MEDICAL BIOCHEMICAL GENETICS
CLINICAL CORE
SEMINAR SERIES

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Carnitine and Fatty Acid Oxidation

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21 July 2023

DISCLOSURES

Company	Financial relationship type
Aeglea	Clinical Trial Support
Alnylam	Advisory Board
Amicus Therapeutics	Clinical Trial support, Advisory Board
ACI Clinical	Data Safety and Monitoring Chair (Applied Ther, Taysha)
Audentes/Astellas	Clinical Trial Support
AvroBio	Clinical Trial Support
BioMarin	Clinical Trial Support, Advisory Board, Travel support
BridgeBio/CoA Ther	Advisory Board
Censa/PTC Ther.	Clinical Trial Support, Advisory Board
Chiesi/Protalix	Clinical Trial Support, Advisory Board
CTI-Clinical Trial	Data Safety and Monitoring Board (Vtesse)
Genzyme/Sanofi	Clinical Trial Support, Advisory Board
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Homology	Clinical Trial Support
Horizon Pharma	Clinical Trial Support, Advisory Board
Jaguar Gene Therapy	Advisory Board
Leadiant Biosciences	Advisory Board
Moderna	Clinical Trial Support, Advisory Board
Nestle' Pharma	Clinical Trials, Advisory Board
Pfizer	Clinical Trial Support
Recordati	Advisory Board
Reneo	Clinical Trial Support, Advisory Board
Retrophin	Clinical Trial Support
Shire/Takeda	Clinical Trial Support, Advisory Board
Stealth Therapeutics	Clinical Trial Support
Synlogic	Clinical trial support, Consultant
Ultragenix	Clinical Trial Support, Advisory Board

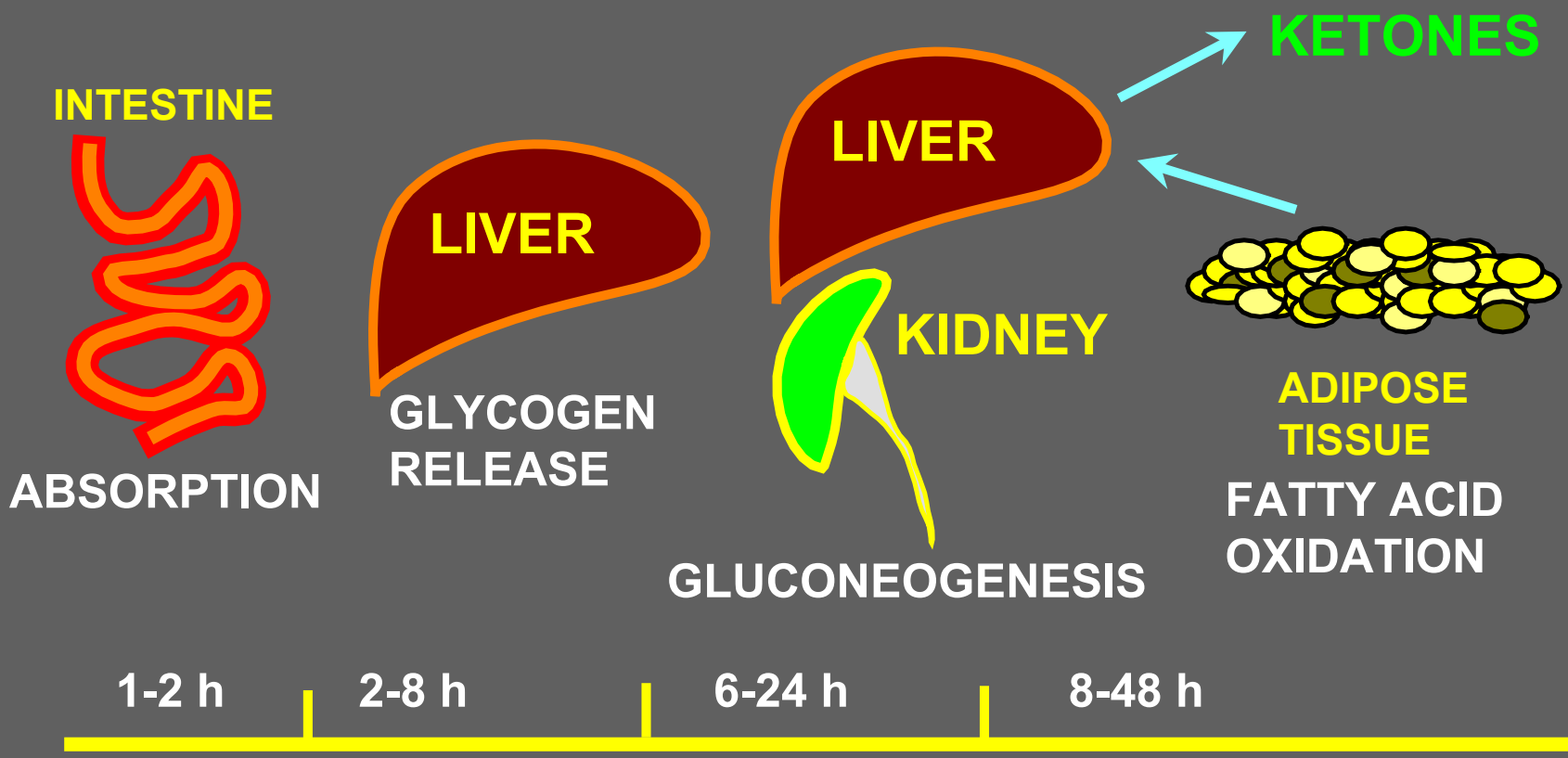
Conflict of interest: managed by the University of Utah Institutional Review Board.

DISORDERS OF FATTY ACID OXIDATION

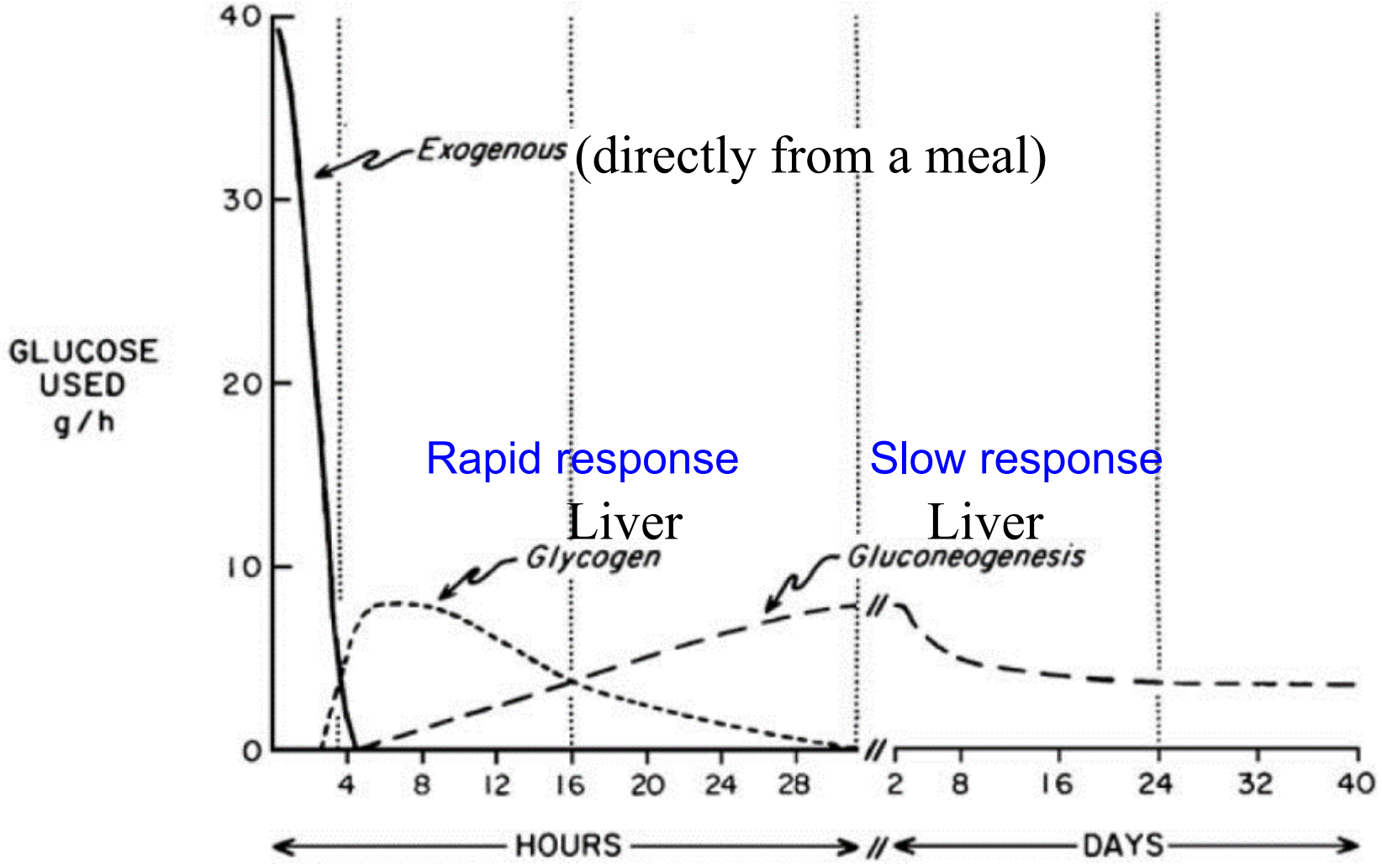
Disorders of fatty acid oxidation

Objectives:
Define role of fatty acid oxidation in fasting
Recognize the role of carnitine in fatty acid oxidation
Define principles of treatment of fatty acid oxidation defects

GLUCOSE HOMEOSTASIS



Phases of blood glucose regulation



Major fuel of the brain:

Glucose

Glucose, Ketone bodies

Ketone bodies Glucose,

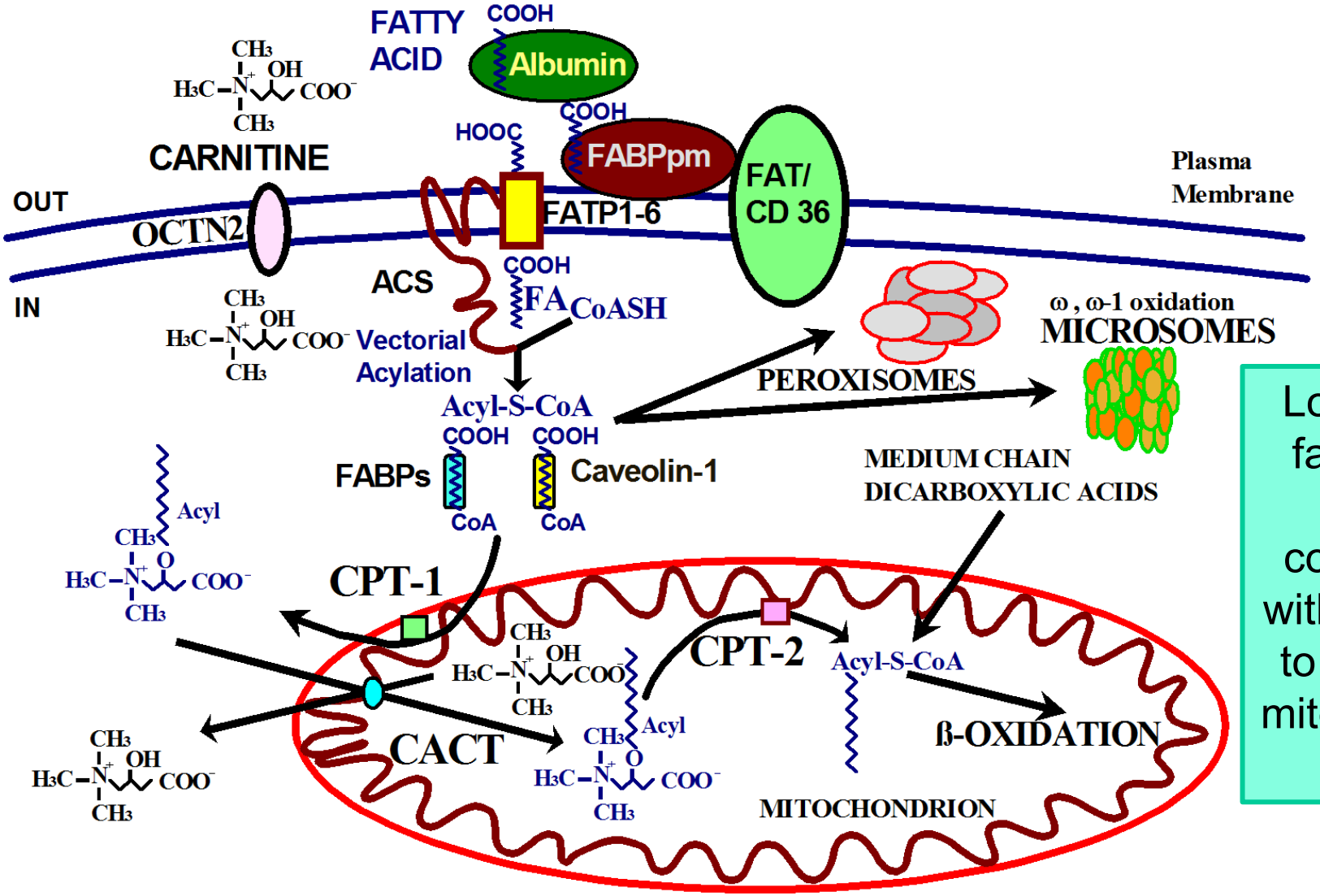
Cahill (2006) Annu. Rev. Nutr. 26:1-22.

Disorders of the carnitine cycle and of fatty acid oxidation

Fatty acid oxidation plays a major role in energy production during fasting. It requires at least 20 individual steps, some of which catalyzed by enzymes with overlapping chain-length specificities.
Carnitine carries fatty acids inside mitochondria and the beta oxidation cycle can extract energy from them.
All known fatty acid oxidation defects are transmitted as autosomal recessive traits.

Longo N, et al. Biochim Biophys Acta. 2016;1863(10):2422-35

THE CARNITINE CYCLE IN FATTY ACID OXIDATION



Long-chain fatty acids are conjugated with carnitine to enter the mitochondrial matrix

Modified from: Longo N, Amat di San Filippo C, Pasquali M (2006) Disorders of carnitine transport and the carnitine cycle. **Am J Med Genet C Semin Med Genet** 142(2):77-85

β-OXIDATION

Acyl-CoA

Acyl-CoA dehydrogenases

FAD

$FADH_2$

2,3-Enoyl-CoA

Hydratases

H_2O

L-3-hydroxyacyl-CoA

Hydroxyacyl-CoA dehydrogenases

NAD

$NADH_2$

3-Ketoacyl-CoA

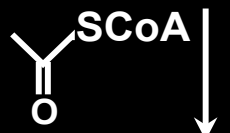
Thiolases

HSCoA

Acyl-CoA + Acetyl-CoA ⟶ TCA cycle

muscle

(n-2)



liver

Recycles

Ketogenesis

VLCAD: C14-C20
LCAD: C12-C18
MCAD: C4-C12
SCAD: C4-C6

TFP C12-C18
Crotonase C4>C14

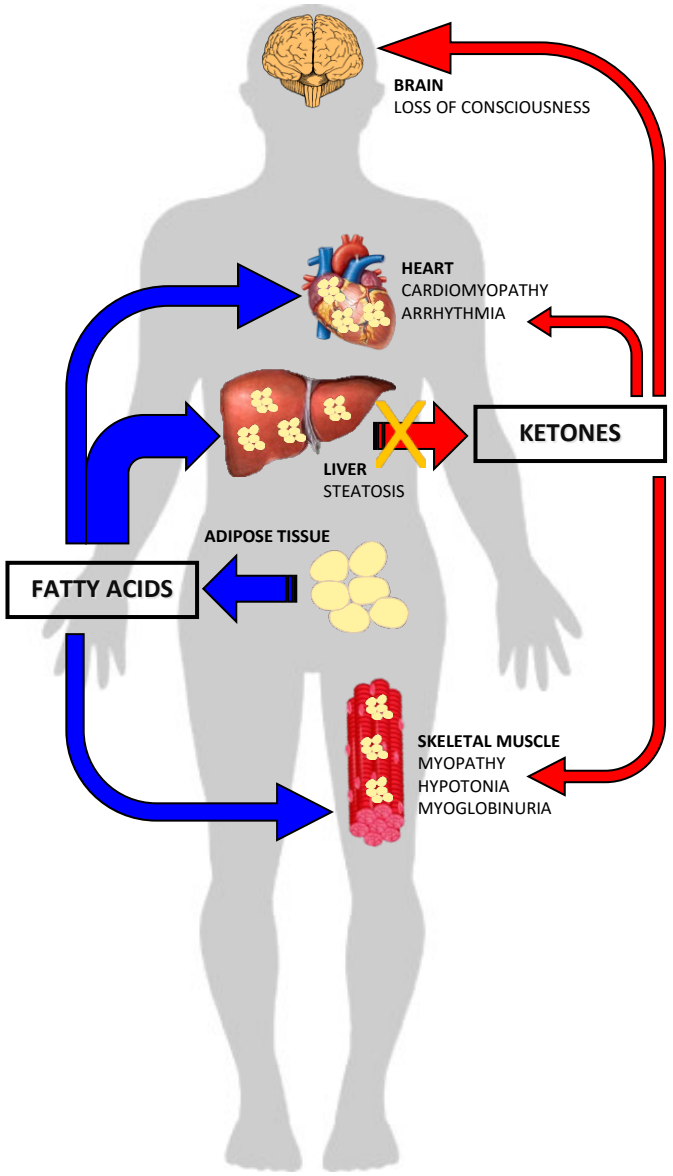
LCHAD (TFP): C12-C18
SCHAD: C4>C16

TFP C6-C16
MKAT C4-C12
β ketothiolase C4

Beta oxidation shortens long-chain fatty acids by 2 carbons at a time, generating energy through the Krebs cycle or ketones in the liver

Pasquali M, Longo N. Newborn Screening and Inborn Errors of Metabolism. Chapter 70. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. St. Louis: Saunders, 2017.

Fatty acid oxidation



During fasting, fatty acids are released from the adipose tissue and used for energy production. The liver partially oxidizes fatty acids to produce acetylCoA. Two molecules of acetylCoA combine together forming ketones that are released by the liver. Ketones can be utilized instead of glucose to produce energy by all organs in the body. The heart and skeletal muscle can fully utilize fatty acids with production of CO_2 and water.

In fatty acid oxidation disorders, ketones cannot be produced by the liver causing excessive glucose utilization (hypoketotic hypoglycemia), the muscle and the heart can suffer from lack of energy (rhabdomyolysis, cardiomyopathy, cardiac arrhythmia), the brain will be energy-deprived (loss of consciousness) not having glucose or ketones.

Modified from: ***Nicola Longo, Marta Frigeni, Marzia Pasquali, Carnitine transport and fatty acid oxidation, BBA - Molecular Cell Research (2016), doi: 10.1016/j.bbamcr.2016.01.023.***

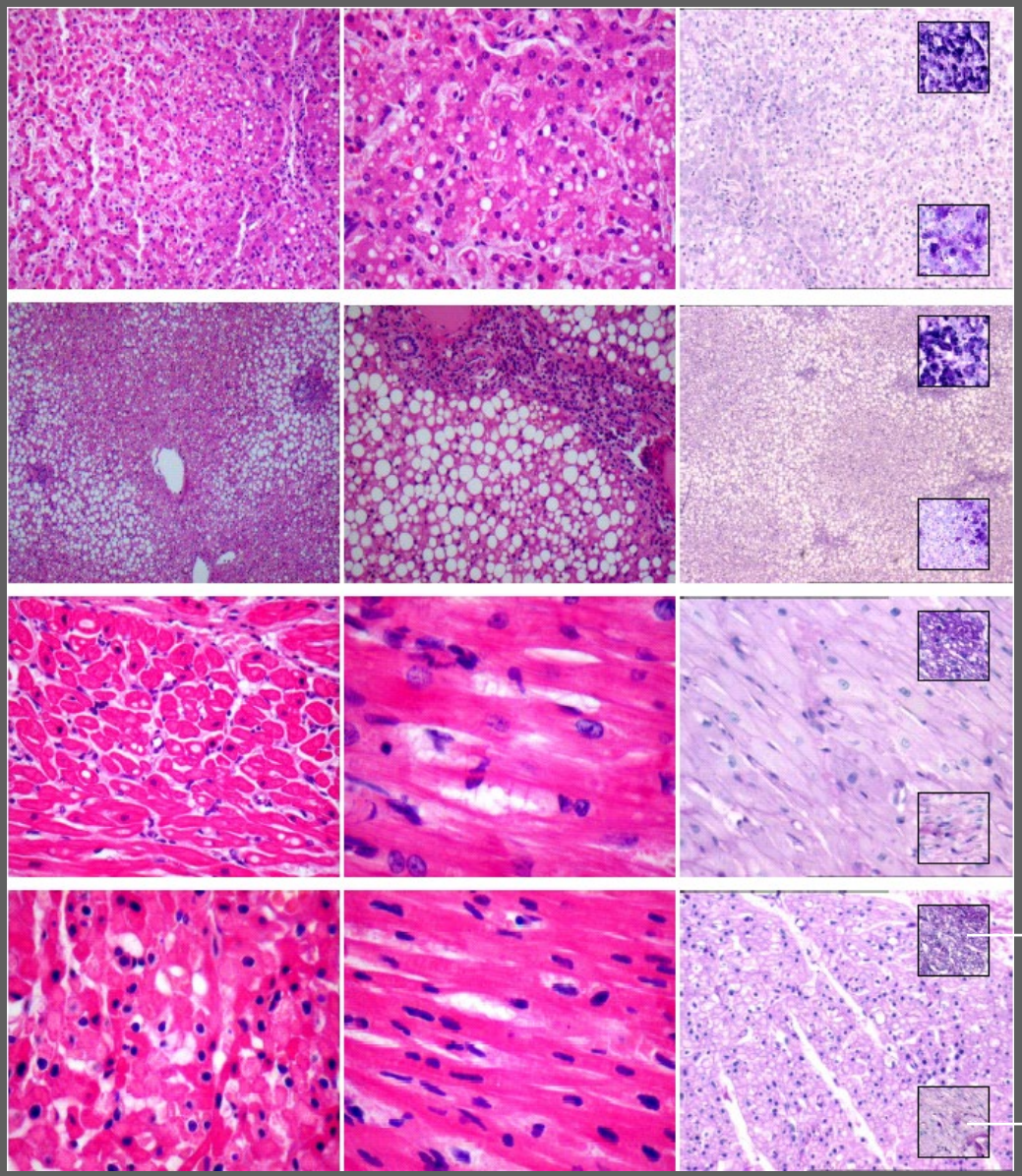
PATHOLOGY IN FATTY ACID OXIDATION DEFECTS

LIVER

Lipid deposition in peripheral areas of lobules

HEART

Focal lipid deposition exp. in subendocardium. Fiber/nuclei size variability (hypertrophy)



Exhaustion of glycogen reserve

control

Control calory-deprived

Hematoxylin-eosin

PAS

Modified from: Melegh et al. (2004) Am J Med Genet A. 2004 Dec 1;131(2):121-6.

TRIGGERS OF FATTY ACID OXIDATION DISORDERS

Most fatty acid oxidation defects are episodic and clinically silent when fat is not utilized.

Triggering conditions include fever, infections, gastroenteritis, reduced caloric intake.

Therefore children present shortly after birth (initiation of breastfeeding) or at any age during an illness causing catabolism.

FATTY ACID OXIDATION DEFECTS

Cause: Deficiency of one of more than 20 enzymes/transporters are involved in FAO. They are all autosomal recessive

Epidemiology: Most frequent is MCAD deficiency (1:10,000)
All others are much rare (1:30,000-1:1,000,000)

Pathogenesis: Accumulation of fat and toxic metabolites, lack of energy, CoA depletion, cell death. On autopsy, fat infiltration of all tissues.

Presentation: Fasting-induced hypoketotic hypoglycemia, liver failure, hyperammonemia (Reye syndrome), cardiomyopathy, myopathy, hypotonia, neuropathy, arrhythmia, sudden death, rhabdomyolysis

Diagnosis: Plasma carnitine and acylcarnitine profile, urine organic acids during acute attack, free fatty acids, DNA studies, in vitro probes, fibroblast enzyme/transport assay.

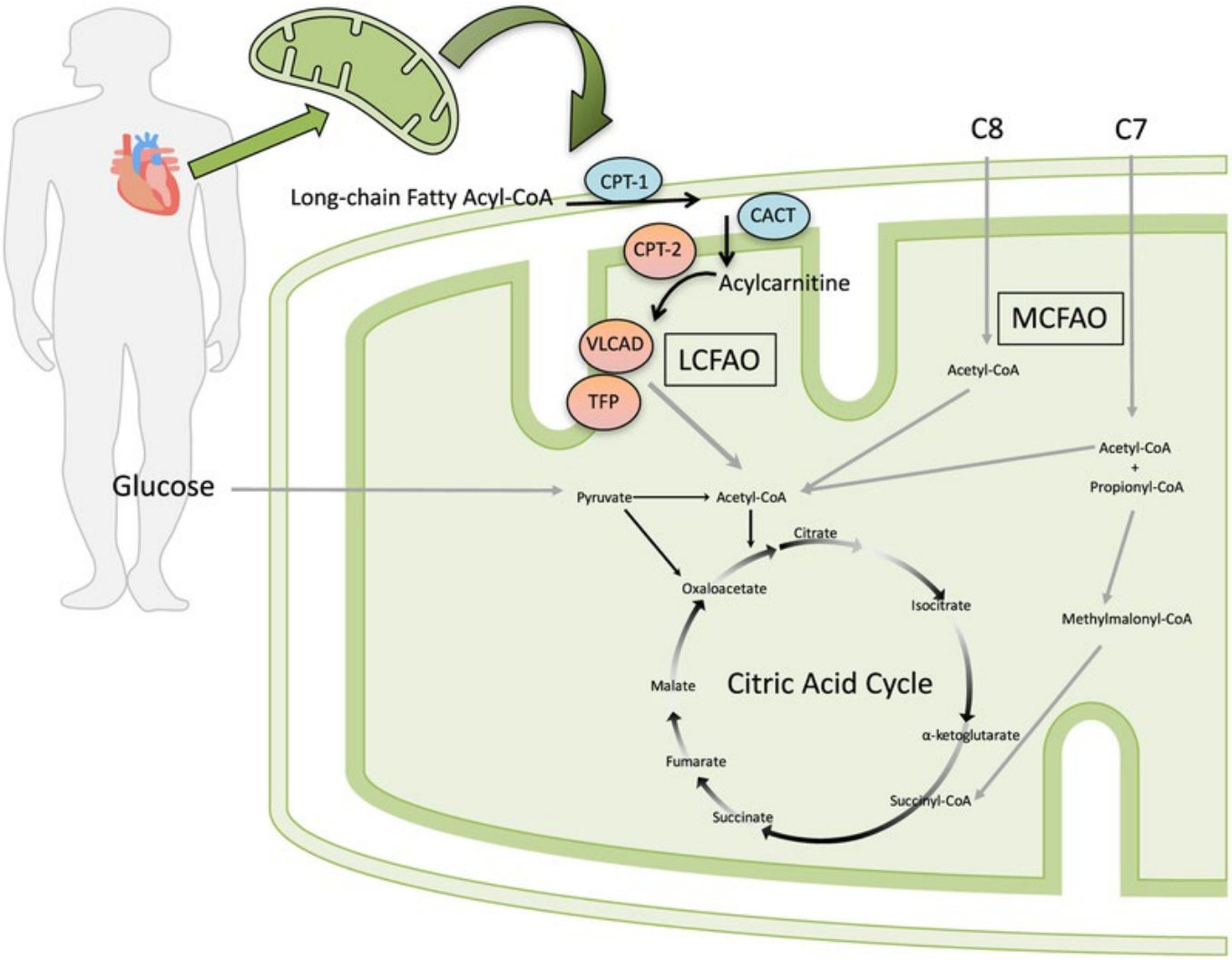
Therapy: Fasting avoidance, prompt treatment of infections, low fat diet, MCT oil/triheptanoin (in some), carnitine supplementation, essential fatty acids, ketones

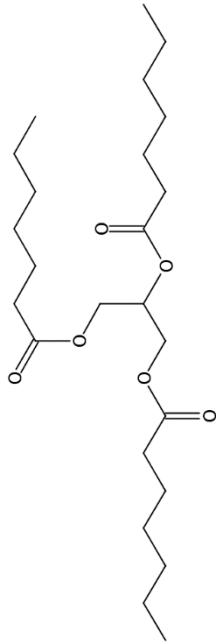
MCT, medium-chain triglyceride.

Pasquali M, Longo N. Newborn Screening and Inborn Errors of Metabolism. Chapter 70. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. St. Louis: Saunders, 2017.

Merritt JL 2nd, MacLeod E, Jurecka A, Hainline B. Clinical manifestations and management of fatty acid oxidation disorders. Rev Endocr Metab Disord. 2020 Dec;21(4):479-493. doi: 10.1007/s11154-020-09568-3. PMID: 32654032

MEDIUM CHAIN TRIGLYCERIDES (C8) AND TRIHEPTANOIN (C7) IN LONG-CHAIN FATTY AXID OXIDATION DISORDERS





Gillingham MB, Heitner SB, Martin J, Rose S, Goldstein A, El-Gharbawy AH, Deward S, Lasarev MR, Pollaro J, DeLany JP, Burchill LJ, Goodpaster B, Shoemaker J, Matern D, Harding CO, Vockley J. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. J Inherit Metab Dis. 2017 Nov;40(6):831-843. doi: 10.1007/s10545-017-0085-8. Epub 2017 Sep 4. PMID: 28871440

ACYLCARNITINES

Acylcarnitines are usually indicated by the letter "C" followed by the number of carbon atoms in the acid esterified with carnitine				
C0	Free carnitine		C6	Hexanoyl-
C2	Acetyl-		C8	Octanoyl-
C3	Propionyl-		C10	Decanoyl-
C4	Isobutyryl/butyryl-		C10:1	Decenoyl-
C5	Isovaleryl/2-methylbutyryl-		C14	Tetradecanoyl (myristoyl)-
C5-OH	3-Hydroxyisovaleryl/2-methyl-3-hydroxybutyryl-		C14:1	Tetradecenoyl-
C3DC	Malonyl-		C16	Hexadecanoyl (palmitoyl)-
C5DC	Glutaryl-		C16-OH	3-Hydroxyhexadecanoyl-

EMERGENCY PROTOCOL FOR PATIENTS WITH FATTY ACID OXIDATION DEFECTS

If unable to eat, give IV Fluids to provide calories:

D10 (10% glucose) + 75-150 mEq/L NaCl + 20 mEq/L KCl at 150 ml/kg per day

Labs: Electrolytes, liver function tests, CK (Creatine Kinase), plasma ammonia, urine analysis.

Labs/Imaging to identify cause of problems, mostly infections (cultures/X-Rays)

Start enteral feeds as soon as tolerated

CHILDHOOD HYPOGLYCEMIA

Eight months old boy with frequent infections and vomiting admitted for low oral intake and lethargy.
Exam: hepatomegaly, lethargy
Labs: nonketotic hypoglycemia (glucose 35 mg/dL), hyperammonemia, and elevated liver function tests (Reye syndrome). Urine organic acids; mild dicarboxylic aciduria, Normal plasma amino acids.
Therapy: he improved with intravenous fluids and glucose.

Table I: Plasma carnitine

	Total carnitine µM	Free carnitine µM	Acyl-carnitine µM
Proband	1	1	0
Mother	21	16	5
Father	24	20	4
Controls	30-70	24-56	6-14

Scaglia et al (1998)
Genet Med 1: 34-39

Carnitine transporter deficiency (Primary carnitine deficiency OMIM 212140)

- **Frequency** 1:142,336 (USA), 1:127,678 (Utah), 1:300 (Faroes)
- **Cause**: Carnitine transporter (OCTN2) defect (*SLC22A5* gene)
- **Pathogenesis**: Loss of carnitine in urine reduces availability of carnitine in liver, muscle and heart, impairing FAO
- **Presentation**: Hepatic encephalopathy, hypoglycemia, cardiomyopathy in childhood, arrhythmia and/or exertional rhabdomyolysis in adults, sudden death in children and adults
- **Diagnosis**: very low plasma carnitine (usually C0<5 mM, can be higher in newborns), decreased urinary carnitine reabsorption, confirmed by DNA testing or transport studies in fibroblasts. Can be detected by newborn screening.
- **Therapy**: Carnitine 100 mg/kg up to 3 g per day PO divided into 3-4 daily doses
- **Monitoring:** Plasma carnitine free and total
- **Prognosis**: Excellent (with treatment)

Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. Biochim Biophys Acta. 2016; 1863(10):2422-35. PMID: 26828774

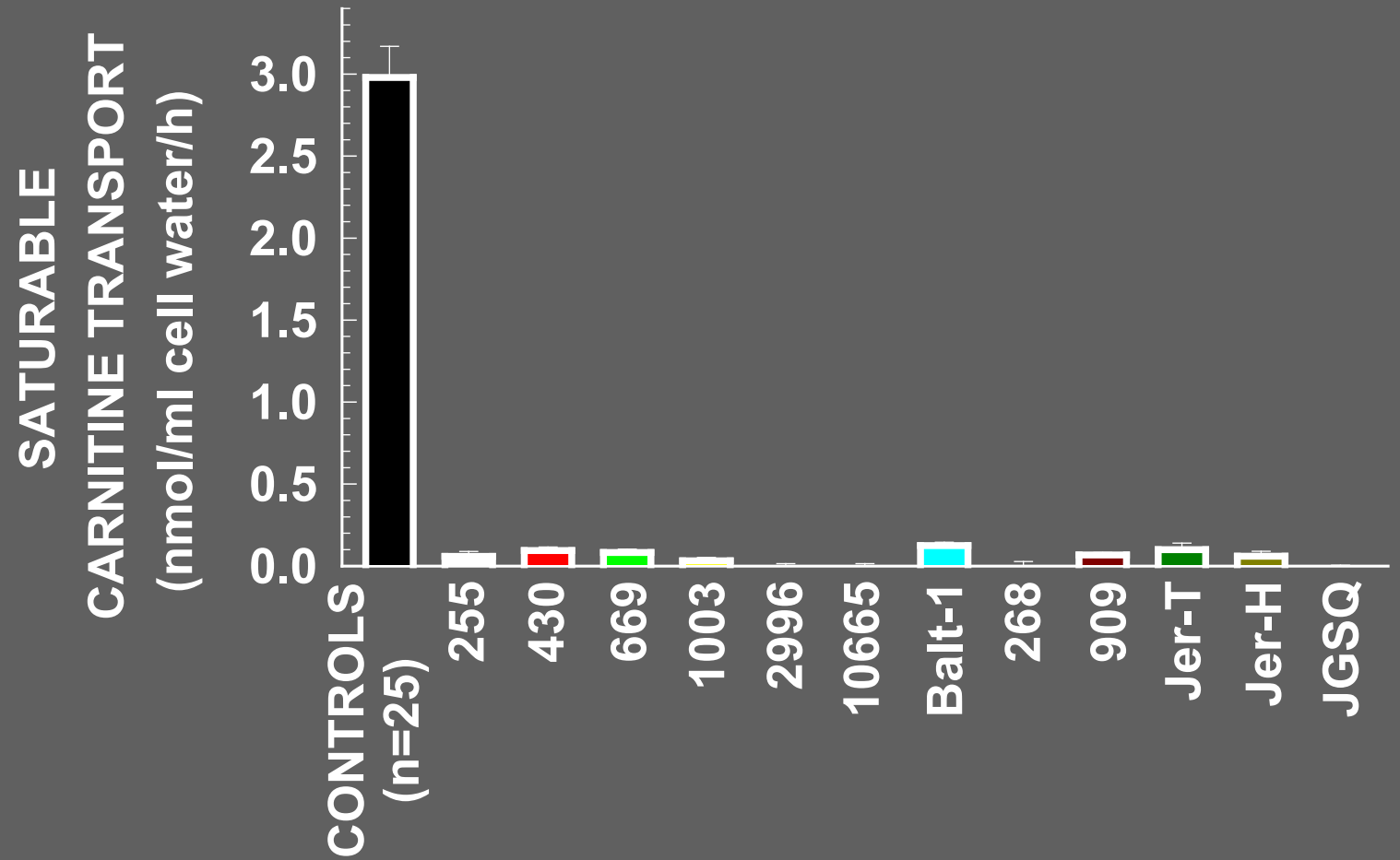
LOW CARNITINE LEVELS IN PRIMARY CARNITINE DEFICIENCY

Free and total carnitine are reduced and remain low with treatment. Goal is to keep free carnitine >15 μmol/L (*SLC22A5* gene: homozygous p.Arg227His).

Carnitine, Free & Total (umol/L)

	Ref. Range	04/07/15 13:23*	03/06/15 15:55*	02/09/15 17:40*	08/04/14 17:20*	02/03/14 12:48	08/03/13 12:39	03/11/13 15:04	02/25/13 12:18	02/13/13 16:55
Carnitine, Free	25-55	24 L	10 L	11 L	9 L	19 L	33	39	9 L	3 L
Carnitine, Total	35-90	35	17 L	15 L	19 L	27 L	61	65	12 L	10 L
Carnitine, Esterified	4-36	11	7	4	10	8	28 H	26 H	3 L	7 L
Carnitine Ester/Free (Ratio)	0.1-0.8	0.5	0.7	0.4	1.1 H	0.4	0.8	0.7	0.3	0.4

DEFECTIVE CARNITINE TRANSPORT IN FIBROBLASTS FROM PATIENTS WITH PRIMARY CARNITINE DEFICIENCY

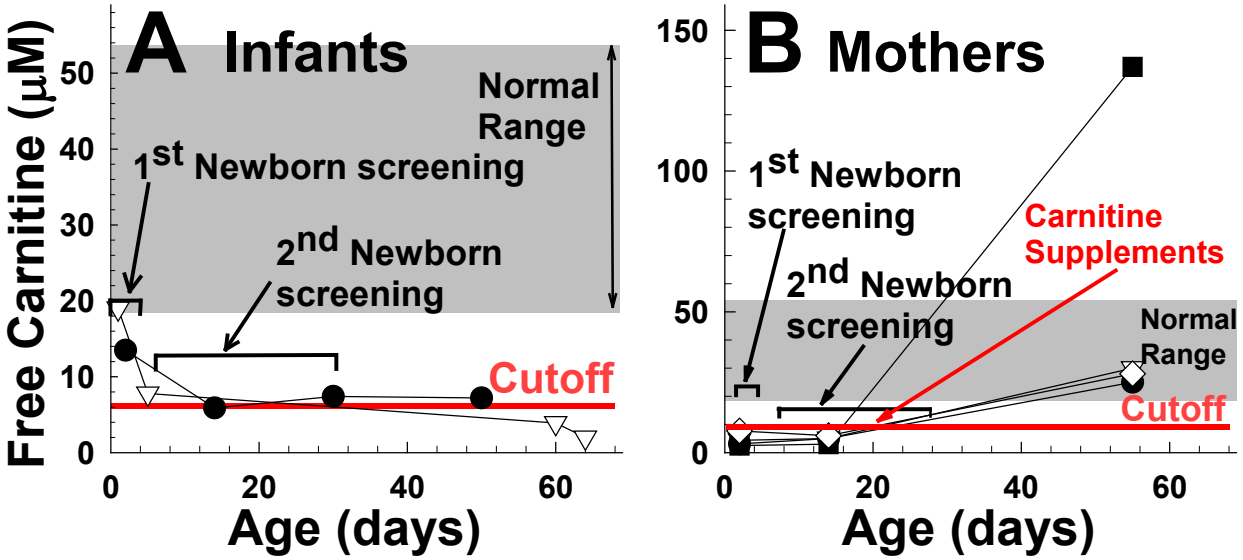


Wang et at (1999) *Proc Natl Acad Sci USA* 96: 2356-2360
Wang et al (2001) *Genet Med* 3: 387-392

Carnitine Transporter Deficiency: Newborn Screening

Carnitine is transferred from the mother to the fetus during pregnancy. Babies can have normal plasma carnitine levels at birth that decline with time.

In maternal primary carnitine deficiency, carnitine levels in the baby are very low at birth. Most mothers are asymptomatic, but at risk of sudden death.



Pasquali M, Longo N. Response to Chen et Al.: carnitine uptake defect (primary carnitine deficiency): risk in genotype-phenotype correlation. Hum Mutat. 2013 Apr;34(4):656

A 5' UTR VARIANT ACCOUNTS FOR ABOUT 20% OF PATHOGENIC VARIANTS

This variant is missed by sequencing exons only (exome) and explains why the functional assay was superior to sequencing for patient identification.

(a) The c.-149G>A variant introduces a novel translation initiation site. The mutant protein is predicted to result in a premature termination codon in exon 1. (b) Comparison of the sequence context surrounding the wild-type and mutant AUG (created by c.-149G>A variant) for the presence of a KOZAK sequence

Ferdinandusse S, Te Brinke H, Ruiter JPN, Haasjes J, Oostheim W, van Lenthe H, IJlst L, Ebberink MS, Wanders RJA, Vaz FM, Waterham HR. A mutation creating an upstream translation initiation codon in SLC22A5 5'UTR is a frequent cause of primary carnitine deficiency. Hum Mutat. 2019 Oct;40(10):1899-1904. doi: 10.1002/humu.23839. Epub 2019 Jul 3. PMID: 31187905

SUDDEN DEATH IN PRIMARY CARNITINE DEFICIENCY

In the Faroe Islands, children and young adults died from cardiac arrhythmia after presenting with altered mental status, psychotic behavior and stupor. In most cases, the episode was triggered by the use of pivalic acid containing antibiotics.

Long or short QT syndrome and cardiac arrhythmia can be seen in pregnancy in patients with the p.N32S mutation. This resolved with carnitine supplements.

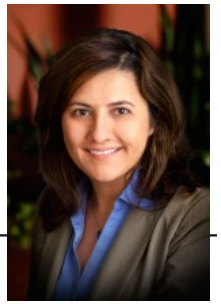
Rasmussen J, Dunø M, Lund AM, Steuerwald U, Hansen SH, Joensen HD, Køber L, Nielsen OW. Increased risk of sudden death in untreated primary carnitine deficiency. J Inherit Metab Dis. 2020 Mar;43(2):290-296. doi: 10.1002/jimd.12158. Epub 2019 Dec 15. PMID: 31373028

J Inherit Metab Dis (2013) 36:35–41
DOI 10.1007/s10545-012-9488-8

ORIGINAL ARTICLE

Primary carnitine deficiency and pivalic acid exposure causing encephalopathy and fatal cardiac events

Jan Rasmussen • Olav W. Nielsen • Allan M. Lund • Lars Køber • Høgni Djurhuus



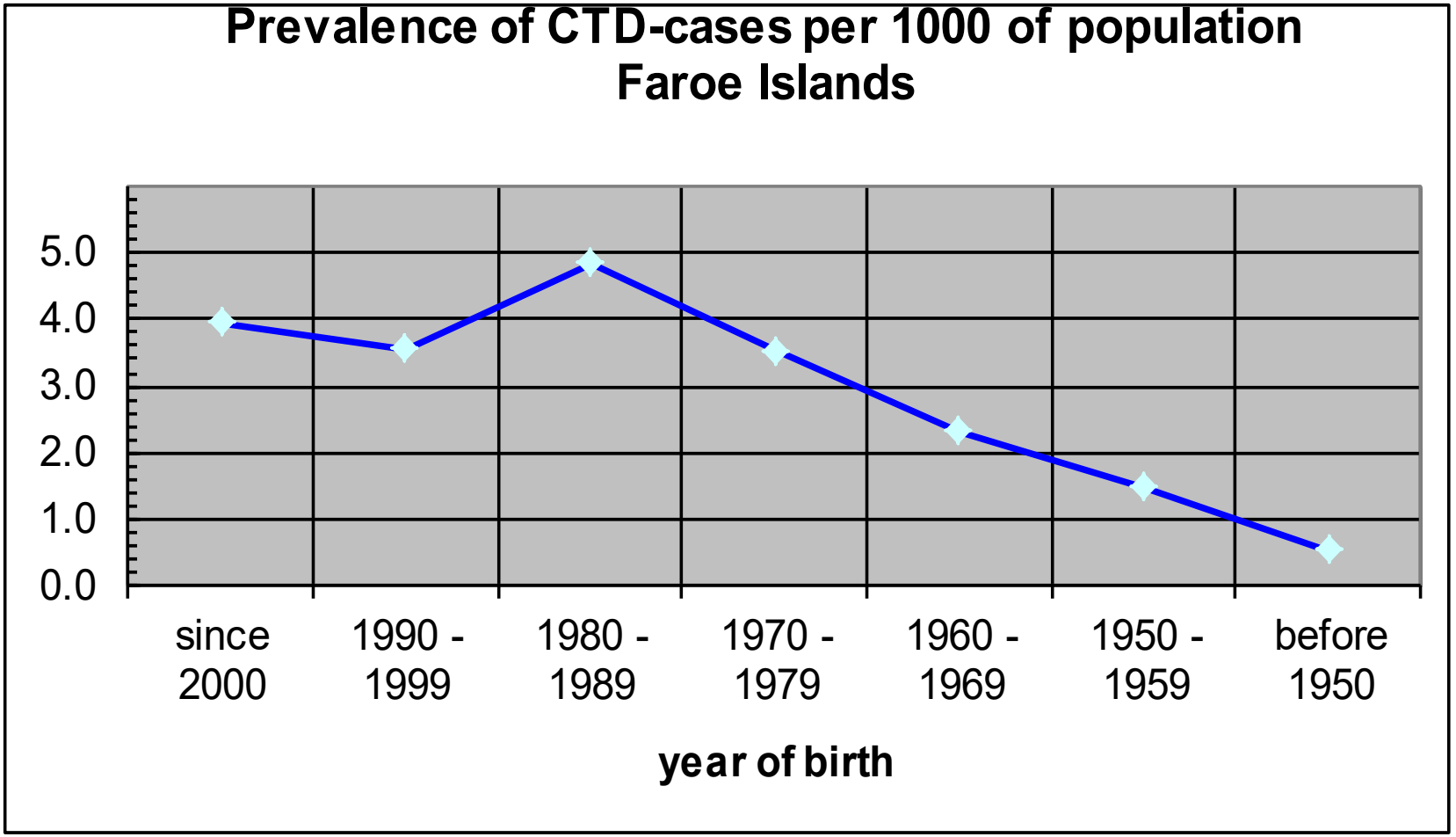
JIMD Reports
DOI 10.1007/8904_2011_52

CASE REPORT

Primary Carnitine Deficiency Presents Atypically with Long QT Syndrome: A Case Report

Irene De Biase • Neena Lorenzana Champaigne • Richard Schroer • Laura Malinda Pollard • Nicola Longo • Tim Wood

Untreated Carnitine Transporter Deficiency: shortened life-expectancy



Screening-Labor Hannover

Courtesy Dr. Ulrike Steuerwald

ACMG
American College of Medical Genetics and Genomics
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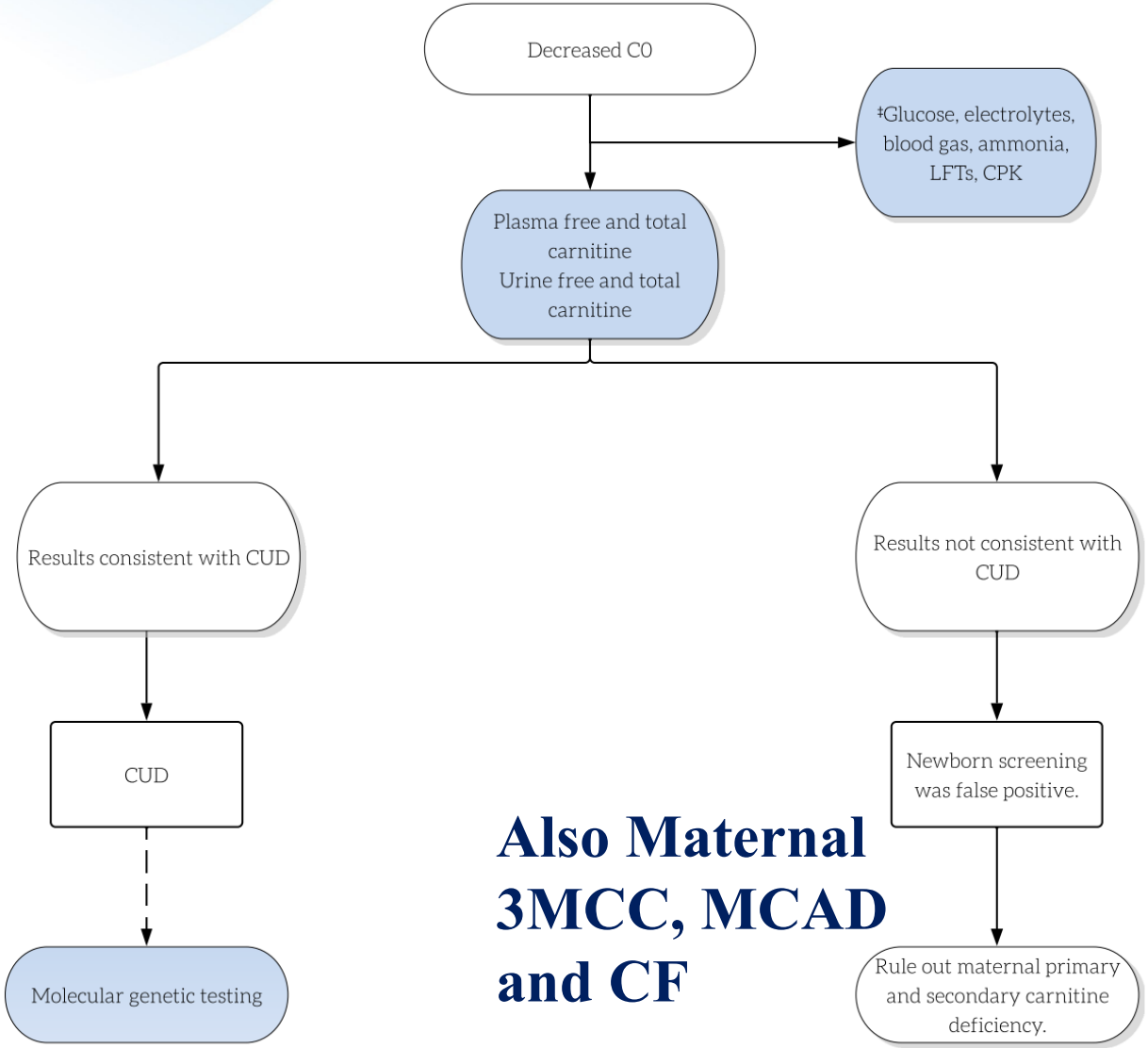
Carnitine Uptake Defect: Decreased C0 (Free Carnitine)



Also Maternal 3MCC, MCAD and CF

Carnitine Uptake Defect

DNA testing: common pathogenic (about 20%) variant 5' to the ATG initiation site is missed by current sequencing

Ferdinandusse S, Te Brinke H, Ruiter JPN, Haasjes J, Oostheim W, van Lenthe H, IJlst L, Ebberink MS, Wanders RJA, Vaz FM, Waterham HR. A mutation creating an upstream translation initiation codon in SLC22A5 5'UTR is a frequent cause of primary carnitine deficiency. Hum Mutat. 2019 Oct;40(10):1899-1904. doi: 10.1002/humu.23839. Epub 2019 Jul 3. PMID: 31187905

Carnitine Palmitoyl Transferase-1A (CPT-1A) deficiency OMIM 255120

Frequency very rare, except in the Alaskan population (1.3:1,000, milder variant)

Cause/Pathogenesis: Deficiency of CPT-1A (liver) impairs synthesis of long-chain acylcarnitine preventing transfer of long-chain fatty acid inside mitochondria.

Presentation: fasting-induced hepatic encephalopathy, hypoglycemia, liver failure, failure to thrive

Diagnosis: Elevated carnitine levels with low C16, C18 (Increased C0/(C16+C18) in blood spots. Free carnitine can be normal or high in plasma: blood is more sensitive. Confirmed by DNA testing. Can be detected by newborn screening.

Therapy: Avoidance of fasting, low-fat diet in which most derive from medium-chain triglycerides (C6-C10 fatty acids) or triheptanoin, cornstarch

Monitoring: liver function tests, glucose, HbA1c

Prognosis: not many data, better with treatment

Bennett MJ, Santani AB. Carnitine Palmitoyltransferase 1A Deficiency. 2005 Jul 27 [Updated 2016 Mar 17]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1527/

Carnitine Palmitoyl Transferase-1A (CPT1A) deficiency (OMIM 255120)

Severe (Classic) cases identified by newborn screening:

***CPT1A* gene: c.222C>A (p.Y74X)/c.222C>A (p.Y74X). C0: 240 on first screen, C0/(C16+C18)=574 (normal <100). 5.5 yo. History of failure to thrive, developmental delays, elevated transaminases while breastfeeding. Formula with MCT oil improved growth and development, normalized liver enzymes. Still mildly behind in development.**

***CPT1A* gene: p.A275T/p.R508X. C0: unknown on first screen (patient from other state). 8 yo. Serum C0= 51-61, total 56-72, very low C16-C18, usually reported as normal in plasma. AST/ALT occasionally elevated. Complications: Seizures, ADHD, unclear compliance with therapy.**

CPT1A DEFICIENCY

Carnitine levels can be normal in plasma, but remain high in whole blood.

Ratio esterified/free carnitine is in the low-normal range.

Carnitine, Free & Total (umol/L)

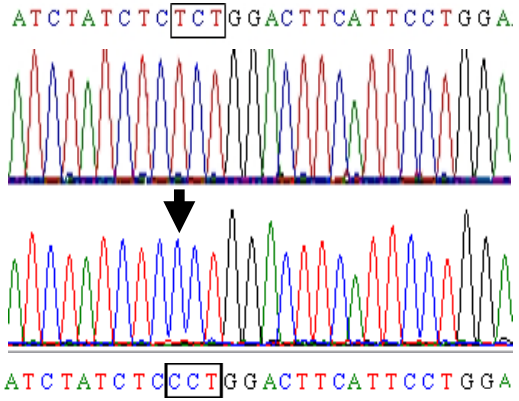
	Ref. Range	02/23/15 14:45*	08/04/14 11:17*	03/03/14 13:30	08/26/13 14:30
Carnitine, Free	22-63	48	61	56	51
Carnitine, Total	31-78	57	72	69	56
Carnitine, Esterified	3-38	9	11	13	5
Carnitine Ester/Free (Ratio)	0.1-0.9	0.2	0.2	0.2	0.1

Acylcarnitine Quantitation, (Plasma)

	Ref. Range	02/23/15 14:45*	08/04/14 11:17*	03/03/14 13:30	08/26/13 14:30
Interpretation:	umol/L	Normal	Normal	Normal	Normal
C2, Acetyl	3.74-16.56	7.53	8.44	6.73	4.94
C3, Propionyl	0.00-0.83	0.81	0.63	0.67	0.39
C4, Iso/Butyryl	0.00-0.45	0.24	0.27	0.34	0.15
C5, Isovaleryl/2Mebutyryl	0.00-0.30	0.18	0.12	0.14	0.10
C5-DC, Glutaryl	0.00-0.09	0.03	0.06	0.02	0.02
C6, Hexanoyl	0.00-0.12	0.05	0.00	0.05	0.05
C5-OH, 3-OH Isovaleryl	0.00-0.07	0.00	0.00	0.03	0.02
C8, Octanoyl	0.00-0.23	0.02	0.09	0.02	0.00
C8:1, Octenoyl	0.00-0.61	0.18	0.17	0.10	0.05
C10, Decanoyl	0.00-0.31	0.03	0.11	0.02	0.00
C10:1, Decenoyl	0.00-0.31	0.06	0.12	0.02	0.02
C12, Dodecanoyl	0.00-0.12	0.04	0.06	0.02	0.01
C12:1, Dodecenoyl	0.00-0.17	0.04	0.07	0.02	0.01
C12-OH, 3-OH Dodecanoyl	0.00-0.02	0.00	0.00	0.00	0.01
C14, Tetradecanoyl	0.00-0.05	0.01	0.01	0.01	0.00
C14:1, Tetradecenoyl	0.00-0.16	0.02	0.04	0.01	0.00
C14:2, Tetradecadienoyl	0.00-0.12	0.02	0.04	0.01	0.00
C14-OH, 3-OH-Tetradecanoyl	0.00-0.02	0.00	0.01	0.00	0.00
C14:1-OH, 3-OH-Tetradecenoyl	0.00-0.02	0.01	0.01	0.00	0.00
C16, Palmitoyl	0.00-0.10	0.00	0.01	0.00	0.00
C16:1, Palmitoleyl	0.00-0.04	0.00	0.01	0.00	0.00
C16-OH, 3-OH-Palmitoyl	0.00-0.01	0.00	0.00	0.00	0.00
C16:1-OH, 3-OH-Palmitoleyl	0.00-0.01	0.00	0.00	0.00	0.00
C18, Stearoyl	0.00-0.04	0.01	0.01	0.01	0.00
C18:1, Oleyl	0.00-0.17	0.01	0.01	0.00	0.00
C18:2, Linoleyl	0.00-0.10	0.00	0.01	0.00	0.00
C18-OH, 3-OH-Stearoyl	0.00-0.01	0.00	0.00	0.00	0.00
C18:1-OH, 3-OH-Oleyl	0.00-0.01	0.00	0.00	0.00	0.00

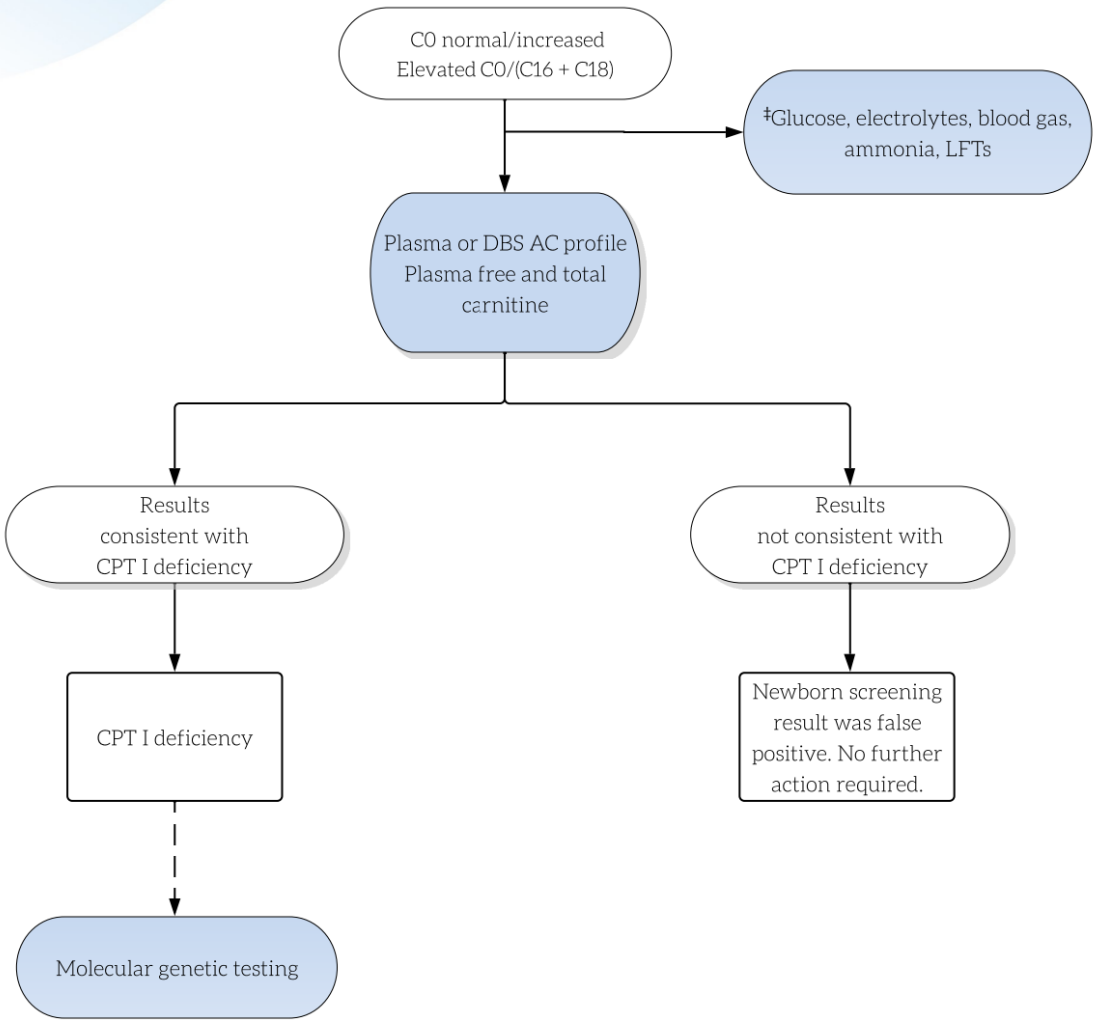
Carnitine Palmitoyl Transferase-1A (CPT-1A) deficiency (OMIM 255120)

Mild variants: Homozygous p.S34P (Marshall Islands).
Carnitine high only in whole blood, not in plasma. Unclear if milder forms in Alaskan natives (p.P479L) or Pacific Islanders (p.S34P) need treatment.
Might increase risk for respiratory infections, Possibly pancreatitis.



Collins SA, Sinclair G, McIntosh S, Bamforth F, Thompson R, Sobol I, Osborne G, Corriveau A, Santos M, Hanley B, Greenberg CR, Vallance H, Arbour L. Carnitine palmitoyltransferase 1A (CPT1A) P479L prevalence in live newborns in Yukon, Northwest Territories, and Nunavut. Mol Genet Metab. 2010 Oct-Nov;101(2-3):200-4. PMID: 20696606

Bernhardt I, Glamuzina E, Dowsett LK, Webster D, Knoll D, Carpenter K, Bennett MJ, Maeda M, Wilson C. Genotype-phenotype correlations in CPT1A deficiency detected by newborn screening in Pacific populations. JIMD Rep. 2022 Mar 26;63(4):322-329. doi: 10.1002/jmd2.12271. PMID: 35822099; PMCID: PMC9259392.



CPT1A Deficiency

Carnitine levels can be normal in plasma, but remain high in whole blood. Need DNA testing (Panel FAOD-DNA testing) to exclude CPT1A deficiency

Carnitine Palmitoyl Transferase-1B (OMIM 601987)

Expressed in the heart and skeletal muscle.

Homozygous deletion of this gene is embryonically lethal in mice Ji S, You Y, Kerner J, Hoppel CL, Schoeb TR, Chick WS, Hamm DA, Sharer JD, Wood PA. Homozygous carnitine palmitoyltransferase 1b (muscle isoform) deficiency is lethal in the mouse. Mol Genet Metab. 2008 Mar;93(3):314-22. Epub 2007 Nov 19. PMID: 18023382

Carnitine Palmitoyl Transferase-1C (OMIM 255120)

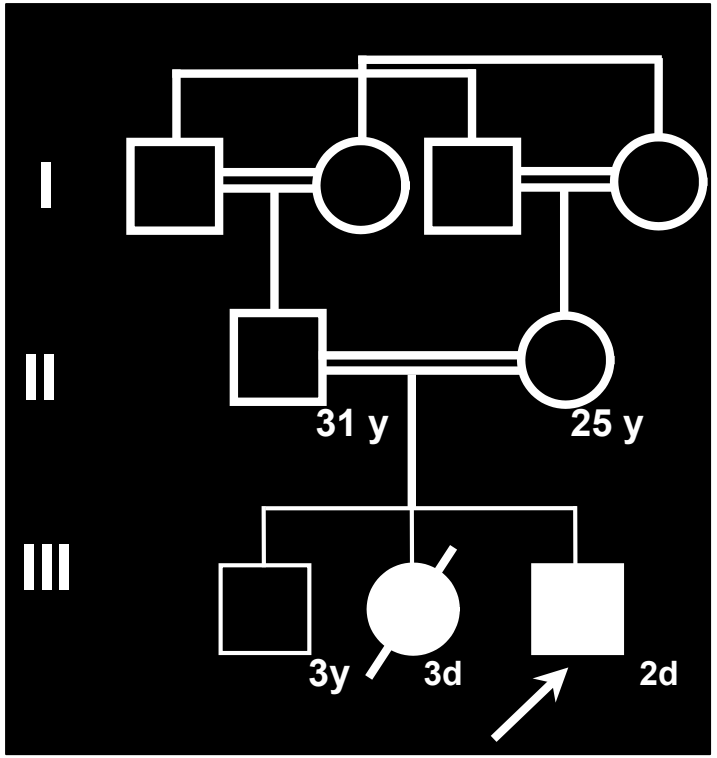
Localizes to the endoplasmic reticulum of neuronal cells and might serve as a sensor for fats.

A mutation (p.R37C) in this gene causes autosomal dominant spastic paraplegia-73, possibly by affecting lipid composition in the brain.

Rinaldi C, Schmidt T, Situ AJ, Johnson JO, Lee PR, Chen KL, Bott LC, Fadó R, Harmison GH, Parodi S, Grunseich C, Renvoisé B, Biesecker LG, De Michele G, Santorelli FM, Filla A, Stevanin G, Dürr A, Brice A, Casals N, Traynor BJ, Blackstone C, Ulmer TS, Fischbeck KH. Mutation in CPT1C Associated With Pure Autosomal Dominant Spastic Paraplegia. JAMA Neurol. 2015 May;72(5):561-70. doi: 10.1001/jamaneurol.2014.4769. Erratum in: JAMA Neurol. 2015 May;72(5):608. PMID: 25751282; PMCID: PMC5612424.

NEONATAL CARDIAC ARREST

Term infant developed hypothermia, desaturations, low blood pressure and hypoglycemia (glucose 7 mg/dL) at 18 h of age. Intubated, developed tachy- and bradycardia. Cardiac ECHO: cardiomyopathy. Had cardiac arrest requiring 5 min of chest compressions. Had mild hyperammonemia with increased liver function tests (ALT/AST up to 400) and mildly increased CPK (up to 350).
Started on IV glucose with stabilization.



ALT, alanine transaminase;
AST, aspartate transaminase;
CPK, creatine phosphokinase;
ECHO, echocardiogram.

Iacobazzi V, Pasquali M, Singh R, Matern D, Rinaldo P, Amat di San Filippo C, Palmieri F, Longo N. Response to therapy in carnitine/acylcarnitine translocase (CACT) deficiency due to a novel missense mutation. Am J Med Genet A. 2004 Apr 15;126A(2):150-5. doi: 10.1002/ajmg.a.20573.PMID: 15057979

Carnitine acylcarnitine translocase (CACT) deficiency OMIM 212138

Frequency: very rare

Cause/Pathogenesis: Deficiency of the acylcarnitine translocator impairs entry of long-chain acylcarnitines into mitochondria, resulting in the accumulation of long-chain acylcarnitine, long-chain fatty acids and defective energy production.

Presentation: Arrhythmia, cardiac arrest shortly after birth, hypoketotic hypoglycemia, cardiomyopathy

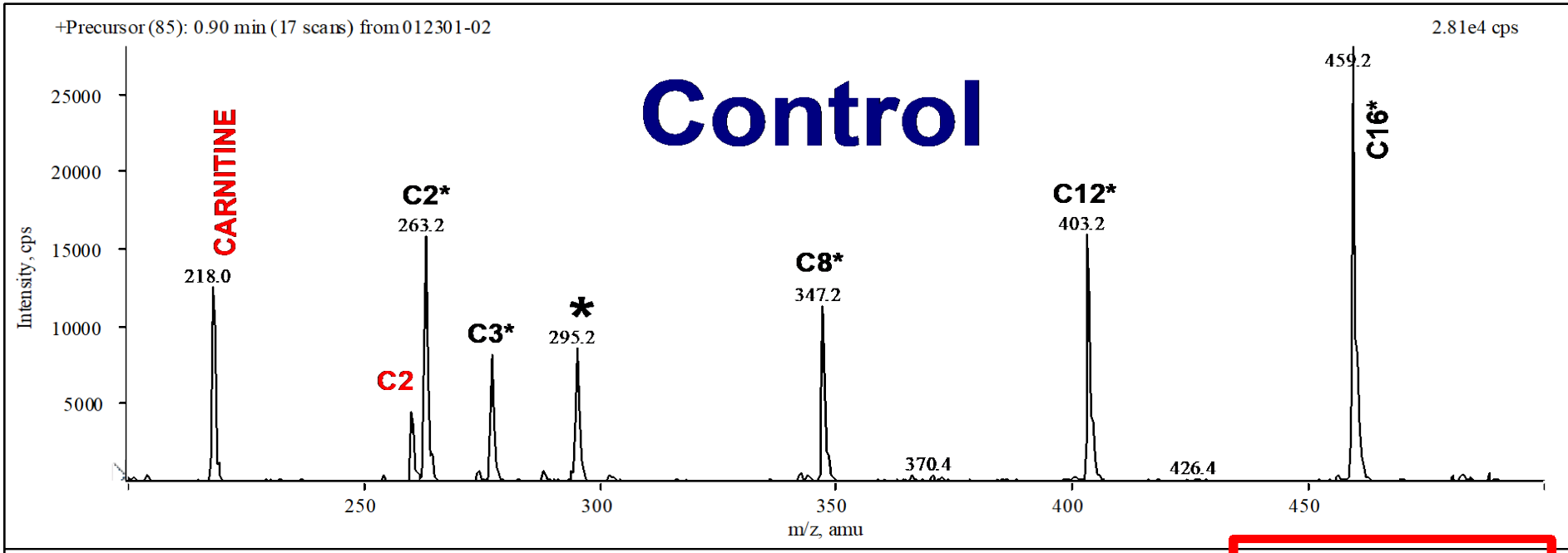
Diagnosis: increased C16, C18, C18:1, C18:2-carnitine, low C0 in plasma, abnormal organic acids (dicarboxylic aciduria), confirmed by DNA testing. Identified by newborn screening, but most infants present before newborn screening is obtained.

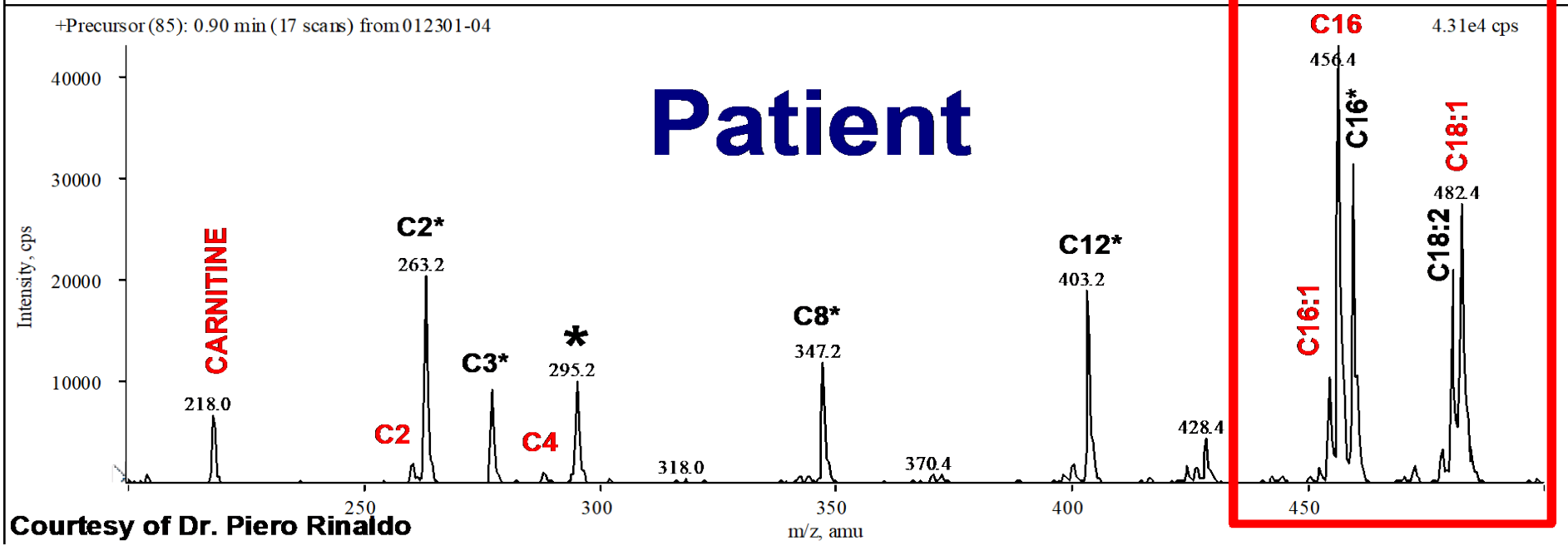
Therapy: fasting avoidance, low fat diet, MCT oil, triheptanoin, carnitine

Monitoring: acylcarnitine profile, carnitine F & T, CK, ALT, AST

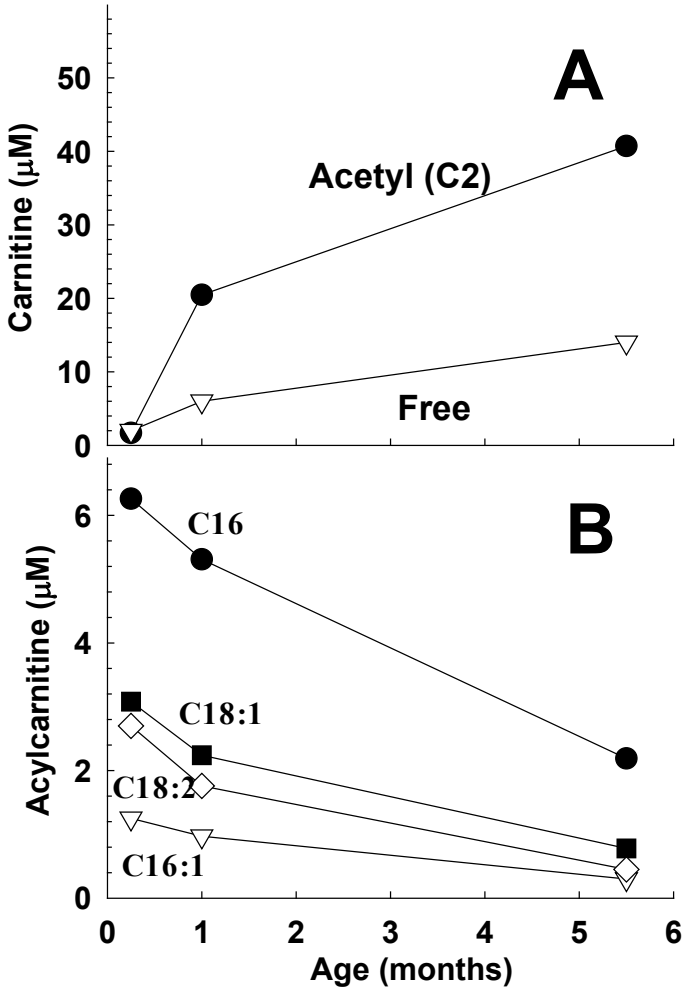
Prognosis: not always good, but there are teenagers with milder variants doing well with therapy.

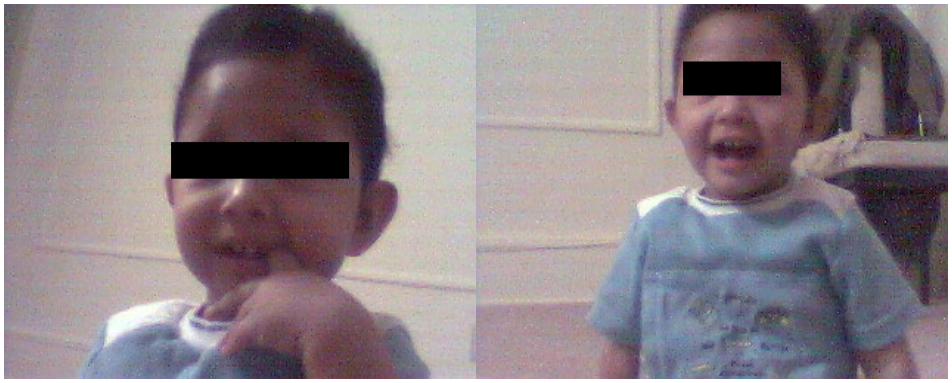
Plasma Acylcarnitine Profile



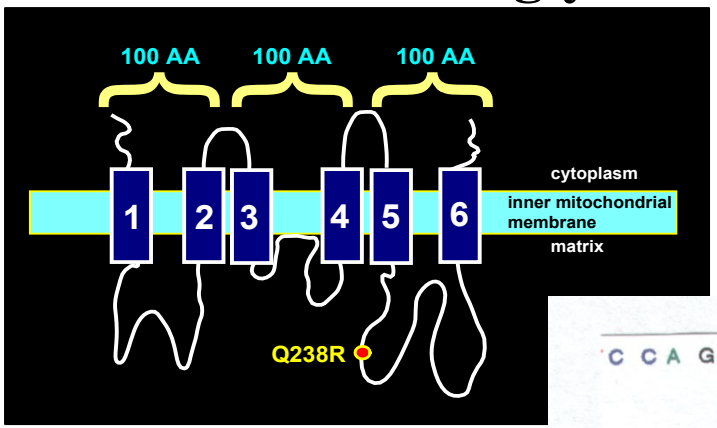


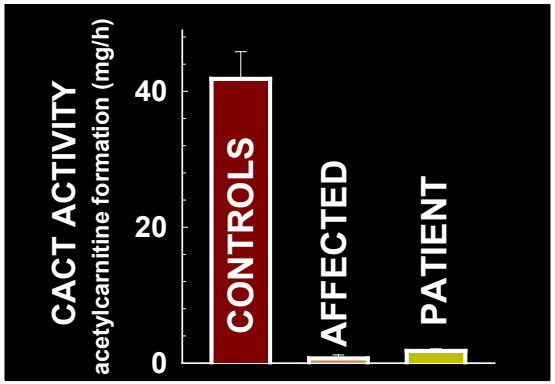
Courtesy of Dr. Piero Rinaldo



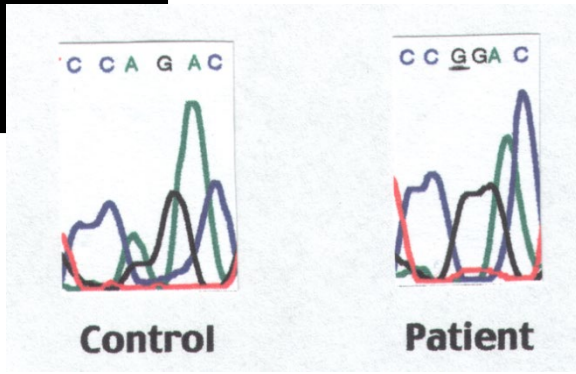


Progressive normalization of carnitine levels in a patient with CACT deficiency with carnitine and medium chain triglycerides.





Iacobazzi V, Pasquali M, Singh R, Matern D, Rinaldo P, Amat di San Filippo C, Palmieri F, Longo N. Response to therapy in carnitine/acylcarnitine translocase (CACT) deficiency due to a novel missense mutation. Am J Med Genet A. 2004 Apr 15;126A(2):150-5.



RHABDOMYOLYSIS

- 78-year-old man with persistent muscle cramps and myoglobinuria
- Not able to run or participate in sustained physical exercise since he was a teenager
- Was in the military during 2 wars but was assigned to an office
- Now, he has diabetes and develops muscle pain and myoglobinuria even without exercise (P50H/unk)

	Last Ref. Range	08/06/07 10:30	12/18/06 12:25	11/09/06 12:00
C2, Acetyl		13.53	* 10.23	* 7.21
C3, Propionyl		0.53	* 0.77	* 0.68
C4, Iso/Butyryl		0.27	* 0.24	* 0.27
C5, Isovaleryl/2Mebutyryl		0.16	* 0.15	* 0.10
C5-DC, Glutaryl		0.04	* 0.03	* 0.08
C6, Hexanoyl		0.09	* 0.10	* 0.12
C8, Octanoyl		0.10	* 0.16	* 0.13
C8:1, Octenoyl		0.24	* 0.36	* 0.14
C10, Decanoyl		0.24	* 0.28	* 0.15
C10:1, Decenoyl		0.16	* 0.21	* 0.22
C12, Dodecanoyl		0.17 H	* 0.18 H	* 0.10
C12:1, Dodecenoyl		0.07	* 0.11	* 0.19 H
C12-OH, 3-OH Dodecanoyl		0.03 H	* 0.06 H	* 0.01
C14, Tetradecanoyl		0.14 H	* 0.10 H	* 0.11 H
C14:1, Tetradecenoyl		0.08	* 0.06	* 0.09
C14:2, Tetradecadienoyl		0.03	* 0.05	* 0.04
C14-OH, 3-OH-Tetradecanoyl		0.02	* 0.02	* 0.00
C14:1-OH, 3-OH-Tetradecenoyl		0.03 H	* 0.05 H	* 0.05 H
C16, Palmitoyl		0.76 H	* 0.46 H	* 0.70 H
C16:1, Palmitoleyl		0.05 H	* 0.06 H	* 0.08 H
C16-OH, 3-OH-Palmitoyl		0.01	* 0.01	* 0.03 H
C16:1-OH, 3-OH-Palmitoleyl		0.03 H	* 0.03 H	* 0.03 H
C18, Stearoyl		0.37 H	* 0.31 H	* 0.36 H
C18:1, Oleyl		0.49 H	* 0.41 H	* 0.82 H
C18:2, Linoleyl		0.25 H	* 0.21 H	* 0.20 H
C18-OH, 3-OH-Stearoyl		0.01	* 0.01	* 0.04 H
C18:1-OH, 3-OH-Oleyl		0.02 H	* 0.01	* 0.03 H
C18:2-OH, 3-OH-Linoleyl		0.02 H	* 0.01	* 0.02 H

Courtesy Marzia Pasquali PhD, ARUP laboratories

Carnitine Palmitoyl Transferase-2 (CPT-2) deficiency

Frequency: Very rare, except for the myopathic form which is still rare, but with several reported cases (>300)

Cause/Pathogenesis: Deficiency of CPT-2 impairs the transfer of long-chain fatty acids from carnitine to CoA resulting in the accumulation of long-chain acylcarnitine, long-chain fatty acids and defective energy production.

Presentation: 1. Lethal Neonatal 608836: respiratory failure, liver failure, cardiomyopathy, arrhythmia, hypoglycemia; 2. severe infantile 600649: hypoglycemia, seizures, hepatomegaly, cardiomyopathy, and arrhythmia; 3. myopathic 255110: muscle pain with exercise.

Diagnosis: increased C16, C18, C18:1, C18:2-carnitine in plasma, confirmed by DNA testing. Can be identified by newborn screening, but infants with late-onset variant can have normal profile at birth.

Therapy: Avoidance of fasting, MCT oil, triheptanoin, sugary drinks with exercise

Monitoring: ALT, AST, CK, acylcarnitines, carnitine free and total

Prognosis: myopathic form compatible with long life

Pasquali M, Longo N. Newborn Screening and Inborn Errors of Metabolism. Chapter 70. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. St. Louis: Saunders; 2017.

ACMG
American College of Medical Genetics and Genomics
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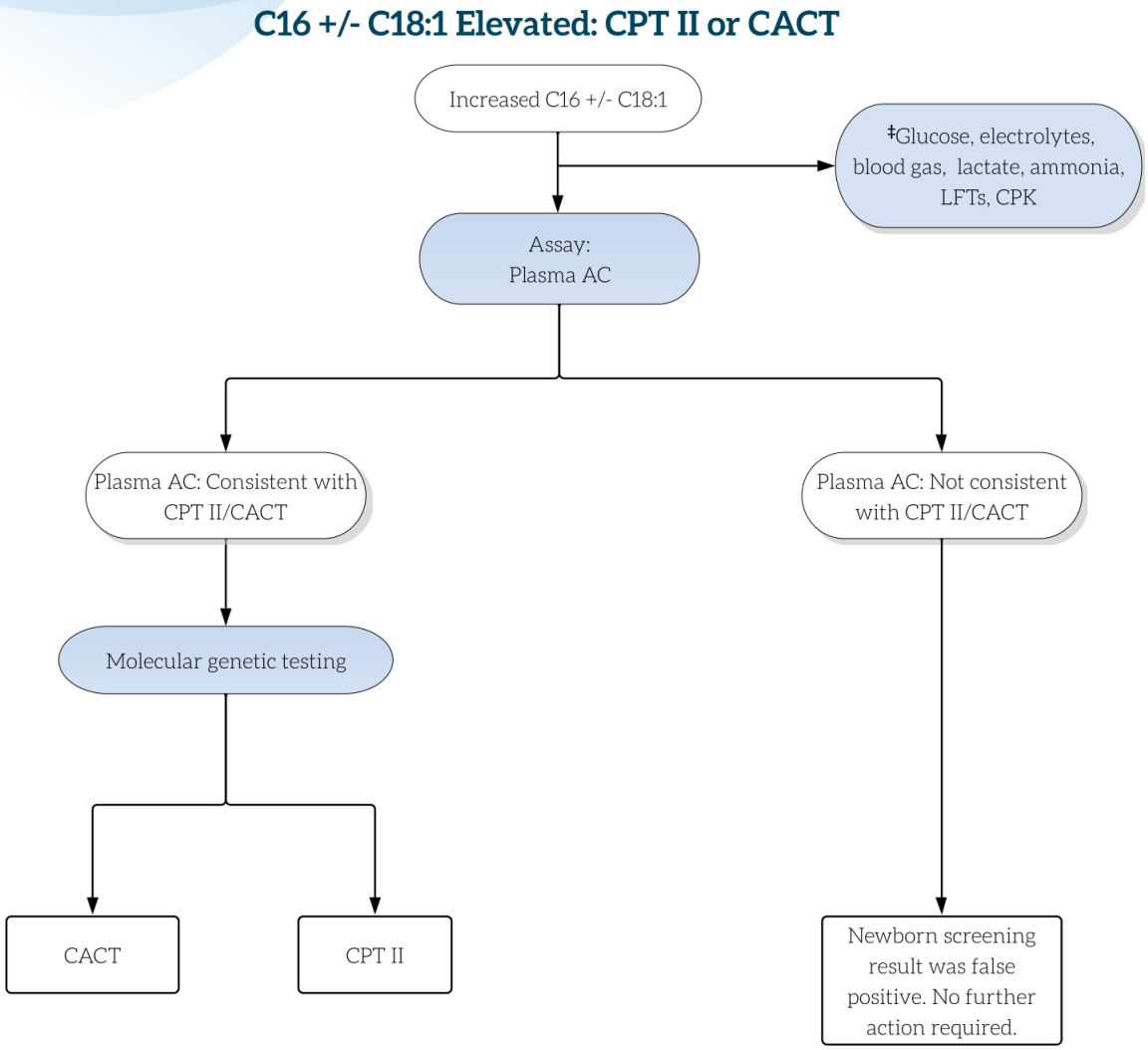


CACT and CPT2 Deficiency

Panel DNA testing has substituted enzyme assay in fibroblasts.
The late-onset form of CPT2 deficiency is usually missed by newborn screening.

MUSCLE PAIN WITH EXERCISE
Differential Diagnosis

- **McArdle disease or other glycogen storage disorder (aldolase A deficiency as well)**
- **FAO Deficiency: CPT-2, Late-Onset MADD, VLCAD, LCHAD/TFP deficiency, carnitine deficiency**
- **Myoadenylate deaminase deficiency (?)**
- **Mitochondrial disorders (cytochrome b, CoQ10 deficiency)**
- **Anesthetic-induced malignant hyperthermia**
- **Autosomal recessive LPIN1 mutations** (Mg(2+)-dependent phosphatidic acid (PA) phosphohydrolase)

Gene panel: ABHD5 ACAD9 ACADM ACADVL AGK AGL AHCY ALDOA AMACR AMPD1 ANO5 ATP2A1 ATP7B B3GALNT2 B4GAT1 C1QBP CACNA1S CAPN3 CASQ1 CAV3 CHAT CHKB COQ2 COQ4 COQ7 COQ8A COQ9 COX15 COX20 COX6B1 CPT1A CPT2 CTDP1 DAG1 DGUOK DMD DNA2 DNAJB6 DPM1 DPM2 DPM3 DYSF EMD ENO3 ETFA ETFB ETFDH FBXL4 FDX2 FHL1 FKRP FKTN FLAD1 GAA GATM GBE1 GFER GMPPB GYG1 GYS1 HADH HADHA HADHB HMBS ISCU ISPD ITGA7 LAMA2 LAMP2 LARGE1 LDHA LPIN1 MAN2B1 MGME1 MICU1 MPV17 MYH3 OPA1 OPA3 PDSS1 PDSS2 PFKM PGAM2 PGK1 PGM1 PHKA1 PHKB PNPLA2 PNPLA8 POLG POLG2 POMGNT1 POMGNT2 POMK POMT1 POMT2 PUS1 PYGM RBCK1 RNASEH1 RRM2B RXYLT1 RYR1 SCN4A SDHA SGCA SGCB SGCD SGCG SIL1 SLC16A1 SLC22A5 SLC25A20 SLC25A3 SLC25A4 SLC25A42 STAC3 SUCLA2 SUCLG1 TANGO2 TCAP TK2 TNPO3 TRIM32 TRMT5 TSFM TWNK TYMP YARS2

Neonatal Hypoglycemia

Full term Caucasian male, first child of healthy, unrelated parents is discharged home from the hospital after uneventful pregnancy and delivery. The mother is breastfeeding. Shortly after arriving at home at 36 hours of life, the infant becomes lethargic and is brought to the emergency room. The infant appears dehydrated and is given normal saline. Blood monitoring indicates glucose of 15 mg/dL.

Medium Chain AcylCoA Dehydrogenase (MCAD) Deficiency OMIM 201450

Most common fatty acid oxidation defect

Frequency: 1:17,759 (USA) 1:7,738 (Utah)

Cause: mutations in *ACADM* gene

Presentation: Fasting-induced hypoketotic hypoglycemia, coma, sudden death. Normal between episodes. Many cases remain asymptomatic until adult life and can still result in unexpected death. Some cases present at birth.

Diagnosis: plasma acylcarnitine profile: elevated C8, C6, C10:1, urine organic acids (hexanoylglycine), DNA testing (common p.K329E mutation)

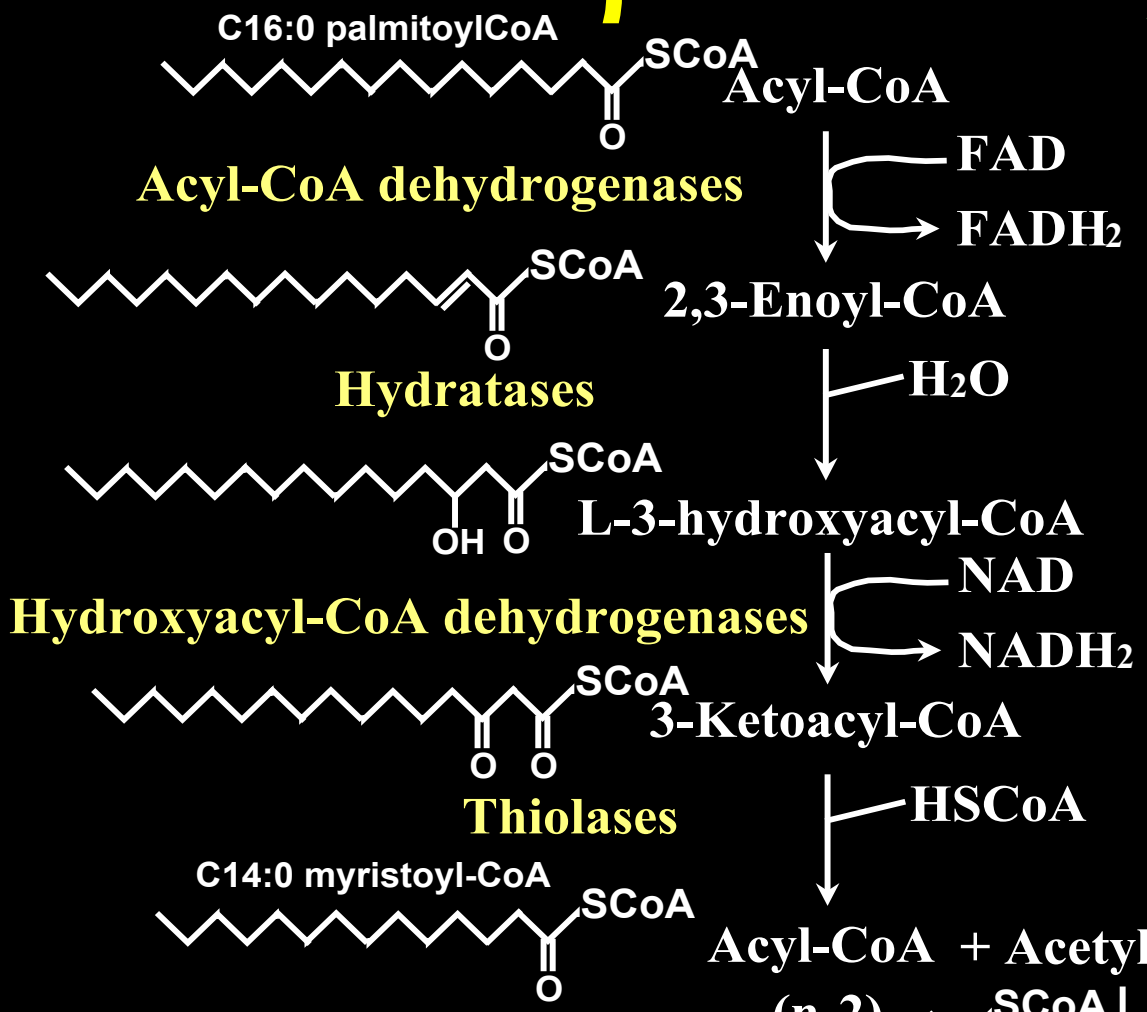
Therapy: avoidance of fasting, prompt treatment of infection, heart-healthy diet at age 1, carnitine supplements (unproven)

Monitoring: free and total carnitine, acylcarnitine profile

Prognosis: Excellent with treatment

Anderson DR, Viau K, Botto LD, Pasquali M, Longo N. Clinical and biochemical outcomes of patients with medium-chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2020 Jan;129(1):13-19. doi: 10.1016/j.ymgme.2019.11.006. Epub 2019 Nov 25. PMID: 31836396

β-OXIDATION



VLCAD: C14-C20
LCAD: C12-C18
MCAD: C4-C12
SCAD: C4-C6

TFP C12-C18
Crotonase C4>C14

LCHAD (TFP): C12-C18
SCHAD: C4>C16

TFP C6-C16
MKAT C4-C12
β ketothiolase C4

Pasquali M, Longo N. Newborn Screening and Inborn Errors of Metabolism. Chapter 70. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. St. Louis: Saunders, 2017.

C2, Acetyl	3.69-24.71	umol/L	10.24	*11.37	*19.51	*16.28
C3, Propionyl	0.00-0.97	umol/L	0.48	*1.28 H	*0.59	*0.38
C4, Iso/Butyryl	0.00-0.50	umol/L	0.19	*0.66 H	*0.94 H	*0.48
C5, Isovaleryl/2Mebutyryl	0.00-0.28	umol/L	0.11	*0.26	*0.10	*0.08
C5-DC, Glutaryl	0.00-0.07	umol/L	0.01	*0.05	*0.03	*0.04
C6, Hexanoyl	0.00-0.12	umol/L	1.00 H	*3.19 H	*2.66 H	*3.84 H
C5-OH, 3-OH Isovaleryl	0.00-0.07	umol/L	0.00	*0.05	*0.05	*0.07
C8, Octanoyl	0.00-0.23	umol/L	2.03 H	*14.81 H	*6.02 H	*10.61 H
C8:1, Octenoyl	0.00-0.63	umol/L	0.27	*0.62	*0.44	*0.74 H
C10, Decanoyl	0.00-0.35	umol/L	0.14	*1.21 H	*0.67 H	*0.79 H
C10:1, Decenoyl	0.00-0.41	umol/L	0.54 H	*3.30 H	*3.02 H	*4.63 H
C12, Dodecanoyl	0.00-0.12	umol/L	0.02	*0.06	*0.10	*0.12
C12:1, Dodecenoyl	0.00-0.16	umol/L	0.00	*0.05	*0.04	*0.05
C12-OH, 3-OH Dodecanoyl	0.00-0.02	umol/L	0.00	*0.01	*0.01	*0.01
C14, Tetradecanoyl	0.00-0.07	umol/L	0.02	*0.03	*0.09	*0.09
C14:1, Tetradecenoyl	0.00-0.23	umol/L	0.02	*0.04	*0.08	*0.07
C14:2, Tetradecadienoyl	0.00-0.12	umol/L	0.01	*0.02	*0.05	*0.03
C14-OH, 3-OH-Tetradecanoyl	0.00-0.02	umol/L	0.00	*0.00	*0.01	*0.01
C14:1-OH, 3-OH-Tetradecenoyl	0.00-0.03	umol/L	0.01	*0.01	*0.01	*0.01
C16, Palmitoyl	0.00-0.10	umol/L	0.09	*0.14 H	*0.14	*0.15
C16:1, Palmitoleyl	0.00-0.05	umol/L	0.02	*0.02	*0.02	*0.03
C16-OH, 3-OH-Palmitoyl	0.00-0.01	umol/L	0.00	*0.00	*0.01	*0.01
C16:1-OH, 3-OH-Palmitoleyl	0.00-0.01	umol/L	0.01	*0.01	*0.01	*0.01
C18, Stearoyl	0.00-0.05	umol/L	0.04	*0.03	*0.07	*0.06
C18:1, Oleyl	0.00-0.16	umol/L	0.04	*0.09	*0.12	*0.13
C18:2, Linoleyl	0.00-0.08	umol/L	0.03	*0.03	*0.09	*0.09
C18-OH, 3-OH-Stearoyl	0.00-0.01	umol/L	0.00	*0.00	*0.01	*0.00
C18:1-OH, 3-OH-Oleyl	0.00-0.01	umol/L	0.01	*0.00	*0.00	*0.01
C18:2-OH, 3-OH-Linoleyl	0.00-0.01	umol/L	*0.00	*0.00	*0.00	*0.00

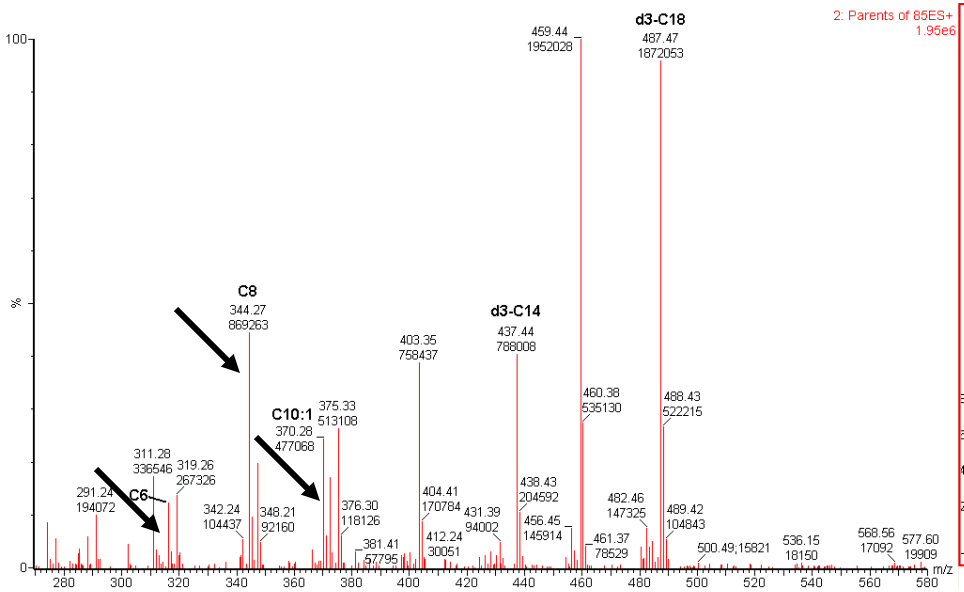
MCAD DEFICIENCY

Plasma acylcarnitine profile

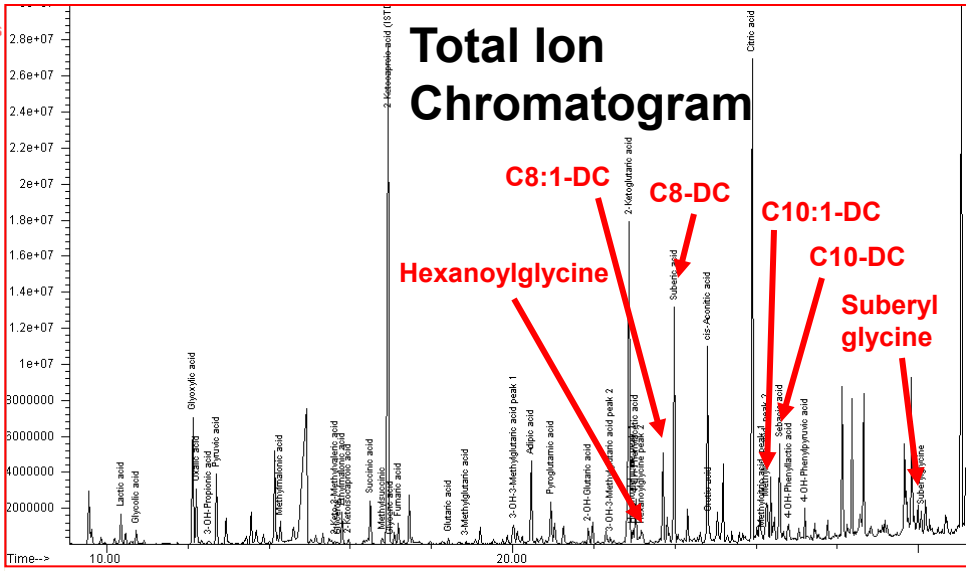
C8-carnitine is the highest

BIOCHEMICAL FINDINGS IN MCAD DEFICIENCY

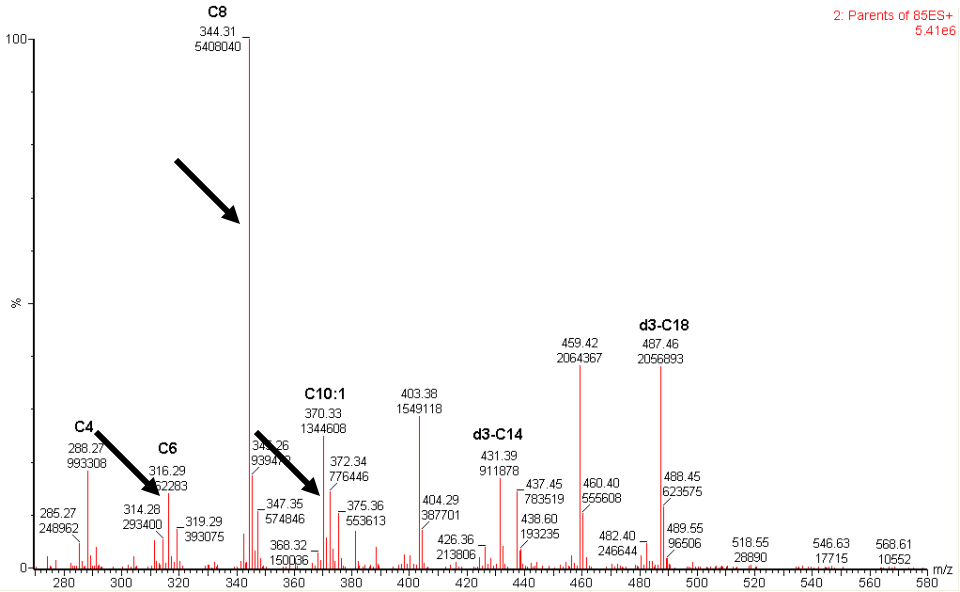
Plasma acylcarnitine profile by MS/MS

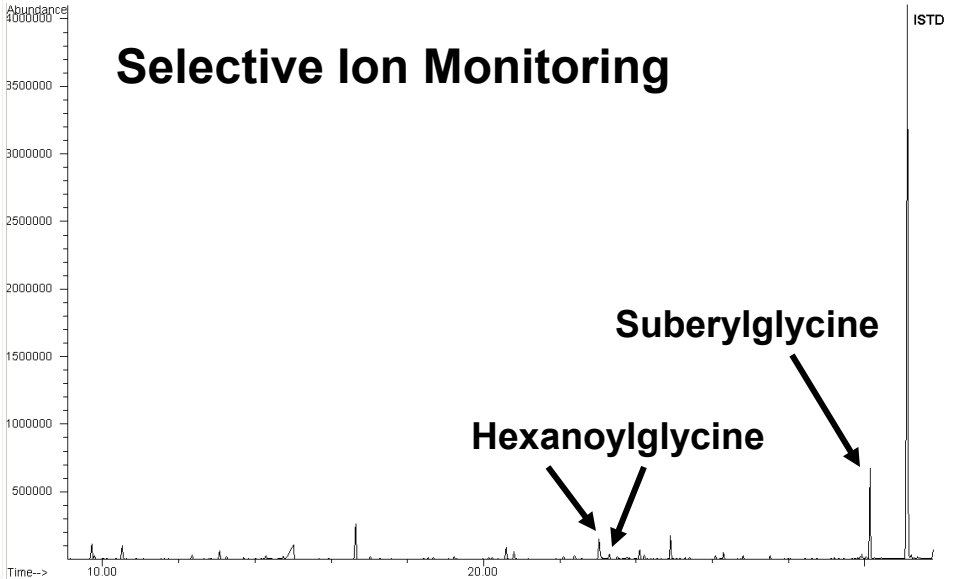


Urine organic acids by GC/MS



Courtesy Marzia Pasquali PhD, ARUP laboratories





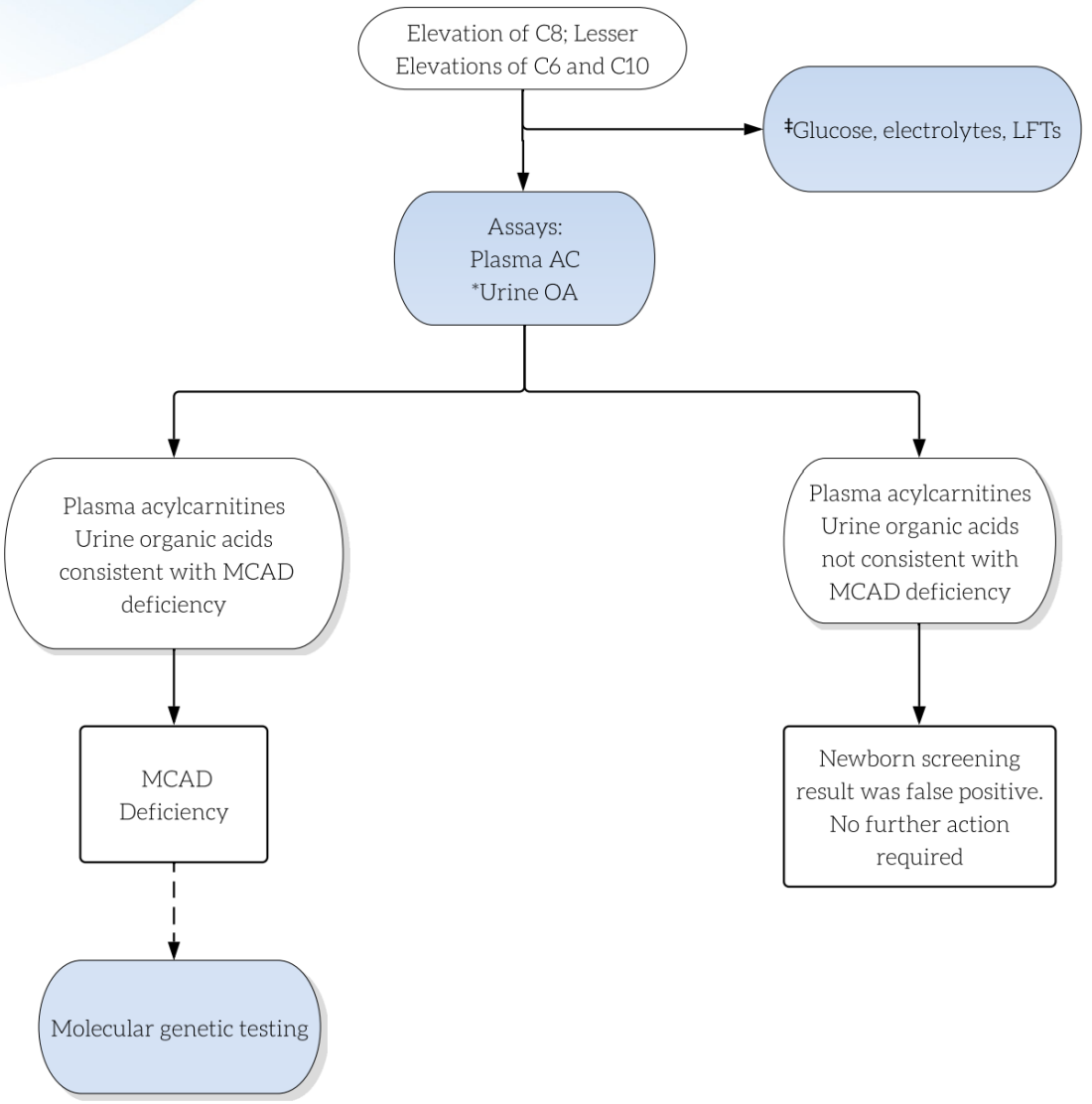
MCAD DEFICIENCY

Causes secondary carnitine deficiency

Carnitine, Free	23-70	* 5 L
Carnitine, Total	26-81	* 10L

Prot	5.9-7.0	g/dL	5.3 L
Alb	3.1-3.9	g/dL	2.9 L
Bili, Total	0.2-1.3	mg/dL	0.2
Bili, Conj	0.0-0.3	mg/dL	0
Bili, Unconj	0.0-1.1	mg/dL	0.3
Alk Phos	145-320	U/L	112L
ALT	May-45	U/L	457 H
AST	20-60	U/L	1241H

MCAD Deficiency



We do DNA testing, but usually Dx can be made without it

CARDIO MYOPATHY

8 yo female hospitalized after being unable to move or wake up completely. She woke up moaning, crying, unable to focus, drink or walk. She was admitted to Intensive Care 6 days and found to have cardiomyopathy with low cardiac ejection fraction, elevated CK, and cardiomegaly on chest X-ray.

	Last Ref. Range	11/12/07 17:25	05/21/07 12:16	12/18/06 12:00	10/23/06 13:15	08/30/06 15:20
C2, Acetyl		* 6.42	* 16.34	* 16.14	* 4.68	* 8.34
C3, Propionyl		* 0.44	* 0.51	* 0.52	* 0.37	* 1.33 H
C4, Iso/Butyryl		* 0.25	* 0.26	* 0.28	* 0.29	* 0.42
C5, Isovaleryl/2Mebutyryl		* 0.10	* 0.08	* 0.04	* 0.05	* 0.13
C5-DC, Glutaryl		* 0.02	* 0.03	* 0.03	* 0.10 H	* 0.04
C6, Hexanoyl		* 0.18 H	* 0.24 H	* 0.30 H	* 0.18 H	* 0.25 H
C8, Octanoyl		* 0.14	* 0.17	* 0.16	* 0.10	* 0.06
C8:1, Octenoyl		* 0.03	* 0.05	* 0.05	* 0.09	* 0.06
C10, Decanoyl		* 0.11	* 0.17	* 0.18	* 0.28	* 0.17
C10:1, Decenoyl		* 0.03	* 0.04	* 0.04	* 0.48 H	* 0.11
C12, Dodecanoyl		* 0.09	* 0.15 H	* 0.21 H	* 0.90 H	* 0.48 H
C12:1, Dodecenoyl		* 0.03	* 0.04	* 0.13	* 0.49 H	* 0.15
C12-OH, 3-OH Dodecanoyl		* 0.00	* 0.01	* 0.02	* 0.09 H	* 0.01
C14, Tetradecanoyl		* 0.37 H	* 0.52 H	* 0.77 H	* 1.90 H	* 0.77 H
C14:1, Tetradecenoyl		* 0.47 H	* 1.31 H	* 1.93 H	* 6.70 H	* 2.78 H
C14:2, Tetradecadienoyl		* 0.13 H	* 0.25 H	* 0.31 H	* 0.96 H	* 0.47 H
C14-OH, 3-OH-Tetradecanoyl		* 0.01	* 0.01	* 0.02	* 0.04 H	* 0.02
C14:1-OH, 3-OH-Tetradecenoyl		* 0.03 H	* 0.03 H	* 0.05 H	* 0.22 H	* 0.05 H
C16, Palmitoyl		* 0.36 H	* 0.46 H	* 0.70 H	* 3.33 H	* 0.99 H
C16:1, Palmitoleyl		* 0.10 H	* 0.22 H	* 0.39 H	* 2.14 H	* 0.50 H
C16-OH, 3-OH-Palmitoyl		* 0.00	* 0.02 H	* 0.02 H	* 0.03 H	* 0.01
C16:1-OH, 3-OH-Palmitoleyl		* 0.03 H	* 0.01	* 0.03 H	* 0.17 H	* 0.05 H
C18, Stearoyl		* 0.13 H	* 0.16 H	* 0.24 H	* 1.40 H	* 0.68 H
C18:1, Oleyl		* 0.14	* 0.25 H	* 0.47 H	* 3.33 H	* 1.07 H
C18:2, Linoleyl		* 0.05	* 0.09	* 0.18 H	* 0.95 H	* 0.29 H
C18-OH, 3-OH-Stearoyl		* 0.01	* 0.01	* 0.01	* 0.05 H	* 0.02 H
C18:1-OH, 3-OH-Oleyl		* 0.01	* 0.01	* 0.01	* 0.11 H	* 0.02 H
C18:2-OH, 3-OH-Linoleyl		* 0.00	* 0.02 H	* 0.01	* 0.11 H	* 0.03 H

Very Long Chain AcylCoA Dehydrogenase (VLCAD) Deficiency OMIM 201450

Frequency: 1:63,481 (USA) 1:27,617 (Utah)

Cause: mutations in *ACADVL* gene

Presentation: 1. Early onset, hypertrophic cardiomyopathy, high morbidity and mortality; 2. Milder form with hypoketotic hypoglycemia, similar to MCAD deficiency with increased LFTs, elevated CPK; 3. Stress-induced rhabdomyolysis, like myopathic CPT2 deficiency.

Diagnosis: plasma acylcarnitine profile (elevated C14:1, normalizes rapidly after stress), DNA testing (part of initial tests), FAO fluxes, VLCAD enzyme assay

Therapy: avoidance of fasting, prompt treatment of infection, MCT oil/triheptanoin with persistently abnormal acylcarnitines, low-fat diet, carnitine (25 mg/kg) with low plasma levels (unproven), MCT oil, triheptanoin, sugary drinks with exercise.

Monitoring: AST, ALT, CK, carnitine F & T, acylcarnitines, heart

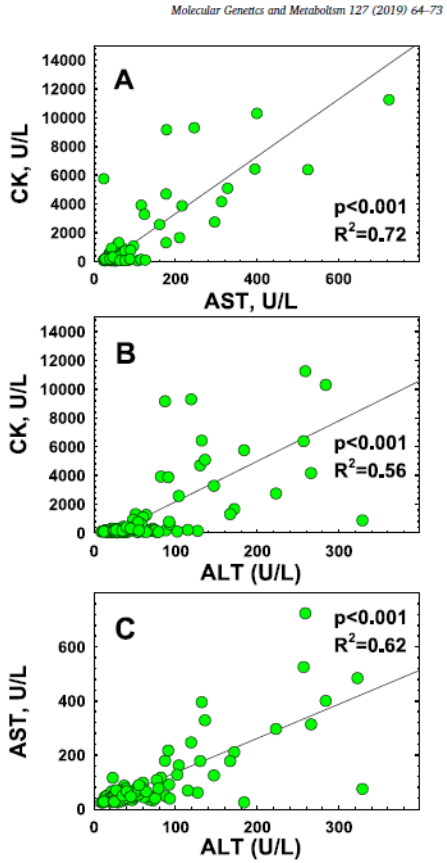
Prognosis: Can be good with treatment

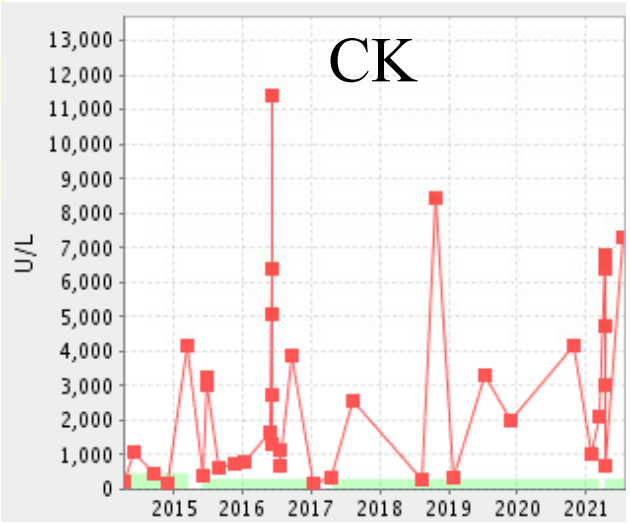
Rovelli V, Manzoni F, Viau K, Pasquali M, Longo N. Clinical and biochemical outcome of patients with very long-chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2019 May;127(1):64-73. doi: 10.1016/j.ymgme.2019.04.001. Epub 2019 Apr 16. PMID: 31031081

VLCAD Deficiency

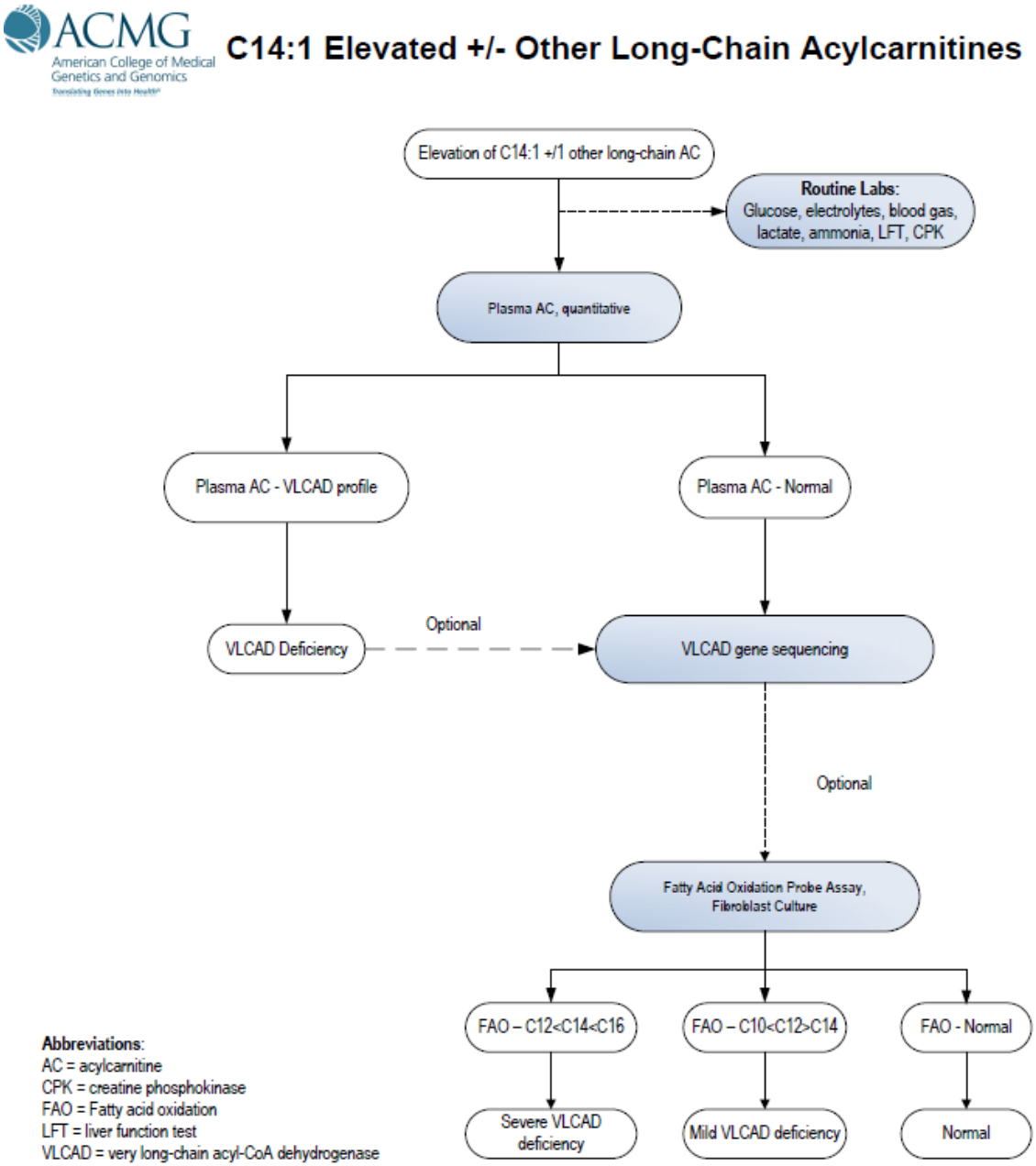
Comprehensive Metabolic Panel Show more...

	Last Ref. Range	Units	07/19/21 13:27	04/10/21 04:57*	04/08/21 22:07*	04/08/21 04:34*
Test Status			Final	Final	Final	Final
Na	137-146	mmol/L	140	139	136 L	138
K	3.4-4.7	mmol/L	4.8 H	4.2	4.9 H	4.3
Cl	102-111	mmol/L	106	107	106	108
CO2	17-25	mmol/L	17	22	19	21
Anion Gap (Na Cl CO2)	3-16	mmol/L	17 H	10	11	9
Glucose	60-115	mg/dL	74	90	134 H	116 H
BUN	9-22	mg/dL	19	2 L	3 L	6 L
Creatinine	0.27-0.73	mg/dL	0.39	0.42	0.64	0.36
GFR, Estimated	>60	mL/min/1.73 sq m	*Not calculated	*Not calculated	*Not calculated	*Not calculated
Ca	8.8-10.1	mg/dL	10.3 H	9.0	9.3	8.6 L
Prot	6.4-7.7	g/dL	7.9 H	5.8 L	6.7	5.6 L
Albumin	3.4-5.3	g/dL	4.7	3.7	4.2	3.8
Bili, Total	0.1-0.4	mg/dL	0.4	0.5 H	0.9 H	0.4
Alk Phos	156-369	U/L	136 L	119 L	135 L	121 L
ALT	11-30	U/L	265 H	385 H	362 H	333 H
AST	22-41	U/L	398 H	363 H	257 H	286 H





Can cause elevation of CK with secondary increase of ALT and AST: ALT and AST are also inside muscle.



VLCAD Deficiency

FAOD Panel DNA testing must be done in all patients with elevated C14:1 carnitine. C14:1 elevated in other FAOD.

Enzyme assay is available in WBC

Long Chain 3-OH-AcylCoA Dehydrogenase (LCHAD) 609016 / Trifunctional Protein (TFP) 609105 Deficiency

LCHAD is part of a trifunctional protein (TFP). Mutations can abolish all 3 functions or only LCHAD activity

Frequency: 1:303,222 (USA) 1: 255,365 (Utah)

Cause: mutations in *HADHA* or *HADHB* gene

Presentation: IUGR, prematurity, fasting-induced vomiting and hypoglycemia, hypotonia, cardiomyopathy, liver dysfunction, sudden death. Rhabdomyolisis with stress/exercise/fasting. Retinitis pigmentosa with time. Neuropathy (more pronounced in TFP deficiency). Preeclampsia in mothers of infants with LCHAD deficiency

Diagnosis: High C16OH (C14OH, C18OH, C18:1OH) and other long-chain carnitines, DNA testing

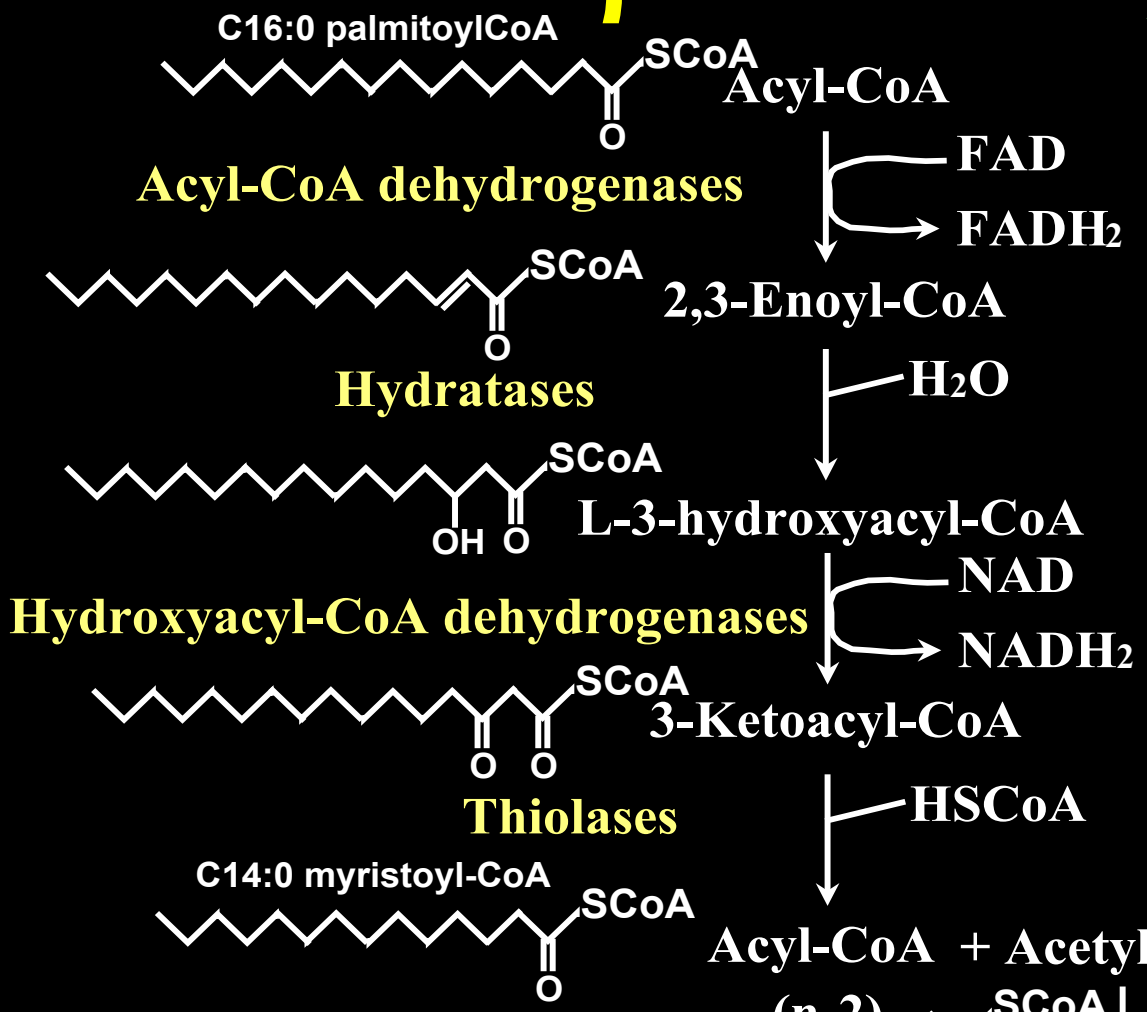
Therapy: avoidance of fasting, MCT oil, triheptanoin, low-fat diet, essential FA, Carnitine (25 mg/kg) with low plasma levels (unproven)

Monitoring: AST, ALT, CK, carnitine F & T, acylcarnitines, essential FA, eye, heart

Prognosis: bad without treatment, even with treatment there are problems (muscle pain, retinitis pigmentosa, neuropathy)

De Biase I, Viau KS, Liu A, Yuzyuk T, Botto LD, Pasquali M, Longo N. Diagnosis, Treatment, and Clinical Outcome of Patients with Mitochondrial Trifunctional Protein/Long-Chain 3-Hydroxy Acyl-CoA Dehydrogenase Deficiency. JIMD Rep. 2017;31:63-71. doi: 10.1007/8904_2016_558. Epub 2016 Apr 28. PMID: 27117294

β-OXIDATION



VLCAD: C14-C20
LCAD: C12-C18
MCAD: C4-C12
SCAD: C4-C6

TFP C12-C18
Crotonase C4>C14

LCHAD (TFP): C12-C18
SCHAD: C4>C16

TFP C6-C16
MKAT C4-C12
β ketothiolase C4

Pasquali M, Longo N. Newborn Screening and Inborn Errors of Metabolism. Chapter 70. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. St. Louis: Saunders, 2017.

Plasma acylcarnitine profile

Useful to determine if we are giving sufficient supplements

TFP deficiency

Appearance of C3 and C5 with triheptanoin

Appearance of C6, C8 with MCT

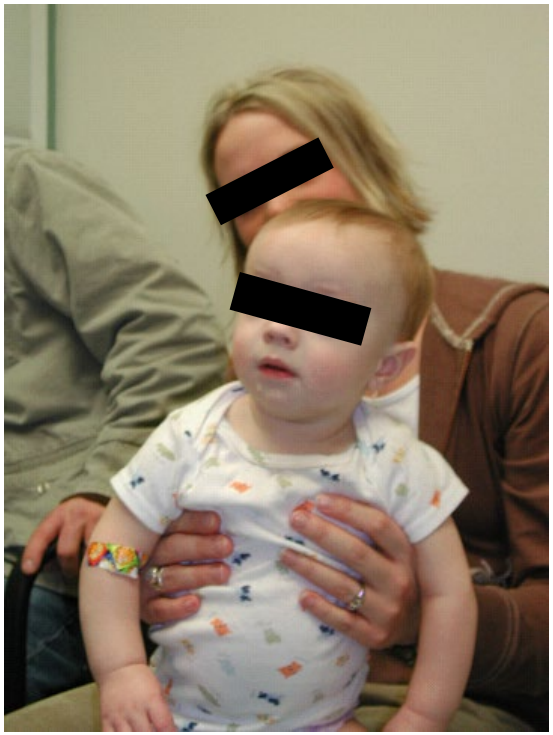
Appearance of C4-OH during catabolism if enough MT or triheptanoin is given

Acylcarnitine Quantitation, (Plasma) Show more...

	Last Ref Range	Units	01/26/21 17:19*	09/11/20 08:58*	09/27/16 09:50*	01/08/16 06:23*	09/28/15 11:40*
Test Status			Final	Final	Final	Final	Final
Interpretation:			*See Comments	*See Comments	*SEE NOTE	*SEE NOTE	*SEE NOTE
C2, Acetyl	3.74-16.56	umol/L	14.84	4.08	5.10	5.53	9.50
C3, Propionyl	0.00-0.83	umol/L	2.55 H	0.33	2.50 H	1.09 H	2.47 H
C4, Iso/Butyryl	0.00-0.45	umol/L	0.26	0.33	0.35	0.35	0.33
C5, Isovaleryl/2Mebutyryl	0.00-0.30	umol/L	0.81 H	0.09	0.26	0.15	0.75 H
C5-DC, Glutaryl	0.00-0.09	umol/L	0.09	0.12 H	0.20 H	0.15 H	0.11 H
C6, Hexanoyl	0.00-0.12	umol/L	0.17 H	0.16 H	0.24 H	0.84 H	0.78 H
C5-OH, 3-OH Isovaleryl	0.00-0.07	umol/L	0.13 H	0.00	0.00	0.07	0.06
C8, Octanoyl	0.00-0.23	umol/L	0.16	0.10	0.25 H	0.26 H	0.26 H
C8:1, Octenoyl	0.00-0.61	umol/L	0.07	0.09	0.30	0.29	0.23
C10, Decanoyl	0.00-0.31	umol/L	0.12	0.13	0.26	0.23	0.15
C10:1, Decenoyl	0.00-0.31	umol/L	0.11	0.15	0.49 H	0.30	0.22
C12, Dodecanoyl	0.00-0.12	umol/L	0.13 H	0.27 H	0.57 H	0.41 H	0.33 H
C12:1, Dodecenoyl	0.00-0.17	umol/L	0.11	0.30 H	0.56 H	0.37 H	0.24 H
C12-OH, 3-OH Dodecanoyl	0.00-0.02	umol/L	0.09 H	0.11 H	0.24 H	0.13 H	0.15 H
C14, Tetradecanoyl	0.00-0.05	umol/L	0.07 H	0.14 H	0.24 H	0.28 H	0.15 H
C14:1, Tetradecenoyl	0.00-0.16	umol/L	0.24 H	0.46 H	0.83 H	1.01 H	0.40 H
C14:2, Tetradecadienoyl	0.00-0.12	umol/L	0.17 H	0.30 H	0.76 H	0.84 H	0.40 H
C14-OH, 3-OH-Tetradecanoyl	0.00-0.02	umol/L	0.10 H	0.13 H	0.27 H	0.24 H	0.15 H
C14:1-OH, 3-OH-Tetradecenoyl	0.00-0.02	umol/L	0.10 H	0.13 H	0.28 H	0.23 H	0.20 H
C16, Palmitoyl	0.00-0.10	umol/L	0.13 H	0.21 H	0.26 H	0.34 H	0.22 H
C16:1, Palmitoleyl	0.00-0.04	umol/L	0.09 H	0.19 H	0.24 H	0.29 H	0.12 H
C16-OH, 3-OH-Palmitoyl	0.00-0.01	umol/L	0.20 H	0.30 H	0.41 H	0.45 H	0.35 H
C16:1-OH, 3-OH-Palmitoleyl	0.00-0.01	umol/L	0.08 H	0.14 H	0.20 H	0.22 H	0.13 H
C18, Stearoyl	0.00-0.04	umol/L	0.04	0.06 H	0.13 H	0.10 H	0.07 H

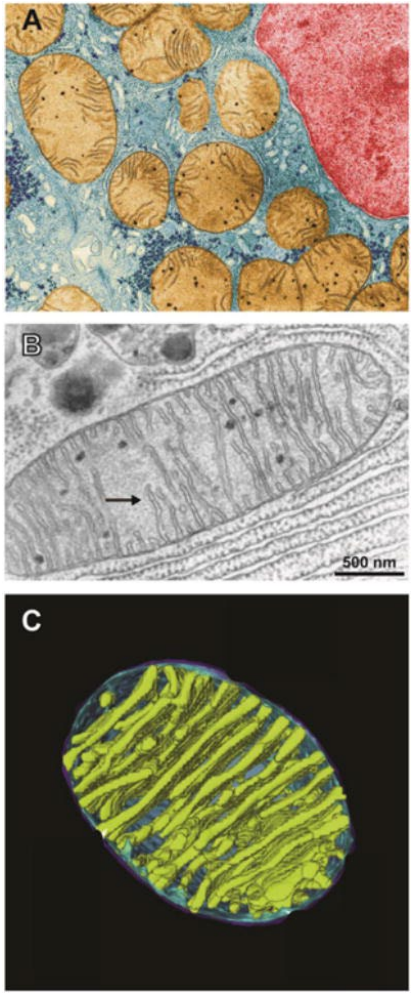
Long Chain 3-OH-AcylCoA Dehydrogenase Deficiency (LCHAD)

AFLP (acute fatty liver of pregnancy) syndrome or HELLP (hypertension, elevated liver functions, and low platelets) are frequent in mothers carrying a fetus with LCHAD deficiency. Patients do very well when treated, but can decompensate with fever, infections and require prompt hospital admission to receive intravenous glucose.

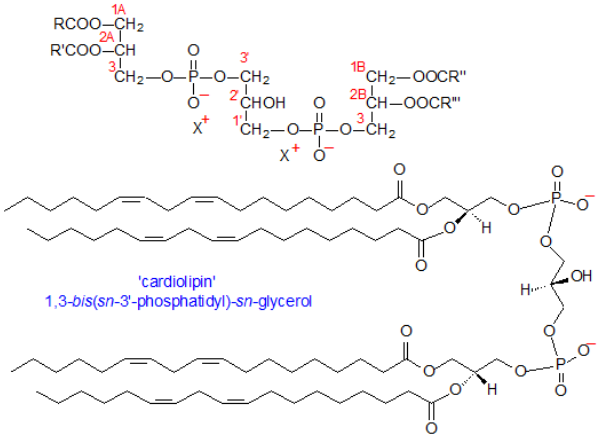


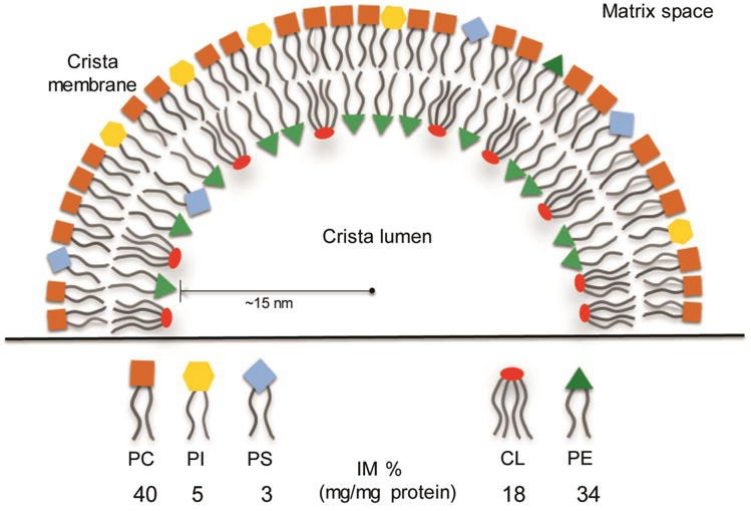
Mentality is normal.

α–TFP MODIFIES CARDIOLIPIN



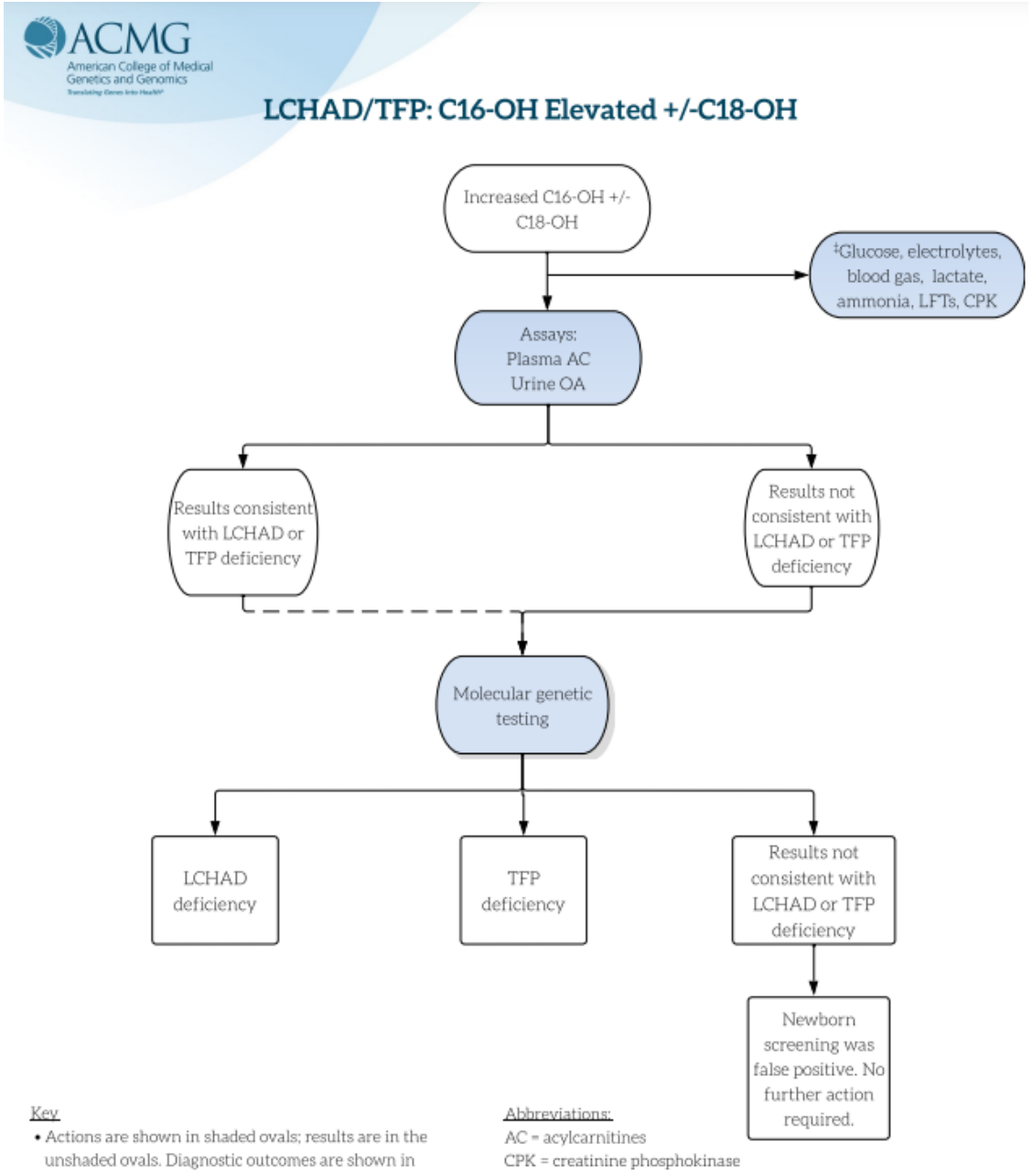
TFP has a fourth enzymatic activity: Monolysocardiolipin (MLCL) acyltransferase (MLCL AT)-1 activity. Cardiolipin constitutes about 20% of the total lipid composition of the inner mitochondrial membrane. Cardiolipin is essential for the formation of cristae.





Ikon N, Ryan RO. Cardiolipin and mitochondrial cristae organization.Biochim Biophys Acta Biomembr. 2017 Jun;1859(6):1156-1163. PMID: 28336315

Taylor WA, Mejia EM, Mitchell RW, Choy PC, Sparagna GC, Hatch GM. Human trifunctional protein alpha links cardiolipin remodeling to beta-oxidation. PLoS One. 2012;7(11):e48628. doi: 10.1371/journal.pone.0048628. Epub 2012 Nov 9. PMID: 23152787



TFP/LCHAD Deficiency

DNA testing (FAOD panel) has substituted functional studies in most cases.

Acylcarnitines can normalize with therapy in some cases of TFP deficiency, not in LCHAD

Short-Chain Acyl-CoA Dehydrogenase (SCAD) deficiency (OMIM 201470)

Biochemical alteration of fatty acid oxidation with unclear clinical significance.

Frequency: 1:40,000-1:100,000. Polymorphisms in this gene are very frequent in the general population.

Cause: Mutations in *ACADS* gene 12q24.31

Presentation: hypotonia, myopathy, most likely no symptoms. This is a non-disease.

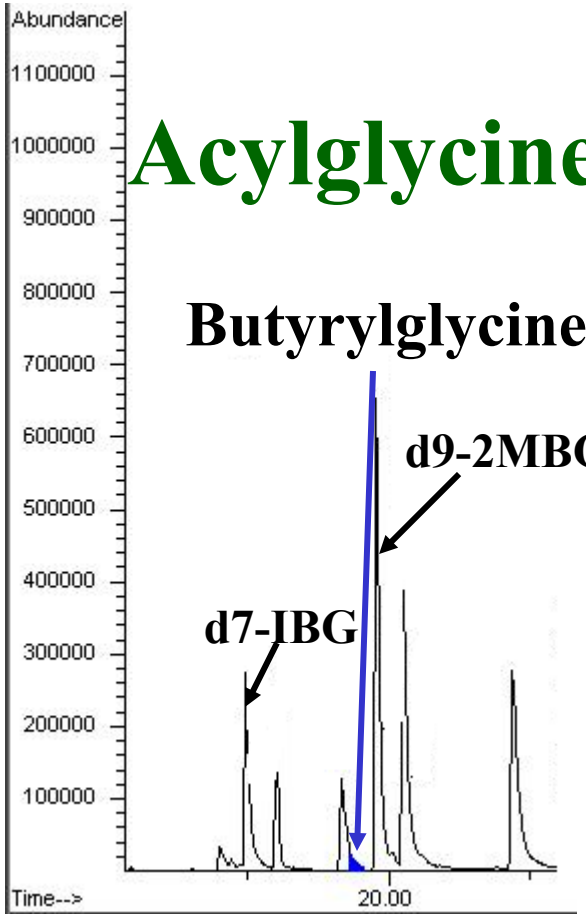
Diagnosis: Urinary organic acids: elevated ethylmalonic and methylsuccinic acids, n-butyrylglycine. Plasma acylcarnitine profile: increased C4 (butyrylcarnitine). Confirmed by DNA testing

Treatment: None. No therapy required.

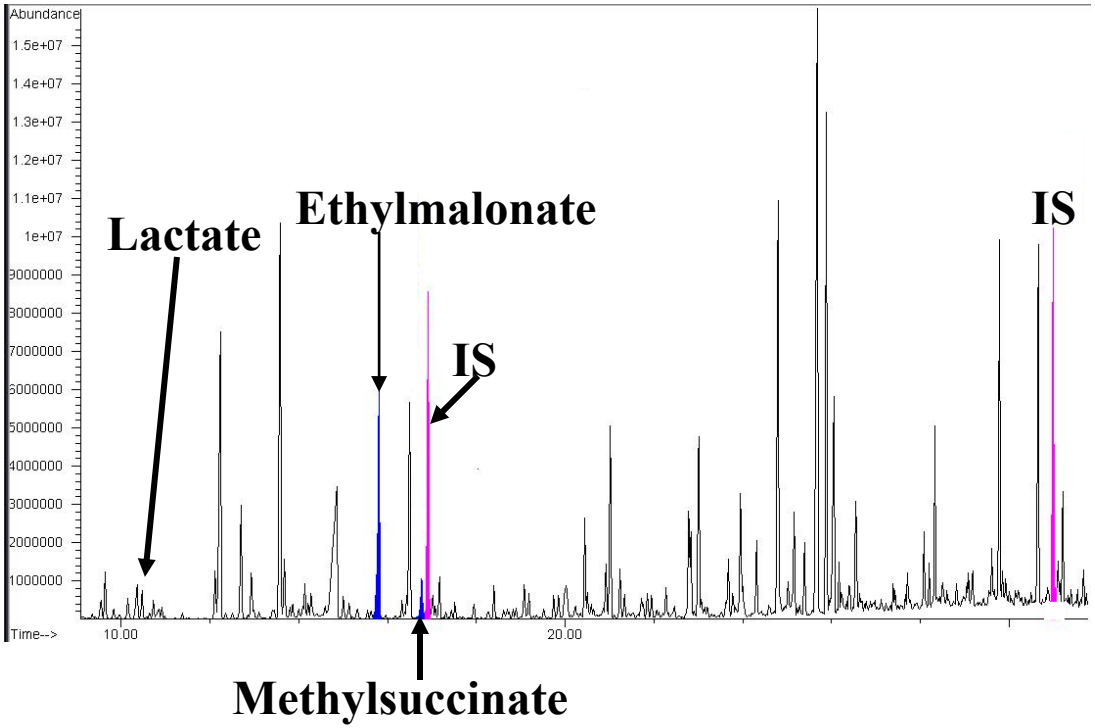
Need to exclude isobutyryl glycinuria (elevated isobutyryl glycine) and ethylmalonic encephalopathy (persistent lactic acidemia).

SCAD Deficiency: Urine acylglycines and urine organic acids

Acylglycines

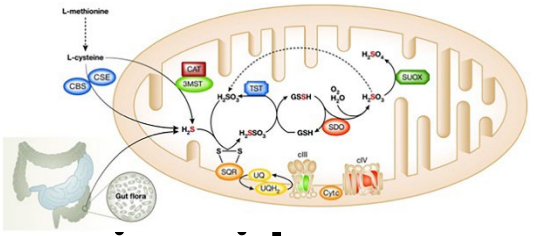


Organic Acids



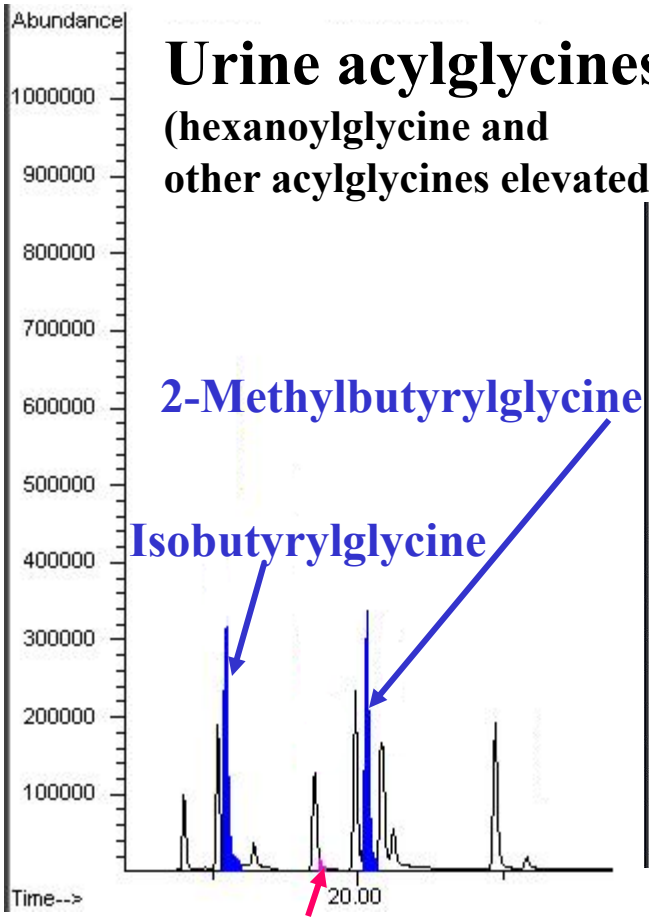
Ethylmalonic encephalopathy

Neurodegenerative disorder affecting the brain, GI tract, and peripheral vessels, caused by mutations in *ETHE1* gene encoding a mitochondrial matrix protein

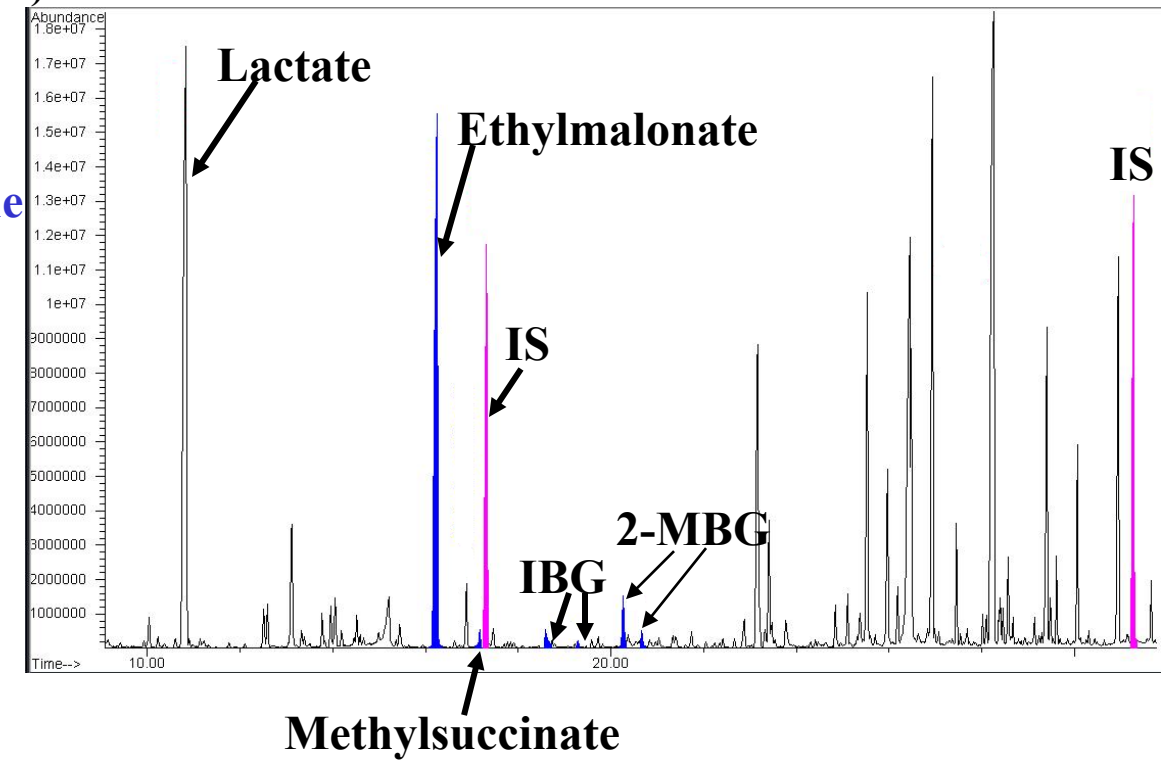


Urine acylglycines

(hexanoylglycine and other acylglycines elevated)

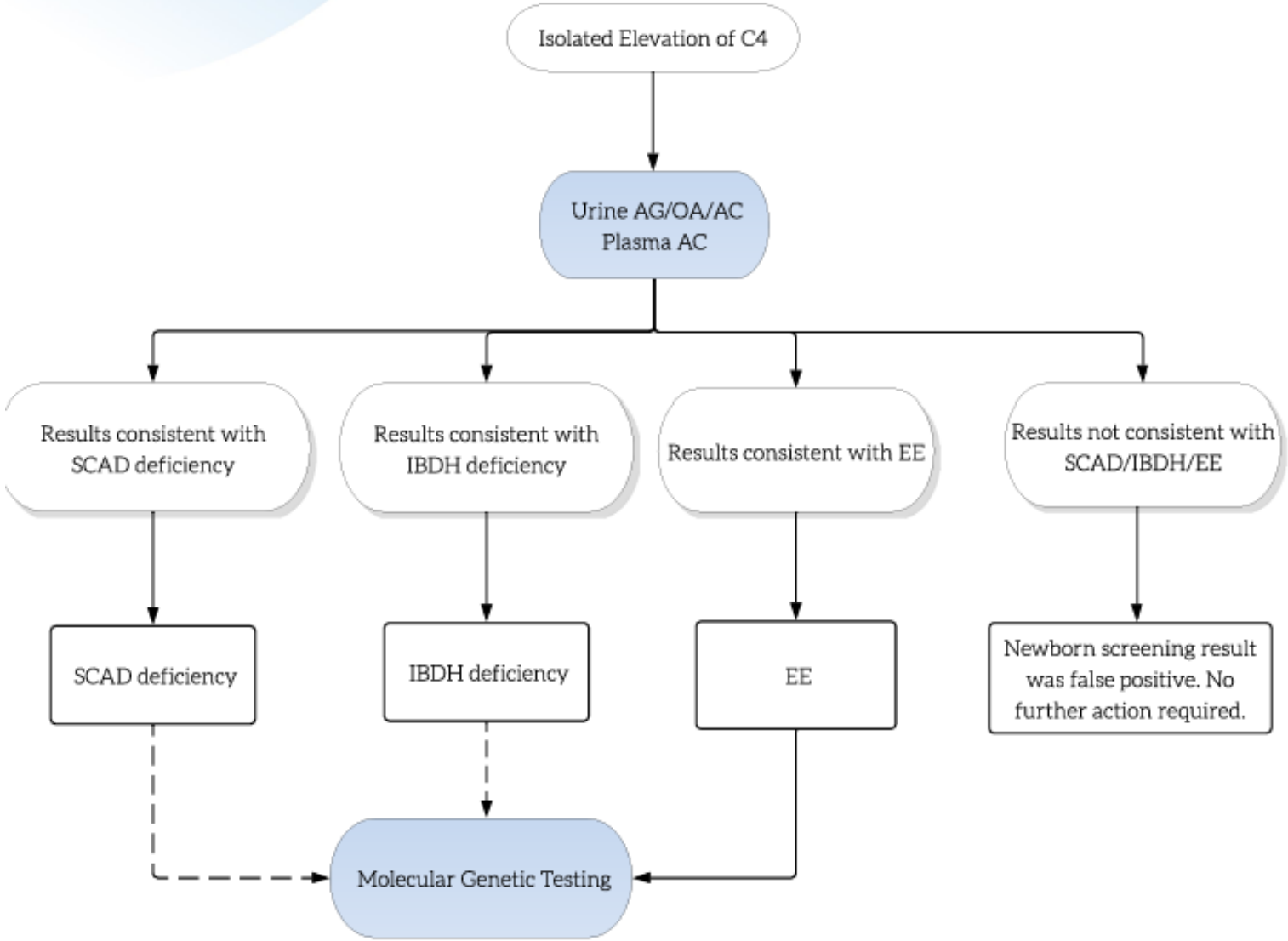


Urine organic acids



ACMG
American College of Medical Genetics and Genomics
Translating Genes into Health®

SCAD Deficiency: C4 Elevated



Glutaric acidemia type 2 (GA-2)/Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

Disorder of mitochondrial fatty acid and organic acid metabolism

Frequency: 1:100,000

Cause: mutations impair the activity of the electron transfer flavoprotein (ETF) (*ETFA* and *ETFB* genes) or ETF ubiquinone oxidoreductase (ETFQO) (*ETFDH* gene) preventing electron transfer from multiple dehydrogenases. Riboflavin deficiency.

Presentation: Neonatal-onset: with or without congenital anomalies (usually fatal): dysmorphic features with multiorgan abnormalities (if present), nonketotic hypoglycemia, metabolic acidosis, multisystem involvement, and excretion of large amounts of abnormal fatty acid and organic acid metabolites.

Late-onset: recurrent episodes of lethargy, vomiting, hypoglycemia, metabolic acidosis, and hepatomegaly often triggered by fever, infection or fasting. Some patients have predominant muscular involvement with pain, weakness, and lipid storage myopathy, neuropathy)

Prasun P. Multiple Acyl-CoA Dehydrogenase Deficiency. 2020 Jun 18. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558236/

Glutaric acidemia type 2 (GA-2)/Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

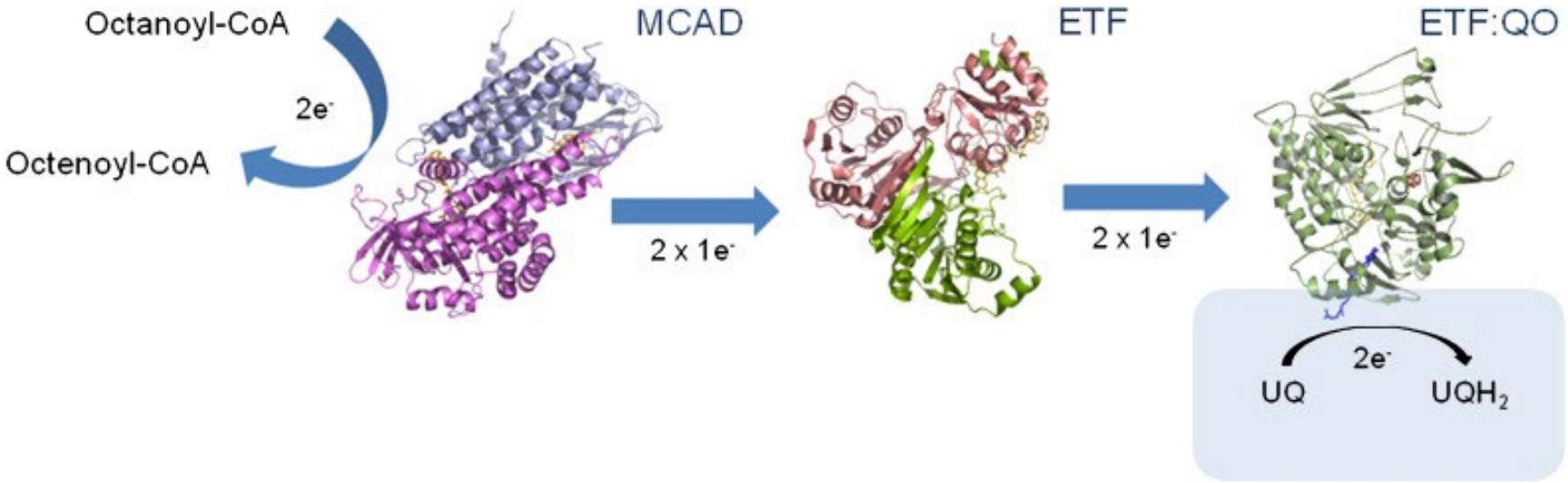
Diagnosis: High C4, C5, C6<C8<C10, C12, C14, C14:1-carnitine, urine organic acids: 2-OH-glutaric, exclude riboflavin deficiency, DNA testing for the 3 genes (*ETFA, ETFB, ETFDH*). *ETFA* mutations are the most frequent followed by *ETFB*. *ETFDH* mutations many times respond to riboflavin

Therapy: avoidance of fasting, prompt treatment of infection, low-fat diet, ketones, riboflavin (100-300 mg/day), ubiquinol (100-400 mg/day) at age 1, carnitine (50-100 mg/kg), essential FA supplements

Monitoring: AST, ALT, CK, carnitine F & T, acylcarnitines, essential FA, heart

Prognosis: severe for neonatal forms; not well characterized for the others.

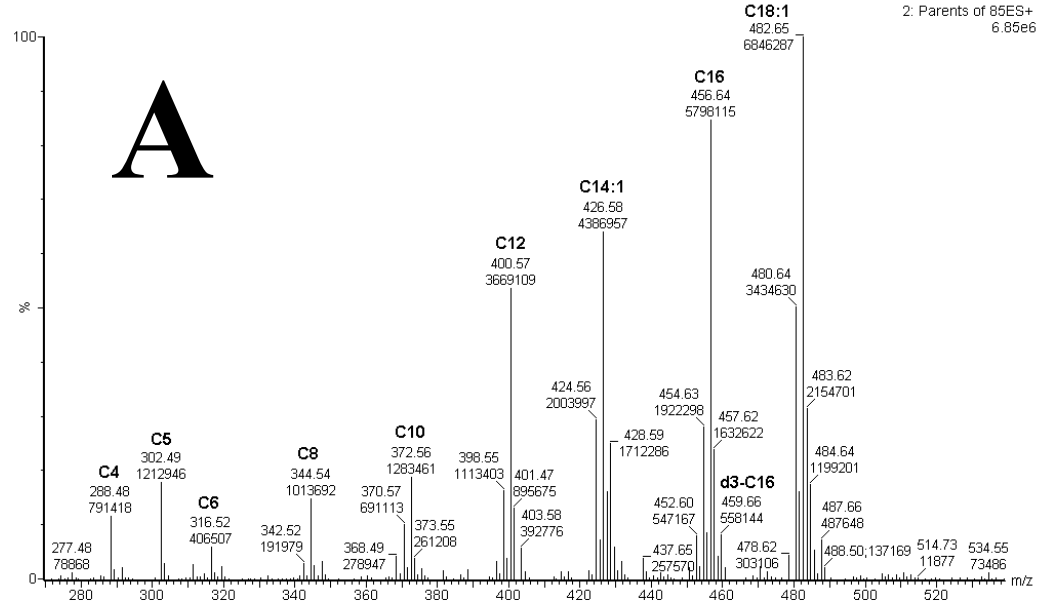
Prasun P. Multiple Acyl-CoA Dehydrogenase Deficiency. 2020 Jun 18. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558236/

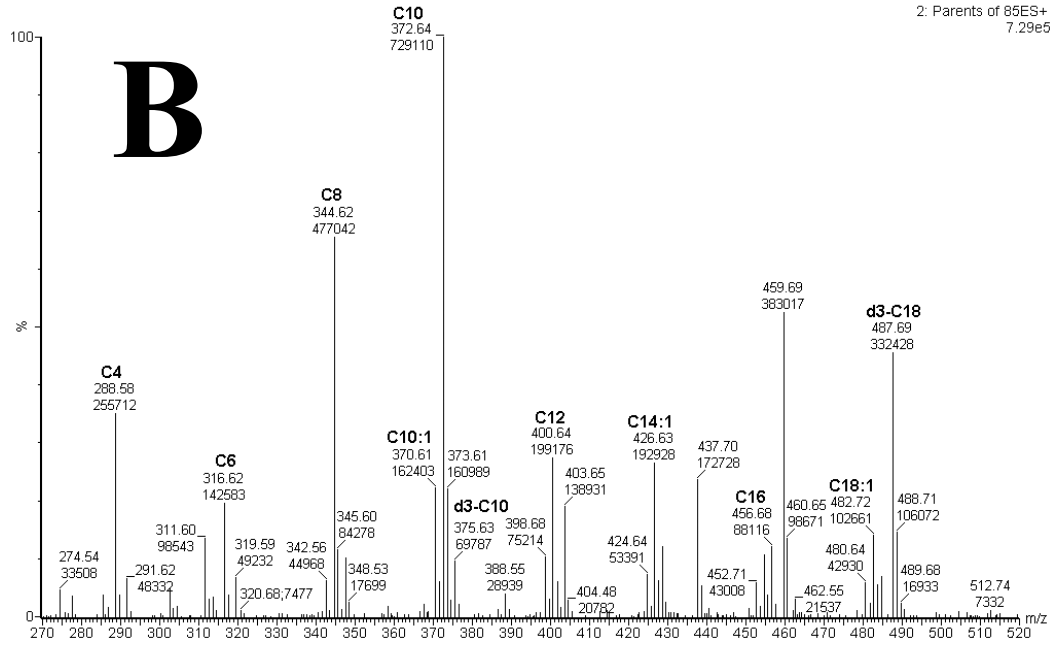


At least 11 different dehydrogenases involved in fatty acid oxidation or amino acid metabolism use flavin adenine nucleotide (FAD) to capture electrons in different reactions. These are transferred to the electron transfer flavoprotein (ETF) and then by the electron transfer flavoprotein oxidoreductase (ETF:QO) to ubiquinone that will carry them along the respiratory chain. A deficiency in this process will impair activity of multiple dehydrogenases (multiple acyl CoA dehydrogenase deficiency – MADD).

Watmough NJ, Frerman FE. The electron transfer flavoprotein: ubiquinone oxidoreductases. Biochim Biophys Acta. 2010 Dec;1797(12):1910-6.

Plasma acylcarnitine profile: MADD





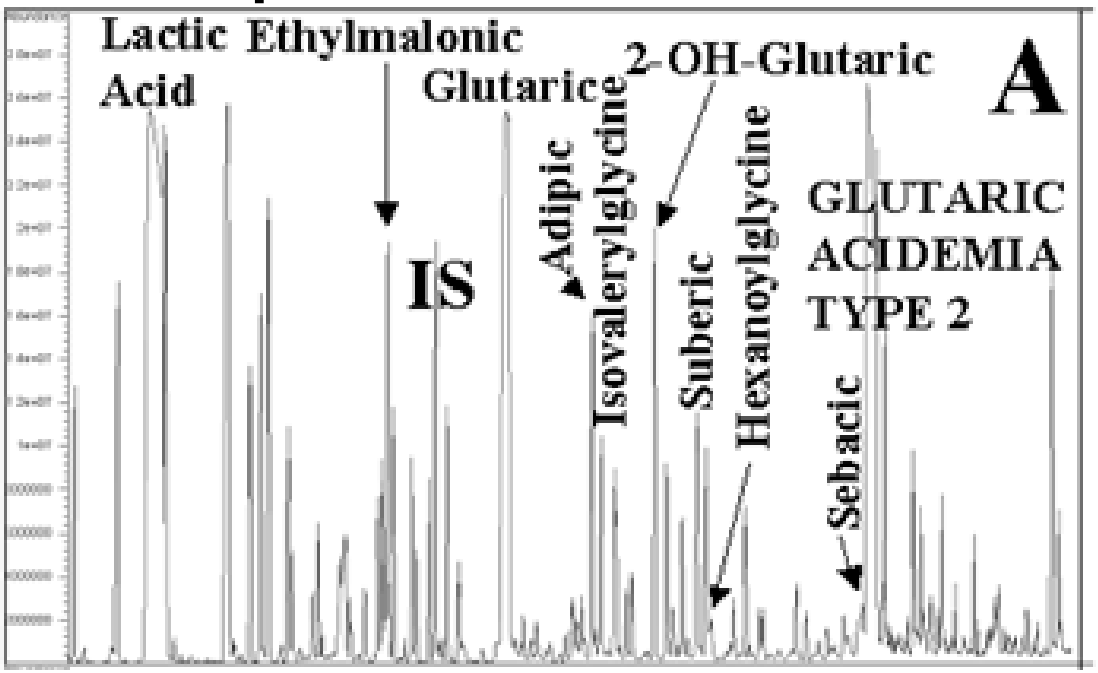
A. Symptomatic at diagnosis (2 days of age).
B. Identified by newborn screening. Similar profile in late-onset patients.

Courtesy of Dr. Marzia Pasquali, ARUP laboratories.

URINE ORGANIC ACIDS: MADD

In addition to glutaric acid, isovaleric, lactic and pyruvic, ethylmalonic, 2-OH-glutaric, dicarboxylic acids are also elevated, reflecting impairment of multiple dehydrogenases.

Urine organic acid and urine acylglycines (elevated hexanoyl- and suberyl-glycine) can normalize when the patient is well compensated.



Hedlund GL, Longo N, Pasquali M. Glutaric acidemia type 1. Am J Med Genet C Semin Med Genet. 2006 May 15;142C(2):86-94

Riboflavin-Deficiency as cause of MADD

Maternal riboflavin deficiency can be due to haploinsufficiency for the high-affinity riboflavin transporter RFT1. Biochemical abnormalities can be absent in some patients.

Riboflavin Metabolism Disorders to Consider in the Differential Diagnosis of MADD: *FLAD1, SLC52A1, SLC52A2, SLC52A3*

Brown-Vialetto-Van Laere Syndrome (MIM 211530, PONTOBULBAR PALSY WITH DEAFNESS) and Fazio-Londe disease (MIM 211500, PROGRESSIVE BULBAR PALSY OF CHILDHOOD) are neurologic conditions linked to deficiency of RFT2 (autosomal recessive).

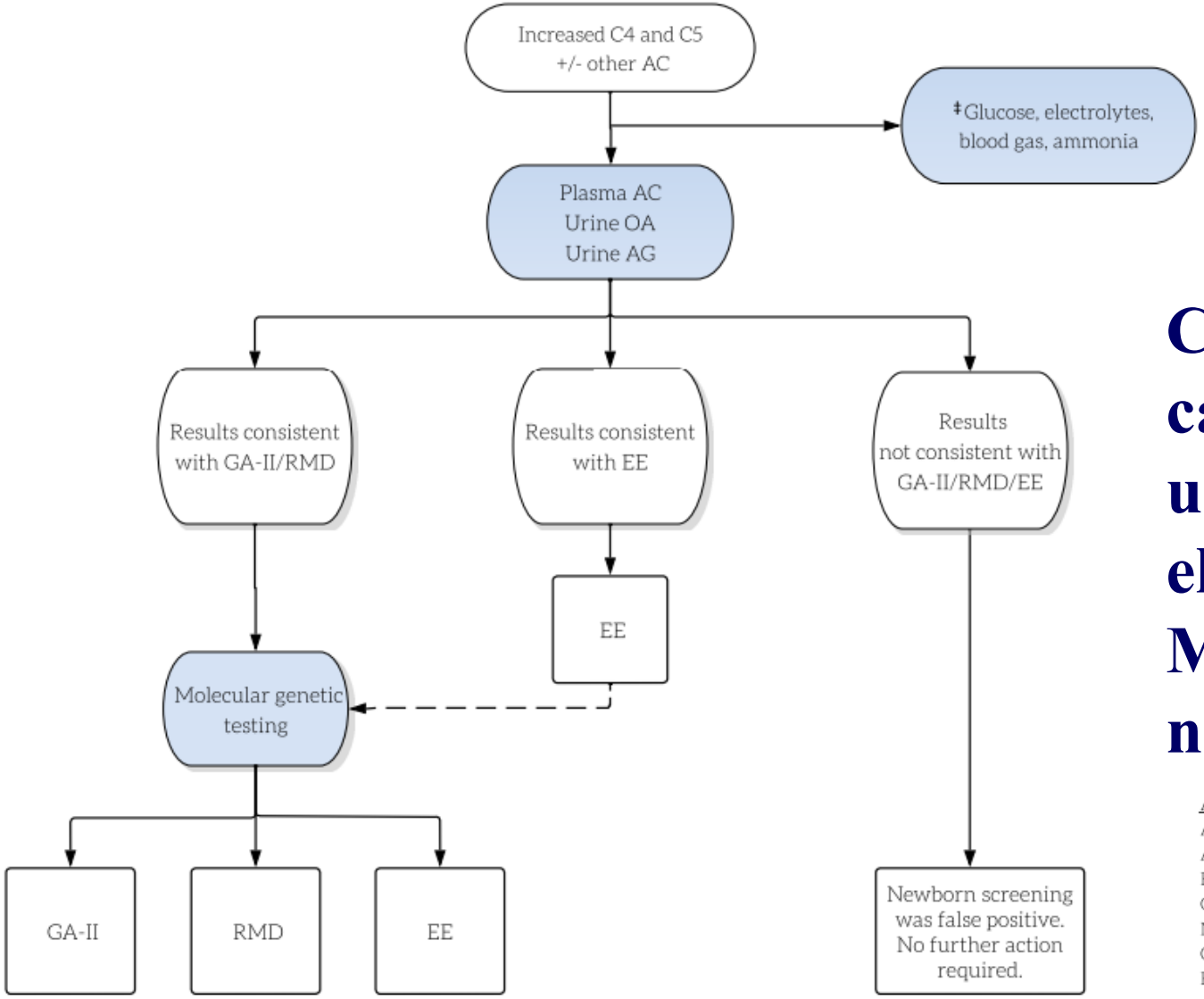
In both conditions, high doses of riboflavin can reverse or improve the biochemical and clinical phenotype.

Bosch AM, Abeling NG, Ijlst L, Knoester H, van der Pol WL, Stroomer AE, Wanders RJ, Visser G, Wijburg FA, Duran M, Waterham HR. Brown-Vialetto-Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment. J Inherit Metab Dis. 2011 Feb;34(1):159-64

Ho G, Yonezawa A, Masuda S, Inui K, Sim KG, Carpenter K, Olsen RK, Mitchell JJ, Rhead WJ, Peters G, Christodoulou J. Maternal riboflavin deficiency, resulting in transient neonatal-onset glutaric aciduria Type 2, is caused by a microdeletion in the riboflavin transporter gene GPR172B. Hum Mutat. 2011 Jan;32(1):E1976-84.

ACMG
American College of Medical Genetics and Genomics

Glutaric Acidemia II (GA-II)/MADD, Riboflavin Metabolism Disorder, Ethylmalonic Encephalopathy:
C4 and C5 elevated +/- other elevated acylcarnitines (AC)



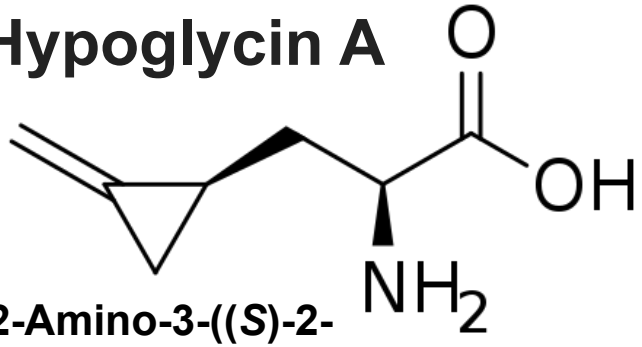
C10 and C12 carnitine are usually the most elevated in MADD (apart neonatal cases)

Abbreviations
AC = acylcarnitines
AG = acylglycines
EE = Ethylmalonic encephalopathy
GA-II = Glutaric acidemia Type 2
MADD = Multiple Acyl-CoA dehydrogenase deficiency
OA = organic acids
RMD = Riboflavin metabolism disorder

MADD-like diseases

Jamaican vomiting sickness: caused by ingestion of unripe akee. Akee tree (Blighia sapida) originates in Western Africa and was brought to Jamaica in 18th century, with the slave ships. It was observed in Ohio with consumption of canned akee.

Hypoglycin A



(*S*)-2-Amino-3-((*S*)-2-methylenecyclopropyl)propanoic acid

Exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and HPTP (the tetrahydropyridinyl analog of haloperidol).

McTague JA, Forney R Jr. Jamaican vomiting sickness in Toledo, Ohio Ann Emerg Med. 1994 May;23(5):1116-8

Mienie LJ, Bergh JJ, Van Staden E, Steyn SJ, Pond SM, Castagnoli N Jr, Van der Schyf CJ. Metabolic defects caused by treatment with the tetrahydropyridine analog of haloperidol (HPTP), in baboons. Life Sci. 1997;61(3):265-72.

SUMMARY

Inherited defects of the carnitine cycle and fatty acid oxidation can present at any age when energy from fat is needed (fasting, infections, fever).

Patients can appear perfectly normal between episodes, for which DNA testing (FAOD panel) is necessary to confirm or exclude the diagnosis.

Therapy requires fasting avoidance, low fat diet, carnitine, MCT oil/triheptanoin.

SUMMARY

Carnitine transporter deficiency causes low carnitine levels and presents with hepatic encephalopathy, cardiomyopathy and sudden death (Low C0).

CPT-1A deficiency causes high carnitine levels with low levels of long-chain acylcarnitine and can cause hypoglycemia and hepatic failure (High C0).

CACT deficiency can present even at birth with hypoglycemia and cardiac arrest (High C16, C18, C18:1, C18:2, Low C0).

The common form of CPT2 deficiency presents with exercise induced muscle pain and myoglobinuria (High C16, C18, C18:1, C18:2). Can be missed by NBS.

SUMMARY

MCAD deficiency is the most frequent FAOD and presents with fasting-induced arrest/hypoglycemia (High C8 (C6<C8>C10,C10:1)).

VLCAD deficiency causes a spectrum of phenotype with hypoglycemia, cardiomyopathy, cardiac arrest, exercise/fasting induced rhabdomyolysis (High C14:1, C14 (C14:1>C14, C16, C18, C18:1)).

LCHAD/TFP deficiency can present even at birth with hypoglycemia and cardiac arrest. Can cause cardiomyopathy, neuropathy retinitis pigmentosa (High C16OH (C14OH, C18OH, C18:1OH)).

SUMMARY

SCAD deficiency is a benign condition. Important to distinguish from isobutyrylglycinuria and ethylmalonic encephalopathy (High C4).

MADD deficiency causes a spectrum of phenotype with hypoglycemia, cardiomyopathy, cardiac arrest, exercise/fasting induced rhabdomyolysis. Can be mimicked by riboflavin deficiency (High C4, C5, C8 (C6<C8<C10, C12, C14, C14:1)).

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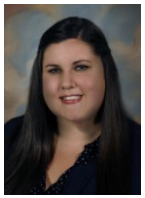



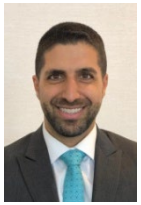


ARUP Laboratories

Marzia Pasquali PhD

Co-Author of all slides

All patients and their families.