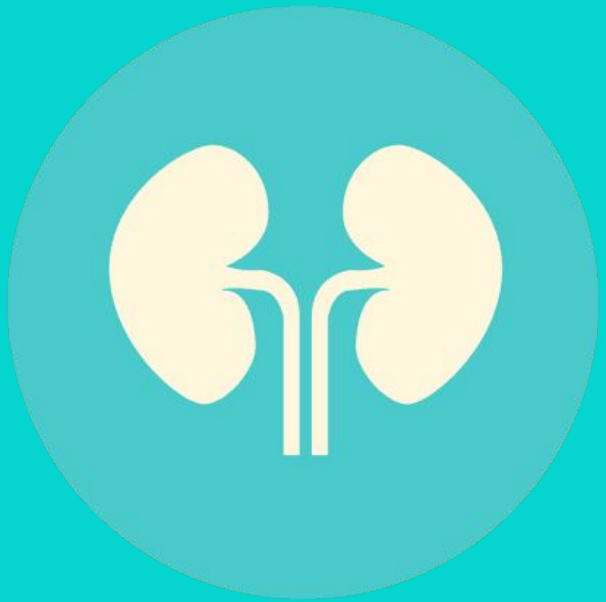
Inborn errors of amino acid metabolism



Editing file

Objectives:

- Identify the amino acid degradation and synthesis of non-essential amino acids
- Recognize the metabolic defects in amino acid metabolism that lead to genetic diseases

Color Index:

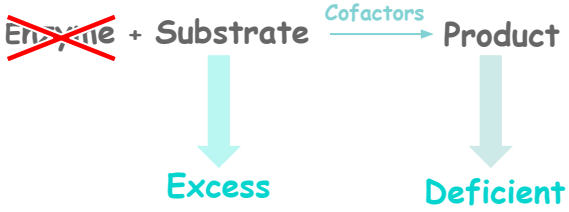
- Important
- Dr's notes
- In females' slides only
- In males' slides only

Take home message:

- Degradation of amino acids involves removal of a-amino group followed by degradation of leftover carbon skeleton by various ways to products that can either enter the biosynthetic athways or TCA
- Glucogenic amino acids whose catabolism yields pyruvate or one of the intermediates of TCA
- Ketogenic amino acids whose catabolism yields either acetoacetate or one of its precursor.
- The essential amino acids are provided in the diet and the non-essential amino acids are synthesized in the body
- Deficiency of the enzymes involved in amino acid metabolism leads to hereditary disorders like: phenylketonuria, alkaptonuria etc.

Inborn errors of amino acid metabolism

Gene mutation → Enzyme loss or deficiency → 1. Accumulation of the substrate 2. Deficiency of the product



Diseases

- Phenylketonuria (most common)
- Maple syrup urine disease
- Albinism
- Homocystinuria
- Alkaptonuria

437 team:

According to the type of mutation, the enzyme might be completely lost or just deficient.

If the enzyme was completely lost, no products will be produced at all, and the substrates will accumulate in huge amounts, leading to a very severe disease.

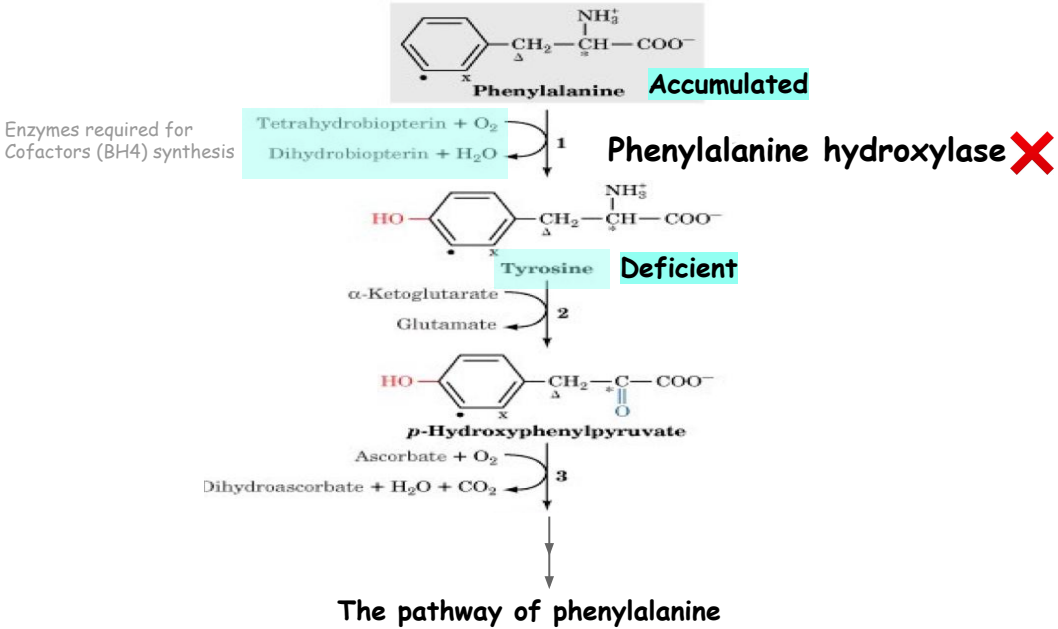
If the enzyme was not completely lost, some substrates will be converted to products and the disease will be less severe.

Deficiency of the product is not always present, because there might be another pathway that results in the same product.

Phenylketonuria (PKU)

Enzyme (deficient)	Substrate (accumulated)	Product (deficient)
Phenylalanine hydroxylase	Phenylalanine (hyperphenylalaninemia)	Tyrosine

Classical PKU



The pathway of phenylalanine

Females' doctor notes:

Tyrosine is normally non-essential
(body can make no need to take it from diet)

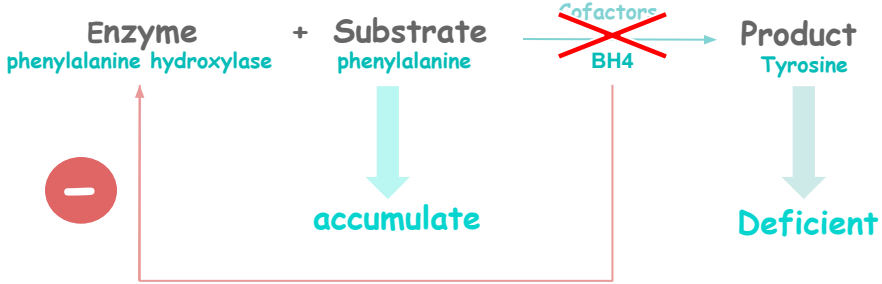
but in case of enzyme deficiency the body can't produce it so it becomes essential
(supplements are needed)

"it is conditional amino acid"

Atypical hyperphenylalaninemia

Due to deficiency of
dihydropteridine reductase, dihydrobiopterin synthetase,
Carbinolamine dehydratase enzymes *

1. Conversion of Phe to Tyr requires tetrahydrobiopterin (BH4)
2. Even if phenylalanine hydroxylase level is normal
3. The enzyme will not function without BH4
4. Hence Phe is accumulated

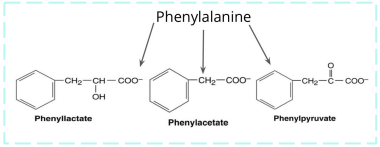


Dr's notes :

* Enzymes required for Cofactors (BH4) synthesis. Thus, in the absence of one of these enzymes → deficiency of BH4

Characteristics of PKU

- **Elevated** phenylalanine in tissues, plasma, urine.
- Phe is **degraded to**:
  phenyllactate, phenylacetate, phenylpyruvate.
- Gives urine a **mousy odor**.



In the absence of BH4 :

1. **Phe will not be converted to Tyrosine.**
   - Melanin will become deficient because Tyrosine is required for synthesis of melanin.
   - Deficiency of tyrosinase will lead to albinism.
   - Causes light skin and photosensitivity in PKU patients.

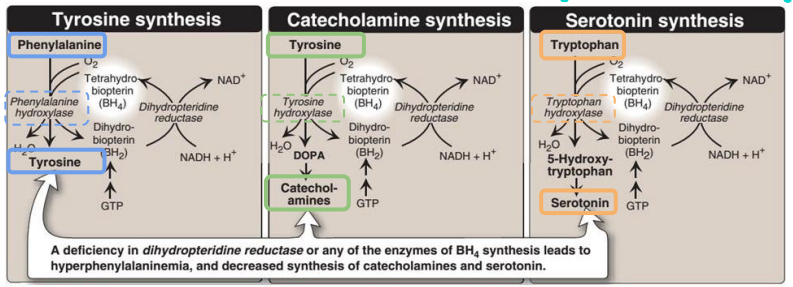
No or less tyrosine/ also inhibited by excess Phe

✖ Tyrosine ➔ DOPA ➔ DOPAquinone ➔ LeucoDOPAchrome➔ DOPAchrome ➔➔ Melanin ✖

No or less melanin Light skin in PKU patients

2. **Tyrosine will not be converted to Catecholamines.**
3. **Tryptophan will not be converted to Serotonin.**
4. Catecholamines & serotonin are **neurotransmitters.**

Amino Acids & Tetrahydrobiopterin

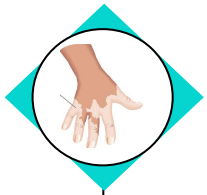


Characteristics of PKU

CNS symptoms

- Mental retardation
- Failure to walk or talk
- Seizures [1]
- Microcephaly [2]

etc.



Hypopigmentation

"Melanin is not synthesized"

- Fair hair
- Light skin colour
- Blue eyes

Urine

musty (mousy) odor.

Diagnosis	
Prenatal "before birth"	detecting gene mutation in fetus.
Neonatal [3] "In infants"	measuring levels of blood Phenylalanine.

Treatment
Lifelong phenylalanine restricted diet
Tyrosine supplementation

Extra info :

1. **Seizure:** Uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms.

2. **Microcephaly:** a medical condition in which the brain doesn't develop properly resulting in a smaller than normal head.

Females' doctor notes:

3. **We measure it after birth after 24-48 hours NOT Immediately**
because the mother clears increased blood phenylalanine in her affected fetus through the placenta.

437 team:

If the treatment is started before 7 days of birth, they might hav near normal life

The problem is that phenylalanine is very abundant in most food, so it is difficult to control

Maple Syrup Urine Disease

Maple syrup odor of urine

deficiency of branched chain a-ketoacid dehydrogenase → The enzyme decarboxylates leucine, isoleucine and valine → These amino acids accumulate in blood

Treatment:

Limited intake of leucine, isoleucine and valine "to prevent toxic effects."

Symptoms

1. Mental retardation
2. Metabolic acidosis
3. Physical disability

..etc

Types

Classic type

- Most common
- Little or no activity of the enzyme

Intermediated and intermittent forms

- Higher enzyme activity
- Symptoms are milder

Thiamine-responsive form

- high doses of thiamine increases the enzyme activity

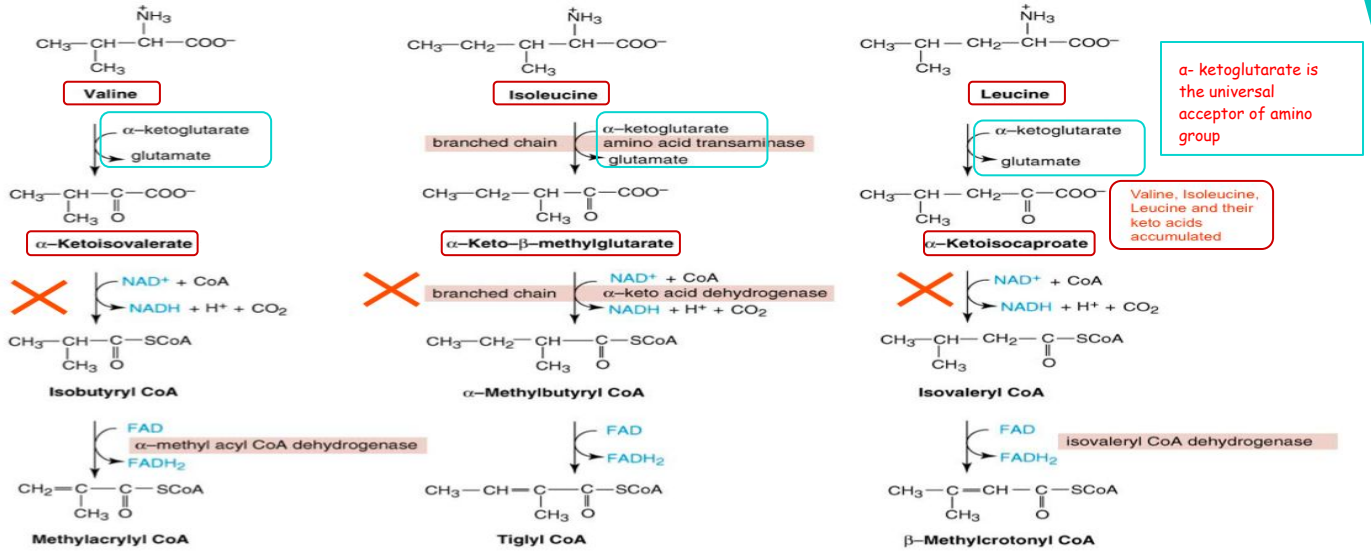
Females' doctor notes:

How to differentiate between the classic type and Thiamine-responsive form?

You give the patient thiamine supplement and see if it works.

Maple Syrup Urine Disease

Degradation of branched-chain amino acids: valine, isoleucine and leucine.
Deficiency of branched chain a-keto acid dehydrogenase leads to MSUD.

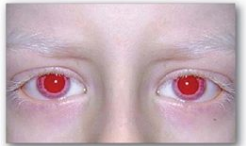


437 team:

In our body we have certain branched chain amino acids.
These amino acids are leucine, isoleucine and valine.
The first step in their degradation is deamination
"Removal of an amino group and introduce a ketone group at
Leucine and their keto acids the alpha carbon".
By the end of this step, each amino acid is converted to
its [a- keto acid].

The a- keto acids are acted on by their a- keto acid dehydrogenases.
If The a- keto acid dehydrogenase is deficient, it will lead to accumulation of the amino acids and their a- keto acid, leading to maple syrup urine disease (MSUD).

Albinism



Albinism

- A disease of tyrosine metabolism

→ Due to **tyrosinase deficiency**

Tyrosine

- Involved in melanin production

Melanin

- A pigment of : hair, skin and eyes.

★ Melanin is absent in albino patients:

Hair

- Appear white

Skin

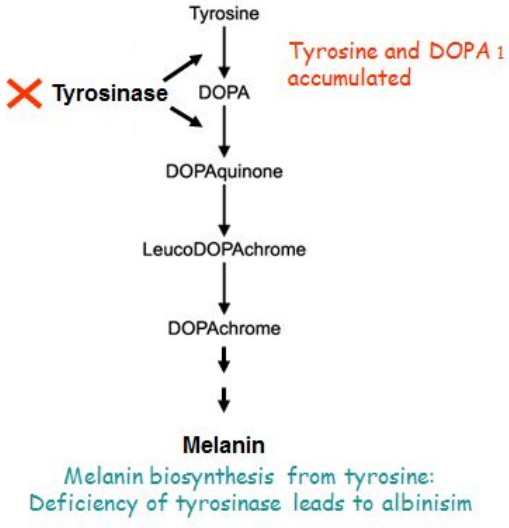
- Appear white

Eyes

- Appear white or red
- Vision defects

Photophobia

Prone to skin cancer.



Melanin biosynthesis from tyrosine:
Deficiency of tyrosinase leads to albinisim

Extra info :

1. DihydrOxyPhenylAlanine: is present in nervous tissue as a precursor of dopamine, used in the treatment of Parkinson's disease.

Homocystinuria

Causes	Defects in homocysteine metabolism • Deficiency of cystathionine β-synthase (converts homocysteine to cystathionine)
Clinical presentations	High plasma and urine levels of homocysteine and methionine Low plasma and urine levels of cysteine
☆ Risk factor for	Atherosclerosis and heart diseases [1]
Symptomes	• Skeletal abnormalities, • Osteoporosis • Mental retardation • Displacement of eye lens
Treatment	• Oral administration of vitamins B6,B12 and folate (folic acid) [2] ➔ Vitamin B6 is a cofactor of cystathionine β-synthase • Methionine-restricted diet

Females' doctor notes:

1. **Increased amounts of homocysteine causes oxidative stress which lead to these diseases**

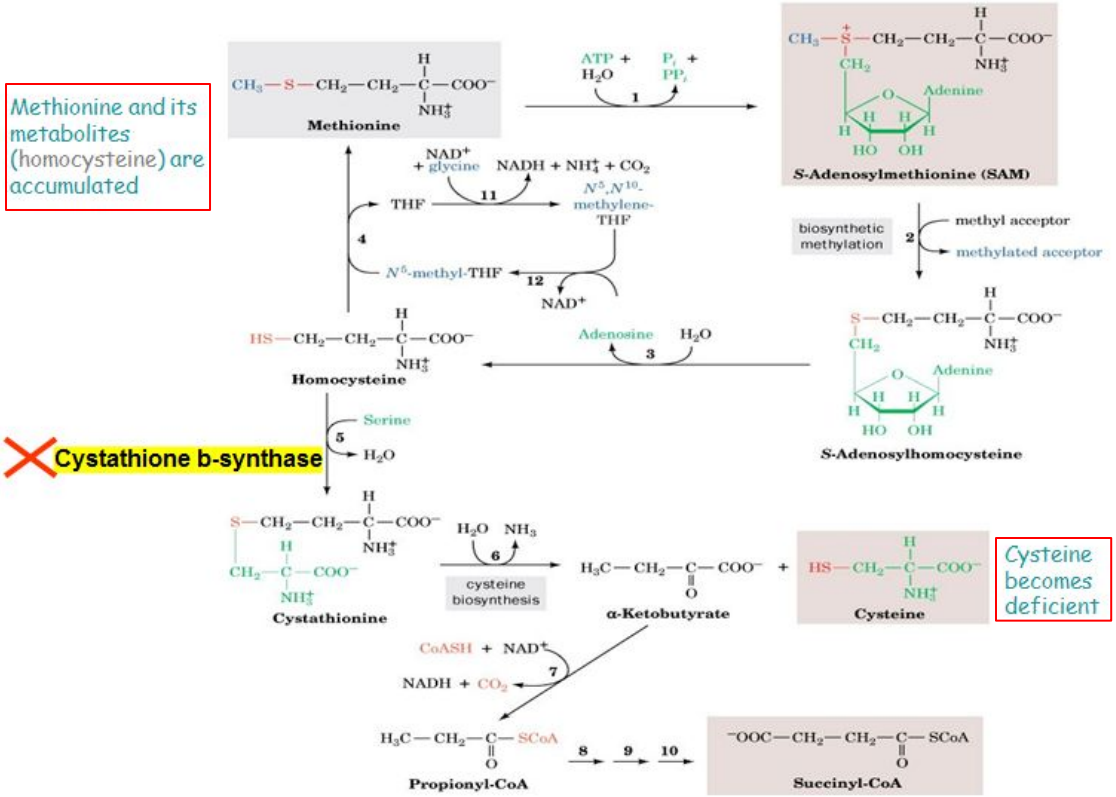
2. When vit B6 and B12 and folate are low homocystine is increased "the exact relation isn't known"

Hyperhomocysteinemia

- Is associated with:

1. Neural tube defect (spina bifida)
2. Vascular diseases (Atherosclerosis)
3. Heart diseases

Homocystinuria



Methionine degradation pathway:

Deficiency of cystathione b-synthase leads to homocystinuria / homocysteinemia

Alkaptonuria

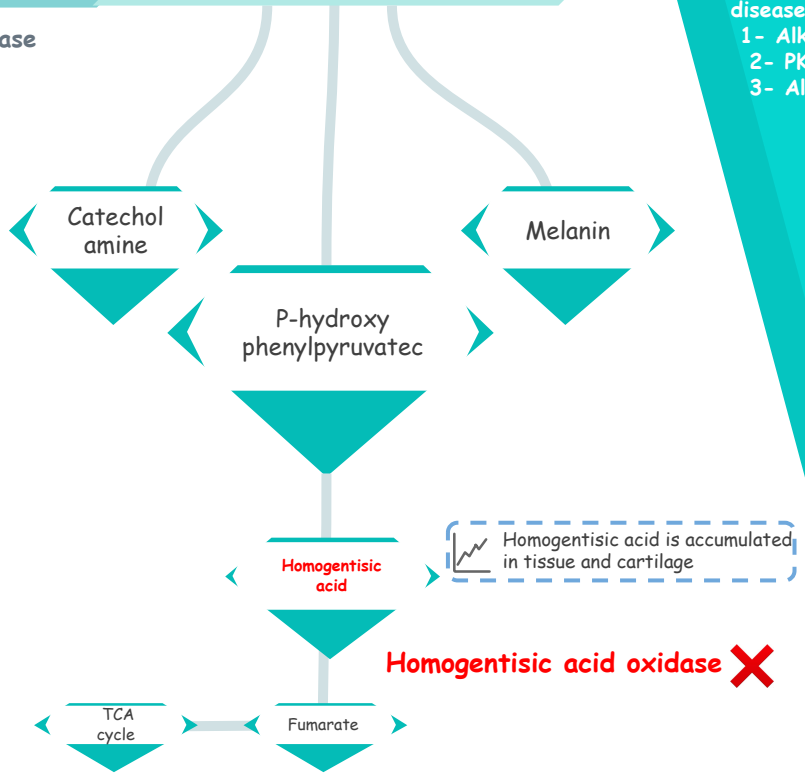
Definition

Rare disease of tyrosine **degradation**

Cause

- **homogentisic acid oxidase deficiency**

Fate of tyrosine



Important to know

The pathway of this disease is the one in the middle where tyrosine is converted to p-hydroxyphenylpyruvate.

Tyrosine is mentioned in 3 diseases:

1- Alkaptonuria
2- PKU
3- Albinism

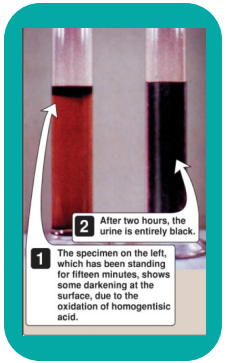
Characteristics of Alkaptonuria

Arthritis

Later; 40 years and beyond

Black pigmentation

Of cartilage and tissues.



Homogentisic aciduria

Elevated homogentisic acid in urine which is oxidized to dark pigment over time

Diagnosis

Usually asymptomatic until adulthood

Treatment

- Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation
- Treat symptoms of arthritis beyond on

Summary

Huge thanks to TEAM 437!

Disease	Enzyme (deficient)	Substrate (Accumulated)	Product (Deficient)	Symptoms	Treatment
Classical phenylketonuria	Phenylalanine hydroxylase	Phenylalanine	Tyrosine Melanin Catecholamines	CNS symptoms Mousy(musty) odor of urine Hypopigmentation	Life long phenylalanine restricted diet and tyrosine supplementation
Atypical phenylketonuria	1. Dihydropteridine reductase 2. Dihydrobiopterin synthetase 3. Carbinolamine dehydratase	Phenylalanine	**BH4 leading to nonfunctional phenylalanine hydroxylase.** Which will lead to tyrosine,catecholamine ,serotonin,melanin deficiency.	Same as the classical PKU	Same as the classical PKU
Maple syrup urine disease	Branched chain a-ketoacid dehydrogenase	1. Leucine 2. Isoleucine 3. valine And their a-ketoacids		Mental retardation,physical disability,metabolic acidosis,maple syrup odor of urine.	Limited intake of leucine,isoleucine,valine
Albinism	Tyrosinase	Tyrosine	Melanin	White hair,skin,and eyes.vision defects,photophobia	
Homocystinuria	Cystathionine Beta-synthase	1. Homocysteine 2. Methionine	Cysteine	Atherosclerosis,heart diseases,skeletal abnormalities,mental retardation	Vitamins B6,B12,and folic acid. Methionine restricted diet.
Alkaptonuria	Homogentisic acid oxidase	Homogentisic acid	Fumarate	Dark urine pigment.Later stages:arthritis	Restricted tyrosine and phenylalanine intake

Quiz

MCQs :

Q1: In case of atypical phenylketonuria, which one won't be deficient:
a) Tyrosine **b)** Cysteine **c)** Neurotransmitters **d)** Serotonin

Q2: Which statement is incorrect in an inborn error of amino acid metabolism:
a) Deficiency in substrate **b)** Excess in product **c)** A&B **d)** None of the above

Q3: In absence of BH4, phenylalanine will not be converted to:
a) Catecholamine **b)** Serotonin **c)** Tryptophan **d)** Tyrosine

Q4: Which amino acid won't be affected by maple syrup urine disease:
a) Cysteine **b)** Valine **c)** Isoleucine **d)** Leucine

Q5: The classic type of maple syrup urine disease is due to:
a) High activity of the enzyme **b)** Little or no activity of the enzyme
c) A&B **d)** the increase of enzyme activity by thiamine.

Q6: Homocystinuria ia a risk factor of:
a) Liver disease **b)** Kidney disease **c)** Heart disease **d)** Nerve injury

Q7: In Alkaptonuria which will most likely be affected?
a) Krebs cycle **b)** glycolysis **c)** ETC **d)** none of the above

Q8: If tyrosine is decreased what will most likely happen to a patient with alkaptonuria?
a) Symptoms become less severe **b)** dark pigmentation decreases
c) Both A and B **d)** None of the above

Q9: Which of the following is the universal acceptor of amino groups?
a) α- ketoglutarate **b)** α-ketoacid dehydrogenase **c)** Valine **d)** none of the above

Q10: All of these enzymes are required for BH4 synthesis except:
a) Dihydropteridine reductase **b)** Dihydropyridine dehydrogenase
c) Dihydrobiopterin synthetase **d)** Carbinolamine dehydratase

SAQs :

Q1: A patient recently suffered from arthritis and in the past he noticed his earlobes becoming slightly blackish in color what's your diagnosis? What's the enzyme that's most probably deficient?

Q2: In PKU phenylalanine is degraded to :

Q3: Treatment of phenylketonuria ?

Q4: What enzyme is deficient in: homocystinuria, alkaptonuria,maple syrup urine disease, albinism, phenylketonuria ?

★ MCQs Answer key:

1) B 2) C 3) D 4) A 5) B 6) C 7) A 8) C 9) A 10) B

★ SAQs Answer key:

1) Alkaptonuria ,Homogentisic acid oxidase.

2) Phenyllactate, Phenylacetate, phenylpyruvate.

3) Phe-restricted diet and tyrosine supplementation.

4) Cystathionine β-synthase, Homogentisic acid oxidase, Branched chain α-ketoacid dehydrogenase, Tyrosinase, Phenylalanine hydroxylase.

[Note:Deficiency of dihydropteridine reductase or any of the enzymes needed for BH4 synthesis can also result in hyperphenylalaninemia.]

بقدر الكد تكسب المعالـي

ومن طلب العلا سهر الليـالـي

ومن طلـب العلا بغيـر كدٍ

أضاع العمر في طلب المحالِ

We hear you

☆ Team members :

Girls team:

- Ajeed Al-rashoud
- Alwateen Albalawi
- ★ Abeer Alkhodair
- ★ Elaf Almusahel
- Haifa Alessa
- Lama Alassiri
- Lina Alosaimi
- ★ Nouf Alhumaidhi
- ★ Noura Alturki
- Nouran Arnous
- Reem Algarni
- ★ Rema Alkahtani
- Shahd Alsalamh
- Taif Alotaibi

Boys team:

- Alkassem Binobaid
- Fahad Alsultan
- Fares Aldokhayel
- Naif Alsolais
- Sultan Alhammad

☆ Team leaders :

Deema Almaziad

Mohannad Alqarni