

***PINK1* Homozygous W437X Mutation in a Patient with Apparent Dominant Transmission of Parkinsonism**

Chiara Criscuolo, MD,^{1*} Giampiero Volpe, MD,¹
 Anna De Rosa, MD,¹ Andrea Varrone, MD,²
 Roberta Marongiu, BSc,^{3,4} Pietro Mancini, BSc, PhD,¹
 Elena Salvatore, MD,¹ Bruno Dallapiccola, MD,^{3,4}
 Alessandro Filla, MD,¹
 Enza Maria Valente, MD, PhD,³
 and Giuseppe De Michele, MD¹

¹Department of Neurological Sciences, Federico II University, Naples, Italy; ² Department of Biomorphological and Functional Sciences, IBB, CNR, Federico II University, Naples, Italy; ³CSS IRCCS, Mendel Institute, Rome, Italy; ⁴Department of Experimental Medicine and Pathology, "La Sapienza" University, Rome, Italy

Abstract: We analyzed the *PINK1* gene in 58 patients with early-onset Parkinsonism and detected the homozygous mutation W437X in 1 patient. The clinical phenotype was characterized by early onset (22 years of age), good response to levodopa, early fluctuations and dyskinesias, and psychiatric symptoms. The mother, heterozygote for W437X mutation, was affected by Parkinson's disease and 3 further relatives were reported affected, according to an autosomal dominant transmission. © 2006 Movement Disorder Society

Key words: PINK1; familial Parkinsonism; PARK6; early onset

Three autosomal recessive genes have been identified to date as causative of early-onset Parkinsonism (EOP). According to a referral based study, the *Parkin* gene represents the most frequent cause of EOP, being responsible for up to 50% of familial cases and 15% of sporadic cases with onset younger than 45 years of age.¹ Mutations in the *DJ-1* gene have a much lower prevalence, not exceeding 1%.² A third gene, *PINK1*, was found mutated in several EOP families and further reports suggest a 1.5% to 2% prevalence in sporadic patients.^{3–9}

In addition to the typical parkinsonian signs, EOP patients present slow progression of the disease, excel-

lent response to levodopa, and early L-dopa-induced fluctuations and dyskinesias. Dementia and dysautonomia are rarely observed, whereas other atypical features occasionally can be present. The range of *Parkin* phenotypes is well known, because a large number of familial and sporadic cases have been described to date.^{10–12} Conversely, only a limited number of patients with *DJ-1* or *PINK1* mutations have been reported, and the associated phenotypic spectrum still needs further definition. We evaluated the presence of *PINK1* mutations in a cohort of 58 EOP cases from Southern Italy and describe the phenotype of 2 patients from a family with apparently dominant inheritance.

PATIENTS AND METHODS

Patients

After obtaining informed consent, 58 consecutive unrelated Italian patients (40 men, 18 women) with EOP (onset < 50 years of age) were recruited as inpatients or outpatients at the Movement Disorder Clinic of the Department of Neurology, Federico II University of Naples, since June 2001. All patients originated from Southern Italy, mostly from Campania. Diagnosis was made according to the UK Brain Bank criteria for Parkinson's disease (PD), except the criterion that excludes familial cases. Patients underwent a detailed neurological examination, including the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr scale.

Mean age at onset \pm SD was 41.3 ± 7.8 years (range, 20–49 years). A total of 34 patients were sporadic, whereas 24 had at least 1 affected relative. An affected first-degree relative was reported in 15 cases (a parent in 9 and a sibling in 6). Parental consanguinity was reported for 7 cases.

Molecular Analysis

Genomic DNA was isolated from peripheral blood using standard techniques. *PINK1* coding sequence was amplified by polymerase chain reaction (PCR) and directly sequenced.⁴ When a homozygous mutation of *PINK1* was found in 1 patient, her parents were analyzed by direct sequencing and by a quantitative PCR-based exon dosage assay, to rule out heterozygous exon rearrangements.⁴ The presence of the mutation was excluded in 50 healthy individuals from Campania.

RESULTS

Of 58 probands, 1 (1.7%) carried a homozygous 1311G>A change in exon 7, resulting in the W437X nonsense mutation. The patient's mother and 3 other relatives in the maternal line were reported to be affected

*Correspondence to: Dr. Chiara Criscuolo, Department of Neurological Sciences, Federico II University, via Pansini 5, 80131 Naples, Italy. E-mail: sky569@libero.it

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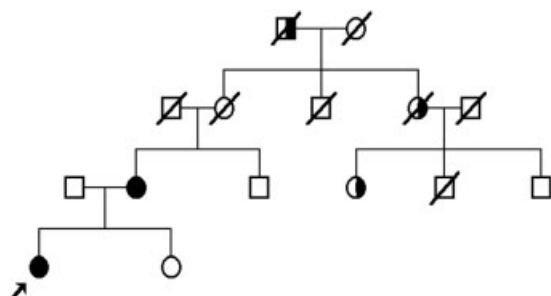


FIG. 1. Pedigree of the family. Black symbols denote definitely affected individuals, half-black symbols denote family members affected by history. A diagonal slash across symbols indicates a deceased individual. The arrow indicates the proband.

by PD (Fig. 1). Both parents of the proband were clinically examined and sampled, whereas the only affected living relative (a proband's cousin) refused to participate in the study. The W437X mutation was detected in the heterozygous state in both parents, who did not carry any other pathogenic changes or gene rearrangements.

CASE REPORTS

Both parents of the proband originated from a small village in Southern Italy, but consanguinity was denied. The proband, a 51-year-old woman, first noted bradykinesia and tremor in the left leg at age 22. Over the next year, symptoms spread to the left arm and subsequently to the right side. Neither dystonia at onset nor sleep benefit were reported. L-Dopa was started approximately 1 year after disease onset, with marked clinical benefit. However, after approximately 2 years of L-dopa therapy, wearing-off occurred leading to compulsive automedication (up to 2,000 mg daily) and painful leg dyskinesias. At the same time, a depressive disorder with severe histrionic and paranoid personality disturbances was diagnosed. Drug withdrawal at 48 years of age caused severe *off* state (Hoehn & Yahr stage 5; UPDRS-III score, 85). Apomorphine was added to L-dopa when she was 50 years of age. On the last examination, she was taking 100 mg of L-dopa and 1 mg of subcutaneous apomorphine 10 times a day. In *on* state, very mild bradykinesia and rigidity were observed (UPDRS-III score, 8). After approximately 2 hours, the patient progressed to an on-off transition state characterized by marked axial rigidity and bradykinesia, hypomimia, and mild postural and action bilateral tremor (UPDRS-III score, 44). Tendon reflexes were brisk. Dementia and autonomic disturbances were absent. A brain magnetic resonance imaging scan revealed slight supratentorial and infratentorial atrophy. [123 I]FP-CIT single-photon emission computed tomography (SPECT) scan showed that striatal DAT density was reduced by 62% in the

caudate and 76% in the putamen compared with average control values. The right striatum was more affected, with a posterior to anterior gradient of DAT decline.

The 73-year-old mother of the proband had onset at 53 years of age, with left arm rest tremor and bradykinesia. L-Dopa was started from the beginning. On the last examination, she was taking 800 mg of L-dopa daily with good response, but motor fluctuations, peak dyskinesias, and early-morning dystonia were present. Examination in *off* state revealed flexed posture, mild postural instability, diffuse bradykinesia and rigidity prevalent on the left side (Hoehn & Yahr stage III, UPDRS-III score: 42), mild dyskinesias, and normal tendon reflexes. She reported urinary urgency and was not demented. Neurological examination of the proband's father at age 79 was entirely normal. None of the subjects on the paternal line was reported to be affected by PD. Both parents refused to undergo further diagnostic procedures, such as [123 I]FP-CIT SPECT scanning. The 3 other affected relatives of the family were reported by history to present tremor, difficulties in gait, and slow movements.

DISCUSSION

We detected a homozygous mutation (W437X) in the PINK1 gene in 1 of 58 EOP patients. The patient reported here carries the same homozygous W437X as the 6 patients from the 2 Italian families originally linked to PARK6.³ All these patients, including the present one, share the same haplotype for markers surrounding the gene (data not shown). Recently, W437X was found in another Italian patient with EOP.¹³ Conversely, this mutation was never identified in EOP patients of different nationality,¹⁴ strongly suggesting a founder effect in Italy. The 7 previously described patients homozygote for W437X presented a fairly typical parkinsonian phenotype, with asymmetric onset in the fourth or fifth decade (range, 30–48 years of age), wearing-off and L-dopa-induced dyskinesias of variable severity, and absence of psychiatric problems. The distinctive features in our patient are earlier age of onset (22 years) and presence of major psychiatric disturbances. Cognitive or autonomic abnormalities were absent in all W437X mutation carriers, whereas dystonia at onset and diurnal fluctuations were rarely observed.

In the family reported here, both parents were heterozygous for the W437X mutation, but only the mother was affected by PD. DNA from the remaining three affected relatives was not available. An increasing number of patients carrying single heterozygous mutations in one of the three EOP genes has been reported.^{1,2,4,7,9,11} The presence of a heterozygous mutation may be coincidental to the disease, or alternatively a second mutation

(for instance, within regulatory untranslated regions) may be missed, despite extensive screening. A third, appealing hypothesis is that a single mutation could lead to a nigrostriatal subclinical dopaminergic defect, which would reach the threshold of disease only in the presence of other genetic or environmental factors. The strongest evidence in favor of this hypothesis comes from positron emission tomographic studies, which concordantly demonstrate a significant decrease of ^{18}F -dopa uptake in *Parkin* and *PINK1* heterozygous healthy carriers.^{15,16} Moreover, some heterozygous carriers present mild signs of Parkinsonism, further supporting the existence of a borderline dopaminergic dysfunction.

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Diffusion-Weighted Magnetic Resonance Imaging in the Syndrome of Acute Bilateral Basal Ganglia Lesions in Diabetic Uremia

Taik-Kun Kim, MD,^{1*} Sang Il Seo, MD,¹
Jung Hyuck Kim, MD,¹ Nam Joon Lee, MD,¹
and Hae Young Seol, MD¹

Department of Diagnostic Radiology, Korea University,
College of Medicine, Seoul, Korea

Abstract: In this report, we have presented a diabetic patient with uremia, in which acute Parkinsonism occurred, coupled with acute mental confusion, after a sudden increase in blood urea nitrogen and serum creatinin levels. Diffusion-weighted magnetic resonance imaging revealed a unique cytotoxic-type edema in the bilateral basal ganglia during the acute phase. Signal alterations were shown to regress in accordance with the normalized apparent diffusion coefficient (ADC) values, but irreversible cystic degeneration developed in the globus pallidus, with the very low preceding ADC values. © 2006 Movement Disorder Society

Key words: diffusion MRI; basal ganglia; diabetes mellitus; uremia

The syndrome of acute bilateral basal ganglia lesions in patients with diabetic uremia is a rare illness, which normally affects Asian patients. Recently, several cases of acute movement disorders with bilateral basal ganglia involvement have been described in uremic-diabetic patients. This syndrome is characterized by reversible, acute-onset Parkinsonism or dyskinesia, together with a variety of symptoms, including disturbances of con-

*Correspondence to: Dr. Taik-Kun Kim, Department of Diagnostic Radiology, Korea University College of Medicine, Ansan Hospital, #516 Kojan-Dong, Ansan City, Kyungki-Do 425-020, Korea. E-mail: tkkim@kumc.or.kr

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