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Case Report

Epilepsy phenotype in patients with Xp22.31 microduplication

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ABSTRACT

The clinical significance of Xp22.31 microduplication is still unclear. We describe a family in which a mother and two children have Xp22.31 microduplication associated with different forms of epilepsy and epileptiform EEG abnormalities. The proband had benign epilepsy with centrotemporal spikes with dysgraphia and dyscalculia (IQ 72), the sister had juvenile myoclonic epilepsy, and both had bilateral talipes anomalies. The mother, who was the carrier of the microduplication, was asymptomatic. The asymptomatic father did not possess the microduplication. These data contribute to delineate the phenotype associated with Xp22.31 microduplication and suggest a potential pathogenic role for an epilepsy phenotype.

1. Introduction

Xp22.31 microduplication is one of the most frequent findings in clinical cytogenetic analysis [1,2]. The frequency varies according to the criteria of sample selection, ranging from 0.04% in multicenter studies based on noninvasive prenatal testing [3], and 2.4% in patients with mental retardation [4]. In patients with epilepsy, Olson et al. [5] found at least one copy number variant on chromosomal microarray in 323 out of 805 studied cases (40%), and 30 of these (9.3%) had Xp22.31 microduplication. Recently, Addis et al. [6] found this duplication in 2.2% of patients with benign childhood epilepsy with centrotemporal spikes (BECTS). Even if the clinical significance of the rearrangement is still debated, the most recent studies confirm its possible pathogenic role, although probably not independently but instead linked to additional genetic factors [7]. The phenotype is variable is prevalent in neurocognitive and behavioral disorders, with seizures reported in 3–44% of cases [2,5–8]. Dysmorphic features, talipes anomalies, and feeding difficulties may also occur [5–8]. Severity and intensity of the phenotypes are variable; intellectual disability ranges from mild to severe mental retardation, in some patients associated with autism spectrum disorder, speech and reading difficulty, dyslexia, and attention deficit hyperactivity disorder. Also, the epilepsy phenotype varies from neonatal seizures to BECTS, Dravet-like epilepsy, and drug-resistant myoclonic epilepsy [2–8]. In the present study we analyzed four members of a family in which two children possess Xp22.31 microduplication associated with different forms of epilepsy.

2. Material and methods

We studied a nuclear family of four members (non-consanguine parents and two children). Underwritten informed consent, all members underwent clinical, EEG, neuro-imaging and laboratory evaluations based on specific clinical indications for each subject. Video-EEG monitoring was recorded in each member at rest and during standardized visual stimuli with intermittent light stimulation (ILS), pattern stimulation (PS) and watching television, according to a protocol used in our center [9]. Genomic DNA of each member was extracted from peripheral blood with standard procedures and analyzed by single nucleotide polymorphism microarray-based analysis (SNP-array Cytoscan; Affymetrix, Santa Clara, CA).

3. Results

The family pedigree is shown in Fig. 1.

3.1. Proband

Six-year-old boy (IV 27, Fig. 1), born at term from normal pregnancy. Normal growth in height, weight and psychomotor development. At 5.7-years of age he started to have focal seizures upon awakening with

Abbreviations: BECTS, Benign epilepsy with centrotemporal spikes; SNP-array, single nucleotide polymorphism microarray; ILS, intermittent light stimulation; PS, pattern stimulation.

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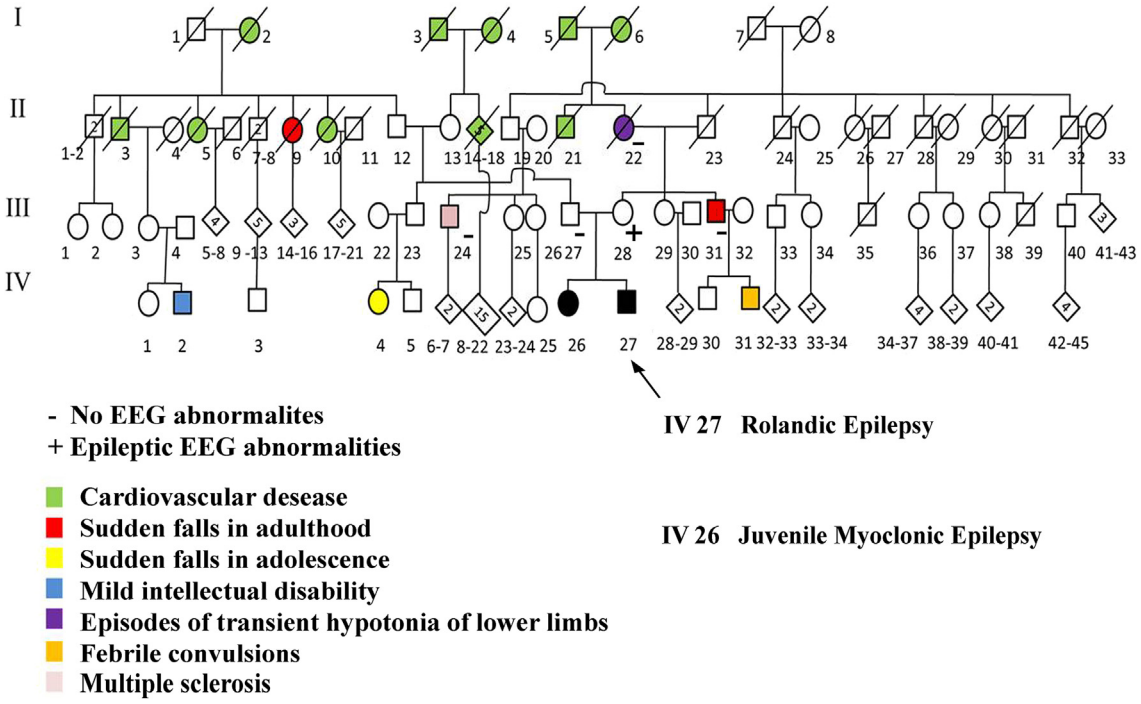

Fig. 1. Pedigree of the family.

sensorimotor symptoms with tonic contraction of one side of the face, oropharyngeal automatisms, sialorrhea, and speech arrest. At school he needed educational support because of learning difficulties, dysgraphia, and dyscalculia. His full-scale intelligence quotient (WAIS-IV test) was 72 (verbal 73, performance 77). General physical examination showed bilateral talo-valgus deformities, reported by the parents to be more prominent in the first months of life. The neurological examination was normal. Waking video-EEG showed rare focal spikes and sharp waves in the centro-occipital regions without changes during ILS, PS and TV. Sleep video-EEG demonstrated bihemispheric independent centrotemporal spikes and sharp waves suggesting BECTS (Fig. 2A). Brain NMR was normal. Therapy was started with valproic acid and titrated to 600 mg/day with complete seizure control (last episode at the age of 7.6 years). At the end of the follow-up (age 18.11 years) he was in remission for about 10 years, with a normalized EEG recorded at the age of 13.4 years, and anti-seizure drug therapy tapered and discontinued over five years.

3.2. Sister

Thirteen-year-old girl (IV 26, Fig. 1) born at term from normal pregnancy. Normal growth in height, weight and psychomotor development. No learning difficulties. She came to medical attention at the age of 14 years for recurrent myoclonic jerks in the upper limbs beginning five months before. Myoclonic jerks predominantly occurred after awakening, with abrupt fall of objects, and rare drop attacks. Some episodes were triggered by visual environmental stimuli, particularly watching TV. Two months after the myoclonic onset, she had a generalized tonic–clonic seizure during wake. General physical examination showed bilateral talo-valgus. Neurological examination was normal. Her total intellectual level (WAIS-IV test) was 95 (verbal 86, performance 108). Wake video-EEG recording showed generalized epileptiform EEG abnormalities with or without concomitant myoclonic jerks at rest (Fig. 2B), activated by ILS (Fig. 2C) and PS. During watching television, she had five seizures characterized by peri-oral or head myoclonia, and an episode of abrupt rhythmic nystagmoid eye movements. The patient's clinical and EEG features were in accordance with the diagnostic criteria for juvenile myoclonic epilepsy (JME) [10]. Lamotrigine therapy was started up, but with poor seizure control, whereby it was gradually replaced with valproic acid up to 600 mg/day with complete seizure remission (normalized EEG at the age of 19.8 years) which still persisted at the end of follow-up (age of 22 years).

3.3. Mother

Fifty-two-year-old woman (III 28, Fig. 1) with unremarkable clinical history (no seizures). The general and neurological examinations were normal. The video-EEG did not show any abnormalities. Brain MRI demonstrated areas of gliosis due to previous involvement of the cerebral microcirculation.

3.4. Father

Sixty-three-year old man (III 27, Fig. 1) with unremarkable clinical history (no seizures). General and neurological examinations were normal. The video-EEG did not show any abnormalities. Brain MRI showed areas of gliosis due to previous involvement of the cerebral microcirculation.

3.5. SNP-array analysis

The analysis detected a microduplication of about 1.7 Mb at Xp22.31, extending from 6,449,233 to 8,135,644 bp (hg19 genomic release) in the two sons and their mother. No SNP-array alterations were found in the father.

4. Discussion

In literature there are no concordant data on the pathogenicity of Xp22.31 microduplication, which has been interpreted in some cases as a variant with an unspecified meaning [1,4] or benign [11,12], in others as a cause of developmental disorders, including autism, intellectual disability, hypotonia and eating disorders [2,7,13]. Cognitive dysfunction and learning difficulties of our proband support a potential pathogenic

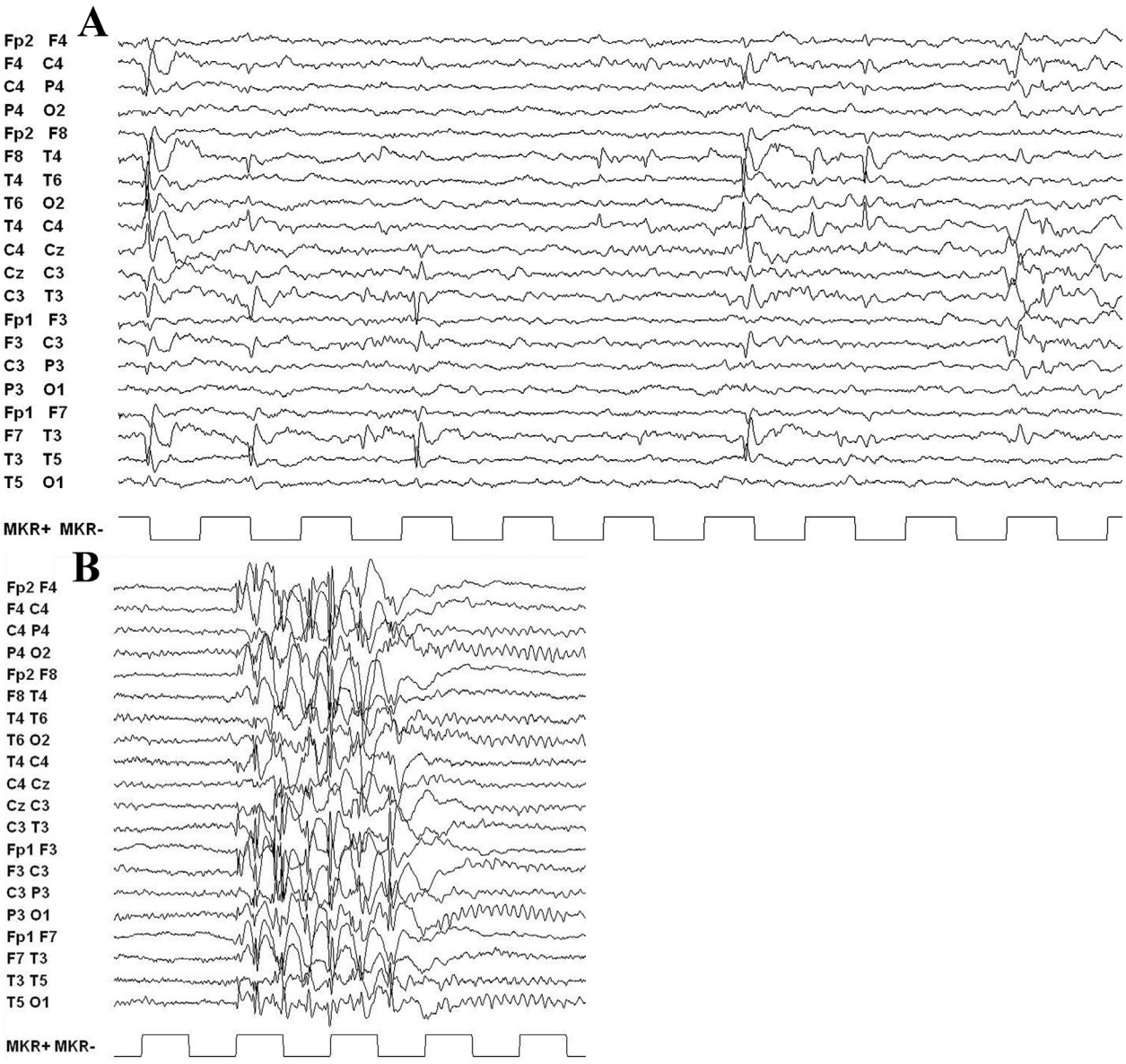

Fig. 2. A. Proband. Sleep EEG: bihemispheric independent centrotemporal spikes and sharp waves. B. Sister. Wake EEG: diffuse burst of spikes, polyspikes, generalized spike-and-wave and generalized polyspike-and-wave complexes at 3–4 Hz of high voltage. Marker amplitude in A and B = 150 μV = 100μ.

role of Xp22.31 microduplication. Regarding the epilepsy phenotype, previous studies reported seizures in 3–17% of cases [2,5,7] and epileptiform EEG abnormalities in 25% [7]. Recently, Esplin et al. [8] described nine patients with this type of mutation, inherited from the mother in all subjects, in which the most frequent phenotypic anomalies were cognitive disability (67%), epilepsy (44%) and talipes anomalies (33%). Epilepsy syndromes are rarely reported in patients with copy number variations at Xp22.31; among 10 cases studied by Olson et al. [5] only 3 had electroclinical features fitting with defined epilepsy syndromes (neonatal seizures, BECTS, Dravet-like onset epilepsy). In the present study, three members had Xp22.31 microduplication, and two of them had epileptiform EEG anomalies associated with a genetic form of epilepsy, with different age-dependent syndromes (BECTS in the proband, JME in the sister). These data support the hypothesis that Xp22.31 microduplication may have a pathogenetic role in the expression of epilepsy phenotype, probably by an additive effect, as suggested by Liu et al. [7].

BECTS and JME have a complex inheritance, probably linked to the interaction of different genes similar to other common forms of genetic epilepsies [14]. In BECTS, the segregation analysis of the 'EEG trait' (centrotemporal spike and sharp waves) fit with a highly penetrant autosomal dominant model of inheritance, with strong evidence of a single genome-wide locus at 11p13 [15–17]. The segregation analysis of JME excluded a simple Mendelian modes of inheritance, while supporting a model involving two genes, one dominant and one recessive [17,18]. Linkage analyses, genome-wide association studies, and fine-mapping resulted in the identification of susceptibility genes ELP4 in BECTS (Pal and Greenberg, 2012). Five mendelian genes have been identified in JME (CACNB4, CASR, GABRa1, GABRD, Myoclonin1/EFHC1) [19]. Three SNP alleles (in BRD2, Cx-36, ME2) and some microdeletions (in 15q13.3, 15q11.2, and 16p13.11) also contribute risk to JME [17,19]. The Xp22.31 microduplication may act in close relationship with both specific epilepsy genes and cerebral maturation processes. Moreover, the phenotypic variability may be related to other modifiers in the genomic background as reduced penetrance, different genes in the region of duplication, and position effect [8,20,21]. In addition, X chromosome inactivation could also play a significant role in the expression of this duplication [8,22]; in fact, both children of the present family had maternal inherited Xp22.31 duplication, but their mother was asymptomatic.

5. Conclusions

The family we studied provides a contribution to the literature and help define a common phenotype related with Xp22.31 duplication, with special attention to the epilepsy. Our result underlines the need for further studies on mechanisms that influence its expressivity.

Declarations of interest

None.

Consent

Informed consent was obtained for all members of the family described in this manuscript.

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Ethical statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained for all members of the family described in this manuscript.

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