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# Report

## Linkage of Benign Familial Infantile Convulsions to Chromosome 16p12-q12 Suggests Allelism to the Infantile Convulsions and Choreoathetosis Syndrome

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**The syndrome of benign familial infantile convulsions (BFIC) is an autosomal dominant epileptic disorder that is characterized by convulsions, with onset at age 3–12 mo and a favorable outcome. BFIC had been linked to chromosome 19q, whereas the infantile convulsions and choreoathetosis (ICCA) syndrome, in which BFIC is associated with paroxysmal dyskinesias, had been linked to chromosome 16p12-q12. BFIC appears to be frequently associated with paroxysmal dyskinesias, because many additional families from diverse ethnic backgrounds have similar syndromes that have been linked to the chromosome 16 ICCA region. Moreover, one large pedigree with paroxysmal kinesigenic dyskinesias only, has also been linked to the same genomic area. This raised the possibility that families with pure BFIC may be linked to chromosome 16 as well. We identified and studied seven families with BFIC inherited as an autosomal dominant trait. Genotyping was performed with markers at chromosome 19q and 16p12-q12. Although chromosome 19q could be excluded, evidence for linkage in the ICCA region was found, with a maximum two-point LOD score of 3.32 for markers D16S3131 and SPN. This result proves that human chromosome 16p12-q12 is a major genetic locus underlying both BFIC and paroxysmal dyskinesias. The unusual phenotype displayed by one homozygous patient suggests that variability of the ICCA syndrome could be sustained by genetic modifiers.**

A large proportion of cases of idiopathic epilepsy are of genetic origin. Mutations in ligand or voltage-gated ion-channel genes have been identified in various epileptic syndromes that are inherited as Mendelian traits (Steinlein et al. 1995; Steinlein et al. 1997; Biervert et al. 1998; Charlier et al. 1998; Singh et al. 1998; Wallace et al. 1998; De Fusco et al. 2000; Escayg et al. 2000). Many other epilepsy genes have been mapped by linkage analyses (Szepetowski and Monaco 1998; Leppert and Singh 1999; Steinlein 1999; Szepetowski 2000) but are not yet known. Identification of these genes is important not only with respect to the corresponding syndromes but for its possible use in studying the more-frequent forms of epilepsy that are inherited as complex traits. Benign familial infantile convulsions (BFIC [MIM 601764]) is one of the numerous epileptic syndromes whose underlying genes remain unknown. It is characterized by nonfebrile convulsions that begin at age 3–12 mo and have a good response to anticonvulsants and a favorable outcome (Vigevano et al. 1992; Lee et al. 1993; Echenne et al. 1994; Caraballo et al. 1997). It is inherited as an autosomal dominant trait, and linkage to chromosome 19q had been found in five Italian families (Guipponi et al. 1997). Since then, several studies have shown evi-

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## Table 1

**Clinical Data on Subjects with BFIC**

| Country | Pedigree | Patient | Sex | Age at Onset (mo) | Seizure | | | EEG | Antiepileptic Drugs[b] | Neurological Examination[c] | CT, MRI | Last Seizure (mo) | Year of Birth |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Type[a] | Distribution | Frequency | | | | | | |
| Argentina | i | I.2 | F | 6 | ND | Awake | ND | N | None | N | N | 6 | 1966 |
| Argentina | i | II.1 | M | 6 | CP | Awake | Isolated | N | PB | N | N | 7 | 1990 |
| Argentina | i | II.2 | F | 5 | CPSG | Awake | Isolated | N | PB | N | N | 6 | 1992 |
| Argentina | O | I.1 | M | 3–6 | GTC | Awake | Clusters | N | PB | N | ND | <12 | 1962 |
| Argentina | O | II.1 | F | 2 | PMSG | Awake | Clusters | N | PB | N | N | 10 | 1989 |
| Argentina | O | II.2 | F | 3 | GTC | Awake | Clusters | N | PB | DS | N | 14 | 1991 |
| Argentina | P | I.4 | M | 8 | PMSG | Awake | ND | N | PB | N | N | 12 | 1969 |
| Argentina | P | II.2 | M | 6 | PMSG | Awake | Clusters | N | CBZ | N | N | 18 | 1997 |
| Argentina | K | II.2 | M | 10 | ND | Awake | ND | ND | PB | N | N | 14 | 1959 |
| Argentina | K | II.5 | M | 6 | GTC | Awake | Clusters | ND | None | N | ND | 6 | 1964 |
| Argentina | K | III.2 | M | 4 | CPSG | Awake | ND | N | PB, CBZ | N | N | 11 | 1991 |
| Argentina | K | III.3 | F | 3 | CPSG | Awake | Clusters | N | PB, CBZ | N | N | BECTS[d] | 1995 |
| Argentina | K | III.4 | F | 5 | GTC | Awake | Clusters | N | None | N | N | 5 | 1996 |
| France | F | I.1 | M | <12 | ND | Awake | ND | ND | None | N | ND | <12 | 1944 |
| France | F | II.2 | F | 3–6 | ND | Awake | ND | ND | PB | N | ND | 6 | 1967 |
| France | F | III.2 | F | 4 | ND | Awake and asleep | Clusters | N | CBZ | N | ND | 4 | 1992 |
| France | F | III.4 | M | 3 | PMSG | Awake and asleep | Clusters | N | None | N | ND | 3 | 1997 |
| France | C1 | II.2 | F | <6 | PMSG | Awake | ND | ND | None | N | ND | <12 | 1953 |
| France | C1 | II.5 | F | <12 | PMSG | Awake | ND | ND | None | N | ND | <12 | 1959 |
| France | C1 | III.2 | F | 6 | PMSG | Awake | Isolated | ND | None | N | ND | 6 | 1975 |
| France | C1 | III.4 | F | 6 | PMSG | Awake | Isolated | ND | None | N | ND | <12 | 1986 |
| France | C1 | IV.1 | M | 3 | PMSG | Awake | Isolated | N | DZP, CBZ, HYD, VGB[e] | DYSK | N | 18 | 1996 |
| France | V | I.1 | M | 4 | GTC | Awake | Clusters | N | PHE | N | N | 11 | 1994 |
| France | V | II.2 | M | <12 | GTC | Awake | Clusters | ND | PB | N | ND | <12 | 1956 |

Note.—N = normal; ND = not determined.

[a] CP = complex partial; CPSG = CP secondary generalized; GTC = generalized tonic-clonic; PMSG = partial motor secondary generalized.

[b] CBZ = carbamazepine; DZP = diazepam; HYD = hydantoin; PB = phenobarbital; PHE = phenytoin; VGB = vigabatrin.

[c] DS = Down syndrome; DYSK = dyskinesia (from age 2 years).

[d] BECTS = benign epilepsy with centrotemporal spikes (from age 3 years).

[e] Treatments were not completely effective.

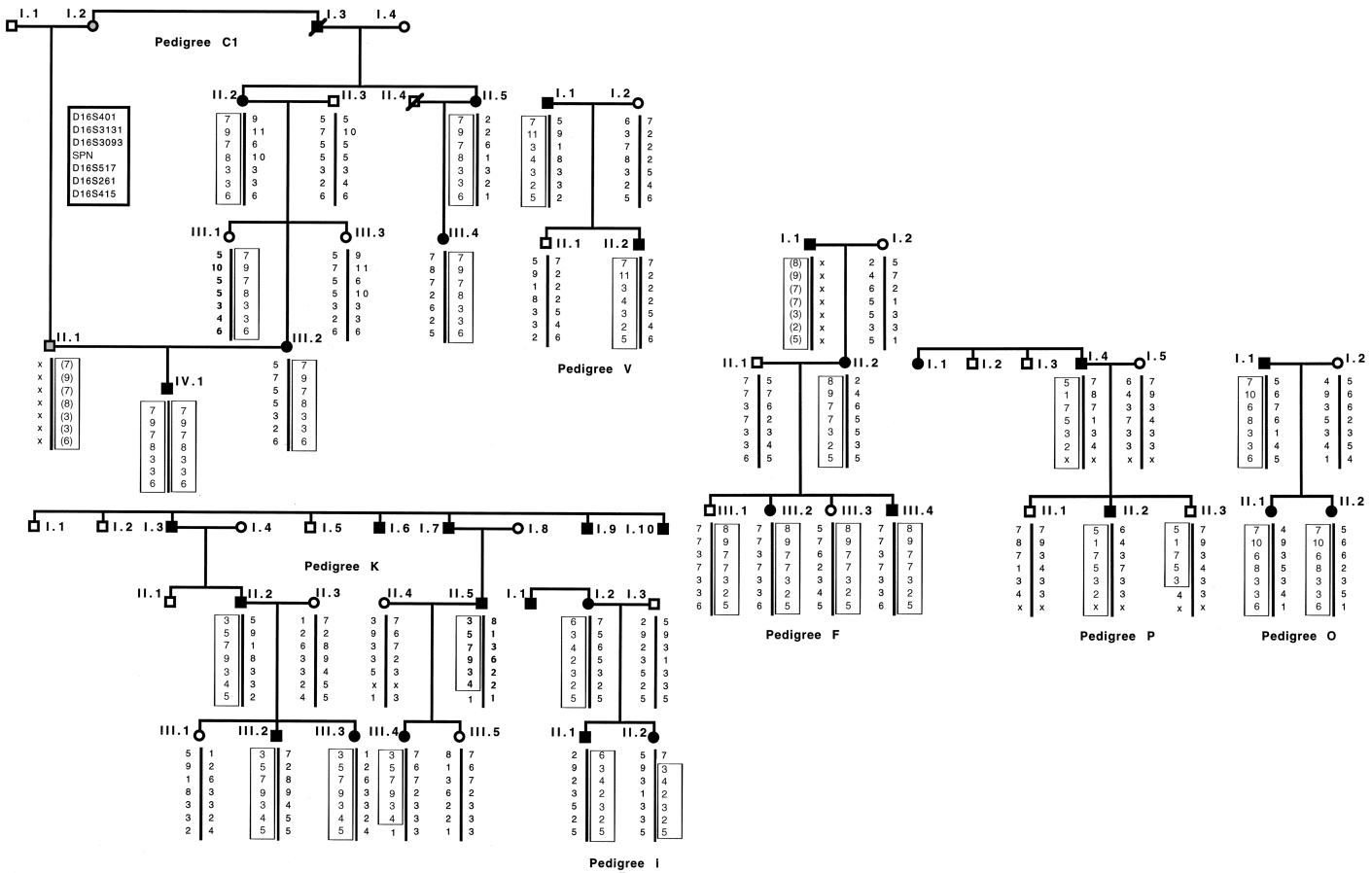


**Figure 1** Pedigree and haplotype analysis of the families with autosomal dominant infantile convulsions. Blackened symbols indicate individuals with BFIC. Gray symbols indicate individuals with an unknown phenotype. Microsatellite markers are listed in box at top left. The haplotype segregating with the disease in the families is boxed.

**Table 2**

**Two-Point LOD Scores for Markers on Chromosomes 19q and 16p12-q12**

| Chromosome and Marker | LOD Score at $\theta$ = | | | | | | |
|---|---|---|---|---|---|---|---|
| | .0 | .01 | .05 | .1 | .2 | .3 | .4 |
| 16 : | | | | | | | |
| D16S401 | −.76 | 1.48 | 1.90 | 1.85 | 1.44 | .94 | .45 |
| D16S3133 | 2.84 | 2.78 | 2.53 | 2.20 | 1.56 | .96 | .44 |
| D16S3131 | 3.32 | 3.25 | 2.95 | 2.58 | 1.83 | 1.12 | .50 |
| D16S3093 | 3.23 | 3.15 | 2.86 | 2.49 | 1.76 | 1.07 | .48 |
| D16S313 | 2.83 | 2.76 | 2.47 | 2.11 | 1.41 | .79 | .31 |
| SPN | 3.32 | 3.25 | 2.95 | 2.58 | 1.83 | 1.12 | .50 |
| D16S517 | 1.53 | 1.49 | 1.30 | 1.07 | .66 | .33 | .11 |
| D16S415 | −2.44 | −.35 | .18 | .29 | .23 | .12 | .04 |
| 19: | | | | | | | |
| D19S250 | −∞ | −4.79 | −2.19 | −1.23 | −.49 | −.22 | −.09 |
| D19S114 | −∞ | −2.33 | −1.06 | −.62 | −.29 | −.16 | −.07 |
| D19S414 | −∞ | −3.78 | −1.83 | −1.10 | −.51 | −.25 | −.09 |
| D19S425 | −∞ | −3.38 | −1.49 | −.83 | −.35 | −.17 | −.07 |
| D19S412 | −∞ | −4.85 | −2.23 | −1.25 | −.47 | −.18 | −.06 |
| D19S606 | −∞ | −4.53 | −1.95 | −1.02 | −.34 | −.11 | −.03 |
| D19S904 | −3.50 | −.96 | −.36 | −.17 | −.08 | −.07 | −.05 |
| D19S926 | −∞ | −3.32 | −1.41 | −.73 | −.25 | −.09 | −.04 |
| D19S210 | −∞ | −3.46 | −1.50 | −.77 | −.20 | .01 | .06 |

dence that the mechanisms underlying paroxysmal movement disorders (dyskinesia) and BFIC are similar (Berkovic 1999). A new autosomal dominant syndrome had been described in four French families in which both BFIC and paroxysmal choreoathetotic dyskinesia occurred. Linkage of this syndrome (ICCA [MIM 602066]) at chromosome 19q was excluded, and evidence for linkage was found at chromosome 16p12-q12, between markers D16S401 and D16S517 (Szepetowski et al. 1997). Infantile convulsions associated with various types of paroxysmal dyskinesias have been linked to the chromosome 16 ICCA region in additional families (Lee et al. 1998; Tomita et al. 1999; Swoboda et al. 2000). Moreover, one large black family with paroxysmal kinesigenic dyskinesia (PKC [MIM 128200]) but without infantile convulsions had been linked to the ICCA region (Bennett et al. 2000). Because patients in the families with ICCA could display either BFIC or paroxysmal dyskinesias or both, it is likely that disease in families with pure BFIC is linked to the ICCA region as well.

In the present study, seven families in Argentina and France with pure BFIC inherited as an autosomal dominant trait were identified and studied. Individuals were considered to be affected with BFIC if they had nonfebrile convulsions (simple partial seizures, complex partial seizures, or apparently generalized seizures), with onset at age 2–12 mo without recognized etiology, with a favorable outcome, and with a familial history of similar seizures (table 1). DNA samples were tested with highly polymorphic markers situated at chromosome 16p12-q12 and at chromosome 19q. Fluorescent PCR products were analyzed on 373A sequencers (PE Applied Biosystems), using the GENESCAN and GENOTYPER softwares. Linkage analysis was performed assuming autosomal dominant mode of inheritance and using an affected-members-only method, and with frequency of the disease allele at .0001, by use of MLINK in the LINKAGE computer package (Lathrop and Lalouel 1984). Markers spaced regularly across 19q (Dib et al. 1996; Généthon Database) gave significant negative LOD scores (table 2), thereby excluding this genomic area. This result also was consistent with previous exclusion of chromosome 19q in several families with BFIC (Gennaro et al. 1999; Giordano et al. 1999; Baralle et al. 2000) and confirmed the genetic heterogeneity of BFIC. By contrast, linkage to chromosome 16p12-q12 was demonstrated with several informative markers, and a maximum two-point LOD score of 3.32 ($\theta = 0$) for D16S3131 and SPN (table 2).

To our knowledge, this is the first time that pure BFIC syndrome has been linked to chromosome 16. Together with data on ICCA and PKC syndromes reported elsewhere, the present study proves that human chromosome 16p12-q12 is a major genetic locus underlying both BFIC and paroxysmal dyskinesias. Alterations at this locus could lead to the various clinical components characterizing the ICCA syndrome. Analysis of meiotic recombination events did not help to narrow the critical ICCA region. Although families had been studied in Argentina and France and although a large proportion of the Argentinian population is of European descent, no evidence could be found for a common origin of the families. Moreover, no common haplotype was significantly shared across the families. Allele 3 for marker D16S517 was present in all affected individuals (fig. 1) but appeared to be very frequent in the white population (71%, according to the Genome Database). No ion-channel gene has been mapped to the critical area. We expect that progress in the sequencing of the human genome will help to identify new candidate genes that can be tested for mutation in the numerous families that are linked to the ICCA region. However, recent data suggested that mutations in more than one gene at chromosome 16p12-q12 may give rise to similar and overlapping syndromes, making the search for the disease gene(s) more complicated. Paroxysmal dyskinesia of the kinesigenic type (PKC [MIM 128200]) has been linked to chromosome 16q13-q22 in a single Indian family (Valente et al. 2000). The critical region showed no overlap with any of the critical regions defined in previous studies (fig. 2). Moreover, a recessive syndrome in which rolandic epilepsy is associated with paroxysmal exertional dyskinesia had been linked to chromosome 16p12 by homozygosity mapping (Guerrini et al. 1999). The condition is also known as the "RE-PED-WC syndrome." Once again, the critical region was not consis-

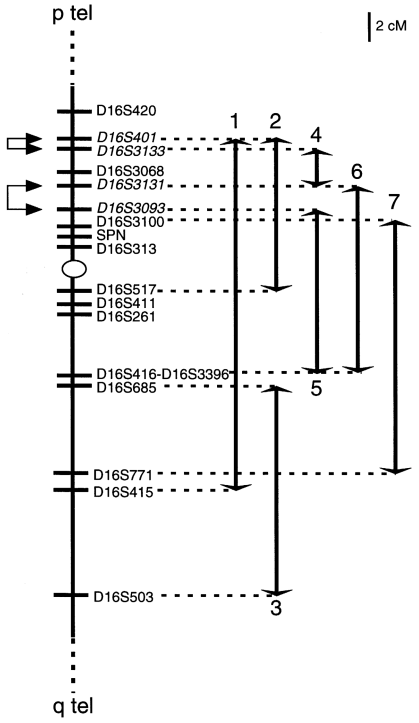


**Figure 2** Schematic representation of the genetic map of human chromosome 16p12-q12. Markers have been located according to Dib et al. (1996) and to data from the present study, as well as according to maps published elsewhere (Szepetowski et al. 1997; Tomita et al. 1999; Valente et al. 2000). Markers shown in italics and marked by arrows are those whose relative locations are controversial. Critical regions are indicated as follows: 1 = BFIC (the present study); 2 = ICCA syndrome (Szepetowski et al. 1997); 3 = PKC (Valente et al. 2000); 4 = RE-PED-WC syndrome (Guerrini et al. 1999); 5 = PKC and BFIC (Tomita et al. 1999); 6 = PKC and BFIC (Swoboda et al. 2000); and 7 = PKC (Bennett et al. 2000).

tent with a single-gene hypothesis (fig. 2). Duplication events could have sustained the existence of two homologous genes lying in close vicinity at 16p12-q12 (Loftus et al. 1999). Other explanations for this apparent complexity cannot be ruled out. Genotyping errors or inconsistencies in the genetic maps (see fig. 2) could have led to misinterpretation in the definition of the overlaps between the critical regions.

Significant LOD scores were obtained, assuming 65% penetrance (data not shown). The highest LOD scores were obtained when only affected members were included in statistical analysis (table 2). This resulted because some families included unaffected individuals carrying the disease haplotypes (fig. 1). Penetrance rates were even lower than in families with ICCA syndrome; this is not surprising, considering that the families with BFIC linked to chromosome 16 display an unusual ICCA syndrome, with no paroxysmal dyskinesia in heterozygous patients. Data reported elsewhere (Szepetowski et al. 1997) clearly showed that the ICCA syndrome could be variably expressed within the same family. It is also noteworthy that infantile convulsions in the families with BFIC cannot be distinguished from those in families with ICCA. Before the analysis, systematic searchers for paroxysmal dyskinesia were conducted in the families with BFIC, making it unlikely that the dyskinesia was present but not detected. We cannot exclude the possibility that the youngest patients (<20 years old) may develop dyskinesia later in life. However, this did not occur for any of the individuals ⩾20 years old in the seven families, including those family members who could not be studied for the present report.

Variable presentation of the ICCA syndrome could be the result of allelic variations. However, the disease could be variably expressed in patients from the same family. It is also well known that paroxysmal disorders can be triggered by a large variety of external stimuli, which could explain the incomplete penetrance and the variable clinical manifestations. Another likely explanation is that modifying genes may be present. This would be consistent with the unexpected findings in one member of pedigree C1 (patient IV.1). This patient belonged to a consanguineous family and appeared to carry two copies of the disease haplotype. The clinical status of his father (II.1) and grandmother (I.2) could not be ascertained, and no DNA was available. However, there is no doubt that I.2 and II.1 inherited the disease haplotype that was transmitted to IV.1, because patient IV.1 was homozygous for all markers at 16p12-q12. This is the first time that a homozygous patient with BFIC has been described. The infantile convulsions of patient IV.1 did not respond well to anticonvulsants, in contrast to all other affected members of his family and to classical BFIC. Moreover, although the families had been selected on the basis of clinical evidence of BFIC only, this patient started having atypical paroxysmal choreic/dystonic dyskinesia at age 2 years; these attacks were detected while the analysis was under way. The patient's age at onset is earlier than that of classical paroxysmal dyskinesias (which usually begins at age 5–16 years). The type of dyskinesia was difficult to assess. Dyskinetic movements sometimes occurred a few seconds after starting exertion, which suggests kinesigenic type. However, the patient did not respond to carbamazepine, a finding that is consistent with an exertional type rather than with a kinesigenic one. Moreover, abnormal movements could occur later in life without any clear triggering factor.

These paradoxical clinical features have already been a matter of debate (Guerrini et al. 2000) and may suggest the existence of overlapping forms of dyskinesia that also may change with time. Homozygous mutation in the putative ICCA gene may thus have led to the appearance, in this unusual patient, of paroxysmal dyskinesia and to

resistance to anticonvulsants, whereas heterozygous mutation in this family would sustain only classical infantile convulsions. This finding could provide interesting clues to understanding the different phenotypes observed in the ICCA syndrome. For example, the ICCA protein could associate with itself as well as with other proteins to form a multimeric functional protein. This has been described for KCNQ2 (*KCNQ2* [MIM 602235]) and KCNQ3 (*KCNQ3* [MIM 602232]) products in the case of benign neonatal familial convulsions (Rogawski 2000). Modifying genes could act similarly in heterozygous ICCA patients and make the clinical manifestations of the ICCA syndrome highly variable.

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## Electronic-Database Information

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

Généthon, http://www.genethon.fr
Genome Database, http://www.gdb.org
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for BFIC [MIM 601764], ICCA [MIM 602066], KCNQ2 [MIM 602235], KCNQ3 [MIM 602232], and PKC [MIM 128200])

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