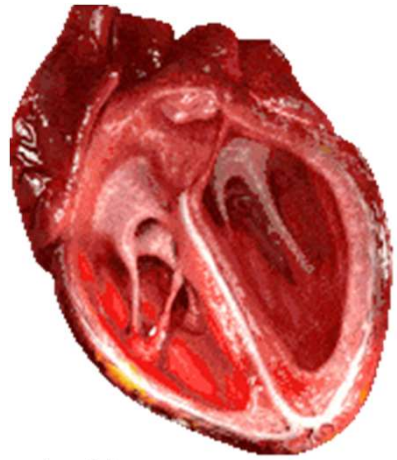
Metabolic Cardiomyopathies

The human heart



Your heart beats:

1. about 100,000 times per day
2. about 35 million times in a year
3. more than 2.5 billion times in an average lifespan

At rest, works about twice as hard as the leg muscles of a person sprinting

Pumps about 5.5 L of blood around the body 3 times per minute

Myocardial metabolism

Largest metabolic demands of any organ

Essential: adequate oxygenation + substrates to generate ATP

Cardiac ATP: Fatty acids 70-90%; glucose; lactate; ketone bodies; amino acids

ATP is used

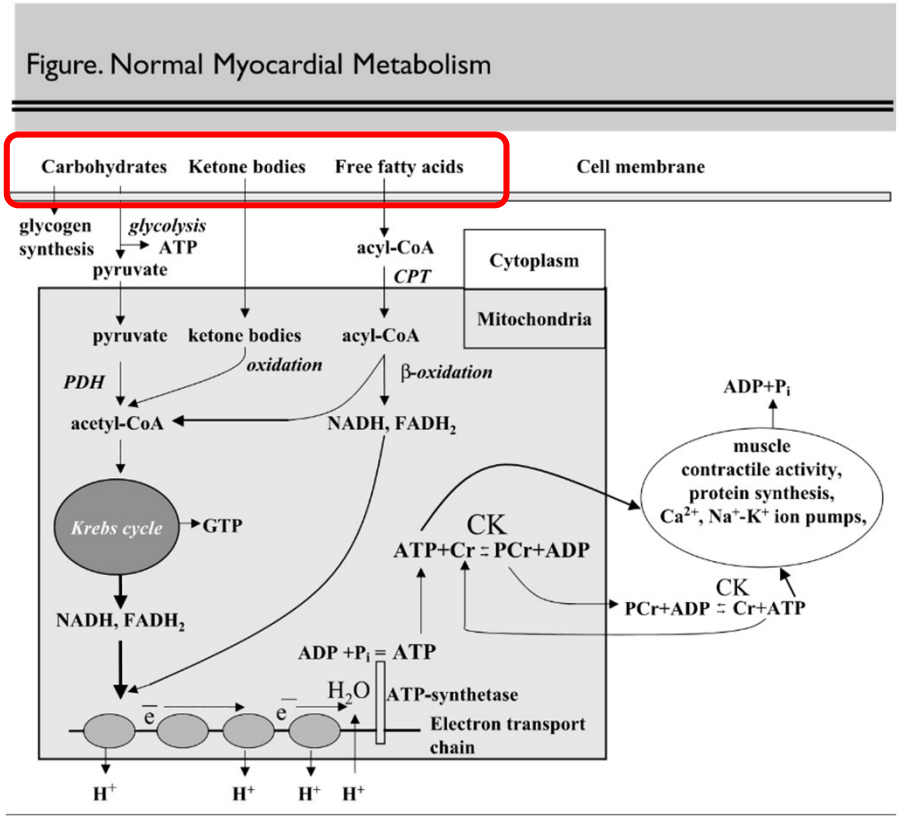
- **To fuel contraction and relaxation (60-70%)**
- **To maintain membrane potential / ion pumps (30-40%)**
- **To fuel anabolic reactions**
- **By signalling system**

But, the ATP pool is small and can be exhausted in a few seconds – it must be continuously synthesized

High demand for ATP

95% of ATP generated by oxidative phosphorylation in mitochondria

The heart has many mitochondria!



Weiss and Maslov, 2004

Cardiomyopathy

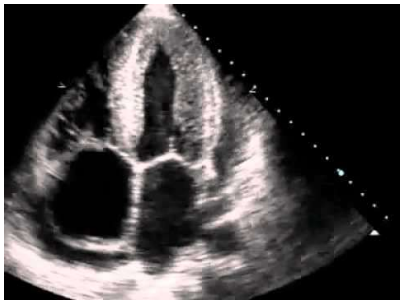
Structural and functional abnormalities of the ventricular myocardium that are unexplained by flow-limiting coronary artery disease or abnormal afterload

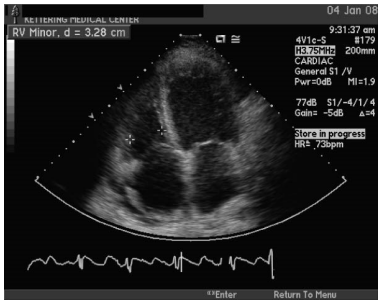
‘primary disease of the heart muscle’

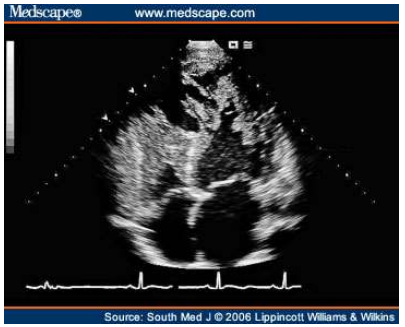
Muscle becomes thickened, or dilated, or rigid, and may be replaced with scar tissue

Types of cardiomyopathy

Hypertrophic	Dilated	Restrictive	Arrhythmogenic Right Ventricle	Noncompaction
Thickening of ventricles. Changes in mitral valve. Harder for heart to pump.	Ventricles enlarge and weaken. Heart failure, valve disease, arrhythmias, clots. (alcohol and diabetes).	Ventricles become stiff and rigid but the walls of the heart do not thicken. Heart failure and valve problems.	Muscle tissue in the right ventricle is replaced with fatty or fibrous tissue. Cause arrhythmias.	Left ventricle has trabeculations, projections of muscle inside the ventricle.







Cardiomyopathy

Inherited metabolic disease causes..

- **Up to 20% of paediatric cardiomyopathies**
- **5-10% of adult cardiomyopathies**

Major complication, leading to death (1/3 of children presenting with heart failure die or require transplantation)

Or

Incidental finding during multisystem evaluation / surveillance

Cox GF. *Prog Pediatr Cardiol.* 2007;24(1):15-25.
Byers SL, Ficicioglu C. *World J Cardiol.* 2014;6(11):1149-1155.
Badertscher A, Bauersfeld U, Arbenz U, Baumgartner MR, Schinzel A, Balmer C. *Acta Paediatr.* 2008;97(11):1523-1528.

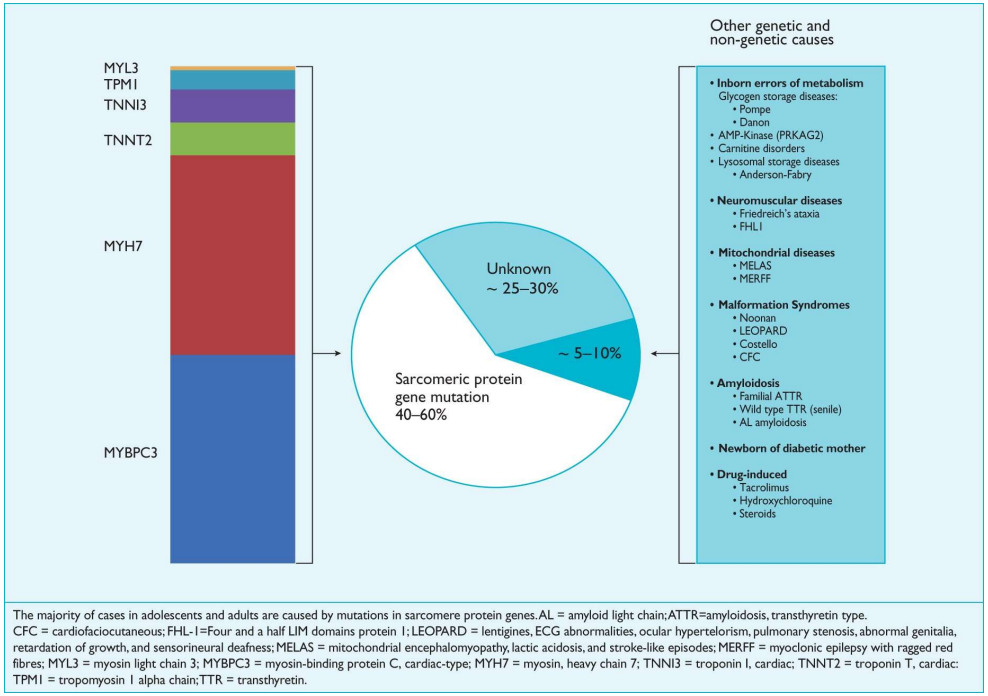
Cardiomyopathy: Paediatric

Incidence per year: 0.3-0.5 per 100,000 children

Dilated	60%	Inflammatory Toxic (chemotherapy) Inherited (Sarcomeric) IMD
Hypertrophic	25%	Infants of diabetic mothers Sarcomeric (60%)[Infants 37%] Noonan syndrome (RASopathy) IMD
Arrhythmogenic right ventricular	15%	
Restrictive		
LV noncompaction		Barth Syndrome

Hypertrophic Cardiomyopathy: adults

Prevalence: 230 per 100,000 adults



The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Eur Heart J, Volume 35, Issue 39, 14 October 2014, Pages 2733–2779, https://doi.org/10.1093/eurheartj/ehu284.

Cardiomyopathy in IMD

Myocardial (ventricular) and / or Electrical defects

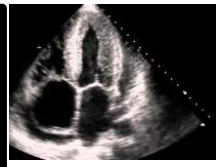
Dilated | Hypertrophic | Other

Conduction | Ventricular arrhythmias

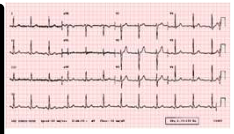
HEART FAILURE

SUDDEN DEATH

Investigations
Echocardiogram
Cardiac MRI



Investigations
ECG, Holter, Loop recorder,
invasive electrophysiology



Treatment
Heart failure medications

Treatment
Pacemaker, Defibrillator (ICD)

Specific enzyme replacement therapy; dietary modifications etc

Cardiomyopathy in IMD

Roles of the metabolic physician / scientist in cardiomyopathy

Assist the cardiologist in making a diagnosis (is the VUS in the cardiomyopathy panel relevant?)
Assist the cardiologist in deciding whether to biochemically screen for IMD (negative genetic panel)

Organise monitoring of known IMD and support the multidisciplinary team in agreeing on therapy

Challenges

The natural history is often unknown
Prognostic risk factor stratification is unknown
The indications for specific interventions are unknown

- **when to operate e.g. for valve disease in mucopolysaccharidoses?**
- **when to implant an cardiac defibrillator?**

Cardiomyopathy in IMD

Type of disorder	Examples
Carnitine shuttle / cycle defects	Primary carnitine deficiency (*SLC22A5*), CACT (*SLC25A20*), *CPT2*
Fatty acid oxidation defects	VLCAD (*ACADVL*), LCHAD (*HADHA, HADHB*)
Mitochondrial disease	Multiple!
Organic acidemias	Propionic and methylmalonic acidemias
Glycogen storage disorders	LAMP2, GSD IIIa (*AGL*)
Polyglucosan body storage disorders	*PRKAG2, RBCK1, GYG1, GBE*
Lysosomal storage disorders	MPSI, MPSII, MPSIV, Mucolipidosis, Pompe, Fabry etc.
Others	Congenital disorders of glycosylation, Refsum disease etc.

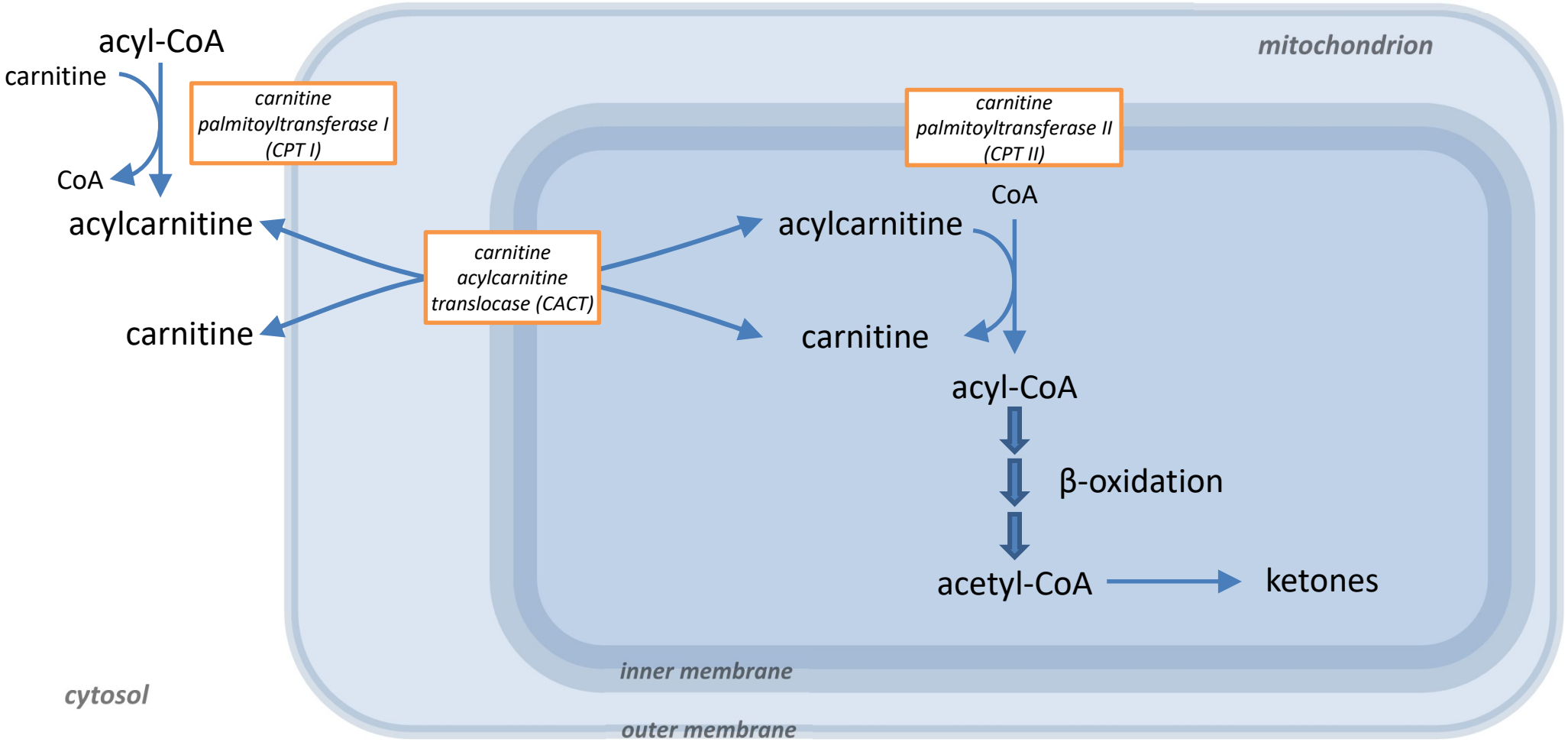
Clues to diagnosis!

Clue	*Comment*	*Disorder*
Hypoglycemia	Suggestive of defect in energy production	Fatty acid oxidation defects Glycogen storage disorders
Hypotonia (feeding difficulties, respiratory distress)	Suggestive of systemic skeletal muscle disease	Pompe disease Mitochondrial disease Congenital disorders of glycosylation
Hepatomegaly	Suggestive of a storage disorder	Mucopolysaccharidoses; GSD
Dysmorphic features		Mucopolysaccharidoses Congenital disorders of glycosylation
Joint contractures / dysostosis		Mucopolysaccharidoses Mucolipidoses
Presenting after acute metabolic stress	eg. fasting, fever, intercurrent illness, surgery	Fatty acid oxidation defects Propionic acidemia; MMA
Hypertrophic cardiomyopathy with ventricular pre-excitation (VPE) or the Wolff–Parkinson–White (WPW) syndrome	Suggestive of a storage disorder	Lysosomal storage disorders Glycogen storage disorders Mitochondrial disorders

Carnitine related defects

Condition	Gene (inheritance)	Incidence	Cardiac involvement	Supportive clinical features	(Non-genetic) diagnostic tests	Treatment options
Carnitine deficiency, systemic primary (#212140)	SLC22A5 (AR)	1:20,000 - 1:70,000. 1 in 300 in the Faroe Islands.	Dilated / hypertrophic cardiomyopathy. Cardiac failure. Arrhythmias. Long QT syndrome.	Episodes of metabolic decompensation, skeletal myopathy, hypoketotic hypoglycemia.	Plasma carnitine. Urine organic acids. Fractional carnitine excretion.	Carnitine supplementation.
Carnitine-acylcarnitine translocase (CACT) deficiency (#212138)	SLC25A20 (AR)	<100 cases reported.	Cardiac arrhythmia, cardiomyopathy, heart block.	Hyperammonemia, liver dysfunction, hypoketotic hypoglycemia.	Plasma acylcarnitine profile. Urine organic acids. Fibroblast studies.	Avoid prolonged fasting. Dietary modification. Medium chain triglyceride supplementation. Carnitine supplementation. Triheptanoin.
Carnitine palmitoyltransferase II (CPT2) deficiency (#255110)	CPT2 (AR)	<500 cases reported.	Hypertrophic / dilated cardiomyopathy. Cardiac arrhythmias. Sudden death.	Exercise intolerance, myalgia, rhabdomyolysis, acute renal failure.	Creatine kinase. Plasma acylcarnitine profile. Urine organic acids. Fibroblast studies.	Avoid prolonged fasting. Dietary modification. Medium chain triglyceride supplementation. Triheptanoin.

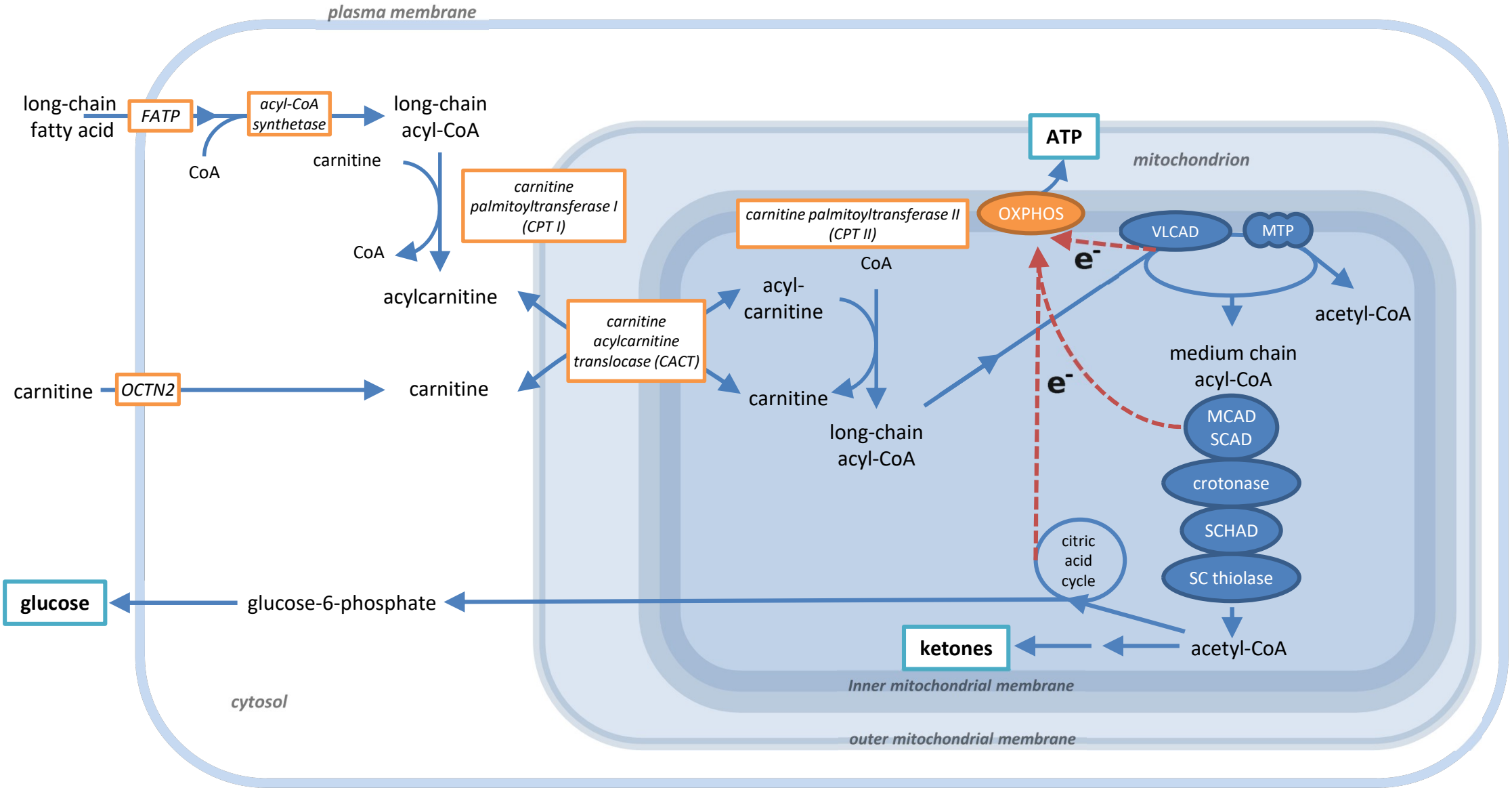
Carnitine shuttle / cycle defects



Fatty acid oxidation defects

Condition	Gene (inheritance)	Incidence	Cardiac involvement	Supportive clinical features	(Non-genetic) diagnostic tests	Treatment options
Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (#201475)	ACADVL (AR)	1:30,000.	Hypertrophic / dilated cardiomyopathy.	Exercise intolerance, myalgia, rhabdomyolysis, acute renal failure, liver dysfunction, hypoketotic hypoglycemia.	Creatine kinase. Plasma acylcarnitine profile. Urine organic acids. Fibroblast studies.	Avoid prolonged fasting. Dietary modification. Medium chain triglyceride supplementation. Triheptanoin.
Long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (#609016)	HADHA (AR)	1:250,000.	Hypertrophic / dilated cardiomyopathy.	Muscle weakness, exercise intolerance, progressive axonal sensorimotor peripheral neuropathy, retinopathy, ataxic gait, episodic rhabdomyolysis, acute renal failure.	Creatine kinase. Plasma acylcarnitine profile. Urine organic acids. Fibroblast studies.	Avoid prolonged fasting. Dietary modification. Medium chain triglyceride supplementation.
Mitochondrial trifunctional protein (MTP) deficiency (#609015)	HADHA or HADHB (AR)	NR				

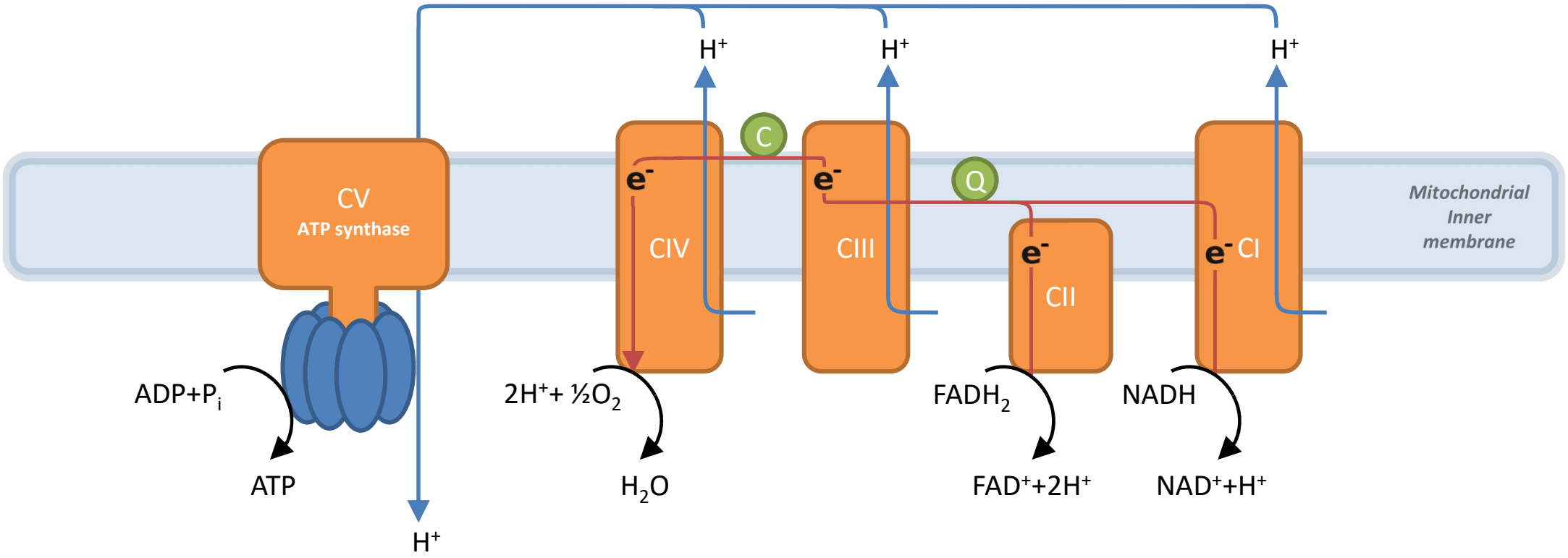
Mitochondrial fatty acid β-oxidation



Mitochondrial disease

Condition	Gene (inheritance)	Incidence	Cardiac involvement	Supportive clinical features	(Non-genetic) diagnostic tests	Treatment options
Mitochondrial disorders	Multiple genes (both nuclear DNA and mitochondrial DNA encoded) (Maternal, AD, AR)	1:5000.	Cardiomyopathy (hypertrophic, dilated, LV noncompaction), heart failure, ventricular tachyarrhythmia, sudden cardiac death.	Multisystem involvement - neuromuscular, renal, endocrinopathy, retinitis pigmentosa, sensorineural hearing loss.	Lactate (Blood / CSF). Supportive features on muscle biopsy. Mitochondrial respiratory chain enzyme activity.	Largely supportive.
Multiple acyl-CoA dehydrogenase (MADD) deficiency (also known as glutaric aciduria II) (#231680)	ETFA or ETFB or ETFDH (AR)	<500 cases reported.	Hypertrophic / dilated cardiomyopathy.	Muscle symptoms predominate - weakness, exercise intolerance. Risk of episodic vomiting, ketoacidosis / loss of appetite, acute encephalopathy. Facial and cerebral malformations.	Plasma acylcarnitine profile. Urine organic acids. Fibroblast studies.	Riboflavin supplementation.

the mitochondrial oxidative phosphorylation system (OXPHOS)



Specific mitochondrial syndromes

Barth syndrome **Dilated CM and LV hypertrabeculation**

(Neutropenia, myopathy, short stature. Gene: *TAFAZZIN*)

Kearns-Sayre syndrome **Arrhythmia (AV cardiac conduction block)**

(PEO, retinopathy, ataxia, endocrine. SLSMDs)

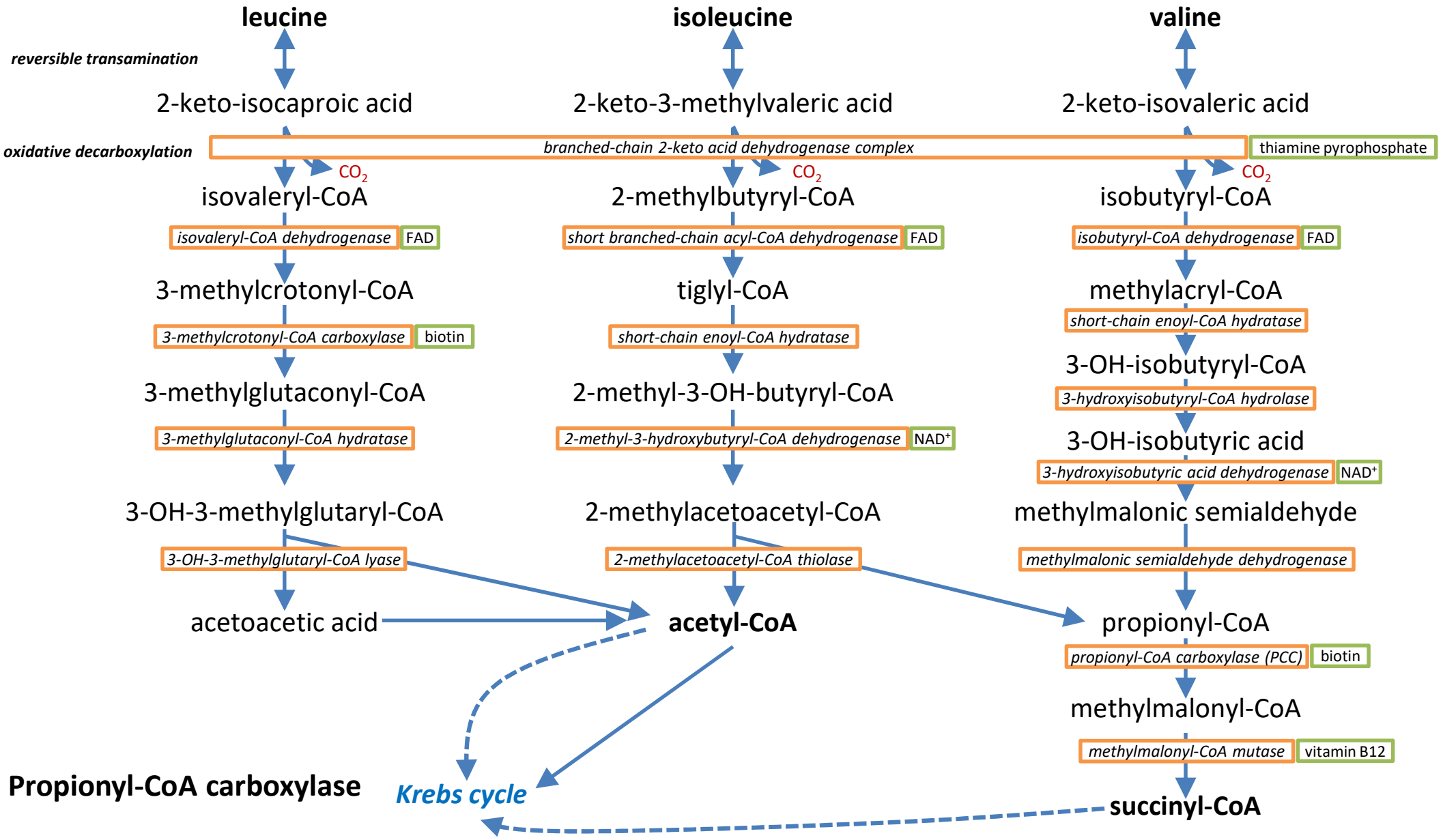
MELAS / MIDD **Dilated CM and LV hypertrabeculation**

(encephalopathy, deafness, PEO, diabetes. m.3243A>G (*MT-TL1*))

Highly heterogeneous

Organic acidemias

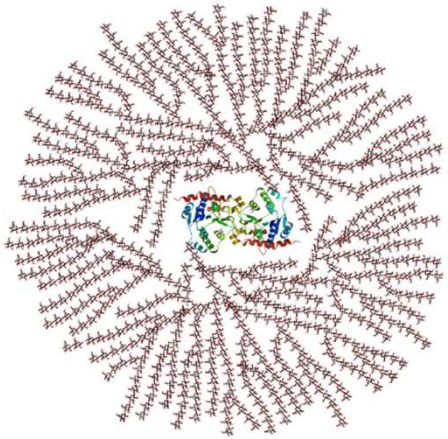
Condition	Gene (inheritance)	Incidence	Cardiac involvement	Supportive clinical features	(Non-genetic) diagnostic tests	Treatment options
Propionic acidemia (#606054)	PCCA or PCCB (AR)	1:50,000 to 1:100,000	Cardiomyopathy. Arrhythmias. Sudden cardiac death.	Metabolic decompensation: ketoacidosis, hypoglycemia, hyperammonemia, pancytopenia, pancreatitis (+/- neurological sequelae), optic atrophy, hearing impairment, renal failure.	Plasma acylcarnitine profile. Urine organic acids. PCC enzyme activity.	Avoid catabolism. Dietary modification. Carnitine supplementation. Carglumic acid.
Methylmalonic acidemia	*cblA*, *cblB*, or *cblD*-MMA (AR)	1:50,000 to 1:100,000	Cardiomyopathy. Arrhythmias.	Metabolic decompensation: respiratory distress, severe ketoacidosis, hyperammonemia, neutropenia, and thrombocytopenia. Developmental delay. Basal ganglia 'stroke'. Pancreatitis, renal impairment, optic atrophy.	Plasma acylcarnitine profile. Plasma amino acids and MMA. Urine organic acids. Fibroblast studies.	Avoid catabolism. Dietary modification. High dose B12. Carnitine supplementation. Carglumic acid.


leucine
isoleucine
valine
reversible transamination
2-keto-isocaproic acid
2-keto-3-methylvaleric acid
2-keto-isovaleric acid
oxidative decarboxylation
branched-chain 2-keto acid dehydrogenase complex
thiamine pyrophosphate
CO2
CO2
CO2
isovaleryl-CoA
2-methylbutyryl-CoA
isobutyryl-CoA
isovaleryl-CoA dehydrogenase
FAD
short branched-chain acyl-CoA dehydrogenase
FAD
isobutyryl-CoA dehydrogenase
FAD
3-methylcrotonyl-CoA
tiglyl-CoA
methylacryl-CoA
3-methylcrotonyl-CoA carboxylase
biotin
short-chain enoyl-CoA hydratase
short-chain enoyl-CoA hydratase
3-OH-isobutyryl-CoA
3-methylglutaconyl-CoA
2-methyl-3-OH-butyryl-CoA
3-hydroxyisobutyryl-CoA hydrolase
3-methylglutaconyl-CoA hydratase
2-methyl-3-hydroxybutyryl-CoA dehydrogenase
NAD+
3-OH-isobutyric acid
3-hydroxyisobutyric acid dehydrogenase
NAD+
3-OH-3-methylglutaryl-CoA
2-methylacetoacetyl-CoA
methylmalonic semialdehyde
3-OH-3-methylglutaryl-CoA lyase
2-methylacetoacetyl-CoA thiolase
methylmalonic semialdehyde dehydrogenase
acetoacetic acid
acetyl-CoA
propionyl-CoA
propionyl-CoA carboxylase (PCC)
biotin
methylmalonyl-CoA
methylmalonyl-CoA mutase
vitamin B12
Propionyl-CoA carboxylase
Krebs cycle
succinyl-CoA

Glycogen storage disorders

Disease	Enzyme / Protein	Gene (Inheritance)	Cardiac involvement	Other supportive clinical features
Glycogen storage disorders				
II (Pompe)	Acid maltase	GAA (AR)	Short PR, wide QRS, cardiomegaly, LVOTO.	Hypotonia. Macroglossia. Feeding difficulties.
IIb (Danon)	LAMP-2	LAMP2 (XL)	Left ventricular hypertrophy. Ventricular preexcitation. Ventricular arrhythmias.	Retinal dystrophy.
IIIa (Cori-Forbes)	Glycogen debranching enzyme	AGL (AR)	Hypertrophic cardiomyopathy. Cardiac failure. Sudden death.	Hypoglycemia. Hepatomegaly.
V (McArdle)	Myophosphorylase	PYGM (AR)	Coronary artery disease.	Exercise intolerance, myalgia, rhabdomyolysis.
Polyglucosan body storage (PGB) disorders				
PRKAG2	gamma subunit of AMP-kinase	PRKAG2 (AD)	Ventricular pre-excitation.	No
RBCK1	RanBP-type and C3HC4-type zinc finger-containing 1	RBCK1 (AR)	Cardiac failure.	Skeletal myopathy. Autoimmunity. Recurrent infections.
GYG1	Glycogenin-1	GYG1 (AR)	(Dilated) cardiomyopathy. Cardiac failure.	Skeletal myopathy.
GSD IV	Glycogen branching enzyme	GBE (AR)	Hypertrophic / dilated cardiomyopathy.	Hypotonia. Neurologic disease. Liver disease.
GSD VII (Tarui)	Phosphofructokinase	PFKM (AR)	Valve disease. Hypertrophic cardiomyopathy.	Haemolytic anemia. Exercise intolerance, myalgia, rhabdomyolysis.

Glycogen



Glycogen
Soluble
Tightly packed, highly organised structure
Accessible source of glucose ie. energy
Reduces osmotic pull of intracellular glucose
Occupies 2% of cardiomyocyte volume of adult and 30% of neonate

Polyglucosan body
Disorganised, elongated chains, poorly branched
Inert – reduced supply of intracellular glucose
Associated with swollen, enlarged cells

Lysosomal storage disorders 1

Condition	Gene (inheritance)	Incidence	Cardiac involvement	Supportive clinical features	(Non-genetic) diagnostic tests	Treatment options
MPS I (Hurler, Scheie disease)(#607015)	IDUA (AR)	1:100,000 (severe from) to 1:500,000 (attenuated form).	Cardiac valve thickening Hypertrophy. Conduction abnormalities. Coronary artery disease. Large vessel arterial narrowing / dilation. Hypertension.	Dysostosis multiplex (arthropathy). Hepatosplenomegaly. Corneal clouding. Hearing impairment. Herniae.	Urine glycosaminoglycans. α-L-iduronidase enzyme activity.	Hematopoietic stem cell transplantation. ERT for systemic features but does not affect CNS disease.
MPS II (Hunter disease)(309900)	IDS (XL)	1:100,000 to 170,000 (males). Some symptomatic females also reported.	Cardiac valve thickening Hypertrophy. Conduction abnormalities. Coronary artery disease. Large vessel arterial narrowing / dilation. Hypertension.	Dysostosis multiplex. Short stature. Hepatosplenomegaly. Herniae. Global developmental delay.	Urine glycosaminoglycans. Iduronate 2-sulfatase enzyme activity.	ERT for systemic features but does not affect CNS disease. Hematopoietic stem cell transplantation.
MPS IV (Morquio disease)(#253000)	MPS IVA - GALNS(AR) MPS IVB - GLB1 (AR)	MPS IVA 1:599,000 (UK). MPS IVB 1:1,000,000.	Similar to other MPS disorders but prevalence of cardiac involvement is lower.	Normal intellect. Short stature. Dysostosis multiplex. Restrictive lung disease. Corneal clouding. Hearing impairment.	Urine glycosaminoglycans. N-acetylgalactosamine 6-sulfatase enzyme activity.	ERT (for MPS IVA).
MPS VI (Maroteaux-Lamy disease)(#253200)	ARSB (AR)	23 in 10,000,000 (Germany). 40 in 10,000,000 (Australia).	Cardiac valve thickening Hypertrophy. Conduction abnormalities. Coronary artery disease.	Normal intellect. Short stature. Dysostosis multiplex.	Urine glycosaminoglycans. N-acetylgalactosamine-4-sulphatase enzyme activity.	ERT.

Valve involvement in adult MPS

Table 2 Type and percentage of valve functional abnormalities in various adult MPSs from reported series

MPS Type	Number of subjects; (age range in years)	% Mitral regurgitation	% Aortic regurgitation	% Mitral stenosis	% Aortic stenosis	Reference/comment
I	6; (18–29)	100	83	50	50	26
	9; (21–43)	100	100	11	22	16
II	10; (21–53)					27
						10 patients: 'valvular heart disease consisting mainly of aortic and/or mitral valve insufficiency'
IV	69; (>18)	28	39	8.7	16	5
VI	10; (18–38)	100	100	90	90	22
	9; (19–29)	22	78	22	11	18

MPS, mucopolysaccharidose.

Multidisciplinary team discussion regarding treatment
(metabolic, spinal, respiratory, airway, cardiology, cardiothoracic surgeon, anaesthetist)

Limited evidence for best timing or type of surgery to perform

Braunlin, Heart 2016

Lysosomal storage disorders 2

Condition	Gene (inheritance)	Incidence	Cardiac involvement	Supportive clinical features	(Non-genetic) diagnostic tests	Treatment options
Mucolipidosis II/III (#252500, #252600, #252605)	GNPTAB (AR); GNPTG (AR)	<1:100,000	Valvular disease. Left and / or right ventricular hypertrophy. Pulmonary hypertension.	Joint stiffness, dysostosis multiplex. Short stature. Restrictive lung disease.	Urine oligosaccharides. Plasma acid hydrolase activities. N-acetylglucosamine-1-phosphotransferase enzyme activity.	Supportive.
Lysosomal acid lipase deficiency (#278000)	LIPA (AR)	1:350,000 (severe infantile form). 1:50,000 (late onset form).	Atherosclerosis.	Infantile: failure to thrive, hepatomegaly, liver failure, adrenal calcification. Late-onset: dyslipidemia, hepatic fibrosis / cirrhosis, atherosclerosis.	Lipid profile. Lysosomal acid lipase enzyme activity.	ERT. Liver transplant.
Fabry disease (#301500)	GLA (XL)	1:50,000 to 1:117,000 males.	Cardiomyopathy. Stroke.	Renal impairment. Acroparathesia. Angiokeratomota.	GLA enzyme activity (men).	ERT. Chaperone therapy.

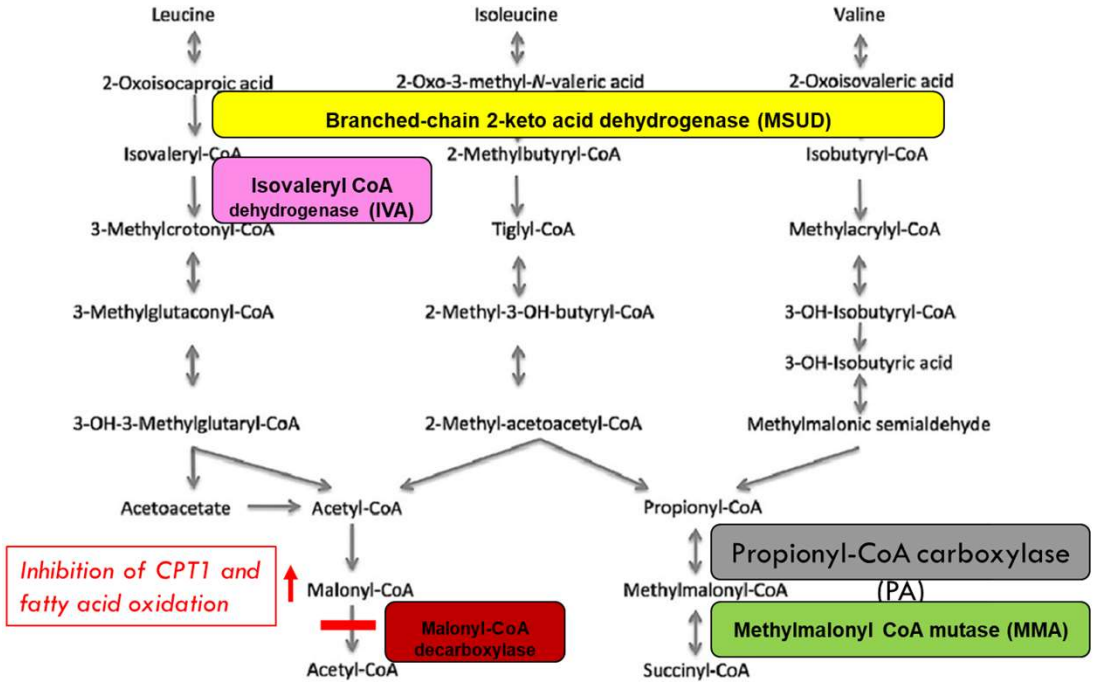
Non-syndromic genetic CM

Isolated cardiomyopathy in disorders typically thought to be associated with multisystem organ involvement

Typically found by genetic testing (WGS, exome, CM panels)

May / may not be associated with biochemical abnormalities

Malonyl-CoA decarboxylase deficiency



Gene: MLYCD

Autosomal recessive

Developmental delay
Hypotonia
Seizures
Metabolic acidosis
Hypoglycemia
Cardiomyopathy

Malonyl-CoA decarboxylase deficiency

30 year old female, CM noted during pregnancy

Homozygous for novel p.Ser241Leufs*17 in *MLYCD* gene (premature stop codon)

Acylcarnitine profile:

Total carnitine	28	(26-62 umol/L)
Free carnitine	24	(22-50 umol/L)
Acylcarnitine	4	(4-12 umol/L), increased C3DC (malonyl carnitine) 0.88 (<0.09 umol/L)

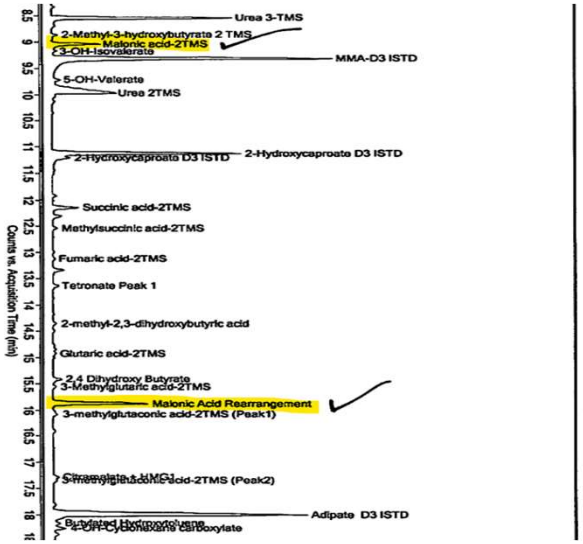
Fibroblast culture, malonyl CoA decarboxylase activity (UMC, Amsterdam):

6.5 nmol/(hour.mg protein) (Normal: 20.4 ± 6.8 nmol/(hour.mg protein))

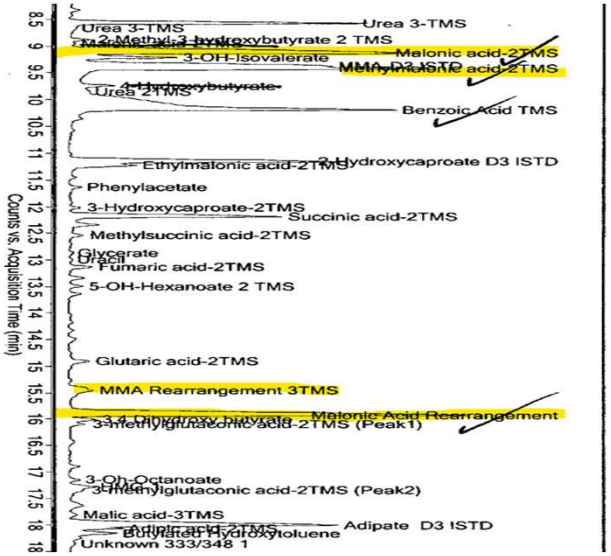
In X5 MCoAD cell lines < 4.3 nmol/(hour.mg protein))

Malonyl-CoA decarboxylase deficiency

Adult



Paediatric

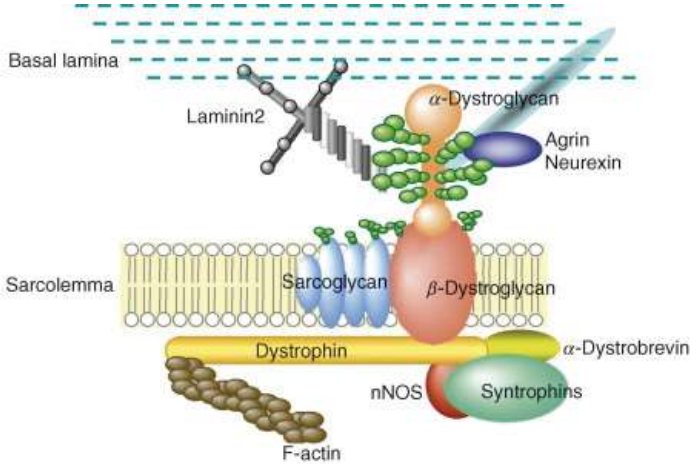


Abnormal metabolites may be more subtle / easily missed in adults

Dolichol kinase-CDG

22 year old female
Presented with progressive exercise intolerance
Diagnosed with dilated CM

Panel of CM genes:
homozygous c.1372G>A p.(Gly458Ser) variant in *DOLK*



No other systemic features
Serum transferrin isoform IEF – abnormal type 1 pattern

Reduces O-mannosylation of alpha-dystroglycan in cardiac muscle – reduced capacity to bind laminin

Dolichol kinase-CDG

Lefeber et al, PLoS Genetics, 2011

11 patients (from 4 families)

5-13 years

CM: asymptomatic – mild – severe

Abnormal transferring IEF for N-glycosylation abnormalities; reduced dolichol kinase activity in fibroblasts

No ataxia, seizures, intellectual disability (except mild in 1 family)

Kapusta et al, Heart Fail Rev, 2013

9 patients, 3 families

All < 10 years

CM: asymptomatic – mild – severe

Abnormal transferrin IEF for N-glycosylation abnormalities

Abnormal coagulation studies

3 patients had cardiac transplant

Investigations

Cardiac function

ECG

ECHO

MRI

Exercise testing

Rhythm and event monitoring

Blood pressure monitoring

Angiogram

Cardiac biopsy

First line testing

Glucose

FBC

Ferritin, transferrin saturation

Electrolytes including calcium

Lipid profile

Blood gas, anion gap

Lactate

Ammonia

Creatine kinase

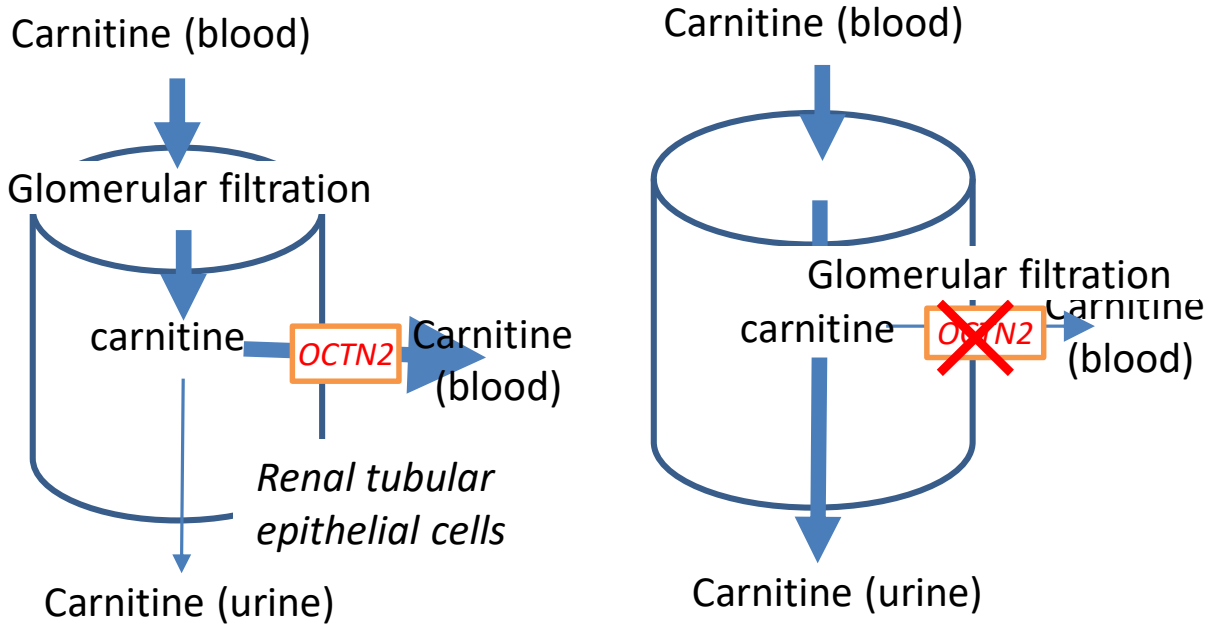
Brain natriuretic peptide (BNP)

Specialist metabolic testing / Genetic tests

Laboratory investigation of metabolic causes of cardiomyopathy

Primary carnitine deficiency

- Organic cation/carnitine transporter 2 deficiency
- Very low plasma/DBS carnitine and acylcarnitines



Primary carnitine deficiency

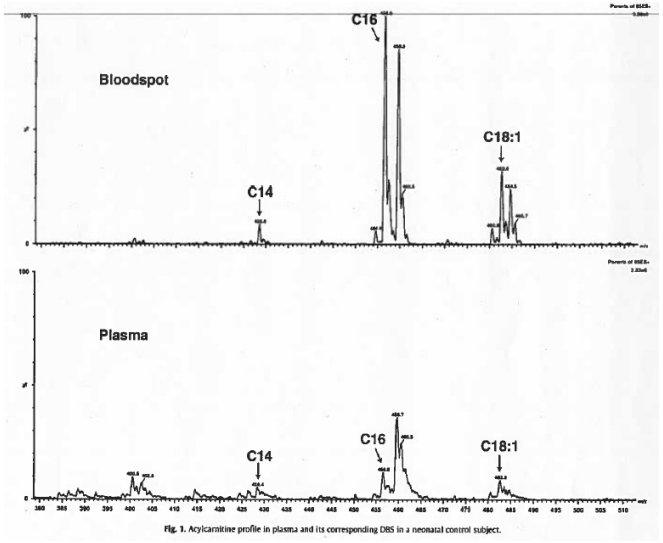
- If patient is on carnitine, may be difficult to identify
- Calculation of fractional excretion of carnitine

$$\text{FEcarn} = \frac{(\text{ur carnitine} \times \text{pl creatinine})}{(\text{pl carnitine} \times \text{ur creatinine})} \times 100$$

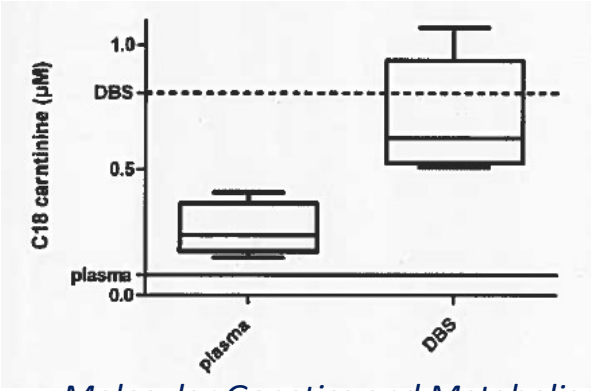
- All analytes in the same units
- Paired samples
- Normal fractional excretion of carnitine <2%
- Exclude renal tubular dysfunction

CACT and CPT2

- Increased long chain fatty acids (C16, C18, C18:1)
- Long-chain FAs associated with red blood cell membranes
- Dried blood spots > plasma
- More difficult to identify increases in DBS than plasma



Acyl-carnitine profiles in paired control samples



C18 results in patients with CPT2 deficiency

Molecular Genetics and Metabolism. Volume 110, 2013, Pages 116-121

CACT and CPT2

- C16+C18:1/C2 ratio increases diagnostic sensitivity in DBS

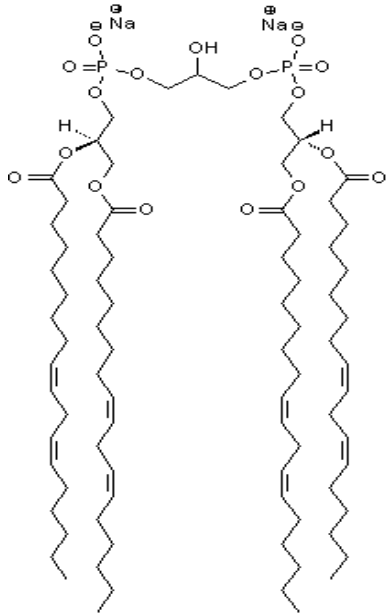
- ERNDIM ACDB-UL-2020-A
  - DBS sample from 1-year old, cardiomyopathy, CACT deficiency
  - Only 15/44 participants suggested CPT2 or CACT

- CACT and CPT2 distinguished by genetic testing

Glycogen storage disorders
Lysosomal storage disorders

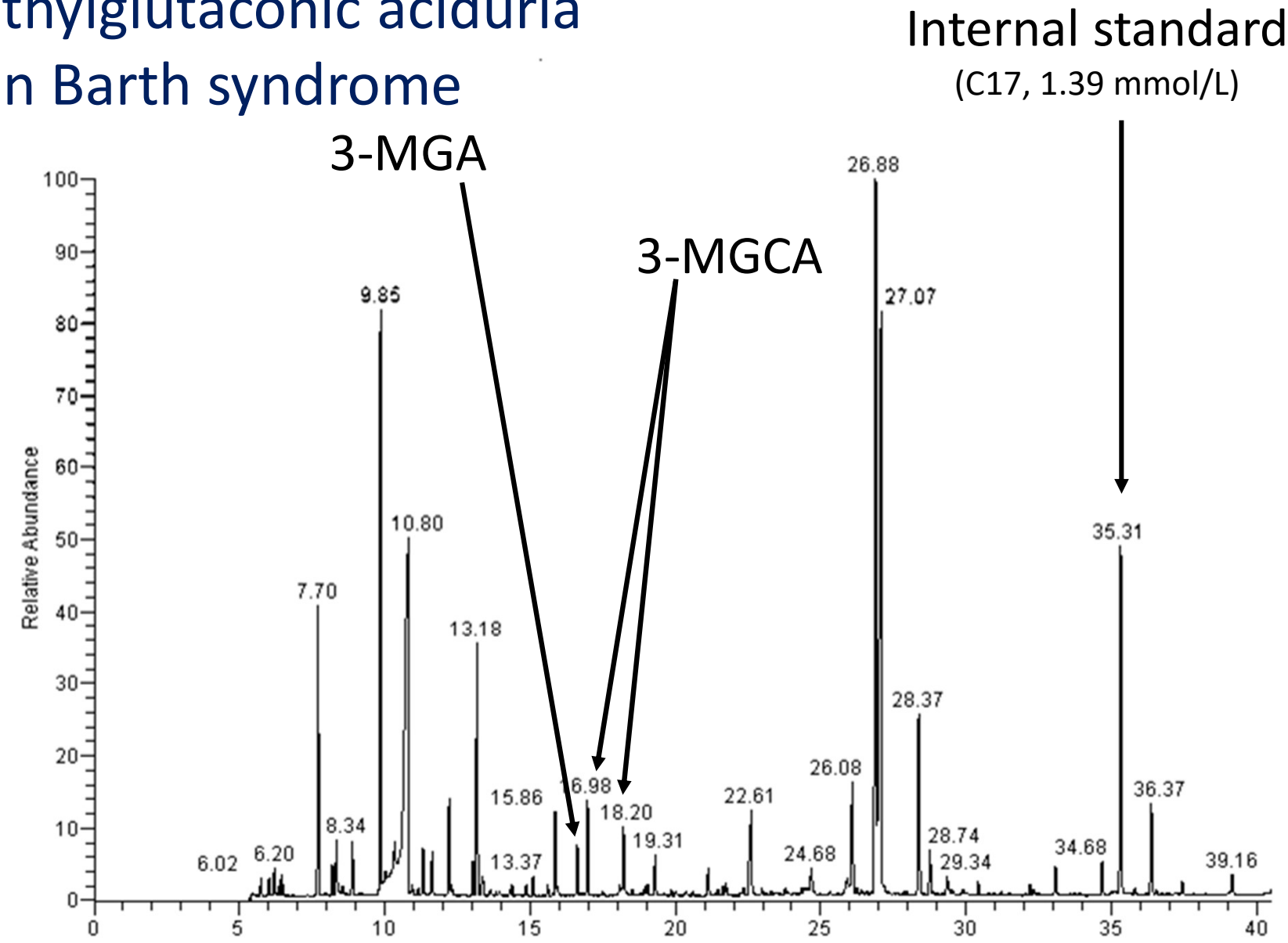
- GSD Enzyme assays
  - Acid maltase (Pompe) in DBS or leucocytes, readily available
  - Others mainly used to confirm results of genetic testing
- In most cases, genetic testing is first-line if GSD suspected
- LSDs
  - Urinary Glycosaminoglycans (GAGS) - mucopolysaccharidoses
  - Specific enzyme activities
  - Metabolites – lyso-GB3
  - Genetic testing

Barth syndrome



- Variable phenotype
  - Cardiomyopathy (most DCM, also HCM)
  - Skeletal muscle weakness
  - Neutropenia
  - Growth retardation
  - 3-methylglutaconic aciduria
- Variants in *TAZAFFIN* gene (X-chromosome) cause abnormalities in cardiolipin, a mitochondrial membrane phospholipid

3-methylglutaconic aciduria in Barth syndrome



Barth syndrome

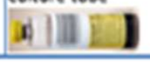
- Diagnostic challenge and delay
- Urine 3-methylglutaconic acid in patient with cardiomyopathy and/or other features should prompt further investigations
- 3-MCG is non-specific and may not be increased
- Analysis of blood spot cardiolipin profile is sensitive and specific for the disorder

Investigation of cardiomyopathy

- Who sees the patient?
  - Acute presentation to cardiac unit
  - Referral to metabolic/genetic service
- Protocol prepared by multi-disciplinary team
  - Helpful for non-metabolic clinician
  - Untargeted
  - Requires a lot of blood

Paediatric Cardiomyopathy Screen

This is not a request form. All tests must be requested on e-record or on paper forms.

Virology & Microbiology			
Test	Sample	Date sent	Result
Influenza CFT (convalescent anti-bodies)	1 x full serum (gold) 		
HIV			
IgM Parvovirus			
IgM CMV			
EBNA IgG (> 1 y)			
EBV VCA IgM (< 1 y)			
ASO			
Based on symptoms and history mycoplasma, HSV, HBV, HCV	1 x EDTA (purple) 		
PCR enterovirus and CMV			
PCR enterovirus: stools	1 stool sample		
PCR in respiratory secretions	Sterile container 		
Throat swab C&S	Culture tube 		
Blood culture if pyrexial	Paediatric blood culture tube 		

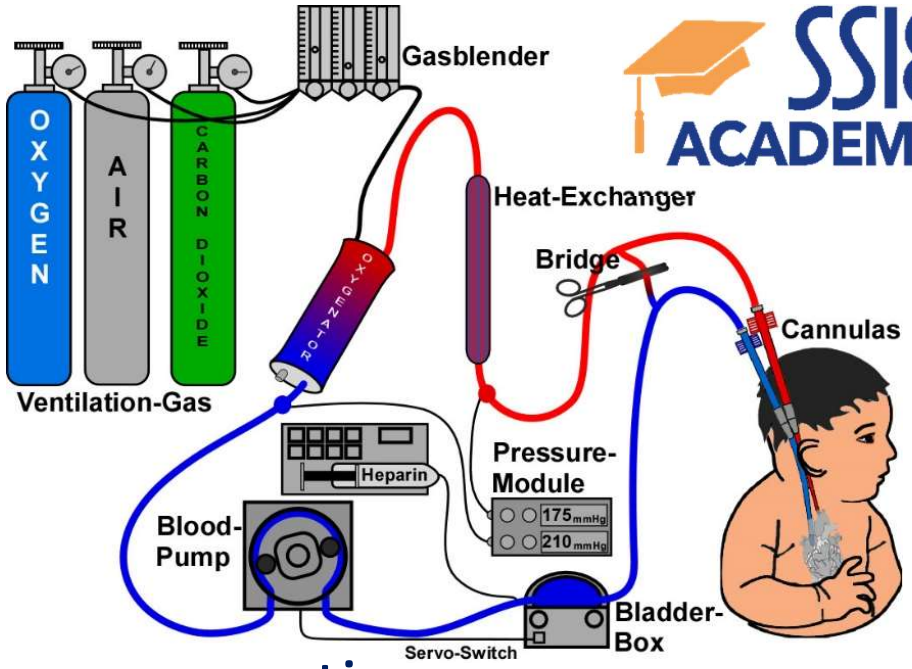
Muscle Biopsy: to be taken with first procedure

Biochemistry			
Test	Sample	Date sent	Result
Glucose	1 x Fl Ox (grey) 		
Lactate			
TSH/FT4	1 x full serum (gold)		
Ca, PO4			
Vitamin D			
Uric acid			
CK			
Total Cholesterol			
Triglyceride			
Ferritin			
Transferrin saturation			
PTH	1 x EDTA (purple) 		
Ammonia	1 x EDTA (purple)  ON ICE		
Biochemistry – Metabolic Tests			
Transferrin isoforms (>3 wks of age or >3 wks post-transfusion)	1 x Serum 		
Acylcarnitines	1 x EDTA (purple)		
Pompe Screen			
Cardiolipin (males)			
Amino acids	1 x Li-hep (green) 		
Urine organic acids	10 ml urine		
Urine MPS screen			

Genetic testing: If dysmorphic features, consanguinity or family history of cardiomyopathy, refer to clinical genetics and take a blood sample for DNA storage, EDTA (purple top) tube.

This protocol was revised in April 2017 by Dr Andres Rico-Armanda (paediatric cardiology), Dr Ann Bowron (Clinical Biochemistry), Dr Danielle Brown (Clinical

Challenges



- Patients < 5 days of age
- Blood transfusion
- Medications
- ECMO
  - extra-corporeal membrane oxygenation
  - mechanical support for heart and lungs
  - blood removed, oxygenated, CO_2 removed, returned to body
  - blood transfusion
  - ?acute phase response due to metal tubing

More challenges

- Have investigations been performed previously? (Variable cardiomyopathy screens)
- Genetics: rapid screens, VUSs
- Collection of samples for storage if patient dies
- Treatment before samples taken
- Mild, late presenting cases

Summary

- Cardiomyopathy is an important feature of many IMD
- Investigation of metabolic cardiomyopathy requires a multi-disciplinary approach (find a friendly cardiologist)
- Metabolic investigations of cardiomyopathy can be a challenge
  - Clinical state of the patient
  - Sample (type, quality and timing) dependent
  - Influence of treatment on results