THE OHIO STATE UNIVERSITY

Classical Citrullinemia

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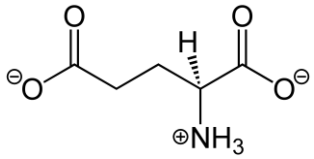
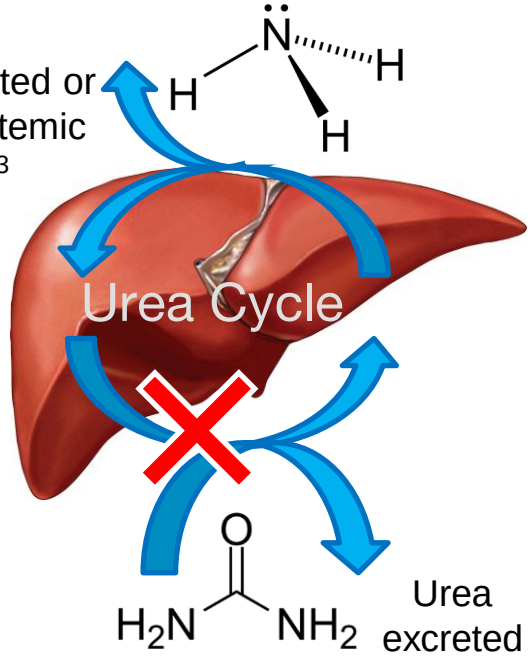
What is classical citrullinemia?

- Classic cirullinemia is a urea cycle disorder affects 1 in 57,000 people worldwide; urea cycle is a metabolic route for disposal of ammonia
- In this disease, the enzyme that metabolizes citrulline, an amino acid made by the body, is inactive, and leads to toxic ammonia buildup in the body

Protein



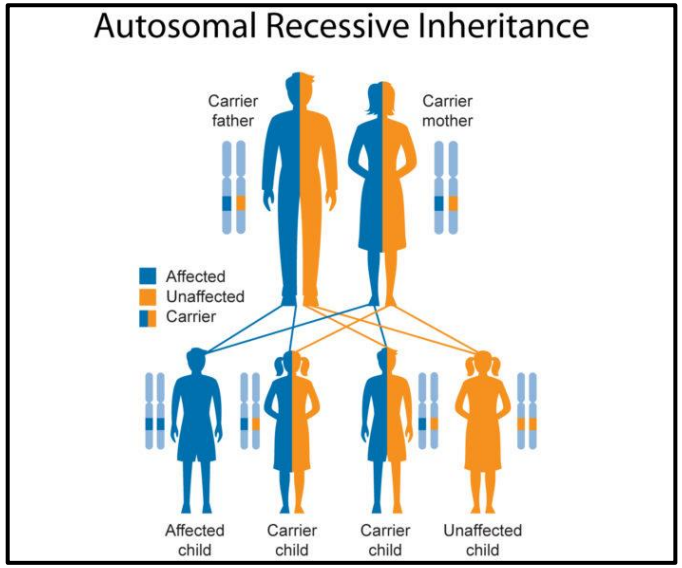
Amino Acids



Digital images retrieved Dec 5, 2020 from https://www.mynetdiary.com/the-benefits-of-eating-protein.html, https://en.wikipedia.org/wiki/Glutamate_(neurotransmitter), https://en.wikipedia.org/wiki/Aspartic_acid , https://www.pcosnutrition.com/fattyliver/

Genetics

- Autosomal recessive inheritance (i.e., both parents must be carriers for a child to inherit the disease)
- Mutations in a gene that codes for an enzyme essential for the urea cycle

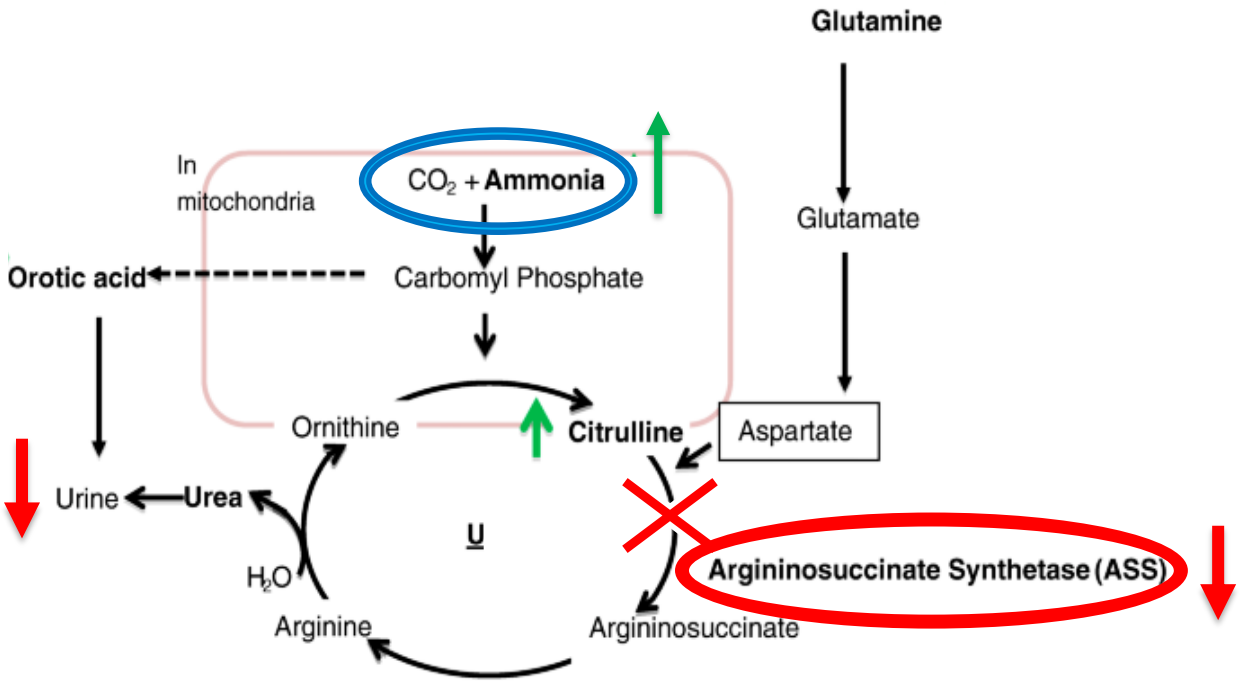


Digital image retrieved Mar 29, 2021 from https://www.nfed.org/learn/genetics-inheritance/

Digital video retrieved Mar 29, 2021 from https://www.youtube.com/watch?v=Nv6qUsKYodA

Biochemical features

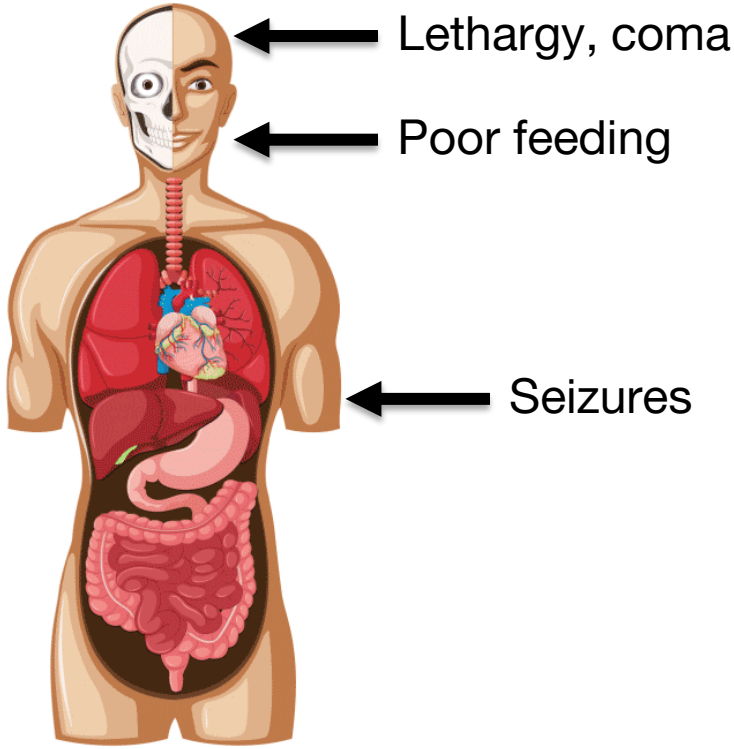
- Argininosuccinate synthetase 1 (ASS1) enzyme deficiency due to ASS1 gene mutations
  - ASS1 converts citrulline and aspartate to argininosuccinate, a central step in the urea cycle
  - ASS1 deficiency leads to ammonia buildup because the urea cycle is blocked



Digital image retrieved Nov 5, 2020
https://link.springer.com/article/10.1007/s12098-019-02905-8?shared-article-renderer

Early symptoms

- The first symptoms will present shortly after birth
- Most symptoms are the result of an excess of ammonia in the blood

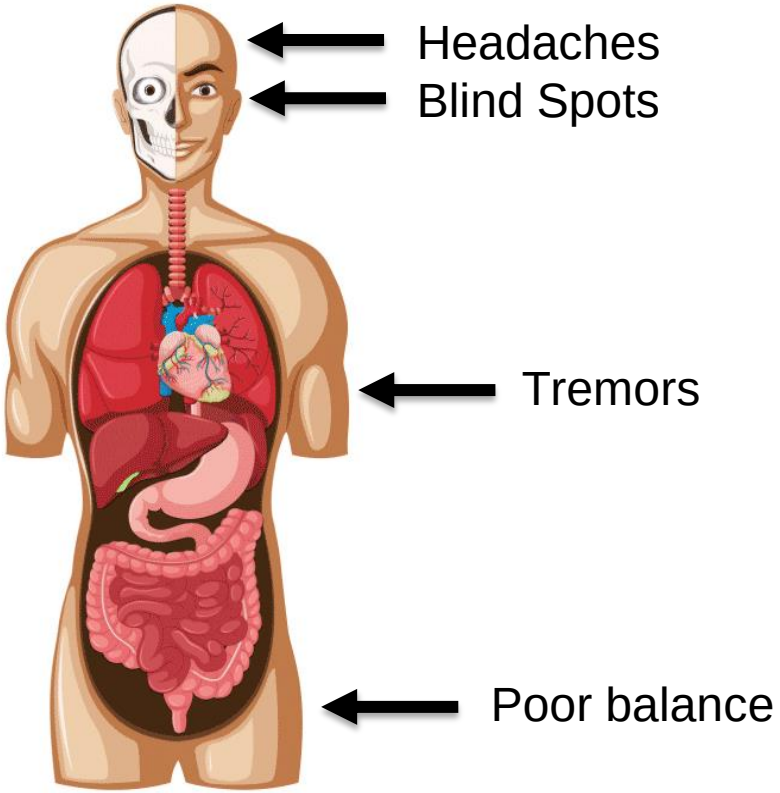


Digital image retrieved Dec 4, 2020 from https://byjus.com/biology/human-body-anatomy/

Late-onset symptoms

- As a child develops, different symptoms can appear as a result of unregulated NH_3 levels building up in the body

- Some individuals will experience no symptoms in their lifetime if their NH_3 levels are properly managed



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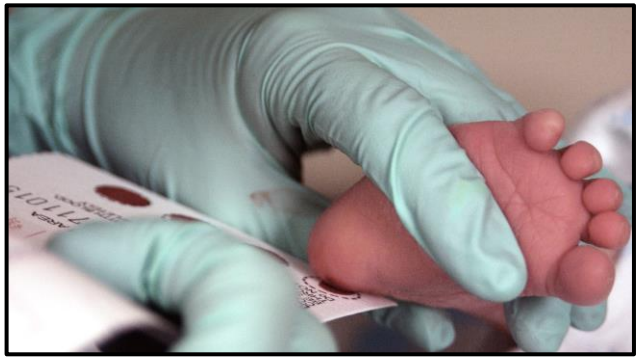
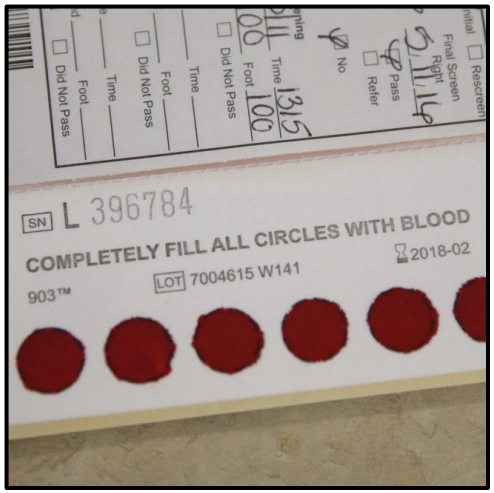
Diagnosis

- Newborn screening
  - Blood (heel-prick) test to assess elevated citrulline levels due to ASS1 enzyme deficiency
  - Follow up tests will be performed to confirm CTLN1 is the cause of the high citrulline levels



Digital image retrieved Dec 4, 2020 from https://en.wikipedia.org/wiki/Newborn_screening



Digital image retrieved Dec 4, 2020 from https://www.statnews.com/2018/04/30/new-newborn-screening-tests-delays/

Diagnosis

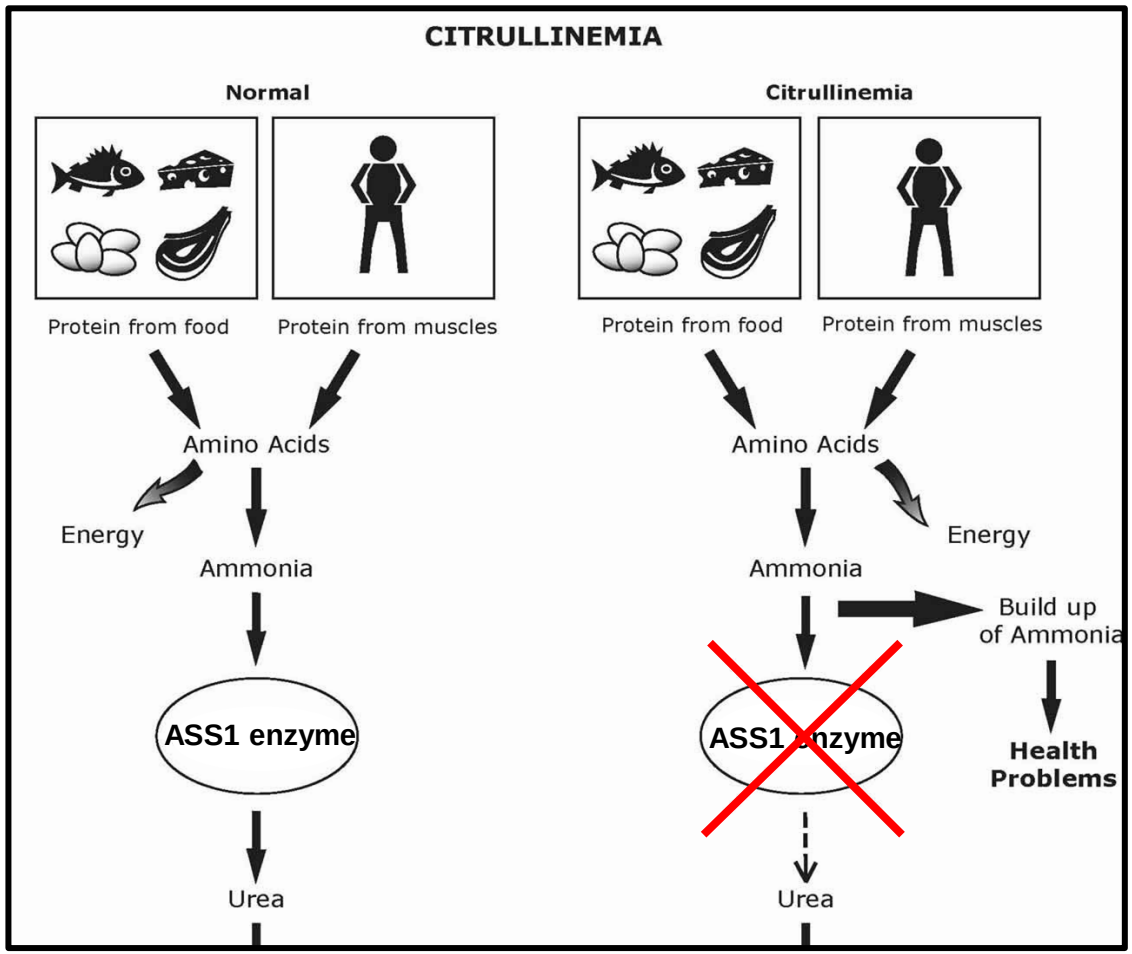
- Elevated plasma ammonia concentration
- Plasma quantitative amino acid analysis
  - Elevated citrulline levels
  - Absence of argininosuccinic acid
  - Low levels of arginine and ornithine
  - Increased levels of lysine, glutamine, and alanine
- Single-gene testing
  - Sequence analysis of the ASS1 gene

Digital image retrieved Dec 4, 2020 from https://www.ghp-news.com/2019-the-future-of-diagnosis-are-blood-tests-soon-to-be-a-thing-of-the-past-450b/

Digital image retrieved Dec 4, 2020 from https://health.clevelandclinic.org/should-you-get-the-genetic-test-for-alzheimers-disease-risk/

Therapy

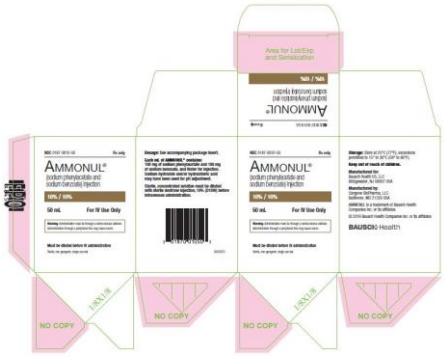
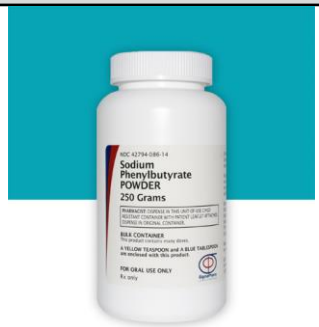
- The goal of therapy is to reduce the levels of ammonia, which is toxic
- Controlled, low-protein diet prevents ammonia buildup



Digital image retrieved Nov. 4, 2020 from https://healthjade.net/citrullinemia/

Therapy

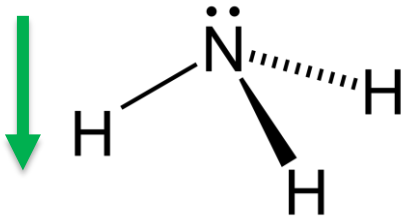
- Different medications can also provide mechanisms for the body to remove excess NH_3 built up due to an ASS1 deficiency

Arginine Supplements	Ammonul	Buphenyl
		
• Arginine is an intermediate of the urea cycle (UC) • Arginine supplements allows partial operation of the UC and helps rid the body of NH_3	• Ammonul is used as an adjunct therapy to treat CTLN1 • Ammonul conjugates with glycine and glutamine to provide an urea alternative for NH_3 excretion	• Buphenyl is metabolized to generate an intermediate • The intermediate conjugates with glutamine and provides a route for nitrogen waste disposal

Digital images retrieved Dec 5, 2020 from https://www.walgreens.com/store/c/nature%27s-bounty-l-arginine-1000-mg-amino-acid-supplement-tablets/ID=prod2497529-product, https://www.sigmapharm.com/products/sodium-phenylbutyrate-powder, https://www.drugs.com/pro/ammonul.html

Prognosis

- Type I patients may have normal growth and development
  - Episodes of high ammonia can lead to permanent brain and nerve damage
  - It is essential to monitor NH_3 levels throughout an affected individual's lifetime to prevent episodes of high ammonia



If ammonia levels are lowered…….

Normal growth and development

Digital images retrieved Apr 4, 2021 from https://en.wikipedia.org/wiki/Ammonia/, https://sites.google.com/site/harrymaofancymove/6-growth-and-development-of-children/2-when-should-i-be-concerned-about-my-child-s-growth-and-development

Additional support

- Along with the patient, family and friends could also use support. Some groups offer that support.

National Urea Cycle Disorders Foundation
75 South Grand Ave.
Pasadena, California, United States 91105
1-(800)-386-8233
Email: info@nucdf.org
Website: http://www.nucdf.org/

Urea Cycle Disorders Consortium
Children's National Medical Center
111 Michigan Avenue, NW
Washington, DC 20010
Phone: (202) 306-6489
Email: jseminar@childrensnational.org
Website: http://rarediseasesnetwork.epi.usf.edu/ucdc/index.html

Citrullinemia: Project Team

Name	Project role
Phoenix Grover	Therapy and team/text lead
Hannah Ackerman	Genetics & figures lead
Lauren Slattery	History and provenance
Serina Smith	Symptoms
Eliza Oser	Diagnosis
Abdel Osman	Prognosis & additional Support
Marilynn Ng	Occurrence frequency
Malvender Jagjit Singh	Biochemical features

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