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Paroxysmal Kinesigenic Choreoathetosis Locus Maps to Chromosome 16p11.2-q12.1

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Summary

Paroxysmal kinesigenic choreoathetosis (PKC), the most frequently described type of paroxysmal dyskinesia, is characterized by recurrent, brief attacks of involuntary movements induced by sudden voluntary movements. Some patients with PKC have a history of infantile afebrile convulsions with a favorable outcome. To localize the PKC locus, we performed genomewide linkage analysis on eight Japanese families with autosomal dominant PKC. Two-point linkage analysis provided a maximum LOD score of 10.27 (recombination fraction [θ] = .00; penetrance [p] = .7) at marker *D16S3081*, and a maximum multipoint LOD score for a subset of markers was calculated to be 11.51 (p = 0.8) at *D16S3080*. Haplotype analysis defined the disease locus within a region of ~12.4 cM between *D16S3093* and *D16S416*. P1-derived artificial chromosome clones containing loci *D16S3093* and *D16S416* were mapped, by use of FISH, to 16p11.2 and 16q12.1, respectively. Thus, in the eight families studied, the chromosomal localization of the PKC critical region (PKCR) is 16p11.2-q12.1. The PKCR overlaps with a region responsible for "infantile convulsions and paroxysmal choreoathetosis" (MIM 602066), a recently recognized clinical entity with benign infantile convulsions and nonkinesigenic paroxysmal dyskinesias.

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Introduction

Paroxysmal kinesigenic choreoathetosis (PKC [MIM 128200]) is a heritable neurological disorder characterized by recurrent and brief attacks of unilateral or bilateral involuntary movement that are usually induced by sudden voluntary movements or, sometimes, by startles. PKC attacks consist of any combinations of dystonic, choreoathetotic, and ballistic components; often occur daily and, frequently, more than once within a day; and usually last seconds to minutes but not >5 min. Consciousness never alters during attacks. The onset of PKC is usually in childhood or in early adolescence, and the frequency and severity generally diminish with age. PKC responds to treatment with anticonvulsants such as phenytoin and carbamazepine. Results of neurological examinations, including electroencephalography and computed tomography (CT) of the brain, have been normal, except in a few patients (Kertesz 1967; Lance 1977; Goodenough et al. 1978; Fahn 1994; Marsden 1996). It has been reported that 40%–70% of PKC cases are familial, and the remaining cases are sporadic. In most reported families with PKC, the disease is inherited in an autosomal dominant fashion with incomplete penetrance (Kertesz 1967; Lance 1977; Goodenough et al. 1978; Fahn 1994; Marsden 1996). Familial cases of PKC may be more common in the Japanese and in the Chinese (Fahn 1994). More males tend to be affected than females, with the male : female ratio being from 3 : 1 to 4 : 1 (Kertesz 1967; Lance 1977; Goodenough et al. 1978; Fahn 1994; Marsden 1996). It has been reported that some PKC patients or their family members have a history of epilepsy (Jung et al.

Table 1

Clinical Findings in Eight Families with PKC

Family and Individual No. (Sex)[a]	Patient Age (years)			Characteristics of PKC				
	At Present	At Onset	At Cessation	Trigger[b]	Duration of Attacks[c]	Involuntary Movement[d]	Response to Anticonvulsants[e]	History of IC (mo)
1:								
II-1 (M)	Dead	14	18–19	SM/S	FS-M	A/D		None
II-3 (F)	82	17	19	SM/S	FS-M	A/D		None
II-4 (M)	79	14	20	SM/S	FS-M	A/D		None
II-11 (F)	68	15	16	SM	FS-M	A		None
III-6 (F)	53	10	Current	SM/S	FS-M	A/D	+ (CBZ)	None
III-8 (F)	50	10	Current	SM/S	FS-M	A/D	+ (CBZ)	6 (Febrile)
III-11 (M)	40	10	30	SM	FS-M	A/D	+ (CBZ)	None
III-14 (M)	50	11	Current	SM	FS-M	A/D	+ (PHT)	0–24
III-18 (F)	43	13	15	SM	FS-M	A		None
III-20 (M)	39	10	20	SM	FS-M	A/D		None
III-21 (F)	36	10	12	SM	FS-M	A/D		0–12
IV-3 (F)	27	10	15	SM	FS-M	A/D	+ (CBZ)	5–24
IV-6 (M)	10	5	Current	SM	FS	A	+ (CBZ)	None
IV-7 (M)	24	13	15	SM	FS-M	A		6–12
IV-8 (M)	22	13	15	SM	FS-M	A		7–12
IV-9 (M)	21	…	…	…	…	…		7–12
2:								
I-2 (F)	72	Childhood	35	SM	FS	C		0–12
II-3 (M)	48	12	15	EX	FS	C		None
II-7 (F)	43	9	Current	SM	…	C		Infancy
III-3 (M)	22	11	Current	SM	FS-M	C	− (PHT/VPA)	9–18
III-7 (M)	17	7	Current	SM	FS	C	+(PB/VPA)	6–9
3:								
I-2 (F)	37	11	22	SM	FS	A		None
II-1 (F)	14	5	Current	SM/S	FS-M	A	+ (PHT)	None
II-2 (M)	12	10	11	SM/S	FS	A		None
4:								
I-1 (M)	85	11	25	SM	FS-M	C		None
II-2 (M)	49	6	20	SM	FS-M	C		None
III-1 (M)	12	8	Current	SM	FS-M	C	+ (CBZ)	None
III-2(M)	8	6	Current	SM	FS-M	C	+ (CBZ)	5
5:								
I-1 (M)	53	Childhood	?	SM	FS-M	C		None
II-1 (M)	24	10	Current	SM	FS-M	C	+ (CBZ)	10
II-2 (M)	13	5	11	SM	FS-M	C	+ (CBZ)	10
6:								
I-3 (M)	40	9	27	SM	FS-M	C	+ (CBZ)	None
II-1 (M)	16	13	Current	SM	FS-M	C	+ (CBZ)	4
II-2 (M)	14	8	Current	SM	FS-M	C	+ (CBZ)	3
7:								
I-1 (M)	71	Childhood	20	SM	FS-M	C		None
II-1 (M)	45	9	30s	SM	FS-M	C		None
II-4 (F)	43	9	30s	SM	FS-M	C		None
III-1 (M)	17	7	12	SM	FS-M	C	+ (CBZ)	None
III-2 (M)	15	10	14	SM	FS-M	C	+ (CBZ)	5
III-3 (F)	12	…	…	…	…	…		11
III-5 (F)	18	11	16	SM	FS-M	C	+ (CBZ)	2
8:								
I-1 (M)	67	10	25	SM	FS-M	C		None
II-2 (F)	42	8	26	SM	FS-M	C		None
II-4 (M)	31	7	25	SM	FS-M	C	+ (PHT)	None
III-1 (M)	13	9	Current	SM	FS-M	C	+ (CBZ)	None

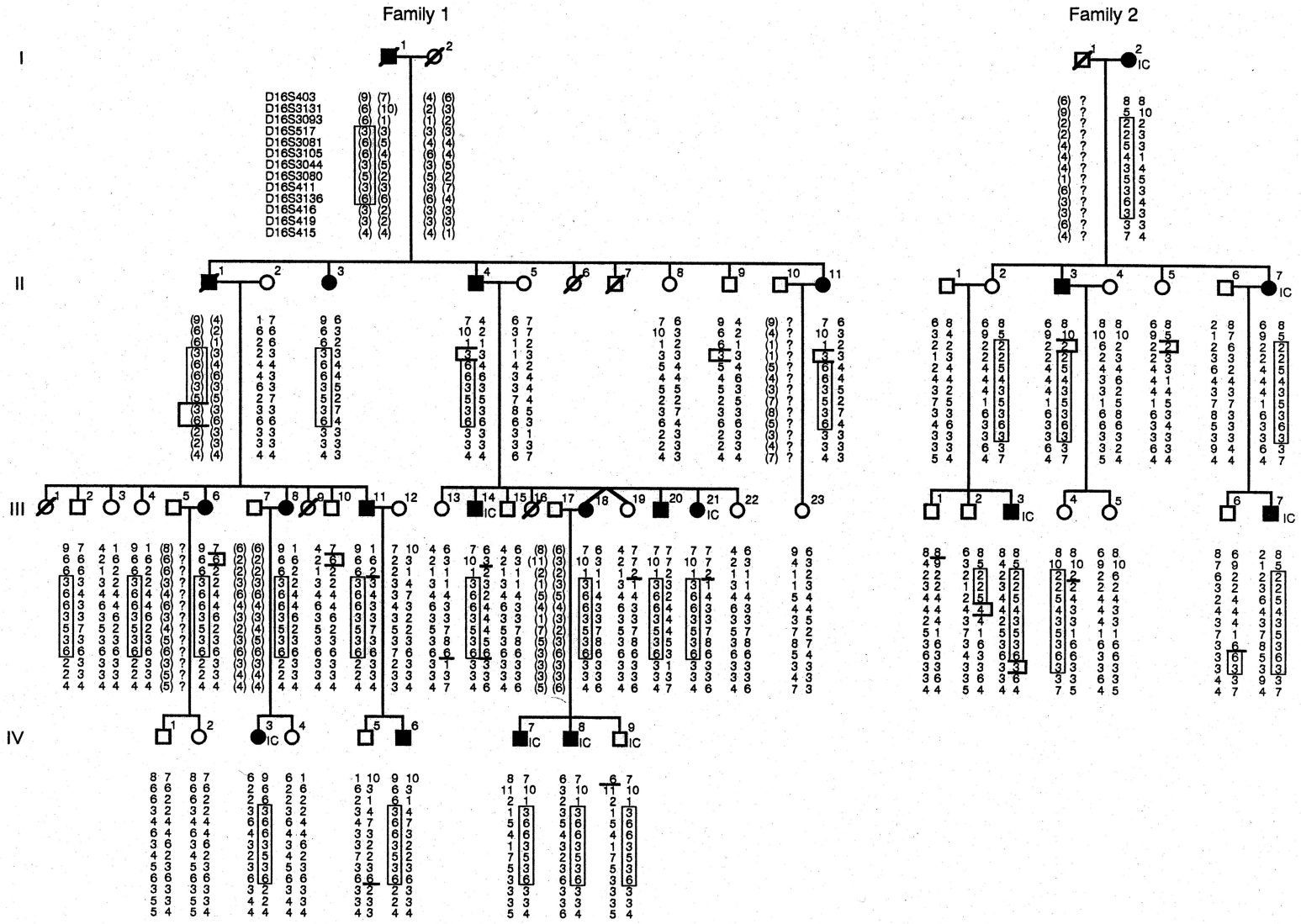
[a] M = male; F = female.

[b] SM = sudden movements, S = startles, and EX = exertion.

[c] FS-M = a few seconds to 1 min.

[d] A = athetoid, D = dystonic, and C = choreoathetotic.

[e] A plus sign (+) denotes effective, and a minus sign (−) denotes not effective; CBZ = carbamazepine, PHT = phenytoin, VPA = valproate, and PB = phenobarbital.


Family 1
Family 2
I
II
III
IV
D16S403
D16S3131
D16S3093
D16S517
D16S3081
D16S3105
D16S3044
D16S3080
D16S411
D16S3136
D16S416
D16S419
D16S415
IC

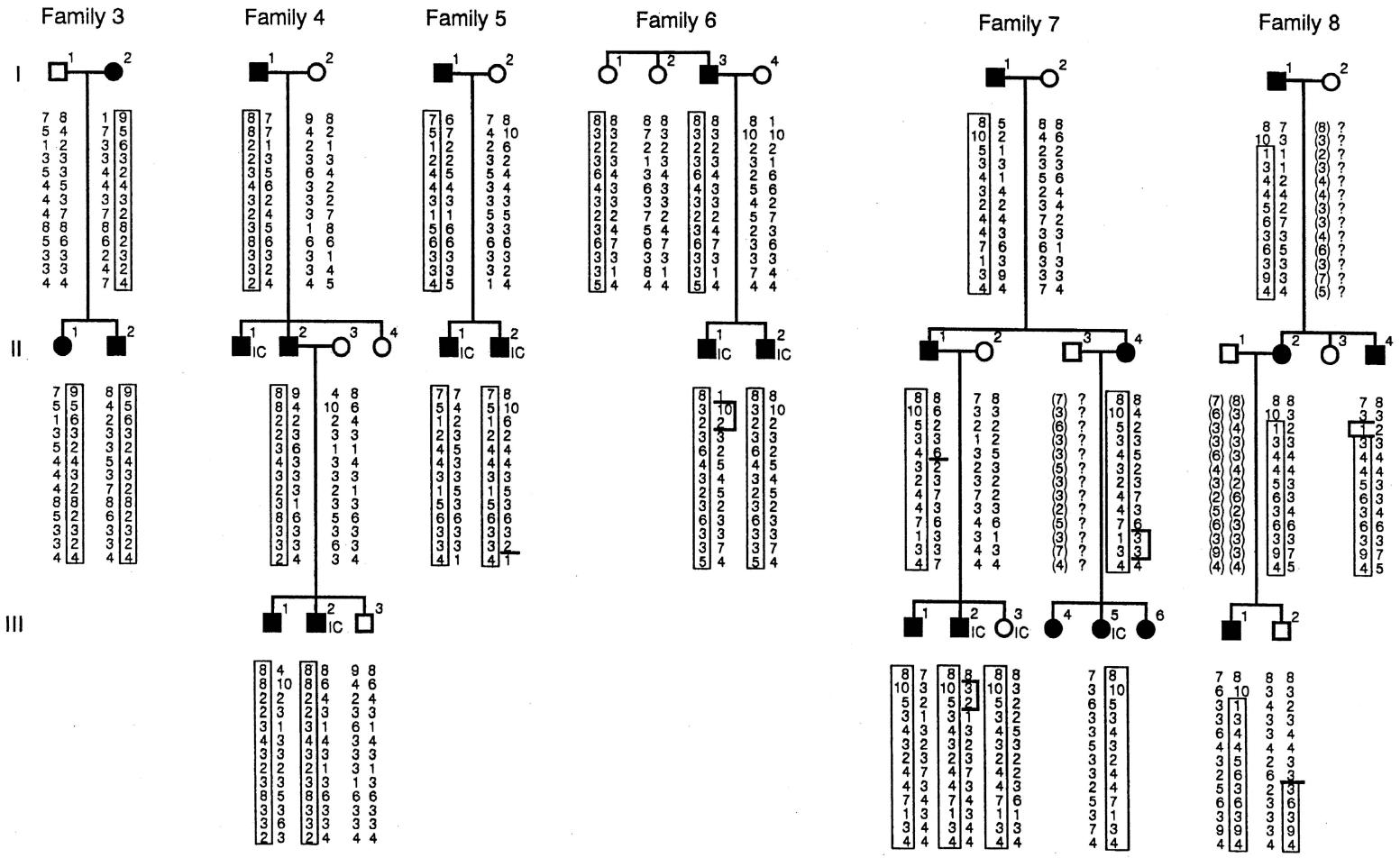


Figure 1 Pedigrees of eight families with PKC. The blackened squares and circles and the letters "IC" denote individuals affected with PKC and those with infantile convulsion, respectively. The numbers in boxes and the numbers in parentheses represent putative disease haplotypes and haplotypes estimated (deduced from data in sibs and/or children), respectively, in family members. Heavy short lines indicate definite recombination sites, and heavy brackets indicate recombination sites that could have occurred on either side of the corresponding marker(s).

Table 2

Two-Point LOD Scores of PKC and/or IC with Various Values of Penetrance (*p*)

Locus and *p* Value	LOD Score at (θ) =							
	.0	.001	.05	.1	.15	.2	.3	.4
D16S403:								
.9	−4.816	−4.675	.806	2.031	2.517	2.635	2.215	1.207
.8	−3.396	−3.324	1.221	2.214	2.561	2.593	2.102	1.115
.7	−2.776	−2.729	1.333	2.226	2.508	2.501	1.985	1.032
.6	−2.458	−2.424	1.315	2.158	2.409	2.384	1.870	.958
D16S3131:								
.9	−6.756	−4.314	1.975	3.097	3.479	3.485	2.822	1.534
.8	−5.182	−2.815	2.654	3.467	3.661	3.549	2.770	1.470
.7	−4.476	−2.161	2.938	3.614	3.714	3.540	2.703	1.412
.6	−4.096	− 1.836	3.044	3.648	3.699	3.493	2.630	1.358
D16S3093:								
.9	−1.370	−1.290	1.356	1.815	1.920	1.849	1.412	.758
.8	−.519	−.481	1.669	1.991	2.010	1.886	1.396	.735
.7	−.121	−.097	1.805	2.066	2.044	1.891	1.374	.713
.6	.107	.123	1.865	2.093	2.048	1.880	1.350	.692
D16S517:								
.9	2.171	2.168	1.994	1.798	1.588	1.367	.895	.415
.8	2.155	2.152	1.957	1.749	1.534	1.312	.850	.392
.7	2.125	2.121	1.915	1.702	1.484	1.263	.812	.372
.6	2.092	2.088	1.875	1.658	1.440	1.220	.778	.354
D16S3081:								
.9	9.615	9.612	9.270	8.656	7.867	6.942	4.773	2.281
.8	10.218	10.205	9.505	8.685	7.775	6.783	4.580	2.154
.7	10.269	10.253	9.442	8.550	7.596	6.583	4.391	2.040
.6	10.126	10.109	9.259	8.343	7.378	6.367	4.211	1.939
D16S3105:								
.9	4.802	4.795	4.425	3.989	3.513	3.007	1.948	.905
.8	4.791	4.782	4.355	3.893	3.409	2.906	1.874	.871
.7	4.690	4.681	4.245	3.782	3.302	2.810	1.808	.842
.6	4.566	4.557	4.125	3.669	3.200	2.720	1.749	.817
D16S3044:								
.9	3.385	3.383	3.200	2.935	2.617	2.258	1.462	.656
.8	3.335	3.331	3.082	2.786	2.458	2.103	1.343	.597
.7	3.207	3.202	2.934	2.631	2.305	1.960	1.238	.547
.6	3.063	3.057	2.782	2.481	2.162	1.830	1.146	.503
D16S3080:								
.9	6.935	6.925	6.398	5.802	5.163	4.488	3.055	1.553
.8	6.655	6.644	6.097	5.503	4.877	4.225	2.860	1.446
.7	6.357	6.346	5.802	5.220	4.613	3.986	2.686	1.353
.6	6.062	6.051	5.519	4.954	4.370	3.769	2.531	1.272
D16S411:								
.9	3.745	3.747	3.715	3.534	3.260	2.923	2.112	1.145
.8	4.338	4.334	4.069	3.745	3.381	2.985	2.109	1.125
.7	4.585	4.578	4.227	3.841	3.433	3.005	2.096	1.105
.6	4.698	4.691	4.296	3.878	3.446	3.002	2.076	1.086
D16S3136:								
.9	3.535	3.535	3.448	3.228	2.926	2.569	1.752	.867
.8	3.951	3.946	3.688	3.364	2.997	2.598	1.740	.849
.7	4.147	4.140	3.806	3.429	3.027	2.604	1.722	.832
.6	4.254	4.247	3.867	3.459	3.034	2.597	1.702	.817
D16S416:								
.9	−3.216	−.261	1.401	1.557	1.520	1.382	.940	.424
.8	−2.322	.018	1.530	1.600	1.511	1.344	.885	.389
.7	−1.894	.082	1.541	1.577	1.467	1.288	.831	.358
.6	−1.644	.071	1.504	1.525	1.407	1.226	.779	.331
D16S419:								
.9	−7.579	−3.116	.590	1.241	1.472	1.486	1.146	.575
.8	−5.717	−1.994	1.253	1.631	1.689	1.590	1.136	.544
.7	−4.793	−1.556	1.526	1.790	1.768	1.614	1.106	.514
.6	−4.222	−1.372	1.627	1.837	1.776	1.595	1.066	.484
D16S415:								
.9	−2.665	.098	1.837	2.022	1.987	1.837	1.342	.706
.8	−1.420	.822	2.299	2.322	2.181	1.958	1.380	.710
.7	−.753	1.159	2.533	2.483	2.288	2.027	1.401	.711
.6	−.324	1.341	2.661	2.572	2.348	2.065	1.412	.711

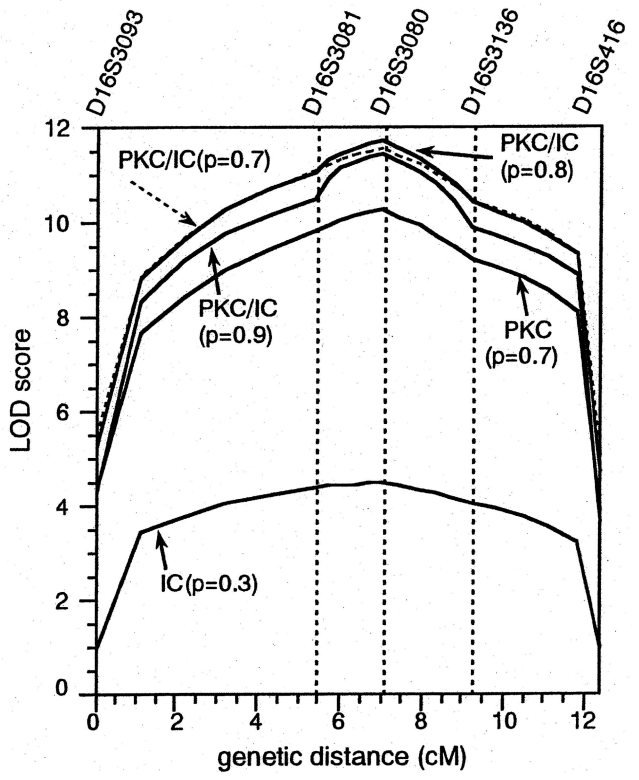


Figure 2 Multipoint LOD scores with various values of penetrance (*p*), calculated with use of the VITTESE program (O'Connell and Weeks 1995). Intermarker distances and marker order are according to Dib et al. (1996). PKC denotes family members affected with PKC; PKC and/or IC denotes inclusion of those affected with PKC and/or IC.

1973; Goodenough et al. 1978; Tan et al. 1998), although a causal relationship between the two abnormalities remains controversial. The frequent occurrence of afebrile infantile convulsions (IC) in patients with PKC or in their relatives has been well recognized in previous reports (Lishman et al. 1962; Hudgins and Corbin 1966; Fukuyama and Okada 1968; Hamada et al. 1998; Sadamatsu et al. 1999). According to a multicenter survey in Japan (Nagamitsu et al. 1999), of 100 patients with PKC who were examined, 17% developed IC with favorable outcome at age <12 mo.

PKC has been described as a form of paroxysmal dyskinesia. Paroxysmal dyskinesias are genetically and clinically heterogeneous, and there are at least seven different forms: (1) PKC; (2) paroxysmal dystonic (nonkinesigenic) choreoathetosis (PDC [MIM 118800]); (3) paroxysmal exertion-induced dyskinesia (PED); (4) nocturnal (hypnogenic) paroxysmal dyskinesia (NPD); (5) paroxysmal choreoathetosis and spasticity (CSE [MIM 601042]); (6) infantile convulsions and paroxysmal choreoathetosis (ICCA [MIM 602066]); and (7) Rolandic epilepsy, paroxysmal exercise-induced dystonia, and writer's cramp (RE-PED-WC). These forms are probably distinct from one another because of the different frequency and duration of attacks, the different triggers or precipitating factors, the different effectiveness of anticonvulsants, and the presence or absence of additional manifestations. Attacks of PDC occur during rest without any triggers, and they last for 2 min to 4 h. PED is characterized by attacks precipitated by prolonged exercise and lasting 5–30 min (Lance 1977; Goodenough et al. 1978; Fahn 1994; Marsden 1996). Attacks of NPD occur during sleep. Most cases of NPD are now regarded as nocturnal frontal-lobe epilepsy (ENFL) (Marsden 1996). CSE and ICCA share a clinical manifestation as a combination of PDC with additional symptoms, constant spastic paraplegia, and benign infantile afebrile convulsions (Auburger et al. 1996; Szepetowski et al. 1997). All but one of the forms are inherited in an autosomal dominant manner, whereas RE-PED-WC is an autosomal recessive condition (Guerrini et al. 1999). Four loci of paroxysmal dyskinesias have been mapped: PDC maps to chromosome 2q33-q35 (Fink et al. 1996; Fouad et al. 1996), CSE to chromosome 1p (Auburger et al. 1996), ICCA

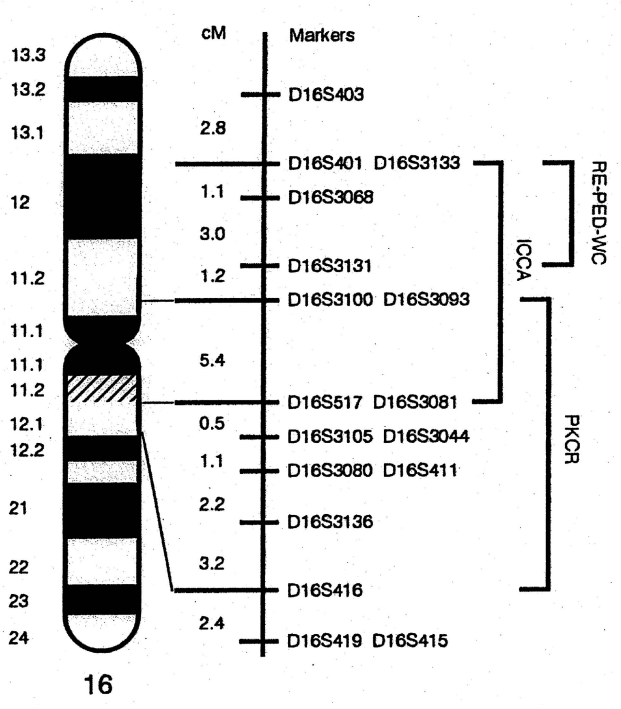


Figure 3 Disease map of paroxysmal dyskinesias on chromosome 16. PKCR is deduced from data from the present study, ICCA is deduced from data from Szepetowski et al. (1997), and RE-PED-WC is deduced from data from Guerrini et al. (1999).

to chromosome 16p12-q12 (Szepetowski et al. 1997), and RE-PED-WC to chromosome 16p12-p11.2 (Guerrini et al. 1999). Nocturnal frontal-lobe epilepsy is genetically heterogeneous, and two loci—ENFL1 (MIM 600513) and ENFL2 (MIM 603204)—have been mapped to 20q13.2 (Phillips et al. 1995) and 15q24 (Phillips et al. 1998), respectively. Here we report the results of a genomewide linkage analysis of eight Japanese families with PKC.

Subjects and Methods

Families and Patients

We collected eight Japanese families that include two or more individuals affected with PKC. A total of 84 members in the eight families (families 1–8) participated in the present study and provided written informed consent. PKC was diagnosed in 43 of the 84 participants (table 1; fig. 1). Detailed clinical manifestations for family 2 and for families 4–8 were reported elsewhere (Nagamitsu et al. 1999; Sadamatsu et al. 1999). Among the 43 patients, mean age at the onset of the disease was 10.0 years (range 5–17 years, with SD score of 2.7 years). Attacks were usually precipitated by sudden voluntary movements and, rarely, by startles, but they never occurred without provocation. The duration of the entire attack ranged from a few seconds to 1 min. Treatment with anticonvulsants completely controlled the attacks in most patients. The attacks in most patients ceased spontaneously in adulthood. Eighteen patients (41.9%) also had afebrile, general convulsions in infancy. The PKC manifestations were not different between patients with and without IC. Two individuals (IV-9 in family 1 and III-3 in family 7) were affected with IC but had no evidence of PKC (table 1).

Direct and vertical transmissions of PKC were observed in all eight families. There was one instance (II-2 in family 2) of an individual in whom disease transmission was skipped, although both the individual's mother (I-2 in family 2) and her son (III-3 in family 2) are both unequivocally affected with PKC. The male : female ratio of the patients in the eight families was 2 : 1. These findings indicate that PKC in the families is inherited in an autosomal dominant fashion with incomplete penetrance.

Genotyping and Linkage Analysis

Genomic DNA was extracted from peripheral blood leukocytes drawn from the 84 participants. We determined genotypes of the participants by using a total of 354 Généthon microsatellite markers distributed in a 5–20-cM interval across the genome (Dib et al. 1996) and a DNA sequencer–assisted method (Mansfield et al. 1994). In brief, DNA was amplified by PCR with primers labeled with fluorescence dye Cy5 (Pharmacia Biotech). Fluorescent PCR products were electrophoresed in an automated DNA sequencer (ALFexpress DNA sequencer) (Pharmacia Biotech). The resulting data were analyzed with software (Fragment Manager™, version 1.2; Pharmacia Biotech) to determine genotypes.

Two-point LOD scores were calculated by MLINK of the FASTLINK software, version 4.0P (Lathrop et al. 1984; Cottingham et al. 1993; Schaffer et al. 1994), with assumptions that, in the eight families, PKC is inherited in an autosomal dominant mode with incomplete penetrance, that the frequency of the mutant allele is .0001, and that each allele frequency of each marker locus is equal. Multipoint LOD scores were calculated by use of the VITTESE program (O'Connell and Weeks 1995). Genetic distances between the marker loci examined were determined on the basis of the Généthon linkage map (Dib et al. 1996). Genetic heterogeneity was tested by use of the HOMOG program (Ott 1991).

FISH

To determine the chromosomal localization of microsatellite markers used for anchors, their corresponding PAC clones were isolated by PCR-based screening of a human PAC library (Roswell Park Cancer Institute-1,3), as described elsewhere (Matsumoto et al. 1997), and were used for FISH to normal metaphase chromosomes, as described elsewhere (Wakui et al. 1999).

Results

We first undertook a genomewide search for the PKC locus. Because PKC and IC are possibly associated with each other, we classified family members who had either form, or both forms, as being "clinically affected." As a result, a high two-point LOD score ($Z_{max} = 6.94$, $\theta = .00$) was obtained at *D16S3080,* when p was assumed to be .9 (table 2). We chose additional markers located near *D16S3080* and analyzed the eight families with these markers. The highest two-point LOD score was calculated to be 10.27 ($\theta = .00$) for *D16S3081,* when p was assumed to be .7 (table 2). A maximum multipoint LOD score for a subset of markers was 11.51 ($p = .8$) at *D16S3080* (fig. 2). Homogeneity was not rejected in a HOMOG test (data not shown).

To confirm the linkage of PKC under more-definite clinical diagnosis, two-point and multipoint LOD scores were calculated again, when two individuals (IV-9 in family 1 and III-3 in family 7) who had IC only but who did not have any episodes of PKC attacks were excluded from the category of "PKC patient." A maximum two-point LOD score of 9.00 was observed at *D16S3081*

(p = .7). We also confirmed a tight linkage by multipoint analysis (fig. 2).

Haplotype analysis of the eight families revealed that all patients with PKC in each family share alleles for loci between *D16S517* and *D16S3136*. Recombinations occurred between *D16S3093* and *D16S3081* in individuals II-4 and II-11 in family 1 and between *D16S3131* and *D16S517* in individual II-3 in family 2 and individual II-4 in family 8. Recombinations were also observed between *D16S3080* and *D16S416* in individual II-1 in family 1 and between *D16S3136* and *D16S419* in individual III-3 in family 2 (fig. 1). These results, along with the high two-point LOD score, indicate that the putative PKC gene is localized to a segment between *D16S3093* and *D16S416* (figs.1 and 3).

We isolated three PAC clones (104-G-3, 158-O-8, and 83-D-21) that correspond to the *D16S3093, D16S517,* and *D16S416* loci, respectively. FISH analysis, with use of these three clones as probes, gave fluorescence signals at 16p11.2, 16q12.1, and 16q12.1, respectively. Thus, in the eight families examined, PKC maps to 16p11.2-q12.1 and, most likely, to 16q12.1.

Discussion

We have assigned the putative PKC gene to 16p11.2-p12.1 and have confined it to a segment between the *D16S3093* and *D16S416* loci, which encompasses the centromere. Since the pericentromeric region of chromosome 16 contains the secondary constriction composed of constitutive heterochromatin and since there were no other polymorphic markers available in this region, we could no longer narrow the PKCR.

The male : female ratio of this disorder has been reported to be from 3 : 1 to 4 : 1 (Kertesz 1967; Lance 1977; Goodenough et al. 1978; Fahn 1994; Marsden 1996). Our study also demonstrated the male predominance. Penetrance of PKC varies between sexes in the eight families studied (.74 for females, .94 for males, and .86 on average), indicating that a mutated allele transmitted to males may show sensitivity 1.27 times higher than the sensitivity of that transmitted to females. This may implicate that there must be a sex-dependent modulating factor to effect the sensitivity to PKC gene mutations, although the association between sex and penetrance is not statistically significant (the two-point P value of Fisher's exact test is .087).

The relationship of the PKCR to the localizations of other forms of paroxysmal dyskinesias merits comment. As shown in figure 3, all the markers that were linked to PKC are located to 16q12.1, and one end of the PKCR is centromeric to *D16S3093* at 16p11.2, whereas all the markers that were linked to ICCA are located to 16p, and one end of an ICCA critical region is centromeric to *D16S517* at 16q12.1 (Szepetowski et al. 1997). Therefore, a 5.4-cM segment between *D16S3093* and *D16S517,* which encompasses the centromere, is overlapped between the two critical regions for the disease (fig. 3). Since both forms of paroxysmal dyskinesias sometimes include IC, it remains to be seen whether they are allelic. If allelic, their common putative gene would be located within the 5.4-cM region. Lee et al. (1998) presented the results of a linkage study of a family that included nine individuals described to be affected with ICCA and to share a haplotype between *D16S420* and *D16S416*. The nine patients had attacks that were triggered not only by excitement and by stresses but also by sudden movements; the attacks lasted only a few seconds. In addition, a low dose of phenytoin was effective in the patients. These characteristics may favor PKC rather than ICCA, and their map data may support the PKCR mapped by us (fig. 3).

The RE-PED-WC locus has been assigned to a 4.1-cM segment between *D16S3133* and *D16S3131* (fig. 3). This segment lies within the ICCA critical region but does not overlap with the PKCR, suggesting that RE-PED-WC may be allelic to ICCA but that it is not allelic to PKC. PDC has been mapped to 2q33-q35 (Fink et al. 1996; Fouad et al. 1996); ENFL1, to 20q13.2 (Phillips et al. 1995); ENFL2, to 15q24 (Phillips et al. 1998); and CSE, to 1p (Auburger et al. 1996); indicating that the four regions are definitely excluded from the PKC locus. Episodic ataxia type 1, which is caused by mutations of the potassium-channel gene *KCNA1* (Browne et al. 1994), was suggested to be associated with PKC (Gancher and Nutt 1986; Brunt and Van Weerden 1990). However, the localization of *KCNA1* to 12p13 (Litt et al. 1994) rules out such an association.

Several disorders representing paroxysmal neurological manifestations and/or idiopathic age-dependent seizures have been known to be caused by mutations in ion-channel–related genes (Doyle and Stubbs 1998). In addition, proteins that are associated with cell signaling and neuronal transduction may also play a role in paroxysmal neurological disorders. Some candidate genes that have been mapped either between *D16S3093* and *D16S416* or to a chromosomal region between 16p11.2 and 16q12.1 include the interleukin-4–receptor α-chain gene (*IL4R* [MIM 147781]), located between *D16S3093* and *D16S409* (Human Genome Resources); the adenylate cyclase-7 gene (*ADCY7* [MIM 600385]), located between *D16S411* and *D16S416* (Human Genome Resources); the protein phosphatase–4 catalytic subunit gene (*PPP4C* [MIM 602035]), located at 16p12-p11; and the monoamine-preferring sulfotransferase gene (*STM* [MIM 600641]), located at 16p11.2. Interleukin-4 can modulate neuronal excitability by potentiating the γ-aminobutyric-acid type-A-receptor–mediated inward currents (Rózsa et al. 1997), and *STM*-protein is responsible for the sulfate conju-

gation of monoamine neurotransmitters such as dopamine. It remains to be seen whether these genes are causally related to PKC.

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Electronic-Database Information

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

Généthon, http://www.genethon.fr/ (for microsatellite markers and genetic distances between the marker loci)

Human Genome Resources, http://www.ncbi.nlm.nih.gov/genome/guide/ (for radiation hybrid mapping information of *ILR4* and *ADCY7*)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ for PKC [MIM 128200], infantile convulsions and paroxysmal choreoathetosis [MIM 602066], PDC [MIM 118800], CSE [MIM 601042], ICCA [MIM 602066], ENFL1 [MIM 600513], ENFL2 [MIM 603204], *IL4R* [MIM 147781], *ADCY7* [MIM 600385], *PPP4C* [MIM 602035], and *STM* [MIM 600641])

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