

Letter to the Editor

Trifunctional Protein Deficiency Due to *HADHB* Mutations Is a Multisystem, β -Oxidation Disorder

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With interest, we read the article by Shahrokhi et al about a new-born with a β -oxidation defect due to a mutation in the *HADHB* gene encoding the β -subunit of the trifunctional protein.¹ We have the following comments and concerns.

A main disadvantage of the study is that the pathogenicity of the *HADHB* mutation was confirmed only by *in silico* techniques.¹ It would have strengthened the results if the pathogenicity had been also confirmed by *in vitro* biochemical methods, such as decreased enzyme activity in fibroblasts or other cell systems, or by *in vivo* studies of knock-in transgenic animals. How can the defect have been confirmed in cultured fibroblasts, as mentioned in the abstract, if only dried blood was available from the index patient?

HADHB mutations not only manifest in the heart and liver as cardiomyopathy, hepatopathy, and hypoketotic hypoglycemia¹ but also with neuropathy, myopathy, recurrent rhabdomyolysis and myoglobinuria, noncompaction, myocardial fibrosis, heart failure, microcephaly, seizures, hydrops, acute fatty liver of pregnancy, hypoparathyroidism, necrotising enterocolitis, respiratory distress syndrome, Raye-like syndrome, lactic acidosis, acute renal failure, or chorio-retinopathy (Table 1). Were any of these additional phenotypic features present in the index case or any of his relatives? Were all first-degree relatives prospectively investigated for these phenotypic manifestations of *HADHB* mutations?

It is unclear what the authors mean with the term "LCTH". The first description of trifunctional protein deficiency (TFPD) dates back to 1992,² and the first causative mutations in the *HADHB* gene were reported in 1996.³ Since then, various types of mutations in the *HADHB* gene have been published.⁴ Among 11 Japanese patients, homozygous missense mutations, compound heterozygote mutations, premature termination

mutations, and frameshift mutations in the *HADHB* gene have been reported.⁴

In previous studies about TFPD, not only an infantile onset type manifesting with hypotonia, lactic acidosis, pulmonary compromise, cardiomyopathy, acute renal failure, and fulminant liver failure, and an adult-onset type manifesting as hypotonia, myalgia, rhabdomyolysis, and peripheral neuropathy, but also a hepatic form of TFPD manifesting with hepatopathy, disseminated intravascular coagulopathy, and recurrent hypoketotic hypoglycemia provoked by prolonged fasting, were differentiated.⁴

Patients with TFPD may die suddenly, particularly those with infantile onset. The cause of sudden death may be sudden cardiac death (SCD) due to acute heart failure from dilated cardiomyopathy, noncompaction, or ventricular arrhythmias, sudden unexplained death in epilepsy (SUDEP) in patients manifesting with seizures, acute respiratory failure due to affection of the respiratory muscles from myopathy, lactic acidosis, or acute, fulminant liver failure. Which was the suspected cause of sudden death in the presented patient?

In a single patient with TFPD, noncompaction has been described.⁵ Noncompaction can be complicated by heart failure, ventricular arrhythmias, and cardioembolic events.⁶ Was the index case investigated for noncompaction, which may be easily missed on echocardiography if the investigator is not familiar with this entity?

Overall, this interesting case would profit from a more detailed description of the phenotype and from revision of the echocardiographic investigations. Confirmation of the pathogenicity of the mutation by investigations other than *in silico* is warranted.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

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Table 1. Phenotype of *HADHB* mutations

Presentation	Mutation	Reference
Brain		
Seizures	c.358dupT + c.1364T>G	7
Microcephaly	c.1109+243_1438-703del	5
Muscle hypotonia	c.1689+2T>G	8
Peripheral nerves		
Hereditary neuropathy	Not accessible	9
Muscles		
Myopathy	c.1689+2T>G	8
Recurrent rhabdomyolysis	Not accessible	1,9
Episodic myoglobinuria	c.210-1G>C + c.686G>T	10
Muscular respiratory insufficiency several		4
Eyes		
Chorio-retinopathy	Not mentioned	11
Endocrine organs		
Hypoglycemia	Not mentioned	12
Hypoparathyroidism	c.1175C>T	13
Heart		
Heart failure	c.358dupT + c.1364T>G	7
Noncompaction	c.1109+243_1438-703del	5
Pericardial effusion	c.1689+2T>G	8
Myocardial fibrosis	Several	4
Lung edema	c.185G>A + c.1292T>C	14
Liver		
Hepatopathy	Not mentioned	15
Acute fatty liver of pregnancy	c.1136A>G	16
Disseminated intravascular coagulopathy	c.1136A>G	16
Gastrointestinal		
Necrotising enterocolitis	c.212+1G>C	17
Kidneys		
Acute renal failure	c.1689+2T>G	8
Other		
Multiorgan failure	c.1154A>C	1
Hydrops	c.1109+243_1438-703del	5
Respiratory distress syndrome (IRDS)	c.212+1G>C	17
Lactic acidosis	c.358dupT + c.1364T>G	7
Raye-like syndrome	c.1689+2T>G	8
Lethargy	c.1689+2T>G	8

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