

The dardarin G2019S mutation is a common cause of Parkinson's disease but not other neurodegenerative diseases

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Abstract

Mutations in the leucine-rich kinase 2 gene (*LRRK2*) encoding dardarin, on chromosome 12, are a common cause of familial and sporadic Parkinson's disease. The most common mutation, a heterozygous 6055G>A transition (G2019S) accounts for approximately 3–10% of familial Parkinson's disease and 1–8% sporadic Parkinson's disease in several European-derived populations. Some families with disease caused by *LRRK2* mutations have been reported to include patients with highly variable clinical and pathological features. We screened for the most common *LRRK2* mutation in a series of patients with Parkinson's Disease, Alzheimer's disease, Progressive Supranuclear Palsy, Multiple System Atrophy and frontotemporal dementia, as well as in neurologically normal controls. The mutation was found only in Parkinson's disease patients or their relatives and not in those with other neurodegenerative disease.

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Parkinson's disease is a common neurodegenerative disorder, affecting 3% of those >75 years of age [3]. It is associated with resting tremor, postural rigidity and bradykinesia. The neuropathologic hallmarks of Parkinson's disease are loss of dopaminergic neurons and deposition of cytoplasmic aggregates termed Lewy bodies, which contain α -synuclein and ubiquitin, especially in the substantia nigra.

Genetic analysis has implicated several genes in parkinsonian syndromes [7]. Most recently, mutations in the *LRRK2* gene were reported [15]. These mutations occurred in several families whose clinical features were usually of Parkinson's disease [8,16,17,19]. However, some families show neuropathological heterogeneity with some affected individuals exhibiting Lewy bodies, in association with neuronal loss and gliosis in the substantia nigra [6] and others having either tau pathology and resembling progressive supranuclear palsy and

Table 1

Number of cases screened for the G2019S dardarin mutation

Diagnosis	G2019S screened
Parkinson's disease	719
Late onset Alzheimer's disease	1444
Progressive Supranuclear Palsy	186
Essential tremor	18
Restless leg syndrome	94
Frontal temporal dementia and CBGD/tauopathy	40
Dystonia	17
Controls	2680

CBGD: cortical-basal ganglionic degeneration.

still others lacking distinctive histopathology; these pathologies occurred in the context of variable clinical phenotypes [5,19]. This variety of clinical and pathological features associated with patients possessing *LRRK2* mutations suggests that they can lead to the central pathogenic event of nigral degeneration, and produce parkinsonian phenotypes, along with variable pathological features [19]. Furthermore, the

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Table 2
Characteristics of cases with mutations

Diagnosis	Age	Age at onset	Gender	Family history	Ancestry
PD	72	58	M	None	Northern European
Dystonia	60	57	M	Positive for PD	Eastern European
PD	Not known	Not known	M	Positive	Northern European
PD	75	70	F	None	Northern European
PD	60	58	F	None	Northern European
Blood relative of PD case	50	Currently well	F	Positive	Eastern European
Blood relative of PD case	53	Currently well	F	Positive	Eastern European
PD	63	62	M	None	South American
PD	43	Not known	M	None	Eastern European

M: male; F: female; PD: Parkinson's disease.

location of the *LRRK2* gene on chromosome 12 close to a linkage peak for late onset Alzheimer's disease has led to the suggestion that variability at *LRRK2* may predispose to Alzheimer's disease [13,19].

The predicted product of the *LRRK2* gene is the large protein, dardarin, which is expected to have 2527 amino acids encoded by 51 exons [19]. One mutation, c.6055G>A in exon 41 of *LRRK2*, encodes a G2109S change in the predicted kinase site of dardarin [8]. This mutation is extremely common in populations of European origin and accounts for between 1 and 10% of Parkinson's disease depending on the geographic location. With this background, we determined to assess whether this mutation occurred in other neurodegenerative diseases. We, therefore, screened a large number of Caucasian Parkinson's disease cases, Alzheimer's disease cases and Progressive Supranuclear Palsy cases for this mutation (Table 1).

DNA was extracted using standard methodologies. Most genotyping was performed using TaqMan single-nucleotide-polymorphism assay (Assays-by-Design Service, Applied Biosystems, Foster City, CA, USA) and an ABI 7900, although some cases were screened directly by sequencing. All variants identified by TaqMan assay were confirmed by direct sequencing. Most of the samples we used are parts of series we have published previously [10,13,18].

The dardarin mutation G2019S was identified primarily in Parkinson's disease cases (7 out of 719; 1% of PD cases tested; this does not include other families we have recently reported; refs. [2,8,10,14–17]) but additionally in a single case presenting with dystonia who had a family history of Parkinson's disease. While our samples series are not population based, these figures are completely concordant with our and others' work detailing the prevalence of the mutation in Parkinson's disease [1,2,4,6,11,12,14]. The mean age at onset noted in the patients studied here is 61 ± 5.4 S.D. years, comparable with the mean age at onset previously reported for G2019S carriers of 57.8 ± 6.7 [1,2,4,6,8,14,16]. In this series, none of the cases had neuropathological confirmation, so we cannot be sure that individuals had Lewy bodies, although statistically, one would assume that the majority would have this pathology [9]. The mutation did not occur in large numbers of cases of late onset Alzheimer's disease, progressive supranuclear palsy or frontal dementia. While we

cannot exclude that other, rare mutations occur in these other conditions, such a finding would suggest that the mutations would have to have subtly different pathogenic mechanisms; however, in our more limited full-gene sequencing efforts (unpublished), we have similarly not found mutations in any circumstance other than Parkinson's disease. Pleomorphic pathology and unusual clinical presentations clearly do occur in cases with dardarin mutations [19]; however, these results suggest that these are the exception not the rule and that most cases with dardarin mutations will develop typical Parkinson's disease (Table 2).

Finally, our continued failure to find this mutation in controls is notable; we have now failed to find the variant in >5000 normal chromosomes mostly from elderly individuals, assuming that a frequency of 1% (1/200 chromosomes) in Parkinson's disease cases suggests that having the mutation increases the risk of developing Parkinson's disease by >25-fold. Given this, the utility of following mutation carriers to determine early symptoms of the disease is clear.

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