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Spectrum of Epilepsy and Electroencephalogram Patterns in Idic (15) Syndrome

Agatino Battaglia,[1]* Laura Bernardini,[2] Isabella Torrente,[2,3] Antonio Novelli,[4] and Gloria Scarselli[1]

[1]Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Calambrone, Pisa, Italy

[2]Mendel Laboratory IRCCS "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Rome, Italy

[3]Department of Experimental Medicine, Sapienza University, Rome, Italy

[4]Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

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Previous reports summarized the seizure types occurring in patients with idic(15) syndrome. To better define this issue, we retrospectively analyzed the evolution of electroencephalogram findings and seizures in 35 patients with confirmed idic(15). Epilepsy occurred in 28 patients (80%), with a median age of onset of 3 years 3 months. The initial seizures were infantile spasms associated with a hypsarrhythmic electroencephalogram (nine patients), focal/generalized tonic (seven patients), or atypical absences (eight patients). High doses of oral steroids were given in all nine children with infantile spasms, with remission of seizures and resolution of electroencephalogram abnormalities. Among them, three were seizure free at the time of evaluation, but six later developed Lennox–Gastaut syndrome or Lennox–Gastaut-like syndrome. The eight patients with atypical absences developed Lennox–Gastaut syndrome or Lennox–Gastaut-like syndrome. Epilepsy was well controlled in 32% of the patients; satisfactorily controlled (seizures reduced >75%) in 21.4%; partially controlled (seizures reduced <50%) in 10.7%; and uncontrolled in 32%. One patient was not taking any anti-epileptic drugs by his parents' choice. Fourteen percent were on monotherapy; whereas the other 82% were on polytherapy. Seizures stopped at a median age of 5 years 5 months. The interictal electroencephalogram showed slow/sharp waves, and/or biphasic spikes-polyspikes, spike/wave complexes, and an excess of fast activity mainly over the fronto-temporal areas. Epilepsy is a major clinical challenge in patients with idic(15), associated with a poor prognosis in 55%. Frontal lobe seizures are a novel finding.

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INTRODUCTION

Epilepsy and intellectual disability are frequently found in chromosomal aberration syndromes. In these conditions epilepsy is usually challenging since it occurs in the context of a pre-existing handicap. In addition, whenever chromosomal rearrangements are associated with frequent and difficult-to-control seizures, long-term cognitive outcome can be seriously impaired [Battaglia and Guerrini, 2005; Parmeggiani et al., 2005]. For these reasons, clinicians should make efforts to characterize the seizures type and/or epilepsy syndrome in individuals with chromosomal anomalies. A thorough evaluation of epilepsy can improve management of patients and also aids in diagnosis. Among chromosomal disorders, distinct epileptic phenotypes have been extensively described in 1p36 deletion syndrome [Bahi-Buisson et al., 2008], Wolf–Hirschhorn (4p-) syndrome [Battaglia and Carey, 2005; Battaglia et al., 2009], Angelman syndrome [Boyd et al., 1988; Laan et al., 1997; Minassian et al., 1998], and ring chromosome 20 syndrome [Inoue et al., 1997; Biraben et al., 2001].

Idic(15) (isodicentric chromosome 15) syndrome is the most common genetic disorder caused by an extra-numerary, structurally abnormal chromosome (ESAC). The syndrome is characterized by an extra chromosome fragment formed by the inverted duplication of proximal chromosome 15, resulting in tetrasomy

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*Correspondence to:
Agatino Battaglia, Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, via dei Giacinti, 2—56128 Calambrone, Pisa, Italy.
E-mail: agatino.battaglia@fsm.unipi.it
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15p and partial tetrasomy 15q. Idic(15) chromosomes of maternal origin, containing the Prader–Willi/Angelman syndrome region (PWS/ASCR) are associated with a neuro-developmental disorder, characterized by early central hypotonia, developmental delay/ intellectual disability, altered behavior, and seizures/epilepsy [Battaglia et al., 1997; Battaglia, 2005, 2008]. Its frequency is estimated as one per 30,000 births, with an equal sex ratio [Schinzel and Niedrist, 2001]. Dysmorphic features are usually subtle and major malformations are rare. As a consequence, chromosome analysis may not be thought to be indicated, and a number of individuals most probably remains undiagnosed.

Epilepsy constitutes a major medical challenge in most patients with idic(15), often requiring multiple anti-epileptic drugs (AEDs), and occurs with a wide variety of seizures [Battaglia et al., 1997; Aguglia et al., 1999; Takeda et al., 2000; Chifari et al., 2002; Battaglia, 2005, 2008, 2011; Conant et al., 2014].

Although several reports concerning the phenotypic spectrum have been published, there are limited published data on the epileptic phenotype, on electroencephalogram (EEG) findings, and particularly, on the natural history of epilepsy, except for one retrospective electronic survey [Conant et al., 2014].

In the present paper, we describe the EEG and the clinical features (electro-clinical phenotype) of 35 patients with idic(15) syndrome, in order to obtain more accurate information on the characteristics of epilepsy, including seizures semiology and EEG features, and on its natural history.

PATIENTS AND METHODS

We retrospectively studied the electro-clinical pattern of 35 patients diagnosed with idic(15). There were 10 females and 25 males. The median age at diagnosis was 20.5 months (from 3 months to 31 years); the median age at first observation was 4 years 4 months (from 9 months to 31 years) and at the final visit was 4 years 6 months (from 11 months to 31 years). The average age at the most recent evaluation was 5 years and 3 months (from 11 months to 46 years).

All patients had supernumerary marker chromosomes formed by the inverted duplication of proximal chromosome 15, resulting in tetrasomy 15p and partial tetrasomy/trisomy 15q, of maternal origin, and containing the PWS/ASCR. The mother's median age at conception was 33 years (from 22 to 40 years). The ESAC(15) was identified on standard cytogenetics and subsequent FISH analyses in all patients. Array-comparative genomic hybridization (A-CGH) was performed in 20 of the 35 patients, in order to better define the size of the region involved.

All patients were personally observed by one of us (A.B.), and we gathered a prenatal/birth history and hereditary/familial history, together with a three-generation pedigree, and a physical, and neurological examination. Depending on the patient's cooperation, half of them also had a standardized cognitive evaluation. Families were also requested to forward copy of any previous hospital files. Those files were reviewed to determine the seizure history and classification, with specific attention to seizure incidence, types, and frequency, and response to treatment. Epilepsies were classified according to the report of the International League Against Epilepsy Commission on classification and terminology [Berg et al., 2010].

All patients were studied with at least one awake and sleep polygraphic-video-EEG recording. Polygraphic video-EEG recordings were carried out while the patients were awake and asleep at 15 or 30 mm/sec on paper, with a 10- or 20-channel EEG apparatus (international 10–20 system, and according to measurements from bony landmarks [Pampiglione, 1965]) with bipolar and referential montages using silver-silver chloride surface electrodes, at the onset of epilepsy and during its course. Activation procedures with intermittent photic stimulation and hyperventilation were performed routinely if patients could cooperate. The results of routine EEG studies performed in other institutions were obtained by chart review.

This study was approved by the Institutional Review Board of the Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Pisa, Italy.

RESULTS

Clinical Findings

All patients showed characteristic early central hypotonia, developmental delay/ apparent or objective intellectual disability, and altered behavior, with autistic-like features. Thirty-four of the 35 patients showed only subtle dysmorphic features, characterized by mildly broad forehead, epicanthal folds, deep-set eyes, downslanting of the palpebral fissures, squint of variable degree, broad and flat nasal bridge, pointed chin, and midface retrusion. These features were more marked and associated with large, malformed, anteverted ears in the remaining patient. All patients presented developmental delay, and different degrees of cognitive/adaptive functioning impairment, varying from profound-severe (87%) to moderate-mild (13%). No significant variation in cognitive ability over time was observed. A distinct "autistic-like" behavior was present in all, as described elsewhere [Battaglia et al., 2010].

None of the 35 patients had a familial history of epileptic seizures. Thirteen percent had transient perinatal distress. Twenty patients have been followed up by us from 4 to 20 years.

Electro-Clinical Pattern

Seizures or epilepsy affected 28 of the 35 patients (80%). The age of the seven patients without seizures ranged between 4 years and 9 years 3 months. The age at seizure onset varied between 2 months and 9 years 9 months (median age of 3 years 3 months). Ten of the 35 patients (28.5%) had the first seizure within the 1st year of life, at the median age of 6 months (from 2 to 10 months). One of ten had tonic seizures, and nine of ten had infantile spasms (ISS) associated with an hypsarrhythmic EEG. High doses of oral steroids were given in eight of the nine patients, with a prompt remission of seizures and resolution of EEG abnormalities. Among them, four were seizure free at the time of evaluation, and the other four developed a Lennox–Gastaut or a Lennox–Gastaut-like syndrome (Table I).

In the other 18 patients, the onset of seizures was varied between 1 year 1 month and 9 years 9 months, with 11 (39.2%) having their first seizure between 4 and 9 years of age. The first seizures were tonic in seven patients, with onset between 6 months and 9 years 9 months. They were either focal or generalized. In all seven patients,

TABLE I. Clinical Features

Pt. No., sex	Age at epilepsy onset	Seizure type	Epilepsy type	AEDs	EEG features	Current status
1, M	6 yr	Atypical absences, tonic, atonic	SGE, LGS	VPA, CBZ, CLB	Awake: multifocal spikes, slow background activity. Slow sleep: diffuse fast recruiting rhythms.	Daily
2, M	7 yr	Atypical absences tonic, atonic, tonic-clonic	SGE, LG-like	VPA, CBZ, PB, CZP, PHT	Frequent bilateral multifocal spikes and diffuse slow spike/polyspike-wave complexes enhanced by slow-wave sleep.	Seizure free from age 16 yr
3, F	7 yr	Atypical absences, tonic, atonic	SGE, LGS	PHT, PB, CZP	Awake: bilateral high amplitude 1.5–2 Hz spike/waves complexes. Slow sleep: diffuse fast recruiting rhythms.	Daily
4, M	4 yr	Atypical absences, tonic, atonic	SGE, LG-like	CBZ, CLB	Low amplitude monomorphic theta activity mixed with diffuse spike/wave. Sleep phases difficult to recognize.	Daily
5, M	5 m	Infantile spasms, tonic	WS, LG-like	GVG, ACTH, NZP, LTG, VPA	Hypsarrhythmia. Fast activity anteriorly, no rythmic activities on eye closure.	Seizure free from age 4 yr 6 m
6, M	10 m	Tonic spasms, tonic	LG-like	VPA, CLB, GVG, ACTH, PB, TPM, LVT, LTG	Frequent bilateral multifocal spikes and diffuse slow spike/polyspike-wave complexes enhanced by slow-wave sleep.	Weekly
7, F	18 m	Tonic	LGS	CBZ, LTG	Multifocal discharges and diffuse large amplitude slow waves enhanced by sleep; no rythmic activities.	Seizure free from age 2 yr 9 m
8, M	4 yr	Atypical absences, tonic	LG-like	VPA, CBZ, LTG	Multifocal discharges and diffuse large amplitude slow waves enhanced by sleep; no rythmic activities.	Monthly
9, F	6 m	Tonic	SGE	VPA	Fast activity anteriorly, multifocal discharges. Diffuse slow spike/ polyspike-wave complexes.	Seizure free from age 3 yr 2 m
10, F	2 yr 4 m	Tonic	SGE	VPA	Fast activity anteriorly, multifocal discharges. Diffuse slow spike/ polyspike-wave complexes.	Seizure free from age 5 yr
11, M	6 yr	Atypical absences, atonic, tonic-clonic	LGS	VPA, CBZ, LTG, RFN	Multifocal discharges and diffuse large amplitude slow waves enhanced by sleep; no rythmic activities.	Monthly
12, M	9 yr 9 m	Tonic-clonic	LG-like	VPA, RFN, CLB	Spike/wave complexes 2–2,5 Hz, over both fronto-temporal areas.	Seizure free from 13 yr
13, M	7 m	Infantile spasms, tonic spasms	WS, LG-like	GVG, ACTH, VPA, CZP, CBZ	Hypsarrhythmia. Slow background activity, slow sharp waves right occipital.	Seizure free from age 10 yr
14, M	6 m	Infantile spasms, focal	WS, LG-like	PB, LTG, CBZ, PHT	Hypsarrhythmia. Multifocal spikes, polyspikes, spike-waves; enhanced and generalized during sleep. Fronto-temporal spikes, spike-waves with secondary generalization.	Yearly
15, F	6 m	Infantile spasms	WS	ACTH, VPA	Hypsarrhythmia. Multifocal sharp waves-spikes.	Seizure free from age 7 yr
16, M	6 m	Infantile spasms, tonic	WS, LG-like	GVG, ACTH, CBZ, VPA	Hypsarrhythmia. Fast activity over both frontal areas. Slow sleep: diffuse fast recruiting rhythms.	Weekly
17, M	3 yr 6 m	Focal with secondary generalization	SGE	CBZ	Fast activity mixed with sharp waves over both frontal areas. Sleep: slow sharp waves/ spikes up to 200 uV over frontal areas.	Daily

(*Continued*)

TABLE I. (*Continued*)

Pt. No., sex	Age at epilepsy onset	Seizure type	Epilepsy type	AEDs	EEG features	Current status
18, M	3 yr 7 m	Atypical absences, tonic, atonic	LGS	VPA, LVT, ESM, RFN, LTG	Multifocal discharges and diffuse large amplitude slow waves enhanced by sleep.	Weekly
19, F	9 yr 9 m	Tonic	FSE	VPA, LTG, RFN	Fast activity over the fronto anterior-temporal regions, spreading to the entire brain.	Yearly
20, M	7 yr 9 m	Tonic, complex focal seizure	SGE	VPA, CZP, LTG	Slowing over the left temporal regions	Monthly
21, F	13 m	Atypical absences, atonic, tonic	LG-like	VPA, CLB	Multifocal spikes, polyspikes, spike-waves; enhanced and generalized during sleep.	Daily
22, M	4 yr	Focal with secondary generalization	SGE	–	Runs of sharp waves/sharp elements at 6–6.5 Hz over both frontal regions.	Monthly
23, M	–	–	–	–	Fast activity prominent over both fronto-temporal regions.	Seizure free at age 8 yr
24, M	–	–	–	–	Fast activity over both fronto-temporal regions. On awakening runs of fast spikes over both fronto-temporal regions.	Seizure free at age 9 yr
25, F	6 yr	Complex focal seizures	FSE	VPA	Focal and generalized spike and wave complex. Poverty of rythmic activities. Fast activity at 14–22 Hz over both fronto temporal regions	Seizure free from age 6 yr 5 m
26, F	6 m	Infantile spasms, tonic	WS, SGE	ACTH, VPA, CBZ	Hypsarrhythmia. Fast activity over frontal regions. Sleep: Brief runs of rhythmic activity over both fronto-central regions	Monthly
27, M	2 m	Tonic spasms, tonic with secondary generalization	FSE	PB, LVT	Spikes-sharp-waves over left fronto-temporal regions.	Daily
28, M	–	–	–	–	Normal	Seizure free at age 5 yr 4 m
29, M	–	–	–	–	Fast activity anteriorly.	Seizure free at age 8 yr
30, M	–	–	–	–	Fast activity over both fronto-temporal regions.	Seizure free at age 9 yr 3 m
31, M	–	–	–	–	Fast activity over both fronto-temporal regions.	Seizure free at age 4 yr 9 m
32, M	–	–	–	–	Fast activity over fronto-temporal regions.	Seizure free at age 4 yr
33, M	7 m	Infantile spasms	WS, LG-like	ACTH, LVT, DZP, VPA	Hypsarrhythmia. Multifocal ill-defined spike-wave complexes and/or spikes.	Weekly
34, M	5 m	Infantile spasms, tonic	WS, LG-like	GVG, ACTH, NZP, VPA, LTG	Hypsarrhythmia. Fast activity over both fronto-anterior temporal areas; Multifocal spikes-polyspikes-spike/waves enhanced by sleep.	Monthly/yearly
35, F	13 m	Infantile spasms, tonic	WS, SGE	ACTH, VPA, LTG	Hypsarrhythmia. Fast activity over both fronto-anterior temporal areas	Seizure free from age 3 yr

SGE, symptomatic generalized epilepsy; LGS, Lennox-Gastaut syndrome; LG-like, Lennox-Gastaut-like; WS, West syndrome; FSE, focal symptomatic epilepsy; VPA, valproic acid; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; CLB, clobazam; LVT, levetiracetam; ESM, ethosuximide; RFN, rufinamide; LTG, lamotrigine; ACTH, adrenocorticotrophic hormone; GVG, vigabatrin; NZP, nitrazepam; TPM, topiramate; DZP, diazepam; CZP, clonazepam.

such seizures were triggered by drowsiness and slow wave sleep, and in one of these seven also by a sonorous stimulus; and initially occurred several times per day. In one patient, the initial focal tonic seizure (at age 9 9/12) was soon followed by several daily episodes of rather bizarre paroxysmal phenomena, with a probable frontal origin. Such episodes could last from a few seconds to 7 minutes; could occur in clusters; were mostly triggered by drowsiness and slow wave sleep, and were characterized by a sudden awakening with the patient raising her head from the bed, screaming, with both arms extended outward, non-responding to the menace, followed by sitting up on the bed with a frightened expression, and abrupt complex body movements in all four limbs and trunk, leading to a bizarre sequence of various brief dystonic postures, and hyperkinetic activity (frantic movements with bipedal activity and pelvic thrushing), in an attempt at fleeing the bed. Clonic jerks involving all four limbs followed (supplementary Fig. S1a and b). These seizures were satisfactorily controlled on valproate and rufinamide.

First seizures were atypical absences in eight patients, with onset between 1 year 1 month and 7 years of age. The atypical absences occurred several times per day and were followed, a few months later, by daily tonic/atonic seizures in all eight patients, showing the electro-clinical picture of the Lennox–Gastaut or Lennox–Gastaut-like syndrome.

The interictal EEG was characterized by: (i) an excess of slow/sharp waves, and/or biphasic spikes-polispikes reaching up to 300 uV over both frontal regions, often in a sub-continuous fashion, on occasions spreading to the entire brain, although prominent over both fronto-temporal areas (Fig. 1A and B); (ii) fast ill-defined spike/wave complexes, reaching up to 250 uV, usually occurring in runs of variable duration, over both fronto-centro-temporal regions (Fig. 2); (iii) a considerable excess of fast activity at 12–20 Hz, reaching up to 200 uV, over both fronto-centro-temporal areas; particularly observed during childhood (Fig. 3); (iv) slow background activity; (v) poverty of the usual rhythmic activities over the rolandic regions; whereas the rhythmic activities evoked on eye closure, over the posterior third of the head, were mostly in keeping with the patients' chronological age (supplementary Fig. S2); (vi) the sleep spindles, well recognizable in most patients, were hardly so in a minority (supplementary Fig. S3).

Long-Term Outcome

Epilepsy was well controlled in 10 of the 28 (35.7%) patients; satisfactorily controlled [seizures reduced >75%] in two of the 28 (7.1%); partially controlled [seizures reduced <50%] in six of the 28 (21.4%); and difficult to control in 10 (35.7%). One patient was not taking any AEDs by his parents' choice. Control was achieved by monotherapy in three of the 28 (10.7%) and polytherapy (two or three antiepileptic drugs-AEDs) in seven of the 28 (25%). All other patients were taking between one and three AEDs. Four out of the 28 (14.2%) patients with epilepsy were on monotherapy; whereas the other 23/28 (82%) were on polytherapy. Valproate, lamotrigine, and rufinamide proved to be the most effective AEDs. Seizures stopped at a median age of 5 years 5 months (between 2 years 9 months and 16 years) (Table I).

Molecular Cytogenetics and Methylation Studies

Detailed characterization and the effective copy number of regions constituting the idic(15) was achieved, in 20 patients, by performing genome wide A-CGH with an average 75 Kb probe spacing (44 K Chip; Agilent Technologies, Walldbronn, Germany) on circulating lymphocytes according to manufacturer's instructions. Six patients had an idic(15)(q13.1q13.1), eight had an idic(15)(q13.3q13.3), and six had an asymmetric idic(15)(q13.2q13.3).

An asymmetric idic(15) copy number was confirmed by quantitative-PCR (qPCR) on the CHRNA7 gene (mapping into the duplicated segment) using an ABI 7000 Sequence Detection System (Applied Biosystem, Foster City, CA), and DNA-binding dye SYBR Green (Invitrogen Corporation, Carlsbad, CA), as described by Carbone et al. [2008]. The maternal origin of idic(15) was assessed by the analysis of the methylation status of the Prader Willi imprinting center (PWS-IC), located around exon 1 of SNRPN gene, using Methylation-Specific-Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) according to the manufacturer's protocol (SALSA MS-MLPA kit ME028-B1 PRADER WILLI/ANGELMAN, MRC-Holland, Amsterdam, The Netherlands).

DISCUSSION

The present series is, to our knowledge, the largest sample of patients with idic(15) syndrome, personally observed, with the best characterized electro-clinical pattern and longest follow-up (up to 20 years), allowing a better delineation of epilepsy phenotype and its evolution in this rare disease. Our results demonstrate that epilepsy is a significant medical challenge in patients with idic(15) syndrome, occurring in 80% of them, with a poor prognosis in about 55% (Table I).

In just over a fourth of patients (28.5%), epilepsy started in infancy, but never in the neonatal period. In all but one of these (32.1%), the first seizures were ISS associated with an hypsarrhythmic EEG. Fifty percent of them had a good response to oral steroids, whereas the others later developed a Lennox–Gastaut or Lennox–Gastaut-like syndrome. Such electro-clinical evolution confirms previous published findings [Conant et al., 2014].

In a further seven patients, their first seizures were tonic, either focal or generalized; triggered by drowsiness and slow wave sleep; with onset up to age 9 years 9 months. About 30% of the patients with epilepsy developed atypical absences, as first seizures, by age 1–7 years. All such patients later developed a Lennox–Gastaut or Lennox–Gastaut-like syndrome. Although generalized seizures have been previously reported for idic (15) syndrome, focal symptomatic epilepsy has only been reported in one individual [Borgatti et al., 2001]. Based on the experience with the patients described here, we believe that focal symptomatic epilepsy is more frequent, and, on occasion, evolving into severe epilepsy of the Lennox–Gastaut type. The frontal regions seem to be particularly involved in most patients with idic(15), with an electro-clinical pattern reminiscent of that seen in familial frontal lobe epilepsies [Picard and Brodtkorb, 2008].

It is intriguing to note that mutations in genes coding for subunits of nicotinic acethylcoline receptors (CHRNA4, CHRNB2) have been identified in Autosomal Dominant Nocturnal Frontal Lobe

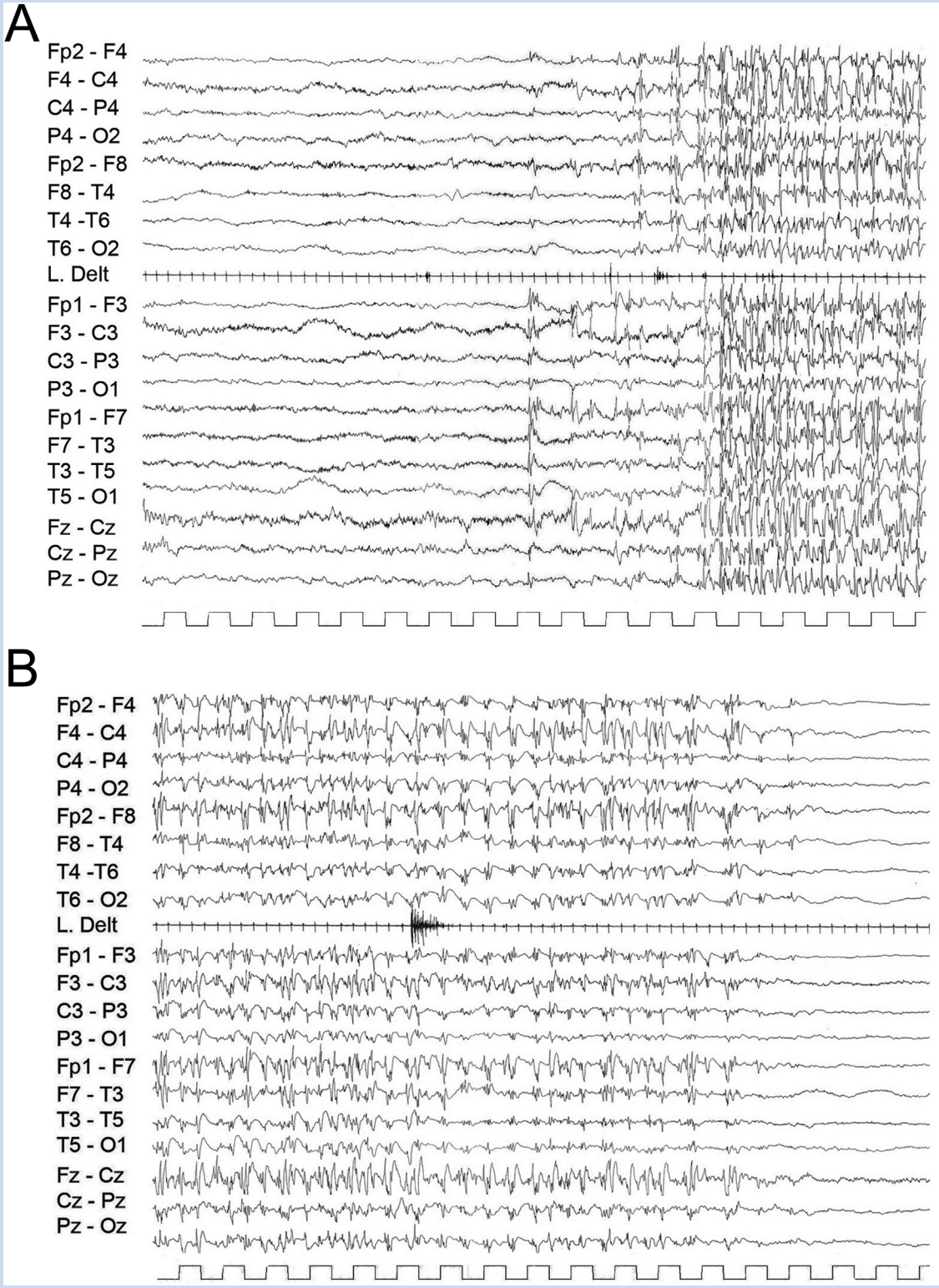

FIG. 1. (A and B) Interictal awake electroencephalogram of a 3-year-old patient. Excess of slow/sharp waves, and/or biphasic spikes-polispikes reaching up to 300 uV over both frontal regions, often in a sub-continuous fashion, on occasions spreading to the entire brain, although prominent over both fronto-temporal areas.

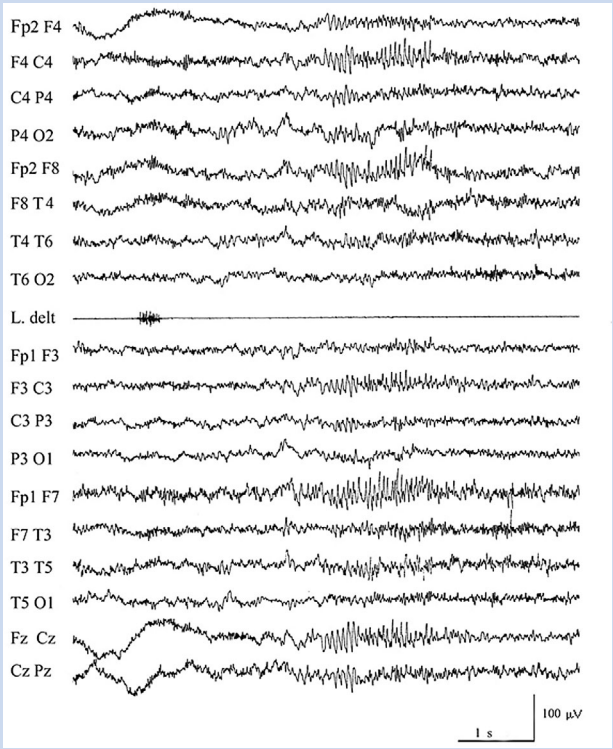

FIG. 2. Interictal awake electroencephalogram of a 2-year-8-month-old patient. Fast ill-defined spike/wave complexes, reaching up to 250 uV, usually occurring in runs of variable duration (1–5 sec), over both fronto-centro-temporal regions.

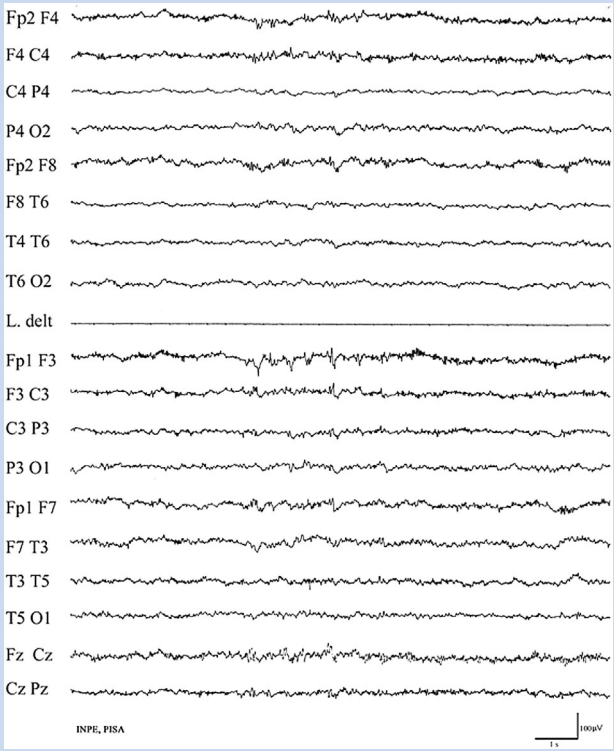

FIG. 3. Interictal awake electroencephalogram of a 6-year-8-month-old patient. Considerable excess of fast activity at 12–20 Hz, reaching up to 200 uV, over both fronto-centro-temporal areas; particularly observed during childhood.

Epilepsy, and that a gene of the same family (CHRNA7) is located on 15q11.2-q13.3, between BP4 and BP5. Linkage studies have suggested mutations in CHRNA7 as a susceptibility factor for both benign focal epilepsy of childhood [Neubauer et al., 1998] and juvenile myoclonic epilepsy [Elmslie et al., 1997]. In addition, mice with a knockout of Chrna7 show a hypersynchronous neocortical EEG phenotype [Orr-Urtreger et al., 1997]. It follows that CHRNA7 represents an excellent candidate gene, dysregulation of which may underlie or contribute to the epilepsy and seizure phenotype observed in patients with idic(15). Furthermore, Szafranski et al. [2010] observed that small microduplications involving only CHRNA7 were associated with developmental delay/intellectual disability, autism spectrum disorder, ADHD, disruptive behavior, bipolar disorder, and, occasionally epilepsy.

We did not find any correlation between type, severity, age at onset, or evolution of epilepsy and the molecular cytogenetic abnormality.

For each patient, we studied several polygraphic-video-EEG recordings during a follow-up lasting up to 20 years. The EEG recordings were abnormal from early on, even in the majority of patients who had not had seizures. Over time, the EEGs showed some similar and rather stereotyped evolutional changes of the brain electrical activity, particularly over the frontal areas. In the medical literature, little is known about the EEG findings in large idic(15) series, nor about their evolution, mainly due to the poor description of these findings, and total lack of serial EEG studies [Gillberg et al., 1991; Crolla et al., 1995; Bingham et al., 1996; Webb et al., 1998; Battaglia, 2005; Kleefstra et al., 2010; Al Ageeli et al., 2014]. Our data show that patients with idic(15) have rather distinctive interictal EEG features, mainly involving the frontal areas. These are characterized by high amplitude slow/sharp waves and/or biphasic spikes-polyspikes; fast ill-defined spike/wave complexes; and, particularly, a considerable excess of fast activity. The latter seems to be an EEG hallmark of idic(15).

The pathophysiological mechanisms of epilepsy and EEG abnormalities in patients with idic(15) remain unknown. Various genetic mechanisms have been hypothesized to explain clinical heterogeneity, such as the size of chromosomal duplication, dosage effect of genes in the region, and the imprinting mechanism regulating gene expression in this critical region. Increased dosage of the PWS/ASC gene region between BP2 and BP3 positively correlates with phenotypic severity [Mann et al., 2004]; however, the clinical heterogeneity among patients cannot be explained by variations in breakpoints, as shown by the patients reported here, suggesting that additional factors contribute to clinical complexity. Gene expression can be altered in unexpected ways through epigenetic changes [Hogart et al., 2007]. Epigenetic differences between individuals with the same genetic copy number variant could be stochastic, environmentally determined, or influenced by genetic background. The study by Hogart et al. [2009] suggested

that the imbalance of 15q11-q13 dosage can disrupt normal parental homolog pairing, DNA methylation, and gene expression patterns within the region. Amongst the genes in the PWS/ASCR, there is an interesting relationship between the α5 and β3 GABA receptor subunit genes and the P gene of the oculocutaneous albinism. A deletion in the p^{cp} mutant mice causes rearrangements of Gaba α5 and Gaba β3 receptors, leading to a phenotype characterized by seizures, jerky gait, and ataxia [Nakatsu et al., 1993]. Similarly, a tetrasomy of these genes, as seen in idic(15), may alter the GABA receptor activity upon which the major central nervous system inhibitory mechanisms rely. The identification of synapse function pathways associated with ISS [Paciorkowski et al., 2011], and the presence of the three non-imprinted biallelically expressed 15q11-13 GABA receptor subunit genes, GABRB3, GABRA5, and GABRG3, could support the hypothesis that abnormalities in GABAergic synapses may play a role in ISS pathogenesis in idic(15). The above-noted GABAa receptor subunit genes are also candidates for the other neurodevelopmental features of this disorder, as Gabrb3 null mice exibit a severe neurological phenotype characterized by seizures, hyperactivity, sleep abnormalities, hypersensitivity to touch stimuli, learning and memory deficits, and behaviors consistent with autism [Homanics et al., 1997; DeLorey et al., 1998, 2008; Hashemi et al., 2007]. Studies of brain samples suggest that additional 15q11.2-q13 copies can disrupt the normal balance of homologous pairing of 15q11.2-q13 alleles in the brain and potentially impact GABRB3 expression in a manner not predicted by gene dosage [Wang et al., 2008; Hogart et al., 2009].

In conclusion, our observations suggest that frontal lobe seizures are a novel finding in idic(15) syndrome, and show once more that epilepsy is a significant medical challenge in patients with this syndrome [Battaglia et al., 1997; Conant et al., 2014], occurring in 80% of them, with a poor prognosis in about 55%. Dysmorphic features are usually subtle or absent, and major malformations are rare. Idic(15) should be searched for in patients presenting with difficult to control seizures/epilepsy, such as Lennox–Gastaut or Lennox–Gastaut-like syndrome without a structural lesion; and, in those with infantile spasms associated with hypsarrhythmic EEG; and in those with frontal lobe seizures, even in the absence of dysmorphic features.

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REFERENCES

Aguglia U, Le Piane E, Gambardella A, Messina D, Russo C, Sirchia SM, Porta G, Quattrone A. 1999. Emotion-induced myoclonic absence-like seizures in a patient with inv-dup(15) syndrome: A clinical, EEG, and molecular genetic study. Epilepsia 40:1316–1319.

Al Ageeli E, Drunat S, Delanoë C, Perrin L, Baumann C, Capri Y, Fabre-Teste J, Aboura A, Dupont C, Auvin S, El Khattabi L, Chantereau D, Moncla A, Tabet AC, Verloes A. 2014. Duplication of the 15q11-q13 region: Clinical and genetic study of 30 new cases. Eur J Med Genet 57:5–14.

Battaglia A, Gurrieri F, Bertini E, Bellacosa A, Pomponi MG, Paravatou-Petsotas M, Mazza S, Neri G. 1997. The inv dup(15) syndrome: A clinically recognizable syndrome with altered behaviour, mental retardation, and epilepsy. Neurology 48:1081–1086.

Battaglia A. 2005. The inv dup(15) or idic(15) syndrome: A clinically recognisable neurogenetic disorder. Brain Devel 27:365–369.

Battaglia A, Carey JC. 2005. Seizure and EEG patterns in Wolf–Hirschhorn (4p-) syndrome. Brain Dev 27:362–364.

Battaglia A, Guerrini R. 2005. Chromosomal disorders associated with epilepsy. Epileptic Disord 7:181–192.

Battaglia A. 2008. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). Orphanet J Rare Dis 3:30. http://www.ojrd.com.

Battaglia A, Filippi T, South ST, Carey JC. 2009. Spectrum of epilepsy and EEG patterns in Wolf–Hirschhorn syndrome: Experience with 87 patients. Dev Med Child Neurol 51:373–380.

Battaglia A, Parrini B, Tancredi R. 2010. The behavioral phenotype of the idic(15) syndrome. Am J Med Genet Part C Semin Med Genet 154C:448–455.

Battaglia A. 2011. Idic(15) syndrome. In: Shorvon S, Andermann F, Guerrini R, editors. "The Causes of Epilepsy". Cambridge, UK: Cambridge University Press, ch. 42:281–284.

Bahi-Buisson N, Gutierrez-Delicado E, Soufflet C, Rio M, Cormier Daire V, Lacombe D, Héron D, Verloes A, Zuberi SM, Burglen L, Afenjar A, Moutard LM, Edery P, Dulac O, Nabbout R, Plouin P, Battaglia A. 2008. Spectrum of epilepsy in terminal 1p36 deletion syndrome. Epilepsia 49:509–515.

Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. 2010. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE commission on classification and terminology, 2005–2009. Epilepsia 51:676–685.

Bingham PM, Spinner NB, Sovinsky L, Zackai EH, Chance PF. 1996. Infantile spasms associated with proximal duplication of chromosome 15q. Pediatr Neurol 15:163–165.

Biraben A, Odent S, Lucas J, Michez F, Lemée, Henry C, Le Berre C, de Grissac N, Bernard AM, Scarabin JM. 2001. Chromosome 20 en anneau et épilepsie: Diversité des crises étudiées en vidéo-EEG. Un mécanisme sous-corticale d'épileptogénèse est-il au premier plan? Epilepsies 13:9–15.

Borgatti R, Piccinelli P, Passoni D, Dalprà L, Miozzo M, Micheli R, Gagliardi C, Balottin U. 2001. Relationship between clinical and genetic features in "inverted duplicated chromosome 15" patients. Pediatr Neurol 24:111–116.

Boyd SG, Harden A, Patton MA. 1988. The EEG in early diagnosis of the Angelman (happy puppet) syndrome. Eur J Pediatr 147:508–513.

Carbone A, Bernardini L, Valenzano F, Bottillo I, De Simone C, Capizzi R, Capalbo A, Romano F, Novelli A, Dallapiccola B, Amerio P. 2008. Array-based comparative genomic hybridization in early-stage mycosis fungoides: Recurrent deletion of tumor suppressor genes BCL7A, SMAC/DIABLO, and RHOF. Genes Chromosomes Cancer 47:1067–1075.

Chifari R, Guerrini R, Pierluigi M, Cavani S, Sgrò V, Elia M, Canger R, Canevini MP. 2002. Mild generalized epilepsy and developmental disorder associated with large inv dup(15). Epilepsia 43:1096–1100.

Conant KD, Finucane B, Cleary N, Martin A, Muss C, Delany M, Murphy EK, Rabe O, Luchsinger K, Spence SJ, Schanen C, Devinsky O, Cook EH, LaSalle J, Reiter LT, Thibert RL. 2014. A survey of seizures and current treatments in 15q duplication syndrome. Epilepsia 55:396–402.

Crolla JA, Harvey JF, Sitch FL, Dennis NR. 1995. Supernumerary marker 15 chromosomes: A clinical, molecular and FISH approach to diagnosis and prognosis. Hum Genet 95:161–170.

DeLorey TM, Handforth A, Anagnostaras SG, Homanics GE, Minassian BA, Asatourian A, Fanselow MS, Delgado-Escueta A, Ellison GD, Olsen

RW. 1998. Mice laking the beta3 subunit of the GABAA receptor have the epilepsy phenotype and many of the behavioural characteristics of Angelman syndrome. J Neurosci 18:8505–8514.

DeLorey TM, Sabhaie P, Hashemi E, Homanics GE, Clark JD. 2008. Gabrb3 gene deficient mice exibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: A potential model of autism spectrum disorder. Behav Brain Res 187:207–220.

Elmslie FV, Rees M, Williamson MP, Kerr M, Kjeldsen MJ, Pang KA, Sundqvist A, Friis ML, Chadwick D, Richens A, Covanis A, Santos M, Arzimanoglou A, Panayiotopoulos CP, Curtis D, Whitehouse WP, Gardiner M. 1997. Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. Hum Mol Genet 6:1329–1334.

Gillberg C, Steffenburg S, Wahlstrom J, Gillberg IC, Sjostedt A, Martinsson T, Liedgren S, Eeg-Olofsson O. 1991. Autism associated with marker chromosome. J Am Acad Child Adolesc Psychiat 30:489–494.

Hashemi E, Sabhaie P, Davies MF, Clark JD, DeLorey TM. 2007. Gabrb3 gene deficient mice exibit increased risk assessment behavior, hypotonia andexpansion of the plexus of locus coeruleus dendrites. Brain Res 1129:191–199.

Hogart A, Nagarajan RP, Patzel KA, Yasui DH, LaSalle JM. 2007. 15q11-13 GABAa receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. Hum Mol Genet 16:691–703.

Hogart A, Leung KN, Wang NJ, Wu DJ, Driscoll J, Vallero RO, Schanen NC, LaSalle JM. 2009. Chromosome 15q11-13 duplication syndrome brain reveals epigenetic alterations in gene expression not predicted from copy number. J Med Genet 46:86–93.

Homanics GE, DeLorey TM, Firestone LL, Quinlan JJ, Handforth A, Harrison NL, Krasowski MD, Rick CE, Korpi ER, Makela R. 1997. Mice devoid of gamma-aminobutyrate type A receptor beta3 subunit have epilepsy, cleft palate, and hypersensitive behavior. Proc Natl Acad Sci USA 94:4143–4148.

Inoue Y, Fujiwara T, Matsuda KS, Kubota H, Tanaka M, Yagi K. 1997. Ring chromosome 20 and nonconvulsive status epilepticus. A new epileptic syndrome. Brain 120:939–953.

Kleefstra T, de Leeuw N, Wolf R, Nillesen WM, Schobers G, Mieloo H, Willemsen M, Perrotta CS, Poddighe PJ, Feenstra I, Draaisma J, van Ravenswaaij-Arts CM. 2010. Phenotypic spectrum of 20 novel patients with molecularly defined supernumerary marker chromosomes 15 and a review of the literature. Am J Med Genet Part A 152A:2221–2229.

Laan LAEM, Renier WO, Arts WFM, Buntinx IM, vd Burgt IJ, Stroink H, Beuten J, Zwinderman KH, van Dijk JG, Brouwer OF. 1997. Evolution of epilepsy and EEG findings in Angelman syndrome. Epilpsia 38:195–199.

Mann SM, Wang NJ, Liu DH, Wang L, Schultz RA, Dorrani N, Sigman M, Schanen NC. 2004. Supernumerary tricentric derivative chromosome 15 in two boys with intractable epilepsy: Another mechanism for partial hexasomy. Hum Genet 115:104–111.

Minassian BA, DeLorey T, Olsen RW, Philippart M, Zhang Q, Bronstein Y, Zhang Q, Guerrini R, van Ness P, Livet MO, Delgado-Escueta AV. 1998. Angelman syndrome: Correlations between epilepsy phenotypes and genotypes. Ann Neurol 43:485–493.

Nakatsu Y, Tyndale RF, De Lorey TM, Durham-Pierre D, Gardner JM, McDanel HJ, Nguyen Q, Wagstaff J, Lalande M, Sikela JM, Olsen RW, Tobin AJ, Brilliant MH. 1993. A cluster of three GABA receptor subunit genes is deleted in a neurological mutant of the mouse p locus. Nature 364:448–450.

Neubauer BA, Fiedler B, Himmelein B, Kämpfer F, Läßker U, Schwabe G, Spanier I, Tams D, Bretscher C, Moldenhauer K, Kurlemann G, Weise S, Tedroff K, Eeg-Olofsson O, Wadelius C, Stephani U. 1998. Centrotemporal spikes in families with rolandic epilepsy: Linkage to chromosome 15q14. Neurology 51:1608–1612.

Orr-Urtreger A, Göldner FM, Saeki M, Lorenzo I, Goldberg L, De Biasi M, Dani JA, Patrick JW, Beaudet AL. 1997. Mice deficient in the α7 neuronal nicotinic acetylcholine receptor lack α-bungarotoxin binding sites and hippocampal fast nicotinic currents. J Neurosci 17: 9165–9171.

Paciorkowski AR, Thio LL, Rosenfeld JA, GajeckaM, Gurnett C, kulkarni S, Chung W, Marsh E, Gentile M, Reggin J, Wheless J, Balasubramanian S, Kumar R, Christian S, Marini C, Guerrini R, Maltsev N, Shaffer L, Dobyns W. 2011. Copy number variants and infantile spasms: Evidence for abnormalities in ventral forebrain development and pathways of synaptic function. Eur J Hum Genet 19:1238–1245.

Pampiglione G. 1965. Brain development and the E.E.G. of normal children of various ethnical groups. Br Med J 2:573–575.

Parmeggiani A, Posar A, Giovannini S, Giovanardi-Rossi P. 2005. Epilepsy in chromosomal abnormalities: An Italian sample. J Child Neurol 20:419–423.

Picard F, Brodtkorb E. 2008. Familial frontal lobe epilepsies. In: Engel J, Pedley TA, editors. Epilepsy. a comprehensive textbook, 2nd edition. Philadelphia, PA: Lippincot Williams & Wilkins vol. III, ch 249 pp:2495–2502.

Schinzel A, Niedrist D. 2001. Chromosome imbalances associated with epilepsy. Am J Med Genet Part C Semin Med Genet 106C:119–124.

Szafranski P, Schaaf C, Person RE, Gibson IB, Xia Z, Mahadevan S, Wiszniewska J, Bacino CA, Lalani S, Potocki L, Kang SH, Patel A, Cheung SW, Probst FJ, Graham BH, Shinawi M, Beaudet AL, Stankiewicz P. 2010. Structures and molecular mechanisms for common 15q13.3 microduplications involving CHRNA7: Benign or pathological? Hum Mutat 31:840–850.

Takeda Y, Baba A, Nakamura F, Ito M, Honma H, Koyama T. 2000. Symptomatic generalized epilepsy associated with an inverted duplication of chromosome 15. Seizure 9:145–150.

Wang NJ, Parokonny AS, Thatcher KN, Driscoll J, Malone BM, Dorrani N, Sigman M, LaSalle JM, Schanen NC. 2008. Multiple forms of atypical rearrangements generating supernumerary derivative chromosome 15. BMC Genet 9:2.

Webb T, Hardy A, King M, Watkiss E, Mitchell C, Cole T. 1998. A clinical, cytogenetic and molecular study of ten probands with inv dup (15) marker chromosomes. Clin Genet 53:34–43.

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