

MANAMA Training, Clinical Genetics

Inborn Errors of Metabolism

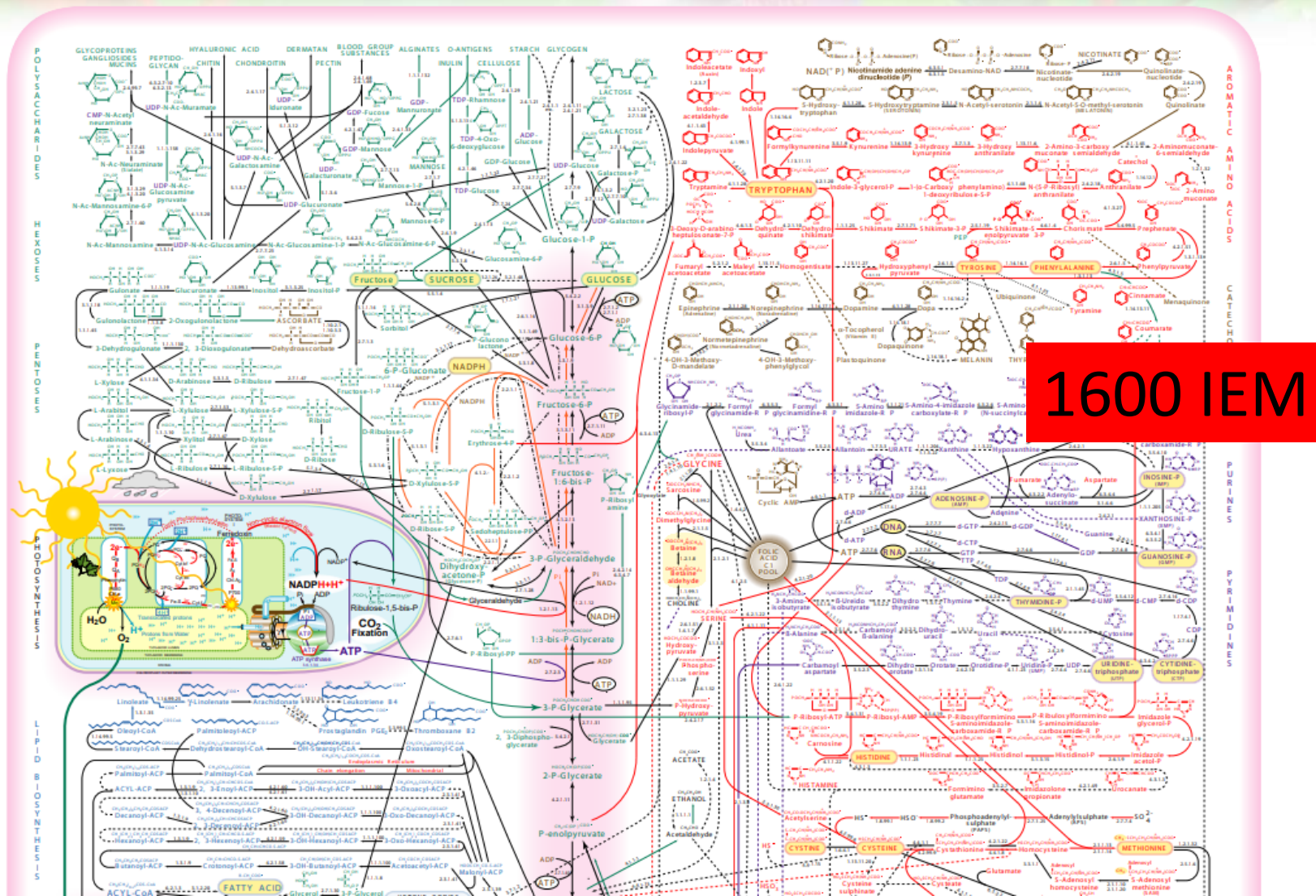
Energy metabolism disorders:
GSD and FAO defects

Stéphanie Paquay
December 9th 2025

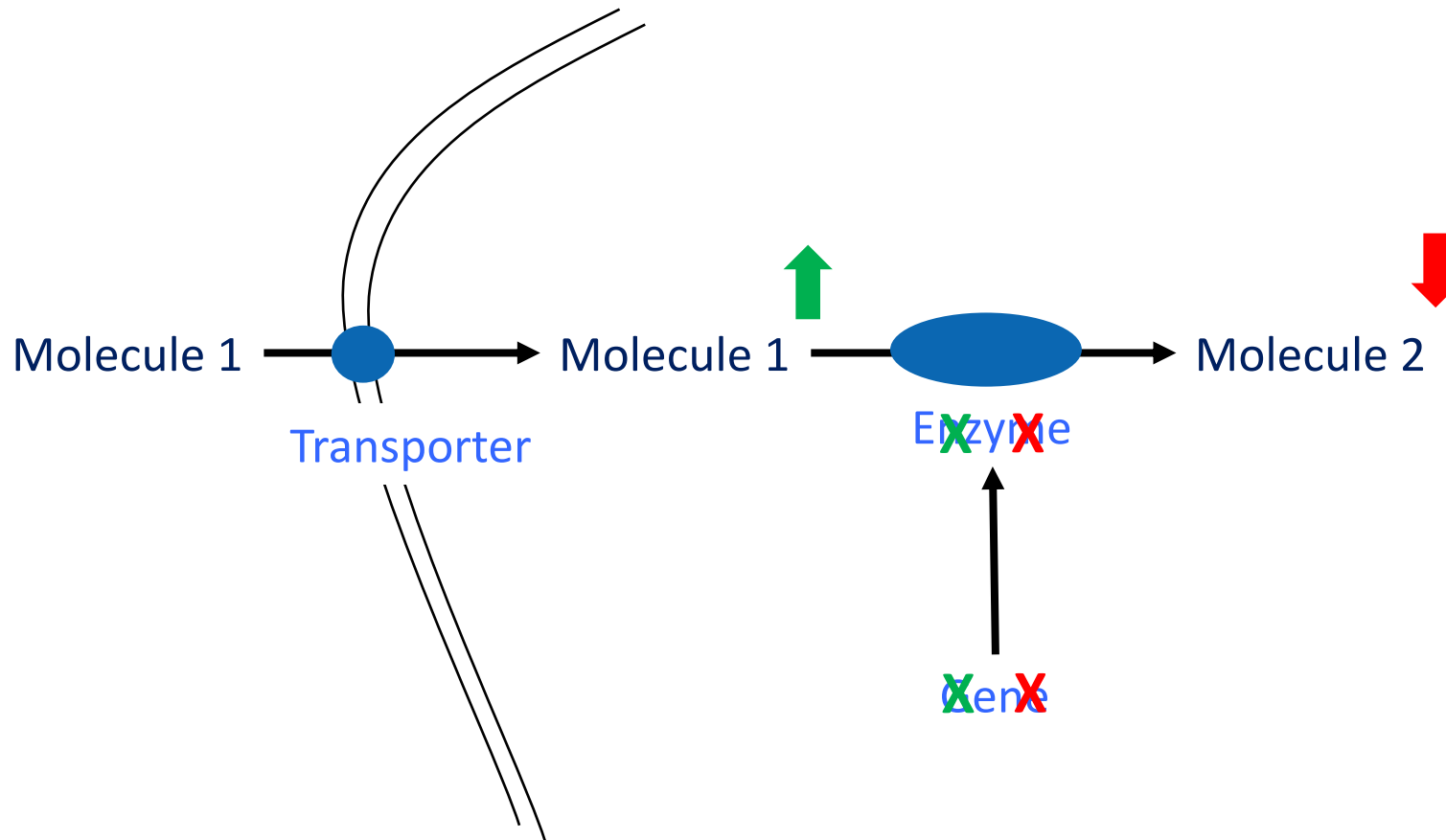
Membre du réseau
Lid van het netwerk

 **Huni**

Metabolic Pathways



Inborn errors of metabolism

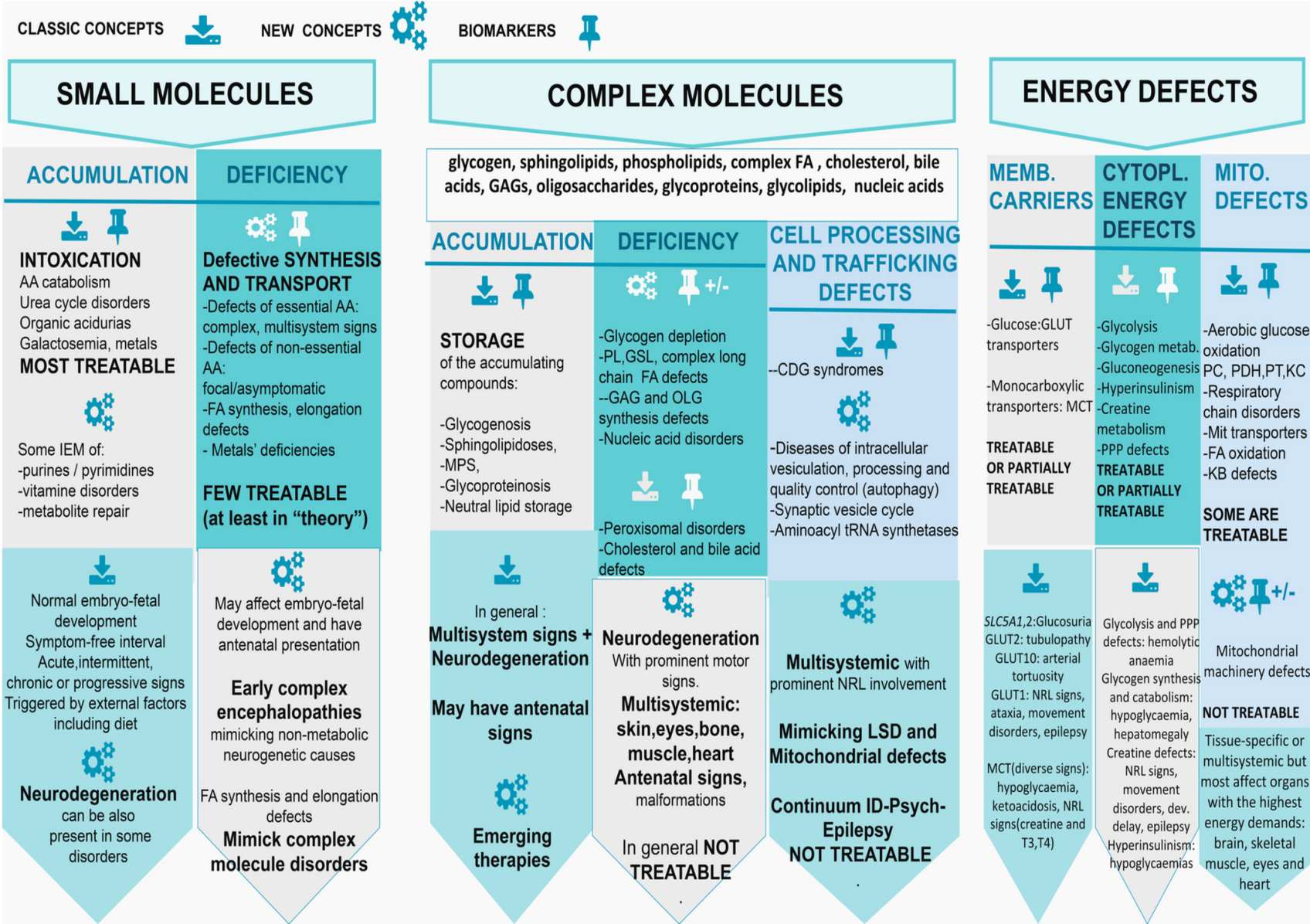


Intoxication : phenylketonuria, urea cycle defects, galactosemia,

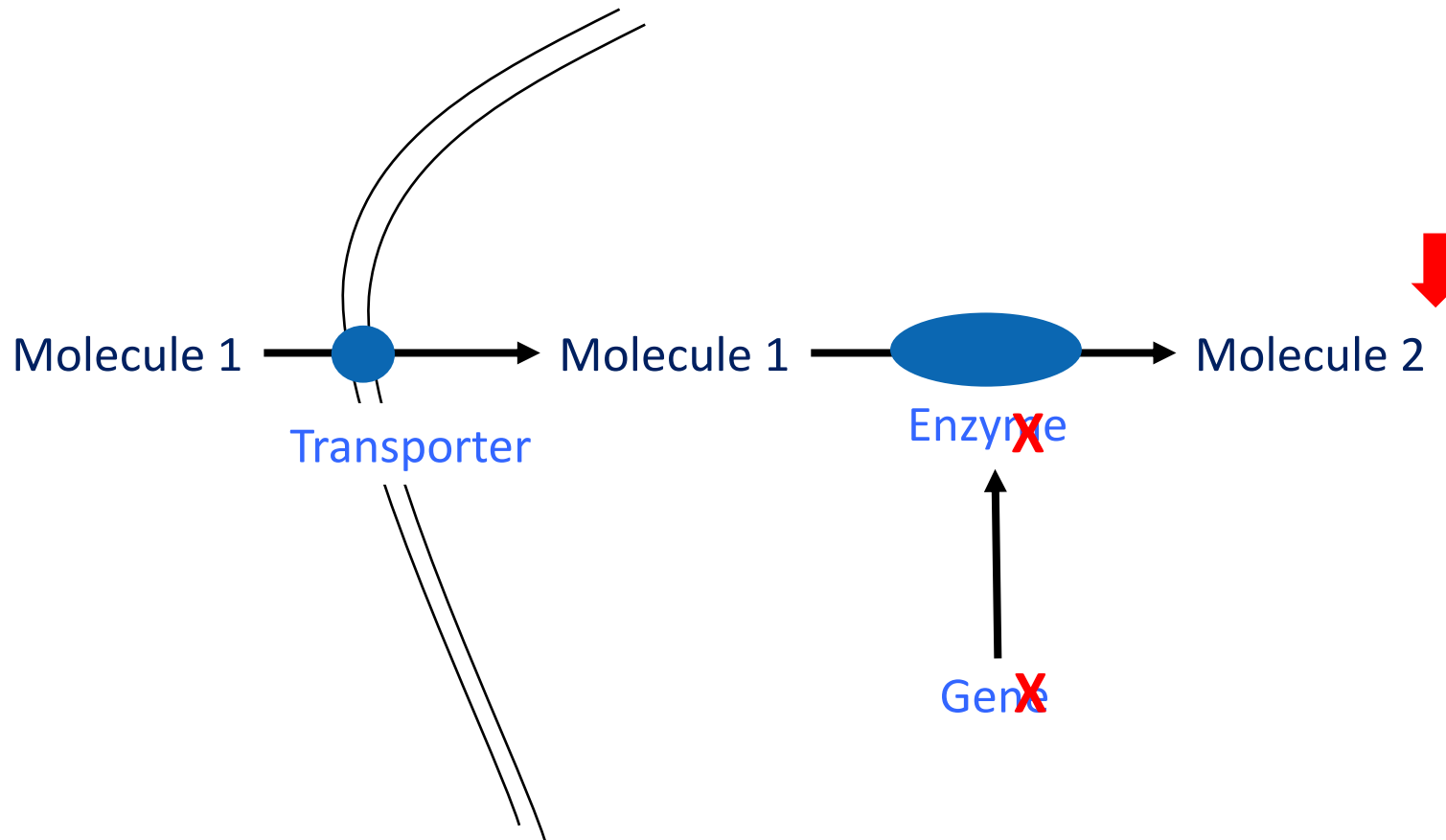
Energy deficiency

Complexes molecules : lysosomal and peroxisomal diseases, CDG,

Proposal for a simplified classification of IMD based on a pathophysiological approach: A practical guide for clinicians

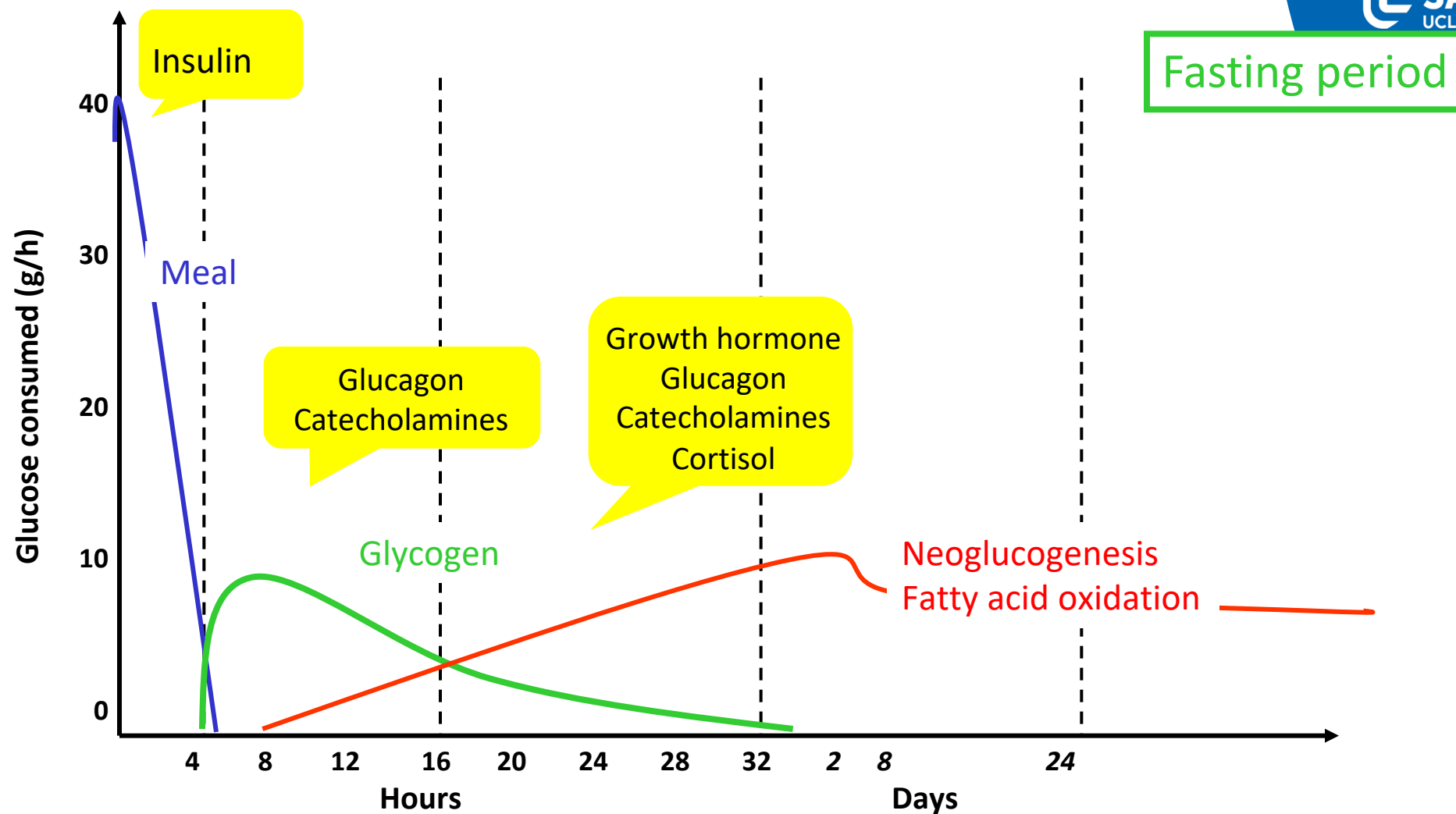


Inborn errors of metabolism



Energy deficiency

- ATP : mitochondrial diseases
- Glucose
 - Glycogenoses
 - Fatty oxidation defects
 - Neoglucogenesis defetcs
 - ...



Fuel used by
the brain

Glucose

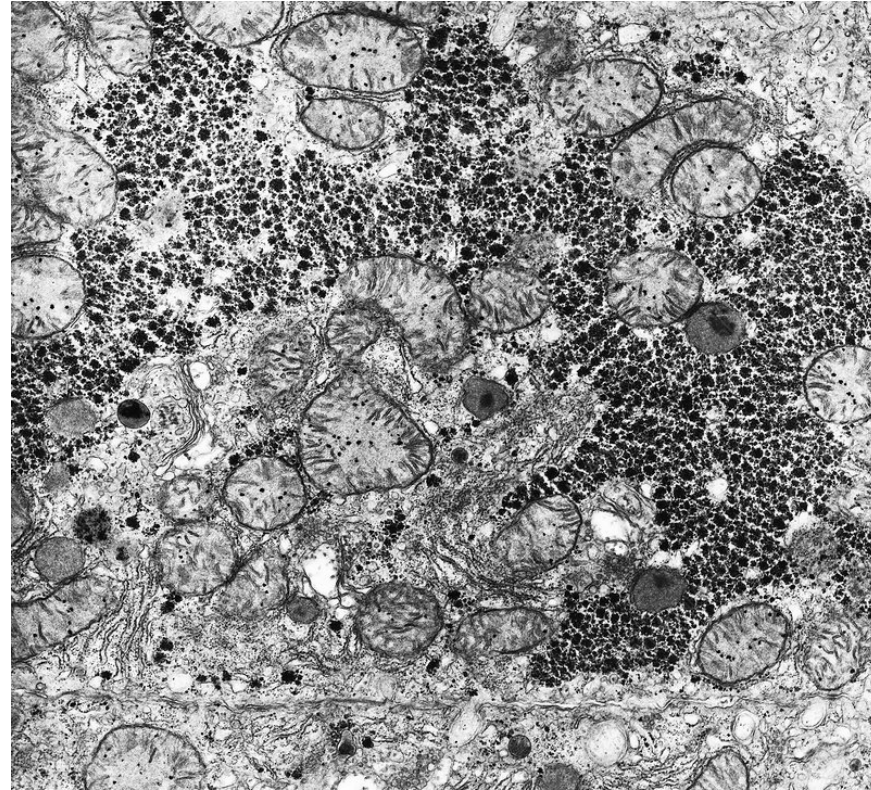
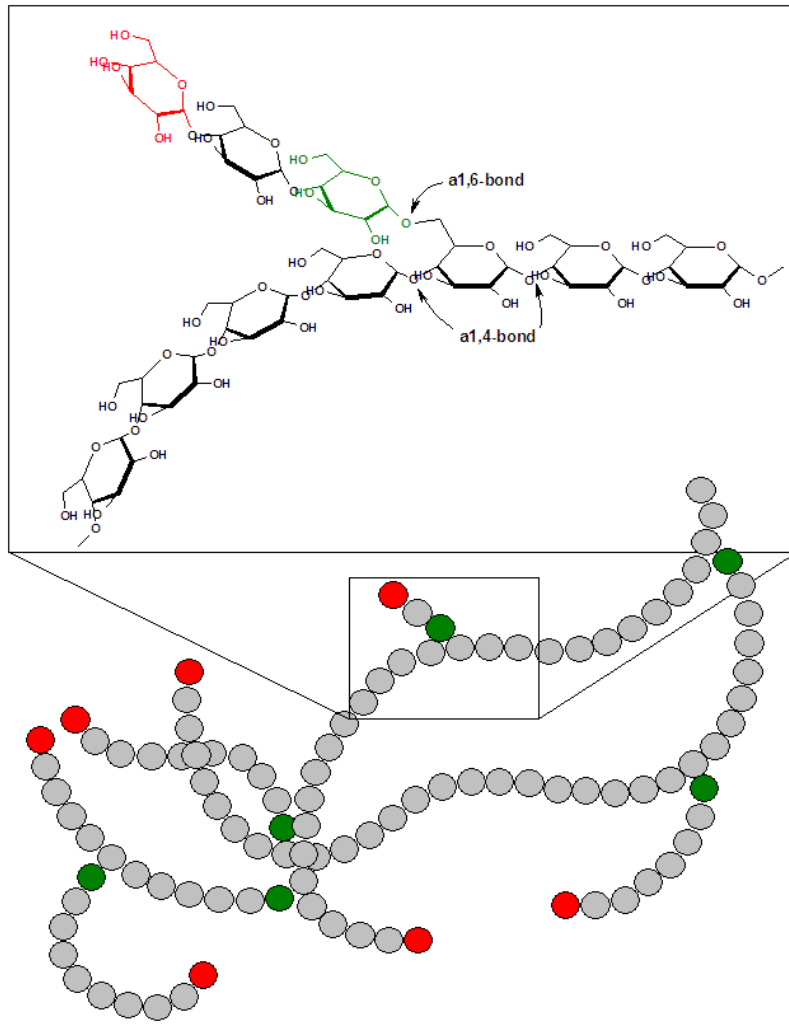
Glucose

Glucose
Ketone bodies

Glucose
Ketones bodies

Ketone bodies
Glucose

Glycogen metabolism



- In the liver : source of glucose for the body
- In the muscles : local source of energy

Glycogenoses

Liver and/or muscle (rare neurological) phenotypes

The hepatic glycogenoses : 80 % : children +++

- hepatomegaly (apart from glycogen synthase 2 deficiency)
- fasting hypoglycaemia

The muscular glycogenoses : 20 % : adults

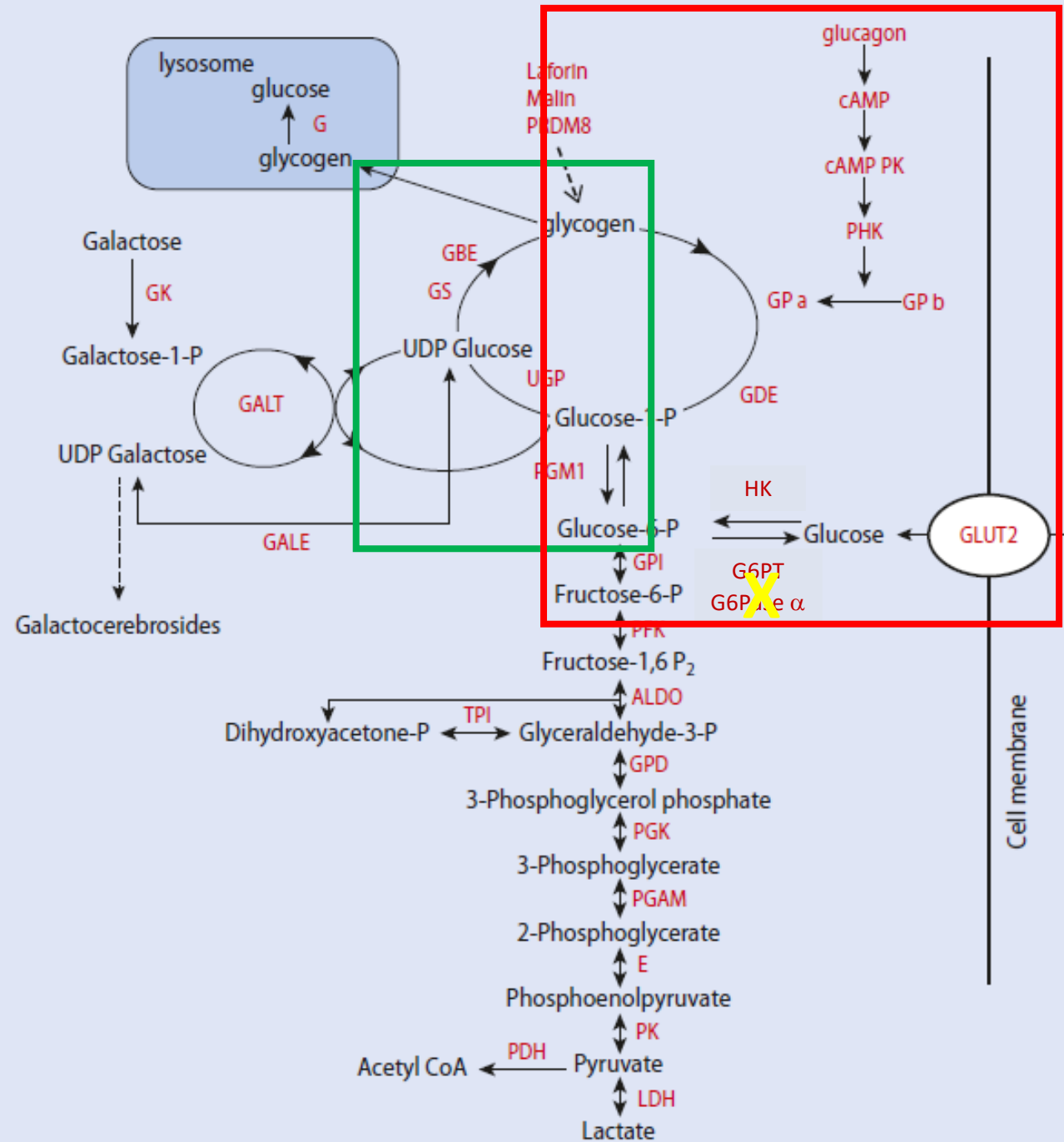
- skeletal myopathy and/or cardiomyopathy

Extremely heterogeneous clinical phenotypes

■ **Table 5.1** Phenotypes associated with enzyme deficiencies

Num- ber	Enzyme deficiency	Gene(s)	Eponym	Main phenotype(s)
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0b	Muscle glycogen synthase	<i>GYS1</i>		Cardiac & skeletal myopathy
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Ib	Glucose-6-phosphate transporter	<i>SLC37A4</i>		As Ia + neutrophil dysfunction, infections/colitis
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VII	Muscle phosphofructokinase	<i>PFKM</i>	Tarui	Skeletal myopathy
IXa	Phosphorylase kinase (various subunits ■ Table 5.2)	<i>PHKA2</i>		Hepatomegaly, hypoglycaemia, growth delay
IXb		<i>PHKB</i>		
IXc		<i>PHKG2</i>		
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XII	Aldolase A	<i>ALDOA</i>		Skeletal myopathy and anaemia
XIII	β -Enolase	<i>ENO3</i>		Skeletal myopathy
XIV	Phosphoglucosmutase	<i>PGM1</i>		Myopathy; PGM1-CDG
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	Lysosomal-associated membrane protein 2 (LAMP2)	<i>LAMP2</i>	Danon	Cardiomyopathy, skeletal myopathy, mental retardation, maculopathy
	Laforin deficiency Malin deficiency PRDM8 deficiency	<i>EPM2A</i> <i>EPM2B</i> <i>PRDM8</i>	Lafora body disease	Epilepsy, dementia

J.-M. Saudubray et al. (eds.),
Inborn Metabolic Diseases,
https://doi.org/10.1007/978-3-662-63123-2_5



Glycogen Storage Disease Type I (GSD I)

2 types

- GSD Ia : deficiency in glucose-6-phosphatase- α
- GSD Ib : deficiency in glucose-6-phosphate (G6P) translocase (G6P transporter).

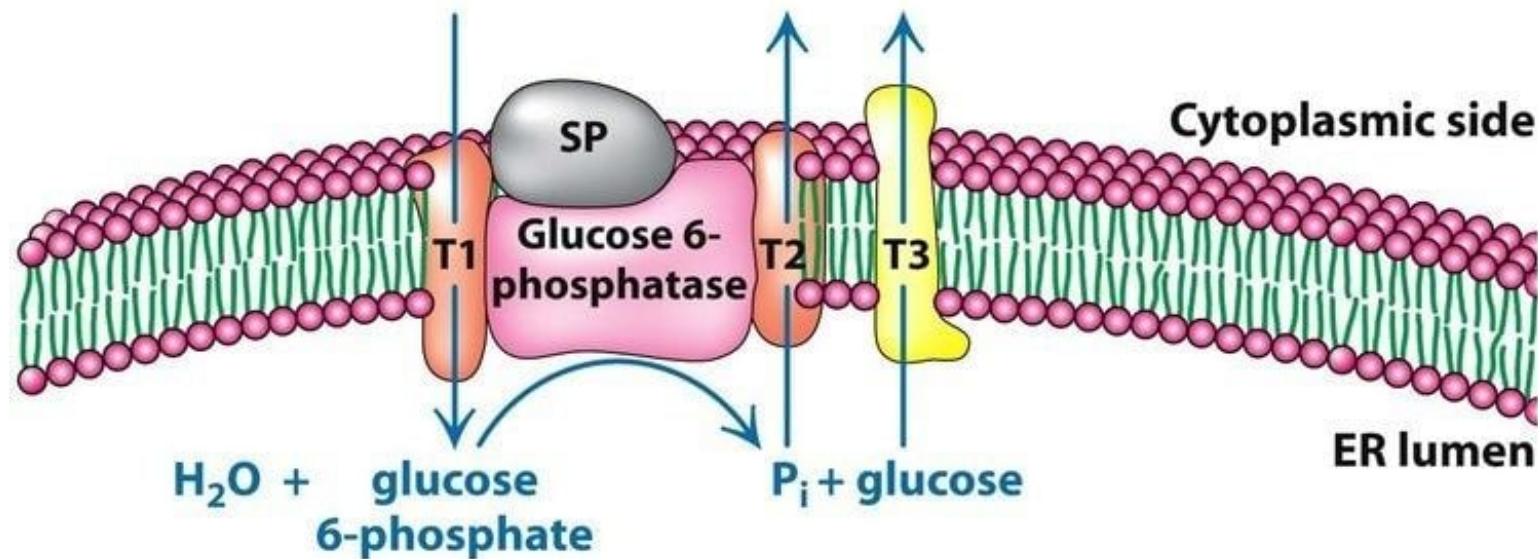
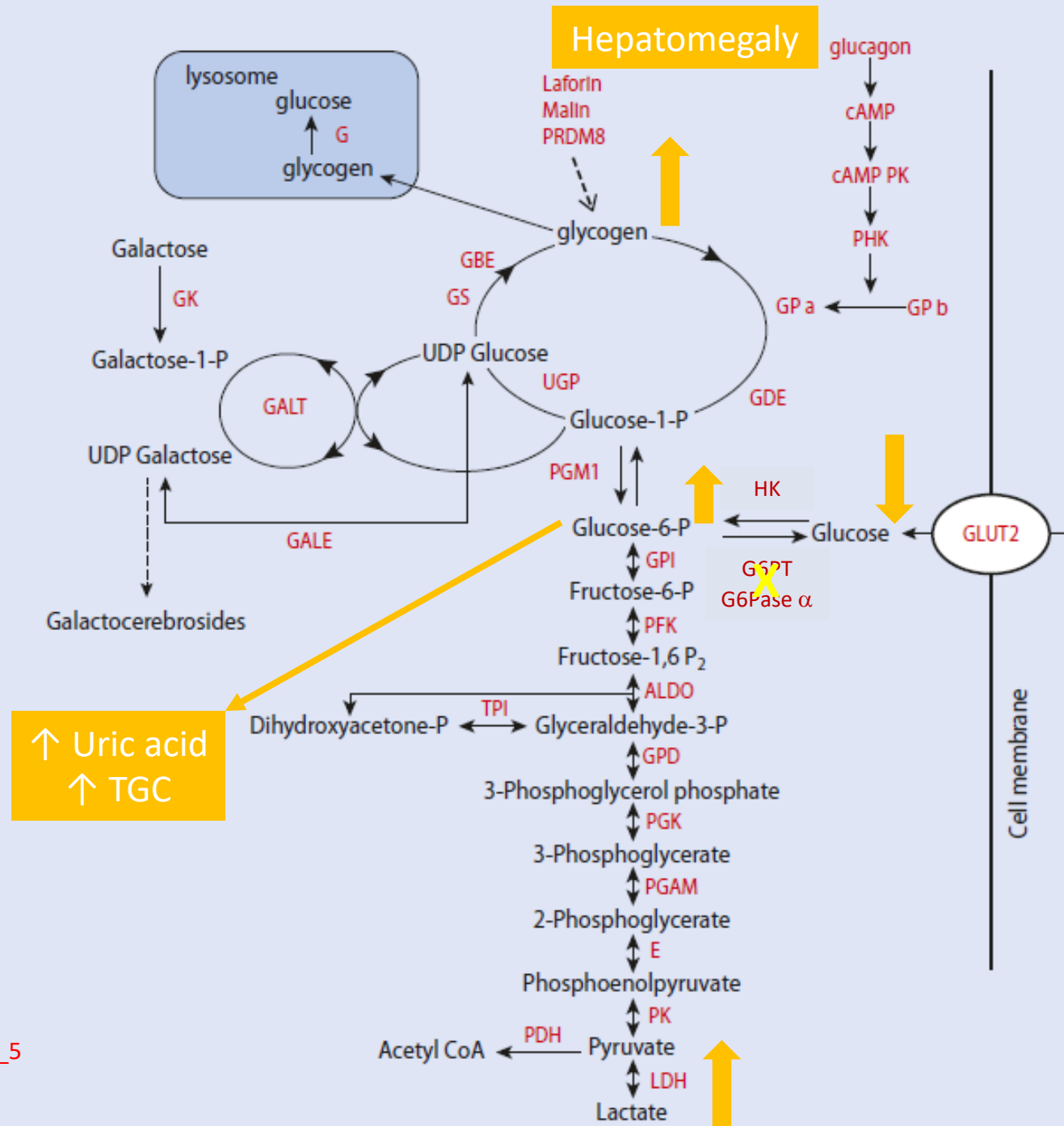


Figure 16.29
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company

! fasting hypoglycaemia, lactic acidosis and hepatomegaly.
GSD Ib : immunological disease due to neutrophil dysfunction.



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Normal at birth

Early infancy

- poor growth, abdominal distension, episodes of tachypnoea, and irritability
- a 'dolls like' face, a large abdomen and thin arms and legs, hepatomegaly
- fasting hypoglycaemia (after a short period of fasting 2-3h), lactic acidosis, hyperlipidaemia, hyperuricaemia
- GSD Ib : frequent severe bacterial infections, neutropenia

Glycogen Storage Disease Type I (GSD I)

2 types

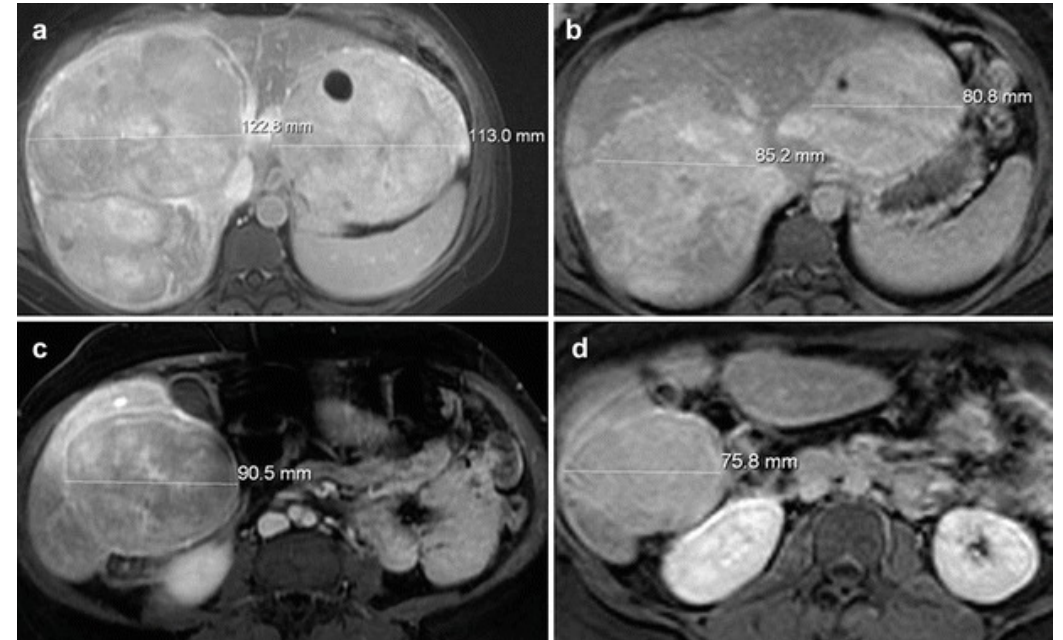
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Long-term complications

- Hepatic Tumors Benign hepatocellular adenoma
- Renal Disease : large kidneys but also impact on proximal and distal renal tubular and glomerular function.
- Systemic hypertension
- Osteoporosis

Neutrophil dysfunction in GSD 1b : Mouth ulcers, chronic and severe periodontitis and inflammatory bowel disease like Crohn disease

Glycogen Storage Disease Type I (GSD I)



JIMD Rep. 2015;18:23-32.

<https://healthjade.net/von-gierke-disease/>

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A frequency of approximately 1 in 100,000 (GSD Ia : 80% of cases).

GSD1a : caused by homozygous or compound heterozygous mutations in *G6PC1*

GSD Ib : caused by homozygous or compound heterozygous mutations in *SLC37A4*.

Glycogen Storage Disease Type I (GSD I)

Treatment : correct the metabolic abnormalities as far as is possible and prevent or manage any complications

Diet

- **Frequent meals** every 120 – 150 minutes : Continuous pumped overnight feeds given via a nasogastric tube or gastrostomy
- Glucose requirements : based on normal, age related, hepatic glucose production (8–9 mg/kg/min in infants, 5–7 mg/kg/min in children, 2–4 mg/kg/min in adolescents and adults)
- **Uncooked cornstarch** prolongs carbohydrate absorption from the gut and can increase the period of normoglycaemia between feeds (> 1 year of age)

Kishnani PS, Austin SL, Abdenur JE et al (2014) Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. Genet Med:1–29

Glycogen Storage Disease Type I (GSD I)

Treatment : correct the metabolic abnormalities as far as is possible and to prevent or manage any complications

Neutrophil dysfunction

- enterocolitis : treatment with 5-aminosalicylic acid and granulocyte colony stimulating factor (GCSF).
- treatment with empagliflozin, an SGLT2 inhibitor

Follow-up

- Renal function
- Abdominal ultrasound or CT/MRI

Veiga-da-Cunha M, Chevalier N, Stephenne X et al (2019) Failure to eliminate a phosphorylated glucose analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. Proc Natl Acad Sci U S A 116(4):1241–1250.

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IV	Glycogen brancher			rhosis; opathy/cardiomyopathy; Adult polyglucosan body disease
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IXb		<i>PHKB</i>		
IXc		<i>PHKG2</i>		
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+muscle and cardiac involvement

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Glycogen Storage Disease Type V (McArdle Disease)

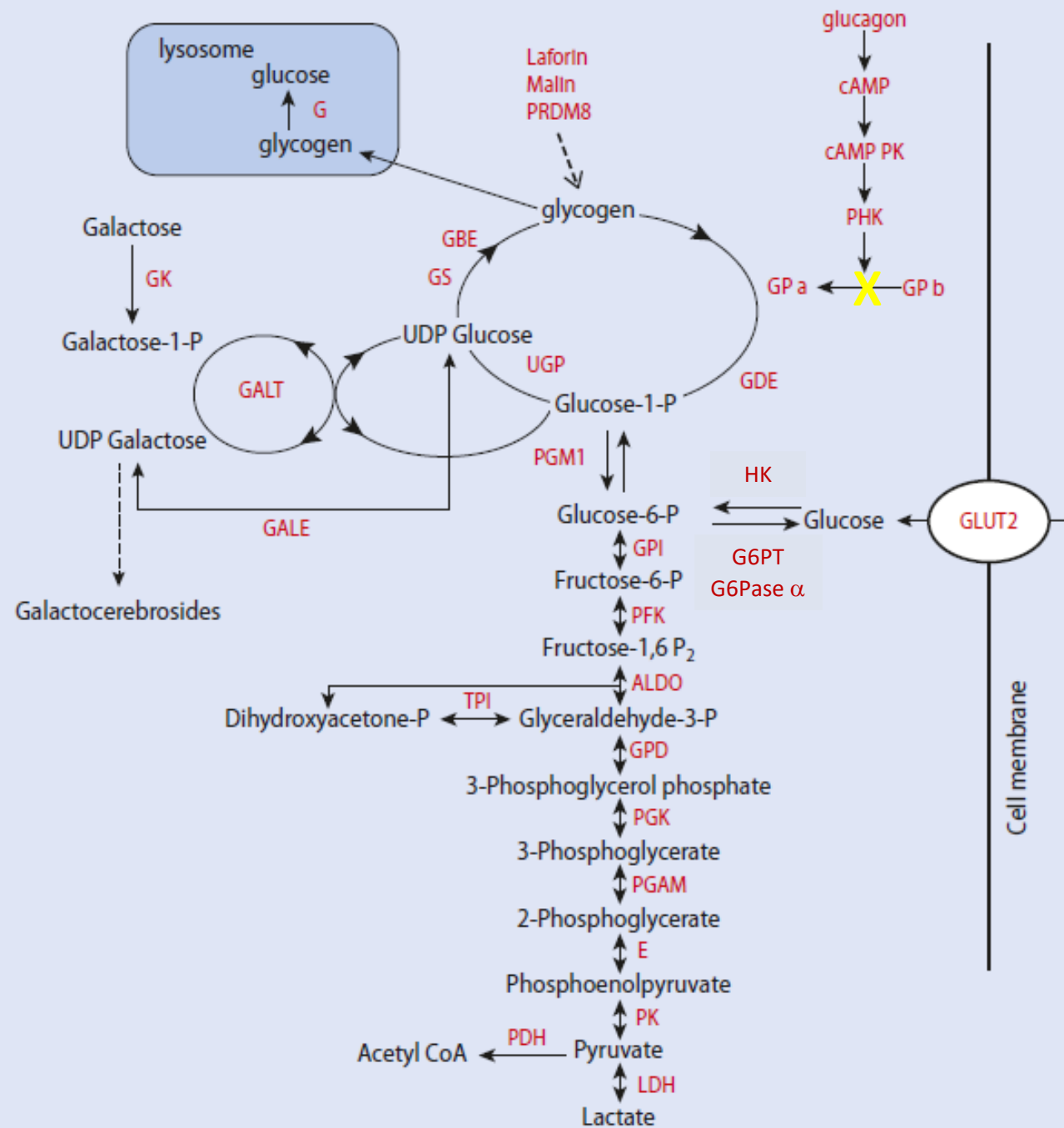
The most common muscle glycogenosis

- **Exercise intolerance** with myalgia and stiffness of exercising muscles, which are relieved by rest
- Onset during childhood, but diagnosis frequently missed at an early age

a constant phenomenon, named the '**second wind**': if they rest briefly after the onset of exercise-induced myalgia, they are then able to continue to exercise with a lower level of pain and fatigue.

Risk of rhabdomyolysis, leading to a risk of developing acute renal failure

Normal clinical exam or mild proximal weakness



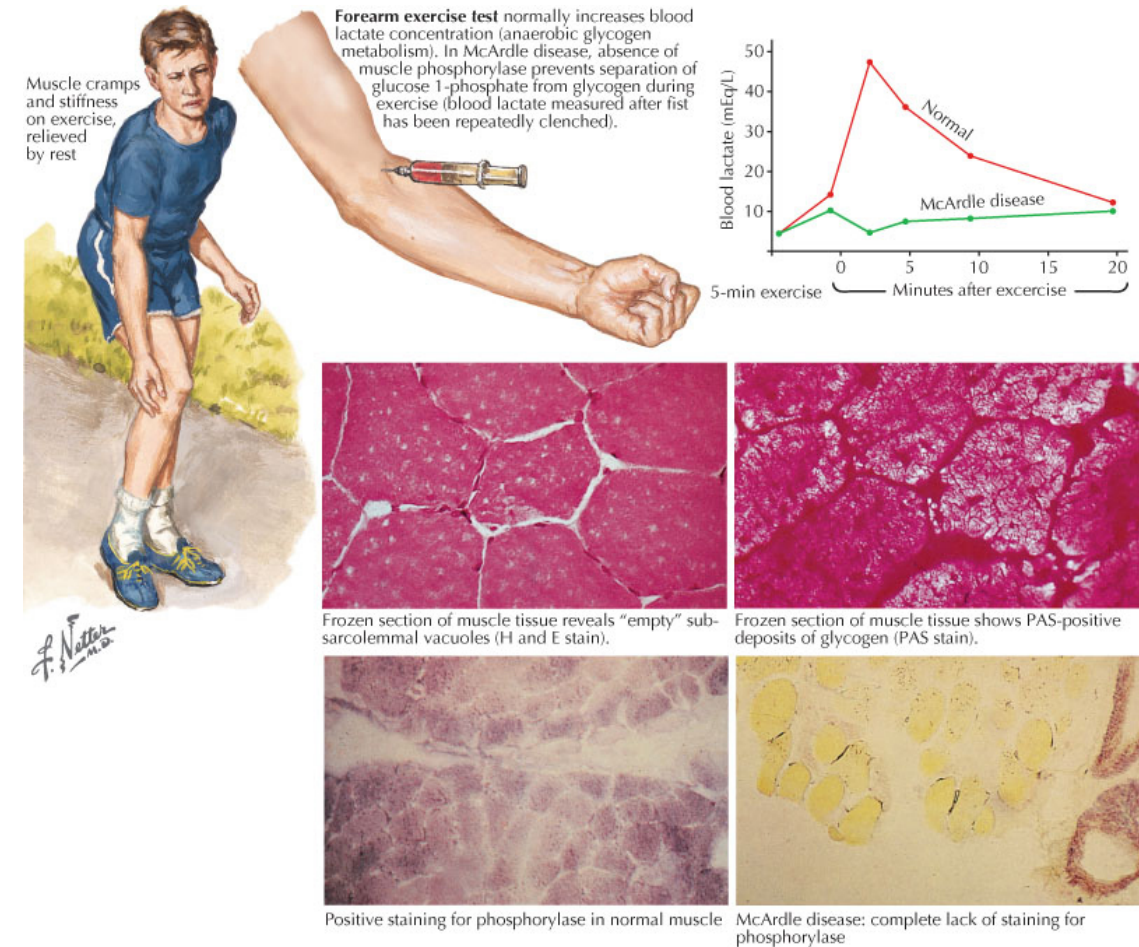
Glycogen Storage Disease Type V (McArdle Disease)

Diagnosis

- ↑ resting serum CK
- Non-ischemic forearm test
- Muscle biopsy :
 - subsarcolemmal accumulation of glycogen
 - Lack of staining for myophosphorylase
- Molecular investigation : *PYGM* gene

Treatment

- no pharmacological treatment
- aerobic conditioning programs
- ingestion of oral sucrose 5 to 15 minutes before planned activity

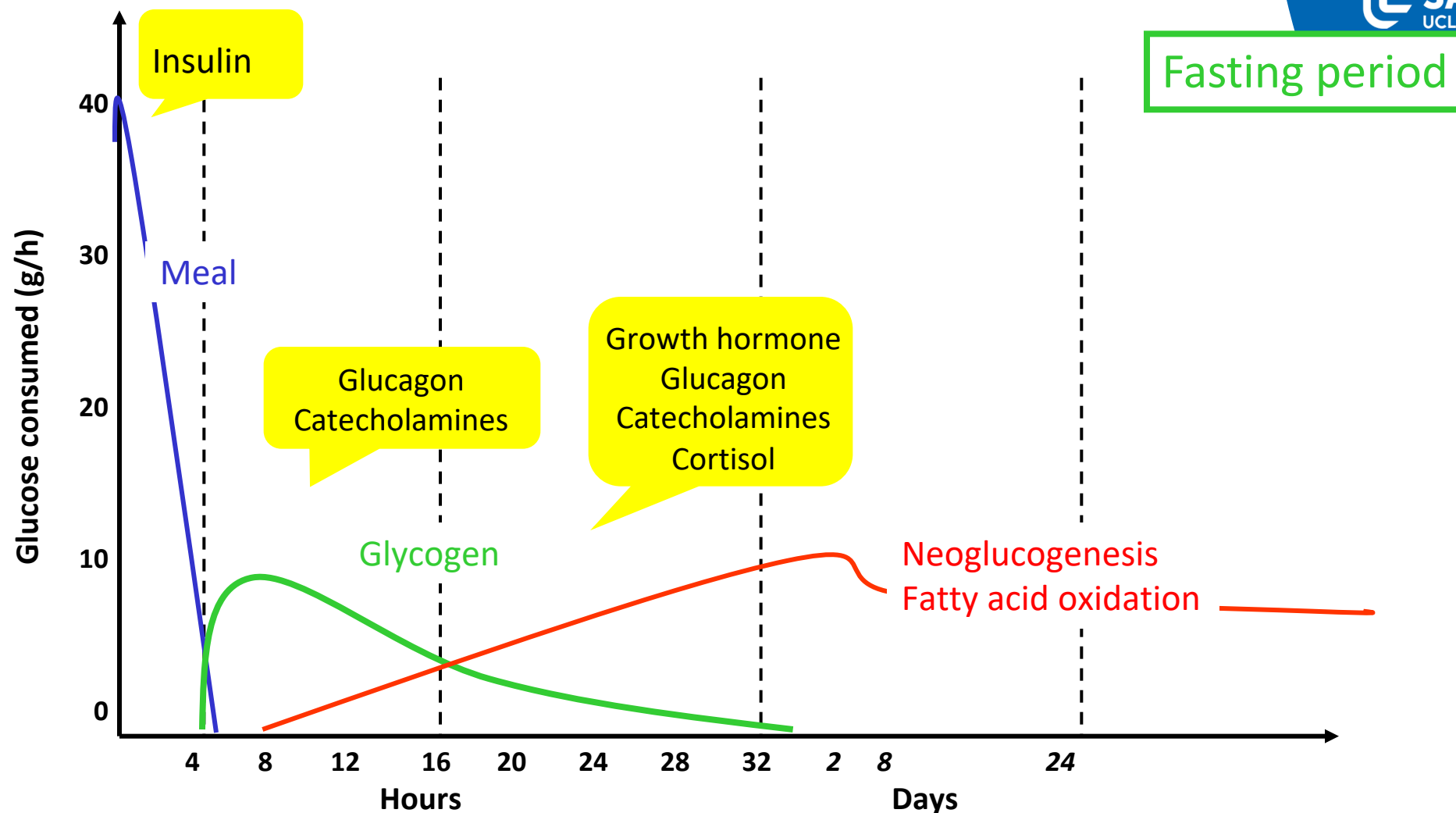


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Fuel used by
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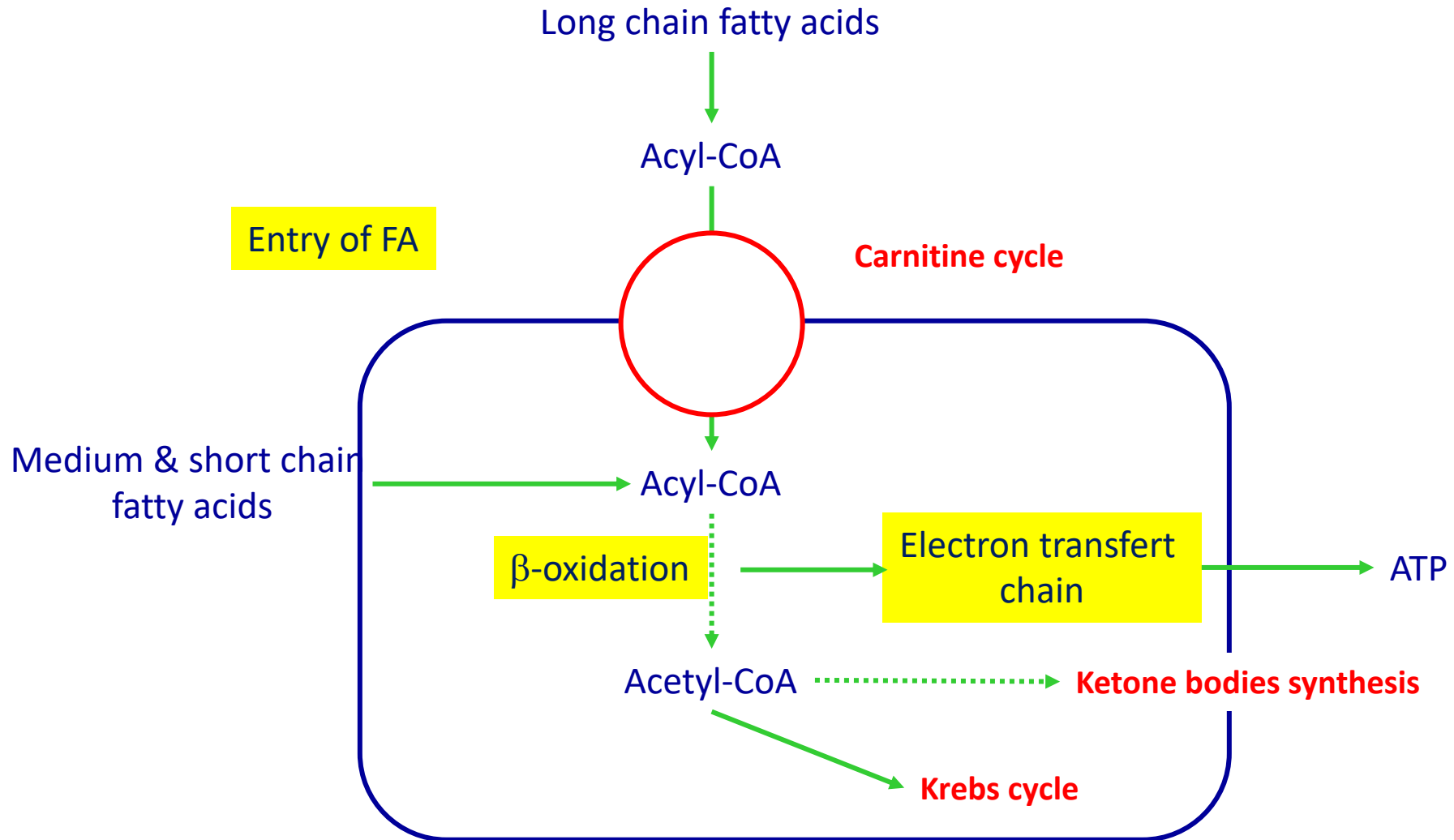
Glucose

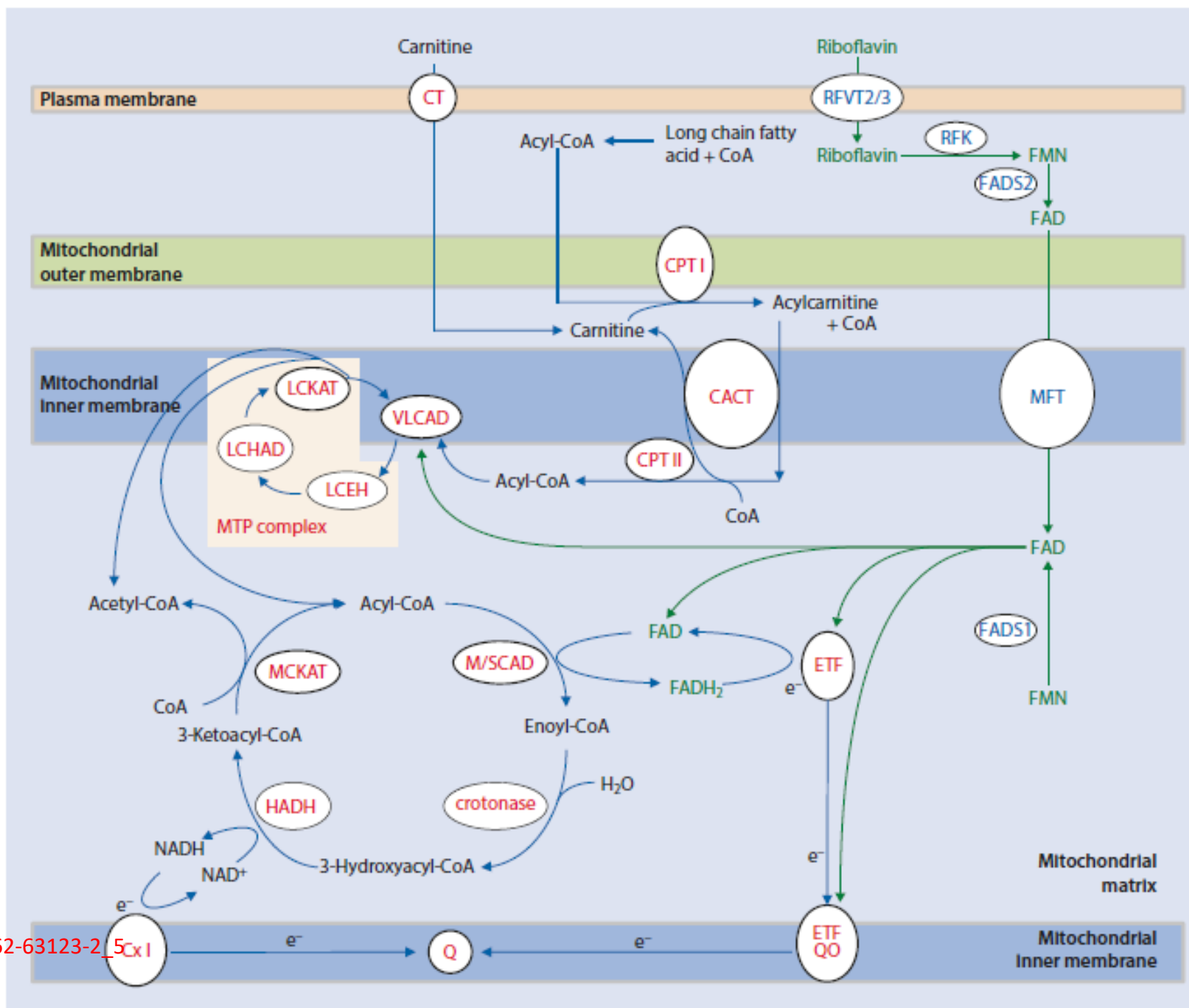
Glucose

Glucose

Glucose
Ketones bodies

Ketone bodies
Glucose





Disorders of Mitochondrial Fatty Acid Oxidation

Julien a boy : 16 months : emergency room : altered consciousness

History

- Tuesday evening : he didn't take his bottle
- On Wednesday morning, he throws up his bottle. Thereafter, he slept
- At noon, he ate shortly before going back to sleep
- Around 4 p.m., he had to be woken up. The child was listless. The lips are blue and he lost consciousness

Personal history

- First child of healthy non-consanguineous parents
- Pregnancy, delivery and neonatal period : uneventful
- In good health until now
- Normal growth and psychomotor development

Disorders of Mitochondrial Fatty Acid Oxidation

Julien a boy : 16 months : emergency room : altered consciousness

Physical examination : Sleepy child

Investigations

- Capillary blood glucose: 25 mg/dl (1.4 mmol/l) Lab-controlled blood glucose: 18 mg/dl (1 mmol/l)
- IV glucose load with marked improvement in clinical examination.
- Very low levels of Insulin and C-peptide. High level of cortisol
- Absence of ketone bodies in urines

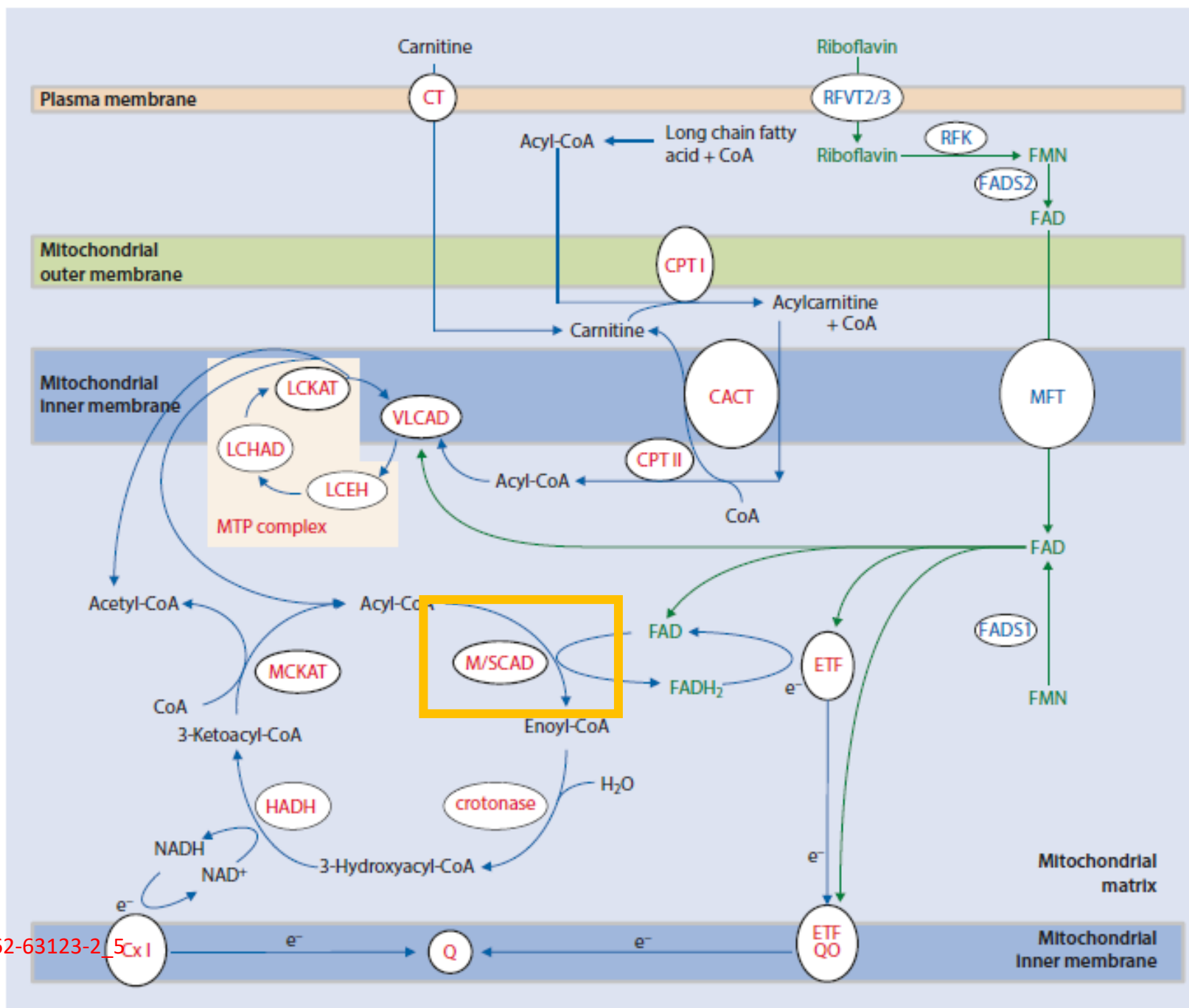
Urinary organic acids: significant medium-chain dicarboxylic aciduria, suberylglycine

Confirmation of MCAD deficiency

Disorders of Mitochondrial Fatty Acid Oxidation

MCAD deficiency : medium-chain acyl-CoA dehydrogenase deficiency

- the commonest fatty acid oxidation disorder in North-West Europe : 1:10,000–20,000
- Between the ages of 4 months and 4 years : acute **hypoglycaemic encephalopathy** and liver dysfunction; some deteriorated rapidly and died.
- Precipitating factors : **prolonged fasting or, more often, by an infection with vomiting.**

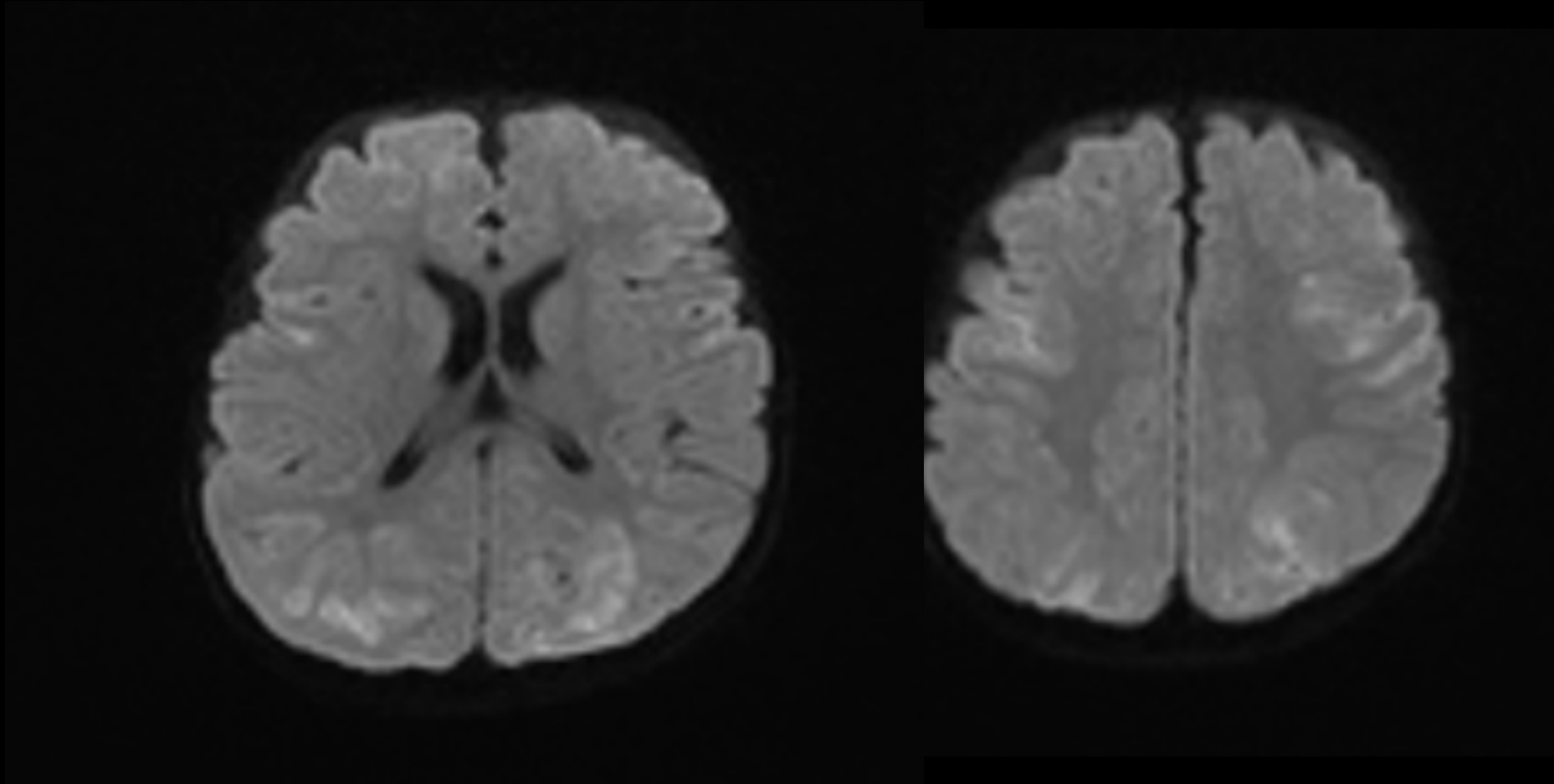


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!! Status epilepticus associated with hypoglycemia

Disorders of Mitochondrial Fatty Acid Oxidation

Adrien : 17 years old

Clinical course

- At the age of 15 : muscle pain following moderate effort. CKs : 140,000 IU/L. 3 days of hyperhydration. Positive serology for mycoplasma. Normalization of the level of CKs
- At the age of 17 : 2nd episode of rhabdomyolysis following moderate exercise. CKs : 70,291 IU/L.
- 3 months later : 3 hours of walking and the next day 1h30 of football. CKs : 246,750 IU/L.

Personal history

- Healthy non-consanguineous parents
- Pregnancy, delivery and neonatal period : uneventful
- In good health until now
- Normal growth and psychomotor development

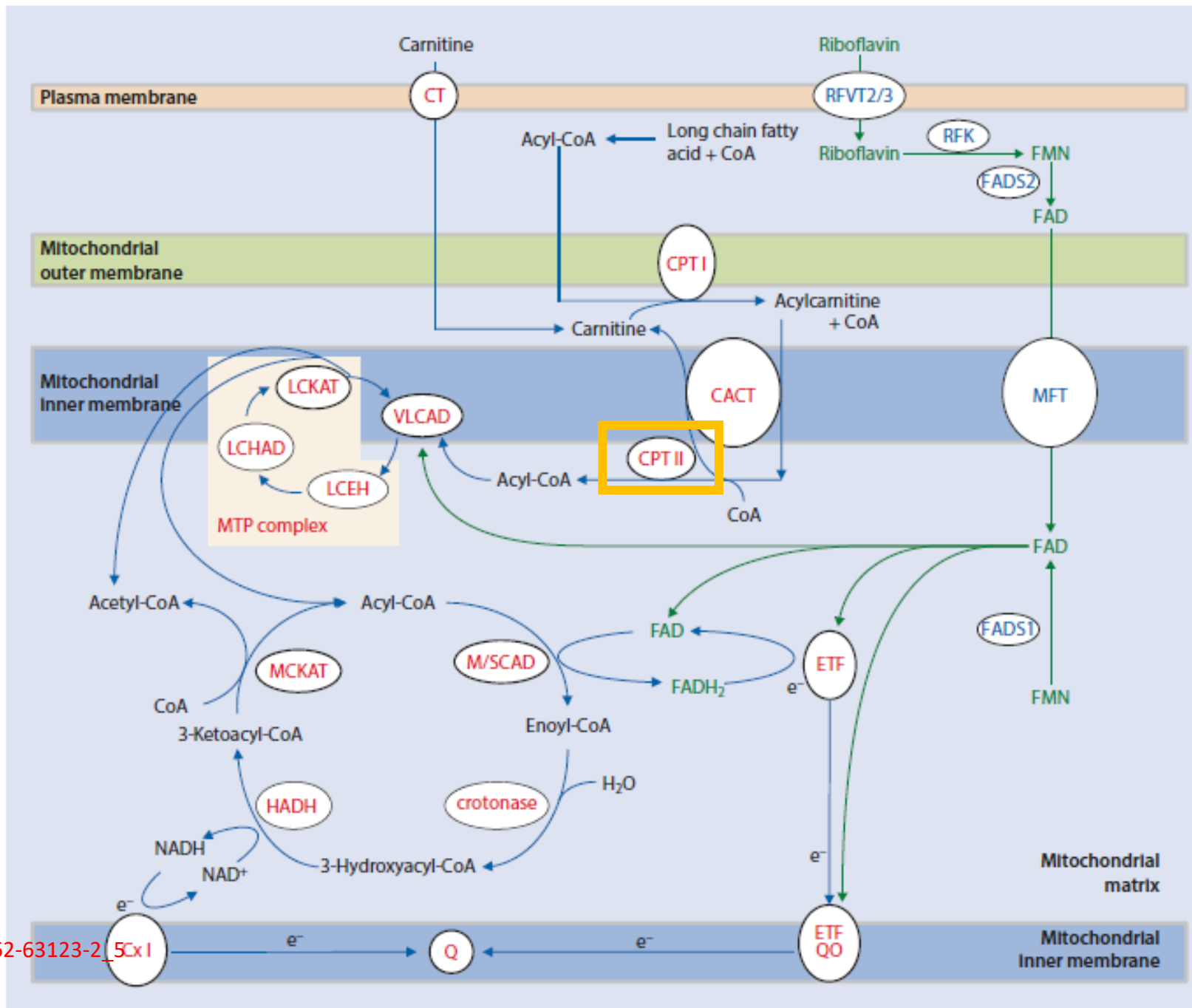
Disorders of Mitochondrial Fatty Acid Oxidation

Adrien : 17 years old

Metabolic investigations

C2 (<u>acetylcarnitine</u>)	2,0 - 19,0 Micromol/L	7.8
C16 (<u>palmitoylcarnitine</u>)	0,02 - 0,20 Micromol/L	4.18
C18 (<u>stearyl</u> carnitine)	0,02 - 0,15 Micromol/L	1.02
C18:1 (<u>oleyl</u> carnitine)	< 0,34 Micromol/L	2.99
C18:2 (<u>linoleyl</u> carnitine)	< 0,15 Micromol/L	0.67

Confirmation of CPT2 deficiency



Disorders of Mitochondrial Fatty Acid Oxidation

CPT 2 deficiency : carnitine palmitoyl deficiency type 2

- The commonest form = partial deficiency with episodes of **rhabdomyolysis in adolescents or young adults**.
- Precipitating factors : prolonged exercise, particularly in the cold or after fasting.
- Sometimes : myoglobinuria → **acute renal failure** requiring dialysis for a few days.
- ↑↑↑↑ plasma CKs during episodes.

Disorders of Mitochondrial Fatty Acid Oxidation

3 characteristic clinical presentations.

- **Acute hypoketotic hypoglycaemia** and encephalopathy, accompanied by hepatomegaly and liver dysfunction. Precipitating factors : fasting or an infection with vomiting. Some patients die unexpectedly during a minor illness. **MCAD deficiency**
- **Cardiomyopathy** (usually hypertrophic), arrhythmias or conduction defects.
- Myopathy, presenting either with weakness or with acute **rhabdomyolysis**, which may be precipitated by exercise or infection. **CPT2 or VLCAD deficiencies**

Table 12.1 Inherited disorders of mitochondrial fatty acid oxidation

Defect	Gene(s)	Potential clinical manifestations ^a					
		Hypoglycaemia & acute liver dysfunction	Cardio-myopathy	Rhabdo-myolysis	Chronic weakness	Other problems	
<i>Carnitine defects</i>							
CT	<i>SLC22A5</i>	+	+		+	J.-M. Saudubray <i>Inborn Metabol</i> https://doi.org/	
CPT I	<i>CPT1</i>	+					RTA
CACT	<i>SLC25A20</i>	+	+		+		
CPT II	<i>CPT2</i>	+	+	+	+	Malformations	
<i>β-oxidation defects</i>							
VLCAD	<i>ACADVL</i>	+	+	+	+		
MCAD	<i>ACADM</i>	+					
SCAD	<i>ACADS</i>						
ACAD9	<i>ACAD9</i>		+		+		
Crotonase	<i>ECHS1</i>		+			Neurodegeneration	
LCHAD & MTP	<i>HADHA, HADHB</i>	+	+	+	+	Retinopathy, Neuropathy	
HADH/SCHAD	<i>HADHSC</i>	+				Hyperinsulinism	
Dienoyl-CoA reductase ^b	<i>NADK2</i>					Neurodegeneration	
Mitochondrial enoyl-CoA reductase deficiency	<i>MECR</i>					Movement disorder & optic atrophy	
<i>Electron transfer defects</i>							
MAD ^c	<i>ETFA, ETFB, ETFDH</i>	+	+		+	Malformations	

J.-M. Saudubray et al. (eds.),
Inborn Metabolic Diseases,
https://doi.org/10.1007/978-3-662-63123-2_5

- All mitochondrial FAODs show an autosomal recessive pattern of inheritance

Disorders of Mitochondrial Fatty Acid Oxidation

Diagnostic Tests

- Accumulation of abnormal metabolites : **acylcarnitines**
 - In most FAODs, acyl-CoA intermediates accumulate proximal to the defect and are transesterified to carnitine.
 - The acylcarnitines profiles are analyzed by tandem mass spectrometry (TMS) on plasma or dried blood spots on filter paper
- Molecular investigations
- Fasting studies : **dangerous: not to be done anymore**

■ **Table 12.2** Abnormal metabolites seen in fatty acid oxidation disorders

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Deficiency	Plasma acylcarnitines	Urinary acylglycines	Urinary organic acids
CT	Low free carnitine		±(DCA)
CPT IA	Virtually absent long- & medium-chain acylcarnitines, high free carnitine		(Variable DCA)
CACT and CPT II severe	C18:1, C18:2, C16, C16-DC, C18:2-DC, C18:1-DC		Variable DCA
CPT II mild	↑(C16 + C18:1)/C2 ^b		
VLCAD	C16:1, C14:2, C14:1, C18:1 ^b		Variable DCA
MCAD	C10:1, C8, C6	Hexanoyl-, suberyl-, phenylpropionyl-	DCA [suberic > adipic], (KB)
SCAD	C4	Butyryl-	Ethylmalonic, methylsuccinic, KB
LCHAD / MTP	C18:1-OH, C18-OH, C16:1-OH, C16-OH ^b		3-Hydroxydicarboxylic acids, DCA
HADH	±C4-OH		±(3-hydroxybutyric, 3-hydroxyglutaric)
NADK2	±C10:2		±Lactic, ethylmalonic, glutaric, fumaric
MAD: severe	C4, C5, C5-DC, C6, C8, C10, C12, C14:1, C16, C18:1	Isobutyryl-, isovaleryl-, hexanoyl-, suberyl-,	Ethylmalonic, glutaric, 2-hydroxyglutaric, DCA
MAD: mild	C6, C8, C10, C12	Isobutyryl-, isovaleryl-, hexanoyl-, suberyl-	Ethylmalonic, adipic, DCA, KB

The diagnostic specificity can be increased by measuring the ratios of different acylcarnitines

Disorders of Mitochondrial Fatty Acid Oxidation

Treatment

- **Avoid prolonged fasting.** > 1 year of age : 12 h if the patient is in good health
- Frequent, regular meals, especially during exercise
- For long-chain fatty acids defects : restriction of long-chain fatty-acids and supplementation with medium-chain triglycerides
- **Careful management during acute illnesses** to prevent metabolic decompensation : provide glucose to stimulate insulin secretion and suppress lipolysis.
 - Drinks containing an appropriate amount of glucose should be started at the first sign of illness and continued every 2–3 hours until the patient starts to improve
 - If the drinks are vomited or the patient deteriorates, intravenous glucose

Disorders of Mitochondrial Fatty Acid Oxidation

Newborn screening

- Acylcarnitines analysis
- Major changes for the prognosis of these diseases, in particular of MCAD deficiency: careful management during periods of illness or fasting: significant reduction in death or long-term disability
- Exception : some babies still present within 72 hours of birth, before newborn screening results are available, with hypoglycaemia and/or arrhythmias

Information : mothers heterozygous for LCHAD deficiency, who may develop AFLP or HELLP syndrome when carrying an affected fetus

(HELLP : Hemolysis, Elevated Liver enzymes, Low Platelet count; AFLP : Acute Fatty Liver of Pregnancy)

Thank you for your attention