Familial Paroxysmal Dystonic Choreoathetosis

Clinical Findings in a Large Japanese Family and Genetic Linkage to 2q

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Background: Paroxysmal dystonic choreoathetosis (PDC) is a rare familial movement disorder that has been mapped to chromosome 2q31-36.

Objective: To study the first Japanese family with PDC clinically and genetically.

Patients and Methods: We studied a large Japanese family in which at least 17 members in 6 generations have been affected by PDC. We interviewed and examined 26 family members, 8 of whom revealed choreoathetosis-like and dystonialike involuntary movement and 1 of whom revealed no involuntary movement but only muscle stiffness such as the aura of paroxysmal dystonic choreoathetosis (PDC). Genetic linkage studies of this family were carried out with polymorphic DNA markers.

Results: The attacks of involuntary movement or muscle stiffness were precipitated by ovulation, menstruation, emotional stress, or caffeine or alcohol ingestion. Magnetic resonance imaging of the brain revealed no abnormalities. Clonazepam therapy was effective for reducing the attacks, and ingestion of garlic was believed by patients to be effective for softening the attacks. An affected woman with only muscle stiffness showed remission after hysterectomy for hysteromyoma. This woman also had the disease haplotype and transferred it to her typical PDC-affected daughter. Maximal pairwise logarithm of odds scores exceeding 2.00 were obtained at D2S2250, D2S1242, D2S377, D2S2148, and D2S126. The PDC gene was demonstrated by linkage analyses to be located in a 15.3-centimorgan interval lying between D2S371 and D2S339 based on pairwise and multipoint logarithm of odds scores and obligate recombination events in affected individuals.

Conclusions: Linkage of PDC to chromosome 2q32-36 was confirmed in a Japanese family. The clinical characterizations of this family with PDC include that ovulation seems also to be a precipitating factor of the attacks and that hysterectomy seems to be effective for softening the attacks. Although low-dose clonazepam treatment was most effective, garlic use was believed by affected members to be effective for softening the attacks. Furthermore, based on the results of clinical and genetic analyses, we suggest that muscle stiffness without involuntary movement may represent a forme fruste of PDC.

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PATIENTS AND METHODS

CLINICAL EVALUATION

Observations were based on a Japanese family with PDC that included 91 members of 6 generations. At least 17 members were affected with autosomal-dominant transmission. After obtaining informed consent, 26 family members (Figure 1) were examined by at least 2 neurologists (H.M., K.K., and Y.T.). Family members underwent a complete history and physical and neurologic examinations, with particular attention to the nature of the involuntary movement or muscle stiffness, age at onset, precipitating factors, and responses to therapy. A detailed family history was obtained through personal interviews with available family members. Most of the affected family members underwent brain magnetic resonance imaging, electroencephalography, and routine laboratory studies.

Oral caffeine loading testing11 and surface electromyographic recording of a typical patient (patient V-27) were performed, after obtaining her additional informed consent, to investigate the nature of her involuntary movement and the effects of caffeine intake. Anticoagulated venous blood samples were obtained from 9 affected family members, including a woman with only muscle stiffness, and 17 unaffected family members and were used for direct DNA preparation.

LINKAGE ANALYSIS

High molecular weight genomic DNA was extracted from peripheral whole blood cells according to standard procedures.12 We used the following 34 microsatellite markers on chromosome 2q: D2S2208, D2S153, D2S371, D2S317, D2S143, D2S128, D2S319, D2S2382, D2S301, D2S434, D2S295, D2S2210, D2S2179, D2S2249, D2S2244, D2S173, D2S2250, D2S433, D2S163, D2S2359, D2S120, D2S2151, D2S424, D2S1242, D2S102, D2S344, D2S377, D2S2372, D2S2148, D2S126, D2S339, D2S130, and D2S159 (Figure 1). We also analyzed a dinucleotide repeat polymorphism in the intron of AE3 (Figure 1)—a candidate PDC gene. A primer pair for the microsatellite markers was fluorescently labeled. The polymerase chain reaction was carried out as described,13 and polymerase chain reaction products were analyzed using fluorescence automated sequence analyzers (Pharmacia ALF2; Pharmacia Biotech, Uppsala, Sweden). Allele frequencies for the markers in the Japanese population were determined by genotyping at least 45 unrelated Japanese individuals. Logarithm of odds (LOD) scores were calculated using MLINK14 and LINKMAP15 subprograms of the LINKAGE (version 5.2) and FASTLINK16 software packages. When necessary, the number of alleles was reduced to save computation time. We assumed a conservative disease allele frequency of 0.001, a penetrance of 0.95, and an autosomal-dominant mode of inheritance.6 Logarithm of odds scores were also calculated with penetrances ranging from 0.7 to 1.0. The order and sex-averaged distances between the marker loci were determined from previously published data.17,18

members of this family, 8 of whom revealed choreothetosilike and dystonialike involuntary movement and 1 of whom revealed only muscle stiffness without involuntary movement. Eight members had had choreothetietic attacks that began between 3 months and 10 years old. Choreothetietic attacks of untreated patients occurred several times per month (minimum, 3 per year; maximum, 1 per day) and never occurred at a frequency of more than 2 per day but tended to taper off in frequency and severity with age. Episodes often began with an aura, such as a feeling of “stiffness,” in the upper or lower extremities or both, the face, or the neck, followed by dystonic posturing and choreoathetosis. Consciousness, vision, and hearing were not disturbed during attacks. Duration of attack ranged from 3 minutes to 4 hours and usually occurred in the afternoon and evening but never during sleep. Episodes were frequently precipitated by emotional stress; ingestion of coffee, green tea, black tea, chocolate, or alcohol; exposure to cold; fasting; epigastric discomfort; or menstruation and ovulation but not by ingestion of roasted green tea or sudden voluntary movement. Most affected family members avoided having coffee, tea, chocolate, or alcohol, and some had abstained from these since birth. Affected family members who required medical attention received low-dose clonazepam therapy, which led to nearly complete resolution of attacks. Some family members believed that use of garlic reduced the frequency and severity of the attacks. Patient IV-9, in whom attacks increased after beginning to drink alcohol at age 20 years, showed complete resolution during 6 months of abstinence at age 32 years.

In contrast, patient IV-18 revealed no involuntary movement but only muscle stiffness such as the aura of PDC. The nature of attacks of muscle stiffness resembled that of involuntary movement observed in other PDC-affected members as follows. She usually experienced attacks of muscle stiffness in either shoulder, the upper extremity, or both that was induced by common precipitatory factors of PDC such as emotional stress, coffee intake, or menstruation. Her attacks began at 7 years old, occurred several times per month, and were reduced in frequency and severity after hysterectomy for hysteromyoma at age 41 years. She experienced no attacks during pregnancy at age 23 years. She also told us that consuming garlic reduced the frequency and severity of attacks.

Results of interictal physical and neurologic examinations were normal or unremarkable in all affected family members and unaffected offspring, except for 3 unaffected family members (patients IV-3, IV-6, and IV-7) with visual field disturbance caused by cone-rod dystrophy. All 17 unaffected members examined were older than 23 years. Results of the following laboratory investigations were normal or unremarkable: complete blood cell count; sedimentation rate; renal and liver function tests; electrolytes, including serum calcium and phosphorus19,20; endocrinologic tests, including parathyroid hormone19,20 and sex hormones; and other routine studies, including glucose,21,22 creatine kinase,20,23 and lactate dehydrogenase.20 Results of routine cerebrospinal fluid studies2 and neopterin, biotin, and homovanillic
acid levels in cerebrospinal fluid were normal in 2 patients (patients IV-18 and IV-27), although the γ-aminobutyric acid level was elevated to 613 pmol/mL (reference range, 144–529 pmol/mL) in patient IV-18 and the 5-hydroxyindoleacetic acid level was decreased to 10.8 ng/mL (reference range, 24.0–74.0 ng/mL) in patient V-27. Neopterin and biotin levels in cerebrospinal fluid, which are low in other diseases such as hereditary progressive dystonia with marked diurnal fluctuation,28,29 were normal. Magnetic resonance imaging studies of 7 affected family members, including patient IV-18, revealed no abnormal findings. Intercital electroencephalography revealed normal findings except in 2 patients (patients V-28 and V-29); abnormal electroencephalographic results showed a 6-Hz wave and spike phantom in patient V-28 and a high-amplitude slow wave, which was also observed during attacks, in patient V-29.

Oral caffeine loading testing13 was performed during recording of the surface electromyogram in patient V-27, who had never drunk coffee but had never experienced choreathetotic attacks after drinking beverages containing as much as 100 mg of caffeine. Five minutes after taking 300 mg of caffeine by mouth, patient V-27 complained of epigastric discomfort followed by nausea and vomiting. Thirty minutes after loading, dystonic movements of the right upper extremity were observed, and the electromyogram showed synergistic discharge of the right biceps and triceps (Figure 2, A). Thirty-three minutes after loading, mild choreoathetotic movements began (Figure 2, B), and these movements became more severe 40 minutes after loading (Figure 2, C). The attack spread to her right lower extremity, and mild dystasia and right blepharospasm were also observed. Attacks were observed only on her left extremities 2 hours after loading and lasted up to 4 hours without loss of consciousness.

**LINKAGE TO CHROMOSOME 2q**

Genotyping of 9 affected and 17 unaffected family members (2 members died) was performed using 35 microsatellites over a region of 25 cM (Figure 1). Haplotype was assigned to minimize the number of recombinations. All affected members shared the same haplotype between D2S337 and D2S126. The maximum pairwise LOD scores for the 12 markers on chromosome 2q, which were obtained using an assumed penetrance of 0.95, are shown in the Table. The highest maximum pairwise LOD score of 2.32 was obtained for D2S2148 at a recombination fraction of 0.05. When analysis was performed with penetrances of 0.7, 0.9, 0.99, and 1.00, the LOD scores

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**Figure 1.** Chromosome 2q haplotypes in a partial pedigree family with paroxysmal dyskinesia. Haplotypes for 35 chromosome 2q microsatellite markers were given with paternal alleles on the left, assuming that minimum recombinations occurred. Precise parental phase was not determined for alleles in parentheses. The latest regional Geneathon linkage map in centimorgans (cM) is given on the right. Duplicated haplotypes of patients II-4 and II-5 are in italics. The full haplotypes are boxed. Crossover points observed in the haplotypes are indicated by horizontal bars, but some precise recombination points could not be determined because of lack of informativity of microsatellites. Obligate recombination events (arrows) in affected individuals were observed at D2S531 (patient III-24) and D2S339 (patient V-28). Four unaffected members in 1 branch (patients III-26, IV-21, IV-23, and IV-24) also have a full or partial disease haplotype. Although a precise recombination point could not be determined because of homogenous haplotypes of patient III-26 between D2S338 and D2S173 (dashed box), 3 patients (patients IV-21, IV-23, and IV-24) do not share the disease haplotype in some region between D2S319 and D2S2250.
were 2.14, 2.27, 2.36, and 2.37, respectively. The maximum LOD scores also exceeded 2.00 for D2S2250, D2S1242, D2S377, and D2S126 with penetrances of 0.7 to 1.0, confirming a localization of the causative gene in this region. For the marker in AE3, the maximum pairwise LOD score of 1.08 was obtained at a recombination fraction of 0.00. The relatively low maximum LOD score was because the allele linked to PDC in this family was common (45.5%) in Japanese control subjects. Obligate recombination events were observed at D2S371 and D2S339 in affected individuals, patients III-24 and V-28, respectively (Figure 1). The precise recombination point of patient III-24 could not be determined because of a lack of informativity of D2S317 and D2S143.

Pairwise LOD scores at a recombination fraction of 0.00 were −5.07 at D2S371 and −1.20 at D2S339 with a penetrance of 0.95 (Table), and both were −infinity with a penetrance of 1.0. Logarithm of odds scores of −infinity with a penetrance of 1.0 were also obtained at the 7 following markers: D2S2208, D2S153, D2S128, D2S301, D2S164, D2S1242, and D2S159. Multipoint LOD scores at D2S371 and D2S339 were less than −2 with a penetrance of 0.95 (data not shown). These findings support that the PDC gene is localized to a 15.3-cM interval lying between D2S371 and D2S339.

Haplotype analysis of the unaffected members (patients IV-21, IV-23, and IV-24), constructed to minimize the numbers of recombination events, suggests the candidate region may narrow to 6.4 cM between D2S2319 and D2S2250—slightly closer to the centromere on the long arm of chromosome 2 than to the previously reported candidate region of the PDC gene.7-10 However,
this is not conclusive given that it is based on nonobligate recombinations.

Furthermore, the alleles of D2S377 and D2S2148 linked to PDC in this family were rare (0.48%) in Japanese controls, indicating the usefulness of these markers for further genetic analyses of PDC.

We described a large Japanese family affected with familial PDC in which we established linkage to chromosome 2q32-36. This is also the first clinical and genetic evidence that only muscle stiffness, ie, the aura of PDC, may represent a forme fruste of PDC.

Patient IV-18, the mother of the proband, suffered from muscle stiffness without involuntary movement or exertional cramping.26 She felt that she had only a kind of “stiff shoulder” so she did not notice that she had attacks like her mother or daughter. Her attacks were also induced by common precipitating factors of PDC. Furthermore, patient III-24, her PDC-affected mother, also experienced only the aura of PDC, which was not followed by involuntary movement. Patient V-27, her PDC-affected daughter, showed nearly complete resolution of involuntary movement attacks when treated with clonazepam and subsequently experienced only the aura of PDC without involuntary movement. We demonstrated that patient IV-18 also had the disease haplotype and transferred it to her typical PDC-affected daughter (patient V-27). These findings demonstrate that her muscle stiffness represented a forme fruste of PDC. Exertional cramping could also be a forme fruste,26,27 but muscle stiffness is more likely. Muscle stiffness may present as milder or variable expression of the PDC gene. Although incomplete inheritance of PDC has been reported,6-7,11,26 some of the uncounted family members might simply have had milder or variable expressions of the PDC gene. Thus, the penetrance of PDC in this family seemed high.

Caffeine is thought to be a major precipitating factor of PDC because ingestion of coffee or tea often induces attacks. Our results support this idea as follows. First, intake of coffee and green or black tea precipitated the attacks, but drinking roasted green tea, which contains lower levels of caffeine, was not a precipitating factor in this family. Second, the oral 300-mg caffeine loading test successfully induced an attack in patient IV-27, although she had never experienced attacks after drinking beverages containing 100 mg of caffeine. Furthermore, she had never drunk coffee. Drinking decaffeinated coffee also induced attacks of PDC,28 but epigastric discomfort also precipitated attacks in this family.

Although endocrinologic test results were unremarkable in affected family members, we also suspect that PDC may be related to endocrinologic abnormalities for the following reasons. First, hysterectomy softened attacks in patient IV-18. Although Kurlan et al26 described a patient with PDC who underwent hysterectomy for pelvic spasm, there have been no previous reports that hysterectomy improved attacks of PDC. Patient IV-18 had not experienced pelvic spasms attributed to dystonia. Second, patient IV-18 did not experience attacks during pregnancy. The effects of pregnancy on PDC attacks vary among reports,29,30 but the attacks were also shown to be reduced after menopause.30 Third, ovulation in addition to menstruation was an additional possible precipitating factor of PDC in this family, especially in patient V-27. Daily measurement of her basal body temperature (data not shown) might support this hypothesis. Thus, there is the possibility that sex hormones such as estrogen may alter the frequency and severity of PDC attacks.

Clonazepam is the most efficacious among the numerous drugs used for PDC.2,23-31 Our affected family members received clonazepam with significant therapeutic effect. The usefulness of garlic for PDC has not been reported previously, but our affected family members told us that garlic use also has an inhibitory effect on attacks of involuntary movement. Garlic contains high levels of allicin and vitamins B and C, especially vitamin B6, which may be a reason why garlic softened the attacks of PDC. However, we need further study to confirm this.

Other paroxysmal neurologic disorders, such as hyperkalemic-24 and hypokalemic periodic paralysis,32 are associated with mutations in the sodium channel SCN4A gene or the calcium channel CACNL1A3 gene. Moreover, choreoathetosis induced by movement can sometimes be observed in patients with periodic ataxia with myokymia, which is associated with mutations in the potassium channel KCNA1 gene.33 A gene for paroxysmal choreoathetosis/spasticity, a clinically similar disorder to PDC, is mapped to a potassium channel gene cluster on chromosome 1p.35 These suggest that PDC may also be a kind of channelopathy. Therefore, AE3, which is mapped to 2q3636 and located between D2S128 and D2S126, is a candidate PDC gene.7 We also performed the linkage analysis of a polymorphic DNA marker in the AE3 gene in this Japanese family, which did not exclude it as the causative gene for PDC.

The PDC gene was demonstrated by linkage analyses to be located in a 15.3-cM interval lying between D2S371 and D2S339 based on pairwise and multipoint LOD scores. The maximum LOD scores of 2.2 to 2.3 were obtained at D2S2250, D2S1242, D2S377, D2S2148, and D2S126. Although these values do not meet strict criteria (LOD score >2.5), the result is consistent with the gene causing this disorder being located on chromosome 2q. Based on haplotypes constructed to minimize numbers of recombination events, an unaffected family member (patient III-26) is assumed to share the whole disease haplotype transferred from her affected father (patient II-4). The 3 children of patient III-26, who are all unaffected and older than 30 years, are assumed to not share the disease haplotype between D2S2382 and D2S173. Although these results might suggest that the PDC gene is located in the region between D2S2319 and D2S2250, the observation is made only on unaffected individuals, and such a conclusion cannot be made unequivocally. Our results were consistent with those of previous reports,6-10 suggesting that the probable location of the gene might be a 2.5-cM interval between D2S295 and D2S2359 (Figure 3).

We can now apply a candidate gene approach or a standard approach of positional cloning for identification of the PDC gene. To identify the causative gene for...
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Figure 3. Candidate region of the paroxysmal dystonic choreoathetosis gene of our family and previous reports (represented by the numbers to the right). A indicates a definite region of our family; B, a probable region of our family based on nonobligate recombination of unaffected members.

PDC would be an important step toward a better understanding of its pathogenesis and developing more effective therapy for paroxysmal choreoathetosis and other paroxysmal neurologic disorders.

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