

Paroxysmal Kinesigenic Dyskinesia and Generalized Seizures: Clinical and Genetic Analysis in a Spanish Pedigree

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Abstract

Familial paroxysmal kinesigenic dyskinesia (PKD) is a rare disorder featuring brief, dystonic or choreoathetotic attacks, typically triggered by sudden movements. Symptoms usually start in mid-childhood, although in several pedigrees infantile convulsions have been reported as the presenting sign. Previous linkage studies have identified two PKD loci on 16p12.1-q21. We report here the clinical features of a Spanish kindred with autosomal dominant PKD, in which haplotype data are compatible with linkage to the pericentromeric region of chromosome 16 and exclude linkage to the locus for Paroxysmal Non Kinesigenic Dyskinesia (PNKD) on chromosome 2q35. In this family, the conservative candidate region for the disease lies between markers D16S3145 and GATA140E03 on 16p12.1-q21 and partially overlaps with both the Paroxysmal Kinesigenic Dyskinesia – Infantile Convulsions (PKD-IC) critical interval and the Episodic Kinesigenic Dyskinesia 2 (EKD2) locus. Unusual findings in our pedigree were early infantile onset of the dyskinesias in one patient and generalized seizures as adults in two, adding to previous observations of phenotypic overlap between epileptic and non-epileptic paroxysmal disorders. Further clinical and genetic studies are needed to elucidate whether PKD and PKD-IC are allelic disorders with age-dependent phenotypic expression.

Key words

Paroxysmal Dyskinesia · Choreoathetosis · Movement Disorders · Childhood · Genetics · Linkage

Abbreviations

ICCA	infantile convulsions and paroxysmal choreoathetosis
PKD	paroxysmal kinesigenic dyskinesia
PKD-IC	paroxysmal kinesigenic dyskinesia and infantile convulsions
BFIC	benign familial infantile convulsions
EKD2	episodic kinesigenic dyskinesia 2
RE-PED-WC	rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp
PNKD	paroxysmal non-kinesigenic dyskinesia

Introduction

The paroxysmal dyskinesias are a broad group of disorders which are best classified on the basis of the dyskinesia precipitating events [6]. The most frequent of these disorders was initially named paroxysmal kinesigenic choreoathetosis and is characterized by attacks lasting from seconds to 5 minutes, typically elicited by sudden voluntary movements. In some instances, however, these attacks can have dystonic rather than choreoathetotic features and be classified as long-lasting (i.e., > 5 minutes) and hence the label paroxysmal kinesigenic dyskinesia (PKD) is currently favoured [2, 6]. PKD is often familial, with autosomal dominant inheritance, although sporadic cases occasionally occur.

All proposed clinical classifications of paroxysmal dyskinesias [6, 9, 14] display a substantial degree of overlap of clinical pheno-

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types. In recent years, the analysis of familial cases has offered a way of categorizing this group of conditions while evidence for genetic heterogeneity has been provided by several studies. In 1997, Szepetowski et al reported four French families with a syndrome of infantile convulsions and paroxysmal choreoathetosis (ICCA), in which genetic linkage to a pericentromeric region on chromosome 16 was found [21]. Linkage to this region was later confirmed in several families with ICCA [17,20,21,25], isolated benign familial infantile convulsions (BFIC) [5] or isolated PKD [2,26]. Given this phenotypic variability, the acronym PKD-IC has been suggested for this genetic locus [20]. A second locus for PKD (EKD2) has been recently mapped to the long arm of chromosome 16 [26]. A related disorder, autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp (RE-PED-WC), maps to a close locus on 16p12–11.2 [10]. On the other hand, several reports have established linkage of paroxysmal non kinesigenic dyskinesia (PNKD), formerly paroxysmal dystonic choreoathetosis, to chromosome 2q31–36 [7,8,11,12,18]. The more rare condition of autosomal dominant paroxysmal choreoathetosis/spasticity and episodic ataxia has been linked to chromosome 1p [1].

In this report we describe the clinical features of a Spanish family with PKD and generalized seizures as an additional sign in two cases. Linkage analysis using microsatellite markers excludes the 2q locus as the one responsible for the disease and suggests linkage to 16p12.1-q21 in this family.

Materials and Methods

Subjects and samples

We have studied a three-generation autosomal dominant pedigree with 17 individuals, 5 of whom were diagnosed as having PKD (Fig. 1). Whole venous blood was drawn from the 5 affected and 8 unaffected cooperative family members, after each subject or parent gave informed consent for DNA analysis and the local IRB approved the study, in accordance with the Helsinki declaration. Genomic DNA was isolated using the QIAamp DNA Blood Maxi Kit (QIAGEN, Hilden, Germany).

DNA analysis

The following microsatellite markers located on chromosome 2q35 and at the pericentromeric region of chromosome 16 were studied in the family to determine potential linkage to loci previously associated with paroxysmal dyskineticias: D2S164–3.7 cM–D2S163 for the PNKD locus [7,8] and D16S401–3.7 cM–D16S3131–1.7 cM–D16S3145–5.5 cM–D16S685–1.9 cM–D16S3080–2.4 cM–D16S3136–3.0 cM–D16S757–5.6 cM–D16S771–7.0 cM–D16S526–7 cM–GATA140E03–2.9 cM–D16S2624, for a region encompassing the RE-PED-WC [10], the PKD-IC [20,21,25] and the EKD2 [26] loci. The distances between the markers are according to the Marshfield map available at research.marshfieldclinic.org [4].

Primers were purchased from the MapPairs set (Research Genetics, Huntsville, AL) or synthesized using sequence data from the Génethon (<ftp.genethon.fr/pub/Gmap>) and the CEPH (www.cephb.fr/bio/cephdb) public databases. The PCR reactions were performed under the following conditions: 50 ng genomic DNA,

0.2 mM dNTPs, 2.5 pmol of each primer, 0.5 U AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, CA) and 1× recommended PCR buffer in a final volume of 25 µl. Amplification conditions were 10 min denaturation at 94°C; then 35 cycles with 1 min at 94°C, 1 min at 56°C and 1 min at 72°C; and finally an extension step at 72°C for 10 min. For markers D2S163, D2S164 and D16S757, the reaction was supplemented with 5% DMSO. The annealing temperature for marker D16S685 was set to 62°C. Amplified products were separated by electrophoresis on a 6% acrylamide/bisacrylamide 19:1 gel and visualized by silver-staining.

Haplotype and linkage analysis

Haplotypes for two markers spanning 3.7 cM on 2q35 and 11 markers spanning 40.7 cM on chromosome 16p12.1-q21 were constructed manually by assuming the minimum number of recombinations. The phase was determined by genotyping all the available family members.

We used the simulation programs SLINK and MSIM, version 2.51 [27] to compute the maximum expected pairwise LOD score in our pedigree, assuming a marker heterozygosity value of 0.7 over 1000 replicates. The family was estimated to provide maximum two-point LOD scores (Z_{\max}) of 1.91 and 1.73 at a recombination fraction (Θ) of 0.00 from the disease gene using penetrance values of 0.95 and 0.80, respectively.

Pairwise LOD scores were calculated by the MLINK program of the LINKAGE package, version 5.2 [16]. An autosomal dominant model of inheritance with penetrance values of either 0.95 or 0.80 was assumed. The population frequency of the disease allele was set to 0.0001 and the allele frequencies of the polymorphic markers were considered to be equal.

We used the GENEHUNTER program [13] to compute multipoint LOD scores for the disease phenotype against fixed maps of marker loci, assuming equilibrium between the marker and test loci. The parameters in the multipoint analysis were the same as those described for the two-point analysis.

All the linkage programs used are available at the Human Genome Mapping Project web site (www.hgmp.mrc.ac.uk).

Results

Clinical data

The proband was a 6-year-old Caucasian girl referred for evaluation of sudden involuntary movements. She was normally born to a gravida 4 para 3 mother after an uneventful pregnancy. Psychomotor development had been normal. At age 5, the patient began experiencing episodes of painful contraction of her right leg, which started in the first toe, extended to the foot and leg and were typically induced by activities such as running or jumping. The attacks lasted from 15 to 20 seconds, during which the patient was unable to walk. The neurological examination between the attacks was normal. Attempts to induce an attack by a sudden command involving a postural change or physical activity did not succeed. An interictal EEG was normal. The episodes disappeared after carbamazepine was started at a dose of

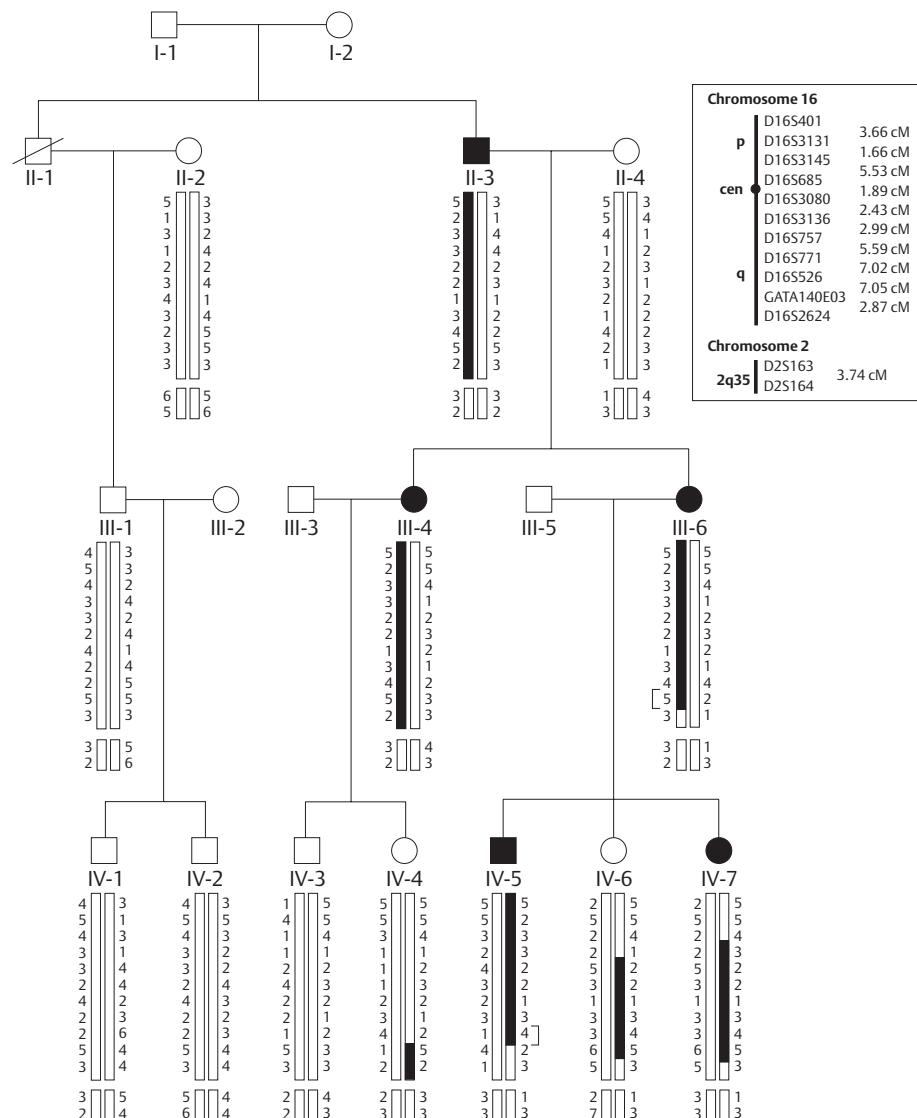


Fig. 1 Spanish pedigree with autosomal dominant paroxysmal kinesigenic dyskinesia (PKD). Affected status is denoted by solid symbols. Haplotypes for microsatellite markers on chromosomes 16 and 2 are depicted below each individual. The disease haplotypes are highlighted by black bars. Alternative recombination points in individuals III-6 and IV-5 are shown by brackets. Boxed genetic distances in centimorgans (cM) are according to the Marshfield map (research.marshfieldclinic.org, [4]).

10 mg/kg/day, but recurred twice when the family discontinued the medication. Reportedly, a typical episode was brought about by an unexpected sound, such as a doorbell or alarm. At age 11 she remains symptom-free on carbamazepine.

The family of the patient (Fig. 1) included 5 individuals affected with paroxysmal dyskinésias, four of whom were interviewed and personally examined by one of the authors (AM). Individual II-3 received a positive affection status after a telephone interview. All individuals reported onset of the dyskinésia before age 10, in the form of attacks limited to the leg. Individuals III-6 and IV-7 had an earlier onset, with the mother of individual III-6 reporting that she witnessed attacks of dystonic limb posturing in her four-month-old daughter. This infant, apparently, had preserved consciousness during the attack and a normal interictal EEG. In all the patients, the attacks increased their frequency in stressful situations. They were brief, as described for the proband, triggered by onset (or even planning) of voluntary limb or body motion and often followed a migratory pattern, with athetoid movements starting in the leg and extending to the ipsilateral arm, neck and facial musculature. Often, the episodes were preceded by tingling or numbness in one extremity. They pre-

cluded normal walking, speaking and, sometimes, staying in an upright position, as in individuals II-3 and III-6. Patient IV-5 reported that he was able to stop some of the attacks through the forceful flexion of the first toe against the floor. The frequency of the attacks peaked around adolescence and early adulthood, when more than 10 attacks per day were reported, and declined progressively after the fourth decade (as in II-3, III-4 and III-6). With increasing age, patient II-3 reported also the emergence of nocturnal episodes characterized by painful involuntary leg movements that awaked him from sleep and that he localized mainly to the first toe, as in the diurnal attacks precipitated by movement. All the affected individuals had normal interictal examinations. In addition to the dyskinésia, individuals II-3 and III-6 suffered as adults from occasional generalized tonic clonic seizures. In the former the seizures were readily controlled with phenobarbital, while the latter responded to adjusting the carbamazepine dose to reach standard antiepileptic blood levels. Interictal awake and sleep EEG (III-6), awake EEG (II-3), and cerebral CT scan were normal in these two cases.

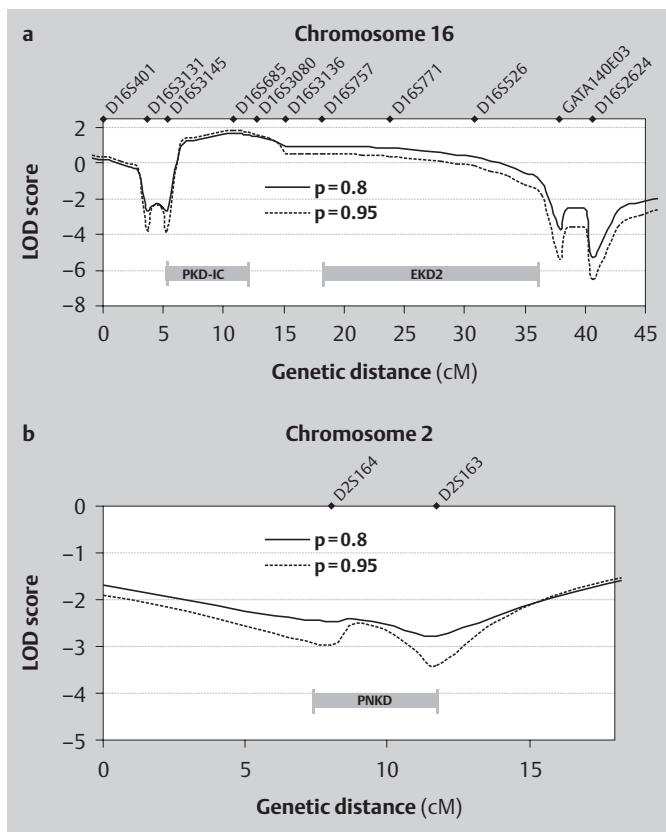


Fig. 2a and b Multipoint LOD scores for linkage of PKD to chromosome 16 p12.1-q21 (a) and to chromosome 2 q35 (b), assuming penetrance values (p) of 0.8 and 0.95. Grey bars indicate critical intervals as inferred from previously reported regions for PKD-IC [20,21,25], EKD2 [26] and PNKD [7,8,11,12,18,19]. Multipoint LOD scores were calculated by means of the GENEHUNTER program [13]. Intermarker distances and marker order are according to the Marshfield map [4].

Genetic analysis

Haplotype analysis of eleven markers on chromosome 16 p12.1-q21, spanning the RE-PED-WC, PKD-IC and EKD2 loci, showed that all the affected individuals shared alleles on the disease chromosome from marker D16S685 to marker D16S526 (Fig. 1). The shared genomic region was bordered by obligatory recombinations, observed with markers D16S3145 on 16 p and GATA140E03 on 16 q in the affected individuals IV-7 and IV-5, respectively. The unaffected members of the family carried a different set of alleles, although individual IV-6, a 19-year-old with no history of dyskinesias, did share with the affected subjects part of the disease haplotype, from D16S3080 to D16S526. We obtained positive two-point LOD scores for the markers situated within the interval bordered by D16S685 and D16S526 (maximum LOD score value of 1.44 at $\Theta = 0$ from D16S685, assuming $p = 0.95$). The multipoint linkage analysis showed positive results in a more than 25-cM interval centromeric to D16S3145 and to GATA140E03, with a maximum LOD score value of 1.85 ($p = 0.95$) and 1.68 ($p = 0.80$) at D16S685 (Fig. 2a).

In contrast, the analysis of haplotypes of two markers on chromosome 2 q35 clearly excluded linkage to the PNKD locus (Fig. 1). This result was statistically significant as shown by two-point analysis: we obtained exclusion LOD score values below -2 in a region of 5.6 cM on both sides of marker D2S164 (includ-

ing marker D2S163) when the penetrance was set to 0.95, and of 4.9 cM when the penetrance was set to 0.80. The multipoint linkage analysis confirmed the results, excluding a genomic region of more than 11 cM that includes the PNKD critical region as defined by the intersection of the genetic intervals described in previous reports [7,8,11,12,18,19] (Fig. 2b).

Discussion

We here report a new family with autosomal dominant PKD and evidence suggesting linkage to the pericentromeric region of chromosome 16 between markers D16S3145 and GATA140E03. This is, to our knowledge, the first Spanish family with familial PKD reported so far. Linkage of PKD to 16 p12.1-q12 in European families has been previously reported in only four French families with the closely related PKD-IC phenotype [21]. In addition, as it could be anticipated from the clinical features, our results allow exclusion of linkage to the PNKD locus on 2 q35 and to the RE-PED-WC locus on 16 p12–11.2.

The phenotype of the family described here fits best into the category of PKD, according to the classification proposed by Demirkiran and Jankovic [6]. Dyskinetic attacks in this family were short-lasting, choreoathetotic or dystonic and, most importantly, elicited by movement. In PNKD, attacks tend to last longer, have precipitating factors other than sudden movement and usually do not respond to treatment with carbamazepine [6]. The clinical features of RE-PED-WC are distinctive and the mode of inheritance is autosomal recessive [10].

Onset of dyskinesias before age 6 is unusual for PKD. In several families with PKD, the age-specific manifestation of the disorder during infancy is thought to be infantile convulsions. In contrast, in the family reported here, one affected subject (III-6) may have had the presentation of dystonic attacks in early infancy. Although in retrospect it might be difficult to differentiate these clinical manifestations from a seizure disorder, the information provided by individual II-4 does not suggest an epileptic nature of the attacks. Interestingly, cases with a similar age of onset, 3 months, are encountered more frequently in PNKD [11,18].

Two of our patients displayed generalized seizures in adulthood. Generalized seizures are unusual in PKD, although they were present in 8% of the patients in a series of familial and sporadic PKD [23] and have been reported in a few patients with the chromosome 16-linked PKD-IC syndrome [17,20]. Age-dependent expression of ion-channel mutations might produce different neurological paroxysmal disorders within a given family or even in a single individual [3].

Although genetic data in our family suggest linkage to the pericentromeric region of chromosome 16, these results should be viewed with caution. We have obtained a maximum multipoint LOD score of 1.85 at D16S685, close to the maximum expected LOD score value for this family. Although a LOD score of 3 is generally accepted as a true linkage in an autosomally inherited trait, a score around 2 is considered sufficient evidence for linkage of a disease to a previously known locus responsible for a similar phenotype [24].

The haplotype shared by all the affected individuals narrows the critical disease interval between markers D16S3145 and GATA140E03, in a genomic region spanning more than 30 cM. However, one unaffected family member, IV-6, harbours part of the disease haplotype, from D16S3080 to D16S526. This individual could be either a non-penetrant carrier of the PKD mutation or a non-carrier. If the first assumption is correct, then the disease interval could be narrowed to a 27 cM region between D16S685 and GATA140E03 (Fig. 3, H). The follow-up of this patient may prove informative to detect potential age-dependent PKD symptoms: onset of idiopathic, genetically determined, PKD is rare after the third decade but it has been reported to occur as late as the age of 41 years [6]. Alternatively, if IV-6 is not a carrier of the PKD mutation segregating in this pedigree, the disease region would then lie within a shorter 7 cM segment between D16S3145 and D16S3080 (Fig. 3, I).

We have compared our results and the previously reported linkage studies performed with PKD and PKD-IC pedigrees using the Marshfield genetic map (research.marshfieldclinic.org/genetics, [4]) (Fig. 3). According to this map, our conservative D16S3145-GATA140E03 disease candidate region, based on affected family members only, partially overlaps with both the PKD-IC critical interval situated in the pericentromeric region of chromosome 16 [20, 21, 25] and the EKD2 locus on 16q13-q22.1 [26]. Two other linkage studies performed in a PKD family [2] and in seven BFIC families [5] show simultaneous overlap with the two putative PKD loci. In these kindreds and also in ours, the question whether the disease-causing gene lies within the PKD-IC, the EKD2, or one as yet undescribed locus, remains open.

An investigation of the critical region on chromosome 16, using the human genome sequence draft, discloses several candidate genes for the disorder that encode proteins involved in ionic transport. The PKD-IC critical region contains the gene for solute (sodium/glucose) carrier protein, *SLC5A2* or *SGLT2*, and two genes coding for ATP-binding cassette proteins (*ABCC11* and *ABCC12*) previously proposed as positional candidates for PKD [22]. The EKD2 locus, in turn, contains *SLC6A5*, the gene for solute carrier family 6, member 2; *CNGB1*, the gene for cyclic-nucleotide-gated cation channel 4, and *SCL12A3*, which causes Gitelman syndrome and encodes member 3 of family 12 of sodium/chloride transporters.

In summary, we have reported a new family with paroxysmal kinesigenic dyskinesia and putative linkage to pericentromeric chromosome 16. The molecular basis of this disorder remains unresolved. Further clinical and genetic studies are needed to elucidate whether PKD and PKD-IC are allelic disorders and, if so, whether the differing phenotypes relate to different mutations or to other genetic or environmental factors.

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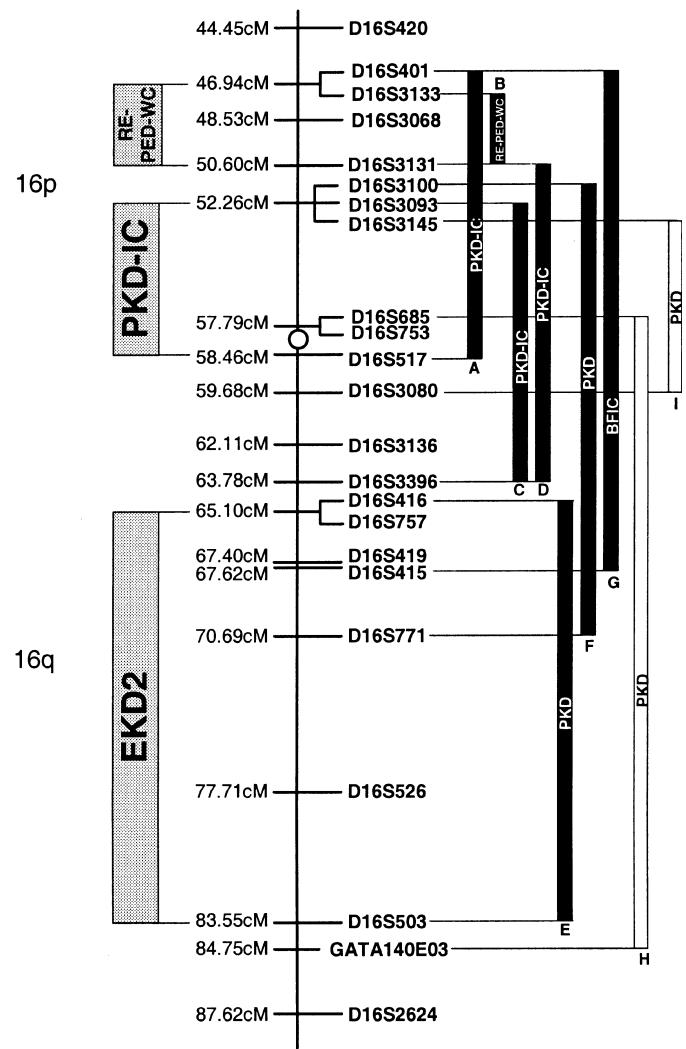


Fig. 3 Schematic representation of the genetic map containing the critical regions (grey bars) of the three paroxysmal dyskinesia loci identified on chromosome 16 p12.1-q21: the PKD-IC region, as determined by (A) Szepetowski et al. [21], (C) Tomita et al. [25] and (D) Swoboda et al. [20]; the RE-PED-WC region (B) as determined by Guerrini et al. [10] and the EKD-2 locus as determined by (E) Valente et al. [26]. The PKD regions defined by (F) Bennet et al. [2] and the present study, and the BFIC region as determined by (G) Caraballo et al. [5] display overlap with more than one locus. Critical intervals considering alternative carrier status for subject IV-6 are indicated (H: carrier, I: non-carrier). The centromere is indicated with an empty circle. Order and distances between markers are according to the Marshfield genetic map [4]. The order of markers concurs with that of the human genome sequence draft (genome.ucsc.edu) [15].

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