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Glutaric Acidemia Type 1

Synonyms: GA-1, GCDH Deficiency, Glutaric Aciduria Type 1, Glutaryl-CoA Dehydrogenase Deficiency

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Summary

Clinical characteristics

The phenotypic spectrum of untreated glutaric acidemia type 1 (GA-1) ranges from the more common form (infantile-onset disease) to the less common form (later-onset disease – i.e., after age 6 years). Of note, the GA-1 phenotype can vary widely between untreated family members with the same genotype, primarily as a function of the age at which the first acute encephalopathic crisis occurred: three months to six years in infantile-onset GA-1 and after age six years in later-onset GA-1. Characteristically these crises result in acute bilateral striatal injury and subsequent complex movement disorders. In the era of newborn screening (NBS), the prompt initiation of treatment of asymptomatic infants detected by NBS means that most individuals who would have developed manifestations of either infantile-onset or later-onset GA-1 remain asymptomatic; however, they may be at increased risk for other manifestations (e.g., renal disease) that are becoming apparent as the understanding of the natural history of treated GA-1 continues to evolve.

Diagnosis/testing

Because the early initiation of treatment dramatically improved the outcome for persons with GA-1, an international guideline group has recommended NBS. The diagnosis of GA-1 in a proband with a positive NBS result or suggestive biochemical and/or clinical findings is confirmed by identification of biallelic pathogenic variants in *GCDH* or, when molecular genetic test results are uncertain, by detection of significantly reduced activity of the enzyme glutaryl-CoA dehydrogenase (GCDH) in cultured fibroblasts or leukocytes.

Management

Prevention of primary manifestations: When GA-1 is suspected during the diagnostic evaluation of a newborn with an elevated concentration of 3-OH-GA in plasma or urine, metabolic treatment should be initiated immediately. Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a

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multidisciplinary approach by experienced subspecialists from a specialized metabolic center. The main principles of treatment are to reduce lysine oxidation and enhance physiologic detoxification of glutaryl-CoA. Combined metabolic therapy includes low-lysine diet, carnitine supplementation, and emergency treatment during episodes with the goal of averting catabolism and minimizing CNS exposure to lysine and its toxic metabolic byproducts.

Surveillance: Regular evaluations by a metabolic specialist and metabolic dietician; routine evaluation of growth parameters and head circumference, developmental progress and educational needs, clinical signs and symptoms of movement disorders, biochemical parameters and renal function (in adolescents and adults).

Agents/circumstances to avoid: Excessive dietary protein or protein malnutrition inducing catabolic state, prolonged fasting, catabolic illness (intercurrent infection; brief febrile illness post vaccination), inadequate caloric provision during other stressors (e.g., surgery or procedure requiring fasting/anesthesia).

Evaluation of relatives at risk: Testing of all at-risk sibs of any age to allow for early diagnosis and treatment. For at-risk newborn sibs when prenatal testing was not performed: in parallel with NBS either test for the familial *GCDH* pathogenic variants or measure urine organic acids, plasma amino acids, and acylcarnitine profile.

Pregnancy management: It is recommended that care for a pregnant woman with GA-1 be provided by a multidisciplinary team including the treating obstetrician, a metabolic physician, and a specialist metabolic dietician.

Genetic counseling

GA-1 is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *GCDH* pathogenic variants in an affected family member are known, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic diagnosis are possible.

Diagnosis

Guidelines for diagnosis and management of glutaric acidemia type 1 (GA-1) due to deficiency or absence of functional glutaryl-CoA dehydrogenase were developed in 2007 and recently revised [Boy et al 2017b].

Suggestive Findings

Scenario 1: Positive Newborn Screening (NBS)

GA-1 **should be suspected** in infants with a positive NBS result. NBS for GA-1 primarily relies on measuring glutarylcarnitine (C5DC) in dried blood spots, which has been shown to have 96% sensitivity [Boy et al 2018]. Positive C5DC values (i.e., those above the cutoff reported by the screening laboratory) require follow-up biochemical testing with **either** urine organic analysis **or** quantitative glutaric and 3-hydroxyglutaric acid, with preference for quantitative studies if available. If either is abnormal, treatment (see Management) and testing to establish a definitive diagnosis (see Establishing the Diagnosis) should be initiated concurrently [Boy et al 2017b].

For more information on false positive and false negative results for NBS for glutaric acidemia type 1 click here (pdf).

Scenario 2: Symptomatic Individuals

GA-1 **should be considered** in symptomatic individuals with the following supportive clinical, neuroimaging, and laboratory findings.

Clinical findings

- Progressive macrocephaly is observed in 75% of affected individuals and may be present prenatally [Bjugstad et al 2000]. Since macrocephaly has many etiologies, additional brain MRI findings characteristic of GA-1 would typically be the indication to consider the diagnosis of GA-1.
- Untreated infantile-onset GA-1 (resulting from false negative NBS, NBS not performed, or caregivers noncompliant with recommended treatment) typically manifests as acute encephalopathic crisis (hypotonia, loss of motor skills, feeding difficulty, and sometimes seizures) usually occurring in the setting of an intercurrent infectious illness, fasting, or other physiological stressor. Acute neurologic injury most commonly occurs between ages three months and three years; it is followed by irreversible basal ganglia injury [Kölker et al 2006]. It may also manifest as insidious-onset basal ganglia injury without a clear acute encephalopathic crisis [Boy et al 2019].
- Untreated late-onset GA-1 may manifest as other nonspecific neurologic abnormalities including headaches, vertigo, dementia, and ataxia [Boy et al 2018].

Brain MRI findings in 18 Dutch individuals ages 11 months to 33 years with GA-1 (most of whom were diagnosed prior to universal GA-1 NBS) included the following [Vester et al 2016]:

- Open opercula (n=15)
- Widening of CSF spaces / ventriculomegaly (9)
- Attenuated signal from basal ganglia (8)
- White matter abnormalities (5)
- Subdural hemorrhage (SDH), probably due to stretching of bridging veins in the enlarged extra-axial fluid spaces (1). SDH is typically associated with frontotemporal hypoplasia.

Preliminary laboratory findings include significantly elevated concentrations of the following metabolites using gas chromatography / mass spectrometry or electrospray-ionization tandem mass spectrometry [Baric et al 1999, Chace et al 2003]:

- Glutaric acid
- 3-hydroxyglutaric acid
- Glutarylcarnitine (C5DC)
- Glutaconic acid

Note: Because elevations of these metabolites individually are not specific to GA-1, additional testing is required to establish the diagnosis of GA-1 (see Establishing the Diagnosis).

Establishing the Diagnosis

The diagnosis of GA-1 in a proband with suggestive biochemical and/or clinical findings **is confirmed** by identification of biallelic pathogenic variants in *GCDH* (Table 1) or, when molecular genetic test results are uncertain, by detection of significantly reduced activity of the enzyme glutaryl-CoA dehydrogenase in cultured fibroblasts or leukocytes.

Molecular genetic testing approaches can include **gene-targeted testing** (single-gene testing or use of a multigene panel) and **comprehensive genomic testing** (typically exome sequencing) depending on the indications for testing. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

- Infants with positive newborn screening and follow-up testing (see Scenario 1) are likely to be diagnosed using gene-targeted testing.

- Symptomatic individuals with nonspecific clinical and imaging findings in whom the diagnosis of GA-1 has not been considered (see Scenario 2) are more likely to be diagnosed using comprehensive genomic testing [Marti-Masso et al 2012].

Scenario 1

When NBS results and other laboratory findings suggest the diagnosis of GA-1, the recommended molecular genetic testing approach is **single-gene testing**. Sequence analysis of *GCDH* is generally performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found. The sensitivity of molecular genetic testing for GA-1 is 98%-99% [Zschocke et al 2000].

Scenario 2

When the diagnosis of GA-1 has not been considered, either a **multigene panel** or **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) are options.

- **A multigene panel** that includes *GCDH* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) includes **exome sequencing** (most commonly used) and **genome sequencing**. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of GA-1.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Glutaric Acidemia Type 1

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GCDH	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	Not available [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Stenson et al [2014]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. While no data on detection rate of gene-targeted deletion/duplication analysis are available, the authors estimate this number to be extremely low based on extensive sequencing of *GCDH* in a multiethnic American population in Dr Goodman's clinical laboratory [SI Goodman, personal communication].

Quantification of glutaryl-CoA dehydrogenase enzyme activity in cultured fibroblasts or leukocytes by a clinical laboratory may help confirm the diagnosis of GA-1 in newborns with positive NBS results when *GCDH* sequencing is equivocal (e.g., only 1 or no detectable pathogenic variants, variants of unknown significance) or glutaric acid (GA) and 3-hydroxyglutaric acid (3-OH-GA) levels in blood and/or urine are equivocal.

Shortcomings of enzymatic testing on fibroblast cultures or leukocytes include the following:

- Difficulty distinguishing carriers (i.e., heterozygotes for one *GCDH* pathogenic variant) – who by definition are not affected – from affected individuals (i.e., those with biallelic *GCDH* pathogenic variants) [Goodman & Kohlhoff 1975, Goodman et al 1975]. This is particularly true for the dominant negative variant (c.553_570del18) [Bross et al 2012].
- The relatively large blood volumes (3-5 mL) required to reliably perform the leukocyte assay
- The limited number of clinical laboratories offering enzymatic testing on leukocytes

Clinical Characteristics

Clinical Description

The phenotypic spectrum of untreated glutaric acidemia type 1 (GA-1) ranges from the more common form (infantile-onset disease) to the less common form (later-onset disease after age 6 years). Of note, the GA-1 phenotype can vary widely among untreated family members with the same genotype, primarily as a function of the age at which the first acute encephalopathic crisis occurred: three months to three years in infantile-onset GA-1 and after age six years in later-onset GA-1 [López-Laso et al 2007, Wang et al 2014]. Characteristically these crises result in acute bilateral striatal injury and subsequent complex movement disorders. Patients may also develop insidious-onset basal ganglia injury in the absence of an identified acute encephalopathic crisis.

In the era of newborn screening (NBS), the prompt initiation of treatment of asymptomatic infants detected by NBS means that most individuals who would have developed manifestations of either infantile-onset or later-onset GA-1 remain asymptomatic.

Infantile-onset GA-1. If untreated, 80%-90% of children with infantile-onset GA-1 will experience an acute encephalopathic crisis, 95% of which occur in the first 24 months of life. These crises can be precipitated by intercurrent febrile illness, febrile reaction to vaccinations, or fasting and catabolic stressors associated with anesthesia and surgical procedures [Kölker et al 2006, Boy et al 2017b]. Characteristically these crises result in

acute bilateral striatal injury and are followed (typically between ages 3 months and 3 years; in rare cases, between ages 3 and 6 years) by progressive complex neurologic movement disorders. Disability and mortality are high after acute crises [Kyllerman et al 2004, Kölker et al 2006].

Dietary treatment and intense emergency treatment during intercurrent illness (see Management) have reduced the frequency of acute encephalopathic crises and movement disorders to 10%-20%.

Subdural hemorrhages, a rare manifestation of GA-1, may develop even in individuals diagnosed on NBS, managed appropriately, and without macrocephaly [Zielonka et al 2015, Ishige et al 2017]. Subdural hemorrhages may appear spontaneously or following mild head trauma in GA-1; they can also resolve spontaneously. Isolated subdural hemorrhage without other features of GA-1 on brain MRI is extremely uncommon [Vester et al 2015, Vester et al 2016].

Seizures are reported in 7% of individuals with GA-1 [Kölker et al 2015a]. While self-limited seizures may accompany the acute encephalopathic crisis, in other instances they may be the presenting manifestation [McClelland et al 2009]. Infantile spasms have been reported in some [Young-Lin et al 2013, Liu et al 2015].

When GA-1 is diagnosed after the onset of neurologic manifestations, outcome is poor and the therapeutic effect of the usual interventions is more limited [Hoffmann et al 1996, Bjugstad et al 2000, Busquets et al 2000a, Kyllerman et al 2004, Kölker et al 2006, Kamate et al 2012, Wang et al 2014]. Nonetheless, therapeutic intervention may prevent additional progressive neurologic deterioration in some [Hoffmann et al 1996, Bjugstad et al 2000, Kölker et al 2006, Badve et al 2015, Fraidakis et al 2015].

With early diagnosis and adherence to treatment, 80%-90% of individuals with GA-1 remain largely asymptomatic [Strauss et al 2011, Viau et al 2012, Couce et al 2013, Lee et al 2013, Boy et al 2018].

Insidious onset of manifestations was previously seen in an estimated 10%-20% of symptomatic individuals [Kölker et al 2006]; it now appears to be more common because early diagnosis and treatment of GA-1 have reduced the incidence of acute encephalopathic crises [Boy et al 2018].

Individuals who adhere to maintenance and emergency treatments rarely develop dystonia; those who do not are at high risk of developing a movement disorder [Kölker et al 2007, Heringer et al 2010, Strauss et al 2011, Kölker et al 2012, Boy et al 2018]. Those who have insidious onset generally have less severe movement disorders and less extensive lesions on brain MRI than those with acute encephalopathic crisis [Boy et al 2019]. The insidious phenotype may correlate with lack of adherence to chronic dietary treatment [Boy et al 2018].

Late-onset GA-1. Late-onset GA-1 is defined as onset of manifestations after age six years. Some individuals with late-onset GA-1 (e.g., mothers diagnosed due to the birth of a child with an abnormal NBS result) are entirely asymptomatic. Others have a variety of neurologic findings. Among eight symptomatic individuals ages eight to 71 years, the following were observed: chronic headaches (4), macrocephaly (4), epilepsy (2), tremor (2), and dementia (2). All had MRI evidence of frontotemporal hypoplasia and abnormal signal of the white matter; five had subependymal nodules. All showed the high excreting phenotype [Boy et al 2017a]. Others have reported clinical and neuroimaging findings [Külkens et al 2005, Pierson et al 2015, Zhang & Luo 2017].

Other reported manifestations of late-onset GA-1 include the following:

- Peripheral neuropathy (1 adult) [Herskovitz et al 2013]
- Brain neoplasms (in several adults and children) [Korman et al 2007, Burlina et al 2012, Herskovitz et al 2013, Pierson et al 2015, Serrano Russi et al 2018]. This finding has led to an as-yet unsubstantiated speculation about possible increased susceptibility to brain neoplasms in adults.

Non-neurologic disease manifestations observed in individuals in GA-1 regardless of age of onset. Chronic kidney disease may occur in those with GA-1, even with adherence to treatment, and may be an extracerebral manifestation in adults with GA-1 [Kölker et al 2015b].

Note: Infants with biochemical findings consistent with GA-1 on NBS, but normal blood levels of GA and 3-OH-GA and only one identifiable *GCDH* pathogenic variant, may warrant close clinical follow up. However, given the high sensitivity of *GCDH* molecular genetic testing, the chances that an infant with these findings is affected and at risk of developing acute striatal necrosis are low.

Genotype-Phenotype Correlations

Most *GCDH* variants reported to date are missense variants [Schmiesing et al 2017].

GA-1 biochemical (excreter) subtypes. GA-1 was originally divided into two arbitrarily defined biochemical subtypes: high excreters of urinary glutaric acid (GA) and low excreters of urinary GA [Baric et al 1999]. High excreters and low excreters are at the same risk for striatal injury [Christensen et al 2004, Kölker et al 2006]. While excreter status has no clear correlation with the clinical phenotype in childhood, evidence suggests that high excreters have higher concentrations of GA and 3-OH-GA in the CNS and have increased prevalence of progressive white matter lesions on MRI [Boy et al 2017a].

- High excreters have no or very low glutaryl-CoA dehydrogenase activity (0%-3%) [Goodman et al 1998, Baric et al 1999, Busquets et al 2000b]. NBS sensitivity for the high excreter biochemical phenotype is 100% [Boy et al 2018].
- Low excreters have up to 30% residual glutaryl-CoA dehydrogenase activity [Goodman et al 1998, Busquets et al 2000b]. They have biallelic *GCDH* pathogenic variants, at least one of which is a hypomorphic missense variant. NBS sensitivity for the low excreter biochemical phenotype is 84% [Boy et al 2018]. See Table 10 for details on variants associated with low excreter status.

Prevalence

Well over 500 individuals with GA-1 have been reported to date [Boy et al 2017b]. Prevalence estimates for GA-1 vary between 1:30,000 and 1:100,000-110,000 [Kyllerman & Steen 1980, Lindner et al 2004, Tsai et al 2017].

Details on founder variants reported in Ojibway-Cree First Nation Canadians of Manitoba and Ontario, South African Xhosa peoples, Pennsylvania Amish, Lumbee Native Americans of North Carolina, and Irish Traveler communities in the Republic of Ireland are included in Table 10.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *GCDH*.

Differential Diagnosis

Table 2. Other Genes of Interest in the Differential Diagnosis of Glutaric Acidemia Type 1 (GA-1)

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features of Differential Diagnosis Disorder		
			Significant overlapping features	Other clinical features	Laboratory/Imaging findings
ETFA *ETFB* *ETFDH*	Glutaric acidemia type 2 (multiple acyl-CoA dehydrogenase deficiency; OMIM 231680)	AR	↑ glutaric acid	• Hypotonia • Liver dysfunction • Muscle weakness • Cardiomyopathy	• May result in suspected GA-1 from NBS result • ↑ plasma GA, 3-OH-GA, & C5DC acylcarnitine as well as many other acylcarnitine species [1] • ↑ ethylmalonic acid • ↑ suberylglycine, hexanoylglycine, isovalerylglycine, isobutyrylglycine • Neuronal migration defects & leukodystrophy on MRI
SUGCT	Glutaric acidemia type 3 (OMIM 231690)	AR	↑ glutaric acid	(No clinical phenotype)	• Key diagnostic marker: massively ↑ GA/3-OH-GA ratio (not seen in GA-1) • ↑ plasma GA • Normal or minimally ↑ 3-OH-GA & C5DC acylcarnitine • May be only a biochemical phenotype
ASPA	Canavan disease	AR	Macrocephaly	• Hypotonia • Developmental delay & regression • Seizures • Optic atrophy	• N-acetyl aspartate in urine • Leukodystrophy on MRI
>60 genes (mt & nuclear) [1]	Leigh syndrome (see Mitochondrial DNA-Associated Leigh Syndrome and NARP & Nuclear Gene-Encoded Leigh Syndrome Overview)	Mat AR (XL)	Metabolic encephalopathy predisposing to basal ganglia disease	• Regression w/illness • Progressive course	• ↑ lactic acid in CSF or blood • ↑ alanine • Metabolic "stroke" &/or basal ganglia injury • Possible white matter abnormality on MRI • Abnormal signal of the brain stem & dentate nuclei

Table 2. continued from previous page.

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features of Differential Diagnosis Disorder		
			Significant overlapping features	Other clinical features	Laboratory/Imaging findings
MCEE *MMAA* *MMAB* *MMADHC* *MMUT*	Isolated methylmalonic acidemia	AR	Metabolic encephalopathy predisposing to basal ganglia disease	• Decompensation w/ illness • DD • Cardiomyopathy • Renal failure • Pancreatitis • Bone marrow suppression • Optic atrophy	• Ketoacidosis • Diagnostic urine organic acid testing • ↑ methylmalonic acid • Metabolic "stroke" &/or basal ganglia injury • Possible white matter abnormality on MRI
PCCA *PCCB*	Propionic acidemia	AR			

3-OH-GA = 3-hydroxyglutaric acid; AR = autosomal recessive; C5DC = glutarylcarnitine; DD = developmental delay; GA = glutaric acid; Mat = maternal; MOI = mode of inheritance; mt = mitochondrial; NBS = newborn screening; XL = X-linked
1. Gerards et al [2016]

In children with **subdural hemorrhage and bitemporal fluid collections** suggestive of bitemporal hypoplasia or arachnoid cysts, targeted investigations for GA-1 should be initiated [Kölker et al 2011]. If subdural hemorrhage is an isolated feature without other findings of GA-1 on MRI, the pretest probability of GA-1 is low and targeted investigations for GA-1 are not necessary [Vester et al 2015, Boy et al 2017b].

Dystonia is a significant sequela for individuals with basal ganglia injury due to glutaric acidemia type 1. For the differential diagnosis of dystonia (i.e., inherited neurodegenerative/metabolic disorders) see Table 4 in Hereditary Dystonia Overview.

Macrocephaly. Benign familial macrocephaly, communicating hydrocephalus, and obstructive hydrocephalus should be considered in a child with macrocephaly.

Management

When glutaric acidemia type 1 (GA-1) is suspected during the diagnostic evaluation (i.e., due to elevated concentration of 3-OH-GA in plasma or urine), metabolic treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach to care including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

The second revision of consensus clinical practice guidelines for the treatment of individuals with GA-1 have recently been published [Boy et al 2017b].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual following diagnosis of GA-1, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of GA-1

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietician [1]	• Transfer to specialist center w/experience in management of inherited metabolic diseases is strongly recommended. • Consider short hospitalization at center of expertise for inherited metabolic conditions to provide detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises) for caregivers.
Gastrointestinal/Feeding	Swallow study as needed for symptomatic patients w/feeding difficulties &/or concern for aspiration
Developmental assessment	Consider referral to developmental pediatrician.
Consultation w/neurologist	As needed to manage dystonia or seizures
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assessment of parental / affected individual's coping skills & resources
Consultation w/physical therapist, occupational therapist, & speech therapist	As needed when developmental delays are present

1. After a new diagnosis of GA-1 in a child, the closest hospital and local pediatrician should also be informed.

Treatment of Manifestations

All children with GA-1 and feeding difficulties require supervision of a specialist metabolic dietitian with experience in managing diet in GA-1. German (D)-Austrian (A)-Swiss (CH) (DACH) recommendations have been used in several clinical trials and have resulted in positive outcomes [Kölker et al 2007, Heringer et al 2010, Kölker et al 2012, Boy et al 2013].

The main principles of treatment are to reduce lysine oxidation and enhance physiologic detoxification of glutaryl-CoA. Combined metabolic therapy includes the following [Boy et al 2013]:

- Low-lysine diet
- Carnitine supplementation
- Emergency treatment during episodes with the goal of averting catabolism and minimizing CNS exposure to lysine and its toxic metabolic byproducts

Table 4. Routine Daily Treatment in Individuals with Glutaric Aciduria Type 1

Principle/Manifestation	Treatment	Consideration/Other
Lys restriction in those age <6 yrs	• Low-Lys diet [1, 2, 3] • Direct calculation of Lys intake (vs total natural protein intake) is more precise & reduces long-term day-to-day variability of Lys intake. [4] • Lys-free, Trp-reduced amino acid formulas [3] to provide adequate supply of EAAs w/minerals, trace elements, & vitamins	• Diet must balance ↓ lysine intake while maintaining sufficient intake of essential nutrients. Goal Lys intake for term infants: • Age 0-6 mos: ~100 mg/kg/day [5] • Age 6-12 mos: ~90 mg/kg/day) (see Table 5) [6]
Natural protein intake in infants	After receiving prescribed quantities of Lys-free, Trp-reduced formula, infants can breastfeed on demand. [7]	• Breastfeeding should be encouraged. • Lys content in breast milk is ~86 mg/100 mL. [8] • Daily Lys intake can be calculated when breast milk is the only natural protein source & breast milk intake is calculated & stable.

Table 4. continued from previous page.

Principle/Manifestation	Treatment	Consideration/Other
Lys restriction in those age >6 yrs [9]	• Controlled protein intake using natural protein w/low Lys content & avoiding Lys-rich foods is advisable even after age 6 yrs (see Table 5, footnote 2). • Diet should follow an age-adapted, protein-controlled protocol w/no requirement for Lys-free, Trp-restricted formula, but w/avoidance or very careful apportioning of Lys-rich natural protein food sources. [10]	Transition from low-Lys diet to protein-controlled diet after age 6 yrs should be accompanied by frequent, supervised input from specialist metabolic dietician w/specific experience w/GA-1.
Maintenance of adequate Trp [11, 12] levels	Formulas should be Trp-reduced but not completely deficient in Trp.	• Depletion may cause severe neurologic deficits. [13] • Quantification of Trp in plasma is technically challenging.
Secondary carnitine deficiency	• Initial oral dosage of 100 mg L-carnitine/kg per day divided into 3-4 doses is typical. [14] • Dose is adjusted on an individual basis to maintain plasma free L-carnitine concentration w/in normal age-appropriate reference range. [15]	• Lifelong carnitine supplementation is generally recommended. [16] • L-carnitine supplementation is considered to contribute to ↓ risk for striatal injury in individuals diagnosed early [17] & may reduce mortality rates in symptomatic individuals w/GA-1. [18]
Addressing ↑ energy/caloric demands [19]	Fundoplication, gastrostomy, or jejunostomy to address feeding issues	Adequate provision of information & education to parents, affected individuals, & caregivers
Dystonic movement disorders	Standard therapeutic options may incl use of benzodiazepines, baclofen, trihexyphenidyl, &/or botulinum toxin type A.	Referral to neurologist for ongoing management

Table 4. continued from previous page.

Principle/Manifestation	Treatment	Consideration/Other
Gross motor delay	• Physical therapy • Aggressive rehabilitation therapy	

EAA = essential amino acid; Lys = lysine; Trp = tryptophan
1. The Lys content in natural protein sources in food varies considerably – e.g., 2%-4% (lysine/protein) in cereals and 9% (lysine/protein) in fish.
2. High-lysine foods include poultry, fish, shrimp, shellfish, pork, beef, soy, nuts, seeds, eggs, beans, and lentils.
3. Consensus recommendations at present state that there is currently insufficient evidence to support routine high-dose arginine (Arg) supplementation orally in addition to (or as a substitute for) the use of a Lys-free, Trp-reduced, Arg-containing amino acid formula as an adjunct to a prescribed daily quantity of natural protein.
4. Yannicelli et al [1994], Müller & Kölker [2004]
5. Data are extremely limited on optimal Lys intake and protein/calorie requirements in premature infants [Goodman & Baker, personal communication].
6. Older children need proportionately less Lys per unit body weight than infants due to decelerating nutritional requirements and growth velocities.
7. Heringer et al [2010], Kölker et al [2012], Boy et al [2013]
8. Souci et al [2008]
9. Long-term outcome in individuals with GA-1 in this age group as a function of dietary management has not been well characterized.
10. Boy et al [2017a]
11. Tryptophan content in natural protein is only 0.6%-2%, depending on source.
12. Foods rich in Trp include poultry, fish, legumes, and dairy products.
13. Hoffmann et al [1991]
14. Kölker et al [2007]
15. Dose reduction may be necessary due to adverse effects, such as diarrhea and a fishy body odor, which can be socially stigmatizing.
16. Boy et al [2017a]
17. Kölker et al [2007], Heringer et al [2010], Viau et al [2012], Couce et al [2013], Lee et al [2013]
18. Kölker et al [2006]
19. Such demands may stem from movement disorders (dystonia, orofacial dyskinesia).

Notes: (1) Riboflavin supplementation is not recommended currently as standard therapy for GA-1 [Boy et al 2017a]. (2) To date, there is no robust evidence that use of other medications, such as phenobarbitone, *N*-acetylcysteine, creatine monohydrate, topiramate, glutamate receptor antagonists, and antioxidants, is beneficial in GA-1 [Greenberg et al 2002, Kyllerman et al 2004, Boy et al 2017a]. (3) Arginine supplementation is not currently recommended in acute or chronic settings [Boy et al 2017b].

Table 5. Nutritional Requirements for L-lysine, L-Carnitine, Calories, and Natural Protein for Infants and Children with GA-1

	0-6 mos	7-12 mos	12-47 mos	48-72 mos	>6 yrs
L-lysine (from dietary natural protein), [1] mg/kg/day	100	90	60-80	50-60	Controlled protein intake w/natural protein & low-Lys content, avoiding Lys-rich foods
Protein from GA-1-specific Lys-free, Trp-restricted formula, [2] g/kg/day	0.8-1.3	0.8-1.0	0.8	0.8	Generally no requirement for GA-1-specific amino acid formula
Energy, kcal/kg/day	80-100	80	81-94	63-86	As per normal pediatric requirements, guided by age & weight

Table 5. continued from previous page.

	0-6 mos	7-12 mos	12-47 mos	48-72 mos	>6 yrs
L-carnitine, mg/kg/day	100	100	100	50-100	30-50

Adapted from Boy et al [2017a]
If normal growth and development are not achieved, these recommendations should be modified according to individual need.
1. Lysine content in natural sources of protein varies significantly; thus, natural protein requirements will vary considerably according to the natural protein source used (e.g., higher natural protein intake will be required if sources have a very low lysine content). High-lysine foods include poultry, fish, shrimp, shellfish, pork, beef, soy, nuts, seeds, eggs, beans, and lentils.
2. Lys-free, Trp-reduced amino acid formulas specifically produced for individuals with GA1 should be supplemented with minerals and micronutrients as needed to maintain normal levels. Adequate intake of essential amino acids is provided from natural protein and Lys-free, Trp-reduced amino acid formula.

If an affected individual is clinically well despite an intercurrent infectious illness or febrile reaction to vaccinations, emergency outpatient management may be considered (see Table 6). If outpatient emergency treatment can be performed adequately and safely and if the child does not develop concerning symptoms during the illness, maintenance treatment and diet should be reintroduced stepwise over the next 48 (-72) hours (see Table 4).

Table 6. Emergency Outpatient Treatment in Individuals with Glutaric Aciduria Type 1

Manifestation/Concern	Treatment	Consideration/Other
Mildly ↑ catabolism [1]	• Carbohydrate supplementation orally or via tube feed [2] • ↓ natural protein intake [3] • ↑ carnitine supplementation [4]	• Trial of outpatient treatment at home for ≤12 hrs • Reassessment (every ~2 hrs) for clinical changes [5]
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperature rises >38.5°C	
Occasional vomiting	Antiemetics [6]	

1. Fever <38.5 °C (101 °F); enteral or gastrostomy tube feeding is tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability, hypotonia, dystonia)
2. Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide nutritional arrangements in the outpatient setting; some centers recommend frequent provision of carbohydrate-rich, protein-free beverages every two hours, with frequent reassessment.
3. Some centers advocate additional steps such as reducing natural protein intake to zero or to 50% of the normal prescribed regimen for short periods (<24 hours) in the outpatient setting during intercurrent illness.
4. Temporarily increasing L-carnitine doses (e.g., to 200 mg/kg/day in infants) is recommended [Boy et al 2017a].
5. Alterations in mentation/alertness, fever, and enteral feeding tolerance, with any new or evolving clinical features discussed with the designated center of expertise for inherited metabolic diseases
6. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

Acute manifestations (e.g., lethargy, encephalopathy, seizures, or progressive coma), often occurring in the setting of intercurrent illness and/or inadequate caloric intake, should be managed symptomatically and with generous caloric support in a hospital setting, with aggressive treatment and supportive care of any identified or clinically suspected acute conditions (see Table 7).

Table 7. Acute In-Patient Treatment in Individuals with Glutaric Aciduria Type 1

Manifestation/Concern	Treatment	Consideration/Other
Catabolic state (due to fever, perioperative/peri-interventional fasting periods, repeated vomiting/diarrhea)	• Administer high-energy fluids &, if needed, insulin. [1, 2] • Intravenous lipid emulsion • ↓ or omit natural protein for 24 hours. [3] • ↑ L-carnitine supplementation. [4]	• Blood glucose, electrolyte concentrations, blood gases, plasma amino acids, plasma carnitine profiling, & urine pH/ketone screening may all be of utility in guiding management.

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Consideration/Other
	• Address electrolytes & pH imbalances w/ intravenous fluid management.	• Ongoing assessment of hemodynamic status & for new neurologic signs is critical. • Inadequate or delayed start of emergency treatment results in a high risk of striatal injury, dystonia, & consequent long-term disability. [5] • No evidence supports use of arginine therapy during acute illness. [6] • In children >6 yrs, adolescents, & adults: emergency treatment adapted from protocols for younger children should be considered during periods of severe illness or prolonged fasting, though risks of encephalopathic illness & striatal injury are probably ↓ in these age groups. [7, 8]
Clinical myalgia, muscle tenderness, &/or urinary discoloration w/↑ CK due to severe dystonia	Intravenous fluids at a rate of 3 L/m^2 body surface area / day for renal protection if CK >5,000 U/L	Regular assessment of CK level & renal function are required for those w/CK >5,000.
New or evolving neurologic symptoms (i.e., muscular hypotonia, irritability, rigors, dystonia, ↓ consciousness, seizures)	• Initiate the treatment listed above for ↑ catabolism. • Neurologic consultation, antiepileptic drugs if needed • MRI of the brain	
Metabolic acidosis	Judicious use of intravenous sodium bicarbonate in order to achieve alkalinization of urine & facilitation of urinary excretion of organic acids	

In-patient emergency treatment should: (1) take place at the closest medical facility, (2) be started without delay, and (3) be supervised by physicians and specialist dieticians at the responsible metabolic center, who should be contacted without delay.
1. Intravenous glucose solutions should provide 12-15 g/kg/day glucose for infants and 10-12 g/kg/day for children 12 months - 6 years.
2. Use of insulin if hyperglycemia emerges; intravenous insulin given at a starting dose of 0.025 IU/kg/hour in the event of persistent hyperglycemia (>150-180 mg/dL in plasma, or glucosuria).
3. Natural protein can be gradually reintroduced, with continuation of enteral Lys-free, Trp-reduced GA-1-specific amino acid formula as tolerated.
4. L-carnitine (with options to increase the dose) can be given intravenously, which enhances bioavailability.
5. Heringer et al [2010]
6. Boy et al [2017a]
7. Hoffmann et al [1996], Bjugstad et al [2000], Kölker et al [2006], Strauss et al [2007], Heringer et al [2010]
8. To date only case reports on emergency treatment in adolescents and adults have been published [Jamuar et al 2012, Ituk et al 2013].

Transitional care from pediatric to adult-centered multidisciplinary care settings. As GA-1 is a lifelong disorder with varying implications according to age, smooth transition of care from the pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties. Standardized procedures for transitional care do not exist for GA-1 due to the absence of multidisciplinary outpatient departments.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with GA-1 together with pediatric metabolic experts, dietitians, psychologists, and social workers.

- In puberty and early adulthood, deficits in adherence to treatment may occur due to deteriorating compliance or other unknown factors, resulting in negative impact on outcomes [Watson 2000].
- As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Prevention of Primary Manifestations

Dietary restriction of lysine intake remains the cornerstone of GA-1 treatment. Although management of any given affected individual is nuanced and managed on a case-by-case basis, minor illnesses, where caloric needs are increased or provision of adequate calories is compromised, should be observed closely and promptly treated with a low threshold for hospital admission (see Treatment of Manifestations).

Prevention of Secondary Complications

One of the most important components of management (as it relates to prevention of secondary complications) is education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors (see also Tables 6 and 7).

Table 8. Prevention of Secondary Manifestations in Individuals with Glutaric Aciduria Type 1

Manifestation/ Situation	Prevention	Considerations/Other
Acute encephalopathic crisis	• Intense & ongoing education of affected individuals & caregivers about worrisome symptoms, natural history, maintenance & emergency treatment, prognosis, & risks of acute encephalopathic crises • Treatment protocols & provision of emergency letters or cards to incl guidance for care in event of illness while on vacation • Medical alert bracelets/pendants or car seat stickers • Always maintain at home: adequate supplies of specialized dietary products (carbohydrate-only formulas or other caloric sources); Lys-free, Trp-reduced amino acid formula; medication required for maintenance & emergency treatment (carnitine, antipyretics).	• Written protocols for maintenance & emergency treatment should be provided to parents & primary care providers / pediatricians, & to teachers & school staff. [1, 2] • Emergency letters/cards should be provided summarizing key information & principles of emergency treatment for GA-1 & containing contact information for the primary treating metabolic center. • For any planned travel or vacations, consider contacting a center of expertise near the destination prior to travel dates.
Surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative management w/ surgeons & anesthesiologists. [3] • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional management).	Consider placing a "flag" in the affected individual's medical record so that all care providers are aware of the diagnosis & the need to solicit opinions & guidance from designated metabolic specialists in the setting of certain procedures.

1. Essential information including written treatment protocols should be provided in anticipation of the possible need for in-patient emergency treatment.
2. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5 °C; (2) vomiting/diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms occur.
3. Perioperative/perianesthetic management precautions may include visitations at specialist anesthetic clinics for affected individuals deemed to be at high risk for perioperative complications.

Surveillance

Regular evaluations by a metabolic specialist and metabolic dietician are appropriate. See Table 9 for additional recommended surveillance.

Table 9. Recommended Surveillance for Individuals with Glutaric Aciduria Type 1

Manifestation/Concern	Evaluation	Frequency/Comment
Poor growth	Measurement of growth, weight, & head circumference	At each visit
Delayed acquisition of developmental milestones	Monitor developmental milestones.	At each visit
	Neuropsychological testing using age-appropriate standardized assessment batteries	As needed
	Standardized quality-of-life assessment tools for affected individuals & parents/caregivers	As needed
Movement disorder	Assessment for clinical symptoms & signs of movement disorders, severity, & responses to treatment, physical therapy, & pharmacologic interventions	At each visit
Abnormal amino acid levels (amino acid deficiencies & ↑ lysine)	Quantitative analysis of plasma amino acids (ideally obtained after a 3-hr protein fast) [1]	• 1st year of life: at least every 3 mos • Ages 1-6 yrs: every 6 mos • >6 yrs of age: annually
Nutritional deficiencies [2]	Calcium, phosphorus, vitamin D, prealbumin, B_{12}, zinc, ferritin	If clinically indicated [3]
Chronic renal insufficiency [4]	Plasma creatinine &/or cystatin C level	Periodically in adolescents & adults
Anemia	Complete blood count, ferritin level	If clinically indicated [3]
Abnormal liver function	ALT/AST , albumin	If clinically indicated [3]
Head injury [5] &/or rapid head growth [6]	Consider head MRI.	If clinically indicated [7]

ALT = alanine transaminase; AST = aspartate transaminase
1. Correlations between plasma lysine concentration and dietary lysine intake are often poor [Kölker et al 2012, Boy et al 2013].
2. Physicians and specialist metabolic dieticians should be alert to changes in growth velocity, or development of new symptoms that may suggest specific micronutrient or amino acid deficiencies.
3. These studies are likely to be normal in an affected individual who is in good compliance with prescribed diet and treatment [Boy et al 2017b].
4. Chronic renal insufficiency may be more common than previously appreciated in adults with GA-1 [Kölker et al 2015b].
5. Zielonka et al [2015]
6. Rapid evolution of macrocephaly may suggest development of subdural fluid collections or hemorrhages, and should be imaged appropriately.
7. Head imaging may have utility in tracking the progression of subependymal mass lesions in individuals with late-onset GA-1 [Herskovitz et al 2013].

Note:

- Because C5DC acylcarnitine values are likely to reflect carnitine concentrations in plasma and not dietary lysine intake, they have no role in biochemical surveillance or ongoing care of persons with GA-1 [Chace et al 2003, Lindner et al 2004].
- Because urinary or plasma concentrations of GA or 3-OH-GA do not correlate with clinical parameters or outcomes [Christensen et al 2004, Kölker et al 2006, Boy et al 2013], they have no role in clinical surveillance or for guidance of ongoing care of persons with GA-1.

Agents/Circumstances to Avoid

Avoid the following:

- Excessive dietary protein or protein malnutrition inducing catabolic state

- Prolonged fasting
- Catabolic illness (intercurrent infection; brief febrile illness post-vaccination)
- Inadequate caloric provision during other stressors, especially when fasting is involved (surgery or procedure requiring fasting/anesthesia)

Although there are no data on which to base such a recommendation, given the increased risk of subdural hemorrhage in individuals with GA-1, avoidance or extreme caution with contact sports and physical activities that involve high risk for minor head injuries would appear to be a sensible precaution.

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment. For at-risk newborn sibs when prenatal testing was not performed: in parallel with NBS, either test for the familial *GCDH* pathogenic variants or measure urine organic acids, plasma amino acids, and acylcarnitine profile.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Although there are no formal published recommendations for dietary or medical management for pregnant women with GA-1, it is recommended that care be provided by a multidisciplinary team including the treating obstetrician, a metabolic physician, and a specialist metabolic dietician. Because the perinatal period is a time of high catabolic stress for women with GA-1, most metabolic physicians would agree that emergency management and close observation are required; however, evidence and/or sufficient clinical data regarding efficacy or necessity of emergency treatment for GA-1 during the peripartum period are not available. Uneventful clinical courses for affected mothers (and their babies) has been reported for women receiving emergency treatment during the peripartum period [Ituk et al 2013], as well as for women who did not receive any specific therapy [Garcia et al 2008].

While to date no specific guidelines are available for surgical procedures and other perinatal stressors, usual perioperative/perianesthetic precautions are likely to be clinically relevant (see Prevention of Secondary Complications).

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Mode of Inheritance

Glutaric acidemia type 1 (GA-1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *GCDH* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing clinical features of the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Note: Phenotype of GA-1 can vary widely among untreated family members who have the same genotype.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the clinical features of the disorder.

Offspring of a proband. Unless an individual with GA-1 has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *GCDH*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *GCDH* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *GCDH* pathogenic variants in the family.

Carriers are asymptomatic and are not at risk of developing clinical features of the disorder.

Quantification of glutaryl-CoA dehydrogenase enzyme activity in fibroblasts or leukocytes is not useful in determining carrier status.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *GCDH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Biochemical testing for prenatal diagnosis of GA-1 is not recommended; molecular genetic testing is preferred.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

Molecular Genetics

Molecular Pathogenesis

Glutaryl-CoA dehydrogenase (GCDH) plays an integral role in degradative metabolism of L-lysine, L-hydroxylysine, and L-tryptophan [Greenberg et al 1995, Fu et al 2004]. Glutaric acidemia type 1 (GA-1) is caused by insufficiency or absence of functional glutaryl-CoA dehydrogenase (GCDH), resulting from biallelic *GCDH* pathogenic variants. Enzymatic insufficiency or absence results in the accumulation of upstream byproducts of L-lysine, L-hydroxylysine, and L-tryptophan degradation: glutaric acid, 3-hydroxyglutaric acid, glutarylcarnitine (C5DC acylcarnitine), and glutaconic acid.

Accumulation of glutaric acid and 3-OH-glutaric acid causes neurotoxicity (especially striatal injury).

Gene structure. *GCDH* comprises 11 exons and spans approximately 7 kb of genomic DNA. Human *GCDH* cDNA encodes a 438-amino acid precursor protein and a 394-amino acid mature protein with a molecular mass of 43.3 kd. Alternative splicing between exons 10 and 11 produces two *GCDH* mRNA transcripts, only one of which is enzymatically active. The precursor protein undergoes cleavage by mitochondrial processing peptidase to form the mature *GCDH* subunit [Goodman et al 1995].

Pathogenic variants. More than 200 (confirmed or likely) pathogenic *GCDH* variants have been reported to date [Stenson et al 2014]. Most *GCDH* variants reported to date are missense variants. It is possible that many of these pathogenic variants affect stability and, hence, heteromeric glutaryl-CoA dehydrogenase enzyme complex formation, and are disruptive to mitochondrial architecture.

Of note, c.91+5G>T (the Ojibway-Cree First Nation founder variant) as well as p.Arg227Pro, p.Val400Met, and p.Met405Val are associated with a low-excreter phenotype and may be more difficult to detect conclusively with biochemical testing (and on NBS utilizing C5DC acylcarnitine). Homozygous p.Arg227Pro and p.Val400Met are both associated with 8%-10% residual enzyme activity [Christensen et al 2004].

The c.553_570del18 (p.Gly185_Ser190del) deletion, a suspected dominant-negative allele, is associated with enzyme activity much lower than 50% [Bross et al 2012]. An individual heterozygous for the deletion did not – to the authors' knowledge – manifest any clinical features of GA-1 [Author, personal observation].

Table 10. Notable *GCDH* Pathogenic Variants

Reference Sequence	Variant Class	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000159.3 NP_000150.1	**Variants w/GPC** [1]	c.91+5G>T		Low-excreter & **founder variant** in Ojibway-Cree First Nations Canadians [Greenberg et al 1995, Greenberg et al 2002]
		c.680G>C	p.Arg227Pro	Low-excreter; 85%-10% residual activity [Christensen et al 2004]
		c.1198G>A	p.Val400Met	• Low-excreter; 8%-10% residual activity [Christensen et al 1997] • A **common variant** among low excreters in Spain [Busquets et al 2000a]

Table 10. continued from previous page.

Reference Sequence	Variant Class	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
		c.1213A>G	p.Met405Val	• Low-excreter [Schillaci et al 2016] • A **common variant** among low-excreter African Americans [Schillaci et al 2016]
	Additional founder & common variants	c.541G>C	p.Glu181Gln	Common variant in Iran & Turkey [Baradaran et al 2014]
		c.877G>A	p.Ala293Thr	Founder variant in South African Xhosa peoples; est. prevalence: 1:5,184 [van der Watt et al 2010]
		c.1093G>A	p.Glu365Lys	Founder variant in Irish Traveler communities in the Republic of Ireland [Naughten et al 2004]
		c.1204C>T	p.Arg402Trp	Most common pan ethnic pathogenic variant [Schwartz et al 1998, Busquets et al 2000b, Gupta et al 2015, Tp et al 2017]
		c.1240G>A	p.Glu414Lys	Founder variant in Lumbee Native Americans of North Carolina [Basinger et al 2006]
		c.1262C>T	p.Ala421Val	Founder variant in Pennsylvania Amish: carrier frequency may be as high as 1 in 10 in some Pennsylvania Amish communities [Morton et al 1991]
	Possible dominant-negative variant	c.553_570del18	p.Gly185_Ser190del	Heterozygosity results in GCDH enzyme activity significantly <50%; a dominant-negative effect has been suggested but no clinical phenotype was present [Bross et al 2012].

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. GPC = genotype-phenotype correlation

Normal gene product. *GCDH* encodes the flavin adenine dinucleotide-dependent mitochondrial matrix protein GCDH, which forms homotetramers and oxidizes and decarboxylates glutaryl-CoA. *GCDH* cDNA encodes a 438-amino acid precursor protein and a 394-amino acid mature protein, with a 44-amino acid mitochondrial targeting sequence at the N terminal [Goodman et al 1998].

Abnormal gene product. GA-1 results from loss of GCDH function, with a mechanism attributed to abnormal surface residues causing impaired stability and impaired GCDH protein interactions and heteromeric complex formation [Schmiesing et al 2017].

Glutaric acid probably derives from hydrolysis of the accumulated enzyme substrate (glutaryl-CoA), but the origin of 3-hydroxyglutaric acid remains unknown. These putative toxins do not cross the blood-brain barrier and thus are probably synthesized within the brain from accumulated glutaryl-CoA, but the reasons why one or both of them preferentially affect the striatum and why there is a period of heightened striatal vulnerability in infancy and early childhood remain a mystery.

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Chapter Notes

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Author Notes

* Dr James Weisfeld-Adams contributed extensively to the early drafts of this *GeneReview*. He died of renal cancer in April 2018. He is survived by his wife and two sons. A biochemical geneticist, Dr Weisfeld-Adams served on the faculties of the University of Colorado School of Medicine and the Mount Sinai School of Medicine. James was a devoted father and husband as well as a compassionate and skilled clinician.

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