Brain & Development 36 (2014) 532–536

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

www.elsevier.com/locate/braindev

Case report

RBPJ is disrupted in a case of proximal 4p deletion syndrome with epilepsy

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Received 16 May 2013; received in revised form 13 July 2013; accepted 20 July 2013

Abstract

Proximal 4p deletion syndrome is characterized clinically by mental retardation, minor dysmorphic facial features, and is occasionally complicated with epilepsy. More than 20 cases of proximal 4p deletion syndrome have been reported, but the causative gene(s) remain elusive. We describe here a 2-year-old female patient with a common manifestation of proximal 4p deletion syndrome and infantile epileptic encephalopathy possessing a *de novo* balanced translocation t(4;13)(p15.2;q12.13). The patient was diagnosed as infantile spasms at 9 months of age. She presented with dysmorphic facial features and global developmental delay, compatible with proximal 4p deletion syndrome. Using fluorescence *in situ* hybridization, we determined the translocation breakpoint at 4p15.2 to be within*RBPJ*. RBPJ is a transcription factor in the Notch/RBPJ signaling pathway, playing a crucial role in the developing human brain, and particularly telencephalon development. Our findings, combined with those of previous studies, strongly suggest that *RBPJ* is causative for proximal 4p deletion syndrome and epilepsy in this case.

Keywords: Balanced translocation; Infantile spasms; Proximal 4p deletion syndrome; *RBPJ*

1. Introduction

Deletions involving the proximal portion of human chromosome 4p15 result in a clinically distinct syndrome characterized by variable degrees of intellectual disability, unusual faces, and minor dysmorphic features [1–3]. More than 20 cases of proximal 4p deletion have been reported. The critical region for proximal 4p deletion syndrome has been localized to 4p15.2–15.33, but the causative gene remains elusive.

Infantile spasms (IS), also known as West syndrome, is the most frequent type of epileptogenic encephalopathy. Various types of epileptic spasms, hypsarrhythmia on electroencephalography (EEG), and psychomotor deterioration constitute the basis for a diagnosis of IS. IS is not a nosological entity but rather constitutes a heterogeneous group of conditions that share this clinical triad. Several genetic abnormalities have been identified among the diverse possible causes of IS. Although the number of mutations identified is small, it gives rise to the intriguing possibility that genetic abnormalities underlie a proportion of IS etiology.

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http://dx.doi.org/10.1016/j.braindev.2013.07.009

Here, we present a patient with IS and profound psychomotor delay with a *de novo* reciprocal translocation t(4;13)(p15.2;q12.13) disrupting the gene that encodes recombination signal binding protein for immunoglobulin kappa J (RBPJ).

2. Case report

The patient, a 2-year-old girl, was born after an uneventful pregnancy to unrelated healthy parents at term without asphyxia. Neither parent had intellectual impairment or epilepsy. She experienced clonic convulsions of the extremities at day 20 after birth. An initial EEG performed at 1 month was normal. Her seizures were not well controlled by a combination of phenobarbital and carbamazepine, and gradually evolved into recurrent brief tonic spasms. IS was diagnosed at 9 months of age by intellectual disability, a series of tonic spasms, and modified hypsarrhythmia described as periodic independent polyspikes-wave bursts on EEG.

On examination at 2 years, her weight was 10.7 kg (−0.8 SD) and her height was 86 cm (+0.6 SD). She presented with dysmorphic facial features; upslanted palpebral fissures, epicanthal folds, a large beaked nose, thick lower lips, and micrognathia (Fig. 1a; Table 1). Other minor anomalies included bilateral fifth finger mild brachydactyly (Fig. 1b). A physical examination revealed mild axial hypotonia. She showed global developmental delays with motor skills equivalent to those normally observed at 5 months of age. She was unable to speak any recognizable words. Routine laboratory and neurometabolic investigations, computed tomography scans, and magnetic resonance imaging findings were normal. No abnormalities were seen on an echocardiogram and electrocardiogram. EEG showed diffuse high voltage slow waves with independent spike waves over the bilateral frontal and parieto-occipital area (Fig. 1c and d).

G-banded chromosomal analysis revealed a balanced translocation t(4;13)(p15.2;q12.13) in the patient. Her parents showed a normal karyotype (data not shown), indicating that the translocation occurred *de novo*. Array CGH, according to a method described elsewhere [4] (Supplementary information), did not show any significant copy number variations (data not shown), suggesting that the balanced translocation did not involve occult changes. FISH, performed as previously described [5] (Supplementary information), demonstrated that the putative breakpoint on chromosome 4

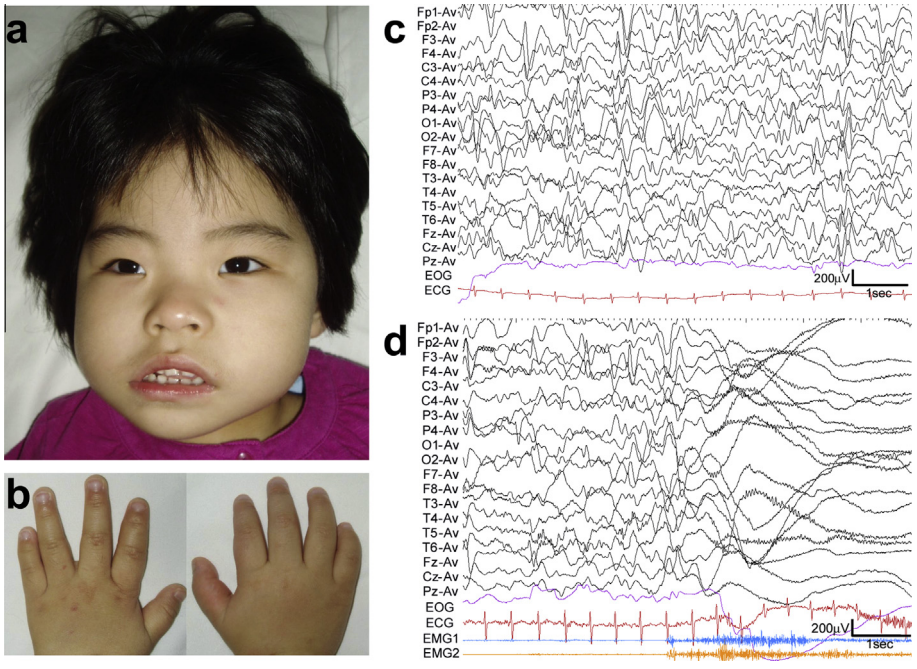

Fig. 1. Characteristics of the patient. (a) Facial appearance of the patient at 4 years. Upslanted palpebral fissures, epicanthal folds, a large beaked nose, thick lower lips, and micrognathia can be observed. Other minor anomalies include strabismus and widely spaced teeth. (b) Digits of the patient at 4 years, showing bilateral fifth finger mild brachydactyly. The parents of the patient gave their consent to publish these photographs in an academic journal. (c) Interictal EEG at 2 years. EEG during wakefulness shows a diffuse high-voltage slow rhythm superimposed with irregular independent spike waves over the bilateral frontal and parieto-occipital area. (d) Ictal EEG during tonic spasms. A diffuse irregular high-voltage slow rhythm is followed by diffuse voltage attenuation with rhythmic fast-wave bursts when tonic axial spasms with symmetric contraction of the deltoid muscles occur. Her daily tonic spasms and subsequent tonic seizures were refractory to pyridoxine, ACTH, valproic acid, clonazepam, lamotrigine, topiramate, and levetiracetam. After undergoing total corpus callosotomy at 2 years and 3 months of age, she showed fewer axial tonic seizures. EOG; electrooculography; ECG; electrocardiography; EMG1; electromyography of left deltoid muscle; EMG2; electromyography of right deltoid muscle.