Glutaric acidemia type I

What is glutaric acidemia type I?

- Glutaric acidemia type I is an inherited disorder in which the body is unable to process certain proteins properly.

- The severity of glutaric acidemia type I varies widely;
- some individuals are only mildly affected, while others have severe problems.

- In most cases, signs and symptoms first occur in infancy or early childhood, but in a small number of affected individuals, the disorder first becomes apparent in adolescence or adulthood.

- Some babies with glutaric acidemia type I are born with unusually large heads (macrocephaly). Affected individuals may have difficulty moving and may experience spasms, jerking, rigidity, or decreased muscle tone.

- Some individuals with glutaric acidemia have developed bleeding in the brain or eyes that could be mistaken for the effects of child abuse.

- Strict dietary control may help limit progression of the neurological damage.

Stress caused by infection, fever or other demands on the body may lead to worsening of the signs and symptoms, with only partial recovery.

- What genes are related to glutaric acidemia type I?

- Mutations in the GCDH("glutaryl-CoA dehydrogenase.") gene cause glutaric acidemia type I.

- The GCDH gene provides instructions for making the enzyme glutaryl-CoA dehydrogenase. This enzyme is involved in processing the amino acids lysine, hydroxylysine, and tryptophan.

- Mutations in the GCDH gene prevent production of the enzyme or result in the production of a defective enzyme that cannot function. This enzyme deficiency allows lysine, hydroxylysine and tryptophan and their intermediate breakdown products to build up to abnormal levels, especially at times when the body is under stress.

- The intermediate breakdown products resulting from incomplete processing of lysine, hydroxylysine, and tryptophan can damage the brain, particularly the basal ganglia, causing the signs and symptoms of glutaric acidemia type I.

Urea Cycle Disorder or Urea Cycle Defects

Carbamoyl phosphate synthetase I deficiency

- Carbamoyl phosphate synthetase I deficiency is an inherited disorder that causes ammonia to accumulate in the blood (hyperammonemia). Ammonia, which is formed when proteins are broken down in the body, is toxic if the levels become too high. The brain is especially sensitive to the effects of excess ammonia.

- In the first few days of life, infants with carbamoyl phosphate synthetase I deficiency typically exhibit the effects of hyperammonemia, which may include unusual sleepiness, poorly regulated breathing rate or body temperature, unwillingness to feed, vomiting after feeding, unusual body movements, seizures, or coma.

- Affected individuals who survive the newborn period may experience recurrence of these symptoms if diet is not carefully managed or if they experience infections or other stressors.
- They may also have delayed development and intellectual disability.
- In some people with carbamoyl phosphate synthetase I deficiency, signs and symptoms may be less severe and appear later in life.
- What genes are related to carbamoyl phosphate synthetase I deficiency?
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- Mutations in the CPS1(CPS1 gene cause carbamoyl phosphate synthetase I, mitochondrial.") gene cause carbamoyl phosphate synthetase I deficiency.

- The CPS1 gene provides instructions for making the enzyme carbamoyl phosphate synthetase I. This enzyme participates in the urea cycle, which is a sequence of biochemical reactions that occurs in liver cells.
- The urea cycle processes excess nitrogen, generated when protein is broken down by the body, to make a compound called urea that is excreted by the kidneys.

- The specific role of the carbamoyl phosphate synthetase I enzyme is to control the first step of the urea cycle, a reaction in which excess nitrogen compounds are incorporated into the cycle to be processed.

- Carbamoyl phosphate synthetase I deficiency belongs to a class of genetic diseases called urea cycle disorders. In this condition, the carbamoyl phosphate synthetase I enzyme is at low levels (deficient) or absent, and the urea cycle cannot proceed normally. As a result, nitrogen accumulates in the bloodstream in the form of toxic ammonia instead of being converted to less toxic urea and excreted.
- Ammonia is especially damaging to the brain, and excess ammonia causes neurological problems and other signs and symptoms of carbamoyl phosphate synthetase I deficiency.

Disorders of organic acid metabolism (organic acidurias)

Alcaptonuria

- Alkaptonuria is an inherited condition that causes urine to turn black when exposed to air. Ochronosis, a buildup of dark pigment in connective tissues such as cartilage and skin, is also characteristic of the disorder. This blue-black pigmentation usually appears after age 30. People with alkaptonuria typically develop arthritis, particularly in the spine and large joints, beginning in early adulthood. Other features of this condition can include heart problems, kidney stones, and prostate stones.

What genes are related to alkaptonuria?

- Mutations in the HGD("homogentisate 1,2-dioxygenase") gene cause alkaptonuria.
- The HGD gene provides instructions for making an enzyme called homogentisate oxidase.
- This enzyme helps break down the amino acids phenylalanine and tyrosine, which are important building blocks of proteins.
- Mutations in the HGD gene impair the enzyme's role in this process.\
- As a result, a substance called homogentisic acid, which is produced as phenylalanine and tyrosine are broken down, accumulates in the body.
- Excess homogentisic acid and related compounds are deposited in connective tissues, which causes cartilage and skin to darken.
- Over time, a buildup of this substance in the joints leads to arthritis.

Homogentisic acid is also excreted in urine, making the urine turn dark when exposed to air.

- More than 65 mutations in the HGD gene have been identified in people with alkaptonuria.

- Most of these mutations change single amino acids used to build the homogentisate oxidase enzyme.

- For example, a substitution of the amino acid valine for the amino acid methionine at protein position 368 (also written as Met368Val) is the most common HGD mutation in European populations.

Disorders of fatty acid oxidation and mitochondrial metabolism

Medium-chain acyl-coenzyme A dehydrogenase deficiency (often shortened to MCADD)

What is MCAD deficiency?

- Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a condition that prevents the body from converting certain fats to energy, particularly during periods without food (fasting).

- Signs and symptoms of MCAD deficiency typically appear during infancy or early childhood and can include vomiting, lack of energy (lethargy), and low blood sugar (hypoglycemia).

- In rare cases, symptoms of this disorder first appear during adulthood. People with MCAD deficiency are at risk for serious complications such as seizures, breathing difficulties, liver problems, brain damage, coma, and sudden death.

- Problems related to MCAD deficiency can be triggered by periods of fasting or by illnesses such as viral infections. This disorder is sometimes mistaken for Reye syndrome, a severe disorder that may develop in children while they appear to be recovering from viral infections such as chicken pox or flu. Most cases of Reye syndrome are associated with the use of aspirin during these viral infections.

Disorders of porphyrin metabolism

Eg:acute intermittent porphyria

- Porphyria is a group of disorders caused by abnormalities in the chemical steps that lead to heme production. Heme is a vital molecule for all of the body's organs, although it is most abundant in the blood, bone marrow, and liver. Heme is a component of several iron-containing proteins called hemoproteins, including hemoglobin (the protein that carries oxygen in the blood).

- Researchers have identified several types of porphyria, which are distinguished

by their genetic cause and their signs and symptoms.

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- Some types of porphyria, called cutaneous porphyrias, primarily affect the skin. Areas of skin exposed to the sun become fragile and blistered, which can lead to infection, scarring, changes in skin coloring (pigmentation), and increased hair growth. Cutaneous porphyrias include congenital erythropoietic porphyria, erythropoietic protoporphyria, hepatoerythropoietic porphyria, and porphyria cutanea tarda.

- Other types of porphyria, called acute porphyrias, primarily affect the nervous system. These disorders are described as "acute" because their signs and symptoms appear quickly and usually last a short time. Episodes of acute porphyria can cause abdominal pain, vomiting, constipation, and diarrhea. During an episode, a person may also experience muscle weakness, seizures, fever, and mental changes such as anxiety and hallucinations. These signs and symptoms can be life-threatening, especially if the muscles that control breathing become paralyzed. Acute porphyrias include acute intermittent porphyria and ALAD deficiency porphyria.
- Two other forms of porphyria, hereditary coproporphyria and variegate porphyria, can have both acute and cutaneous symptoms.
- The porphyrias can also be split into erythropoietic and hepatic types, depending on where damaging compounds called porphyrins and porphyrin precursors first build up in the body. In erythropoietic porphyrias, these compounds originate in the bone marrow. Erythropoietic porphyrias include erythropoietic protoporphyria and congenital erythropoietic porphyria. Health problems associated with erythropoietic porphyrias include a low number of red blood cells (anemia) and enlargement of the spleen (splenomegaly). The other types of porphyrias are considered hepatic porphyrias. In these disorders, porphyrins and porphyrin precursors originate primarily in the liver, leading to abnormal liver function and an increased risk of developing liver cancer.
- Environmental factors can strongly influence the occurrence and severity of signs and symptoms of porphyria. Alcohol, smoking, certain drugs, hormones, other illnesses, stress, and dieting or periods without food (fasting) can all trigger the signs and symptoms of some forms of the disorder. Additionally, exposure to sunlight worsens the skin damage in people with cutaneous porphyrias.
- What genes are related to porphyria?
- Each form of porphyria results from mutations in one of these genes:
- ALAD,
- ALAS2,
- CPOX,
- FECH,
- HMBS,
- PPOX,

- UROD, or UROS.

- The genes related to porphyria provide instructions for making the enzymes needed to produce heme. Mutations in most of these genes reduce enzyme activity, which limits the amount of heme the body can produce. As a result, compounds called porphyrins and porphyrin precursors, which are formed during the process of heme production, can build up abnormally in the liver and other organs. When these substances accumulate in the skin and interact with sunlight, they cause the cutaneous forms of porphyria. The acute forms of the disease occur when porphyrins and porphyrin precursors build up in and damage the nervous system.
- One type of porphyria, porphyria cutanea tarda, results from both genetic and nongenetic factors. About 20 percent of cases are related to mutations in the UROD gene. The remaining cases are not associated with UROD gene mutations and are classified as sporadic. Many factors contribute to the development of porphyria cutanea tarda. These include an increased amount of iron in the liver, alcohol consumption, smoking, hepatitis C or HIV infection, or certain hormones. Mutations in the HFE gene (which cause an iron overload disorder called hemochromatosis) are also associated with porphyria cutanea tarda. Other, as-yet-unidentified genetic factors may also play a role in this form of porphyria.

Disorders of purine or pyrimidine metabolism -E.g., Lesch-Nyhan syndrome

What is Lesch-Nyhan syndrome?

- Lesch-Nyhan syndrome is a condition that occurs almost exclusively in males. It is characterized by neurological and behavioral abnormalities and the overproduction of uric acid. Uric acid is a waste product of normal chemical processes and is found in blood and urine. Excess uric acid can be released from the blood and build up under the skin and cause gouty arthritis (arthritis caused by an accumulation of uric acid in the joints). Uric acid accumulation can also cause kidney and bladder stones.
- The nervous system and behavioral disturbances experienced by people with Lesch-Nyhan syndrome include abnormal involuntary muscle movements, such as tensing of various muscles (dystonia), jerking movements (chorea), and flailing of the limbs (ballismus). People with Lesch-Nyhan syndrome usually cannot walk, require assistance sitting, and generally use a wheelchair. Self-injury (including biting and head banging) is the most common and distinctive behavioral problem in individuals with Lesch-Nyhan syndrome.
- What genes are related to Lesch-Nyhan syndrome?
- Mutations in the HPRT1 gene cause Lesch-Nyhan syndrome. The HPRT1 gene provides instructions for making an enzyme called hypoxanthine phosphoribosyltransferase 1. This enzyme is responsible for recycling purines, a type of building block of DNA and its chemical cousin RNA. Recycling purines

ensures that cells have a plentiful supply of building blocks for the production of DNA and RNA.

- HPRT1 gene mutations that cause Lesch-Nyhan syndrome result in a severe shortage (deficiency) or complete absence of hypoxanthine phosphoribosyltransferase 1. When this enzyme is lacking, purines are broken down but not recycled, producing abnormally high levels of uric acid. For unknown reasons, a deficiency of hypoxanthine phosphoribosyltransferase 1 is associated with low levels of a chemical messenger in the brain called dopamine. Dopamine transmits messages that help the brain control physical movement and emotional behavior, and its shortage may play a role in the movement problems and other features of this disorder. However, it is unclear how a shortage of hypoxanthine phosphoribosyltransferase 1 causes the neurological and behavioral problems characteristic of Lesch-Nyhan syndrome.
- Some people with HPRT1 gene mutations produce some functional enzyme. These individuals are said to have Lesch-Nyhan variant. The signs and symptoms of Lesch-Nyhan variant are often milder than those of Lesch-Nyhan syndrome and do not include self-injury.

Disorders of steroid metabolism

E.g., lipoid congenital adrenal hyperplasia, congenital adrenal hyperplasia

- Congenital adrenal hyperplasia (CAH) due to 11-beta-hydroxylase deficiency is one of a group of disorders (collectively called congenital adrenal hyperplasia) that affect the adrenal glands. The adrenal glands are located on top of the kidneys and produce a variety of hormones that regulate many essential functions in the body. In people with CAH due to 11-beta-hydroxylase deficiency, the adrenal glands produce excess androgens, which are male sex hormones.
- There are two types of CAH due to 11-beta-hydroxylase deficiency, the classic form and the non-classic form. The classic form is the more severe of the two types.
- Females with the classic form of CAH due to 11-beta-hydroxylase deficiency have external genitalia that do not look clearly male or female (ambiguous genitalia). However, the internal reproductive organs develop normally. Males and females with the classic form of this condition have early development of their secondary sexual characteristics such as growth of facial and pubic hair, deepening of the voice, appearance of acne, and onset of a growth spurt. The early growth spurt can prevent growth later in adolescence and lead to short stature in adulthood. In addition, approximately two-thirds of individuals with the classic form of CAH due to 11-beta-hydroxylase deficiency have high blood pressure (hypertension). Hypertension typically develops within the first year of life.
- Females with the non-classic form of CAH due to 11-beta-hydroxylase deficiency have normal female genitalia. As affected females get older, they may develop excessive body hair growth (hirsutism) and irregular menstruation. Males with the non-classic form of this condition do not typically have any signs or

symptoms except for short stature. Hypertension is not a feature of the non-classic form of CAH due to 11-beta-hydroxylase deficiency.

- What genes are related to congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency?
- Mutations in the CYP11B1 gene cause CAH due to 11-beta-hydroxylase deficiency. The CYP11B1 gene provides instructions for making an enzyme called 11-beta-hydroxylase. This enzyme is found in the adrenal glands, where it helps produce hormones called cortisol and corticosterone. Cortisol has numerous functions, such as maintaining blood sugar levels, protecting the body from stress, and suppressing inflammation. Corticosterone gets converted to the hormone aldosterone, which helps control blood pressure by maintaining proper salt and fluid levels in the body.
- CAH due to 11-beta-hydroxylase deficiency is caused by a shortage (deficiency) of the 11-beta-hydroxylase enzyme. When 11-beta-hydroxylase is lacking, precursors that are used to form cortisol and corticosterone build up in the adrenal glands and are converted to androgens. The excess production of androgens leads to abnormalities of sexual development, particularly in females with CAH due to 11-beta-hydroxylase deficiency. A buildup in the precursors used to form corticosterone increases salt retention, leading to hypertension in individuals with the classic form of CAH due to 11-beta-hydroxylase deficiency.
- The amount of functional 11-beta-hydroxylase enzyme that an individual produces typically determines the extent of abnormal sexual development. Individuals with the classic form of the condition usually have CYP11B1 gene mutations that result in the production of an enzyme with low levels of function or no function at all. Individuals with the non-classic form of the condition typically have CYP11B1 gene mutations that lead to the production of an enzyme with moderately reduced function. The severity of the signs and symptoms of sexual development do not appear to be related to the severity of the hypertension.