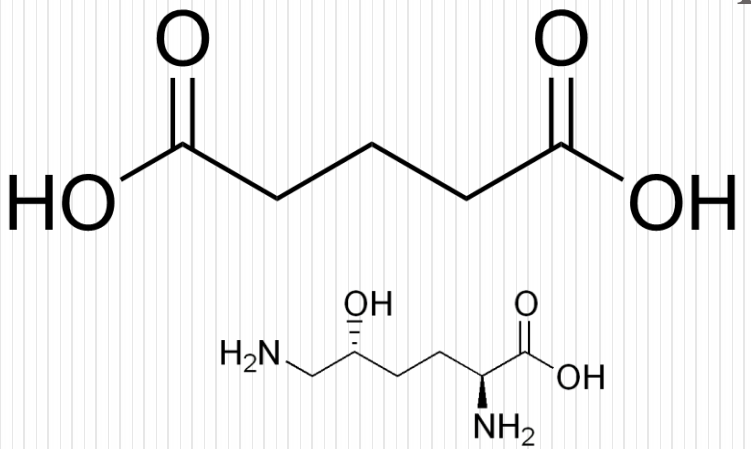
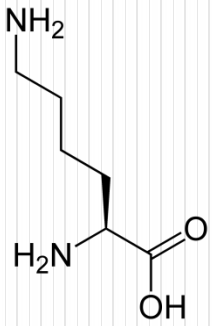
"The boy had been healthy until age 14 months, when he suffered a mild bout of diarrhea. A few hours later his body went limp. He never regained control of his muscles."

Glutaric Acidemia Type I

Linyi Gao

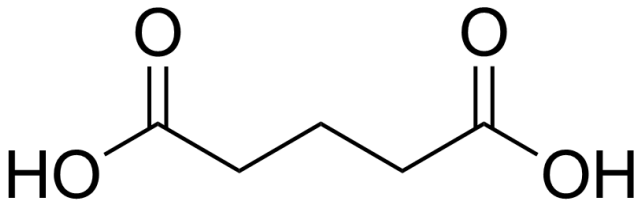


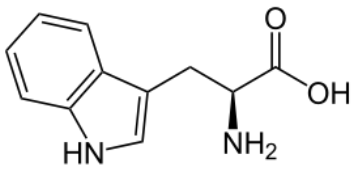


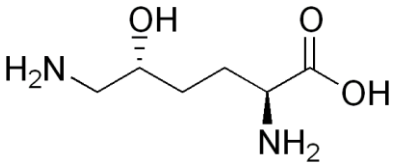
BIOC 118Q—Genomics and Medicine
Prof. Doug Brutlag
September 28, 2010

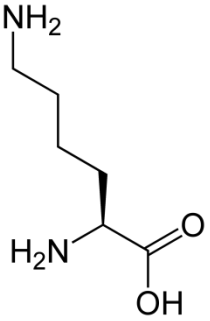
Glutaric Acidemia 1: Overview

- Inherited metabolic disorder
  - Old Order Amish, 1970s
- Defective metabolic enzyme (glutaryl-CoA dehydrogenase) → toxic products in cells, esp. glutaric acid (top left)
- Key: ages 6 months to 5 years
- Stress/illness → sudden brain damage & nervous system injury
  - Often fatal, may be progressive



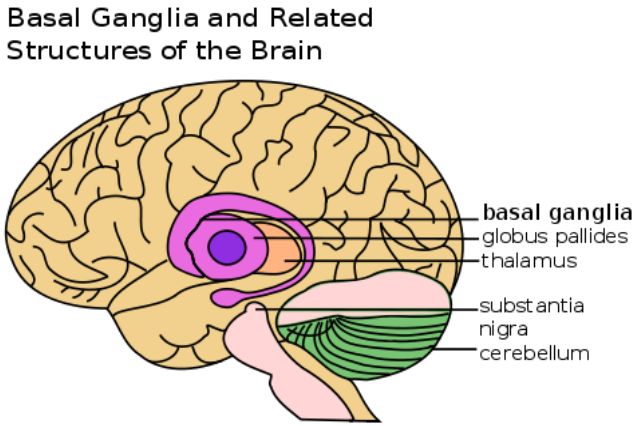


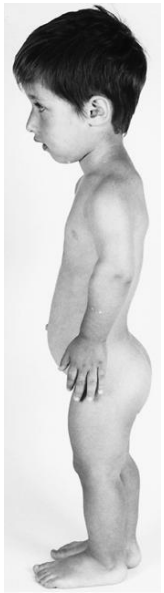




Classical Symptoms: A Sudden Killer

- I. Before crisis (~healthy):
  - Unusually large head (macrocephaly)
  - High glutaric acid in urine
- II. Sudden **encephalopathic crisis**
  - **6 months to 5 years of age**
  - Damage to the **basal ganglia** (Goodman et al. (1995)) **within hours**
  - **Preventable, but permanent once it has occurred**
- III. After crisis:
  - Movement disorders, paralysis, spasms, jerking, weakness
  - Body damaged for life; **intellect may remain intact**





http://www.nature.com/ejhg/journal/v14/n12/images/5201700f4.jpg

Key:
Avoid sudden brain damage before age 5

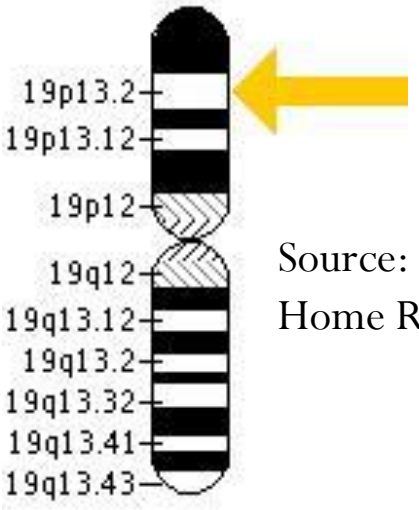
- After this age, the brain is more resistant to sudden damage
- Once damage has occurred, it is more or less permanent
- This is the main goal of diagnosis/treatment

Classical Diagnosis & Treatment

- **Diagnosis of GA1:**
  - **Examine urine** for excess glutaric acid and 3-hydroxyglutaric acid (GC/mass spectrometry)
    - Prenatal diagnosis
  - Confirmed by a deficiency of glutaryl-CoA dehydrogenase in **cultured fibroblasts**
- **Treatment—prevention:**
  - **Diet control**—Low lysine/tryptophan
  - Carnitine & riboflavin supplements
  - Aggressive management of fevers, vomiting, etc.
  - Brain injury rate 85-94% → 35% (Strauss et al. (2003))

Molecular Genetics

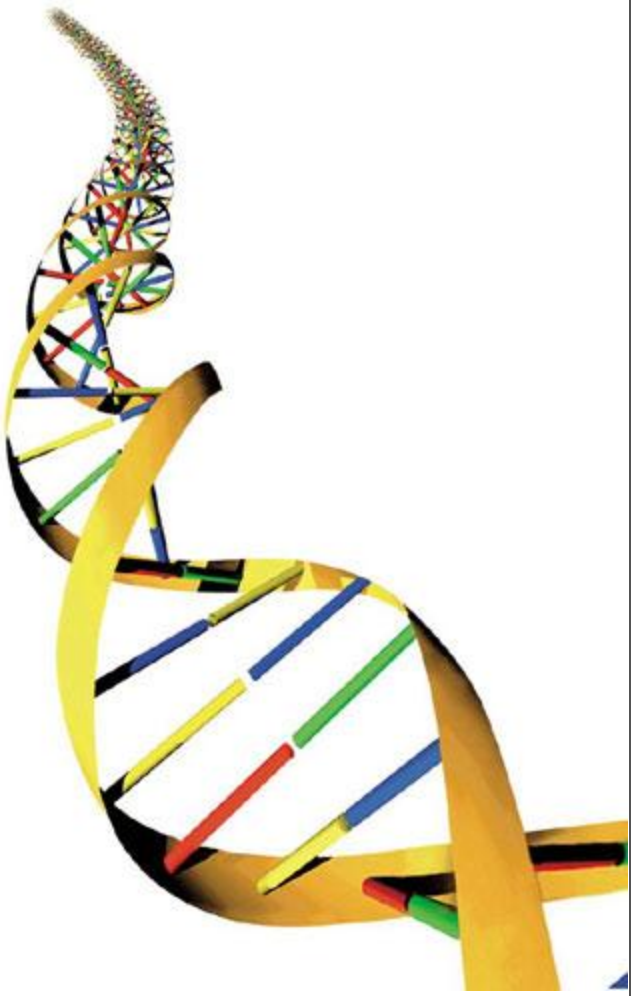
- Autosomal **recessive** (Mendelian)
- Defect in **GCDH gene** coding for glutaryl-CoA dehydrogenase
  - Chromosome 13
- >38 different mutations (Zschocke et al. (2000))
- Old Order Amish
  - 10% carrier frequency
- Worldwide: 1 in 100,000 infants
- High penetrance; variable expressivity



Source: Genetics Home Reference

Genetics, Diagnostics, & Therapies

- I. Genetics → better diagnostics?
  - Yes—**sequence analysis** of the entire coding region (offered by 13 of 32 labs) can verify presence of the disease
  - **Carrier testing** (13 labs)
  - Prenatal diagnosis (14 labs)
- II. Genetic information → new therapies?
  - Therapies not yet tailored toward specific genetic information, but genetics aid diagnosis, which is paramount to treatment



Laboratory information: GeneTests

References & Resources

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