Brain & Development 37 (2015) 874–879

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

# Three patients manifesting early infantile epileptic spasms associated with 2q24.3 microduplications

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Received 15 August 2014; received in revised form 7 March 2015; accepted 12 March 2015

**Abstract**

*Background:* Recent development of genetic analyses enabled us to reveal underlying genetic causes of the patients with epileptic encephalopathy in infancy. Mutations of voltage-gated sodium channel type I alpha subunit gene (*SCN1A*) are to be causally related with several phenotypes of epilepsy, generalized epilepsy with febrile seizure plus (GEFS+), Dravet syndrome, and other infantile epileptic encephalopathies. In addition to *SCN1A*, contiguous genes such as *SCN2A* and *SCN3A* in 2q24.3 are also reported to have contribution to epileptic seizures. Therefore, gene abnormality involving this region is reasonable to contribute to epilepsy manifestation.

*Results:* We encountered three patients with 2q24.3 microduplication diagnosed by Array comparative genomic hybridization array (aCGH). They developed partial seizures and epileptic spasms in their early infantile periods and showed remarkable developmental delay, although their seizures disappeared from 11 to 14 months of age. One of three patients had 2q24.3 microduplication which excludes *SCN1A*. Therefore, characteristics of epilepsy with 2q24.3 microduplication do not necessarily need duplication of *SCN1A*. This study suggested that 2q24.3 microduplication is one of the causes for early infantile epileptic spasms. Epileptic spasms associated with 2q24.3 microduplications may have better seizure outcome comparing with other etiologies.


*Keywords:* 2q24.3 microduplication; Epileptic spasms; Array comparative genomic hybridization array (aCGH); *SCN1A*; *SCN2A*; *SCN3A*

## 1. Introduction

Recent development of genetic analyses enabled us to reveal underlying genetic causes of the patients with epileptic encephalopathy in infancy effectively. Several genes including the syntaxin binding protein 1 gene (*STXBP1*) [1,2], the cyclin-dependent kinase-like 5 gene (*CDKL5*) [3], the potassium channel subfamily T member 1 gene (*KCNT1*) [4], the protocadherin 19 gene (*PCDH19*) [5], the aristaless related homeobox gene

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http://dx.doi.org/10.1016/j.braindev.2015.03.001

(*ARX*) [6], the potassium voltage-gated channel, KQT-like subfamily, member 2 gene (*KCNQ2*) [7], the Cdc42 guanine nucleotide exchange factor 9 gene (*ARHGEF9*) [8], the gamma-aminobutyric acid A receptor, alpha 1 gene (*GABRA1*) [9] and the spectrin, alpha, non-erythrocytic 1 gene (*SPTAN1*) [10] have been identified as the major genes responsible for epileptic encephalopathy in infancy. Although the voltage-gated sodium channel type I alpha subunit gene (*SCN1A*) is not only related to epileptic encephalopathy in infancy, i.e., Dravet syndrome, but to other epileptic syndromes, i.e., generalized epilepsy with febrile seizure plus (GEFS+), etc., *SCN1A* is located on chromosomal region of 2q24.3, which includes clustering of other sodium channel genes, i.e., *SCN2A* and *SCN3A*. Latter two genes are also reported to have contribution to epileptic seizures. Although missense mutations in *SCN2A* have been reported to be associated with benign familial neonatal–infantile seizures (BFNIS) [11–13], recent reports also revealed *SCN2A* is one of causal genes for early-onset epileptic encephalopathies such as Ohtahara syndrome and West syndrome [14]. Furthermore, *SCN3A* is confirmed to be correlated to focal epilepsy in children [15,16]. Therefore, contiguous gene abnormality involving the region of 2q24.3 is reasonable to contribute to epilepsy manifestation. Here, we report three patients with 2q24.3 duplications associated with epileptic encephalopathy in infancy.

## 2. Patient reports

### 2.1. Patient 1

A male infant was born at 38 weeks of gestation by caesarean section with no distress, because of repeated caesarean section. At the birth his weight was 2790 g, and neurologic examination was normal, and no dysmorphic feature was noticed. He had no particular family history except for his elder brother's simple febrile seizure. He developed partial seizures consisting of tonic posture and deviation of the eyes to the left or right at 7 days after birth. He developed combined epileptic spasms occurring in cluster at 30 days of age, with the interictal EEG showing the bursts of high voltage slow and spikes, and following diffuse background attenuation (suppression-burst pattern) (Fig. 1A). His seizures did not respond to valproate (VPA), pyridoxal phosphate, zonisamide, levetiracetam (LEV), or ACTH. Carbamazepine (CBZ) was added to LEV at 8 months of age, because of asymmetric spasms and combined partial seizures. Thereafter both types of seizures disappeared from 11 months of age. His EEG at 12 months of age showed remarkable improvement without epileptic discharge ( Fig. 1A). His development was remarkably delayed, and head control was incomplete at even 12 months. Brain magnetic resonance imaging (MRI) at 12 months showed nonspecific mild brain atrophy, large cavum septi pellucidi and cavum vergae (Fig. 2A).

### 2.2. Patient 2

A female infant was born at 38 weeks of gestation by caesarean section with no distress. Her birth weight was 2728 g, head circumference was 34.5 cm. Neurologic examination was normal, and no dysmorphic feature was noticed. She had no family history of neurological disease. She developed partial seizures with deviation of the eyes to the right at 3 days after birth, and combined epileptic spasms occurring in cluster joined at the age of 30 days. Her EEG at 2 months of age showed multifocal spikes, sharp waves, and high voltage slow background (Fig. 1B). Treatment with ZNS and VPA resulted in gradual control of seizures by 11 months of age. Her EEG at 12 months of age showed improvement without epileptic discharge (Fig. 1B). Her development was considerably delayed, with no head control at the age of 18 months. Brain MRI at the age of 18 months showed moderate atrophy of bilateral frontal lobes (Fig. 2B).

### 2.3. Patient 3

A female infant was born at 37 weeks of gestation without distress and dysmorphic features. Her birth weight was 2934 g, and head circumference was 31.5 cm. She had no family history of neurological disease. She developed clustering epileptic spasms and partial seizures with upward deviation of the eyes from several hours after birth. Her EEG at 5 months of age showed spikes at right parietal and left occipital regions (Fig. 1C). At 5 months of age, new partial seizure developed, consisting of eyes opening and slow deviation of eyes to the left during sleep, and then disappeared by 7 months. After the addition of lamotrigine (LTG) to VPA from 8 months, epileptic spasms disappeared gradually, and she became seizure-free at 14 months of age. Her brain MRI at 12 months showed hypoplastic corpus callosum, bilateral diffuse atrophy and possible delay of myelination ( Fig. 2C). Her development was extremely delayed, with no complete head control at the age of 14 months.

### 2.4. Molecular cytogenetic analysis

Chromosomal microarray testing was performed according to the method described previously [18]. The present three patients showed genomic copy number gains in 2q24.3 region (Fig. 3). Fluorescence in situ hybridization (FISH) analyses confirmed the signal duplications of this region on the same chromosome, indicating no translocation (data not shown). All of