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Autosomal dominant Parkinson's disease in a large German pedigree

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Objective – While several genes have been identified to cause Parkinson's disease (PD), monogenic forms explain only a small proportion of cases. We report clinical and genetic results in a large family with late-onset autosomal dominant PD. *Methods* – Thirty-eight family members of a five-generation Northern German PD family underwent a detailed neurologic examination, and transcranial sonography was performed in fifteen of them. Comprehensive mutation analysis of known PD-causing genes and a genome-wide linkage analysis were performed. *Results* – Late-onset definite PD was found in five subjects with a mean age at onset of 63 years. Another six individuals presented either with probable/possible PD or with subtle parkinsonian signs. Six members with a mean age of 79 years had an essential tremor phenotype. Mode of PD inheritance was compatible with autosomal dominant transmission. One of three examined patients with definite PD demonstrated an increased area of substantia nigra hyperechogenicity upon transcranial sonography. Comprehensive linkage and mutational analysis excluded mutations in known PD-causing genes. Genome-wide linkage analysis suggested a putative disease gene in an 11.3-Mb region on chromosome 7p15–21.1 with a multipoint LOD score of 2.0. *Conclusions* – The findings in this family further demonstrate genetic heterogeneity in familial autosomal dominant late-onset PD.

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Key words: genetics; linkage analysis; movement disorders; parkinson's disease

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Introduction

Parkinson's disease (PD) is a common disabling neurodegenerative disorder characterized by bradykinesia, rest tremor, rigidity, and postural instability with a prevalence of 2% in elderly persons (1). Although the causative mechanisms are poorly understood for the classical form of PD, a genetic contribution to its etiology has unambiguously been demonstrated. To date, at least eight genes have been identified in families with inherited parkinsonism, either with an autosomal recessive mode of inheritance [*Parkin/PARK2* (2), *PINK1/-PARK6* (3), *DJ-1/PARK7* (4), *ATP13A2/PARK9* (5), *PLA2G6/PARK14* (6), and *FBXO7/PARK15* (7)] or dominant transmission [*SNCA/PARK1* (8) and *LRRK2/PARK8* (9, 10)]. Moreover, several genes were shown to influence the susceptibility to or the age of onset of PD although the results are partially inconsistent, for example, as for polymorphisms in the apolipoprotein E gene (11, 12).

Although parkinsonism is the clinical hallmark of all of these inherited forms, there is evidence for marked intrafamilial phenotypic variability including cognitive and psychiatric disturbances, dystonia, or isolated tremor in at least a subset of pedigrees. In some cases, there is also phenotypic overlap with a subtype of hereditary frontotemporal lobar degeneration combined with parkinsonism, caused by mutations in the

microtubule-associated protein tau (*MAPT*) and *Progranulin* (*GRN*) genes on chromosome 17 (FTD-P17) (13, 14).

Despite the detection of all of these PD- or parkinsonism-causing genes, monogenic forms explain only a minority of cases. Most of these forms are associated with early onset or atypical features. The exclusion of known genetic causes in families with autosomal dominantly transmitted PD suggests an even larger genetic heterogeneity and the existence of yet unknown genes involved in the etiology of PD (15, 16).

In this report, we present clinical characteristics and genetic results of a new five-generation Northern German pedigree with autosomal dominantly inherited late-onset PD.

Patients and methods

Patients

The study protocol was approved by the local ethics committee of the University of Lübeck, Germany. After obtaining written informed consent, 38 members of a multigenerational PD family from Northern Germany underwent a detailed neurologic examination by at least one experienced movement disorders specialist (NB, VT). There was no history of consanguinity in this family. Five additional subjects (V:2, V:3, V:5, VI:1, and VI:2), aged 11–48 years, were not available for personal clinical examination. Information on clinical status was obtained through a telephone interview with one of these five family members who works as an internist. The pedigree of this family was constructed using the CYRILLIC 2.0 software (Fig. 1).

All personally examined family members were videotaped using the Unified Parkinson's Rating Scale (UPDRS) Part III protocol. A consensus diagnosis was obtained based on the findings of the onsite examiner and the results of the videotape review by two additional blinded members of the movement disorders team (JH, CK). Clinical evaluation comprised the UPDRSIII rating scale and Hoehn and Yahr classification in all examined participants and, additionally, UPDRSI, II, and IV in selected cases. A definite diagnosis of PD was established according to the United Kingdom Brain Bank Criteria with the exception that a positive family history was not regarded an exclusion criterion (17). At least three supportive criteria were required for the diagnosis of definite PD.

Subjects presenting with the combination of at least mild bradykinesia (sum of UPDRS III items 24–26 and 31 ≥ 2) and one additional cardinal PD sign with an unknown response to levodopa were considered to have probable parkinsonism. Possible parkinsonism was diagnosed when only bradykinesia was present. Presence of subtle motor signs such as reduced arm swing (passive and on walking) and isolated tremor was noted separately. Family members who were aware of their motor signs were classified as 'symptomatic'.

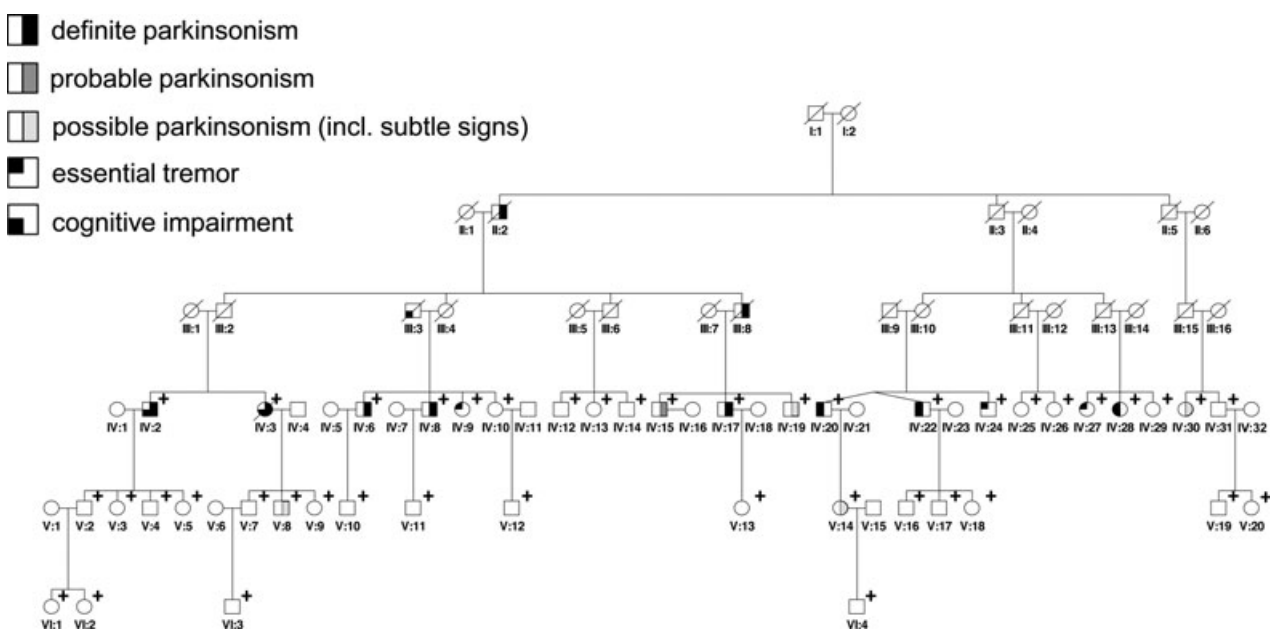

Figure 1. Pedigree of the described Northern German multigenerational family. All investigated individuals are marked with a plus sign. Slashes indicate deceased individuals.

Cognitive function was established by history and using the Mini Mental State Examination Test (MMSE) as well as the Montreal Cognitive Assessment (MoCA) in 28 family members. MMSE and MoCA scores below 26 were regarded pathologic. The University of Pennsylvania Smell Identification Test [UPSIT, Haddonfield, NJ, USA (18)] was used to test olfaction in 20 family members. Scores ranged from 0 to 40; subjects with scores >33 (man) and >34 (woman), respectively, were considered to have normosmia. Color discrimination was tested with the Farnsworth Munsell 100 Hue Test in 19 cases. A total error score of 0–16 was classified as superior discrimination, 20–100 as average, and more than 100 as low discrimination according to normative data. Clinical status of unavailable and deceased relatives was gathered by family history interview and analysis of a handwriting sample in one individual (micrography in II:2).

Transcranial sonography

Transcranial sonography (TCS) of the brain parenchyma was performed by an experienced sonographer (J. H.) blinded for the clinical status using a SONOS 5500 ultrasound system (Philips Healthcare, Amsterdam, The Netherlands) in connection with a 2.0–2.5 MHz sector transducer (S3 probe; Philips) on 15 family members including three patients with PD. Examinations were conducted through the temporal bone window from both sides. Only the ipsilateral side was evaluated in a standardized axial mesencephalic plane (landmark: butterfly-shaped brainstem) with a maximum depth of 14 cm. Images were digitally stored. The area of SN signal (aSN) was manually encircled and calculated by an independent rater (NB) with a public domain graphics software tool (Scion Image Beta 4.02 Win software package). The maximum aSN (aSNmax) was selected for further statistical analysis. Values >0.27 cm^2 were considered abnormally increased.

Genetic testing

For genetic experiments, blood samples were collected from 43 family members and genomic DNA was extracted according to standard procedures. The proband (IV:6) was comprehensively tested for mutations by sequence analysis of all coding exons and exon–intron boundaries in *SNCA, Parkin, PINK1, DJ-1, MAPT,* and *GRN* and exons 19-51 in *LRRK2*. Gene dosage variations were tested for by MLPA of all exons of *SNCA*, *Parkin*, *PINK1,* and *DJ-1* as well as of *LRRK2* exons 1, 2, 10, 15, 27, 41, and 49. The proband and individual IV:22 with predominant severe tremor and cognitive decline were tested for premutations (55–200 CGG repeats) in the *fragile X mental retardation 1* gene (*FMR1*).

In addition, linkage to *SNCA, Parkin, PINK1, DJ-1, ATP13A2,* and *LRRK2* was excluded using microsatellite markers in the respective genomic regions.

Furthermore, we tested genomic DNA of patient IV:8 for subtle chromosomal imbalances by array comparative genomic hybridization using the Human Genome Microarray 244A platform, which contains 238,381 60-mer oligonucleotides distributed across the human genome (Agilent, Santa Clara, CA, USA). Array CGH was performed according to standard protocols (19). For evaluation, we applied the Aberration Detection Method-2 (ADM-2) algorithm of the Agilent CGH Analytics software with a threshold of 6.0. Significant chromosomal gains and deletions were defined by a log2 ratio of 10 neighboring oligonucleotides exceeding 0.4 and corresponding to an average resolution of approximately 100 kb. Known copy number variations/polymorphisms were identified with the database integrated into the Agilent CGH Analytics software.

In a next step, we performed a genome-wide linkage analysis on 13 family members with 423 short tandem repeat markers and an average distance of about 10 cM (WK). For statistical linkage analysis, we performed model-based two-point and multipoint calculations using the ALLEGRO 2.0 software (20). Allele frequencies for all markers were set to be equal. Definitely and probably affected individuals were considered as 'affected', married-ins as 'unaffected', and all others (including individuals with possible parkinsonism and/or subtle motor signs) as 'unknown', to reflect the reduced and age-dependent penetrance of PD (Fig. 2). An autosomal dominant mode of inheritance was assumed with a penetrance of 0.95, a frequency of the disease allele of 0.01, and a phenocopy rate of 0.03. We performed a fine-mapping analysis in regions with a multipoint LOD score of 0.5 and higher with 84 microsatellite markers. Haplotypes were constructed manually based on the smallest number of inferred recombinations. Based on our pedigree, the power to detect a LOD score >2 was $<20\%$ (this was obtained for a simulated marker explaining 100% of a total heritability of 0.90, placed at 2-cM distance from the disease marker). The power was estimated with SOLAR version 4.2.0 (21). Biallelic markers were simulated with minor allele frequencies ranging between 0.10 and 0.30. For each scenario, we assumed that the total heritability of PD was 0.30, 0.40, 0.50, 0.70, and 0.90.

	Criteria	Individual no.	Condition state *	Symptom state
Definite parkinsonism	United Kingdom Parkinson's Disease Society brain bank diagnostic criteria [15]	IV:2 IV:3 IV:6 IV:8 IV:17	'affected'	symptomatic
Probable parkinsonism	Mild bradykinesia, one additional cardinal sign, unknown response to levodopa	IV:15	'affected'	symptomatic
Possible parkinsonism	Bradykinesia only, unknown response to levodopa	IV:19	'unknown'	symptomatic
Subtle motor signs	e.g. unilaterally reduced armswing, slight rigidity	IV:25 IV:30 V:8 V:14	'unknown'	asymptomatic

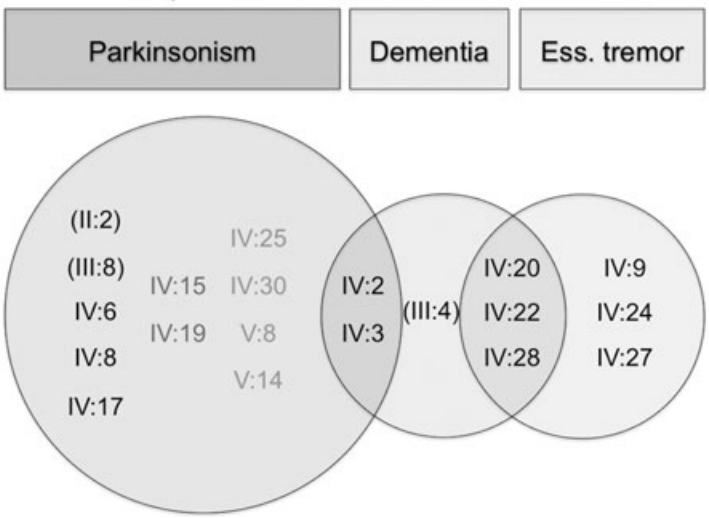

Figure 2. Phenotypic overlap of the different motor and non-motor phenotypes of the family. In the group with parkinsonism, definitely affected patients are marked in black, probably or possibly affected patients in dark gray, and individuals with subtle signs in light gray. Individuals in parenthesis have not been personally examined. Note that none of the individuals in the parkinsonism group had ET and *vice versa*. *The clinical status of individuals with possible parkinsonism and subtle motor signs was labeled 'unknown' for the genome-wide linkage analysis.

All coding exons and exon–intron boundaries of five genes in the linked region [*ATP-binding cassette, subfamily B, member 5* (*ABCB5*), *Serine/threonine kinase 31* (*STK31*), *cAMP response element-binding protein 5* (*CREB5*), *interleukin 6* (*IL6*), *cytochrome C, and somatic* (*CYCs*)] were sequenced bidirectionally in two affected individuals using a *Genetic Analyzer 3130* (Applied Biosystems, Foster City, CA, USA). Primer sequences are available on request.

Results

Clinical findings

Late-onset definite PD was found in five personally examined subjects, four of them men, with a mean age of 72 years (range 61–78), mean age at onset of 63 years (range 53–70), and a mean disease duration of 8.4 years (Table 1, Figs 1 and 2). PD was associated with severe hyposmia in this family. Four patients were treated for PD and responded well to dopaminergic medication at least in the early stages of the disease. One man (IV:15), aged 65 years, was probably and his 56-year-old brother (IV:19) was possibly affected. Another four family members showed subtle motor signs but were asymptomatic (one man, mean age 59 years, range 44–71 years).

Six individuals with a mean age of 79 years (three men, range 70–83) had postural and action tremor in terms of an essential tremor (ET) (Table 2). Response to alcohol was unknown; propanolol moderately improved tremor in one

Table 1 Clinical features and test results of the five definitely affected patients with PD

	IV:2	IV:3	IV:6	IV:8	IV:17
Gender	Male	Female	Male	Male	Male
Age at examination (years)	78	76, deceased in 2008	74	71	61
Age at PD onset (years)	70	62	65	66	53
Symptom state	Sympt.	Sympt.	Sympt.	Sympt.	Sympt.
Parkinsonian signs	B, R, PI	B, R, PI	B, R	B, R, RT	B, R, PI
Asymmetry	Initially asymmetric, meanwhile symmetric	Initially asymmetric, meanwhile symmetric	Left	Right	Right
Response to levodopa/DA	Good	Moderate (initially good)	Good	Not tested	Moderate, tremor responded only partially
UPDRSI	n.t.	n.t.	4	0	2
UPDRSII	n.t.	n.t.	11	2	4
UPDRSIII	64	>60	25	10	34
UPDRSIV	n.t.	n.t.	0	0	0
Hoehn and Yahr stage	5	5	3	1,5	2,5
Levodopa-induced dyskinesia	–	–	–	n.a.	–
UPSIT (max 40)	Reported anosmia for >40 years	n.t.	4	13	22
Dementia	+	+	–	–	– (MMSE 23[a], MoCA 27)
Frontal release signs	+	+	+	–	–
Visual hallucinations	+	+	+	–	–
Falls	+	+	–	–	–
Depression	–	+	–	–	–
TCS aSN max (cm^2)	n.t.	n.t.	0.32	0.250	0.18
Neuroimaging	Initially regular MRI	Global brain atrophy[b]	Global brain atrophy[b]	Marked perisylvian brain atrophy[b]	–

B, bradykinesia; R, rigidity; RT, rest tremor; PI, postural instability; MoCA, Montreal Cognitive Assessment; n.t. , not tested; n.a., not applicable.

[a]Poor school education.

[b]Performed in an advanced diseased stage.

Table 2 Clinical features and additional test results of the six affected patients with essential tremor

	VI:9	VI:20	VI:22	VI:24	VI:27	VI:28
Gender	Female	Male	Male	Male	Female	Female
Age at examination (years)	70	82	82	78	83	80
Symptom state	Sympt.	Sympt.	Sympt.	Sympt.	Asmpt.	Sympt.
Duration of tremor	≈10 years	≈10 years	Decades	≈20 years	n/a	≈30 years
Rest tremor	No	No	No	No	No	Head/jaw tremor
Postural tremor	Moderate	Moderate	Moderate	Moderate	Mild	Marked
Action tremor	Moderate	Mild	Marked	Moderate	Mild	Marked
Asymmetry of tremor	(Right)	No	No	(Left)	No	(Right)
UPSIT (max 40)	35	n.t.	n.t.	28	n.t.	n.t.
Age at onset of cognitive decline	n.a.	80	75	n.a.	n.a.	unknown
Frontal release signs	–	+	+	–	+	–
MMSE	n.t.	25	14	30	28 (MoCA 28)	26 (MoCA 22)

Sympt., Symptomatic; Asympt., Asymptomatic; n.t. , not tested; n.a., not applicable.

subject (IV:29). The tremor had been present for more than 5 years in all cases.

At a mean age of 80 years, five subjects (three men, range of age 76–82 years) presented with cognitive decline, ranging from mild cognitive impairment to severe dementia. Two of them had PD (IV:2 and IV:3), whereas the remaining three patients presented with isolated postural and kinetic tremor (IV:20, IV:22, and IV:28) (Figs 1 and 2). The onset of dementia did not precede the onset of PD.

Among the deceased relatives, two male subjects were described to have late-onset PD (II:2 and III:8); another subject had suffered from amyotrophic lateral sclerosis (ALS, III:11). One female patient had had dementia and a history of anosmia for decades without evidence for clear PD (III:4).

Case reports of two selected patients with PD

Case IV:2 – This 78-year-old male patient developed mild dysfunction of his short-term memory, spontaneous weight loss, and depressive symptoms at the age of 70 years. His medical history was remarkable for anosmia since the age of 30 years. By the age of 72 years, he developed asymmetric hypokinetic-rigid parkinsonism. Neurologic examination 3 years after onset of first motor symptoms revealed hypomimia, dysarthrophonia, micrography, generalized bradykinesia, moderate impairment of fine motor skills, and rigidity predominantly in the right extremities. Gait was small-stepped and shuffling with absence of arm swing on the right. Rest tremor and marked postural instability were absent. At this stage, he had an MMSE score of 25 points, indicative of mild dementia. The patient's wife reported that his motor symptoms were responsive to levodopa (at the last visit 700 mg daily). FP-CIT-SPECT revealed absence of presynaptic tracer uptake in the left putamen corresponding to the clinically more affected right side and massive reduction in the right putamen and caudate nucleus bilaterally. Cognitive function deteriorated gradually over the years resulting in severe disorientation to place and time. Approximately 5 years after disease onset, he suffered from medication-induced visual hallucinations, fluctuating vigilance, and frequent falls because of impaired postural reflexes. At the age of 77 years, he developed a spontaneous coma for 4 days unrelated to medication and metabolic changes. At the last visit at the age at 78, the patient was almost completely wheelchair-bound. He presented with a severe, symmetric akinetic-rigid syndrome, stooped posture, and loss of postural reflexes (UPDRSIII 64/108). He was able to follow simple instructions but did not speak spontaneously.

Case IV:6 – This 74-year-old retired architect noticed first problems while Nordic walking at the age of 65 years. He further complained about a reduced sense of smell for approximately 35 years. Following an unrelated surgery 2 years later, symptoms of impaired fine motor skills on the left advanced substantially but showed a good response to levodopa. At the last visit, he presented with decreased facial expression and hypophonia, stooped posture, moderate arm rigidity predominantly of the left arm, and bradykinesia in the ON-state (UPDRSIII 25). He developed visual delusions with full insight and REM-sleep behavior disorder, which was successfully treated with clonazepame. He displayed anosmia and low color discrimination (TES 368).

TCS of the brain parenchyma

We analyzed the SN of 15 family members and a control group consisting of 64 unrelated healthy probands. One definitely affected patient (IV:6) showed a distinctly increased aSN max of 0.32 cm^2, whereas the remaining 14 members, including another two definite patients with PD and one proband with unilateral tremor, had aSN max values < 0.27 cm^2. The aSN max values of all examined family members in relation to the regression (±95% confidence interval) of age and hyperechogenicity of the control group are shown in Fig. 3.

Genetic findings

Mutations in *SNCA, Parkin, PINK1, DJ-1, LRRK2, ATP13A2, MAPT,* and *GRN* were excluded in the proband. Likewise, premutations in the *FMR1* gene were absent in both tested individuals. Linkage analysis confirmed exclusion of the known gene loci.

High-resolution array CGH revealed six common copy number variants without known pathogenetic relevance and a 500-kb deletion on chromosome 5q21.1 [arr cgh 5q (101516850 → 102020144)×1 (NCBI Build 35)]. Part of this deletion corresponds to another common copy number variant without known pathogenicity. The deletion was investigated by linkage analysis and did not segregate with the PD phenotype in the family.

By genome-wide linkage analysis, we observed 13 regions with multipoint LOD scores of 0.5 and higher. Four of them on chromosomes 1, 3, 4, and

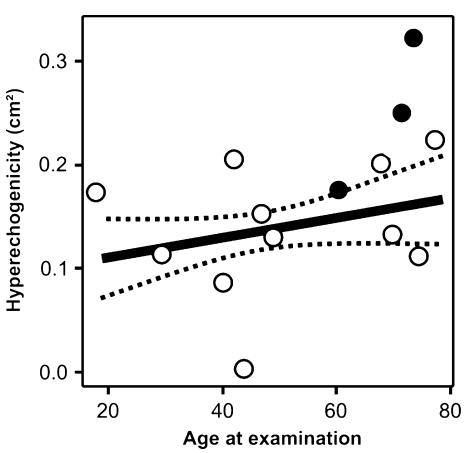

Figure 3. Values for the aSN max of three definitely affected patients (black dots) and 11 unaffected family members (white dots) in relation to the regression of age and hyperechogenicity of the control group.

7 showed multipoint LOD scores of at least 1.5 (Fig. 4). Fine mapping revealed a shared haplotype in all affected family members only on chromosome 7. It comprised an 11.3-cM region (according to the Marshfield map) between markers D7S3051 (at 18.3 Mb, 7p21.1) and D7S2496 (at 29.6 Mb, 7p15) in all definitely and probably affected family members. This haplotype was also found in one possibly affected family member (IV:19) and one member with subtle motor signs (V:8) in the 'PD branch' of the family as well as in the unaffected individual V:9, currently aged 40 years, but not in individuals with isolated tremor, irrespective of the presence of cognitive decline. A maximum multipoint LOD score of 2.0 was obtained for markers D7S3048 and D7S2562.

In the candidate regions on chromosomes 3, 4, and 22, at least one affected individual did not share the disease haplotype. At the remaining loci, two to five affected subjects did not carry the disease haplotype.

In the linked region on chromosome 7, 91 genes have been reported including several candidate genes for PD based on their known function or expression pattern. Of these, we chose *ABCB5, STK31, CREB5, IL6,* and *CYCs* as candidates, but did not detect any potential disease-associated variant.

Discussion

We here present a German family with autosomal dominant PD, in whom detailed mutational analysis excluded known genetic factors pointing toward the existence of a yet unknown PD-causing gene.

There are several clinical features consistent with idiopathic PD including late-onset, severe hyposmia prior to the first motor symptoms, asymmetric symptom distribution, absence of pyramidal and cerebellar signs, a (slowly) progressive disease course, and cognitive impairment in some affected individuals. In contrast, some features are not typical of idiopathic disease, such as the absence of levodopa-induced dyskinesias even after 10 years. Several clinical characteristics overlap with *LRRK2*- and, in part, *SNCA*-associated PD (8–10, 22–25). Apart from rare point mutations in the *SNCA* gene, *SNCA* duplications and triplications can also cause PD and are more common than point mutations (22, 26, 27). While triplications are associated with an early onset, rapid progression, and dementia in up to 100% of cases, duplications are causing a less-severe phenotype, more similar to idiopathic disease, and the PD phenotype in our family (22, 26, 27).

The dramatically reduced basal ganglia FP-CIT uptake in patient IV:2 shows the presynaptic involvement in this family. Although post-synaptic striatal dopaminergic function was not investigated by neuroimaging, the sustained response to dopaminergic treatment argues against relevant post-synaptic degeneration. Upon TCS, the area of SN hyperechogenicity was increased in only one of three definitely affected patients, which was unexpected given the overall resemblence to idiopathic

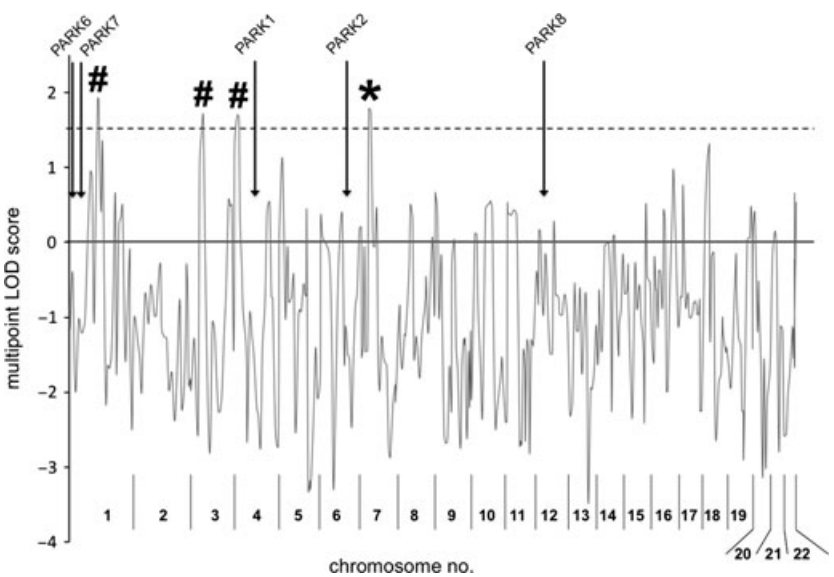

Figure 4. Multipoint LOD score curves for the genome-wide linkage analysis in this family. Four regions on chromosomes 1, 3, 4, and 7 showed multipoint LOD scores of at least 1.5 (dotted line). Fine mapping excluded three of them (#), leaving one region (*) on chromosome 7. The chromosomal locations of known monogenic causes are marked with an arrow.

PD, where 90% of patients clearly show this sonographic hallmark (28). Similarly, patients with *LRRK2*-, *SNCA*-, *Parkin*-, and *PINK1*-associated PD have an increased area of SN hyperechogenicity comparable with idiopathic PD (29). Currently, Kufor-Rakeb syndrome, an atypical recessively inherited form of parkinsonism with mutations in the *ATP13A2* gene, is the only known monogenic form that is not associated with this echofeature (30).

Apart from the PD phenotype in this family, there were other potential phenotypes such as probable ET and dementia in the expanded pedigree (Fig. 2). Occasionally, familial ET and familial PD co-occur within the same pedigree as presented here, and it is well known that ET is more frequent in relatives of patients with PD (31, 32). In a Mexican family with early-onset monogenic PD, however, ET did not co-segregate with homozygous or heterozygous *Parkin* mutations (33). There was also no co-segregation in a large Cuban PD family with linkage to chromosome 19 (34). Despite recent efforts and advances in genetic research, no shared monogenic cause has yet been identified and not even a single gene has so far been linked with familial essential tremor. Based on this (lack of) evidence from the literature, we conclude that the presence of a shared genetic cause is unlikely in this family.

The genome-wide linkage analysis in the patients with the PD phenotype did not reach the threshold of 3.0 indicating significant linkage as only five definitely affected individuals were available, instead of the eight to ten required to establish significant linkage. Novel molecular techniques such as next generation sequencing will be helpful to identify the exact underlying genetic variation for PD in this family.

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Conflict of interest

There are no conflicts of interests.

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