بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 18

Carbon Skeletons Disorders

Written & reviewed by : NST member

- This lecture is the **second part** of amino acid metabolism, focusing on **carbon skeleton metabolism**.
- We ended the previous lecture by introducing **inborn errors of amino acid metabolism**.
- These diseases occur due to **genetic mutations affecting enzymes** that catalyze steps in amino acid carbon skeleton processing.
- Each enzyme can have **many reported mutations**, and:
- Different mutations → **different severity**
- Clinical outcomes are **variable between patients**

AMINO ACID METABOLISM DISORDERS

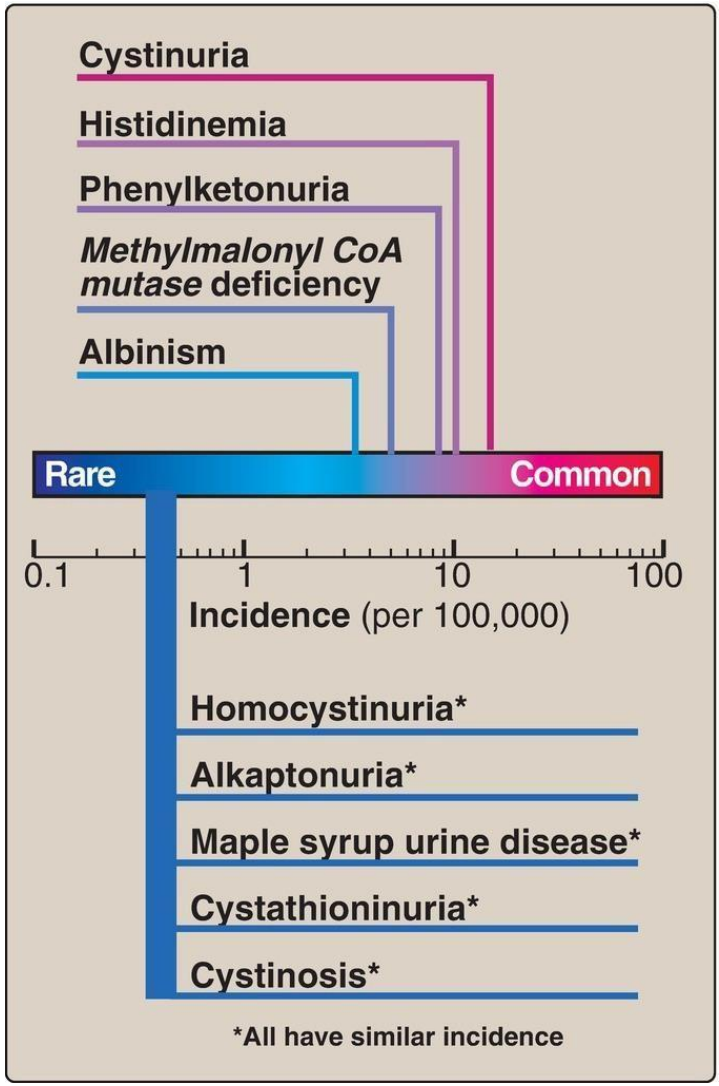
- Single gene disorders (inborn errors of metabolism)
- Variable activity of the enzymes
- Without treatment → intellectual disability or other developmental abnormalities
  Replacement therapy and dietary management exist for many disorders.
- >50 of these disorders have been described (most are rare , <1 per 250,000). so the lecture focuses on the **most common ones**.

•Collectively, however, they constitute a very significant portion of pediatric genetic diseases

The **main medical specialty** dealing with these disorders is **Pediatrics**.

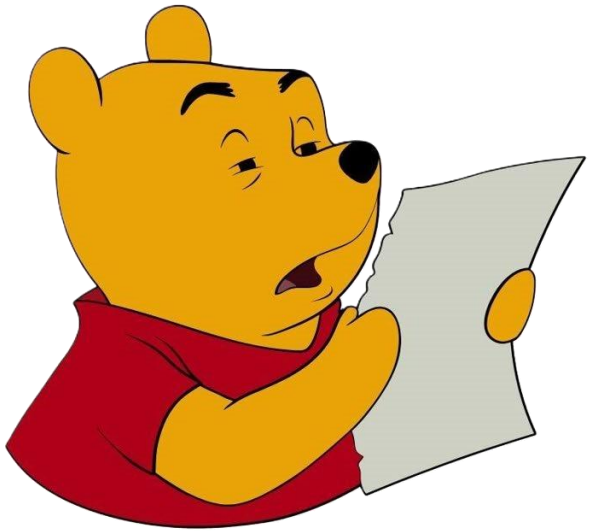
•Reason:

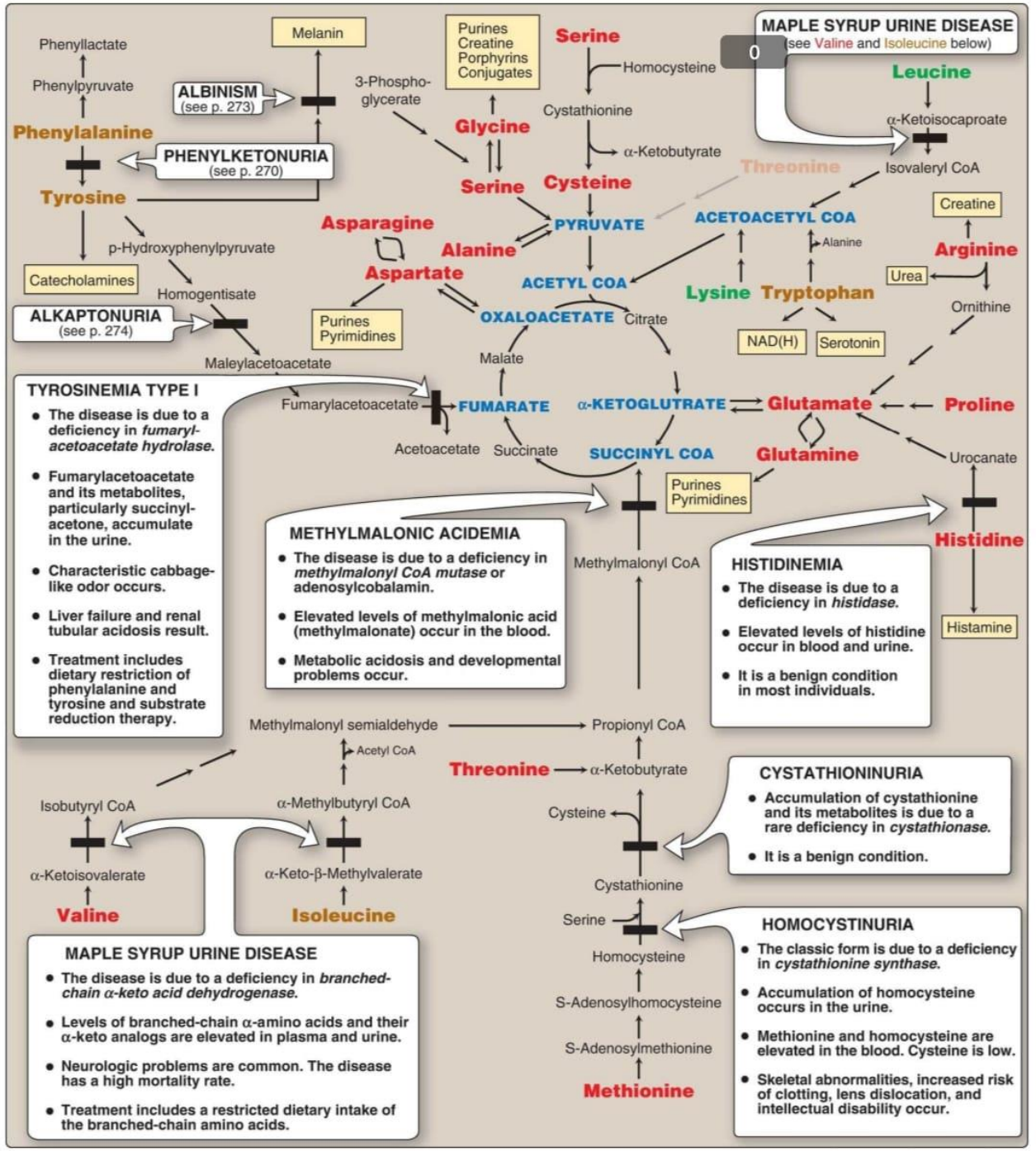
→ These diseases **appear early in life**, usually in infancy or childhood.



وَإِلَيْهِ يُرْجَعُ ٱلْأَمْرُ كُلُّهُۥ فَٱعْبُدْهُ وَتَوَكَّلْ عَلَيْهِ

Explanation of the Amino Acid Metabolism Disorders Diagram next slides





General Idea of the Diagram

This diagram shows **amino acid metabolism pathways** and how a **defect at any enzymatic step** leads to a **specific disease**.

Each boxed disease represents a **block in metabolism**, leading to **accumulation of intermediates** and characteristic clinical features

Phenylalanine → Tyrosine Pathway (Left Upper Side)

Phenylalanine is normally converted to **tyrosine**.

If this conversion does not occur:

- Phenylalanine is diverted to produce:
- **Phenylpyruvate**
- **Phenyllactate**
- **Phenylacetate**

This causes **phenylketonuria**.

Tyrosine is also required for:

- **Melanin synthesis**
- **Catecholamine synthesis**

So, deficiency of tyrosine leads to:

- **Hypopigmentation**
- Neurologic manifestations

If there is a defect in melanin synthesis itself:

- This leads to **albinism**.

Tyrosine Degradation Pathway

Tyrosine is a **mixed amino acid**.

It is broken down to produce:

- **Fumarate**
- **Acetoacetate**

During this pathway, **homogentisic acid** is formed.

If homogentisic acid is not oxidized due to deficiency of:

- **Homogentisic acid oxidase**

This leads to:

- **Alkaptonuria**
- Accumulation of homogentisic acid
- Darkening of urine on standing

Further down the pathway:

- **Fumarylacetoacetate** should be converted into fumarate and acetoacetate

If **fumarylacetoacetate hydrolase** is deficient:

- **Tyrosinemia type I** occurs
- Toxic metabolites accumulate
- Characteristic **cabbage-like odor of urine**
- Liver and renal damage occur

Branched-Chain Amino Acids (Bottom Left)
The branched-chain amino acids are:
- **Valine**
- **Isoleucine**
- **Leucine**

These amino acids are first converted to their corresponding **α-keto acids**.
They all require the enzyme:
- **Branched-chain α-keto acid dehydrogenase**

If this enzyme is deficient:
- **Maple syrup urine disease** occurs
- Branched-chain amino acids and their α-keto acids accumulate
- Neurologic problems are common
- High mortality rate if untreated

Leucine is strictly ketogenic,
Valine is glucogenic,
Isoleucine is mixed.

Methionine → Homocysteine Pathway (Lower Middle)
Methionine is converted to **homocysteine**.
Homocysteine normally combines with serine to form **cystathionine** via:
- **Cystathionine β-synthase**

If this enzyme is deficient:
- **Homocystinuria** occurs
- Homocysteine accumulates in urine
- Methionine levels are high
- Cysteine levels are low
- Skeletal abnormalities, thrombosis, and intellectual disability occur

If cystathionine is not further metabolized:
- **Cystathioninuria** occurs
- Accumulation of cystathionine
- Usually a benign condition

Histidine Pathway (Right Side)
Histidine is normally converted to **urocanate**.
If there is a deficiency in **histidase**:
-Histidinemia occurs -Elevated histidine in blood and urine -Usually a benign condition in most individuals

Integration with Central Metabolism

Many amino acids feed into central metabolic intermediates such as:

- **Pyruvate**
- **Acetyl-CoA**
- **α-ketoglutarate**
- **Succinyl-CoA**
- **Fumarate**
- **Oxaloacetate**

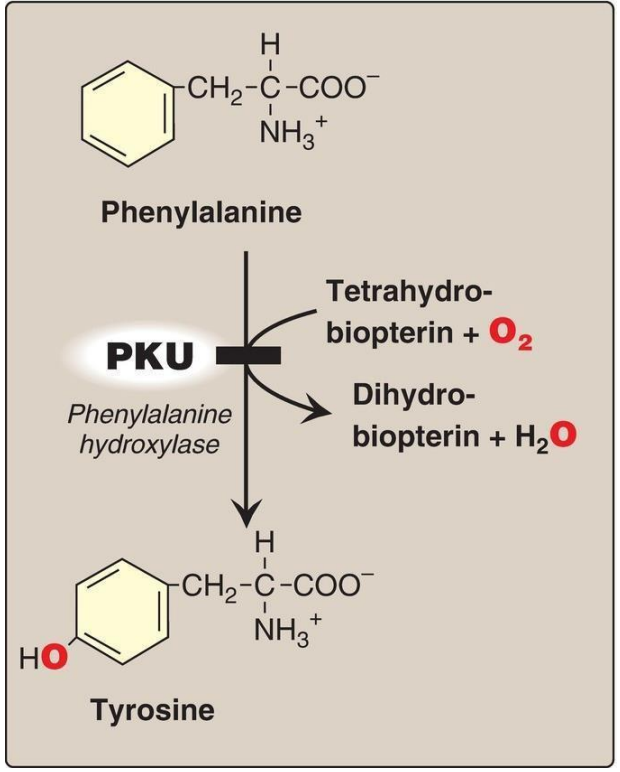
This explains why defects in amino acid metabolism affect:

- CNS function
- Energy production
- Growth and development

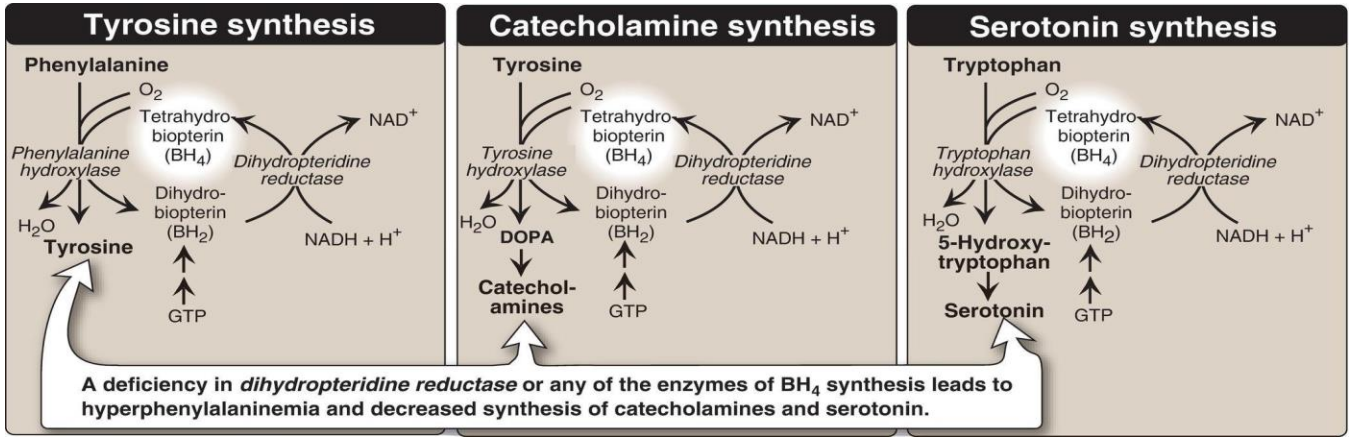
So, what this diagram shows is that:

- Amino acids are interconnected with central metabolism
- A defect in **one enzyme** leads to:
- Accumulation of specific metabolites
- Characteristic **clinical picture**
- Recognizable **urine odor or color**
- These disorders present early in life and are mainly managed by **dietary restriction and supplementation**

A. Phenylketonuria



- The most common clinically encountered inborn error of amino acid metabolism (incidence 1:15,000) live births
- Deficiency of PAH (Phenylalanine hydroxylase) and hyperphenylalaninemia (10 folds; plasma, urine, tissues), Tyrosine is deficient
- Management!
- Other causes of Hyperphenylalaninemia (indirect) and management!



Next slide for more clarification

Role of Tetrahydrobiopterin (BH_4)

- Required coenzyme for:
- Phenylalanine → tyrosine
- BH_4 → dihydrobiopterin
- Regenerated by:
- **Dihydropteridine reductase**
- Similar concept to:
- Dihydrofolate reductase in folate metabolism

Diagnosis

- Newborn screening:
- **Hyperphenylalaninemia**
- After **48–78 hours of birth**:
- Phenylalanine ↑ up to **10× normal**
- Tyrosine ↓
- Elevated in:
- Plasma
- Urine
- Tissues

Management

- **Low-phenylalanine diet**
- **Tyrosine supplementation**
- Needed to synthesize:
- Dopamine, Epinephrine, Norepinephrine,& Melanin

Other Causes of Hyperphenylalaninemia

- Not only phenylalanine hydroxylase deficiency:
- Deficiency of **BH_4**
- Deficiency of **dihydropteridine reductase**

Why BH_4 Is Important?

- Required for hydroxylation of:
- Phenylalanine → tyrosine
- Tyrosine → DOPA → dopamine
- Tryptophan → serotonin

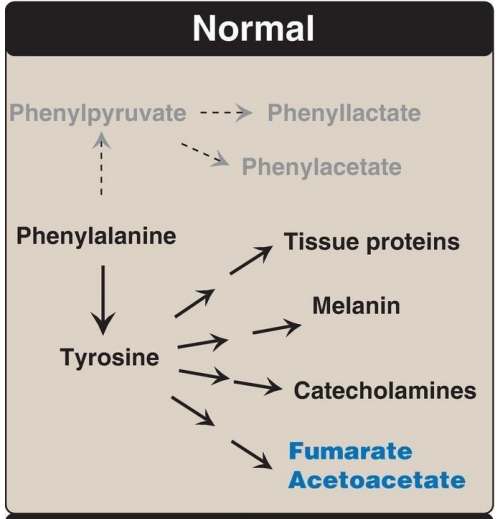
Differentiation

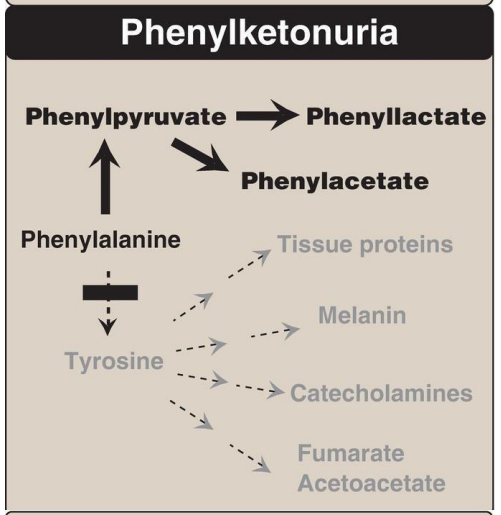
- If **only PAH deficiency**:
- Tyrosine supplementation works
- Normal dopamine & serotonin synthesis
- If **BH_4 or reductase deficiency**:
- Impaired synthesis of:
- Dopamine
- Serotonin
- Catecholamines

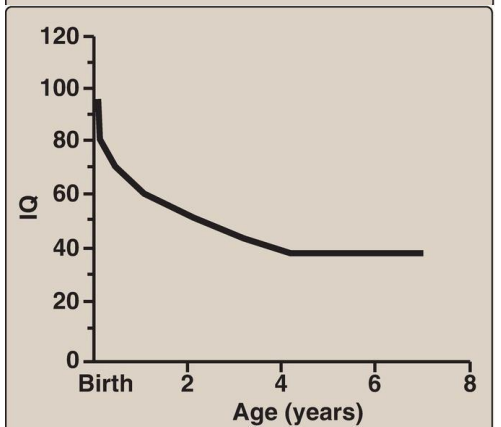
A. Phenylketonuria

Name of the disease?

- Elevated levels of phenylketones
- Phenylpyruvate (a phenylketone), phenylacetate, and phenyllactate, which are not normally produced in significant amounts
- **These phenylketones accumulate in blood, tissues, and brain cells**
- **Brain cells cannot handle these metabolites, leading to cellular damage**
- These metabolites give urine a characteristic musty (“mousy”) odor
- **The odor becomes noticeable by around 1 year of age**
- CNS effects:
- Severe intellectual disability, developmental delay, microcephaly, and seizures
- **Neurologic damage is progressive if untreated**
- Symptoms of intellectual disability by age 1 year and
- Rarely achieves an intelligence quotient (IQ) >50
- **Even with treatment, normal IQ is rarely achieved if diagnosis is delayed**

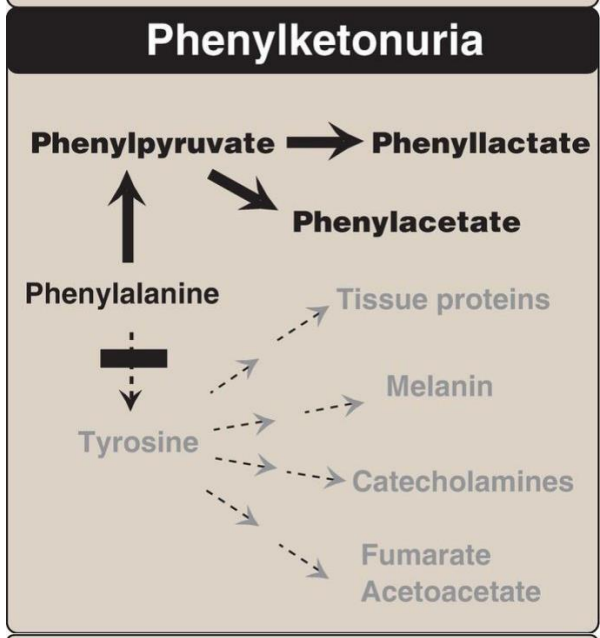


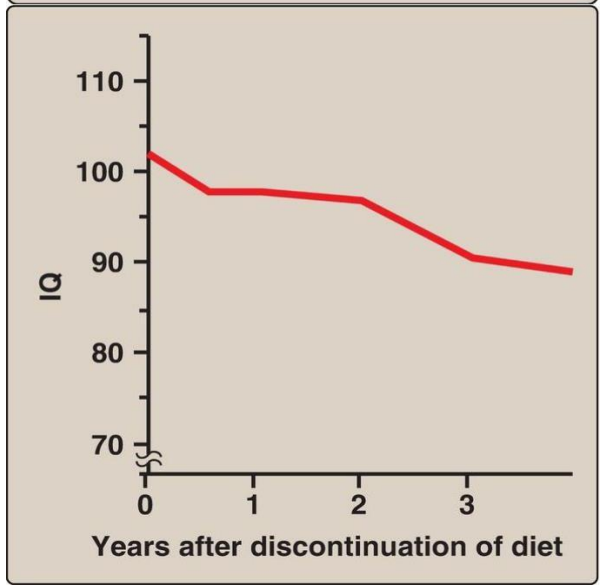




A. Phenylketonuria

- Hypopigmentation
  - (fair hair, light skin color, and blue eyes) Because phenylalanine is not getting converted to tyrosine, we have low levels of melanin
  - The hydroxylation of tyrosine by copper- requiring tyrosinase, is decreased due to low tyrosine availability
- Newborn screening and diagnosis (24-48h)
  If diagnosed early in newborn screening, this disease is manageable
- Management! Aspartame
  Patients are not allowed to take aspartame as a replacement sweetener because it includes phenylalanine
- Maternal phenylketonuria syndrome:
  - Teratogenic مُسبِّب للتشوهات الخلقية(microcephaly and congenital heart abnormalities) **High levels of phenylketones are teratogenic to the babies**
    - Prior to conception **Phenylalanine levels must be controlled prior to conception, not only during pregnancy but also before it.**





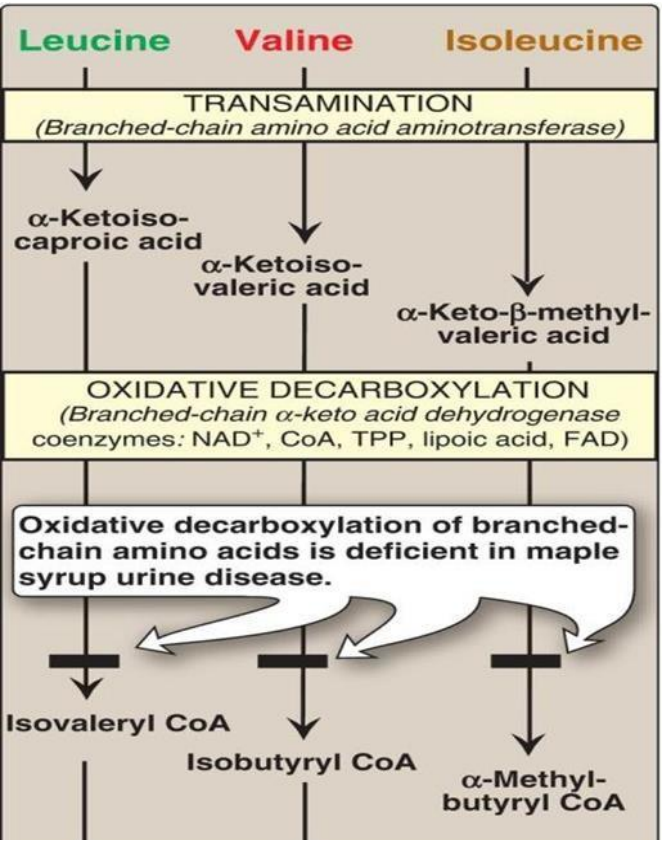
B. Maple syrup urine disease

- Autosomal recessive
- Deficiency in BCKD (Branched-Chain α-Ketoacid Dehydrogenase)
- BCAA (*Branched-Chain Amino Acids (Leucine, Isoleucine, Valine)*) and their corresponding α- keto acids accumulate causing CNS effects
- Feeding problems, vomiting, ketoacidosis, changes in muscle tone, neurologic problems
- Characteristic maple syrup–like urine odor (Ile)

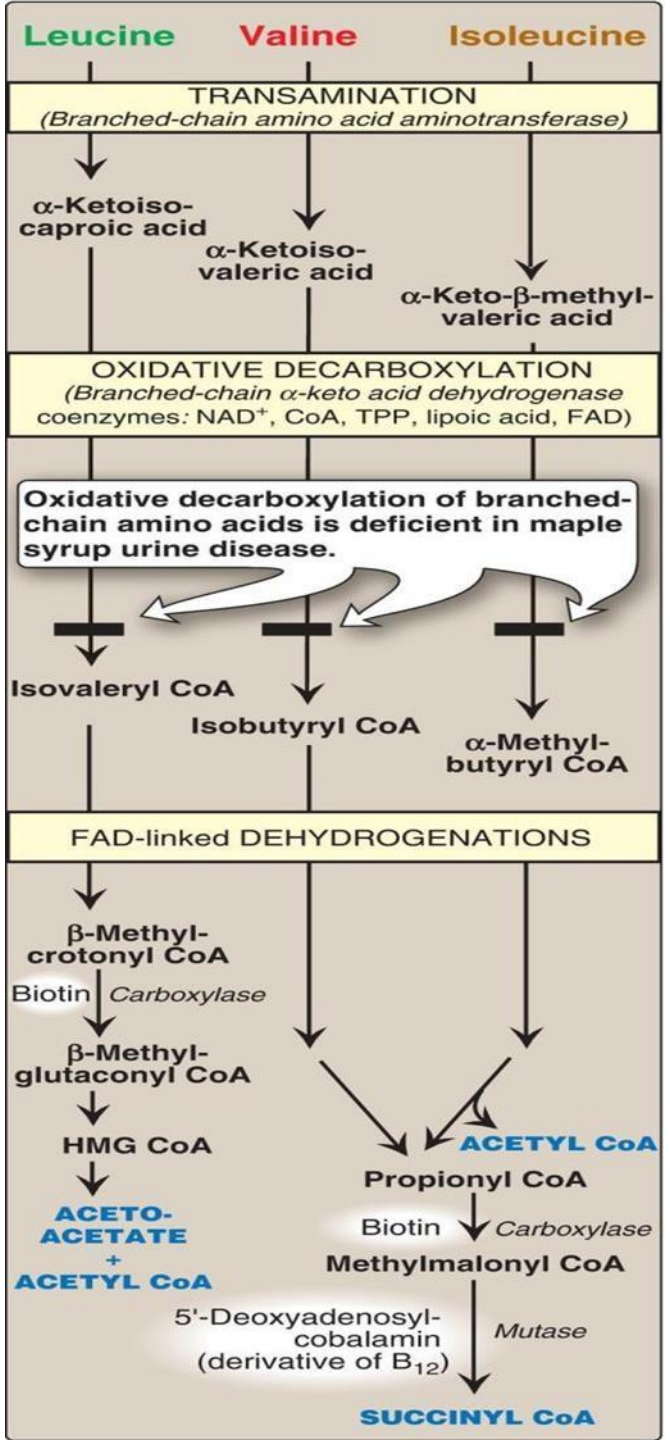
-Isoleucine (responsible for the maplesyrup-like urine odor)

- If untreated, the disease is fatal
- If treatment is delayed, intellectual disability results
- Screening and diagnosis

B. Maple syrup urine disease



Deficiency in these patients is in a disease which is called **branched-chain alpha keto acid dehydrogenase**.
This enzyme is the same as the enzyme **pyruvate dehydrogenase** or **alpha-ketoglutarate dehydrogenase** that we have taken before.
Those branched-chain amino acids are getting converted to their corresponding **alpha-keto acids**.
Then the branched-chain alpha-keto acid dehydrogenase works on them to produce their corresponding molecule coupled to **coenzyme A**.
NADH is being produced and CO_2 is being produced, and we have taken that before.
That enzyme is defective, mutated, and according to the mutation, the expression of this disease is variable among patients.



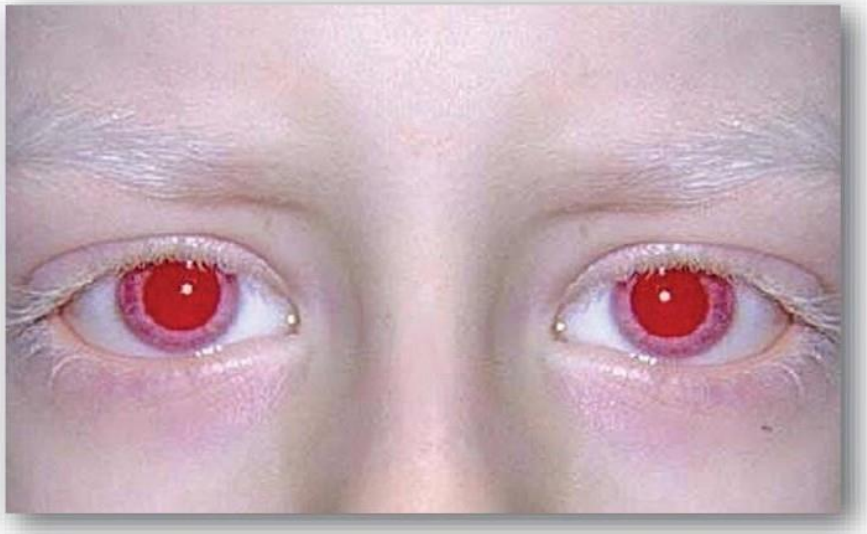
C. Albinism

- A group of conditions in which a defect in tyrosine metabolism results in a deficiency in the production of melanin

  Albinism is a phenotype that includes more than one disease underneath it

  More than one mutation affecting more than one enzyme in the journey of converting tyrosine to melanin

- Partial or full absence of pigment from the skin, hair, and eyes
- Albinism appears in different forms, and it may be inherited as: autosomal recessive(primary mode), autosomal dominant, or X-linked



- Total absence of pigment (tyrosinase-negative oculocutaneous albinism, type 1 albinism), results from an absent or defective copper-requiring tyrosinase
- Hypopigmentation, vision defects, photophobia, increased risk for skin cancer

· **Inheritance depends on the mutation that affects the enzyme**

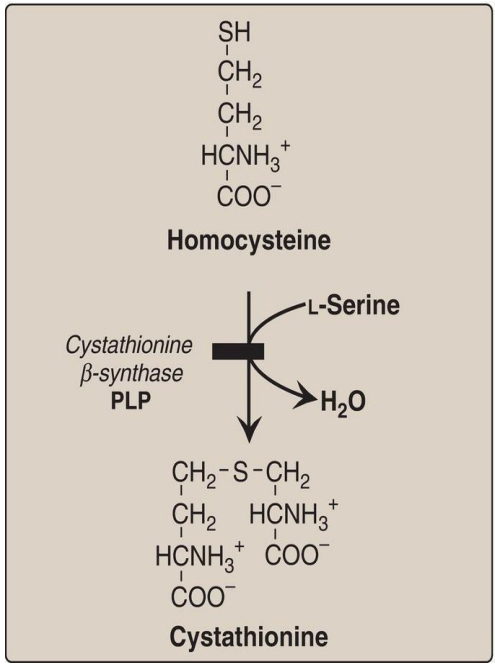
D. Homocystinuria

Homocysteine urea is the elevated levels of homocysteine

- A group of disorders, autosomal-recessive, high urinary levels of Hcy, high plasma levels of Hcy and methionine, and low plasma levels of cysteine
- Most common cause: cystathionine β-synthase

  Homocysteine is converted to cystathionine through the action of cystathionine beta synthase

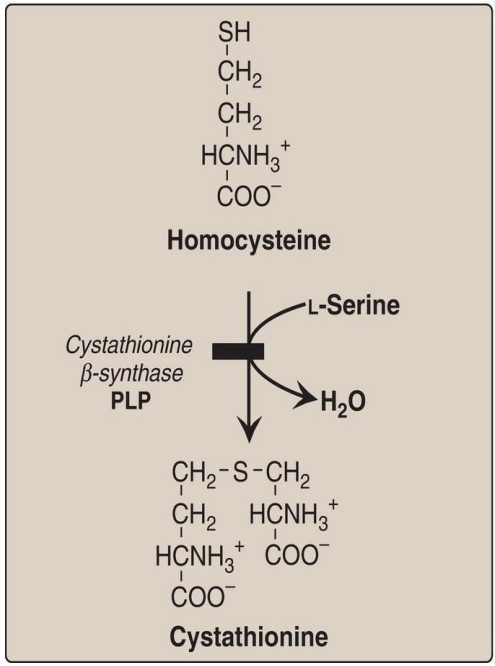
  This enzyme requires vitamin B6 and PLP as a co-enzyme
- Homozygous patients exhibit increased risk for developing thrombi (the major cause of early death)



D. Homocystinuria

وَأَمَّا مَنْ خَافَ مَقَامَ رَبِّهِ وَنَهَى النَّفْسَ عَنِ الْهَوَىٰ
فَإِنَّ الْجَنَّةَ هِيَ الْمَأْوَىٰ

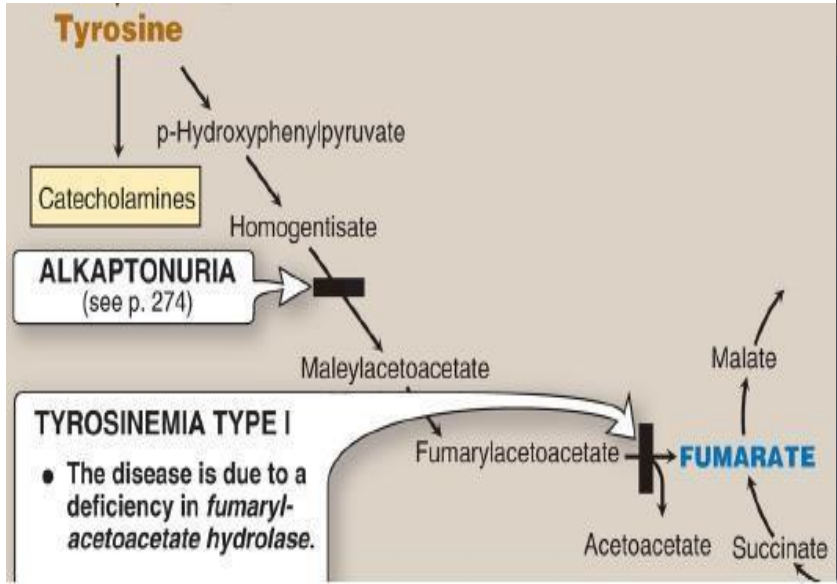
- Management: restriction of methionine and supplementation with vitamin B12 and folate
  Supplementation with vitamin B12, vitamin B9, and vitamin B6 decreases the levels of homocysteine and its effects
- Some patients are responsive to oral administration of pyridoxine (milder form)
- Deficiencies in methylcobalamin or MTHF reductase [MTHFR]; also result in elevated Hcy
  Homocysteine levels can also be elevated if the remethylation pathway is defective

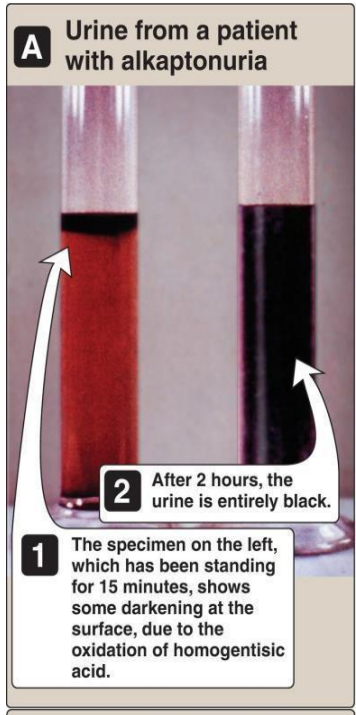


E. Alkaptonuria and Tyrosinemia Type 1

- A rare organic aciduria: a deficiency in **homogentisic** acid oxidase (accumulation of HA) **Homogentisic acid is formed in the tyrosine pathway**
  This conversion requires the enzyme homogentisic acid oxidase
  This enzyme might be defective or mutated, causing alkaptonuria
- Symptoms: homogentisic aciduria (oxidized to a dark pigment), early onset of arthritis in the large joints, and deposition of black pigment (ochronosis) in cartilage and collagenous tissue
- Management!

- Deficiencies in fumarylacetoacetate hydrolase, result in tyrosinemia type I and a characteristic cabbage-like odor to urine

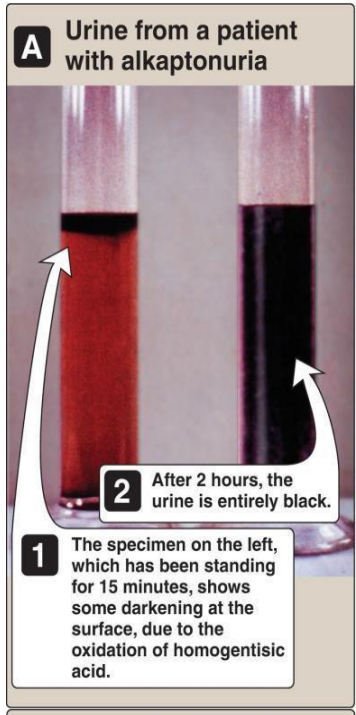




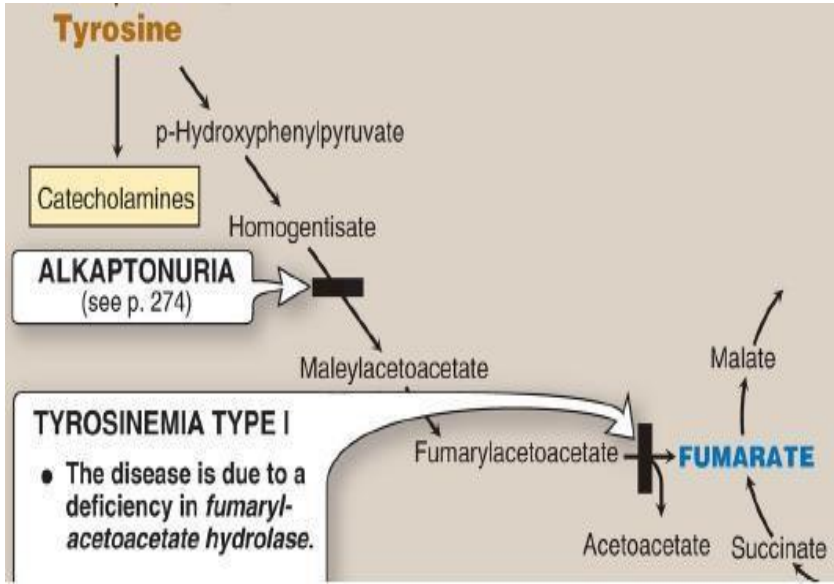
E. Alkaptonuria and Tyrosinemia Type 1

There are high levels of homogentisic acid inside the blood and accordingly inside urine
This material gets oxidized easily and with oxygen it gets converted to brown then deep black color
If you take a urine or blood sample and leave it, it gets converted to deep black color
Homogentisic acid can also accumulate in the vertebrae and can be shown by radiograph

- Deficiencies in fumarylacetoacetate hydrolase, result in tyrosinemia type I and a characteristic cabbage-like odor to urine



Tyrosine is converted at the end of the pathway to fumarate and acetoacetate
If this enzyme is defective, everything will be backed up and tyrosine levels will be high
Fumarylacetoacetate will accumulate
This causes a characteristic cabbage-like odor of urine



AMINO ACID METABOLISM DISORDERS – SUMMARY TABLE

Disease	Enzyme Defect	Main Accumulation	Key Clinical Features	Characteristic Finding
Phenylketonuria (PKU)	Phenylalanine hydroxylase (or BH_4-related enzymes)	Phenylalanine → phenylpyruvate, phenylacetate, phenyllactate	Severe intellectual disability, developmental delay, microcephaly, seizures, hypopigmentation	Musty (mousy) urine odor
Maternal PKU	Same as PKU	Phenylketones	Teratogenic effects on fetus	Microcephaly, congenital heart defects
Maple Syrup Urine Disease (MSUD)	Branched-chain α-ketoacid dehydrogenase	BCAA (Leu, Ile, Val) and their α-keto acids	Feeding problems, vomiting, ketoacidosis, neurologic problems	Maple syrup–like urine odor (Ile)
Albinism	Tyrosinase or other enzymes in tyrosine → melanin pathway	↓ Melanin	Partial or total absence of pigment, vision defects, photophobia	Hypopigmentation, ↑ skin cancer risk
Homocystinuria	Cystathionine β-synthase (most common)	Homocysteine ↑, methionine ↑, cysteine ↓	Thromboembolism, skeletal abnormalities, intellectual disability	High homocysteine in blood & urine
Alkaptonuria	Homogentisic acid oxidase	Homogentisic acid	Early arthritis, ochronosis, pigmentation of cartilage	Urine turns dark/black on standing
Tyrosinemia Type 1	Fumarylacetoacetate hydrolase	Fumarylacetoacetate, tyrosine	Liver and renal problems	Cabbage-like urine odor

رسالة من الفريق العلمي:

اعتنِ بصلاتك

فإحداهن ستكون الأخيرة

وأنت لا تعلم

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide #**15**	This enzyme requires vitamin B6 and PLP as a core enzyme	This enzyme requires vitamin B6 and PLP as a co-enzyme
V1 → V2			