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Corticobasal syndrome and primary progressive aphasia as manifestations of *LRRK2* gene mutations

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Abstract

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Background—Mutations in the *LRRK2* gene are an important cause of familial and nonfamilia parkinsonism. Despite pleomorphic pathology, *LRRK2* mutations are believed to manifest clinically as typical Parkinson disease (PD). However, most genetic screens have been limited to PD clinic populations.

Objective—To clinically characterize *LRRK2* mutations in cases recruited from a spectrum of neurodegenerative diseases.

Methods—We screened for the common G2019S mutation and several additional previously reported *LRRK2* mutations in 434 individuals. A total of 254 patients recruited from neurodegenerative disease clinics and 180 neurodegenerative disease autopsy cases from the University of Pennsylvania brain bank were evaluated.

Results—Eight cases were found to harbor a *LRRK2* mutation. Among patients with a mutation, two presented with cognitive deficits leading to clinical diagnoses of corticobasal syndrome and primary progressive aphasia.

Conclusion—The clinical presentation of *LRRK2*-associated neurodegenerative disease may be more heterogeneous than previously assumed.

In the last 10 years, multiple genetic loci have been linked to parkinsonism, and mutations in five genes have been shown to be associated with Mendelian inheritance of disease. Of these, mutations in leucine-rich repeat kinase 2 (*LRRK2*) are the most common, with the frequency of a single mutation (G2019S) ranging from 1.6% to >10% in Parkinson disease (PD) clinic-based populations.[1-3] The importance of *LRRK2* is further underscored by the fact that mutations are found in many apparently sporadic cases of PD, blurring the lines between genetic and sporadic causes of disease.

LRRK2 mutations have been associated histopathologically with Lewy body disease, neurofibrillary tangles, and nonspecific neuronal loss.[4] Despite the pleomorphic pathology, *LRRK2* mutations are believed to manifest clinically in a manner that is indistinguishable from idiopathic PD.[5-9] However, to date, most genetic screens have been limited to PD clinic populations, with only a few studies examining the frequency of *LRRK2* mutations in other neurodegenerative diseases.[10-14] We therefore evaluated patients recruited from multiple neurodegenerative disease clinics including those not specializing in PD (254 patients), and cases from the brain bank at the Center for Neurodegenerative Disease Research (CNDR) at the University of Pennsylvania (UPenn) with a variety of pathologically proven neurodegenerative diseases (180 cases) for nine previously reported *LRRK2* mutations, including the common G2019S mutation.

Methods

Subjects

A total of 254 patients were recruited from neurodegenerative disease clinics at UPenn and the University of California San Francisco (UCSF). These patients carried diagnoses of frontotemporal dementia (FTD, n = 114), corticobasal syndrome (CBS, n = 31), Alzheimer disease (AD, n = *56),* PD or dementia with Lewy-bodies (PD/DLB, n = 20), amyotrophic lateral sclerosis (ALS, n = 13), progressive supranuclear palsy (PSP, n = 1), or dementia not otherwise specified (n = 19). A total of 180 autopsy cases from the UPenn CNDR brain bank were also genetically evaluated. These autopsy cases had the following neuropathologic diagnoses: Lewy body disease (PD or DLB, n = 78), AD with some Lewy bodies (n = 40), Lewy body variant of AD (LBVAD, n = 5), argyrophilic grain disease (n = 3), multiple system atrophy (n = 10), ALS (n = 2), corticobasal degeneration (CBD, n = 4), FTD (n = 13), and frontotemporal lobar degeneration with motor neuron disease (n = 25). In the

autopsy cases, the average age at death was 73 years (range 43 to 99 years). In addition to the disease cases, 35 controls were tested.

Molecular genetic analysis

DNA was extracted from blood (patients) or brain tissue (autopsy cases) using standard methods (Qiagen Inc., Valencia, CA). All cases were genotyped for the following *LRRK2* mutations (notation based on AY792511) with corresponding predicted protein variants: c.6055>A (exon [Ex] 41, p.G2019S), c.6059T>C (Ex41, p.I2020T), c.5606T>C (Ex38, p.M1869T), c.2378G>T (Ex19, p.R793M), c.5096A>G (Ex35, p.Y1699C). Genotyping was performed using a TaqMan chemistry-based allelic discrimination assay with "Assay by Design" (Applied Biosystems, Foster City, CA) probes on an Applied Biosystems 7900 followed by analysis with Sequence Detection System 2.2.1 software (Applied Biosystems) as described.[15] PCR amplification and genotyping were performed according to the manufacturer's protocol (Applied Biosystems) with appropriate positive and negative controls. A subset (n = 114) of the autopsy cases which included all of the Lewy body disease cases were additionally evaluated for substitutions at codon R1441 in Ex 31 of *LRRK2* (c.4322G>A [p.R1441H], c.4321C>G [p.R1441G], and c.4321C>T [p.R1441C]) using restriction fragment length polymorphism analysis with *Bst*UI (60 °C, New England Biolabs) as described.[16] Finally, in the Lewy body disease autopsy cases, bi-directional DNA sequencing of a 251 bp product containing exon 25 (primers E25F: GACTA-GAAATAAAATATCAGGGGA and E25R: TGC-CACTTTTAAATCCACAAC) was used to evaluate for the presence of the c.3364A>G (p.I1122V) mutation. This also allowed for the identification of novel variants within the exon 25 region. All cases with *LRRK2* mutations found by screening were subsequently confirmed by bidirectional DNA sequencing using standard methods on a CEQ8000 (Beckman Coulter).

Patients 1 and 2, who presented with dementia, were additionally screened for progranulin (*GRN*) and tau (*MAPT*) mutations as previously described.[17,18]

Imaging analysis

Volumetric MRI analysis was performed using a previously described voxel-based morphometry (VBM) method.[19] In brief, volumes of an image acquired on a 1.5 T MRI scanner and another acquired on a 3 T MRI scanner were normalized by registration to the T1 template[20] of 305 averaged brain volumes in SPM2 (www.fil.ion.ucl.ac.uk/spm/). VBM was performed by first segmenting brain volumes into four tissue types (gray matter, white matter, CSF, and other). Then gray matter volumes were smoothed with a 12 mm full width at half maximum (FWHM) Gaussian filter to minimize individual gyral variations. The gray matter volume of the image acquired on the 1.5 T scanner was compared against a control group of 12 healthy seniors, and the gray matter image acquired from the 3 T scanner was compared with 19 healthy seniors. Z-scores were calculated to determine areas of significant relative atrophy ($z > 3.09$, $p < 0.001$). Coordinates were converted to Talairach space using SPM2′s Talairach conversion utility.[21]

Results

In the 180 autopsy cases, five cases with mutations were identified (table 1). All five were found in cases of neuropathologically confirmed Lewy body disease (5/78, 6.4%), with no mutations identified in autopsy cases with neurodegenerative diseases other than Lewy body disease. In the 254 clinical patient cases, three were found to have mutations (table 1). Thus, eight total cases with *LRRK2* mutations were identified.

Of the eight cases, the common G2019S mutation was found in five. Four of the G2019S mutation cases were heterozygotes, but one patient with early onset PD with a strong family history was homozygous for the G2019S mutation. We found the R793M mutation[23] in two cases and additionally identified one novel missense variant in exon 25 (c.3494T>C, p.L1165P) which is currently being studied further. The G2019S mutation was also found in one of 35 controls (2.8%, age 74), consistent with the incomplete penetrance reported for this mutation.

Of the three clinical patient cases, only one manifested with parkinsonism. In the remaining two cases, the clinical presentation was dominated by cognitive deficits. One G2019S mutation heterozygote (Patient 1) carries a clinical diagnosis of corticobasal syndrome (CBS), with some extrapyramidal symptoms (EPS) and no response to carbidopa/levodopa. One R793M mutation heterozygote (Patient 2) carries a clinical diagnosis of primary progressive aphasia (PPA), with minimal EPS, and has never had a trial of carbidopa/levodopa.

Patient 1

This right-handed woman with a family history of dementia in her mother and paternal grandmother presented with difficulties in planning, organization, and memory at age 52. She did not have visual hallucinations, and her social behavior was appropriate. When she was seen by a behavioral neurologist for the first time at age 57, 5 years into her illness, she was noted to have prominent deficits in attention, memory, praxis, and language. She also exhibited extrapyramidal features of increased tone, worse on the right, and a shuffling gait. Her neurologic examination was otherwise unremarkable (table 2). On the basis of the asymmetric EPS, cognitive deficits, and apraxia, she was given a clinical diagnosis of corticobasal syndrome (CBS) likely representing corticobasal degeneration (CBD). She had no response to a trial of carbidopa/levodopa 25/100 TID. Serum testing and CSF analysis were unremarkable, as was genetic screening for mutations in *MAPT* or *GRN* (table 2). Volumetric brain MRI showed asymmetric cortical atrophy affecting the parietal, frontal, and temporal regions of the left hemisphere more than the right hemisphere (table 3, figure).

Over the next 2 years, her symptoms worsened. Her right upper extremity apraxia became severe to the point of her having a useless “alien hand.” She developed cortical sensory loss, especially in the right hand. Her language impairment became severe, with word-finding difficulty, poor naming, and inability to comprehend more than single words. She has never had a tremor. Ten years into her illness, she continues to carry a clinical diagnosis of CBS. On genetic testing, she is a *LRRK2* G2019S heterozygote.

Patient 2

This right-handed woman with a family history of PD in her father presented with speech difficulties at age 66. Because of a pre-existing seizure disorder (generalized myoclonic seizures since childhood), she initially underwent evaluation for possible seizures manifesting as speech arrest. However, on continuous EEG monitoring, during which she had frequent difficulty speaking, she had no epileptiform activity. Besides her seizure disorder, which was well-controlled on levetiracetam, her past neurologic history was also notable for an intention tremor, present since her 40s, which was responsive to propranolol. She did not have visual hallucinations, and her social behavior was appropriate.

On neurologic examination 3 years into her illness, she showed moderate expressive aphasia and mild deficits in visual executive function. She had normal tone. An intention but no rest tremor was apparent. She had mild flattening of her right nasolabial fold. Otherwise, her examination was unremarkable (table 2). Two independent neurologists diagnosed her with

PPA (non-fluent type), a form of FTD. Detailed neuropsychological testing revealed moderate expressive language deficit characterized by dysfluency, anomia, inefficient word retrieval, and halting output. Serum testing and CSF analysis were unremarkable, as was testing for mutations in the *MAPT* or *GRN* gene (table 2). Volumetric brain MRI showed cortical atrophy, initially worse on the left side, especially affecting the temporal lobe. EEG was non-specifically abnormal bilaterally.

Over the next 20 months, her mental status continued to decline. She ceased speaking spontaneously and responded to direct questions with single words only. On a neurologic examination 3 and a half years into her illness, a rest tremor was noted. Her tone remained normal. Her gait remained normal until 5 years into her illness, when it became slightly slowed. Repeat volumetric brain imaging showed marked frontal and temporal cortical atrophy, worse on the right side (table 3, figure). Six years into her illness, she continues to carry a clinical diagnosis of PPA/FTD. On genetic testing, she is heterozygous for *LRRK2* R793M.

Discussion

LRRK2 mutations are believed to cause a form of neurodegenerative disease that is indistinguishable clinically[5-9] and radiographically[25,26] from idiopathic PD. Only a few exceptions exist in the literature. First, the large German-Canadian family later associated with a *LRRK2* Y1699C mutation[4,27] had two members who manifested primarily with dementia. Unfortunately, very little clinical information is available for these individuals. Second, a *LRRK2* intronic variant of uncertain significance from a Chinese population (IVS33 + 6 T>A) was found in one patient who developed typical parkinsonian signs after an 8-year course of isolated essential tremor.[28] More recently, a *LRRK2* G2019S mutation case has been reported with pathologic findings consistent with frontotemporal dementia with ubiquitin-immunoreactive inclusions.[29] Clinical information is scant, but the patient had advanced dementia at the time of death.

We report here the detailed clinical findings of two *LRRK2* mutation carriers who presented with cognitive difficulties, leading to clinical diagnoses of CBS and PPA, a subtype of FTD. Neither patient had PD clinically. *LRRK2* mutations have not been clinically linked to either of these disorders, nor to other types of FTD. Of note, mutations in *GRN* or *MAPT,* which are associated with familial FTD, were excluded in both of these patients by DNA sequencing of the coding regions of these genes.

What might account for the relatively large proportion (2/8 or 25%) of our *LRRK2* mutation patients manifesting as a non-parkinsonian clinical phenotype? Close scrutiny reveals that most of the >25 reported genetic screens have focused on patients from PD or movement disorders clinics or on kindreds with familial PD. Indeed, only a handful of studies have included other neurodegenerative diseases at all,[11-14] with no *LRRK2* mutations found in cohorts of patients with AD or ALS. Only one study has examined multiple neurodegenerative diseases.[10] This study included 40 patients with CBD/FTD but focused exclusively on the G2019S mutation, which was not found in any of these patients. In contrast, our *LRRK2* mutation screen was comprehensive both in terms of mutations screened and populations tested, which might account for the higher yield of atypical *LRRK2* phenotypes.

Our patients with CBS harbored the *LRRK2* G2019S mutation, the most common *LRRK2* mutation, reported to be pathogenic, with incomplete penetrance. This mutation has been previously linked to some cases of tau-predominant pathology,[30] and CBD, the usual

neuropathologic correlate of clinical CBS, is characterized by tau-immunoreactive inclusion bodies in gray and white matter.[31]

Our patient with PPA harbored the R793M mutation, a change of putative pathogenicity reported previously in two familial PD cases, one sporadic PD case, and one 40-year-old asymptomatic individual.[23] This mutation occurs within the ankyrin domain of *LRRK2,* which possesses no other pathogenic or putative pathogenic mutations. In keeping with the likely multifunctional nature of *LRRK2,* mutations in different functional domains could manifest heterogeneously.

The diagnoses of CBS and PPA made here are clinical, with as yet no pathologic confirmation. The diagnosis of CBS as a manifestation of underlying neuropathologic CBD is further complicated by the lack of clinical consensus criteria. However, our CBS patient's combination of levodopa-resistant asymmetric akinetic-rigidity, “alien hand” phenomenon, cortical sensory loss, and cognitive decline are consistent with both classic[32] and more recent[31,33] clinical-pathologic studies of CBD. The radiographic pattern of atrophy, especially affecting Brodmann areas 6 and 7, is also consistent with patterns of atrophy in CBS/CBD reported by us and others.[19,34] Finally, the CSF findings of normal to low tau and normal Aβ42 corroborate the diagnosis of a non-AD dementia. As we have previously shown, in CBD and in PPA, CSF tau levels are normal to low in comparison to controls and CSF Aβ42 levels slightly less than in controls, while in AD, tau levels tend to be increased and Aβ42 levels decreased relative to controls.[24]

In the case of our patient with PPA, the clinical presentation meets several sets of consensus clinical criteria for the overlapping diagnoses of PPA, FTD, and frontotemporal lobar degeneration (FTLD) of the progressive nonfluent aphasia sub-type. These include the McKhann criteria for FTD of the language deficit variety,[35] the Neary criteria for progressive nonfluent aphasia as a subtype of FTLD,[36] and the Mesulam criteria for PPA.[37] In addition, the striking frontal and temporal atrophy seen on MRI strongly suggests a diagnosis of FTD or FTLD. Finally, as for our patient with CBS, CSF findings of low tau and normal Aβ42 corroborate a diagnosis of non-AD dementia.

LRRK2 mutations have been associated with pleomorphic pathology, leading some to speculate on an “upstream” role for *LRRK2* in the cascade of events leading to disease. In this article, we provide a potential clinical accompaniment to this heterogeneous pathology and extend the clinical spectrum of *LRRK2*-associated disease.

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Glossary

AD	Alzheimer disease
ALS	amyotrophic lateral sclerosis
CBD	corticobasal degeneration
CBS	corticobasal syndrome
CDNR	Center for Neurodegenerative Disease Research
DLB	dementia with Lewy-bodies
EPS	extrapyramida symptoms
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FWHM	full width at half maximum
LBVAD	Lewy body variant of AD
PD	Parkinson disease
PPA	primary progressive aphasia
PSP	rogressive supranuclear palsy
UPenn	University of Pennsylvania
UCSF	University of California San Francisco

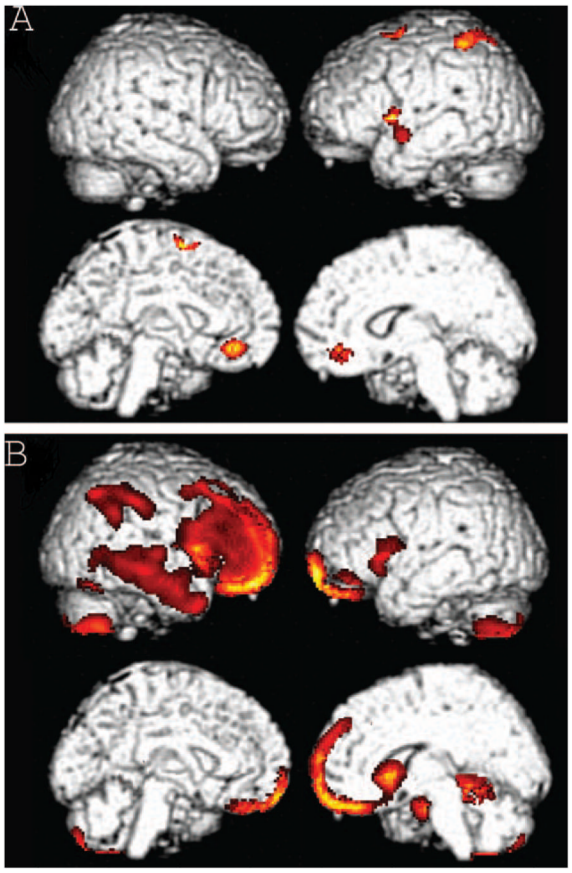

Figure. Distribution of cortical atrophy on MRI studies of Patients 1 and 2

Patient 1 is a *LRRK2* G2019S heterozygote and carries a clinical diagnosis of corticobasa syndrome. Patient 2 is a *LRRK2* R793M heterozygote and carries a clinical diagnosis of primary progressive aphasia/frontotemporal dementia. Areas of relative atrophy compared to control groups of healthy seniors are shown in color (statistical threshold for display $p < 0.001$).

Table 1

Summary of cases with *LRRK2* mutations

Patient/case	Clinical or pathologic diagnosis	Sample	Age at onset, y	Gender	*LRRK2* mutations
1	CBS	Blood	52	F	p.G2019S
2	FTD (PPA)	Blood	66	F	p.R793M
3	PD	Blood	44	F	p.G2019S
4	PD	Brain	47	M	p.G2019S
5	PD	Brain	59	M	p.G2019S
6	PD	Brain	77	F	p.R793M
7	PD	Brain	76	M	p.G2019S
8	PD	Brain	47	M	p.L1165P

Case 3 is homozygous for G2019S. Cases 4, 5, and 7 are described in detail in a previous publication.[22] Cases 4 through 8 are autopsy cases, while Cases 1 through 3 are clinical. Case 8 has a *LRRK2* variant which has not been previously reported and is under further study.

CBS = corticobasal syndrome; FTD = frontotemporal dementia; PPA = primary progressive aphasia; PD = Parkinson disease.

Table 2
Clinical and laboratory features of Patients 1 and 2

	Patient 1	Patient 2
LRRK2 mutation	G2019S	R793M
Clinical diagnosis	Corticobasal syndrome	Primary progressive aphasia
Age at onset, y/sex	52/F	66/F
Family history	Dementia (mother, grandmother)	Parkinson (father)
Chief complaint	Poor planning, memory	Hesitant speech
Parkinsonian features		
Bradykinesia	Yes	No
Rigidity	Yes	No
Rest tremor	No	No
Response to levodopa	No	N/T
Cognitive features		
Digit span	3 forward, 0 backward	5 forward, 3 backward
Recall of six-word list	0/6	4/6
Naming	Impaired	Impaired
Repetition	Impaired	Intact
Comprehension	Impaired	Mildly impaired
Written sentence	N/T	Intact
Reading	N/T	Mildly impaired
Other clinical features	None	Intention tremor
Laboratory features		
CSF protein (mg/dL)	30	55
CSF glucose (mg/dL)	62	63
CSF WBC (cells/mm^3)	0	0
CSF RBC (cells/mm^3)	0	4
CSF total tau (pg/mL)	189.1	Too low to quantify
CSF phosphorylated tau (pg/mL)	70.6	49.5
CSF Aβ42 (pg/mL)	51.2	68.7
Serum testing	B12, folate, RPR, Lyme, TSH, ANA within normal limits	B12, TSH within normal limits
Progranulin gene testing	No mutation	No mutation
Tau gene testing	No mutation	No mutation

Examination findings are from initial neurologic examination. Recall of six-word list is best of three tries. As reported previously, mean levels in normal controls (with standard deviations) are CSF tau = 260.4 (±93.8) pg/mL, CSF phosphorylated tau = 50.1 (±14.3) pg/Ml, and CSF Aβ42 = 95.2 (±29.7) pg/mL.[24]

N/T = not tested; CSF Aβ42 = CSF amyloid $\beta_{1\text{-}42}$.

Table 3

Distribution of cortical atrophy on MRI studies of Patients 1 and 2

		Coordinates				
	Anatomic region (Brodmann area)	**X**	**Y**	**Z**	**No. voxels**	**Z-score**
Patient 1	Left superior parietal (7)	−34	−48	59	245	4.44
	Left medial frontal gyrus (11)	−2	36	−10	227	4.04
	Left mid frontal gyrus (6)	−16	7	59	132	4.02
	Left parahippocampal gyrus (19)	−28	−51	−3	194	3.70
	Left frontal gyrus (6)	−61	4	9	205	3.56
Patient 2	Right temporal fusiform gyrus (37)	28	−45	−11	14,106	6.50
	Right posterior cerebellar tonsil	44	−58	−39	796	6.11
	Right mid temporal gyrus (21)	65	−24	−7	2,175	5.55
	Right inferior parietal (40)	55	−56	43	948	5.15
	Left posterior cerebellar tonsil	−44	−62	−40	1,031	4.70
	Left temporal fusiform gyrus (37)	−32	−45	−10	668	4.26
	Left frontal gyrus (44)	−55	14	9	510	4.00

Patient 1 is a *LRRK2* G2019S heterozygote and carries a clinical diagnosis of corticobasal syndrome. Patient 2 is a *LRRK2* R793M heterozygote and carries a clinical diagnosis of primary progressive aphasia/frontotemporal dementia. Z-score is based on comparison to healthy controls as described previously.[19]