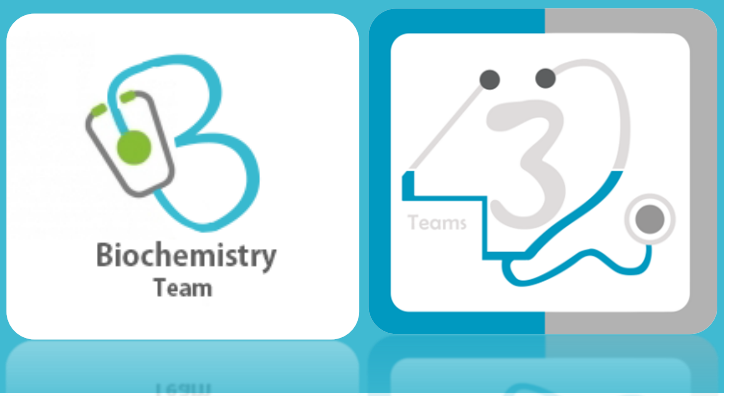
[lecture 4]

Inborn Errors of Amino Acid Metabolism



The Objectives

1. Phenylketonuria (PKU)
2. Maple Syrup Urine Disease (MSUD)
3. Albinism
4. Homocyteinuria
5. Alkaptonuria

Red = Import-ant

Blue = explain

Green = addition notes

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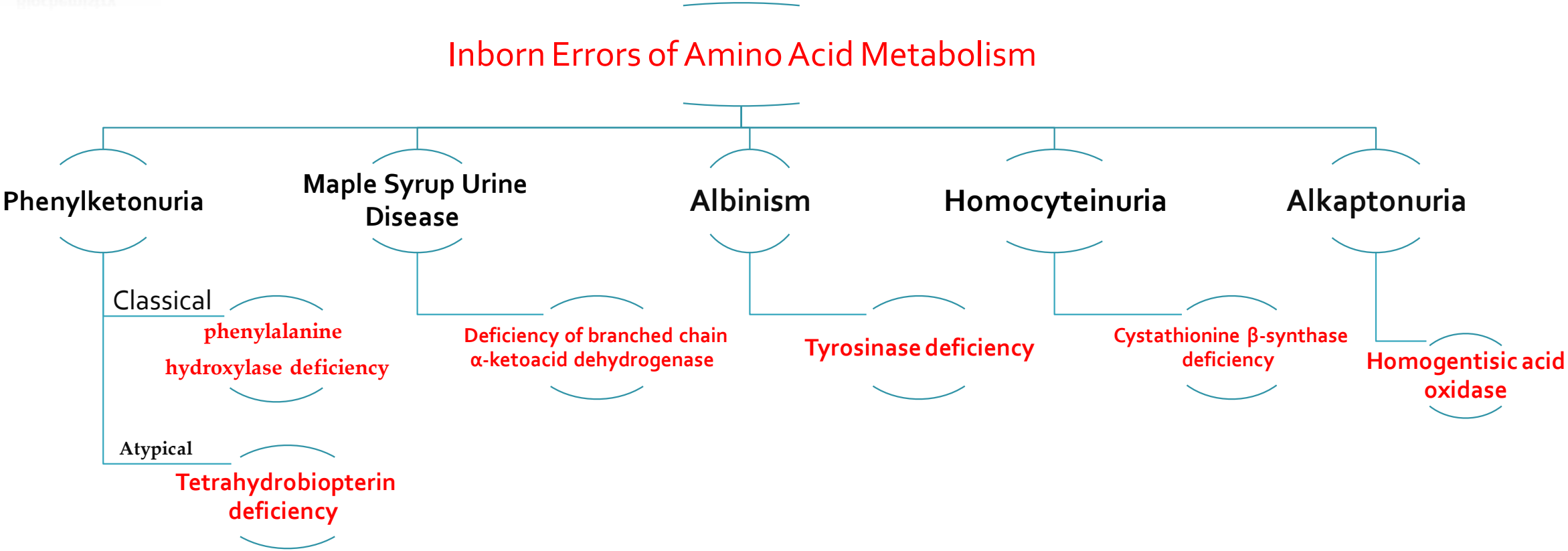
Mind Map


Inborn Errors of Amino Acid Metabolism
Phenylketonuria
Classical
phenylalanine hydroxylase deficiency
Atypical
Tetrahydrobiopterin deficiency
Maple Syrup Urine Disease
Deficiency of branched chain α-ketoacid dehydrogenase
Albinism
Tyrosinase deficiency
Homocyteinuria
Cystathionine β-synthase deficiency
Alkaptonuria
Homogentisic acid oxidase

Inborn Errors of Amino Acid Metabolism

Caused by enzyme loss or deficiency due to gene loss or gene mutation

Normal amino acid metabolism

Enzyme + Substrate —(**Cofactors**)→ **Product**

But if there are any deficiency of either enzyme or cofactor →
There will be abnormality of amino acid metabolism

There are five examples for these abnormality:

1. Phenylketonuria (PKU)
2. Maple Syrup Urine Disease (MSUD)
3. Albinism
4. Homocyteinuria
5. Alkaptonuria

Amino acid involved	phenylalanine
Cause	Due to deficiency of phenylalanine hydroxylase enzyme
symptoms	1)CNS symptoms: Mental retardation, failure to walk or talk, seizures, etc. 2)Hypopigmentation Deficiency of melanin Hydroxylation of tyrosine by tyrosinase is inhibited by high phe conc.
diagnosis	Prenatal diagnosis is done by detecting gene mutation in fetus Neonatal diagnosis in infants is done by measuring blood phe levels
treatment	Life long phe-restricted diet

Phenylketonuria (PKU)

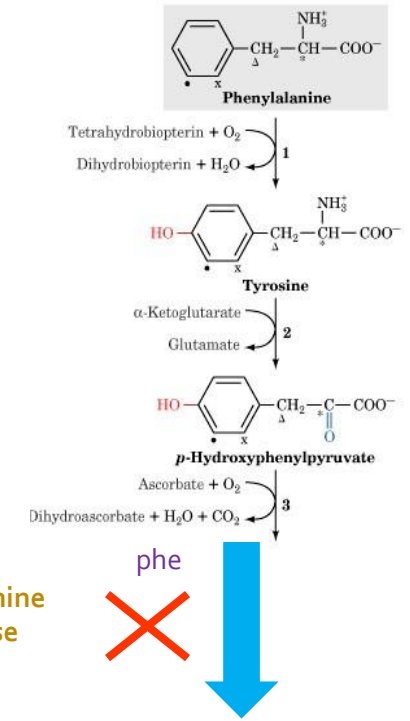
types

Classic PKU

Duo to deficiency of enzyme

Due to deficiency of phenylalanine hydroxylase

Hence Phenylalanine is accumulated



phe

Phenylalanine hydroxylase

Atypical hyperphenylalaninemia

Duo to deficiency of cofactor

Due to deficiency of BH_4

Conversion of Phe to Tyr requires tetrahydrobiopterin (BH_4)

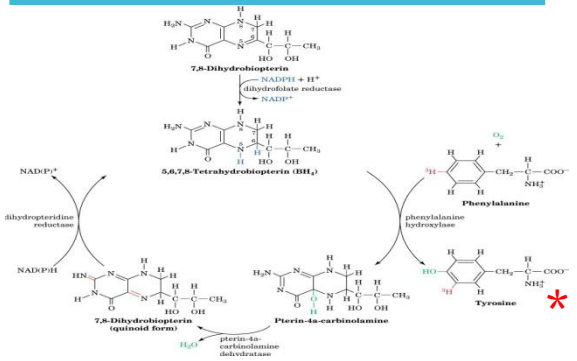
Even if phenylalanine hydroxylase level is normal, the enzyme will not function without BH_4

deficiency of BH_4Caused by the deficiency of:

Dihydropteridine reductase

Dihydrobiopterin synthetase

Carbinolamine dehydratase

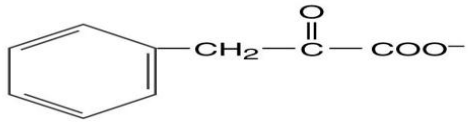


*not imp just memorize the names

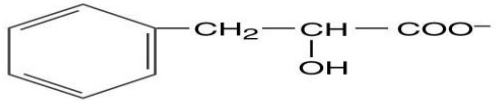
Tyrosine so there will be no tyrosine

Characteristics of PKU

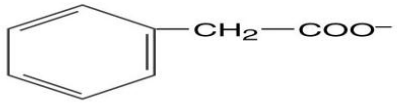
- In the absence or deficiency of BH_4
  - Phe will not be converted to Tyr
  - No or less melanin
    Light skin in PKU patients
  - Tyr will not be converted to catecholamine (neurotransmitter)
    Synthesis of catecholamines requires BH_4
  - Trp will not be converted to serotonin (a neurotransmitter) as it requires BH_4
- In the absence or deficiency of phenylalanine hydroxylase
  - Elevated phenylalanine in tissues, plasma, urine
  - Gives urine a mousy odor
    Because of >
    Phe is degraded to>
    1& 2&3



1 Phenylpyruvate



2 Phenyllactate

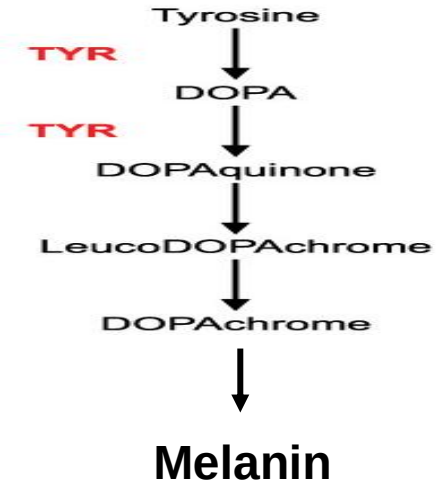


3 Phenylacetate

tryptophan

Tryptophan hydroxylase Which required BH_4

serotonin



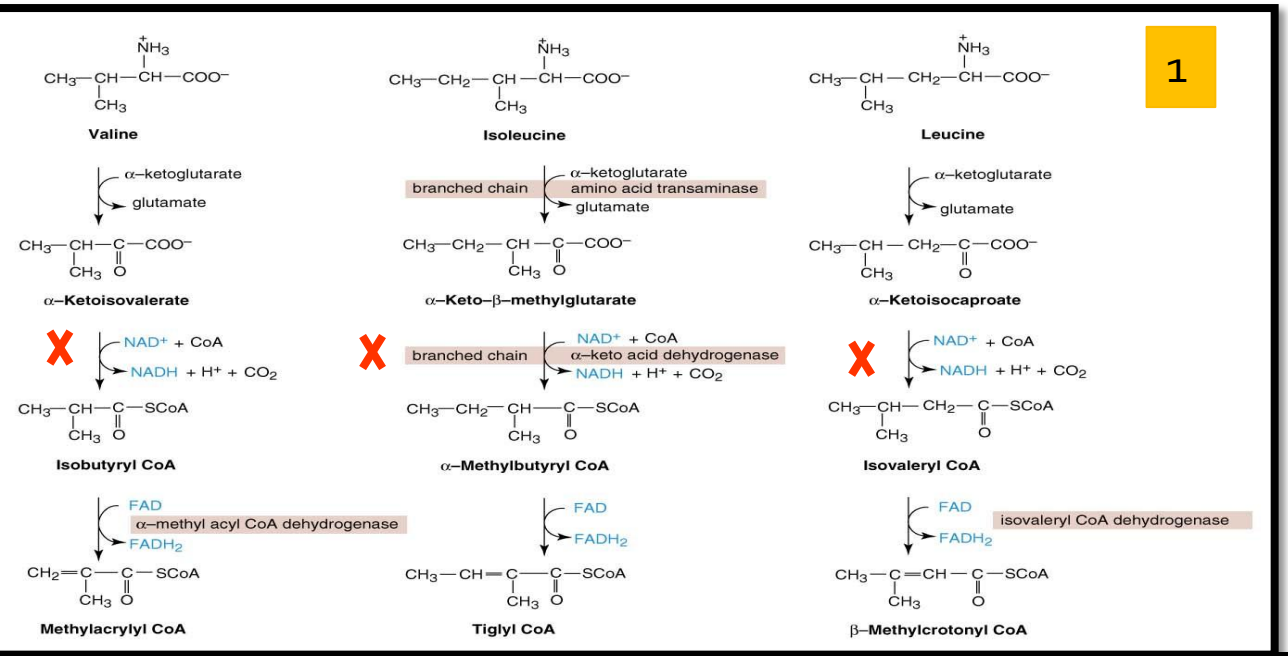
Melanin biosynthesis from tyrosine

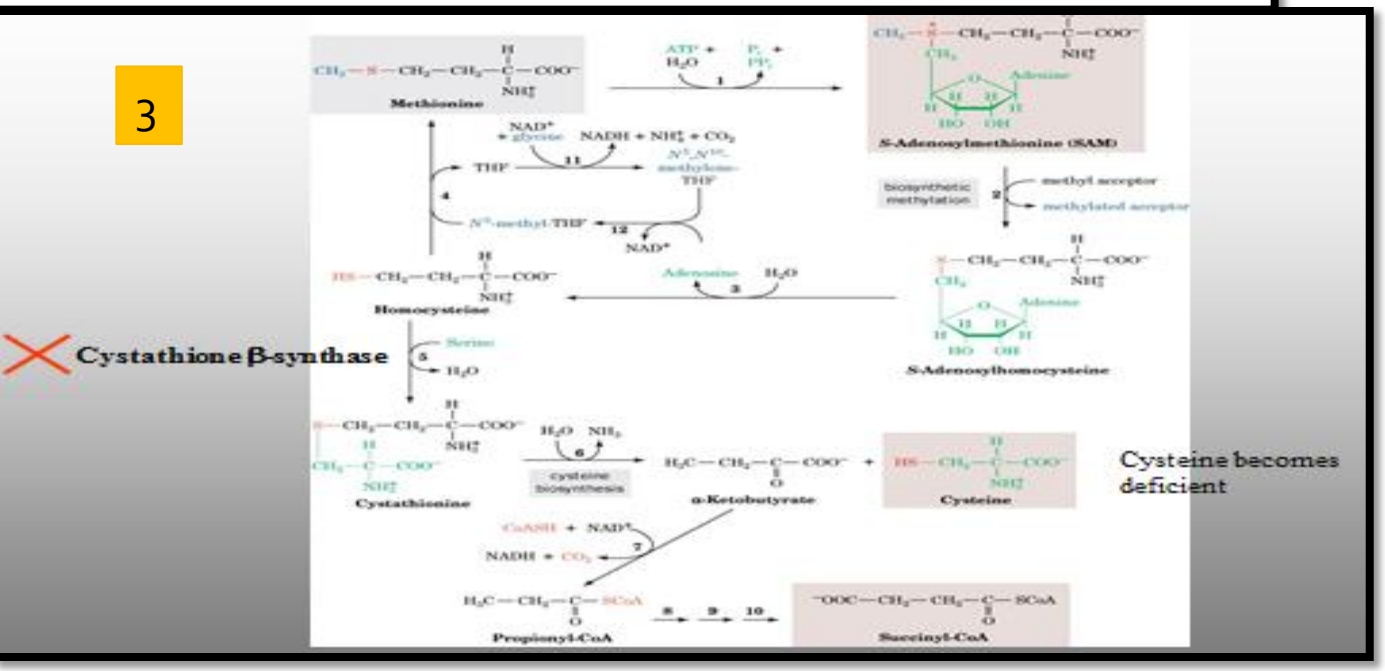
serotonin biosynthesis from tryptophan

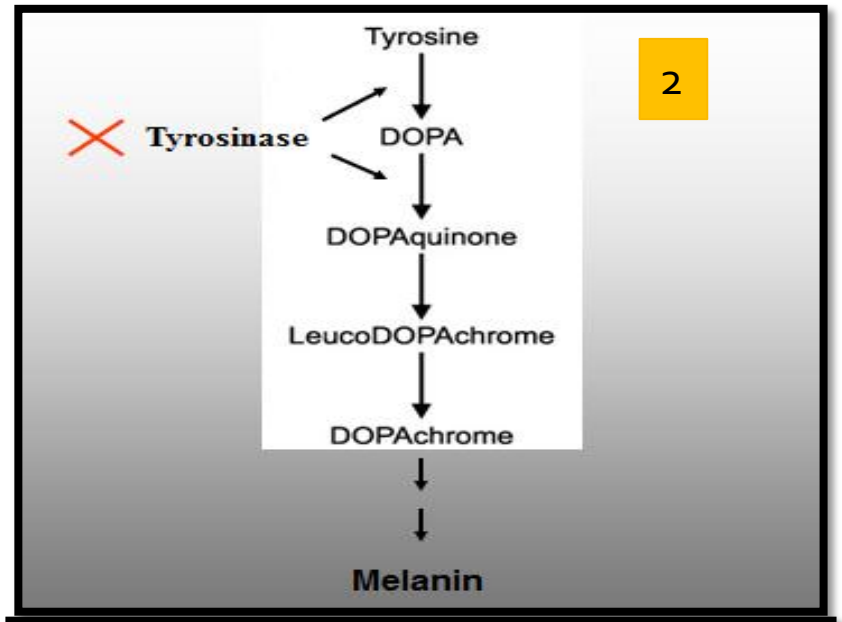
OTHER PIC s<is not imp
Just look at it

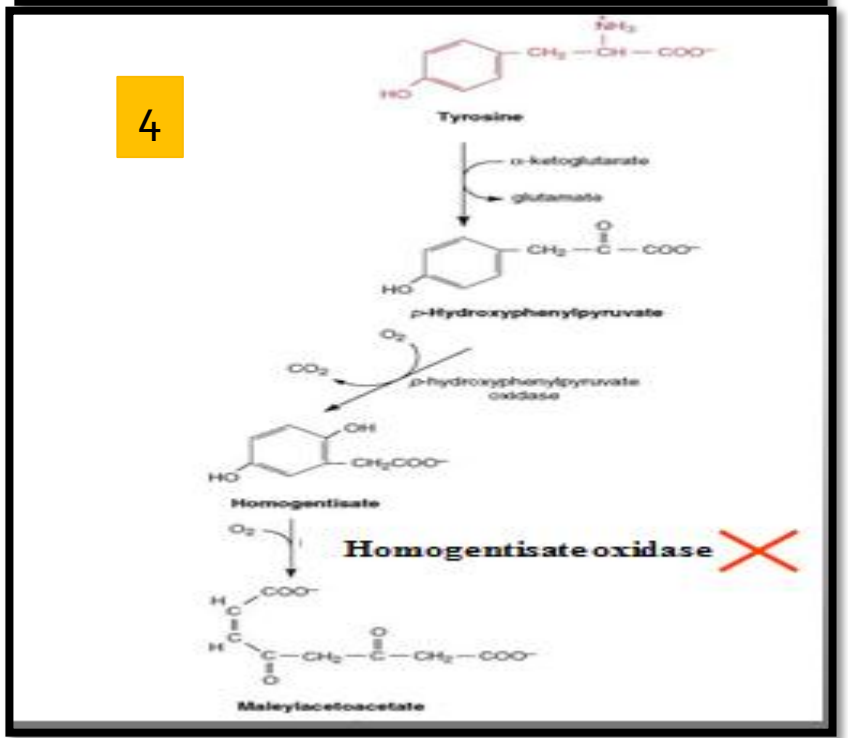
Disease	Maple syrup urine disease	Albinism
Enzyme	Branched chain α-ketoacid dehydrogenase	Tyrosinase
Amino acids involved	Isoleucine, leucine and valine	Tyrosine ✓ Tyrosine is involved in melanin production
Place of accumulation	In blood	—
symptoms	• mental retardation. • physical disability . • metabolic acidosis.	• Hair and skin appear white. • Vision defects . • Photophobia.
Clinical features	Maple syrup odor .	Melanin is absent
types	1. Classic type: Most common, due to little or no activity of a-ketoacid dehydrogenase. 2. Intermediate and intermittent forms. 3. Thiamin-responsive form.	—
treatment	Limited intake of leucine, isoleucine and valine	—

Disease	Homocystinuria	Alkaptonuria
Enzyme	Cystathionine β-synthase	Homogentisic acid oxidase
Amino acids involved	Methionine	Tyrosine and phenylalanine
Place of accumulation	In plasma and urine .	in tissue and cartilage
symptoms	• Skeletal abnormalities. • Osteoporosis. • mental retardation. • displacement of eye lens. *is also associated with: 1. Neural tube defect (spina bifida) 2. Vascular disease (atherosclerosis) 3. Heart disease.	• Usually asymptomatic until adulthood • Arthritis may will be seen
Clinical features	• High plasma and urine levels of homocysteine. • Has a risk factor for atherosclerosis and heart disease.	• urine is oxidized to dark pigment over time. • Black pigmentation of cartilage, tissue.
treatment	1. Oral administration of vitamins B6, B12 and folate. 2. Methionine-restricted diet	1. Restricted intake of tyrosine. 2. phenylalanine reduces homogentisic acid and dark pigmentation.

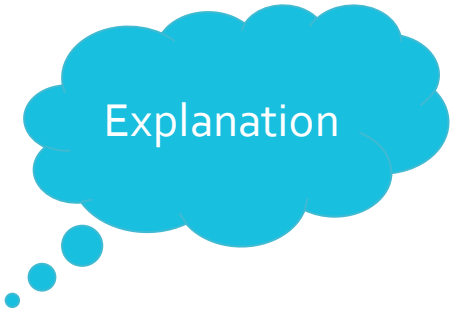

1
Valine
Isoleucine
Leucine
α–ketoglutarate
glutamate
branched chain
amino acid transaminase
α–Ketoisovalerate
α–Keto–β–methylglutarate
α–Ketoisocaproate
NAD+ + CoA
NADH + H+ + CO2
α–keto acid dehydrogenase
Isobutyryl CoA
α–Methylbutyryl CoA
Isovaleryl CoA
FAD
FADH2
α–methyl acyl CoA dehydrogenase
isovaleryl CoA dehydrogenase
Methylacrylyl CoA
Tiglyl CoA
β–Methylcrotonyl CoA


3
Cystathione β-synthase
Methionine
S-Adenosylmethionine (SAM)
Homocysteine
S-Adenosylhomocysteine
Cystathionine
α-Ketobutyrate
Cysteine
Propionyl-CoA
Succinyl-CoA
Cysteine becomes deficient


2
Tyrosine
Tyrosinase
DOPA
DOPAquinone
LeucoDOPAchrome
DOPAchrome
Melanin


4
Tyrosine
p-Hydroxyphenylpyruvate
Homogentisate
Homogentisate oxidase
Maleylacetoacetate

disease	Defect	Due to
1 **MSUD**	Valine, Isoleucine,Leucine and their keto acids accumulated.	deficiency of branched chain a-keto acid dehydrogenase leads to.
2 **Albinism**	Absents of Melanin.	Deficiency of tyrosinase. *Melanin biosynthesis from tyrosine.
3 **Homocystinuria**	Methionine and its metabolites are accumulated . **(homocystinuria / homocysteinemia)**	Deficiency of cystathione b-synthase .
4 **Alkaptonuria**	**Homogentisic aciduria** *(elevated homogentisic acid in urine)*	deficiency of homogentisic acid oxidase



Qs

1- In a patient with MAPLE SYRUP URNIE DISEASE there is a deficiency of enzyme … :

A) Tyrosinase
B) Branched chain α-ketoacid dehydrogenase
C) phenylalanine hydroxylase enzyme
D) Homogentisic acid oxidase

2- The most obvious clinical feature in ALBINISM is :

A) Tissue damage.
B) Osteoporosis.
C) Mental retardation.
D) Melanin absence.

3- The patient with HOMOCYSTINURIA may present with :

A) Displacement of eye lens .
B) Seizures .
C) Metabolic acidosis .
D) Vision defects .

4- The doctor can treat Phenylketonuria (PKU) with :

A) Life long phe-restricted diet.
B) Intake of vitamin B6 .
C) Intake of tyrosine .
D) Intake of leucine.

Answers ☺

1 --- B
2 --- D
3 --- A
4 --- A

Biochemistry
Team

If you find any mistake, please contact us:)

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