

The PARK8 Locus in Autosomal Dominant Parkinsonism: Confirmation of Linkage and Further Delineation of the Disease-Containing Interval

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Recently, a new locus (PARK8) for autosomal dominant parkinsonism has been identified in one large Japanese family. Linkage has been shown to a 16-cM centromeric region of chromosome 12, between markers D12S1631 and D12S339. We tested 21 white families with Parkinson disease and an inheritance pattern compatible with autosomal dominant transmission for linkage in this region. Criteria for inclusion were at least three affected individuals in more than one generation. A total of 29 markers were used to saturate the candidate region. One hundred sixty-seven family members were tested (84 affected and 83 unaffected). Under the assumption of heterogeneity and through use of an affecteds-only model, a maximum multipoint LOD score of 2.01 was achieved in the total sample, with an estimated proportion of families with linkage of 0.32. This LOD score is significant for linkage in a replication study and corresponds to a *P* value of .0047. Two families (family A [German Canadian] and family D [from western Nebraska]) reached significant linkage on their own, with a combined maximum multipoint LOD score of 3.33, calculated with an affecteds-only model (family A: LOD score 1.67, *P* = .0028; family D: LOD score 1.67, *P* = .0028). When a penetrance-dependent model was calculated, the combined multipoint LOD score achieved was 3.92 (family A: LOD score 1.68, *P* = .0027; family D: LOD score 2.24, *P* = .0007). On the basis of the multipoint analysis for the combined families A and D, the 1-LOD support interval suggests that the most likely disease location is between a CA repeat polymorphism on genomic clone AC025253 (44.5 Mb) and marker D12S1701 (47.7 Mb). Our data provide evidence that the PARK8 locus is responsible for the disease in a subset of families of white ancestry with autosomal dominant parkinsonism, suggesting that it could be a more common locus.

Introduction

Parkinsonism (MIM 168600) is a clinical syndrome defined by a characteristic constellation of signs and symptoms, including bradykinesia, rigidity, resting tremor, and postural instability. The most common cause of parkinsonism is Parkinson disease (PD). Patients with PD respond to dopaminergic therapy. PD is pathologically characterized by a selective degeneration of dopaminergic

neurons of the substantia nigra, leading to a deficiency of dopamine in their striatal projection areas. Characteristic eosinophilic inclusions, termed "Lewy bodies" (LBs) are the pathological hallmark required for a diagnosis of definite PD (Gibb and Lees 1989).

A major breakthrough in recent years was the mapping and cloning of a number of genes that cause monogenically inherited forms of parkinsonism with different associated pathologies and a variable, but overlapping, spectrum of clinical signs and symptoms. Mutations in the gene for α -synuclein are responsible for disease in a small number of families with autosomal dominantly inherited parkinsonism (PARK1 [MIM 168601]) (Polymeropoulos et al. 1997; Kruger et al. 1998). Patients with this mutation show typical levodopa-responsive parkinsonism, but they also frequently show dementia and, in some cases, other neurologic abnormalities

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(Spira et al. 2001). Pathologically, α -synuclein aggregates in LBs, as in typical sporadic PD, but tau pathology has also been recognized (Duda et al. 2002; Ishizawa et al. 2003). Tau deposits in neurons and glial cells are the major pathological abnormality observed in affected individuals with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17 [MIM 600274]). Some of these families present clinically with parkinsonism, although it is poorly responsive to levodopa therapy. There are now >30 known tau mutations found in >80 kindreds (Ghetti et al. 2003).

Although only two disease-causing mutations have been found in the α -synuclein gene, a large number of pathogenic mutations have been identified in the parkin gene on chromosome 6 (PARK2 [MIM 60254]) (Kitada et al. 1998). These mutations cause autosomal-recessive early-onset parkinsonism, a form of the disease that is characterized pathologically by a severe and selective degeneration of dopaminergic neurons, usually without LBs (Ishikawa and Takahashi 1998; Mori et al. 1998), although alternate pathologies have been described in compound heterozygous cases (Farrer et al. 2001a; van der Warrenburg et al. 2001; Morales et al. 2002). Parkin has been found to function as a ubiquitin ligase (Shimura et al. 2000), suggesting a key role of the ubiquitin-protein degradation pathway in the molecular pathogenesis of dopaminergic cell death. The importance of this pathway is further emphasized by the discovery of a mutation in another gene involved in protein ubiquitination, ubiquitin C-terminal hydrolase (UCHL1; PARK5 [MIM 191342]), in a small family with parkinsonism (Leroy et al. 1998). A nonsynonymous polymorphism (S18Y) in that gene was found to be associated with a reduced risk for developing PD (Maraganore et al. 1999).

Recently, mutations in the gene DJ-1 have been found to cause another recessive form of early-onset parkinsonism (PARK7 [MIM 602533]) (Bonifati et al. 2003). Several other loci for monogenic recessive and dominant forms of inherited parkinsonism have been mapped, but the respective genes have not been identified yet. One such locus for levodopa-responsive parkinsonism has been identified on chromosome 12, in a large Japanese family with autosomal-dominant inheritance (PARK8 [MIM 607060]) (Funayama et al. 2002). Affected individuals in this family showed typical levodopa-responsive parkinsonism with onset in their 50s. Pathologically, nigral degeneration was found without distinctive inclusions.

Here we provide evidence that the PARK8 locus is responsible for disease in a subset of families of white ancestry with autosomal-dominant parkinsonism. However, on careful clinical examination, signs of dementia, supranuclear gaze palsy, and motoneuron degeneration were also found in some affected individuals, and path-

ological examination showed a range of α -synuclein and tau pathology, suggesting a remarkably wide spectrum of phenotypes of PARK8-linked parkinsonism.

Material and Methods

Clinical Studies

Twenty-one families with three or more affected persons, consistent with autosomal dominant inheritance, were included in the study. A description of the genealogical and clinical methods used in the study of parkinsonian kindreds are detailed elsewhere (Denson and Wszolek 1995). Some of the families had been included into linkage previously, with no evidence for linkage to PARK1 and PARK3 in families A, D, M3, and M6. (Gasser et al. 1997, 1998; T.G. and A.Z., unpublished observations). Disease in patients was diagnosed according to the U.K. Brain Bank or Calne's criteria (Calne et al. 1992; Daniel and Lees 1993).

Positron Emission Tomography (PET) Studies

PET studies were performed through use of an ECAT 953B scanner in 3-D mode with 6- 18 F]fluoro-L-dopa (FD) on two affected and two unaffected members of family D and with 11 C]raclopride (RAC) on one affected family member. Details on the PET studies will be presented elsewhere (D.B.C., J.S., and Z.W., unpublished data).

Pathological Studies

Every effort was made to obtain fixed and frozen brain at autopsy, through use of standard methods (Ishizawa et al. 2003). Previously collected pathological material was retrieved and reexamined.

Genetic Studies

The following microsatellite markers on chromosome 12, spanning the published disease locus, were used (the sex-averaged map positions, in centimorgans, are given in parentheses): D12S310 (34.62), D12S1042 (46.52), D12S87 (49.42), D12S345 (50.67), D12S1592 (54.17), D12S1653 (54.54) D12S291 (54.99), D12S1301 (55.52), D12S1663 (55.68), AC024934, AC025253, AC018923, AC079033, AC08127, AC084878, AC025031, AC008014, AC080136, D12S85 (58.42), AC0044861, D12S1701 (59.70), AC008083, D12S1661 (60.66), D12S2196 (60.67), D12S339, (60.84), D12S1635 (61.82), D12S1629 (62.43), D12S368 (63.15), and D12S398 (65.69). The map positions of these markers were obtained by calculating the arithmetic mean of the sex-specific distances taken from the Genetic Location Database, through use of MAP-O-MAT version 1.0b (MAP-O-MAT Web site). To saturate the PARK8 region,

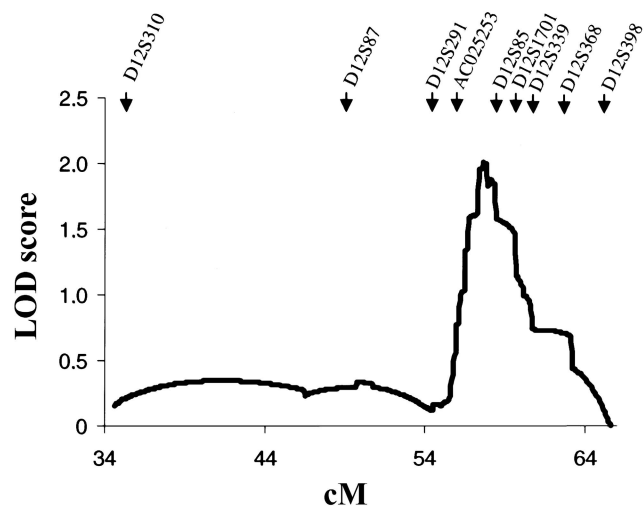


Figure 1 Linkage analysis of all 21 pedigrees with autosomal dominant Parkinson disease. Affecteds-only multipoint LOD scores are summed across families.

we developed new polymorphic markers (underlined in the above list) by searching the database for CA repeats through use of *in silico* BAC sequence (University of California Santa Cruz [UCSC] Human Genome Browser Web site). Since the genetic positions for these markers are not defined in the database, their positions were estimated by linear interpolation.

Genomic DNA from peripheral blood lymphocytes was extracted after obtaining informed consent from all participating family members. DNA fragments containing the polymorphic marker sequences were amplified by PCR (primer sequences are available upon request). Fluorescently labeled PCR products were analyzed on ABI 310 and ABI 377 automated sequencers with a fluorescence detection system. Linkage analysis was performed using MLINK for pairwise and FASTMAP for multipoint LOD scores in all families, allowing for genetic heterogeneity. The admixture test was applied as developed by Smith (1963).

Marker allele frequencies were based on all individuals genotyped. If allele frequencies were based on founders (estimated using ILINK), the results were not significantly different throughout. Differences were usually markedly less than 0.1 LOD units.

We assumed autosomal-dominant inheritance with an age-dependant penetrance. Penetrance was set at 20% for the decade between 20 and 30 years, 30% for the decade between 30 and 40 years, and so forth. Individuals aged ≥ 70 years were assigned to the class with the highest penetrance, 70%. The frequency of the deleterious allele was set at 0.001. The estimates for the age-dependent penetrances were based on two observations: (1) that ages at onset seemed uniformly distributed over

all age decades except for the very youngest ones, indicating a constant increase in penetrance over all relevant age decades; and (2) that an overall estimate resulted in a penetrance of 69.2% at the age of 70 years (18/26 putative gene carriers affected). It should be noted that these estimates are necessarily based on a selected sample (pedigrees ascertained for linkage analysis) and that this sample size is also limited. In two affected individuals, date of birth, age at death, and age at onset were not available. These individuals were classified in a separate liability class that contained only affected persons. The phenocopy rate was set at 2% in individuals, on the basis of the population prevalence of PD at >60 years (de Rijk et al. 1997). The *P* values given are nominal *P* values. Since the models used here (affecteds-only model, penetrance-dependent model, and penetrance-dependent model with individuals classified as affected on the basis of PET criteria) are not independent models, we did not perform a Bonferroni correction. Nevertheless, the results would still be significant even if Bonferroni correction were applied.

Results

All 21 families were analyzed with a first set of known polymorphic markers (D12S310, D12S1042, D12S87, D12S345, D12S1592, D12S1653, D12S291, D12S1301, D12S1663, D12S85, D12S1701, D12S1661, D12S2196, D12S339, D12S1635, D12S1629, D12S368, D12S398). Significant evidence for linkage was found, with a maximum multipoint LOD score of 2.01, corresponding to a *P* value of .0047, considering affected members only and allowing for genetic heterogeneity (fig. 1). The corresponding *P* value for the analysis with age-dependent penetrance is .00119 (LOD score 2.56). Since this is a replication study and only a defined chromosomal region is investigated, this LOD score exceeds the level of significance, $P = .01$, required for this type of analysis (Lander and Kruglyak 1995). Thus, both of our models give significant evidence for linkage under heterogeneity, even when a correction for multiple tests (two models here) is performed.

Of these 21 families, 10 showed positive LOD scores in this region, with the bulk of the evidence being derived from two large families (family D, from western Nebraska, and family A, of German Canadian origin) that had previously been characterized clinically and pathologically (Wszolek et al. 1995, 1997), whereas 11 families had negative LOD scores, of which 4 had LOD scores < -2 , fulfilling the formal criteria for exclusion. The estimate for the proportion of families with linkage was 0.32, with the 95% CI ranging from 0.03 to 1.00. This leaves open the possibility that some of the other families may also have linkage to PARK8, although

Table 1

Clinical Features of the 10 Families with Positive LOD Scores

	FAMILY									
	D	A	3211	198	194	3082	M3	3083	3081	281
Country of origin	United States	Canada	Ireland	Germany	Norway/Holland	Norway	Austria	Norway	Norway	United States
No. of generations	6	6	3	5	5	3	3	3	2	3
No. of family members	190	208	11	23	21	6	13	9	5	6
Affected Individuals	22	15	3	4	3	4	4	5	4	3
No. of typed individuals affected (unaffected)	9 (24)	7 (7)	2 (6)	2 (7)	2 (2)	2 (0)	2 (0) ^a	2 (0)	2 (0)	3 (0)
No. of typed generations	3	2	1	2	2	1	1	1	1	3
M:F ratio	8:14	10:5	1:2	2:4	1:2	3:1	7:6	1:4	2:3	0:3
Mean (range) age at onset in years	65 (48–78)	55 (35–65)	45 (40–50)	69 (63–76)	68 (61–74)	58.5 (55–62)	64 (60–68)	48 (47–49)	59 (56–62)	44 (12–78)
Mean (range) disease duration in years	13 (4–26)	13 (5–18)	NA	NA	NA	NA	7 (4–10)	NA	NA	NA
Initial signs	B, RT, PI	RT, B	Tremor	Tremor	Tremor	NA	NA	NA	NA	Writing cramp
Bradykinesia	+	+	+	NA	+	+	+	+	+	+
Rigidity	+	+	+	NA	+	+	+	+	+	+
Resting tremor	+	+	+	+	+	+	+	+	+	NA
Postural instability	+	+	–	+	+	–	+	+	+	+
Response to levodopa	+	+	NA	+	+	+	+	NA	+	NA
Long-term complication	+	+	NA	NA	NA	NA	NA	+	+	NA
Other features	None	Anyotrophy in 2, dementia in 2	None	Dementia	None	None	Dementia in 1	None	None	None
Pathological features	LBs in SN only in 1, diffuse LBs in 1, tau deposition and no LBs in 1, gliosis in SN and LC and no LBs in 1	Neuronal loss and gliosis in SN, thalamus and LC, ubiquitin and eosinophilic positive granules	NA	NA	NA	NA	NA	NA	NA	NA
Maximum LOD score at position of maximum HETLOD ^b	1.67	1.67	.29	.26	.31	.34	.57	.26	.21	.13
Posterior probability of linkage	.96	.96	.48	.46	.49	.51	.64	.46	.43	.39
Maximum LOD score obtainable using affecteds-only model ^c	3.46	1.79	.3	.3	.35	.38	.58	.38	.3	.29

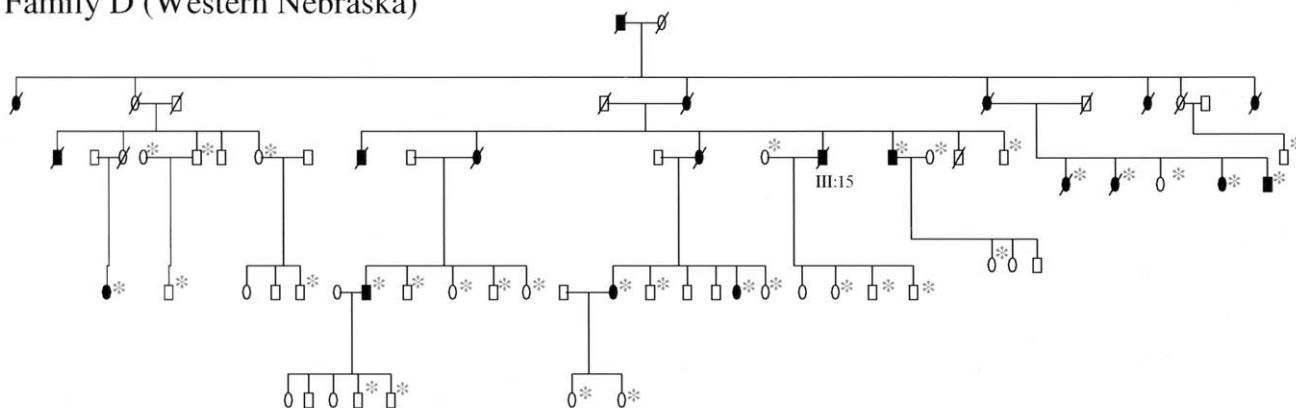
NOTE.—NA = not applicable; B = bradykinesia; R = rigidity; RT = resting tremor; PI = postural instability; SN = substantia nigra.

^a Affected individuals were cousins.

^b Affecteds-only analysis; position of maximum LOD score under heterogeneity (HETLOD) was 57.68 cM.

^c Determined using SIMULATION with SLINK.

Family D (Western Nebraska)



Family A (German Canadian)

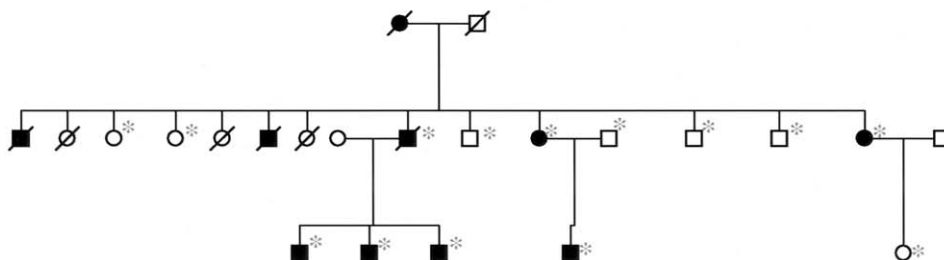


Figure 2 Pedigree structure of families A and D. Blackened symbols denote affected family members, and asterisks (*) indicate individuals typed with polymorphic markers. For clarity, only part of each pedigree is shown. The complete pedigrees with detailed clinical descriptions are shown elsewhere (Wszolek and Markopoulou 1999).

these families are too small to draw any definitive conclusion.

The clinical characteristics of the 10 families with positive scores are shown in table 1. The two largest families (family A and family D; fig. 2) showed significant linkage on their own by the Lander and Kruglyak (1995) criteria. Therefore, they were chosen for further delineation of the critical region. To refine the candidate region, new microsatellite repeats were identified from the following chromosome 12 BAC clones: AC024934, AC025253, AC018923, AC079033, AC08127, AC084878, AC025031, AC008014, AC080136, AC0044861, and AC008083. Two-point LOD scores were calculated and showed the highest value for the combined families (families A and D) at marker D12S85, with a value of 4.89 (penetrance-dependent model; table 2), and at marker AC08127, with value of 3.14 (affecteds-only model; data not shown).

To define the candidate region further, parametric multipoint linkage analysis was performed. The highest values in an affecteds-only multipoint analysis were achieved with LOD scores of 1.67 for family D ($P = .0028$) and 1.77 for family A ($P = .0022$), with the

respective peak in each family being 1.2 cM apart. When we forced both peaks to occur at the same point, the LOD scores were 1.67 for each family, with P values of .0028 in each of the families (fig. 3a). When we calculated a penetrance-dependent model, the multipoint analysis remained stable for family A, with the highest LOD score value being 1.68 ($P = .0027$), whereas the LOD score in family D increased to 2.24 ($P = .0007$); both peaks were at an identical location, only 0.24 cM away from the peak in the affecteds-only analysis. (fig. 3b). It is noteworthy that two clinically unaffected individuals in family D who are aged >60 years carry the putative disease haplotype. One of these two individuals was found to be affected on the basis of PET criteria. To protect the privacy of these individuals, the position in the pedigree is not shown. When we considered this patient as affected, the LOD score in family D increased from 2.24 to 2.79 (penetrance-dependent model). The LOD score allowing for heterogeneity, calculated through use of this classification and all families, rises to 3.02 ($P < .0004$).

The 1-LOD support interval for the disease-causing locus, based on the affecteds-only multipoint analysis

Table 2

Parametric Two-Point LOD Scores, for the Combined Families A and D, between Autosomal Dominant Parkinsonism and Markers of the PARK8 Region, Calculated under the Penetrance-Dependent Model

MARKER (POSITION IN cM)	LOD SCORE AT A RECOMBINATION FRACTION OF						
	.00	.01	.05	.1	.2	.3	.4
D12S1592 (54.17)	-.05	.5	1.19	1.37	1.19	.75	.23
D12S291 (54.99)	.59	-.4	.35	.63	.68	.47	.16
D12S1301 (55.52)	2.05	2.0	1.38	1.61	1.13	.63	.19
D12S1663 (55.68)	-1.80	-1.04	.03	.48	.66	.49	.20
AC024943	3.54	3.73	3.78	3.5	2.61	1.54	.47
AC025253	.65	.64	.60	.53	.37	.22	.07
AC018293	-.08	-.08	-.06	-.02	.03	.03	.01
AC079033	2.9	2.84	2.6	2.27	1.58	.85	.23
AC08127	1.95	1.90	1.72	1.5	1.03	.57	.17
AC084878	4.29	4.22	3.9	3.47	2.52	1.47	.49
AC025031	2.19	2.42	2.62	2.5	1.97	1.25	.48
AC080140	4.67	4.60	4.28	3.86	2.88	1.78	.66
AC080136	1.56	1.52	1.38	1.20	.82	.43	.11
D12S85 (58.42)	4.89	4.79	4.39	3.85	2.71	1.51	.43
AC0044861	1.80	2.10	1.99	1.46	.82	.25	1.28
D12S1701 (59.70)	2.51	2.45	2.22	1.90	1.26	.65	.16
D12S1661 (60.66)	-.41	-.07	.38	.55	.56	.38	.14
D12S2196 (60.67)	-.58	-.03	.48	.63	.58	.36	.12

for the combined families A and D, is defined by markers AC025253 (44.5 Mb) to D12S1701 (47.7 Mb). In family A, LOD scores were close to the theoretical maximum. In family D, the maximum multipoint LOD score was 2.24, substantially lower than the theoretical maximum of 6.27 (when we assumed the age-dependent model) that could be obtained in this pedigree. This is due to one deceased individual (individual III:15 in fig. 2), whose haplotype was reconstructed from his three living unaffected children and his living spouse. This individual was affected with PD at age 49 years and was treated with stereotactic surgery. His children carried four different haplotypes, but none of them was identical to the haplotype shared by all other affected individuals in this pedigree. It therefore must be assumed that this individual suffered from parkinsonism of another cause. A similar case of a phenocopy was found in the Contursi kindred (Polymeropoulos et al. 1996), the family in which α -synuclein was identified as the disease gene.

Haplotype analysis in all 10 families supporting linkage did not show any evidence, at the present resolution, of allele sharing for the cosegregating chromosome, indicating that, most likely, independent mutational events have occurred.

It is interesting that neuropathologic examination of affected individuals of families A and D showed variable α -synuclein and tau pathology, indicating that the PARK8 mutation may be associated with a range

of pathological phenotypes. Details on these examinations are presented elsewhere (Wszolek et al. 2003).

Discussion

Genetic progress in unraveling the etiology of parkinsonism has been rapid, with the identification of α -synuclein (PARK1), parkin (PARK2), UCH-L1 (PARK5), and DJ-1 (PARK7) gene mutations. Although many families with dominant inheritance have been described, to date, each of the mapped genetic loci accounts only for a very small number of kindreds (Skipper and Farrer 2002).

PARK8 (Funayama et al. 2002) may be an exception. Although linkage could be proven for only two of the families in our study individually, LOD score calcula-

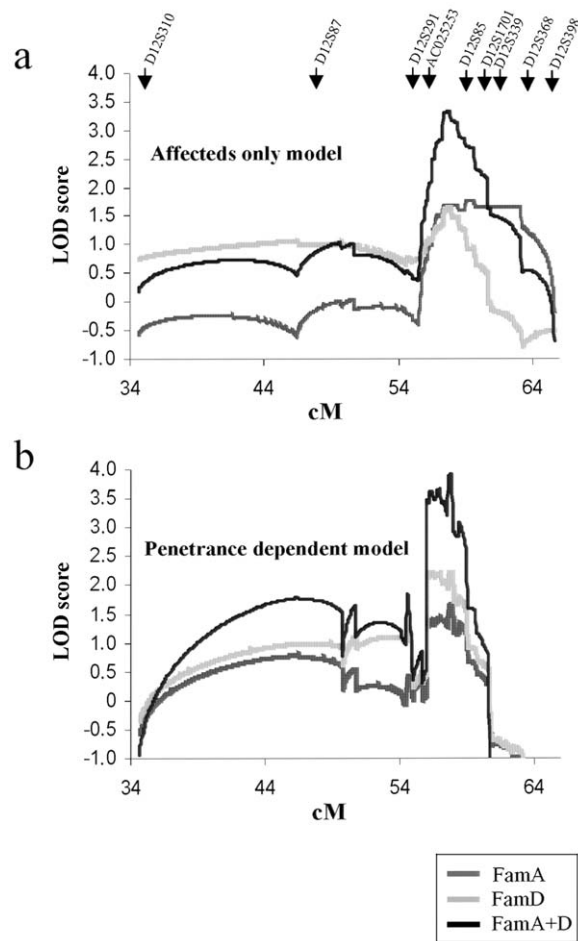


Figure 3 Multipoint LOD score plots for families A and D. The X-axis represents location in centimorgans, and the Y-axis represents LOD scores. LOD scores are shown for family A, family D, and both families combined (A+D). *a*, Affected-only model. *b*, Penetrance-dependent model.

tions in the total sample of families under the assumption of genetic heterogeneity leave open the possibility that mutation(s) in the underlying disease gene, yet to be identified, may explain a broader subset of the families with dominantly inherited PD. However, even if the disease only in the two largest families of this study were due to PARK8 mutations, this would be quite remarkable, given the fact that only two mutational events have been identified worldwide in the α -synuclein gene and that other dominant PD loci also seem to be restricted to a very small number of families.

All individuals included in the study as affected family members satisfy criteria for the cardinal signs and symptoms of PD with positive response to L-dopa. However, closer examination and longitudinal follow-up over many years showed a broader range of phenotypes, including dementia and amyotrophy (Wszolek et al. 1997, 2003). This is consistent with recent reports indicating that clinical features associated with the Ala53Thr mutation of the α -synuclein gene may clearly exceed the core syndrome of parkinsonism and include dementia, autonomic dysfunction, and other neurologic deficits (Spira et al. 2001).

The relationship between rare monogenic variants of parkinsonism and the common sporadic disease is still unclear. It is assumed that relatively common genetic variants may increase susceptibility to the sporadic disease. To identify these polymorphisms, several genome-wide screens have been performed in large numbers of small families (usually affected sib pairs). These investigations provided suggestive evidence for linkage with a number of chromosomal regions. So far, none of these regions comprised the gene loci mapped in families with dominant monogenic inheritance, indicating that these genes may not contribute significantly to the etiology of PD in larger patient populations without clear Mendelian inheritance (DeStefano et al. 2001; Scott et al. 2001; Li et al. 2002; Pankratz et al. 2002). On the other hand, there is some evidence that polymorphisms in the promoter region of α -synuclein may be associated with a higher risk for PD (Farrer et al. 2001*b*). This question also remains to be investigated for the PARK8 locus on chromosome 12. It is interesting that genetic support for the importance of this locus comes from the study of Pankratz et al. (2002), in which evidence for linkage to PARK8 is found in a subset of Parkin-positive families. Furthermore, an overlapping locus on chromosome 12 has recently been linked to dementia in families containing at least one affected individual with LB disease (Scott et al. 2000). This raises the exciting possibility that one and the same gene in the centromeric region of chromosome 12 may cause both dominant parkinsonism and dementia with LBs. This is, in fact,

supported by the pathological studies in the families in our study (see below).

Despite the recent progress in gene identification, the molecular pathogenesis of PD is still unknown. However, genetic and biochemical evidence indicates that the abnormal accumulation and aggregation of α -synuclein (and possibly other proteins) and/or a deficiency of ubiquitinylation-dependent proteasomal protein degradation may play an important role in the process of nigral cell death.

The demonstration of tau pathology in parkinsonism caused by α -synuclein (Duda et al. 2002; Ishizawa et al. 2003) and parkin (van de Warrenburg et al. 2001; Morales et al. 2002) mutations indicates that pathways to neurodegeneration may overlap; although there may be a variety of insults, the cellular responses may be more limited.

Autopsies were performed on several affected individuals from families A and D, shown here to have linkage to PARK8. It is interesting that four different types of pathological features were observed in family D: one individual had LB pathology restricted to the brain stem, as in idiopathic PD; one had widespread LB pathology, as in dementia with LBs; one had tau pathology resembling PSP; and one had only nigral degeneration (Wszolek et al. 2003). Two individuals from family A also demonstrated the presence of ubiquitin and eosinophilic inclusions, but without classic LBs seen in affected brain areas (Wszolek et al. 1997).

These observations may shed light on the complex genotype-phenotype relationship in neurodegenerative disorders. The findings in the families in our study indicate that a single genetic defect may cause a remarkably wide range of pathology. On the other hand, distinct biologic insults may lead to similar pathology: although LBs are described as the pathological hallmark of PD, they are also found at autopsy in prion disease, type 1 neurodegeneration with brain iron accumulation, Down syndrome, and in some patients with Alzheimer disease who carry an amyloid precursor protein mutation (Lantos et al. 1994; Bugiani et al. 2000; Neumann et al. 2000; Simard and van Reekum 2001). Identification of the gene product of PARK8 will undoubtedly contribute to our understanding the basis of variable clinicopathological findings found in these kindreds.

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Electronic-Database Information

The URLs for data presented herein are as follows:

Genetic Location Database, http://cedar.genetics.soton.ac.uk/public_html/ldb.html

MAP-O-MAT, <http://compngen.rutgers.edu/mapomat/> (for marker information)

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for parkinsonism, PARK1, FTDP-17, PARK2, PARK5, PARK7, and PARK8)

UCSC Human Genome Browser, Human Genome Working Draft, <http://genome.ucsc.edu/goldenPath/septTracks.html> (for new polymorphic markers, developed by searching the database for CA repeats using *in silico* BAC sequence)

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