Long-Chain Fatty Acid Oxidation Disorders

Fatty acid oxidation disorders (FAOD) are a group of autosomal recessive genetic disorders that impair the metabolism of dietary fat to energy.[1]

Long-chain FAOD (LC-FAOD) are a specific group of FAOD that are caused by defective mitochondrial carnitine shuttle or β-oxidation enzymes that are required to convert long chain fatty acids into energy and can result in severe energy deficit.[2,3]

The most common types of LC-FAOD, the symptoms of which can vary in severity and age of onset, are[1,4]:

Enzyme Deficiency	Gene
Carnitine palmitoyltransferase I (CPT I) deficiency	*CPT1A*
Carnitine-acylcarnitine translocase (CACT) deficiency	*SLC25A20*
Carnitine palmitoyltransferase II (CPT II) deficiency	*CPT2*
Very long–chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency	*ACADVL*
Trifunctional protein (TFP) deficiency	*HADHA and HADHB*
Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency	*HADHA*

Energy production from long-chain fatty acids is impaired in LC-FAOD[5]:

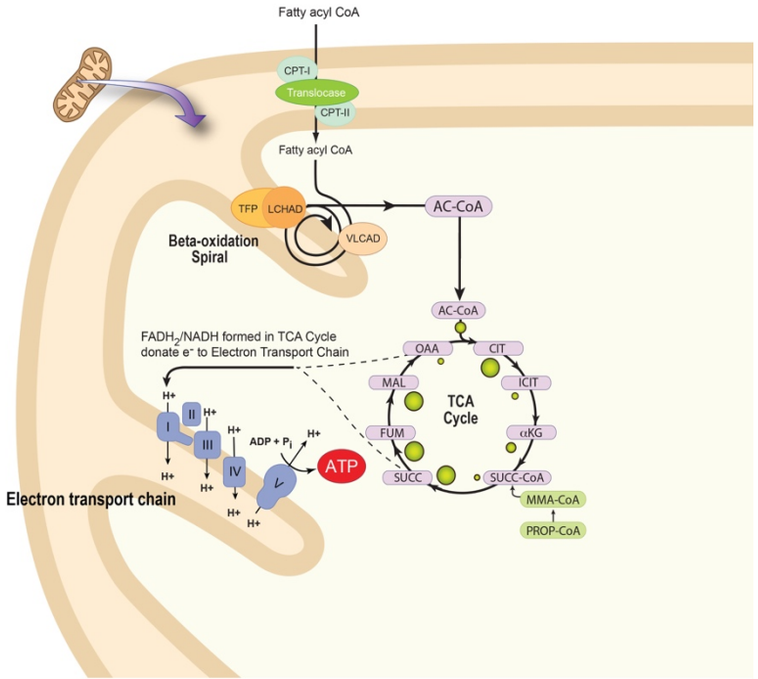

Figure modified from Vockley J, et al. *Mol Genet Metab*. 2015;116(1-2):53-60.

Prevalence:

LC-FAOD are rare and therefore limited epidemiological data is available. It is believed that approximately 100 babies are born each year with a confirmed diagnosis of LC-FAOD in the United States. It is estimated that there are 2,000-3,500 patients living with LC-FAOD in the United States.[6]

LC-FAOD Clinical Presentation

LC-FAOD are included in newborn screening panels across the United States and in certain other countries.[1] Patients not detected by newborn screening typically present clinically with severe life-threatening events or chronic, intermittent muscle fatigue and/or pain.[3]

Patients that present with clinical features of LC-FAOD or, if born after the introduction of NBS, with an abnormal screen result (acylcarnitine elevations in dried blood spot sample), further evaluation is necessary, such as glucose, electrolytes, blood gas, ammonia, liver function tests, and a plasma acylcarnitine assay. Confirmatory type-specific gene sequencing may be done if available.[4,7,8] In some cases, the same acylcarnitine pattern is the same for 2 different disorders, or non-specific in a symptomatic patient so sequencing is necessary for confirmation.[4,7,8]

Illness, fasting, and physical activity can trigger symptoms.[3]

LC-FAOD signs and symptoms may include[1-3,9-12]:

Musculoskeletal

- Muscle pains, cramps, weakness, fatigue
- Rhabdomyolysis, elevated creatine kinase (CK)
- Myoglobinuria
- Acute tubular necrosis
- Hypotonia
- Myopathy

Heart

- Dilated and/or hypertrophic cardiomyopathy
- Heart failure
- Arrhythmia, sudden death

Liver

- Hypoketotic hypoglycemia
- Hepatomegaly, fatty infiltration
- Elevated aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH)
- Hyperammonemia

Other Signs and Symptoms of LC-FAOD

- Retinitis pigmentosa (LCHAD)
- Peripheral neuropathy (TFP/LCHAD)
- Maternal hemolysis, elevated liver enzymes, low platelet count (Maternal HELLP syndrome) syndrome during the last trimester of pregnancy
- Sudden infant death syndrome (SIDS)
- Gastrointestinal distress
- Nausea
- Drowsiness
- Fussiness
- Lack of appetite

To learn more about our ongoing LC-FAOD development program, contact **medinfo@ultragenyx.com** or visit **www.ultragenyx.com.**

References

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