# Neuromuscular Symptoms of LC-FAOD (Long-Chain Fatty Acid Oxidation Disorders)

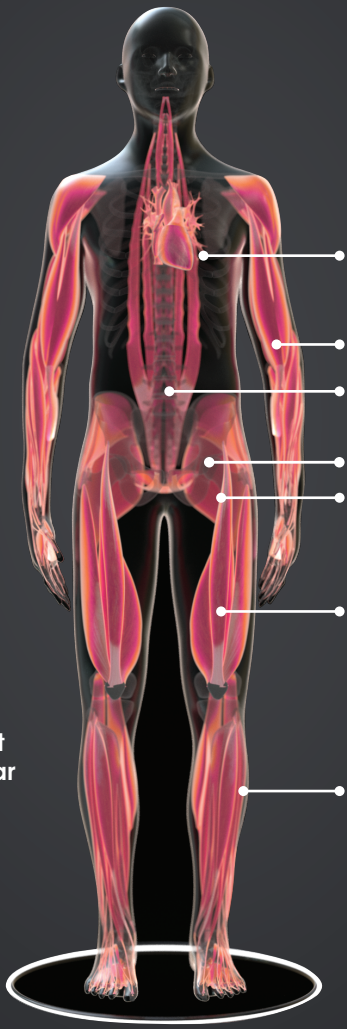
Key neuromuscular symptoms that should increase suspicion of LC-FAOD[1,2]

- Exercise intolerance
- Rhabdomyolysis
- Elevated CK
- Muscle weakness
- Myalgia
- Myoglobinuria

**CPT II** deficiency

**VLCAD** deficiency

Primary LC-FAOD types featuring clinical signs that overlap with neuromuscular disorders[1,2]



Major muscle groups affected by LC-FAOD

- heart[3]
- arms[4]
- thoracic extensors[5]
- gluteus maximus[5]
- pelvic girdle to lower leg[6]
- quadriceps[7]
- calves[8]

CPT=carnitine palmitoyltransferase; VLCAD=very long-chain acyl-CoA dehydrogenase.

**More inside:**

# What are LC-FAOD?

## LC-FAOD: A group of rare, life-threatening autosomal recessive disorders[9-12]

CPT II and VLCAD deficiencies feature clinical signs that overlap with neuromuscular disorders.[1,2]

## CARNITINE TRANSPORT DISORDERS[13,14]

**CPT II deficiency**[10,13]
**Cause:** Mutations in the *CPT2 gene*
**Estimated incidence:** 1:750,000 to 1:2,000,000

**CPT I deficiency**[10,13]
**Cause:** Mutations in the *CPT1A gene*
**Estimated incidence:** 1:750,000 to 1:2,000,000

**CACT deficiency**[10,15]
**Cause:** Mutations in the *SLC25A20 gene*
**Estimated incidence:** 1:750,000 to 1:2,000,000

## BETA-OXIDATION DISORDERS[13]

**VLCAD deficiency**[10,13]
**Cause:** Mutations in the *ACADVL gene*
**Estimated incidence:** 1:85,000

**TFP deficiency**[10,13]
**Cause:** Mutations in both the *HADHA and HADHB genes*, leads to defects in the entire TFP complex
**Estimated incidence:** 1:750,000

**LCHAD deficiency**[10,13]
**Cause:** Mutations in the *HADHA gene*, which encodes for a subunit of TFP
**Estimated incidence:** 1:250,000

CACT=carnitine-acylcarnitine translocase; CPT=carnitine palmitoyltransferase; LCHAD=long-chain 3-hydroxyacyl-CoA; TFP=trifunctional protein; VLCAD=very long-chain acyl-CoA dehydrogenase.

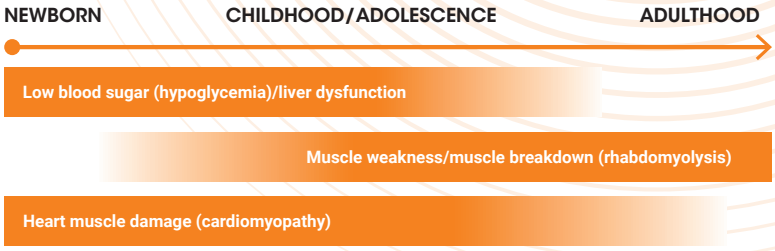
# The Impact

## Patients with LC-FAOD face acute episodes and chronic symptoms that lead to:[12,16-19]

- **High mortality rates**
- **Substantial medical burdens**
- **Difficult challenges**

Although symptoms can appear within a few hours of birth, they may also not appear until adulthood[12,20,21]

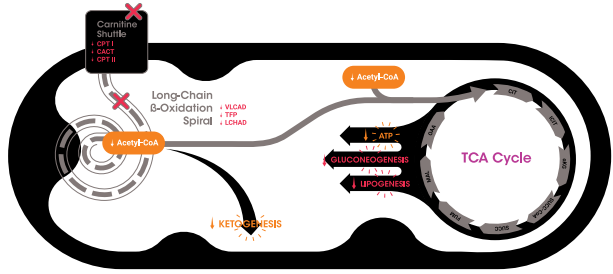
## A SPECTRUM OF PRESENTATION[12,16,20]




- Adolescents and adults with CPT II and VLCAD deficiencies reported clinical signs that overlap with neuromuscular disorders, including muscle myopathy, rhabdomyolysis, elevated creatine kinase, and myoglobinuria.[2]
- Adolescent and adult patients may not have received newborn screening for LC-FAOD, genetic testing can help with diagnosis for symptomatic patients of all ages.[2]

# The Cause

## Unbalanced metabolism in LC-FAOD impairs energy production[11,12,22]




### 1. ENZYME DEFICIENCIES

LC-FAOD are caused by specific enzyme deficiencies in the carnitine shuttle system or the long-chain β-oxidation spiral.[9,16]

### 2. COMPROMISED LCFA METABOLISM

Impaired enzyme activity limiting normal metabolism of LCFAs into acetyl-CoAs results in[12,24,25]

- Lower ATP production
- Impaired ketogenesis

### 3. TCA CYCLE IMBALANCE

Enzyme deficiencies can disrupt the anaplerosis/cataplerosis balance, leading to[12,23]

- Accumulation of toxic metabolites
- Lack of replenishing substrates in the TCA intermediate pools

### 4. IMPAIRED ENERGY PRODUCTION

Incomplete TCA cycle processing may impair[11,12,22,26,27]

- Gluconeogenesis
- Lipogenesis

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Acetyl-CoA=acetyl coenzyme A; αKG=alpha-ketoglutarate; ATP=adenosine triphosphate; CACT=carnitine-acylcarnitine translocase; CITR=citrate; CPT=carnitine palmitoyltransferase; FUM=fumarate; ICIT=isocitrate; LCHAD=long-chain 3-hydroxyacyl-CoA dehydrogenase; MAL=malate; OAA=oxaloacetate; SUCC=succinate; SCoA=succinyl-CoA; TCA=tricarboxylic acid; TFP=mitochondrial trifunctional protein; VLCAD=very long-chain acyl-CoA dehydrogenase.

# Case studies in CPT II and VLCAD with neuromuscular symptoms[1]

## CASE 1

**CPT II deficiency**

A 13-year old female presents with:

- myalgia
- weakness
- dark urine

## CASE 2

**VLCAD deficiency**

A 16-year old female presents with:

- Severe leg pain and weakness
- Elevated CK
- History of exercise intolerance


Topçu: CPT II and VLCAD Case Studies

Importance of acylcarnitine profile analysis for disorders of lipid metabolism in adolescent patients with recurrent rhabdomyolysis: report of two cases

Yasemin Topçu, Erhan Bayram, Pelinsu Kasapoğlu, Ulaş Pa, Semra Hız Kurul

Abstract

Case 1 (CPT II):

Case 2 (VLCAD):

Conclusion

REVIEW THE CASE REPORT

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# Genetic testing for patients with neuromuscular symptoms suggesting LC-FAOD

- ACADVL
- CPT1A
- CPT2
- HADHA
- HADHB
- SLC25A20

Genetic Testing Panels are available to confirm a diagnosis of LC-FAOD.

When ordering a genetic test, look for the six genes associated with LC-FAOD.

## If you see one or more of these neuromuscular symptoms:

- Exercise intolerance
- Elevated CK
- Myalgia
- Rhabdomyolysis
- Muscle weakness
- Myoglobinuria[1,2]

## Consider Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD), particularly CPT II and VLCAD[1,2]

**CPT II** deficiency[10,13] | **CPT I** deficiency[10,13] | **CACT** deficiency[10,15] | **VLCAD** deficiency[10,13] | **TFP** deficiency[10,13] | **LCHAD** deficiency[10,13]

**IF YOU SUSPECT LC-FAOD, SPEAK WITH AN ULTRAGENYX REPRESENATIVE ABOUT HOW TO DIAGNOSE LC-FAOD.**

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**References:**

**1.** Topçu Y, Bayram E, Karaoğlu P, Yis U, and Kurul SH. *Ann Indian Acad Neurol.* 2014;17(4):437-440. **2.** Rangel Miller V, Chettiath T, Johnson B, Marsden D, McKnight D, Sarafrazi S, Willcock A, and Miller N. Muscular Dystrophy Association Conference, March 2022. Poster Number 130. **3.** Spiekerkoetter U, Mueller M, Cloppenburg E, et al. *Mol Genet Metab.* 2008;94:428-430. **4.** Uzun Ö, Çavdarlı B and Karalök S. *Turk J Pediatr.* 2021;63:1097-1102. **5.** Avila-Smirnow D, Boutron A, Beyfia-Reyes M, et al. *J Med Case Rep.* 2018;12: 249. **6.** Diekman EF, van der Pol WL, Nievelstein RA, et al. *J Inherit Metab Dis* 2014;37:405-413. **7.** Diekman EF, Visser G, Schmitz JP, et al. *PLoS One.* 2016;11:e0147818. **8.** Madsen KL, Stemmerik MG, Buch AE, et al. *J Clin Endocrin Metab.* 2019;104:3610-3613. **9.** Wanders RJ, Ruiter JP, IJLst L, Waterham HR, Houten SM. *J Inherit Metab Dis.* 2010;33(5):479-494. **10.** Lindner M, Hoffmann GF, Matern D. *J Inherit Metab Dis.* 2010;33(5):521-526. **11.** Wajner M, Amaral AU. *Biosci Rep.* 2015;36(1):e00281. **12.** Knottnerus SJG, Bleeker JC, Wüst RCI, et al. *Rev Endocr Metab Disord.* 2018;19(1):93-106. **13.** Vockley J. *Am J Manag Care.* 2020;26(7 Suppl):S147-S154. **14.** Merritt JL 2nd, Norris M, Kanungo S. *Ann Transl Med.* 2018;6(24):473. **15.** Pennisi EM, Garibaldi M, Antonini G. *J Clin Med.* 2018;7(12):472. **16.** Vockley J, Burton B, Berry GT, et al. *Mol Genet Metab.* 2017;120(4):370-377. **17.** Saudubray JM, Martin D, de Lonlay P, et al. *J Inherit Metab Dis.* 1999;22(4):488-502. **18.** Siddiq S, Wilson BJ, Graham ID, et al. *Orphanet J Rare Dis.* 2016;11(1):168. **19.** Shekhawat PS, Matern D, Strauss AW. *Pediatr Res.* 2005;57(5 Pt 2):78R-86R. **20.** Spiekerkoetter U. *J Inherit Metab Dis.* 2010;33(5):527-532. **21.** Vockley J, Marsden D, McCracken E, et al. [published correction appears in *Mol Genet Metab.* 2015 Nov;116(3):221]. *Mol Genet Metab.* 2015;116(1-2):53-60. **22.** Owen OE, Kalhan SC, Hanson RW. *J Biol Chem.* 2002;277(34):30409-30412. **23.** Longo N, Amat di San Filippo C, Pasquali M. *Am J Med Genet C Semin Med Genet. 2006:142C(2):77-85.* **24.** Brunengraber H, Roe CR. *J Inherit Metab Dis.* 2006;29(2-3):327-331. **25.** Janeiro P, Jotta R, Ramos R, et al. *Eur J Pediatr.* 2019;178(3):387-394. **26.** Roe CR, Brunengraber H. *Mol Genet Metab.* 2015;116(4):260-268. **27.** Houten SM, Wanders RJ. *J Inherit Metab Dis.* 2010;33(5):469-477.


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