Disease Name	**Citrullinemia type I**
Alternate name(s)	Argininosuccinic acid synthetase deficiency
Acronym	CIT type I
Disease Classification	Amino Acid Disorder
Variants	Yes
Variant name	Citrullinemia type I (adult and neonatal onset forms) – caused by *SLC25A13* mutations
Symptom onset	Neonatal with some variability
Symptoms	Potential lethal coma, seizures, anorexia, vomiting, lethargy, apnea and hypertonia. Possible enlarged liver.
Natural history without treatment	Mental delays due to hyperammonemia.
Natural history with treatment	Normal IQ and development are possible if no damage from initial or subsequent hyperammonemic episodes.
Treatment	Management of hyperammonemic cases with sodium benzoate and/or phenylacetate and arginine. Dietary restriction of protein, arginine and essential amino acid supplementation.
Physical phenotype	None
Inheritance	Autosomal recessive
General population incidence	Rare
Ethnic differences	Yes
Population	Citrullinemia type II is common in Japan
Ethnic incidence	N/A
Enzyme location	Widely expressed in tissues; liver, kidney and fibroblasts.
Enzyme Function	Catalyzes the conversion of citrulline and aspartic acid to argininosuccinic acid.
Missing Enzyme	Argininosuccinic acid synthetase
Metabolite changes	Hyperammonemia
Prenatal testing	Linkage analysis and enzyme testing
MS/MS Profile	N/A
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/215700
Genetests Link	www.genetests.org
Support Group	National Urea Cycle Disorders Foundation http://www.nucdf.org/ National Coalition for PKU and Allied Disorders http://www.pku-allieddisorders.org/ Children Living with Inherited Metabolic Diseases http://www.climb.org.uk/

Newborn Screening ACT Sheet
[Increased Citrulline]
Amino Aciduria/Urea Cycle Disorder

Differential Diagnosis: Citrullinemia I, argininosuccinic acidemia, citrullinemia II (citrin deficiency), pyruvate carboxylase deficiency.

Condition Description: The urea cycle is the enzyme cycle whereby ammonia is converted to urea. In citrullinemia and in argininosuccinic acidemia, defects in argininosuccinic acid (ASA) synthetase and lyase, respectively, in the urea cycle result in hyperammonemia and elevated citrulline

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YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- Immediate consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, vomiting, lethargy, hypotonia, tachypnea, seizures, and signs of liver disease). Measure blood ammonia. If any sign is present or infant is ill initiate emergency treatment for hyperammonemia in consultation with metabolic specialist.
- Transport to hospital for further treatment in consultation with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- Provide family with basic information about hyperammonemia.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma **ammonia** to determine presence of hyperammonemia. In citrullinemia, plasma amino acid analysis will show increased **citrulline** whereas in argininosuccinic acidemia, **argininosuccinic acid** will also be present. **Orotic acid**, which may be detected by urine organic analysis, may be increased in both disorders. **Note:** "Urine organic analysis" may not identify orotic acid in some laboratories because of the tests employed. In citrin deficiency, liver enzymes, lactic acid and bilirubin may be elevated. Blood lactate and pyruvate will be elevated in pyruvate carboxylase deficiency.

Clinical Considerations: Citrullinemia and argininosuccinic acidemia can present acutely in the newborn period with hyperammonemia, seizures, failure to thrive, lethargy, and coma. Later signs include mental retardation. Citrin deficiency may present with cholestatic liver disease in the newborn period. Pyruvate carboxylase deficiency produces coma seizures and life-threatening ketoacidosis. Treatment for ASA and citrullinemia is to promote normal growth and developmental and to prevent hyperammonemia.

Additional Information:

Gene Reviews
Genetics Home Reference

Referral (local, state, regional and national):

Testing
Clinical Services