

Novel familial cases of ICCA (infantile convulsions with paroxysmal choreoathetosis) syndrome

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ABSTRACT – Epilepsy and paroxysmal dyskinesia are two episodic cerebral disorders that can share a common genetic basis. Rare families with infantile seizures and paroxysmal dyskinesia [predominantly paroxysmal kinesigenic dyskinesia (PKD)], co-inherited as a single autosomal dominant trait, have been described (infantile convulsions with paroxysmal choreoathetosis; ICCA syndrome) and a disease gene has been mapped at chromosome 16p12-q12 (ICCA region). We report the clinical picture of seven previously unreported families with ICCA syndrome. The identification of novel ICCA families should contribute to better knowledge regarding the clinical manifestations of ICCA syndrome as well as the search for the underlying genetic defect(s).

Key words: infantile seizures, epilepsy, paroxysmal dyskinesia, ICCA syndrome

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The relationship between human epilepsies and non-epileptic cerebral disorders, whether paroxysmal (migraine, episodic ataxia, paroxysmal dyskinesia, paroxysmal kinesigenic dyskinesia), or non-paroxysmal (autism, speech impairment, mental retardation), has long been known. In

a given family, two or more of these cerebral disorders may be variably co-inherited as a single trait, indicating that common genetic mechanisms may underlie at least the pathogenesis of a subset of these clinically different entities. For instance, mutations in the sodium/potassium channel pump

gene *ATP1A2* have been found in patients with infantile seizures with hemiplegic migraine (Vanmolkot *et al.*, 2003). Benign infantile seizures (BIS) are afebrile seizures which commence at age 3-12 months and are associated with a favourable outcome and a normal psychomotor development. Typical seizures are brief with motor arrest, deviation of the head and eyes to one side, generalised hypertonia, cyanosis, and limb jerks. Seizures are focal with or without secondary generalisation and usually occur in clusters. In most cases interictal electroencephalogram (EEG) is normal while ictal EEG shows abnormalities that may originate from various cerebral lobes. Familial forms with autosomal dominant inheritance, namely benign familial infantile seizures (BFIS) and non-familial forms (referred to as BIS), have been reported (Vigevano *et al.*, 1992; Caraballo *et al.*, 2003; Caraballo, 2007).

Paroxysmal dyskinesia (PD) is a rare disorder characterized by the episodic occurrence of involuntary abnormal movements which manifest as attacks of choreoathetosis or dystonia. They are clinically and genetically heterogeneous and various classifications have been proposed (Bruno *et al.*, 2004). Paroxysmal non-kinesigenic dyskinesia (PNKD) can be due to mutations in a gene (*MR1*) of unknown function (Lee *et al.*, 2004), while three genes for paroxysmal kinesigenic dyskinesia (PKD) have been mapped to 1p34-p33 (PKD with episodic ataxia and spasticity; Auburger *et al.*, 1996), 16p11.2-q12 (Bennett *et al.*, 2000), and 16q13-q22.1 (Valente *et al.*, 2000). More recently, mutations in the *SLC2A1* gene encoding the glucose transporter GLUT-1 were found in patients with PD of the exercise-induced type (Suls *et al.*, 2008, 2009; Weber *et al.*, 2008).

The relationship of PD with epileptic seizures has long been suspected (Pryles *et al.*, 1952; Hudgins and Corbin, 1966). In 1997, genetic linkage to chromosome 16 of a newly defined syndrome (infantile convulsions and paroxysmal choreoathetosis, ICCA) demonstrated that typical infantile seizures (*i.e.* afebrile seizures with onset at age 3-12 months and a favourable outcome) and PD might share common molecular mechanisms (Szepietowski *et al.*, 1997). Since then, several studies have confirmed the importance of the ICCA locus at chromosome 16 (Szepietowski, 2007; Rochette *et al.*, 2008). In addition to the rare large families that independently led to significant LOD scores for each (Szepietowski *et al.*, 1997; Lee *et al.*, 1998), cumulative LOD scores have also indicated linkage to human chromosome 16 in small to medium-size ICCA families with infantile seizures and PD (Tomita *et al.*, 1999; Bennett *et al.*, 2000; Swoboda *et al.*, 2000). To date, the identity of the ICCA gene remains unknown. The diagnosis and collection of data from additional families with ICCA syndrome will help future screening strategies; from classical sequencing approaches to the search for large-scale rearrangements such as deletions and duplications (Rochette *et al.*, 2008). In the present study we describe seven geographically dispersed families with features of ICCA.

Patients and families

The seven pedigrees are depicted in *figure 1*. Inclusion criteria for this study included familial association of IS (afebrile seizures with onset at age 3-12 months without recognized aetiology and with a favourable outcome) with PD. Age at onset, neurological examination, type of PD, as well as characteristics of epileptic seizures, were evaluated in all paediatric patients and, whenever possible, in their affected relatives. Interictal EEGs were also performed in the patients according to the international 10-20 system. Clinical family studies were performed when relatives gave informed consent according to local regulations.

Results and discussion

Family 1

Patient II.3, of French origin, was first diagnosed with recurrent afebrile seizures at age 18 months. At eight years old, she was referred to the specialized clinic for attacks triggered by sudden movement that lasted for a maximum of 30 seconds and could be as frequent as ten per day. The attacks started with transient irregular twitching of the upper extremities. Typically, the paroxysms consisted of dystonic posturing affecting the trunk in a convex manner followed by ballistic movements. At the same time, she had the sensation of "pins and needles" in both feet while maintaining full consciousness. Her brother (II.1) presented with the same clinical picture of PKD at ten years of age but had no known history of epilepsy. Both the children had normal interictal EEG as well as normal radiological and neurological findings. Their mother (I.2) had afebrile epilepsy when she was two to three years old with a favourable outcome and never displayed abnormal movements.

Family 2

All the patients in this French family experienced benign infantile seizures before 12 months and all displayed PKD with onset between nine and ten years of age. Seizures were partial with secondary generalisation and were characterised by head and eye deviation, cyanosis and bilateral limb jerks. Attacks of dyskinesia were brief (less than two minutes), occurred more than ten times a day on average and were precipitated by sudden movements.

Family 3

Patient III.1 developed afebrile recurrent seizures at age five months when she presented seven seizures during a period of 36 hours. Three seizures were recorded by video EEG monitoring. These seizures were partial with secondary generalisation. The patient responded well to

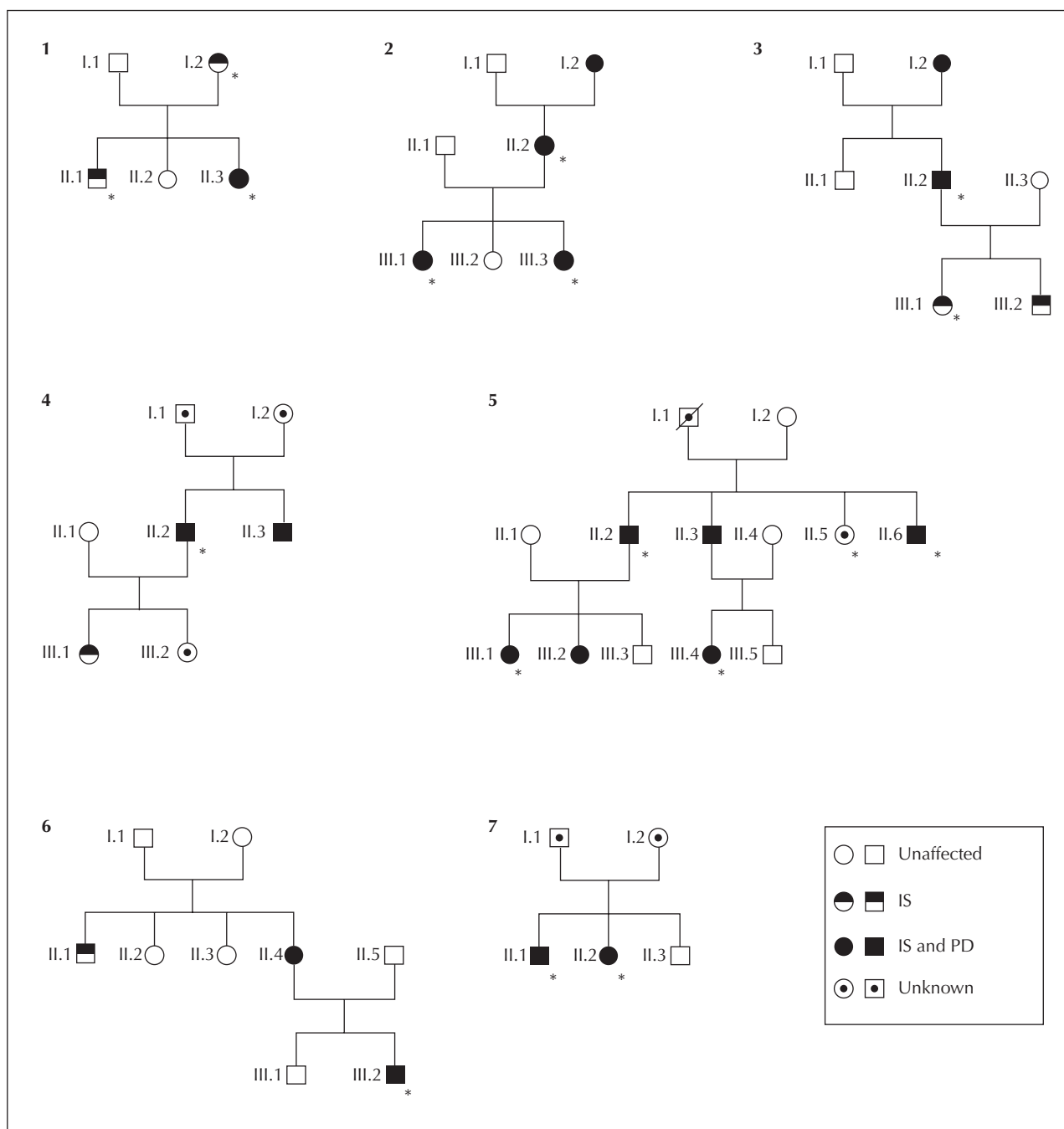


Figure 1. Seven novel pedigrees with ICCA syndrome.

The asterisks indicate the patients with blood samples collected with the corresponding available DNA.

IS: infantile seizures; PD: paroxysmal dyskinesia.

low doses of carbamazepine and has been seizure-free with normal development since then. In this family of French origin, patient III.2 also had three seizures at age four months; low doses of carbamazepine had the same efficacy with complete stoppage of the seizures. The

father (II.2) also had similar seizures at age six months and received phenobarbital for six months. He had episodes of paroxysmal dystonic (non-kinesigenic) choreoathetosis that sometimes lasted for more than one hour, later in life.

Family 4

Patient II.2, from India, had afebrile seizures in infancy. Onset of brief spells (less than a minute) appeared at age 23 years triggered by sudden movements such as standing up to answer the telephone or when starting to run. Stress, fatigue and hunger were reported by the patient to be aggravating factors. The spells included both choreoathetotic and dystonic movements and were well controlled with 200 mg of phenytoin/day. His brother (II.3), who was reported to have a similar phenotype, and his daughter (III.1) developed infantile convulsions at age three months. Investigations of the daughter were normal, including brain MRI and EEG.

Family 5

The index case (III.1) was a Turkish female presenting with episodes of involuntary abnormal movements that corresponded to attacks of choreoathetosis or dystonia, at four years of age. The attacks were brief (less than a minute) and consistently started with initiation of rapid movements like "jumping up to get the phone". The attacks were primarily choreoathetotic with some dystonia. Her sister (III.2) had a very similar disorder with onset at age eight years. Their father (II.2), uncle (II.6), and cousin (III.4) were reported to have the same phenotype. Seizures in both girls were well controlled with 100mg of carbamazepine/day. Neurological workups were completely normal including MRI. All patients in the family had benign infantile convulsions between the ages of four months to three years.

Family 6

Patient III.2 was a Malaysian male with mixed Chinese-Caucasian origin. He had uncomplicated antenatal, intra-partum and postnatal histories with normal development. At four months of age, he presented with recurrent afebrile seizures. Further investigations were normal. The patient responded well to phenytoin, which was stopped at age 10 months without further recurrence of seizures. The patient presented again at age eight years complaining of 'numbness' of the right forearm. Paroxysmal kinesigenic choreoathetosis was diagnosed. The episodes had increased in frequency and occurred almost daily. These were precipitated by unanticipated sudden movement, with his right arm stuck in a dystonic posture that lasted for a few seconds. His mother (II.4) also had similar symptoms starting at around six to seven years of age. She described her lower limb as being stuck in an abnormal posture associated with irregular jerking, spreading to her upper limb and face. Again, these were brought on by sudden unexpected movement and could be avoided if she slowed down her movement or planned before executing the movements. Symptoms resolved for many

years, and then recurred during her university years in Wales. Extensive EEGs and videotelemetry led to diagnosis of epilepsy and sodium valproate was prescribed as antiepileptic treatment. Her brother (II.1) also presented with an afebrile seizure at three years of age.

Family 7

Patient II.1 was a male of Caucasian-Canadian origin who developed afebrile seizures at the age of 3.5 months. Investigations including EEG were normal. At the age of 10 years he presented with a two-year history of a sensation that his legs were out of control. He began to have problems with standing and initiating movement, loss of balance and tripping. There were episodes of flexing at the elbow, extensor rotation at the shoulder and finger flexion. His face and head also became involved. The episodes occurred five to six times per day and lasted about five seconds. Paroxysmal kinesigenic choreoathetosis was diagnosed. In this Canadian family of Caucasian origin, the sister (II.2) presented with seizures at four months. She began to stumble at age six years, which progressed to "freeze-ups". At the age of seven years she began to have mild dystonia whilst standing or sitting for a while. She progressed to the same PD diagnosis as her brother.

Inter- and intra-familial variability in the ICCA patients has already been described and is largely sustained by the type of PD (kinesigenic, exercise-induced, or non-kinesigenic). More than 30 families with the clinical characteristics of ICCA syndrome have been described worldwide so far (Pryles *et al.*, 1952; Hudgins and Corbin, 1966; Szepetowski *et al.*, 1997; Lee *et al.*, 1998; Sadamatsu *et al.*, 1999; Tomita *et al.*, 1999; Bennett *et al.*, 2000; Swoboda *et al.*, 2000; Hattori *et al.*, 2000; Thiriaux *et al.*, 2002; Kato *et al.*, 2006; Striano *et al.*, 2006), and seven families are reported here, which have not previously been described. Overall, the seven ICCA families studied here showed a relatively homogeneous association between infantile seizures and PD inherited as an autosomal dominant trait (*figure 1*). Of note, while the familial presentation of ICCA syndrome may variably include patients with PD, infantile seizures, or both, all patients reported here in the seven families presented with PD had infantile seizures earlier in life. PD was of the kinesigenic type (PKD) in all families but one (family 3: non-kinesigenic type, PNKD). This is in agreement with previous findings, as both the predominance of PKD, as part of the ICCA syndrome, and the possible occurrence of other types of PD have been reported (Guerrini, 2001; Szepetowski, 2007). Hence, patients had spontaneous (PNKD) or exercise-induced (PED) dyskinesia in some ICCA families (Szepetowski *et al.*, 1997), while PD was clearly of the kinesigenic type in other families (Pryles *et al.*, 1952; Hudgins and Corbin, 1966; Sadamatsu *et al.*, 1999; Tomita *et al.*, 1999; Swoboda *et al.*, 2000;

Kato *et al.*, 2006). Interestingly also, the type of PD changed with time in one particular patient of a family with BIS inherited as an autosomal trait (Caraballo *et al.*, 2001).

Each separate family detected here was too small in size to enable successful genetic linkage; moreover, DNA from several affected individuals was lacking in most families (figure 1). Although we cannot exclude linkage elsewhere in the genome for a minority of the small ICCA families so far, no ICCA family has ever been excluded from linkage to the ICCA genomic area amongst the 27 families that have been genotyped so far (Szepetowski *et al.*, 1997; Lee *et al.*, 1998; Sadamatsu *et al.*, 1999; Tomita *et al.*, 1999; Bennett *et al.*, 2000; Swoboda *et al.*, 2000; Thiriaux *et al.*, 2002; Striano *et al.*, 2006). Hence, it is very likely that the novel families are linked to the chromosome 16 ICCA area, assuming that the ICCA syndrome is genetically homogeneous. These families will help in future gene and genome screening strategies. Together with better knowledge of the clinical manifestations of ICCA syndrome, they will also help in establishing phenotype/genotype correlations when the genetic defect(s) underlying the ICCA syndrome is identified. □

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Disclosure.

None of the authors has any conflict of interest to disclose.

References

Auburger G, Ratzlaff T, Lunkes A, *et al.* A gene for autosomal dominant paroxysmal choreoathetosis/spasticity (CSE) maps to the vicinity of a potassium channel gene cluster on chromosome 1p, probably within 2 cM between D1S443 and D1S197. *Genomics* 1996; 31: 90-4.

Bennett LB, Roach ES, Bowcock AM. A locus for paroxysmal kinesigenic dyskinesia maps to human chromosome 16. *Neurology* 2000; 54: 125-30.

Bruno MK, Hallett M, Gwinn-Hardy K, *et al.* Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. *Neurology* 2004; 63: 2280-7.

Caraballo R. Benign familial and non familial infantile seizures. In: Fejerman N, Caraballo R, eds. *Benign focal epilepsies in infancy, childhood and adolescence*. Paris: John Libbey Eurotext, 2007: 31-49.

Caraballo RH, Cersósimo RO, Espeche A, Fejerman N. Benign familial and non-familial infantile seizures: a study of 64 patients. *Epileptic Disord* 2003; 5: 45-9.

Caraballo R, Pavsek S, Lemainque A, *et al.* Linkage of benign familial infantile convulsions to chromosome 16p12-q12 suggests allelism to the infantile convulsions and choreoathetosis syndrome. *Am J Hum Genet* 2001; 68: 788-94.

Guerrini R. Idiopathic epilepsy and paroxysmal dyskinesia. *Epilepsia* 2001; 42 (Suppl. 3): 36-41.

Hattori H, Fujii T, Nigami H, Higuchi Y, Tsuji M, Hamada Y. Co-segregation of benign infantile convulsions and paroxysmal kinesigenic choreoathetosis. *Brain Dev* 2000; 22: 432-5.

Hudgins RL, Corbin KB. An uncommon seizure disorder: familial paroxysmal choreoathetosis. *Brain* 1966; 89: 199-204.

Kato N, Sadamatsu M, Kikuchi T, Niikawa N, Fukuyama Y. Paroxysmal kinesigenic choreoathetosis: from first discovery in 1892 to genetic linkage with benign familial infantile convulsions. *Epilepsy Res* 2006; 70 (Suppl 1): S174-84.

Lee HY, Xu Y, Huang Y, *et al.* The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway. *Hum Mol Genet* 2004; 13: 3161-70.

Lee WL, Tay A, Ong HT, Goh LM, Monaco AP, Szepetowski P. Association of infantile convulsions with paroxysmal dyskinesias (ICCA syndrome): confirmation of linkage to human chromosome 16p12-q12 in a Chinese family. *Hum Genet* 1998; 103: 608-12.

Pryles CV, Livingston S, Ford FR. Familial paroxysmal choreoathetosis of Mount and Reback: study of a second family in which this condition is found in association with epilepsy. *Pediatrics* 1952; 9: 44-7.

Rochette J, Roll P, Szepetowski P. Genetics of infantile seizures with paroxysmal dyskinesia: the infantile convulsions and choreoathetosis (ICCA) and ICCA-related syndromes. *J Med Genet* 2008; 45: 773-9.

Sadamatsu M, Masui A, Sakai T, Kunugi H, Nanko S, Kato N. Familial paroxysmal kinesigenic choreoathetosis: an electrophysiologic and genotypic analysis. *Epilepsia* 1999; 40: 942-9.

Striano P, Lispi ML, Gennaro E, *et al.* Linkage analysis and disease models in benign familial infantile seizures: a study of 16 families. *Epilepsia* 2006; 47: 1029-34.

Suls A, Mullen SA, Weber YG, *et al.* Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann Neurol* 2009; 66: 415-9.

Suls A, Dedeken P, Goffin K, *et al.* Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1. *Brain* 2008; 131: 1831-44.

Swoboda KJ, Soong B, McKenna C, *et al.* Paroxysmal kinesigenic dyskinesia and infantile convulsions: clinical and linkage studies. *Neurology* 2000; 55: 224-30.

Szepetowski P. Benign familial infantile seizures and paroxysmal choreoathetosis. In: Fejerman N, Caraballo R, eds. *Benign focal epilepsies in infancy, childhood and adolescence*. Paris: John Libbey Eurotext, 2007: 51-62.

Szepetowski P, Rochette J, Berquin P, Piussan C, Lathrop GM, Monaco AP. Familial infantile convulsions and paroxysmal choreoathetosis: a new neurological syndrome linked to the pericentromeric region of human chromosome 16. *Am J Hum Genet* 1997; 61: 889-98.

Thiriaux A, de St Martin A, Vercueil L, *et al.* Co-occurrence of infantile epileptic seizures and childhood paroxysmal choreoathetosis in one family: clinical, EEG, and SPECT characterization of episodic events. *Mov Disord* 2002; 17: 98-104.

Tomita H, Nagamitsu S, Wakui K, *et al.* Paroxysmal kinesigenic choreoathetosis locus map to chromosome 16p11.2-q12.1. *Am J Hum Genet* 1999; 65: 1688-97.

Valente EM, Spacey SD, Wali GM, *et al.* A second paroxysmal kinesigenic choreoathetosis locus (EKD2) mapping on 16q13-q22.1 indicates a family of genes which give rise to paroxysmal disorders on human chromosome 16. *Brain* 2000; 123: 2040-5.

Vanmolkot KR, Kors EE, Hottenga JJ, *et al.* Novel mutations in the Na⁺, K⁺-ATPase pump gene ATP1A2 associated with familial

hemiplegic migraine and benign familial infantile convulsions. *Ann Neurol* 2003; 54: 360-6.

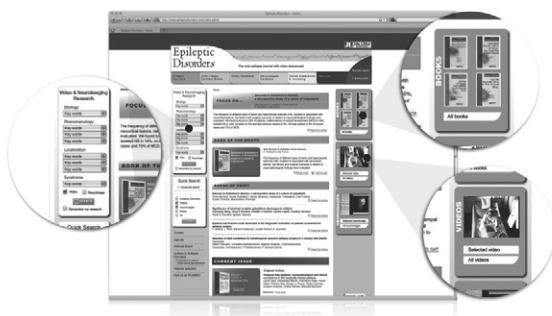
Vigevano F, Fusco L, Di Capua M, Ricci S, Sebastianelli R, Lucchini P. Benign infantile familial convulsions. *Eur J Pediatr* 1992; 151: 608-12.

Weber YG, Storch A, Wuttke TV, *et al.* GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. *J Clin Invest* 2008; 118: 2157-68.

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