Glutaric Aciduria

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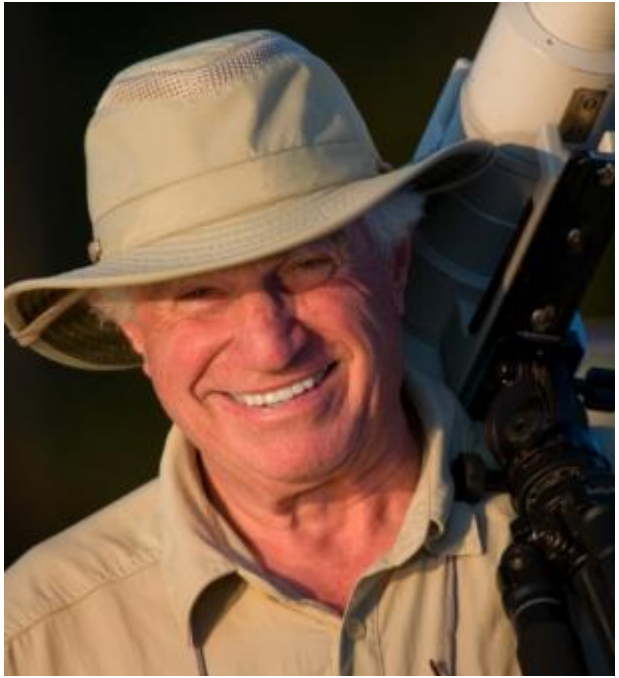
History

- Two siblings with a distinctive neuro-degenerative disorder were first reported in 1975 by Goodman and co-workers at the University of Colorado's Medical Center in Denver, Colorado

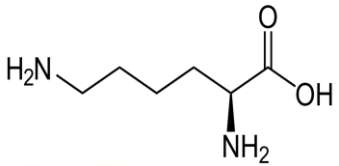
- Soon after the initial discovery, more than 200 cases were reported

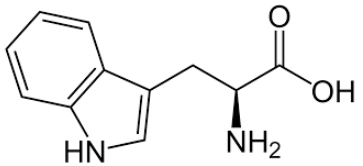


Dr. Stephen I. Goodman
Digital Image retrieved 12/03/20 from
http://www.simd.org/messages/StephenGoodmanSIMDTribute.pdf

Glutaric aciduria

- A disease that affects protein utilization
- Essential* amino acids lysine and tryptophan cannot be broken down





Digital Image retrieved 12/03/2020 from https://www.dailymail.co.uk/health/article-8074087/Eating-egg-day-NOT-increase-heart-disease-stroke-risk.html

Digital Image retrieved 12/03/2020 from https://www.cookinglight.com/news/white-stuff-in-raw-chicken-tendons

Digital Image retrieved 12/30/2020 from https://nuts.com/nuts/mixednuts/organic-raw.html

* Essential refers to those amino acids that the body cannot make and must therefore be obtained from the diet

Occurrence frequency

- 1/100,000 newborns worldwide
- 1/40,000 newborns in United States

Occurs more frequently in these communities:

- 1/250 Old Order Amish Community in Pennsylvania
- 1/300 Oji-Cree First Nations in Manitoba and Western Ontario, Canada
- 1/250 Irish Travellers in Ireland and the United Kingdom
- 1/250 Lumbee Tribe in North Carolina, United States
- 1/250 Xhosa Ethnic Group in South Africa

Symptoms

- Affected babies are born healthy, but may have an enlarged head
- As they grow older, the mental health of most of these babies will be altered and there will be functional alterations, which can trigger symptoms such as:
  - Excessive crying
  - Easy bruising
  - Low blood sugar
  - Nausea, vomiting, diarrhea
  - Hypotonia (floppiness)
  - Poor appetite
  - Low energy

Digital Image retrieved 12/03/20 from https://www.parents.com/baby/care/crying/understanding-baby-cries1/

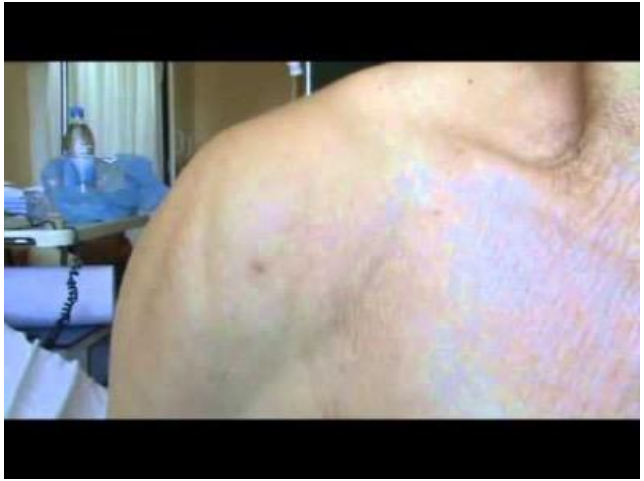
Digital Image retrieved 12/03/20 from https://www.spectrumnews.org/news/study-questions-large-head-size-in-autism/

Symptoms

Neurologic symptoms could include:

- Uncontrollable muscle spasms/contractions
- Repetitive, uncontrollable eye movements
- Developmental delay (highly variable)
- Coma, loss of consciousness

Muscle Twitching and Spasms

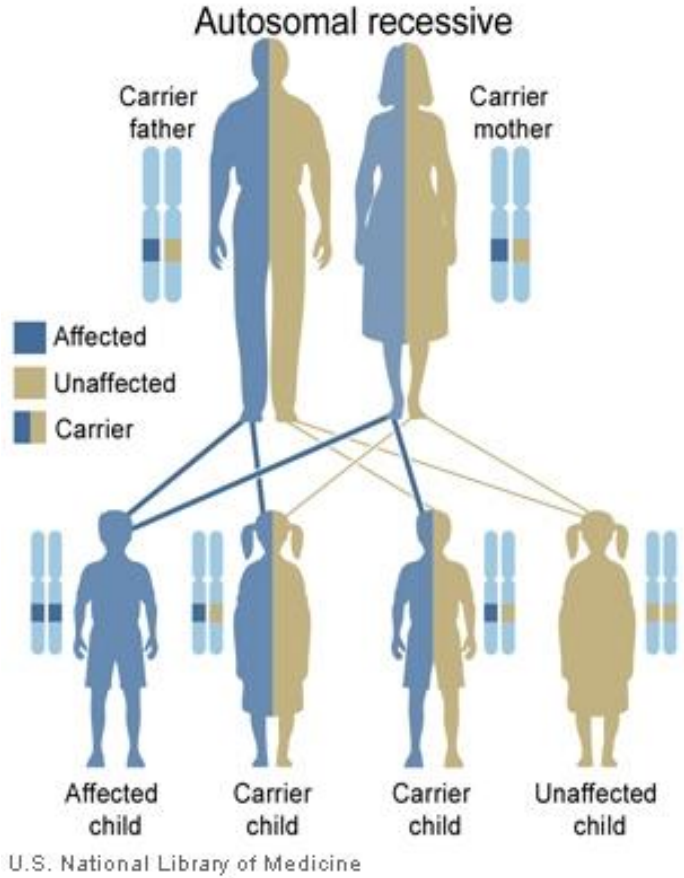


Video retrieved 12/03/20 from
https://www.youtube.com/watch?v=bt9VC-yD3RE

Genetics

- Inherited in an autosomal recessive pattern (i.e., requires two copies of the mutated gene to manifest disease)

- Mutation in the glutaryl-CoA dehydrogenase (GCDH) gene impairs activity of the GCDH enzyme



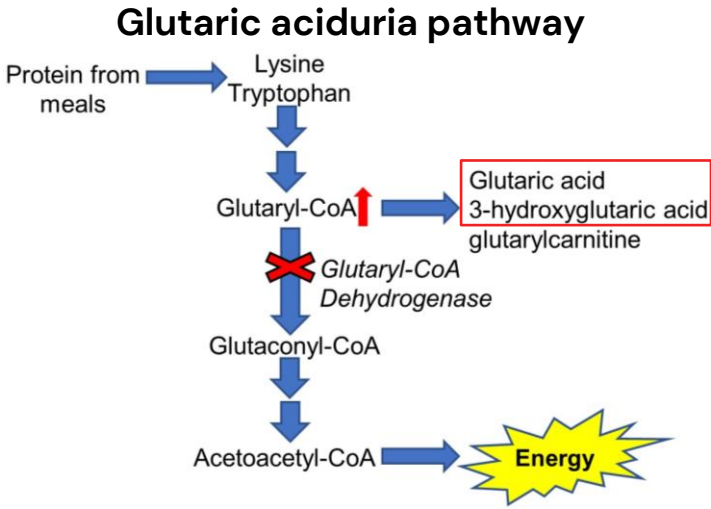
Digital Image retrieved 4/12/21 from https://treat-nmd.org/autosomal-recessive-inheritance/

Genetics

Digital video retrieved Apr 13, 2021 from
https://www.youtube.com/watch?v=Nv6qUsKYodA

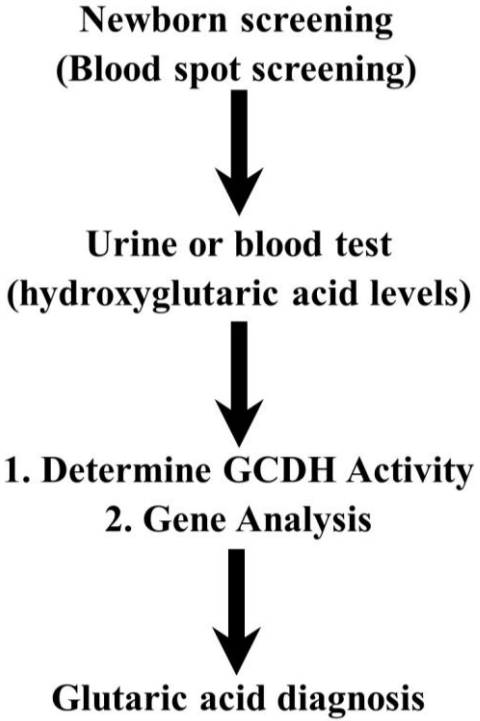
Biochemical features

- Glutaryl-coenzyme A dehydrogenase (GCDH) deficiency
- GCDH is needed to break down amino acids—lysine and tryptophan—when they are present in excess and they are broken down to yield energy
- Mutant GCDH is unable to completely breakdown lysine and tryptophan
  - Build-up of glutaric acid and 3-hydroxyglutaric acid, which are tissue irritants/neurotoxins
  - Basal ganglia, the brain structure involved in motor control, is affected by these built-up metabolites



Diagnosis

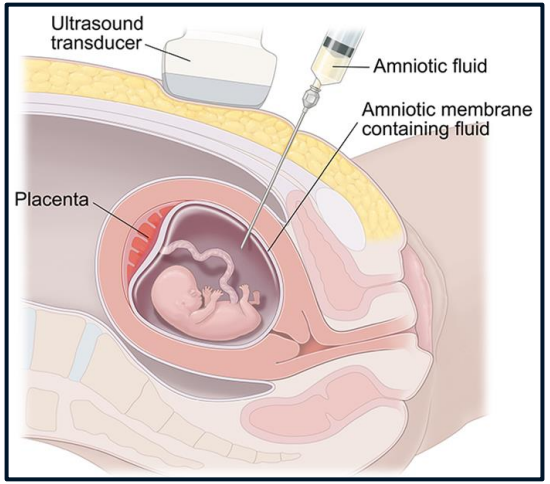
- Blood spot screening → further testing
  - Measure glutarylcarnitine levels
- Test urine or blood
  - Assess levels of 3-hydroxyglutaric acid
- GCDH enzyme activity and gene analysis confirm a diagnosis
  - Two mutations in GCDH gene needed for a diagnosis



GCDH: Glutaryl-CoA dehydrogenase

Prenatal diagnosis

- Available for parents with previously diagnosed child
- Week 16 to 20 during pregnancy
- Analyze amniotic fluid
  - GCDH mutation analysis
  - Metabolite analysis
    - Accumulation of C5DC (non-toxic) and glutaric acid (toxic) indicates glutaric aciduria
    - C5DC and glutaric acid result from excess glutaryl-CoA, which is caused by a GCDH deficiency



Digital image retrieved and modified 12/03/20 from https://www.babycenter.com/pregnancy/health-and-safety/amniocentesis_327

GCDH: Glutaryl-CoA Dehydrogenase
C5DC: glutarylcarnitine

Therapy

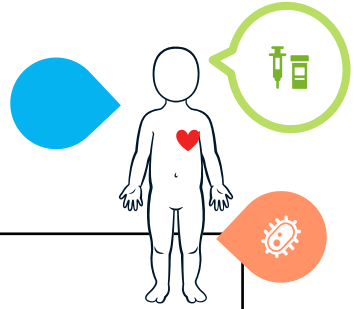
- Monitor levels of glutaric and 3-hydroxyglutaric acid in urine
  - Oral L-carnitine treatment
    - Promotes formation of C5DC (non-toxic)
    - Leads to lowering of glutaric and 3-hydroxyglutaric acids
  - Lysine-restricted diet
  - Amino acid supplements (with the exception of Lysine and Tryptophan)

C5DC: glutarylcarnitine

Lysine-rich foods

Digital Image retrieved 12/03/2020 from https://en.paperblog.com/foods-rich-or-high-in-lysine-you-can-eat-1776434/

Prognosis



	If treated at birth	If treated after 6 years of age	If not treated
Neurological damage	None - however, future complications are not known at this time	Irreversible damage; no further progression	Irreversible damage worsens: - Inability to control movement - Seizures - Comatose
Life expectancy	Normal	Between 25 years to normal (depending on when treatment begins)	Short (~25 years)

Available support

ORGANIZATIONS

Organic Acidemia Association
https://www.oaanews.org/ga-i.html

NIH Genetic and Rare Disease (GARD) Information Center
https://rarediseases.info.nih.gov/diseases/6522/glutaric-acidemia-type-i

FAMILY STORIES AND SUPPORT

Glutaric Acidemia: Hope & Help for Parents
https://theholymess.com/glutaric-acidemia-hope-help-for-parents/

Newborn Screening
http://www.newbornscreening.info/Parents/organicaciddisorders/GA2.html#5

Metabolic Diet App
https://www.metabolicdietapp.org/GA1.html

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Glutaric aciduria: Project team

Student	Project Role
Lauren Etzkorn	History
Natalie Hitt	Occurrence frequency
Jisoo Kim	Symptoms
Faith Beke	Genetics
Max Zywica	Biochemical features
Jack Millot	Diagnosis
Kendra Polson	Prognosis
Alexa Shin	Therapy
Jocelyn Hsu	Available support