

# The *PINK1* phenotype can be indistinguishable from idiopathic Parkinson disease

**Abstract**—Mutations in the *PINK1* gene cause autosomal recessive parkinsonism characterized by early onset and a variable phenotypic presentation. A patient homozygous for the Ala168Pro mutation has been fully characterized clinically. Apart from onset at age 39 years and the excellent and sustained response to levodopa, all clinical and laboratory features, including SPECT and assessment of autonomic function, were indistinguishable from typical idiopathic Parkinson disease.

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The phenotypic core of Parkinson disease (PD) (resting tremor, rigidity, bradykinesia, and postural instability) is often associated with other signs, such as sleep disturbances, depression, and mild autonomic dysfunction. Autosomal recessive early-onset parkinsonism (EOP) can be indistinguishable from sporadic, late-onset idiopathic PD, yet patients often show atypical features such as dystonia at onset, hyperreflexia, sleep benefit, early occurrence of levodopa-induced dyskinesias, and behavioral or psychiatric abnormalities. Mutations in the *PINK1* gene, encoding a putative serine-threonine kinase with likely mitochondrial localization, have recently been identified as responsible for familial and sporadic EOP,<sup>1,5</sup> but the spectrum of *PINK1*-associated phenotypes needs further definition. In most Italian patients, the phenotype closely resembles typical idiopathic PD, with unilateral onset and absence of atypical signs, the only distinguishing feature being a more benign course.<sup>1,2</sup> We report here a detailed clinical and laboratory analysis of the sporadic Italian patient carrying the *PINK1* homozygous Ala168Pro mutation, including SPECT and assessment of autonomic and mitochondrial functions.

**Case reports.** This patient is a 54-year-old carpenter who was born in central Italy. He denied parental consanguinity, albeit both parents had the same family name.

Parkinsonian signs started at age 39 years, with gait impairment due to akinesia of the right leg. A year later, he noticed motor impairment of the right upper limb and started levodopa treatment (50 mg QID), with immediate improvement. After 6

years, the patient consulted us complaining of freezing of gait. Pergolide (1 mg TID) was added with sustained benefit, and the patient remained in this combination therapy until now.

Upon observation after 15 years from onset, the patient had a typical parkinsonian picture with right-side prevalence and reported excellent response to treatment. Characteristic features of EOP, such as dystonia at onset, early or severe levodopa-induced dyskinesias, sleep benefit, and hyperreflexia, were absent. He had facial hypomimia, mild akinesia in the upper limbs, and mild “on” period right-foot dystonia. Mood was normal with no behavioral abnormalities. The patient was in excellent motor condition; in his best “on” state (after the first morning dose of treatment) the Unified Parkinson’s Disease Rating Scale (UPDRS) motor score was 12 (see video E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)). He could appreciate the wearing-off of the first morning dose. “Off” period motor fluctuations occurred occasionally in the afternoon as festination without freezing. He had mild urinary urgency but reported no other autonomic dysfunction; drug intake was not associated with hypotension.

To assess the motor condition in the “off” state, antiparkinsonian medication was withdrawn. The patient’s motor condition gradually worsened and mood became depressed. On the fifth day, he had a UPDRS motor score of 49 that decreased to 12 after a single challenge of 200/50 mg levodopa/benserazide. During drug withdrawal, there was no dysautonomia and urinary complaints did not change; on examination, he had a moderate impairment of speech and facial hypomimia, significant akinesia and rigidity in all four limbs, and a severe disturbance of gait with festination, freezing, and postural instability (see video E-2).

A complete neuropsychological profile was obtained by administering a battery for global mental status examination, in addition to specific tests for memory, executive functions, verbal fluency, and comprehension. All test results were normal. A psychiatric interview was unremarkable and the Neuropsychiatric Inventory was normal.

SPECT after administration of methyl-3-β-(4-β[<sup>123</sup>I]iodophenyl)tropane-2-β-carboxylate ([<sup>123</sup>I]β-CIT) was performed to visualize the nigrostriatal projections in three regions of interest (ROI) for each hemisphere, corresponding to the anterior putamen, the posterior putamen, and the caudate nucleus. Striatal [<sup>123</sup>I]β-CIT uptake was severely decreased on both sides in a similar manner. Compared with occipital background activity, dopaminergic denervation was more severe in the putamen (ratio: 1.5 on each side) than in the caudate nucleus (ratio: 2.5 on the right, 2.9 on the left).

Mitochondrial function was assessed by dosing the respiratory chain enzymatic activity, citric acid cycle, and electron transport rate on a biopsy sample of the left quadriceps muscle. At rest, blood lactate was slightly elevated (1906 μmol/L; normal 500 to 1800), whereas pyruvate was within normal limits. No other abnormality of mitochondrial function was detected. EMG and nerve conduction study results were normal. Muscle morphology and histochemistry revealed normal tissue organization and distribution of the oxidative enzymes activity. Degeneration, ragged red fibers, and pathologic accumulation of lipids or carbohydrates were not observed.

Assessment of autonomic function showed a mild impairment of sympathetic nervous system function. Systolic blood pressure dropped to borderline normal values (up to 20 mm Hg after 7

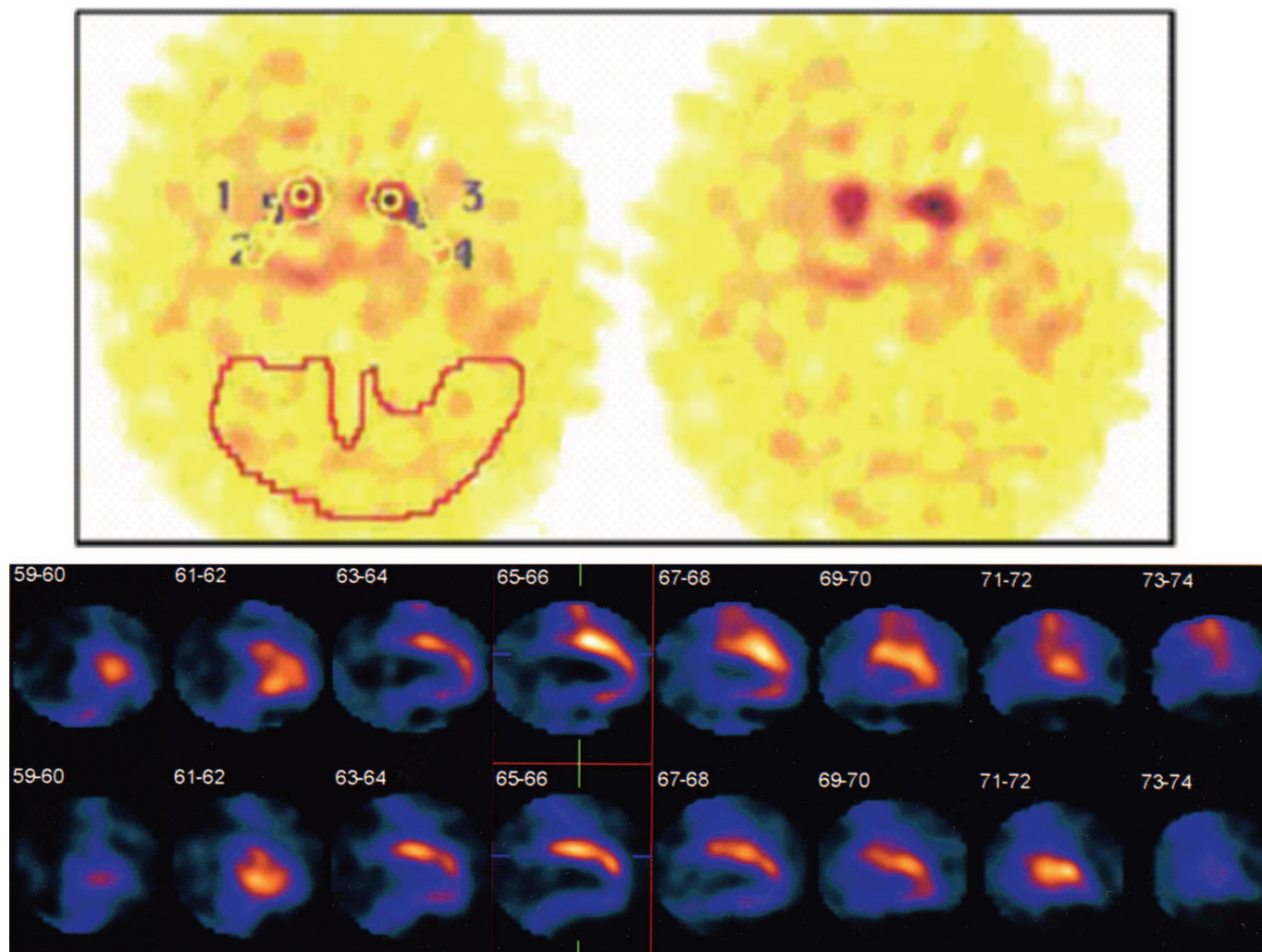
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**Figure 1.** Top: Methyl-3-β-(4-[<sup>123</sup>I]iodophenyl)tropane-2β-carboxylate SPECT scan of the patient; six regions of interest (ROI), three in each hemisphere (ROI 1, 2, and 5 on the right; ROI 3, 4, and 6 on the left) are superimposed on the left panel. ROI 1 and 3 correspond to the striatal region, ROI 2 and 4 to the putamen, and ROI 5 and 6 to the caudate nucleus. Dopaminergic denervation is almost complete in the putamen, whereas the caudate nucleus is comparatively less affected. Bottom: Analysis of regional radiolabeled <sup>123</sup>I-metaiodobenzylguanidine uptake shows a reduced metaiodobenzylguanidine activity in the laterobasal and inferior walls of the left ventricle compared with the upper mediastinum, indicating partial β-adrenergic denervation.

minutes) during the head-up tilt to 60 degrees. Heart rate increase compensated adequately. The Valsalva maneuver was altered: There was no blood pressure overshoot and postmaneuver bradycardia was detected, indicating an initial sympathetic vasoconstrictor failure. An abnormality of the sympathetic efferent pathways was confirmed by the lack of reflex blood pressure increase on the skin cold test, whereas the Valsalva ratio was normal, indicating preserved parasympathetic function.

Sympathetic innervation to the heart was evaluated with cardiac scintigraphy using radiolabeled <sup>123</sup>I-meta-iodobenzylguanidine ([<sup>123</sup>I]MIBG). Global [<sup>123</sup>I]MIBG uptake was assessed by measuring the ratio of [<sup>123</sup>I]MIBG uptake in the left heart ventricle compared with that in the upper mediastinum on planar scintigraphic data. In the laterobasal and inferior walls of the left ventricle, there was a 1.71 ratio indicating partial β-adrenergic denervation (normal values 2.2 ± 0.2) (figure 1).

**Discussion.** The patient reported here received a diagnosis of typical PD with early onset. After 15 years of disease duration, the phenotype had slowly progressed without the appearance of atypical features. Clinical and laboratory examination results

were in keeping with the findings commonly observed in idiopathic PD, including dopaminergic denervation, mild dysautonomia, and absence of cognitive or psychiatric disturbances. Unlike an earlier report of fluorodeoxyglucose-DOPA PET scans in *PINK1* familial cases,<sup>6</sup> the striatal dopaminergic denervation observed with [<sup>123</sup>I]β-CIT SPECT was similar to that reported in late-onset PD.<sup>7</sup>

There is increasing evidence that impairment of mitochondrial function and oxidative damage are contributing factors for PD, and all EOP genes seem to be involved in mitochondrial activity.<sup>8</sup> Yet muscle mitochondrial function in this patient was normal, indicating that the putative influence of *PINK1* defect on brain mitochondrial function is not detectable in the periphery, at least under basal conditions.

So far, 21 patients with *PINK1* homozygous or compound heterozygous mutations have been re-

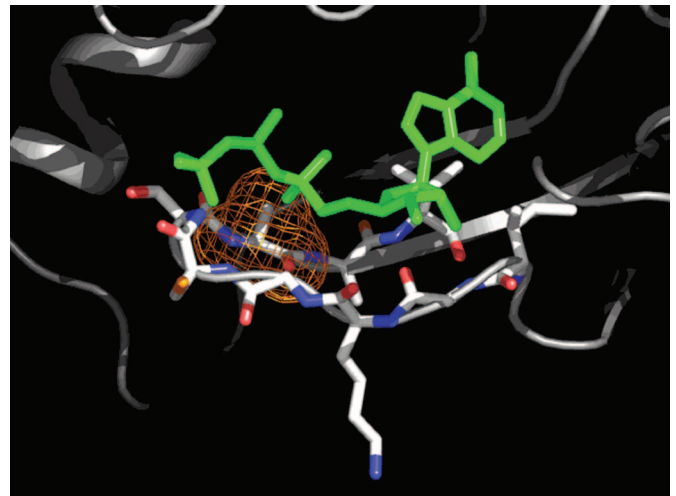
**Table** Prevalence of clinical features in the 21 *PINK1*-positive cases reported in literature

| Clinical feature                             | Prevalence (%)    |
|----------------------------------------------|-------------------|
| Sex                                          | 8M/11F/2 unknown  |
| Mean age at onset (range)                    | 31.6 y (18 to 48) |
| Excellent and sustained response to levodopa | 21/21 (100)       |
| Slow disease progression                     | 21/21 (100)       |
| Bradykinesia                                 | 20/20 (100)       |
| Rigidity                                     | 19/20 (95)        |
| Wearing off                                  | 18/19 (95)        |
| Levodopa-induced dyskinesias                 | 16/19 (84)        |
| Resting tremor                               | 16/20 (80)        |
| Asymmetry at onset                           | 14/19 (74)        |
| Postural instability                         | 12/19 (63)        |
| "On"/"off"                                   | 12/20 (60)        |
| Gait impairment                              | 11/20 (55)        |
| Urinary urgency                              | 4/9 (44)          |
| Hyperreflexia                                | 6/18 (33)         |
| Sleep benefit                                | 6/19 (31)         |
| Psychiatric disturbances                     | 5/20 (25)         |
| Orthostatic hypotension                      | 2/9 (22)          |
| Dystonia at onset                            | 3/19 (16)         |
| Dementia                                     | 1/20 (5)          |

For each feature, percentages were calculated on the total number of patients for whom clinical data were available.

ported (table).<sup>1-5,9</sup> Although the phenotypic spectrum of *PINK1* disease is rather wide, typical features of PD predominate. The present case shows that orthostatic hypotension (a rare occurrence) was associated with postsynaptic sympathetic denervation, as observed in typical PD. Excellent and sustained response to levodopa therapy has been reported in all patients with *PINK1* disease; we observed here that this response was still sustained after 15 years of disease, when withdrawal produced a marked worsening of motor condition.

Genotype-phenotype correlates in *PINK1* disease have not been fully elucidated. A large proportion of mutations are missense changes, whose pathogenetic role in sporadic cases remains unclear in the absence of a functional assay on the protein. Bioinformatic analysis of the *PINK1* protein showed that alanine 168 is localized inside the conserved adenosine triphosphate-binding region (amino acids 162 to 170), which is characterized by rich  $\beta$ -sheet content (figure 2). Mutation of this residue might influence the local nonbonded interactions implied in adenosine triphosphate/adenosine diphosphate binding and therefore alter the kinase activity. This is particularly true in the specific mutation A168P because proline is an amino acid with disruptive effects in the hydrogen-bonding patterns of  $\alpha$ -helices and  $\beta$ -sheets.<sup>10</sup> The identification of the role by which different mutant *PINK1* proteins produce their phe-



**Figure 2.** Model of the nucleotide phosphate-binding region of *PINK1* in the presence of an adenosine triphosphate (ATP) ligand. The protein structure has been obtained from ModBase (residues 151 to 501 modeled on the PDB structure 1gjo as template). ATP has been positioned according to the experimental docking geometry found in the structure of a homologous kinase complexed with this ligand (PDB structure 1h1w) and subjected to energy optimization. The protein is represented as ribbons, residues 162 to 170 in the ATP-binding region, and ATP is depicted as sticks (alanine 168 is highlighted by the orange mesh and ATP is in green). The model has been rendered with the program PyMOL (<http://www.pymol.org>).

notypic aftermath will contribute to a better understanding of the pathogenesis of variants of EOP.

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