MEDICAL BIOCHEMICAL GENETICS
CLINICAL CORE
SEMINAR SERIES

Hosted by:

University of Colorado
Anschutz Medical Campus

Fatty Acid Oxidation, Carnitine, Ketone disorders – Part 2

Nicola Longo MD PhD

Professor of Pediatrics

Adjunct Professor of Pathology and Nutrition and Integrative Physiology

Chief, Division of Medical Genetics

Co-Director Biochemical Genetics Lab, ARUP

University of Utah, Salt Lake City UT, USA

20 August 2021
2 September 2021

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

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 or deficiency of riboflavin transporters.

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)

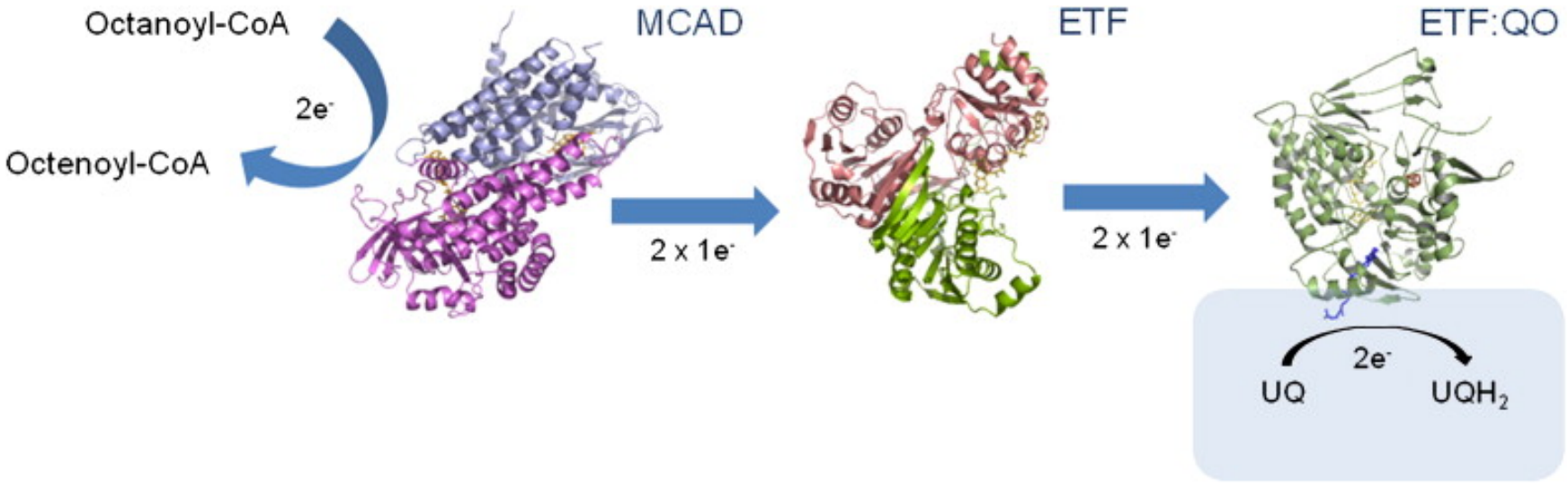
Glutaric acidemia type 2 (GA-2)/Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

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 (100-400 mg/day), ubiquinol (100-400 mg/day) at age 1, carnitine (100 mg/kg), essential FA supplements

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

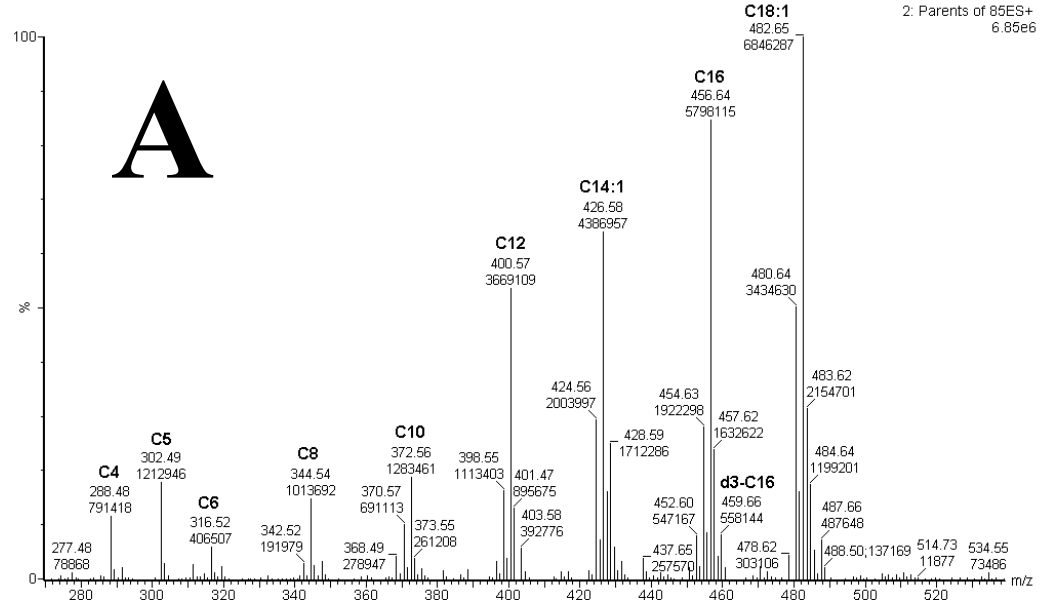
Prognosis: severe for neonatal forms; not well characterized for the others.

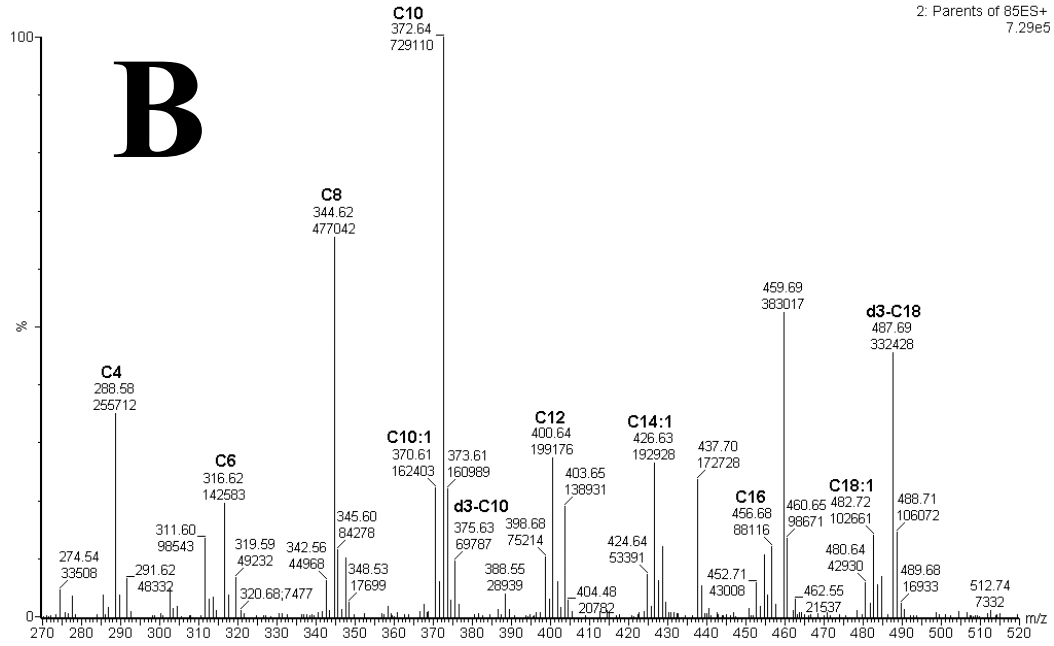


At least 11 different dehydrogenases involved in fatty acid oxidation or amino acid metabolism use flavin adenine nucleotide (FAD) to capture electrons in different reactions. These are transferred to the electron transfer flavoprotein (ETF) and then by the electron transfer flavoprotein oxidoreductase (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





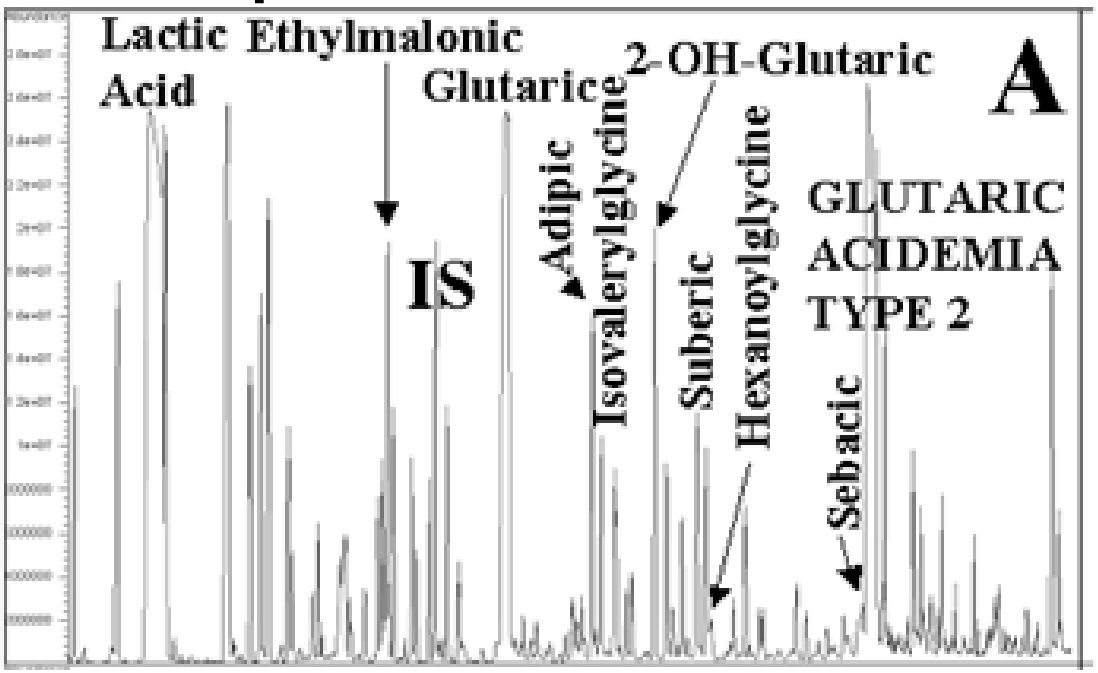
A. Symptomatic at diagnosis (2 days of age).
B. Identified by newborn screening. Similar profile in late-onset patients.

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.

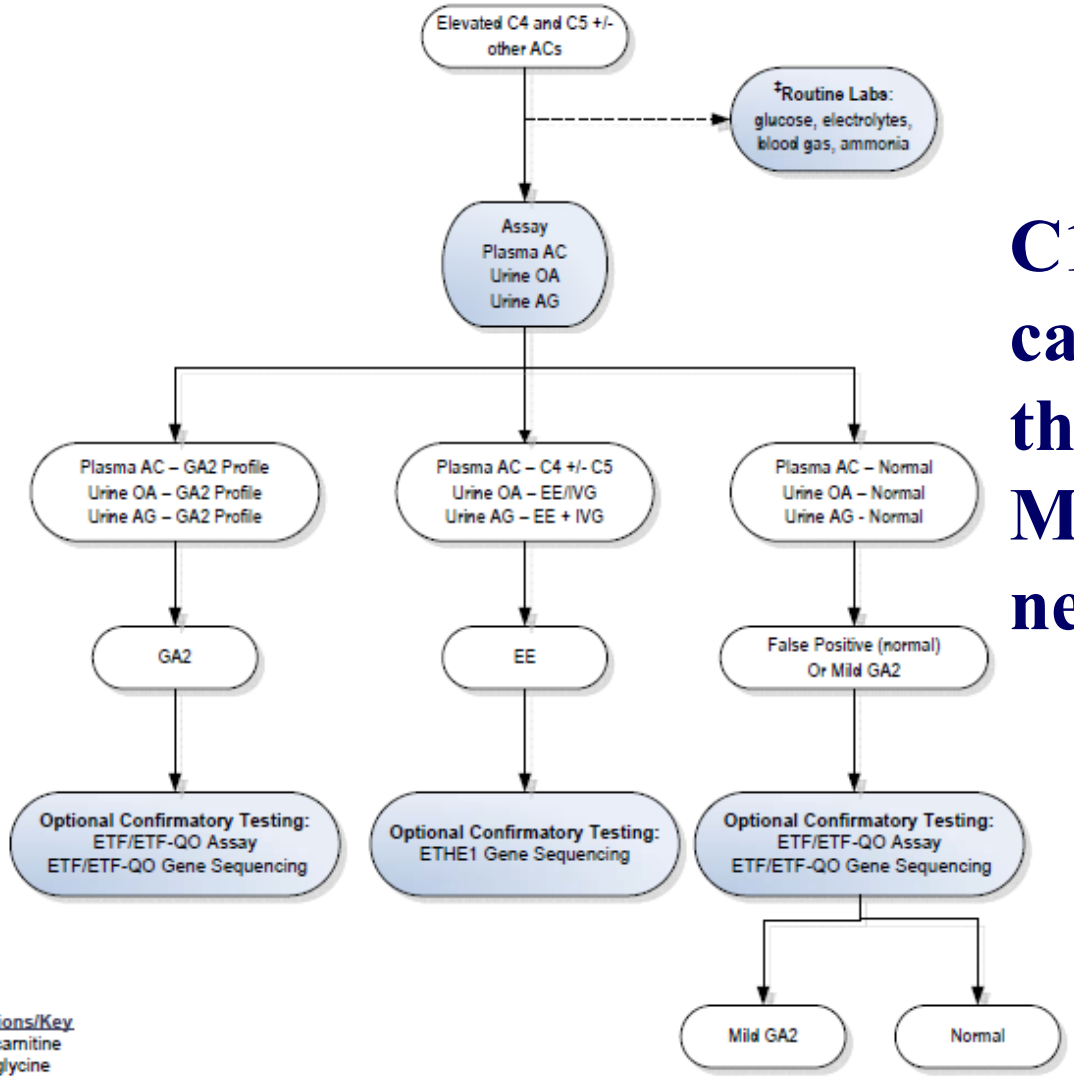
Urine organic acid and urine acylglycines (elevated hexanoyl- and suberyl-glycine) can normalize when the patient is well compensated.



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

ACMG
American College of Medical Genetics and Genomics

C4 and C5 +/- Other Acylcarnitines Elevated



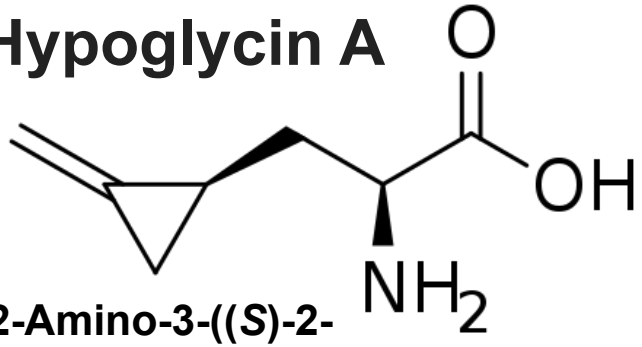
C10 and C12 carnitine are usually the most elevated in MADD (apart neonatal cases)

Abbreviations/Key
AC = Acylcarnitine
AG = Acylglycine
EE = Ethylmalonic encephalopthy 1
ETF = Electron transfer flavoprotein
GA2 = Glutaric aciduria Type
IVG = Isovaleryl glycine
OA = Organic acid

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 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).

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)).

DISORDERS OF KETONE BODIES SYNTHESIS AND UTILIZATION

Objectives

Understand why and where ketones are synthesized

Define enzymes involved in ketone synthesis and utilization

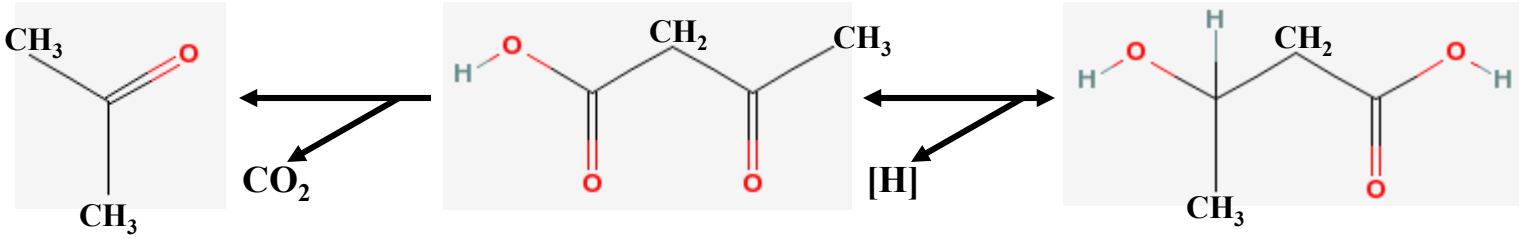
List therapies for disorders of ketone body synthesis and utilization

KETONE BODIES METABOLISM

- Ketone bodies are important in energy transfer during fasting or other lypolitic stresses.
- They derive from beta-oxidation of fatty acids and from ketogenic amino acid (leucine, lysine, isoleucine) catabolism.
- They are produced in liver mitochondria and are transported to extrahepatic tissues where they are utilized.
- Ketogenesis (hepatic ketone body formation) and ketolysis (extra hepatic ketone body utilization) are important processes, especially for the brain, to provide energy when glucose can not meet the metabolic need.
- Physiological levels of ketone bodies in plasma range from <0.1 mM (post-prandial) to 6 mM (prolonged fasting), they can reach 25 mM in diabetic ketoacidosis.
- Most of the ketone bodies are taken up by the extra hepatic tissues, 10-20% are lost in the urine during ketosis.

KETONE BODIES

- Three compounds are usually listed as “ketone bodies”: 3-hydroxybutyrate, acetoacetate, acetone.
- Acetoacetate is the main ketone body, acetone derives from its decarboxylation, while 3-hydroxybutyrate derives from its reduction.



Acetone **Acetoacetic acid** **3-Hydroxybutyric acid**

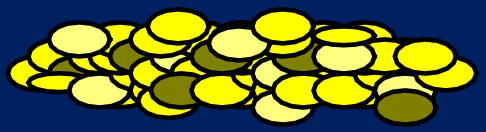
KETONE BODIES METABOLISM

- Rate of utilization of ketone bodies is proportional to their circulating levels.
- Heart and kidney have the greatest capacity for ketone utilization.
- The ketogenic pathway provides fat-derived fuel for the brain when glucose is low.
- Patients with defects in ketone synthesis or degradation are asymptomatic unless they are fasting:
  - **Defects of ketogenesis: hypoketotic hypoglycemia**
  - **Defects of ketolysis: ketoacidosis (severe) ± hypoglycemia**

HSL (Hormone Sensitive Lipase) Releases Fatty Acids from adipocytes. Transcription of HSL is increased during fasting and suppressed by insulin and glucose.

FATTY ACID OXIDATION DURING FASTING

ADIPOSE TISSUE



FATTY ACIDS

HEART

SKELETAL MUSCLE

LIVER

KETONES

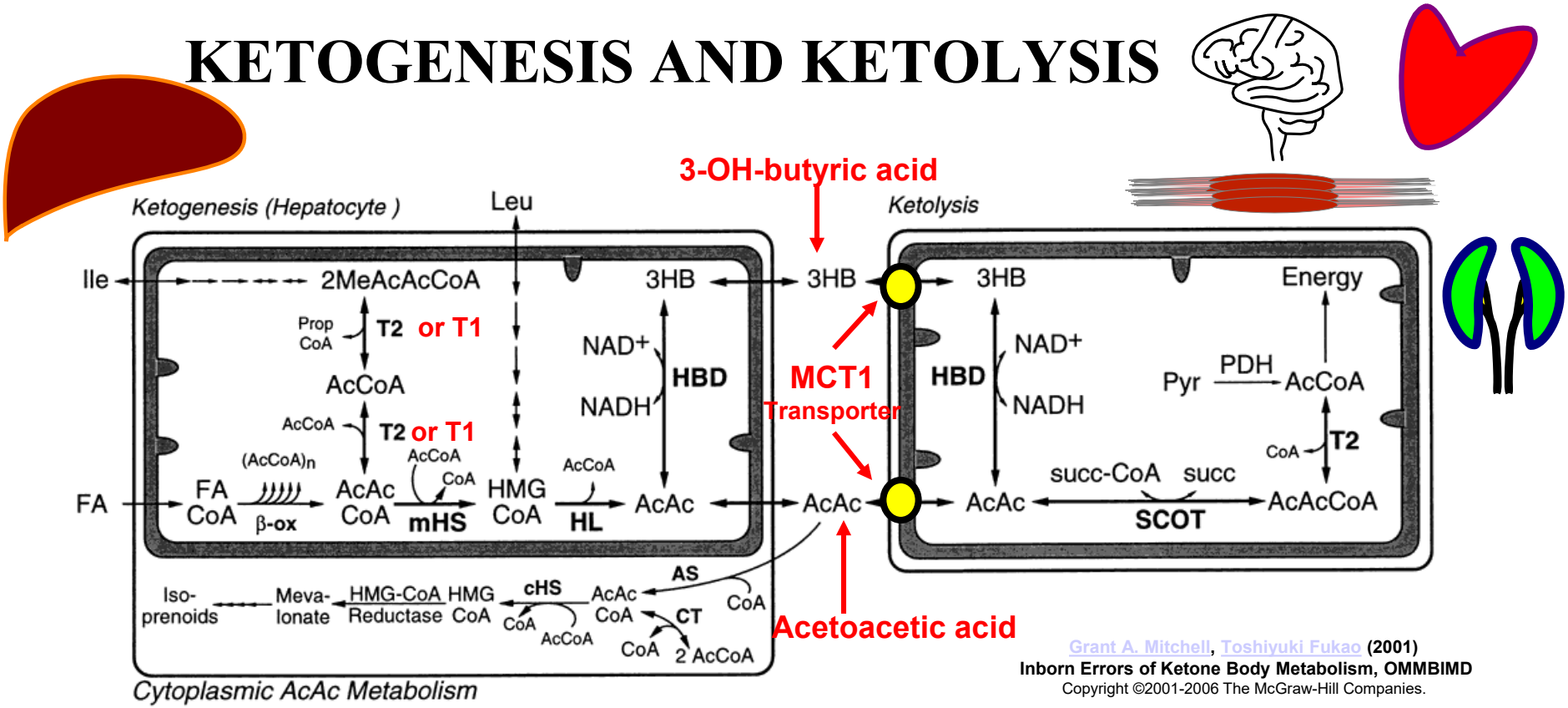
ß-hydroxybutyrate
acetoacetate

BRAIN

KETOGENESIS AND KETOLYSIS

- Ketogenesis is regulated by two hepatic mitochondrial enzymes:
  - **3-hydroxy-3-methylglutaryl-CoA synthase (mHS)**
  - **3-hydroxy-3-methylglutaryl-CoA lyase (HL)**
- Ketolysis in extra hepatic mitochondria is mediated by reversible reactions catalyzed by:
  - **The MCT1 transporter (*SLC16A1*): entry of ketones into tissues**
  - **SuccinylCoA:3-ketoacid(oxoacid) CoA transferase (SCOT)**
  - **Mitochondrial acetoacetyl-CoA thiolase (T2)(*ACAT1*)**
- Deficiencies of mHS or HL cause disorders of ketogenesis; deficiencies of MCT1, SCOT or T2 cause disorders of ketolysis.
- All are inherited as autosomal recessive traits

KETOGENESIS AND KETOLYSIS



Acetoacetate is synthesized from acetylCoA by cytosolic acetoacetyl-CoA thiolase (*ACAT2* gene, T1). Acetoacetyl-CoA (AcAc-CoA) and acetyl-CoA via two enzymatic steps (mitochondrial Hydroxy Methyl Glutaryl CoA synthase (mHS), a highly regulated enzyme, and Hydroxy Methyl Glutaryl CoA lyase (HL)) form ketones. The liver has both T2 (*ACAT1*, mitochondrial) and T1 (*ACAT2,* cytosolic) thiolase. R-3-hydroxybutyrate dehydrogenase (3HBD) catalyzes the reduction of Acetoacetate to 3-OH-butyrate.

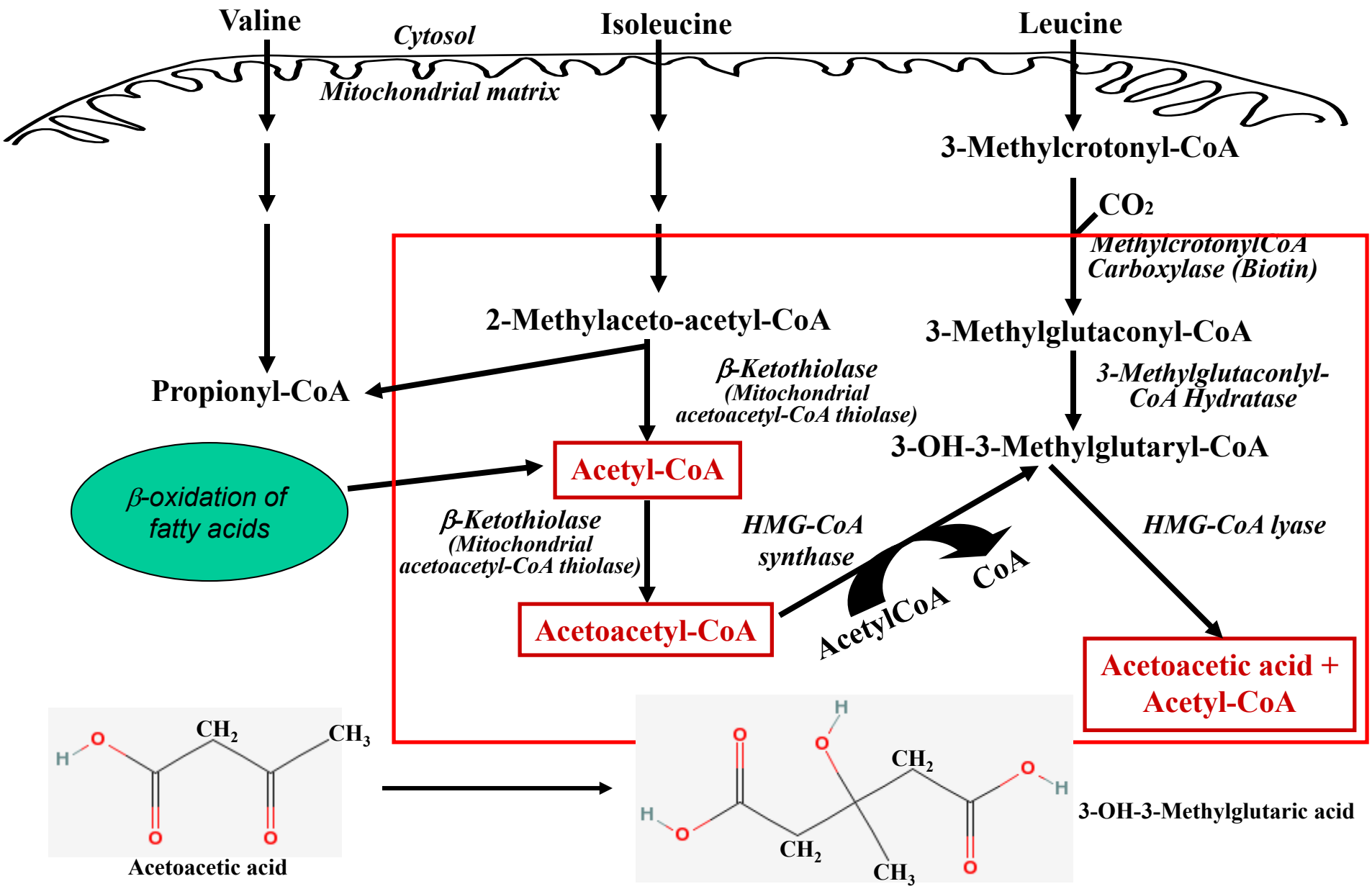
The MCT1 transporter mediates the uptake of ketones by peripheral tissues

HBD: 3-Hydroxy Butyrate Dehydrogenase

T1: *ACAT2*: cytosolic acetoacetyl-CoA thiolase

T2: *ACAT1*: mitochondrial acetoacetyl-CoA thiolase : MAT

BRANCHED-CHAIN AMINO ACID METABOLISM



DISORDERS OF KETOGENESIS

Mitochondrial 3-Hydroxy-3-Methyl-Glutaryl-CoA Synthase deficiency, mHS (OMIM 605911)

Frequency: rare

Presentation: hypoketotic hypoglycemia, metabolic acidosis, encephalopathy progressing to coma after fasting or infections, hepatomegaly. Can present without hypoglycemia.

Labs: Elevated serum free fatty acids and triglycerides at time of hypoglycemia, elevated acetylcarnitine, but acylcarnitines may be normal, dicarboxylic aciduria can be seen, 4-hydroxy-6-methyl-2-pyrone and 3-hydroxyglutarate can be present, ketones absent or barely present, normal lactate

Diagnosis: DNA testing: *HMGCS2* gene (1p13-p12)

Therapy: Fasting avoidance, cornstarch

DISORDERS OF KETOGENESIS

3-Hydroxy-3-Methyl-Glutaryl-CoA Lyase deficiency, HL (OMIM 246450)

Presentation early in life with vomiting, seizures, unconsciousness, hepatomegaly.

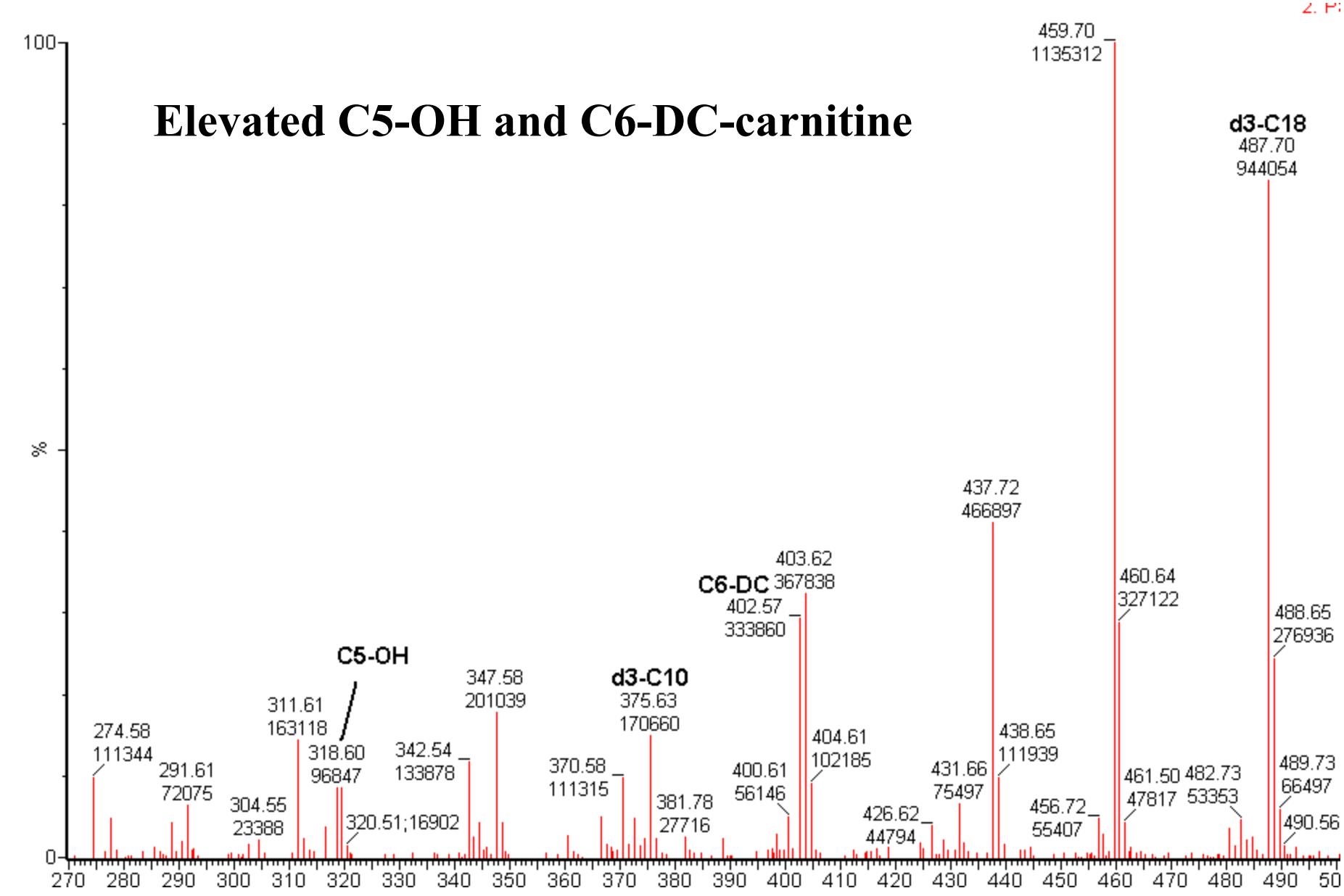
Labs: Hyperammonemia, acidosis, increased anion gap, elevated transaminases, hypoglycemia. Organic acids: Elevated excretion of 3-hydroxy-3-methylglutaric acid, 3-methylglutaconic acid, 3-methylglutaric acid, (3-hydroxyisovaleric acid, 3-methylcrotonylglycine); elevated 3-methylglutaryl (C6-DC) and 3-OH-isovaleryl- (C5OH) carnitine.

Diagnosis: DNA testing: *HMGCL* gene (1pter-p33)

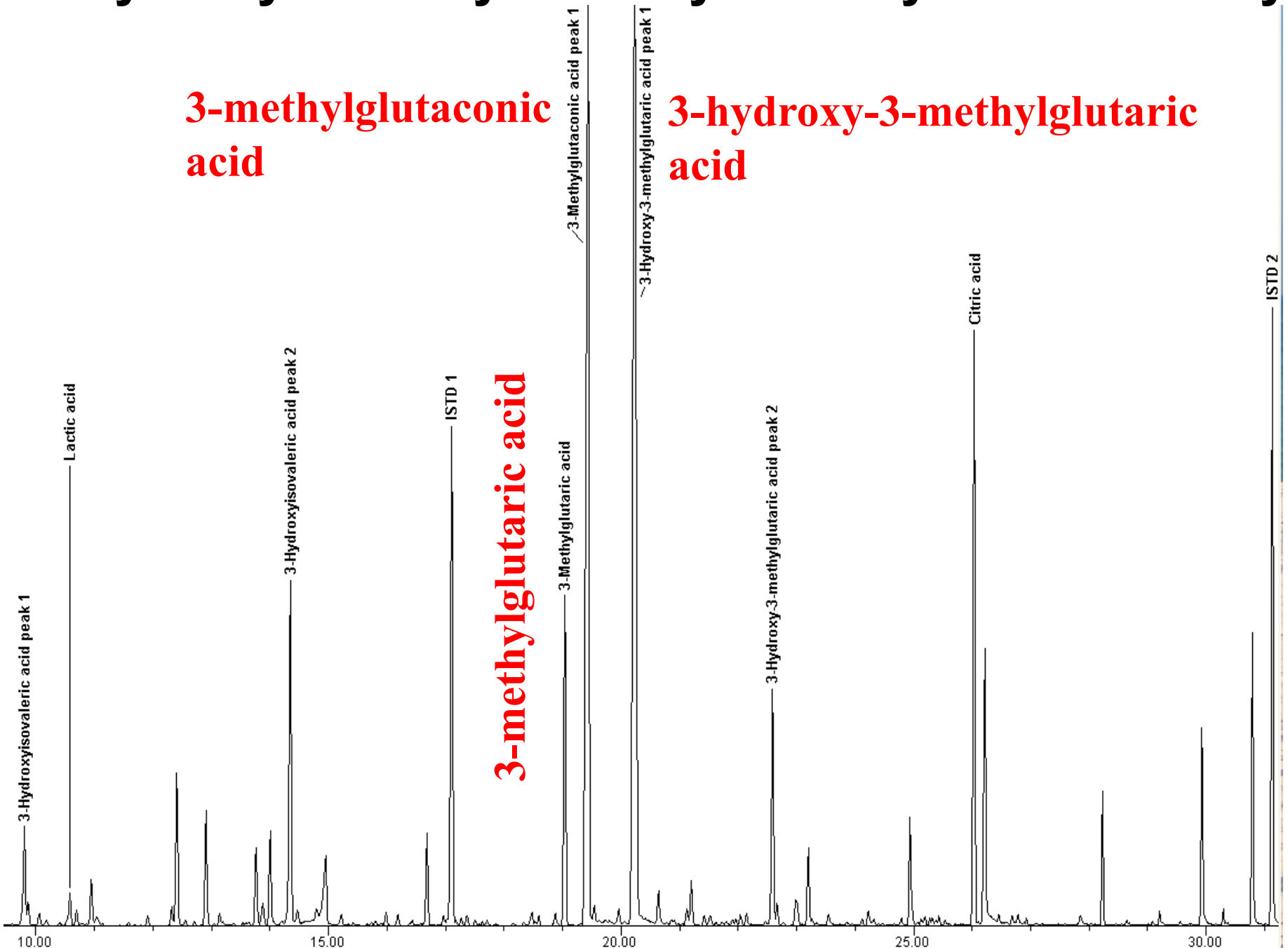
Therapy: Fasting avoidance, carnitine, moderate protein restriction early in life, reduce fat calories to <30%, cornstarch supplements.

Grünert SC, Schlatter SM, Schmitt RN, Gemperle-Britschgi C, Mrázová L, Balcı MC, Bischof F, Çoker M, Das AM, Demirkol M, de Vries M, Gökçay G, Häberle J, Uçar SK, Lotz-Havla AS, Lücke T, Roland D, Rutsch F, Santer R, Schlune A, Staufner C, Schwab KO, Mitchell GA, Sass JO. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: Clinical presentation and outcome in a series of 37 patients. Mol Genet Metab. 2017 Jul;121(3):206-215. doi: 10.1016/j.ymgme.2017.05.014. Epub 2017 May 22. PMID: 28583327

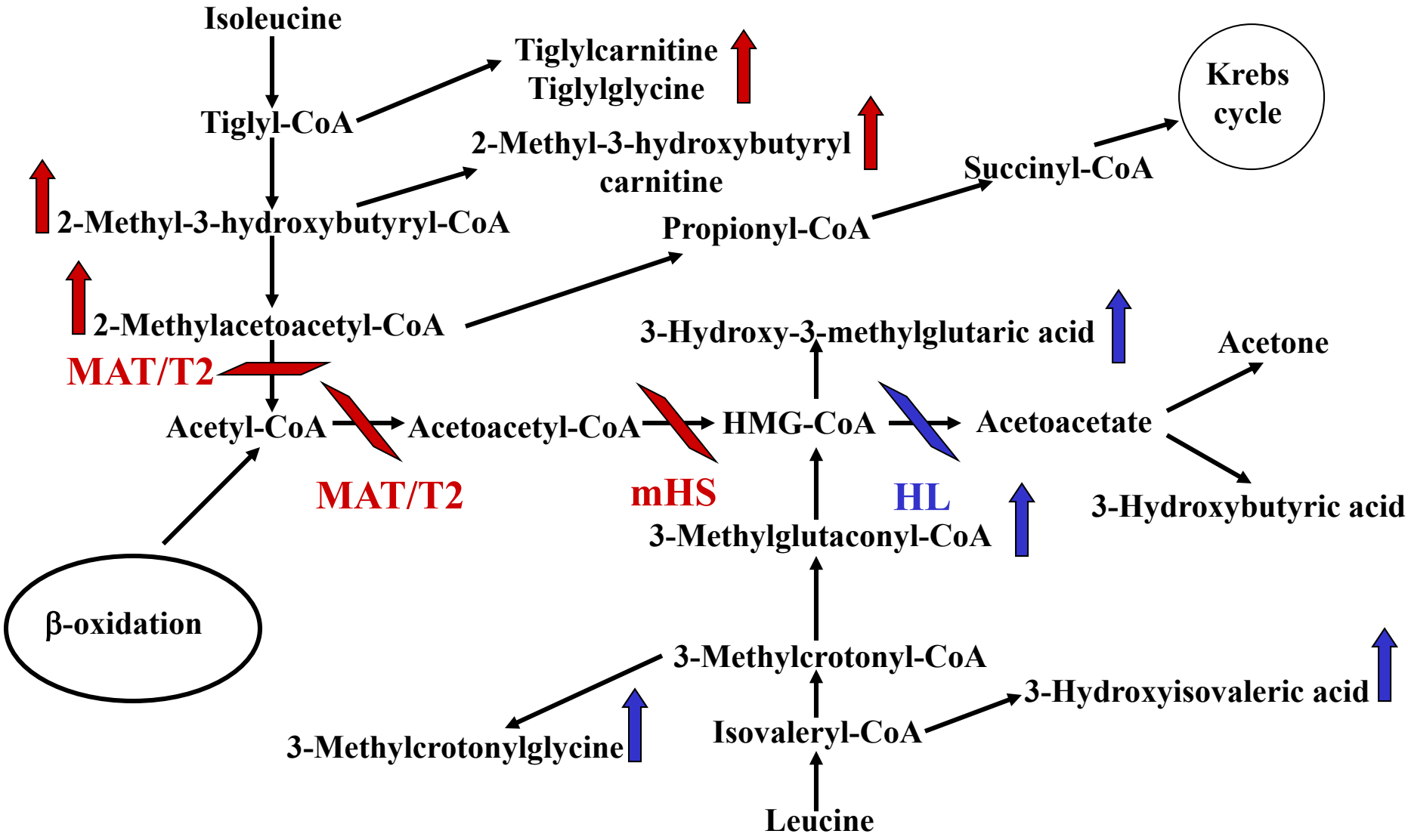
3-Hydroxy-3-Methyl-Glutaryl-CoA Lyase deficiency

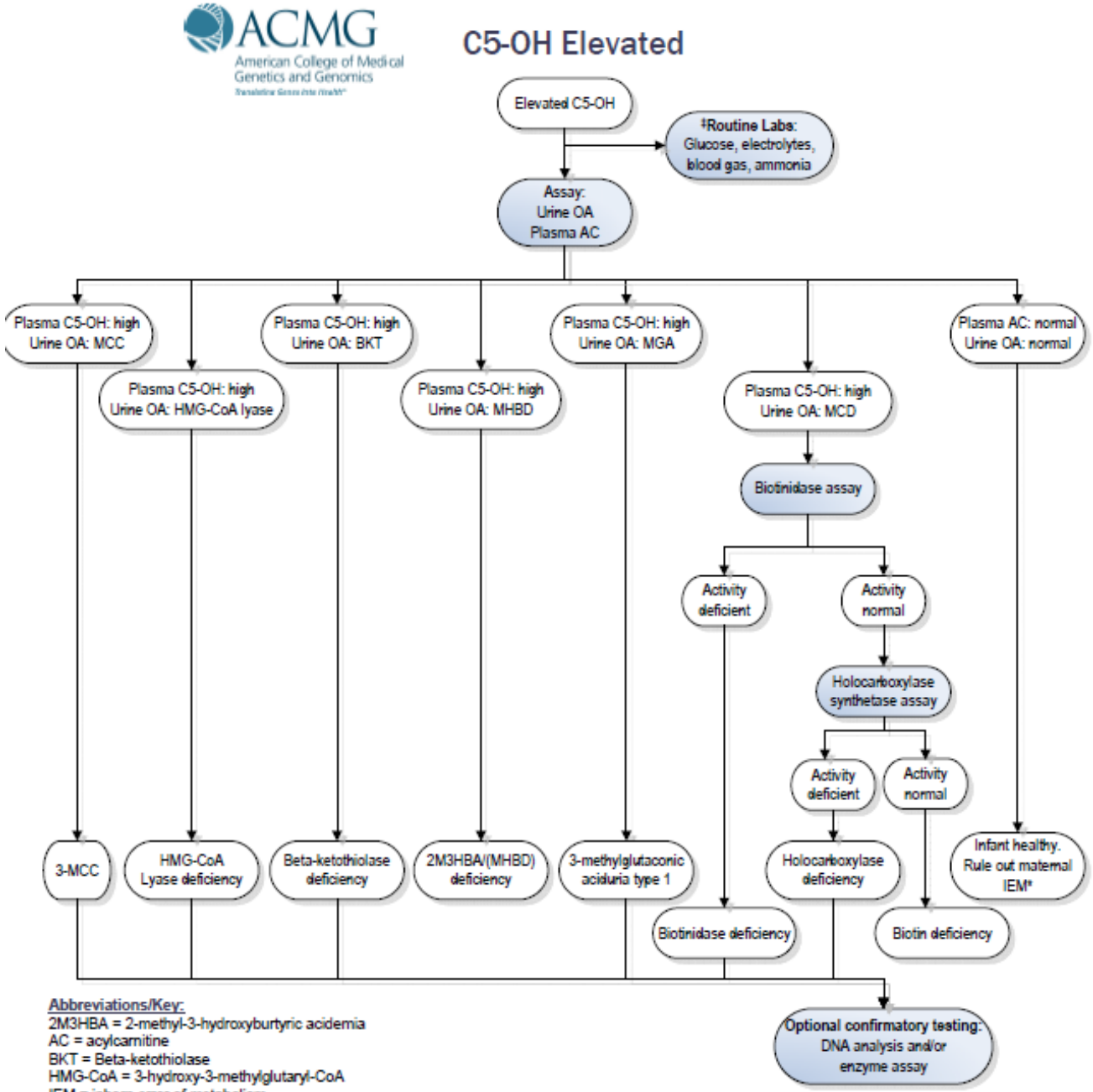


3-Hydroxy-3-Methyl-Glutaryl-CoA Lyase deficiency



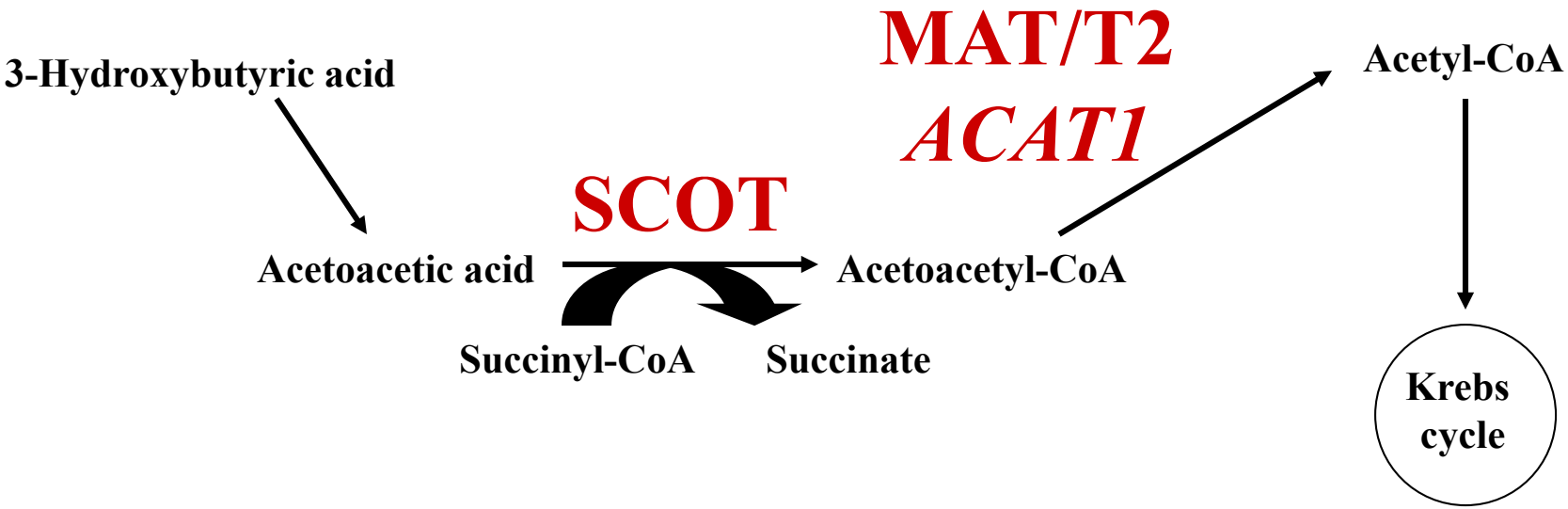
DISORDERS OF KETOGENESIS





3-methylglutaryl (C6-DC) can be elevated as well in HMG-CoA Lyase deficiency

BETA KETOTHIOLASE DEFICIENCY



Mitochondrial acetoacetyl-CoA thiolase, MAT/T2 (OMIM 203750): has a ketolytic role (converts acetoacetyl-CoA and CoA in two molecules of acetyl-CoA) and a ketogenic role (converts 2-methylacetoacetyl-CoA and CoA in acetyl-CoA and propionyl-CoA).

Presentation: ketoacidosis, therefore the ketolytic process is more dependent upon adequate function of MAT/T2 (ACAT1): CAT/T1 (ACAT2) might bypass the defect in ketone body synthesis.

METABOLIC ACIDOSIS

3-Year-old male with a 24-hour history of vomiting, lethargy, starting the day of admission. In the emergency department, he had a blood glucose of 15 with 3+ ketones in the urine, metabolic acidosis (pH 6.8), bicarbonate <5, and BMP glucose of 7. Head CT was normal. Described as poor eater, very active in his sleep. No previous hospitalizations or surgeries. Has speech delay.

		Units	07/30/07	05/22/07
Na	137-146	mmol/L	139	144
K	3.4-4.7	mmol/L	3.9	4.4
Cl	98-109	mmol/L	106	120 H
CO2	18-24	mmol/L	24	* <5 L
Anion Gap	3-16	mmol/L	9	19 H
Glucose	60-115	mg/dL	91	95
BUN	5-17	mg/dL	12	32 H
Creatinine	0.3-0.7	mg/dL	0.4	0.6
Ca	8.7-9.8	mg/dL	9.4	7.8 L
Prot	5.9-7.0	g/dL	7.5 H	6.1
Alb	3.1-3.9	g/dL	4.7 H	3.6
Bili, Total	0.2-1.3	mg/dL	0.2	<0.1 L
Alk Phos	145-320	U/L	200	235
ALT	5-45	U/L	16	52 H
AST	20-60	U/L	55	69 H
Ammonia	21-50	umol/L	21	* 54 H

METABOLIC ACIDOSIS

Ketolytic enzymes, Fibroblasts:

Enzyme	Activity	Ref. range	Units
Beta-Ketothiolase	**10.3**	**(8.9-20.6)**	**nmol/min/mg protein**
Succinyl-CoA 3-ketotransferase	7.5	(2.6-8.6)	nmol/min/mg protein

- Interpretation: Beta-ketothiolase activity was in the low normal range, but not stimulated by potassium (normally K doubles enzyme activity).
- DNA *ACAT1* gene: c.T99A, p.Y33X; c.T155C, p.I52T
- Treatment: fasting avoidance, cornstarch and carnitine supplements.

BETA KETOTHIOLASE DEFICIENCY

Mitochondrial acetoacetyl-CoA thiolase deficiency

Presentation: intermittent ketoacidotic episodes during intercurrent illnesses, triggered by vomiting, fever.

Labs: Two groups of patients:

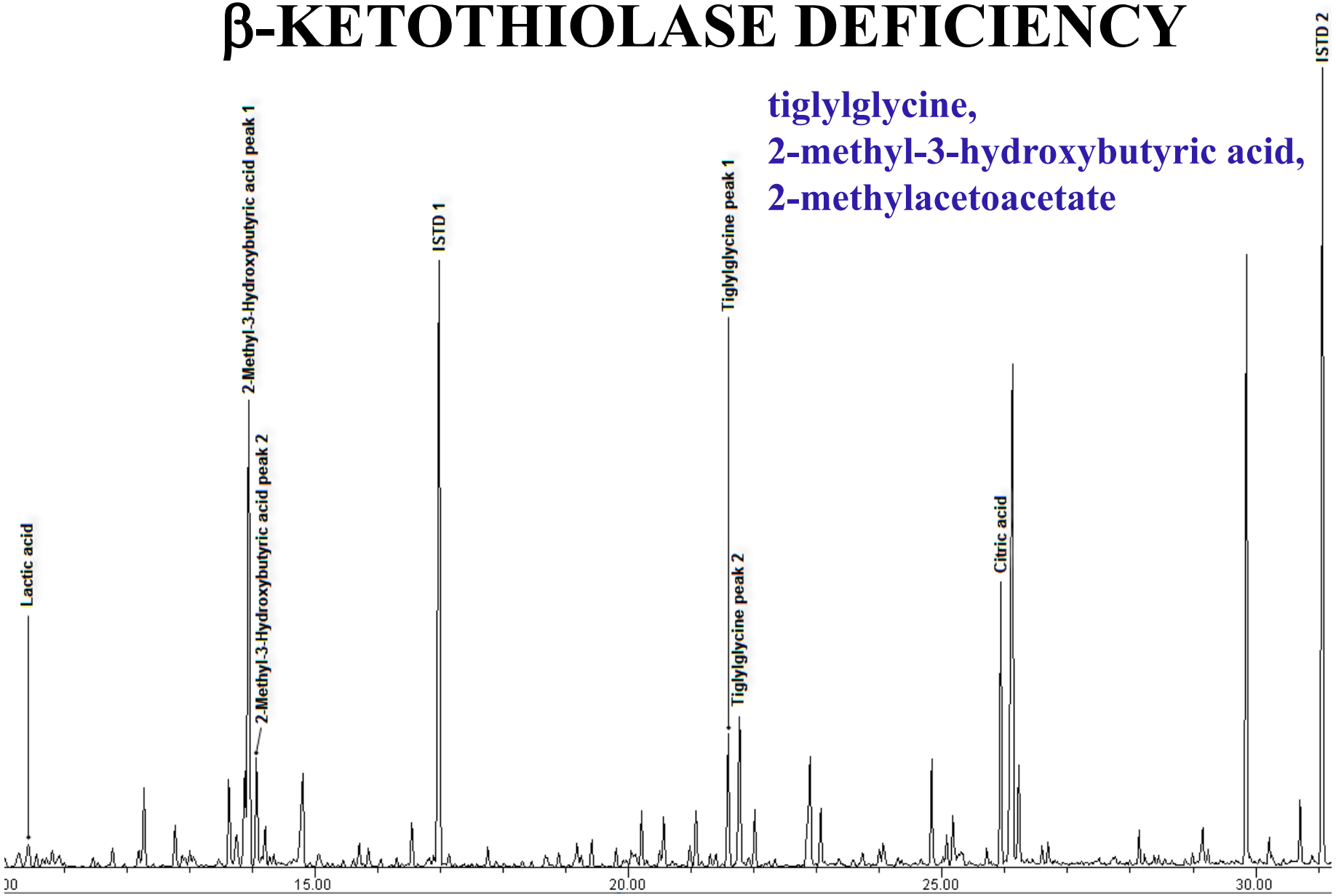
Group 1: no residual enzyme activity; urine organic acids ALWAYS show elevated tiglylglycine, 2-methyl-3-hydroxybutyric acid, 2-methylacetoacetate (unstable, rarely seen) with or without ketoacidosis; elevated tiglylcarnitine (C5:1) and 2-methyl-3-hydroxybutyrylcarnitine (C5OH).

Group 2: some residual enzyme activity; urine organic acids may be normal when stable; elevated tiglylcarnitine (C5:1) and 2-methyl-3-hydroxybutyrylcarnitine (C5OH). Newborn screening (and even acylcarnitine profile in plasma) can miss these patients .

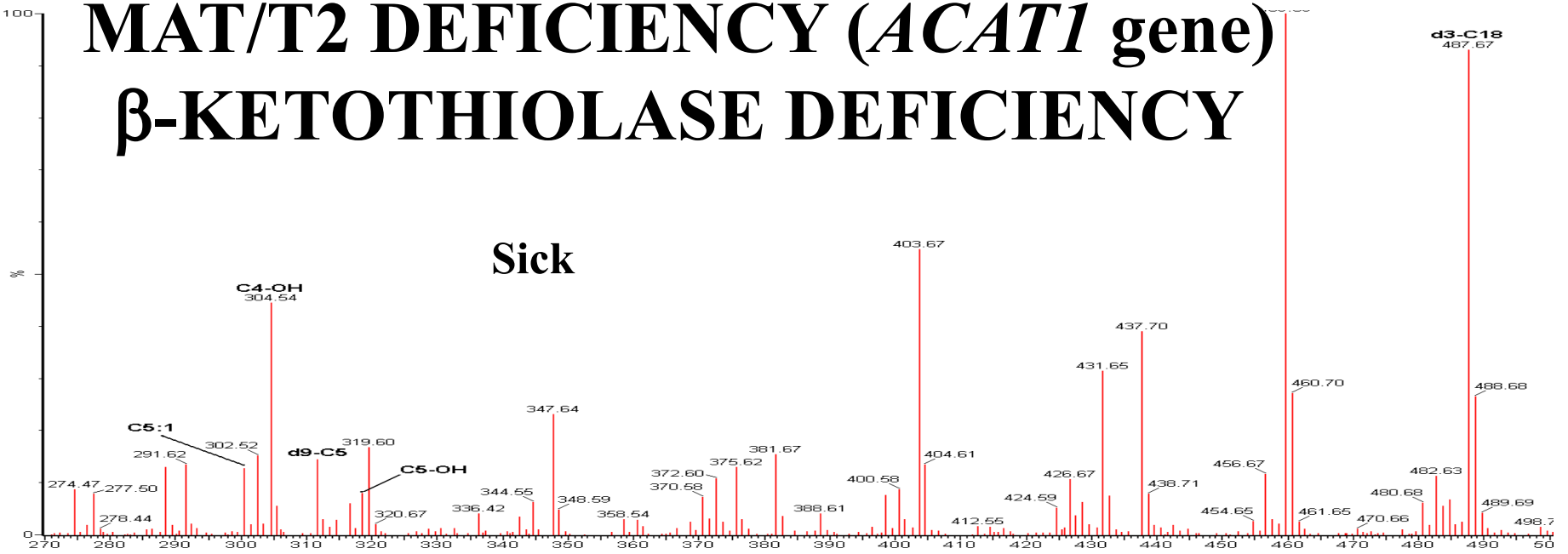
Diagnosis: DNA testing *ACAT1* gene (11q22.3-q23.1), enzyme assay

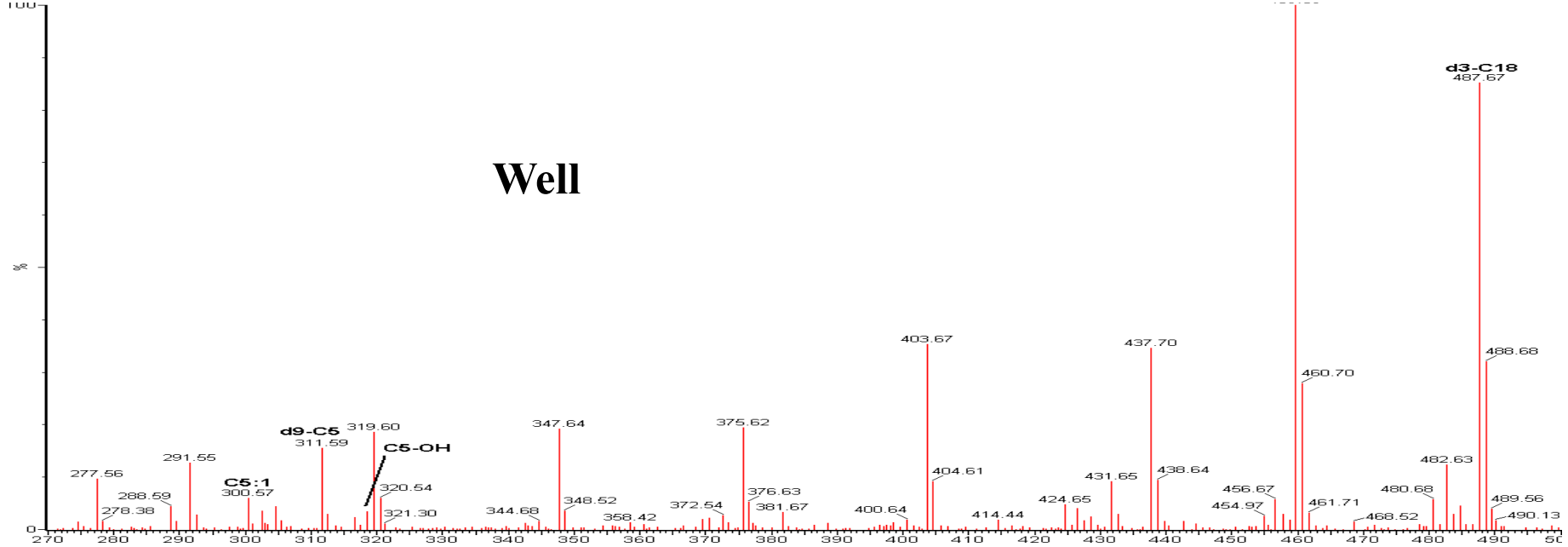
Therapy: Fasting avoidance, cornstarch, carnitine

MAT/T2 DEFICIENCY (*ACAT1* gene)
β-KETOTHIOLASE DEFICIENCY

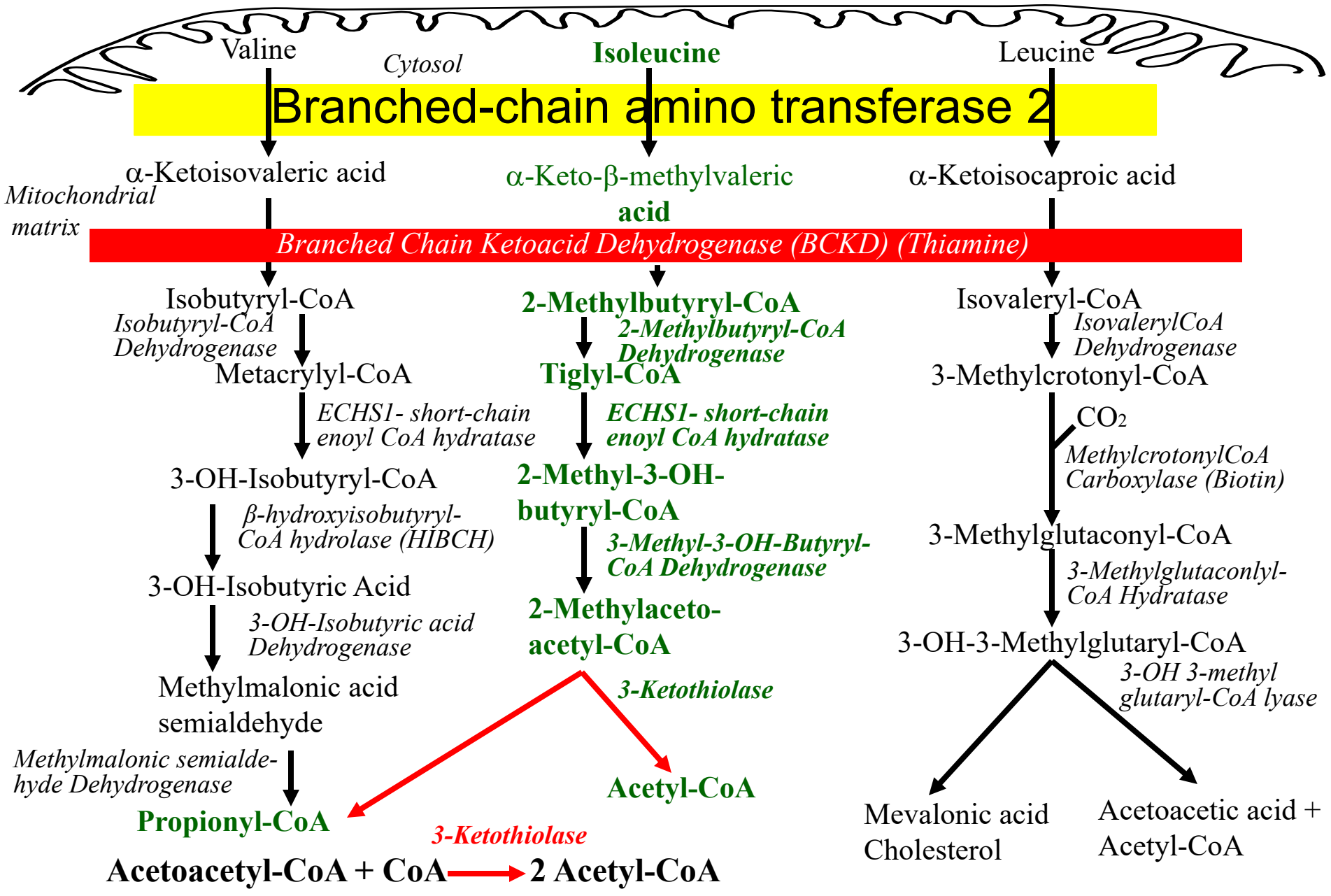


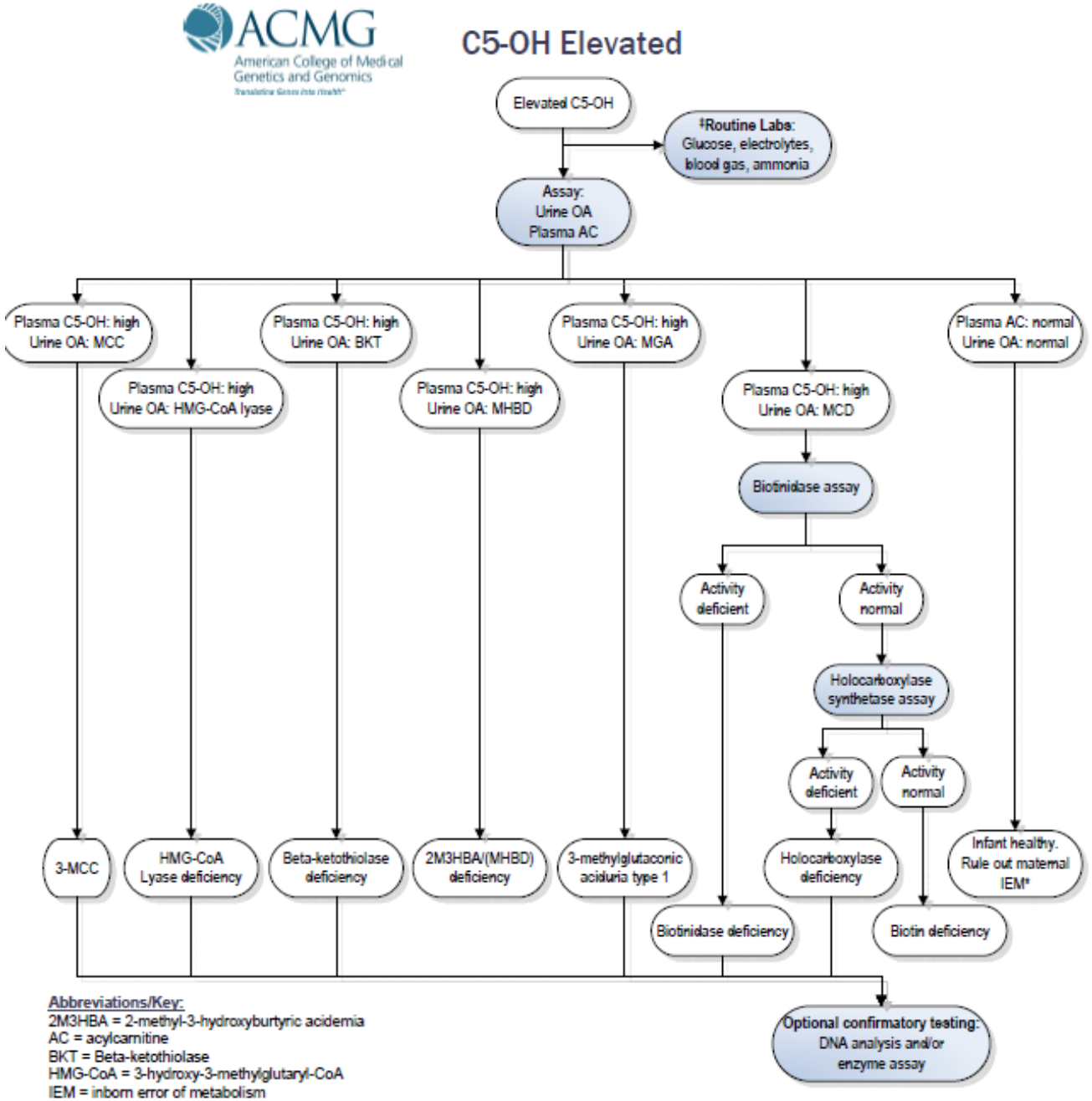
MAT/T2 DEFICIENCY (*ACAT1* gene)
β-KETOTHIOLASE DEFICIENCY





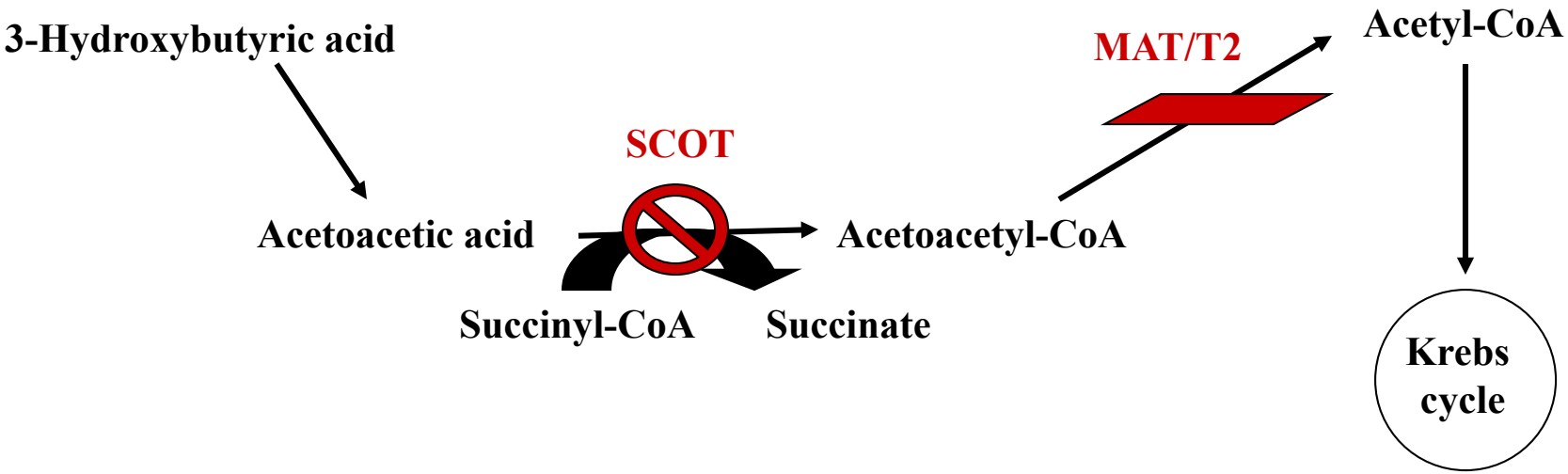
3-KETOTHIOLASE DEFICIENCY





C5-OH can be elevated, but we have seen combination of elevations of different species (C5:1, C4-OH) one at a time

SCOT deficiency



SCOT, Succinyl-CoA:3-ketoacid-CoA transferase (OMIM 245050) catalyzes the reversible rate-limiting step of ketolysis.

Cause: mutations in *OXCT* gene (5p12-p13).

OXCT gene not expressed in liver.

SCOT deficiency

Presentation: episodic, non-physiologic or exaggerated physiologic ketoacidosis: Tachypnea, lethargy, coma, severe ketoacidosis with elevated anion gap, persistent ketonemia/ketonuria even when stable or post-prandially, no diagnostic metabolites in urine or plasma. Ketones are present in fed state.

Diagnosis: Urine organic acids: increased Acetoacetate and 3-OH-Butyric acid, without other abnormal urine organic acids. It is differentiated from physiological ketosis for the absence of adipic, suberic, and sebacic acids, usually seen during severe physiologic ketosis.

Confirmation: DNA testing *OXCT1* gene on 5p13.

Therapy: prevention of fasting, alkali to prevent acidosis, mild protein and fat restriction, cornstarch, carnitine.

METABOLIC ACIDOSIS

- **Hispanic female, the first child of first cousin parents. Born prematurely with birth weight of 1.96 kg. Hospitalized for the first two months to achieve normal birth weight and for unspecified respiratory problems.**
- **At 8 months of age she had tachypnea, vomiting and lethargy following fever (39C). Severe metabolic acidosis with pH of 6.98, low CO2 (<5 mEq/L), an elevated anion gap (22-27 mEq/L), and hypokalemia (1.4-2 mEq/L). Glucose and ammonia were normal. Urine ketones were strongly positive.**
- **Acidosis was corrected by intravenous bicarbonate and peritoneal dialysis was initiated. Acidosis reappeared when dialysis was discontinued, for which she was kept on a regimen of daily dialysis.**
- **At 15 months of age, her growth and development were only mildly delayed. Hypoglycemia (glucose 1.22 mmol/L – 22 mg/dL) after overnight fasting but not during daytime was noted, with hypokalemia (2.5 mEq/L), normal bicarbonate and elevated anion gap (23.5 mEq/L). Urinary organic acid analysis showed excess ketone bodies without dicarboxylic aciduria or other abnormal metabolites.**

LABORATORY FINDINGS

URINE ORGANIC ACIDS

ABNORMAL: Severe ketonuria suggesting severe catabolic state. No abnormal organic acids identified.

Organic acid quantitation in mmol/mol creatinine:

Analyte	Result	1 mo-12 yrs
Lactic acid	676	<370
Pyruvic acid	22	<34
Succinic acid	81	<80
Fumaric acid	31	<10
2-Ketoglutaric	180	<150
3-OH-butyric acid	10,563	<4
Acetoacetic acid	17,704	<4
2-Keto-3-methylvaleric	26	<10
2-Keto-isocaproic	9	<4
Ethylmalonic acid	8	<15
Adipic acid	23	<100
Suberic acid	14	<10
Sebacic acid	0	<3
4-OH-phenylacetic acid	81	<100
4-OH-phenylpyruvic acid	8	<2

SICK $CO_2 = 5$

URINE ORGANIC ACIDS

ABNORMAL: Severe ketonuria. Abnormal products of fatty acid oxidation are not present in this sample.

Organic acid quantitation in mmol/mol creatinine:

Analyte	Result	1 mo-12 yrs
Lactic acid	349	<370
Pyruvic acid	83	<34
Succinic acid	117	<80
Fumaric acid	33	<10
2-Ketoglutaric	577	<150
3-OH-butyric acid	6,380	<4
Acetoacetic acid	6,192	<4
2-Keto-3-methylvaleric	23	<10
2-Keto-isocaproic	8	<4
Ethylmalonic acid	21	<15
Adipic acid	28	<100
Suberic acid	11	<10
Sebacic acid	9	<3
4-OH-phenylacetic acid	216	<100
4-OH-phenylpyruvic acid	8	<2

WELL $CO_2 = 27$

Normal plasma and urine amino acids

Plasma carnitine: excess acylcarnitines while on supplements.

LABORATORY FINDINGS

- **Ketolytic enzymes, Fibroblasts:**

Enzyme	Activity	Ref. range	Units
Beta-Ketothiolase	8.4	(5.6-15.9)	nmol/min/mg protein
Succinyl-CoA 3-ketotransferase	0.0	(4.1-8.1)	nmol/min/mg protein

- **Interpretation: SCOT deficiency.**
- **DNA *OXCT* gene: homozygous c.649C>T; p.R217X.**

MONOCARBOXYLIC TRANSPORTER 1 (MCT1) DEFICIENCY

Presentation: episodic, non-physiologic or exaggerated physiologic ketoacidosis: Tachypnea, lethargy, coma, severe ketoacidosis with elevated anion gap. Cyclic vomiting.
Diagnosis: Urine organic acids: increased Acetoacetate and 3-OH-Butyric acid, without abnormal urine organic acids. It is differentiated from physiological ketosis for the absence of adipic, suberic, and sebacic acids, usually seen during severe physiologic ketosis.
Confirmation: DNA testing *SLC16A1* gene on 1p13.2. Possible milder phenotype in heterozygotes with incomplete penetrance.
Therapy: prevention of fasting, alkali to prevent acidosis, mild protein and fat restriction, cornstarch, carnitine.

MJ, Duran K, Harakalova M, van der Zwaag B, Monavari AA, Okur I, Sharrard MJ, Cleary M, O'Connell N, Walker V, Rubio-Gozalbo ME, de Vries MC, Visser G, Houwen RH, van der Smagt JJ, Verhoeven-Duif NM, Wanders RJ, van Haaften G. Monocarboxylate transporter 1 deficiency and ketone utilization. van Hasselt PM, Ferdinandusse S, Monroe GR, Ruiter JP, Turkenburg M, Geerlings N Engl J Med. 2014 Nov 13;371(20):1900-7. doi: 10.1056/NEJMoa1407778. PMID: 25390740

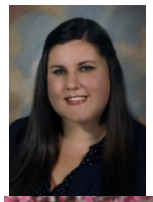
SUMMARY

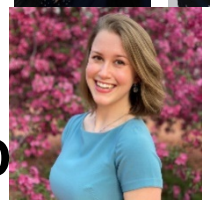
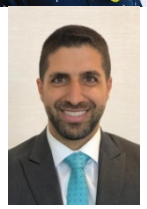
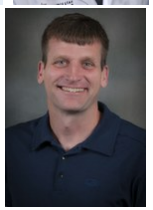
- **Fatty acids oxidation and ketogenic amino acids produce ketones (liver) that can be used by the body to produce energy.**
- **Disorders of ketogenesis (Mitochondrial 3-Hydroxy-3-Methyl-Glutaryl-CoA Synthase (mHs) and lyase (HL) deficiency) present as fatty acid oxidations defects with hypoketotic hypoglycemia.**
- **Disorders of ketolysis (MCT1, SCOT and MAT/T2 (*ACAT1*) deficiency) present with acute metabolic acidosis during fasting.**
- **Urine organic acids and plasma acylcarnitine profile can identify abnormal metabolites in HL and MAT/T2 deficiency. No diagnostic metabolites might be seen in mHS, SCOT and MCT1 deficiency. All require DNA studies for diagnosis.**

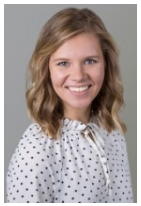
University of Utah

Biochemical Genetics Service

Ashley Andrews NP
Abbey Bentley NP
Lorenzo Botto MD
Sarah Roberts RD
Brian Shayota MD
Hunter Underhill MD PhD
Ashley Williams RD
Julia Wilmarth RD





ARUP Laboratories

Marzia Pasquali PhD

Co-Author of all slides

All patients and their families.