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Iranian Society of Pediatricians

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# Ammonia

- Ammonia (NH<sub>3</sub>) is a small metabolite that results predominantly from protein and amino acid degradation. It is highly membrane-permeant and readily crosses epithelial barriers in its nonionized form.

## Ammonia(NH3) vs Ammonium(NH4+)

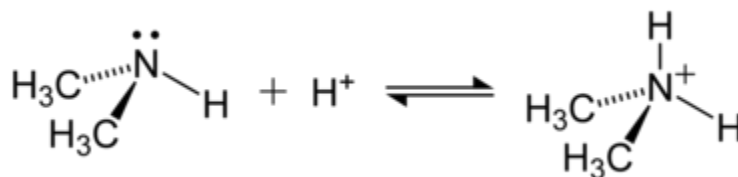
Ammonia is un-ionized, and has the formula NH<sub>3</sub>. Ammonium is ionized, and has the formula NH<sub>4</sub><sup>+</sup>.

The major factor that determines the proportion of ammonia or ammonium in water is water pH.

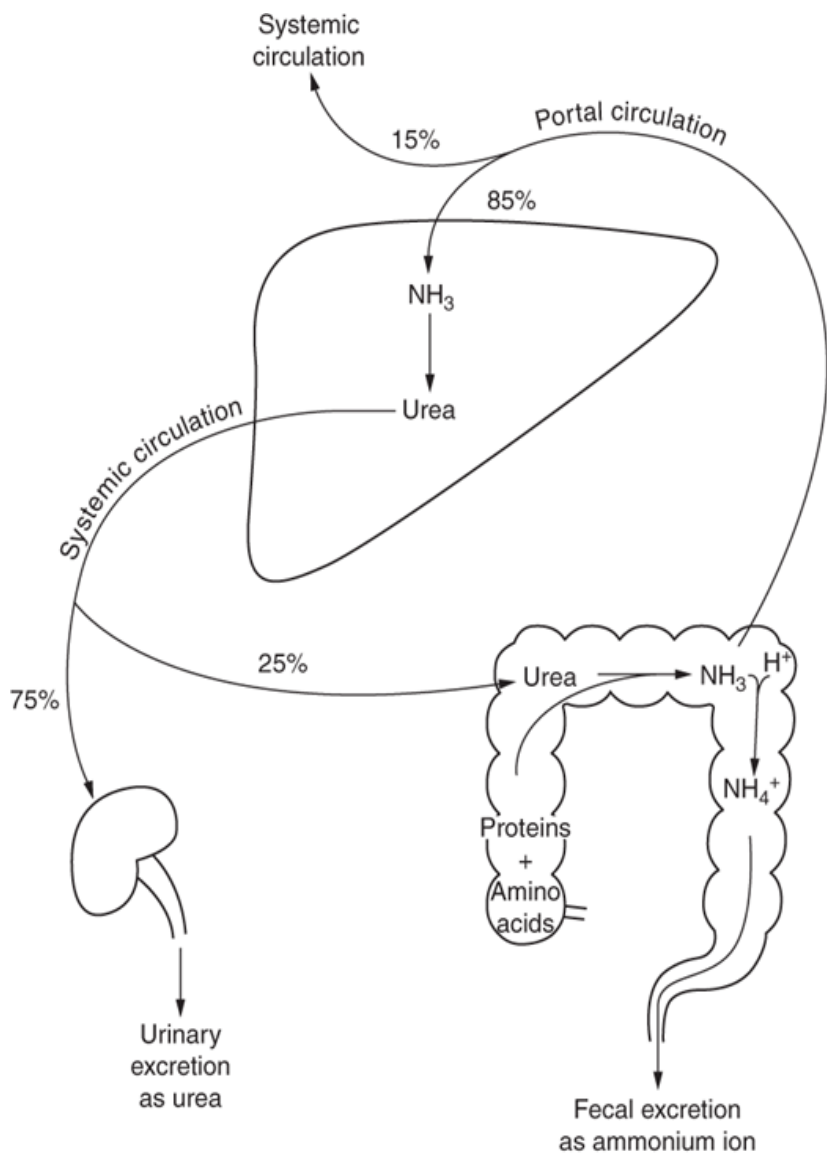
The activity of ammonia also is influenced by temperature and ionic strength. This is important as the unionized NH<sub>3</sub> is the form that can be toxic to aquatic organisms.

The ionized NH<sub>4</sub> is basically harmless to aquatic organisms.

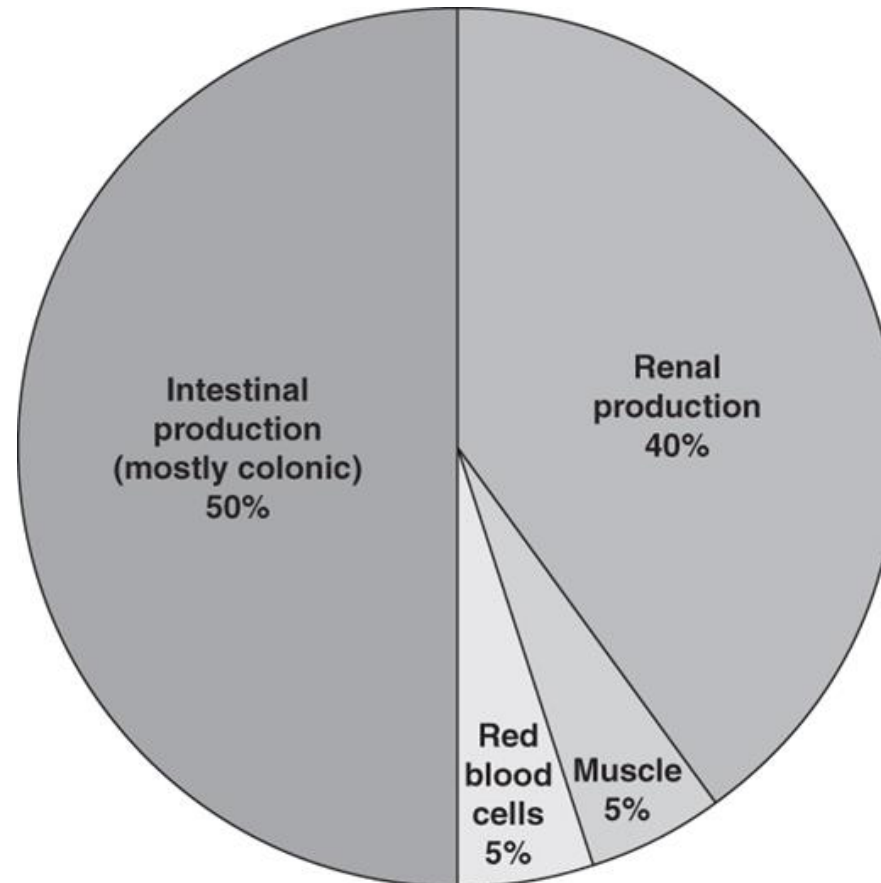
The chemical equation that drives the relationship between ammonia and ammonium is:



- Ammonia is produced primarily from breakdown of amino acids in various cells of the body (“endogenous” ammonia or  $\text{NH}_3$ ).
- The ammonia is taken up by hepatocytes and converted, in the urea cycle, to urea, which is then exported into blood. Urea is primarily excreted in the kidneys (75%, and is a marker of glomerula filtration rate) and the intestine (around 25%). Once in the intestinal system, urea is broken down by bacteria (rumen in ruminants, colon in other species) forming ammonia, which is then absorbed into the portal circulation. The liver efficiently extracts (85%) of the ammonia from portal blood, leaving only 15% to enter the systemic circulation. Bacterial metabolism of other proteins (e.g. soybean meal in cattle), also produces ammonia from “exogenous” sources. Defects in hepatic function, portal blood flow and urea cycle enzymes or intermediates can result in hyperammonemia, as can excess production of ammonia in the gastrointestinal tract.



Ammonia in the circulation originates in a number of different sites. A diagram showing the major contributors to ammonia levels is shown in

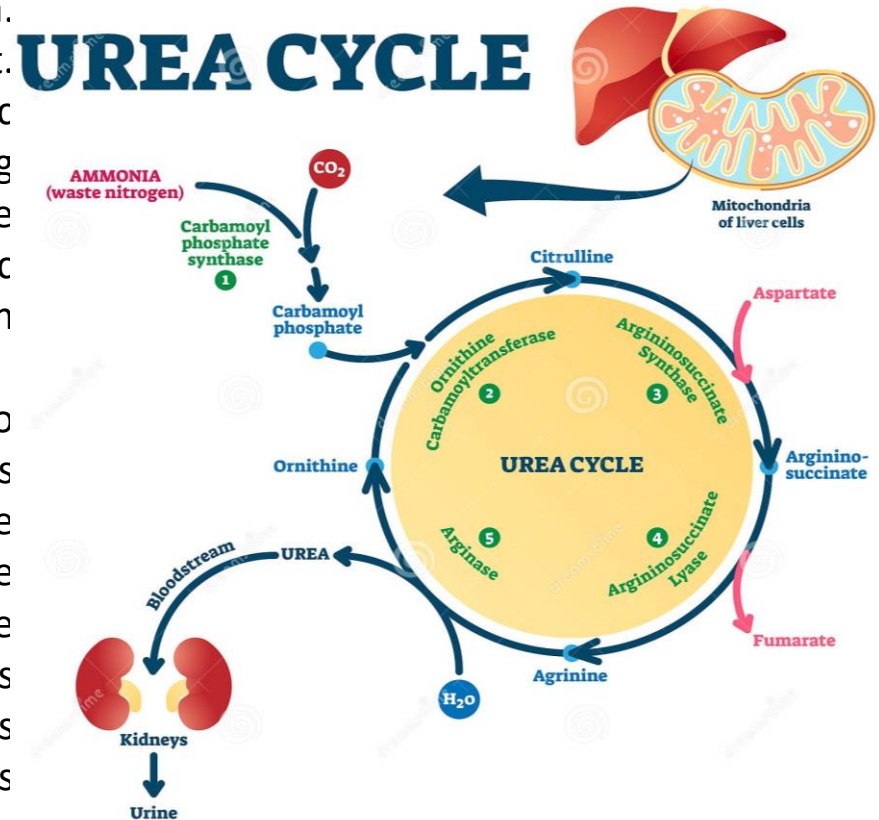


Source: Barrett KE: *Gastrointestinal Physiology, Second Edition*:  
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# Urea cycle

Amino acid catabolism results in waste ammonia. All animals need a way to excrete this product. Most aquatic organisms, or ammonotelic organisms, excrete ammonia without converting it. Organisms that cannot easily and safely remove nitrogen as ammonia convert it to a less toxic substance such as urea via the urea cycle, which occurs mainly in the liver.

Urea produced by the liver is then released into the bloodstream where it travels to the kidneys and is ultimately excreted in urine. The urea cycle is essential to these organisms, because if the nitrogen or ammonia are not eliminated from the organism it can be very detrimental. In species including birds and most insects, the ammonia is converted into uric acid or its urate salt, which is excreted in solid form.



**Urea cycle disorders (UCDs)** result from inherited deficiencies in any one of the six enzymes or two transporters of the urea cycle pathway (CPS1, OTC, ASS1, ASL, ARG1, NAGS, ORNT1, or citrin):

**Five catalytic enzymes:**

- Carbamoyl phosphate synthetase I deficiency (CPS1 deficiency)
- Ornithine transcarbamylase deficiency (OTC deficiency)
- Citrullinemia type I (Argininosuccinic acid synthetase (ASS1) deficiency).
- Argininosuccinic aciduria (Argininosuccinic acid lyase (ASL) deficiency)
- Hyperargininemia (Arginase deficiency)

**One cofactor-producing enzyme:**

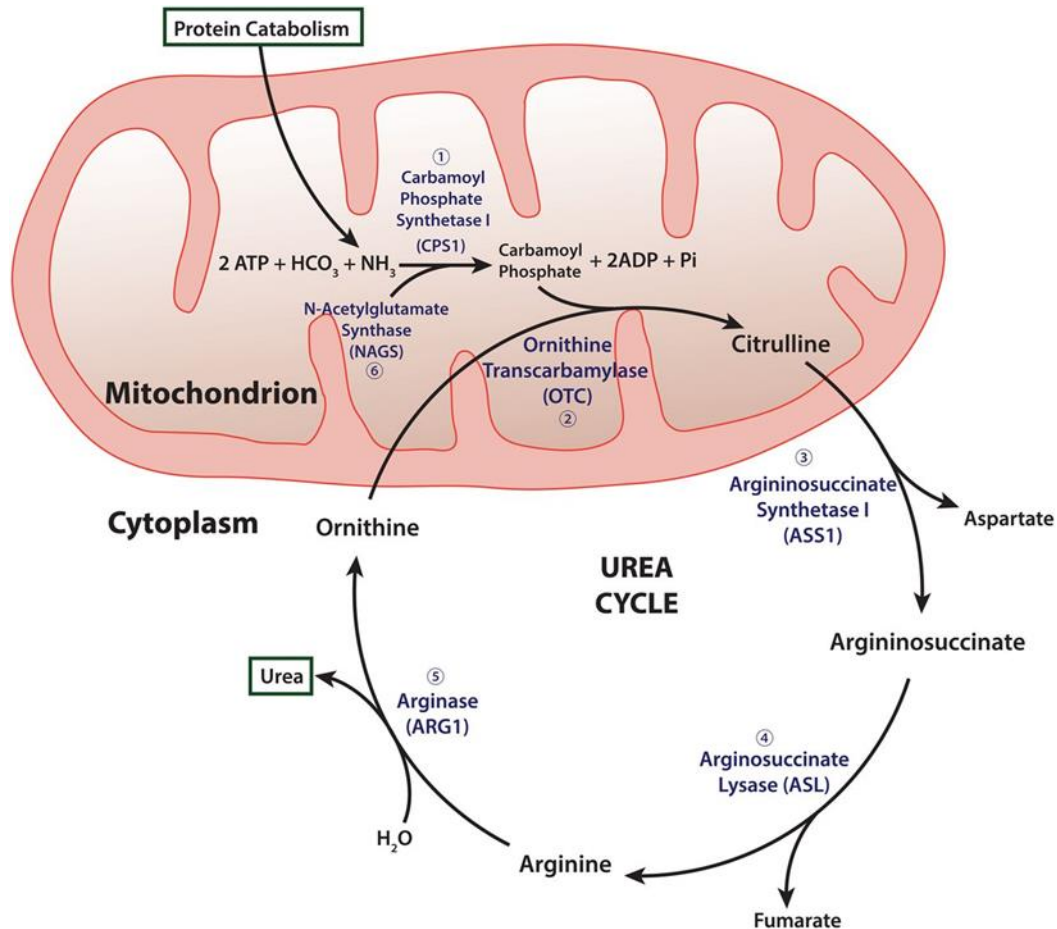
- N-acetylglutamate synthase deficiency (NAGS deficiency)

**Two amino acid transporters:**

- Ornithine translocase deficiency (ORNT1 deficiency, hyperornithinemia - hyperammonemia-homocitrullinuria syndrome)
- Citrullinemia type II (Citrin deficiency)

# Urea cycle disorders

## Carbamoyl phosphate synthetase I deficiency (CPS1 deficiency)

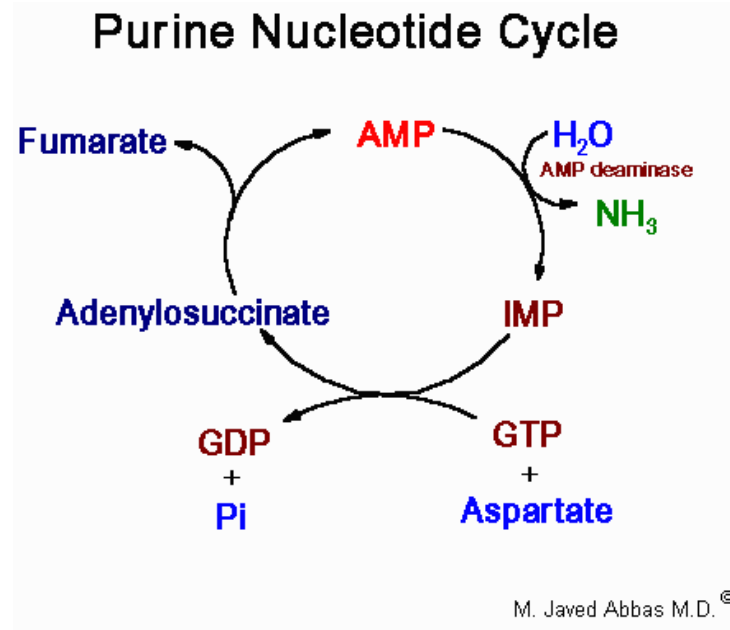


# Ammonia Generation

- Ammonia is generated by amino acids obtained from the diet, from catabolism of glutamine by enterocytes, or from peripheral tissues such as skeletal muscle.
- In mammals, at least 20 metabolic reactions generate ammonia, with the glutaminase, glutamate dehydrogenase, and purine nucleotide cycle pathways producing most of the ammonia!
- Additionally, urea diffuses into the gastrointestinal tract and may be degraded to ammonia by urease-producing microorganisms, recycling approximately 25% of synthesized urea.
- Dietary glutamine is an important metabolic “fuel” for enterocytes. The **catabolism of glutamine** (via glutaminase) by enterocytes produces energy and releases large amounts of ammonia that is then carried to the liver via the portal vein.

# Ammonia Generation

- During vigorous exercise, **skeletal muscle** may produce significant amounts of ammonia, which is detoxified by glutamine synthesis in other peripheral tissues.
- The primary source of ammonia in exercised muscle is the **purine nucleotide cycle**, which releases energy through the conversion of adenine monophosphate (AMP) to inosine monophosphate (IMP). Ammonia production by **skeletal muscle** during exercise contrasts to ammonia metabolism in resting muscle, when myocytes synthesize glutamine from circulating ammonia.



# Urea cycle disorders

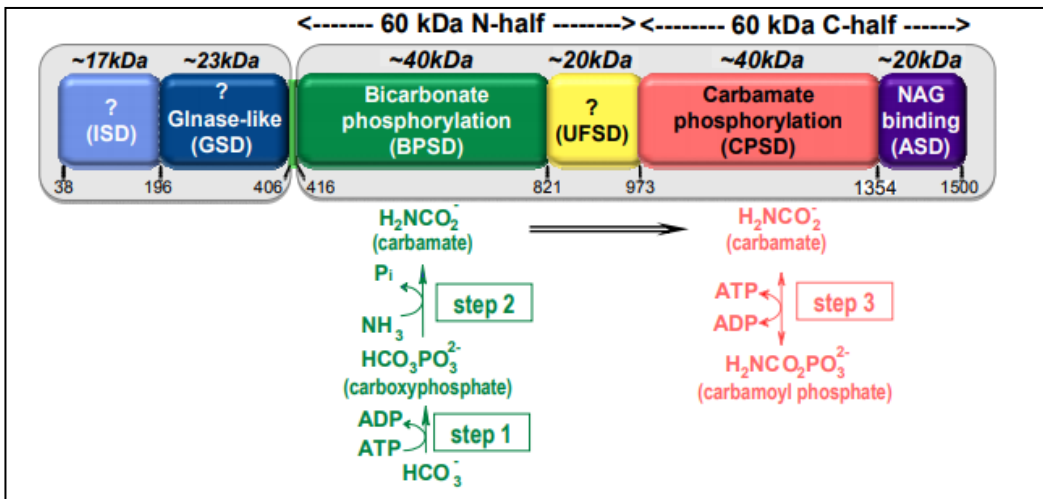
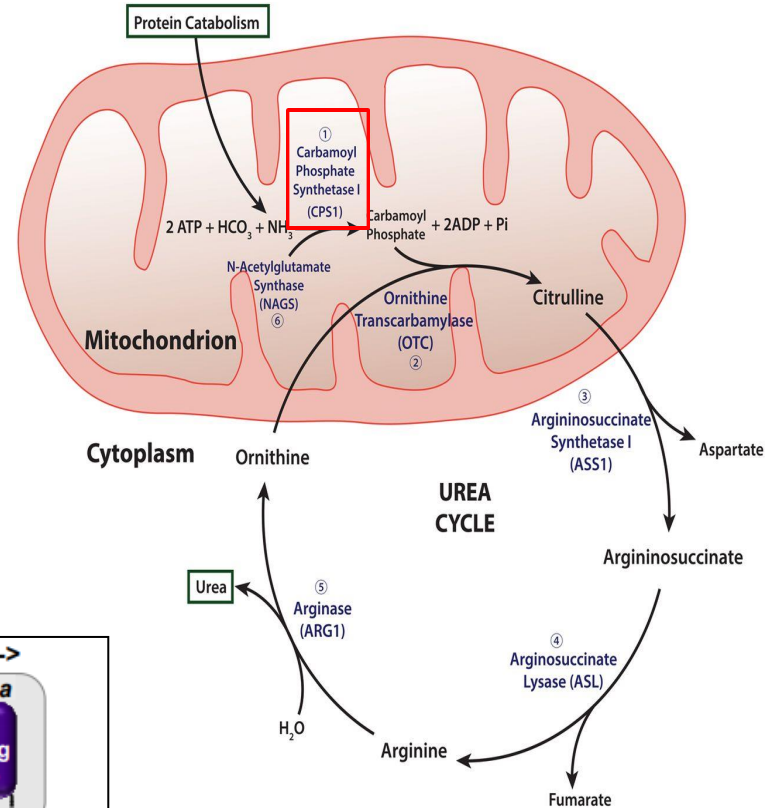
## Carbamoyl phosphate synthetase I deficiency (CPS1 deficiency)

### Causes:

**CPSI** is inherited as an autosomal recessive genetic disorder and is caused by **mutations in the CPSI gene**. Mutations in the CPSI gene result in production of an abnormal carbamoyl phosphate synthetase enzyme.

### Affected Populations:

The estimated frequency of CPSID is **1 in 150-200,000 births**.



Linear scheme of multidomain organization and reaction steps of mature human CPS1.

# Urea cycle disorders

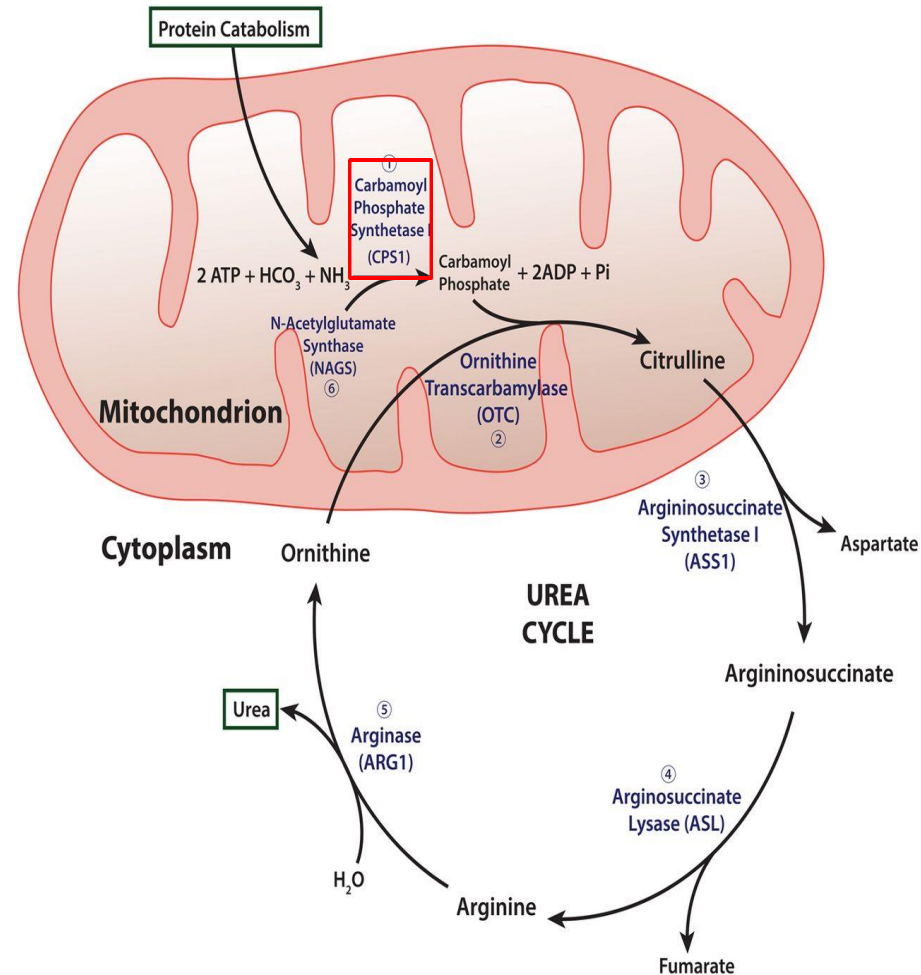
## Carbamoyl phosphate synthetase I deficiency (CPS1 deficiency)

### Symptoms:

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.



# Urea cycle disorders

## Carbamoyl phosphate synthetase I deficiency (CPS1 deficiency)

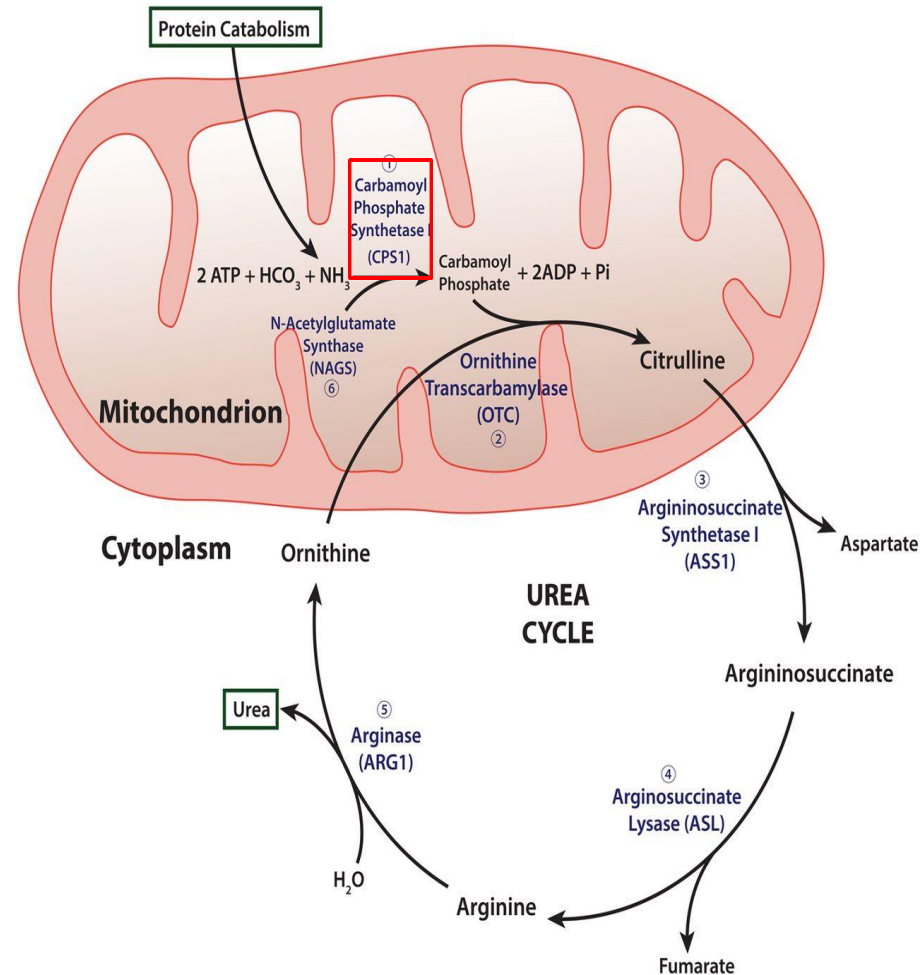
### Diagnosis:

A diagnosis of a urea cycle disorder, such as CPSID, should be considered in any newborn who has an undiagnosed illness characterized by **vomiting**, **progressive lethargy**, and **irritability**.

**Blood tests** may reveal excessive amounts of **ammonia** in the blood, which is the main criterion for a diagnosis of urea cycle disorders including CPSID.

**Genetic sequencing** of the CPS1 gene is the main form of diagnosis at this time (typically combined with sequence of the other urea cycle enzymes).

**Measurement of CPSID1 enzyme activity** on cells obtained from a liver biopsy can confirm the diagnosis but is rarely employed currently.



# Urea cycle disorders

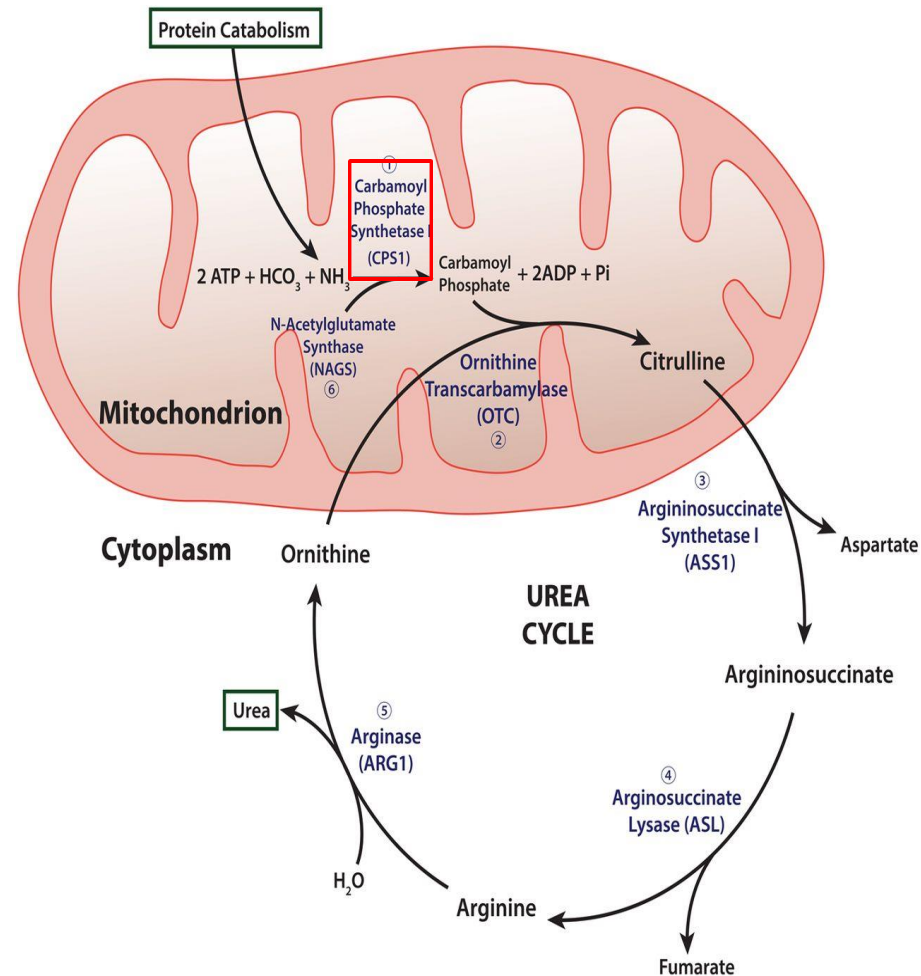
## Carbamoyl phosphate synthetase I deficiency (CPS1 deficiency)

**Treatment** is very complex and is based on reducing plasma ammonia concentration, preventing excess ammonia from being formed, and reducing the amount of nitrogen in the diet while supplying enough for growth.

Treatment may also include **Citrulline** or **Arginine**, to maintain a normal rate of protein formation (synthesis).

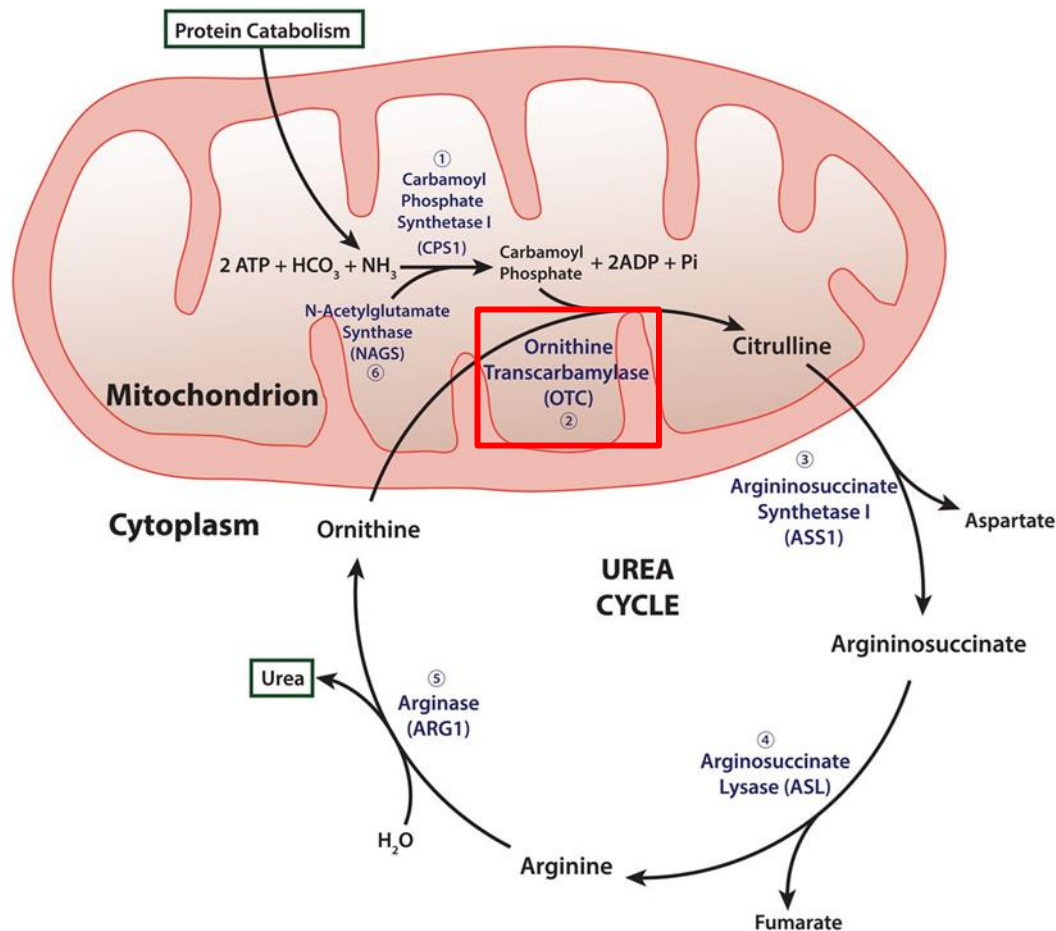
In many centers **liver transplantation** is offered as a more permanent solution to severe CPSID. Seizures are treated with phenobarbital or carbamazepine.

Valproic acid and intravenous steroids should be avoided, as it can increase blood ammonia levels. steroid compounds like **Prednisone** should also be avoided because they will trigger a protein catabolic state and hyperammonemia.



# Urea cycle disorders

## Ornithine transcarbamylase deficiency (OTC deficiency)



# Urea cycle disorders

## Ornithine transcarbamylase deficiency (OTC deficiency)

### Causes:

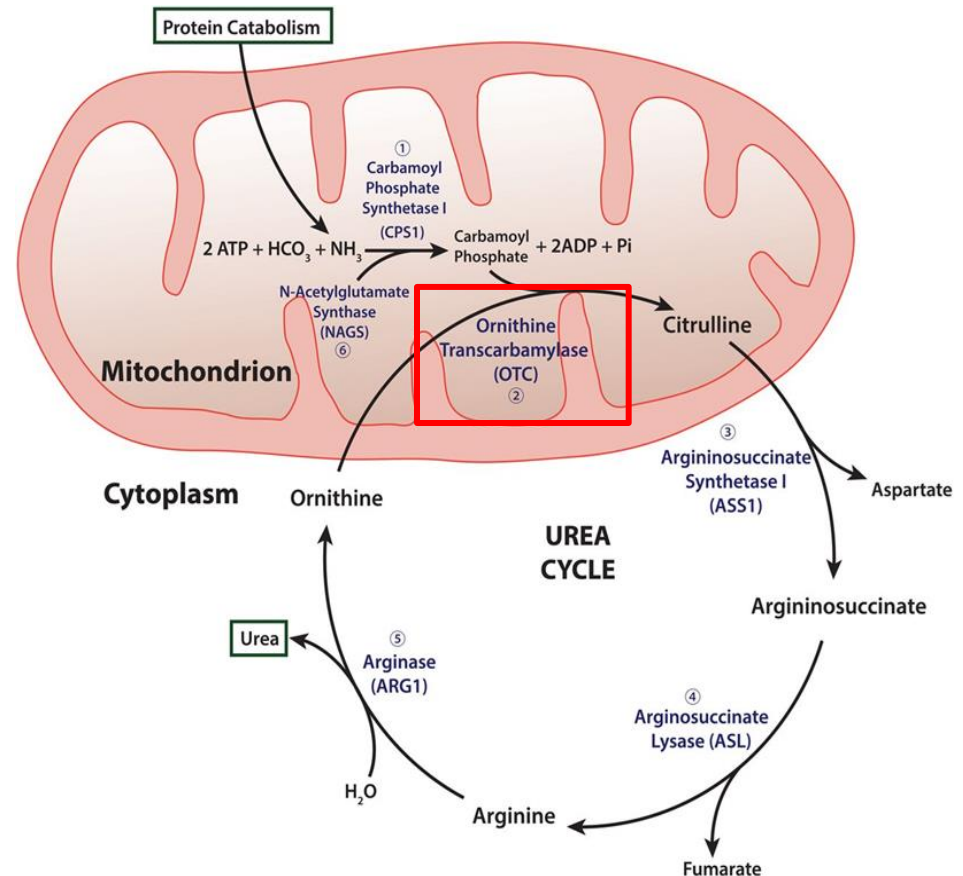
Ornithine transcarbamylase (OTC) deficiency is a **rare X-linked** genetic disorder characterized by complete or partial lack of the enzyme ornithine transcarbamylase (OTC).

The lack of the OTC enzyme results in excessive accumulation of nitrogen, in the form of ammonia (**hyperammonemia**), in the blood.

### Affected Populations:

OTC deficiency affects **males more often than females** and is fully expressed in males only.

The estimated frequency of OTC deficiency is **1/50,000 – 80,000**.

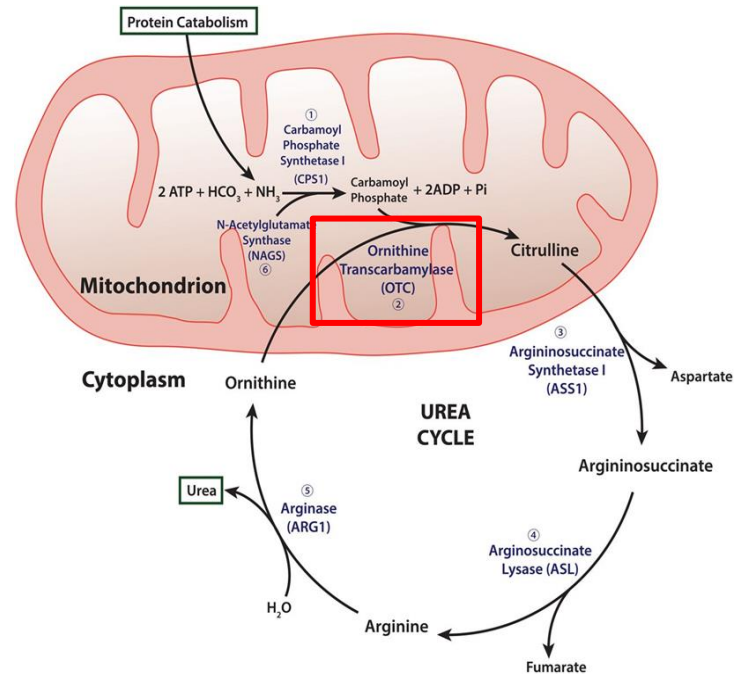


# Urea cycle disorders

## Ornithine transcarbamylase deficiency (OTC deficiency)

### Symptoms:

- The severity and age of onset of OTC deficiency vary from person to person, even within the same family.
- Both males and females may develop symptoms of OTC deficiency during childhood. Most carrier females are healthy, but may be prone to severe headaches following protein intake.
- The severe form of OTC deficiency usually following a protein feeding. Initial symptoms may include **refusal to eat**, **poor suck**, **vomiting**, **progressive lethargy**, and **irritability**.
- The disorder may rapidly progress to include **seizures**, diminished muscle tone (**hypotonia**), an enlarged liver (**hepatomegaly**) and **respiratory abnormalities**. Affected infants and children may also exhibit the accumulation of fluid (**edema**) within the brain.
- Some infants and children may have a **milder** form of OTC deficiency. These infants and children may not exhibit symptoms of OTC deficiency **until later during life**.



# Urea cycle disorders

## Ornithine transcarbamylase deficiency (OTC deficiency)

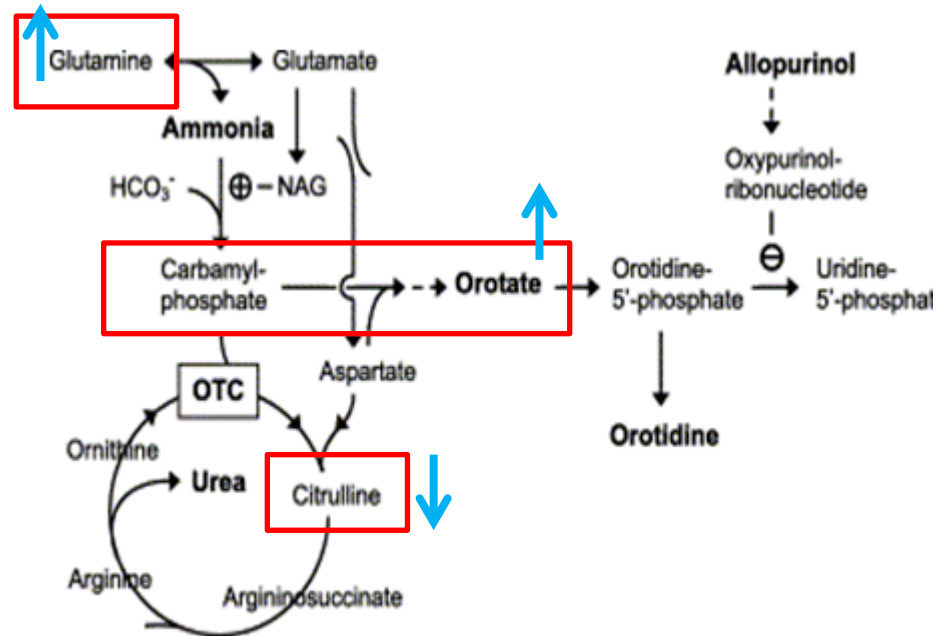
### Diagnosis:

A diagnosis of OTC deficiency should be considered in any newborn that has an undiagnosed illness characterized by vomiting, progressive lethargy, and irritability.

**Blood tests** may reveal excessive amounts of **ammonia** in the blood. Individuals with OTC deficiency usually have both **low levels of citrulline** and **high glutamine** in the blood and **high levels of orotic acid** in the **urine**.

In rare cases, OTC deficiency may be detected by surgical removal (**biopsy**) and microscopic examination of tissue samples from the **liver**, **duodenum**, and **rectum** where deficient enzyme activity may be seen.

**DNA genetic** testing is available to confirm the diagnosis.



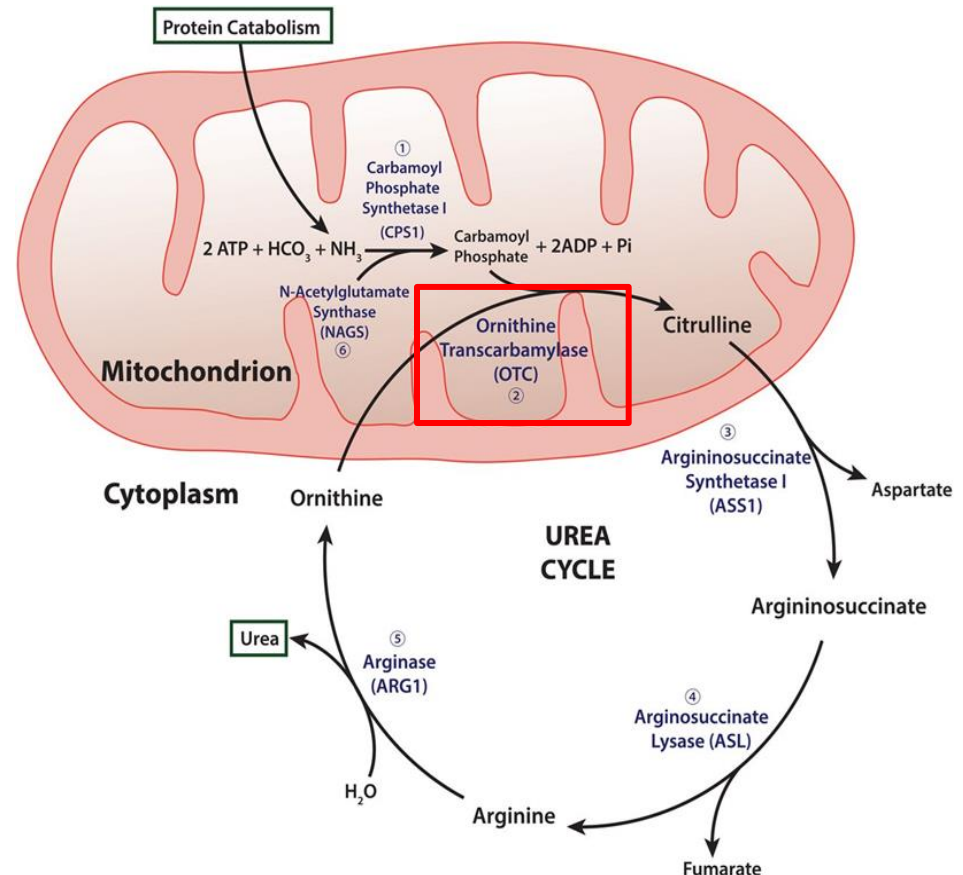
| High level         | Low level  |
|--------------------|------------|
| Glutamine          | citrulline |
| Orotic acid(urine) |            |

# Urea cycle disorders

## Ornithine transcarbamylase deficiency (OTC deficiency)

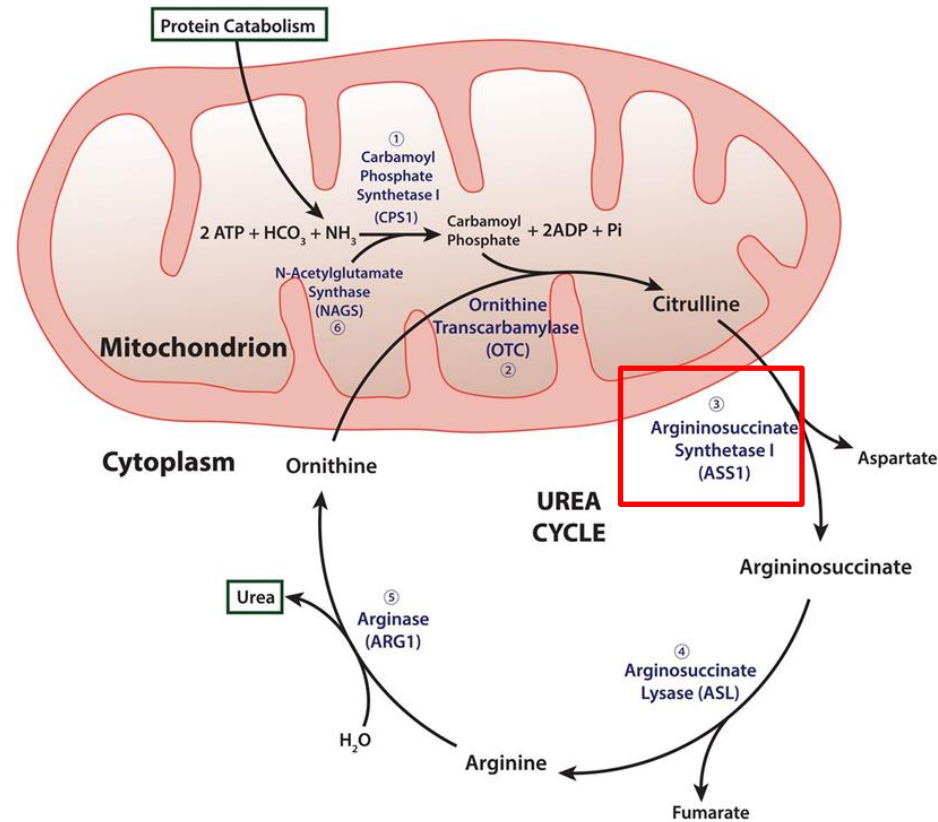
### Treatment

- preventing excessive ammonia from being formed or from **removing excessive ammonia** during a hyperammonemic episode.
- **dietary restrictions** through limiting the amount of protein intake to avoid the development of excess ammonia.
- Prescription of medications that stimulate the removal of nitrogen from the body.
- **Multiple vitamins** and **calcium** supplements may also be used in the treatment of OTC deficiency.
- In some cases, **liver transplantation**, either cadaveric or from a living donor, may be an appropriate treatment option. Liver transplantation can cure the hyperammonemia in OTC deficiency. However, this operation is risky and may result in post-operative complications. Also, after liver transplantation, patients will need to take medications life-long for immunosuppression.



# Urea cycle disorders

## Citrullinemia type I (Argininosuccinic acid synthetase (ASS1) deficiency)



# Urea cycle disorders

## Citrullinemia type I (Argininosuccinic acid synthetase (ASS1) deficiency)

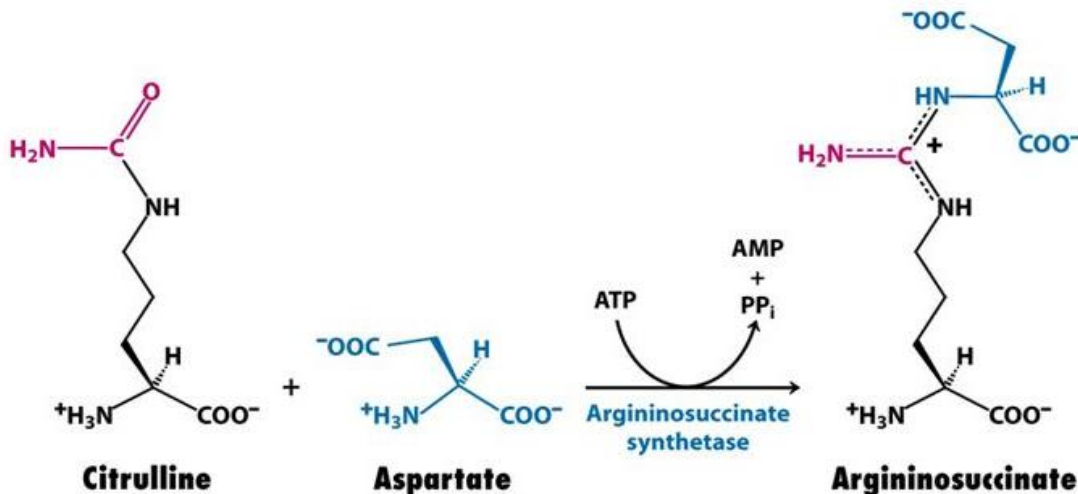
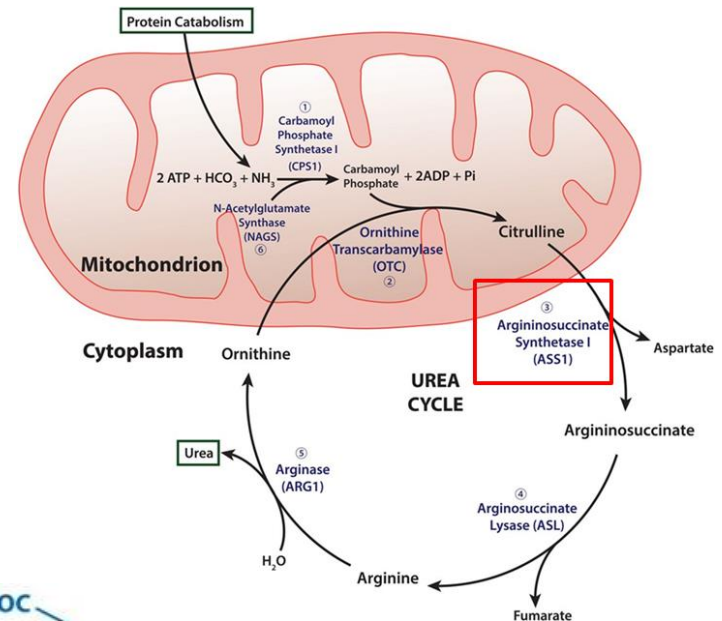
### Causes:

Citrullinemia type I (CTLN1) is caused by mutations in the **ASS1 gene** that is responsible for production of the argininosuccinate synthetase (ASS) enzyme.

CTLN1 is inherited as an **autosomal recessive** genetic condition.

### Affected Populations:

CTLN1 occurs in approximately **1/57,000 births**.



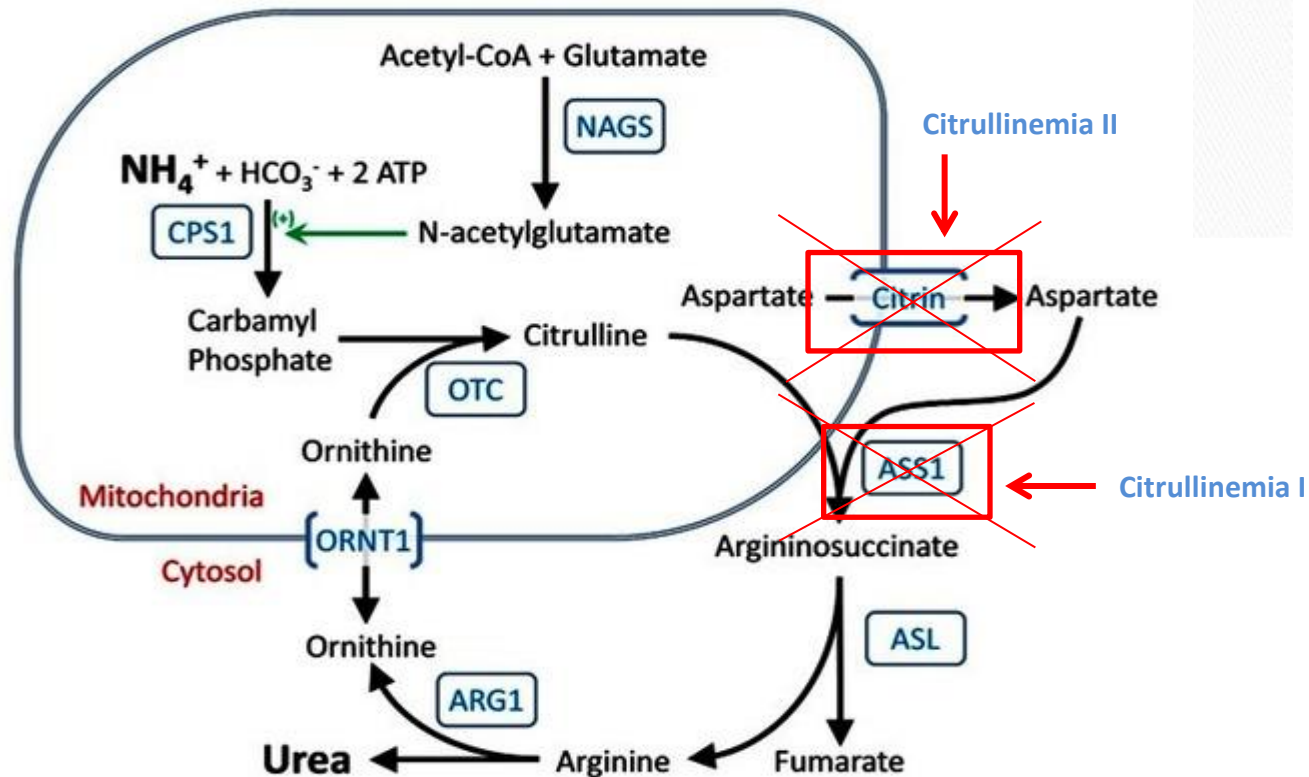
# CITRULLINEMIA

## TYPE I

- ✓ Argininosuccinate Synthase def.
- ✓ Autosomal Recessive
- ✓ Lethargy progressing to coma
- ✓ Mental Retardation
- ✓ Hyperammonemia

## TYPE II

- ✓ Defect in mitochondrial aspartate /glutamate carrier(CTLN2)
- ✓ Autosomal Recessive
- ✓ Neonatal Intrahepatic Cholestasis
- ✓ Adult- Sudden behavioral changes
- ✓ Hyperammonemia
- ✓ Stupor
- ✓ Coma

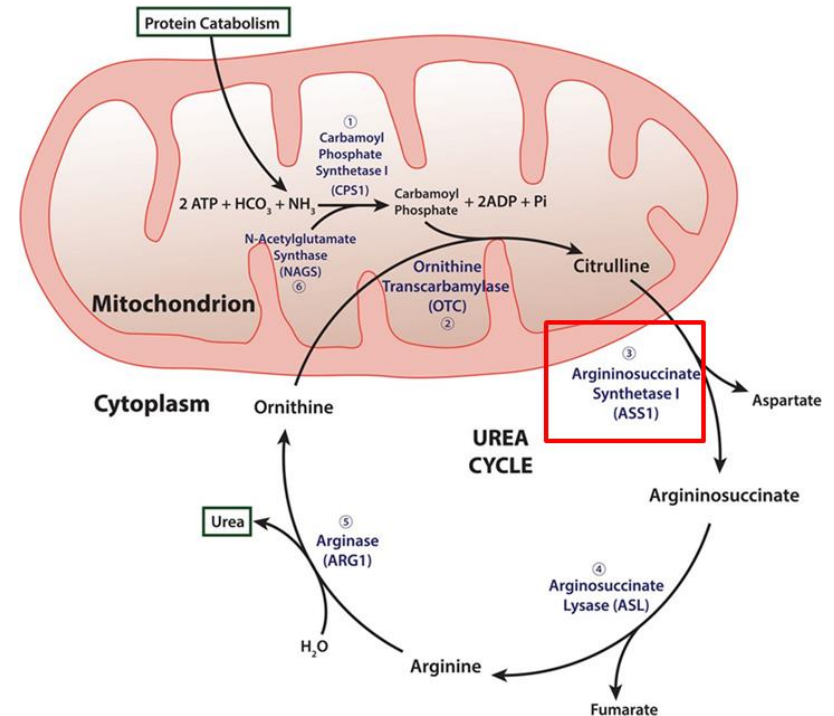


# Urea cycle disorders

## Citrullinemia type I (Argininosuccinic acid synthetase (ASS1) deficiency)

### Symptoms:

- The severity of CTLN1 varies from patient to patient. **accumulation of ammonia** in the blood and cerebrospinal fluid (CSF).
- **The classic form** occurs within 24-72 hours after birth, usually following a protein feeding and is initially characterized by **refusal to eat**, **lethargy**, **lack of appetite**, **vomiting**, and **irritability**.
- Affected infants may also experience **seizures**, diminished **muscle tone (hypotonia)**, **respiratory distress**, accumulation of fluid in the brain (**cerebral edema**), and **liver failure**.
- **Neurological abnormalities including:** developmental delays, intellectual disability, cerebral palsy,...

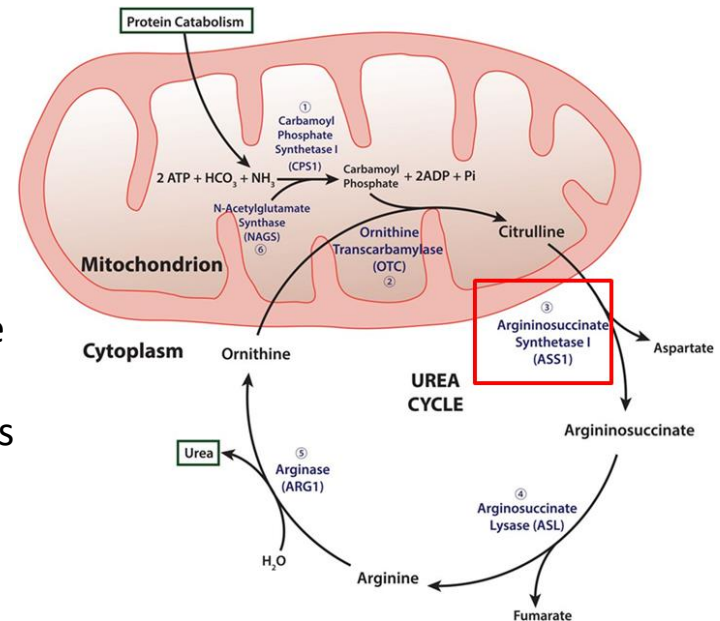


# Urea cycle disorders

## Citrullinemia type I (Argininosuccinic acid synthetase (ASS1) deficiency)

### Diagnosis:

- A diagnosis of citrullinemia can be confirmed by a detailed **patient/family history**, identification of characteristic findings, and a variety of specialized tests.
- Excessive amounts of **ammonia** and **citrulline** in the blood strongly suggests the diagnosis of CTLN1.
- **Molecular genetic** testing for *ASS1* gene mutations is available to confirm the diagnosis.
- CTLN1 may also be diagnosed **through newborn screening** programs. Early detection is important because prompt identification and treatment may prevent the hyperammonemia that causes brain damage.
- **Carrier testing** and prenatal diagnosis are available if the specific gene-causing mutation has been identified in the family.

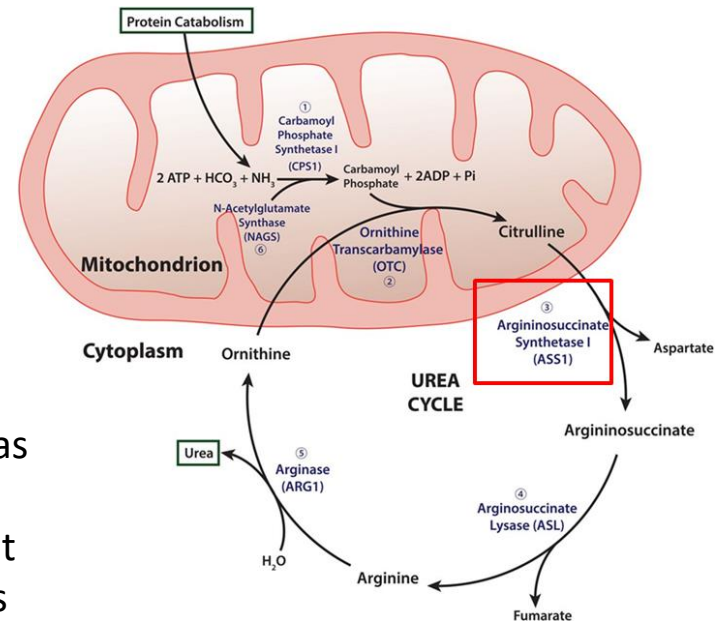


# Urea cycle disorders

## Citrullinemia type I (Argininosuccinic acid synthetase (ASS1) deficiency)

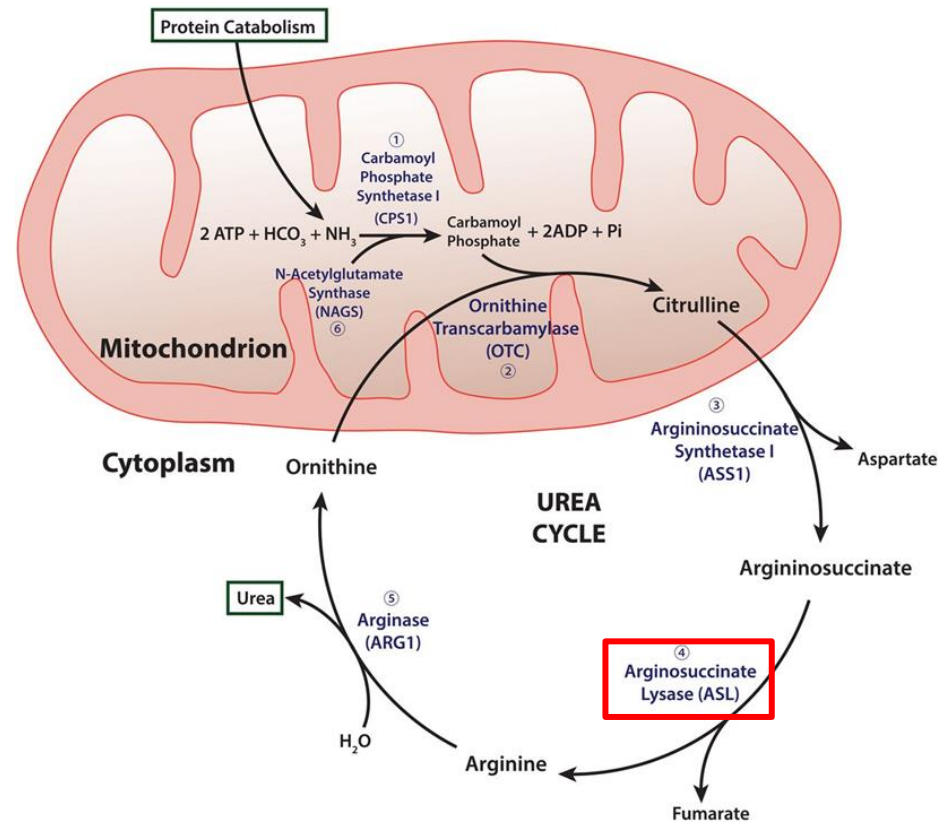
### Treatment:

- Management involves prompt diagnosis, **control of hyperammonemia** and **control of intracranial pressure**.
- Medications that assist in the removal of nitrogen from the body by providing an alternative means of waste nitrogen removal are employed. Available medications are **Buphenyl**, **Ammonul**, and **Raviciti**, as well as arginine.
- **Dietary restrictions** are aimed at limiting the amount of protein intake to avoid the development of excess ammonia. However, enough protein must be taken in by an affected infant to ensure proper growth.
- **Hemodialysis** is also used to treat infants, children, and adults who are first diagnosed with CTLN1 during hyperammonemic coma.
- **Liver transplantation** has been reported to improve quality of life and prolong survival in some patients.



# Urea cycle disorders

## Argininosuccinic aciduria (Argininosuccinic acid lyase (ASL) deficiency)

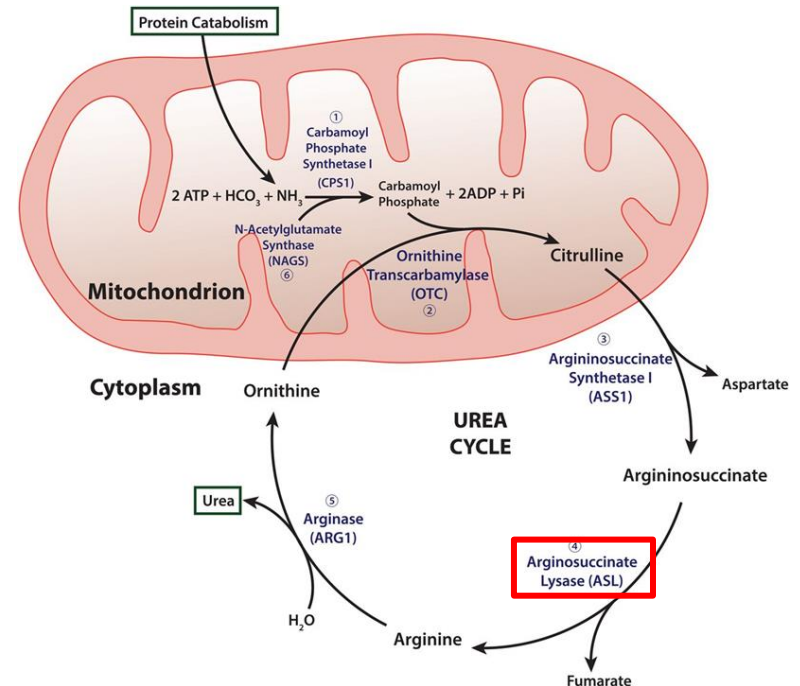


# Urea cycle disorders

## Argininosuccinic aciduria (Argininosuccinic acid lyase (ASL) deficiency)

### Causes:

- Argininosuccinic aciduria is caused by alterations (mutations) in the **ASL gene**.
- The alteration in the **ASL** gene is inherited in an **autosomal recessive** manner.
- Symptoms of argininosuccinic aciduria develop due to the near **complete or partial lack** of the enzyme argininosuccinate lyase.
- The **ASL** gene is responsible for **regulating** the production of this enzyme. Alterations in the **ASL** gene lead to low levels of functional argininosuccinate lyase.



### Affected Populations:

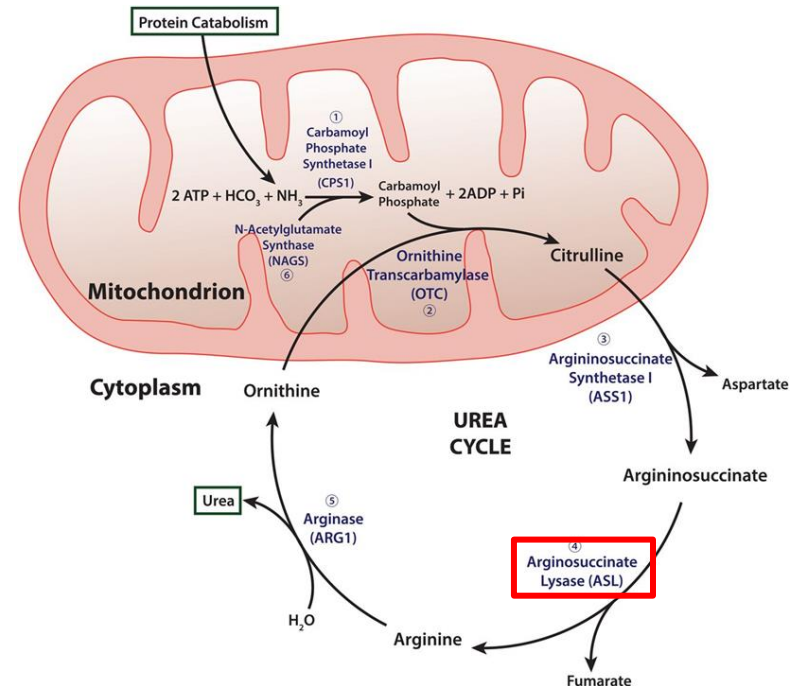
It is estimated to affect anywhere between approximately one in **70,000** to **1 in 218,000** live births.

# Urea cycle disorders

## Argininosuccinic aciduria (Argininosuccinic acid lyase (ASL) deficiency)

### Symptoms:

- The severity and specific symptoms of argininosuccinic aciduria varies from one person to another.
- Symptoms are caused by the accumulation of ammonia in the blood.
- A **severe** form of the disorder, which is characterized by a complete or near complete lack of the ASL enzyme, occurs shortly after birth (neonatal period) and characterized by a **refusal to eat**, **lethargy**, **lack of appetite**, **vomiting**, and **irritability**.
- A **milder** form of the disorder, which is characterized by partial lack of the ASL enzyme, affects some individuals later during infancy or childhood or even adulthood (late-onset form). **failure to grow and gain weight** at the expected rate (**failure to thrive**), avoidance of protein from the diet, inability to **coordinate voluntary movements (ataxia)**, **lethargy**, and **vomiting**.
- **Less commonly**: **progressive liver disease** and dysfunction such as the buildup of scar tissue (**fibrosis**) and **cirrhosis**/ **chronic kidney (renal)** disease.
- high levels of ammonia in the blood (**hyperammonemic coma**)

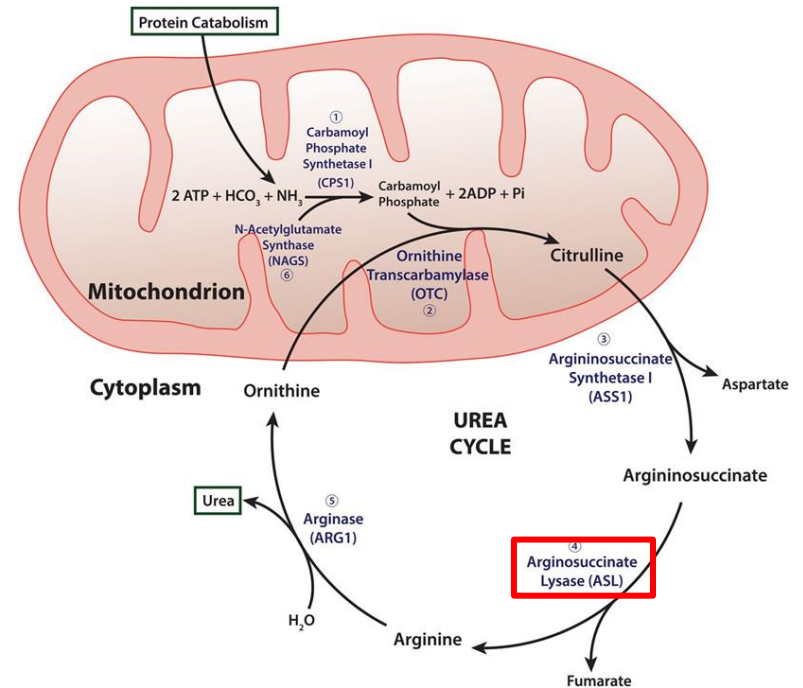


# Urea cycle disorders

## Argininosuccinic aciduria (Argininosuccinic acid lyase (ASL) deficiency)

### Diagnosis:

- diagnosis of argininosuccinic aciduria, should be considered in any newborn that has an undiagnosed illness characterized by vomiting, progressive lethargy, and irritability.
- **Blood tests** may reveal excessive amounts of **ammonia** in the blood, which is the main criterion for a diagnosis of urea cycles disorders including argininosuccinic aciduria.
- **Blood tests** may also reveal high levels of an amino acid called **citruiline**.
- A diagnosis can be confirmed by identifying elevated levels of **argininosuccinic acid in blood or urine** samples.
- A diagnosis can also be confirmed by **molecular genetic** testing, which detects the gene alteration that causes the disorder.

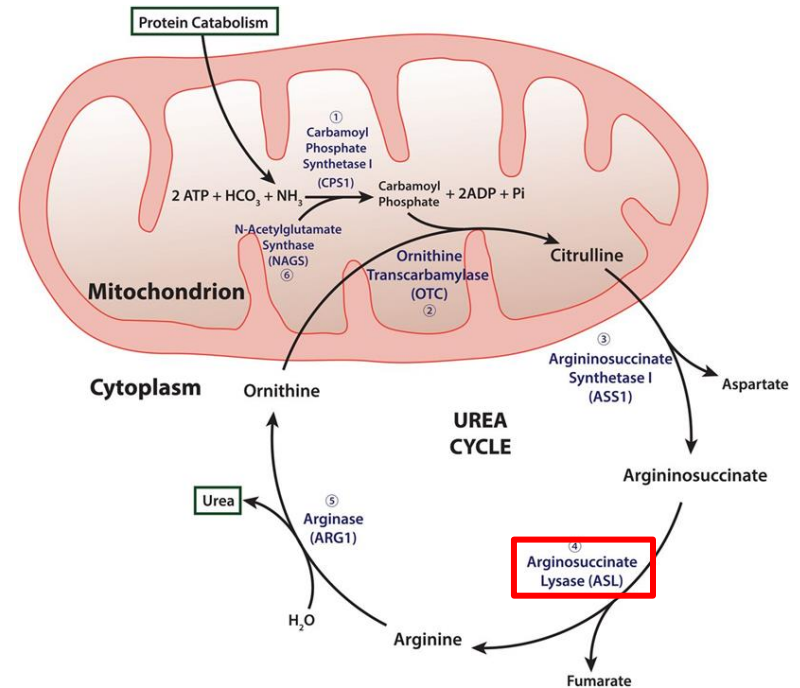


# Urea cycle disorders

## Argininosuccinic aciduria (Argininosuccinic acid lyase (ASL) deficiency)

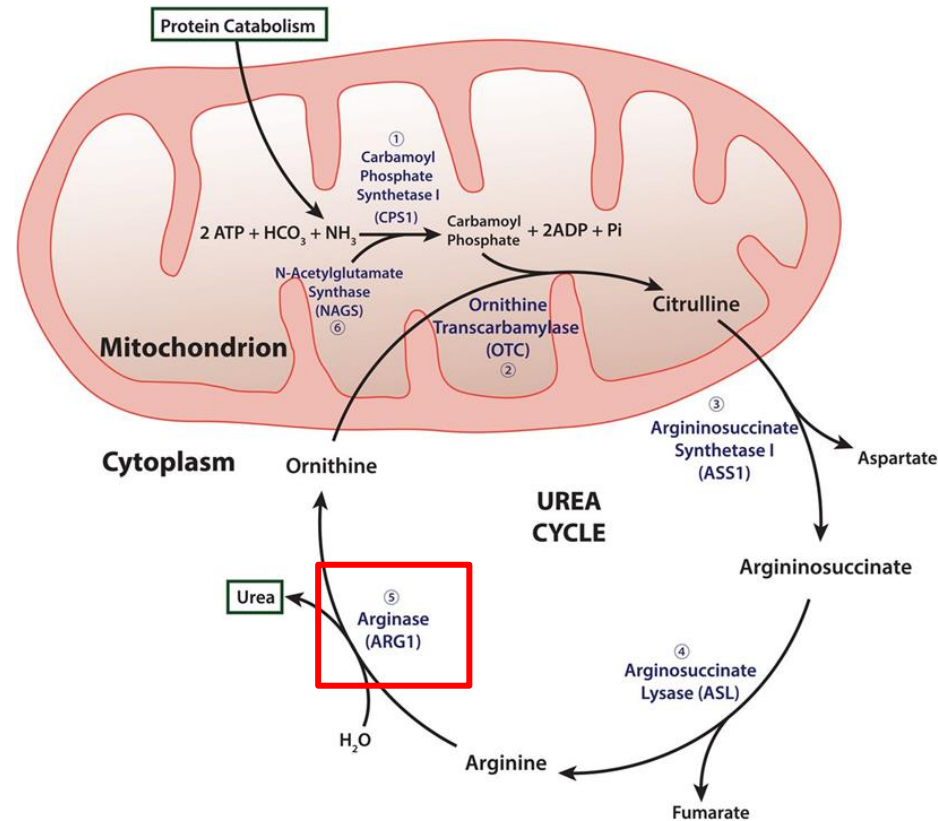
### Treatment:

- Management involves prompt diagnosis, **control of hyperammonemia** and **control of intracranial pressure**.
- **Dietary restrictions** are aimed at limiting the amount of protein intake to avoid the development of excess ammonia. However, enough protein must be taken in by an affected infant to ensure proper growth.
- Individuals with argininosuccinic aciduria benefit from treatment with arginine, which helps to promote the excretion of nitrogen.
- **Hemodialysis** is also used to treat infants, children, and adults who are first diagnosed with CTLN1 during hyperammonemic coma.
- **Liver transplantation** has been reported to improve quality of life and prolong survival in some patients.



# Urea cycle disorders

## Hyperargininemia (Arginase deficiency)



# Urea cycle disorders

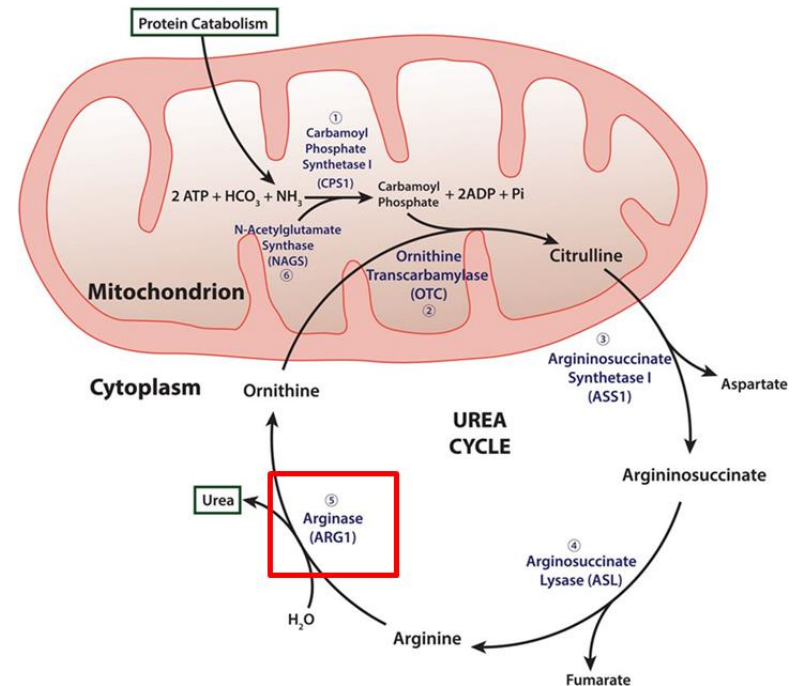
## Hyperargininemia (Arginase deficiency)

### Causes:

Arginase-1 deficiency is inherited as an **autosomal recessive** genetic disorder and is caused by **mutations in the ARG1 gene**. Mutations in the ARG1 gene result in production of an **abnormal arginase enzyme**.

### Affected Populations:

Arginase-1 deficiency has been estimated to occur in approximately **1 in 300,000-1,000,000** births.

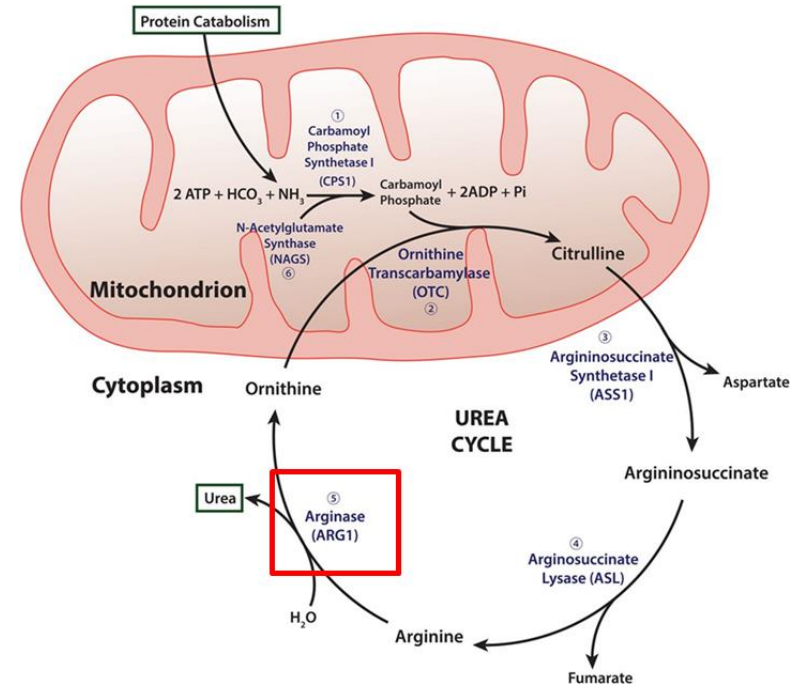


# Urea cycle disorders

## Hyperargininemia (Arginase deficiency)

### Symptoms:

- Symptoms associated with arginase-1 deficiency differ from those associated with other disorders of the urea cycle. Most infants with arginase-1 deficiency **do not exhibit an symptoms during the** first few months to a year of life.
- Infants with arginase-1 deficiency infrequently experience **severe hyperammonemia** or **hyperammonemic coma**, which are characteristic of the other urea cycle disorders.
- Affected children may experience a **lag in growth** between one and three years and may **walk on their toes** and **develop progressive stiffness** and lack of control of voluntary movements of the legs (**spastic diplegia**). Cognitive development slows or stops and if untreated, children develop severe spasticity, an **inability to walk**, **loss of bowel** and **bladder control** and **severe intellectual disability**.
- Almost all affected children have **growth deficiency** and many also experience **seizures**.



# Urea cycle disorders

## Hyperargininemia (Arginase deficiency)

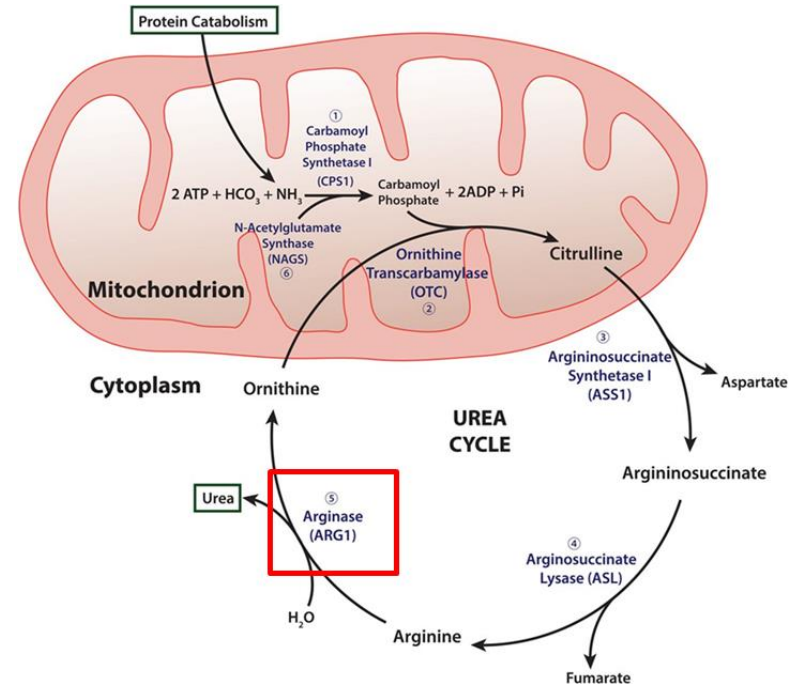
### Diagnosis:

Most affected infants are now identified at birth through newborn screening.

Arginase enzyme activity is usually **not detectable in red blood cells** from affected individuals.

**Molecular genetic** testing is available to confirm the diagnosis.

If two mutations are not found, red blood cell **enzyme testing** is used to confirm the diagnosis.

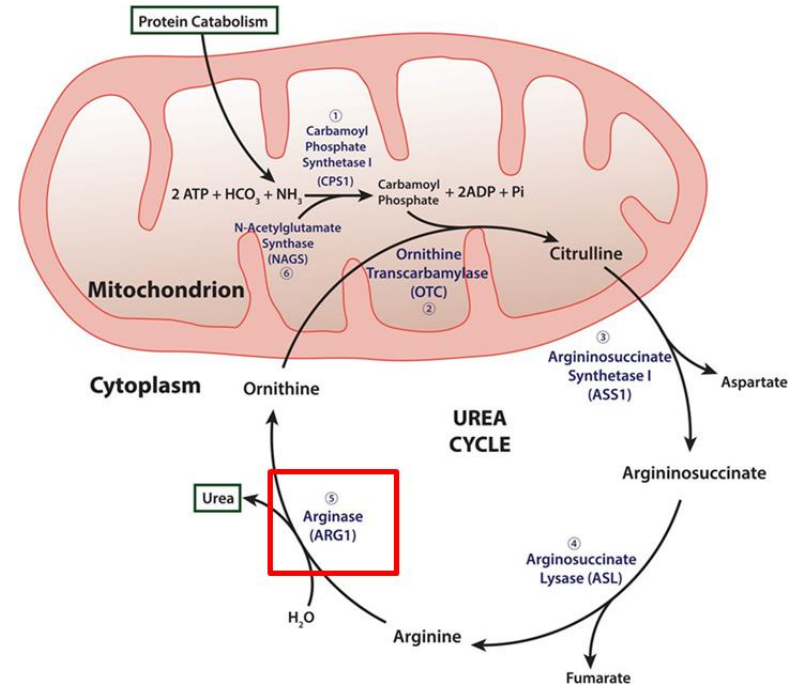


# Urea cycle disorders

## Hyperargininemia (Arginase deficiency)

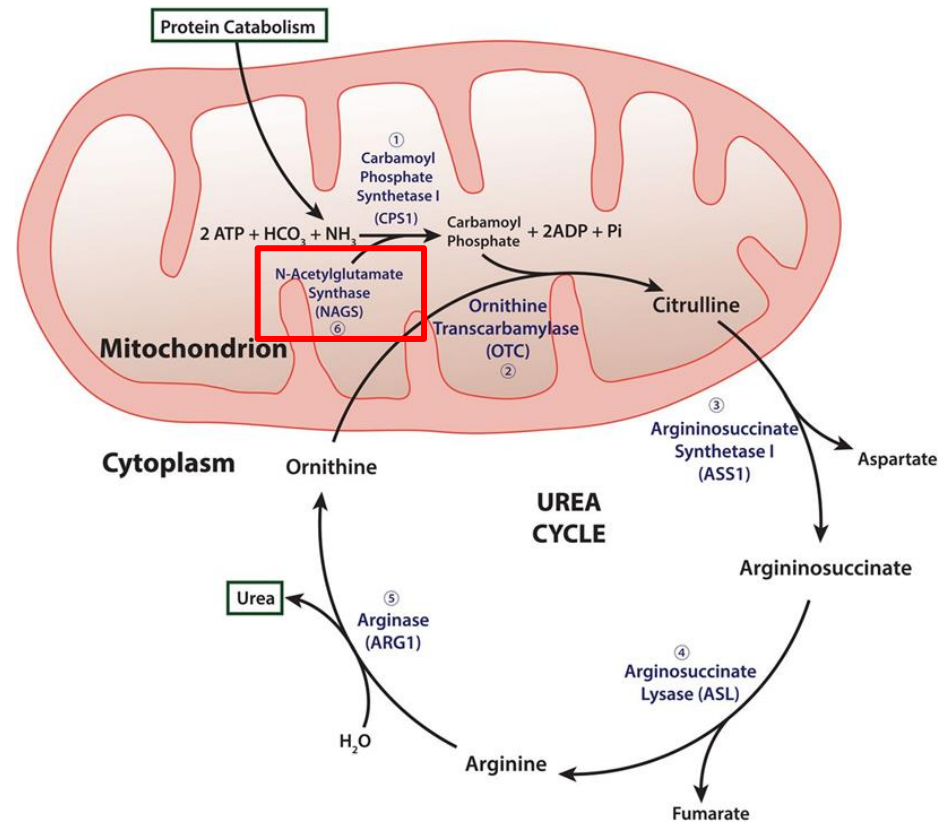
### Treatment:

- **Reduction of plasma ammonia** concentration is accomplished by dialysis and several different methods are available. This should be used only when the high levels are producing severe symptoms.
- The **nitrogen scavenger drugs sodium phenylacetate** and **sodium benzoate** provide an alternative pathway for removing excess nitrogen.
- **Dietary restrictions** in individuals with arginase-1 deficiency are aimed at limiting the amount of arginine and protein intake.
- **Seizures** are treated with **phenobarbital** or **carbamazepine**. **Valproic acid should be avoided**, as it can increase blood ammonia levels.
- Affected individuals should receive periodic blood tests to determine the levels of **ammonia** and **arginine** in the blood and to be sure that liver function is not impaired.



# Urea cycle disorders

## N-acetylglutamate synthase deficiency (NAGS deficiency)



# Urea cycle disorders

## N-acetylglutamate synthase deficiency (NAGS deficiency)

### Causes:

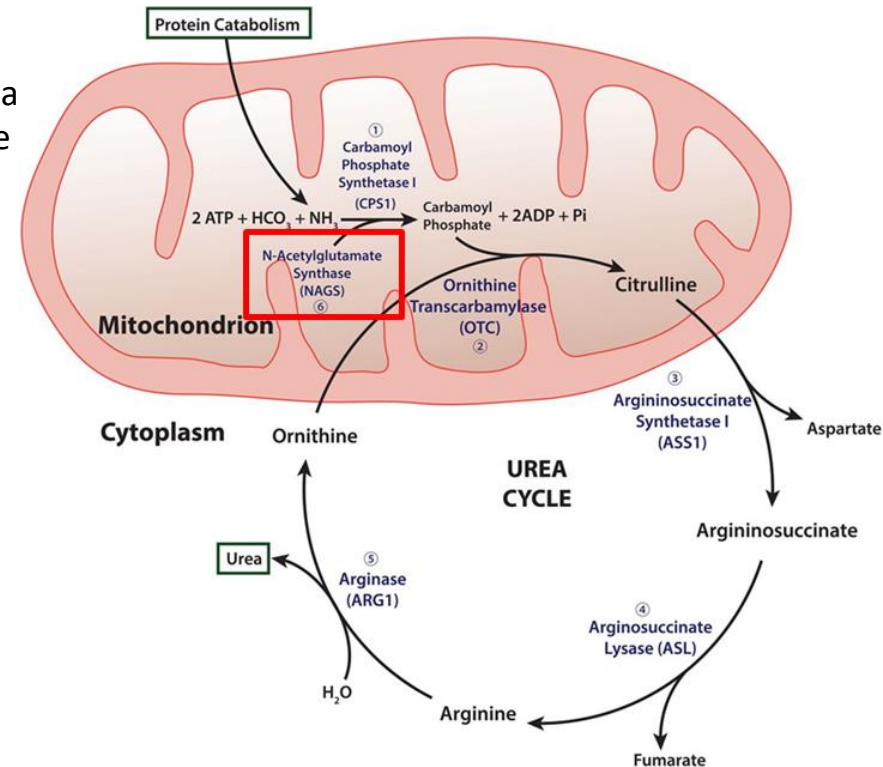
- N-acetylglutamate synthetase deficiency affects the body's ability to make n-acetylglutamate (NAG) which is a required cofactor for the function of carbamyl phosphate synthetase I.
- Without NAG, **CPSI cannot convert ammonia into carbamyl phosphate**.
- Patients with complete NAGS deficiency rapidly develop hyperammonemia in the newborn period.
- NAGS deficiency is an **autosomal recessive** genetic disorder caused by mutations of the NAGS gene.

### Affected Populations:

NAGS deficiency **is a rare disorder** that affects males and females in equal numbers.

In most cases, onset of symptoms occurs at, or shortly following, birth.

The estimated frequency of urea cycle disorders collectively is **one in 30,000** births. However, because urea cycle disorders like **NAGS deficiency often go unrecognized**, these disorders are under-diagnosed, making it difficult to determine the true frequency of urea cycle disorders in the general population.



# Urea cycle disorders

## N-acetylglutamate synthase deficiency (NAGS deficiency)

### Symptoms:

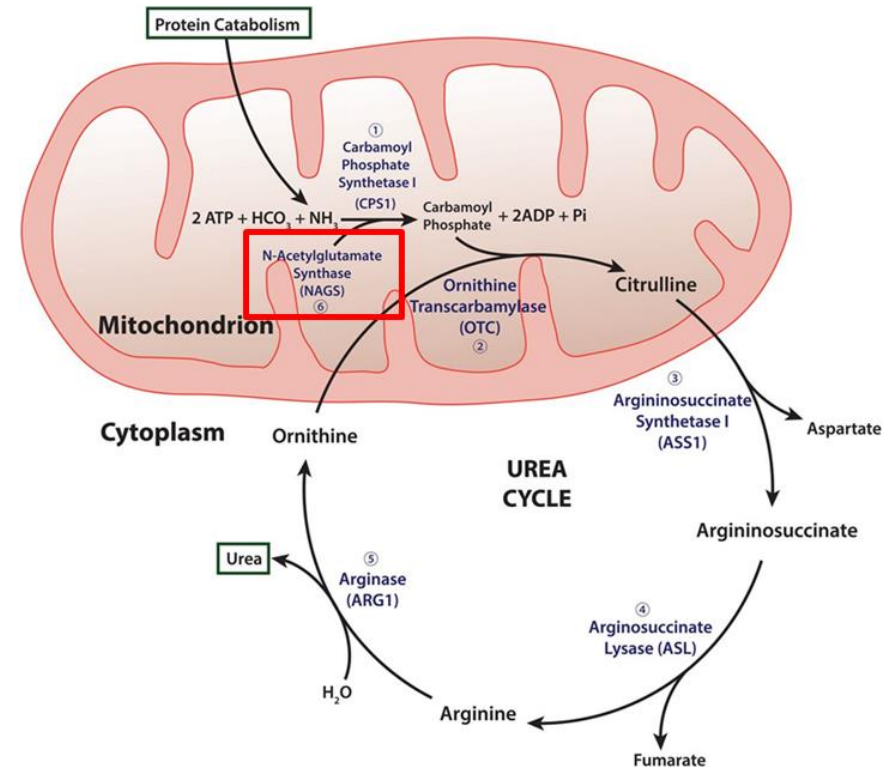
**Complete lack** of the NAGS enzyme results in the severe form of the disorder, in which symptoms occur shortly after birth (neonatal period).

**Partial lack** of the NAGS enzyme results in a milder form of the disorder that occurs later during infancy or childhood or even adulthood in some cases.

The symptoms of NAGS deficiency are caused by the **accumulation of ammonia** in the blood.

Affected infants may exhibit **refusal to eat** and **poor feeding habits**, **progressive lethargy**, **recurrent vomiting**, **diarrhea**, **irritability** and an **abnormally enlarged liver (hepatomegaly)**. More severe complications can also develop including **seizures**, **confusion**, **respiratory distress**, and the **abnormal accumulation of fluid in the brain (cerebral edema)**.

In some cases, the symptoms of NAGS deficiency may progress to **coma** and **neurological abnormalities** including **developmental delays**, **learning disabilities** and **intellectual disability**.

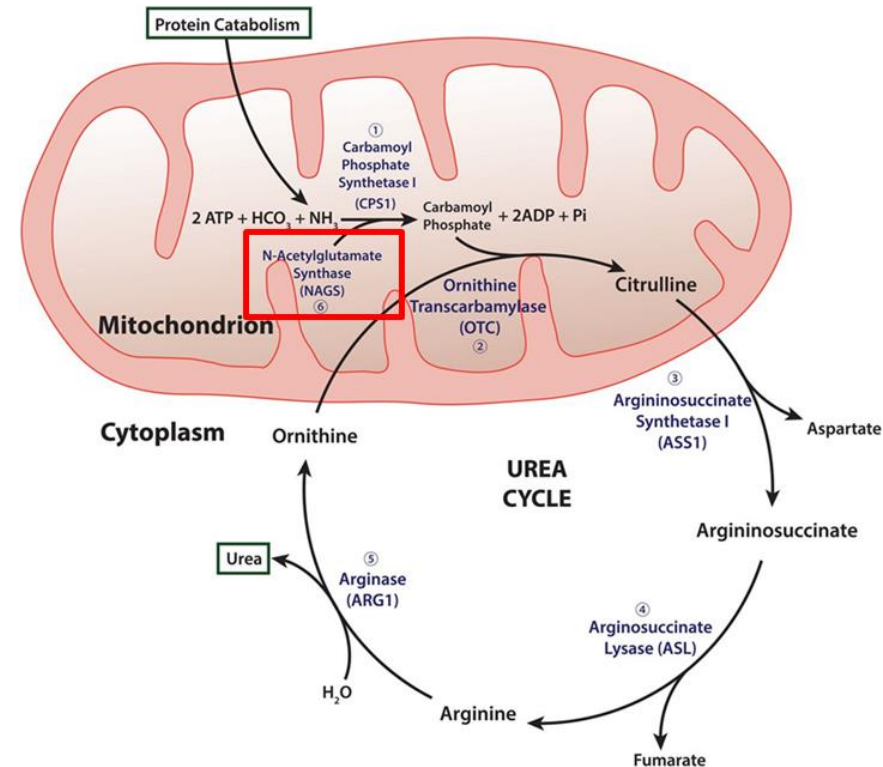


# Urea cycle disorders

## N-acetylglutamate synthase deficiency (NAGS deficiency)

### Diagnosis:

- A diagnosis of NAGS deficiency (or any urea cycle disorder) should be considered in any newborn that has an undiagnosed illness characterized by **vomiting, progressive lethargy, and irritability**.
- **Blood tests** may reveal excessive amounts of ammonia in the blood, the characteristic finding of urea cycle disorders.
- A diagnosis of NAGS deficiency can be confirmed through **molecular genetic testing** that reveals a mutation of the *NAGS* gene that characterizes this disorder.

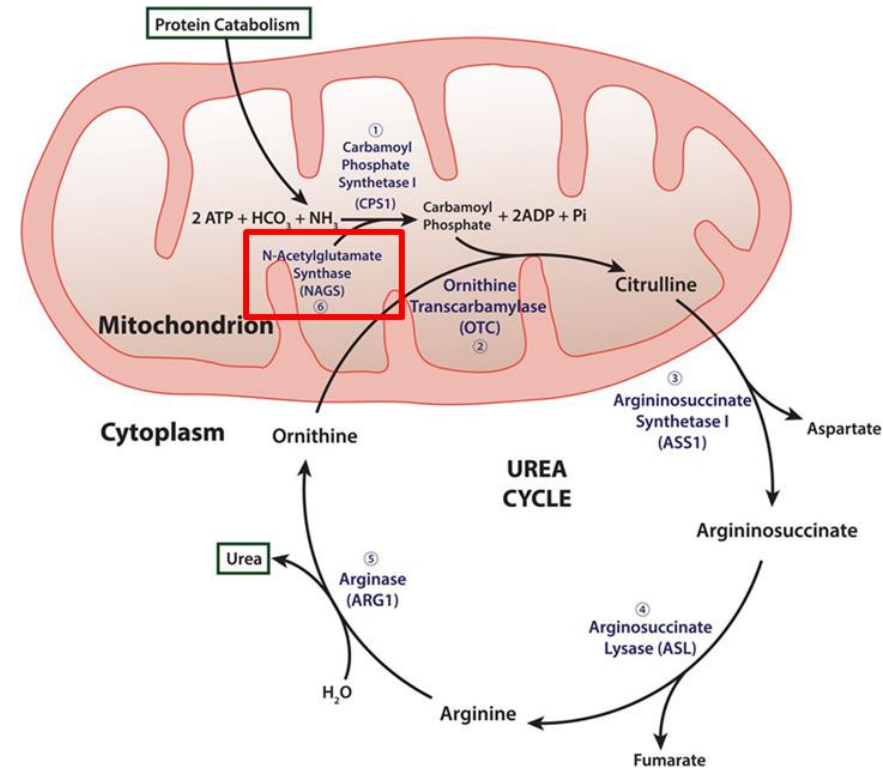


# Urea cycle disorders

## N-acetylglutamate synthase deficiency (NAGS deficiency)

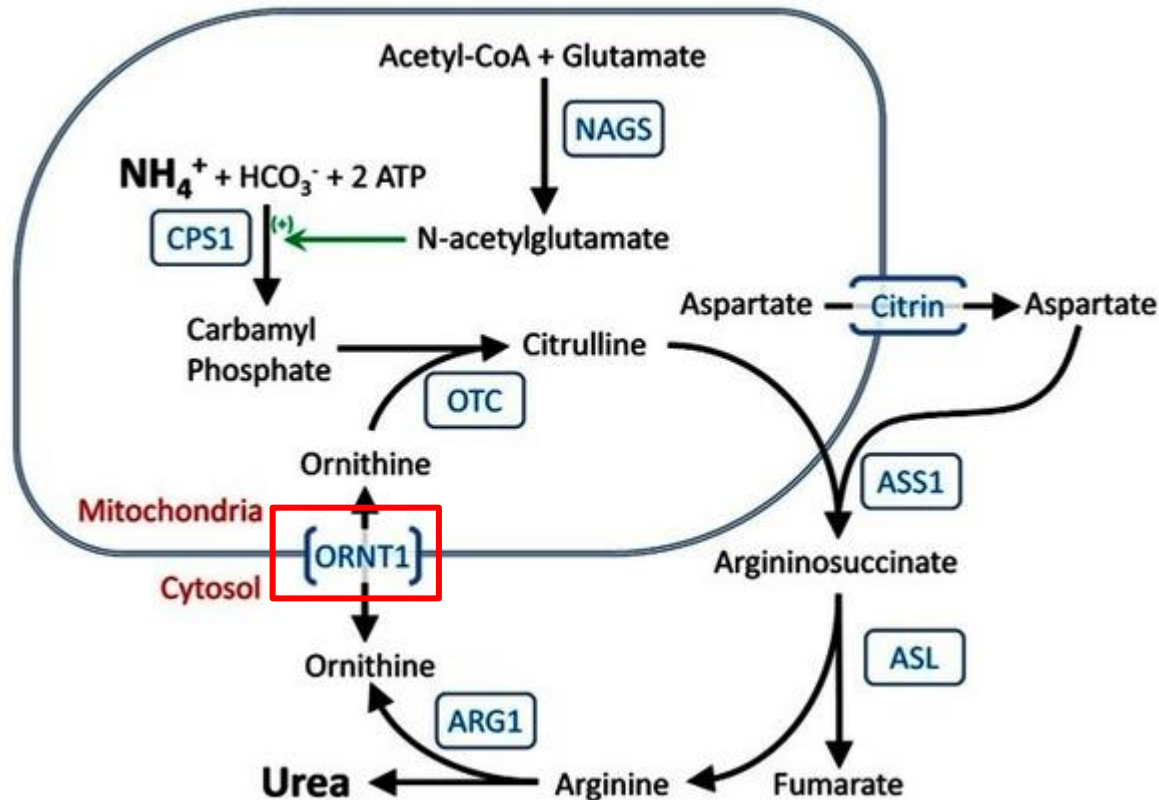
### Treatment:

- The treatment of NAGS deficiency is aimed at **preventing excessive ammonia** from being formed or from removing excessive ammonia during a hyperammonemic episode. Long-term therapy for NAGS deficiency had combined **dietary restrictions** and the stimulation of alternative methods of **converting and excreting nitrogen** from the body (alternative pathways therapy).
- In 2010, the U.S. Food and Drug Administration (FDA) approved the use of **Carbaglu®** (carbamylglutamate) tablets to reduce blood ammonia levels in patients with NAGS deficiency.
- elevated levels of an amino acid (**glutamine**) in the blood often precede the development of hyperammonemia by days or weeks. Affected individuals should receive periodic tests to measure the amount of amino acids such as glutamine in the blood. Detection of elevated levels of ammonia or glutamine may allow treatment before clinical symptoms appear.



## Urea cycle disorders

### Ornithine translocase deficiency(ORNT1 deficiency)



## Urea cycle disorders

### Ornithine translocase deficiency(ORNT1 deficiency)

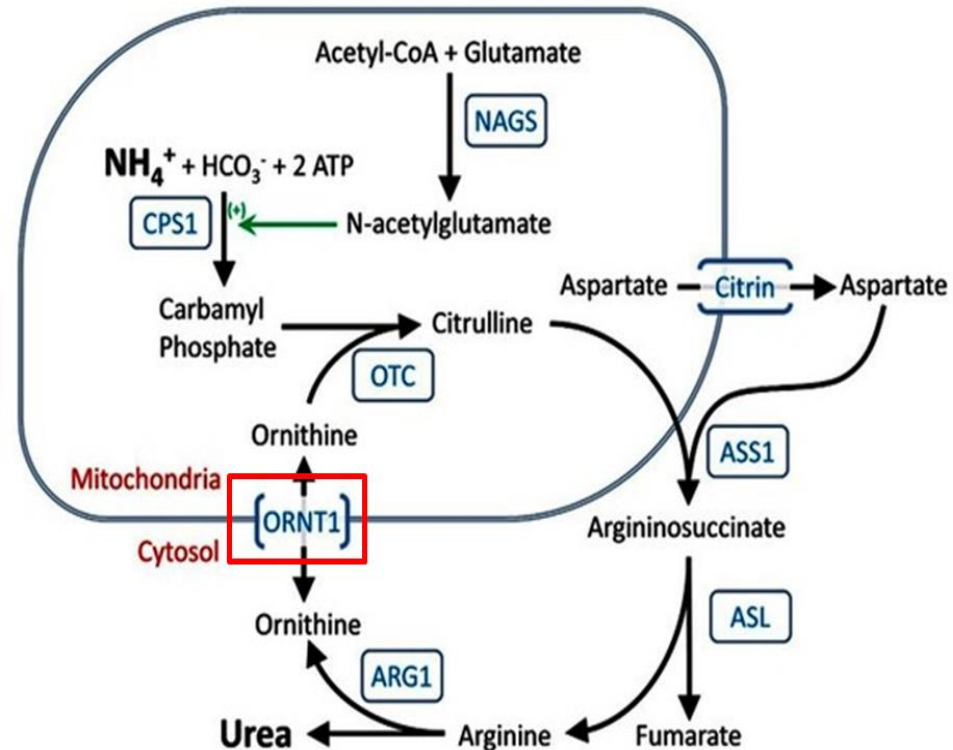
#### Causes:

Mutations in the SLC25A15 gene cause ornithine translocase deficiency.

Mutations in the *SLC25A15* gene cause the production of a mitochondrial ornithine transporter 1 with reduced or absent function

#### Affected Populations:

Ornithine translocase deficiency is a very rare disorder. More than 100 affected individuals have been described in the scientific literature.



## Urea cycle disorders

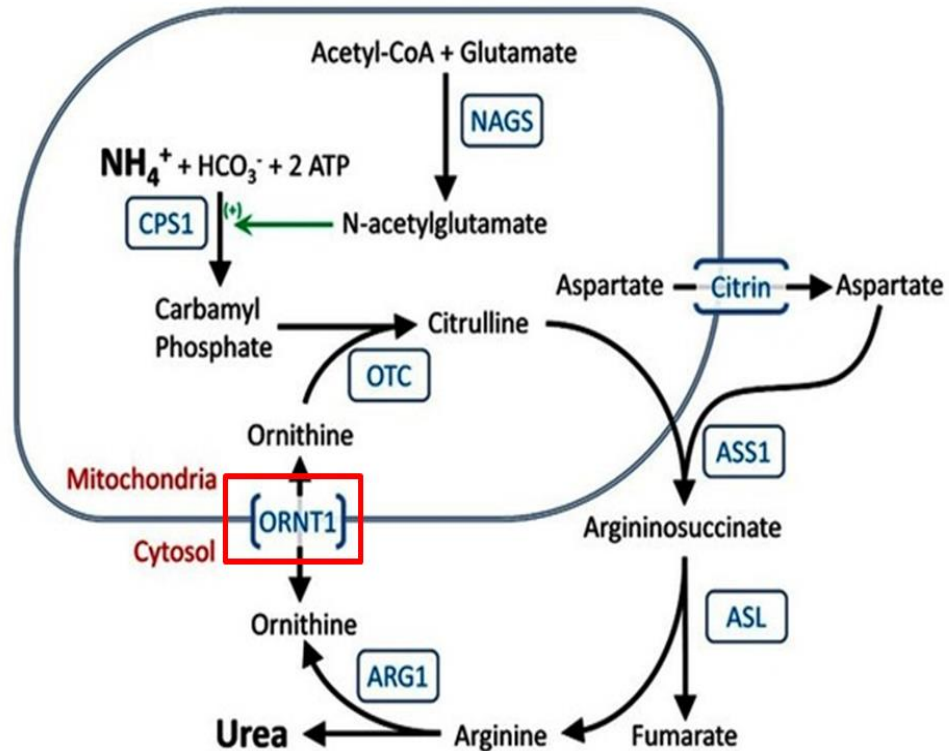
# Ornithine translocase deficiency(ORNT1 deficiency)

### Symptoms:

Infants with ornithine translocase deficiency may **lack energy (be lethargic)**, **refuse to eat**, **vomit frequently**, or have **poorly controlled breathing or body temperature**.

**Seizures** or **unusual body movements** are common in these individuals. Some people with this condition have **intellectual disability** or **developmental delay**, but others have normal intelligence. Severe cases may result in **coma**.

Some people with **later-onset** ornithine translocase deficiency have episodes of **vomiting**, **lethargy**, problems with coordination (**ataxia**), **vision problems**, episodes of brain dysfunction (**encephalopathy**), **developmental delay**, **learning disabilities**, or **stiffness** caused by abnormal tensing of the muscles (spasticity). Affected individuals may have **chronic liver problems** and **mild abnormal bleeding**.



## Urea cycle disorders

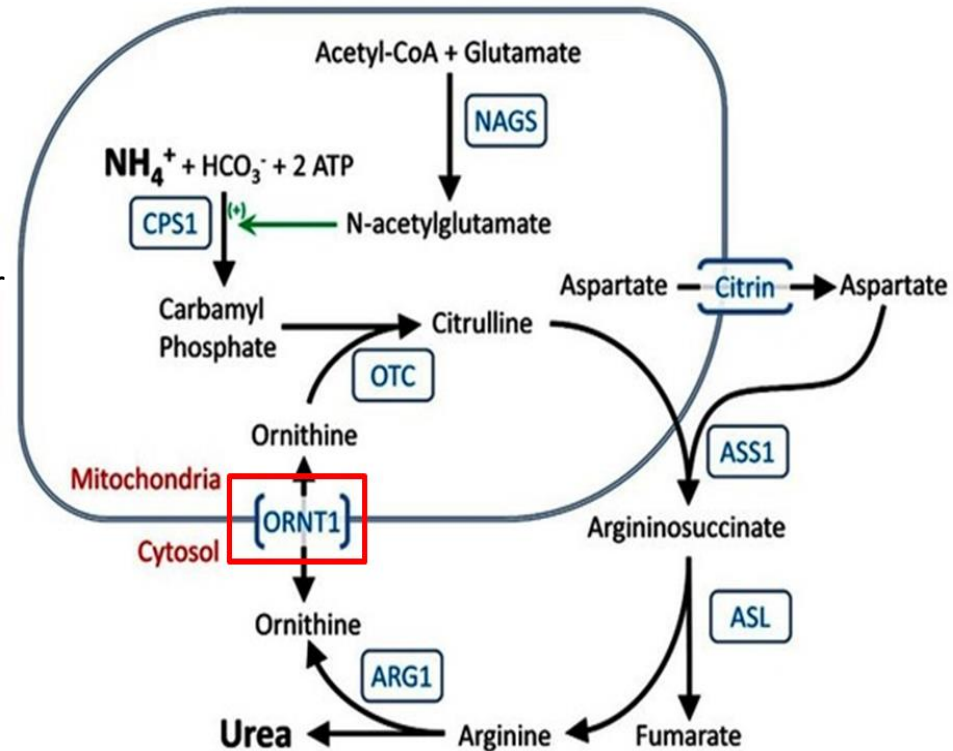
### Ornithine translocase deficiency(ORNT1 deficiency)

#### Diagnosis:

Laboratory tests usually reveal increased urinary excretion of **orotic acid**, **homocitrulline** and **uracil**, and a rise in the levels of **plasma polyamines**, **ornithine**, **glutamine**, **alanine**, and **liver transaminases**.

**Plasma ammonia** levels are elevated episodically or postprandially and plasma ornithine is chronically elevated and is a hallmark of the disease as is the presence of homocitrulline in urine.

**Molecular genetic** testing confirms diagnosis.



## Urea cycle disorders

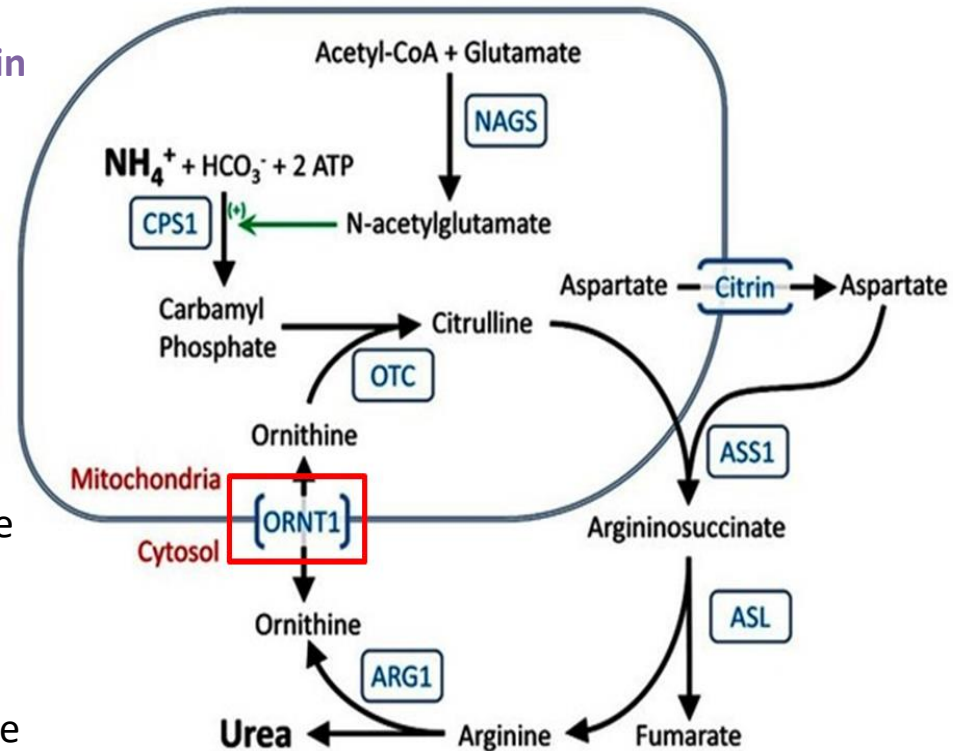
### Ornithine translocase deficiency (ORNT1 deficiency)

#### Treatment:

Treatment involves the **adherence to a low protein diet** along with **citrulline** or **arginine** supplementation. In resistant cases, **sodium benzoate and/or sodium or glycerol phenylbutyrate** may be necessary for control of plasma ammonia levels.

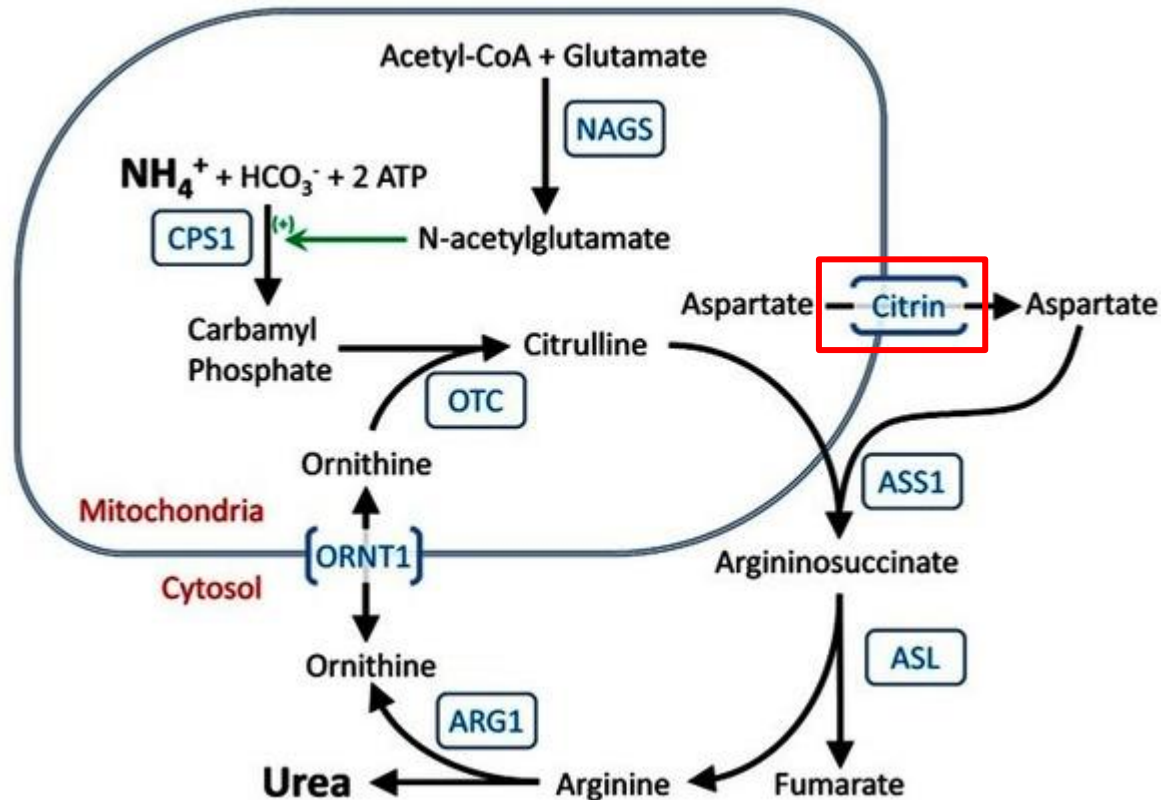
Patients should be monitored during times of stress (e.g. pregnancy, surgery, intercurrent infections) and when taking certain medications (i.e. corticosteroids) as they can trigger an episode of hyperammonemia.

Hyperammonemic coma is treated in a tertiary care center where plasma ammonia levels must be lowered (by **hemodialysis** or **hemofiltration**), ammonia scavenger therapy implemented, **catabolism reversed** (with glucose and lipid infusions) and special care taken to **reduce the risk of neurological damage**.



# Urea cycle disorders

## Citrullinemia type II (Citrin deficiency)



# Urea cycle disorders

## Citrullinemia type II (Citrin deficiency)

### Causes:

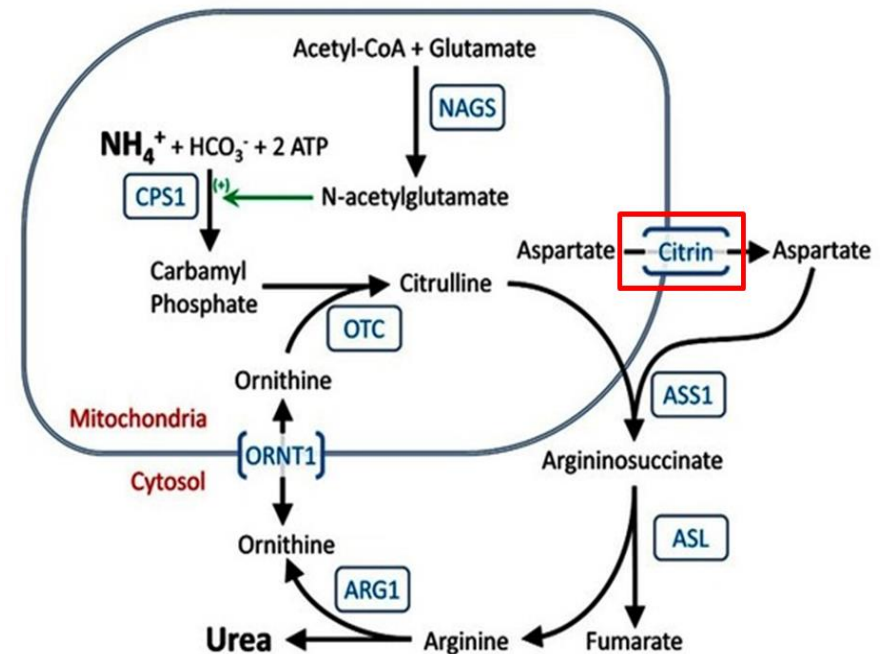
Mutations in the **SLC25A13 gene** are responsible for adult-onset type II citrullinemia.

This gene provides instructions for making a protein called **citrin**.

Within cells, citrin helps transport molecules used in the production and breakdown of simple sugars, the production of proteins, and the urea cycle.

### Affected Populations:

Type II citrullinemia is found primarily in the Japanese population, where it occurs in an estimated 1 in 100,000 to 230,000 individuals. Type II also has been reported in other populations, including other people from East Asia, the Middle East, the United States, and the United Kingdom.

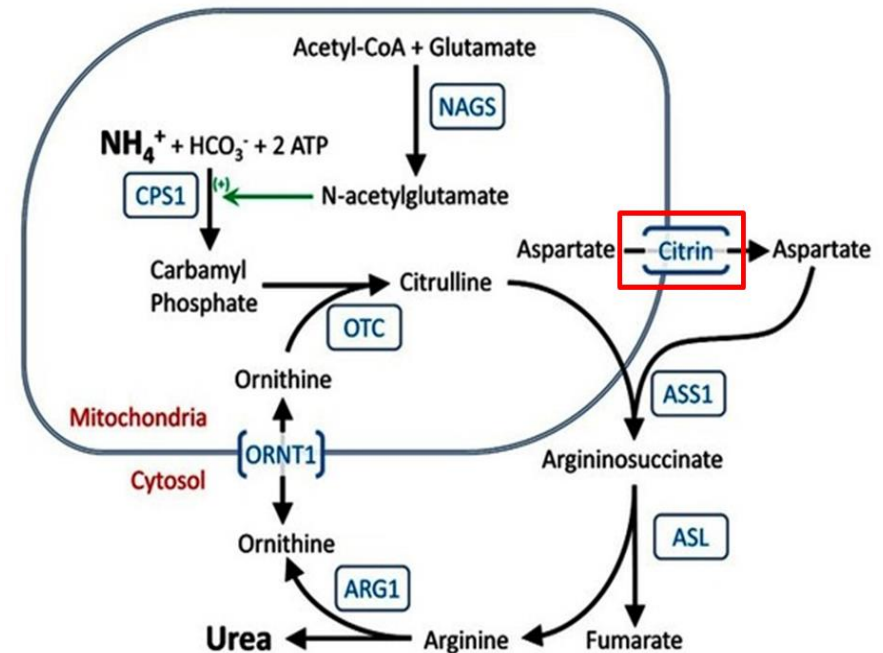


# Urea cycle disorders

## Citrullinemia type II (Citrin deficiency)

### Symptoms:

- Type II citrullinemia chiefly affects the **nervous system**, causing **confusion**, **restlessness**, **memory loss**, **abnormal behaviors** (such as aggression, irritability, and hyperactivity), **seizures**, and **coma**.
- The signs and symptoms of this disorder typically appear during adulthood (adult-onset) and can be triggered by certain medications, infections, surgery, and alcohol intake.
- Adult-onset type II citrullinemia may also develop in people who as infants had a liver disorder called **neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)**. NICCD blocks the flow of **bile** and prevents the body from processing certain nutrients properly.
- In rare cases, affected individuals develop other signs and symptoms in early childhood after seeming to recover from NICCD, including delayed growth, extreme tiredness (fatigue), specific food preferences (mentioned above), and abnormal amounts of fats (lipids) in the blood (dyslipidemia). This condition is known as **failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD)**. Years or even decades later, some people with NICCD or FTTDCD develop the features of adult-onset type II citrullinemia.

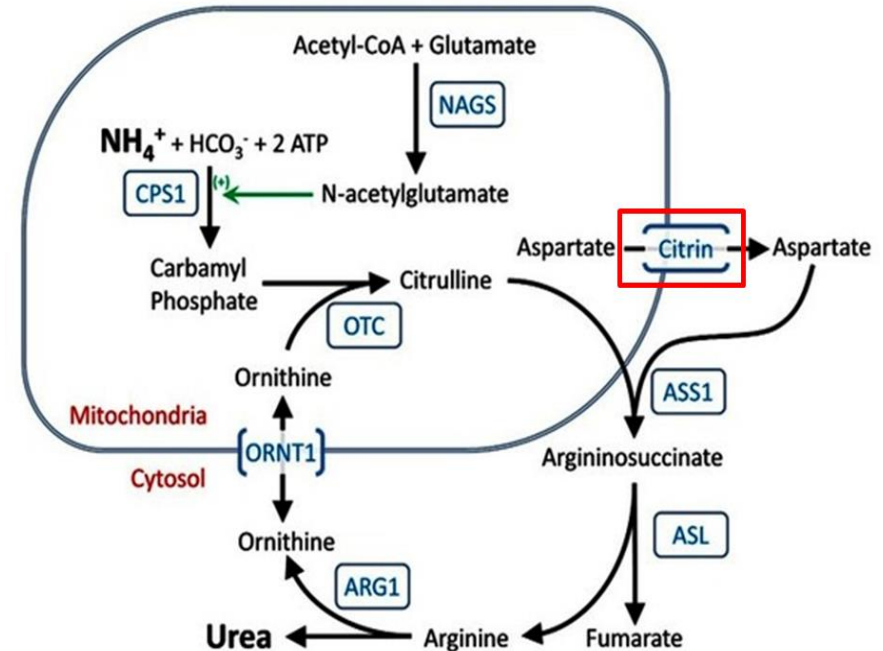


# Urea cycle disorders

## Citrullinemia type II (Citrin deficiency)

### Diagnosis:

Making a diagnosis for a genetic or rare disease can often be challenging. Healthcare professionals typically look at a person's medical history, symptoms, physical exam, and laboratory test results in order to make a diagnosis. The following resources provide information relating to diagnosis and testing for this condition.



# Urea cycle disorders

## Citrullinemia type II (Citrin deficiency)

### Treatment:

**Liver transplantation** for adult-onset citrullinemia type II prevents hyperammonemic crises, corrects metabolic disturbances, and eliminates preferences for protein-rich foods.

**Administration of arginine** decreases blood ammonia concentration.

**Reduction in calorie and/or carbohydrate intake** can lessen high triglycerides. Individuals with adult-onset citrullinemia type II are encouraged to consume a diet rich in lipids and protein and low in carbohydrates. This may help to prevent hyperammonemia.

