Lecture 15

BT 203

Biochemistry

3-0-0-6

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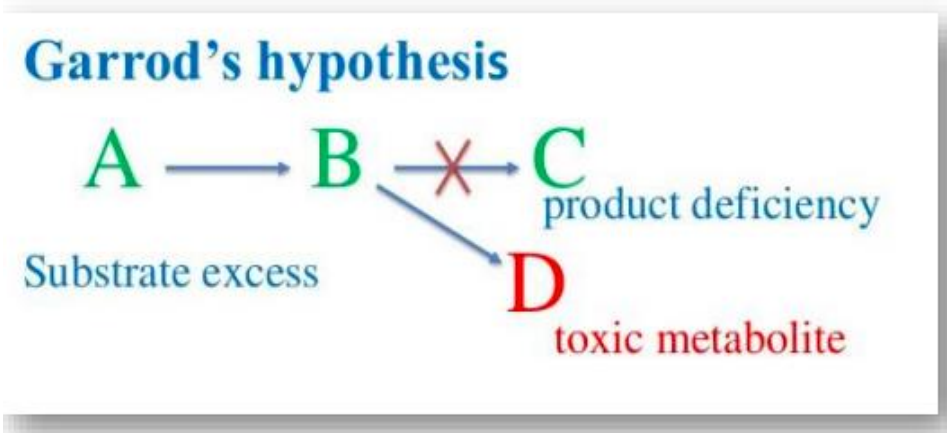
Key Concepts

- What are Inborn error of metabolism?
- Disorders of carbohydrate, protein and lipid metabolism
- Which are the pathways affected?
- What are the symptoms, diagnostic investigations and Available therapies?

Inborn Errors of Metabolism

- Inborn errors of metabolism are inherited biochemical disorders with defect in specific enzyme that interferes with the normal metabolism



Subgroups

Carbohydrate Disorders

- **Galactosemia**
- **Glycogen Storage Disease**

Protein Disorders

- **Amino Acids**
  - **Phenylketonuria**
  - **Maple Syrup Urine Disease**
- **Organic Acids**
  - **Methylmalonic Aciduria**
  - **Propionic Aciduria**
- **Urea Cycle**
  - **Citrullinemia**
  - **Argininosuccinic Aciduria**

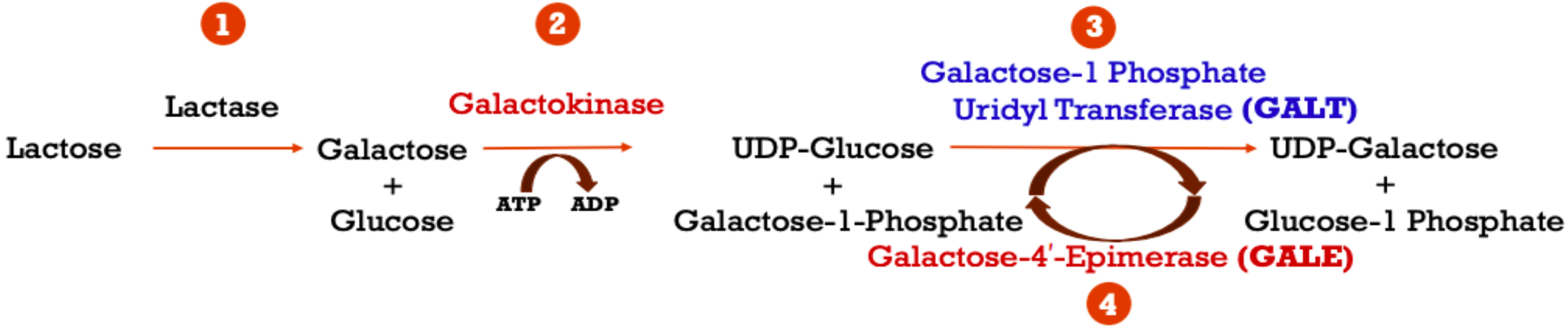
Fatty Acid Disorders

- **Medium Chain Acyl CoA Dehydrogenase Deficiency**
- **Long Chain Acyl CoA Dehydrogenase Deficiency**
- **Very Long Chain Acyl CoA Dehydrogenase Deficiency**

Disorders of Carbohydrate Metabolism

Galactosemia

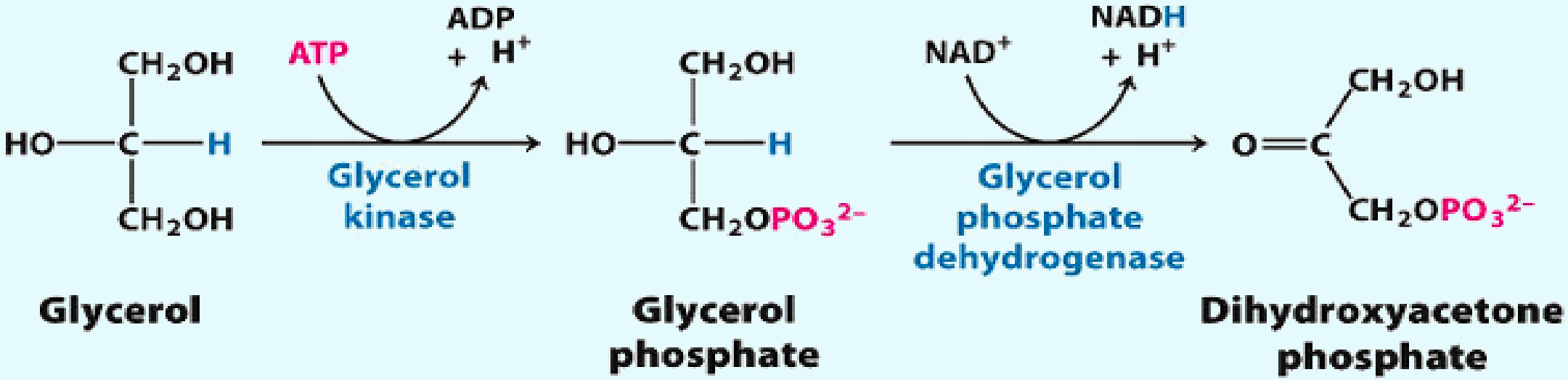
- **Autosomal recessive disorder of galactose metabolism**
- **1/40,000 live births**
- **Three forms: classic galactosemia, galactokinase deficiency, galactose-4' –epimerase deficiency**
- **Symptoms: lethargy, poor feeding, jaundice, cataracts, prone to sepsis, mild growth failure, ataxia, learning disabilities, ovarian failure, probable infertility**
- **Screening: GALT activity, glucose, LFTs, total bilirubin, galactose-1-phosphate, normal lactate, normal pyruvate**
- **Treatment : Strict dietary lactose/galactose restriction**



Disorders of Carbohydrate Metabolism

Glycerol kinase (GK) deficiency

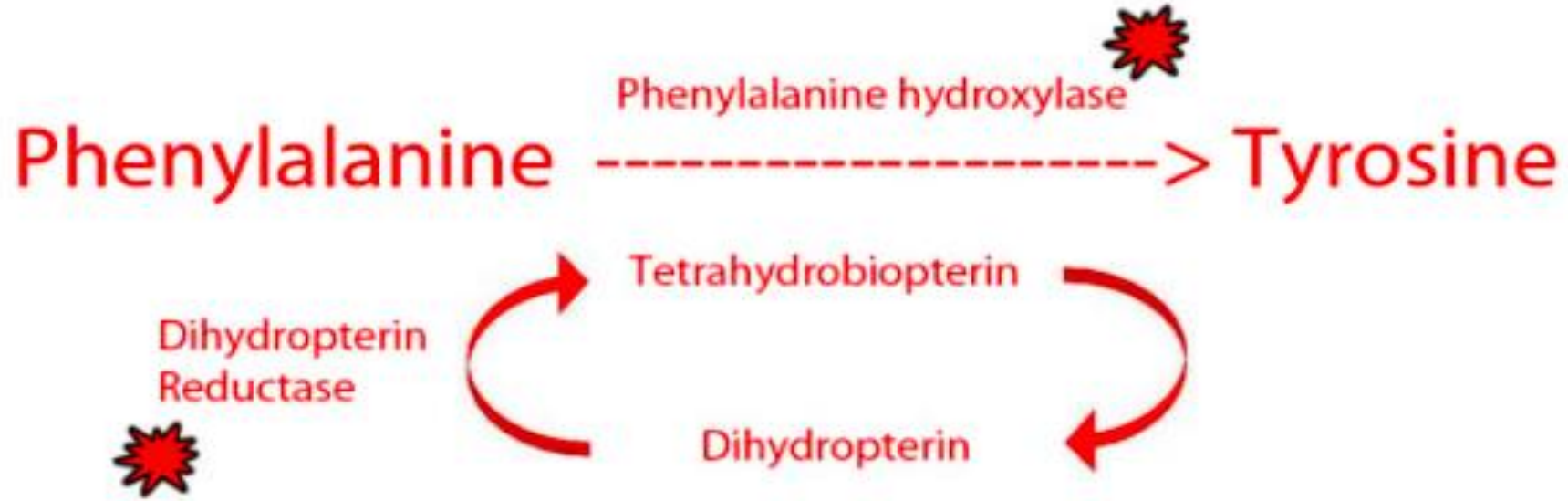
- **X-linked recessive defect in GK**
- **Symptoms: lethargy, vomiting, acidosis, ketotic hypoglycemia, developmental delay, cryptorchidism, seizures, adrenal hypoplasia, Duchnne muscular dystrophy**
- **Screening: elevated glycerol, deletion in glycerol kinase gene**
- **Treatment : Symptoms management by using corticosteroids, mineralocorticoids and/or glucose infusion**



Disorders of Protein Metabolism

Phenylketonuria

- **Autosomal recessive disorder in which phenylalanine can not be converted to tyrosine**
- **1/20,000 live births**
- **Enzyme defect: Phenylalanine Hydroxylase (Chr 12q24.1)**
- **Symptoms: vomiting, irritability, peculiar ‘musty’ odor, eczematoid rash, fair-hair and skin**
- **Screening: Elevated Serum Phenylalanine**
- **Treatment : Strict dietary phenylalanine restriction**



Disorders of Protein Metabolism

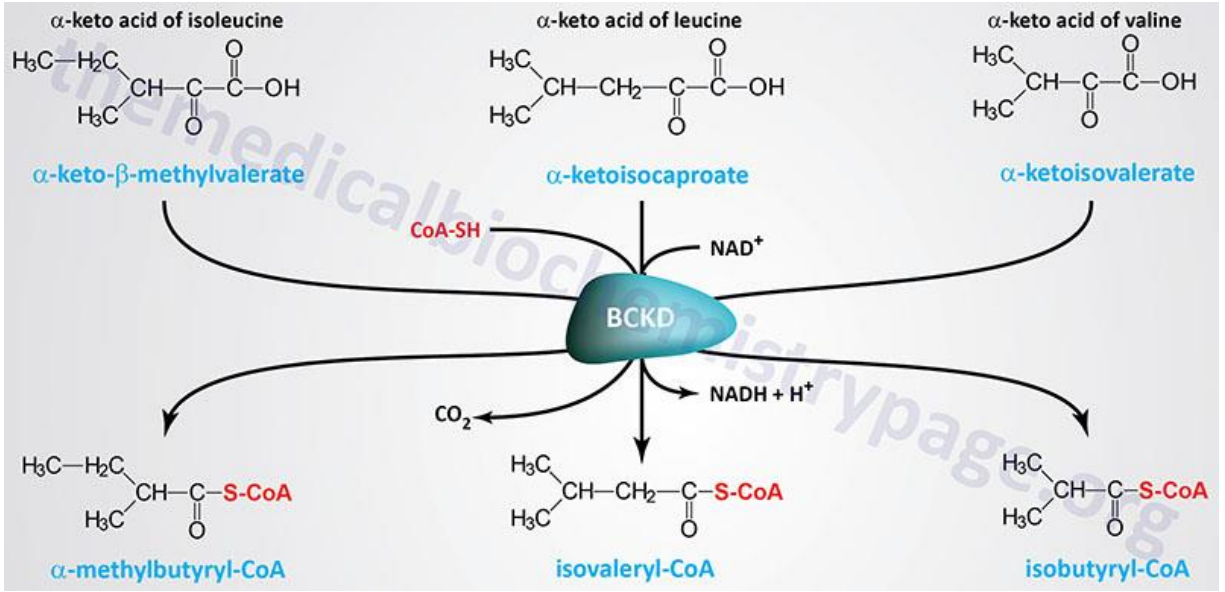
Tyrosinemia

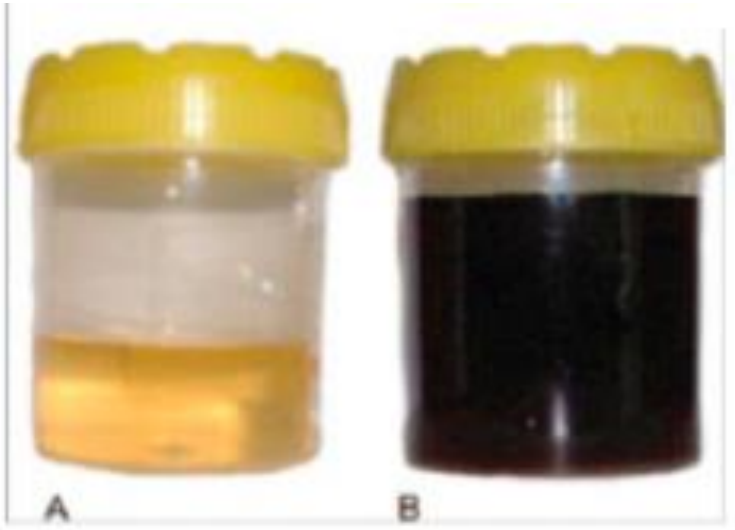
	Enzyme Defect	Clinical Presentation	Diagnostic Studies	Treatment	Prognosis
Type I	Fumarylacetoacetate hydroxylase	Failure to thrive (FTT) Hepatomegaly Hepatoblastoma RTA Rickets	Succinylacetone in urine ↑ levels of tyrosine in plasma	Diet low in tyrosine and phenylalanine -NTBC	Infants are affected early with high risk of mortality
Type II	Tyrosine Aminotransferase	Corneal ulcers or dendritic keratitis 50% with intellectual disability Red papular lesions on their palms and soles No liver toxicity		Diet low in tyrosine	Diet may not be curative

Disorders of Protein Metabolism

Maple Syrup Urine Disease

- Autosomal recessive disorder of branched chain amino acid (valine, leucine and isoleucine metabolism
- 1/50,000 live births
- Enzyme defect: Defect in oxidative decarboxylation of keto acids- branched chain ketoacid dehydrogenase (BCKD)
- Symptoms: feeding difficulty, irregular respiration, loss of Moro reflex, severe seizures and rigidity
- Screening: Elevated Serum valine, leucine and isoleucine, presence of alloisoleucine, elevated urine organic acids- branched chain 2-keto and 2-hydroxy acids
- Treatment : Strict dietary control of valine, leucine and isoleucine intake



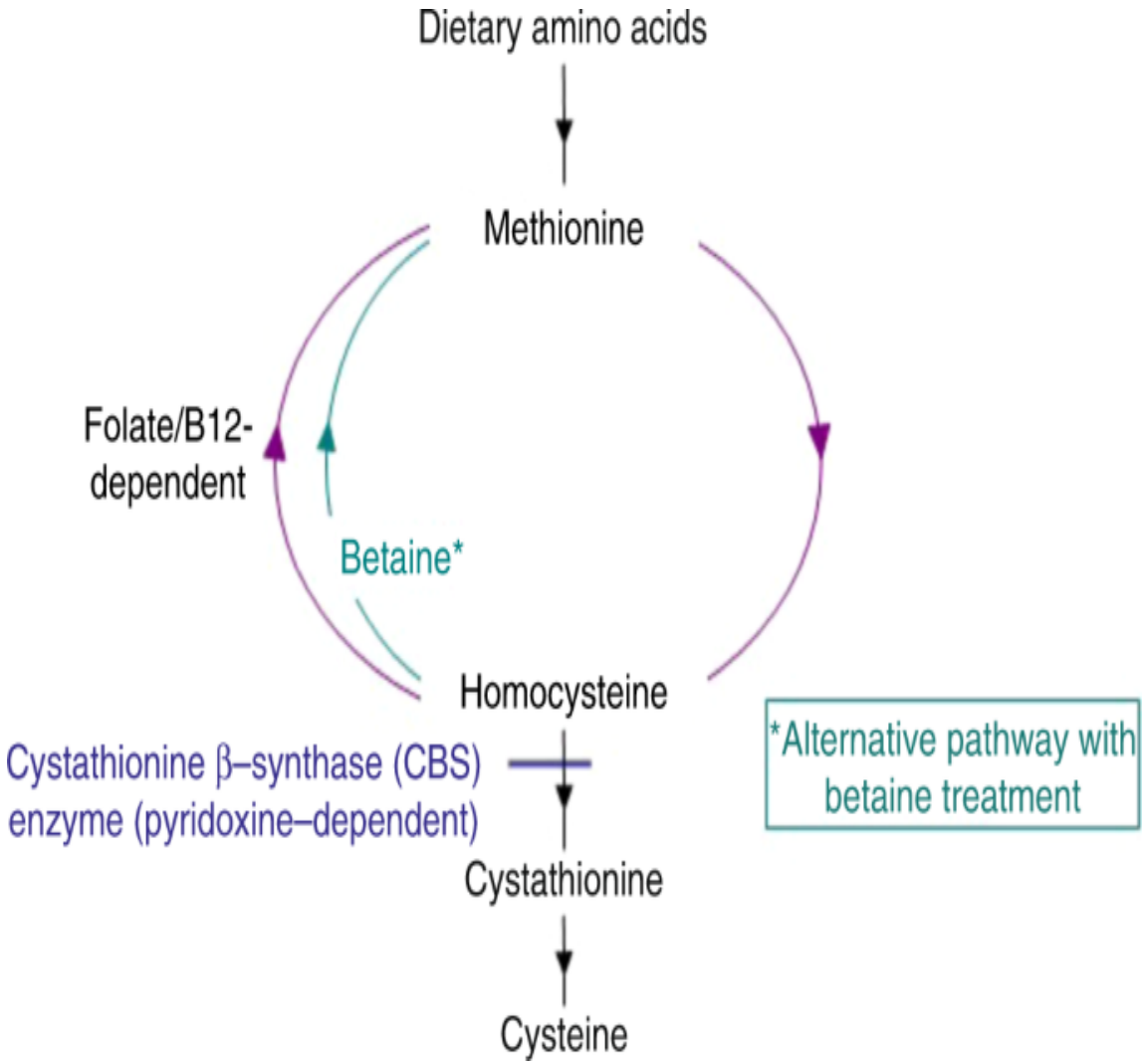


Urine of the diseased look like **Maple Syrup**

Disorders of Protein Metabolism

Homocystinuria

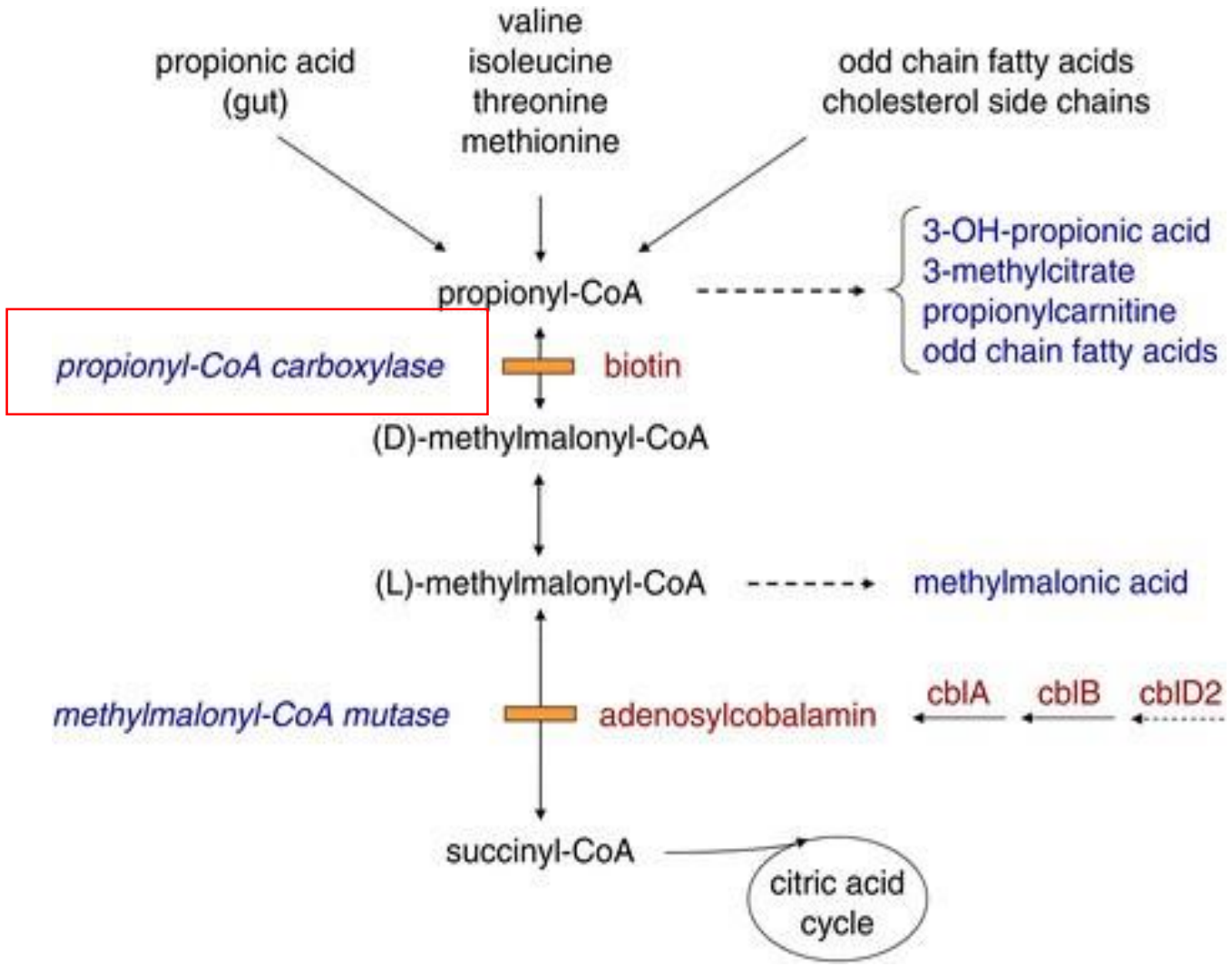
- Autosomal recessive disorder of methionine metabolism
- 1/200-335000 live births
- Enzyme defect: Cystathionine-*β*-synthase
- Symptoms: developmental delay, osteoporosis and increased risk of thromboembolism, intellectual disability
- Screening: Elevated Serum methionine and homocsyteine
- Treatment : pyridoxine (vitamin B6), vitamin B12, folic acid



Disorders of Protein Metabolism

Propionic acidemia

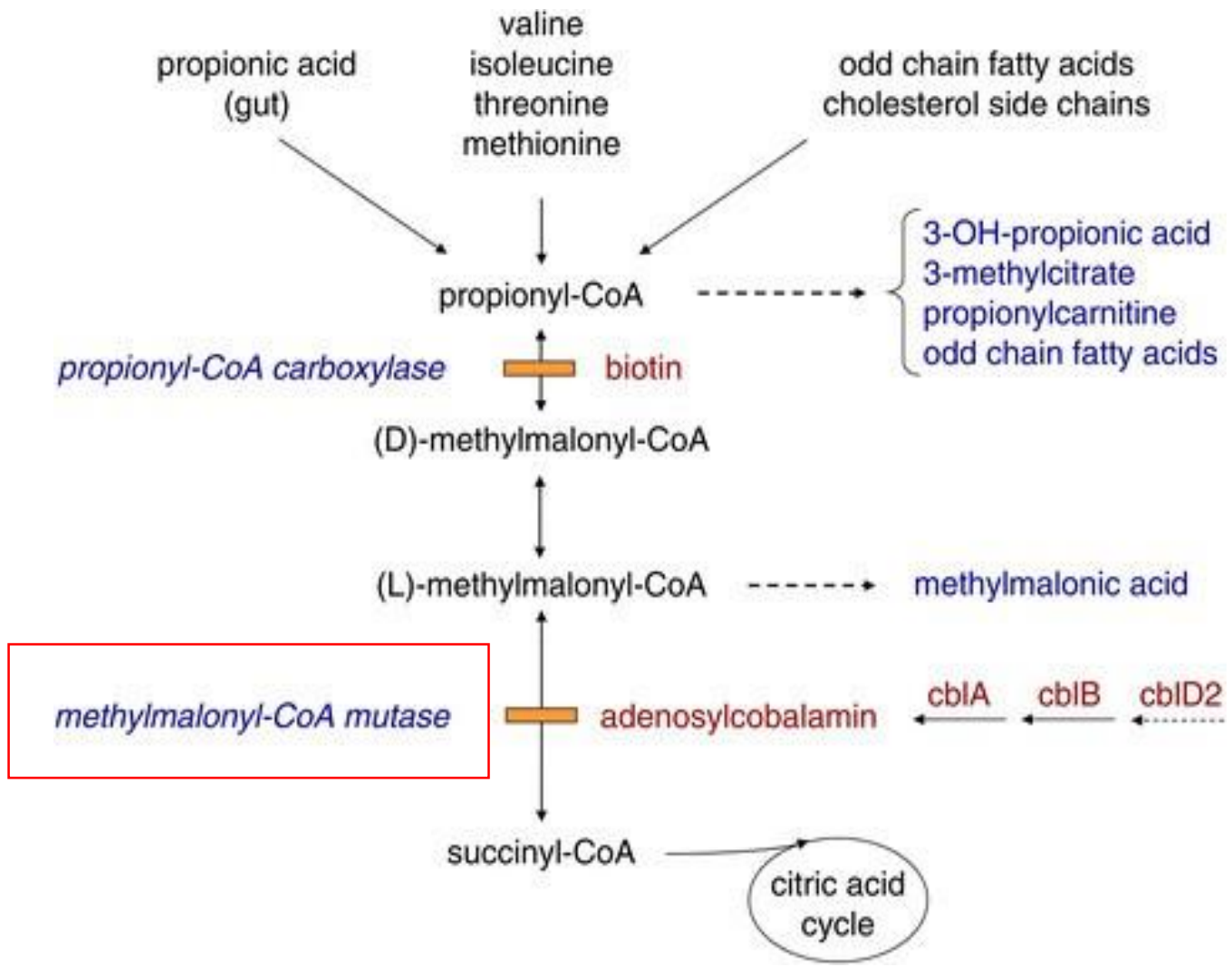
- Autosomal recessive disorder of propionyl CoA carboxylase
- Enzyme defect: propionyl CoA carboxylase
- Symptoms: lethargy, acidosis, neutropenia, thrombocytopenia, coma
- Screening: Elevated Serum propionyl carnitine, glycine, methylcitrate
- Treatment : Diet control, carnitine and biotin (cofactor for enzyme)



Disorders of Protein Metabolism

Methylmalonic acidemia

- Autosomal recessive disorder of methylmalonyl CoA dismutase
- Enzyme defect: methylmalonyl CoA dismutase and cobalamin deficiency
- Symptoms: hyperammonemia, ketoacidosis, thrombocytopenia, cardiomyopathy
- Screening: Elevated Serum homocysteine, methylmalonic acid, ketone bodies
- Treatment : Diet control, B12 and betaine



Highlights

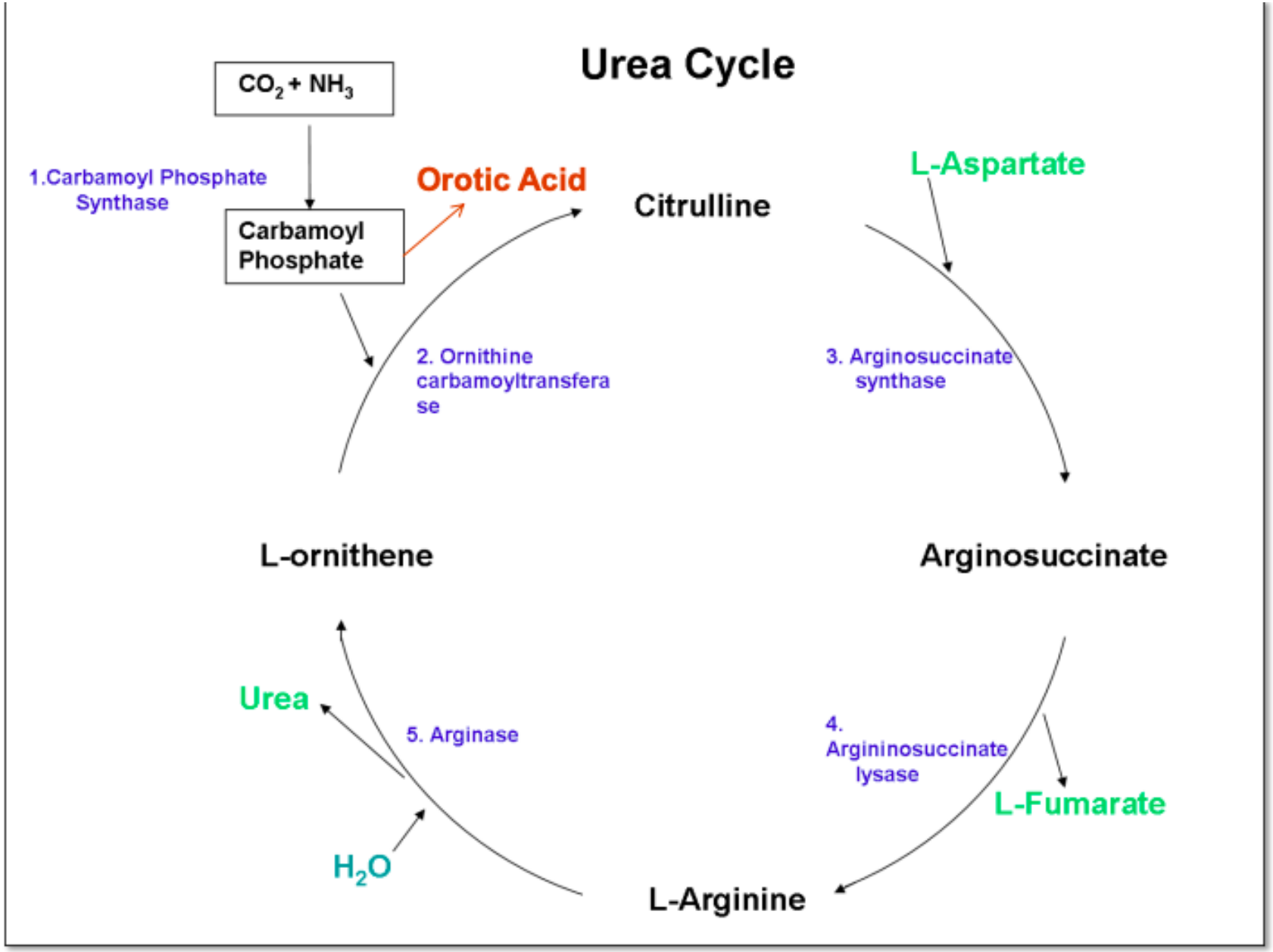
- Inborn error of metabolism are inherited disorders
- Occurs mainly due to defect in enzyme involved in particular pathway
- Symptoms are generally serious and require immediate treatment
- Screening includes either the elevated or accumulated substrate or deficiency of end product
- Treatment :No permanent cure available; symptoms are controlled via dietary restrictions

Disorders of Carbohydrate Metabolism

Glycogen Storage Disorders

Type	Enzyme defect	Eponym	Hypoglycemia	Hyperlipidemia	Symptoms	Others
GSD type 1	Glucose-6-phosphatase	Von Gierke's	Yes	Yes	Growth failure	Lactic acidosis, hyperuricemia
GSD type 2	Acid maltase	Pompe's	No	No	Death by age ~ 2 years	Heart failure Myopathy
GSD type 3	Glycogen debrancher	Cori's or Forbes'	Yes	Yes		Myopathy
GSD type 4	Glycogen branching enzyme	Andersen	No	No	Failure to thrive, death at age ~ 5 years	Liver cirrhosis
GSD type 5	Muscle glycogen phosphorylase	McArdle	No	No		Renal failure by myoglobinuria
GSD type 6	Liver glycogen phosphorylase	Hers' disease	Yes	No		
GSD type 7	Muscle phosphofructokinase	Tarui's disease	No	No	Growth retardation	Hemolytic anemia
GSD type 9	Phosphorylase kinase PHKA2		No	Yes	Delayed motor development, growth retardation	
GSD type 11	Glucose transporter GLUT2	Fanconi-Bickel Syndrome	Yes	No		
GSD type 12	Aldolase A	Red cell aldolase deficiency	?	?		Exercise intolerance
GSD type 13	B-enolase		?	?		Exercise intolerance

Urea Cycle Defects



Urea Cycle Defects

Urea Cycle Defects	Incidence/ Inheritance	Deficiency	Symptom Onset	Presentation	Labs
CPS Deficiency	1:70-100,000 AR	Carbamoyl phosphate synthetase I	By 5 days of age	Lethargy, hypotonia, vomiting and poor feeding Death if undiagnosed	**↑Ammonia** ↑CSF Glutamine Respiratory alkalosis Low BUN ↑Glutamine, alanine, asparagine ↓Citrulline ↓Argninine **↓Urine orotic acid**
Ornithine Transcarbamylase (OTC) Deficiency	1:70,000 **X-linked** (Most common)	Ornithine Transcarbamylase	24-48 hours	Lethargy, hypotonia, vomiting and poor feeding Death if undiagnosed	**↑Ammonia** ↑CSF Glutamine Respiratory alkalosis Low BUN ↑Glutamine, Alanine, Asparagine ↓Citrulline ↓Argninine **↑Urine orotic acid**
Citrillinemia	AR	Arginoinosuccinate synthetase deficiency	Late onset; preceded by stressor		**↑Ammonia** ↓Argninine
Argininosuccinic Aciduria	AR	Argininocuccinate lyase deficiency	Late onset; preceded by stressor	Trichorrhexis nodosa Episodic coma	**↑Ammonia** ↓Argninine
Argininemia	AR	Arginase deficiency	Late onset; preceded by stressor	Progressive splastic diplegia, tremor, ataxia	**↑Ammonia** Normal Argninine

Disorders of Lipid Metabolism

PHENOTYPE	I	IIa	IIb	III	IV	V
Lipoprotein, elevated	Chylomicrons	LDL	LDL and VLDL	Chylomicron and VLDL remnants	VLDL	Chylomicrons and VLDL
Triglycerides	↑↑↑	N	↑	↑↑	↑↑	↑↑↑
Cholesterol (total)	↑	↑↑↑	↑↑	↑↑	N/↑	↑↑
LDL-cholesterol	↓	↑↑↑	↑↑	↓	↓	↓
HDL-cholesterol	↓↓↓	N/↓	↓	N	↓↓	↓↓↓
Plasma appearance	Lactescent	Clear	Clear	Turbid	Turbid	Lactescent
Xanthomas	Eruptive	Tendon, tuberous	None	Palmar, tuberoeruptive	None	Eruptive
Pancreatitis	+++	0	0	0	0	+++
Coronary atherosclerosis	0	+++	+++	+++	+/–	+/–
Peripheral atherosclerosis	0	+	+	++	+/–	+/–
Molecular defects	LPL and ApoC-II	LDL receptor, ApoB-100, PCSK9, LDLRAP, ABCG5, and ABCG8		ApoE	ApoA-V	ApoA-V and GPIHBP1
Genetic nomenclature	FCS	FH, FDB, ADH, ARH, sitosterolemia	FCHL	FDBL	FHTG	FHTG

Abbreviations: ADH, autosomal dominant hypercholesterolemia; Apo, apolipoprotein; ARH, autosomal recessive hypercholesterolemia; FCHL, familial combined hyperlipidemia; FCS, familial chylomicronemia syndrome; FDB, familial defective ApoB; FDBL, familial dysbetalipoproteinemia; FH, familial hypercholesterolemia; FHTG, familial hypertriglyceridemia; LPL, lipoprotein lipase; LDLRAP, LDL receptor associated protein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein1; N, normal.

Disorders of Lipid Metabolism

GENETIC DISORDER	PROTEIN (GENE) DEFECT	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETIC TRANSMISSION	ESTIMATED INCIDENCE
Lipoprotein lipase deficiency	LPL (*LPL*)	Chylomicrons	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	1/1,000,000
Familial apolipoprotein C-II deficiency	ApoC-II (*APOC2*)	Chylomicrons	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
ApoA-V deficiency	ApoA-V (*APOA5*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AD	<1/1,000,000
GPIHBP1 deficiency	*GDIHBP1*	Chylomicrons	Eruptive xanthomas, pancreatitis	AD	<1/1,000,000
Familial hepatic lipase deficiency	Hepatic lipase (*LIPC*)	VLDL remnants	Pancreatitis, CHD	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (*APOE*)	Chylomicron and VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR AD	1/10,000
Familial hypercholesterolemia	LDL receptor (*LDLR*)	LDL	Tendon xanthomas, CHD	AD	1/500
Familial defective apoB-100	ApoB-100 (*APOB*)	LDL	Tendon xanthomas, CHD	AD	<1/1000
Autosomal dominant hypercholesterolemia	PCSK9 (*PCSK9*)	LDL	Tendon xanthomas, CHD	AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	*LDLRAP*	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	*ABCG5 or ABCG8*	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low density lipoprotein.