CATEGORIES OF INHERITED METABOLIC DISEASES:

- Disorders of carbohydrate metabolism

E.g., glycogen storage disease

- Disorders of amino acid metabolism

E.g., phenylketonuria, maple syrup urine disease, glutaric acidemia type 1

- Urea Cycle Disorder or Urea Cycle Defects

E.g., Carbamoyl phosphate synthetase I deficiency

- Disorders of organic acid metabolism (organic acidurias)

E.g., alcaptonuria

- Disorders of fatty acid oxidation and mitochondrial metabolism

E.g., Medium-chain acyl-coenzyme A dehydrogenase deficiency (often shortened to MCADD.)

- Disorders of porphyrin metabolism

E.g., acute intermittent porphyria

- Disorders of purine or pyrimidine metabolism

E.g., Lesch-Nyhan syndrome

- Disorders of steroid metabolism

E.g., congenital adrenal hyperplasia

- Disorders of mitochondrial function

E.g., Kearns-Sayre syndrome

- Disorders of peroxisomal function

E.g., Zellweger syndrome

- Lysosomal storage disorders

E.g., Gaucher's disease

E.g., Niemann Pick disease

Disorders of carbohydrate metabolism :

Glycogen storage disease (GSD, also glycogenosis and dextrinosis):

- GSD has two classes of cause:
- Genetic
- Acquired

- Genetic GSD is caused by any inborn error of metabolism (genetically defective enzymes) involved in these processes.

- In livestock, acquired GSD is caused by intoxication with the alkaloid castanospermine.

Glycogen storage disease type I /von Gierke disease

- Glycogen storage disease type I (also known as GSDI or von Gierke disease) is an inherited disorder caused by the buildup of a complex sugar called glycogen in

the body's cells. The accumulation of glycogen in certain organs and tissues, especially the liver, kidneys, and small intestines, impairs their ability to function normally.

What genes are related to glycogen storage disease type I?

- Mutations in two genes cause GSDI
- G6PC (glucose-6-phosphatase, catalytic subunit)- mutations cause GSDIa
- The G6PC gene is located on the long (q) arm of chromosome 17 at position 21. (17q21)

2. SLC37A4 (solute carrier family 37 (glucose-6-phosphate transporter), member 4)- mutations cause GSDIb.(cytogenetic location 11q23.3)

- Normal function: The proteins produced from the G6PC and SLC37A4 genes work together to break down a type of sugar molecule called glucose 6-phosphate and produce the simple sugar glucose, which is the primary energy source for most cells in the body.
- Mutations: G6PC and SLC37A4 genes mutation prevent the effective breakdown of glucose 6-phosphate. Glucose 6-phosphate that is not broken down means then converted to glycogen and fat so it can be stored within cells. Too much glycogen and fat stored within a cell can be toxic. This buildup damages organs and tissues throughout the body, particularly the liver and kidneys, leading to the signs and symptoms of GSDI.
- 85 mutations in the G6PC gene have been found to cause glycogen storage disease type Ia (GSDIa).
- 80 mutations in the SLC37A4 gene have been found to cause glycogen storage disease type Ib (GSDIb)

GSD type II/ Pompe disease

- Pompe disease is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells.
- The accumulation of glycogen in certain organs and tissues, especially muscles, impairs their ability to function normally.
- Researchers have described three types of Pompe disease, which differ in severity and the age at which they appear.
- These types are known as
- classic infantile-onset,
- non-classic infantile-onset,
- late-onset.
- The classic form of infantile-onset Pompe disease begins within a few months of birth. Infants with this disorder typically experience muscle weakness (myopathy), poor muscle tone (hypotonia), an enlarged liver (hepatomegaly), and heart defects. Affected infants may also fail to gain weight and grow at the expected rate (failure to thrive) and have breathing problems. If untreated, this form of Pompe disease leads to death from heart failure in the first year of life.

- The non-classic form of infantile-onset Pompe disease usually appears by age 1.

It is characterized by delayed motor skills (such as rolling over and sitting) and progressive muscle weakness. The heart may be abnormally large (cardiomegaly), but affected individuals usually do not experience heart failure. The muscle weakness in this disorder leads to serious breathing problems, and most children with non-classic infantile-onset Pompe disease live only into early childhood.

- The late-onset type of Pompe disease may not become apparent until later in childhood, adolescence, or adulthood. Late-onset Pompe disease is usually milder than the infantile-onset forms of this disorder and is less likely to involve the heart. Most individuals with late-onset Pompe disease experience progressive muscle weakness, especially in the legs and the trunk, including the muscles that control breathing. As the disorder progresses, breathing problems can lead to respiratory failure.

What genes are related to Pompe disease?

- Mutations in the GAA gene cause Pompe disease.
- GAA gene-(glucosidase, alpha; acid)

Normal function of the GAA gene:

- The GAA gene provides instructions for producing an enzyme called acid alpha-glucosidase (also known as acid maltase). This enzyme is active in lysosomes, which are structures that serve as recycling centers within cells. Lysosomes use digestive enzymes to break down complex molecules into simpler ones that can be used by cells. Acid alpha-glucosidase normally breaks down a complex sugar called glycogen into a simpler sugar called glucose. Glucose is the main energy source for most cells.
- Mutations of GAA gene :
- Mutations in the GAA gene prevent acid alpha-glucosidase from breaking down glycogen effectively, which allows this sugar to build up to toxic levels in lysosomes. This buildup damages organs and tissues throughout the body, particularly the muscles, leading to the progressive signs and symptoms of Pompe disease.
- More than 200 mutations in the GAA gene have been identified in people with Pompe disease.
- Where is the GAA gene located?
- Cytogenetic Location: 17q25.2-q25.3

Glycogen storage disease type III/ Cori disease

- Glycogen storage disease type III (also known as GSDIII or Cori disease) is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulated glycogen is structurally abnormal and impairs the function of certain organs and tissues, especially the liver and muscles.

- GSDIII is divided into types IIIa, IIIb, IIIc, and IIId, which are distinguished by their pattern of signs and symptoms.
- GSD types IIIa and IIIc mainly affect the liver and muscles,
- GSD types IIIb and IIId typically affect only the liver.

- GSD types IIIa and IIIb are the most common forms of this condition.

- Beginning in infancy, individuals with any type of GSDIII may have low blood sugar (hypoglycemia), excess amounts of fats in the blood (hyperlipidemia), and elevated blood levels of liver enzymes. As they get older, children with this condition typically develop an enlarged liver (hepatomegaly). Liver size usually returns to normal during adolescence, but some affected individuals develop chronic liver disease (cirrhosis) and liver failure later in life. People with GSDIII often have slow growth because of their liver problems, which can lead to short stature. In a small percentage of people with GSDIII, noncancerous (benign) tumors called adenomas may form in the liver.

- Individuals with GSDIIIa may develop muscle weakness (myopathy) later in life. These muscle problems can affect both heart (cardiac) muscle and the muscles that are used for movement (skeletal muscles). Muscle involvement varies greatly among affected individuals. The first signs and symptoms are typically poor muscle tone (hypotonia) and mild myopathy in early childhood. The myopathy may become severe by early to mid-adulthood. Some people with GSDIIIa have a weakened heart muscle (cardiomyopathy), but affected individuals usually do not experience heart failure. Other people affected with GSDIIIa have no cardiac muscle problems.

What genes are related to glycogen storage disease type III?

Mutations in the AGL("amylo-alpha-1, 6-glucosidase, 4-alpha glucanotransferase") gene cause GSDIII.

What is the normal function of the AGL gene?

- The AGL gene provides instructions for making the glycogen debranching enzyme. This enzyme is involved in the breakdown of a complex sugar called glycogen, which is a major source of stored energy in the body. Glycogen is made up of several molecules of a simple sugar called glucose. Some glucose molecules are linked together in a straight line, while others branch off and form side chains. The glycogen debranching enzyme is involved in the breakdown of these side chains. The branched structure of glycogen makes it more compact for storage and allows it to break down more easily when it is needed for fuel.
- Mutations in the AGL gene cause GSDIII.
- Most AGL gene mutations lead to the production of a nonfunctional glycogen debranching enzyme.
- These mutations typically cause GSD types IIIa and IIIb.

- The mutations that cause GSD types IIIc and IIId are thought to lead to the production of an enzyme with reduced function.
- 100 mutations in the AGL gene have been found to cause glycogen storage disease type III (also called GSDIII or Cori disease)
- Cytogenetic Location: 1p21

glycogen storage disease type IV

- Glycogen storage disease type IV (GSD IV) is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulated glycogen is structurally abnormal and impairs the function of certain organs and tissues, especially the liver and muscles.

- There are five types of GSD IV, which are distinguished by their severity, signs, and symptoms.

- The fatal perinatal neuromuscular type is the most severe form of GSD IV, with signs developing before birth.
- Excess fluid may build up around the fetus (polyhydramnios) and in the fetus' body. Affected fetuses have a condition called fetal akinesia deformation sequence, which causes a decrease in fetal movement and can lead to joint stiffness (arthrogryposis) after birth. Infants with the fatal perinatal neuromuscular type of GSD IV have very low muscle tone (severe hypotonia) and muscle wasting (atrophy). These infants usually do not survive past the newborn period due to weakened heart and breathing muscles.

- The congenital muscular type of GSD IV is usually not evident before birth but develops in early infancy. Affected infants have severe hypotonia, which affects the muscles needed for breathing. These babies often have dilated cardiomyopathy, which enlarges and weakens the heart (cardiac) muscle, preventing the heart from pumping blood efficiently. Infants with the congenital muscular type of GSD IV typically survive only a few months.

- The progressive hepatic type is the most common form of GSD IV. Within the first months of life, affected infants have difficulty gaining weight and growing at the expected rate (failure to thrive) and develop an enlarged liver (hepatomegaly). Children with this type develop a form of liver disease called cirrhosis that often is irreversible. High blood pressure in the vein that supplies blood to the liver (portal hypertension) and an abnormal buildup of fluid in the abdominal cavity (ascites) can also occur. By age 1 or 2, affected children develop hypotonia. Children with the progressive hepatic type of GSD IV often die of liver failure in early childhood.

- The non-progressive hepatic type of GSD IV has many of the same features as the progressive hepatic type, but the liver disease is not as severe. In the non-progressive hepatic type, hepatomegaly and liver disease are usually evident in early childhood, but affected individuals typically do not develop cirrhosis. People with this type of the disorder can also have hypotonia and muscle weakness (myopathy). Most individuals with this type survive into adulthood, although life expectancy varies depending on the severity of the signs and symptoms.

- The childhood neuromuscular type of GSD IV develops in late childhood and is characterized by myopathy and dilated cardiomyopathy. The severity of this type of GSD IV varies greatly; some people have only mild muscle weakness while others have severe cardiomyopathy and die in early adulthood.

What genes are related to glycogen storage disease type IV?

Mutations in the GBE1("glucan (1,4-alpha-), branching enzyme 1") gene cause GSD IV.

Normal function of the GBE1 gene?

- The GBE1 gene provides instructions for making the glycogen branching enzyme. This enzyme is involved in the last step of the production of a complex sugar called glycogen, which is a major source of stored energy in the body. Glycogen is made up of many molecules of a simple sugar called glucose; some glucose molecules are linked together in a straight line, while others branch off the main line and form side chains. The glycogen branching enzyme is involved in the formation of these side chains. The branched structure of glycogen makes it more compact for storage and allows it to break down more easily when it is needed for fuel.

- Mutations in the GBE1 gene cause GSD IV. The GBE1 gene provides instructions for making the glycogen branching enzyme. This enzyme is involved in the production of glycogen, which is a major source of stored energy in the body. GBE1 gene mutations that cause GSD IV lead to a shortage (deficiency) of the glycogen branching enzyme. As a result, glycogen is not formed properly. Abnormal glycogen molecules called polyglucosan bodies accumulate in cells, leading to damage and cell death.

- Polyglucosan bodies accumulate in cells throughout the body, but liver cells and muscle cells are most severely affected in GSD IV. Glycogen accumulation in the liver leads to hepatomegaly and interferes with liver functioning. The inability of muscle cells to break down glycogen for energy leads to muscle weakness and wasting.
- 40 mutations in the GBE1 gene have been found to cause glycogen storage

disease type IV (GSD IV).

Glycogen storage disease type V /McArdle disease:

- Glycogen storage disease type V (also known as GSDV or McArdle disease) is an inherited disorder caused by an inability to break down a complex sugar called glycogen in muscle cells. A lack of glycogen breakdown interferes with the function of muscle cells.

- People with GSDV typically experience fatigue, muscle pain, and cramps during the first few minutes of exercise (exercise intolerance). Exercise such as weight lifting or jogging usually triggers these symptoms in affected individuals. The discomfort is generally alleviated with rest. If individuals rest after brief exercise and wait for their pain to go away, they can usually resume exercising with little or no discomfort (a characteristic phenomenon known as "second wind").

- Prolonged or intense exercise can cause muscle damage in people with GSDV. About half of people with GSDV experience breakdown of muscle tissue (rhabdomyolysis).

- In severe episodes, the destruction of muscle tissue releases a protein called myoglobin, which is filtered through the kidneys and released in the urine (myoglobinuria).
- Myoglobin causes the urine to be red or brown. This protein can also damage the kidneys, and it is estimated that half of those individuals with GSDV who have myoglobinuria will develop life-threatening kidney failure.

- The signs and symptoms of GSDV can vary significantly in affected individuals. The features of this condition typically begin in a person's teens or twenties, but they can appear anytime from infancy to adulthood. In most people with GSDV, the muscle weakness worsens over time; however, in about one-third of affected individuals, the muscle weakness is stable. Some people with GSDV experience mild symptoms such as poor stamina; others do not experience any symptoms.

What is the normal function of the PYGM gene?

- The PYGM(phosphorylase, glycogen, muscle) gene provides instructions for making an enzyme called myophosphorylase. This enzyme breaks down a complex sugar called glycogen. Myophosphorylase is found only in muscle cells, where it breaks down glycogen into a simpler sugar called glucose-1-phosphate. Additional steps convert glucose-1-phosphate into glucose, a simple sugar that is the main energy source for most cells.
- What genes are related to glycogen storage disease type V?
- Mutations in the PYGM gene cause GSDV.
- PYGM gene mutations prevent myophosphorylase from breaking down glycogen effectively. As a result, muscle cells cannot produce enough energy, so muscles

become easily fatigued. Reduced energy production in muscle cells leads to the major features of GSDV.

- Cytogenetic Location: 11q12-q13.2

Glycogen storage disease type

What is glycogen storage disease type VI?

- Glycogen storage disease type VI (also known as GSDVI or Hers disease) is an inherited disorder caused by an inability to break down a complex sugar called glycogen in liver cells. A lack of glycogen breakdown interferes with the normal function of the liver.
- The signs and symptoms of GSDVI typically begin in infancy to early childhood. The first sign is usually an enlarged liver (hepatomegaly). Affected individuals may also have low blood sugar (hypoglycemia) or a buildup of lactic acid in the body (lactic acidosis) during prolonged periods without food (fasting).

- The signs and symptoms of GSDVI tend to improve with age; most adults with this condition do not have any related health problems.

What genes are related to glycogen storage disease type VI?

Mutations in the PYGL("phosphorylase, glycogen, liver.")gene cause GSDVI

What is the normal function of the PYGL gene?

The PYGL gene provides instructions for making an enzyme called liver glycogen phosphorylase. This enzyme breaks down a complex sugar called glycogen. Liver glycogen phosphorylase is one of three related enzymes that break down glycogen in cells; the other glycogen phosphorylases are found in the brain and in muscles. Liver glycogen phosphorylase is found only in liver cells, where it breaks down glycogen into a type of sugar called glucose-1-phosphate. Additional steps convert glucose-1-phosphate into glucose, a simple sugar that is the main energy source for most cells in the body.

PYGL GENE MUTATION RELATED TO HEALTH CONDITIONS?

- At least 17 mutations in the PYGL gene have been found to cause glycogen storage disease type VI (GSDVI).

- Most mutations change single protein building blocks (amino acids) in liver glycogen phosphorylase, affecting the normal function of the enzyme.

- A defective liver glycogen phosphorylase enzyme impairs the normal breakdown of glycogen. As a result, liver cells cannot use glycogen for energy, so liver function becomes impaired. A lack of glycogen breakdown within liver cells leads to the major features of GSDVI.
- At least 17 mutations in the PYGL gene have been found to cause glycogen

storage disease type VI (GSDVI).

Glycogen Storage Disease Type VII

- Also known as muscle phosphofructokinase deficiency or Tarui disease.
- The clinical features of Type VII are similar to those of Type V with onset of more severe fatigue and muscle pain early in exercise. Symptoms are evident in childhood.
- Type VII is caused by a deficiency of the phosphofructokinase enzyme which is needed to facilitate the breakdown of glucose into energy in muscle during exercise.
- The body breaks down muscle (rhabdomyolysis) when trying to attain energy, which causes symptoms such as muscle pain, cramping, fatigue and tenderness. The red protein myoglobin is released and red-brown urine may be seen.

Glycogen Storage Disease Type VIII:

Type VIII - There used to be a GSD Type VIII but this is now classified as a sub type of Type VI.

Glycogen storage disease type IX:

- Glycogen storage disease type IX (also known as GSD IX) is a condition caused by the inability to break down a complex sugar called glycogen. The different forms of the condition can affect glycogen breakdown in liver cells or muscle cells or sometimes both. A lack of glycogen breakdown interferes with the normal function of the affected tissue.
- When GSD IX affects the liver, the signs and symptoms typically begin in early childhood.
- The initial features are usually an enlarged liver (hepatomegaly) and slow growth. Affected children are often shorter than normal. During prolonged periods without food (fasting), affected individuals may have low blood sugar (hypoglycemia) or elevated levels of ketones in the blood (ketosis). Ketones are molecules produced during the breakdown of fats, which occurs when stored sugars are unavailable.
- Affected children may have delayed development of motor skills, such as sitting, standing, or walking, and some have mild muscle weakness. Puberty is delayed in some adolescents with GSD IX.
- In the form of the condition that affects the liver, the signs and symptoms usually improve with age. Typically, individuals catch up developmentally, and adults reach normal height.

- However, some affected individuals have a buildup of scar tissue (fibrosis) in the liver, which can rarely progress to irreversible liver disease (cirrhosis).
- GSD IX can affect muscle tissue, although this form of the condition is very rare and not well understood. The features of this form of the condition can appear anytime from childhood to adulthood. Affected individuals may experience fatigue, muscle pain, and cramps, especially during exercise (exercise intolerance). Most affected individuals have muscle weakness that worsens over time.

- GSD IX can cause myoglobinuria, which occurs when muscle tissue breaks down abnormally and releases a protein called myoglobin that is excreted in the urine. Myoglobinuria can cause the urine to be red or brown.
- In a very small number of people with GSD IX, the liver and muscles are both affected. These individuals develop a combination of the features described above, although the muscle problems are usually mild.
- What genes are related to glycogen storage disease type IX?
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- Mutations in the PHKA1("phosphorylase kinase, alpha 1 (muscle)."), PHKA2("phosphorylase kinase, alpha 2 (liver)."), PHKB("phosphorylase kinase, beta."), or PHKG2("phosphorylase kinase, gamma 2 (testis).") genes are known to cause GSD IX.
- These genes provide instructions for making pieces (subunits) of an enzyme called phosphorylase b kinase. The enzyme is made up of 16 subunits, four each of the alpha, beta, gamma, and delta subunits. At least two different versions of phosphorylase b kinase are formed from the subunits: one is most abundant in liver cells and the other in muscle cells.
- The PHKA1 and PHKA2 genes provide instructions for making alpha subunits of phosphorylase b kinase. The protein produced from the PHKA1 gene is a subunit of the muscle enzyme, while the protein produced from the PHKA2 gene is part of the liver enzyme. The PHKB gene provides instructions for making the beta subunit, which is found in both the muscle and the liver. The PHKG2 gene provides instructions for making the gamma subunit of the liver enzyme.
- Whether in the liver or the muscles, phosphorylase b kinase plays an important role in providing energy for cells. The main source of cellular energy is a simple sugar called glucose. Glucose is stored in muscle and liver cells in a form called glycogen. Glycogen can be broken down rapidly when glucose is needed, for instance to maintain normal levels of glucose in the blood between meals or for energy during exercise. Phosphorylase b kinase turns on (activates) the enzyme that breaks down glycogen.
- Although the effects of gene mutations on the respective protein subunits are unknown, mutations in the PHKA1, PHKA2, PHKB, and PHKG2 genes reduce the activity of phosphorylase b kinase in liver or muscle cells and in blood cells.

Reduction of this enzyme's function impairs glycogen breakdown. As a result, glycogen accumulates in and damages cells, and glucose is not available for energy. Glycogen accumulation in the liver leads to hepatomegaly, and the liver's inability to break down glycogen for glucose contributes to hypoglycemia and ketosis. Reduced energy production in muscle cells leads to muscle weakness, pain, and cramping.

Glycogen storage disease type XI

- Glycogen storage disease type XI is a form of glycogen storage disease.
- It is also known as "Fanconi–Bickel syndrome", for Guido Fanconi and Horst Bickel.
- It is associated with GLUT2(Glucose transporter 2 (GLUT2)
- GLUT2 is a transmembrane carrier protein that enables protein facilitated glucose movement across cell membranes. It is the principal transporter for transfer of glucose between liver and blood, and for renal glucose reabsorption
- Glycogen storage disease type 0
- Glycogen storage disease type 0 (also known as GSD 0) is a condition caused by the body's inability to form a complex sugar called glycogen, which is a major source of stored energy in the body.

- GSD 0 has two types:
- in muscle GSD 0, glycogen formation in the muscles is impaired,
- in liver GSD 0, glycogen formation in the liver is impaired.

- The signs and symptoms of muscle GSD 0 typically begin in early childhood.

- Affected individuals often experience muscle pain and weakness or episodes of fainting (syncope) following moderate physical activity, such as walking up stairs. The loss of consciousness that occurs with fainting typically lasts up to several hours. Some individuals with muscle GSD 0 have a disruption of the heart's normal rhythm (arrhythmia) known as long QT syndrome.

- In all affected individuals, muscle GSD 0 impairs the heart's ability to effectively pump blood and increases the risk of cardiac arrest and sudden death, particularly after physical activity. Sudden death from cardiac arrest can occur in childhood or adolescence in people with muscle GSD 0.

- Individuals with liver GSD 0 usually show signs and symptoms of the disorder in infancy. People with this disorder develop low blood sugar (hypoglycemia) after going long periods of time without food (fasting). Signs of hypoglycemia become apparent when affected infants begin sleeping through the night and stop late-night feedings; these infants exhibit extreme tiredness (lethargy), pale skin (pallor), and nausea. During episodes of fasting, ketone levels in the blood may increase (ketosis). Ketones are molecules produced during the breakdown of fats,

which occurs when stored sugars (such as glycogen) are unavailable. These short-term signs and symptoms of liver GSD 0 often improve when food is eaten and sugar levels in the body return to normal. The features of liver GSD 0 vary; they can be mild and go unnoticed for years, or they can include developmental delay and growth failure.

What genes are related to glycogen storage disease type 0?

- Mutations in the GYS1("glycogen synthase 1 (muscle)) gene cause muscle GSD 0, and mutations in the GYS2("glycogen synthase 2 (liver). These genes provide instructions for making different versions of an enzyme called glycogen synthase.
- Both versions of glycogen synthase have the same function, to form glycogen molecules by linking together molecules of the simple sugar glucose, although they perform this function in different regions of the body.

- The GYS1 gene provides instructions for making muscle glycogen synthase; this form of the enzyme is produced in most cells, but it is especially abundant in heart (cardiac) muscle and the muscles used for movement (skeletal muscles). During cardiac muscle contractions or rapid or sustained movement of skeletal muscle, glycogen stored in muscle cells is broken down to supply the cells with energy.

- The GYS2 gene provides instructions for making liver glycogen synthase, which is produced solely in liver cells. Glycogen that is stored in the liver can be broken down rapidly when glucose is needed to maintain normal blood sugar levels between meals.

- Mutations in the GYS1 or GYS2("glycogen synthase 2 (liver)") gene lead to a lack of functional glycogen synthase, which prevents the production of glycogen from glucose.

- Mutations that cause GSD 0 result in a complete absence of glycogen in either liver or muscle cells. As a result, these cells do not have glycogen as a source of stored energy to draw upon following physical activity or fasting. This shortage of glycogen leads to the signs and symptoms of GSD 0.

Disorders of amino acid metabolism

- Phenylketonuria
- Maple syrup urine disease
- Glutaric acidemia type 1

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.

- The signs and symptoms of PKU vary from mild to severe.
- The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Untreated individuals may have a musty or mouse-like odor as a side effect of excess phenylalanine in the body. Children with classic PKU tend to have lighter skin and hair than unaffected family members and are also likely to have skin disorders such as eczema.

- Less severe forms of this condition, sometimes called variant PKU and non-PKU hyperphenylalaninemia, have a smaller risk of brain damage. People with very mild cases may not require treatment with a low-phenylalanine diet.

- Babies born to mothers with PKU and uncontrolled phenylalanine levels (women who no longer follow a low-phenylalanine diet) have a significant risk of intellectual disability because they are exposed to very high levels of phenylalanine before birth. These infants may also have a low birth weight and grow more slowly than other children.

- Other characteristic medical problems include heart defects or other heart problems, an abnormally small head size (microcephaly), and behavioral problems.

- Women with PKU and uncontrolled phenylalanine levels also have an increased risk of pregnancy loss.

What is the normal function of the PAH gene?

- The PAH gene provides instructions for making an enzyme called phenylalanine.

- 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 smaller molecules that are used to produce energy.

What genes are related to phenylketonuria?

- The PAH gene ("phenylalanine hydroxylase."),
- Mutations in the PAH gene cause phenylketonuria.
- The PAH gene provides instructions for making an enzyme called phenylalanine hydroxylase. This enzyme converts the amino acid phenylalanine to other tyrosine in the body. If gene mutations reduce the activity of phenylalanine hydroxylase, phenylalanine from the diet is not processed 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 hyperphenylalaninemia.
- Changes in other genes may influence the severity of PKU, but little is known about these additional genetic factors.

Maple syrup urine

What is maple syrup urine disease?

- Maple syrup urine disease is an inherited disorder in which the body is unable to process certain protein building blocks (amino acids) properly. The condition gets its name from the distinctive sweet odor of affected infants' urine.

- Beginning in early infancy, this condition is characterized by poor feeding, vomiting, lack of energy (lethargy), and developmental delay. If untreated, maple syrup urine disease can lead to seizures, coma, and death.

- Maple syrup urine disease is often classified by its pattern of signs and symptoms.
- The most common and severe form of the disease is the classic type, which becomes apparent soon after birth.

- Variant forms of the disorder become apparent later in infancy or childhood and are typically milder, but they still involve developmental delay and other medical problems if not treated.

What genes are related to maple syrup urine disease?

- BCKDHA -"branched chain keto acid dehydrogenase E1, alpha polypeptide."
- BCKDHB -"branched chain keto acid dehydrogenase E1, beta polypeptide."
- DBT -"dihydrolipoamide branched chain transacylase E2."
- DLD-"dihydrolipoamide dehydrogenase."

- Mutations in the BCKDHA, BCKDHB, DBT, and DLD genes can cause maple syrup urine disease. These four genes provide instructions for making proteins that work together as a complex called branched-chain alpha-keto acid dehydrogenase, or BCKD.
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- The protein complex is essential for breaking down the amino acids leucine, isoleucine, and valine, which are present in many kinds of food (particularly protein-rich foods such as milk, meat, and eggs).
- Mutations in any of these four genes reduce or eliminate the function of the protein complex, preventing the normal breakdown of leucine, isoleucine, and valine.

- As a result, these amino acids and their byproducts build up in the body. Because high levels of these substances are toxic to the brain and other organs, their accumulation leads to the serious medical problems associated with maple syrup urine disease.