induced motor complications
8 earlier in the treatment [Deng et al., 2008b; Khan et al., 2005a; Lucking et al., 2000]. Further,
9 *PARK2* mutations were also identified in patients with a clinical diagnosis of PSP, PD plus
10 essential tremor (ET), as well as ET and restless legs syndrome (RLS) [Adel et al., 2006; Deng et
11 al., 2007; Limousin et al., 2009; Pellecchia et al., 2007; Pigullo et al., 2004; Sanchez et al., 2002]
12
13 Homozygous *PINK1* mutation carriers are clinically indistinguishable from homozygous *PARK2*
14 mutation carriers [Bentivoglio et al., 2001; Valente et al., 2004a]. Although rare, *PINK1*
15 mutations were also associated with late onset PD, RLS with parkinsonism and dopa-responsive
16 dystonia [Gelmetti et al., 2008; Leutenegger et al., 2006; Tan et al., 2005; Tan et al., 2006b].
17
18 Further, a few *PINK1* homozygous mutation carriers also presented with cognitive and
19 psychiatric problems in addition to parkinsonism [Ephraty et al., 2007; Reetz et al., 2008;
20 Savettieri et al., 2008].
21
22

23
24 Clinical features of carriers with a homozygous mutation in the recessive *PARK7* gene are also
25 similar to those of homozygous *PARK2* and *PINK1* carriers [Bonifati et al., 2003]. Also here,
26 clinical heterogeneity with a wide range of clinical phenotypes among unrelated and related
27 carriers was reported. For example, in one family segregating two distinct homozygous
28 variations were diagnosed with early onset parkinsonism, dementia and amyotrophic lateral
29 sclerosis (ALS) [Annesi et al., 2005]. In addition, the initially reported 14 kb deletion of the 5'
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 region of *PARK7* linked to typical PD was also observed heterozygously in two dementia
4 patients without signs of parkinsonism [Arias et al., 2004].
5

6
7
8 The available clinical data showed us that mutations in these five PD genes are not only present
9 in patients but also in patients diagnosed with related disorders. Some clinical features are known
10 to overlap between these disorders, so clinical diagnoses may not always be accurate or different
11 disorders might share a common etiology. In both cases, it might be worthwhile screening for
12 mutations in “PD-associated-genes” in larger groups of patients with clinical diagnoses related to
13 PD to further explore the genotype-phenotype correlations. Alternatively, no information was
14 provided on mutation analyses of additional genes so other currently unknown mutations might
15 still explain this range of clinical features for these patients.
16
17

18
19
20 When discussing genotype-phenotype correlations, one needs to take into account that at times it
21 can be difficult to comprehend the clinical implications of some genetic variants. Although
22 homozygous mutations in the recessive genes have a penetrance of 100% with only two carriers
23 older than the onset age of affected relatives reported in literature (*PARK2* p.Trp74fsCysX8
24 [Pineda-Trujillo et al., 2001] and *PARK7* p.Glu64Asp [Hering et al., 2004]), the effect of
25 heterozygous mutations is far less clear. The presence of these mutations in *PARK2*, *PINK1* and
26 *PARK7* has instigated a debate on the role of heterozygous recessive mutations as risk factors for
27 disease. In many studies the prevalence of these heterozygous rare variants is (significantly)
28 higher in patients than in control individuals (*PARK2*: [Brooks et al., 2009; Clark et al., 2006;
29 Lesage et al., 2008; Nuytemans et al., 2009; Sun et al., 2006] / *PINK1*: [Abou-Sleiman et al.,
30 2006; Bonifati et al., 2005; Brooks et al., 2009; Marongiu et al., 2008; Rogaeva et al., 2004;
31 Valente et al., 2004b]), implying that the presence of a heterozygous recessive mutation might
32 increase the carrier’s susceptibility to develop PD. In addition, several families reported affected
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 heterozygous family members of a homozygous proband creating a false impression of dominant
4 inheritance and indicating a possible predisposition of *PARK2* or *PINK1* variants to PD (*PARK2*:
5 [Maruyama et al., 2000; Munhoz et al., 2004; Tan et al., 2003] / *PINK1*: [Criscuolo et al., 2006;
6 Djarmati et al., 2006; Hedrich et al., 2006a; Ibanez et al., 2006]). Investigation of clinical
7 features in patients with digenic combinations of heterozygous mutations might provide us with
8 more insight in the effects of these variants (Table 4). For example, the clinical presentation and
9 onset of PD does not differ between patients carrying a heterozygous *LRRK2* mutation and
10 patients carrying a digenic combination of *LRRK2* and *PARK2* mutations [Bras et al., 2008;
11 Ferreira et al., 2007; Gao et al., 2009; Illarioshkin et al., 2007; Lesage et al., 2006; Marras et al.,
12 2008]. Illarioshkin and coworkers, though, reported early occurrence of dyskinesias during
13 treatment, more common in *PARK2* mutation carriers, in a *LRRK2/PARK2* digenic mutation
14 carrier [Illarioshkin et al., 2007]. Reports of carriers with digenic mutations of two recessive
15 genes are rare, mostly because many mutation studies reported so far have not analysed all five
16 PD genes. One study describing patients carrying a single heterozygous *PINK1* mutation on top
17 of a homozygous *PARK2* mutation indicated nevertheless that these patients present with a
18 significant earlier onset age than patients carrying only *PARK2* mutations [Funayama et al.,
19 2008]. This suggested that heterozygous *PINK1* mutations might indeed effect the development
20 of PD, although more research into their biological role is warranted.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **BIOLOGICAL AND PATHOLOGICAL RELEVANCE**

49
50 The pathology in PD brain generally consists of progressive neuronal depigmentation and
51 dopaminergic cell loss in the substantia nigra, accompanied by presence of LB in the residual
52 neurons (Table 5). Interestingly, the LB are common to all disorders in the LBD spectrum,
53
54
55
56
57
58
59
60

1
2
3 although their location in the patient's brain can help specify the exact disorder. In non-demented
4
5 PD patients the LB are usually confined to the brainstem, whereas more widespread cortical LB
6
7 point to PDD or DLB. It is not fully understood yet how mutations in the causal PD genes might
8
9 cause such pathology. Since SNCA is the main constituent of LB [Baba et al., 1998], many
10
11 studies have tried elucidating the biological processes that trigger SNCA aggregation. Direct
12
13 investigation of SNCA itself has provided evidence that mutant SNCA has a greater tendency to
14
15 acquire a misfolded conformation [Conway et al., 2000; Cookson, 2005; Kazantsev et al., 2008],
16
17 stabilized by oligomerisation [Uversky et al., 2001b; Uversky et al., 2001a]. But overexpression
18
19 of wildtype SNCA produces the same effect by triggering a shift from natively unfolded SNCA
20
21 to small oligomers due to concentration burden [Kazantsev et al., 2008; Uversky et al., 2001b].
22
23 Aggregation of SNCA has been shown to be neurotoxic for the cell through the formation of
24
25 intermediate aggregates called protofibrils [Conway et al., 2000; Spillantini et al., 1998].
26
27 Because of their conformation these protofibrils can bind lipid membranes and cause membrane
28
29 permeabilisation. It is suspected that LB sequester these protofibrils as part of a defense
30
31 mechanism of the cell against toxic effects [Bodner et al., 2006; Kazantsev et al., 2008].
32
33 Although a few studies reported the presence of LRRK2 in ubiquitin-positive inclusion bodies
34
35 [Greggio et al., 2006; Perry et al., 2008], it is generally perceived that LRRK2 does not reside in
36
37 LB in affected brains. Interestingly though, associated LRRK2 pathology comprises variable
38
39 lesions; (diffuse) LBs and/or PSP-like tau aggregation or none of the above [Zimprich et al.,
40
41 2004a], suggesting that LRRK2 dysfunction might be an upstream event in neurodegeneration
42
43 and causing disturbances in different pathways. The biological function of LRRK2 however is
44
45 still largely unknown. Mutations in the kinase domain of LRRK2 (p.e. p.Gly2019Ser and
46
47 p.Ile2020Thr) were reported to increase kinase activity [Anand et al., 2009; Gloeckner et al.,
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 2006; Greggio et al., 2006; Guo et al., 2007; Imai et al., 2008; West et al., 2005; West et al.,
4
5
6 2007], but these results were based on autophosphorylation or phosphorylation of heterologous
7
8 substrates, warranting caution in interpreting these data. The mutations in the Roc domain, the
9
10 GTPase regulating the kinase domain, are suspected to impair the function of the GTPase,
11
12 therefore inducing sustained kinase activity of LRRK2 [Guo et al., 2007; Lewis et al., 2007; Li et
13
14 al., 2007]. Furthermore, mutations like the substitutions at codon p.Arg1441 and p.Arg1442Pro
15
16 are located at key positions for the formation of functional LRRK2 dimers; possibly also
17
18 resulting in a decreased GTPase activity [Gotthardt et al., 2008]. As the exact functions of the
19
20 other domains in LRRK2 in relation to kinase activity are unclear, it is difficult to assess the
21
22 impact of mutations in these domains.
23
24
25

26
27 The proteins encoded by the recessive PD genes are all involved in the cell's response
28
29 mechanism to cellular and oxidative stress, implying cell dysfunction or increased vulnerability
30
31 to neurodegeneration in patients carrying mutations in these genes. Mutations in *PARK2* were
32
33 reported to impair the E3 ubiquitin ligase activity of parkin [Shimura et al., 2000], which resulted
34
35 in insufficient protein clearance and the subsequent formation of protein aggregates. On the other
36
37 hand *PINK1* mutations were shown to interfere with its protein stability and kinase activity [Sim
38
39 et al., 2006], possibly causing disrupted mitochondrial trafficking [Wang et al., 2009; Weihofen
40
41 et al., 2009], reduced performance of the electron transport complexes [Gandhi et al., 2009; Liu
42
43 et al., 2009] and elevated ROS formation [Gandhi et al., 2009] due to disturbed calcium
44
45 homestasis, as well as activation of cell death proteins [Plun-Favreau et al., 2007; Pridgeon et al.,
46
47 2007; Wang et al., 2007]. Together parkin and PINK1 are thought to be involved in the same
48
49 pathway upstream of the mitochondrial fission/fusion machinery and mutations in both have
50
51 been shown to result in an increase of mitochondrial fission in mammalian cells [Exner et al.,
52
53
54
55
56
57
58
59
60

1
2
3 2007; Weihofen et al., 2009]. In addition, parkin was shown to be recruited to dysfunctional
4 mitochondria pointing towards a possible role of parkin in the induction of mitophagy [Narendra
5 et al., 2008; Narendra et al., 2009]. Mutations in *PARK2* might impair this function and
6 eventually result in increased cellular toxicity. This hypothesis was supported by a parkin null
7 *Drosophila* model which showed mitochondrial defects and elevated oxidative stress rather than
8 UPS impairment [Greene et al., 2003; Pesah et al., 2004], implying that parkin's involvement in
9 mitochondria might be its primary activity. Nonetheless more studies are needed to investigate
10 the contribution of parkin to this pathogenic pathway.

11
12 In light of this, it seems plausible that digenic combinations of heterozygous mutations in
13 *PARK2* and *PINK1* could be sufficient to cause disease as they might enhance each other's
14 pathogenic effect by concomitant partial loss-of-function of two important enzymes active in the
15 same pathway. Further, mutations in *PARK7* were suspected to contribute to neuronal death
16 through loss of antioxidant activity of DJ-1 and subsequent increase in oxidative stress of the cell
17 [Moore et al., 2003; Ramsey et al., 2008; Taira et al., 2004]. It is not clear yet how the *PARK7*
18 mutations can lead to this impaired functionality. As concomitant deficits in mitochondrial
19 function and UPS activity have been observed, one might suspect a feedback loop between both
20 cellular processes ultimately resulting in cell death and protein excess and aggregation.

21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 **DIAGNOSTIC RELEVANCE**

46
47 The past decade has been very exciting for molecular genetic research of PD. Genetic variants in
48 at least 11 genes have been associated with increased risk for PD and study of the corresponding
49 proteins has been critical for our knowledge of the disease mechanisms underlying PD
50 pathogenesis. For 5 genes there is extensive evidence of causality but screening them all 5 for
51
52
53
54
55
56
57
58
59
60

1
2
3 diagnostic or research purposes is a laborious undertaking. Therefore, mutation studies have been
4
5 often restricted to sequence analyses of the two most frequently mutated genes – *LRRK2* and
6
7 *parkin* – and sometimes even further restricted to sequences coding for functional domains
8
9 within these genes. Therefore, we have incomplete data to calculate the precise contribution of
10
11 mutations in different PD genes together with an underestimation of more complex mutations
12
13 like CNVs.
14
15

16
17 Ideally mutation analyses of the 5 major PD genes should include both sequence analysis and
18
19 dosage analyses to detect CNVs. We investigated 310 Flanders-Belgian patients [Nuytemans et
20
21 al., 2009], and showed high frequencies of heterozygous variants in *PARK2* (9.0%) and *LRRK2*
22
23 (6.1%) and low contributions for *SNCA*, *PINK1* and *PARK7* mutations (0.3%, 0.3% and 0.6%
24
25 respectively). In contrast to other populations, we did not observe the most frequent mutation in
26
27 *LRRK2*, p.Gly2019Ser.
28
29

30
31 It is difficult to compare mutation frequencies between patient groups of different ethnic
32
33 background since even the more recent and extensive mutation analyses in Brazilian, Dutch,
34
35 Korean, Australian or Portugese patient groups [Aguiar et al., 2008; Bras et al., 2008; Camargos
36
37 et al., 2009; Choi et al., 2008; Macedo et al., 2009; Mellick et al., 2009] employed different
38
39 study set ups (selection of patients, genes of interest, domains of interest,..). Here, we provided a
40
41 comprehensive presentation of the mutation frequencies, based on the published studies (Table 3
42
43 and Table 4; PDmutDB: <http://www.molgen.ua.ac.be/PDmutDB>). When analyzing these data it
44
45 became clear that, as in our Flanders-Belgian study, the contributions of *SNCA*, *PINK1* and
46
47 *PARK7* are relatively low. Remarkably, the mutation burden of *PINK1* was increased almost
48
49 twofold in Asian patient groups. *LRRK2* remains the most frequently mutated gene, even when
50
51 heterozygous *PARK2* mutation carriers were included in the equation. These data reinforced the
52
53
54
55
56
57
58
59
60

1
2
3 guidelines on molecular diagnosis of PD that were proposed by the European Federation of
4
5 Neurological Sciences (EFNS [Harbo et al., 2009]). It is important to stress that the frequency
6
7 data depicted here, were extracted from reported studies only, and therefore is likely biased since
8
9
10 *SNCA*, *PINK1* and *PARK7* analyses were often incomplete or even absent.

11
12 Influences of ethnicity on mutation frequencies as well as founder effects have been documented
13
14 for several PD genes. Consequently, only a complete mutation analysis of these genes will allow
15
16 the identification of all relevant mutations both for the individual patient as well as a population
17
18 of interest. In addition, it is important to go on with the genetic characterization of patients even
19
20 if they have been shown to carry a mutation in one gene, since unexpected digenic combinations
21
22 might explain some atypical clinical presentations of individual PD patients. Despite that not all
23
24 studies implemented CNV analyses the observed CNV frequencies are higher than expected,
25
26 implying that gene dosage is a major feature of the genetic etiology of PD. For *PARK2* for
27
28 instance, in approximately 50% of mutation carriers, deletions or duplications of (single) exons
29
30 were identified. For *SNCA*, multiplications were observed not only in familial (~88%) but also in
31
32 seemingly sporadic patients (~12%), resulting in higher CNV frequencies than originally
33
34 anticipated. These data indicate that dosage analysis should be considered in all mutation
35
36 screenings. On the other hand, when performing extensive mutation analyses, problems with
37
38 pathogenicity assessment can occur for some types of mutations. For example genetic variants
39
40 appearing in *LRRK2* domains with unclear biological function or heterozygous *PARK2*
41
42 mutations. The current efforts aiming at developing novel functional assays should be helpful in
43
44 obtaining sufficient evidence to support a pathogenic role – and thus clinical implication – of
45
46 individual mutations in the near future.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

A PD MUTATION DATABASE (PDmutDB)

A huge amount of information on genetic variability in *SNCA*, *PARK2*, *PINK1*, *PARK7* and *LRRK2* and corresponding clinical phenotypes is present in the scientific literature though contained within numerous articles published over the last two decades. In addition, the data provided is often incomplete, fragmented or sometimes even hard to interpret since for example clinical and genetic data of one family or group of patients are reported in separate papers and/or in different formats. Some of the current mutation databases do not systematically provide information on clinical features, familial history and so on, while others are maintained by the goodwill of the researchers themselves and consequently are often incomplete or not up to date. Therefore, we decided to construct a novel PD mutation database, called PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>). This database will be publicly available and will hold information of reported variants with correct nomenclature and references to original studies. To allow for genotype-phenotype correlations, we added detailed familial and clinical data. Importantly, all informative family members are linked to their individual clinical features and identified variants in multiple genes with indication of zygosity. Also, we make an effort to provide an indication of pathogenicity for each variant, whenever sufficient data are available. Data from new publications will be included in the database whenever they contain sufficient genetic information to correctly link each individual to the respective mutations. Individual researchers can submit genetic and/or clinical information using an additional file when their publications do not permit excessive tables. Contact: PDmutDB@molgen.vib-ua.be.

CONCLUSION AND FUTURE PROSPECTS

During the last two decades molecular genetic research has lead to the identification of five important PD genes bearing approximately 500 different DNA variants. These variants make up a wide mutation spectrum including different simple mutations as well as genomic rearrangements. Gathering this information from literature is very laborious since it is scattered across many publications and different studies employ different study designs. Here we present a novel publicly available mutation database PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>). Next to the systematic organization of all DNA variants, this database provides information on family history, clinical features and mutation zygosity. At this time data on approximately 1900 families of sporadic and familial patients is available. Data meta-analysis indicated both high genetic and clinical heterogeneity among mutation carriers. Mutations have been identified in patients with PD but also clinically related disorders such as LBD and Parkinson-plus syndromes. These data underline the complex genetic nature of these neurodegenerative diseases linking them together in spectrum disorders. As only few studies have included patients with PD-related disorders in their mutation analyses, the exact contribution of PD genes to the etiology of other neurodegenerative diseases remains unclear. Even for PD itself, this assessment is not straightforward as most mutation reports present fragmented data on only one or few PD genes. Since more recent data support that dosage plays a major role in PD pathogenesis (e.g. higher frequency of multiplications for *SNCA* than missense mutations and significant contribution of dosage effects in recessive genes), a lot of attention is drawn to gene expression regulation. Non-coding sequence variants in the promoter and UTR regions of PD genes are all potential disease associated variants. Indeed, variants in the *SNCA* promoter and UTR regions (both 5' and 3') were reported to be associated with increased risk for PD [Brighina et al., 2008; Farrer et al.,

1
2
3 2001bb; Hadjigeorgiou et al., 2006; Izumi et al., 2001; Kay et al., 2008; Maraganore et al., 2006;
4
5 Mizuta et al., 2006; Mueller et al., 2005; Myhre et al., 2008b; Pals et al., 2004b; Parsian et al.,
6
7 2007; Ross et al., 2007; Tan et al., 2004; Winkler et al., 2007]. Moreover, recent genome-wide
8
9 association studies (GWAS) in PD patient and control groups confirmed the *SNCA* region as a
10
11 major player in PD susceptibility [Pankratz et al., 2009; Satake et al., 2009; Simon-Sanchez et
12
13 al., 2009]. Also, variants located upstream of *LRRK2* were identified to be associated with
14
15 increased risk for PD, suggesting that variants causing transcriptional upregulation of *LRRK2*
16
17 might be part of PD etiology [Satake et al., 2009; Simon-Sanchez et al., 2009]. Given that not all
18
19 is known about the cell's transcription and translation mechanisms, variants detected in
20
21 previously unexplored genomic regions might turn out to represent a novel group of pathogenic
22
23 variations. It is clear that the research field should keep an open mind when performing mutation
24
25 analyses and interpreting its results as exemplified by the variants in the promoter and UTR
26
27 regions which were previously overlooked. Unfortunately, it is difficult to assess the pathogenic
28
29 nature of these new subtypes of genetic variants without relevant functional assays. This concern
30
31 already exists for several other groups of mutations in known PD genes. For example, we do not
32
33 have unambiguous information on the actual involvement of *PARK2* heterozygotes in PD
34
35 pathogenicity or on the implications of mutations in *LRRK2* regions with less known
36
37 functionality. Even the current functional analyses of putative pathogenicity of *LRRK2* mutations
38
39 might be misleading since no physiological substrate has yet been identified. These concerns
40
41 signify the urgent need of the molecular genetics field to invest more time and efforts in the
42
43 development of relevant functional assays.
44
45
46
47
48
49
50
51

52
53 In order for the novel PDmutDB database to be usable in the broader research field, data on other
54
55 genes associated with PD will be added in the near future. Functional data will also be included
56
57
58
59
60

1
2
3 in the database when these data become available. This way we strive to develop a valuable, easy
4
5 accessible and up to date instrument for future research or diagnostic purposes.
6
7

8 In conclusion, it is clear that our knowledge on underlying genetics of PD gathered in the last
9
10 two decades has provided researchers with incredible amounts of information on the different
11
12 biological pathways involved in the pathogenesis of PD. There are still a large number of
13
14 unanswered questions residing amongst the few solved mysteries, which will need further
15
16 attention in order to fully understand PD in all its facets.
17
18
19

20 21 22 23 24 **ACKNOWLEDGMENTS**

25
26 The research in the authors' research group was supported in part by by the Special Research
27
28 Fund of the University of Antwerp, the Fund for Scientific Research Flanders (FWO-F), the
29
30 Institute for Science and Technology – Flanders (IWT-F), the Foundation for Alzheimer
31
32 Research (SAO/FRMA) and a Methusalem excellence grant of the Flemish Government; K.N.
33
34 was holder of a PhD fellowship of the IWT-F and J.T. holds a postdoctoral fellowships of the
35
36 FWO-V.
37
38
39
40
41
42
43
44
45

46 **REFERENCES**

47
48
49
50
51 Abbas N, Lucking CB, Ricard S, Durr A, Bonifati V, De MG, Bouley S, Vaughan JR, Gasser T,
52
53 Marconi R, Broussolle E, Brefel-Courbon C, Harhangi BS, Oostra BA, Fabrizio E, Bohme GA,
54
55 Pradier L, Wood NW, Filla A, Meco G, Deneffe P, Agid Y, Brice A. 1999. A wide variety of
56
57
58
59
60

1
2
3 mutations in the parkin gene are responsible for autosomal recessive parkinsonism in Europe.
4
5 French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic
6
7 Susceptibility in Parkinson's Disease. *Hum.Mol.Genet.* 8:567-574.
8
9

10
11 Abeliovich A, Schmitz Y, Farinas I, Choi-Lundberg D, Ho WH, Castillo PE, Shinsky N,
12
13 Verdugo JM, Armanini M, Ryan A, Hynes M, Phillips H, Sulzer D, Rosenthal A. 2000. Mice
14
15 lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron*
16
17 25:239-252.
18
19

20
21 Abou-Sleiman PM, Healy DG, Quinn N, Lees AJ, Wood NW. 2003. The role of pathogenic DJ-1
22
23 mutations in Parkinson's disease. *Ann.Neurol.* 54:283-286.
24
25

26
27 Abou-Sleiman PM, Muqit MM, McDonald NQ, Yang YX, Gandhi S, Healy DG, Harvey K,
28
29 Harvey RJ, Deas E, Bhatia K, Quinn N, Lees A, Latchman DS, Wood NW. 2006. A
30
31 heterozygous effect for PINK1 mutations in Parkinson's disease? *Ann.Neurol.* 60:414-419.
32
33

34
35 Adel S, Djarmati A, Kabakci K, Pichler I, Eskelson C, Lohnau T, Kock N, Hagenah J, Hedrich
36
37 K, Schwinger E, Kramer PL, Pramstaller PP, Klein C. 2006. Co-occurrence of restless legs
38
39 syndrome and Parkin mutations in two families. *Mov Disord.* 21:258-263.
40
41

42
43 Aguiar PC, Lessa PS, Godeiro C, Jr., Barsottini O, Felicio AC, Borges V, Silva SM, Saba RA,
44
45 Ferraz HB, Moreira-Filho CA, Andrade LA. 2008. Genetic and environmental findings in early-
46
47 onset Parkinson's disease Brazilian patients. *Mov Disord.* 23:1228-1233.
48
49

50
51 Ahn TB, Kim SY, Kim JY, Park SS, Lee DS, Min HJ, Kim YK, Kim SE, Kim JM, Kim HJ, Cho
52
53 J, Jeon BS. 2008. alpha-Synuclein gene duplication is present in sporadic Parkinson disease.
54
55 *Neurology* 70:43-49.
56
57
58
59
60

- 1
2
3 Alvarez V, Guisasola LM, Moreira VG, Lahoz CH, Coto E. 2001. Early-onset Parkinson's
4 disease associated with a new parkin mutation in a Spanish family. *Neurosci.Lett.* 313:108-110.
5
6
7
8
9 An XK, Peng R, Li T, Burgunder JM, Wu Y, Chen WJ, Zhang JH, Wang YC, Xu YM, Gou YR,
10 Yuan GG, Zhang ZJ. 2008. LRRK2 Gly2385Arg variant is a risk factor of Parkinson's disease
11 among Han-Chinese from mainland China. *Eur.J.Neurol.* 15:301-305.
12
13
14
15
16
17 Anand VS, Reichling LJ, Lipinski K, Stochaj W, Duan W, Kelleher K, Pungaliya P, Brown EL,
18 Reinhart PH, Somberg R, Hirst WD, Riddle SM, Braithwaite SP. 2009. Investigation of leucine-
19 rich repeat kinase 2 : enzymological properties and novel assays. *FEBS J.* 276:466-478.
20
21
22
23
24
25 Annesi F, Rocca EF, Ciro C, I, Carrideo S, Tarantino P, Provenzano G, Civitelli D, De Marco
26 EV, Quattrone A, Annesi G. 2007. Novel human pathological mutations. Gene symbol: PARK2.
27 Disease: Parkinson's disease. *Hum.Genet.* 122:415.
28
29
30
31
32
33 Annesi G, Savettieri G, Pugliese P, D'Amelio M, Tarantino P, Ragonese P, La B, V, Piccoli T,
34 Civitelli D, Annesi F, Fierro B, Piccoli F, Arabia G, Caracciolo M, Ciro C, I, Quattrone A. 2005.
35 DJ-1 mutations and parkinsonism-dementia-amyotrophic lateral sclerosis complex. *Ann.Neurol.*
36 58:803-807.
37
38
39
40
41
42
43
44 Arias VA, Sleegers K, Dekker MC, van Gool WA, van Swieten JC, Aulchenko YS, Oostra BA,
45 van Duijn CM. 2004. A deletion in DJ-1 and the risk of dementia--a population-based survey.
46 *Neurosci.Lett.* 372:196-199.
47
48
49
50
51
52 Athanassiadou A, Voutsinas G, Psiouri L, Leroy E, Polymeropoulos MH, Ilias A, Maniatis GM,
53 Papapetropoulos T. 1999. Genetic analysis of families with Parkinson disease that carry the
54 Ala53Thr mutation in the gene encoding alpha-synuclein. *Am.J.Hum.Genet.* 65:555-558.
55
56
57
58
59
60

1
2
3 Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, Trojanowski JQ, Iwatsubo T. 1998.
4
5 Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia
6
7 with Lewy bodies. *Am.J.Pathol.* 152:879-884.
8
9

10
11 Bardien S, Keyser R, Yako Y, Lombard D, Carr J. 2009. Molecular analysis of the parkin gene
12
13 in South African patients diagnosed with Parkinson's disease. *Parkinsonism.Relat Disord.*
14
15 15:116-121.
16
17

18
19 Bayrakli F, Bilguvar K, Mason CE, DiLuna ML, Bayri Y, Gungor L, Terzi M, Mane SM, Lifton
20
21 RP, State MW, Gunel M. 2007. Rapid identification of disease-causing mutations using copy
22
23 number analysis within linkage intervals. *Hum.Mutat.* 28:1236-1240.
24
25
26

27
28 Bentivoglio AR, Cortelli P, Valente EM, Ialongo T, Ferraris A, Elia A, Montagna P, Albanese A.
29
30 2001. Phenotypic characterisation of autosomal recessive PARK6-linked parkinsonism in three
31
32 unrelated Italian families. *Mov Disord.* 16:999-1006.
33
34

35
36 Berg D, Schweitzer K, Leitner P, Zimprich A, Lichtner P, Belcredi P, Brussel T, Schulte C,
37
38 Maass S, Nagele T. 2005. Type and frequency of mutations in the LRRK2 gene in familial and
39
40 sporadic Parkinson's disease*. *Brain* 128:3000-3011.
41
42

43
44 Bertoli-Avella AM, Giroud-Benitez JL, Akyol A, Barbosa E, Schaap O, van der Linde HC,
45
46 Martignoni E, Lopiano L, Lamberti P, Fincati E, Antonini A, Stocchi F, Montagna P, Squitieri F,
47
48 Marini P, Abbruzzese G, Fabbrini G, Marconi R, Dalla LA, Trianni G, Guidi M, De GA, Boff
49
50 MG, De LA, Gallai V, de RG, Vanacore N, Mecocci G, van Duijn CM, Oostra BA, Heutink P,
51
52 Bonifati V. 2005. Novel parkin mutations detected in patients with early-onset Parkinson's
53
54 disease. *Mov Disord.* 20:424-431.
55
56
57
58
59
60

1
2
3 Biswas A, Gupta A, Naiya T, Das G, Neogi R, Datta S, Mukherjee S, Das SK, Ray K, Ray J.
4
5 2006. Molecular pathogenesis of Parkinson's disease: identification of mutations in the Parkin
6
7 gene in Indian patients. *Parkinsonism.Relat Disord.* 12:420-426.
8
9

10
11 Bodner RA, Housman DE, Kazantsev AG. 2006. New directions for neurodegenerative disease
12
13 therapy: using chemical compounds to boost the formation of mutant protein inclusions. *Cell*
14
15 *Cycle* 5:1477-1480.
16
17

18
19 Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MC, Squitieri F,
20
21 Ibanez P, Joesse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn
22
23 CM, Oostra BA, Heutink P. 2003. Mutations in the DJ-1 gene associated with autosomal
24
25 recessive early-onset parkinsonism. *Science* 299:256-259.
26
27

28
29
30 Bonifati V, Rohe CF, Breedveld GJ, Fabrizio E, De MM, Tassorelli C, Tavella A, Marconi R,
31
32 Nicholl DJ, Chien HF, Fincati E, Abbruzzese G, Marini P, De GA, Horstink MW, Maat-Kievit
33
34 JA, Sampaio C, Antonini A, Stocchi F, Montagna P, Toni V, Guidi M, Dalla LA, Tinazzi M, De
35
36 PF, Fabbrini G, Goldwurm S, de KA, Barbosa E, Lopiano L, Martignoni E, Lamberti P,
37
38 Vanacore N, Meco G, Oostra BA. 2005. Early-onset parkinsonism associated with PINK1
39
40 mutations: frequency, genotypes, and phenotypes. *Neurology* 65:87-95.
41
42
43
44

45 Bostantjopoulou S, Katsarou Z, Papadimitriou A, Veletza V, Hatzigeorgiou G, Lees A. 2001.
46
47 Clinical features of parkinsonian patients with the alpha-synuclein (G209A) mutation. *Mov*
48
49 *Disord.* 16:1007-1013.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Bras J, Guerreiro R, Ribeiro M, Morgadinho A, Januario C, Dias M, Calado A, Semedo C,
4
5 Oliveira C, Hardy J, Singleton A. 2008. Analysis of Parkinson disease patients from Portugal for
6
7 mutations in SNCA, PRKN, PINK1 and LRRK2. *BMC.Neurol.* 8:1.
8
9

10
11 Brighina L, Frigerio R, Schneider NK, Lesnick TG, de AM, Cunningham JM, Farrer MJ,
12
13 Lincoln SJ, Checkoway H, Rocca WA, Maraganore DM. 2008. Alpha-synuclein, pesticides, and
14
15 Parkinson disease: a case-control study. *Neurology* 70:1461-1469.
16
17

18
19 Brooks J, Ding J, Simon-Sanchez J, Paisan-Ruiz C, Singleton AB, Scholz SW. 2009. Parkin and
20
21 PINK1 mutations in early-onset Parkinson's disease: comprehensive screening in publicly
22
23 available cases and control. *J.Med.Genet.* 46:375-381.
24
25
26

27
28 Bruggemann N, Mitterer M, Lanthaler AJ, Djarmati A, Hagenah J, Wiegers K, Winkler S,
29
30 Pawlack H, Lohnau T, Pramstaller PP, Klein C, Lohmann K. 2009. Frequency of heterozygous
31
32 Parkin mutations in healthy subjects: need for careful prospective follow-up examination of
33
34 mutation carriers. *Parkinsonism.Relat Disord.* 15:425-429.
35
36
37

38
39 Camargos ST, Dornas LO, Momeni P, Lees A, Hardy J, Singleton A, Cardoso F. 2009. Familial
40
41 Parkinsonism and early onset Parkinson's disease in a Brazilian movement disorders clinic:
42
43 phenotypic characterization and frequency of SNCA, PRKN, PINK1, and LRRK2 mutations.
44
45 *Mov Disord.* 24:662-666.
46
47

48
49 Carmine Belin A, Westerlund M, Sydow O, Lundstromer K, Hakansson A, Nissbrandt H, Olson
50
51 L, Galter D. 2006. Leucine-rich repeat kinase 2 (LRRK2) mutations in a Swedish Parkinson
52
53 cohort and a healthy nonagenarian. *Mov Disord.* 21:1731-1734.
54
55
56
57
58
59
60

- 1
2
3 Cazeneuve C, San C, Ibrahim SA, Mukhtar MM, Kheir MM, Leguern E, Brice A, Salih MA.
4
5 2009. A new complex homozygous large rearrangement of the PINK1 gene in a Sudanese family
6
7 with early onset Parkinson's disease. *Neurogenetics*. 10:265-270.
8
9
10
11 Chan DK, Mok V, Ng PW, Yeung J, Kwok JB, Fang ZM, Clarke R, Wong L, Schofield PR,
12
13 Hattori N. 2008. PARK2 mutations and clinical features in a Chinese population with early-onset
14
15 Parkinson's disease. *J.Neural Transm*. 115:715-719.
16
17
18
19 Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C,
20
21 Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destee A.
22
23 2004. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet*
24
25 364:1167-1169.
26
27
28
29
30 Chaudhary S, Behari M, Dihana M, Swaminath PV, Govindappa ST, Jayaram S, Goyal V,
31
32 Maitra A, Muthane UB, Juyal RC, Thelma BK. 2006. Parkin mutations in familial and sporadic
33
34 Parkinson's disease among Indians. *Parkinsonism.Relat Disord*. 12:239-245.
35
36
37
38 Chen R, Gosavi NS, Langston JW, Chan P. 2003. Parkin mutations are rare in patients with
39
40 young-onset parkinsonism in a US population. *Parkinsonism.Relat Disord*. 9:309-312.
41
42
43
44 Chen-Plotkin AS, Yuan W, Anderson C, McCarty WE, Hurtig HI, Clark CM, Miller BL, Lee
45
46 VM, Trojanowski JQ, Grossman M, Van D, V. 2008. Corticobasal syndrome and primary
47
48 progressive aphasia as manifestations of LRRK2 gene mutations. *Neurology* 70:521-527.
49
50
51
52 Chishti MA, Bohlega S, Ahmed M, Loualich A, Carroll P, Sato C, St George-Hyslop P,
53
54 Westaway D, Rogaeva E. 2006. T313M PINK1 mutation in an extended highly consanguineous
55
56 Saudi family with early-onset Parkinson disease. *Arch.Neurol*. 63:1483-1485.
57
58
59
60

1
2
3 Choi JM, Woo MS, Ma HI, Kang SY, Sung YH, Yong SW, Chung SJ, Kim JS, Shin HW, Lyoo
4 CH, Lee PH, Baik JS, Kim SJ, Park MY, Sohn YH, Kim JH, Kim JW, Lee MS, Lee MC, Kim
5 DH, Kim YJ. 2008. Analysis of PARK genes in a Korean cohort of early-onset Parkinson
6 disease. *Neurogenetics*. 9:263-269.
7

8
9
10
11
12
13
14 Chung SJ, Park HK, Ki CS, Kim MJ, Lee MC. 2008. Marked diurnal fluctuation and rest benefit
15 in a patient with parkin mutation. *Mov Disord*. 23:624-626.
16

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Ciro C, I, Annesi F, Rocca EF, Carrideo S, Tarantino P, Provenzano G, Civitelli D, De Marco
EV, Quattrone A, Annesi G. 2007. Novel human pathological mutations. Gene symbol: PARK2.
Disease: Parkinson's disease. *Hum.Genet*. 122:416.

Clarimon J, Johnson J, Dogu O, Horta W, Khan N, Lees AJ, Hardy J, Singleton A. 2005.
Defining the ends of Parkin exon 4 deletions in two different families with Parkinson's disease.
Am.J.Med.Genet.B Neuropsychiatr.Genet. 133B:120-123.

Clarimon J, Pagonabarraga J, Paisan-Ruiz C, Campolongo A, Pascual-Sedano B, Marti-Masso
JF, Singleton AB, Kulisevsky J. 2008. Tremor dominant parkinsonism: Clinical description and
LRRK2 mutation screening. *Mov Disord*. 23:518-523.

Clark LN, Afridi S, Karlins E, Wang Y, Mejia-Santana H, Harris J, Louis ED, Cote LJ, Andrews
H, Fahn S, Waters C, Ford B, Frucht S, Ottman R, Marder K. 2006. Case-control study of the
parkin gene in early-onset Parkinson disease. *Arch.Neurol*. 63:548-552.

Clark LN, Afridi S, Mejia-Santana H, Harris J, Louis ED, Cote LJ, Andrews H, Singleton A,
Wavrant De-Vrieze F, Hardy J, Mayeux R, Fahn S, Waters C, Ford B, Frucht S, Ottman R,

1
2
3 Marder K. 2004. Analysis of an early-onset Parkinson's disease cohort for DJ-1 mutations. *Mov*
4
5 *Disord.* 19:796-800.
6
7

8
9 Conway KA, Lee SJ, Rochet JC, Ding TT, Williamson RE, Lansbury PT, Jr. 2000. Acceleration
10
11 of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations
12
13 linked to early-onset Parkinson's disease: implications for pathogenesis and therapy.
14
15 *Proc.Natl.Acad.Sci.U.S.A* 97:571-576.
16
17

18
19 Cookson MR. 2005. The biochemistry of Parkinson's disease. *Annu.Rev.Biochem.* 74:29-52.
20
21

22
23 Criscuolo C, Volpe G, De RA, Varrone A, Marongiu R, Mancini P, Salvatore E, Dallapiccola B,
24
25 Filla A, Valente EM, De MG. 2006. PINK1 homozygous W437X mutation in a patient with
26
27 apparent dominant transmission of parkinsonism. *Mov Disord.* 21:1265-1267.
28
29

30
31 Dachsel JC, Mata IF, Ross OA, Taylor JP, Lincoln SJ, Hinkle KM, Huerta C, Ribacoba R,
32
33 Blazquez M, Alvarez V, Farrer MJ. 2006. Digenic parkinsonism: investigation of the synergistic
34
35 effects of PRKN and LRRK2. *Neurosci.Lett.* 410:80-84.
36
37

38
39 Dachsel JC, Ross OA, Mata IF, Kachergus J, Toft M, Cannon A, Baker M, Adamson J, Hutton
40
41 M, Dickson DW, Farrer MJ. 2007. Lrrk2 G2019S substitution in frontotemporal lobar
42
43 degeneration with ubiquitin-immunoreactive neuronal inclusions. *Acta Neuropathol.* 113:601-
44
45 606.
46
47

48
49 Davidson WS, Jonas A, Clayton DF, George JM. 1998. Stabilization of alpha-synuclein
50
51 secondary structure upon binding to synthetic membranes. *J.Biol.Chem.* 273:9443-9449.
52
53
54
55
56
57
58
59
60

1
2
3 Deng H, Dodson MW, Huang H, Guo M. 2008a. The Parkinson's disease genes pink1 and parkin
4 promote mitochondrial fission and/or inhibit fusion in Drosophila. *Proc.Natl.Acad.Sci.U.S.A*
5
6 105:14503-14508.
7
8

9
10
11 Deng H, Le W, Shahed J, Xie W, Jankovic J. 2008b. Mutation analysis of the parkin and PINK1
12 genes in American Caucasian early-onset Parkinson disease families. *Neurosci.Lett.* 430:18-22.
13
14

15
16
17 Deng H, Le WD, Hunter CB, Mejia N, Xie WJ, Jankovic J. 2007. A family with Parkinson
18 disease, essential tremor, bell palsy, and parkin mutations. *Arch.Neurol.* 64:421-424.
19
20

21
22
23 Di Fonzo A, Dekker MC, Montagna P, Baruzzi A, Yonova EH, Correia GL, Szczerbinska A,
24
25 Zhao T, Dubbel-Hulsman LO, Wouters CH, de GE, Oyen WJ, Simons EJ, Breedveld GJ, Oostra
26
27 BA, Horstink MW, Bonifati V. 2009. FBXO7 mutations cause autosomal recessive, early-onset
28 parkinsonian-pyramidal syndrome. *Neurology* 72:240-245.
29
30

31
32
33 Di Fonzo A, Rohe CF, Ferreira J, Chien HF, Vacca L, Stocchi F, Guedes L, Fabrizio E, Manfredi
34
35 M, Vanacore N, Goldwurm S, Breedveld G, Sampaio C, Meco G, Barbosa E, Oostra BA,
36
37 Bonifati V. 2005. A frequent LRRK2 gene mutation associated with autosomal dominant
38 Parkinson's disease. *Lancet* 365:412-415.
39
40
41

42
43
44 Di Fonzo A, Tassorelli C, De MM, Chien HF, Ferreira J, Rohe CF, Riboldazzi G, Antonini A,
45
46 Albani G, Mauro A, Marconi R, Abbruzzese G, Lopiano L, Fincati E, Guidi M, Marini P,
47
48 Stocchi F, Onofrj M, Toni V, Tinazzi M, Fabbrini G, Lamberti P, Vanacore N, Meco G, Leitner
49
50 P, Uitti RJ, Wszolek ZK, Gasser T, Simons EJ, Breedveld GJ, Goldwurm S, Pezzoli G, Sampaio
51
52 C, Barbosa E, Martignoni E, Oostra BA, Bonifati V. 2006a. Comprehensive analysis of the
53
54 LRRK2 gene in sixty families with Parkinson's disease. *Eur.J.Hum.Genet.* 14:322-331.
55
56
57
58
59
60

1
2
3 Di Fonzo A, Wu-Chou YH, Lu CS, van Doeselaar M, Simons EJ, Rohe CF, Chang HC, Chen
4
5 RS, Weng YH, Vanacore N, Breedveld GJ, Oostra BA, Bonifati V. 2006b. A common missense
6
7 variant in the LRRK2 gene, Gly2385Arg, associated with Parkinson's disease risk in Taiwan.
8
9

10 Neurogenetics. 7:133-138.

11
12
13 Djarmati A, Hedrich K, Svetel M, Lohnau T, Schwinger E, Romac S, Pramstaller PP, Kostic V,
14
15 Klein C. 2006. Heterozygous PINK1 mutations: a susceptibility factor for Parkinson disease?
16
17 Mov Disord. 21:1526-1530.
18
19

20
21
22 Djarmati A, Hedrich K, Svetel M, Schafer N, Juric V, Vukosavic S, Hering R, Riess O, Romac
23
24 S, Klein C, Kostic V. 2004. Detection of Parkin (PARK2) and DJ1 (PARK7) mutations in early-
25
26 onset Parkinson disease: Parkin mutation frequency depends on ethnic origin of patients.
27
28 Hum.Mutat. 23:525.
29
30

31
32 Ephraty L, Porat O, Israeli D, Cohen OS, Tunkel O, Yael S, Hatano Y, Hattori N, Hassin-Baer S.
33
34 2007. Neuropsychiatric and cognitive features in autosomal-recessive early parkinsonism due to
35
36 PINK1 mutations. Mov Disord. 22:566-569.
37
38

39
40 Exner N, Treske B, Paquet D, Holmstrom K, Schiesling C, Gispert S, Carballo-Carbajal I, Berg
41
42 D, Hoepken HH, Gasser T, Kruger R, Winklhofer KF, Vogel F, Reichert AS, Auburger G, Kahle
43
44 PJ, Schmid B, Haass C. 2007. Loss-of-function of human PINK1 results in mitochondrial
45
46 pathology and can be rescued by parkin. J.Neurosci. 27:12413-12418.
47
48

49
50 Farrer M, Chan P, Chen R, Tan L, Lincoln S, Hernandez D, Forno L, Gwinn-Hardy K, Petrucelli
51
52 L, Hussey J, Singleton A, Tanner C, Hardy J, Langston JW. 2001a. Lewy bodies and
53
54 parkinsonism in families with parkin mutations. Ann.Neurol. 50:293-300.
55
56
57
58
59
60

1
2
3 Farrer M, Kachergus J, Forno L, Lincoln S, Wang DS, Hulihan M, Maraganore D, Gwinn-Hardy
4
5 K, Wszolek Z, Dickson D, Langston JW. 2004. Comparison of kindreds with parkinsonism and
6
7 alpha-synuclein genomic multiplications. *Ann.Neurol.* 55:174-179.
8
9

10
11 Farrer M, Maraganore DM, Lockhart P, Singleton A, Lesnick TG, de AM, West A, de SR, Hardy
12
13 J, Hernandez D. 2001b. alpha-Synuclein gene haplotypes are associated with Parkinson's disease.
14
15 *Hum.Mol.Genet.* 10:1847-1851.
16
17

18
19 Farrer M, Stone J, Mata IF, Lincoln S, Kachergus J, Hulihan M, Strain KJ, Maraganore DM.
20
21 2005. LRRK2 mutations in Parkinson disease. *Neurology* 65:738-740.
22
23

24
25 Farrer MJ, Stone JT, Lin CH, Dachsel JC, Hulihan MM, Haugarvoll K, Ross OA, Wu RM. 2007.
26
27 *Lrrk2* G2385R is an ancestral risk factor for Parkinson's disease in Asia. *Parkinsonism.Relat*
28
29 *Disord.* 13:89-92.
30
31

32
33 Ferreira JJ, Guedes LC, Rosa MM, Coelho M, van DM, Schweiger D, Di FA, Oostra BA,
34
35 Sampaio C, Bonifati V. 2007. High prevalence of LRRK2 mutations in familial and sporadic
36
37 Parkinson's disease in Portugal. *Mov Disord.* 22:1194-1201.
38
39

40
41 Foroud T, Uniacke SK, Liu L, Pankratz N, Rudolph A, Halter C, Shults C, Marder K, Conneally
42
43 PM, Nichols WC. 2003. Heterozygosity for a mutation in the parkin gene leads to later onset
44
45 Parkinson disease. *Neurology* 60:796-801.
46
47

48
49 Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schule B, Langston JW, Middleton FA,
50
51 Ross OA, Hulihan M, Gasser T, Farrer MJ. 2007. Phenotypic variation in a large Swedish
52
53 pedigree due to SNCA duplication and triplication. *Neurology* 68:916-922.
54
55
56
57
58
59
60

1
2
3 Funayama M, Hasegawa K, Kowa H, Saito M, Tsuji S, Obata F. 2002. A new locus for
4 Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann.Neurol.* 51:296-301.
5
6

7
8
9 Funayama M, Li Y, Tsoi TH, Lam CW, Ohi T, Yazawa S, Uyama E, Djaldetti R, Melamed E,
10 Yoshino H, Imamichi Y, Takashima H, Nishioka K, Sato K, Tomiyama H, Kubo S, Mizuno Y,
11 Hattori N. 2008. Familial Parkinsonism with digenic parkin and PINK1 mutations. *Mov Disord.*
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

23:1461-1465.

Fung HC, Chen CM, Hardy J, Singleton AB, Lee-Chen GJ, Wu YR. 2006a. Analysis of the
PINK1 gene in a cohort of patients with sporadic early-onset parkinsonism in Taiwan.
Neurosci.Lett. 394:33-36.

Fung HC, Chen CM, Hardy J, Singleton AB, Wu YR. 2006b. A common genetic factor for
Parkinson disease in ethnic Chinese population in Taiwan. *BMC.Neurol.* 6:47.

Gaig C, Ezquerra M, Marti MJ, Munoz E, Valldeoriola F, Tolosa E. 2006. LRRK2 mutations in
Spanish patients with Parkinson disease: frequency, clinical features, and incomplete penetrance.
Arch.Neurol. 63:377-382.

Gaig C, Ezquerra M, Marti MJ, Valldeoriola F, Munoz E, Llado A, Rey MJ, Cardozo A,
Molinuevo JL, Tolosa E. 2008. Screening for the LRRK2 G2019S and codon-1441 mutations in
a pathological series of parkinsonian syndromes and frontotemporal lobar degeneration.
J.Neurol.Sci. 270:94-98.

Gaig C, Marti MJ, Ezquerra M, Rey MJ, Cardozo A, Tolosa E. 2007. G2019S LRRK2 mutation
causing Parkinson's disease without Lewy bodies. *J.Neurol.Neurosurg.Psychiatry* 78:626-628.

1
2
3 Gandhi S, Wood-Kaczmar A, Yao Z, Plun-Favreau H, Deas E, Klupsch K, Downward J,
4
5 Latchman DS, Tabrizi SJ, Wood NW, DuChen MR, Abramov AY. 2009. PINK1-associated
6
7 Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Mol.Cell*
8
9 33:627-638.

10
11
12
13 Gao L, Gomez-Garre P, az-Corrales FJ, Carrillo F, Carballo M, Palomino A, az-Martin J, Mejias
14
15 R, Vime PJ, Lopez-Barneo J, Mir P. 2009. Prevalence and clinical features of LRRK2 mutations
16
17 in patients with Parkinson's disease in southern Spain. *Eur.J.Neurol.*
18
19

20
21
22 Gelmetti V, Ferraris A, Brusa L, Romano F, Lombardi F, Barzaghi C, Stanzione P, Garavaglia
23
24 B, Dallapiccola B, Valente EM. 2008. Late onset sporadic Parkinson's disease caused by PINK1
25
26 mutations: clinical and functional study. *Mov Disord.* 23:881-885.
27
28

29
30 Giasson BI, Covy JP, Bonini NM, Hurtig HI, Farrer MJ, Trojanowski JQ, Van D, V. 2006.
31
32 Biochemical and pathological characterization of Lrrk2. *Ann.Neurol.* 59:315-322.
33
34

35
36 Gilks WP, bou-Sleiman PM, Gandhi S, Jain S, Singleton A, Lees AJ, Shaw K, Bhatia KP,
37
38 Bonifati V, Quinn NP, Lynch J, Healy DG, Holton JL, Revesz T, Wood NW. 2005. A common
39
40 LRRK2 mutation in idiopathic Parkinson's disease. *Lancet* 365:415-416.
41
42

43
44 Giordana MT, D'Agostino C, Albani G, Mauro A, Di FA, Antonini A, Bonifati V. 2007.
45
46 Neuropathology of Parkinson's disease associated with the LRRK2 Ile1371Val mutation. *Mov*
47
48 *Disord.* 22:275-278.
49

50
51
52 Gloeckner CJ, Kinkl N, Schumacher A, Braun RJ, O'Neill E, Meitinger T, Kolch W, Prokisch H,
53
54 Ueffing M. 2006. The Parkinson disease causing LRRK2 mutation I2020T is associated with
55
56 increased kinase activity. *Hum.Mol.Genet.* 15:223-232.
57
58
59
60

1
2
3 Godeiro-Junior C, de Carvalho-Aguiar PM, Felicio AC, Barsottini OG, Silva SM, Borges V,
4
5 Andrade LA, Ferraz HB. 2009. PINK1 mutations in a Brazilian cohort of early-onset Parkinson's
6
7 disease patients. *Mov Disord*.
8
9

10
11 Goldwurm S, Di FA, Simons EJ, Rohe CF, Zini M, Canesi M, Tesei S, Zecchinelli A, Antonini
12
13 A, Mariani C, Meucci N, Sacilotto G, Sironi F, Salani G, Ferreira J, Chien HF, Fabrizio E,
14
15 Vanacore N, Dalla LA, Stocchi F, Diroma C, Lamberti P, Sampaio C, Meco G, Barbosa E,
16
17 Bertoli-Avella AM, Breedveld GJ, Oostra BA, Pezzoli G, Bonifati V. 2005. The G6055A
18
19 (G2019S) mutation in LRRK2 is frequent in both early and late onset Parkinson's disease and
20
21 originates from a common ancestor. *J.Med.Genet*. 42:e65.
22
23
24
25

26
27 Gonzalez-Fernandez MC, Lezcano E, Ross OA, Gomez-Esteban JC, Gomez-Busto F, Velasco F,
28
29 varez-Alvarez M, Rodriguez-Martinez MB, Ciordia R, Zarranz JJ, Farrer MJ, Mata IF, de
30
31 Pancorbo MM. 2007. Lrrk2-associated parkinsonism is a major cause of disease in Northern
32
33 Spain. *Parkinsonism.Relat Disord*. 13:509-515.
34
35

36
37 Gorostidi A, Ruiz-Martinez J, de Munain AL, Alzualde A, Masso JF. 2009. LRRK2 G2019S and
38
39 R1441G mutations associated with Parkinson's disease are common in the Basque Country, but
40
41 relative prevalence is determined by ethnicity. *Neurogenetics*. 10:157-159.
42
43
44

45
46 Gosal D, Lynch T, Ross OA, Haugarvoll K, Farrer MJ, Gibson JM. 2007. Global distribution and
47
48 reduced penetrance: Lrrk2 R1441C in an Irish Parkinson's disease kindred. *Mov Disord*. 22:291-
49
50 292.
51
52
53
54
55
56
57
58
59
60

1
2
3 Gotthardt K, Weyand M, Kortholt A, Van Haastert PJ, Wittinghofer A. 2008. Structure of the
4 Roc-COR domain tandem of *C. tepidum*, a prokaryotic homologue of the human LRRK2
5
6 Roc-COR domain tandem of *C. tepidum*, a prokaryotic homologue of the human LRRK2
7
8 Parkinson kinase. *EMBO J.* 27:2352.
9

10
11 Gouider-Khouja N, Larnaout A, Amouri R, Sfar S, Belal S, Ben HC, Ben HM, Hattori N,
12
13 Mizuno Y, Hentati F. 2003. Autosomal recessive parkinsonism linked to parkin gene in a
14
15 Tunisian family. Clinical, genetic and pathological study. *Parkinsonism.Relat Disord.* 9:247-251.
16
17

18
19 Greene JC, Whitworth AJ, Kuo I, Andrews LA, Feany MB, Pallanck LJ. 2003. Mitochondrial
20
21 pathology and apoptotic muscle degeneration in *Drosophila* parkin mutants.
22
23 *Proc.Natl.Acad.Sci.U.S.A* 100:4078-4083.
24
25

26
27
28 Greggio E, Jain S, Kingsbury A, Bandopadhyay R, Lewis P, Kaganovich A, van der Brug MP,
29
30 Beilina A, Blackinton J, Thomas KJ, Ahmad R, Miller DW, Kesavapany S, Singleton A, Lees A,
31
32 Harvey RJ, Harvey K, Cookson MR. 2006. Kinase activity is required for the toxic effects of
33
34 mutant LRRK2/dardarin. *Neurobiol.Dis.* 23:329-341.
35
36

37
38 Greggio E, Zambrano I, Kaganovich A, Beilina A, Taymans JM, Daniels V, Lewis P, Jain S,
39
40 Ding J, Syed A, Thomas KJ, Baekelandt V, Cookson MR. 2008. The Parkinson disease-
41
42 associated leucine-rich repeat kinase 2 (LRRK2) is a dimer that undergoes intramolecular
43
44 autophosphorylation. *J.Biol.Chem.* 283:16906-16914.
45
46

47
48 Guo JF, Xiao B, Liao B, Zhang XW, Nie LL, Zhang YH, Shen L, Jiang H, Xia K, Pan Q, Yan
49
50 XX, Tang BS. 2008. Mutation analysis of Parkin, PINK1, DJ-1 and ATP13A2 genes in Chinese
51
52 patients with autosomal recessive early-onset Parkinsonism. *Mov Disord.* 23:2074-2079.
53
54
55
56
57
58
59
60

1
2
3 Guo L, Gandhi PN, Wang W, Petersen RB, Wilson-Delfosse AL, Chen SG. 2007. The
4
5 Parkinson's disease-associated protein, leucine-rich repeat kinase 2 (LRRK2), is an authentic
6
7 GTPase that stimulates kinase activity. *Exp.Cell Res.* 313:3658-3670.
8
9

10
11 Gwinn-Hardy K, Mehta ND, Farrer M, Maraganore D, Muentner M, Yen SH, Hardy J, Dickson
12
13 DW. 2000. Distinctive neuropathology revealed by alpha-synuclein antibodies in hereditary
14
15 parkinsonism and dementia linked to chromosome 4p. *Acta Neuropathol.* 99:663-672.
16
17

18
19 Hadjigeorgiou GM, Xiromerisiou G, Gourbali V, Aggelakis K, Scarmeas N, Papadimitriou A,
20
21 Singleton A. 2006. Association of alpha-synuclein Rep1 polymorphism and Parkinson's disease:
22
23 influence of Rep1 on age at onset. *Mov Disord.* 21:534-539.
24
25

26
27 Hague S, Rogaeva E, Hernandez D, Gulick C, Singleton A, Hanson M, Johnson J, Weiser R,
28
29 Gallardo M, Ravina B, Gwinn-Hardy K, Crawley A, PH SG-H, Lang AE, Heutink P, Bonifati V,
30
31 Hardy J, Singleton A. 2003. Early-onset Parkinson's disease caused by a compound heterozygous
32
33 DJ-1 mutation. *Ann.Neurol.* 54:271-274.
34
35

36
37 Harbo HF, Finsterer J, Baets J, Van BC, Di DS, Fontaine B, De JP, Lossos A, Lynch T, Mariotti
38
39 C, Schols L, Spinazzola A, Szolnoki Z, Tabrizi SJ, Tallaksen C, Zeviani M, Burgunder JM,
40
41 Gasser T. 2009. EFNS guidelines on the molecular diagnosis of neurogenetic disorders: general
42
43 issues, Huntington's disease, Parkinson's disease and dystonias. *Eur.J.Neurol.* 16:777-785.
44
45

46
47 Hatano Y, Li Y, Sato K, Asakawa S, Yamamura Y, Tomiyama H, Yoshino H, Asahina M,
48
49 Kobayashi S, Hassin-Baer S, Lu CS, Ng AR, Rosales RL, Shimizu N, Toda T, Mizuno Y,
50
51 Hattori N. 2004. Novel PINK1 mutations in early-onset parkinsonism. *Ann.Neurol.* 56:424-427.
52
53
54
55
56
57
58
59
60

1
2
3 Hattori N, Kitada T, Matsumine H, Asakawa S, Yamamura Y, Yoshino H, Kobayashi T,
4
5 Yokochi M, Wang M, Yoritaka A, Kondo T, Kuzuhara S, Nakamura S, Shimizu N, Mizuno Y.
6
7 1998a. Molecular genetic analysis of a novel Parkin gene in Japanese families with autosomal
8
9 recessive juvenile parkinsonism: evidence for variable homozygous deletions in the Parkin gene
10
11 in affected individuals. *Ann.Neurol.* 44:935-941.
12
13

14
15
16 Hattori N, Matsumine H, Asakawa S, Kitada T, Yoshino H, Elibol B, Brookes AJ, Yamamura Y,
17
18 Kobayashi T, Wang M, Yoritaka A, Minoshima S, Shimizu N, Mizuno Y. 1998b. Point
19
20 mutations (Thr240Arg and Gln311Stop) [correction of Thr240Arg and Ala311Stop] in the
21
22 Parkin gene. *Biochem.Biophys.Res.Comm.* 249:754-758.
23
24

25
26 Haubenberger D, Bonelli S, Hotzy C, Leitner P, Lichtner P, Samal D, Katzenschlager R,
27
28 Djamshidian A, Brucke T, Steffelbauer M, Bancher C, Grossmann J, Ransmayr G, Strom TM,
29
30 Meitinger T, Gasser T, Auff E, Zimprich A. 2007. A novel LRRK2 mutation in an Austrian
31
32 cohort of patients with Parkinson's disease. *Mov Disord.* 22:1640-1643.
33
34

35
36 Haugarvoll K, Rademakers R, Kachergus JM, Nuytemans K, Ross OA, Gibson JM, Tan EK,
37
38 Gaig C, Tolosa E, Goldwurm S, Guidi M, Riboldazzi G, Brown L, Walter U, Benecke R, Berg
39
40 D, Gasser T, Theuns J, Pals P, Cras P, De Deyn PP, Engelborghs S, Pickut B, Uitti RJ, Foroud T,
41
42 Nichols WC, Hagenah J, Klein C, Samii A, Zabetian CP, Bonifati V, Van BC, Farrer MJ,
43
44 Wszolek ZK. 2008. Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson
45
46 disease. *Neurology* 70:1456-1460.
47
48

49
50
51 Hayashi S, Wakabayashi K, Ishikawa A, Nagai H, Saito M, Maruyama M, Takahashi T, Ozawa
52
53 T, Tsuji S, Takahashi H. 2000. An autopsy case of autosomal-recessive juvenile parkinsonism
54
55 with a homozygous exon 4 deletion in the parkin gene. *Mov Disord.* 15:884-888.
56
57
58
59
60

1
2
3 Healy DG, bou-Sleiman PM, Gibson JM, Ross OA, Jain S, Gandhi S, Gosal D, Muqit MM,
4
5 Wood NW, Lynch T. 2004. PINK1 (PARK6) associated Parkinson disease in Ireland. *Neurology*
6
7 63:1486-1488.
8
9

10
11 Hedrich K, Djarmati A, Schafer N, Hering R, Wellenbrock C, Weiss PH, Hilker R, Vieregge P,
12
13 Ozelius LJ, Heutink P, Bonifati V, Schwinger E, Lang AE, Noth J, Bressman SB, Pramstaller
14
15 PP, Riess O, Klein C. 2004a. DJ-1 (PARK7) mutations are less frequent than Parkin (PARK2)
16
17 mutations in early-onset Parkinson disease. *Neurology* 62:389-394.
18
19

20
21 Hedrich K, Eskelson C, Wilmot B, Marder K, Harris J, Garrels J, Meija-Santana H, Vieregge P,
22
23 Jacobs H, Bressman SB, Lang AE, Kann M, Abbruzzese G, Martinelli P, Schwinger E, Ozelius
24
25 LJ, Pramstaller PP, Klein C, Kramer P. 2004b. Distribution, type, and origin of Parkin mutations:
26
27 review and case studies. *Mov Disord.* 19:1146-1157.
28
29

30
31 Hedrich K, Hagenah J, Djarmati A, Hiller A, Lohnau T, Lasek K, Grunewald A, Hilker R,
32
33 Steinlechner S, Boston H, Kock N, Schneider-Gold C, Kress W, Siebner H, Binkofski F, Lencer
34
35 R, Munchau A, Klein C. 2006a. Clinical spectrum of homozygous and heterozygous PINK1
36
37 mutations in a large German family with Parkinson disease: role of a single hit? *Arch.Neurol.*
38
39 63:833-838.
40
41
42
43

44
45 Hedrich K, Kann M, Lanthaler AJ, Dalski A, Eskelson C, Landt O, Schwinger E, Vieregge P,
46
47 Lang AE, Breakefield XO, Ozelius LJ, Pramstaller PP, Klein C. 2001. The importance of gene
48
49 dosage studies: mutational analysis of the parkin gene in early-onset parkinsonism.
50
51 *Hum.Mol.Genet.* 10:1649-1656.
52
53
54
55
56
57
58
59
60

1
2
3 Hedrich K, Marder K, Harris J, Kann M, Lynch T, Meija-Santana H, Pramstaller PP, Schwinger
4 E, Bressman SB, Fahn S, Klein C. 2002. Evaluation of 50 probands with early-onset Parkinson's
5 disease for Parkin mutations. *Neurology* 58:1239-1246.
6
7

8
9
10
11 Hedrich K, Winkler S, Hagenah J, Kabakci K, Kasten M, Schwinger E, Volkmann J, Pramstaller
12 PP, Kostic V, Vieregge P, Klein C. 2006b. Recurrent LRRK2 (Park8) mutations in early-onset
13 Parkinson's disease. *Mov Disord.* 21:1506-1510.
14
15

16
17
18
19 Hering R, Strauss KM, Tao X, Bauer A, Woitalla D, Mietz EM, Petrovic S, Bauer P, Schaible
20 W, Muller T, Schols L, Klein C, Berg D, Meyer PT, Schulz JB, Wollnik B, Tong L, Kruger R,
21 Riess O. 2004. Novel homozygous p.E64D mutation in DJ1 in early onset Parkinson disease
22 (PARK7). *Hum.Mutat.* 24:321-329.
23
24
25

26
27
28
29 Hernandez D, Paisan RC, Crawley A, Malkani R, Werner J, Gwinn-Hardy K, Dickson D,
30 Wavrant DF, Hardy J, Singleton A. 2005. The dardarin G 2019 S mutation is a common cause of
31 Parkinson's disease but not other neurodegenerative diseases. *Neurosci.Lett.* 389:137-139.
32
33
34

35
36
37
38 Hertz JM, Ostergaard K, Juncker I, Pedersen S, Romstad A, Moller LB, Guttler F, Dupont E.
39 2006. Low frequency of Parkin, Tyrosine Hydroxylase, and GTP Cyclohydrolase I gene
40 mutations in a Danish population of early-onset Parkinson's Disease. *Eur.J.Neurol.* 13:385-390.
41
42
43

44
45
46 Hoenicka J, Vidal L, Morales B, Ampuero I, Jimenez-Jimenez FJ, Berciano J, del ST, Jimenez
47 A, Ruiz PG, de Yebenes JG. 2002. Molecular findings in familial Parkinson disease in Spain.
48
49
50
51 *Arch.Neurol.* 59:966-970.
52

53
54
55 Huang Y, Halliday GM, Vandebona H, Mellick GD, Mastaglia F, Stevens J, Kwok J, Garlepp M,
56 Silburn PA, Horne MK, Kotschet K, Venn A, Rowe DB, Rubio JP, Sue CM. 2007. Prevalence
57
58
59

1
2
3 and clinical features of common LRRK2 mutations in Australians with Parkinson's disease. *Mov*
4
5 *Disord.* 22:982-989.
6
7

8
9 Ibanez P, Bonnet AM, Debarges B, Lohmann E, Tison F, Pollak P, Agid Y, Durr A, Brice A.
10
11 2004. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease.
12
13 *Lancet* 364:1169-1171.
14
15

16
17 Ibanez P, Lesage S, Janin S, Lohmann E, Durif F, Destee A, Bonnet AM, Brefel-Courbon C,
18
19 Heath S, Zelenika D, Agid Y, Durr A, Brice A. 2009. Alpha-synuclein gene rearrangements in
20
21 dominantly inherited parkinsonism: frequency, phenotype, and mechanisms. *Arch.Neurol.*
22
23 66:102-108.
24
25

26
27 Ibanez P, Lesage S, Lohmann E, Thobois S, De MG, Borg M, Agid Y, Durr A, Brice A. 2006.
28
29 Mutational analysis of the PINK1 gene in early-onset parkinsonism in Europe and North Africa.
30
31 *Brain* 129:686-694.
32
33

34
35 Ikeuchi T, Kakita A, Shiga A, Kasuga K, Kaneko H, Tan CF, Idezuka J, Wakabayashi K,
36
37 Onodera O, Iwatsubo T, Nishizawa M, Takahashi H, Ishikawa A. 2008. Patients homozygous
38
39 and heterozygous for SNCA duplication in a family with parkinsonism and dementia.
40
41 *Arch.Neurol.* 65:514-519.
42
43
44

45
46 Illarioshkin SN, Periquet M, Rawal N, Lucking CB, Zagorovskaya TB, Slominsky PA,
47
48 Miloserdova OV, Markova ED, Limborska SA, Ivanova-Smolenskaya IA, Brice A. 2003.
49
50 Mutation analysis of the parkin gene in Russian families with autosomal recessive juvenile
51
52 parkinsonism. *Mov Disord.* 18:914-919.
53
54
55
56
57
58
59
60

1
2
3 Illarioshkin SN, Shadrina MI, Slominsky PA, Bespalova EV, Zagorovskaya TB, Bagyeva GK,
4
5 Markova ED, Limborska SA, Ivanova-Smolenskaya IA. 2007. A common leucine-rich repeat
6
7 kinase 2 gene mutation in familial and sporadic Parkinson's disease in Russia. *Eur.J.Neurol.*
8
9 14:413-417.

10
11
12
13 Imai Y, Gehrke S, Wang HQ, Takahashi R, Hasegawa K, Oota E, Lu B. 2008. Phosphorylation
14
15 of 4E-BP by LRRK2 affects the maintenance of dopaminergic neurons in *Drosophila*. *EMBO J.*
16
17 27:2432-2443.

18
19
20
21 Imai Y, Soda M, Takahashi R. 2000. Parkin suppresses unfolded protein stress-induced cell
22
23 death through its E3 ubiquitin-protein ligase activity. *J.Biol.Chem.* 275:35661-35664.

24
25
26
27 Izumi Y, Morino H, Oda M, Maruyama H, Udaka F, Kameyama M, Nakamura S, Kawakami H.
28
29 2001. Genetic studies in Parkinson's disease with an alpha-synuclein/NACP gene polymorphism
30
31 in Japan. *Neurosci.Lett.* 300:125-127.

32
33
34
35 Johnson J, Paisan-Ruiz C, Lopez G, Crews C, Britton A, Malkani R, Evans EW, Inerney-Leo A,
36
37 Jain S, Nussbaum RL, Foote KD, Mandel RJ, Crawley A, Reimsnider S, Fernandez HH, Okun
38
39 MS, Gwinn-Hardy K, Singleton AB. 2007. Comprehensive screening of a North American
40
41 Parkinson's disease cohort for LRRK2 mutation. *Neurodegener.Dis.* 4:386-391.

42
43
44
45 Kachergus J, Mata IF, Hulihan M, Taylor JP, Lincoln S, Aasly J, Gibson JM, Ross OA, Lynch T,
46
47 Wiley J, Payami H, Nutt J, Maraganore DM, Czyzewski K, Styczynska M, Wszolek ZK, Farrer
48
49 MJ, Toft M. 2005. Identification of a novel LRRK2 mutation linked to autosomal dominant
50
51 parkinsonism: evidence of a common founder across European populations. *Am.J.Hum.Genet.*
52
53 76:672-680.
54
55
56
57
58
59
60

1
2
3 Kann M, Jacobs H, Mohrmann K, Schumacher K, Hedrich K, Garrels J, Wiegers K, Schwinger
4
5 E, Pramstaller PP, Breakefield XO, Ozelius LJ, Vieregge P, Klein C. 2002. Role of parkin
6
7 mutations in 111 community-based patients with early-onset parkinsonism. *Ann.Neurol.* 51:621-
8
9 625.

10
11
12
13 Kay DM, Factor SA, Samii A, Higgins DS, Griffith A, Roberts JW, Leis BC, Nutt JG,
14
15 Montimurro JS, Keefe RG, Atkins AJ, Yearout D, Zabetian CP, Payami H. 2008. Genetic
16
17 association between alpha-synuclein and idiopathic Parkinson's disease. *Am.J.Med.Genet.B*
18
19 *Neuropsychiatr.Genet.* 147B:1222-1230.

20
21
22
23 Kay DM, Kramer P, Higgins D, Zabetian CP, Payami H. 2005. Escaping Parkinson's disease: a
24
25 neurologically healthy octogenarian with the LRRK2 G2019S mutation. *Mov Disord.* 20:1077-
26
27 1078.

28
29
30
31 Kay DM, Moran D, Moses L, Poorkaj P, Zabetian CP, Nutt J, Factor SA, Yu CE, Montimurro
32
33 JS, Keefe RG, Schellenberg GD, Payami H. 2007. Heterozygous parkin point mutations are as
34
35 common in control subjects as in Parkinson's patients. *Ann.Neurol.* 61:47-54.

36
37
38
39 Kazantsev AG, Kolchinsky AM. 2008. Central role of alpha-synuclein oligomers in
40
41 neurodegeneration in Parkinson disease. *Arch.Neurol.* 65:1577-1581.

42
43
44
45 Khan NL, Horta W, Eunson L, Graham E, Johnson JO, Chang S, Davis M, Singleton A, Wood
46
47 NW, Lees AJ. 2005a. Parkin disease in a Brazilian kindred: Manifesting heterozygotes and
48
49 clinical follow-up over 10 years. *Mov Disord.* 20:479-484.

50
51
52
53 Khan NL, Jain S, Lynch JM, Pavese N, bou-Sleiman P, Holton JL, Healy DG, Gilks WP,
54
55 Sweeney MG, Ganguly M, Gibbons V, Gandhi S, Vaughan J, Eunson LH, Katzenschlager R,
56
57
58
59
60

1
2
3 Gayton J, Lennox G, Revesz T, Nicholl D, Bhatia KP, Quinn N, Brooks D, Lees AJ, Davis MB,
4
5 Piccini P, Singleton AB, Wood NW. 2005b. Mutations in the gene LRRK2 encoding dardarin
6
7 (PARK8) cause familial Parkinson's disease: clinical, pathological, olfactory and functional
8
9 imaging and genetic data. *Brain* 128:2786-2796.
10
11

12
13
14 Ki CS, Stavrou EF, Davanos N, Lee WY, Chung EJ, Kim JY, Athanassiadou A. 2007. The
15
16 Ala53Thr mutation in the alpha-synuclein gene in a Korean family with Parkinson disease.
17
18 *Clin.Genet.* 71:471-473.
19

20
21
22 Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M,
23
24 Mizuno Y, Shimizu N. 1998. Mutations in the parkin gene cause autosomal recessive juvenile
25
26 parkinsonism. *Nature* 392:605-608.
27
28

29
30 Klein C, Djarmati A, Hedrich K, Schafer N, Scaglione C, Marchese R, Kock N, Schule B, Hiller
31
32 A, Lohnau T, Winkler S, Wiegers K, Hering R, Bauer P, Riess O, Abbruzzese G, Martinelli P,
33
34 Pramstaller PP. 2005. PINK1, Parkin, and DJ-1 mutations in Italian patients with early-onset
35
36 parkinsonism. *Eur.J.Hum.Genet.* 13:1086-1093.
37
38

39
40 Klein C, Pramstaller PP, Kis B, Page CC, Kann M, Leung J, Woodward H, Castellan CC,
41
42 Scherer M, Vieregge P, Breakefield XO, Kramer PL, Ozelius LJ. 2000. Parkin deletions in a
43
44 family with adult-onset, tremor-dominant parkinsonism: expanding the phenotype. *Ann.Neurol.*
45
46 48:65-71.
47
48

49
50
51 Kobayashi T, Wang M, Hattori N, Matsumine H, Kondo T, Mizuno Y. 2000. Exonic deletion
52
53 mutations of the Parkin gene among sporadic patients with Parkinson's disease.
54
55 *Parkinsonism.Relat Disord.* 6:129-131.
56
57

1
2
3 Kruger R, Kuhn W, Muller T, Woitalla D, Graeber M, Kosel S, Przuntek H, Eppelen JT, Schols
4
5 L, Riess O. 1998. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's
6
7 disease. *Nat.Genet.* 18:106-108.
8
9

10
11 Kumazawa R, Tomiyama H, Li Y, Imamichi Y, Funayama M, Yoshino H, Yokochi F, Fukusako
12
13 T, Takehisa Y, Kashihara K, Kondo T, Elibol B, Bostantjopoulou S, Toda T, Takahashi H,
14
15 Yoshii F, Mizuno Y, Hattori N. 2008. Mutation analysis of the PINK1 gene in 391 patients with
16
17 Parkinson disease. *Arch.Neurol.* 65:802-808.
18
19

20
21 Latourelle JC, Sun M, Lew MF, Suchowersky O, Klein C, Golbe LI, Mark MH, Growdon JH,
22
23 Wooten GF, Watts RL, Guttman M, Racette BA, Perlmutter JS, Ahmed A, Shill HA, Singer C,
24
25 Goldwurm S, Pezzoli G, Zini M, Saint-Hilaire MH, Hendricks AE, Williamson S, Nagle MW,
26
27 Wilk JB, Massood T, Huskey KW, Laramie JM, DeStefano AL, Baker KB, Itin I, Litvan I,
28
29 Nicholson G, Corbett A, Nance M, Drasby E, Isaacson S, Burn DJ, Chinnery PF, Pramstaller PP,
30
31 Al-hinti J, Moller AT, Ostergaard K, Sherman SJ, Roxburgh R, Snow B, Slevin JT, Cambi F,
32
33 Gusella JF, Myers RH. 2008. The Gly2019Ser mutation in LRRK2 is not fully penetrant in
34
35 familial Parkinson's disease: the GenePD study. *BMC.Med.* 6:32.
36
37
38
39

40
41 Lautier C, Goldwurm S, Durr A, Giovannone B, Tsiaras WG, Pezzoli G, Brice A, Smith RJ.
42
43 2008. Mutations in the GIGYF2 (TNRC15) gene at the PARK11 locus in familial Parkinson
44
45 disease. *Am.J.Hum.Genet.* 82:822-833.
46
47
48

49
50 Lee MJ, Mata IF, Lin CH, Tzen KY, Lincoln SJ, Bounds R, Lockhart PJ, Hulihan MM, Farrer
51
52 MJ, Wu RM. 2009. Genotype-phenotype correlates in Taiwanese patients with early-onset
53
54 recessive Parkinsonism. *Mov Disord.* 24:104-108.
55
56
57
58
59
60

1
2
3 Leroy E, Anastasopoulos D, Konitsiotis S, Lavedan C, Polymeropoulos MH. 1998a. Deletions in
4 the Parkin gene and genetic heterogeneity in a Greek family with early onset Parkinson's disease.
5 Hum.Genet. 103:424-427.
6
7

8
9
10
11 Leroy E, Boyer R, Auburger G, Leube B, Ulm G, Mezey E, Harta G, Brownstein MJ,
12 Jonnalagada S, Chernova T, Dehejia A, Lavedan C, Gasser T, Steinbach PJ, Wilkinson KD,
13 Polymeropoulos MH. 1998b. The ubiquitin pathway in Parkinson's disease. Nature 395:451-452.
14
15
16

17
18
19 Lesage S, Condroyer C, Lannuzel A, Lohmann E, Troiano A, Tison F, Damier P, Thobois S,
20 Ouvrard-Hernandez AM, Rivaud-Pechoux S, Brefel-Courbon C, Destee A, Tranchant C,
21 Romana M, Leclere L, Durr A, Brice A. 2009. Molecular analyses of the LRRK2 gene in
22 European and North-African autosomal dominant Parkinson's disease. J.Med.Genet.
23
24
25
26

27
28
29 Lesage S, Durr A, Tazir M, Lohmann E, Leutenegger AL, Janin S, Pollak P, Brice A. 2006.
30 LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. N.Engl.J.Med.
31
32
33
34
35
36
37

38 Lesage S, Janin S, Lohmann E, Leutenegger AL, Leclere L, Viallet F, Pollak P, Durif F, Thobois
39 S, Layet V, Vidailhet M, Agid Y, Durr A, Brice A, Bonnet AM, Borg M, Broussolle E, Damier
40 P, Destee A, Martinez M, Penet C, Rasco O, Tison F, Tranchan C, Verin M. 2007a. LRRK2
41
42
43
44
45
46
47
48

49 Lesage S, Lohmann E, Tison F, Durif F, Durr A, Brice A. 2008. Rare heterozygous parkin
50 variants in French early-onset Parkinson disease patients and controls. J.Med.Genet. 45:43-46.
51
52
53
54
55
56
57
58
59
60

1
2
3 Lesage S, Magali P, Lohmann E, Lacomblez L, Teive H, Janin S, Cousin PY, Durr A, Brice A.
4
5 2007b. Deletion of the parkin and PACRG gene promoter in early-onset parkinsonism.
6
7
8 Hum.Mutat. 28:27-32.
9

10
11 Leutenegger AL, Salih MA, Ibanez P, Mukhtar MM, Lesage S, Arabi A, Lohmann E, Durr A,
12
13 Ahmed AE, Brice A. 2006. Juvenile-onset Parkinsonism as a result of the first mutation in the
14
15 adenosine triphosphate orientation domain of PINK1. Arch.Neurol. 63:1257-1261.
16
17

18
19 Lev N, Ickowicz D, Barhum Y, Lev S, Melamed E, Offen D. 2009. DJ-1 protects against
20
21 dopamine toxicity. J.Neural Transm. 116:151-160.
22
23

24
25 Lewis PA, Greggio E, Beilina A, Jain S, Baker A, Cookson MR. 2007. The R1441C mutation of
26
27 LRRK2 disrupts GTP hydrolysis. Biochem.Biophys.Res.Comm. 357:668-671.
28
29

30
31 Li X, Kitami T, Wang M, Mizuno Y, Hattori N. 2005a. Geographic and ethnic differences in
32
33 frequencies of two polymorphisms (D/N394 and L/I272) of the parkin gene in sporadic
34
35 Parkinson's disease. Parkinsonism.Relat Disord. 11:485-491.
36
37

38
39 Li X, Tan YC, Poulouse S, Olanow CW, Huang XY, Yue Z. 2007. Leucine-rich repeat kinase 2
40
41 (LRRK2)/PARK8 possesses GTPase activity that is altered in familial Parkinson's disease
42
43 R1441C/G mutants. J.Neurochem. 103:238-247.
44
45

46
47 Li Y, Tomiyama H, Sato K, Hatano Y, Yoshino H, Atsumi M, Kitaguchi M, Sasaki S,
48
49 Kawaguchi S, Miyajima H, Toda T, Mizuno Y, Hattori N. 2005b. Clinicogenetic study of PINK1
50
51 mutations in autosomal recessive early-onset parkinsonism. Neurology 64:1955-1957.
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Limousin N, Konofal E, Karroum E, Lohmann E, Theodorou I, Durr A, Arnulf I. 2009. Restless legs syndrome, rapid eye movement sleep behavior disorder, and hypersomnia in patients with two parkin mutations. *Mov Disord*.

Liu S, Ninan I, Antonova I, Battaglia F, Trinchese F, Narasanna A, Kolodilov N, Dauer W, Hawkins RD, Arancio O. 2004. alpha-Synuclein produces a long-lasting increase in neurotransmitter release. *EMBO J*. 23:4506-4516.

Liu W, Vives-Bauza C, Acin P, Yamamoto A, Tan Y, Li Y, Magrane J, Stavarache MA, Shaffer S, Chang S, Kaplitt MG, Huang XY, Beal MF, Manfredi G, Li C. 2009. PINK1 defect causes mitochondrial dysfunction, proteasomal deficit and alpha-synuclein aggregation in cell culture models of Parkinson's disease. *PLoS.ONE*. 4:e4597.

Lucking CB, Abbas N, Durr A, Bonifati V, Bonnet AM, de BT, De MG, Wood NW, Agid Y, Brice A. 1998. Homozygous deletions in parkin gene in European and North African families with autosomal recessive juvenile parkinsonism. The European Consortium on Genetic Susceptibility in Parkinson's Disease and the French Parkinson's Disease Genetics Study Group. *Lancet* 352:1355-1356.

Lucking CB, Durr A, Bonifati V, Vaughan J, De MG, Gasser T, Harhangi BS, Meco G, Deneffle P, Wood NW, Agid Y, Brice A. 2000. Association between early-onset Parkinson's disease and mutations in the parkin gene. *N.Engl.J.Med*. 342:1560-1567.

Macedo MG, Verbaan D, Fang Y, van Rooden SM, Visser M, Anar B, Uras A, Groen JL, Rizzu P, van Hilten JJ, Heutink P. 2009. Genotypic and phenotypic characteristics of Dutch patients with early onset Parkinson's disease. *Mov Disord*. 24:196-203.

1
2
3 Madegowda RH, Kishore A, Anand A. 2005. Mutational screening of the parkin gene among
4 South Indians with early onset Parkinson's disease. *J.Neurol.Neurosurg.Psychiatry* 76:1588-
5
6 1590.
7
8

9
10
11 Maraganore DM, de AM, Elbaz A, Farrer MJ, Ioannidis JP, Kruger R, Rocca WA, Schneider
12 NK, Lesnick TG, Lincoln SJ, Hulihan MM, Aasly JO, Ashizawa T, Chartier-Harlin MC,
13
14 Checkoway H, Ferrarese C, Hadjigeorgiou G, Hattori N, Kawakami H, Lambert JC, Lynch T,
15
16 Mellick GD, Papapetropoulos S, Parsian A, Quattrone A, Riess O, Tan EK, Van BC. 2006.
17
18 Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease.
19
20 *JAMA* 296:661-670.
21
22
23

24
25
26 Marongiu R, Brancati F, Antonini A, Ialongo T, Ceccarini C, Scarciolla O, Capalbo A, Benti R,
27
28 Pezzoli G, Dallapiccola B, Goldwurm S, Valente EM. 2007. Whole gene deletion and splicing
29
30 mutations expand the PINK1 genotypic spectrum. *Hum.Mutat.* 28:98.
31
32
33

34
35 Marongiu R, Ferraris A, Ialongo T, Michiorri S, Soleti F, Ferrari F, Elia AE, Ghezzi D, Albanese
36
37 A, Altavista MC, Antonini A, Barone P, Brusa L, Cortelli P, Martinelli P, Pellicchia MT,
38
39 Pezzoli G, Scaglione C, Stanzione P, Tinazzi M, Zecchinelli A, Zeviani M, Cassetta E,
40
41 Garavaglia B, Dallapiccola B, Bentivoglio AR, Valente EM. 2008. PINK1 heterozygous rare
42
43 variants: prevalence, significance and phenotypic spectrum. *Hum.Mutat.* 29:565.
44
45
46

47
48 Marras C, Klein C, Lang AE, Wakutani Y, Moreno D, Sato C, Yip E, Munhoz RP, Lohmann K,
49
50 Djarmati A, Bi A, Rogaeva E. 2008. LRRK2 and Parkin mutations in a family with
51
52 parkinsonism-Lack of genotype-phenotype correlation. *Neurobiol.Aging*.
53
54
55

1
2
3 Maruyama M, Ikeuchi T, Saito M, Ishikawa A, Yuasa T, Tanaka H, Hayashi S, Wakabayashi K,
4
5 Takahashi H, Tsuji S. 2000. Novel mutations, pseudo-dominant inheritance, and possible
6
7 familial affects in patients with autosomal recessive juvenile parkinsonism. *Ann.Neurol.* 48:245-
8
9 250.

10
11
12
13 Mata IF, Alvarez V, Coto E, Blazquez M, Guisasola LM, Salvador C, Kachergus JM, Lincoln
14
15 SJ, Farrer M. 2005a. Homozygous partial genomic triplication of the parkin gene in early-onset
16
17 parkinsonism. *Neurosci.Lett.* 380:257-259.

18
19
20
21 Mata IF, Kachergus JM, Taylor JP, Lincoln S, Aasly J, Lynch T, Hulihan MM, Cobb SA, Wu
22
23 RM, Lu CS, Lahoz C, Wszolek ZK, Farrer MJ. 2005b. Lrrk2 pathogenic substitutions in
24
25 Parkinson's disease. *Neurogenetics.* 6:171-177.

26
27
28
29 Mata IF, Taylor JP, Kachergus J, Hulihan M, Huerta C, Lahoz C, Blazquez M, Guisasola LM,
30
31 Salvador C, Ribacoba R, Martinez C, Farrer M, Alvarez V. 2005c. LRRK2 R1441G in Spanish
32
33 patients with Parkinson's disease. *Neurosci.Lett.* 382:309-311.

34
35
36
37 Meeus B, Theuns J, Van Broeckhoven C. 2010. GIGYF2 in Parkinson's disease: Innocent until
38
39 proven otherwise. *Neurobiol.Aging* (in press).

40
41
42
43 Mellick GD, Siebert GA, Funayama M, Buchanan DD, Li Y, Imamichi Y, Yoshino H, Silburn
44
45 PA, Hattori N. 2009. Screening PARK genes for mutations in early-onset Parkinson's disease
46
47 patients from Queensland, Australia. *Parkinsonism.Relat Disord.* 15:105-109.

48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

55

1
2
3 Mitsumoto A, Nakagawa Y. 2001. DJ-1 is an indicator for endogenous reactive oxygen species
4 elicited by endotoxin. *Free Radic.Res.* 35:885-893.
5
6

7
8
9 Mizuta I, Satake W, Nakabayashi Y, Ito C, Suzuki S, Momose Y, Nagai Y, Oka A, Inoko H,
10 Fukae J, Saito Y, Sawabe M, Murayama S, Yamamoto M, Hattori N, Murata M, Toda T. 2006.
11 Multiple candidate gene analysis identifies alpha-synuclein as a susceptibility gene for sporadic
12 Parkinson's disease. *Hum.Mol.Genet.* 15:1151-1158.
13
14
15

16
17
18
19 Moore DJ, Zhang L, Dawson TM, Dawson VL. 2003. A missense mutation (L166P) in DJ-1,
20 linked to familial Parkinson's disease, confers reduced protein stability and impairs homo-
21 oligomerization. *J.Neurochem.* 87:1558-1567.
22
23
24
25

26
27
28 Moro E, Volkmann J, Konig IR, Winkler S, Hiller A, Hassin-Baer S, Herzog J, Schnitzler A,
29 Lohmann K, Pinsker MO, Voges J, Djarmatic A, Seibler P, Lozano AM, Rogaeva E, Lang AE,
30 Deuschl G, Klein C. 2008. Bilateral subthalamic stimulation in Parkin and PINK1 parkinsonism.
31
32
33
34
35
36
37

38
39
40 Mueller JC, Fuchs J, Hofer A, Zimprich A, Lichtner P, Illig T, Berg D, Wullner U, Meitinger T,
41 Gasser T. 2005. Multiple regions of alpha-synuclein are associated with Parkinson's disease.
42
43
44
45
46
47

48
49
50 Munhoz RP, Sa DS, Rogaeva E, Salehi-Rad S, Sato C, Medeiros H, Farrer M, Lang AE. 2004.
51
52
53
54
55
56

57
58
59 Munoz E, Pastor P, Marti MJ, Oliva R, Tolosa E. 2000. A new mutation in the parkin gene in a
60 patient with atypical autosomal recessive juvenile parkinsonism. *Neurosci.Lett.* 289:66-68.

- 1
2
3 Munoz E, Tolosa E, Pastor P, Marti MJ, Valldeoriola F, Campdelacreu J, Oliva R. 2002.
4
5 Relative high frequency of the c.255delA parkin gene mutation in Spanish patients with
6
7
8 autosomal recessive parkinsonism. *J.Neurol.Neurosurg.Psychiatry* 73:582-584.
9
10
11 Myhre R, Steinkjer S, Stormyr A, Nilsen GL, Abu ZH, Horany K, Nusier MK, Klungland H.
12
13 2008a. Significance of the parkin and PINK1 gene in Jordanian families with incidences of
14
15 young-onset and juvenile parkinsonism. *BMC.Neurol.* 8:47.
16
17
18
19 Myhre R, Toft M, Kachergus J, Hulihan MM, Aasly JO, Klungland H, Farrer MJ. 2008b.
20
21 Multiple alpha-synuclein gene polymorphisms are associated with Parkinson's disease in a
22
23 Norwegian population. *Acta Neurol.Scand.* 118:320-327.
24
25
26
27
28 Narendra D, Tanaka A, Suen DF, Youle RJ. 2008. Parkin is recruited selectively to impaired
29
30 mitochondria and promotes their autophagy. *J.Cell Biol.* 183:795-803.
31
32
33 Narendra D, Tanaka A, Suen DF, Youle RJ. 2009. Parkin-induced mitophagy in the pathogenesis
34
35 of Parkinson disease. *Autophagy.* 5:706-708.
36
37
38
39 Nichols WC, Elsaesser VE, Pankratz N, Pauciulo MW, Marek DK, Halter CA, Rudolph A,
40
41 Shults CW, Foroud T. 2007. LRRK2 mutation analysis in Parkinson disease families with
42
43 evidence of linkage to PARK8. *Neurology* 69:1737-1744.
44
45
46
47 Nichols WC, Pankratz N, Hernandez D, Paisan-Ruiz C, Jain S, Halter CA, Michaels VE, Reed T,
48
49 Rudolph A, Shults CW, Singleton A, Foroud T. 2005. Genetic screening for a single common
50
51 LRRK2 mutation in familial Parkinson's disease. *Lancet* 365:410-412.
52
53
54
55
56
57
58
59
60

1
2
3 Nichols WC, Pankratz N, Uniacke SK, Pauciulo MW, Halter C, Rudolph A, Conneally PM,
4
5 Foroud T. 2002. Linkage stratification and mutation analysis at the Parkin locus identifies
6
7 mutation positive Parkinson's disease families. *J.Med.Genet.* 39:489-492.
8
9

10
11 Nishioka K, Hayashi S, Farrer MJ, Singleton AB, Yoshino H, Imai H, Kitami T, Sato K, Kuroda
12
13 R, Tomiyama H, Mizoguchi K, Murata M, Toda T, Imoto I, Inazawa J, Mizuno Y, Hattori N.
14
15 2006. Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease.
16
17 *Ann.Neurol.* 59:298-309.
18
19

20
21 Nishioka K, Ross OA, Ishii K, Kachergus JM, Ishiwata K, Kitagawa M, Kono S, Obi T,
22
23 Mizoguchi K, Inoue Y, Imai H, Takanashi M, Mizuno Y, Farrer MJ, Hattori N. 2009. Expanding
24
25 the clinical phenotype of SNCA duplication carriers. *Mov Disord.*
26
27

28
29 Nisipeanu P, Inzelberg R, Abo MS, Carasso RL, Blumen SC, Zhang J, Matsumine H, Hattori N,
30
31 Mizuno Y. 2001. Parkin gene causing benign autosomal recessive juvenile parkinsonism.
32
33 *Neurology* 56:1573-1575.
34
35

36
37 Nuytemans K, Meeus B, Crosiers D, Brouwers N, Goossens D, Engelborghs S, Pals P, Pickut B,
38
39 Van den BM, Corsmit E, Cras P, De Deyn PP, Del-Favero J, Van BC, Theuns J. 2009. Relative
40
41 contribution of simple mutations vs. copy number variations in five Parkinson disease genes in
42
43 the Belgian population. *Hum.Mutat.*
44
45

46
47 Nuytemans K, Rademakers R, Theuns J, Pals P, Engelborghs S, Pickut B, de PT, Peeters K,
48
49 Mattheijssens M, Van den BM, Cras P, De Deyn PP, Van BC. 2008. Founder mutation
50
51 p.R1441C in the leucine-rich repeat kinase 2 gene in Belgian Parkinson's disease patients.
52
53
54
55
56 *Eur.J.Hum.Genet.* 16:471-479.
57
58
59
60

1
2
3 Obi T, Nishioka K, Ross OA, Terada T, Yamazaki K, Sugiura A, Takanashi M, Mizoguchi K,
4
5 Mori H, Mizuno Y, Hattori N. 2008. Clinicopathologic study of a SNCA gene duplication patient
6
7
8 with Parkinson disease and dementia. *Neurology* 70:238-241.
9

10
11 Okubadejo N, Britton A, Crews C, Akinyemi R, Hardy J, Singleton A, Bras J. 2008. Analysis of
12
13 Nigerians with apparently sporadic Parkinson disease for mutations in LRRK2, PRKN and
14
15 ATXN3. *PLoS.ONE.* 3:e3421.
16

17
18
19 Oliveira SA, Scott WK, Martin ER, Nance MA, Watts RL, Hubble JP, Koller WC, Pahwa R,
20
21 Stern MB, Hiner BC, Ondo WG, Allen FH, Jr., Scott BL, Goetz CG, Small GW, Mastaglia F,
22
23 Stajich JM, Zhang F, Booze MW, Winn MP, Middleton LT, Haines JL, Pericak-Vance MA,
24
25 Vance JM. 2003. Parkin mutations and susceptibility alleles in late-onset Parkinson's disease.
26
27
28 *Ann.Neurol.* 53:624-629.
29

30
31
32 Orr-Urtreger A, Shifrin C, Rozovski U, Rosner S, Bercovich D, Gurevich T, Yagev-More H,
33
34 Bar-Shira A, Giladi N. 2007. The LRRK2 G2019S mutation in Ashkenazi Jews with Parkinson
35
36 disease: is there a gender effect? *Neurology* 69:1595-1602.
37

38
39
40 Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, Hunt AL,
41
42 Klein C, Henick B, Hailpern SM, Lipton RB, Soto-Valencia J, Risch N, Bressman SB. 2006.
43
44 LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N.Engl.J.Med.* 354:424-
45
46 425.
47

48
49
50 Paisan-Ruiz C. 2009. LRRK2 gene variation and its contribution to Parkinson disease.
51
52
53 *Hum.Mutat.* 30:1153-1160.
54

1
2
3 Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, Hardy J, Houlden H,
4
5 Singleton A, Schneider SA. 2009. Characterization of PLA2G6 as a locus for dystonia-
6
7 parkinsonism. *Ann.Neurol.* 65:19-23.
8
9

10
11 Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der BM, Lopez de MA, Aparicio S,
12
13 Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Pena AS, de SR, Lees A,
14
15 Marti-Masso JF, Perez-Tur J, Wood NW, Singleton AB. 2004. Cloning of the gene containing
16
17 mutations that cause PARK8-linked Parkinson's disease. *Neuron* 44:595-600.
18
19

20
21 Paisan-Ruiz C, Lang AE, Kawarai T, Sato C, Salehi-Rad S, Fisman GK, Al-Khairallah T, St
22
23 George-Hyslop P, Singleton A, Rogaeva E. 2005. LRRK2 gene in Parkinson disease: mutation
24
25 analysis and case control association study. *Neurology* 65:696-700.
26
27

28
29 Paisan-Ruiz C, Nath P, Washecka N, Gibbs JR, Singleton AB. 2008. Comprehensive analysis of
30
31 LRRK2 in publicly available Parkinson's disease cases and neurologically normal controls.
32
33 *Hum.Mutat.* 29:485-490.
34
35

36
37 Pals P, Lincoln S, Manning J, Heckman M, Skipper L, Hulihan M, Van den Broeck M, De
38
39 Pooter T, Cras P, Crook J, Van Broeckhoven C, Farrer MJ. 2004a. alpha-Synuclein promoter
40
41 confers susceptibility to Parkinson's disease. *Ann.Neurol.* 56:591-595.
42
43

44
45 Pals P, Lincoln S, Manning J, Heckman M, Skipper L, Hulihan M, Van den BM, de PT, Cras P,
46
47 Crook J, Van BC, Farrer MJ. 2004b. alpha-Synuclein promoter confers susceptibility to
48
49 Parkinson's disease. *Ann.Neurol.* 56:591-595.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Pankratz N, Pauciulo MW, Elsaesser VE, Marek DK, Halter CA, Rudolph A, Shults CW, Foroud
4
5 T, Nichols WC. 2006a. Mutations in LRRK2 other than G2019S are rare in a north American-
6
7 based sample of familial Parkinson's disease. *Mov Disord.* 21:2257-2260.
8
9

10
11 Pankratz N, Pauciulo MW, Elsaesser VE, Marek DK, Halter CA, Wojcieszek J, Rudolph A,
12
13 Shults CW, Foroud T, Nichols WC. 2006b. Mutations in DJ-1 are rare in familial Parkinson
14
15 disease. *Neurosci.Lett.* 408:209-213.
16
17

18
19 Pankratz N, Wilk JB, Latourelle JC, DeStefano AL, Halter C, Pugh EW, Doheny KF, Gusella JF,
20
21 Nichols WC, Foroud T, Myers RH. 2009. Genomewide association study for susceptibility genes
22
23 contributing to familial Parkinson disease. *Hum.Genet.* 124:593-605.
24
25
26

27
28 Papadimitriou A, Veletza V, Hadjigeorgiou GM, Patrikiou A, Hirano M, Anastasopoulos I.
29
30 1999. Mutated alpha-synuclein gene in two Greek kindreds with familial PD: incomplete
31
32 penetrance? *Neurology* 52:651-654.
33
34

35
36 Papapetropoulos S, Ellul J, Paschalis C, Athanassiadou A, Papadimitriou A, Papapetropoulos T.
37
38 2003. Clinical characteristics of the alpha-synuclein mutation (G209A)-associated Parkinson's
39
40 disease in comparison with other forms of familial Parkinson's disease in Greece. *Eur.J.Neurol.*
41
42 10:281-286.
43
44

45
46 Papapetropoulos S, Paschalis C, Athanassiadou A, Papadimitriou A, Ellul J, Polymeropoulos
47
48 MH, Papapetropoulos T. 2001. Clinical phenotype in patients with alpha-synuclein Parkinson's
49
50 disease living in Greece in comparison with patients with sporadic Parkinson's disease.
51
52 *J.Neurol.Neurosurg.Psychiatry* 70:662-665.
53
54
55
56
57
58
59
60

1
2
3 Papapetropoulos S, Singer C, Ross OA, Toft M, Johnson JL, Farrer MJ, Mash DC. 2006.

4
5 Clinical heterogeneity of the LRRK2 G2019S mutation. *Arch.Neurol.* 63:1242-1246.

6
7
8
9 Park J, Lee G, Chung J. 2009. The PINK1-Parkin pathway is involved in the regulation of
10
11 mitochondrial remodeling process. *Biochem.Biophys.Res.Comm.* 378:518-523.

12
13
14
15 Parsian AJ, Racette BA, Zhao JH, Sinha R, Patra B, Perlmutter JS, Parsian A. 2007. Association
16
17 of alpha-synuclein gene haplotypes with Parkinson's disease. *Parkinsonism.Relat Disord.*
18
19 13:343-347.

20
21
22
23 Pchelina SN, Yakimovskii AF, Emelyanov AK, Ivanova ON, Schwarzman AL, Singleton AB.
24
25 2008. Screening for LRRK2 mutations in patients with Parkinson's disease in Russia:
26
27 identification of a novel LRRK2 variant. *Eur.J.Neurol.* 15:692-696.

28
29
30
31 Pellecchia MT, Varrone A, Annesi G, Amboni M, Cicarelli G, Sansone V, Annesi F, Rocca FE,
32
33 Vitale C, Pappata S, Quattrone A, Barone P. 2007. Parkinsonism and essential tremor in a family
34
35 with pseudo-dominant inheritance of PARK2: an FP-CIT SPECT study. *Mov Disord.* 22:559-
36
37 563.

38
39
40
41 Periquet M, Latouche M, Lohmann E, Rawal N, De MG, Ricard S, Teive H, Fraix V, Vidailhet
42
43 M, Nicholl D, Barone P, Wood NW, Raskin S, Deleuze JF, Agid Y, Durr A, Brice A. 2003.
44
45
46
47 Parkin mutations are frequent in patients with isolated early-onset parkinsonism. *Brain*
48
49 126:1271-1278.

50
51
52 Periquet M, Lucking C, Vaughan J, Bonifati V, Durr A, De MG, Horstink M, Farrer M,
53
54 Illarioshkin SN, Pollak P, Borg M, Brefel-Courbon C, Deneffe P, Meco G, Gasser T, Breteler
55
56
57
58
59
60 MM, Wood N, Agid Y, Brice A. 2001. Origin of the mutations in the parkin gene in Europe:

1
2
3 exon rearrangements are independent recurrent events, whereas point mutations may result from
4
5 Founder effects. *Am.J.Hum.Genet.* 68:617-626.
6
7

8
9 Perry G, Zhu X, Babar AK, Siedlak SL, Yang Q, Ito G, Iwatsubo T, Smith MA, Chen SG. 2008.
10
11 Leucine-rich repeat kinase 2 colocalizes with alpha-synuclein in Parkinson's disease, but not tau-
12
13 containing deposits in tauopathies. *Neurodegener.Dis.* 5:222-224.
14
15

16
17 Pesah Y, Pham T, Burgess H, Middlebrooks B, Verstreken P, Zhou Y, Harding M, Bellen H,
18
19 Mardon G. 2004. *Drosophila parkin* mutants have decreased mass and cell size and increased
20
21 sensitivity to oxygen radical stress. *Development* 131:2183-2194.
22
23

24
25 Pigullo S, De LA, Barone P, Marchese R, Bellone E, Colosimo A, Scaglione C, Martinelli P, Di
26
27 ME, Pizzuti A, Abbruzzese G, Dallapiccola B, Ajmar F, Mandich P. 2004. Mutational analysis
28
29 of parkin gene by denaturing high-performance liquid chromatography (DHPLC) in essential
30
31 tremor. *Parkinsonism.Relat Disord.* 10:357-362.
32
33

34
35 Pineda-Trujillo N, Carvajal-Carmona LG, Buritica O, Moreno S, Uribe C, Pineda D, Toro M,
36
37 Garcia F, Arias W, Bedoya G, Lopera F, Ruiz-Linares A. 2001. A novel Cys212Tyr founder
38
39 mutation in parkin and allelic heterogeneity of juvenile Parkinsonism in a population from North
40
41 West Colombia. *Neurosci.Lett.* 298:87-90.
42
43
44

45
46 Plun-Favreau H, Klupsch K, Moiso N, Gandhi S, Kjaer S, Frith D, Harvey K, Deas E, Harvey
47
48 RJ, McDonald N, Wood NW, Martins LM, Downward J. 2007. The mitochondrial protease
49
50 HtrA2 is regulated by Parkinson's disease-associated kinase PINK1. *Nat.Cell Biol.* 9:1243-1252.
51
52
53
54
55
56
57
58
59
60

1
2
3 Polymeropoulos MH, Higgins JJ, Golbe LI, Johnson WG, Ide SE, Di IG, Sanges G, Stenroos ES,
4
5 Pho LT, Schaffer AA, Lazzarini AM, Nussbaum RL, Duvoisin RC. 1996. Mapping of a gene for
6
7 Parkinson's disease to chromosome 4q21-q23. *Science* 274:1197-1199.
8
9

10
11 Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H,
12
13 Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos
14
15 T, Johnson WG, Lazzarini AM, Duvoisin RC, Di IG, Golbe LI, Nussbaum RL. 1997. Mutation
16
17 in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 276:2045-
18
19 2047.
20
21

22
23
24 Poole AC, Thomas RE, Andrews LA, McBride HM, Whitworth AJ, Pallanck LJ. 2008. The
25
26 PINK1/Parkin pathway regulates mitochondrial morphology. *Proc.Natl.Acad.Sci.U.S.A*
27
28 105:1638-1643.
29
30

31
32 Poorkaj P, Nutt JG, James D, Gancher S, Bird TD, Steinbart E, Schellenberg GD, Payami H.
33
34 2004. parkin mutation analysis in clinic patients with early-onset Parkinson [corrected] disease.
35
36 *Am.J.Med.Genet.A* 129A:44-50.
37
38

39
40 Pramstaller PP, Schlossmacher MG, Jacques TS, Scaravilli F, Eskelson C, Pepivani I, Hedrich K,
41
42 Adel S, Gonzales-McNeal M, Hilker R, Kramer PL, Klein C. 2005. Lewy body Parkinson's
43
44 disease in a large pedigree with 77 Parkin mutation carriers. *Ann.Neurol.* 58:411-422.
45
46
47

48
49 Prestel J, Gempel K, Hauser TK, Schweitzer K, Prokisch H, Ahting U, Freudenstein D,
50
51 Bueltmann E, Naegele T, Berg D, Klopstock T, Gasser T. 2008. Clinical and molecular
52
53 characterisation of a Parkinson family with a novel PINK1 mutation. *J.Neurol.* 255:643-648.
54
55
56
57
58
59
60

1
2
3 Pridgeon JW, Olzmann JA, Chin LS, Li L. 2007. PINK1 protects against oxidative stress by
4 phosphorylating mitochondrial chaperone TRAP1. *PLoS.Biol.* 5:e172.
5
6
7

8
9 Puschmann A, Ross OA, Vilarino-Guell C, Lincoln SJ, Kachergus JM, Cobb SA, Lindquist SG,
10 Nielsen JE, Wszolek ZK, Farrer M, Widner H, van WD, Hagerstrom D, Markopoulou K, Chase
11 BA, Nilsson K, Reimer J, Nilsson C. 2009. A Swedish family with de novo alpha-synuclein
12 A53T mutation: Evidence for early cortical dysfunction. *Parkinsonism.Relat Disord.*
13
14
15

16
17
18
19 Rajput A, Dickson DW, Robinson CA, Ross OA, Dachsel JC, Lincoln SJ, Cobb SA, Rajput ML,
20 Farrer MJ. 2006. Parkinsonism, Lrrk2 G2019S, and tau neuropathology. *Neurology* 67:1506-
21 1508.
22
23
24
25

26
27
28 Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin
29 AF, Wriekat AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI,
30 Kubisch C. 2006. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2,
31 encoding a lysosomal type 5 P-type ATPase. *Nat.Genet.* 38:1184-1191.
32
33
34
35

36
37
38 Ramsey CP, Giasson BI. 2008. The E163K DJ-1 mutant shows specific antioxidant deficiency.
39 *Brain Res.*
40
41
42

43
44 Rawal N, Periquet M, Lohmann E, Lucking CB, Teive HA, Ambrosio G, Raskin S, Lincoln S,
45 Hattori N, Guimaraes J, Horstink MW, Dos Santos BW, Brousolle E, Destee A, Mizuno Y,
46 Farrer M, Deleuze JF, De MG, Agid Y, Durr A, Brice A. 2003. New parkin mutations and
47 atypical phenotypes in families with autosomal recessive parkinsonism. *Neurology* 60:1378-
48 1381.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Reetz K, Lencer R, Steinlechner S, Gaser C, Hagenah J, Buchel C, Petersen D, Kock N, Djarmati
4
5 A, Siebner HR, Klein C, Binkofski F. 2008. Limbic and frontal cortical degeneration is
6
7 associated with psychiatric symptoms in PINK1 mutation carriers. *Biol.Psychiatry* 64:241-247.
8
9

10
11 Rocca FE, Annesi F, Ciro C, I, Carrideo S, Tarantino P, Provenzano G, Civitelli D, De Marco
12
13 EV, Quattrone A, Annesi G. 2007. Novel human pathological mutations. Gene symbol: PARK2.
14
15 Disease: Parkinson's disease. *Hum.Genet.* 122:415.
16
17

18
19 Rogaeva E, Johnson J, Lang AE, Gulick C, Gwinn-Hardy K, Kawarai T, Sato C, Morgan A,
20
21 Werner J, Nussbaum R, Petit A, Okun MS, McInerney A, Mandel R, Groen JL, Fernandez HH,
22
23 Postuma R, Foote KD, Salehi-Rad S, Liang Y, Reimsnider S, Tandon A, Hardy J, St George-
24
25 Hyslop P, Singleton AB. 2004. Analysis of the PINK1 gene in a large cohort of cases with
26
27 Parkinson disease. *Arch.Neurol.* 61:1898-1904.
28
29

30
31
32 Rohe CF, Montagna P, Breedveld G, Cortelli P, Oostra BA, Bonifati V. 2004. Homozygous
33
34 PINK1 C-terminus mutation causing early-onset parkinsonism. *Ann.Neurol.* 56:427-431.
35
36

37
38 Romito LM, Contarino MF, Ghezzi D, Franzini A, Garavaglia B, Albanese A. 2005. High
39
40 frequency stimulation of the subthalamic nucleus is efficacious in Parkin disease. *J.Neurol.*
41
42 252:208-211.
43
44

45
46 Ross OA, Gosal D, Stone JT, Lincoln SJ, Heckman MG, Irvine GB, Johnston JA, Gibson JM,
47
48 Farrer MJ, Lynch T. 2007. Familial genes in sporadic disease: common variants of alpha-
49
50 synuclein gene associate with Parkinson's disease. *Mech.Ageing Dev.* 128:378-382.
51
52
53
54
55
56
57
58
59
60

1
2
3 Ross OA, Wu YR, Lee MC, Funayama M, Chen ML, Soto AI, Mata IF, Lee-Chen GJ, Chen CM,
4
5 Tang M, Zhao Y, Hattori N, Farrer MJ, Tan EK, Wu RM. 2008. Analysis of Lrrk2 R1628P as a
6
7 risk factor for Parkinson's disease. *Ann.Neurol.* 64:88-92.
8
9

10
11 Samaranch L, Lorenzo-Betancor O, Arbelo JM, Ferrer I, Lorenzo E, Irigoyen J, Pastor MA,
12
13 Marrero C, Isla C, Herrera-Henriquez J, Pastor P. 2010. PINK1-linked parkinsonism is
14
15 associated with Lewy body pathology. *Brain.*
16
17

18
19 Sanchez MP, Gonzalo I, Avila J, de Yébenes JG. 2002. Progressive supranuclear palsy and tau
20
21 hyperphosphorylation in a patient with a C212Y parkin mutation. *J.Alzheimers.Dis.* 4:399-404.
22
23

24
25 Santos-Reboucas CB, Abdalla CB, Baldi FJ, Martins PA, Correa JC, Goncalves AP, Cunha MS,
26
27 Borges MB, Pereira JS, Laks J, Pimentel MM. 2008. Co-occurrence of sporadic parkinsonism
28
29 and late-onset Alzheimer's disease in a Brazilian male with the LRRK2 p.G2019S mutation.
30
31 *Genet.Test.* 12:471-473.
32
33

34
35 Sasaki S, Shirata A, Yamane K, Iwata M. 2004. Parkin-positive autosomal recessive juvenile
36
37 Parkinsonism with alpha-synuclein-positive inclusions. *Neurology* 63:678-682.
38
39

40
41 Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T,
42
43 Watanabe M, Takeda A, Tomiyama H, Nakashima K, Hasegawa K, Obata F, Yoshikawa T,
44
45 Kawakami H, Sakoda S, Yamamoto M, Hattori N, Murata M, Nakamura Y, Toda T. 2009.
46
47 Genome-wide association study identifies common variants at four loci as genetic risk factors for
48
49 Parkinson's disease. *Nat.Genet.* 41:1303-1307.
50
51

52
53 Savettieri G, Annesi G, Civitelli D, Ciro C, I, Salemi G, Ragonese P, Annesi F, Tarantino P,
54
55 Terruso V, D'Amelio M, Quattrone A. 2008. Identification of the novel D297fsX318 PINK1
56
57
58
59
60

1
2
3 mutation and phenotype variation in a family with early-onset Parkinson's disease.

4
5 Parkinsonism.Relat Disord. 14:509-512.

6
7
8
9 Scherfler C, Khan NL, Pavese N, Eunson L, Graham E, Lees AJ, Quinn NP, Wood NW, Brooks
10 DJ, Piccini PP. 2004. Striatal and cortical pre- and postsynaptic dopaminergic dysfunction in
11 sporadic parkin-linked parkinsonism. Brain 127:1332-1342.

12
13
14
15
16
17 Schlitter AM, Voitalla D, Mueller T, Epplen JT, Dekomien G. 2006. The LRRK2 gene in
18 Parkinson's disease: mutation screening in patients from Germany.

19
20 J.Neurol.Neurosurg.Psychiatry 77:891-892.

21
22
23
24
25 Shimura H, Hattori N, Kubo S, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba
26 T, Tanaka K, Suzuki T. 2000. Familial Parkinson disease gene product, parkin, is a ubiquitin-
27 protein ligase. Nat.Genet. 25:302-305.

28
29
30
31
32
33 Shyu WC, Lin SZ, Chiang MF, Pang CY, Chen SY, Hsin YL, Thajeb P, Lee YJ, Li H. 2005.
34 Early-onset Parkinson's disease in a Chinese population: 99mTc-TRODAT-1 SPECT, Parkin
35 gene analysis and clinical study. Parkinsonism.Relat Disord. 11:173-180.

36
37
38
39
40
41 Sim CH, Lio DS, Mok SS, Masters CL, Hill AF, Culvenor JG, Cheng HC. 2006. C-terminal
42 truncation and Parkinson's disease-associated mutations down-regulate the protein
43 serine/threonine kinase activity of PTEN-induced kinase-1. Hum.Mol.Genet. 15:3251-3262.

44
45
46
47
48
49 Simon-Sanchez J, Marti-Masso JF, Sanchez-Mut JV, Paisan-Ruiz C, Martinez-Gil A, Ruiz-
50 Martinez J, Saenz A, Singleton AB, Lopez de MA, Perez-Tur J. 2006. Parkinson's disease due to
51 the R1441G mutation in Dardarin: a founder effect in the Basques. Mov Disord. 21:1954-1959.

1
2
3 Simon-Sanchez J, Scholz S, Matarin MM, Fung HC, Hernandez D, Gibbs JR, Britton A, Hardy
4 J, Singleton A. 2008. Genomewide SNP assay reveals mutations underlying Parkinson disease.
5 Hum.Mutat. 29:315-322.
6
7

8
9
10
11 Simon-Sanchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P,
12 Scholz SW, Hernandez DG, Kruger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M,
13 Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR,
14 Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozi R, Gwinn K, van der
15 BM, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW,
16 Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T. 2009. Genome-wide
17 association study reveals genetic risk underlying Parkinson's disease. Nat.Genet. 41:1308-1312.
18
19
20
21

22
23 Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna
24 T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson
25 MR, Muentner M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. 2003. alpha-
26 Synuclein locus triplication causes Parkinson's disease. Science 302:841.
27
28

29
30 Sironi F, Primignani P, Zini M, Tunesi S, Ruffmann C, Ricca S, Brambilla T, Antonini A, Tesei
31 S, Canesi M, Zecchinelli A, Mariani C, Meucci N, Sacilotto G, Cilia R, Isaias IU, Garavaglia B,
32 Ghezzi D, Travi M, Decarli A, Coviello DA, Pezzoli G, Goldwurm S. 2008. Parkin analysis in
33 early onset Parkinson's disease. Parkinsonism.Relat Disord. 14:326-333.
34
35
36

37
38
39
40 Skipper L, Shen H, Chua E, Bonnard C, Kolatkar P, Tan LC, Jamora RD, Puvan K, Puong KY,
41 Zhao Y, Pavanni R, Wong MC, Yuen Y, Farrer M, Liu JJ, Tan EK. 2005. Analysis of LRRK2
42 functional domains in nondominant Parkinson disease. Neurology 65:1319-1321.
43
44
45
46
47
48
49

1
2
3 Spanaki C, Latsoudis H, Plaitakis A. 2006. LRRK2 mutations on Crete: R1441H associated with
4 PD evolving to PSP. *Neurology* 67:1518-1519.
5
6

7
8
9 Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. 1998. alpha-Synuclein in
10 filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies.
11 *Proc.Natl.Acad.Sci.U.S.A* 95:6469-6473.
12
13
14

15
16
17 Spira PJ, Sharpe DM, Halliday G, Cavanagh J, Nicholson GA. 2001. Clinical and pathological
18 features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation.
19 *Ann.Neurol.* 49:313-319.
20
21
22

23
24
25 Strauss KM, Martins LM, Plun-Favreau H, Marx FP, Kautzmann S, Berg D, Gasser T, Wszolek
26 Z, Muller T, Bornemann A, Wolburg H, Downward J, Riess O, Schulz JB, Kruger R. 2005. Loss
27 of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. *Hum.Mol.Genet.*
28 14:2099-2111.
29
30
31
32

33
34
35 Sun M, Latourelle JC, Wooten GF, Lew MF, Klein C, Shill HA, Golbe LI, Mark MH, Racette
36 BA, Perlmutter JS, Parsian A, Guttman M, Nicholson G, Xu G, Wilk JB, Saint-Hilaire MH,
37 DeStefano AL, Prakash R, Williamson S, Suchowersky O, Labelle N, Growdon JH, Singer C,
38 Watts RL, Goldwurm S, Pezzoli G, Baker KB, Pramstaller PP, Burn DJ, Chinnery PF, Sherman
39 S, Vieregge P, Litvan I, Gillis T, MacDonald ME, Myers RH, Gusella JF. 2006. Influence of
40 heterozygosity for parkin mutation on onset age in familial Parkinson disease: the GenePD study.
41 *Arch.Neurol.* 63:826-832.
42
43
44
45
46
47
48
49
50

51
52
53 Taira T, Saito Y, Niki T, Iguchi-Ariga SM, Takahashi K, Ariga H. 2004. DJ-1 has a role in
54 antioxidative stress to prevent cell death. *EMBO Rep.* 5:213-218.
55
56
57
58
59
60

1
2
3 Tan EK, Chai A, Teo YY, Zhao Y, Tan C, Shen H, Chandran VR, Teoh ML, Yih Y, Pavanni R,
4
5 Wong MC, Puvan K, Lo YL, Yap E. 2004. Alpha-synuclein haplotypes implicated in risk of
6
7 Parkinson's disease. *Neurology* 62:128-131.
8
9

10
11 Tan EK, Peng R, Wu YR, Wu RM, Wu-Chou YH, Tan LC, An XK, Chen CM, Fook-Chong S,
12
13 Lu CS. 2009. LRRK2 G2385R modulates age at onset in Parkinson's disease: A multi-center
14
15 pooled analysis. *Am.J.Med.Genet.B Neuropsychiatr.Genet.*
16
17

18
19 Tan EK, Skipper L, Chua E, Wong MC, Pavanni R, Bonnard C, Kolatkar P, Liu JJ. 2006a.
20
21 Analysis of 14 LRRK2 mutations in Parkinson's plus syndromes and late-onset Parkinson's
22
23 disease. *Mov Disord.* 21:997-1001.
24
25

26
27 Tan EK, Tan LC, Lim HQ, Li R, Tang M, Yih Y, Pavanni R, Prakash KM, Fook-Chong S, Zhao
28
29 Y. 2008. LRRK2 R1628P increases risk of Parkinson's disease: replication evidence.
30
31 *Hum.Genet.* 124:287-288.
32
33

34
35 Tan EK, Yew K, Chua E, Puvan K, Shen H, Lee E, Puong KY, Zhao Y, Pavanni R, Wong MC,
36
37 Jamora D, de SD, Moe KT, Woon FP, Yuen Y, Tan L. 2006b. PINK1 mutations in sporadic
38
39 early-onset Parkinson's disease. *Mov Disord.* 21:789-793.
40
41

42
43 Tan EK, Yew K, Chua E, Shen H, Jamora RD, Lee E, Puong KY, Zhao Y, Pavanni R, Wong
44
45 MC, Puvan K, Yih Y, Tan LC. 2005. Analysis of PINK1 in Asian patients with familial
46
47 parkinsonism. *Clin.Genet.* 68:468-470.
48
49

50
51 Tan EK, Zhao Y, Skipper L, Tan MG, Di FA, Sun L, Fook-Chong S, Tang S, Chua E, Yuen Y,
52
53 Tan L, Pavanni R, Wong MC, Kolatkar P, Lu CS, Bonifati V, Liu JJ. 2007. The LRRK2
54
55
56
57
58
59
60

1
2
3 Gly2385Arg variant is associated with Parkinson's disease: genetic and functional evidence.

4
5 Hum.Genet. 120:857-863.
6
7

8
9 Tan LC, Tanner CM, Chen R, Chan P, Farrer M, Hardy J, Langston JW. 2003. Marked variation
10 in clinical presentation and age of onset in a family with a heterozygous parkin mutation. Mov
11 Disord. 18:758-763.
12
13

14
15 Tang B, Xiong H, Sun P, Zhang Y, Wang D, Hu Z, Zhu Z, Ma H, Pan Q, Xia JH, Xia K, Zhang
16 Z. 2006. Association of PINK1 and DJ-1 confers digenic inheritance of early-onset Parkinson's
17 disease. Hum.Mol.Genet. 15:1816-1825.
18
19

20
21 Tarantino P, Ciro C, I, Annesi F, Rocca FE, Carrideo S, Provenzano G, Civitelli D, De Marco
22 EV, Quattrone A, Annesi G. 2007. Novel human pathological mutations. Gene symbol: PARK2.
23 Disease: Parkinson's disease. Hum.Genet. 122:415.
24
25

26
27 Tarantino P, Civitelli D, Annesi F, De Marco EV, Rocca FE, Pugliese P, Nicoletti G, Carrideo S,
28 Provenzano G, Annesi G, Quattrone A. 2009. Compound heterozygosity in DJ-1 gene non-
29 coding portion related to parkinsonism. Parkinsonism.Relat Disord. 15:324-326.
30
31

32
33 Terreni L, Calabrese E, Calella AM, Forloni G, Mariani C. 2001. New mutation (R42P) of the
34 parkin gene in the ubiquitinlike domain associated with parkinsonism. Neurology 56:463-466.
35
36

37
38 Toft M, Myhre R, Pielsticker L, White LR, Aasly JO, Farrer MJ. 2007. PINK1 mutation
39 heterozygosity and the risk of Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 78:82-84.
40
41

42
43 Tomiyama H, Li Y, Funayama M, Hasegawa K, Yoshino H, Kubo S, Sato K, Hattori T, Lu CS,
44 Inzelberg R, Djaldetti R, Melamed E, Amouri R, Gouider-Khouja N, Hentati F, Hatano Y, Wang
45
46

1
2
3 M, Imamichi Y, Mizoguchi K, Miyajima H, Obata F, Toda T, Farrer MJ, Mizuno Y, Hattori N.
4
5 2006. Clinicogenetic study of mutations in LRRK2 exon 41 in Parkinson's disease patients from
6
7 18 countries. *Mov Disord.* 21:1102-1108.
8
9

10
11 Tomiyama H, Mizuta I, Li Y, Funayama M, Yoshino H, Li L, Murata M, Yamamoto M, Kubo S,
12
13 Mizuno Y, Toda T, Hattori N. 2008. LRRK2 P755L variant in sporadic Parkinson's disease.
14
15 *J.Hum.Genet.* 53:1012-1015.
16
17

18
19 Uversky VN, Lee HJ, Li J, Fink AL, Lee SJ. 2001a. Stabilization of partially folded
20
21 conformation during alpha-synuclein oligomerization in both purified and cytosolic preparations.
22
23 *J.Biol.Chem.* 276:43495-43498.
24
25

26
27 Uversky VN, Li J, Fink AL. 2001b. Evidence for a partially folded intermediate in alpha-
28
29 synuclein fibril formation. *J.Biol.Chem.* 276:10737-10744.
30
31

32
33 Valente EM, Bentivoglio AR, Dixon PH, Ferraris A, Ialongo T, Frontali M, Albanese A, Wood
34
35 NW. 2001. Localization of a novel locus for autosomal recessive early-onset parkinsonism,
36
37 PARK6, on human chromosome 1p35-p36. *Am.J.Hum.Genet.* 68:895-900.
38
39

40
41 Valente EM, bou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, Ali Z, Del TD,
42
43 Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, Gonzalez-Maldonado R, Deller T, Salvi
44
45 S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G, Wood NW.
46
47 2004a. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science*
48
49 304:1158-1160.
50
51

52
53 Valente EM, Brancati F, Ferraris A, Graham EA, Davis MB, Breteler MM, Gasser T, Bonifati V,
54
55 Bentivoglio AR, De MG, Durr A, Cortelli P, Wassilowsky D, Harhangi BS, Rawal N, Caputo V,
56
57
58
59
60

1
2
3 Filla A, Meco G, Oostra BA, Brice A, Albanese A, Dallapiccola B, Wood NW. 2002. PARK6-
4 linked parkinsonism occurs in several European families. *Ann.Neurol.* 51:14-18.
5
6

7
8
9 Valente EM, Salvi S, Ialongo T, Marongiu R, Elia AE, Caputo V, Romito L, Albanese A,
10
11 Dallapiccola B, Bentivoglio AR. 2004b. PINK1 mutations are associated with sporadic early-
12 onset parkinsonism. *Ann.Neurol.* 56:336-341.
13
14

15
16
17 van Duijn CM, Dekker MC, Bonifati V, Galjaard RJ, Houwing-Duistermaat JJ, Snijders PJ,
18
19 Testers L, Breedveld GJ, Horstink M, Sandkuijl LA, van Swieten JC, Oostra BA, Heutink P.
20
21 2001. Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome
22 1p36. *Am.J.Hum.Genet.* 69:629-634.
23
24

25
26
27 Varrone A, Pellecchia MT, Amboni M, Sansone V, Salvatore E, Ghezzi D, Garavaglia B, Brice
28
29 A, Brunetti A, Bonavita V, De MG, Salvatore M, Pappata S, Barone P. 2004. Imaging of
30 dopaminergic dysfunction with [123I]FP-CIT SPECT in early-onset parkin disease. *Neurology*
31
32 63:2097-2103.
33
34

35
36
37 Wakabayashi K, Hayashi S, Ishikawa A, Hayashi T, Okuizumi K, Tanaka H, Tsuji S, Takahashi
38
39 H. 1998. Autosomal dominant diffuse Lewy body disease. *Acta Neuropathol.* 96:207-210.
40
41

42
43
44 Wang HL, Chou AH, Yeh TH, Li AH, Chen YL, Kuo YL, Tsai SR, Yu ST. 2007. PINK1
45
46 mutants associated with recessive Parkinson's disease are defective in inhibiting mitochondrial
47
48 release of cytochrome c. *Neurobiol.Dis.* 28:216-226.
49
50

51
52 Wang M, Hattori N, Matsumine H, Kobayashi T, Yoshino H, Morioka A, Kitada T, Asakawa S,
53
54 Minoshima S, Shimizu N, Mizuno Y. 1999. Polymorphism in the parkin gene in sporadic
55
56 Parkinson's disease. *Ann.Neurol.* 45:655-658.
57
58
59
60

1
2
3 Wang X, Schwarz TL. 2009. The mechanism of Ca²⁺ -dependent regulation of kinesin-mediated
4
5 mitochondrial motility. *Cell* 136:163-174.
6
7

8
9 Wang Y, Clark LN, Louis ED, Mejia-Santana H, Harris J, Cote LJ, Waters C, Andrews H, Ford
10
11 B, Frucht S, Fahn S, Ottman R, Rabinowitz D, Marder K. 2008. Risk of Parkinson disease in
12
13 carriers of parkin mutations: estimation using the kin-cohort method. *Arch.Neurol.* 65:467-474.
14
15

16
17 Waters CH, Miller CA. 1994. Autosomal dominant Lewy body parkinsonism in a four-
18
19 generation family. *Ann.Neurol.* 35:59-64.
20
21

22
23 Weihofen A, Thomas KJ, Ostaszewski BL, Cookson MR, Selkoe DJ. 2009. Pink1 forms a
24
25 multiprotein complex with Miro and Milton, linking Pink1 function to mitochondrial trafficking.
26
27 *Biochemistry* 48:2045-2052.
28
29

30
31 Weng YH, Chou YH, Wu WS, Lin KJ, Chang HC, Yen TC, Chen RS, Wey SP, Lu CS. 2007.
32
33 PINK1 mutation in Taiwanese early-onset parkinsonism : clinical, genetic, and dopamine
34
35 transporter studies. *J.Neurol.* 254:1347-1355.
36
37

38
39 West AB, Moore DJ, Biskup S, Bugayenko A, Smith WW, Ross CA, Dawson VL, Dawson TM.
40
41 2005. Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase
42
43 activity. *Proc.Natl.Acad.Sci.U.S.A* 102:16842-16847.
44
45

46
47 West AB, Moore DJ, Choi C, Andrabi SA, Li X, Dikeman D, Biskup S, Zhang Z, Lim KL,
48
49 Dawson VL, Dawson TM. 2007. Parkinson's disease-associated mutations in LRRK2 link
50
51 enhanced GTP-binding and kinase activities to neuronal toxicity. *Hum.Mol.Genet.* 16:223-232.
52
53
54
55
56
57
58
59
60

1
2
3 Winkler S, Hagenah J, Lincoln S, Heckman M, Haugarvoll K, Lohmann-Hedrich K, Kostic V,
4 Farrer M, Klein C. 2007. alpha-Synuclein and Parkinson disease susceptibility. *Neurology*
5
6 69:1745-1750.
7
8

9
10
11 Wu RM, Bounds R, Lincoln S, Hulihan M, Lin CH, Hwu WL, Chen J, Gwinn-Hardy K, Farrer
12 M. 2005. Parkin mutations and early-onset parkinsonism in a Taiwanese cohort. *Arch.Neurol.*
13
14 62:82-87.
15
16

17
18
19 Xiong H, Wang D, Chen L, Choo YS, Ma H, Tang C, Xia K, Jiang W, Ronai Z, Zhuang X,
20
21 Zhang Z. 2009. Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting
22
23 unfolded protein degradation. *J.Clin.Invest* 119:650-660.
24
25

26
27
28 Xiromerisiou G, Hadjigeorgiou GM, Gourbali V, Johnson J, Papakonstantinou I, Papadimitriou
29
30 A, Singleton AB. 2007. Screening for SNCA and LRRK2 mutations in Greek sporadic and
31
32 autosomal dominant Parkinson's disease: identification of two novel LRRK2 variants.
33
34 *Eur.J.Neurol.* 14:7-11.
35
36

37
38 Xu Y, Liu Z, Wang Y, Tao E, Chen G, Chen B. 2002. [A new point mutation on exon 2 of parkin
39
40 gene in Parkinson's disease]. *Zhonghua Yi.Xue.Yi.Chuan Xue.Za Zhi.* 19:409-411.
41
42

43
44 Zabetian CP, Samii A, Mosley AD, Roberts JW, Leis BC, Yearout D, Raskind WH, Griffith A.
45
46 2005. A clinic-based study of the LRRK2 gene in Parkinson disease yields new mutations.
47
48 *Neurology* 65:741-744.
49
50

51
52 Zabetian CP, Yamamoto M, Lopez AN, Ujike H, Mata IF, Izumi Y, Kaji R, Maruyama H,
53
54 Morino H, Oda M, Hutter CM, Edwards KL, Schellenberg GD, Tsuang DW, Yearout D, Larson
55
56
57
58
59
60

1
2
3 EB, Kawakami H. 2009. LRRK2 mutations and risk variants in Japanese patients with
4
5 Parkinson's disease. *Mov Disord.* 24:1034-1041.
6
7

8
9 Zarranz JJ, Alegre J, Gomez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J,
10
11 Rodriguez O, Atares B, Llorens V, Gomez TE, del ST, Munoz DG, de Yebenes JG. 2004. The
12
13 new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia.
14
15 *Ann.Neurol.* 55:164-173.
16
17

18
19 Zhang Y, Gao J, Chung KK, Huang H, Dawson VL, Dawson TM. 2000. Parkin functions as an
20
21 E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-
22
23 associated protein, CDCrel-1. *Proc.Natl.Acad.Sci.U.S.A* 97:13354-13359.
24
25
26

27
28 Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti
29
30 RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Muller-
31
32 Myhsok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T. 2004a. Mutations in
33
34 LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* 44:601-
35
36 607.
37
38

39
40 Zimprich A, Muller-Myhsok B, Farrer M, Leitner P, Sharma M, Hulihan M, Lockhart P,
41
42 Strongosky A, Kachergus J, Calne DB, Stoessl J, Uitti RJ, Pfeiffer RF, Trenkwalder C, Homann
43
44 N, Ott E, Wenzel K, Asmus F, Hardy J, Wszolek Z, Gasser T. 2004b. The PARK8 locus in
45
46 autosomal dominant parkinsonism: confirmation of linkage and further delineation of the
47
48 disease-containing interval. *Am.J.Hum.Genet.* 74:11-19.
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

Figure 1. Representation of *SNCA* on genomic and transcript level. All three transcripts coding for the same protein SNCA are depicted (t1: NM_001146055.1 /t2: NM_000345.2 /t3: NM_007308.2). On transcript level exons are colored alternately.

Figure 2. Representation of *LRRK2* on genomic and transcript level and the functional domains of the LRRK2 protein. On transcript level exons are colored alternately (NM_198578.2). (LRR: leucine-rich repeat; Roc: Ras-of-complex protein; COR: C-terminal of Roc)

Figure 3. Representation of *PARK2* on genomic and transcript level and the functional domains of the parkin protein. On transcript level exons are colored alternately (NM_004562.2). (UBL: ubiquitin-like; IBR: in-between-ring)

Figure 4. Representation of *PINK1* on genomic and transcript level and the functional domains of the PINK1 protein. On transcript level exons are colored alternately (NM_032409.2). (TM: transmembranair)

Figure 5. Representation of *PARK7* on genomic and transcript level. On transcript level exons are colored alternately (NM_007262.4).

Table 1. Overview of the five major PD genes

Gene	MIM number	Inheritance	Position	Gene size	Number of exons	Transcript length	Mutation spectrum	
							Classic mutations	Copy number variations
<i>SNCA</i>	163890	AD	4q21	112kb	6	1543bp	Missense (0.9%)	Whole gene duplication and triplication (0.6%)
<i>LRRK2</i>	609007	AD	12q12	144kb	51	9225bp	Missense (18.2%)	-
<i>PARK2</i>	602544	AR	6q26	1.38Mb	12	4073bp	Nonsense, Frameshift (indels and splice site), missense (32.4%)	Single or multiple exon deletions and duplications (15.8%)
<i>PINK1</i>	608309	AR	1p35-36	18kb	8	2660bp	Nonsense, frameshift (indels), missense (24.7%)	Single or multiple exon deletions; whole gene deletion (1.2%)
<i>PARK7</i> or <i>DJ-1</i>	602533	AR	1p36	34kb	7	961bp	Missense (4.4%)	Single or multiple exon deletions and duplications (1.2%)
(%) number of (possible) pathogenic mutations for this gene / total number of (possible) pathogenic mutations								

Table 2. Features of the proteins coded by the five major genes

Gene	Protein	Number of aa	Functional domains	(Putative) function
<i>SNCA</i>	α -synuclein	144aa	-	Neurotransmitter release
<i>LRRK2</i>	LRRK2	2527aa	Ank (ankyrin-like), LRR (leucine rich repeat), Roc (Ras-of-complex proteins), COR (C-terminal of Roc), Kinase, WD40	-
<i>PARK2</i>	Parkin	465aa	UBL (ubiquitin-like), RING1, IBR (in-between-ring), RING2	Target proteins for degradation, maintenance mitochondrial function
<i>PINK1</i>	PINK1	581aa	Target sequence, kinase	Oxidative stress response, maintenance mitochondrial function
<i>PARK7</i> or <i>DJ-1</i>	DJ-1	189aa	-	Redox sensor, anti-oxidant

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Table 3. Relative frequencies of mutation categories dependent on ethnicity and familial history

Ethnic origin		<i>SNCA</i> (%)		<i>LRRK2</i> (%)		<i>PARK2</i> (%)			<i>PINK1</i> (%)		<i>PARK7</i> (%)	
		Classic	CNV	Classic	CNV	Classic	mixed	CNV	Classic	CNV	Classic	CNV
Caucasian	F	4.13	2.07	67.36	0	10.12	3.51	7.44	3.93	0.21	0.83	0.41
	S	0.99	0.33	52.48	0	18.15	2.97	11.88	10.89	0.33	0.99	0.66
Asian	F	1.01	8.08	9.09	0	10.10	10.10	42.42	17.17	0	3.03	0
	S	0	3.13	10.42	0	28.13	1.04	38.54	17.71	1.04	0	0
Arab	F	0	0	88.61	0	1.27	1.27	3.80	3.80	1.27	0	0
	S	0	0	97.06	0	1.47	0	0.74	0	0	0.74	0
Latin-American	F	0	0	57.14	0	14.29	4.76	23.81	0	0	0	0
	S	0	0	41.67	0	41.67	0	8.33	0	8.33	0	0
Ashkenazi Jews	F	0	0	100.00	0	0	0	0	0	0	0	0
	S	0	0	98.04	0	0	0	0	0	0	1.96	0

(%) Number of unrelated mutation carriers with this category of mutation / Total number of unrelated mutation carriers (for each ethnicity and familial history). Each row of this table equals 100%.

Table 4. Relative frequencies of homozygotes or compound heterozygotes and digenic combinations dependent on ethnicity and familial history

Ethnic origin			Homozygotes (%)		Compound heterozygotes (%)		Digenic combinations (%)
Caucasian	F	10.33	<i>LRRK2, PARK2, PINK1</i> and <i>DJ-1</i>	8.06	<i>LRRK2, PARK2</i> and <i>PINK1</i>	0.20	<i>LRRK2-PARK2</i>
	S	8.58	<i>PARK2, PINK1</i> and <i>DJ-1</i>	6.60	<i>LRRK2, PARK2</i> and <i>PINK1</i>	1.65	<i>LRRK2-PARK2</i>
Asian	F	41.41	<i>SNCA, PARK2, PINK1</i> and <i>DJ-1</i>	22.22	<i>PARK2</i> and <i>PINK1</i>	1.01	<i>PINK1-DJ-1</i>
	S	38.54	<i>PARK2</i> and <i>PINK1</i>	6.25	<i>PARK2</i>	0	
Arab	F	50.63	<i>LRRK2, PARK2</i> and <i>PINK1</i>	1.27	<i>PARK2</i>	0	
	S	13.97	<i>LRRK2, PARK2</i> and <i>DJ-1</i>	0		0	
Latin-American	F	23.81	<i>PARK2</i>	14.29	<i>PARK2</i>	0	
	S	16.67	<i>LRRK2</i> and <i>PINK1</i>	25.00	<i>PARK2</i>	0	
(% Number of unrelated mutation carriers with this category of mutation / Total number of unrelated mutation carriers (for each ethnicity and familial history))							

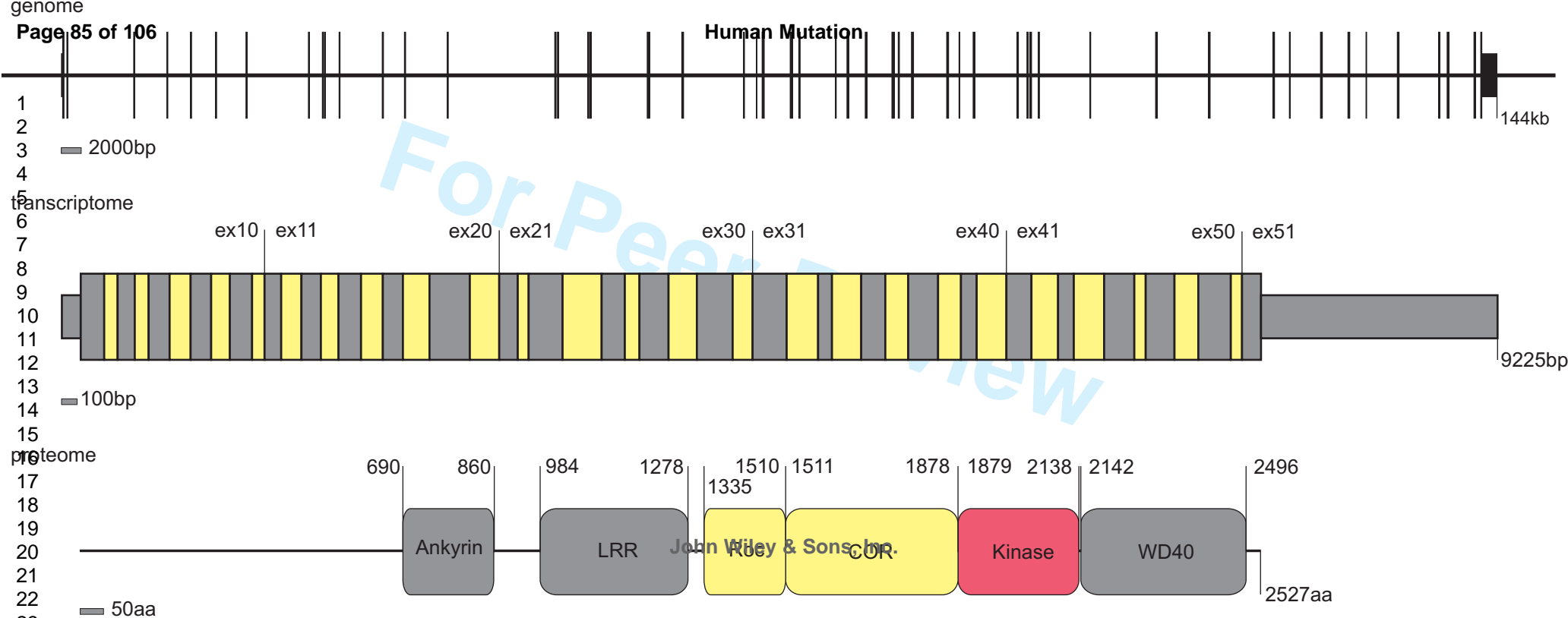
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

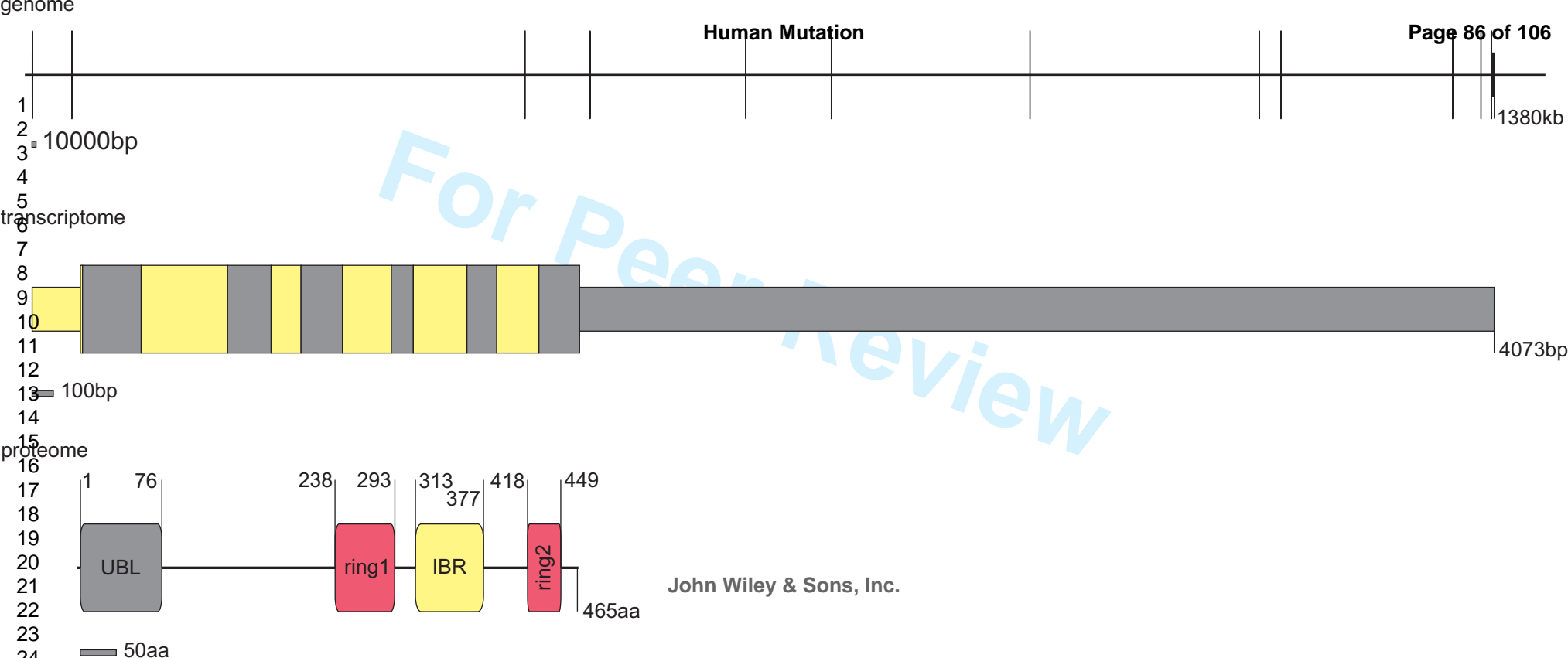
Table 5. Overview of pathology associated with mutations in the 5 different PD genes

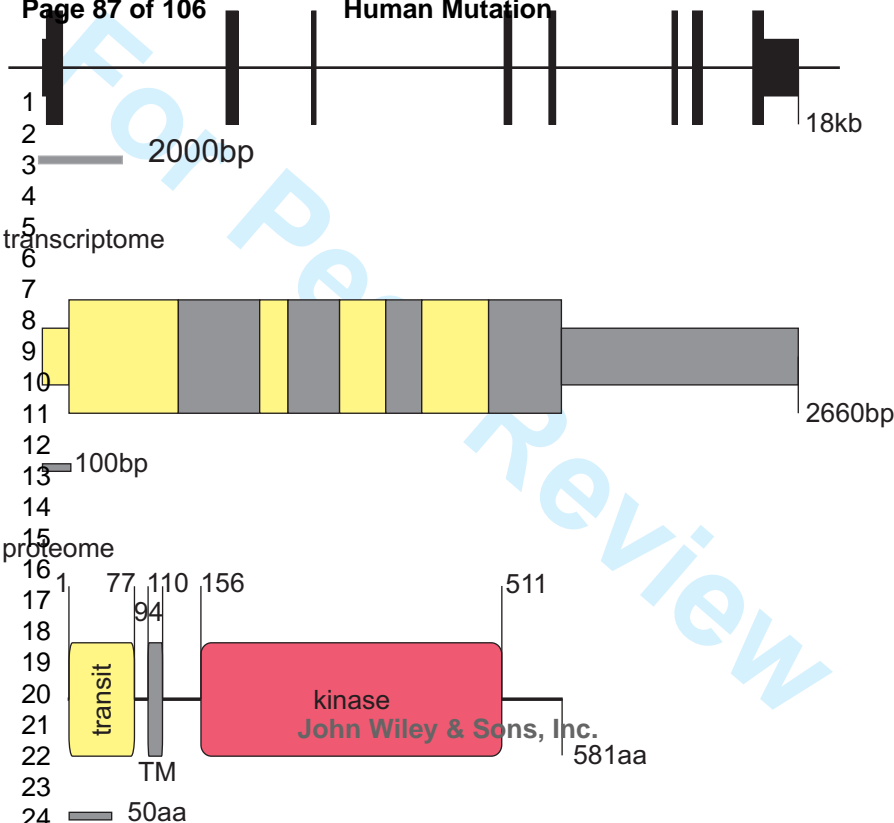
Gene	Pathology	Reference(s)
<i>SNCA</i>	Typical LB disease	[Spira et al., 2001]
	Brainstem and cortical LB and neuritic staining	[Farrer et al., 2004; Fuchs et al., 2007; Gwinn-Hardy et al., 2000; Ikeuchi et al., 2008; Obi et al., 2008; Wakabayashi et al., 1998; Waters et al., 1994; Zarranz et al., 2004]
<i>LRRK2</i>	Typical LB disease	[Giasson et al., 2006; Giordana et al., 2007; Papapetropoulos et al., 2006]
	Tau-positive pathology without LB	[Gaig et al., 2007; Rajput et al., 2006; Zimprich et al., 2004a]
<i>PARK2</i>	Nigral degeneration, with neither LB nor NFT	[Dachsel et al., 2007; Gaig et al., 2008; Giasson et al., 2006]
	Loss of dopaminergic neurons in SN and LC without LB or NFT pathology	[Gouider-Khouja et al., 2003; Hayashi et al., 2000; Kitada et al., 1998; Sasaki et al., 2004]
<i>PINK1</i>	Typical LB disease	[Pramstaller et al., 2005]
<i>PARK7</i> or <i>DJ-1</i>	Remains to be determined	[Samaranch et al., 2010]

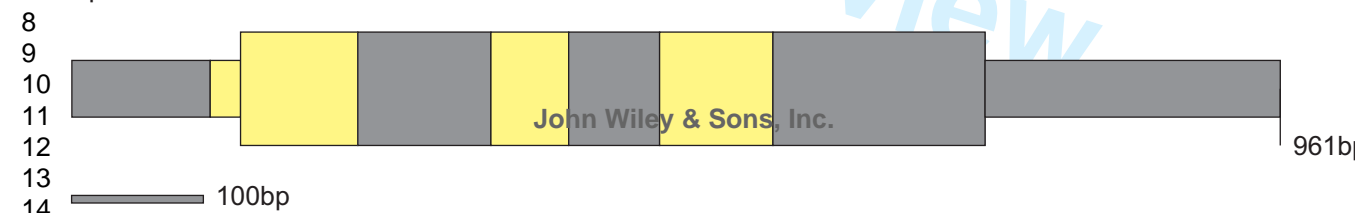
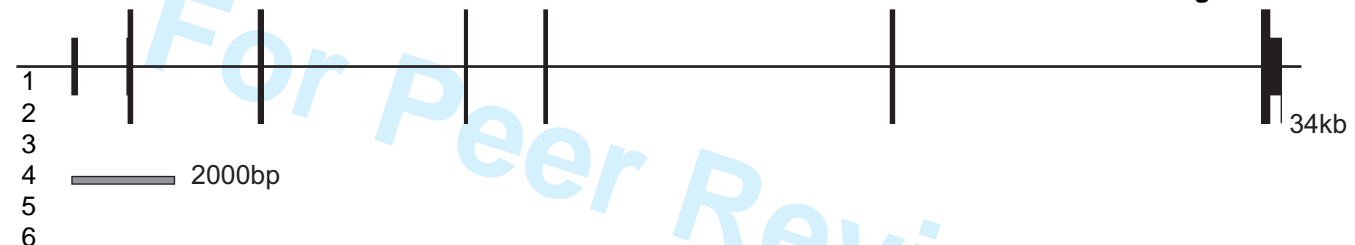
LB: lewy body; NFT: neurofibrillary tangles; SN: Substantia nigra, LC: locus ceruleus











Nuytemans et al., *Human Mutation***Supp. Table S1-1. SNCA Classic mutations**^(a)

(a) Missense, nonsense and frameshift mutations

Region	NG Numbering	cDNA Numbering	Protein Numbering	dbSNP number	Reference
EX2	g.07717G>C	c.88G>C	p.A30P	-	[Kruger et al., 1998]
EX3	g.15127G>A	c.136G>A	p.E46K	-	[Zarranz et al., 2004]
EX3	g.15148G>A	c.157G>A	p.A53T	-	[Polymeropoulos et al., 1997]

(b) Splice, silent and UTR variants					
Region	NG Numbering	cDNA Numbering	Alias	dbSNP number	Reference
IVS2	g.07759A>C	-	IVS2+9A>C†	-	[Nuytemans et al., 2009]
EX3	g.15138G>A	c.193G>A	p.V49	-	[Nuytemans et al., 2009]
EX6	g.116654C>T	c.454C>T	p.Y136	-	[Nuytemans et al., 2009]
3'UTR	g.117170C>T	c.*501C>T	Ex6+534C>T	rs17016074	[Mueller et al., 2005]
3'UTR	g.117562C>T	c.*893C>T	Ex6+926C>T	rs356165	[Pals et al., 2004a]

Supp. Table S1-2. SNCA Copy number variations^(a)

Region	cDNA Numbering	Alias	Mutation Description	Reference
Complete gene	c.(?_70)_(*2533_?)[3]	tripSNCA	Chromosome 4q genomic triplication of unknown size containing <i>SNCA</i> and including <i>HERC5</i> , <i>PIGY</i> , <i>HERC3</i> , <i>NAPIL5</i> , <i>FAM13A0S</i> , <i>AX748242</i> , <i>FAM13A1</i> , <i>KIAA0914</i> , <i>TIGD2</i> , <i>AK026379</i> , <i>GPRIN3</i>	[Singleton et al., 2003]
Complete gene	c.(?_70)_(*2533_?)[3]	tripSNCA	Chromosome 4q genomic triplication of unknown size containing <i>SNCA</i> and including <i>CR05611</i> , <i>AK123890</i> , <i>MMRN1</i> , <i>MGC48628</i> and <i>KIAA1680</i>	[Farrer et al., 2004]
Complete gene	c.(?_70)_(*2533_?)[3]	tripSNCA	Chromosome 4q genomic triplication of unknown size containing <i>SNCA</i> and including <i>AK026379</i> , <i>GPRIN3</i> , <i>CR05611</i> , <i>AK123890</i> , <i>MMRN1</i> , <i>MGC48628</i> , <i>KIAA1680</i> and <i>TMSL3</i>	[Ibanez et al., 2009]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including <i>CR05611</i> , <i>AK123890</i> , <i>MMRN1</i> , <i>MGC48628</i> and <i>KIAA1680</i>	[Fuchs et al., 2007]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including at least <i>FAM13A1</i> , <i>KIAA0914</i> , <i>TIGD2</i> , <i>AK026379</i> , <i>GPRIN3</i> and <i>CR05611</i>	[Chartier-Harlin et al., 2004]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including at least <i>CR05611</i> and <i>AK123890</i>	[Ibanez et al., 2004]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including at least <i>CR05611</i> , <i>AK123890</i> and <i>MMRN1</i>	[Ibanez et al., 2004]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including <i>CR05611</i> , <i>AK123890</i> and <i>MMRN1</i>	[Nishioka et al., 2006]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including at least <i>CR05611</i> , <i>AK123890</i> , <i>MMRN1</i> , <i>MGC48628</i> and <i>KIAA1680</i>	[Nishioka et al., 2006]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing at least <i>SNCA</i>	[Ahn et al., 2008; Nuytemans et al., 2009]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including 32 more known or predicted genes	[Ikeuchi et al., 2008]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including 44 more known or predicted genes	[Ibanez et al., 2009]
Complete gene	c.(?_70)_(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including 34 more known or predicted genes	[Ibanez et al., 2009]

Nuytemans et al., *Human Mutation*

2

Region	cDNA Numbering	Alias	Mutation Description	Reference
Complete gene	c.(?_-70)(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including <i>CR05611</i> , <i>AK123890</i> , <i>MMRN1</i> , <i>MGC48628</i> and <i>KIAA1680</i>	[Ibanez et al., 2009]
Complete gene	c.(?_-70)(*2533_?)dup	dupSNCA	Chromosome 4q genomic duplication of unknown size containing <i>SNCA</i> and including <i>CR05611</i> and <i>AK123890</i>	[Ibanez et al., 2009]

For all references please visit the Parkinson Disease mutation database PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>).

^(a) NG numbering: NG_011851.1; cDNA numbering: NM_001146055.1; protein numbering: NP_000336.1. Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.

† Also observed in control individuals

For Peer Review

Nuytemans et al., *Human Mutation***Supp. Table S2. *LRRK2* Classic mutations^(a)**

(a) Missense, nonsense and frameshift mutations

Region	NG numbering	cDNA Numbering	Protein Numbering	dbSNP number	Reference
EX1	g.5149G>A	c.28G>A	p.E10K	-	[Nichols et al., 2007]
EX2	g.5548C>T	c.155C>T	p.S52F§	rs72546335	[Lesage et al., 2009]
EX4	g.15624T>C	c.356T>C	p.L119P	rs33995463	[Zimprich et al., 2004a]
EX6	g.20533C>T	c.632C>T	p.A211V†	-	[Xiromerisiou et al., 2007]
EX6	g.20584G>C	c.647G>C	p.C228S*	rs56108242	[Paisan-Ruiz et al., 2008]
EX9	g.31263G>A	c.1000G>A	p.E334K	-	[Nichols et al., 2007]
EX9	g.31351A>G	c.1088A>G	p.N363S	rs72546336	[Lesage et al., 2009]
EX9	g.31359G>A	c.1096G>A	p.V366M§	-	[Nuytemans et al., 2009]
EX11	g.32974C>T	c.1256C>T	p.A419V	rs34594498	[Di Fonzo et al., 2006b]
EX13	g.39568G>A	c.1517G>A	p.R506Q	-	[Nuytemans et al., 2009]
EX14	g.43865A>G	c.1630A>G	p.K544E	-	[Xiromerisiou et al., 2007]
EX14	g.43888C>G	c.1653C>G	p.N551K	rs7308720	[Mata et al., 2005b]
EX18	g.58157C>T	c.2147C>T	p.A716V*	-	[Paisan-Ruiz et al., 2008]
EX18	g.58144A>G	c.2134A>G	p.M712V	-	[Paisan-Ruiz et al., 2008]
EX18	g.58177A>G	c.2167A>G	p.I723V	rs10878307	[Mata et al., 2005b]
EX19	g.63887C>T	c.2264C>T	p.P755L	rs34410987	[Di Fonzo et al., 2006b]
EX19	g.64001G>T	c.2378G>T	p.R793M†	rs35173587	[Zimprich et al., 2004a]
EX19	g.64051A>G	c.2428A>G	p.I810V	rs72546337	[Lesage et al., 2009]
EX20	g.67451A>G	c.2611A>G	p.K871E*	-	[Paisan-Ruiz et al., 2008]
EX21	g.73614G>x	c.2769G>x	p.Q923H	rs58559150	[Camargos et al., 2009]
EX21	g.73634A>G	c.2789A>G	p.Q930R	-	[Berg et al., 2005]
EX25	g.75456G>A	c.2918G>A	p.S973N	-	[Haubenberger et al., 2007]
EX23	g.75556A>G	c.3018A>G	p.I1006M	-	[Nuytemans et al., 2009]
EX24	g.78336G>A	c.3200G>A	p.R1067Q†	-	[Skipper et al., 2005]
EX24	g.78423C>G	c.3287C>G	p.S1096C	-	[Berg et al., 2005]
EX24	g.78469G>T	c.3333G>T	p.Q1111H	-	[Nichols et al., 2007]
EX25	g.79115A>G	c.3364A>G	p.I1122V	rs34805604	[Zimprich et al., 2004a]
EX25	g.79202G>A	c.3451G>A	p.A1151T	-	[Schlitter et al., 2006]
EX25	g.79245T>C	c.3494T>C	p.L1165P	-	[Chen-Plotkin et al., 2008]
EX26	g.82856A>G	c.3574A>G	p.I1192V	-	[Nichols et al., 2007]
EX27	g.83994A>G	c.3647A>G	p.H1216R	rs72546324	[Lesage et al., 2009]
EX27	g.84030G>C	c.3683G>C	p.S1228T	rs60185966	[Berg et al., 2005]
EX28	g.85781C>G	c.3784C>G	p.P1262A*,§	rs4640000	[Paisan-Ruiz et al., 2008]

Nuytemans et al., *Human Mutation*

12

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

EX29	g.88471G>A	c.3974G>A	p.R1325Q	rs72546338	[Nuytemans et al., 2008]
EX29	g.88608A>G	c.4111A>G	p.I1371V	rs17466213	[Paisan-Ruiz et al., 2005]
EX30	g.89099G>A	c.4193G>A	p.R1398H	rs7133914	[Paisan-Ruiz et al., 2005]
EX30	g.89135C>T	c.4229C>T	p.T1410M	rs72546327	[Lesage et al., 2009]
EX30	g.89164G>A	c.4258GA	p.D1420N	-	[Gao et al., 2009]
EX31	g.90424C>G	c.4321C>G	p.R1441G	-	[Paisan-Ruiz et al., 2004]
EX31	g.90424C>T	c.4321C>T	p.R1441C	rs33939927	[Zimprich et al., 2004a]
EX31	g.90425G>A	c.4322G>A	p.R1441H	rs34995376	[Mata et al., 2005b]
EX31	g.90427G>C	c.4324G>C	p.A1442P	-	[Huang et al., 2007]
EX31	g.90440C>T	c.4337C>T	p.P1446L	-	[Zabetian et al., 2009]
EX31	g.90451G>A	c.4348G>A	p.V1450I	-	[Zabetian et al., 2009]
EX31	g.90505A>G	c.4402A>G	p.K1468E	-	[Nuytemans et al., 2008]
EX31	g.90551G>A	c.4448G>A	p.R1483Q	-	[Nuytemans et al., 2008]
EX32	g.93966G>A	c.4541G>A	p.R1514Q	rs35507033	[Zimprich et al., 2004a]
EX32	g.94049C>T	c.4624C>T	p.P1542S	rs33958906	[Mata et al., 2005b]
EX34	g.99988T>C	c.4838T>C	p.V1613A	-	[Pchelina et al., 2008]
EX34	g.100036G>C	c.4883G>C	p.R1628P	rs33949390	[Mata et al., 2005b]
EX34	g.100087T>C	c.4937T>C	p.M1646T	rs35303786	[Paisan-Ruiz et al., 2004]
EX34	g.100089T>A	c.4939T>A	p.S1647T	rs11564148	[Mata et al., 2005b]
EX35	g.101104A>T	c.5096A>G	p.Y1699C	rs35801418	[Paisan-Ruiz et al., 2004]
EX36	g.102037G>A	c.5183G>A	p.R1728H	-	[Paisan-Ruiz et al., 2008]
EX36	g.102037G>T	c.5183G>T	p.R1728L	-	[Paisan-Ruiz et al., 2008]
EX37	g.102376G>T	c.5385G>T	p.L1795F	-	[Nichols et al., 2007]
EX38	g.103245A>G	c.5605A>G	p.M1869V	-	[Di Fonzo et al., 2006b]
EX38	g.103246T>C	c.5606T>C	p.M1869T†	rs35602796	[Farrer et al., 2005]
EX38	g.103250G>T	c.5610G>T	p.L1870F*	-	[Paisan-Ruiz et al., 2008]
EX38	g.103260G>T	c.5620G>T	p.E1874X	-	[Di Fonzo et al., 2006b]
EX40	g.115021G>A	c.5822G>A	p.R1941H	-	[Khan et al., 2005b]
EX41	g.120351T>C	c.6016T>C	p.Y2006H	-	[Lesage et al., 2007a]
EX41	g.120370T>C	c.6035T>C	p.I2012T	rs34015634	[Tomiya et al., 2006]
EX41	g.120390G>A	c.6055G>A	p.G2019S†	rs34637584	[Di Fonzo et al., 2005]
EX41	g.120394T>C	c.6059T>C	p.I2020T	rs35870237	[Zimprich et al., 2004a]
EX41	g.120426A>T	c.6091A>T	p.T2031S	-	[Lesage et al., 2007a]
EX42	g.126874A>G	c.6241A>G	p.N2081D	rs33995883	[Zimprich et al., 2004a]
EX44	g.131569C>T	c.6422C>T	p.T2141M	-	[Paisan-Ruiz et al., 2008]
EX44	g.131575G>A	c.6428G>A	p.R2143H	-	[Paisan-Ruiz et al., 2008]

Nuytemans et al., *Human Mutation*

EX44	g.131713A>G	c.6566A>G	p.Y2189C	rs35658131	[Nuytemans et al., 2008]
EX48	g.143430C>T	c.7067C>T	p.T2356I	-	[Khan et al., 2005b]
EX48	<i>g.143516G>A</i>	<i>c.7153G>A</i>	<i>p.G2385R</i>	<i>rs34778348</i>	[Mata et al., 2005b]
EX48	g.143531G>A	c.7168G>A	p.V2390M	-	[Clarimon et al., 2008]
EX49	g.144833G>A	c.7183G>A	p.E2395K*,§	-	[Paisan-Ruiz et al., 2008]
EX49	<i>g.144840T>C</i>	<i>c.7190T>C</i>	<i>p.M2397T</i>	<i>rs3761863</i>	[Paisan-Ruiz et al., 2005]
EX50	g.147002T>A	c.7397T>A	p.L2466H	-	[Paisan-Ruiz et al., 2008]
EX51	g.147639delC	c.7468delC	p.Q2490NfsX3†	-	[Nuytemans et al., 2009]

(b) Splice, silent and UTR variants

Region	NG numbering	cDNA Numbering	Alias	dbSNP number	Reference
5'UTR	g.5078G>T	c.-44G>T	c.-44G>T	-	[Paisan-Ruiz et al., 2008]
5'UTR	g.5092G>C	c.-30G>C	c.-30G>C	rs72546314	[Lesage et al., 2009]
EX5	<i>g.17979T>C</i>	<i>c.457T>C</i>	<i>p.L153</i>	<i>rs10878245</i>	[Mata et al., 2005b]
EX5	<i>g.18068A>G</i>	<i>c.546A>G</i>	<i>p.K182</i>	<i>rs35517158</i>	[Mata et al., 2005b]
EX7	<i>g.23658T>C</i>	<i>c.825T>C</i>	<i>p.H275</i>	-	[Paisan-Ruiz et al., 2008]
EX8	g.29844C>T	c.867C>T	p.N289	rs17490713	[Paisan-Ruiz et al., 2008]
EX8	g.29913G>T	c.936G>T	p.A312	rs41286466	[Nuytemans et al., 2009]
IVS9	<i>g.31445G>A</i>	-	<i>IVS9-10C>A</i>	<i>rs7955902</i>	[Di Fonzo et al., 2006a]
IVS10	g.32896A>G	-	IVS10-4A>G*	rs7135747	[Paisan-Ruiz et al., 2008]
EX12	<i>g.37332T>C</i>	<i>c.1383T>C</i>	<i>p.S461</i>	<i>rs35847451</i>	[Mata et al., 2005b]
EX13	<i>g.39515A>T</i>	<i>c.1464A>T</i>	<i>p.L488</i>	-	[Nichols et al., 2007]
IVS16	g.57864delT	-	IVS16-14delT*	-	[Paisan-Ruiz et al., 2008]
EX17	g.57958A>C	c.2022A>C	p.V674	rs72546319	[Lesage et al., 2009]
EX18	g.58131C>T	c.2121C>T	p.Y707*	-	[Paisan-Ruiz et al., 2008]
EX19	<i>g.64106T>C</i>	<i>c.2481T>C</i>	<i>p.S827</i>	-	[Nichols et al., 2007]
IVS19	g.64128_64131delGTAA	-	IVS19+5_8delGTAA	-	[Johnson et al., 2007]
IVS19	<i>g.67332_67333insT</i>	-	<i>IVS19-9_8insT</i>	<i>rs36220740</i>	[Di Fonzo et al., 2006a]
EX22	<i>g.74883T>C</i>	<i>c.2857T>C</i>	<i>p.L953</i>	<i>rs7966550</i>	[Paisan-Ruiz et al., 2005]
EX24	<i>g.78478A>G</i>	<i>c.3342A>G</i>	<i>p.L1114§</i>	<i>rs35808389</i>	[Zimprich et al., 2004a]
IVS25	g.82771delT	-	IVS25-8delT†	-	[Paisan-Ruiz et al., 2008]
IVS27	g.85764C>T	-	IVS27-9C>T	-	[Paisan-Ruiz et al., 2008]
EX30	<i>g.89175G>A</i>	<i>c.4269G>A</i>	<i>p.K1423</i>	<i>rs11175964</i>	[Mata et al., 2005b]
EX30	g.89196C>T	c.4290C>T	p.A1430	-	[Paisan-Ruiz et al., 2008]
IVS30	<i>g.89235delT</i>	-	<i>IVS30+12delT†</i>	-	[Di Fonzo et al., 2006a]
IVS30	g.90415C>T	-	IVS30-6C>T	rs56082834	[Nuytemans et al., 2009]
EX31	g.90426C>T	c.4323C>T	p.R1441§	-	[Gaig et al., 2008]

IVS31	g.90642A>G	-	IVS31+3A>G	rs41286476	[Zabetian et al., 2005]
IVS32	g.94177G>A	-	IVS32+14G>A	rs72546328	[Lesage et al., 2009]
IVS33	g.95296T>A	-	IVS33+6T>A	-	[Skipper et al., 2005]
<i>EX34</i>	<i>g.100022C>A</i>	<i>c.4872C>A</i>	<i>p.G1624</i>	<i>rs1427263</i>	[Paisan-Ruiz et al., 2005]
<i>EX34</i>	<i>g.100061A>G</i>	<i>c.4911A>G</i>	<i>p.K1637</i>	<i>rs11176013</i>	[Mata et al., 2005b]
<i>EX37</i>	<i>g.102448T>C</i>	<i>c.5457T>C</i>	<i>p.G1819</i>	<i>rs10878371</i>	[Mata et al., 2005b]
IVS37	g.103141A>G	-	IVS37-9A>G†	rs41286460	[Di Fonzo et al., 2006a]
IVS38	g.103303C>T	-	IVS38+7C>T	rs36212069	[Paisan-Ruiz et al., 2008]
<i>EX41</i>	<i>g.120348C>T</i>	<i>c.6013C>T</i>	<i>p.L2005*</i>	-	[Orr-Urtreger et al., 2007]
<i>EX41</i>	<i>g.120389C>T</i>	<i>c.6054C>T</i>	<i>p.Y2018*</i>	-	[Orr-Urtreger et al., 2007]
<i>EX43</i>	<i>g.128442G>A</i>	<i>c.6324G>A</i>	<i>p.E2108</i>	<i>rs10878405</i>	[Mata et al., 2005b]
<i>EX44</i>	<i>g.131657C>A</i>	<i>c.6510C>A</i>	<i>p.G2170</i>	<i>rs34869625</i>	[Mata et al., 2005b]
IVS46	g.139236T>A	-	IVS46-14T>A	rs72546333	[Lesage et al., 2009]
IVS46	g.139242delT	-	IVS46-8delT	rs72546334	[Lesage et al., 2009]
IVS47	g.143383delT	-	IVS47-9delT	rs11317573	[Di Fonzo et al., 2006a]
<i>EX48</i>	<i>g.143518A>G</i>	<i>c.7155A>G</i>	<i>p.G2385</i>	<i>rs33962975</i>	[Mata et al., 2005b]
<i>EX49</i>	<i>g.144946C>G</i>	<i>c.7296C>G</i>	<i>p.G2432*</i>	-	[Paisan-Ruiz et al., 2008]

For all references please visit the Parkinson Disease mutation database PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>).

^(a) NG numbering: NG_011709.1; cDNA numbering: NM_198578.2; protein numbering: NP_940980.3. Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.

* Only observed in control individuals;

† Also observed in control individuals;

§ In proximity to exon/intron boundary;

Italic: known polymorphism

Nuytemans et al., *Human Mutation***Supp. Table S3-1. *PARK2* Classic mutations** ^(a)

(a) Missense, nonsense and frameshift mutations						
Region	NG numbering	cDNA Numbering	Protein Numbering	Alias	dbSNP number	Reference
EX1	g.0005135A>T	c.1A>T	p.0?	Met1Leu	-	[Rawal et al., 2003]
EX	g.0289335G>A	c.13G>A	p.V5I	Val5Ile	-	[Camargos et al., 2009]
EX2	g.0289351G>A	c.29G>A	p.S10N	Ser10Asn	-	[Nuytemans et al., 2009]
EX2	g.0289356G>C	c.34G>C	p.G12R	Gly12Arg	-	[Mellick et al., 2009]
EX2	g.0289365G>A	c.43G>A	p.V15M	Val15Met	-	[Munoz et al., 2002]
EX2	g.0289374G>A	c.52G>A	p.D18N	Asp18Asn	-	[Annesi et al., 2007]
EX2	g.0289414C>A	c.92C>A	p.A31D	Ala31Asp	-	[Chaudhary et al., 2006]
EX2	g.0289417A>C	c.95A>C	p.K32T	Lys32Thr	-	[Tarantino et al., 2007]
EX2	g.0289419C>T	c.97C>T	p.R33X	Arg33Stop	-	[Maruyama et al., 2000]
EX2	g.0289420G>A	c.98G>A	p.R33Q	Arg33Gln	-	[Hertz et al., 2006]
EX2	g.0289423delA	c.101delA	p.Q34RfsX10	Gln34fs	-	[Nisipeanu et al., 2001]
EX2	g.0289423_0289424delAG	c.101_102delAG	p.Q34RfsX5	Gln34fs	rs55777503	[Abbas et al., 1999]
EX2	g.0289423A>G	c.101A>G	p.Q34R	Gln34Arg	-	[Biswas et al., 2006]
EX2	g.0289432C>T	c.110C>T	p.P37L	Pro37Leu	-	[Kann et al., 2002]
EX2	g.0289440C>T	c.118C>T	p.Q40X	Gln40Stop	-	[Choi et al., 2008]
EX2	g.0289446C>T	c.124C>T	p.R42C	Arg42Cys	-	[Biswas et al., 2006]
EX2	g.0289447G>A	c.125G>A	p.R42H	Arg42His	-	[Madegowda et al., 2005]
EX2	g.0289447G>C	c.125G>C	p.R42P	Arg42Pro	-	[Terreni et al., 2001]
EX2	g.0289458G>A	c.136G>A	p.A46T	Ala46Thr	-	[Okubadejo et al., 2008]
EX2	g.0289458G>C	c.136G>C	p.A46P	Ala46Pro	-	[Xu et al., 2002]
EX2	g.0289477delA	c.155delA	p.N52MfsX29	Asn52fs	-	[Lucking et al., 2000]
EX2	g.0289478_0289479insT	c.156_157insT	p.D53X	Asp53Stop	-	[Aguiar et al., 2008]
EX2	g.0289482T>A	c.160T>A	p.W54R	Trp54Arg	-	[Camargos et al., 2009]
EX2	g.0289486C>T	c.164C>T	p.T55I	Thr55Ile	-	[Rocca et al., 2007]
EX2	g.0289489T>A	c.167T>A	p.V56E	Val56Glu	-	[Hoenicka et al., 2002]
EX3	g.0470086_0470087insGT	c.220_221insGT	p.W74CfsX8	Trp74fs	-	[Abbas et al., 1999]
EX3	g.0470101G>T	c.235G>T	p.E79X	Glu79Stop	-	[Foroud et al., 2003]
EX3	g.0470111C>A	c.245C>A	p.A82E†	Ala82Glu	rs55774500	[Hedrich et al., 2001]
EX3	g.0470122G>A	c.256G>A	p.D86N	Asp86Asn	-	[Ciro, I et al., 2007]
EX3	g.0470166G>C	c.300G>C	p.Q100H	Gln100His	-	[Chen et al., 2003]
EX3	g.0470176C>T	c.310C>T	p.R104W	Arg104Trp	-	[Varrone et al., 2004]
EX3	g.0470203_0470242del40	c.337_376del40	p.P113TfsX51	Pro113fs / ex3 Δ40bp	-	[Farrer et al., 2001a]
EX3	g.0470263_0470265delCCA	c.397_399delCCA	p.P133del	Pro133del	-	[Hedrich et al., 2004b]

Nuytemans et al., *Human Mutation*

16

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

EX3	g.0531566A>G	c.428A>G	p.Y143C	Tyr134Cys	-	[Biswas et al., 2006]
EX4	g.0531572G>A	c.434G>A	p.S145N	Ser145Asn	-	[Varrone et al., 2004]
EX4	g.0531596C>G	c.458V>G	p.P153R†	Pro153Arg	rs55654276	[Wang et al., 2008]
EX4	g.0531621A>T	c.483A>T	p.K161N	Lys161Asn	-	[Abbas et al., 1999]
EX4	g.0531635G>A	c.497G>A	p.C166T	Cys166Tyr	-	[Brooks et al., 2009]
EX4	g.051638G>A	c.500G>A	p.S167N	Ser167Asn	rs1801474	[Hattori et al., 1998a]
EX4	g.0531649C>T	c.511C>T	p.Q171X	Gln171Stop	-	[Brooks et al., 2009]
EX4	g.0531656C>T	c.518C>T	p.T173M*	Thr173Met	-	[Kay et al., 2007]
EX5	g.0678630delG	c.536delG	p.G179VXfs9	Gly179fs	-	[Hattori et al., 1998a]
EX5	g.0678668A>C	c.574A>C	p.M192L	Met192Leu	rs9456735	[Hedrich et al., 2002]
EX5	g.0678668A>G	c.574A>G	p.M192V	Met192Val	-	[Dachsel et al., 2006]
EX5	g.0678694C>G	c.600C>G	p.H200Q	His200Gln	rs72480421	[Bardien et al., 2009]
EX6	g.0759399A>G	c.632A>G	p.K211R	Lys211Arg	-	[Periquet et al., 2001]
EX6	g.0759400A>T	c.633A>T	p.K211N	Lys211Asn	-	[Lucking et al., 2000]
EX6	g.0759401delT	c.634delT	p.C212VfsX13	Cys212fs	-	[Sironi et al., 2008]
EX6	g.0759401T>G	c.634T>G	p.C212G	Cys212Gly	-	[Shyu et al., 2005]
EX6	g.0759402G>A	c.635G>A	p.C212Y	Cys212Tyr	-	[Pineda-Trujillo et al., 2001]
EX6	g.0759412C>A	c.645C>A	p.H215Q	His215Gln	-	[Pigullo et al., 2004]
EX6	g.0759455G>A	c.688G>A	p.A230T	Ala230Thr	-	[Sironi et al., 2008]
EX6	g.0759468G>A	c.701G>A	p.R234Q	Arg234Gln	-	[Hertz et al., 2006]
EX6	g.0759481C>G	c.714G>A	p.C238W	Cys238Trp	-	[Sironi et al., 2008]
EX6	g.0759486C>G	c.719C>G	p.T240R	Thr240Arg	-	[Hattori et al., 1998b]
EX6	g.0759486C>T	c.719C>T	p.T240M	Thr240Met	-	[Periquet et al., 2003]
EX6	g.0759494G>A	c.727G>A	p.D243N†	Asp243Asn	-	[Romito et al., 2005]
EX6	g.0759497G>A	c.730G>A	p.V244I*,§	Val244Ile	-	[Kay et al., 2007]
EX7	g.0946918G>A	c.758G>A	p.C253Y	Cys253Tyr	-	[Sironi et al., 2008]
EX7	g.0946918G>T	c.758G>T	p.C253F	Cys253Phe	-	[Guo et al., 2008]
EX7	g.0946919C>G	c.759C>G	p.C253W	Cys253Trp	-	[Oliveira et al., 2003]
EX7	g.0946926C>T	c.766C>T	p.R256C	Arg256Cys	-	[Abbas et al., 1999]
EX7	g.0946932G>A	c.772G>A	p.V258M	Val258Met	-	[Shyu et al., 2005]
EX7	g.0946954A>G	c.794A>G	p.H265R	His265Arg	-	[Nuytemans et al., 2009]
EX7	g.0946959T>C	c.799T>C	p.Y267H	Tyr267His	-	[Lee et al., 2009]
EX7	g.0946964T>A	c.804T>A	p.C268X	Cys268Stop	-	[Lucking et al., 2000]
EX7	g.0946973A>T	c.813A>T	p.R271S	Arg271Ser	-	[Chen et al., 2003]
EX7	g.0946974C>A	c.814C>A	p.L272I	Leu272Ile	-	[Li et al., 2005a]
EX7	g.0946978A>G	c.818A>G	p.N273S†	Asn273Ser	-	[Lesage et al., 2008]

Nuytemans et al., *Human Mutation*

1							
2							
3							
4	EX7	g.0946983C>T	c.823C>T	p.R275W†	Arg275Trp	rs34424986	[Abbas et al., 1999]
5	EX7	g.0946998G>A	c.838G>A	p.D280N	Asp280Asn	rs72480422	[Lucking et al., 2000]
6	EX7	g.0947008T>C	c.848T>C	p.L283P	Leu283Pro	rs56754308	[Macedo et al., 2009]
7	EX7	g.0947010G>C	c.850G>C	p.G284R	Gly284Arg	-	[Wu et al., 2005]
8	EX7	g.0947025T>G	c.865T>G	p.C289G§	Cys289Gly	rs55961220	[Lucking et al., 2000]
9	EX7	g.0947031delG	c.871delG	p.A291LfsX7	Ala291fs	-	[Munoz et al., 2000]
10	EX8	g.1163407A>C	c.892A>C	p.I298L	Ile298Leu	-	[Wang et al., 2008]
11	EX8	g.1163408T>G	c.893T>G	p.I298S	Ile298Ser	-	[Lesage et al., 2008]
12	EX8	g.1163445G>C	c.930G>C	p.E310D	Glu310Asp	rs72480423	[Bardien et al., 2009]
13	EX8	g.1163446C>T	c.931C>T	p.Q311X	Gln311Stop	-	[Hattori et al., 1998b]
14	EX8	g.1163448G>T	c.933G>T	p.Q311H§	Gln311His	-	[Shyu et al., 2005]
15	EX9	g.1183834_1183839del6	c.968_973delGTGTCC	p.C323_V324del	Cys323fs	-	[Guo et al., 2008]
16	EX9	g.1183837delT	c.971delT	p.V324AfsX111	Val324fs	-	[Klein et al., 2000]
17	EX9	g.1183849G>A	c.983G>A	p.G328E	Gly328Glu	-	[Lucking et al., 2000]
18	EX9	g.1183866C>T	c.1000C>T	p.R334C†	Arg334Cys	-	[Lucking et al., 2000]
19	EX9	g.1183867G>A	c.1001G>A	p.R334H	Arg334His	-	[Okubadejo et al., 2008]
20	EX9	g.1183881G>T	c.1015G>T	p.A339S	Ala339Ser	-	[Chen et al., 2003]
21	EX9	g.1183907_1183908delGA	c.1041_1042delGA	p.R348EfsX21	Arg348fs	-	[Lucking et al., 2000]
22	EX9	g.1183912_1183913delAA	c.1046_1047delAA	p.K349SfsX20	Lys349fs	-	[Hedrich et al., 2001]
23	EX9	g.1183917A>C	c.1051A>C	p.T351P	Thr351Pro	-	[Kann et al., 2002]
24	EX9	g.1183942G>A	c.1076G>A	p.G359D†	Gly359Asp	-	[Madegowda et al., 2005]
25	EX10	g.1345938C>T	c.1096C>T	p.R366W	Arg366Trp	rs56092260	[Wang et al., 1999]
26	EX10	g.1345939G>A	c.1097G>A	p.R366Q	Arg366Gln	-	[Wang et al., 2008]
27	EX10	g.1345980G>C	c.1138G>C	p.V380L	Val380Leu	rs1801582	[Abbas et al., 1999]
28	EX11	g.1372605delGA	c.1175_1176delGA	p.R392SfsX3	Arg392fs	-	[Alvarez et al., 2001]
29	EX11	g.1372610G>A	c.1180G>A	p.D394N	Asp394Asn	rs1801334	[Abbas et al., 1999]
30	EX11	g.1372613G>T	c.1183G>T	p.E395X	Glu395Stop	-	[Bras et al., 2008]
31	EX11	g.1372616A>G	c.1186A>G	p.R396G	Arg396Gly	-	[Wu et al., 2005]
32	EX11	g.1372622G>A	c.1192G>A	p.A398T	Ala398Thr	-	[Periquet et al., 2003]
33	EX11	g.1372634C>T	c.1204C>T	p.R402C†	Arg402Cys	rs55830907	[Poorkaj et al., 2004]
34	EX11	g.1372635G>A	c.1205G>A	p.R402H	Arg402His	-	[Sun et al., 2006]
35	EX11	g.1372655G>T	c.1225G>T	p.E409X	Glu409Stop	-	[Sironi et al., 2008]
36	EX11	g.1372674C>A	c.1244C>A	p.T415N†	Thr415Asn	-	[Abbas et al., 1999]
37	EX11	g.1372682T>C	c.1252T>C	p.C418R	Cys418Arg	-	[Bertoli-Avella et al., 2005]
38	EX11	g.1372691_1372692insA	c.1283_1284insA	p.N428KfsX141	Asn428fs	-	[Rawal et al., 2003]
39	EX12	g.1382592G>A	c.1286G>A	p.G429E§	Gly429Glu	-	[Bruggemann et al., 2009]
40							
41							
42							
43							
44							
45							
46							
47							
48							
49							

Nuytemans et al., *Human Mutation*

18

EX12	g.1382595G>A	c.1289G>A	p.G430D	Gly430Asp	-	[Lucking et al., 2000]
EX12	g.1382598G>T	c.1292G>T	p.C431F	Cys431Phe	-	[Maruyama et al., 2000]
EX12	g.1382616C>T	c.1310C>T	p.P437L†	Pro437Leu	-	[Hedrich et al., 2002]
EX12	g.1382627T>C	c.1321T>C	p.C441R	Cys441Arg	-	[Shyu et al., 2005]
EX12	g.1382636G>C	c.1330G>C	p.E444Q	Glu444Gln	-	[Madegowda et al., 2005]
EX12	g.1382641G>A	c.1335G>A	p.W445X	Trp445Stop	-	[Rawal et al., 2003]
EX12	g.1382664G>A	c.1358G>A	p.W453X	Trp453Stop	rs34424986	[Abbas et al., 1999]
EX12	g.1382678A>C	c.1372A>C	p.M458L	Met458Leu	-	[Brooks et al., 2009]
EX12	g.1382684_1382685insG	c.1378_1379insG	p.D460GfsX109	Asp460fs	-	[Chan et al., 2008]
EX12	g.1382699G>A	c.1393G>A	p.V465M	Val465Met	-	[Pigullo et al., 2004]

(b) Splice, silent and UTR variants

Region	NG numbering	cDNA Numbering	Protein Numbering	Alias	dbSNP number	Reference
5'UTR	g.0005082C>T	c.-53C>T	p.?*	c.-53C>T	-	[Kay et al., 2007]
5'UTR	g.0005091C>A	c.-44C>A	p.?	c.-44C>A	-	[Kay et al., 2007]
5'UTR	g.0005096G>T	c.-39G>T	p.?	c.-39G>T	-	[Bruggemann et al., 2009]
5'UTR	g.0005114G>T	c.-21G>T	p.?	c.-21G>T	-	[Hedrich et al., 2002]
5'UTR	g.0005129G>C	c.-6G>C	p.?	c.-6G>C	-	[Varrone et al., 2004]
IVS1	g.0005142G>A	-	p.?	IVS1+1G>A	-	[Illarioshkin et al., 2003]
EX2	g.0289370G>A	c.48G>A	p.E16†	Glu16	-	[Okubadejo et al., 2008]
EX3	g.0289373C>x	c.51C>x	p.V17	Val17	-	[Myhre et al., 2008a]
EX3	g.0289433G>A	c.111G>A	p.P37	Pro37	-	[Okubadejo et al., 2008]
EX3	g.047238C>T	c.372C>T	p.H124	His124	-	[Chen et al., 2003]
EX4	g.0531660C>T	c.522C>T	p.L174	Leu174	-	[Brooks et al., 2009]
EX4	g.0531669C>A	c.531C>A	p.T177*,§	Thr177	-	[Kay et al., 2007]
IVS4	g.0531682T>C	-	p.?	IVS4+10T>C	-	[Chan et al., 2008]
IVS5	g.0678714T>A	-	p.?	IVS5+2T>A	-	[Scherfler et al., 2004]
EX7	g.0946925A>T	c.765A>T	p.S255†	Ser255	-	[Kay et al., 2007]
EX7	g.0946943A>G	c.783A>G	p.L261	Leu261	rs9456711	[Hedrich et al., 2002]
EX7	g.0946976C>T	c.816C>T	p.L272	Leu272	-	[Chaudhary et al., 2006]
EX7	g.0946997C>T	c.837C>T	p.H279	His279	-	[Pigullo et al., 2004]
IVS7	g.1163384C>G	-	p.?	IVS7-3C>G	-	[Nuytemans et al., 2009]
IVS7	g.1163386G>C	-	p.?	IVS7-1G>C	-	[Rawal et al., 2003]
EX8	g.1163434C>T	c.919C>T	p.L307	Leu307	-	[Sironi et al., 2008]
IVS8	g.1183797C>T	-	p.?	IVS8-3C>T	-	[Pigullo et al., 2004]
EX9	g.1183823T>C	c.957T>C	p.G319	Gly319	-	[Okubadejo et al., 2008]
EX9	g.1183883G>A	c.1017G>A	p.A339	Ala339	-	[Abbas et al., 1999]

Nuytemans et al., *Human Mutation*1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

IVS9	g.1345925G>A	-	p.?	IVS9-1G>A	-	[Nuytemans et al., 2009]
EX11	g.1372636T>C	c.1206T>C	p.R402	Arg402	-	[Bardien et al., 2009]
IVS11	g.1382589C>G	-	p.*/p.G429EfsX5	IVS11-3C>G	-	[Bertoli-Avella et al., 2005]
3'UTR	g.1382720G>A	c.*16G>A	p.?	*16G>A	rs61730194	[Bardien et al., 2009]
3'UTR	g.1382798A>G	c.*94A>G	p.†	*94A>G	rs62637702	[Sironi et al., 2008]
3'UTR	g.1382798_1382799delins4	c.*94_*95delinsGCGC	p.?	*94_95delinsGCGC	-	[Sironi et al., 2008]
3'UTR	g.1382807C>T	c.*103C>T	p.?	*103C>T	-	[Bardien et al., 2009]

Supp. Table S3-2. *PARK2* copy number variations^(a)

Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	Reference
Prom+EX1	-	c.(8-?)_oPACRG:(157-?)del	p.0	prom+ex1del (NP)	[Lesage et al., 2007b]
EX1	-	c.(-134-?)_(7+?)del	p.?	ex1del (NP)	[Hedrich et al., 2002]
EX1	-	c.(-134-?)_(7+?)del	p.?	ex1dup (NP)	[Sun et al., 2006]
EX1-4	-	c.(-134-?)_(534+?)del	p.?	ex1-4del (NP)	[Chung et al., 2008]
EX2	-	c.(8-?)_(171+?)del	p.V3EfsX3	ex2del (NP)	[Lucking et al., 2000]
EX2	-	c.(8-?)_(171+?)dup	p.*/p.N58CfsX41†	ex2dup (NP)	[Simon-Sanchez et al., 2008]
EX2	-	c.(8-?)_(171+?) [3]	p.N58CfsX41	ex2trip (NP)	[Lucking et al., 2000]
EX2-3	-	c.(8-?)_(412+?)del	p.V3AfsX329	ex2-3del (NP)	[Lucking et al., 2000]
EX2-3	-	c.(8-?)_(412+?)dup	p.*/p.A138VfsX464	ex2-3dup (NP)	[Nichols et al., 2002]
EX2-4	-	c.(8-?)_(534+?)del	p.V3GfsX7	ex2-4del (NP)	[Maruyama et al., 2000]
EX2-4	-	c.(8-?)_(534+?)dup	p.*/p.G179CfsX41†	ex2-4dup (NP)	[Periquet et al., 2003]
EX2-4	-	c.(8-?)_(534+?) [3]	p.*/p.G179CfsX41	ex2-4trip (NP)	[Mata et al., 2005a]
EX2-5	-	c.(8-?)_(618+?)del	p.V3GfsX5	ex2-5del (NP)	[Kann et al., 2002]
EX2-12	-	c.(8-?)_(3939+?)dup	p.?	ex2-12dup (NP)	[Nuytemans et al., 2009]
EX3	-	c.(172-?)_(412+?)del	p.N58QfsX39	ex3del (NP)	[Hattori et al., 1998a]
EX3	-	c.(172-?)_(412+?)dup	p.*/p.A138EfsX3	ex3dup (NP)	[Lucking et al., 2000]
EX3-4	-	c.(172-?)_(534+?)del	p.N58_Q178del	ex3-4del (NP)	[Hattori et al., 1998a]
EX3-4	-	c.(172-?)_(534+?)dup	p.*/p.N58_Q178dup	ex3-4dup (NP)	[Periquet et al., 2003]
EX3-5	-	c.(172-?)_(618+?)del	p.N58_A206del	ex3-5del (NP)	[Kobayashi et al., 2000]
EX3-6	-	c.(172-?)_(734+?)del	p.N58EfsX29	ex3-6del (NP)	[Lucking et al., 2000]
EX3-7	-	c.(172-?)_(871+?)del	p.A291LfsX7	ex3-7del (NP)	[Kitada et al., 1998]
EX3-9	-	c.(172-?)_(1083+?)del	p.N58_G361del	ex3-9del (NP)	[Lucking et al., 2000]
EX4	g.0484957_0641130del	c.(413-46594)_(534+109486)del156202	p.A138GfsX7	ex4del	[Clarimon et al., 2005]
EX4	g.0529909_0531657del1749	c.(413-1642)_519del1749	p.G139HfsX11	partial ex4del	[Khan et al., 2005a]
EX4	-	c.(413-?)_(534+?)del	p.A138GfsX7	ex4del (NP)	[Kitada et al., 1998]
EX4	-	c.(413-?)_(534+?)dup	p.*/p.G179QfsX39	ex4dup (NP)	[Hedrich et al., 2001]

1						
2						
3	EX4-5	-	c.(413-?)_(618+?)del	p.G139NfsX18	ex4-5del (NP)	[Kann et al., 2002]
4	EX4-6	-	c.(413-?)_(734+?)del	p.A138GfsX14	ex4-6del (NP)	[Nichols et al., 2002]
5	EX4-7	-	c.(413-?)_(871+?)del	p.R140CXfs174	ex4-7del (NP)	[Rawal et al., 2003]
6	EX5	g.0574670_0702743del12813	c.(535-104015)_(618+24031)del128130	p.G179_A206del	ex5del	[Bayrakli et al., 2007]
7	EX5	-	c.(535-?)_(618+?)del	p.G179_A206del	ex5del (NP)	[Hattori et al., 1998a]
8	EX5	-	c.(535-?)_(618+?)dup	p.~/p.G179_A206dup	ex5dup (NP)	[Hedrich et al., 2002]
9	EX5-6	-	c.(535-?)_(734+?)del	p.G179EfsX29	ex5-6del (NP)	[Lucking et al., 2000]
10	EX5-7	-	c.(535-?)_(871+?)del	p.G179LfsX7	ex5-7del (NP)	[Leroy et al., 1998a]
11	EX5-8	-	c.(535-?)_(933+?)dup	p.~/p.G179_Q311dup	ex5-8dup (NP)	[Hertz et al., 2006]
12	EX5-9	-	c.(535-?)_(1083+?)dup	p.~/p.G179_G361dup	ex5-9dup (NP)	[Brooks et al., 2009]
13	EX5-12	-	c.(535-?)_(3939+?)del	p.G179_V465del	ex5-12del (NP)	[Moro et al., 2008]
14	EX6	-	c.(619-?)_(734+?)del	p.F208PfsX28†	ex6del (NP)	[Nichols et al., 2002]
15	EX6	-	c.(619-?)_(734+?)dup	p.~/p.S246NfsX18	ex6dup (NP)	[Lucking et al., 2000]
16	EX6-7	-	c.(619-?)_(871+?)del	p.E207LfsX7	ex6-7del (NP)	[Maruyama et al., 2000]
17	EX6-8	-	c.(619-?)_(933+?)dup	p.~/p.F207_Q311dup	ex6-8dup (NP)	[Sun et al., 2006]
18	EX7	-	c.(735-?)_(871+?)del	p.R245SfsX9	ex7del (NP)	[Klein et al., 2000]
19	EX7	-	c.(735-?)_(871?)dup	p.~/p.A291GfsX14†	ex7dup (NP)	[Lucking et al., 2000]
20	EX7-8	-	c.(735-?)_(933+?)del	p.R245SfsX124	ex7-8del (NP)	[Sun et al., 2006]
21	EX7-9	-	c.(735-?)_(1083+?)del	p.R245SfsX74	ex7-9del (NP)	[Lucking et al., 2000]
22	EX8	-	c.(872-?)_(933+?)del	p.A291VfsX35	ex8del (NP)	[Lucking et al., 2000]
23	EX8	-	c.(872-?)_(933+?)dup	p.~/p.Y312LfsX7	ex8dup (NP)	[Nichols et al., 2002]
24	EX8-9	-	c.(872-?)_(1083+?)del	p.A291VfsX8	ex8-9del (NP)	[Lucking et al., 1998]
25	EX8-10	-	c.(872-?)_(1167+?)del	p.A291GfsX6	ex8-10del (NP)	[Bertoli-Avella et al., 2005]
26	EX8-11	-	c.(872-?)_(1285+?)del	p.A291GfsX38	ex8-11del (NP)	[Bras et al., 2008]
27	EX9	-	c.(934-?)_(1083+?)dup	p.~/p.Y312_G361dup	ex9dup (NP)	[Kann et al., 2002]
28	EX10	-	c.(1084-?)_1167+?)del	p.F339AfsX77	ex10del (NP)	[Periquet et al., 2003]
29	EX10	-	c.(1084-?)_1167+?)dup	p.~/p.A390FfsX105	ex10dup (NP)	[Foroud et al., 2003]
30	EX10-12	-	c.(1084-?)_(3939+?)del	p.?	ex10-12del (NP)	[Shyu et al., 2005]
31	EX10-12	-	c.(1084-?)_(3939+?)dup	p.~/p.F362_V466dup	ex10-12dup (NP)	[Macedo et al., 2009]
32	EX11	-	c.(1168-?)_(1285+?)del	p.A390EfsX6	ex11del (NP)	[Hertz et al., 2006]
33	EX11	-	c.(1168-?)_(1285+?)dup	p.~/p.G430LfsX4	ex11dup (NP)	[Lucking et al., 2000]
34	EX12	-	c.(1286-?)_(3939+?)dup	p.?	ex12dup (NP)	[Sun et al., 2006]

For all references please visit the Parkinson Disease mutation database PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>).

^(a) NG numbering: NG_008289.1; cDNA numbering: NM_004562.2; protein numbering: NP_004553.2. Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.

Nuytemans et al., *Human Mutation*

* Only observed in control individuals;
 † Also observed in control individuals;
 § In proximity to exon/intron boundary;
 NP: breakpoints not mapped
Italic: known polymorphism

Supp. Table S4-1. *PINK1* Classic mutations ^(a)

(a) Missense, nonsense and frameshift mutations

Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	dbSNP Number	Reference
EX1	g.05164_05195del32	c.70_101del32	p.K24GfsX31	Lys24fs	-	[Chaudhary et al., 2006]
EX1	g.05188G>A	c.94G>A	p.G32R	Gly32Arg	-	[Choi et al., 2008]
EX1	g.05249C>T	c.155C>T	p.P52L	Pro52Leu	-	[Brooks et al., 2009]
EX1	g.05293C>T	c.199C>T	p.L67F	Leu67Phe	-	[Marongiu et al., 2008]
EX1	g.05297_05298GC>CT	c.203_204G>C	p.R68P	Arg68Pro	-	[Valente et al., 2004b]
EX1	g.05327C>T	c.233C>T	p.A78V	Ala78Val	-	[Kumazawa et al., 2008]
EX1	g.05369G>T	c.275G>T	p.C92F	Cys92Phe	-	[Valente et al., 2004b]
EX1	g.05376C>T	c.282C>T	p.R98W	Arg98Trp	-	[Marongiu et al., 2008]
EX1	g.05426T>G	c.332T>G	p.I111S	Ile111Ser	-	[Marongiu et al., 2008]
EX1	<i>g.05438A>T</i>	<i>c.344A>T</i>	<i>p.Q115L</i>	<i>Gln115Leu</i>	-	[Bonifati et al., 2005]
EX1	g.05465C>T	c.371C>T	p.A124V	Ala124Val	-	[Marongiu et al., 2008]
EX1	g.05467T>G	c.373T>G	p.C125G	Cys125Gly	-	[Ibanez et al., 2006]
EX1	g.05471A>C	c.377A>C	p.Q126P	Gln126Pro	-	[Prestel et al., 2008]
EX2	g.09434C>T	c.434C>T	p.T145M	Thr145Met	rs45604240	[Marongiu et al., 2008]
EX2	g.09440G>A	c.440G>A	p.R147H	Arg147His	-	[Healy et al., 2004]
EX2	g.09502G>C	c.502G>C	p.A168P	Ala168Pro	-	[Valente et al., 2004b]
EX2	g.09509T>G	c.509T>G	p.V170G	Val170Gly	-	[Toft et al., 2007]
EX2	g.09558G>C	c.558G>C	p.K186N	Lys186Asn	-	[Djarmati et al., 2006]
EX2	g.09577G>A	c.577G>A	p.G193R	Gly193Arg	-	[Weng et al., 2007]
EX2	g.09587delC	c.587delC	p.P196QfsX25	Pro196fs	-	[Kumazawa et al., 2008]
EX2	g.09587C>T	c.587C>T	p.P196L	Pro196Leu	rs35802484	[Bonifati et al., 2005]
EX2	g.09625C>G	c.625C>G	p.P209A	Pro209Ala	rs17852513	[Lee et al., 2009]
EX2	g.09626C>T	c.626C>T	p.P209L	Pro209Leu	rs34677717	[Djarmati et al., 2006]
EX2	g.09650C>A	c.650C>A	p.A217D	Ala217Asp	-	[Leutenegger et al., 2006]
EX3	g.11454A>G	c.692A>G	p.E231G	Glu231Gly	-	[Djarmati et al., 2006]
EX3	g.11466A>T	c.704A>T	p.N235I*	Asn235Ile	-	[Djarmati et al., 2006]

Nuytemans et al., *Human Mutation*1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

EX3	g.11471A>G	c.709A>G	p.M237V†	Met237Val	-	[Macedo et al., 2009]
EX3	g.11477C>T	c.715C>T	p.Q239X	Glu239Stop	-	[Hatano et al., 2004]
EX3	g.11480G>A	c.718G>A	p.E240K	Glu240Lys	-	[Rogaeva et al., 2004]
EX3	g.11498C>T	c.736C>T	p.R246X	Arg246Stop	-	[Hatano et al., 2004]
EX3	g.11493C>G	c.731C>G	p.A244G	Ala244Gly	-	[Gelmetti et al., 2008]
EX3	g.11532C>T	c.770C>T	p.T257I	Thr257Ile	-	[Marongiu et al., 2008]
EX3	g.11536C>A	c.774C>A	p.Y258X	Tyr258Stop	-	[Tan et al., 2006b]
EX4	g.16046A>G	c.787A>G	p.R263G*	Arg263Gly	-	[Rogaeva et al., 2004]
EX4	g.16061C>G	c.802C>G	p.L268V	Leu268Val	-	[Tan et al., 2005]
EX4	g.16072C>A	c.813C>A	p.H271Q	His271Gln	rs28940284	[Hatano et al., 2004]
EX4	g.16086G>A	c.827G>A	p.R276Q	Arg276Gln	-	[Marongiu et al., 2008]
EX4	g.16095G>A	c.836G>A	p.R279H	Arg279His	rs61735932	[Klein et al., 2005]
EX4	g.16097G>A	c.838G>A	p.A280T	Ala280Thr	-	[Tan et al., 2006b]
EX4	g.16146C>T	c.887C>T	p.P296L*	Pro296Leu	-	[Valente et al., 2004b]
EX4	g.16148delG	c.889delG	p.D297MfsX22	Asp297fs	-	[Kumazawa et al., 2008]
EX4	g.16173C>T	c.914C>T	p.P305L	Pro305Leu	rs7349186	[Healy et al., 2004]
EX4	g.16185G>A	c.926G>A	p.G309D	Gly309Asp	-	[Valente et al., 2004a]
EX4	g.16197C>T	c.938C>T	p.T313M	Thr313Met	-	[Chishti et al., 2006]
EX4	g.16208G>A	c.949G>A	p.V371I	Val371Ile	-	[Abou-Sleiman et al., 2006]
EX4	g.16211A>T	c.952A>T	p.M318L	Met318Leu	-	[Rogaeva et al., 2004]
EX5	g.17111C>T	c.965C>T	p.P322L	Pro322Leu	-	[Marongiu et al., 2008]
EX5	g.17161G>A	c.1015G>A	p.A339T	Ala339Thr	rs55831733	[Rogaeva et al., 2004]
EX5	g.17164G>A	c.1018G>A	p.A340T	Ala340Thr	rs3738136	[Valente et al., 2004a]
EX5	g.17169G>A	c.1023G>A	p.M341I	Met341Ile	rs35813094	[Lee et al., 2009]
EX5	g.17170A>G	c.1024A>G	p.M342V	Met342Val	-	[Kumazawa et al., 2008]
EX5	g.17172G>A	c.1026G>A	p.M342I	Met342Ile	-	[Nuytemans et al., 2009]
EX5	g.17186T>C	c.1040T>C	p.L347P†	Leu347Pro	rs28940285	[Hatano et al., 2004]
EX5	g.17230G>C	c.1084G>C	p.D362H*	Asp362His	-	[Rogaeva et al., 2004]
EX5	g.17246A>G	c.1100A>G	p.N367S	Asn367Ser	-	[Choi et al., 2008]
EX5	g.17252T>C	c.1106T>C	p.L369P	Leu369Pro	-	[Ibanez et al., 2006]
EX6	g.20074G>A	c.1147G>A	p.A383T	Ala383Thr	rs45515602	[Abou-Sleiman et al., 2006]
EX6	g.20080T>C	c.1153T>C	p.F385L	Phe385Leu	-	[Choi et al., 2008]
EX6	g.20084G>C	c.1157G>C	p.G386A	Gly386Ala	-	[Ibanez et al., 2006]
EX6	g.20089T>C	c.1162T>C	p.C388R	Cys388Arg	-	[Li et al., 2005b]
EX6	g.20111G>T	c.1184G>T	p.G395V	Gly395Val	-	[Marongiu et al., 2008]
EX6	g.20123C>T	c.1196C>T	p.P399L	Pro399Leu	-	[Tang et al., 2006]
EX6	g.20147G>A	c.1220G>A	p.R407Q	Arg407Gln	-	[Fung et al., 2006a]
EX6	g.20153G>T	c.1226G>T	p.G409V	Gly409Val	-	[Ibanez et al., 2006]
EX6	g.20158G>A	c.1231G>A	p.G411S	Gly411Ser	rs45478900	[Abou-Sleiman et al., 2006]

Nuytemans et al., *Human Mutation*

1							
2							
3	EX6	g.20174C>G	c.1247C>G	p.P416R	Pro416Arg	-	[Myhre et al., 2008a]
4	EX6	g.20177A>G	c.1250A>G	p.E417G	Glu417Gly	-	[Hatano et al., 2004]
5	EX7	g.20539_20561del23	c.(1252-2)_1274del23	p.?	23bp del acceptor site ex7	-	[Marongiu et al., 2007]
6	EX7	g.20544T>C	c.1255T>C	p.S419P	Ser419Pro	-	[Myhre et al., 2008a]
7	EX7	g.20569C>A	c.1280C>A	p.A427E	Ala427Glu	-	[Brooks et al., 2009]
8	EX7	g.20562C>T	c.1273C>T	p.P425S	Pro425Ser	-	[Rogaeva et al., 2004]
9	EX7	g.20580T>C	c.1291T>C	p.Y431H	Tyr431His	-	[Abou-Sleiman et al., 2006]
10	EX7	g.20598T>C	c.1309T>C	p.W437R	Trp437Arg	-	[Kumazawa et al., 2008]
11	EX7	g.20600G>A	c.1311G>A	p.W437X†	Trp437Stop	-	[Valente et al., 2004a]
12	EX7	g.20614T>C	c.1325T>C	p.I442T	Ile442Thr	-	[Valente et al., 2004b]
13	EX7	g.20641A>G	c.1352A>G	p.N451S	Asn451Ser	-	[Abou-Sleiman et al., 2006]
14	EX7	g.20655C>T	c.1366C>T	p.Q456X	Gln456Stop	rs45539432	[Bonifati et al., 2005]
15	EX7	g.20671T>G	c.1382T>G	p.L461R*	Leu461Arg	-	[Abou-Sleiman et al., 2006]
16	EX7	g.20680G>A	c.1391G>A	p.R464H	Arg464His	-	[Valente et al., 2004b]
17	EX7	g.20715G>A	c.1426G>A	p.E476K†	Glu476Lys	-	[Myhre et al., 2008a]
18	EX7	g.20733G>A	c.1444G>A	p.V482M	Val482Met	-	[Kumazawa et al., 2008]
19	EX7	g.20755T>C	c.1466T>C	p.L489P	Leu489Pro	-	[Rogaeva et al., 2004]
20	EX7	g.20763C>T	c.1474C>T	p.R492X	Arg492Stop	rs34208370	[Hatano et al., 2004]
21	EX8	g.21984C>T	c.1493C>T	p.P498L	Pro498Leu	-	[Toft et al., 2007]
22	EX8	g.21993G>A	c.1502G>A	p.R501Q*	Arg501Gln	-	[Abou-Sleiman et al., 2006]
23	EX8	g.22048delG	c.1557delG	p.K520RfsX3	Leu519fs	-	[Ibanez et al., 2006]
24	EX8	g.22053A>C	c.1562A>C	p.N521T	Asn521Thr	rs1043424	[Myhre et al., 2008a]
25	EX8	g.22064G>A	c.1573G>A	p.D525N†	Asp525Asn	-	[Valente et al., 2004b]
26	EX8	g.22064_22065insTTAG	c.1473_1574insTTAG	p.D525VfsX38	Asp525fs	-	[Rohe et al., 2004]
27	EX8	g.22093_22094insCAA	c.1602_1603insCAA	p.Q534_S535insQ	534_535insQ	-	[Klein et al., 2005]
28	EX8	g.22100G>A	c.1609G>A	p.A537T	Ala537Thr	-	[Marongiu et al., 2008]
29	EX8	g.22116A>G	c.1625A>G	p.N542S	Asn542Ser	-	[Kumazawa et al., 2008]
30	EX8	g.22138_22141delTGTG	c.1647_1650delTGTG	p.C549WfsX5	Cys549fs	-	[Ibanez et al., 2006]
31	EX8	g.22214T>C	c.1723T>C	p.C575R	Cys575Arg	-	[Abou-Sleiman et al., 2006]
32	EX8	g.22236G>T	c.1745G>T	p.X582L†	Stop582Leu	-	[Toft et al., 2007]

(b) Splice, silent and UTR variants

Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	dbSNP Number	Reference	
35	5'UTR	g.05013G>A	c.-82G>A	p.? *	c.-82G>A	-	[Bonifati et al., 2005]
36	5'UTR	g.05074G>A	c.-21G>A	p.?	c.-21G>A	-	[Klein et al., 2005]
37	5'UTR	g.05075C>T	c.-20C>T	p.? *	c.-20C>T	-	[Bonifati et al., 2005]
38	EX1	g.05283C>T	c.189C>T	p.L63	Leu63	rs45530340	[Valente et al., 2004b]
39	IVS1	g.09381A>G	-	p.?	IVS1-7A>G	rs2298298	[Valente et al., 2004a]
40	EX3	g.11470A>C	c.708A>C	p.T236	Thr236	-	[Rogaeva et al., 2004]

Nuytemans et al., *Human Mutation*

EX4	g.16063A>G	c.804A>G	p.L268	Leu268	-	[Weng et al., 2007]
EX4	g.16096C>T	c.837C>T	p.R279	Arg279	-	[Toft et al., 2007]
EX4	g.16111C>T	c.852C>T	p.S284*	Ser284	-	[Bonifati et al., 2005]
EX4	g.16138C>A	c.879C>A	p.V293	Val293	-	[Godeiro-Junior et al., 2009]
EX4	g.16147T>G	c.888T>G	p.P296	Pro296	-	[Rogaeva et al., 2004]
EX4	g.16195G>A	c.936G>A	p.R312	Arg312	rs56200357	[Valente et al., 2004a]
EX4	g.16207C>T	c.948C>T	p.L316	Leu316	-	[Rogaeva et al., 2004]
<i>IVS4</i>	<i>g.17101G>A</i>	-	p.?	<i>IVS4-5G>A</i>	<i>rs3131713</i>	[Valente et al., 2004a]
EX5	g.17211A>G	c.1065A>G	p.Q355	Gln355	-	[Valente et al., 2004b]
EX5	g.17241C>T	c.1095C>T	p.S365	Ser365	-	[Valente et al., 2004b]
EX6	g.20100T>C	c.1173T>C	p.D391†	Asp391	rs45499398	[Myhre et al., 2008a]
EX6	g.20139C>T	c.1212C>T	p.Y404	Tyr404	-	[Weng et al., 2007]
EX	g.20157C>T	c.1230C>T	p.N410	Asn410	-	[Godeiro-Junior et al., 2009]
EX7	g.20549G>A	c.1260G>A	p.T420	Thr420	-	[Brooks et al., 2009]
EX7	g.20651C>T	c.1362C>T	p.Y454	Tyr454	rs56383368	[Weng et al., 2007]
IVS7	g.20791C>G	-	p.?	IVS7+14C>G	-	[Valente et al., 2004b]
EX8	g.22219A>G	c.1728A>G	p.S576*	Ser576	-	[Rogaeva et al., 2004]
3'UTR	g.22274T>A	c.*37T>A	p.?	c.*37T>A	rs686658	[Rogaeva et al., 2004]
3'UTR	g.22277G>A	c.*40G>A	p.?	c.*40G>A	-	[Rogaeva et al., 2004]

Supp. Table S4-2. *PINK1* Copy number variations^(a)

Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	Reference
Complete gene	-	c.(?-94)_(*2566_?)del	Complete protein	delPINK1 (NP)	[Marongiu et al., 2007]
EX4-8	-	c.(777-?)_(2566+?)del	p.?	ex4-8del (NP)	[Cazeneuve et al., 2009]
EX6-8	-	c.(1124-?)_(2566+?)del	p.?	ex6-8del (NP)	[Li et al., 2005b]
EX7	-	c.(1252-?)_(1488+?)del	p.V418_K496del	ex7del (NP)	[Camargos et al., 2009]

For all references please visit the Parkinson Disease mutation database PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>).

^(a) NG numbering: NG_008164.1; cDNA numbering: NM_032409.2, protein numbering: NP_115785.1. Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.

* Only observed in control individuals;

† Also observed in control individuals;

§ In proximity to exon/intron boundary;

NP: breakpoints not mapped

Italic: known polymorphism

Nuytemans et al., *Human Mutation***Supp. Table S5-1. PARK7 Classic mutations** ^(a)

(a) Missense, nonsense and frameshift mutations						
Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	dbSNP Number	Reference
EX2	g.06161T>C	c.29T>C	p.L10P	Leu10Pro	-	[Guo et al., 2008]
EX2	g.06210G>A	c.78G>A	p.M26I	Met26Ile	-	[Abou-Sleiman et al., 2003]
EX3	g.08695G>T	c.115G>T	p.A39S	Ala39Ser	-	[Tang et al., 2006]
EX3	g.08772G>C	c.192G>C	p.E64D§	Glu64Asp	-	[Hering et al., 2004]
EX5	g.14281G>A	c.293G>A	p.R98Q	Arg98Gln	rs71653619	[Abou-Sleiman et al., 2003]
EX5	g.14298G>A	c.310G>A	p.A104T§	Ala104Thr	-	[Clark et al., 2004]
EX7	g.28277A>C	c.446A>C	p.D149A	Asp149Ala	-	[Abou-Sleiman et al., 2003]
EX7	g.28302_28304delGCC	c.471_473delGCC	p.P158del	Pro158del	-	[Macedo et al., 2009]
EX7	g.28318G>A	c.487G>A	p.E163K	Glu163Lys	-	[Annesi et al., 2005]
EX7	g.28328T>C	c.497T>C	p.L166P	Leu166Pro	rs28938172	[Bonifati et al., 2003]
EX7	g.28342G>T	c.511G>T	p.A171S*	Ala171Ser	-	[Clark et al., 2004]
EX7	g.28354A>G	c.523A>G	p.K175E	Lys175Glu	-	[Nuytemans et al., 2009]
EX7	g.28366G>A	c.535G>A	p.A179T	Ala179Thr	rs71653622	[Nuytemans et al., 2009]
(b) Splice, silent and UTR variants						
Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	dbSNP Number	Reference
EX4	g.12733C>T	c.234C>T	p.G78	Gly78	rs11548937	[Abou-Sleiman et al., 2003]
IVS4	g.12759_12760insA	-	p.?	IVS4+8_9insA	-	[Tarantino et al., 2009]
EX5	g.14282G>A	c.294G>A	p.R98	Arg98	-	[Abou-Sleiman et al., 2003]
IVS5	g.14312_14322del11	-	p.?	IVS5+2_12del	-	[Hedrich et al., 2004a]
EX7	g.28311C>A	c.480C>A	p.T160	Thr160	-	[Pankratz et al., 2006b]
EX7	g.28332A>G	c.501A>G	p.A167	Ala167	rs71653621	[Abou-Sleiman et al., 2003]
EX7	g.28389T>C	c.558T>C	p.V186	Val186	-	[Hering et al., 2004]
EX7	g.28521_28522insA	c.690_691insA	p.?	c.*120insA	-	[Abou-Sleiman et al., 2003]
EX7	g.28604G>A	c.773G>A	p.?	c.*203G>A	-	[Abou-Sleiman et al., 2003]

Supp. Table S5-2. PARK7 Copy number variations ^(a)

Region	NG Numbering	cDNA Numbering	Protein Numbering	Alias	Reference
EX1-5	g.02064_16161del14098	c.1_322del	p.? [†]	ex1-5del	[Bonifati et al., 2003]
EX1-5	-	c.(-129-?)(322+?)dup	p.?	ex1-5dup (NP)	[Macedo et al., 2009]
EX5	-	c.(253-?)(107+?)del	p.S85VfsX10	ex5del (NP)	[Djarmati et al., 2004]
EX5-7	-	c.(253-?)(795+?)del	p.?	ex5-7del (NP)	[Hedrich et al., 2004a]

For all references please visit the Parkinson Disease mutation database PDmutDB (<http://www.molgen.ua.ac.be/PDmutDB>).

Nuytemans et al., *Human Mutation*

26

^(a) NG numbering: NG_008271.1; cDNA numbering: NM_007262.4; protein numbering: NP_009193.2. Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.

* Only observed in control individuals;

† Also observed in control individuals;

§ In proximity to exon/intron boundary;

NP: breakpoints not mapped

Italic: known polymorphism

For Peer Review