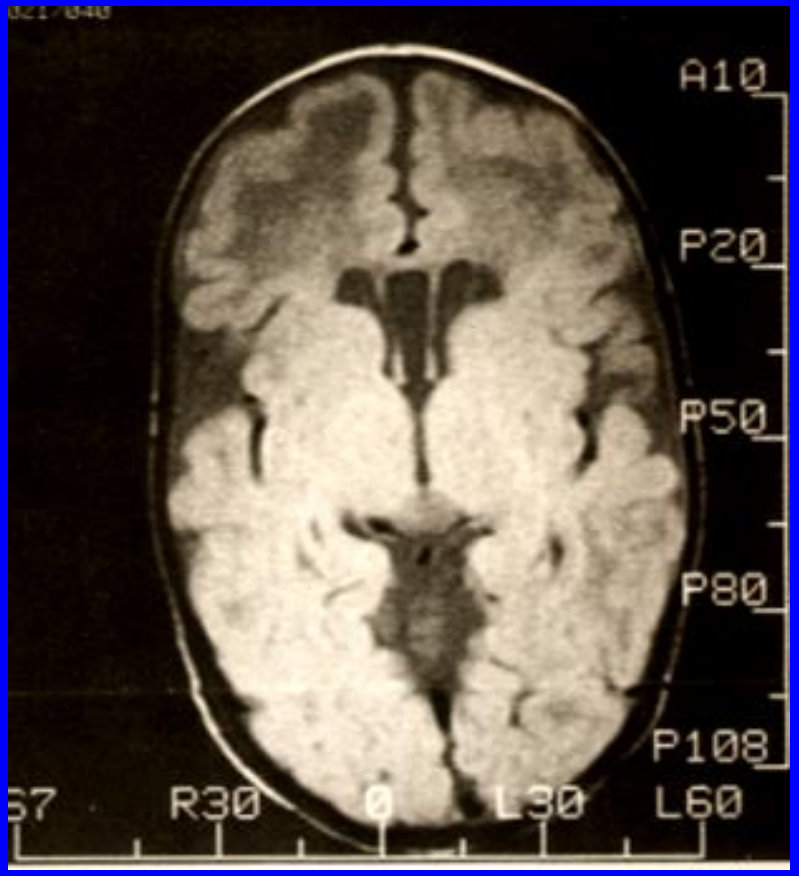
Glutaric Acidemia (type 1)
Overview

- Macrocephaly at birth
- Extrapyramidal movement disorder between 4 months and 3 years
- Acute neuronal loss in striatum
- Glutaric and 3-hydroxyglutaric acid in urine, serum and cerebrospinal fluid
- Glutaryl-CoA dehydrogenase deficiency
- Autosomal recessive; 1:100,000

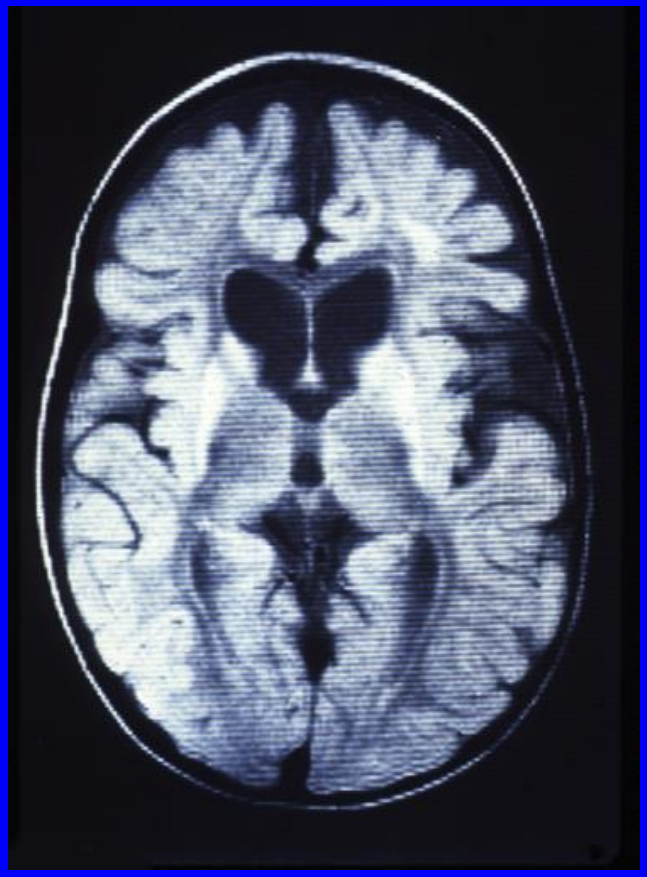
Glutaric acidemia (type 1)
Early Features

- 2/3 clinically normal at birth, and for months to years thereafter
- MRI shows frontal and temporal atrophy
- Basal ganglia normal



Glutaric acidemia (type 1)
MRI scan when symptomatic

- Acute encephalopathy before 3 years of age
- Acute degeneration, with loss of medium spiny neurons, and gliosis, in caudate and putamen

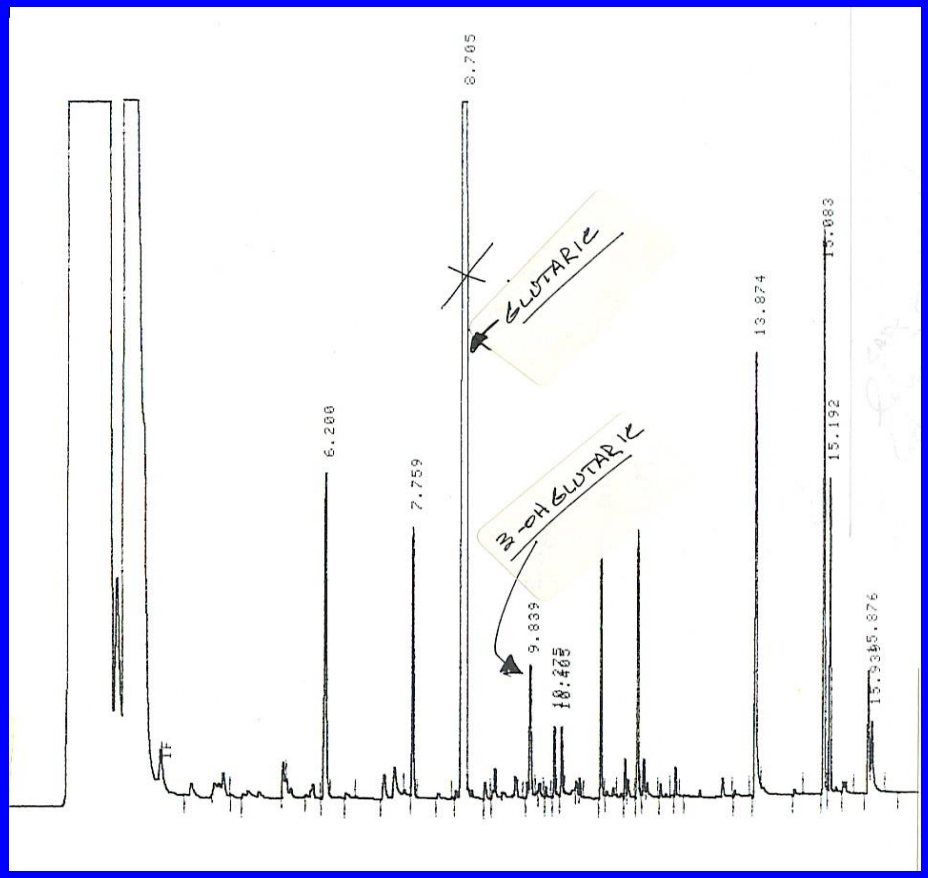


Glutaric acidemia (type 1)
Clinical features

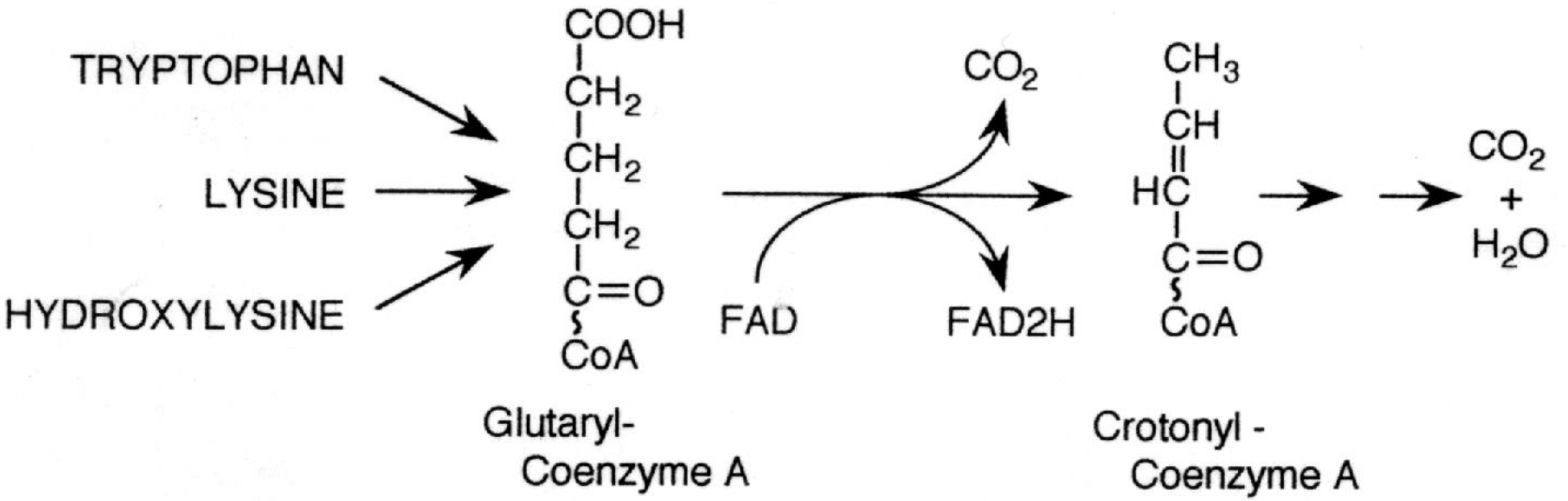
- Sudden extrapyramidal movement disorder, with dystonia and athetosis
- Static cerebral palsy
- Some, perhaps 10 percent, do not develop striatal damage but may develop very different symptoms as adults

Glutaric acidemia (type 1)
Urine Organic acids

- Glutaric and 3-OH-glutaric acid in urine, serum, and CSF
- May be consistent, intermittent, absent – or only 3-OH-glutaric
- Organic acid pattern depends on mutations



Glutaric acidemia (type 1)
Glutaryl-CoA Dehydrogenase

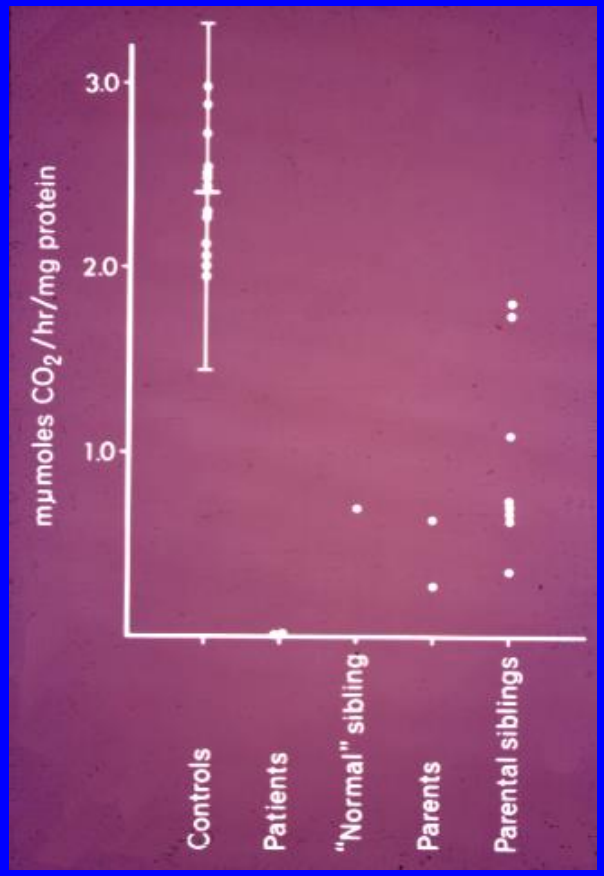


Glutaric acidemia (type 1)
Origin of 3-hydroxyglutaric

- Diagnostic metabolite, found only in GA1 and SCHAD deficiency, and physiological ketosis)
- Possibly due to oxidation of glutaryl-CoA to glutaconyl-CoA by another ETF-linked acyl-CoA dehydrogenase
- Not found in GA2, when all ETF-dependent dehydrogenases are deficient
- No direct supporting evidence

Glutaric acidemia (type 1)
Autosomal recessive inheritance

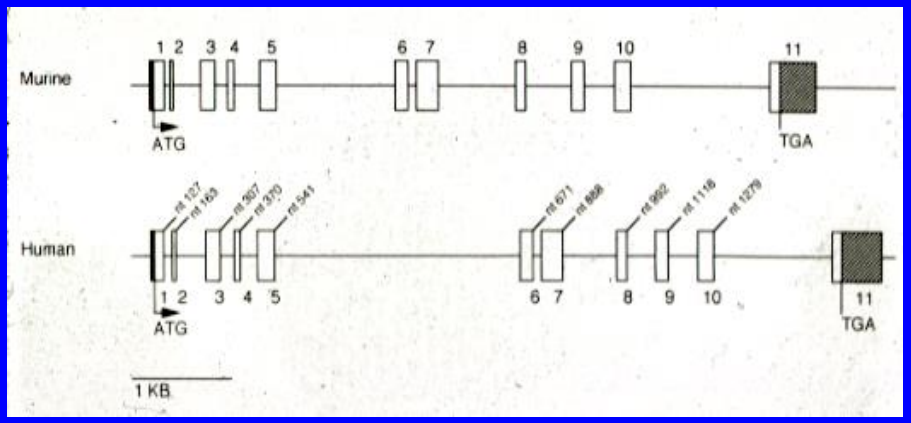
- No GCDH activity in WBC and fibroblasts of early patients
- Residual GCDH activity in patients with leaky mutations
- 20-25% activity in parents (obligate heterozygotes)



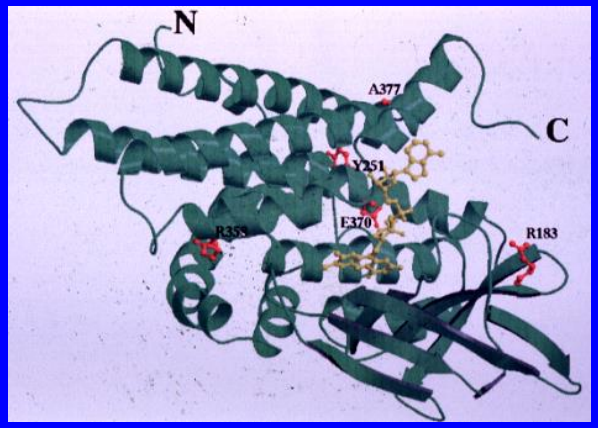
Glutaric acidemia (type 1)
Molecular biology

GCDH cloned

7kb gene on 19p, with 11 exons



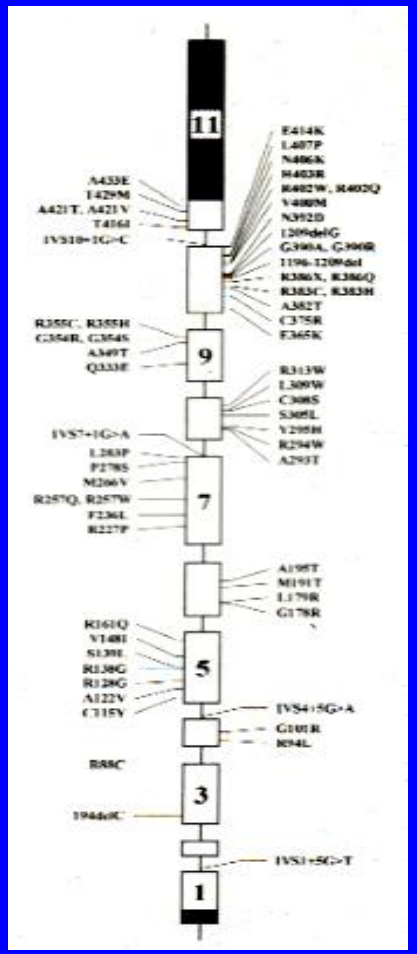
- GCDH overexpressed, crystallized, and structure resolved



- Mutations delineated

Glutaric acidemia (type 1)
GCDH mutations

- > 230 mutations
- R402W most common (25%)
- Some, eg, R227P and M415V, associated with minimal organic aciduria and c 25% activity in fibroblasts
- Genetic isolates



Glutaric acidemia (type 1)
Treatment

- Treatment after striatal injury ineffective
- Presymptomatic treatment prevents striatal injury in 65-90 % of patients; hence newborn screening
- Rx includes low lysine and tryptophan diet, oral arginine and L-carnitine, and prevention and early treatment of ketosis

Glutaric acidemia (type 1)
Newborn screening

- Screening newborn blood spots for glutarylcarnitine by tandem mass spectrometry detects most, but not all, GA1 patients

- A few patients with leaky mutations (and particular mutations) are missed

Glutaric acidemia (type 1)
Pathogenesis of brain damage

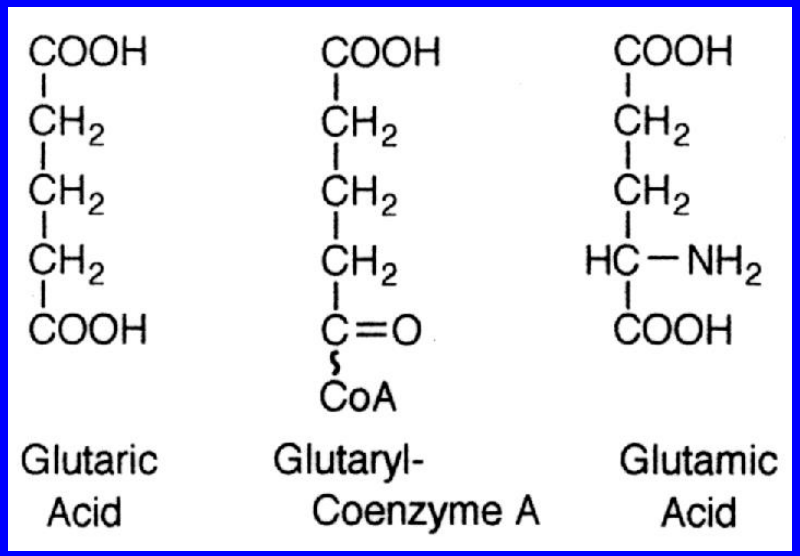
- Theory of pathogenesis must explain
  - in-utero damage to frontal and temporal lobes
  - post-natal neuronal death restricted to striatum
  - striatal window of vulnerability

Glutaric acidemia (type 1)
Pathogenesis - 1

- Glutaric and 3-hydroxyglutaric concentrations in brain exceed those in blood and CSF
- Glutaric and 3HG cannot cross blood-brain barrier, so glutaric and 3HG in brain are made in brain
- Glutaric and 3HG increase in brain during catabolism, when blood lysine increases and crosses blood-brain barrier

Glutaric acidemia (type 1)
Pathogenesis - 2

- Glutaric and 3-hydroxy-glutaric acids are similar to glutamate
- an excitatory neuro-transmitter, and
- source of GABA (γ-amino-butyric acid), an inhibitory neurotransmitter

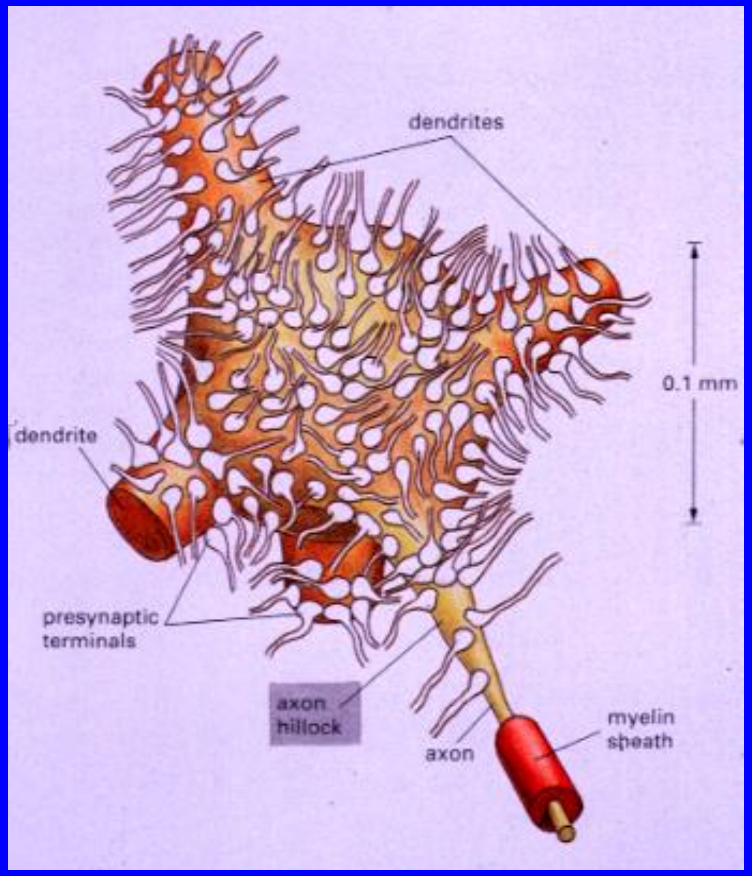


Glutaric acidemia (type 1)
Pathogenesis - 3

- Striatal vulnerability may be due in some way to its higher dependence on glutamate as a neurotransmitter
- Glu (and 3HG) inhibit GABA synthesis
- Glu inhibits synaptosomal glutamate uptake
- 3HG (and ?G) kill striatal neurons in culture and in vivo; this is prevented by NMDA-receptor antagonists

Glutaric acidemia (type 1)
Pathogenesis - 4

- Combined effects may be to lower resting potential, causing …
- hyperexcitability and "soft" neurological signs
- ? Sustained depolarization when hypoglycemic
- Temporal vulnerability may be due to developmental changes in NMDA receptor subunits



Glutaric acidemia (type 1)
Cause of abnormal CT/MRI at birth

- Hypothesis
- Neuronal damage and brain swelling in-utero causes macrocephaly
- Subsequent cell death and cortical atrophy leaves enlarged cranium with hydrocephalus ex-vacuo

Glutaric acidemia (type 1)
Successes

- Recognition, and resolution of biochemical and molecular basis
- Development of treatment algorithms
- Success of expanded newborn screening

Glutaric acidemia (type 1)
Questions

- Pathogenesis of acute striatal toxicity
- Origin of 3-hydroxyglutaric, particularly if it is the most important neurotoxin
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- Treatment of infants damaged in-utero
- Pathogenesis and treatment of adult-onset disease