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Chromosome 6–Linked Autosomal Recessive Early-Onset Parkinsonism: Linkage in European and Algerian Families, Extension of the Clinical Spectrum, and Evidence of a Small Homozygous Deletion in One Family

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Summary

The gene for autosomal recessive juvenile Parkinsonism (AR-JP) recently has been mapped to chromosome 6q25.2–27 in Japanese families. We have tested one Algerian and 10 European multiplex families with early-onset Parkinson disease for linkage to this locus, with marker D6S305. Homogeneity analysis provided a conditional probability in favor of linkage of >.9 in eight families, which were analyzed further with eight microsatellite markers spanning the 17-cM AR-JP region. Haplotype reconstruction for eight families and determination of the smallest region of homozygosity in two consanguineous families reduced the candidate interval to 11.3 cM. If the deletion of two microsatellite markers (D6S411 and D6S1550) that colocalize on the genetic map and that segregate with the disease in the Algerian family is taken into account, the candidate region would be reduced to <1 cM. These findings should facilitate identification of the corresponding gene. We have confirmed linkage of AR-JP, in European families and in an Algerian family, to the PARK2 locus. PARK2 appears to be an important locus for AR-JP in European patients. The clinical spectrum of the disease in our families, with age at onset ⩽58 years and the presence of painful dystonia in some patients, is broader than that reported previously.

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Introduction

Parkinson disease (PD), a frequent disorder with a lifetime risk of 2%, is characterized mainly by degeneration of brain dopaminergic pathways. The main clinical features are rigidity, bradykinesia, and tremor, with an initial good response to levodopa (Agid 1991). Genetic risk factors probably are involved in the pathogenesis of the idiopathic form (Wood 1997), and several families with clearly established monogenic inheritance have been reported. An autosomal dominant type of PD has been mapped to chromosome 4q (PD1) in a large Italian kindred (Polymeropoulos et al. 1996) in which a missense mutation of the α-synuclein gene has been identified (Polymeropoulos et al. 1997). A different missense mutation was detected in a German kindred (Krüger et al. 1998). It is probably, however, an uncommon locus for familial PD (The French Parkinson's Disease Genetics Study Group 1998; Vaughan et al., in press). Another locus for autosomal dominant PD recently has been mapped to chromosome 2p13 (Gasser et al. 1998). An autosomal recessive form of Parkinsonism (AR-JP [autosomal recessive juvenile Parkinsonism]) has been described in several Japanese families (Yamamura et al. 1973; Yamamura et al. 1993; Takahashi et al. 1994; Ishikawa and Tsuji 1996) and recently has been mapped to chromosome 6q25.2-27 (Matsumine et al. 1997). This locus is also designated "PARK2" (MIM 600116). The 17-cM interval defined by the study by Matsumine et al. (1997) contains the Mn-superoxide dismutase gene (SOD2), which was excluded as a candidate gene, by sequence analysis of 13 patients. Prominent clinical features are early onset, mostly at <40 years of age, Parkinsonism with rigidity, resting and/or postural tremor, bradykinesia, postural instability, excellent response to levodopa but with levodopa-induced dyskinesias and

wearing-off phenomenon associated with foot dystonia and sleep benefit (Ishikawa and Tsuji 1996). Selective neurodegeneration and gliosis were observed in the substantia nigra pars compacta, but Lewy bodies, the pathological hallmark of idiopathic PD, were not detected in the few patients examined (Yamamura et al. 1993; Takahashi et al. 1994). In order to determine if this genetic entity was restricted to Japan, we performed linkage analysis with markers from the PARK2 region in one Algerian and 10 European multiplex families with early-onset Parkinsonism compatible with autosomal recessive inheritance.

Patients and Methods

Patients

Families were selected according to the following criteria: (1) presence, in all examined patients, of two of the three cardinal signs of PD (akinesia, rigidity, and tremor); (2) marked improvement with levodopa treatment, except in two untreated secondary cases; (3) age at onset $\leqslant$40 years for at least one affected sib; and (4) family history compatible with autosomal recessive inheritance—that is, with the presence of the disease in at least two patients in a single generation and/or consanguinity. There were 11 families: five Italian (IT-1-005, IT-1-006, IT-2-021, IT-2-022, and IT-1-031), four French (GRE-017, SAL-028, LYO-119, and SAL-727), one Portuguese (SAL-711), and one Algerian (DEL-001). These families were selected from among 104 kindreds comprising at least one affected sib pair fulfulling criteria 1 and 2. Blood samples were taken, with informed consent, from 30 patients and from 22 clinically unaffected first-degree relatives.

Genotypes

Genotypes were determined with either [^{32}P]-labeled primers (Stevanin et al. 1994) or fluorescent primers analyzed on an ABI377 automated sequencer with the GENESCAN and GENOTYPER software. The PCR conditions were as described in the Genome Database (GDB). All families were genotyped for microsatellite D6S305. After linkage and HOMOG analysis, families with a high posterior probability in favor of linkage were genotyped for eight additional microsatellite markers spanning the ~17-cM PARK2 locus (Matsumine et al. 1997) on chromosome 6q: cen–D6S419–2.3 cM–D6S1581–1.6 cM–D6S1579–0 cM–D6S411–0 cM–D6S1550–0 cM–D6S305–3.6 cM–D6S1599–7.7 cM–D6S1719–1.2 cM–D6S264–tel (Dib et al. 1996). Haplotypes were reconstructed manually. The primers used for analysis of SOD2 were those described in Genbank (accession number X07834).

Linkage and Homogeneity Analysis

Linkage analysis was performed with the LINKAGE and FASTLINK software packages (Lathrop et al. 1985; Schäffer et al. 1994), with the same parameters used by Matsumine et al. (1997), except for the liability classes, which were derived from the cumulative age-dependent penetrance in our 11 families: class I, 0–25 years of age, penetrance .0665; class II, 26–35 years of age, penetrance .3165; class III, 36–40 years of age, penetrance .615; class IV, 41–50 years of age, penetrance .815; class V, >50 years of age, penetrance .95. Allele frequencies were derived from the GDB. Linkage homogeneity was tested by use of the HOMOG program of Ott (1991), with the two-point LOD scores obtained, for the 11 families, with marker D6S305.

Statistical Analysis

Means were compared by use of nonparametric tests, and frequencies were compared by use of the χ^2 test, with the Yates correction used when appropriate.

Results

Linkage Analysis

Linkage to PARK2 was first tested with marker D6S305, in the 52 members of the 11 families, including the 30 patients. Two-point LOD scores at a recombination fraction (θ) of .00 were positive (range 0.70–1.92) in 8 families and were negative over the entire tested interval in the other 3 families (table 1). The odds, calculated with the HOMOG program, in favor of linkage with heterogeneity (H_2) as opposed to no linkage (H_0) and to linkage and homogeneity (H_1) were 1.1×10^7:1 and 11.3:1, respectively. The conditional probability in favor of linkage to marker D6S305 was equal to zero for the three families with negative LOD scores at all tested values of θ. In addition, negative scores at

Table 1

Two-Point LOD Scores for D6S305 Marker in 11 Families with Autosomal Recessive Early-Onset Parkinsonism

	LOD Score at θ =						
Family	.00	.01	.05	.10	.20	.30	.40
IT-2-021	1.92	1.88	1.73	1.52	1.08	.61	.19
IT-1-005	1.56	1.52	1.38	1.20	.82	.45	.13
LYO-119	1.51	1.47	1.34	1.17	.82	.50	.21
DEL-001	1.15	1.12	1.01	.88	.61	.37	.15
IT-2-022	1.06	1.04	.93	.80	.53	.28	.08
SAL-711	1.00	.97	.87	.75	.50	.26	.07
GRE-017	.84	.82	.73	.62	.40	.20	.05
IT-1-006	.70	.68	.61	.51	.32	.16	.04
SAL-028	−5.57	−1.28	−.61	−.36	−.14	−.05	−.01
IT-1-031	−5.94	−1.30	−.63	−.37	−.15	−.06	−.01
SAL-727	−11.38	−2.69	−1.36	−.84	−.37	−.15	−.04

all values of θ tested with markers D6S419 and D6S264 also were obtained for these three families, supporting the hypothesis that these families do not present evidence for linkage to the PARK2 locus (data not shown). This was confirmed by multipoint LOD scores computed for markers D6S419, D6S305, and D6S264, which generated LOD scores below −1.20 for the entire candidate interval in each of these families (data not shown). In eight families for which the conditional probability in favor of linkage was >.9 (range .92–.99), eight other microsatellite markers spanning the 17-cM AR-JP candidate region were genotyped. The maximum two-point LOD scores for a marker within the PARK2 candidate region were within the range 0.84–1.92, with a cumulative maximum of 9.73 at D6S305 (table 2). The maximum multipoint LOD score calculated with data for D6S419, D6S305, and D6S264 was 10.76 at D6S305.

Table 2

Cumulative Pairwise LOD Scores between Nine Chromosome 6q Markers and the PARK2 Locus in Eight Families

	LOD Score at θ =								
Marker	.00	.01	.05	.1	.2	.3	.4	Z_{max}	θ_{max}
D6S419	−8.19	1.99	3.43	3.49	2.66	1.52	.48	3.54	.077
D6S1581	−5.88	.67	1.66	1.75	1.32	.72	.21	1.76	.084
D6S1579	2.33	4.49	4.58	4.11	2.87	1.59	.50	4.66	.029
D6S411	−2.39	1.55	1.98	1.89	1.35	.73	.22	1.98	.059
D6S1550	−1.17	2.99	3.21	2.90	1.96	.98	.25	3.24	.036
D6S305	9.73	9.51	8.59	7.43	5.09	2.82	.94	9.73	.0
D6S1599	8.76	8.55	7.71	6.64	4.49	2.45	.80	8.76	.0
D6S1719	3.55	5.70	5.71	5.13	3.62	2.01	.63	5.84	.025
D6S264	−7.50	.97	1.97	2.06	1.59	.93	.34	2.68	.073

Note.—Markers are ordered from centromere to telomere. Markers D6S1579 and D6S305 were positioned on the basis of recombination events determined by haplotype reconstruction (see fig. 1). Markers D6S411 and D6S1550 were ordered arbitrarily.

Haplotype Reconstruction

Haplotypes were reconstructed for nine microsatellite markers spanning 17 cM on chromosome 6q in the eight families presenting evidence for linkage to the PARK2 locus (fig. 1). Recombination events were detected in affected members of four families. In family IT-1-005, a recombination event detected in patient 12 situated the gene telomeric to D6S411, D6S1550, and D6S1579, which are at the same locus, and demonstrated that D6S305, which also mapped to the same locus, is telomeric to these three markers. More-centromeric recombination events, observed with marker D6S419, in patients from families DEL-001 (individual 14) and IT-2-021 (individual 5) confirmed this telomeric localization. A distal recombination event in patient 8 from family IT-2-021 defined D6S1719 as the telomeric boundary. This was confirmed by a more telomeric recombination event observed with marker D6S264 in patient 4 from family SAL-711. The candidate interval between markers D6S411/D6S1550/D6S1579 and marker D6S1719 is ~11.3 cM.

Homozygosity was observed in patients from two consanguineous families, DEL-001 and LYO-119. In the former, the entire region was homozygous except for marker D6S419, whereas in the latter the region of homozygosity was restricted to four markers (D6S1550, D6S411, D6S305, and D6S1599). The lack of homozygosity at locus D6S1579 and at more-proximal markers suggested recombination between this marker and D6S1550, D6S411, and D6S305, at the same locus, and showed that D6S1579 is centromeric to the three other markers at the same locus. These data restricted the candidate interval to the 11.3-cM region between D6S1579 and D6S1719. Regions of homozygosity spanning 2–7 markers were found in families SAL-711, IT-1-005, IT-1-006, and IT-2-021, which originate from regions in rural Portugal and Italy, and may result from undocumented consanguinity. The haplotype of each family is different, suggesting that the haplotypes derived from independent ancestral mutations.

Characterization of Homozygous Deletion in Family DEL-001

A single allele was detected with markers D6S411 and D6S1550 in the mother and the unaffected sibs of family DEL-001 (fig. 1). The three affected children received no parental contribution at these loci, suggesting that the disease segregated with a deletion, in this family. Markers D6S305 and D6S1579, which colocalize on the genetic map, were shown by recombination events to represent the centromeric and the telomeric boundaries, respectively. They were not included in the deletion. The deletion therefore is located in a <1-cM interval flanked by these markers. Two additional microsatellite markers (AFMA155TD9 and AFMB281WF1) and one sequence-tagged site (STS; WI4940) that map to the region, but not the SOD2 gene, were found by PCR analysis to be within the deletion. The existence of the deletion was confirmed by Southern blot hybridization with the STS in the three affected sibs (data not shown). Deletions of the microsatellite markers or of STS WI4940 were not detected in the other linked families.

Phenotype-Genotype Correlations

Evidence in favor of linkage was found in eight families of different geographical origins. The characteristics of 23 patients from the chromosome 6–linked families were compared with those of the 17 Japanese patients with AR-JP reported elsewhere (Matsumine et al. 1997) and the 7 patients from the three families in this study that did not show evidence of linkage to chromosome 6q (table 3). The mean age at onset was 35 ± 11 years,

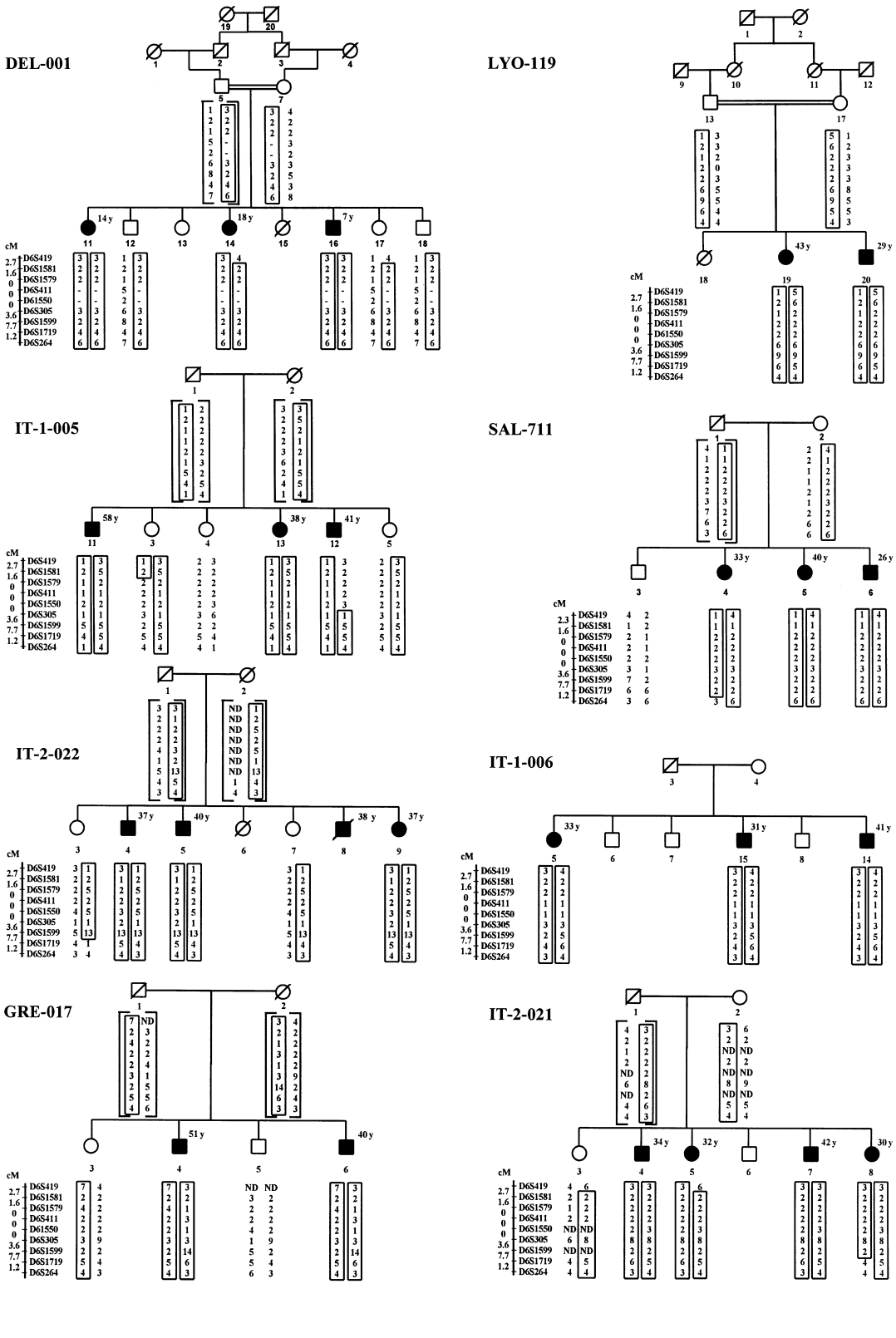

Figure 1 Simplified pedigrees of the eight families showing linkage to the PARK2 locus, with haplotypes for nine chromosome 6q markers. Blackened squares (men) and circles (women) represent affected individuals. Age at onset (in years) is indicated above the patient's symbol. Haplotypes were reconstructed to minimize the number of recombination events in each family. Genetic distances are indicated in centimorgans, and markers are listed top to bottom from centromere to telomere. The order of D6S411 and D6S1550 at the same locus was defined arbitrarily. Alleles are numbered as in the GDB. Haplotypes segregating with the disease are boxed. Reconstructed genotypes are within brackets. Note that when both parents were not genotyped their haplotypes were assigned arbitrarily. A hyphen (-) indicates a deleted marker. ND = not determined.

Table 3

Clinical Comparison among Patients with Autosomal Recessive Early-Onset Parkinsonism Linked to Chromosome 6q, from Europe and Algeria and from Japan, and Patients with Early-Onset PD Not Linked to Chromosome 6q

	Early-Onset PD Linked to Chromosome 6, Present Study (23 Patients, 8 Families)	Early-Onset PD Not Linked to Chromosome 6q (7 Patients, 3 Families)	Japanese AR-JP (17 Patients, 12 Families)[a]
No. of men:no. of women	12:11	2:5	5:12
Mean (range) age at onset [years]	35 ± 11 (7–58)*	36 ± 10 (21–52)	28 ± 9 (9–43)
Mean (range) disease duration [years]	15 ± 7 (3–29)*	22 ± 10 (4–36)	23 ± 11 (7–52)
Hoehn and Yahr score	2.6 ± 1	2.7 ± .8	2.7 ± .9
Percentage of patients with:[b]			
Bradykinesia	97 (22/23)	100 (7/7)	76 (13/17)
Rigidity	97 (22/23)	100 (7/7)	71 (12/17)
Tremor	83 (19/23)	57 (4/7)	94 (16/17)
Response to levodopa	Good 71 (15/21) Excellent 29 (6/21)	Good 3/7 Excellent 4/7	Satisfactory 100 (17/17)
Diurnal fluctuations of levodopa response	63 (10/16)	100 (4/4)	87 (13/15)
Dopa-induced dyskinesias	73 (16/22)	57 (4/7)	93 (14/15)
Other symptoms[b]	Dystonia (5/11) Brisk reflexes (4/16)* Axonal neuropathy (1/16) Painful dystonia (3/16)	Dystonia (2/3)	Dystonia (10/16) Brisk reflexes (14/17) Retropulsion (15/17)

[a] From Ishikawa and Tsuji (1996).

[b] The number of patients for whom specific information was available is indicated in parentheses.

* $P < .05$, for comparison between the families with early-onset PD linked to chromosome 6 and the Japanese AR-JP families.

with a range of 7–58 years, in the chromosome 6–linked families, which is significantly older than that in the Japanese families (28 ± 9; $P < .05$). The overall clinical picture was a mild to moderate parkinsonian syndrome that responded well to levodopa, with the appearance of dyskinesias in 73% of the patients, after a mean disease duration of 15 ± 7 years. Signs at onset were one or two of the parkinsonian triad ($n = 21$), dystonia in the foot ($n = 1$), and difficulty walking ($n = 1$). Impassive face was frequent (7/8 patients). Scores on the Mini Mental State (MMS) examination were normal ($\geqslant 25$/30) for 20 patients. For three patients, abnormal MMS scores of 15, 20, and 24, after disease durations of 17, 12, and 27 years, respectively, were seen. Brisk reflexes were present in 4/16 patients, which is significantly less than the number of Japanese patients (14/17; $P < .05$) with brisk reflexes. Additional signs were painful dystonia in three patients from two families (DEL-001 and SAL-711) and pronounced anxiety, requiring treatment, in eight patients.

Discussion

We have identified eight families with a high posterior probability of linkage to the PARK2 locus on chromosome 6, determined from two-point LOD scores for marker D6S305, which maps to the same genetic locus as the disease. The high proportion of families (7/10) that present with evidence of linkage indicates that the AR-JP locus is a common locus for early-onset Parkinsonism in Europeans. The clinical features of AR-JP in patients from the European and Algerian families studied could not be distinguished from those in patients from families that did not show linkage to chromosome 6 and were, for the most part, similar to those in patients from Japanese families (Yamamura et al. 1973; Takahashi et al. 1994; Ishikawa and Tsuji 1996)—namely, early onset in some family members, marked and sustained response to low doses of levodopa, early appearance of dyskinesia, and slow disease progression. However, the clinical spectrum of the disease was larger and the phenotype corresponded better to the clinical definition of early-onset PD than did the juvenile form (Quinn et al. 1987). Age at onset, which did not exceed 43 years in Japanese families (Yamamura et al. 1973; Takahashi et al. 1994; Ishikawa and Tsuji 1996), was >50 years for several of our patients, with 58 years being the oldest. Sleep benefit was not a prominent feature, and dystonia was rare in our families. However, painful dystonia, which has not been reported previously for AR-JP, was observed in two families, including DEL-001, which has a homozygous deletion; this symptom might result from complete loss of function because of the deletion. This also may explain why age at onset

was markedly earlier in patients from family DEL-001 (mean 13 ± 6 years) than in those without detectable deletions (mean 38 ± 8 years; $P < .01$). Alternatively, painful dystonia in family DEL-001 could result from the deletion or disruption of a contiguous gene (contiguous-gene syndrome). Since autopsies were not performed on patients from the eight families that showed linkage to the PARK2 locus, we cannot confirm that Lewy bodies are absent in this disease (Yamamura et al. 1993; Takahashi et al. 1994).

With the assumption that the deletion in family DEL-001 encompasses the gene responsible for AR-JP, this study of eight families enabled us to reduce the candidate interval from 17 cM between markers D6S437 and D6S264 (Matsumine et al. 1997) to <1 cM between markers D6S411/D6S1550 and microsatellite D6S305. Recombination events reduced the candidate interval to an 11.3-cM region between the locus defined by markers D6S411/D6S1550/D6S1579 and marker D6S1719. The minimal region of homozygosity in two consanguineous families (DEL-001 and LYO-119) defined markers D6S1579 and D6S1719 as the centromeric and the telomeric boundaries of the candidate interval, which was restricted further, by a deletion in family DEL-001, to a small region containing D6S411 and D6S1550 and flanked by D6S1579 and D6S305, which colocalize on the genetic map. This deletion also contains one STS and two other microsatellite markers. Although its physical size has not yet been determined, it is probably small. Two of the several markers that colocalize on the genetic map were not deleted. Several expressed sequence tags have been identified in the PARK2 region, but none have been mapped to the <1-cM candidate interval. Our results are in good agreement with those of Saito et al. (1998), who restricted the candidate interval to the 13-cM region flanked by D6S1579 and D6S264 and suggested, on the basis of linkage-desequilibrium studies, that the AR-JP gene most likely is located near the 4-cM interval between D6S1579 and D6S1599. Interestingly, the small deletion detected in family DEL-001 is contained within their proposed 4-cM interval.

In conclusion, we have shown that AR-JP is not restricted to Japan and that the AR-JP locus represents a common locus for early-onset PD in European and Algerian patients. The clinical features in the European and Algerian families are indistinguishable from those of early-onset idiopathic PD, and the clinical spectrum is larger than that reported in Japan. The latter could be explained by allelic heterogeneity. This hypothesis is supported by the observation of different haplotypes among families, suggesting the occurrence of independent ancestral mutations. The Parkin gene at the PARK2 locus on chromosome 6 was identified very recently (Kitada et al. 1998). We now are able to confirm that this gene is also implicated in our families with AR-JP.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Web/Genbank (for primers used for SOD2 [X07834])
Genome Database, http://www.gdb.org
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for PARK2 [MIM 600116])

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