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Autosomal Recessive Juvenile Parkinsonism Maps to 6q25.2-q27 in Four Ethnic Groups: Detailed Genetic Mapping of the Linked Region

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Summary

Parkinson disease (PD) is a common neurodegenerative condition associated with degeneration of dopaminergic neurons in the zona compacta of the substantia nigra. There is increasing evidence that genetic factors play a role in the etiology of PD, although genetic heterogeneity is likely. An autosomal dominant syndrome with many similarities to sporadic PD has been mapped to 4q21-22 in a large Italian pedigree and has been found to be due to mutation of the alpha-synuclein gene. However, this gene appears to account for only a minority of PD, and a susceptibility locus for autosomal dominant parkinsonism has recently been mapped, on 2p13. Autosomal recessive juvenile parkinsonism (JP), which shows marked clinical similarity to PD, maps to 6q25.2-q27. We found linkage to this region in a group of 15 families from four distinct ethnic backgrounds. A full genomic screen excluded other candidate regions. We have constructed a detailed genetic map of the linked region and have mapped the position of the manganese superoxide dismutase gene (SOD2). Recombination events restricted the JP locus to a 6.9-cM region and excluded SOD2. The apparent homozygosity for null alleles at D6S955 in one family suggested a deletion and finer localization of the JP locus.

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Introduction

Parkinson disease (PD) affects 1.6% of those >65 years of age (de Rijk et al. 1997). It is characterized clinically by rigidity, bradykinesia, and tremor. Pathology studies have demonstrated selective degeneration of dopaminergic neurons in the substantia nigra of the midbrain, but the etiology of PD remains unknown. Community-based (Marder et al. 1996) and clinic-based (De Michele et al. 1996) studies support the importance of an inherited component in its pathophysiology, and an autosomal dominant form of inheritance seems likely (Maraganore et al. 1991; Lazzarini et al. 1994). Polymeropoulos et al. (1996) mapped a locus for a rapidly progressive, early-onset, autosomal dominant form of familial PD (MIM 168601) to 4q21-q23 and, subsequently, identified a mutation in the alpha-synuclein gene as its cause (Polymeropoulos et al. 1997). They found no alpha-synuclein mutations in a group of 50 sporadic cases of PD. A second susceptibility locus for autosomal dominant inheritance of parkinsonism recently has been localized to 2p13 (Gasser et al. 1998).

Patients and families affected with parkinsonism in the earlier decades of life (early-onset or juvenile parkinsonism [JP]) have long been considered separately from PD. Other than an earlier age at onset, the clinical characteristics of JP closely mirror those of classical PD, with rigidity, bradykinesia and tremor, and a slow progressive course (Ishikawa and Tsuji 1996; Yamamura et al. 1996). Both diurnal fluctuation of symptoms and mild dystonia are common in JP. Initial response to therapy is usually good, but on-off phenomena and dopa-induced dyskinesia often develop early. Results of fluorodopa positron-emission tomography (Snow et al. 1993) have shown changes similar to those seen in PD. In contrast, the pathology and pattern of inheritance in JP seem different from those in PD. Pathology studies have shown that the affected brain regions in JP are

similar to those in PD, but without the characteristic Lewy bodies (Mizutani et al. 1991; Takahashi et al. 1994) that are the hallmark of PD. In >40% of reported index cases of JP, there is a family history of the condition (Nygaard 1993). There has been a high frequency of parental consanguinity in these families, and the recurrence risk of JP is virtually confined to the siblings of cases (Yamamura et al. 1973; Tanaka et al. 1991; Ishikawa and Tsuji 1996).

We have performed linkage studies in 15 families, from four distinct ethnic backgrounds, that have autosomal recessive JP. Our full-genome screen, in three Japanese families, mapped the locus responsible for JP to 6q25.2-27, with a maximum pairwise LOD score of 3.11 for D6S1035. At that time, Matsumine et al. (1997) reported the results of a candidate-gene approach to investigate the role of the manganese superoxide dismutase gene (SOD2) in JP. Although they could not identify any SOD2 mutations in affected individuals, they found linkage of JP to a 17-cM region containing the gene, on 6q25.2-q27. We have now extended our observations to show cosegregation in four ethnic groups, with a maximum pairwise LOD score of 11.60, 1 cM from marker D6S1599. Recombination events between the JP locus and a marker within SOD2 specifically excluded this gene. The genomic screen excluded regions containing other candidate genes, as well as susceptibility loci on 4q21-22 and 2p13. We have established a detailed genetic map of the linked region, which localized the JP locus to a 6.9-cM region bounded by D6S1277 and D6S1579.

Subjects and Methods

This study was approved by the institutional review board at Columbia-Presbyterian Medical Center. All family members gave informed consent prior to their participation in the study. In each case, the diagnosis of parkinsonism was made by the family's attending neurologist, but inclusion within the study required both the presence of three of the four most typical clinical features (bradykinesia, rigidity, rest tremor, or dystonia) and a typical JP course over a follow-up period of $\geqslant 5$ years. Ten families (F1–F10; fig. 1) were from Japan. Families F2–F4 (Yamamura et al. 1973) and F5 (including histopathological findings from F5) (Yamamura et al. 1993) have been reported elsewhere. Four of the families were known to be consanguineous. Two families (F11 and F12; fig. 2), one of which was consanguineous, were from Turkey. Two families (F13 and F14; fig. 2) were from the United States, of northern European descent, and had no known consanguinity. One family (F15; fig. 2), which had several instances of intermarriage, was from Saudi Arabia.

All families were judged to show the characteristic features of JP, including early age at onset (mean 23.6 years), with rigidity, bradykinesia, rest tremor, or foot dystonia. Previous reports had shown a mean age at onset of $\sim 28 \pm 8$ years for autosomal recessive JP (Tanaka et al. 1991; Ishikawa and Tsuji 1996). The upper age limit for onset of JP in this study was therefore set at 45 years (mean + 2 SD, calculated on the basis of previous reports). Affected individuals had a disease course of $\geqslant 5$ years, with characteristic progression marked by dopa responsiveness, diurnal fluctuation, and a high frequency of dopa-related dyskinesia. There were a total of 34 affected individuals (21 female and 13 male) among 61 siblings examined. With the exception of F13, all families showed either consanguinity or several affected members of a single sibship with unaffected parents. This is consistent with an autosomal recessive mode of inheritance.

DNA was extracted from either venous blood samples or lymphoblastoid cell lines, and genotyping was performed according to standard protocols (Nygaard et al. 1993). The genomic screen used commercially available primers for 217 short tandem repeats (STRs), with an average interlocus separation of 22 cM and an average heterozygosity of 80% (Research Genetics). Locus map distances were obtained from genetic maps published by the Center for Medical Genetics, Marshfield Medical Research and Education Foundation. Additional primers—for example, to amplify an STR within the SOD2 gene (GenBank L34215)—were designed by use of published genomic sequences. All families were genotyped by use of X- and Y-chromosome markers, to verify identity and paternity. Apparently non-Mendelian inheritance of marker alleles was verified by repeat reactions; if this did not resolve the problem, the genotype was attributed to a new mutation, and the data were omitted from analysis. If an aberrant genotype pattern was observed for markers within the linked region (an apparent "null" allele), reactions were repeated with redesigned primer pairs, under varying PCR conditions. When this resolved an apparent null allele, all genotyping was repeated with optimal primers and under optimized PCR conditions.

For a genomic screen, the three Japanese families with known consanguinity (F4–F6; fig. 1) were selected as those likely to be maximally informative. The region identified in this screen was then tested by use of additional, closely spaced markers and all available families. To assist in the estimation of allele frequencies, 10 Japanese controls were also genotyped for markers in the linked region. In view of the complexity of the family structure, only one of the affected sibships in F15 was included with the other families, for pairwise and multipoint analyses (see fig. 2).

Two-point analyses were performed by use of the MLINK option of FASTLINK 4.0 (Cottingham et al.

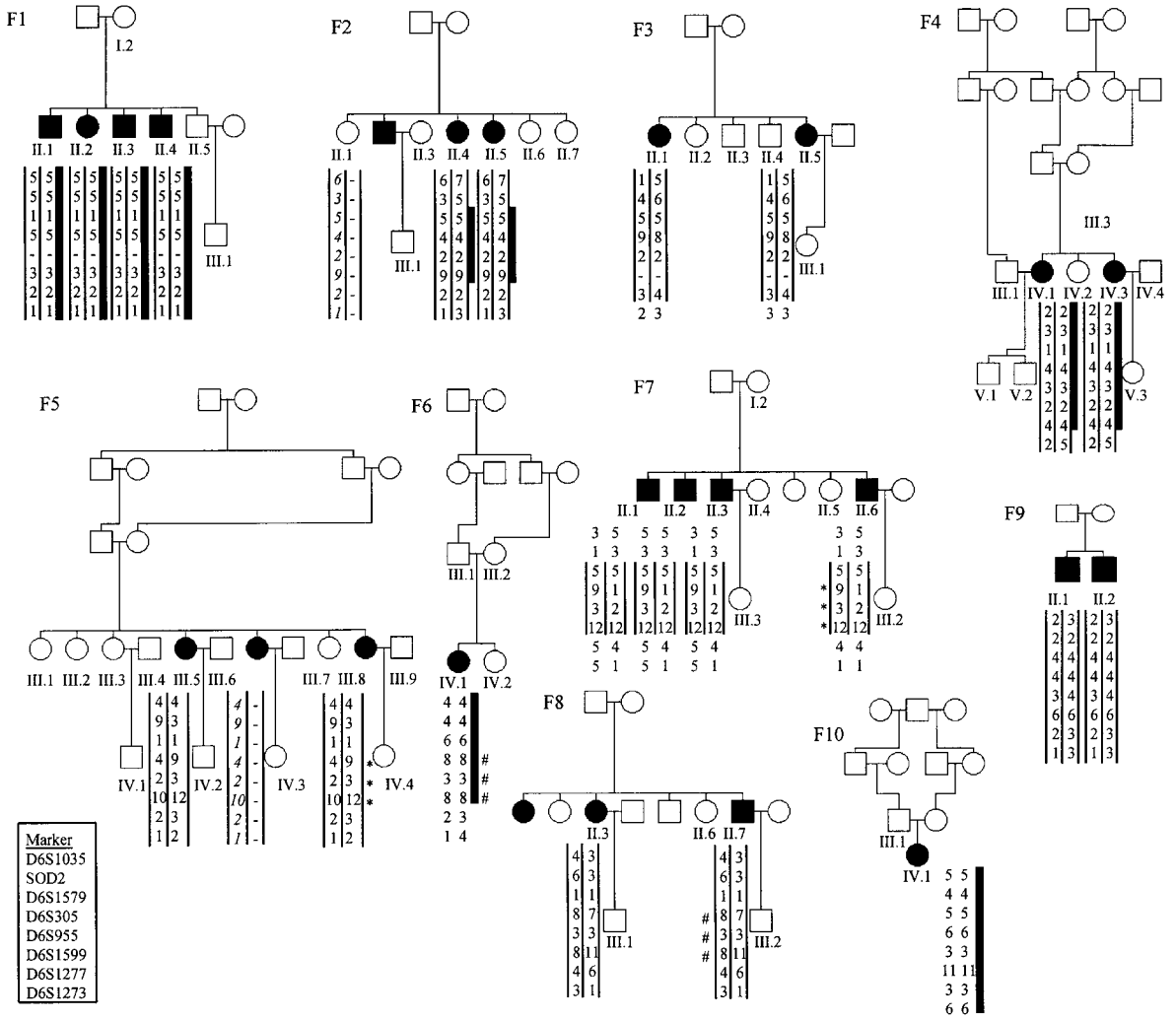

Figure 1 Ten Japanese pedigrees (F1–F10) used to show linkage to 6q25.2-q27. F4–F6 were used for an initial genomic screen. All individuals shown with a pedigree number were genotyped. Affected family members are denoted by blackened squares and circles. Inferred haplotypes for markers D6S1035, SOD2, D6S1579, D6S305, D6S955, D6S1599, D6S1277, and D6S1273 are shown for affected individuals; those in italics have been inferred from other family data. Haplotypes that are shared by all affected members of a family are boxed; those for which affected individuals show homozygosity are indicated by the thicker vertical bars. Haplotypes that are shared between families (i.e., between F5 and F7 and between F6 and F8) are also indicated (by asterisks [*] and number signs [#], respectively). Data for D6S955 in F1 and for D6S1599 in F3 are not shown; genotypes suggested null alleles in members of these families.

1993; Becker et al. 1998). Multipoint LOD scores and marker-allele haplotypes were generated by use of GENEHUNTER (Kruglyak et al. 1996). The entire data set, including all of F15, was also analyzed by use of SIMWALK2 (Sobel and Lange 1996). This program can generate approximate multipoint location scores for complex pedigrees, with all consanguinity and marriage loops intact. Homogeneity analyses used the HOMOG program (Ott 1991). Linkage disequilibrium was considered by use of the method of Risch et al. (1995). Marker-allele frequencies were estimated by allele counting within our data. An autosomal recessive model of transmission was specified, with a JP-gene frequency of .001 and a penetrance of .90. An individual was classified as unaffected only if he or she had been examined, did not fulfill any of the diagnostic criteria for JP, and was >45 years of age. All others were classified as "unknown" with regard to JP status. Individual II.1 in F14 had late onset (age >65 years) of parkinsonism, and V.3 in F15 had a short history of dystonia with diurnal fluctuation but had developed no other symptoms of JP and had not received treatment. These two individuals were also classified as "unknown" with regard to JP status.

A detailed genetic map of the candidate region was

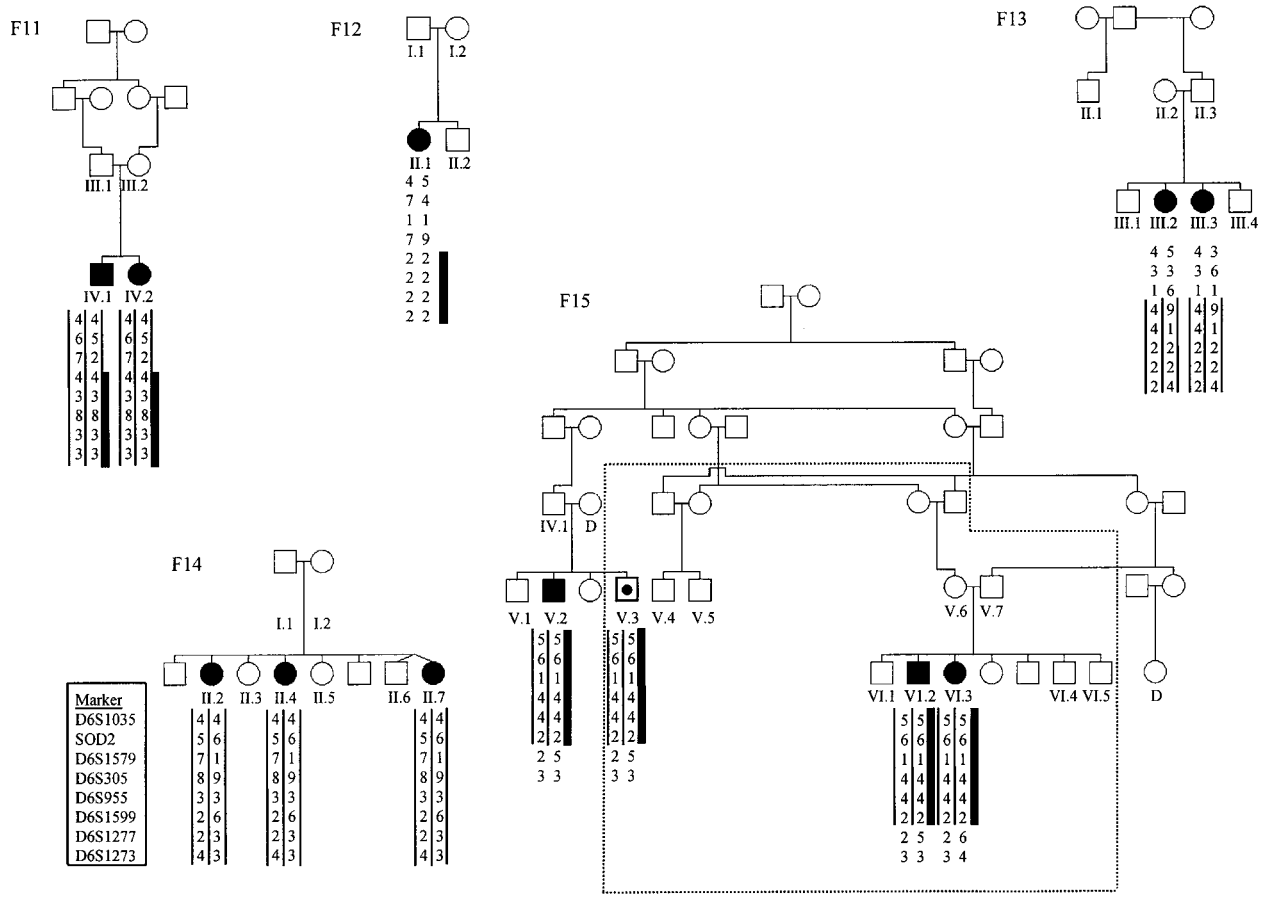

Figure 2 Turkish (F11 and F12), American (F13 and F14), and Saudi Arabian (F15) families genotyped for markers across the linked region on 6q25.2-q27. All individuals shown with a pedigree number were genotyped. Affected family members are denoted by blackened squares and circles. Inferred haplotypes for markers D6S1035, SOD2, D6S1579, D6S305, D6S955, D6S1599, D6S1277, and D6S1273 are shown for affected individuals; those in italics have been inferred from other family data. Haplotypes that are shared by all affected members of a family are boxed; those for which affected individuals show homozygosity are indicated by the thicker vertical bars. Individual D in F15 is shown twice and represented a further instance of intermarriage. V.3 in F15 had possible JP but was assigned "unknown" status for purposes of linkage analysis. In view of the complexity of the family structure, the part of F15 enclosed by the dotted line was not included along with all other families for purposes of pairwise (MLINK) and multipoint (GENEHUNTER) analyses. All of F15 was included in the analysis using SIMWALK2.

constructed on the basis of the genotyping of 61 of the CEPH reference families (Dausset et al. 1990), and these data (1,036 meioses) were analyzed by use of MultiMap (Matise et al. 1994). The map order was also verified by use of the Stanford G3 radiation-hybrid panel (Research Genetics [Cox et al. 1990]).

Results

The genomic screen with three consanguineous Japanese families (F4–F6) identified a region with a maximal two-point LOD score of 2.83 for marker D6S441. Further analyses, with additional markers for this region, confirmed linkage, with a pairwise LOD score of 3.11 for marker D6S1035. The close proximity of this locus to SOD2 (Church et al. 1992), an important candidate gene for JP, led us to look for a genetic marker for this gene. We designed a primer pair to amplify an STR within SOD2. Seven additional Japanese families were then genotyped by use of this and all other markers reported to localize within the candidate region. We confirmed cosegregation with JP in all 10 families, with a maximal pairwise LOD score of 8.44, 1 cM from marker D6S1599 (table 1).

There was a recombination between the SOD2 marker and the JP locus in F7 (individual II.2). A second recombination event, between D6S1277 and JP, was observed in a different member of this family (individual II.6). CEPH-family genotypes allowed us to map 10 markers, including SOD2, to unique positions across the

Table 1

Pairwise LOD Scores for Markers across 6q25.2-q27 in 10 Japanese Families with Autosomal Recessive JP

	Pairwise LOD at Recombination Fraction of						
Marker	.0	.01	.05	.1	.2	.3	.4
D6S419	−.18	2.84	3.86	3.73	2.71	1.48	.45
D6S959	−3.68	.44	1.82	1.98	1.49	.81	.25
D6S437	−3.01	−.78	.62	.95	.81	.43	.11
D6S363	6.27	6.56	6.35	5.63	3.92	2.17	.72
D6S1035	6.42	8.17	7.84	6.87	4.69	2.60	.90
SOD2	2.62	4.95	5.38	4.90	3.39	1.80	.54
D6S1579	7.72	7.52	6.73	5.75	3.86	2.11	.69
AFMb281wf1	2.48	2.96	3.10	2.82	1.98	1.11	.36
AFMa155td9	5.84	5.70	5.15	4.45	3.05	1.70	.55
D6S1550	4.18	4.08	3.68	3.18	2.20	1.25	.43
D6S253	5.14	5.60	5.51	4.91	3.43	1.89	.56
D6S411	4.43	4.29	3.78	3.17	2.04	1.09	.37
D6S305	6.66	7.09	6.88	6.12	4.30	2.43	.82
D6S955	2.21	2.62	2.74	2.44	1.61	.81	.23
D6S1599	8.08	8.44	8.08	7.14	4.96	2.75	.88
D6S1277	−1.20	1.19	2.44	2.52	1.87	1.00	.28
D6S1273	−4.47	.56	2.91	3.30	2.64	1.48	.42

candidate region (LOD >3.0) and suggested that D6S955 was most likely to lie between D6S1559 and D6S305 (table 2). The marker position was supported by radiation-hybrid mapping, which placed D6S955 with LOD >3.0. Using this detailed map, we restricted the JP locus to a 7.2-cM region bounded by recombination events at D6S1277 and SOD2, in F7. Multipoint analyses produced a maximal LOD score of 11.20, at the position of D6S1579 (fig. 3).

Initial genotyping for markers AFMa342vb5 (D6S1599), UT1349 (D6S955), UT681 (D6S980), and SOD2 showed either a non-Mendelian pattern of inheritance or persistent failure of amplification in one or more families. Marker afm207wa1 (D6S411) also showed a non-Mendelian pattern of inheritance in a number of CEPH families. UT681, which was extremely polymorphic in both groups, had a high mutation rate (0.010 mutations/gamete/generation) in the CEPH families. The mutation rate for the other markers (0.0019 mutations/locus/gamete/generation) was consistent with those in previous reports (Weber and Wong 1993). Since it did not show stable inheritance, UT681 was not used in linkage analysis. The use of alternative primers for SOD2 (forward, CCA AGA GTT CAT GGC TGC; and reverse, TTC TCC TGT AGG TAC AGA ATT GC) and D6S411 (forward, TGG TTG ATT GAC CCA C) demonstrated new alleles, which resolved apparent null alleles. Genotype data for D6S1599 in F3 showed non-Mendelian inheritance consistent with a null allele. All the affected individuals in F1 appeared to be homozygous for a null allele of D6S955. The data for D6S1599 in F3 and for D6S955 in F1 were therefore excluded from linkage analyses.

Haplotype analyses showed cosegregation of the linked region with JP in each family. There was no evidence of a founder effect, although the affected members of F5 and F7, who were from the same geographical region, had the same haplotype for markers D6S305, D6S955, and D6S1599. F6 and F8 shared a different JP-associated haplotype for these markers. The affected members of F1 and F2 (families without known consanguinity) were homozygous for marker alleles across the linked region, suggesting that their parents may, in fact, have a common ancestor. F5, which was consanguineous, showed segregation of marker alleles with JP, without homozygosity. Haplotypes were also used to compare the frequencies of marker alleles on JP-associated and non–JP-associated chromosomes. There was no obvious excess of a particular marker allele on JP-associated chromosomes. The greatest difference was for allele 10 of D6S1599, but this was not statistically significant ($\chi^2 = 0.13$, $P = .71$). There was, therefore, no evidence of linkage disequilibrium. The same comparison was also made for the most common three-marker haplotype, which showed no significant association.

All of the non-Japanese families were genotyped for markers across the linked region. There was cosegregation with JP in each of the other three ethnic groups. Inclusion of these families produced a maximum two-point LOD score of 11.60, 1 cM from D6S1599, and a multipoint LOD score of 15.20 at the map position of D6S1599 (fig. 3). Analyses of the entire data set (including all of F15) by use of SIMWALK2 strongly supported linkage to this location. Homogeneity testing revealed no evidence of genetic heterogeneity. There was

Table 2

High-Resolution Genetic Map of Markers across the Linked Region on 6q25.2-q27

Marker[a]	Recombination Fraction[b]	Map Distance[c] (cM)	Colocalizing Marker(s)[d]
D6S419	.010	.0	D6S959
D6S437	.019	.9	D6S363
D6S1035	.002	2.9	
SOD2	.003	3.0	
D6S1579	.017	3.3	
D6S1550	.002	5.1	AFMb281wf1, AFMa155td9
D6S305	.012	5.2	D6S253, D6S411
D6S955	.005	6.4	
D6S1599	.031	6.9	
D6S1277	.010	10.2	
D6S1273		11.2	

[a] Order is from most centromeric to least centromeric.

[b] Distance to next marker listed.

[c] From first marker listed (distances are derived by means of the Haldane function).

[d] Shown in order of decreasing heterozygosity. Radiation-hybrid mapping suggested the following map order for colocalizing markers: (AFMa155td9/AFMb281wf1)-D6S1550-(D6S253/D6S411)-D6S305.

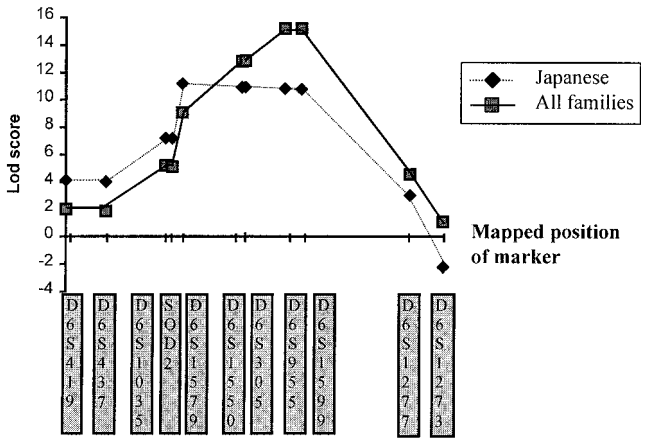

Figure 3 Multipoint LOD scores for Japanese and all families, across 6q25.2-q27.

recombination between the JP locus and markers D6S1579–D6S419 in F13, supporting exclusion of SOD2 from the linked region. A recombination event between D6S1277 and JP in F15 confirmed the other regional boundary. Haplotype analyses did not suggest a founder effect in these groups. In F11, which was consanguineous, JP-associated genotypes were concordant across the entire region, but they were only homozygous for markers telomeric to D6S253, suggesting a recombination event between D6S253 and D6S305.

The genomic screen specifically excluded regions on chromosomes 3, 11, 21, and 22, which contain genes previously considered as candidate genes in familial parkinsonism (Gasser et al. 1994). The regions of 2p13 (Gasser et al. 1998) and 4q21-q22 (Polymeropoulos et al. 1996), which have been linked to autosomal dominant parkinsonism, were excluded also.

Discussion

We have conducted a full genomic screen in three Japanese families with JP and have identified a single region segregating with JP, on 6q25.2-27. This confirms the finding reported by Matsumine et al. (1997), who had implicated the same region on the basis of their examination of SOD2 as a candidate gene for JP. Furthermore, our data from the Turkish, American, and Saudi Arabian families extends to other ethnic groups the significance that this region has for autosomal recessive JP. We have constructed a detailed genetic map of the linked region and have restricted it to a 6.9-cM region bounded by recombination events at D6S1277 and D6S1579. We have developed a polymorphic marker within SOD2 and have identified recombination events between it and JP in two of our families (F7 and F13), suggesting that SOD2 is not the JP locus.

In our study group, only D6S1579 showed homozygosity in all affected individuals. However, 6 of 15 of the unaffected family members were also homozygous for D6S1579, reflecting low heterozygosity of this marker. The examination of marker-allele haplotypes showed no evidence of a founder effect; nor was there evidence of linkage disequilibrium, despite the high density of the markers. Homozygosity of marker alleles in families not known to be consanguineous (F1 and F2) suggested that the parents of affected individuals could have a common ancestor. Shared marker-allele haplotypes for D6S305, D6S955, and D6S1599, both in F5 and F7 and in F6 and F8, suggested the existence of a common ancestor for each of these family pairs. F5, which showed linkage but not homozygosity, could represent allelic heterogeneity of JP. Two of the consanguineous families studied by Matsumine et al. (1997) also had apparent segregation without homozygosity.

Among the other families, a recombination at D6S1579 was observed in F13 (North American). The homozygosity of JP-associated genotypes in the consanguineous F11 (Turkish) was restricted to markers telomeric to D6S253. This suggests that the JP locus may lie within the 5 cM between D6S253 and D6S1277.

For several markers in this study, apparent homozygosity resulted from failure to amplify one or more alleles and was corrected by the design and use of alternative primers. In F1, D6S955 could not be amplified for any of the affected family members, despite the use of alternative primer pairings and PCR conditions. The unaffected sibling showed heterozygosity for all markers across the region. Only the mother was available for genotyping, and she showed a single allele size for D6S955. This could indicate the presence of a homozygous microdeletion, including the D6S955 locus, in affected members of F1. The maximum multipoint LOD score was associated with D6S1599, with a three-unit–LOD-score (Zmax-3) support interval of 2.9 cM in the region between D6S1550 and D6S1277. The same region was highlighted by shared haplotypes (between F5 and F7 and between F6 and F8) and homozygosity data (F11) and included the site of a possible homozygous microdeletion, in F1. If JP in F1 resulted from such a microdeletion, then the gene defect would lie within the 1.7 cM between D6S305 and D6S1599.

Family studies of JP have suggested a major-gene effect and an autosomal recessive mode of transmission. Our genomic screen revealed a single region of interest, consistent with these suggestions, and excluded all other previously considered candidate regions (Gasser et al. 1994). The regions on 2p13 (Gasser et al. 1998) and 4q21-q23 (Polymeropoulos et al. 1996), which other studies had linked to autosomal dominant forms of familial parkinsonism, were specifically excluded. We have confirmed the finding, reported by Matsumine et al.

(1997), that JP is indeed localized to 6q25.2-27. Our data show recombination between JP and a marker within SOD2, providing further evidence that SOD2 is not the gene responsible for JP. Recombination events limited the linked region to 6.9 cM. We have shown both cosegregation with JP and genetic homogeneity of JP in four ethnic groups, suggesting that this will prove to be an important JP locus. A number of our observations suggested that particular attention should be directed toward the region surrounding D6S955. Indeed, Kitada et al. (1998) have now described deletions in a novel gene within this region of 6q25.2-q27, in four Japanese families with JP.

Note added in proof.—Additional clinical data from the Japanese families reported here appear as part of an independent study by Matsumine et al. (1998).

Acknowledgments

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Electronic-Database Information

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

Center for Medical Genetics, Marshfield Medical Research and Education Foundation, http://www.marshmed.org/genetics/
GenBank, http://www.ncbi.nlm.nih.gov/Web/Genbank/ (for SOD2 [L34215])
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim
(for familial PD [MIM 168601])

References

Becker A, Geiger D, Schäffer AA (1998) Automatic selection of loop breakers for genetic linkage analysis. Hum Hered 48:49–60

Church SL, Grant JW, Meese EU, Trent JM (1992) Sublocalization of the gene encoding manganese superoxide dismutase (MnSOD/SOD2) to 6q25 by fluorescence in situ hybridization and somatic cell hybrid mapping. Genomics 14: 823–825

Cottingham RW Jr, Idury RM, Schäffer AA (1993) Faster sequential genetic linkage computations. Am J Hum Genet 53: 252–263

Cox DR, Burmeister M, Price ER, Kim S, Waters EM (1990) Radiation hybrid mapping: a somatic cell genetic method for constructing high-resolution maps of mammalian chromosomes. Science 250:245–250

Dausset J, Cann H, Cohen D, Lathrop M, Lalouel JM, White R (1990) Centre d'Étude du Polymorphisme Humain (CEPH) collaborative genetic mapping of the human genome. Genomics 6:575–577

De Michele G, Filla A, Volpe G, De Marco V, Gogliettino A, Ambrosio G, Marconi R, et al (1996) Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Mov Disord 11:17–23

de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, Manubens-Bertran JM, et al (1997) Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study—European Community Concerted Action on the Epidemiology of Parkinson's Disease. J Neurol Neurosurg Psychiatry 62:10–15

Gasser T, Müller-Myhsok B, Wsolek Z, Oehlmann R, Calne D, Bonifati V, Bereznai B, et al (1998) A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nat Genet 18:262–265

Gasser T, Wszolek ZK, Trofatter J, Ozelius L, Uitti RJ, Lee CS, Gusella J, et al (1994) Genetic linkage studies in autosomal dominant parkinsonism: evaluation of seven candidate genes. Ann Neurol 36:387–396

Ishikawa A, Tsuji S (1996) Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. Neurology 47:160–166

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, et al (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392:605–608

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lazzarini AM, Myers RH, Zimmerman TR Jr, Mark MH, Golbe LI, Sage JI, Johnson WG, et al (1994) A clinical genetic study of Parkinson's disease: evidence for dominant transmission. Neurology 44:499–506

Maraganore DM, Harding AE, Marsden CD (1991) A clinical and genetic study of familial Parkinson's disease. Mov Disord 6:205–211

Marder K, Tang MX, Mejia H, Alfaro B, Cote L, Louis E, Groves J, et al (1996) Risk of Parkinson's disease among first-degree relatives: a community-based study. Neurology 47:155–160

Matise TC, Perlin M, Chakravarti A (1994) Automated construction of linkage genetic maps using an expert system (MultiMap): a human genome linkage map. Nat Genet 6: 384–390

Matsumine H, Saito M, Shimoda-Matsubayashi S, Tanaka H, Ishikawa A, Nakagawa-Hattori Y, Yokochi M, et al (1997) Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. Am J Hum Genet 60:588–596

Matsumine H, Yamamura Y, Kobayashi T, Nakamura S, Kuzuhara S, Mizuno Y (1998) Early onset parkinsonism with diurnal fluctuation maps to a locus for juvenile parkinsonism. Neurology 50:1340–1345

Mizutani Y, Yokochi M, Oyanagi S (1991) Juvenile parkin-

sonism: a case with first clinical manifestation at the age of six years and with neuropathological findings suggesting a new pathogenesis. Clin Neuropathol 10:91–97

Nygaard TG (1993) Idiopathic dystonia-Parkinsonism. In: Stern MB, Koller WC (eds) Parkinsonian syndromes. Marcel Dekker, New York, pp 451–466

Nygaard TG, Wilhelmsen KC, Risch NJ, Brown DL, Trugman JM, Gilliam TC, Fahn S, et al (1993) Linkage mapping of dopa-responsive dystonia (DRD) to chromosome 14q. Nat Genet 5:386–390

Ott J (1991) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore

Polymeropoulos MH, Higgins JJ, Golbe LI, Johnson WG, Ide SE, Di Iorio G, Sanges G, et al (1996) Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. Science 274:1197–1199

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, et al (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276:2045–2047

Risch N, de Leon D, Ozelius L, Kramer P, Almasy L, Singer B, Fahn S, et al (1995) Genetic analysis of idiopathic torsion dystonia in Ashkenazi Jews and their recent decent from a small founder population. Nat Genet 9:152–159

Snow BJ, Okada A, Martin WRW, Duvoisin RC, Calne DB (1993) PET scanning in dopa-responsive dystonia, parkinsonism-dystonia and young-onset parkinsonism. In: Segawa M (ed) Hereditary progressive dystonia. Parthenon Publishing, Carnforth, UK, pp 181–186

Sobel E, Lange K (1996) Descent graphs in pedigree analysis: applications to haplotyping, location scores, and marker-sharing statistics. Am J Hum Genet 58:1323–1337

Takahashi H, Ohama E, Suzuki S, Horikawa Y, Ishikawa A, Morita T, Tsuji S, et al (1994) Familial juvenile parkinsonism: clinical and pathologic study in a family. Neurology 44:437–441

Tanaka H, Ishikawa A, Ginns EI, Miyatake T, Tsuji S (1991) Linkage analysis of juvenile parkinsonism to tyrosine hydroxylase gene locus on chromosome 11. Neurology 41: 719–722

Weber JL, Wong C (1993) Mutation of human short tandem repeats. Hum Mol Genet 2:1123–1128

Yamamura Y, Arihiro K, Kohriyama T, Nakamura S (1993) Early-onset parkinsonism with diurnal fluctuation–clinical and pathological studies (in Japanese). Rinsho Shinkeigaku 33:491–496

Yamamura Y, Kohriyama T, Kaseda Y, Kawakami H, Katayama S, Yanagi T, Uchida M, et al (1996) Clinical manifestations of autosomal recessive early-onset parkinsonism with diurnal fluctuation. In: Ohye C, Kimura M, McKenzie JS (eds) Advances in behavioral biology. Vol 47: The basal ganglia. Part 5. Plenum Press, New York, pp 485–489

Yamamura Y, Sobue I, Ando K, Iida M, Yanagi T (1973) Paralysis agitans of early onset with marked diurnal fluctuation of symptoms. Neurology 23:239–244