MEDICAL ACADEMY NAMED AFTER S.I. GEORGIEVSKY OF VERNADSKY CFU

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GROUP ;LA1-202(2)

TOPIC; AMINO ACID METABOLIC DISORDERS

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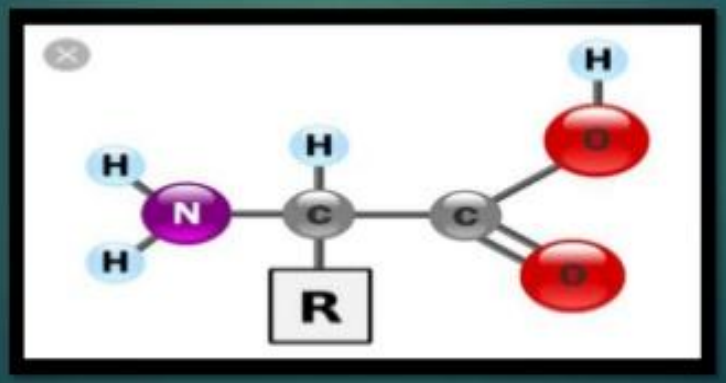
What is amino acid?

- Amino acids are building blocks of protein. Amino acid are organic compound which contain amine and carboxyl as a functional groups along with the side chain which is specific for each amino acid.



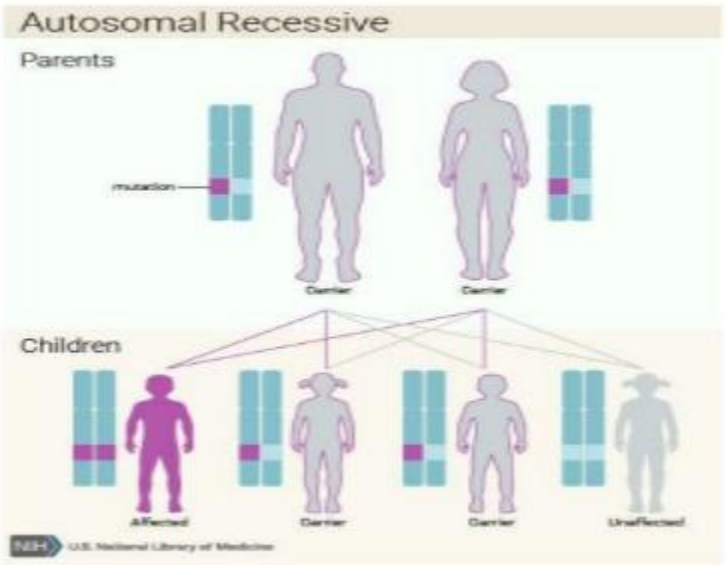
Amino acid disorders

- Something goes wrong with metabolic process is called as disorder. But when something goes wrong with metabolism of amino acid specifically at that time it is termed as disorders associated with amino acid metabolism.

- **There are many disorders associated with amino acid metabolism such as:**
  - Albinism
  - Alkaptonuria
  - Phenylketonuria etc.

Albinism

- Albinism is **a congenital** disorder in which humans have complete or partial absence of pigment in skin, hair & eyes. Due to lack of skin pigment the person get more susceptible to sunburn & **Skin cancer.** It is very rare disease. It is chronic. It is an inherited disease which is occur due to receive a defective recessive gene allels from parent. Albinism occur in all vertebrates including human also. Albinism is an autosomal recessive disoreder.


Autosomal Recessive
Parents
mutation
Carrier
Carrier
Children
Affected
Carrier
Carrier
Unaffected
NIH
U.S. National Library of Medicine

Cause of Albinism

- It is occur due to absence or defect in tyrosinase enzyme. This is an enzyme which involved in the production of melanin. This condition is totally opposite of **melanism**. An organism with complete absence of melanin is called an **albino.**

11/10/2018

Genetics of albinism

- A mutation occur in **TRP-1** gene may result in the deregulation of melanocytes tyrosinase enzyme. The sub type of albinism is **ocular albinism** which is **X linked inherited** disease. So, ocular albinism is more observe in male compare to female.
- Two forms of albinism:1.Partial lack of melanin which is known as hypomelanism or hypomelanosis & 2.The total absence of melanin is known as amelanosis.

In normal condition

Tyrosine

↓ Tyrosinase

Melanin

In Albinism

Tyrosine

⊘ Tyrosinase

Melanin

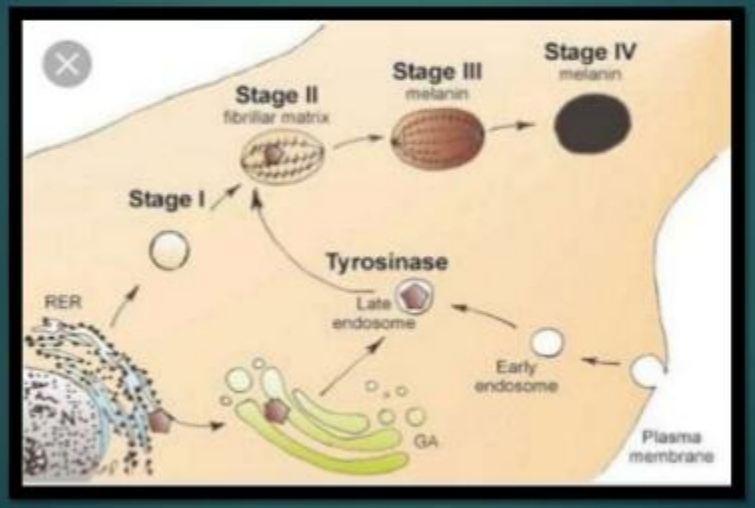
Tyrosinase also called as Tyrosine-3-monooxygenase.

Symptoms and effects:

Lack of pigmentation, White hair, Pink skin etc.

Patients of Albinism

Melanin production pathway



Alkaptonuria

- It is also known as black bone or black urine disease. It is also an inherited disease.
- Alkaptonuria is an autosomal recessive genetic disease meaning that patients have two defective copies of a gene; one from each parent.

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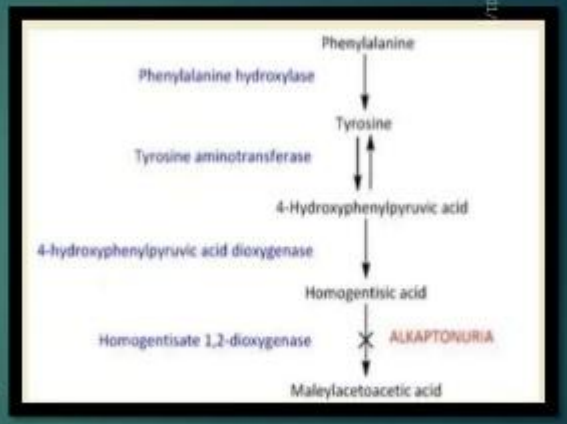
Genetics of alkaptonuria

- The defects is occur in chromosome 3, between regions 3q21-3q23.
- In human, this is the site of the homogentisate-1,2-dioxygenase enzyme(HGD) which play the key role in tyrosine metabolism.
- Homogentisic acid → Maleylacetoacetic acid
- ★ - indicates HGD enzyme
- If HGD is not working properly at that time the accumulation of Homogentisic acid (HGA) is increase.

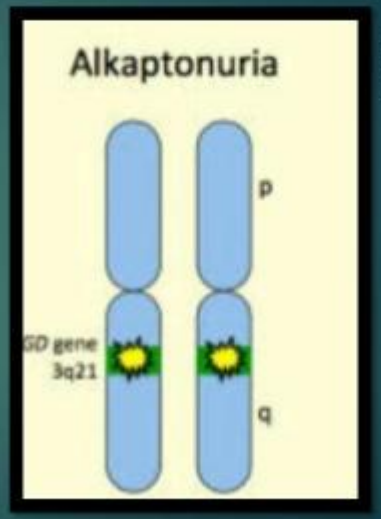
Pathway for tyrosine metabolism

- In figure there is shown that HGD enzyme is deficient so HGA is accumulate which lead to AKU. If we want to treat the AKU, inhibit the 4-hydroxyphenylpyruvic acid dioxygenase which inhibits the production of HGA.



Genetics of AKU

- In figure the chromosome no 3 is shown in which the region 3q21 is present and shown by yellow color. This region contain gene for HGD enzyme which is defective in alkaptonuria. It is recessive disease so two copies of defective gene is present one from each parent.



Why called black urine disease?

- Initially the Homogentisic acid(HGA) only accumulates in blood. In childhood this results in only one symptom: Urine turns black when left stand in air.
- When time goes, less amount of HGA is excreted out via urine and most is deposited in cartilage and bone.
- HGA → OXIDIZED → Black pigment {benzoquinone acetic acid}

- One deposited HGA polymerizes to ubiquinines & binds to individual collagen fibers in cartilage which resulting in a pigmentation known as Ochronosis.
- This make the cartilage more stiff, brittle & black. So, it is called black bone disease.
- This lead to joint pain, cartilage damage.
- As all joints collapse, the only current medical treatment is joint replacement surgery have been done.
- HGA also can accumulate at other places in our body.

- One of the more sign of alkaptonuria is the decolouration under skin particularly in pinna of the ears. This is due to ochronosis of auricular cartilage and giving it a black appearance.
- There is no cure for alkaptonuria. The biggest hope for a future treatment of AKU lies with a drug Nitisinone.
- It is rare disorder in which the body can not process the amino acids phenylalanine and tyrosine, which occur in protein.

Signs and symptoms

- Patient with black bone disease are asymptomatic as children or young adults, but their urine may turn brown or even inky black if collected and left exposed to open air.
- After the age of thirty people begin to develop pain in weight bearing joints of the spine, hips and knees.
- In longer term the involvement of the spinal joints leads to reduced movement of the rib cage and affect breathing.
- Also heart failure occurs.

Treatment

- There is no treatment. Such commonly recommended treatment include dietary restriction of amino acids phenylalanine, tyrosine.
- Several studies suggested that the herbicide nitisinone may be effective in treatment.
- Nitisinone inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase which is responsible for converting tyrosine to HGA. So it blocks the production and accumulation of HGA.
- The main draw back is that accumulation of tyrosine occur which damage to cornea of eye.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Normal urine
Urine from patients with alkaptonuria
Patients may display painless bluish darkening of the outer ears, nose and whites of the eyes. Longer term arthritis often occurs.

Phenylketonuria

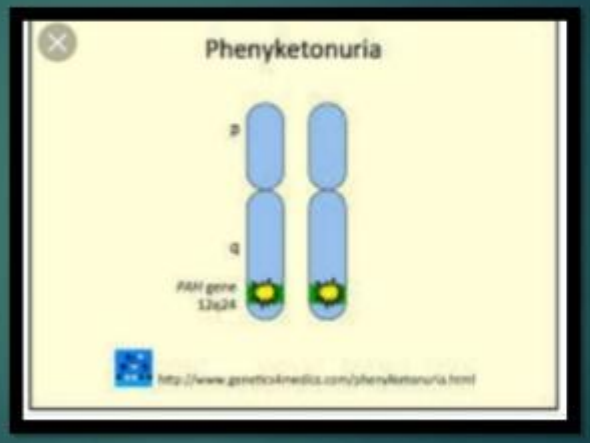
- Phenylketonuria is a rare genetic disease that is lead to the accumulation of phenylalanine in the body. Phenylalanine is found in all proteins and some artificial sweeteners.
- Phenylalanine hydroxylase is an enzyme which convert phenylalanine into tyrosine which is further need to create neurotransmitters such as epinephrine, dopamine, and norepinephrine.
- PKU is caused due to defect in gene that helps create phenylalanine hydroxylase.
- When this enzyme was not proper working at that time the phenylalanine is not convert to tyrosine. So there is an accumulation of phenylalanine in the body occur.

Causes of Phenylketonuria

- PKU is an inherited condition caused by a defect in the PAH gene. The PAH gene helps to create the enzyme which is responsible for phenylalanine conversion.
- It is an autosomal recessive disease.
- When PAH activity is reduce, phenylalanine accumulates and is converted into phenylpyruvate which is detected in urine.

GENETICS OF PKU

- The PAH gene is located on chromosome no12 in the bands 12q22-q24.1.

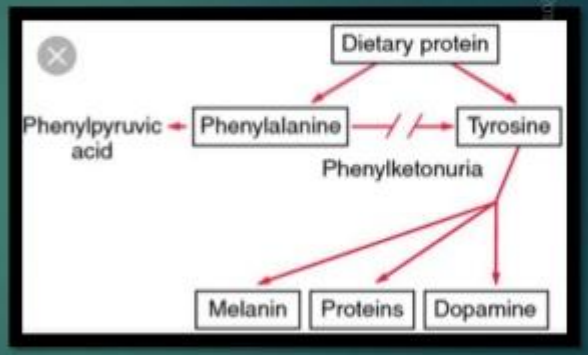


Signs and symptoms

- **Seizures**
- Trembling and shaking
- Skin condition such as **eczema**
- A **musty odor** of their breath, urine or skin.
- Mental retardation etc.
- There is no cure for PKU. The best treatment to manage the symptoms of the disorder is a diet that is low in protein.

How PKU is occur?

- The accumulated phenylalanine gets converted to phenylpyruvic acid in PKU disorder.



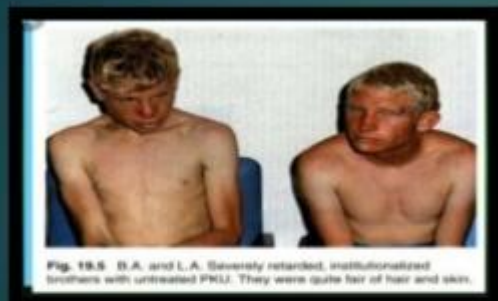


Fig. 19.5 D.A. and L.A. Severely retarded, institutionalized brothers with untreated PKU. They were quite fair of hair and skin.

Laura Davis-Keppen, MD,
Clinical Geneticist at Sanford Children's,
with PKU patients

Photo courtesy of Sanford Health


Thank
you!