

CITRIN DEFICIENCY

Citrin deficiency or citrulinemia type II is an inherited metabolic disease caused by **mutations in the SLC25A13 gene** encoding **mitochondrial transporter citrin**. It causes a different clinical presentation regarding to age, from **neonatal cholestasis** (impaired liver function) to **citrullinemia** (elevated levels of citrulline in blood) in adults.

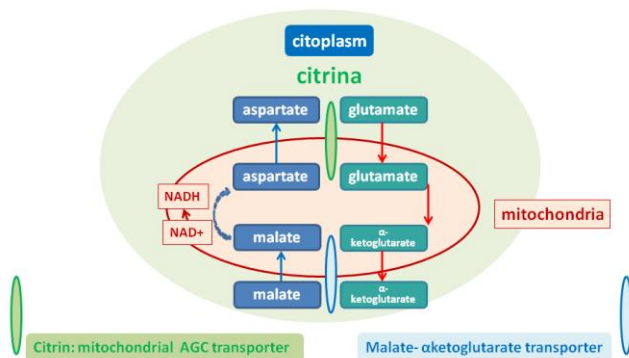
Citrin deficiency was initially described only in individuals of East Asia but in recent years some patients in America and Europe have been reported, so it can be considered a pan-ethnic distribution disease, although it is much more common in Asia.

WHAT IS CITRIN?

Citrin is the isoform 2 (different forms of the same protein) **liver mitochondrial aspartate/glutamate transporter (AGC2)**. Citrin is involved in important metabolic functions:

Citrina

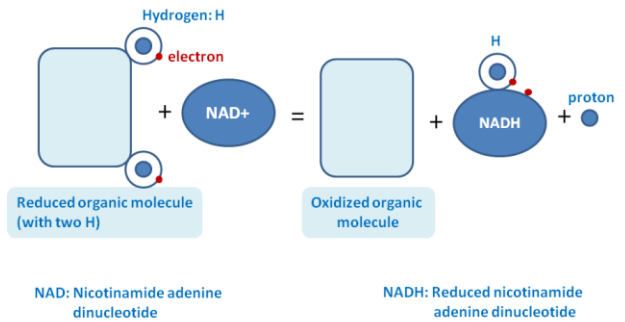
Mitochondrial aspartate/glutamate transporter (AGC)



- The **transfer of reducing equivalents** to the mitochondria for **energy generation as ATP** by oxidative phosphorylation.
- The maintenance of a balanced redox (oxidation/reduction) cytosolic and mitochondrial NADH/ NAD relationship.
- The **gluconeogenesis** or glucose generation from 3-carbon precursors such as lactate, pyruvate and gluconic amino acids.
- The **urea cycle**, providing **aspartate** to form argininsuccinate.

Oxidation of an organic molecule

What role do play NAD/NADH?



WHAT ARE THE METABOLIC CONSEQUENCES OF CITRIN DEFICIENCY?

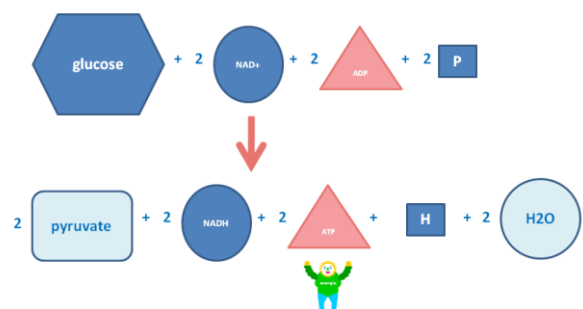
Given the metabolic importance of citrin, its deficiency interferes in important metabolic functions: glycolysis, gluconeogenesis, urea cycle, the metabolism of galactose and NAD / NADH nucleotides.

WHY DOES CITRIN DEFICIENCY INTERFERE IN GLYCOLYSIS?

Glycolysis (breakdown of glucose sugar) is responsible for **oxidizing glucose** in order to produce energy (as ATP) for the cell.

Citrin deficiency may cause the glycolysis impairment due to an increase in the cytosolic NADH/NAD relationship, leading to a shortage of energy in the liver (see figure).

Glycolysis

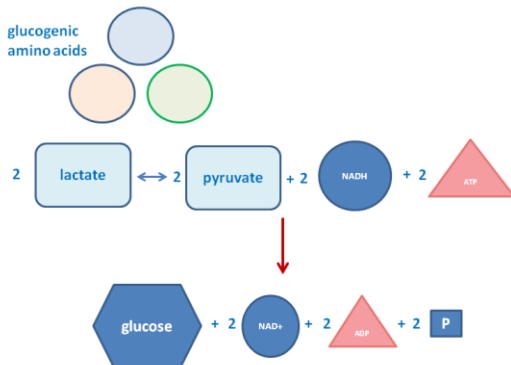


Glucose is broken down (glycolysis) generating energy as ATP.

WHY DOES CITRIN DEFICIENCY INTERFERE IN GLUCONEOGENESIS?

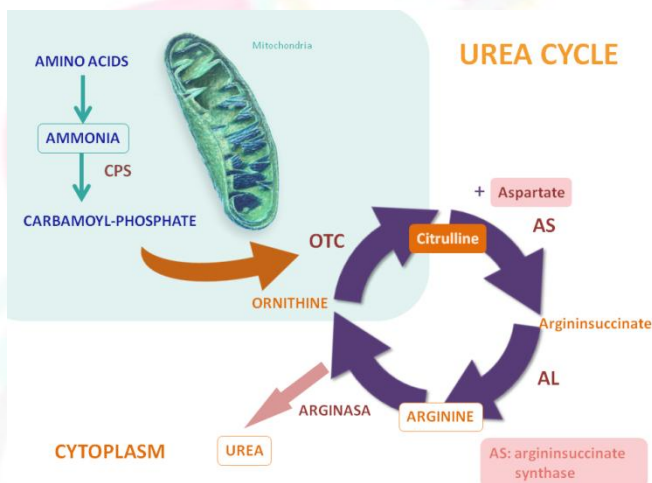
Glucose production from lactate, pyruvate and glucogenic amino acids occurs in the liver and requires NADH and energy as ATP. Therefore, citrin defect causes **impaired gluconeogenesis**.

Gluconeogenesis



WHY DOES CITRIN DEFICIENCY INTERFERE IN UREA CYCLE?

Urea cycle is the set of reactions leading to remove **ammonium as urea**. Ammonium comes from the metabolism of proteins and is neurotoxic.



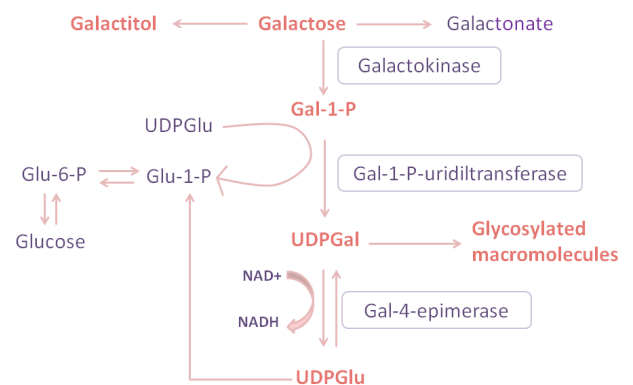
In the first reaction of the urea cycle that occurs in the cytoplasm, **aspartate** binds **citrulline** by means of the argininsuccinate synthase enzyme to form argininsuccinic acid, which continues the cycle to finally produce **urea**. If the cytosolic aspartate is scarce because the carrier protein (citrin) that leads it out of the mitochondria is deficient, this reaction is inefficient and citrulline accumulates, causing hyperammonemia by poor function of the urea cycle. This accumulation of

citrulline gives the name to the adult form of the disease: **type II citrullinemia**.

WHY DOES CITRIN DEFICIENCY INTERFERE IN GALACTOSE METABOLISM?

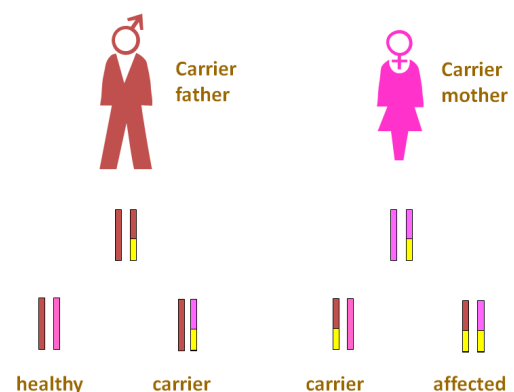
One galactose molecule generates one of NADH in the step of UDP-galactose to UDP-glucose by the liver enzyme epimerase, and then UDP-glucose enters the glycolytic pathway. If the NAD/NADH ratio is altered due to citrin deficiency, galactose is not effectively metabolised and accumulates in blood and urine, and causing **galactosuria and galactosemia**, respectively.

Galactose metabolism



WHY DOES CITRIN DEFICIENCY OCCUR?

Autosomal recessive inheritance



Citrin deficiency occurs due to **mutations** (stable and heritable changes) in the **SLC25A13** gene encoding the transporter protein **AGC2**.

Citrin deficiency is transmitted with an **autosomal recessive inheritance**, ie, both parents are carriers of a mutation in the **SLC25A13** gene, although they do not suffer any clinical sign for it. If both parents pass the

child a mutant allele of this gene, the child will suffer a citrin deficiency.

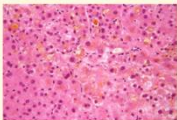
WHICH ARE THE CLINICAL FEATURES OF CITRIN DEFICIENCY?

Two major phenotypes (set of clinical features) in citrin deficiency have been described:

- "Neonatal intrahepatic cholestasis caused by citrin deficiency" (NICCD) and
- "Adult onset citrullinemia type II" (CTLN2).

However, lately a few patients with clinical presentation characterized by "**delayed development and dyslipemia caused by citrin deficiency**" (FTDCCD) have been reported, appearing subsequently to the NICCD form and preceding the adult CTLN2 form.

Clinical symptoms of citrin deficiency

NICCD type	Neonatal hepatic cholestasis	
FTDCCD type	Hypoglycemia	Growth retardation
CTLN2 type	Aggressiveness	Delirium

NICCD: It occurs in children under one year of age with growth retardation and intrahepatic cholestasis, hepatomegaly, diffuse fatty liver and parenchymal cell infiltration associated with hepatic fibrosis, variable hepatic dysfunction, hypoproteinemia, decreased clotting factors, hemolytic anemia and/or hypoglycemia. Equinocitosis (red blood cells with short spicules evenly distributed over the entire surface) is present in a group of children with more severe biochemical alterations. Although NICCD form is usually not severe and the symptoms are generally resolved by the first year of age with proper treatment, may even be fatal in some children due to infection and liver cirrhosis and some of them may need a liver transplant.

FTDCCD: Appears around one to two years of age in children with citrin deficiency showing preference for protein-rich and/or lipid-rich foods and aversion to carbohydrate-rich foods. Some children have growth retardation, hypoglycemia and fatigue as well as hyperlipidemia, pancreatitis, fatty liver and hepatoma.

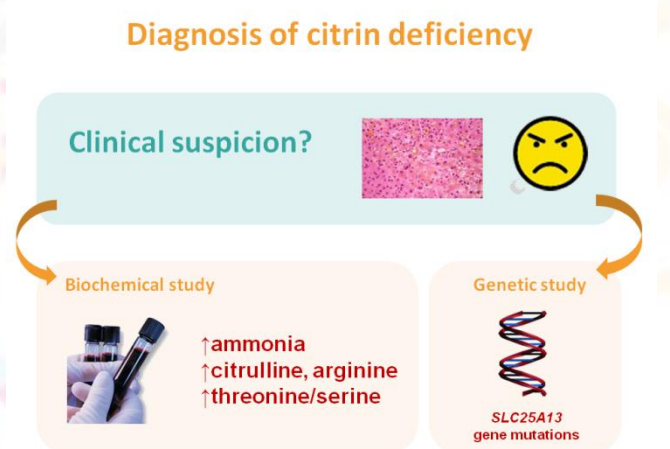
One or several decades later, some individuals develop NICCD or FTTDCD CTLN2.

CTLN2: The onset is sudden, usually from adolescence to adulthood. Manifestations include recurrent hyperammonemia with neuropsychiatric symptoms including delirium, aggressiveness, irritability, hyperactivity, disorientation, agitation, drowsiness, memory loss, tremors, convulsions, and coma; in some cases cerebral edema can lead to death. The symptoms are often caused by triggers such as alcohol and sugar intake, medication and/or surgery. Affected individuals may or may not have a previous history of NICCD or FTTDCD.

HOW IS CITRIN DEFICIENCY DIAGNOSED?

The diagnosis is based on clinical and biochemical suspicion. The biochemical analysis shows hyperammonemia, altered blood profile of amino acids with increased concentration of citrulline and arginine as well as threonine/serine ratio.

The diagnosis is confirmed by mutational study of the **SLC25A13 gene**, allowing genetic counseling.



IS THERE A TREATMENT FOR CITRIN DEFICIENCY?

The treatment is somewhat different depending on the age of onset of the disease.

In NICCD, a diet supplemented with vitamins and lactose-free formula (in children with increased excretion of galactose) supplemented with medium chain triglycerides (MCT) is administered. The restriction of lactose reduces galactosemia/uria and MCT administration improves cholestasis. Indeed, the pathophysiology of citrin deficiency seems to be an energy defect in the liver due to altered glycolysis. The

MCT rapidly hydrolyzes and absorbs as free medium-chain fatty acids.

In **FTTDCD**, in addition of dietary treatment, the administration of sodium pyruvate can improve growth.

In **CTLN2**, liver transplantation prevents the hyperammonemia crisis, corrects the metabolic abnormalities, and eliminates the preference for protein-rich foods; arginine decreases the concentration of ammonia in the blood and reduces hypertriglyceridemia by a yet unidentified mechanism. Arginine and sodium pyruvate can effectively treat hyperammonemia and fatty liver, thus delaying the need for a liver transplant.

Translation

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Treatment of citrin deficiency

NICCD type	Lactose-free supplemented with MCT	
FTTDCD type	Protein-rich Lactose-free diet MCT Sodium pyruvate	
CTLN2 type	Protein-rich Lactose-free diet MCT Liver transplantation	

Citrin deficiency is a metabolic disease that can have serious consequences in some patients. Early diagnosis and treatment can improve the quality of life of individuals with the disease.