Disorders of mitochondrial function E.g., Kearns-Sayre syndrome

What is Kearns-Sayre syndrome?

- Kearns-Sayre syndrome is a condition that affects many parts of the body, especially the eyes. The features of Kearns-Sayre syndrome usually appear before age 20, and the condition is diagnosed by a few characteristic signs and symptoms. People with Kearns-Sayre syndrome have progressive external ophthalmoplegia, which is weakness or paralysis of the eye muscles that impairs eye movement and causes drooping eyelids (ptosis). Affected individuals also have an eye condition called pigmentary retinopathy, which results from breakdown (degeneration) of the light-sensing tissue at the back of the eye (the retina) that gives it a speckled and streaked appearance. The retinopathy may cause loss of vision. In addition, people with Kearns-Sayre syndrome have at least one of the following signs or symptoms: abnormalities of the electrical

signals that control the heartbeat (cardiac conduction defects), problems with coordination and balance that cause unsteadiness while walking (ataxia), or abnormally high levels of protein in the fluid that surrounds and protects the brain and spinal cord (the cerebrospinal fluid or CSF).

- People with Kearns-Sayre syndrome may also experience muscle weakness in their limbs, deafness, kidney problems, or a deterioration of cognitive functions (dementia). Affected individuals often have short stature. In addition, diabetes mellitus is occasionally seen in people with Kearns-Sayre syndrome.
- When the muscle cells of affected individuals are stained and viewed under a microscope, these cells usually appear abnormal. The abnormal muscle cells contain an excess of structures called mitochondria and are known as ragged-red fibers.

- A related condition called ophthalmoplegia-plus may be diagnosed if an individual has many of the signs and symptoms of Kearns-Sayre syndrome but not all the criteria are met.
- What are the genetic changes related to Kearns-Sayre syndrome?
- Kearns-Sayre syndrome is a condition caused by defects in mitochondria, which are structures within cells that use oxygen to convert the energy from food into a form cells can use. This process is called oxidative phosphorylation. Although most DNA is packaged in chromosomes within the nucleus (nuclear DNA), mitochondria also have a small amount of their own DNA, called mitochondrial DNA (mtDNA). This type of DNA contains many genes essential for normal mitochondrial function. People with Kearns-Sayre syndrome have a single, large deletion of mtDNA, ranging from 1,000 to 10,000 DNA building blocks (nucleotides). The cause of the deletion in affected individuals is unknown.
- The mtDNA deletions that cause Kearns-Sayre syndrome result in the loss of genes important for mitochondrial protein formation and oxidative phosphorylation. The most common deletion removes 4,997 nucleotides, which includes twelve mitochondrial genes. Deletions of mtDNA result in impairment of oxidative phosphorylation and a decrease in cellular energy production. Regardless of which genes are deleted, all steps of oxidative phosphorylation are affected. Researchers have not determined how these deletions lead to the specific signs and symptoms of Kearns-Sayre syndrome, although the features of the condition are probably related to a lack of cellular energy. It has been suggested that eyes are commonly affected by mitochondrial defects because they are especially dependent on mitochondria for energy.
- Disorders of peroxisomal function ,E.g., Zellweger syndrome
- The Zellweger spectrum is a group of conditions that have overlapping signs and symptoms and affect many parts of the body. This group of disorders includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. These conditions were once thought to be distinct disorders but are now considered to be part of the same disease spectrum. Zellweger syndrome is the most severe form of the Zellweger spectrum, NALD is intermediate in

severity, and infantile Refsum disease is the least severe form. In some cases, it can be difficult to distinguish between the three conditions that make up the Zellweger spectrum.

- Individuals with Zellweger syndrome develop signs and symptoms of the condition during the newborn period. These infants experience weak muscle tone (hypotonia), feeding problems, hearing loss, vision loss, and seizures. These problems are caused by the degeneration of myelin, which is the covering that protects nerves and promotes the efficient transmission of nerve impulses. The part of the brain and spinal cord that contains myelin is called white matter. Destruction of the myelin (demyelination) leads to loss of white matter (leukodystrophy). Children with Zellweger syndrome also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys. They may have skeletal abnormalities, including a large space between the bones of the skull (fontanels) and characteristic bone spots known as chondrodysplasia punctata that can be seen with an x-ray. Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with Zellweger syndrome typically do not survive beyond the first year of life.
- People with NALD or infantile Refsum disease have more variable features than those with Zellweger syndrome and usually do not develop signs and symptoms of the disease until late infancy or early childhood. They may have many of the features seen in more severely affected individuals; however, their condition typically progresses more slowly. Children with these less severe conditions often have hypotonia, vision problems, hearing loss, liver dysfunction, developmental delay, and some degree of intellectual disability. Most people with NALD survive into childhood, and those with infantile Refsum disease may reach adulthood. In rare cases, individuals at the mildest end of the Zellweger spectrum have developmental delay in childhood and hearing loss or vision problems beginning in adulthood.
- What genes are related to Zellweger spectrum?
- Mutations in 12 genes have been found to cause the Zellweger spectrum. These genes provide instructions for making a group of proteins known as peroxins, which are essential for the formation and normal functioning of cell structures called peroxisomes. Peroxisomes are sac-like compartments that contain enzymes needed to break down many different substances, including fatty acids and certain toxic compounds. They are also important for the production of fats (lipids) used in digestion and in the nervous system. Peroxins assist in the formation (biogenesis) of peroxisomes by producing the membrane that separates the peroxisome from the rest of the cell and by importing enzymes into the peroxisome.
- Mutations in the genes that cause the Zellweger spectrum prevent peroxisomes from forming normally. Diseases that disrupt the formation of peroxisomes, including the Zellweger spectrum, are called peroxisome biogenesis disorders. If

the production of peroxisomes is altered, these structures cannot perform their usual functions. The signs and symptoms of Zellweger syndrome are due to the absence of functional peroxisomes within cells. NALD and infantile Refsum disease are caused by mutations that allow some peroxisomes to form.

- Mutations in the PEX1 gene are the most common cause of the Zellweger spectrum and are found in nearly 70 percent of affected individuals. The other genes associated with the Zellweger spectrum each account for a smaller percentage of cases of this condition.

Lysosomal storage disorders E.g., Gaucher's disease, Niemann Pick disease

Gaucher's disease

- Gaucher disease is an inherited disorder that affects many of the body's organs and tissues. The signs and symptoms of this condition vary widely among affected individuals. Researchers have described several types of Gaucher disease based on their characteristic features.
- Type 1 Gaucher disease is the most common form of this condition. Type 1 is also called non-neuronopathic Gaucher disease because the brain and spinal cord (the central nervous system) are usually not affected. The features of this condition range from mild to severe and may appear anytime from childhood to adulthood. Major signs and symptoms include enlargement of the liver and spleen (hepatosplenomegaly), a low number of red blood cells (anemia), easy bruising caused by a decrease in blood platelets (thrombocytopenia), lung disease, and bone abnormalities such as bone pain, fractures, and arthritis.
- Types 2 and 3 Gaucher disease are known as neuronopathic forms of the disorder because they are characterized by problems that affect the central nervous system. In addition to the signs and symptoms described above, these conditions can cause abnormal eye movements, seizures, and brain damage. Type 2 Gaucher disease usually causes life-threatening medical problems beginning in infancy. Type 3 Gaucher disease also affects the nervous system, but tends to progress more slowly than type 2.
- The most severe type of Gaucher disease is called the perinatal lethal form. This condition causes severe or life-threatening complications starting before birth or in infancy. Features of the perinatal lethal form can include extensive swelling caused by fluid accumulation before birth (hydrops fetalis); dry, scaly skin (ichthyosis) or other skin abnormalities; hepatosplenomegaly; distinctive facial features; and serious neurological problems. As its name indicates, most infants with the perinatal lethal form of Gaucher disease survive for only a few days after birth.
- Another form of Gaucher disease is known as the cardiovascular type because it primarily affects the heart, causing the heart valves to harden (calcify). People with the cardiovascular form of Gaucher disease may also have eye abnormalities, bone disease, and mild enlargement of the spleen (splenomegaly).
- What genes are related to Gaucher disease?

- Mutations in the GBA gene cause Gaucher disease.
- The GBA gene provides instructions for making an enzyme called beta-glucocerebrosidase. This enzyme breaks down a fatty substance called glucocerebroside into a sugar (glucose) and a simpler fat molecule (ceramide). Mutations in the GBA gene greatly reduce or eliminate the activity of beta-glucocerebrosidase. Without enough of this enzyme, glucocerebroside and related substances can build up to toxic levels within cells. Tissues and organs are damaged by the abnormal accumulation and storage of these substances, causing the characteristic features of Gaucher disease.

Niemann-Pick disease

- Niemann-Pick disease is an inherited condition involving lipid metabolism, which is the breakdown, transport, and use of fats and cholesterol in the body. In people with this condition, abnormal lipid metabolism causes harmful amounts of lipids to accumulate in the spleen, liver, lungs, bone marrow, and brain.
- This disorder is divided into four main types based on the genetic cause and the signs and symptoms. Niemann-Pick disease type A appears during infancy and is characterized by an enlarged liver and spleen (hepatosplenomegaly), failure to gain weight and grow at the expected rate (failure to thrive), and progressive deterioration of the nervous system. Due to the involvement of the nervous system, Niemann-Pick disease type A is also known as the neurological type. Children affected by this condition generally do not survive past early childhood.
- Niemann-Pick disease type B has a range of features that may include hepatosplenomegaly, growth retardation, and problems with lung function including frequent lung infections. Other signs include blood abnormalities such as elevated levels of cholesterol and other lipids (fats), and decreased numbers of blood cells involved in clotting (platelets). Niemann-Pick disease type B is also known as the non-neurological type because the nervous system is not usually affected. People with Niemann-Pick disease type B usually survive into adulthood.
- Niemann-Pick disease type C usually appears in childhood, although infant and adult onsets are possible. Signs of Niemann-Pick disease type C include severe liver disease, breathing difficulties, developmental delay, seizures, poor muscle tone (dystonia), lack of coordination, problems with feeding, and an inability to move the eyes vertically. People with this disorder can survive into adulthood. Niemann-Pick disease type C is further subdivided into types C1 and C2, each caused by a different gene mutation.
- What genes are related to Niemann-Pick disease?
- Mutations in the NPC1, NPC2, and SMPD1 genes cause Niemann-Pick disease.
- Mutations in the SMPD1 gene cause Niemann-Pick disease types A and B. This gene provides instructions for producing an enzyme called acid sphingomyelinase. This enzyme is found in the lysosomes (compartments that digest and recycle materials in the cell), where it processes lipids such as sphingomyelin. Mutations in this gene lead to a deficiency of acid

sphingomyelinase and the accumulation of sphingomyelin, cholesterol, and other kinds of lipids within the cells and tissues of affected individuals.

- Mutations in either the NPC1 or NPC2 gene cause Niemann-Pick disease type C. The NPC1 gene provides instructions for producing a protein that is involved in the movement of cholesterol and lipids within cells. A deficiency of this protein leads to the abnormal storage of lipids within cells as seen in people with Niemann-Pick disease type C1. The NPC2 gene provides instructions to produce a protein that binds and transports cholesterol. Reduced or absent levels of this protein lead to the abnormal accumulation of lipids and cholesterol in the cells as seen in people with Niemann-Pick disease type C2. The exact functions of the NPC1 and NPC2 proteins are not fully understood.

NEONATAL AMINOACIDOPATHIES

- Aminoacidopathies are diseases caused by a genetically determined, biochemical abnormality in the metabolic pathway of amino acids.
- In most cases, the defects implicate the alteration of an enzyme interrupting the normal catabolism of an amino acid; in a few cases, the defects implicate a protein mediator required for amino acids transport.
- These disorders account for a non-negligible portion of neonatal and paediatric diseases.
- They are, however, relatively rare globally and give rise to a wide range of clinical manifestations.
- Neurological manifestations appear to be the main symptoms, often indicative of the underlying metabolic disease, and they may be more or less associated with other, sometimes cutaneous, manifestations.
- Broadly, three main forms of aminoacidopathies can be distinguished based on physical expression:

- — acute neonatal forms. These forms are observed in newborns who, after a disease-free period of a few hours to a few days, undergo progressive, unexplained neurological deterioration resulting in reduced consciousness and coma in extreme cases;
- acute delayed onset forms. These forms of the disease are observed in infants or children and even in adults and manifest as neurological disorders occurring during acute regressive attacks while between episodes the child is normal and suffers from no mental retardation. Onset at a late age and an absence of mental retardation are therefore not exclusion criteria as regards diagnosis. These acute attacks may be severe, giving rise, for example, to repeated, unexplained comas;
- progressive chronic forms. Numerous aminoacidopathies of late onset are accompanied, in retrospect, by relatively non-specific, insidious, often neurologic signs such as progressive mental retardation, hypotonia, muscle weakness, muscle atrophy and non-specific, extraneurologic symptoms. Gastrointestinal symptoms such as chronic anorexia, recurring vomiting, delayed growth, etc., and

cutaneous, hematologic, nephrologic, hepatic, ophthalmologic signs…can be associated

PHENYL KETONURIA

- Phenylketonuria (commonly known as PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. Phenylalanine is a building block of proteins (an amino acid) that is obtained through the diet.
- It is found in all proteins and in some artificial sweeteners.

- If PKU is not treated, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems.

History:

- Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Følling in 1934 when he noticed hyperphenylalaninemia (HPA) was associated with intellectual disability.

- In Norway, this disorder is known as Følling's disease, named after its discoverer. Dr. Følling was one of the first physicians to apply detailed chemical analysis to the study of disease.

- His careful analysis of the urine of two affected siblings led him to request many physicians near Oslo to test the urine of other affected patients. This led to the discovery of the same substance he had found in eight other patients.
- Disease characteristics.
- Phenylalanine hydroxylase (PAH) deficiency results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces a spectrum of disorders including
- Classic phenylketonuria (PKU),
- non-PKU hyperphenylalaninemia (non-PKU HPA), and
- variant PKU.

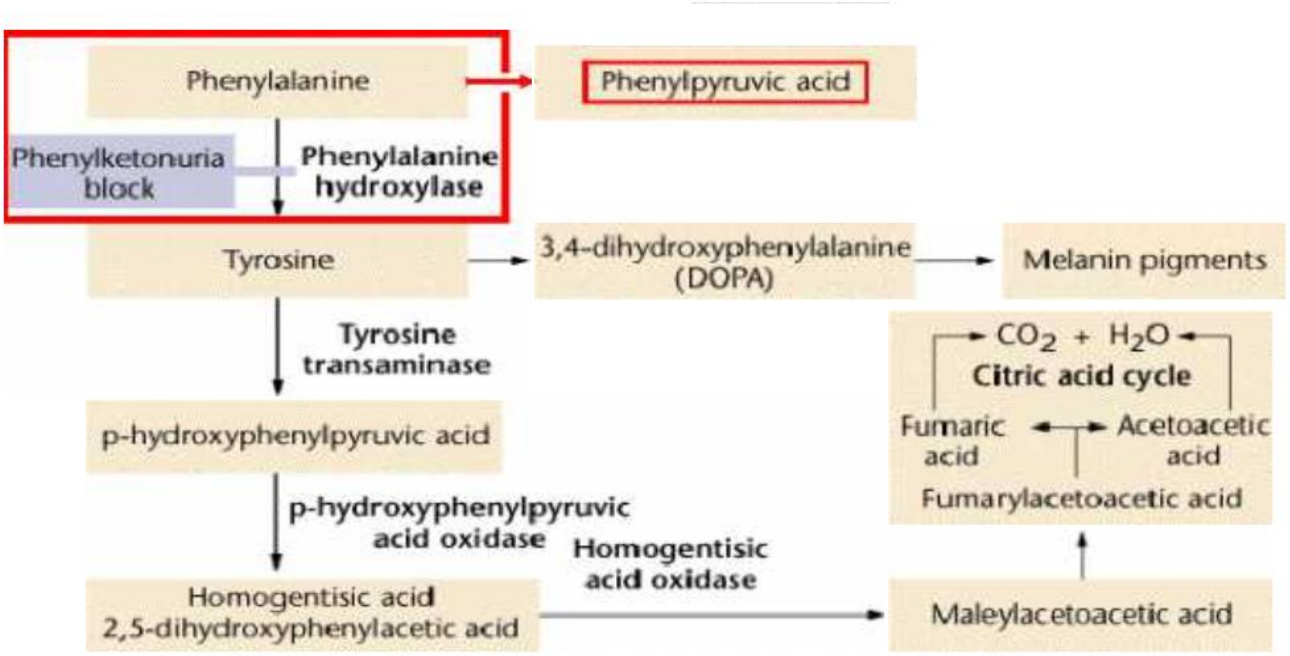
- Classic PKU is caused by a complete or near-complete deficiency of phenylalanine hydroxylase activity; without dietary restriction of phenylalanine, most children with PKU develop profound and irreversible intellectual disability.

- Non-PKU HPA is associated with a much lower risk of impaired cognitive development in the absence of treatment.

What genes are related to phenylketonuria?

- Mutations in the PAH gene cause phenylketonuria.
- PAH- “phenylalanine hydroxylase.”

- The PAH gene provides instructions for making an enzyme called phenylalanine hydroxylase.
- This enzyme is responsible for the first step in processing phenylalanine, which is a building block of proteins (an amino acid) obtained through the diet.
- Phenylalanine hydroxylase is responsible for the conversion of phenylalanine to another amino acid, tyrosine. The enzyme works with a molecule called tetrahydrobiopterin (BH4) to carry out this chemical reaction.
- Tyrosine is used to make several types of hormones, certain chemicals that transmit signals in the brain (neurotransmitters), and a pigment called melanin, which gives hair and skin their color. Tyrosine can also be broken down into



Phenylketonuria

(Klug & Cummings 1997)

smaller molecules that are used to produce energy.

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Tetrahydrobiopterin-deficient hyperphenylalaninemia

- A rarer form of hyperphenylalaninemia occurs when the PAH enzyme is normal, but there is a defect in the biosynthesis or recycling of the cofactor tetra hydrobiopterin (BH4).

- BH4 (called biopterin) is necessary for proper activity of the enzyme PAH, and this coenzyme can be supplemented as treatment. Those who suffer from PKU as well may also have a deficiency of tyrosine (which is created from phenylalanine by PAH). These patients must also be supplemented with tyrosine to account for this deficiency.

- Levels of dopamine can be used to distinguish between these two types.

- Tetrahydrobiopterin is required to convert phenylalanine to tyrosine, but is also required to convert tyrosine to L-DOPA (L-3,4-dihydroxyphenylalanine)via the enzyme tyrosine hydroxylase.

- L-DOPA (L-3,4-dihydroxyphenylalanine)in turn is converted to dopamine. Low levels of dopamine lead to high levels of prolactin. (luteotropic hormone or luteotropin, is a protein-related to mental health)
- By contrast, in classical PKU (without dihydrobiopterin involvement), prolactin levels would be relatively normal.
- More than 500 mutations in the PAH gene have been identified in people with phenylketonuria (PKU).

- Most of these mutations change single amino acids in phenylalanine hydroxylase.
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- For example, the most common mutation in many populations replaces the amino acid arginine with the amino acid tryptophan at position 408 (written as Arg408Trp or R408W).

- Other PAH mutations delete small amounts of DNA from the gene or disrupt the way the gene's instructions are used to make phenylalanine hydroxylase.
- PAH mutations reduce the activity of phenylalanine hydroxylase, preventing it from processing phenylalanine effectively.
- As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage.
- Classic PKU, the most severe form of the disorder, occurs when phenylalanine hydroxylase activity is severely reduced or absent.

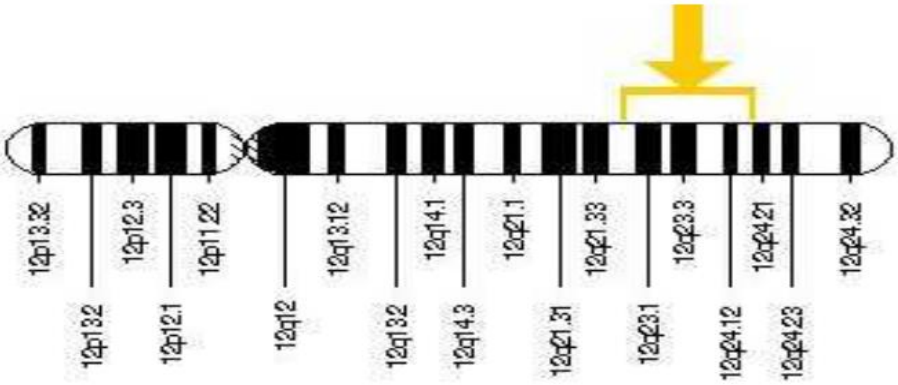
- People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious medical problems.

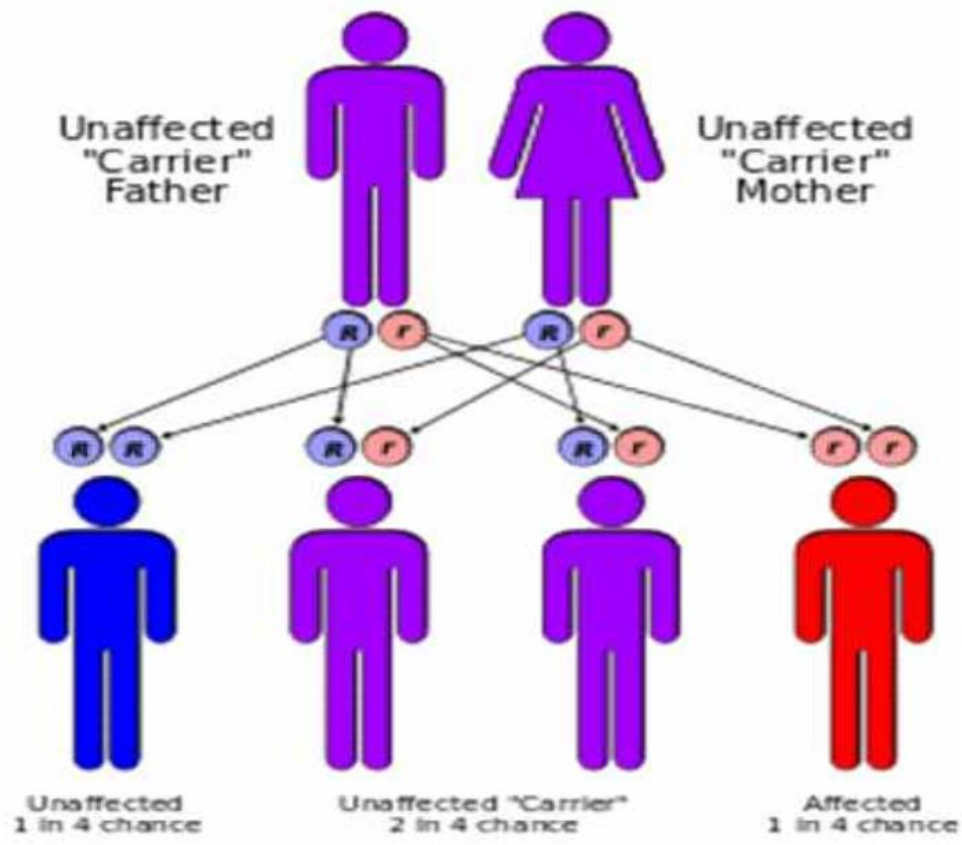
- Mutations in the PAH gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyper phenylalaninemia.

Where is the PAH gene located?

- Cytogenetic Location: 12q22-q24.2
- Molecular Location on chromosome 12: base pairs 102,838,325 to 102,917,602
- The PAH gene is located on the long (q) arm of chromosome 12 between positions 22 and 24.2.

Phenylketonuria is inherited in an autosomal recessive fashion





Symptoms

- Elevated phenylalanine, phenylpyruvate, phenyllactate and phenylacetate in blood and urine **(musty odor of urine).**
- **Neurological problems** (mental retardation, seizures, tremors, microcephaly etc) due to reduced production of catecholamines.
- **Hypopigmentation** (light skin, hair, blue eyes) due to reduced melatonin production. NO COMPLETE LOSS OF PIGMENT B/C WILL STILL HAVE SOME TYROSINE FROM DIET