# Chapter 1
# Leucine-Rich Repeat Kinase (*LRRK2*) Genetics and Parkinson's Disease

**Edoardo Monfrini and Alessio Di Fonzo**

**Abstract** The discovery of *LRRK2* mutations as a cause of Parkinson's disease (PD), including the sporadic late-onset form, established the decisive role of genetics in the field of PD research. Among *LRRK2* mutations, the G2019S, mostly lying in a haplotype originating from a common Middle Eastern ancestor, has been identified in different populations worldwide. The G2385R and R1628P variants represent validated risk factors for PD in Asian populations. Here, we describe in detail the origin, the present worldwide epidemiology, and the penetrance of *LRRK2* mutations. Furthermore, this chapter aims to characterize other definitely/probably pathogenic mutations and risk variants of *LRRK2*. Finally, we provide some general guidelines for a *LRRK2* genetic testing and counseling. In summary, *LRRK2* discovery revolutionized the understanding of PD etiology and laid the foundation for a promising future of genetics in PD research.

**Keywords** Leucine-rich repeat kinase 2 • *LRRK2* • Dardarin • Parkinson's disease • PARK8 • Parkinson's disease genetics • Familial Parkinson's disease • *LRRK2* mutations

Until the discovery of leucine-rich repeat kinase 2 (*LRRK2*) mutations as a genetic cause of Parkinson's disease (PD), the hereditary influences on PD were limited to observation of rare autosomal dominant familial cases harboring highly penetrant *SNCA* (alpha-synuclein) mutations and juvenile or young onset autosomal recessive forms carrying *PRKN*, *PINK1*, and *DJ-1* mutations. This scenario was more suggestive of a minor role played by genetic factors in PD, especially considering the common sporadic late-onset form. The innovative finding of *LRRK2* low penetrant mutations in common forms of PD revolutionized this outdated view.

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## Genetic Contribution in Etiology of PD

Epidemiological studies reveal that 10–15% of PD have a positive familial history for the disease, while the majority of cases are sporadic. Through linkage analysis and positional cloning approaches, five genes have been definitely implicated in the etiology of PD. Mutations in the *SNCA* [1, 2], *LRRK2* [3, 4], and *VPS35* [5, 6] genes cause autosomal dominant forms, whereas mutations in the *PRKN* [7], *DJ-1* [8], and *PINK1* [9] genes cause autosomal recessive forms of PD. Furthermore, mutations in the *ATP13A2* [10], *PLA2G6* [11], *FBXO7* [12, 13], *DNAJC6* [14], and *SYNJ1* [15] have been reported as rare causes of early-onset parkinsonism with atypical clinical features which might be mechanistically distinct from classical PD. Finally, mutations in *UCH-L1* [16], *Omi/HtrA2* [17], *GIGYF2* [18], *EIF4G1* [19], and *DNAJC13* [20] genes have also been described in PD cases, but their role in the disease remains uncertain. Another three PD loci have also been mapped (PARK3, PARK10, PARK12, PARK16) [21–23], but the defective genes remain unknown (Table 1.1).

**Table 1.1** List of loci, genes, patterns of inheritance, and clinical presentations of genetic forms of Parkinson's disease

| Locus | Gene | Chromosome | Inheritance | Clinical presentation |
|---|---|---|---|---|
| PARK1-4 | α-Synuclein | 4q21 | AD | PD, Lewy body dementia |
| PARK2 | *PRKN* | 6q25.2-27 | AR | Early-onset PD |
| PARK3 | Unknown | 2p13 | AD | Typical PD |
| PARK5 | *UCH-L1*[a] | 4p14 | AD | Typical PD |
| PARK6 | *PINK1* | 1p36 | AR | Early-onset PD |
| PARK7 | *DJ-1* | 1p36 | AR | Early-onset PD |
| PARK8 | *LRRK2* | 12q12 | AD | Typical PD |
| PARK9 | *ATP13A2* | 1p36 | AR | Early-onset parkinsonian–pyramidal syndrome with dementia |
| PARK10 | Unknown | 1p32 | Unknown | Typical PD |
| PARK11 | *GIGYF2*[a] | 2q36-37 | AD | Typical PD |
| PARK12 | Unknown | Xq21-q25 | Unknown | Typical PD |
| PARK13 | *Omi/HTRA2*[a] | 2p12 | Unknown | Typical PD |
| PARK14 | *PLA2G6* | 22q | AR | Adult-onset dystonia-parkinsonism |
| PARK15 | *FBXO7* | 22q | AR | Early-onset parkinsonian-pyramidal syndrome |
| PARK16 | Unknown | 1q32 | Unknown | Typical PD |
| PARK17 | *VPS35* | 16q11.1 | AD | Typical PD |
| PARK18 | *EIF4G1*[a] | 3q27.1 | AD | Typical PD |
| PARK19 | *DNAJC6* | 1p31.3 | AR | Early-onset PD atypical |
| PARK20 | *SYNJ1* | 21q22 | AR | Early-onset PD atypical |
| PARK21 | *DNAJC13*[b] | 3q21.3-q22.2 | AD | Typical PD |
| PARK22 | *CHCHD2*[a] | 7p11.2 | AD | Typical PD |
| PARK23 | *VPS13C* | 15q22.2 | AR | Early-onset PD atypical |

[a]Not confirmed by other studies
[b]Needs confirmation by independent studies

In addition to the Mendelian forms of PD, genetic risk factors for the disease have been investigated in several candidate genes and, more recently, in genome-wide association studies [24]. With the exceptions of *SNCA*, microtubule-associated protein tau (*MAPT*), and HLA region [25–32], none of the loci reported have so far been convincingly replicated in independent studies.

Another exception is represented by the glucocerebrosidase gene (*GBA*) involved in a recessive neurometabolic disease (Gaucher's disease). Screening of PD patients for *GBA* mutations showed a higher number of heterozygous mutations carriers as compared to healthy controls. Mutations have been found in about 2–4% of Caucasian PD patients and less than 1% of controls [33].

## The *LRRK2* Gene: Mapping and Cloning

Although the discovery of mutations in the *SNCA*, *PRKN*, *PINK1*, and *DJ-1* genes clearly contributed to our understanding of the pathogenesis of PD, they were identified in a limited number of PD cases, often with early-onset or pathologically atypical features.

A new locus for PD, termed PARK8, was identified in a large family with autosomal dominant PD, known as the "Sagamihara family" from the region in Japan where the family originated from [34]. The clinical features in affected individuals of the kindred were reported to resemble very closely classical PD, with an average of symptoms onset at 51 ± 6 years. A pattern of "pure nigral degeneration" without Lewy bodies (LB) was found at autopsy in six PD patients examined, another carrier of the disease haplotype developed multiple system atrophy type P-like pathology, and one showed classical LB pathology [35]. In this family, a genome-wide linkage scan yielded significant evidence for linkage of PD to the centromeric region of chromosome 12 (12p11.2-q13.1). The haplotype analysis suggested an incomplete penetrance of the mutation [34, 35]. In 2004 the linkage to PARK8 was confirmed in two Caucasian families, "family A" (a German–Canadian kindred) and "family D" (from Western Nebraska) with dominantly inherited neurodegeneration [36], and thereafter in several Basque PD [37] families suggesting PARK8 to be a relatively common locus and refining the critical region. A wide clinical–pathological spectrum was shown in these families, including typical PD but also dementia and amyotrophy, diffuse LB and tau pathology, nigral degeneration without inclusions, and atypical, ubiquitin-positive inclusions [38].

In 2004 two independent groups, by positional cloning, identified mutations in a gene at that time annotated as DKFZp434H2111, which cosegregated with PD in several PARK8-linked pedigrees [3, 4]. The gene was renamed *LRRK2* (leucine-rich repeat kinase 2) and the encoded protein LRRK2 or dardarin (from the Basque term *dardara*, meaning tremor, since resting tremor was a consistent clinical feature of the Basque patients who carried *LRRK2* mutations).

Subsequently, early in 2005, several groups identified a single *LRRK2* mutation (c.G6055A) leading to a G2019S substitution in the encoded protein, which was

present in familial and sporadic PD with unprecedented high frequency [39–42]. The following years have seen an explosion of research into the *LRRK2* gene in PD and related disorders. The I2020T mutation was detected as the cause of disease in the original "Sagamihara family" [43].

## *The G2019S Mutation*

### Prevalence of G2019S Across Populations

G2019S is particularly important among the PD-causing mutations in *LRRK2*. This mutation was identified by several groups as a common cause of the disease, being detected initially in ~5–6% of large cohorts of familial PD in Europe and the USA [39, 41] and in ~1–2% of sporadic PD from the UK [40]. Due to the unprecedented high frequency in familial and late-onset classical parkinsonism, which in the past would have been identified as "idiopathic PD," this specific mutation has been extensively studied worldwide (Fig. 1.1).

So far, large screenings revealed that the frequency of G2019S is population specific. The G2019S mutation has been reported at the highest frequency (up to 37%) among familial PD cases of North African descent and in familial Ashkenazi Jewish patients (23%) [44, 45]. Similar frequencies were replicated in independent studies on PD cases from Tunisia [46–48] and in Ashkenazi Jews [48–51]. Remarkably, the frequency of this mutation was considerably high among sporadic cases (41% North Africans and 13% Ashkenazi Jews) and rarely identified in healthy controls too (3% North Africans and 1.3% Ashkenazi Jews). Other studies reported the presence of the G2019S among 1–2% of healthy North Africans, Ashkenazi, and

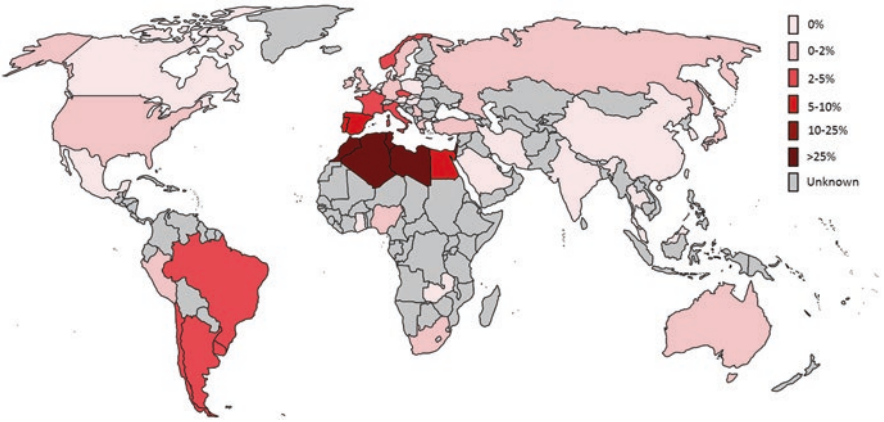


**Fig. 1.1** Rough estimates of worldwide G2019S prevalence in PD patients (familial and sporadic)

Sephardic Jewish subjects [49, 50, 52, 53]. So far the G2019S mutation has not been found in sub-Saharan Africans, with exceptions of South Africans where the mutation was present in subjects with European and Jewish ancestry only [54–57]. Little is known about the prevalence in Middle Eastern populations. G2019S is rare in Turkey [58] and has not been identified so far in Yemenite Jews [51] and in Iran [59].

In Western Europe there is a south–north gradient of frequency. The G2019S is found in 9–16% of familial and 3–4% of sporadic PD patients in Portugal [60, 61]; it accounts for 6–16% of familial and 2–6% of sporadic PD in different regions of Spain: Catalonia [62], Cantabria [63, 64], Asturias [65], Galicia [63], and Basque regions (patients without Basque ancestry) [66], while it is less common in patients of Basque origin (1–2%) [66].

In Italy, the G2019S mutation has been reported up to 6–7% of familial and ~1–2% of sporadic cases [39, 67–71]. Similarly, in France the mutation accounts for ~3.5% of familial and ~1.9% of sporadic cases [44, 72–75]. Two independent screening in Sardinians, an isolated population, reported a frequency of ~1.5% in both familial and sporadic cases [76, 77]. Interestingly, the mutation that appeared to be common in the western Mediterranean basin is instead very rare in Greece and Crete [78–81].

A slightly lower frequency was reported in UK screenings of PD patients of Caucasian ethnicity (2.5% familial and 0.3–1.6% sporadic) [40, 82, 83] and also in populations of Celtic and Baltic origin (Ireland 1.1% of familial PD [42, 84], Norway ~1.5% of familial PD [85], and Sweden 1.4% of sporadic cases [86]). Mutation analyses in more than 300 familial and 1200 sporadic PD in Germany suggested a very low frequency of this mutation (0.8% of familial cases [87, 88] 0.2–0.9% of sporadic) [87–89], as well as in Belgium [90], the Netherlands [91], Denmark [92], and Austria [93].

In Poland, Serbia, Hungary, Czech Republic, and Slovakia, the G2019S appeared to be rare (or found in a single subject) [87, 94–98]. On the contrary, four studies have been performed in Russia, where the mutation accounts for 4–7% of familial and 1% of sporadic cases [99–102]. However, subjects were included from a mixed ethnic background, since at least two PD families and one sporadic case reported their ethnic origin as Ashkenazi Jews [101].

An analogous observation can be done when analyzing patients from the USA, where the frequency of the G2019S in Caucasian PD reaches 2–3.5% in familial and 0.5–1.6% in sporadic cases [46, 49, 103–109]; it seems to be rare among American Indians and Afro-Americans (but the sample size for these two ethnic groups is still insufficient to make firm conclusions) [108, 109], whereas it was reported to be higher when patients of Ashkenazi Jewish ancestry were included [49]. In Canadian PD patients, the G2019S is rare/absent [110, 111].

Four different populations of South America, where the Spanish, Portuguese, and Italian ethnic backgrounds are strong, have been studied for this mutation. In Uruguay [112], Chile [113], and Argentina [114], G2019S accounts for 3.5–5.5% of familial and 2.9–4.2% of sporadic cases. The 5.45% of a PD cohort from Argentina was found to carry the mutation, all of them being of Jewish ancestry. While in Peru, the G2019S appears to be rare [112]. Controversial results came from large screening

in Brazil (from 3 to 6.8% in familial and 0 to 1.7% in sporadic cases), probably due to the high degree of ethnic heterogeneity within the study cohorts [115–117].

G2019S is rare/absent among Chinese patients with familial and sporadic PD [118–121], as well as in Korea [122, 123] and in India [121, 124]. So far, only three patients have been reported with this mutation in Japan (0.7% of sporadic cases) [48, 125].

Finally, the mutation is present in Australia, among PD patients with European ancestry (2–6% of familial, 0.4% of sporadic PD) [126, 127], while it has not been identified in Australian Aboriginal.

Taken together, these data show that a single *LRRK2* mutation represents the most frequent known genetic determinant of PD. The frequency of the G2019S mutation varies widely across populations, indicating that ethnicity is an important factor. For some populations, independent studies on the prevalence of the mutation are already available, and often, the reported results are consistent. These observations imply that most neurologists who treat patients with movement disorders will see patients with *LRRK2*-related PD that may be addressed to genetic testing. This estimation could be even higher if we include the other *LRRK2* definitely pathogenic mutations.

## Origins of the G2019S Mutation

So far three different haplotypes have been identified in patients carrying the G2019S mutation.

### Haplotype 1

The first studies on unrelated carriers of the G2019S of European or Middle Eastern–North African origin revealed that all shared the same haplotype, consistent with a common founder [42, 44, 45, 70, 128, 129].

Subsequently, the same haplotype has been identified among subjects carrying the G2019S mutation from Italy (independent subset) [71], France [47], Germany [87], Russia [99] Sardinia [76, 77], Spain [65], Portugal [61, 70], Brazil [70], Chile [113], Uruguay and Peru [112], and Australia [126].

According to a general rule in population genetics, the geographic center of the origin of a mutation corresponds to the area where that mutation is most frequent [130]. The highest prevalence of the G2019S mutation has been reported in Berbers [52], followed by North African Arabs, Ashkenazi, and Sephardic Jews. The frequency data combined with the identification of a common haplotype among these populations support the hypothesis that the mutation of haplotype I originated in North Africa or in the Middle East and then spread to other countries following the patterns of migration.

Further studies provided important insights on the estimated age of the common founder for the haplotype 1 carriers. Analyzing the haplotypes of European and Ashkenazi Jews [129] and Tunisian G2019S carriers [131], the age estimated of the common ancestor (using the 30-year intergeneration interval) was 2250 (95% CI 1650–3120) and 3120 (95% CI 2340–4620) years ago, respectively. A third study, on Ashkenazi Jews only, estimated a more recent founder approximately 1525–1830 years ago (150–450 A.D.) [132]. This estimation would fit with the absence of the G2019S in Yemenite Jews [51]. The Yemenite Jews evolved completely separate from all of the other Jewish populations. Most of them arrived in Yemen in the early second century A.D. (~160 A.D.). Finally, a multicentric study proposed a consensus of haplotype 1 origin, estimating the founding mutational event in Ashkenazi Jews ancestors in a period ranging from 4500 to 9100 years. In this scenario, being the Ashkenazi Jews history more recent (at most 2000 years old), it is possible that the G2019S have arisen at least 4000 years ago in the Near East and then Ashkenazi ancestors may have kept the mutation through the different diasporas. Thereafter, the mutation may have been reintroduced by gene flow from Ashkenazi Jews to other European and North African populations [133].

### Haplotype 2

A different G2019S haplotype was identified in three families from Western Europe, which appeared to share a more recent founder than haplotype 1. The geographic origin of this haplotype is less certain [129].

### Haplotype 3

The third haplotype has been found in Japanese patients carrying the G2019S mutation [125]. This haplotype differs across the markers closest to the mutation, which would suggest an independent origin of the mutation in Japanese and European populations rather than a single ancient founder. Interestingly, the haplotype 3 has also been observed in a single sporadic Turkish patient [134]. This may be the result of a common ancestry (plausibly explained by the large centuries-long migration of the Turkic people across Central Asia) or coincidental presence of Japanese ancestors.

### Incomplete Penetrance of G2019S

Incomplete penetrance was already suspected for the mutations underlying the PARK8 locus at the time of the linkage studies. Most of the penetrance analyses have been performed on the frequent G2019S mutation.

Analyses performed on Ashkenazi Jews from the USA revealed a lifetime penetrance of 31.8% [45]. A slighter lower penetrance (24–26% at 80 years) was estimated in independent groups of US Ashkenazi Jews [49, 135].

The International *LRRK2* Consortium performed a penetrance study on the largest dataset of G2019S carriers. By analyzing a large sample of PD patients, they calculated a 28% risk of PD at 59 years, 51% at 69 years, and 74% at 79 years for *LRRK2* G2019S carriers without differences in penetrance by sex or ethnic group [136]. Interestingly a penetrance study in Tunisian G2019S PD cases, after stratifying by homozygous ($n = 23$) and heterozygous carriers, reported a penetrance consistently higher in homozygotes in each age group. Considering possible biases in estimating penetrance only from families, this finding, if true, would indicate a gene dosage effect, although the age of onset was not dissimilar between the two groups [46]. However, subsequent studies collecting clinical data of homozygous carriers showed no phenotype differences between heterozygous and homozygous carriers ruling out a gene dosage effect [44, 137, 138].

The reduced penetrance of this frequent mutation is in keeping with the *LRRK2* G2019S being the most important genetic determinant, known so far, of sporadic PD. Penetrance can also be expressed in terms of risk (calculated as odd ratio) to develop the disease. For an Ashkenazi Jew who carries the G2019S, the risk of developing PD increases ~18-fold [45]. By analyzing the G2019S in North Africans, a lifetime odds ratio for developing PD of 48.6 (CI 11.2–211.0) [44] has been calculated.

Nevertheless, additional studies in different populations are warranted before G2019S genetic counseling can be implemented, since the precise estimation of the penetrance in some countries is still controversial.

Dissimilar results across the abovementioned Ashkenazi Jews from the USA and other G2019S carriers might be influenced by different methodological approaches (e.g. including only patients with both parents genotyped, excluding patients with *GBA* mutations, etc.) or by additional genetic or nongenetic factors that can act as modifiers.

The analysis of candidate genes involved in neurodegeneration as potential genetic modifiers of *LRRK2* has been reported. The first to be explored was *PRKN*, since patients who simultaneously harbored *PRKN* mutations and *LRRK2* G2019S have been mentioned in several studies [61, 73, 99, 139–141]. However, the clinical and cosegregation analysis of patients carrying heterozygous *PRKN* mutations and the G2019S revealed that the combination of the two does not influence the symptoms or the age at disease onset [142].

Polymorphic variations in the microtubule-associated protein tau (*MAPT*) have been proposed to be significantly associated with age of disease onset in individuals with *LRRK2* mutations [143]. Moreover, SNCA variants have been found as determinant of age of onset in G2019S carriers [144]. It is a common observation among neurologists of the different penetrance of *LRRK2* mutations in affected families, implying the great importance of genetic modifiers. Further analyses, especially on large samples and families carrying the G2019S, are warranted to identify genetic factors that can act as modifiers of *LRRK2* mutations.

## *The R1441 Mutational Hot Spot*

The *LRRK2* R1441 residue is the second most common spot of pathogenic *LRRK2* mutations, after G2019S. Three non-synonymous substitutions (R1441C, R1441G, and R1441H) and the synonymous R1441R have been reported in several patients.

### R1441C: The Second Most Frequent Pathogenic *LRRK2* Mutation

This mutation (c. 4321C > T) represents the second known most common mutation of the *LRRK2* gene. The R1441C was identified as causative mutation of the PARK8-linked "family D" (Western Nebraska) [4]. Cosegregation was reported also in smaller PD families from Germany [4, 87], Italy [69], Belgium [90], the USA [42, 145], and Iran [59]. The mutation has also been reported in a few other families, but additional affected relatives were not available for cosegregation analysis [62, 69, 90, 146]. The R1441C is also found among sporadic cases and has been reported in patients from Italy [70], Sardinia [77], Russia (Slavic origin) [100], China [147], and Belgium [90]. The variant was absent in large cohorts of ethnically matched controls (>1000 German, 530 Italian, 208 Sardinian, 400 Chinese, 178 Belgian, and 300 American). Interestingly, the R1441C has been found to be more common than G2019S in southern Italy [148].

Haplotype analysis of *LRRK2* R1441C carriers from 20 families of different geographical areas revealed in total four classes of haplotypes. Only for the two major haplotypes, the phase could be established [149]. A first haplotype was identified in the Italian carriers, as well as in German, Spanish, and American patients. A second haplotype was present in the American family D (Western Nebraska) and in Belgian R1441C families. A German and an Irish patient shared a third haplotype for which phase could not be unambiguously determined. Finally, a Chinese proband carried alleles that could not be assigned to any of three previous haplotype classes.

The phenotype associated with this mutation is similar to that of classic PD [149]. The mutation exhibits incomplete penetrance, which could explain its presence in sporadic cases, but calculations performed so far must be interpreted with caution as only a small number of R1441C mutation carriers have been identified until now.

### R1441G: A Founder Pathogenic Mutation in the Basques

The *LRRK2* R1441G (c. 4321C > G) was initially described in patients with autosomal dominant late-onset PD in PARK8-linked families of Basque ethnicity [3]. The Basques are a homogeneous ethnic group who historically were isolated by linguistic and geographical barriers. The first report on the frequency of this mutation in Basque PD (~8% of familial cases) [3] and the absence in other large populations screened (except for a US patient reported to be of Hispanic descent [50]) suggested that this variant was population specific. Further studies investigated the prevalence

of this mutation in Basque. One group detected the R1441G in 16.4% and 4.0% of familial and sporadic Basque PD, respectively [150], while a more recent study reported a prevalence of 46% in familial Basque patients and 2.5% of sporadic cases [66]. It has also been identified at lower frequencies in patients from nearby provinces in Spain who did not report Basque ancestry (6% of non-Basques living in the Basque countries [66], 2.7% in Asturias [151], 0.7% in Catalonia [62], two families from the neighboring region of Navarre, and one from La Rioja [63]), while it is rare in Cantabria [64]. Haplotype analysis on R1441G carriers from Basque and neighborhood regions [63, 150, 152] indicates that this mutation occurred in a single common ancestor, which in one study was estimated to have lived 1350 (95% CI, 1020–1740) years ago [152]. Since the Basque population has a history of emigration to Europe and North, Central, and South Americas, it would not be surprising to find isolated cases in those countries. However, a single case from Uruguay and a family from Japan carrying the R1441G have been reported with a different haplotype than the Basque, suggesting in these cases independent mutational events [112, 153].

### R1441H and R1441R: Uncommon but also Likely Pathogenic

This variant, c.G4322A on *LRRK2* cDNA, occurs immediately adjacent to the two previously reported pathogenic mutations, c.C4321T (R1441C) and c.C4321G (R1441G), resulting in a different substitution of the same amino acid residue (R1441H).

R1441H has been described in a US PD family, but only the proband and an unaffected sibling were available for testing [146]. It was also reported in PD families from Crete [81], Portugal [61], and Taiwan [84], all not large enough to demonstrate definitive cosegregation with the disease.

Haplotype analysis of the abovementioned R1441H carriers showed diversity suggesting a number of independent founders [154]. Subsequently, the R1441H mutation has been identified in two cases from Australia, both of British origin and with a possible common haplotype, although in these cases the phase was not assessed [126]. A further proof in favor of a pathogenic role of this variant came from the identification of R1441H in two slightly larger French families [72].

R1441H was not found in 281 Americans, 300 Cretans, 200 Portugueses, 174 Europeans, and a set of 1000 control samples (600 North Americans, 200 Taiwaneses, 200 Norwegians, 200 Irish, and 200 Spanish). Moreover several studies screened by sequence the *LRRK2* exon 31 in a large sample of healthy controls (>3000 Caucasian [3, 4, 69, 90]) in order to check for the R1441C and R1441G, and none reported mutation in the adjacent nucleotide.

The clinical presentation of affected R1441H carriers appears to be similar to typical Parkinson's disease with an age at onset range of 32–66 years. All display levodopa-responsive parkinsonism; however, the disease in one of the siblings from the Greek R1441H family appeared to transition into a progressive supranuclear palsy-like disorder [81].

To further highlight the nature of codon 1441 as a mutational hot spot, two groups reported a R1441R (c.C4323T) in a sporadic PD patient [101] from Russia

and a PD patient with ascertained LB pathology who additionally developed dementia and dysautonomia (PDD) [155]. As for the R1441H, we can indirectly assume that the variant is rare in the Caucasian population, since sequencing controls for the other mutations at the same codon did not reveal any R1441R carriers. This variant is predicted to lead to a synonymous substitution, which would suggest a nonpathogenic role. Moreover, being the nucleotide change close to the splice site, cDNA analysis from the brain of the PDD patient was performed and did not reveal any aberrations on the *LRRK2* transcript [155]. Taken together these results suggest that R1441R is likely to represent a rare but nonpathogenic polymorphism.

Mutations in *LRRK2* are associated with pleomorphic pathology, although the Lewy bodies (LB)-positive pathology is the most common pattern, particularly for the G2019S mutation [38, 40, 82, 156, 157].

In a large screen of 405 LB-positive brains, eight (~2%) have been found to be carriers of the G2019S mutation, including four with brainstem type, three with transitional type, and one with diffuse LB pathology. In two G2019S-positive brains, Alzheimer-type pathology was also present, and it was of enough severity to make a concomitant pathological diagnosis of Alzheimer's disease [157].

A further study on 80 brains with PD or LB dementia screened for the G2019S mutation, and three were found to be carriers. Typical brainstem-type LB-positive pathology was found in one, while the Lewy body variant of Alzheimer's disease was diagnosed in the second. The third brain showed only cell loss in the substantia nigra and locus coeruleus, but no α-synuclein inclusions were detected. There were only rare tau-positive tangles and occasional plaques. No other ubiquitin-positive inclusions were present either [156].

In family D (Western Nebraska), all R1441C carriers examined showed substantia nigra neuronal loss. Two cases had LB pathology, one brainstem type, and the other one diffuse type. The third case had "nonspecific" substantia nigra degeneration with ubiquitin-positive neuronal inclusions. The final case had PSP-like changes with tau-immunoreactive neuronal and glial lesions [4].

The neuropathological examination of R1441G Basque carriers displayed "nonspecific" nigral degeneration in the substantia nigra without α-synuclein, tau, or ubiquitin inclusions [158].

Japanese cases with the I2020T mutation were found to display hyperphosphorylated tau aggregates [159]. Therefore, despite LBs represent the predominant feature in neuropathological studies, the overall *LRRK2*-associated pathology has revealed great variability, probably recapitulating the heterogeneity of PD itself, which can be a more complex disease than what we thought until now.

## *The Other* LRRK2 *Variants: Which Are Pathogenic?*

Besides the most recurrent G2019S and R1441C/R1441G/R1441H, more than 50 different *LRRK2* sequence variants have been reported in familial and sporadic PD cases so far; moreover, few novel *LRRK2* substitutions have been found in healthy control subjects only (Fig. 1.2).

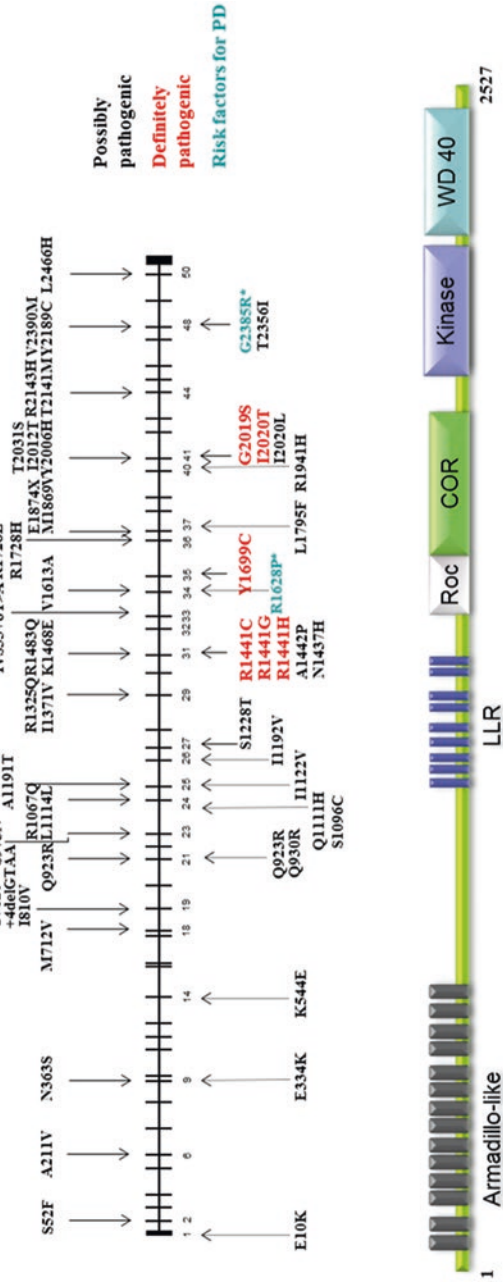


**Fig. 1.2** Schematic representation of the *LRRK2* gene, the dardarin protein, and its known functional domains. *LRRK2* 83 coding variants and three putative splice variants are grouped according to evidence of pathogenicity (see main text)

The Y1699C and I2020T mutations are considered as definitely pathogenic. The Y1669C was identified in two independent large families, the Lincolnshire kindred [3, 82] (family PL) of European ancestry, and "family A" (German–Canadian) [4, 38]. The I2020T was identified in "family 32" [4] and "T10738" [89], both of German ancestry. Additionally the same mutation was identified segregating in the large PARK8-linked Sagamihara kindred [43] and in two smaller Japanese families coming from the neighborhood of the Sagamihara region [48].

The role of several other variants remains unclear, since often no family members were available to assess cosegregation and a limited number of ethnically matched controls were screened. Overall, the criteria that may be applied to consider the pathogenicity of the *LRRK2* variants should consider several standpoints: frequency in healthy subjects, cosegregation in families, confirmation in independent studies, and pathogenic consequences on cellular and animal models.

## Association Studies on *LRRK2*

In the past few years, many groups put special effort in search of common risk factors for complex diseases. Among these, PD and other neurodegenerative disorders have been extensively studied. However, even using high-throughput techniques allowing to genotype hundreds of thousands of SNPs and covering the whole genome in cases and controls (genome-wide association studies, GWA), no reproducible risk loci have been reported so far.

One caveat is that the GWA approach can be problematic because the massive number of statistical tests performed presents an unprecedented potential for false-positive results.

After the discovering of mutations in the *LRRK2* gene, several studies aimed to explore whether common variant of this gene could represent a risk factor for PD.

Two association studies on *LRRK2* have been performed in Caucasians. The first enrolled 340 PD patients and 608 controls from Germany. 121 SNPs (81 tagging SNPs) were genotyped attempting to represent the complete DNA variation of the *LRRK2* gene [160]. The second study analyzed four common coding SNPs (L953L, R1398H, G1624G, and T2397M) in 250 controls and 121 unrelated PD, mostly with early-onset and positive family history [141]. Neither of these studies revealed any evidences of association between PD and the *LRRK2* SNPs at both allelic and genotypic levels.

In 2005, one study performed in Singapore yielded a significant association. A set of 21 tagging SNPs covering the *LRRK2* gene were genotyped in 466 sporadic PD and 374 control individuals all of Chinese ancestry. The authors identified a common haplotype that was highly overrepresented within cases ($p = 0.005$) and, when present in two copies, significantly increased the risk of PD (OR = 5.5, 95% C.I. = 2.1–14.0, $P = 0.0001$) [161]. However, no *LRRK2* variants within the risk haplotype were reported as the biologically relevant factors.

## *The G2385R Variant*

The *LRRK2* G2385R represents the first common genetic risk factor for PD in the Asian population. This variant was first reported in a small PD family from Taiwan [84]. Evidence for cosegregation with PD in that family was limited due to the small pedigree size; however, the mutation was reported to be absent in 200 ethnically matched controls and, therefore, interpreted as putatively pathogenic. At that time very limited data were available on the nature and frequency of *LRRK2* mutations and on the polymorphism content of the gene in patients from Asia.

Several groups conducted a mutational screening of three known PD-causing mutations (I2012T, G2019S, and I2020T) which appeared to be very rare or absent in Asian PD patients [43, 118, 120, 121]. A sequence of the whole *LRRK2* in Chinese Han patients revealed four coding variants (A419V, P755L, M1869V which were novel substitutions, and the G2385R) that were tested for association with PD in 608 Chinese Han cases and 373 ethnically matched controls.

The heterozygosity for the G2385R variant was significantly higher among PD cases than controls (10% vs 4% $p$ 0012). This suggested that the G2385R variant, or another variant in linkage disequilibrium, is associated with PD in the Taiwanese population.

Since then, several association studies on Asian populations from Taiwan, Singapore, Mainland China, Korea, and Malaysia replicated this finding with a similar size effect. Interestingly the association was also reported in Japanese PD patients and controls, giving a risk of developing PD increased of ~twofold [125, 166] (Table 1.2).

Two groups performed a haplotype analysis of G2385R carriers in a cohort of Chinese Han from Taiwan [165, 168]. A single common haplotype shared by carriers has been identified, likely originated from a single ancestor who lived approximately 4800 years ago. Also all Japanese G2385R carriers shared the same haplotype, with a set of markers (D12S2516, D12S2519, and D12S2521) which overlapped with the Chinese haplotype. This might suggest that the G2385R of Chinese Han and Japanese ancestry has arisen from a common ancestor [125].

## *The R1628P Variant*

The *LRRK2* R1628P has been identified in a multicentric study which combined 1986 Chinese individuals from three independent centers in Taiwan and Singapore and so far represents the second most frequent genetic risk factor for PD in Asia [184]. This variant was approximately twice as frequent in affected individuals as control subjects (~6% of PD and ~3.5% of controls, odds ratio 1.84, 95% C.I.: 1.20–2.83, nominal $p$ value = 0.006) [184].

**Table 1.2** Association studies on Asian populations (from Taiwan, Singapore, China, Korea, Japan, and Malaysia) showing the G2385R variant as significantly associated with Parkinson's disease

| Geographical location | Ethnicity | PD | Controls | OR (95% CI) | References |
|---|---|---|---|---|---|
| Taiwan | Chinese Han | 61/608 (10%) | 18/373 (4.8%) | 2.20 (1.28–3.78) | [162] |
| Singapore | Chinese | 37/495 (7.5%) | 18/494 (3.6%) | 2.14 (1.20–3.81) | [163] |
| Taiwan | Chinese Han | 27/305 (9%) | 1/176 (0.5%) | 17.00 (2.29–126.20) | [164] |
| Taiwan | Chinese | 34/410 (9.3%) | 13/335 (3.9%) | 2.24 (1.16–4.32) | [165] |
| Japan | Japanese | 52/448 (11.6%) | 22/457 (4.8%) | 2.60 (1.55–4.35) | [166] |
| Singapore | Malay | 2/98 (2%) | 2/173 (1.2%) | 1.75 (0.25–12.85) | [167] |
| | Indian | 0/66 (0%) | 0/133 (0%) | | |
| Shanghai | Chinese Han | 14/235 (6%) | 0/214 (0%) | 28.08 (1.66–473.72) | [168] |
| Mainland of China | Chinese Han | 71/600 (11.8%) | 11/334 (3.3%) | 3.94 (2.06–7.55) | [169] |
| Japan and USA | Japanese | 69/601 (11.5%) | 101/1628 (6.2%) | 1.96 (1.42–2.70) | [170] |
| Japan | Japanese | 30/229 (13.1%) | 23/358 (6.4%) | 2.06 | [171] |
| Korea | Koreans | 82/923 (8.9%) | 21/422 (5%) | 1.83 | [172] |
| Asia | Taiwanese | 369 (NA) | 300 (NA) | 1.62 | [173] |
| | Korean | 844 (NA) | 587 (NA) | 1.87 | |
| | Japanese | 173 (NA) | 95 (NA) | 1.44 | |
| Malaysia | Malaysian | 695 (NA) | 507 (NA) | 2.22 | [174] |
| Total | | 479/5018 (9.6%) | 230/5097 (4.5%) | 2.23 (1.89–2.62) $p$ value < 0.0001 | |

This finding was replicated in two independent Chinese Han cohorts from Singapore [185] and Taiwan [186]. On the contrary, the R1628P is rare in Japan and in non-Chinese Asians [170, 184, 187].

Haplotype analysis strongly indicates that carriers of the R1628P variant share an extended haplotype, indicative of a founder effect [184]. The mutation has been estimated to arise ~2500 years ago and, in contrast to the older G2385R, has remained confined to subjects of Chinese Han ethnicity.

Like for the G2385R, the clinical phenotype of the affected R1628P carriers is that of typical late-onset L-dopa-responsive PD [184, 186, 187].

Taken together, these studies indicate for the first time that common population specific genetic risk factors for PD exist. The association of both *LRRK2* variants with PD in Asia has been extensively confirmed in independent dataset of patients. These findings open several opportunities of studies for researchers and clinicians. Discovering how those variants can increase the risk of death of dopaminergic neurons might provide important insight into the pathogenesis of the disease. Other interesting prospects can be provided in clinical practice, for example, studying the effect of neuroprotective drugs in large cohorts of asymptomatic carriers of these two *LRRK2* variants, in order to explore whether the risk of developing PD would decrease in the treated subjects.

In conclusion, the *LRRK2* gene displays a high polymorphic content in terms of single nucleotide substitutions. No deletions or duplications have been identified until now. Variants identified in patients are located in almost all exons. However, most of them still lack a definite proof of pathogenicity (Tables 1.3). This has direct

**Table 1.3** *LRRK2* genetic variants associated with Parkinson's disease that are possibly pathogenic, but need more evidence to be definitely associated with the disease

| Possibly pathogenic *LRRK2* variants | | | |
|---|---|---|---|
| cDNA change | Protein change | Protein domain | References |
| 28G > A | E10K | LRRK2 repeats | [175] |
| 155C > T | S52F | LRRK2 repeats | [72] |
| 632C > T | A211V | LRRK2 repeats | [176] |
| 1000G > A | E334K | LRRK2 repeats | [175] |
| 1088A > G | N363S | LRRK2 repeats | [72] |
| 1630A > G | K544E | LRRK2 repeats | [176] |
| 2134A > G | M712V | LRRK2 repeats | [106] |
| 2242119_2242122delGTAA | – | LRRK2 repeats | [104] |
| 2769G > C | Q923R | LRRK2 repeats | [115] |
| 2789A > G | Q930R | LRRK2 repeats | [89] |
| 2918G > A | S973N | LRRK2 repeats | [93] |
| 3200G > A | R1067Q | LRRK2 repeats | [177] |
| 3287C > G | S1096C | LRRK2 repeats | [89] |
| 3333G > T | Q1111H | LRRK2 repeats | [175] |
| 3364A > G | I1122V | LRRK2 repeats | [4] |
| 3574A > G | I1192V | LRRK2 repeats | [175] |
| 3451G > A | A1191T | LRRK2 repeats | [178] |
| 3494 T > C | L1165P | LRRK2 repeats | [179] |
| 3287G > C | S1228T | LRRK2 repeats | [89] |
| 3974G > A | R1325Q | | [90] |
| 4111A > G | I1371V | | [69] |
| 4309A > C | N1437H | Roc domain | [180] |
| 4324G > C | A1442P | Roc domain | [126] |
| 4402A > G | K1468E | Roc domain | [90] |
| 4448G > A | R1483Q | Roc domain | [90] |
| 45,361 + 3A > G | – | | [146] |

(continued)

**Table 1.3** (continued)

| Possibly pathogenic *LRRK2* variants | | | |
|---|---|---|---|
| cDNA change | Protein change | Protein domain | References |
| 48,271 + 6 T > A | – | | [177] |
| 4838 T > C | V1613A | COR | [100] |
| 5183G > T | R1728L | COR | [106] |
| 5183G > A | R1728H | COR | [106] |
| 5281A > C | S1761R | COR | [181] |
| 5385G > T | L1795F | COR | [175] |
| 5605A > G | M1869V | | [69] |
| 5620G > T | E1874X | | [69] |
| 5822G > A | R1941H | Kinase | [82] |
| 6016 T > C | Y2006H | Kinase | [73] |
| 6035 T > C | I2012T | Kinase | [90] |
| Unknown | I2020L | Kinase | [182] |
| 6091A > T | T2031S | Kinase | [73] |
| 6422C > T | T2141M | | [106] |
| 6428G > A | R2143H | | [106] |
| 6566A > G | Y2189C | WD40 | [90] |
| 7168G > A | V2390M | WD40 | [183] |
| 7397 T > A | L2466H | WD40 | [106] |
| 7067C > T | T2356I | WD40 | [82] |

**Table 1.4** *LRRK2* variants that are definitely associated with Parkinson's disease (upper panel: causative mutations, lower panel: risk variants)

| dbSNP rs # | cDNA change | Protein change | Protein domain | References |
|---|---|---|---|---|
| *Definitely pathogenic LRRK2 mutations* | | | | |
| | 4321C > G | R1441G | Roc domain | [3] |
| rs33939927 | 4321C > T | R1441C | Roc domain | [4] |
| rs34995376 | 4322G > A | R1441H | Roc domain | [146] |
| rs35801418 | 5096A > G | Y1699C | COR domain | [3, 4] |
| rs34637584 | 6055G > A | G2019S | Kinase domain | [39–41] |
| rs35870237 | 6059 T > C | I2020T | Kinase domain | [4] |
| *LRRK2 variants associated with increased risk* | | | | |
| rs33949390 | 4883G > C | R1628P | COR domain | [184] |
| rs34778348 | 7153G > A | G2385R | | [162] |

practical consequences for the genetic studies. *LRRK2* is a large gene containing 51 exons. A time-/cost-saving strategy to perform the mutational analysis could be to first screen for the frequent G2019S mutation. If negative, other validated mutations (R1441G/R1441C/R1441H, I2020T, and Y1699C) can be tested next (Tables 1.4). Where a considerable number of affected family members are available for testing, an option is to screen the entire *LRRK2* gene, which raises the possibility of discovering one of the above-reported doubtful variants, or even a novel mutation that

could be tested for cosegregation in order to verify its pathogenic role. Concerning the significance of these data for the genetic counseling, it is worth to consider that screening the whole coding region or single variants of uncertain role in unselected cases is still a matter of debate, since the identification of any variant would result in more questions than answers for both clinicians and patients. *LRRK2* mutations penetrance is a key piece of information for a proper genetic counseling. Only a minority of *LRRK2* mutation carriers will develop the disease, making the predictive genetic testing more similar to *BRCA* test for breast cancer than to presymptomatic test in Huntington's disease. Dominant transmission involves more subjects and generations inside the family. The involvement of the offspring and the absence of neuroprotective therapy make the offer of predictive/presymptomatic genetic tests in neurodegenerative disease controversial. However, whenever presymptomatic testing is offered, detailed information and counseling at a center with expertise in this area are required [188, 189].

**Conflict of Interest** The author declares no conflicts of interest.

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