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Case Report

Clinical variations of epileptic syndrome associated with *PACS2* variant

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Abstract

Background: Recent studies have suggested that two *PACS2* pathogenic variants, c.625G > A (p.Glu209Lys) and c.631G > A (p.Glu211Lys), have been causally linked to the characteristic developmental and epileptic encephalopathy, including autistic behaviors, hypotonia, cerebellar dysgenesis and facial dysmorphism. Their seizures appear most difficult to control in neonatal and infant period, but improve after the first year of life. We herein report three patients with the same *PACS2* variant, c.625G > A (p.Glu209Lys), showing different characteristics from previous reports.

Case report: Case 1, a 2-year-old girl, developed frequent tonic convulsions 2 weeks after birth. Brain magnetic resonance imaging showed a decrease in posterior periventricular white matter volume, an enlargement of the inferior horn of lateral ventricles and old subependymal hemorrhage. Epilepsy is now controlled with antiepileptic drugs. Case 2, a 12-year-old girl, developed generalized tonic convulsions 3 days after birth. Although epilepsy had been controlled since the age of 4, she developed Lennox–Gastaut syndrome at 9 years old. Case 3, a 3-year-old girl, developed tonic convulsions 3 days after birth. She now exhibits normal psychomotor development, and epilepsy is controlled without medicine.

Conclusion: *PACS2*-related epileptic syndrome presents variable phenotypes than previously reported. We think that our findings expand the clinical spectrum of this disease, and provide important information about the differential diagnosis of neonatal-onset epileptic syndrome.

Keywords: *PACS2*; Developmental and epileptic encephalopathy; Neonatal-onset; Facial dysmorphism; MRI

1. Introduction

PACS2, phosphofurin acidic cluster sorting protein 2, is a multifunctional protein which mainly expresses in the brain and acts as a traffic modulator by controlling communication between the endoplasmic reticulum and the mitochondria, with nuclear gene expression [1,2]. Recent studies have showed that two *PACS2*

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pathogenic variants, c.625G > A (p.Glu209Lys) and c.631G > A (p.Glu211Lys), have been causally linked to neonatal/early-infantile-onset developmental and epileptic encephalopathy with cerebellar dysgenesis, facial dysmorphism and some other features [3,4]. Here we report three patients with the same *PACS2* variant, c.625G > A (p.Glu209Lys), and present a wider range of clinical variations than previously reported in *PACS2*-related epileptic syndrome.

2. Case report

Patient 1: The proband was a 2-year-old girl who was born to nonconsanguineous parents at 37 weeks of gestation. She had facial dysmorphism, including hypertelorism, downward-slanting palpebral fissures, thin upper lip, down-turned corners of the mouth, and broad nasal root (Fig. 1A). Frequent tonic convulsions with head turning appeared 2 weeks after birth. Electroencephalography (EEG) revealed high-voltage slow waves over the left posterior-temporal areas. Brain magnetic resonance imaging (MRI) showed a decrease in posterior periventricular white matter volume, an enlargement of the inferior horn of lateral ventricles, and old subependymal hemorrhage, which were suggestive of perinatal injury (Fig. 2). Epilepsy was refractory in early infancy, but seizures decreased in frequency from 8 months of age and were almost controlled with carbamazepine and clobazam from 2 years of age. The patient now shows hypotonia and mild psychomotor developmental delay. Whole-exome sequencing (WES) , which was performed as previously described [5], identified the *de novo* heterozygous variant in *PACS2* (c.625G > A:p.Glu209Lys).

Patient 2: The proband was a 12-year-old girl who was born to nonconsanguineous parents. She had facial dysmorphism, including hypertelorism, downward-slanting palpebral fissures, thin upper lip, down-turned corners of the mouth, and broad nasal root (Fig. 1B). Seizures appeared 3 days after birth. She repeatedly exhibited focal or generalized tonic convulsions. EEG revealed spikes over the right frontal areas. Brain MRI findings were normal. Although epilepsy had been controlled with topiramate, zonisamide and clonazepam since she was 4 years old, several types of seizures including atypical absence and tonic convulsion appeared when she was 9 years old. EEG revealed a characteristic appearance of Lennox–Gastaut syndrome with diffuse slow polyspike-and-wave complexes and fast rhythms (Fig. 2B). WES identified the *de novo* heterozygous variant in *PACS2* (c.625G > A:p.Glu209 Lys). Her seizures are almost controlled with lamotrigine, valproic acid and clonazepam. She is now diagnosed with autism spectrum disorder and severe intellectual disability. Although she shows hypotonia, she can walk alone.

Patient 3: The proband was a 3-year-old girl who was born to nonconsanguineous parents. She had facial dysmorphism, including hypertelorism, downward-slanting palpebral fissures, everted vermillion of lower lip and broad nasal root (Fig. 1C). Seizures appeared 3 days after birth. She suffered from repeated tonic convulsions monthly. Brain MRI showed right venous sinus thrombosis at 3 days of age, which disappeared at 4 months. When she was 6 months old, ictal EEG showed epileptic discharges from the left hemisphere. Epilepsy was controlled with carbamazepine at 9 months of age. The patient now exhibits normal psychomotor development, and epilepsy is controlled without medicine. WES identified the *de novo* heterozygous variant in *PACS2* (c.625G > A:p.Glu209Lys).

In all 3cases, the analysis by WES was approved by the ethical committee at Showa University School of Medicine and the Faculty of Medicine, Yokohama City University. Written informed consent was obtained from the parents of each patient.

3. Discussion

Recently, a recurrent *de novo* missense variant in *PACS2* has been reported in 14 unrelated individuals with neonatal/early-infantile-onset epilepsy, developmental delay, autistic behaviors, hypotonia, and facial dysmorphism including coarse features, hypertelorism, broad nasal root, and thin upper lip [3]. The seizures, which are mainly focal seizures, appear most difficult to control in infancy despite the treatment such as phenobarbital, levetiracetam, carbamazepine and valproate, but improve after the first year of life. Early EEG often shows an excess of sharp waves, but more severe encephalopathic patterns, such as burst suppression or hypsarrhythmia, are not reported. The typical findings of brain MRI are reported to be dysgenesis of the cerebellar folia, megacisterna magna and inferior vermian hypoplasia. Other features include ocular abnormalities such as nystagmus, myopia and strabismus, congenital heart disease, minor distal limb anomalies including fifth finger brachyclinodactyly, and hemaological disturbances with anemia and neutropenia. Functional studies demonstrate that the p.Glu209Lsy in *PACS2* alters the ability of the autoregulatory domain to modulate the interaction between the PACS2 and client proteins, which may disturb cellular function [3].

Here, we report three additional patients with the same *PACS2* variant who showed a wide range of clinical phenotypes, although all patients had the common feature of neonatal-onset epilepsy. Patient 1 had a phenotype similar to that of previously reported cases, but the MRI findings were suggestive of perinatal injury, without imaging features such as dysgenesis of the cerebellar folia, megacisterna magna and inferior vermian hypoplasia being reported. Recently, Dentici et al.

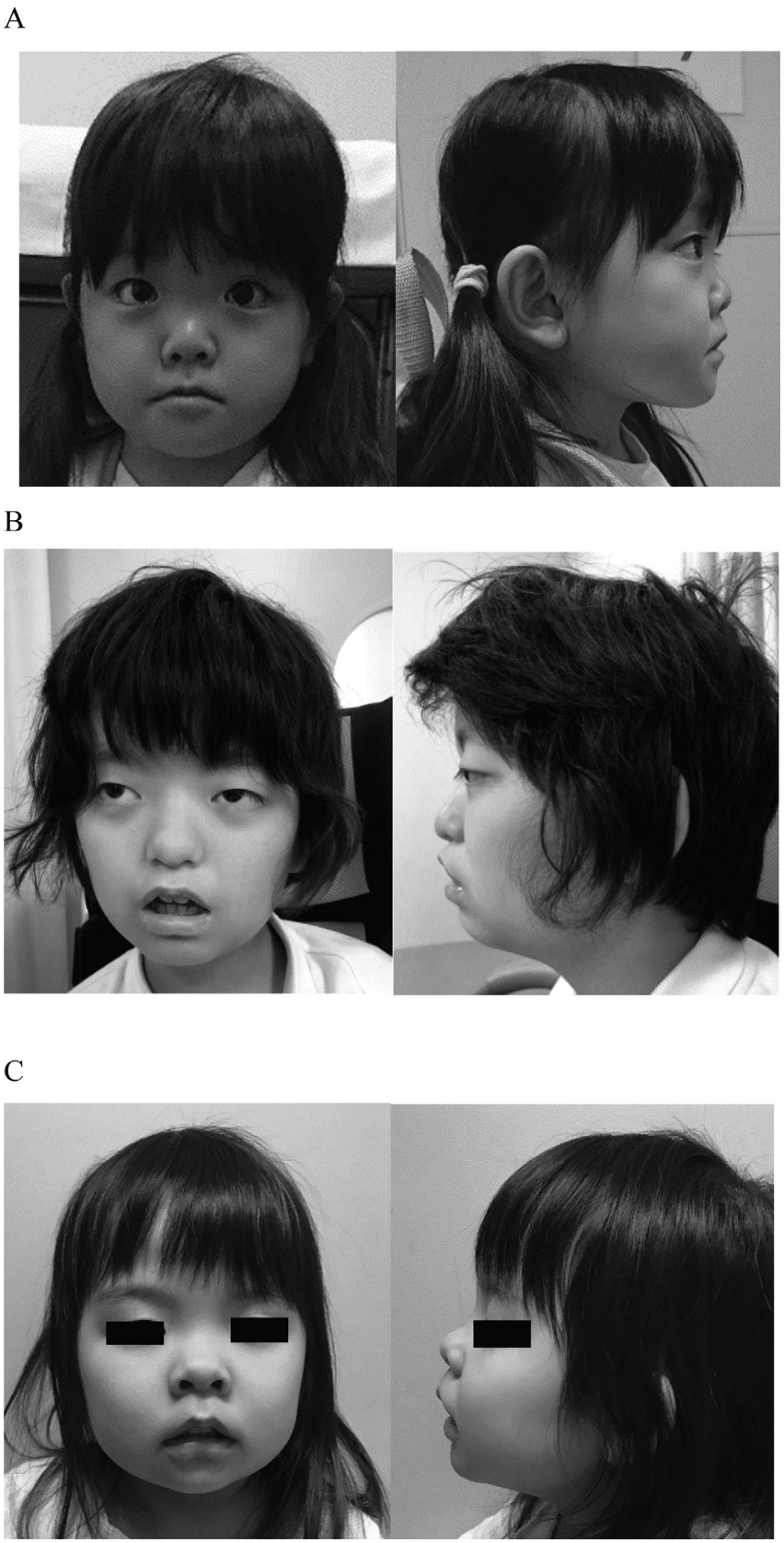

Fig. 1. Pictures of patients 1 (A), 2 (B) and 3 (C): facial dysmorphism including hypertelorism, downward-slanting palpebral fissures, thin upper lip, down-turned corners of the mouth, and broad nasal root. The informed consent was obtained from the parents of each patient for the use of the pictures.

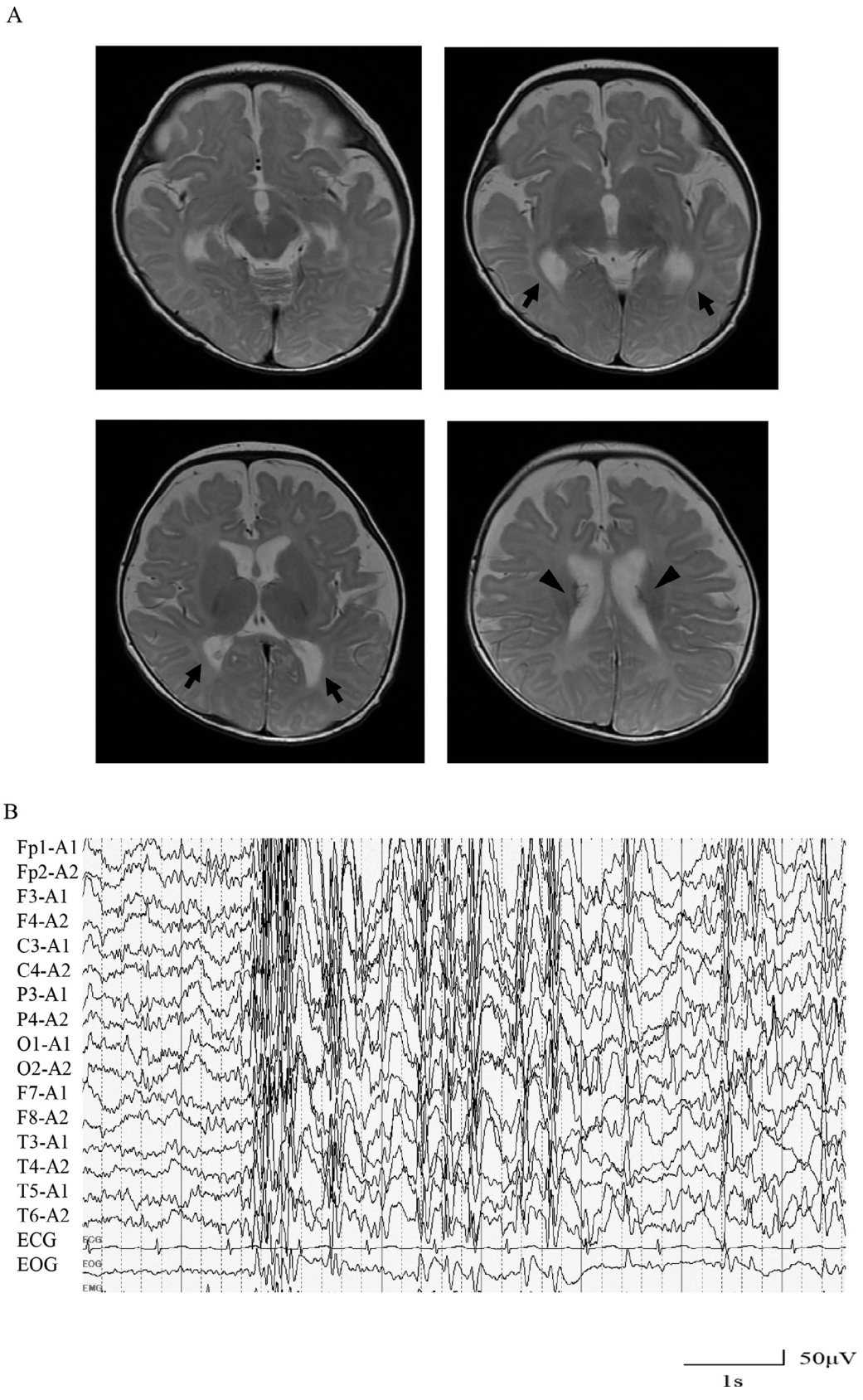

Fig. 2. T2-weighted brain MRI of patient 1 at the age of 4 months (A) showed a decrease in posterior periventricular white matter volume, an enlargement of the inferior horn of lateral ventricles (arrows), and old subependymal hemorrhage (triangular arrows). EEG of patient 2 at the age of 9 years (B) revealed a characteristic appearance of Lennox–Gastaut syndrome with diffuse slow polyspike-and-wave complexes and fast rhythms.

reported the case of a patient with developmental and epileptic encephalopathy who had a missense *PACS2* variant, c.631G > A (p.Glu211Lys) [4]. In this patient, MRI findings were similar to those in our patient 1, including quantitative reduction of the parietal region and posterior periventricular white matter and asymmetry of the lateral ventricles. Furthermore, our patient 2 exhibited Lennox–Gastaut syndrome, which has not been reported in patients with *PACS2* variant. In contrast, our patient 3 showed normal psychomotor development, although all the other patients reported so far have had psychomotor delay. *PACS2*-related epileptic syndrome appears to manifest with more variable phenotypes than previously reported, and thus, further accumulation of the patients is needed to delineate the characteristics of this disorder. Furthermore, we should consider the possibility of *PACS2*-related epileptic syndrome in patients with neonatal/early-infantile-onset epilepsy, developmental delay and facial dysmorphism.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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