


CASE REPORT

Phenotypic overlap between pyruvate dehydrogenase complex deficiency and FOXG1 syndrome

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Abstract

Pyruvate dehydrogenase complex (PDHC) deficiency is a mitochondrial disorder. We report two cases of PDHC deficiency with clinical symptoms and brain imaging findings reminiscent of FOXG1 syndrome, suggesting a phenotypic overlap of these disorders.

KEYWORDS

FOXG1 syndrome, MRI, PDHC deficiency, phenotype

1 | INTRODUCTION

Developmental encephalopathy (DE) is associated with developmental impairment, intellectual disability, and other neurological disorders such as epilepsy and movement disorders.¹ DE has developmental consequences arising directly from the effect of genetic variants. The clinical features of patients with DE overlap with those of many neurodevelopmental disorders, and one disorder is difficult to distinguish from the others.

FOXG1 syndrome is one of the DEs, caused by a loss-of-function variant of *FOXG1*, that encodes a brain-specific transcriptional factor critical for forebrain development.^{2,3} Patients with FOXG1 syndrome show microcephaly, hyperkinetic movement disorder, severe psychomotor delay without regression, and characteristic brain imaging findings.^{2,4} Because hyperkinetic movement disorders commonly

develop by 1 year of age, they are proposed as a diagnostic marker for FOXG1 syndrome.⁵

Pyruvate dehydrogenase complex (PDHC) deficiency is a mitochondrial disorder associated with lactic acidosis and various neurological symptoms. PDHC catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, a critical step in energy production.⁶

The clinical spectrum of PDHC deficiency ranges from episodic ataxia to severe fatal neonatal lactic acidosis, but involuntary movements are rare.⁷

Here, we report two cases of PDHC deficiency with clinical symptoms and brain imaging findings reminiscent of FOXG1 syndrome. They exhibited hyperkinetic involuntary movements and hand stereotypies, which are unusual for PDHC deficiency.⁷ This study demonstrates phenotypic overlap between PDHC deficiency and FOXG1 syndrome.

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2 | CASE PRESENTATION

2.1 | Patient 1

This 31-year-old female patient was born to nonconsanguineous, healthy Japanese parents at 40 weeks of gestation after an uneventful pregnancy. Her birthweight and length were 2650 g (- 1.1 SD) and 44.2 cm (- 2.8 SD), respectively. Her occipitofrontal circumference (OFC) was 32 cm (- 1.1 SD). She had no significant family medical history. Because of floppiness and inability to suck, she was fed through a nasogastric tube from the first day of life. At the age of 3 months, psychomotor delay, hypotonia, and strabismus were noted, and myoclonic seizures from the age of 11 months. The seizures were eventually controlled with phenytoin and phenobarbital. Developmental milestones were severely delayed; she acquired head control and turned over at 3 years and was never able to walk unaided and never acquired speech sounds. She displayed hand stereotypies with hand-to-mouth movements. Her OFC was 43.5 cm (- 6.6 SD) at 8 years, indicating that microcephaly had become more evident with time. Magnetic resonance imaging (MRI) scans of the brain showed ventricular dilatation and hypoplasia of the frontal lobe and the corpus callosum (Figure 1A,B). Based on the clinical and brain MRI features, *FOXG1* syndrome was initially suspected. However, genetic testing identified

a disease-associated variant in *PDHAI* but not in *FOXG1*. Metabolic investigations revealed increased levels of lactate (25.1 mg/dL) and pyruvate (1.93 mg/dL) in blood, leading to a definite diagnosis of PDHC deficiency. Lactate and pyruvate accumulation were reduced to 12.9 and 1.06 mg/dL, respectively, by administration of thiamine at a dose of 150 mg a day; however, her neurological condition did not improve.

2.2 | Patient 2

This female patient, aged 8 years, was born to nonconsanguineous, healthy Japanese parents at 41 weeks of gestation after an uneventful pregnancy. Her birthweight and OFC were 3156 g (0.1 SD) and 32.0 cm (- 1.2 SD), respectively. She had no significant family medical history. During the neonatal period, she showed hypotonia, sleep disturbance, and inconsolable crying. The developmental milestones were severely delayed with no regression; she acquired head control at 6 months, turned over at 15 months, and sat up at 2 years. Because of feeding problems due to swallowing difficulties, she was fed via a nasogastric tube from 1 year and 9 months. Her head growth was postnatally decelerated and microcephaly became evident (OFCs of 40.2, 41.0, and 43.0 cm at 7 months, 1 year, and 2 years, respectively, all below - 2 SD). At the age of 3 years, she remained incapable of standing up, acquiring speech

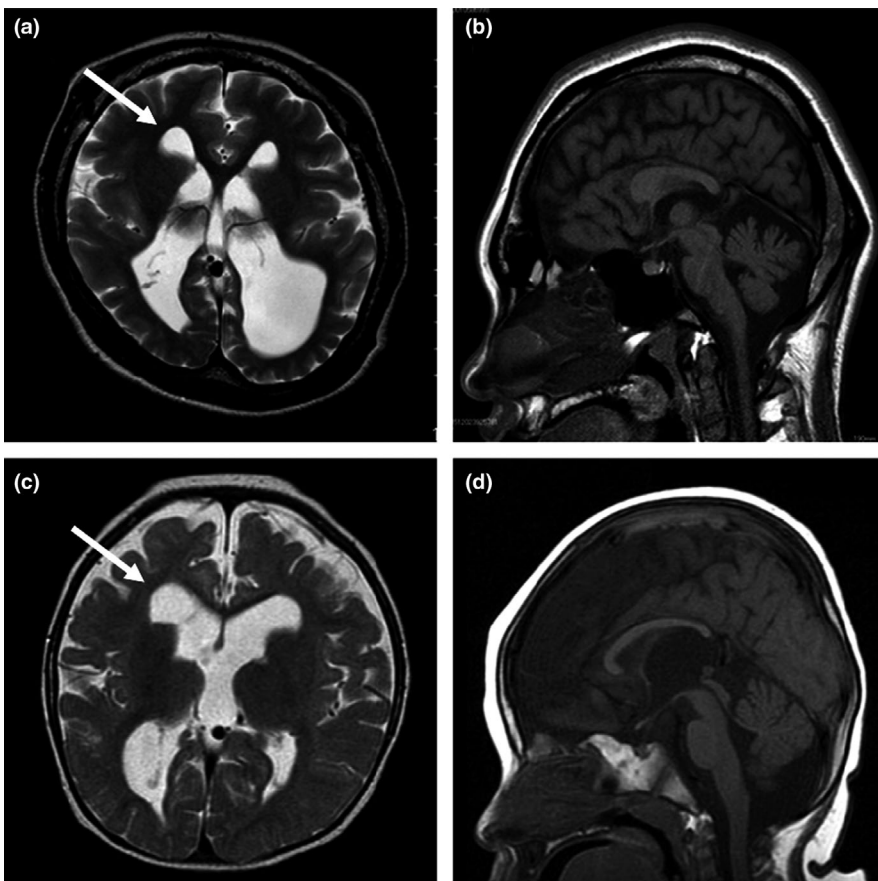
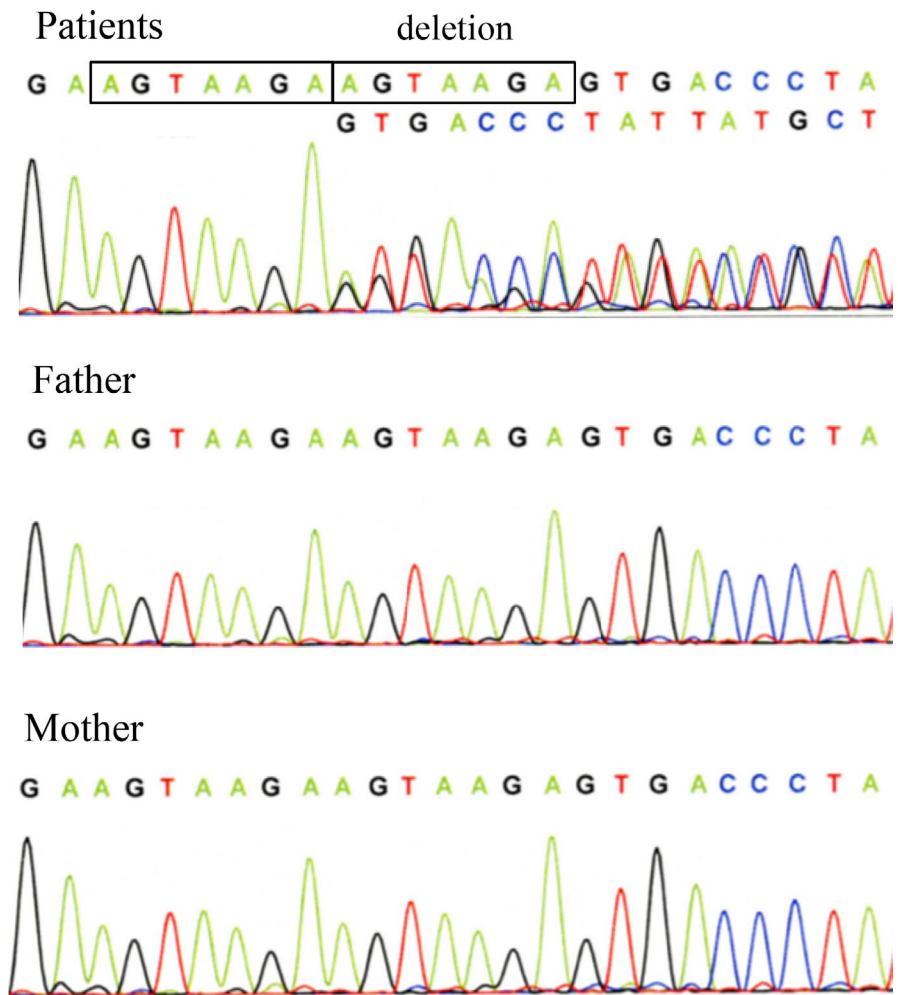


FIGURE 1 (A-D) Images obtained when patient 1 (A and B) and patient 2 (C and D) were 29 and 3 years old, respectively. T1- and T2-weighted images of patients with PDHC deficiency show asymmetrical ventriculomegaly with subependymal cysts (A, arrows), ventricular septation (C, arrow), and hypoplasia of the corpus callosum (B and D)

FIGURE 2 Sequencing analysis revealed the heterozygous deletion of a 7-bp repeat sequence (AGTAAGA) in exon 10 of *PDHA1* (NM_000284.3:c.934_940del) in patients 1 and 2, which resulted in a reading frame shift and introduction of a premature stop codon (p.Ser312Valfs*12). The parents of patients 1 and 2 did not harbor this variant



sounds, and purposeful hand skills. She displayed prominent hyperkinetic movement disorders with hand stereotypies. Brain MRI scans showed microcephaly with hypoplasia of the frontal lobe and the corpus callosum (Figure 1C,D). She showed clinical features and brain MRI findings that were reminiscent of FOXP1 syndrome; however, she had increased lactate and pyruvate levels in blood (lactate 18.2 mg/dL, pyruvate 2.5 mg/dL) and cerebrospinal fluid (CSF) (lactate 32.6 mg/dL, pyruvate 3.3 mg/dL), although the lactate/pyruvate molar ratio was normal. Genetic testing revealed a disease-associated variant of *PDHA1*, leading to a diagnosis of PDHC deficiency. She was enrolled in a clinical trial of pyruvate therapy for mitochondrial diseases,⁸ which was effective in promoting motor development, but not the cognitive impairment. She was able to walk a few steps at 7 years of age, but remained unable to speak any meaningful words.

2.3 | Identification of *PDHA1* variants

Blood samples were collected from the patients and their parents after obtaining written informed consent from

the parents. This study was approved by the Committee for Ethical Issues at Asahikawa Medical University. We performed whole exome sequencing in patient 1 as previously described⁹ and direct sequencing of *PDHA1* in patient 2 and, in both, identified a same frameshift variant in *PDHA1*, NM_000284.3:c.934_940del, p.(Ser312Valfs*12) (Figure 2). Testing of the patients' parents confirmed that the *PDHA1* variant emerged de novo.

3 | DISCUSSION

We identified a disease-associated variant in the X-linked *PDHA1* in two female patients who were clinically suspected to have FOXP1 syndrome. Both had the same heterozygous deletion of a 7-bp repeat sequence in exon 10 of *PDHA1*. Gene deletions preferentially occur either within or in the vicinity of such tandem repeats.¹⁰ This mutation was also repeatedly reported in female patients with PDHC deficiency who exhibited variations in clinical severity, most probably due to different patterns of X-chromosome inactivation.¹¹ Our patients exhibited similar clinical features, including microcephaly,

TABLE 1 Phenotypic overlap between PDHC deficiency and FOXG1 syndrome

	Patient 1	Patient 2	FOXG1 syndrome (n = 29) ^a
Sex	female	female	21 females; 8 males
Age at least follow-up	31 years	8 years	10 months to 34 years
Growth			
Failure to thrive	(+)	(+)	21/22
Postnatal microcephaly	(+)	(+)	24/24
Development			
Intellectual disability	(+)	(+)	29/29
Absent language	(+)	(+)	27/28
Sitting	(−)	(+)	6/26
Walking	(−)	(−)	2/29
Motor and dyskinesias			
Hypotonia	(+)	(+)	19/19
Involuntary movements	(+)	(+)	21/23
Stereotypic movements	(+)	(+)	11/14
Strabismus	(+)	(−)	11/12
Bruxism	(−)	(+)	18/24
Epilepsy	(+)	(−)	20/28
Feeding difficulties	(+)	(+)	15/20
Brain MRI			
Hypoplasia of corpus callosum	(+)	(+)	21/23

^aClinical features of 29 patients with FOXG1 syndrome have previously reported.^{11–13}

hypotonia, feeding difficulties, abnormal involuntary movements, stereotypic hand movements, and a profound delay in psychomotor development. Brain MRI scans revealed cerebral atrophy, ventriculomegaly, and hypoplasia of the corpus callosum. These features have been reported in patients with FOXG1 syndrome,^{12–14} suggesting a phenotypic overlap between PDHC deficiency and FOXG1 syndrome (Table 1).

Although patients with PDHC deficiency shared clinical features with FOXG1 syndrome, specific brain MRI findings may distinguish PDHC deficiency from FOXG1 syndrome. Corpus callosum hypogenesis was observed in both diseases. However, the corpus callosum in FOXG1 syndrome was affected mostly the anterior parts,¹⁵ whereas in PDHC deficiency, the posterior body and splenium were preferentially affected.¹⁶

Moreover, patients with PDHC deficiency had dilated ventricles with ventricular septations and/or subependymal cysts (Figure 1), probably due to a destructive process secondary to a metabolic defect, which were absent in FOXG1 syndrome. Subependymal cysts were also described in other metabolic disorders that cause primary lactic acidosis.¹⁷ Intraventricular septations probably reflect the evolution of subependymal cysts. Thus, none of the MRI findings described here is unique to PDHC deficiency. The detection of these MRI findings should prompt further investigation, including metabolic analysis and genetic testing for *PDHA1* variants.

Most importantly, PDHC deficiency is commonly associated with lactic acidosis.⁶ Specific structural brain abnormalities, with the characteristic clinical features, may allow distinction of PDHC deficiency from FOXG1 syndrome if the lactate and pyruvate levels are elevated in the blood and/or CSF. The correct diagnosis will lead to effective treatment. The therapeutic options that may be beneficial in some patients with PDHC deficiency include ketogenic diet, supplementation with thiamine, and dichloroacetate.¹⁸ Therefore, this study further reinforces the necessity of measuring the lactate and pyruvate levels in blood and/or CSF even in the cases of clinically suspected FOXG1 syndrome.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

YA: contributed to collecting all the clinical data and writing of the draft manuscript. ST: contributed to literature review and revision of the manuscript. RT, RT, SN, HS, and NM critically reviewed the manuscript. All Authors approved the contents of the submitted manuscript.

ETHICAL APPROVAL

Institutional approval was obtained. No identifiable patient information was presented in this report.

DATA AVAILABILITY STATEMENT

Not applicable.

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