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Mild Phenotype in a Male with Pyruvate Dehydrogenase Complex Deficiency Associated with Novel Hemizygous In-Frame Duplication of the E1α Subunit Gene (*PDHA1*)

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Abstract

Pyruvate dehydrogenase complex (PDHC) deficiency is an inborn error of metabolism that occurs most commonly due to mutations in the X-linked E1α subunit gene (*PDHA1*). We report a novel duplication of *PDHA1* associated with a mild phenotype in a 15-year-old boy who was diagnosed with PDHC deficiency at 4 years of age following a history of seizures and lactic acidosis. The novel c.1087_1119 mutation in exon 11 resulted in an in-frame duplication of 11 amino acids. Measurements of PDHC activity in cultured skin fibroblasts were low, corresponding to 18.6 and 11.6% of the mean with respect to prior controls, whereas the E1 PDH component was absent. He has borderline intellectual functioning and maintains normal lactate levels on a ketogenic diet in between relapses due to illness. Review of the literature reveals wide variation of clinical phenotype in patients with mutations of the E1α subunit gene (*PDHA1*). There appears to be a higher incidence of normal or borderline intellectual ability in individuals who have insertions or deletions that are in-frame versus those that are out-of-frame. Furthermore, there is no correlation between mean residual PDH activity and phenotype in these patients.

Keywords
- pyruvate dehydrogenase
- complex deficiency
- lactic acidosis
- ataxia
- neuropathy

Introduction

The pyruvate dehydrogenase complex (PDHC, PDC)—consisting of the pyruvate dehydrogenase (E1), lipoamide transacetylase (E2), and dihydrolipoamide dehydrogenase (E3) subunits—is located in the mitochondrial matrix and catalyze the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA. It is an essential and rate-limiting enzyme for connecting glycolysis with the tricarboxylic acid cycle and oxidative phosphorylation, and defects are an important cause of lactic acidosis. Clinically, this may present heterogeneously with mild ataxia to progressive neuropathy, or congenital brain malformation to early death in neonates, and typically manifests differently in the two sexes.

Although mutations have been found in the genes encoding E2, E3, E3-binding protein, PDHC, and pyruvate dehydrogenase (PDH) phosphatase, the majority of reported mutations occur in the gene encoding E1α subunit that contains the E1 active site and plays a key role in the function

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of the PDH complex. This gene, known as *PDHA1*, located on Xp22 may be inherited in an X-linked recessive or dominant manner depending upon the mutation type and the random X-inactivation pattern in female patients.[1–5] We report the case of a male patient with a mild phenotype and a novel hemizygous in-frame duplication of 11 amino acids in exon 11: c.1087_1119dup33 (p.E363_P373dup11).

Case Report

At 4½ years of age, our proband was diagnosed with PDHC deficiency following seizures and acute lactic acidosis. A computed tomography (CT) of the brain at that time reportedly showed bilateral asymmetric prominence of the lateral ventricles, deviation of the septum pellucidum, and hypoattenuation in the basal ganglia. Prior to his diagnosis, he had been meeting all developmental milestones appropriately, and was in the third percentile in height and weight. He had previously presented to the emergency room at 2 years of age when he had stopped walking after having a fever for 2 days at home. As per the report of the patient's mother, our proband had started walking alone at 12 months, used his first words at 18 months, was speaking in two-word sentences, and had no feeding, sleeping, or behavior problems prior to this presentation. Following negative blood work, CT of the head, and lumbar puncture, he was discharged home from the emergency room and returned to baseline in 3 days. His pediatrician placed a referral to neurology (who did not complete any further work-up) and to genetics; however, the patient was unfortunately never seen prior to his hospitalization at 4½ years of age. It is additionally noted by his mother that, at that age, the proband had been speaking in sentences (although without perfect clarity), completed potty training, and enjoyed playtime with his playmates. During the subsequent 13 years, he has been admitted to the emergency department on multiple occasions for seizures and/or confusion and multiple upper respiratory tract infections. On one occasion, he was diagnosed with "metabolic stroke," resulting in new-onset stuttering of speech. During these visits, his lactate levels ranged from 1.8 to 9.9 mM (reference range: 0.8 to 2 M). Magnetic resonance imaging (MRI) of the brain at 7 and 9 years of age showed the same findings of bilateral prominence of the lateral ventricles (right more than left), deviation of the septum pellucidum, and mild thinning of the corpus callosum and new patchy white matter signal abnormality in the cerebellar hemispheres, brachium pontis, and brainstem. There was also a bright

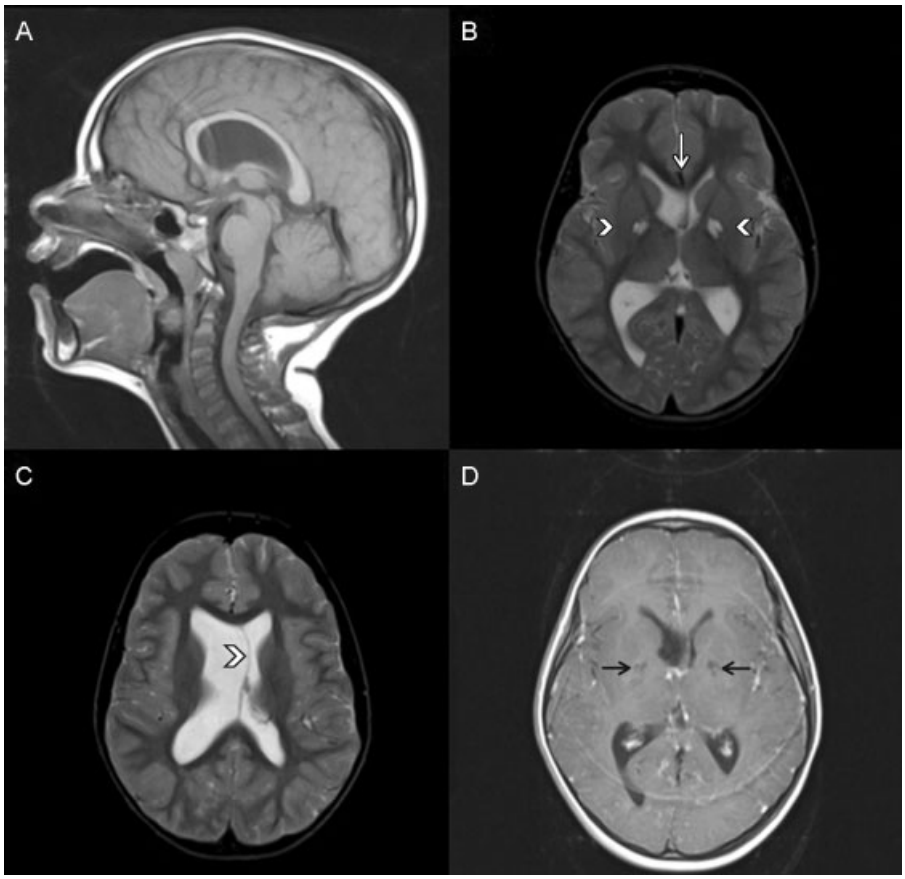

Fig. 1 Magnetic resonance images at 7 years of age. (A) Midline sagittal T1 spin-echo without fat saturation of our patient showing arching and mild thinning of the corpus callosum. (B) Axial T2 spin-echo showing bilateral symmetric necrosis in the globus pallidus (arrowheads) and asymmetric thinning of the corpus collosam (arrow). (C) Axial T2 and a T1 postcontrast showing the asymmetric prominence of the lateral ventricles with deviation of the septum pellucidum (arrowhead) to the left suggesting hypoplasia in the white matter, left more than right. (D) Noncontrast enhancement of the focal necrotic areas in the globus pallidus (arrows).

T2 signal without enhancement in the bilateral globus pallidus suggestive of necrosis (►**Fig. 1**).

Although our proband is now 17 years of age, his most recent presentation to the hospital was at 15 years with confusion and seizures. He was admitted to the pediatruc intensive care unit (PICU) in severe lactic acidosis and respiratory distress, and a diagnosis of pertussis was made. His laboratory findings during that hospitalization were significant for elevated lactate levels (9.9 mM; reference range: 0.80 to 2.00 mM), elevated pyruvate levels (0.34 mM; reference range: 0.05 to 0.14 mM) and a lactate:pyruvate ratio of 30:1 (reference range: 10 to 20:1). He was noted to have had a normal carnitine profile, 2+ (moderate) ketones, and elevated alanine (969 mM; reference range: 152 to 547 mM) and proline (866 mM; reference range: 59 to 369 mM). An MRI showed a new patchy white matter signal abnormality in the cerebellar hemispheres (not thought to be of significance), brachium pontis, and brainstem; abnormal signal in the mammillary body/distal fornices and hypothalamus; and no change in signal intensity in the globus pallidus and cerebral peduncles (►**Fig. 2**). There was mild thinning of the body of the corpus callosum attributed to stretching by enlarged ventricles. All of these findings were consistent with PDHC deficiency with associated Leigh syndrome.[6] He was discharged from the hospital with levocarnitine, thiamine, sodium citrate, and levetiracetam and was treated with azithromycin for pertussis. He is also taking a multivitamin, Actikroll (ARSA Distributing, Inc. in El Paso, TX), which provides approximately 1 mg of thiamine and pyridoxal phosphate. The patient was previously taking methylphenidate briefly for a 1-year period for the diagnosis of attention deficit hyperactivity disorder at 14 years of age.

Although previous neuropsychological data could not be obtained, our proband underwent an individualized education program (IEP) meeting during his senior year of high school where the review team found that he has completed all credits necessary to progress toward graduation with a GPA of 2.83. He actively participates in class, shows up on time, and has decent classroom behavior; however, it is noted that according to his state reading and math examinations, his scores indicate that he has borderline intellectual functioning. The speech pathologist noted that though our proband is intelligible at the conversational level, verbal communication has become more difficult for our proband during recent years and that he speaks with an inconsistent rate and diminished intonation. His fine and gross motor skills, social/emotional development, daily living skills, and vocational skills were found to be within normal limits.

Over the years, despite being maintained on a ketogenic diet of 62% fat, 16% protein, and 22% carbohydrate, his weight gain has remained poor with his stature –3 to –4 standard deviations below the mean. Recurrent organic acid evaluations throughout his life have revealed elevated lactic acid, 3-OH-butyric, and 2-OH butyric acid levels upon hospital admission with an elevated amino acid profile. Childhood measurements of PDC enzyme activity in cultured skin fibroblasts were low (0.45 and 0.28 nmol/min/mg protein), corresponding to 18.6 and 11.6% of the mean with respect to prior controls (2.42 ± 0.88 nmol/min/mg protein); activity of the E1 PDH component was absent (0.0 nmol/min/mg protein) and activity of the E2 and E3 components were within the normal range. A high concentration of thiamine pyrophosphate (TPP) in the assay mix did not result in restoration of activity to a significant degree (activated activity was 12 and 19% of control mean in two separate assays). However, although our patient showed poor thiamine responsiveness on the assay, he has always been maintained on 100 to 400 mg of thiamine. Muscle biopsy showed normal muscle architecture without evidence of abnormal mitochondrial size, localization, or distribution by light and electron microscopy. Routine immunohistochemistry stains were normal. Sequencing of the *PDHA1* gene was performed from peripheral blood and revealed a novel hemizygous in-frame duplication in exon 11: c.1087_1119dup33 (p.E363_P373dup11) resulting potentially in the duplication of 11 amino acids. The exons and the immediately adjacent intronic regions of the *PDHA1* gene located at Xp22.1-p22.2 were amplified by polymerase chain reaction (PCR) and sequenced in the forward and reverse directions using automated fluorescent dideoxy sequencing methods. GenBank (NCBI) ID NM_000284.1 was used as the reference sequence. Although the c.1087_1119dup33 is novel, various other duplications in this region have been reported in PDH deficiency patients.[1,2] Genetic testing of the mother did not reveal a mutation of the *PDHA1* gene.

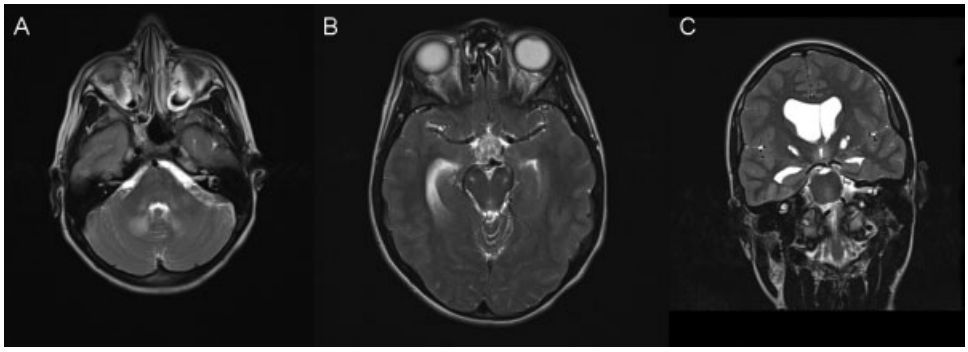

Fig. 2 Follow-up magnetic resonance images at 15 years of age. (A) Axial T2 image showing new patchy white matter signal abnormality in the cerebellar hemispheres. (B) Axial T2 with redemonstration of abnormal signal in the cerebral peduncles. (C) Coronal T2 showing unchanged abnormality in the globus pallidus bilaterally.

Table 1 Characterization of pyruvate dehydrogenase complex deficiency cases identified with normal or borderline intellectual function in patients with insertions and deletions

Mutation	In-frame vs. frameshift	Cognitive functioning	Other phenotypic features	PDH activity (%)	Age at report (y)	Patients	Source
c.1167_1170del4 (Exon 11)	FS	Normal	Exercise intolerance	24.6	9	1	Endo (1989)[10]
c.1162_1163ins4 (Exon 11)	FS	Normal	Mild ataxia, dysarthria	2.9	35	14	Cameron (1994)[9]
c.1159_1162dup4 (Exon 11)	FS	Normal	None reported	44.0	4.4	54	DeBrosse (2012)[7]
c.1159_1162dup4 (Exon 11)	FS	Normal	None reported	41.0	14	55	DeBrosse (2012)[7]
c.977_978ins15 (Exon 10)	IF	Normal	Periodic weakness, ataxia, cramps	23.0	4	1	Fugii (1996)[8]
c.1143_1144ins24 (Exon 11)	IF	BIF	Dystonia	8.0	10	M-8	Quintana (2010)[4]
c.961_975dup15 (Exon 10)	IF	Normal	None reported	32.0	35	37	DeBrosse (2012)[7]
c.1087_1119dup33 (Exon 11)	IF	BIF	Seizures, dysarthria	18.6, 11.6	17	1	This report

Abbreviations: BIF, borderline intellectual functioning; FS, frameshift; IF, in-frame; PDH, pyruvate dehydrogenase.

Discussion

To date, there are over 371 cases and 140 known mutations in *PDHA1* inclusive of insertions, deletions, missense mutations, nonsense mutations, exon skipping, tandem repeats, and duplications, which together lead to a very heterogeneous clinical presentation.[5] Clinically, when compared with other similar mutations located on exon 11, our proband has presented similarly with dilated ventricles and encephalopathy; however, despite his health complications, he has shown a markedly better clinical course.[1–5] We compared the relatively mild clinical features in our patient with other reported patients with in-frame insertions and deletions, and although limited clinical information was available in many of the case reports, there appeared to be a higher incidence of individuals with higher intellectual ability when they displayed duplications rather than deletions and when they displayed indels that were in-frame rather than out-of-frame. Including our proband, in all case reports for which we can confirm cognitive functioning, 4 out of 21 (19.0%) in-frame indels resulted in normal or borderline intellectual functioning[4,7,8] and 4 out of 46 (8.7%) frameshift mutations resulted in normal or borderline intellectual functioning[9,10] (►**Table 1**). In addition, it is noted that in the entire literature for which we can obtain information on cognitive functioning, there is only one reported individual with a deletion whereas there are seven PDHC-deficient patients with duplications who have normal or borderline intellectual functioning. Thus, it appears that deletions of the *PDHA1* gene tend to be more severe. Furthermore, we found no correlation between residual enzymatic function and phenotype. In fact, even between the eight individuals we report with mild phenotypes, the mean residual PDH activity varied between 2.9 and 44%. His particular duplication has not been previously reported in *PDHA1*, and this article serves to present a novel duplication to help advance the understanding of PDHC deficiency.

Acknowledgment

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