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ORIGINAL ARTICLE

Paroxysmal kinesigenic choreoathetosis (PKC): confirmation of linkage to 16p11-q21, but unsuccessful detection of mutations among 157 genes at the PKC-critical region in seven PKC families

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Abstract Paroxysmal kinesigenic choreoathetosis (PKC) is a paroxysmal movement disorder of unknown cause. Although the PKC-critical region (PKCCR) has been assigned to the pericentromeric region of chromosome 16 by several studies of families from various ethnic backgrounds, the causative gene has not yet been identified. In the present study, we performed linkage and haplotype analysis in four new families with PKC, as well as an intensive polymerase chain reaction (PCR) based mutation analysis in seven families for a total of 1,563 exons from 157 genes mapped around the PKCCR. Consequently, the linkage/haplotype analysis revealed that PKC was assigned to a 24-cM segment between *D16S3131* and *D16S408*, the result confirming the previously defined PKCCR, but being unable to narrow it down. Although the mutation analysis of the 157 genes was unsuccessful at identifying any mutations that were shared by patients from the seven families, two nonsynonymous substitutions, i.e., 6186C>A in exon 3 of *SCNN1G* and 45842A>G in exon 29 of *ITGAL*, which were segregated with the disease in Families C and F, respectively, were not observed in more than 400 normal controls. Thus, one of the two genes, *SCNN1G* and *ITGAL*, could be causative for PKC, but we were not able to find any other mutations that explain the PKC phenotype.

Keywords Paroxysmal kinesigenic choreoathetosis (PKC) · PKC-critical region · Linkage analysis · Mutation analysis · *SCNN1G* · *ITGAL*

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Introduction

Paroxysmal kinesigenic choreoathetosis (PKC; MIM 128200) is a paroxysmal movement disorder characterized by recurrent and brief attacks of unilateral or bilateral involuntary movements, including dystonic posturing, chorea, athetosis, and ballism, which are precipitated by the sudden onset of movements (Kato et al. 2006). The attacks can last as long as a few seconds to a few minutes, occur up to 100 times daily, but usually manifest in childhood or early adolescents, and commonly decrease with age. There is no loss of consciousness during these attacks. The attacks are responsive to anticonvulsants such as carbamazepine or phenytoin. Electroencephalogram (EEG) analysis demonstrates normal or nonspecific abnormalities. Neuroimaging and neuropathological studies resulted in unremarkable findings (Sadamatsu et al. 1999; Nagamitsu et al. 1999). The etiology and pathophysiology of PKC still remain unclear. Some neurologists consider PKC as a form of reflex epilepsy, whereas others believe that basal ganglia dysfunction may play a role in its cause (Kato et al. 2006). Most (40–70%) were familial cases in which PKC was transmitted in an autosomal dominant mode of inheritance with incomplete penetrance (Tomita et al. 1999; Valente et al. 2000). Males are affected more often than females, with an estimated ratio of 3–4:1 (Bhatia 1999).

We previously performed a genome-wide linkage and haplotype analysis in eight Japanese families with PKC and defined the disease locus within a 12.4-cM region between *D16S3093* and *D16S416* at 16p11.2-q12.1 (Tomita et al. 1999). This PKC-critical region (PKCCR) was confirmed by others (Bennett et al. 2000; Swoboda et al. 2000; Valente et al. 2000; Cuenca-Leon et al. 2002). In addition, mapped regions for other conditions probably allelic to PKC, such as infantile convulsions and paroxysmal choreoathetosis (ICCA; MIM 602066) and benign familial infantile convulsions (BFIC2; MIM 605751), shared with that for PKC (Lee et al. 1998; Hattori et al. 2000; Swoboda et al. 2000; Caraballo et al. 2001; Weber et al. 2004). Nevertheless, mutations in any genes within the PKCCR have remained uncovered.

Here, we describe the results of the mutation analyses of seven PKC families for a total of 157 genes located at or around the PKCCR, together with linkage/haplotype analysis of four newly identified families.

Materials and methods

Subjects

The subjects studied included seven families (Families A–G) with PKC. Two of them (Families F and G) corresponded respectively to Families 1 and 3 in our previous report (Tomita et al. 1999), and five other families (Families A–E, Fig. 1) were those which were newly collected. A total of 21 members, including 16 PKC patients from four of the five families (Families A–D), underwent a linkage and haplotype analysis. In addition, one of each affected individual (we further call them representative patients) chosen from all seven families was subjected to mutation analysis. Blood samples were collected from all participants after obtaining written informed consent, and the study protocol was approved by the Committee for Ethical Issues on Human Genome and Gene Analysis at Nagasaki University.

Genotyping and linkage analysis

Genomic DNA was isolated from the blood lysate of the 21 participants by phenol-chloroform extraction, followed by ethanol precipitation. To try to narrow down the PKCCR, we performed genotyping and haplotype analysis in the four newly collected PKC families, using 13 microsatellite markers (Table 1) located to a 36-cM region at 16p12-q21 to which PKC has been shown to be linked, as well as using three

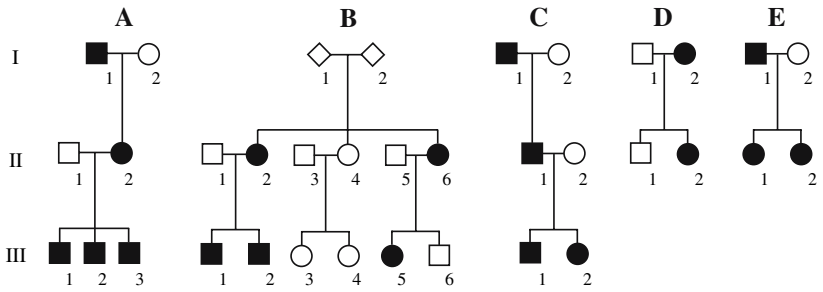

Fig. 1 Pedigree of the five families (Families A–E) with paroxysmal kinesigenic choreoathetosis (PKC). The *closed squares* and *circles* denote individuals affected with PKC. Although not shown here, Families F and G correspond to Families 1 and 3 reported previously (Tomita et al. 1999)

Table 1 Primer sequences of the 12 microsatellite markers used for genotyping and linkage analysis

Markers	Forward primer (5′–3′)	Reverse primer (5′–3′)
D16S403	CAAGACTAACGCTGATGGCT	GACAGTGAGGTGGGAATCAAA
D16S417	CTGTCCAACATGCAGCC	TGAAGTCAATCCCACTTGAA
D16S3131	CTGCTTCCATCTTGCC	CTAGCCCCCAAATGTG
D16S3093	CAAGGGCAAAACTCCAT	CCAAAAGGTTGATTCTCTG
AC007353-M1	GCTTAACTACATTTTATTCAAGGTTG	TCTGTGGTAGAGAGGCAAAGA
AC092368-M1	GTTTACCAGCCATTTTTAATCAACA	TGAATAAGTGTGTCTTTCAACAAAATT
AC092721-M3	GCCCTGTAATATAATTTGAAGTTG	GGGTTCAAGTGATTCTCCTG
D16S3136	CTCACCTATTGCCCTCAAGAA	CAGAATCTTATGCCATTATT
D16S416	CATAGGACCCTCAGATGTATA	CTGCCTATGGCTAAGAGGACA
D16S408	TGTAACCTTGTGTGCATCCT	CACTCTTATCCCAGGAACCC
D16S514	CAATTCCTTGATGCTACCAT	CTTGTCTAGTGGCTGGAATA
D16S3143	GCTACTGAGGAAACCTTATCC	GGCCATTACAGGAAGTGC

Primers of D16S3068 were purchased from the ABI PRISM Linkage Mapping Sets LMS (Applied Biosystems, Foster City, CA)

additional markers (AC007353-M1, AC092368-M1, and AC092721-M3) that were designed by us according to the human genome sequence (http://genome.cse.ucsc.edu/). Sample DNA was polymerase chain reaction (PCR) amplified for each marker locus with fluorescence-labeled primers. PCR was performed on DNA Thermal Cycler Model 9700 (Applied Biosystems, Foster City, CA) in a 10-μl reaction mixture containing 1×PCR buffer (Takara Bio, Otsu, Japan), 200 μM each of dNTP, 0.5 μM each of primer, 10 ng DNA, and 0.25 units ExTaq DNA polymerase HS-version (Takara Bio, Otsu, Japan) under the conditions of denaturation at 94°C for 2 min, 35 cycles of 94°C for 30 s, 58°C for 30 s, and 72°C for 1 min, and final extension at 72°C for 7 min. PCR products were run on an auto-sequencer Model 3100 (Applied Biosystems, Foster City, CA). Allele sizes were analyzed by GeneScan and Genotyper software (Applied Biosystems, Foster City, CA) to determine the genotypes.

Mutation analysis

We performed PCR-based mutation analysis of the seven representative patients with typical features of PKC. Sequences examined for mutations among the seven patients included those of 1,371 coding exons, excluding the 3′-UTR and 5′-UTR in 117 genes, located at the PKCCR between *D16S3093* and *D16S416* (Table 1). The analysis in five families (Families A and C–F) was expanded to an additional 192 exons of 40 other genes, whereas because of depletion of genomic DNA, an expanded analysis was not done in the remaining two families. Thus, a total of 1,563 exons in 157 genes were analyzed for mutation (primer sequences are available on request).

Real-time quantitative PCR

We performed real-time quantitative PCR in six representative patients from Families A and C–G. Six pairs of primers and TaqMan probes were designed for exons 1, 6, and 13 of *SCNN1G*, and for exons 1, 16, and 30 of *ITGAL*. PCR was carried out in a 10-μl reaction mixture containing 5 μl of 2×TaqMan Universal PCR Master mix (Applied Biosystems, Foster City, CA), 0.4 μM each of primer, a 0.2-μM probe, and 10 ng DNA under the conditions of 2 min at 50°C, 10 min at 95°C, 40 cycles of 15 s at 95°C, and 1 min at 60°C, with a 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA).

Results

The haplotype analysis showed that all affected individuals in the four new families share an allele at each locus examined between *D16S3131* and *D16S408* (Fig. 2). One end of the shared region was defined by a recombination between *D16S3131* and *D16S3093* in individual III-3 in Family A, and the other end by a recombination between *D16S514* and *D16S408* in individual III-1 in the same family. These results defined a minimum PKCCR in the four new families within an approximately 24-cM segment between *D16S3131* and *D16S408*. Therefore, the present linkage/haplotype analysis did not contribute to narrow down the previously defined PKCCR.

Among a total of 1,563 exons of 157 genes analyzed, we detected 243 base alterations in the seven representative patients (Fig. 3), 36 of which were base substitutions in coding regions and have not been reported in the dbSNP database (http://www.ncbi.nlm.-

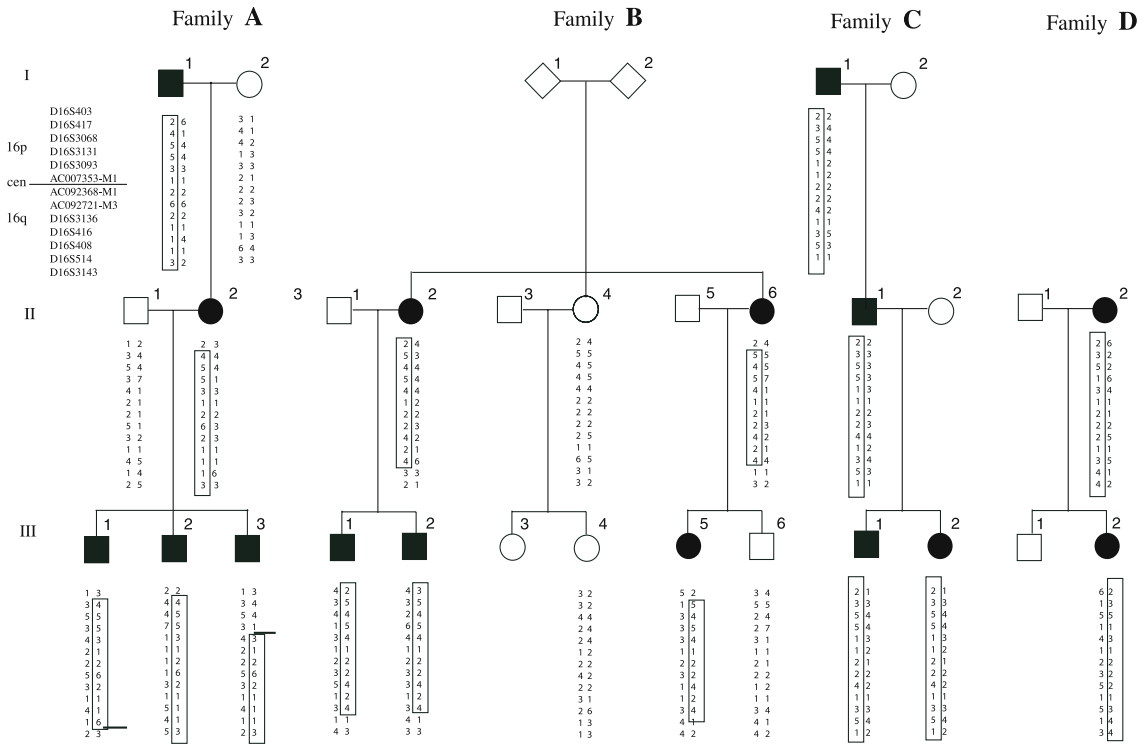

Fig. 2 Haplotype analysis of the four new PKC families (Families A–D). The *numbers in boxes* represent putative disease haplotypes. The *heavy short lines* indicate recombination sites

nih.gov/SNP/). Seven of the alterations in six genes were nonsynonymous substitutions resulting in amino-acid substitutions (Table 2). Five of such nonsynonymous substitutions in four genes were observed both in some patients and among 100 normal control individuals. The remaining two, i.e., 6186C>A in exon 3 of *SCNN1G* (the gene for sodium channel, nonvoltage-gated 1, gamma) and 45842A>G in exon 29 of *ITGAL* (the integrin alpha L precursor gene), observed in Families C and F, respectively, were not observed among more than 400 normal controls. The real-time quantitative PCR analysis did not detect a duplication or a deletion within the two genes. Of the 35 intronic base changes we identified in the seven patients, none were located at the acceptor or donor splice sites (Fig. 3).

G-banding chromosome analysis at the 400-band level and C-banding analysis revealed that all five patients from Families B–D, F, and G had a normal-sized heterochromatin block on chromosome 16 without an inversion (data not shown).

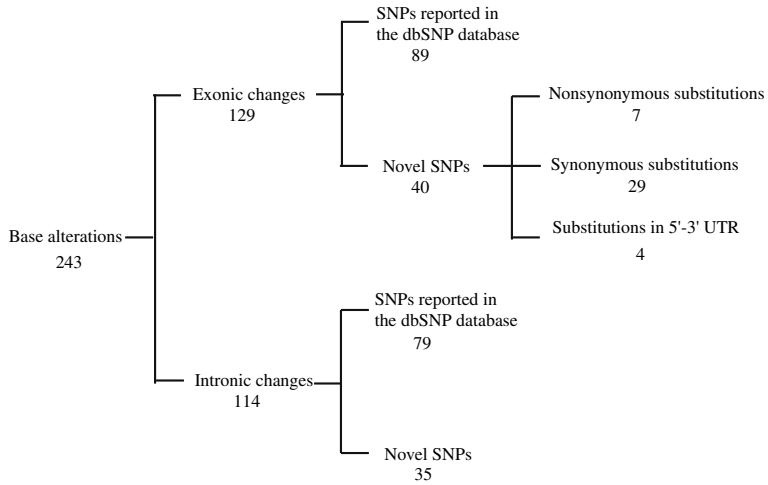

Fig. 3 Classification of 243 base alterations in 157 candidate genes. Information of the newly found single nucleotide polymorphisms (SNPs) is shown in Table 2. None of the novel intronic SNPs are located at any of the acceptor or donor splice sites

Table 2 List of genes for mutation analysis in the PKC patients, and novel SNPs identified, their positions, nucleotide changes, and amino acid changes

Gene	E/I	SNP definition	AA	Gene	E/I	SNP definition	AA	Gene	E/I	SNP definition	AA
HS3ST2*				ASPHD1	E1	515insTGG		ITGAX*			
SCNN1G*	E3	6185G>T	Y241Y	KCTD13*	I2	INV2-74A>T		ITGAD*	5′U	5'U-13G>C[a]	
	E3	6186C>A	P242T	LOC124446					E2	943C>T	G33G
SCNN1B*				TAOK2*					I7	INV7+38C>T	
UBPH*				HIRIP3*					E8	14188A>G	R246R
NDUFAB1*				CCDC95					E8	14253A>G	Y268C
PRKCB1*	E1	79C>A	R27R	DOC2A*					I9	INV10-43G>A	
	I15	INV15+85G>T		FAM57B	I2	INV2+66G>T			E16	19819A>G	S644G
CACNG3*				ALDOA*					I17	INV17+139G>A	
TNRC6A*	E1	5′U-12079T>A		PPP4C*	E1	5′U-355-347del(CGG)3			I19	INV19+71C>T	
	E21	33511C>T	H1551H	TBX6*					I27	INV27+87G>A	
SLC5A11*	I1	5′U-12193T>C		YPEL3*				ARMC5*			
	I2	INV2+6C>G		GDPD3				TGFB1I1*	E5	753C>T	P119S
	I5	INV5-30G>A		MAPK3*				SLC5A2*			
	I5	INV5+65T>C		CORO1A*				C16orf58*	I5	INV5+53G>A	
LCMT1*				SULT1A3*				ERAF*	3′U	3′U+570T>C[a]	
IL4R*	I3	INV3+72T>A		CD2BBP2*	I1	INV1+493C>T		MGC3020*			
	E11	22448T>C	L433L	TBC1D10B*				ZNF720*			
IL21R*	I4	INV4+51C>T		MYLPF	I5	INV5+27G>A		ZNF267			
GTF3C1*				SEPT1*				TP53TG3*	E3	1232insG	
KIAA0556*	I16	INV16+4T>C		ZNF553	E2	2434G>A	T326T	FLJ43855			
	E18	204044A>G	Q1198Q	ZNF771				POL3S			
GSGIL*				XTP3TPA*				FLJ46121			
XPO6*	I9	INV9+31insT		SEPHS2*				FLJ43980	E1	5′U-15C>G	
	I15	INV15+23G>C		ITGAL*	E1	5′U-86C>T		SHCBP1*	E5	12986C>T	N204N
	E16	69120T>C	N740N		E29	45842A>G	K1063R	VPS35*			
SBK-1				ZNE768				ORC6L	E6	6328A>G	V193V
LOC440350				ZNF747				MLCK*			
LOC440348				ZNF764				LOC388272*			
CLN3*	I12	INV12+36C>T		ZNF688				GPT2*			
	E15	14138A>G	H404R	ZNF785				DNAJA2*			
APOB48R*				ZNF689				NETO2*	I3	INV3-34G>A	
IL27*	I5	INV5-12C>T		PRR14				ITFG1 *			
NUPR1*				FBS1*				PHKB*	I28	INV28+37C>T	
CCDC101*				SRCAP*				ABCC12*			
SULTIA2*				PHKG2*				ABCC11*			
SULT1A1*				LOC90835				LONPL*			
EIF3S8*	E16	20499C>T	P725P	RNF40*				SIAH1			
ATXN2L*	I13	INV13+55G>A		BCL7C*				N4BP1*			
TUFM*				CTF1*				CBLN1*			
SH2B*				LOC283932				FLJ44674	E1	3′U+905C>G	
ATP2A1*				FBXL19*				C16orf78*	E1	45G>A	K15K
RABEP2*	I3	INV4-56C>T		TMEM142C					I3	INV3+27A>G	
CD19*	E4	1379G>T	P206P	SETD1A*				ZNF423 *			
SPIN1*	E7	6897C>T	S319S	HSD3B7*				C16orf69			
	I7	INV7+278Cdel		STX1B2*				HEATR3 *	I11	INV11-44A>G	
	3′U	3′U+9285C>A[a]		STX4A*	I8	INV8+55C>A		PAPD5*			
LAT	E7	1259G>A	A120A		I8	INV8+65C>T		ADCY7*	E22	24951T>C	Y875Y
BOLA2				ZNF668				BRD7*	I9	INV9-26insT	
GDYD1*				ZNF646*	I1	5′U-108T>G			E16	48481G>A	T570T
SPN*					E2	2722G>C	G907A	NKD1*			
QPRT*				VKORC1*	3′U	3′U+3730G>C[a]		SLIC1*			
C16orf54				BCKDK*				CARD15*			
KIF22*	I12	INV12+70A>G		MYST1*				CYLD*	E17	43909C>T	D805D
MAZ*				PRSS8*	E3	2163C>T	V46V	SALL1*			
PRRT2				PRSS36				FTS*			
MVP*	E10	11504C>T	D525D	FUS*				CAPNS2*			
C16orf53				TRIM72				SLC6A2*			
CDIPT*				PYCARD*				GNAO1*			
PSK-1*				PYDC1*				CNGB1*	E22	51134C>T	N725N
				ITGAM*	I2	INV2+11T>C					

A total of 75 SNPs not reported in the dbSNP database were found in this study

Four SNPs found in 5′-UTR or 3′-UTR happened to be included in the sequenced regions

*Analyzed in seven representative patients: E/I=exon or intron; AA=inferred amino acid change from nonsynonymous SNP; U=UTR

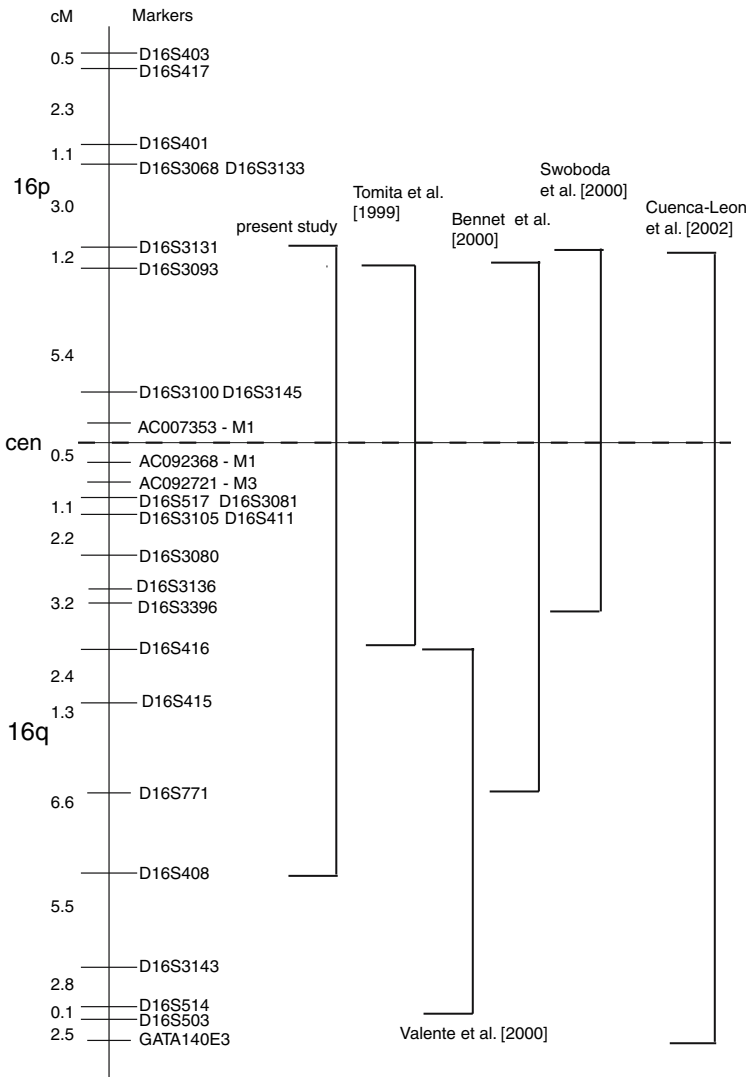

Fig. 4 The PKC-critical region (PKCCR) summarized by five mapping studies (Tomita et al. 1999; Bennett et al. 2000; Swoboda et al. 2000; Cuenca-Leon et al. 2002, present study), as well as a seemingly second PKC locus (EKD2) by Valente et al. (2000). The location of markers and intermarker distances are from the Généthon map (Dib et al. 1996)

Table 3 List of exons that have not been sequenced in the mutation analysis

Gene	Exon
COX6A2	Exon 2, Exon 3
MAZ	Exon 1, Exon 2, Exon 3
VPS35	Exon 9, Exon 10, Exon 11
SULT1A1	Exon 7
SALL1	Exon 2
MGC2474	Exon 2
FLJ43855	Exon 5, Exon 7, Exon 9

Discussion

The PKCCR was assigned to a segment between *D16S3093* and *D16S416* in eight Japanese families (Tomita et al. 1999). It was also mapped between *D16S3100* and *D16S771* in an Afro-Caribbean family (Bennett et al. 2000), between *D16S3131* and *D16S3396* in 11 families of diverse ethnicity (Swoboda et al. 2000), between *D16S3145* and *GATA140E03* in a Spanish family (Cuenca-Leon et al. 2002), and a 24-cM segment between *D16S3131* and *D16S408* in the present study (Fig. 4). Thus, the shortest region of overlap (SRO) did not become narrower than a 12.4-cM segment detected by Tomita et al. (1999). Valente et al. (2000) assigned a form of PKC (a second PKC locus, EKD2), in an Indian family, to a segment between *D16S416* and *D16S503*, the region distinct from those mapped by Tomita et al. (1999) and by Swoboda et al. (2000). Furthermore, two other clinical entities, ICCA and BFIC2, were assigned to a region encompassing the centromere of chromosome 16 (Lee et al. 1998; Hattori et al. 2000; Swoboda et al. 2000; Caraballo et al. 2001; Weber et al. 2004). Since all of these loci were confined to a relatively small region, it is likely that all of these paroxysmal movement dis-

orders actually belong to one disorder and are allelic, as suggested previously (Tomita et al. 1999).

We searched for mutations in almost all protein-coding genes mapped at the PKCCR. In addition, we also analyzed four ion-channel-related genes (*CACNG3*, *SCNN1B*, *SCNN1G*, and *CNGB1*), albeit located outside the PKCCR, since many episodic neurologic disorders, such as muscle diseases, epilepsy, and movement disorders, are known as ion-channel abnormalities (Bhatia et al. 2000). However, 14 coding exons in seven genes (Table 3) were not analyzed because of difficulties in PCR-amplification.

In the present study on a total of 157 genes, we failed to identify any causative mutations that can explain PKC in all of the seven families examined. However, two nonsynonymous substitutions, 6186C>A in exon 3 of *SCNN1G* and 45842A>G in exon 29 of *ITGAL*, which were co-segregated with PKC in Families C and F, respectively, which were not found in normal control individuals, might be implicated in PKC. In other words, they were not able to be totally ruled out from the candidacy for PKC. It thus remains to be investigated whether another mutation in either gene is found in other PKC families.

Although the mapping of PKC was successful in at least nine studies, causative mutations have been uncovered. This may imply that PKC is caused by aberrations other than exonic mutations, such as a deletion or insertion, in the promoter regions, including the 5′-UTR or 3′-UTR. However, there is still a possibility for usual exonic mutations in a novel gene not annotated in public databases. As PKC itself is, generally, a viable disorder with which patients may show high reproductive fitness, such a mutated allele may be transmitted through many generations. A chromosomal rearrangement is another possibility. The pericentromeric region of chromosome 16 has a large heterochromatin (C-band) block that contains several duplicated regions, through which, frequent chromosomal rearrangements occur (Loftus et al. 1999). It remains also to be seen whether PKC patients within a family share such a variant.

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