



Expedited Publication

Phenotypic Characterisation of Autosomal Recessive PARK6-Linked Parkinsonism in Three Unrelated Italian Families

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Abstract: The clinical features of nine patients (three women and six men) affected by PARK6-linked parkinsonism, belonging to three unrelated Italian families, are reported. The occurrence of affected men and women within one generation suggested an autosomal recessive mode of inheritance in all three families. Mean age at disease onset was 36 ± 4.6 years; all cases except one presented with asymmetrical signs, consisting of tremor and akinesia of one upper limb or unilateral short step gait. Affected individuals had a mean age of 57 ± 8.5 years, and average disease duration was 21 ± 7.8 years. Parkinsonian features included benign course, early onset of drug-induced dys-

kinesias, and a good and persistent response to levodopa. There were no other associated features (i.e., pyramidal or cerebellar signs, dysautonomia, or diurnal fluctuations unrelated to drug treatment). Cognition was unaffected. The clinical picture was remarkably similar in all patients; no relevant family-related differences were found. PARK6 disease is a new form of early-onset parkinsonism without other atypical clinical features.
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Key Words: autosomal recessive parkinsonism; Parkinson's disease; early onset; family study; genetics; PARK6

Parkinson's disease (PD) is a neurodegenerative disorder with characteristic clinical features mainly resulting from defective dopaminergic transmission in the nigrostriatal system. The cause of PD is unknown, but it is probably attributable to a combination of genetic and environmental factors.¹ Genetic linkages have been identified in families with PD, but the extent to which sporadic PD cases are inherited has not yet been determined. Genetic contribution is thought to play a more important

role in early-onset (symptoms shown before age 50 years)² PD cases.

Familial parkinsonism can be inherited as a dominant or recessive trait. Although autosomal dominant forms may have a sporadic presentation because of reduced penetrance or clinical expression, sporadic PD patients are more likely to carry autosomal recessive genes. Two autosomal recessive parkinsonisms have been described. Mutations of the *parkin* gene (chromosome 6q25.2–q27) are responsible for Lewy body-negative, autosomal-recessive early-onset parkinsonism, first described in Japanese families.³ In a recent study,⁴ mutations in the *parkin* gene occurred in about 50% of families with autosomal recessive parkinsonism with onset before age 45 years. A high incidence of mutation was also found among a subset of sporadic cases with onset before age 30 years.⁴

A videotape accompanies this article.

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We recently identified a new locus for autosomal recessive parkinsonism on chromosome 1p35-36 (PARK6) in a large family originating from Marsala (Sicily, Italy).⁵ We report in detail on the clinical features of three Italian families linked to the PARK6 locus.

SUBJECTS AND METHODS

The Gemelli registry for movement disorders was screened for *parkin*-negative families with at least two members in the same generation affected by parkinsonism with onset before 45 years of age. Among five families analysed so far, we identified three families with parkinsonism due to PARK6 disease. Family 1 allowed us to map the PARK6 locus to a 12.5-cM interval on chromosome 1p35-36.⁴ Genotyping of 11 microsatellite markers spanning the PARK6 region on chromosome 1p35-p36 allowed us to identify further two families (family 2, registry number 105, and family 3, registry number 36) in which the affected sibs shared identical haplotypes across the entire PARK6 interval. No unaffected relative within either of these two families showed the same haplotypes as the affected siblings, and positive logarithm of odds (LOD) scores at all recombination fractions were obtained in both families.⁶

The three Italian families linked to PARK6 were studied in detail; members older than 18 had signed an informed consent and donated a blood sample for genetic analysis. Minors were examined but their blood was not sampled. All subjects provided detailed information on the following: birth, growth and development, education, use of well-water, medications, drug misuse, exposure to toxins or chemicals (particularly regarding organophosphorous compounds and other substances used in agriculture), previous illnesses, previous hospitalisations, any neurological or psychiatric disease, and any head or body injuries. The levodopa equivalent daily dose (LEDD) was calculated in order to have comparable data on drug therapy.⁷

All participating family members had a complete on-site neurological examination that included the Unified Parkinson's Disease Rating Scale (UPDRS) motor scale in the *on* condition (and in the *off* condition when possible), the Mini-Mental State Examination (MMSE), and tasks aimed to disclose dystonia or paroxysmal dyskinesias. Each subject was videotaped during the assessment. The diagnosis of parkinsonian syndrome was made when at least two of the following were present: resting tremor (4–6 Hz), bradykinesia or akinesia (with fatigue), or rigidity (with or without cog-wheeling).

RESULTS

In total, 73 subjects were examined, nine of whom (three women and six men) were affected by early-onset

parkinsonism linked to the PARK6 locus. Mean age was 55 ± 12 years (range, 40–74 years). The clinical features of PARK6 patients were remarkably similar, and are described hereafter in some detail.

The families originated from different Italian regions. Crossed interviews and genealogical investigation did not relate them to common ancestors. Family 1 comprised 122 members (35 examined and blood-sampled), originating from Marsala (Sicily, Italy). Figure 1 shows a simplified pedigree of the family. The affected individuals descended, both on the maternal and the paternal side, from subjects I:1 and I:2, who lived in the late nineteenth century. Their descendants remained in the same region and frequently had consanguineous marriages in subsequent generations. The high rate of inbreeding and the occurrence of affected men and women within one generation suggest an autosomal recessive mode of inheritance. All family members were farmers, who denied the use of pesticides. Four subjects were diagnosed with early-onset parkinsonism. Mean age at disease onset was 40.8 ± 7.2 years; average disease duration was 16.5 ± 6.4 years (age at time of study: 59.8 ± 13.5 years). The clinical features of the four affected individuals are illustrated in Table 1.

Family 2 comprised 43 family members (Fig. 2), who originated from a small village in Abruzzo (central eastern Italy). The affected individuals descended from two first-degree cousins. We examined and blood-sampled 12 subjects. Two subjects (IV:2 and IV:3) received a diagnosis of early-onset parkinsonism (Table 1). There were no other affected family members, as shown in Figure 2. All family members denied the use of pesticides, and were not exposed to toxins known to induce parkinsonism.

Family 3 comprised 87 members; at the time of the study 66 were alive (26 were examined, of whom 12 were blood-sampled). The family (see Figure 3) originated from a small village close to Siena. No consanguineous marriages were reported in the past generations, but all marriages occurred within the population of the same small village where the proband lived. All family members denied the use of pesticides, and none were exposed to toxins known to produce parkinsonism. Three siblings, two men and a woman who are descendants of III:11, were diagnosed with early-onset parkinsonism (Table 1). The grandfather of the affected family members was reported to have been affected by young-onset postural tremor of the upper limbs, which had started in young adulthood; all living family members denied that he may have had gait impairment, slowness of movement, or motor impairment reminiscent of akinesia. Mean age at disease onset was 36 ± 4.6 years. At the time

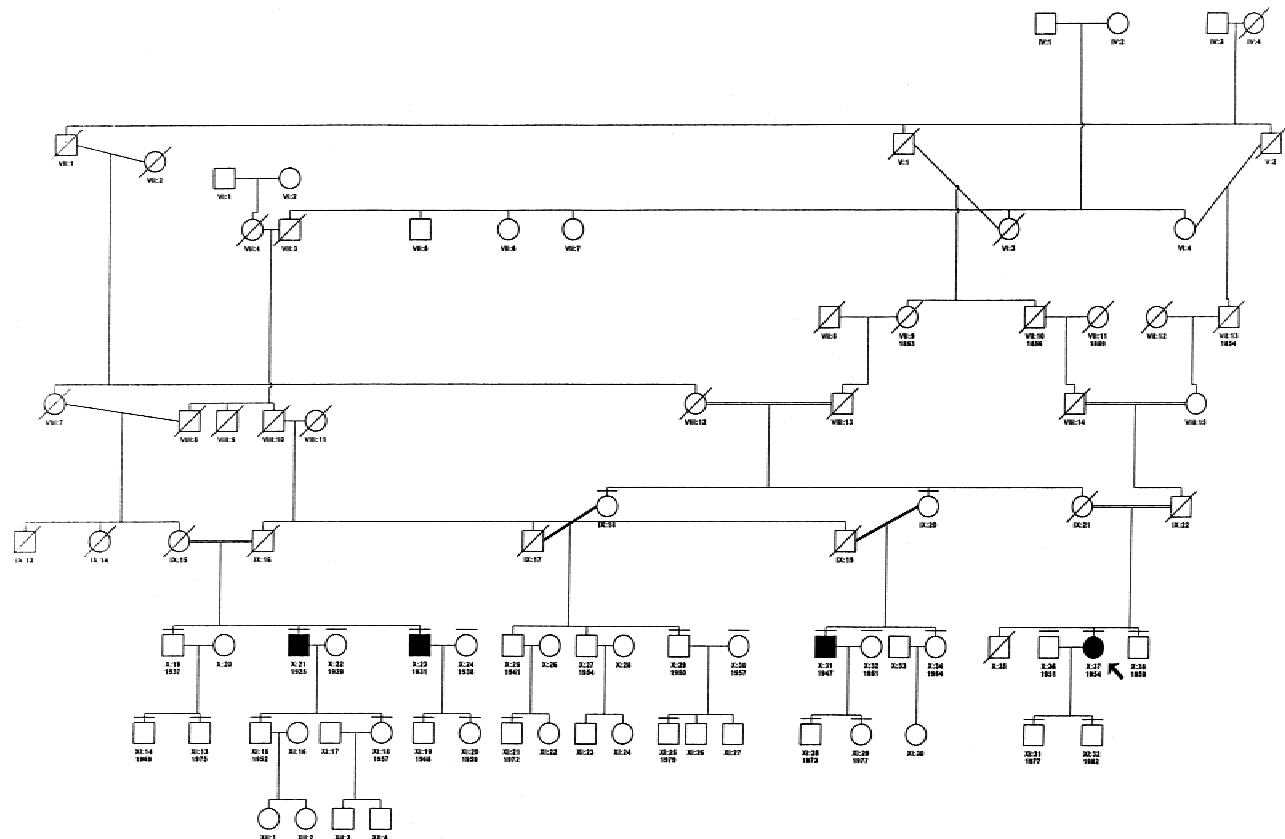


FIG. 1. Simplified pedigree of Family 1. Black symbols denote individuals affected by parkinsonism; deceased members are marked with a diagonal bar. A thin horizontal bar above symbols indicates members of the family who were examined clinically. The arrow indicates the index case.

of study, the average duration of the disease was 21 ± 7.81 years, and the affected individuals had a mean age of 57 ± 8.5 years.

The parkinsonian picture started before the age of 50 in all cases, mean age at disease onset being 38.6 ± 6 years (range, 30–48 years). In seven of nine patients, onset was before age 40 years. In all but one, the presenting parkinsonian picture was asymmetrical; among the nine patients, the presenting sign was in the arm(s) in four cases, in the leg in four cases, and in the leg and arm in one case. No patient reported dystonia, sleep benefit, or diurnal fluctuations before starting treatment. Cognitive functions were normal in all patients. The MMSE was above 25 in all cases.

The clinical evaluation was performed after average disease duration of 15 ± 8 years (range, 2–26 years). All patients had resting tremor, akinesia, rigidity and gait impairment (associated with freezing). There were no atypical features, such as cerebellar signs (ataxia, intention tremor, dysmetria), supranuclear gaze palsy, cognitive impairment, or symptomatic orthostatic hypoten-

sion. Pyramidal signs were absent, but deep tendon reflexes in the lower limbs were brisk in three patients; plantar responses were flexor in all cases.

All patients were under antiparkinsonian treatment; seven were taking oral medication (levodopa or dopamine agonists). The mean LEDD was 974 ± 512.3 mg (range, 220–2,500 mg). Antiparkinsonian medication was started within 2 years after disease onset in all patients. Two patients (family 3, IV:31 and IV:27) were under subcutaneous infusion of apomorphine and oral levodopa; in these two patients, the parkinsonian picture was not particularly severe when compared with the other patients; their UPDRS motor scores in the *on* condition were 3 and 10, respectively. Clinical response to treatment was excellent and sustained in all cases. The average UPDRS motor score in the *on* condition was $14.3 (\pm 6.6)$. The UPDRS motor score (in the *on* condition) was remarkably low (average, 16.6 ± 12 ; range, 3–31) in PARK6 patients with long disease duration (≥ 19 years). For example, Patient IV:31 of Family 3, with 25 years of disease duration, had an UPDRS motor

TABLE 1. Clinical features of the patients belonging to the three *PARK6* families

	Family 1				Family 2		Family 3		
Patient	X:37	X:21	X:23	X:31	IV:7	IV:8	IV:27	IV:31	IV:33
Gender	F	M	M	M	F	M	F	M	M
Age at onset	38	45	48	32	30	38	40	31	37
Age at time of study	45	74	68	52	42	40	66	56	49
Disease duration	7	19	20	20	10	2	26	25	12
Asymmetric signs at onset	+	+	–	+	+	+	+	+	+
Dystonia at onset	–	–	–	–	–	–	–	–	–
Diurnal fluctuations before therapy	–	–	–	–	–	–	–	–	–
Cerebellar signs	–	–	–	–	–	–	–	–	–
Progression	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow
Clinical presentation at time of study									
Resting tumor	+	+	+	+	+	+	+	+	+
Bradykinesia/akinesia	+	+	+	+	+	+	+	+	+
Rigidity	+	+	+	+	+	+	+	+	+
Gait impairment	+	+	+	+	+	+	+	+	+
Postural abnormality	–	+	+	+	–	–	–	–	–
Orthostatic hypotension	–	–	–	–	–	–	–	–	–
Incontinence	–	–	–	–	–	–	–	–	–
Urinary urgency	+	+	–	+	–	–	+	–	–
Hyperreflexia	+	–	–	–	+	–	+	–	+
Clinical response to levodopa	Good	Good	Good	Good	Good	Good	Good	Good	Good
Levodopa-induced dyskinesias	+	+	+	+	*	+	+	+	+
UPDRS III (<i>on-state</i>)	6	31	27	12	25	10	3	10	5
MMSE	30/30	27/30	26/30	30/30	30/30	29/30	–	29/30	29/30
LEDD	500	700	600	1,100	400	220	2,500	2,500	250
PD: exclusion criteria	–	–	–	–	–	–	–	–	–

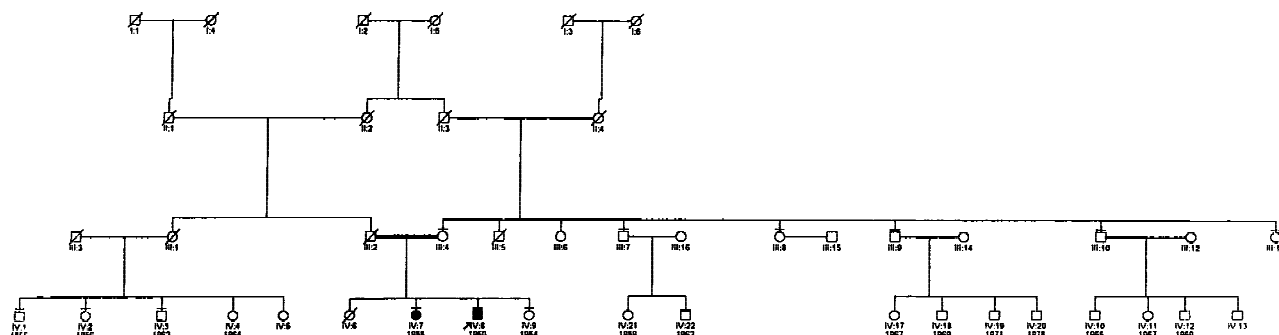
*Never treated with levodopa.

UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease.

score of 34 in the *off* condition and of 10 in the *on* condition. All patients were able to deal efficaciously with everyday life occupations while in the *on* condition, and none had retired prematurely due to motor impairment.

Motor fluctuations were common. Wearing-off phenomena occurred in all patients. Subject IV:8 of Family 2, who was examined after 2 years of disease duration and after only a few months of medical treatment, presented wearing-off phenomena of mild intensity. His sister, Subject IV:7, was never treated with levodopa, and had mild early morning akinesia relieved by the first dose of dopamine agonist.

On-state dyskinesias were reported by all patients, except for IV:7 of Family 2. It is noteworthy, however, that this woman had only received dopamine agonists. The duration of levodopa therapy and the severity of dyskinesias were variable. In two *PARK6* patients (Family 1, X:37; Family 2, IV:8) dyskinesias occurred as early as 4 months after starting antiparkinsonian treatment. In others, dyskinesias started after several years of levodopa administration. Severe *on-off* fluctuations occurred in three subjects (Family 1, X:31; and Family 3, IV:27 and IV:31), who also experienced severe choreiform *on-state* dyskinesias.

**FIG. 2.** Simplified pedigree of Family 2. Symbols as for Figure 1.

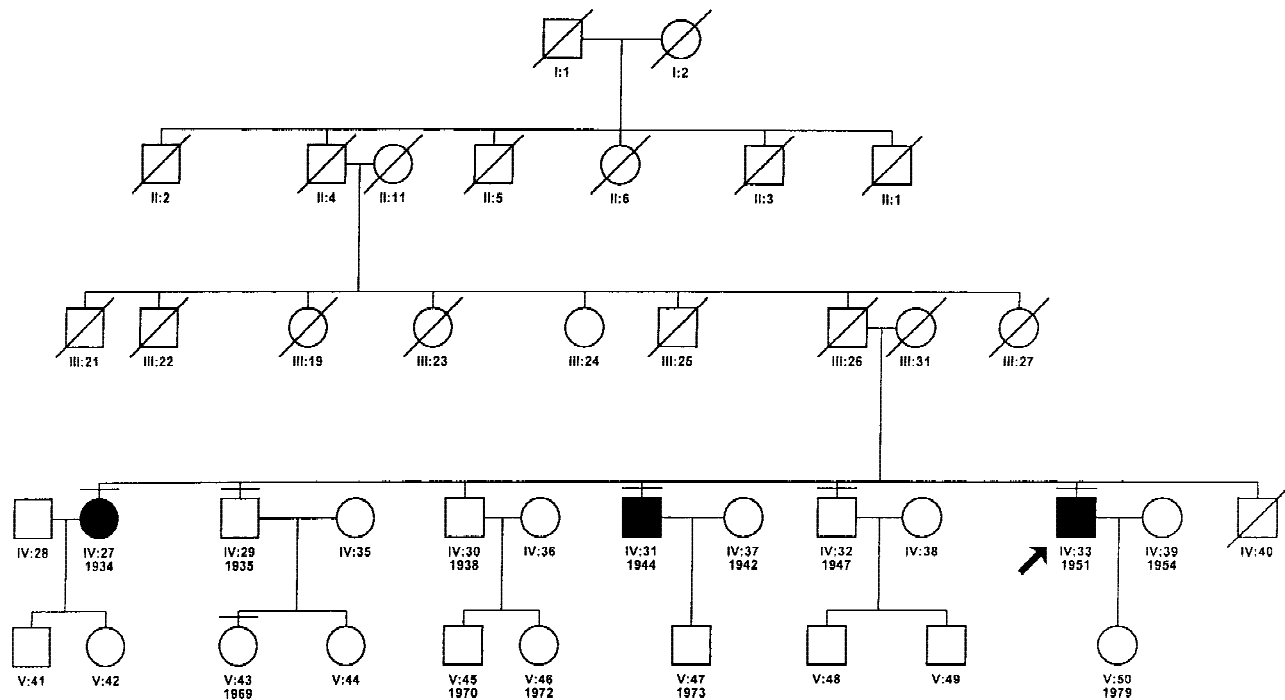


FIG. 3. Pedigree of Family 3. Symbols as for Figure 1.

DISCUSSION

The clinical features of PARK6 parkinsonism in the first three recognised Italian families are described here. Compared with sporadic, classic Lewy body PD, this autosomal recessive parkinsonism has a remarkable overlap and few distinctive features. The main differences are a younger age at disease onset and early occurrence of *on*-state dyskinesias. In typical PD, the mean age at disease onset is between 58 and 62 years.⁸ The terms “juvenile” or “young-onset” PD have been used to indicate PD cases with onset at a younger age than average, not considering their possible genetic origin. In clinical studies, early-onset PD cases have been arbitrarily defined as having onset before the age of 40 years (“young onset” when beginning between 21 and 40 years, “juvenile” when onset was before the age of 21 years).^{9,10} Early-onset PD is characterised by dyskinesias and fluctuations presenting early in the disease course, and low incidence of dementia.⁹ Others confirmed that few peculiar features differentiate parkinsonism presenting below 35 years (early occurrence of dyskinesias and occurrence of dystonia at onset), and that there are no remarkable differences from adult onset PD, even after prolonged follow-up.¹¹

The clinical features of PARK6 disease are clearly different from those of autosomal dominant parkinsonisms (see Table 2). At variance with most autosomal

dominant parkinsonisms, PARK6 patients do not have a rapid progression and do not develop cognitive abnormalities.

Apart from an earlier age at onset, most PARK6 patients have a remarkably typical parkinsonian picture that matches the current clinical diagnostic criteria for PD.^{12,13} Leg onset occurs in four of nine patients, and further observations will allow us to understand if it might represent a peculiar sign of PARK6 disease. The clinical course of PARK6 disease is benign. The average UPDRS motor score in the *on* condition was 14.3 (± 6.6); in those subjects with 19 years or more of disease duration, the UPDRS motor score in the *on* condition was on average 16.6 (range, 3–31). All patients were able to deal efficaciously with everyday life occupations while in the *on* condition, and none of them retired prematurely due to the parkinsonian state. In some PARK6 patients, *on*-state dyskinesias occurred earlier than expected in a typical PD patient; thus, two patients developed dyskinesias within 4 months after starting levodopa and 2 years after disease onset; however, this is also seen in many patients with nonfamilial young-onset PD. Nevertheless, the majority of patients had dyskinesias only after several years of disease course. Response to drug treatment was excellent in all PARK6 patients and did not wane with time; dopaminergic treatment induced a satisfactory *on*

TABLE 2. Summary of the relevant phenotypic features of monogenic parkinsonisms

Name	Locus	Gene	Transmission	Onset	Progression	Peculiar features	Lewy bodies	Ref.
PARK1	4q21–22	α -synuclein	AD	46 $\pm$ 13 (20–85)	Rapid	Early onset Rapid disease progression	Yes	18
PARK2	6q25.2–q27	<i>Parkin</i>	AR	Juvenile* Variable (3–70)	Slow	Early onset Symmetric involvement Dystonia Sleep benefit	—	4
PARK3	2p13	Unknown	AD	Mean 54–63 (37–89)	Slow	Early dyskinesias Variable onset Dementia (in 2 families)	Yes	19
PARK4	4p14–15	Ubiquitin C-terminal hydrolase	AD	<45	Rapid	Early onset No rest tremor Early weight loss Late hypotension and dementia	Yes	20
PARK6	1p35–36	Unknown	AR	38 $\pm$ 6 (30–48)	Slow	Early onset Benign course Early dyskinesias	?	5
PARK7	1p36	Unknown	AR	27–40	Slow	Early onset Neurotic signs in 2 over 4 individuals	?	21
FT dementia and parkinsonism	17q21–22	Tau	AD	>30	Rapid	FT dementia Dystonia Pyramidal signs Amiotrophy Vocalisation	—	22
RDP	19q13	Unknown	AD	14–45	Rapid	Acute/subacute onset Levodopa unresponsive	—	23
Dystonia- parkinsonism	Xq13.1	Unknown	X-linked	35 $\pm$ 8 (12–56)	Slow	Early onset Prominent dystonia	—	24

*Juvenile in Japanese families; variable in European families.

AD, autosomal dominant; AR, autosomal recessive; FT, frontotemporal; RDP, rapid-onset dystonia-parkinsonism.

state using average doses of medication, even when patients had a disease course of 20 years or more.

PARK6 disease clinically overlaps also with the classic presentation of *parkin* disease, another early-onset parkinsonism with autosomal recessive transmission. The most obvious overlapping features are a prolonged and sustained response to relatively small doses of dopaminergic medication and the early occurrence of on-state dyskinesias. Other clinical features, such as symmetric involvement or the occurrence of dystonia at disease onset commonly observed in European *parkin* patients,⁴ have not been observed in the present series. Dystonia (unrelated to therapy) is a clinical hallmark of a number of genetically determined parkinsonian disorders with early onset, such as *parkin* disease, levodopa-responsive dystonia, and Lubag,^{14,15} and it is remarkable that PARK6 patients did not present with dystonia. The study of additional PARK6 families will allow us to consolidate this observation.

PARK6 and *parkin* diseases both present at an early age. The average age at disease onset in the present series is older than that of *parkin* patients. European *parkin* disease patients have an average age at disease onset of 32 $\pm$ 11 years,⁴ while age at onset in PARK6 patients in

the present series averaged 38.6 $\pm$ 6 years. Taken as a whole, the clinical presentation of PARK6 patients is in between that of idiopathic, Lewy body, classic PD and that of *parkin* disease. As it has been reckoned that *parkin* disease only accounts for approximately 30% of autosomal recessive familial cases of parkinsonism,¹⁶ PARK6 disease may possibly account for a large share of autosomal recessive parkinsonism. How many patients with sporadic parkinsonism are indeed affected by PARK6 disease, and how many of the patients who receive a clinical diagnosis of PD do actually carry the PARK6 haplotype, are two intriguing questions that remain unanswered. Interestingly, in a recent study,¹⁷ PD patients previously thought to be largely unrelated could be traced to a common ancestor, six generations before the oldest patient.

In conclusion, PARK6 disease appears to be a new form of inherited parkinsonism with early onset but no other atypical clinical features.

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LEGENDS TO THE VIDEOTAPE

Segment 1. Family 1; Subject X:37. An *on* state is demonstrated. This 45-year-old woman noted a short-stepped gait and stiffness of the left leg at the age of 38 years. She had no diurnal fluctuations of symptoms nor sleep-induced benefit. The parkinsonian picture slowly progressed; at the age of 41 years, low doses of levodopa were started with excellent improvement of symptoms, and 4 months later, dyskinesias and wearing-off phenomenon appeared. At the age of 41 years, she had typical features of bilateral Parkinson's disease (PD) and brisk deep tendon reflexes, particularly in the lower limbs. She is presently being treated with levodopa (500 mg/day plus peripheral decarboxylase inhibitor [PDI]) and selegiline (10 mg/day). Mild right hemifacial hypomimia and mild bradykinesia of the right limbs are visible while sitting. Reduced arm swinging and typical posturing of the right hand are evident during gait. On the pull test she recovers unaided.

Segment 2. Family 1, Subject X:21. The *on* condition is demonstrated. This 74-year-old man noted tremor and stiffness in the legs, particularly on the left, at the age of 45 years. Over the following 8 years the symptoms progressed to involve all four limbs; tremor, akinesia, and rigidity worsened. Since age 45 years, he has been taking levodopa and trihexyphenidyl. After a few years of treatment, he developed dyskinesias; levodopa was reduced and dopamine agonists were started. At the time of clinical evaluation, he had a 29-year history of PD and was taking levodopa (300 mg/day plus PDI) and pergolide (4 mg/day). When the patient is sitting, a resting tremor in the legs, both abduction-adduction and flexion-extension, is apparent, and is more pronounced on the right leg. Hypokinesia is revealed by hand and finger tapping and by rapid alternating movements of the hands (more pronounced on the right). Foot tapping is impaired bilaterally. When the patient is standing, an abnormal stooped posture of the trunk is evident.

Segment 3. Family 1; Subject X:31. An *on-off* transition occurring 2½ hours after levodopa intake is shown. This 52-year-old man noted tremor and impaired movements in the right arm at the age of 32 years. During the following 5 years, he developed bilateral, tremulous PD. At the time of clinical evaluation, he presented with severe tremor, akinesia, and severe parkinsonian gait. Response to levodopa and dopamine agonists was good, but in the *on* condition, he had disabling, drug-induced dyskinesias. The patient is currently being treated with levodopa (800 mg/day plus PDI) and per-

golide (3 mg/day). While the patient is sitting, there are severe dyskinesias affecting the head, trunk, and limbs, and a brief run of resting tremor in the right hand. Brief intermittent involuntary upward deviations of the eyes accompanied by mild retrocollis movements appear several times during the recorded segment. Voluntary eye movements are normal. Dyskinesias interfere with the task of foot tapping. When the patient walks, steps are short and freezing occurs.

Segment 4. Family 2; Subject IV:7. An incomplete *off* condition is shown. This 42-year-old woman started complaining of gait problems, caused by stiffness and short steps in the left leg, at the age of 30 years. No diurnal fluctuations of symptoms were reported. The parkinsonian picture slowly progressed, and at the age of 33 years she started dopamine agonists. She is now being treated with pramipexole (5 mg daily). No drug-induced dyskinesias have occurred. Pramipexole was discontinued for 12 hours before video recording; hence, the *off* condition is incomplete. Moderate hypomimia is evident and blinking is almost absent. With the arms outstretched, inconstant tremor occurred in the right hand (not visible in this sequence). Finger and hand tapping are impaired; foot tapping is moderately slowed (akinesia is more pronounced in the right limbs). When the patient walks, posture is stooped, steps are short, she drags the right leg slightly, and right arm swinging is reduced compared with the left.

Segment 5. Family 3; Subject IV:31. The *on* state is illustrated. This 56-year-old man presented left-dominant resting tremor in the arms at the age of 31 years. During the following months, rigidity and akinesia became evident. Symptoms progressed in the following 15 years but were efficaciously controlled by levodopa. Drug-induced dyskinesias and the wearing-off phenomenon appeared late in the disease course, about 15 years after starting levodopa. Currently the patient is treated by continuous infusion of apomorphine, as oral drugs failed to control his fluctuations. In the first part of the recording, the patient is singing. His facial expression, the volume of his voice, and the prosody are normal. Dyskinesias are evident involving the shoulders (left more than right). During hand movements, a mild tremor is intermittently present in the right hand (not shown here). Finger tapping is smoothly performed in both sides; during finger tapping a trunkal dyskinesia resembling a myoclonic jerk is visible. Hand tapping is normal. The patient stands up from a low sofa after two attempts.

Segment 6. Family 3; Subject IV:33. Examination 5 hours after levodopa intake (100 mg plus PDI). This 49-year-old man reported resting tremor and akinesia in the left limbs since the age of 37 years. He was treated

early with a low dosage of levodopa (100 mg/day plus PDI); the same doses were effective in controlling symptoms for the following 5 years. The patient also reported mild *on-state* dyskinesias that were not observed during examination. He is currently treated daily with levodopa (300 mg) and trihexyphenidyl (4 mg). While sitting there is no resting tremor in the hands, and mild left hemifacial hypomimia is appreciable; a mild tremor of the left hand appears at the end of hand movements. There is fatiguing of alternating wrist movements (more in the left hand) which then develops a tremor. Finger tapping looks almost normal. Arm swing is inconstantly reduced on the left side while walking.

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