SCAD and GA-II: Truths and Confusions

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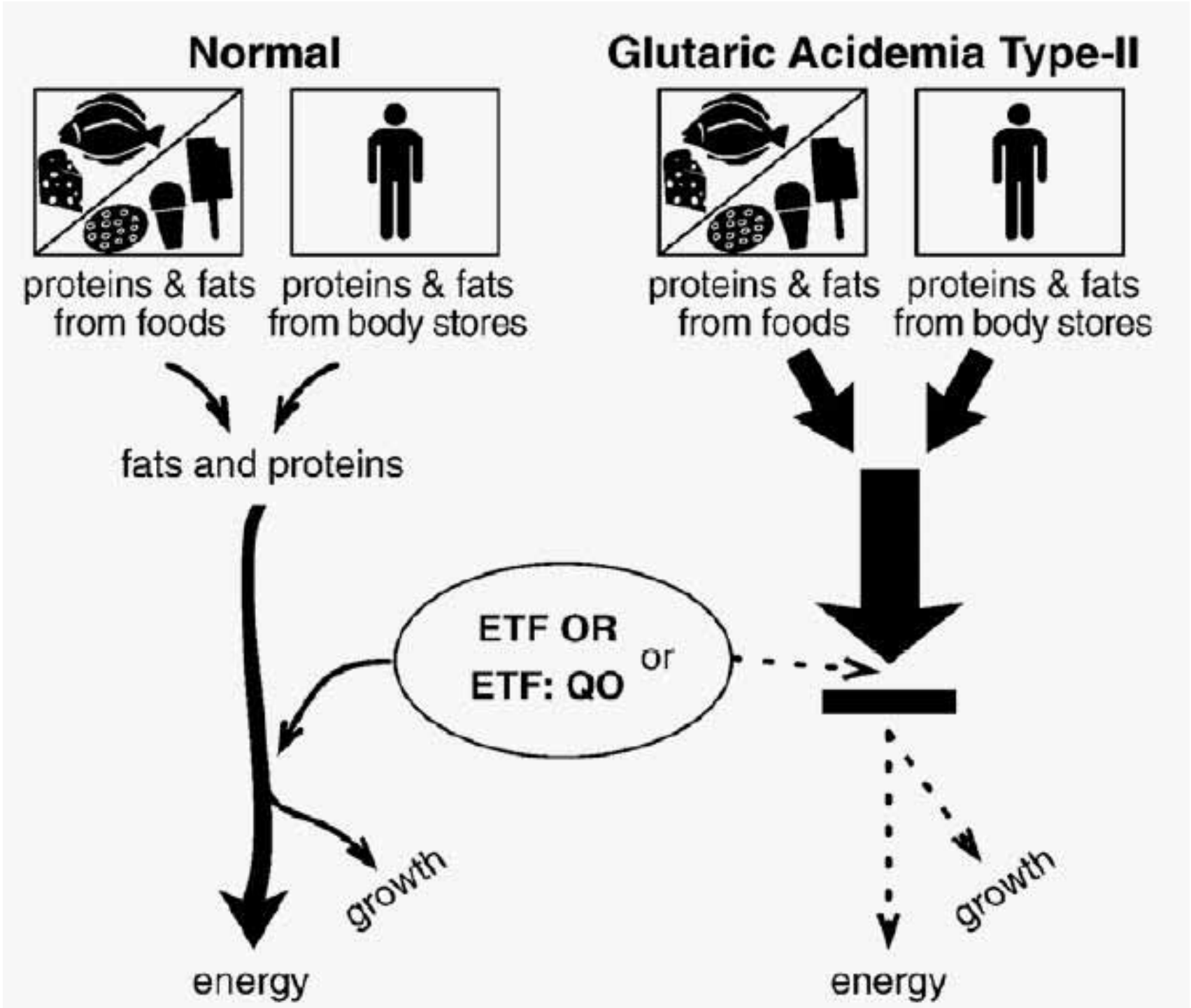
*MD, PhD

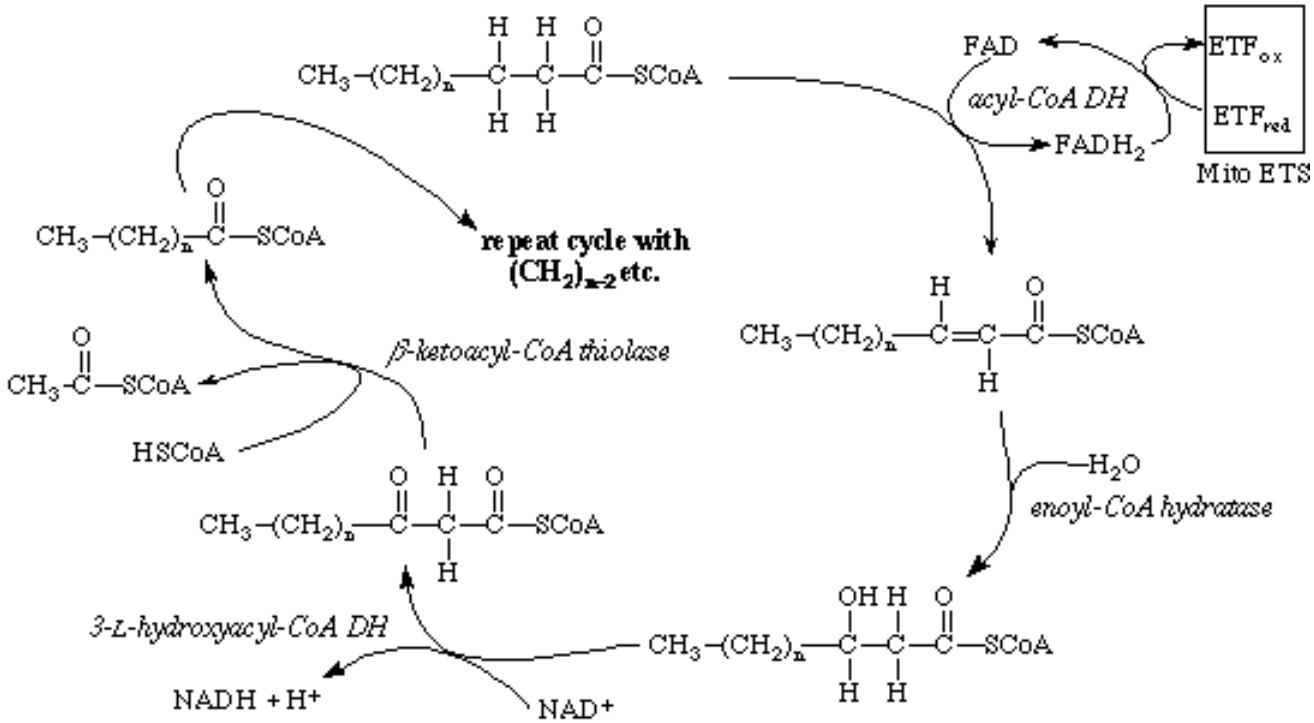
GA-II

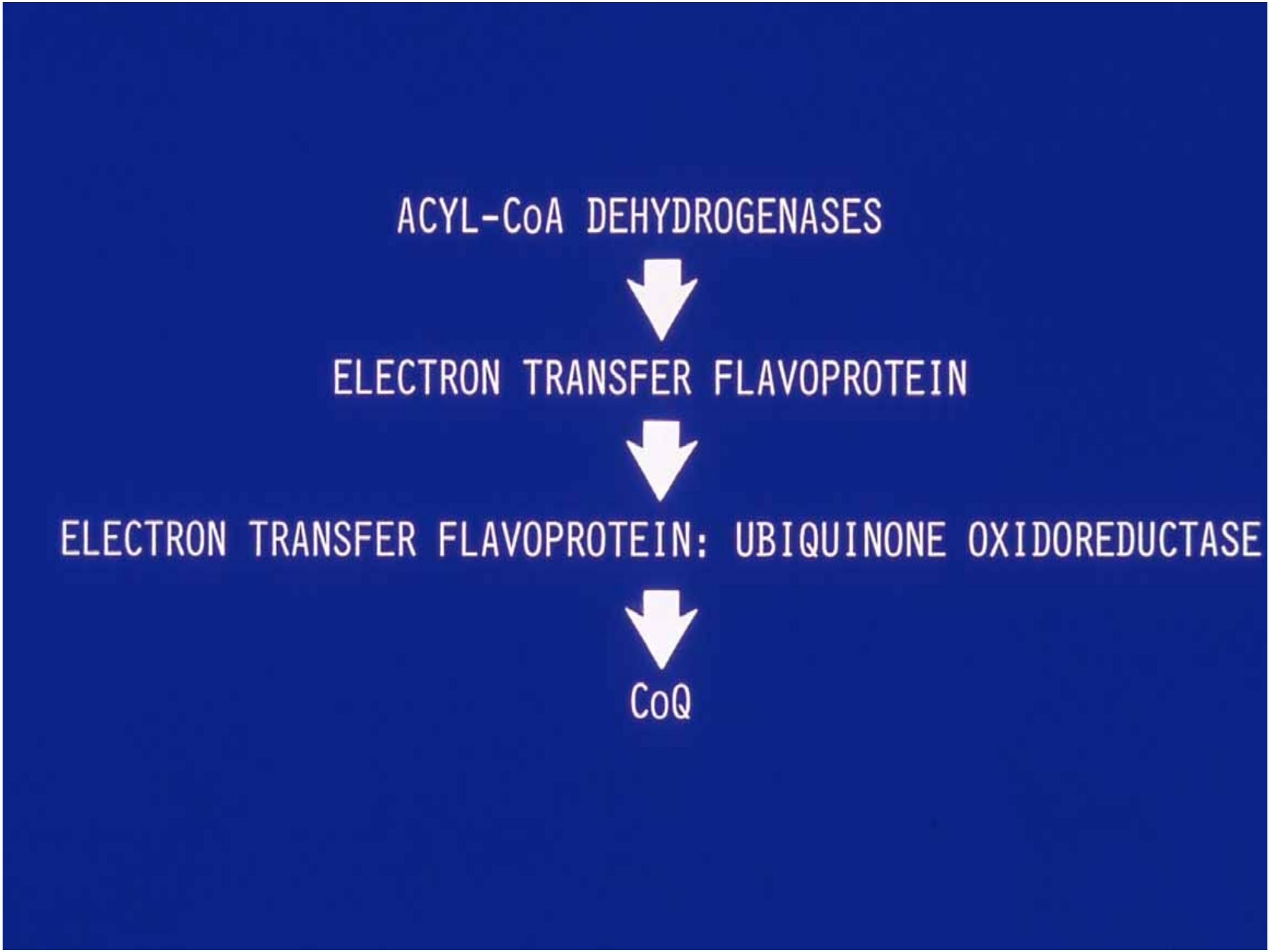
What other names do people use for glutaric acidemia type II?

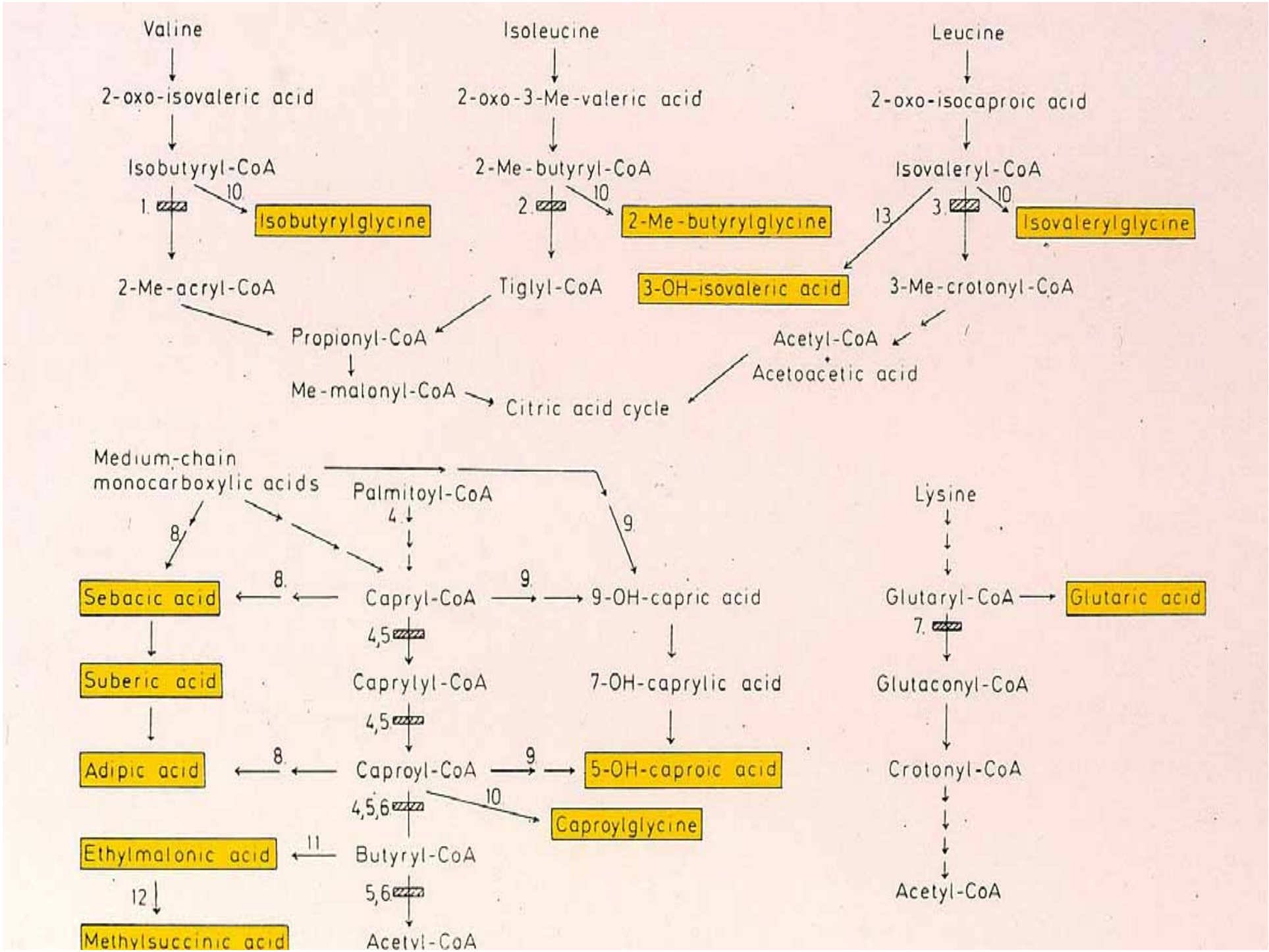
- Electron transfer flavoprotein deficiency
- EMA
- ETFA deficiency
- ETFB deficiency
- ETFDH deficiency
- Ethylmalonic-adipicaciduria
- GA II
- Glutaric acidemia, type 2
- Glutaric aciduria, type 2
- MAD
- MADD
- Multiple acyl-CoA dehydrogenase deficiency

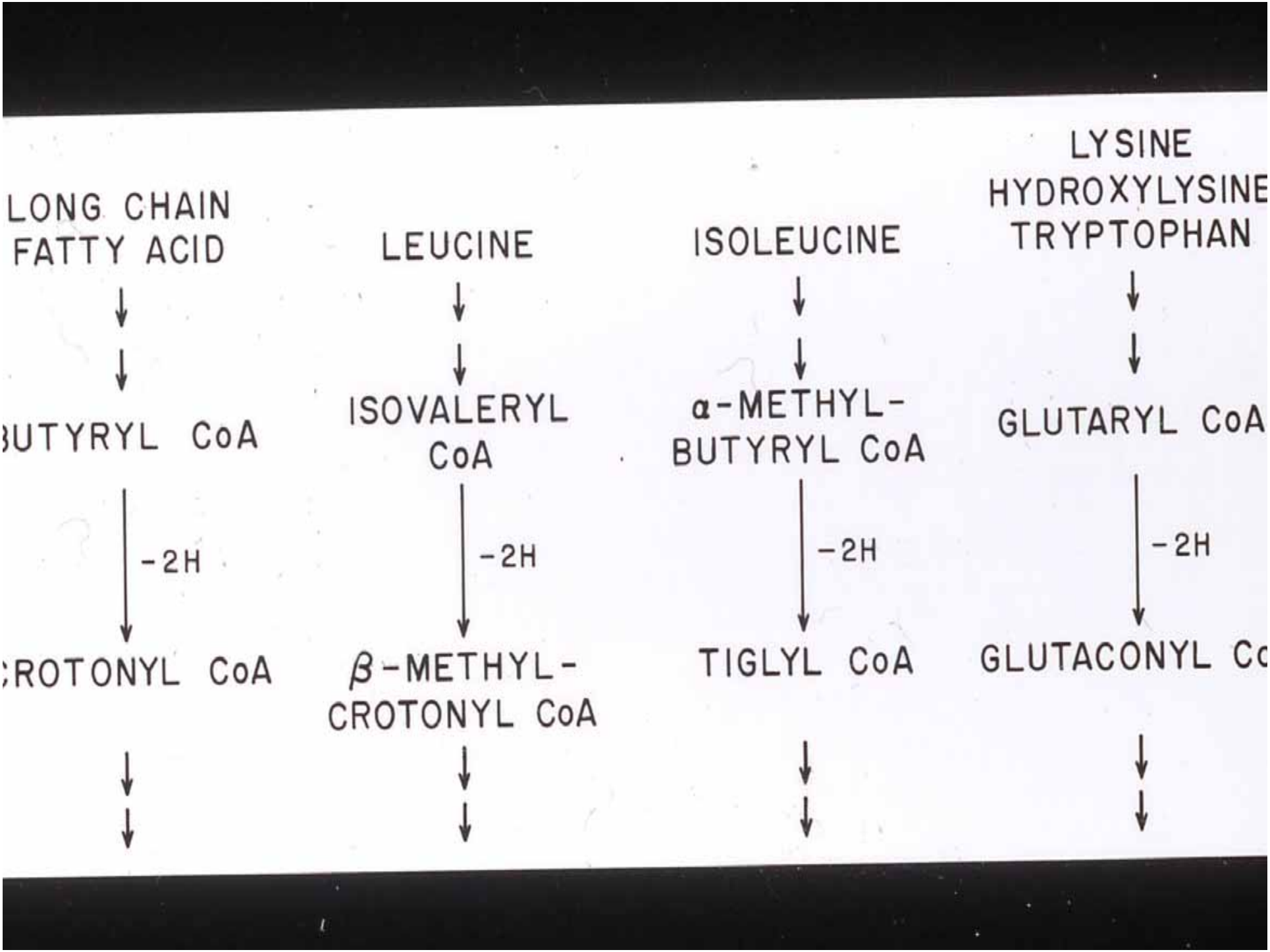

Normal
Glutaric Acidemia Type-II
proteins & fats from foods
proteins & fats from body stores
proteins & fats from foods
proteins & fats from body stores
fats and proteins
ETF OR
ETF: QO
or
growth
energy
growth
energy

β-Oxidation of Fatty Acids




ACYL-CoA DEHYDROGENASES
ELECTRON TRANSFER FLAVOPROTEIN
ELECTRON TRANSFER FLAVOPROTEIN: UBIQUINONE OXIDOREDUCTASE
CoQ


Valine
2-oxo-isovaleric acid
Isobutyryl-CoA
1
10
Isobutyrylglycine
2-Me-acryl-CoA
Isoleucine
2-oxo-3-Me-valeric acid
2-Me-butyryl-CoA
2
10
2-Me-butyrylglycine
Tiglyl-CoA
Leucine
2-oxo-isocaproic acid
Isovaleryl-CoA
13
3
10
Isovalerylglycine
3-OH-isovaleric acid
3-Me-crotonyl-CoA
Propionyl-CoA
Me-malonyl-CoA
Acetyl-CoA
Acetoacetic acid
Citric acid cycle
Medium-chain monocarboxylic acids
Palmitoyl-CoA
4
8
9
Sebacic acid
Capryl-CoA
9-OH-capric acid
4,5
Caprylyl-CoA
7-OH-caprylic acid
Suberic acid
Adipic acid
Caproyl-CoA
5-OH-caproic acid
4,5,6
10
Caproylglycine
Ethylmalonic acid
11
Butyryl-CoA
12
Methylsuccinic acid
5,6
Acetyl-CoA
Lysine
Glutaryl-CoA
Glutaric acid
7
Glutaconyl-CoA
Crotonyl-CoA
Acetyl-CoA


LONG CHAIN FATTY ACID
BUTYRYL CoA
-2H
CROTONYL CoA
LEUCINE
ISOVALERYL CoA
-2H
β-METHYL-CROTONYL CoA
ISOLEUCINE
α-METHYL-BUTYRYL CoA
-2H
TIGLYL CoA
LYSINE
HYDROXYLYSINE
TRYPTOPHAN
GLUTARYL CoA
-2H
GLUTACONYL Co

Severe GA-II is as bad as:

SCAD

+

MCAD

+

VLCAD

+

IVA

+

GA-I

COMBINED!

PATIENT	SEX	AFFECTED RELATIVES	AGE PRESENTATION/DEATH	MALFORMATIONS/ PATHOLOGY
1441/Q	F	SIBS: F;DEAD 19d M;" " 2d	3d/7 wks	NONE NOTED/ FATTY CHANGES: HEART LIVER KIDNEY
C.W.	M	NONE	1d/4d	NONE NOTED/?
P.K.	M	SIB: M;DEAD 1d	1d/3d	NONE NOTED/?
A.F.	M	SIBS: M;DEAD 1d M;" " 2d F;" " ∿6mo	1d/7 mo.	NONE NOTED/ CARDIOMYOPATHY ON ECHO; NO AUTOPSY
E.R.	M	4 M DEAD UNDER 4d	1d/4d	NONE NOTED/ FATTY CHANGES: LIVER BRAIN
A.L.	F	NONE	1d/3d	DYSMORPHIC FACIES/POLY- CYSTIC KIDNEYS, DYSPLASIA OF CEREBRAL CORTEX, NEUROBLASTOMA
K.H.	F	NONE	1d/3d	NONE NOTED/ FATTY LIVER

ATIENT	SEX	AFFECTED RELATIVES	PRESENTATION/ SYMPTOMS	LABORATORY STUDIES	PRESENT CONDITION
493	F	SIB: F;DEAD3d, FATTY LIVER	SEIZURES, KETOACIDOSIS & HYPOGLYCEMIA AT 7 wks, 1 yr, 4 yrs, & 5 yrs	$NH_3$276;↑ALA/GLY$_s$ ↑LFT's CHALLENGES: MCT/LEU ⊕ LYS ⊖	NORMAL IQ & GROWTH
632	F	SIBS: F;DEAD 7mo, HYPOGLY-CEMIA F;DEAD HYPOGLYCEMIA AT 10 yrs; SUDDEN DEATH AT 12 yrs	19 yrs, PREGN: 4 EPISODES: HYPOGLYCEMIA VOMITING HEPATIC DIS. PROX. MYOPATHY MINIM. ACIDOSIS	↑↑↑LFTs SEVERE HEPATIC FATTY CHANGES & PATCHY NECROSIS. SL. ↓CARNITINE$_s$	NORMAL IQ & ADULT SIZE
741	M	NONE	BIRTH: IRRITABILITY, FEEDING DIFFICULTIES; NO ACIDOSIS OR HYPOGLYCEMIA	CHALLENGES: MCT/LYS ⊖	NORMAL DEV'T & GROWTH SINCE 6 mo; NO THERAPY
M.L.	M	SIBS: M;6 yrs, ↓COORDI-NATION M; 14 yrs, HYPERKINETIC	3yrs: SEIZURES, COMA,&ACIDOSIS BUT NO HYPOGLYCEMIA. 3 PREVIOUS EPISODES OF IRRITABILITY, TREMORS	?CEREBRAL ATROPHY ON CT SCAN ↑ALA/GLY$_s$	?DELAYED DEVELOPMENT ACCENTUATED BY CRISIS
K.O.	M	NONE	18mo: POOR DEV'T, GROWTH, &	CHALLENGES: MCT ⊕ LYS ⊖	DELAYED DEVELOPMENT

Severe GA-II is always fatal

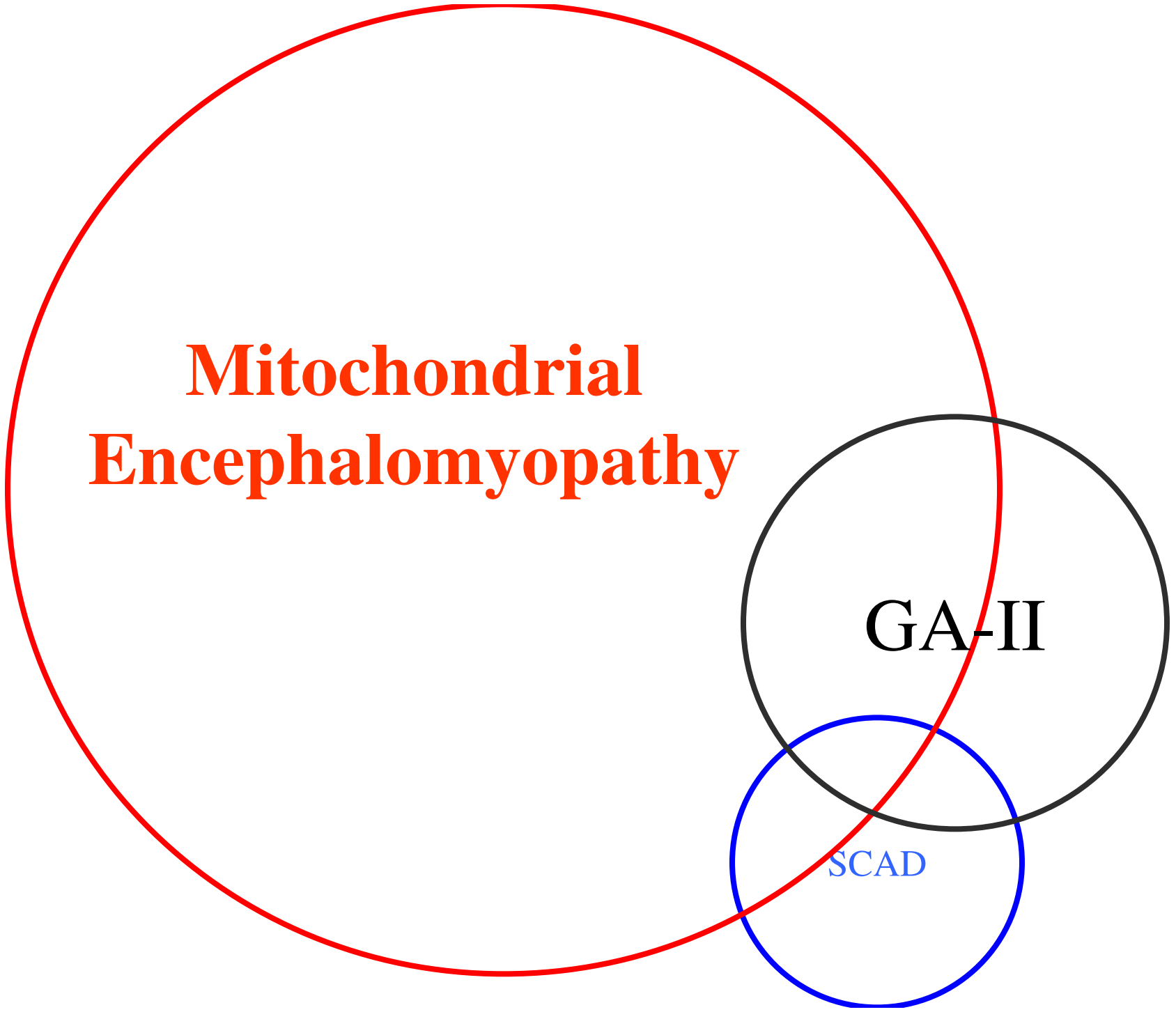
Mild GA-II is clinically like MCAD
(…usually…)

Table 1. *ETF and ETF-QO activity in GA2 fibroblasts*

	ETF mU/mg protein	ETF-QO mU/mg protein
Control range	1.10–2.50	5.4–20.5
(mean ± SD)	1.70 ± 0.40; $n = 11$	14.1 ± 3.9; $n = 20$
ETF deficiency		
Neonatal onset		
1441	0.20	12.7
1196	0.05	13.5
1728	0.32	9.8
1902	≤0.01	13.0
1803	0.11	5.5
1863	≤0.01	11.3
1894	0.08	9.1
1916	0.05	4.4
1918	0.15	9.3
Late onset		
1851	0.48	15.3
1903	0.10	18.6
1966	0.03	10.7
ETF-QO deficiency		
Neonatal Onset		
1730	3.8	≤0.1
1691	2.7	≤0.1
1692	1.8	≤0.1
1808	2.3	0.4
1846	1.8	≤0.1
1865	2.6	≤0.1
1879	1.5	≤0.1
1890	1.3	≤0.1
Late Onset		
1591	0.7	2.5
1592	1.2	2.9
1935	1.8	2.9
Parental lines		

Confusions and Overlaps

The blood and urine metabolites of GA-II, especially of the mild form, can be found in other diseases.


Mitochondrial
Encephalomyopathy
GA-II
SCAD

If the clinical problems can be explained by tissue (especially brain) damage caused by episodic hypoglycemia, acidosis and/or carnitine deficiency, then GA-II may be a reasonable diagnosis.

However……

……if the clinical problems affect many different body systems and are BEST explained by ongoing, continuing problems with tissue energy supply (GI dysmotility, TRUE muscle weakness, liver dysfunction, CNS decline, etc.), then a mitochondrial encephalomyopathy is much more likely than GA-II.

The same warnings apply even MORE strongly to SCAD

SCAD

Short-Chain Acyl-CoA Dehydrogenase Deficiency

Butyryl-CoA Dehydrogenase Deficiency

I have a selfish interest in SCAD being a “Disease”

Short-chain acyl-coenzyme A dehydrogenase deficiency. Clinical and biochemical studies in two patients.

B A Amendt, C Greene, L Sweetman, J Cloherty, V Shih, A Moon, L Teel, and W J Rhead

Abstract

We describe two patients with short-chain acyl-coenzyme A (CoA) dehydrogenase (SCADH) deficiency. Neonate I excreted large amounts of ethylmalonate and methylsuccinate; ethylmalonate excretion increased after a medium-chain triglyceride load. Neonate II died postnatally and excreted ethylmalonate, butyrate, 3-hydroxybutyrate, adipate, and lactate. Both neonates' fibroblasts catabolized [1-14C]

SCAD

Short-chain Acyl-CoA Dehydrogenase Deficiency

Butyryl-CoA Dehydrogenase Deficiency

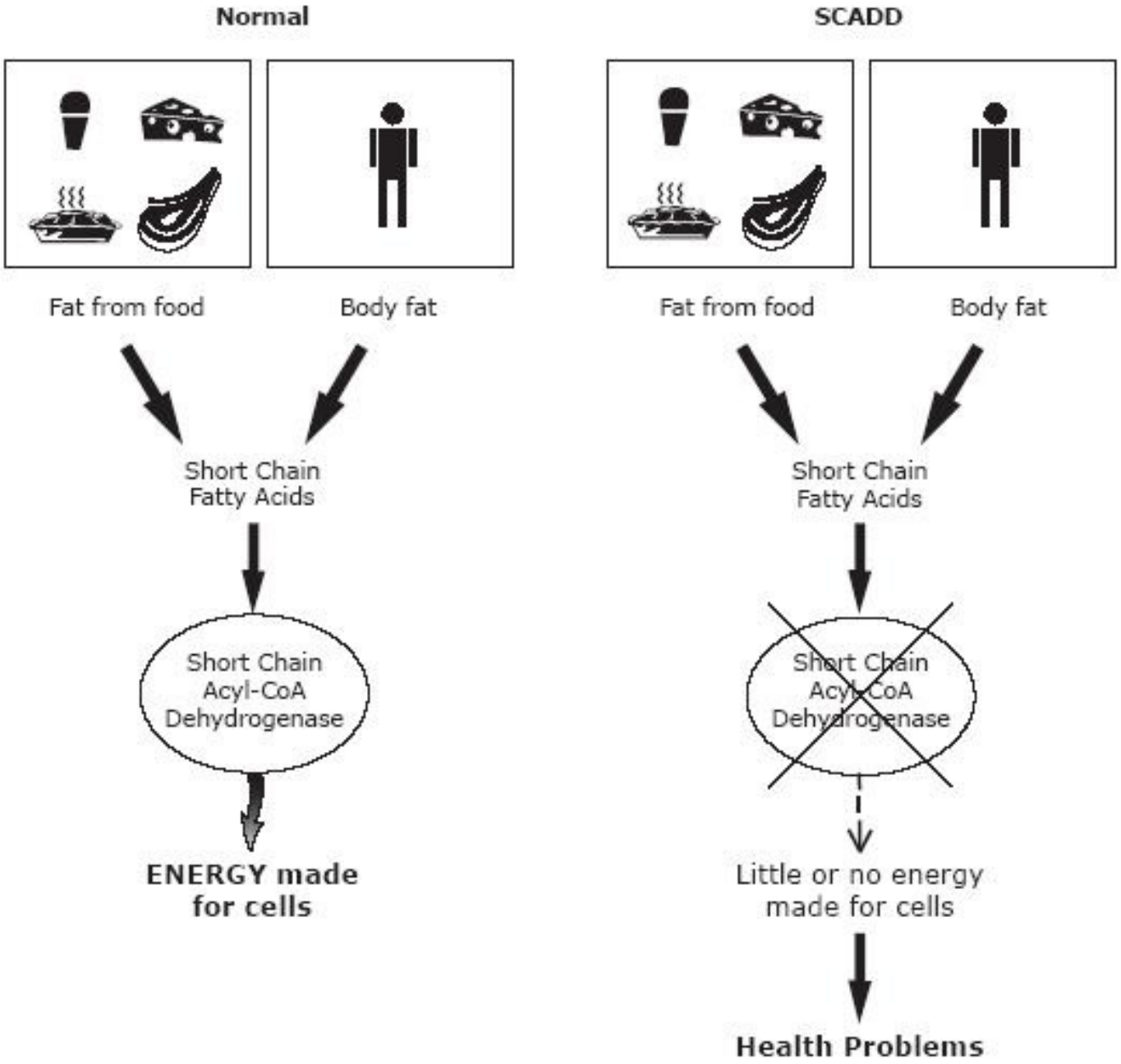
SCAD

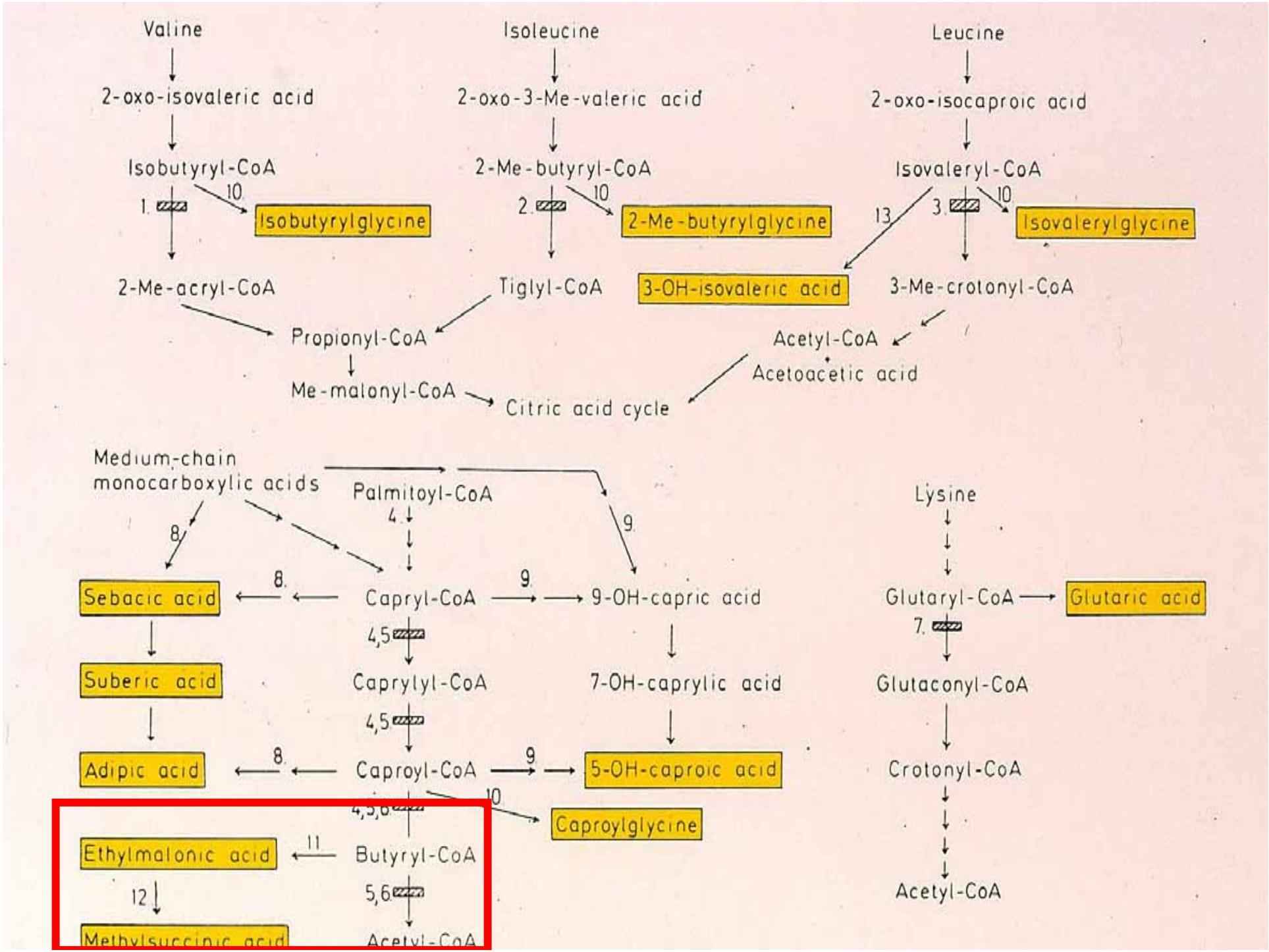
SUPER-CONFUSING
ALMOST-DISEASE

Clinical Problems in SCAD

- Hypoglycemia
- Acidosis/Lactic acidosis
- Lipid myopathy
- Muscle carnitine deficiency
- Seizures
- Developmental delay
- ADHD
- Cerebral palsy
- Unusual facial features
- Scoliosis
- Nystagmus
- Muscle loss (wasting)
- Ophthalmoplegia
- Ptosis
- Petechiae
- Axonal neuropathy

Short Chain Acyl-CoA Dehydrogenase Deficiency
SCADD

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Acetyl-CoA
Lysine
Glutaryl-CoA
Glutaric acid
7.
Glutaconyl-CoA
Crotonyl-CoA
Acetyl-CoA

“True” SCAD deficiency only lowers overall fatty acid oxidation by 40-60%, and “Variant” SCAD by 10-20%

Ethylmalonic acid (EMA) Excretion is found in:

SCAD

GA-II

Mitochondrial Encephalomyopathies

EMA Encephalopathy

Catabolic (fasting) state

etc.

Incidence of SCAD gene variants in the US population

The distribution of genotypes determined for the 511C > T variant was highly in favor of wild type alleles. In 41 of the 694 newborns at least one copy of the 511C > T variant was identified. Two newborns (0.3%) were homozygous for the 511C > T variant, 39 (6%) were heterozygous, and 653 (94%) were wild type (Table 1). In contrast, 260 of the 694 newborns carried at least one copy of the 625G > A variant; 39 (6%) were homozygous for the 625G > A variant, 221 (32%) were heterozygous, and 434 (62%) were wild type (Table 1). Overall, these gene variants were detected in either homozygous or compound heterozygous form in 7% (48/694) of the study population.

Gender	Age at onset	Clinical presentation	Urine ethylmalonic acid*	Fibroblast SCAD activity†	Allele 1‡	Allele 2
M	3 months	Hypotonia, hypoglycemia Developmental delay	19	Undetectable§	511T	511T
F	<1 week	Hypotonia Respiratory distress	Increased‖	Undetectable	**268G>A** 625A	625A
M	<1 week	Hypotonia, seizures Developmental delay	Increased‖	Undetectable	**575C>T** 625A	**973C>T** 625A
F	<1 week	Dysmorphic features Developmental delay	20	Undetectable	511T	625A
M	<1 week	Hypotonia Developmental delay	48,75	Undetectable	**310–312delGAG**	625A
F	15 months	Hypotonia	69	12–14%¶, 260%**	625A	625A
F	1 month	Hypotonia Developmental delay	22	Undetectable	625A	625A
M	3 months	Hypotonia Developmental delay	34,200	10%	**1058C>T**	625A
F	<1 week	Hypotonia, seizures Developmental delay	45,68	20%	**1138C>T**	625A
F		Low average IQ (identified by newborn screening)	43,74 <18	Undetectable	1147C>T 625A	625A

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F		Low average IQ (identified by newborn screening)	43,74 <18	Undetectable	1147C>T 625A	625A

Only patient with 2 "TRUE" mutations

“True” SCAD deficiency only lowers overall fatty acid oxidation by 40-60%, and “Variant” SCAD by 10-20%

ASCERTAINMENT BIAS (AB) IN SCAD DETECTION

AB means that HOW you find a SCAD patient FALSELY leads you to assume that SCAD caused the patient's problem, rather than showing the true cause.

For example, if you only do studies on developmentally delayed children, then finding SCAD (or webbed toes) does not mean it IS the cause of the DD.

(18 million people in the US have 2 SCAD gene "Variants", of whom 1 million have DD; 1/1000-1/2000 of persons with DD will have a common SCAD gene "Variant" and a "TRUE" mutation by accident. Since there are at least 6 million DD persons in the US, 3000-6000 of them will be in this category by accident.)

L.N.: Oldest SCAD patient

Urinary Levels of Organic Acids in Neonate I

no.	Collection date	Condition/treatment	Ethylmalonic acid	Methylsuccinic acid
			μmol/mg creatinine	*μmol/mg creatinine*
	1/17/83	Baseline/none	6.48	—*
	1/30/83	Baseline/none	4.82	0.41
	5/2/83	Baseline/before MCT	6.02	0.49
	5/2/83	Post-MCT	8.32	0.90
	5/4/83	Glycine only	1.61	0.61
	5/5/83	Glycine and MCT	8.26	0.52
	5/17/83	Baseline	3.82	0.20
	5/17/83	Postlysine	10.19	0.36
	5/18/83	Baseline	4.91	0.21
	5/19/73	Postleucine	4.44	0.20
controls			<0.03	<0.03

L. N.

- Was hypotonic as an infant.
- Has NEVER been sick from SCAD since birth.
- Was (and still is) smart.
- Barrel-raced quarter horses for fun.
- Graduated from Stanford.
- Has 2 “TRUE” inactivating mutations.

I have seen SCAD with other genetic disorders*:

- Rett syndrome (2)*
- Ondine's curse (CCHS)*
- How many other so-called "SCAD's" like S.H.?

*Proven by DNA studies.

Mild or absent clinical signs in twin sisters with short-chain acyl-CoA dehydrogenase deficiency.

Ribes A, Riudor E, Garavaglia B, Martinez G, Arranz A, Invernizzi F, Briones P, Lamantea E, Sentis M, Barcelo A, Roig M.

Department of Inborn Errors of Metabolism, Corporacio Sanitaria Edificio Helios III, Barcelona, Spain.

Two HLA-identical twin sisters are reported, of whom one has remained essentially asymptomatic, and an episode of hypotonia and decreased level of conciousness being the only relevant clinical finding in the other. Organic acid-analysis revealed that ethylmalonate was constantly, although sometimes only slightly, increased. No abnormal acylglycines or acylcarnitines could be detected. Enzyme assay in cultured skin fibroblasts confirmed short-chain acyl-CoA dehydrogenase deficiency. CONCLUSION: The lack of appropriate biochemical markers for this deficiency makes the diagnosis difficult and consequently, the low number of patients described may be the result of underdiagnosis.

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Short-Chain Acyl-CoA Dehydrogenase Deficiency: Studies in a Large Family Adding to the Complexity of the Disorder

Levinus A. Bok, MD[*], Peter Vreken, PhD[‡,†], Frits A. Wijburg, MD, PhD[‡], Ronald J. A. Wanders, PhD[‡], Niels Gregersen, PhD[§], Morten J. Corydon, PhD[§], Hans R. Waterham, PhD[‡] and Marinus Duran, PhD[‡]

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[§] Research Institute for Molecular Medicine, Faculty of Health Sciences and Aarhus University Hospital, Aarhus N, Denmark

NBS Criteria

- Disease
    - High incidence and severity
    - Sequelae treatable and preventable
- Tests
    - Simple, reliable, accurate, and cheap
- Program
    - Universal and uniform
    - Comprises follow-up, diagnosis, management and treatment
    - Favorable risk/benefit ratio to patient, family and society

SCAD Newborn Screeening

- Most SCAD patients found in NBS are normal and healthy.
- 5-10% have hypoglycemia, hypotonia and/or problems unrelated to SCAD or FAOD.
- SCAD mutations have been done in very few patients; most of those studied are “Variant” SCAD, not severe/classic/totally deficient “TRUE” SCAD.
- Australia and Bavaria refuse to do NBS for SCAD.
- NBS has profoundly changed our attitude towards SCAD.

Clinical Problems in SCAD

- Hypoglycemia
- Acidosis/Lactic acidosis
- Lipid myopathy
- Muscle carnitine deficiency
- Seizures
- Developmental delay
- ADHD
- Cerebral palsy
- Unusual facial features
- Scoliosis
- Nystagmus
- Muscle loss (wasting)
- Ophthalmoplegia
- Ptosis
- Petechiae
- Axonal neuropathy

Which were found due to Ascertainment Bias?

Making the diagnosis of SCAD is NOT the end of a diagnostic evaluation!

(when a child has neurologic disease or problems in multiple body systems)

It is the midpoint!!

(Full evaluation by neurology, GI, clinical genetics, and/or dysmorphology MD's is essential)

Treatment Strategies

- Avoidance of Fasting
- Fat Restriction
- Energy Supplementation
  - Carbohydrates and Proteins
  - MCT Oil
  - Cornstarch
- Prevent Catabolism
- Carnitine Supplementation
- Healthy Diet promotes growth & development

SCAD

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Butyryl-CoA Dehydrogenase Deficiency

SCAD

SUPER-CONFUSING
ALMOST-DISEASE