



## Pompe Disease

**Synonyms:** Acid Alpha-Glucosidase Deficiency, Acid Maltase Deficiency, GAA Deficiency, Glycogen Storage Disease Type II (GSD II), Glycogenosis Type II

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## Summary

### Clinical characteristics

Pompe disease is classified by age of onset, organ involvement, severity, and rate of progression.

- *Infantile-onset Pompe disease* (IOPD; individuals with onset before age 12 months with cardiomyopathy) may be apparent in utero but more typically onset is at the median age of four months with hypotonia, generalized muscle weakness, feeding difficulties, failure to thrive, respiratory distress, and hypertrophic cardiomyopathy. Without treatment by enzyme replacement therapy (ERT), IOPD commonly results in death by age two years from progressive left ventricular outflow obstruction and respiratory insufficiency.
- *Late-onset Pompe disease* (LOPD; including: (a) individuals with onset before age 12 months without cardiomyopathy; and (b) all individuals with onset after age 12 months) is characterized by proximal muscle weakness and respiratory insufficiency; clinically significant cardiac involvement is uncommon.

### Diagnosis/testing

The diagnosis of GSD II is established in a proband with either deficiency of acid alpha-glucosidase enzyme activity or biallelic pathogenic variants in *GAA* on molecular genetic testing.

### Management

*Treatment of manifestations:* Management guidelines from the American College of Medical Genetics: individualized care of cardiomyopathy as standard drugs may be contraindicated and risk for tachyarrhythmia and sudden death is high; physical therapy for muscle weakness to maintain range of motion and assist in ambulation; surgery for contractures as needed; nutrition/feeding support. Respiratory support may include inspiratory/expiratory training in affected adults, CPAP, BiPAP, and/or tracheostomy.

*Prevention of primary manifestations:* Begin enzyme replacement therapy (ERT) with alglucosidase alfa as soon as the diagnosis is established. Of note, ERT can be accompanied by infusion reactions (which are treatable) as

well as anaphylaxis. Infants at high risk for development of antibodies to the therapeutic enzyme are likely to need immunomodulation early in the treatment course.

- **IOPD.** In the pivotal trial, a majority of infants in whom ERT was initiated before age six months and before the need for ventilatory assistance showed improved survival, ventilator-independent survival, improved acquisition of motor skills, and reduced cardiac mass compared to untreated controls. More recent data suggest that initiation of ERT before age two weeks may improve motor outcomes in the first two years of life, even when compared to infants in whom treatment was initiated only ten days later.
- **LOPD.** ERT may stabilize the functions most likely to be lost: respiration and motor ability.

*Prevention of secondary complications:* Aggressive management of infections; keeping immunizations up to date; annual influenza vaccination of the affected individual and household members; respiratory syncytial virus (RSV) prophylaxis (palivizumab) in the first two years of life; use of anesthesia only when absolutely necessary.

*Surveillance:* Routine monitoring of respiratory status, cardiovascular status, musculoskeletal function (including bone densitometry), nutrition and feeding, kidney function, and hearing.

*Agents/circumstances to avoid:* Digoxin, ionotropes, diuretics, and afterload-reducing agents, as they may worsen left ventricular outflow obstruction in some stages of the disease; hypotension and volume depletion; exposure to infectious agents.

*Evaluation of relatives at risk:* Evaluate at-risk sibs to permit early diagnosis and treatment with ERT.

## Genetic counseling

Pompe disease 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. If the *GAA* pathogenic variants in an affected family member are known, carrier testing for at-risk family members, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

## Diagnosis

Pompe disease can be classified by age of onset, organ involvement, severity, and rate of progression:

- **Infantile-onset Pompe disease (IOPD).** Individuals with onset before age 12 months with cardiomyopathy
- **Late-onset Pompe disease (LOPD)**
  - Individuals with onset before age 12 months without cardiomyopathy; and
  - All individuals with onset after age 12 months

## Suggestive Findings

Infantile-onset and late-onset Pompe disease **are suspected** in individuals with the following clinical findings and supportive laboratory findings.

## Clinical Findings

**Infantile-onset Pompe disease (IOPD)** is suspected in infants with the following [van den Hout et al 2003, Kishnani et al 2006a]:

- Poor feeding/failure to thrive (44%-97% of cases)
- Motor delay/muscle weakness (20%-63%)
- Respiratory infections/difficulty (27%-78%)

- Cardiac issues (shortened PR interval with a broad, wide QRS complex, cardiomegaly, left ventricular outflow obstruction, cardiomyopathy) (50%-92%)

**Late-onset Pompe disease (LOPD)** is suspected in infants, children, and adults with proximal muscular weakness and respiratory insufficiency without clinically apparent cardiac involvement.

## Supportive Laboratory Findings

**Positive newborn screening (NBS) results.** Rapid and sensitive analysis of acid alpha-glucosidase (GAA) enzyme activity can be performed on dried blood spots when using standard conditions [Chamoles et al 2004, Zhang et al 2006, Winchester et al 2008].

Confirmation of deficiency of GAA enzyme activity detected on dried blood spots is recommended by molecular genetic testing [Winchester et al 2008]. Although measurement of GAA activity in another tissue (e.g., cultured skin fibroblasts) has been regarded as a "gold standard" for enzymatic diagnosis of Pompe disease, newer methodology using mass spectrometry suggests that blood-based assays may be comparable [Lin et al 2017].

Countries engaged in NBS include Taiwan, Austria [Mechtler et al 2012], Japan [Oda et al 2011] and the US (currently New York, Missouri, Kentucky, and Illinois; many more states are planning to implement NBS) [Hopkins et al 2015].

**Serum creatine kinase (CK) concentration** is elevated (as high as 2000 IU/L; normal: 60-305 IU/L) in all individuals with IOPD and in some with LOPD (it may be normal in LOPD) [Laforêt et al 2000, Kishnani et al 2006b]. Because elevated serum CK concentration is observed in many conditions, it must be considered nonspecific.

**Urinary oligosaccharides.** Elevation of the specific urinary glucose, tetrasaccharide, is a highly sensitive finding in IOPD; however, it is also seen in other glycogen storage diseases [An et al 2000, Kallwass et al 2007, Young et al 2012]. Sensitivity is diminished in LOPD [Young et al 2009]. Of note: Urinary oligosaccharides have been useful in evaluating infants with an abnormal result on NBS [Chien et al 2015].

## Establishing the Diagnosis

The diagnosis of GSD II is **established** in a proband with either deficiency of acid alpha-glucosidase enzyme activity or biallelic pathogenic (or likely pathogenic) variants in *GAA* on molecular genetic testing (see Table 1).

Note: (1) A single abnormal NBS result is not regarded as sufficient for diagnosis of Pompe disease. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) Identification of biallelic *GAA* variants of uncertain significance (or of one known *GAA* pathogenic variant and one *GAA* variant of uncertain significance) does not establish or rule out the diagnosis.

- The diagnosis of IOPD can be established rapidly after a positive NBS result when physical examination, echocardiography, and elevated CPK support the diagnosis.
- It is recommended that the diagnosis be confirmed either by molecular genetic testing [Winchester et al 2008] or by measurement of GAA activity in another tissue, such as isolated lymphocytes or mixed leukocytes. Note: Because of longer turn-around times, analysis of GAA enzyme activity in cultured skin fibroblasts is less ideal than molecular genetic testing or blood-based enzyme testing; however, it may be helpful when LOPD is suspected or when asymptomatic individuals are ascertained through screening tests.

**Acid alpha-glucosidase (GAA) enzyme activity.** Rapid and sensitive analysis of GAA enzyme activity can be performed on dried blood spots when using standard conditions [Chamoles et al 2004, Zhang et al 2006, Winchester et al 2008]. Although other tissues such as muscle and peripheral leukocytes can be used, both have limitations.

As a general rule, the lower the GAA enzyme activity, the earlier the age of onset of disease:

- Complete deficiency of GAA enzyme activity (<1% of normal controls) is associated with IOPD.
- Partial deficiency of GAA enzyme activity (2%-40% of normal controls) is associated with LOPD [Hirschhorn & Reuser 2001].

**Molecular testing approaches** can include **single-gene testing**, **targeted analysis for pathogenic variants**, and use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of GAA is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

Note: Caution must be exercised in correlating results from molecular genetic testing and enzyme analysis in the absence of clinical features of Pompe disease as the pseudodeficiency allele c.1726 G>A (p.Gly576Ser), which is relatively common in Asian populations, interferes with interpretation of enzyme testing in NBS programs (confirmed by screening programs in Missouri and New York) [Hopkins et al 2015, Lin et al 2017].

- **Targeted analysis for pathogenic variants** can be performed before sequence analysis in individuals with the following ancestry and clinical findings:
  - **African Americans with IOPD.** An estimated 50%-60% have the pathogenic variant p.Arg854Ter [Becker et al 1998, Hirschhorn & Reuser 2001].
  - **Chinese with IOPD.** An estimated 40%-80% have the pathogenic variant p.Asp645Glu [Shieh & Lin 1998, Ko et al 1999, Hirschhorn & Reuser 2001].
  - **Adults with LOPD.** An estimated 50%-85% have the pathogenic variant c.-32-13T>G typically in the compound heterozygous state [Laforêt et al 2000, Hirschhorn & Reuser 2001, Winkel et al 2005, Montalvo et al 2006].
- **A multigene panel** that includes GAA and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

**Table 1.** Molecular Genetic Testing Used in Glycogen Storage Disease Type II

Gene <sup>1</sup>	Method	Proportion of Probands with Pathogenic Variants <sup>2</sup> Detectable by Method
GAA	Sequence analysis <sup>3</sup>	83%-93% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	5%-13% <sup>6</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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. Detection rate of two pathogenic variants in sequencing of the genomic DNA in individuals with confirmed reduced or absent GAA enzyme activity [Hermans et al 2004, Montalvo et al 2006].

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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. Deletion of exon 18 comprises approximately 5%-7% of alleles [Van der Kraan et al 1994]. Although other exon and multiexon deletions have been reported, they are rare [McCready et al 2007, Pittis et al 2008, Bali et al 2012, Amiñoso et al 2013].

## Clinical Characteristics

### Clinical Description

Traditionally, Pompe disease has been separated into two major phenotypes – infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD) –based on age of onset, organ involvement (i.e., presence of cardiomyopathy), severity, and rate of progression. As a general rule, the earlier the onset of manifestations, the faster the rate of progression; thus, the two general classifications – IOPD and LOPD – tend to be clinically useful in determining prognosis and treatment options.

Although LOPD has been divided into childhood-, juvenile-, and adult-onset disease, many individuals with adult-onset disease recall symptoms beginning in childhood and, thus, late onset is often the preferred term for those presenting after age 12 months [Laforêt et al 2000]. Most likely, LOPD represents a clinical continuum in which age of onset cannot reliably distinguish subtype [Kishnani et al 2013].

**IOPD** may be apparent in utero but more often is recognized at a median age of four months as hypotonia, generalized muscle weakness, feeding difficulties, failure to thrive, and respiratory distress (see Table 2).

Feeding difficulties may result from facial hypotonia, macroglossia, tongue weakness, and/or poor oromotor skills [van Gelder et al 2012].

Hearing loss is common, possibly reflecting cochlear or conductive pathology or both [Kamphoven et al 2004, van Capelle et al 2010].

Without treatment by enzyme replacement therapy, the cardiomegaly and hypertrophic cardiomyopathy that may be identified in the first weeks of life by echocardiography progress to left ventricular outflow obstruction. Enlargement of the heart can also result in diminished lung volume, atelectasis, and sometimes bronchial compression. Progressive deposition of glycogen results in conduction defects as seen by shortening of the PR interval on EKG.

In untreated infants, death commonly occurs in the first two years of life from cardiopulmonary insufficiency [van den Hout et al 2003, Kishnani et al 2006a].

**Table 2.** Common Findings at Presentation of Infantile-Onset Pompe Disease

Physical Signs	Proportion of Individuals <sup>1</sup>
Hypotonia/muscle weakness	52%-96%
Cardiomegaly	92%-100%
Hepatomegaly	29%-90%
Left ventricular hypertrophy	83%-100%
Cardiomyopathy	88%
Respiratory distress	41%-78%
Murmur	46%-75%
Enlarged tongue (macroglossia)	29%-62%
Feeding difficulties	57%
Failure to thrive	53%
Absent deep tendon reflexes	33%-35%
Normal cognition	95%

1. Hirschhorn & Reuser [2001], van den Hout et al [2003]

Death from ventilatory failure typically occurs in early childhood.

**LOPD** can manifest at various ages with muscle weakness and respiratory insufficiency. Disease progression is often predicted by the age of onset, as progression is more rapid if symptoms are evident in childhood.

While initial manifestations in late childhood-onset to adolescent-onset Pompe disease do not typically include cardiac complications, some adults with late-onset disease have had arteriopathy, including dilatation of the ascending thoracic aorta [El-Gharbawy et al 2011]. Of note, echocardiography alone (without specific measurement of the diameter of the thoracic aorta) may not be sufficient to visualize this complication. In addition, ectasia of the basilar and internal carotid arteries may be associated with clinical signs, such as transient ischemic attacks and third nerve paralysis [Sacconi et al 2010].

Progression of skeletal muscle involvement is slower than in the infantile forms and eventually involves the diaphragm and accessory respiratory muscles [Winkel et al 2005]. Affected individuals often become wheelchair users because of lower limb weakness. Respiratory failure causes the major morbidity and mortality [Hagemans et al 2005, Güngör et al 2011]. Male sex, severity of skeletal muscle weakness, and duration of disease are all risk factors for severe respiratory insufficiency [van der Beek et al 2011].

LOPD may present from the first decade to as late as the seventh decade of life with progressive proximal muscle weakness primarily affecting the lower limbs, as in a limb-girdle muscular dystrophy or polymyositis. Affected adults often describe symptoms beginning in childhood that resulted in difficulty participating in sports. Later, fatigue and difficulty with rising from a sitting position, climbing stairs, and walking prompt medical attention. In an untreated cohort of individuals with LOPD, the median age at diagnosis was 38 years, the median survival after diagnosis was 27 years, and the median age at death was 55 years (range 23-77 years) [Güngör et al 2011].

Evidence of advanced osteoporosis in adults with LOPD is accumulating; while this is likely in large part secondary to decreased ambulation, other pathologic processes cannot be overlooked [Oktenli 2000, Case et al 2007].

#### **Clinical manifestations of LOPD** [Hirschhorn & Reuser 2001]

- Progressive proximal muscle weakness (95%) [Winkel et al 2005]
- Respiratory insufficiency



- Exercise intolerance
- Exertional dyspnea
- Orthopnea
- Sleep apnea
- Hyperlordosis and/or scoliosis
- Hepatomegaly (childhood and juvenile onset)
- Macroglossia (childhood onset)
- Difficulty chewing and swallowing
- GI symptoms, including irritable bowel-like symptoms
- Chronic pain
- Increased respiratory infections
- Decreased deep tendon reflexes
- Gower sign
- Joint contractures

**Electrophysiologic studies.** Myopathy can be documented by electromyography (EMG) in all forms of Pompe disease although some muscles may appear normal. In adults, needle EMG of the paraspinal muscles may be required to demonstrate abnormalities [Hobson-Webb et al 2011].

Nerve conduction velocity studies are normal for both motor and sensory nerves, particularly at the time of diagnosis in IOPD and in LOPD. However, an evolving motor axonal neuropathy has been demonstrated in a child with IOPD [Burrow et al 2010].

**Muscle biopsy.** In contrast to the other glycogen storage disorders, Pompe disease is also a lysosomal storage disease. In Pompe disease glycogen storage may be observed in the lysosomes of muscle cells as vacuoles of varying severity that stain positively with periodic acid-Schiff. However, 20%-30% of individuals with LOPD with documented partial GAA enzyme deficiency may not show these muscle-specific changes [Laforêt et al 2000, Winkel et al 2005]. Furthermore, while histochemical evidence of glycogen storage in muscle is supportive of a glycogen storage disorder it is not specific for Pompe disease.

## Genotype-Phenotype Correlations

GAA enzyme activity may correlate with age of onset and rate of progression as a "rough" general rule:

- It is assumed that biallelic GAA pathogenic variants that produce essentially no enzyme activity result in infantile-onset Pompe disease (IOPD). Infants who have IOPD with no cross-reactive material (CRIM-negative) (see Management, Prevention of Primary Manifestations) are likely to have two null variants [Bali et al 2012].
- Various combinations of other pathogenic variants resulting in some residual enzyme activity likely cause disease but the age of onset and progression are most likely directly proportional to the residual GAA enzyme activity.

Some generalizations about genotype-phenotype correlations by type of pathogenic variant:

- GAA pathogenic variants that introduce mRNA instability, such as nonsense variants, are more commonly seen in IOPD as they result in nearly complete absence of GAA enzyme activity.
- GAA pathogenic missense and splicing variants may result in either complete or partial absence of GAA enzyme activity and therefore may be seen in both IOPD and LOPD [Zampieri et al 2011].

Some observations about genotype-phenotype correlations with specific pathogenic variants (see Table 3):

- p.Glu176ArgfsTer45 (c.525delT) is an especially common pathogenic variant among the Dutch [Van der Kraan et al 1994]. It results in negligible GAA enzyme activity and must be considered one of the more

severe alterations. Either in the homozygous state or in the compound heterozygous state with another severe pathogenic variant, p.Glu176ArgfsTer45 predicts IOPD, although the correlation is not absolute.

- Deletion of exon 18 (p.Gly828\_Asn882del; c.2481+110\_2646+39del538) is also a common pathogenic variant, particularly among the Dutch [Van der Kraan et al 1994]. It results in negligible GAA enzyme activity and must be considered one of the more severe pathogenic variants. Deletion of exon 18, either in the homozygous state or in the compound heterozygous state with another severe pathogenic variant, predicts IOPD.
- c.-32-13T>G is seen in 36% to 90% of late-onset GSD II and is not associated with IOPD [Hermans et al 2004, Montalvo et al 2006]. The pathogenic variant leads to a leaky splice site resulting in greatly diminished, but not absent, GAA enzyme activity.
- The pathogenic variant p.Asp645Glu, seen in a high proportion ( $\leq 80\%$ ) of IOPD in Taiwan and China, is associated with a haplotype, suggesting a founder effect [Shieh & Lin 1998].
- The pathogenic variant p.Arg854Ter is frequently associated with IOPD. Although present in several different ethnicities, this pathogenic variant has been observed in up to 60% of individuals of African descent who had a common haplotype, suggesting a founder effect [Becker et al 1998].

**Table 3.** Proportion of Individuals with Selected GAA Pathogenic Variants

GAA Pathogenic Variant	% of Affected Individuals	Reference
p.Glu176ArgfsTer45	34% of Dutch population	Van der Kraan et al [1994]
	9% of US population	Hirschhorn & Huie [1999]
p.Gly828_Asn882del	25% of Dutch & Canadian infants	Van der Kraan et al [1994]
	5% of US population	Hirschhorn & Huie [1999]
c.-32-13T>G	36%-90% of persons w/late-onset GSD II	Hermans et al [2004], Montalvo et al [2006]
p.Asp645Glu	$\leq 80\%$ of Taiwanese & Chinese infants	Shieh & Lin [1998]
p.Arg854Ter	$\leq 60\%$ of persons of African descent w/a common phenotype	Becker et al [1998]

## Nomenclature

Historically, IOPD (now defined as onset before age 12 months with cardiomyopathy) was further divided into classic form (severe with onset age  $<12$  months with clinically significant cardiomyopathy) and "non-classic" or infantile form (onset age  $<12$  months but without cardiomyopathy) [Slonim et al 2000]. Most children with "non-classic IOPD" are now classified as LOPD (i.e., onset age  $<12$  months without cardiomyopathy as well as all individuals with onset of myopathy age  $>12$  months).

## Prevalence

The incidence of Pompe disease varies, depending on ethnicity and geographic region, from 1:14,000 in African Americans to 1:100,000 in individuals of European descent (see Table 4).

**Table 4.** Incidence of Pompe Disease in Different Populations

Population	Incidence	Reference
African American	1:14,000	Hirschhorn & Reuser [2001]
Netherlands	1:40,000 combined <sup>1</sup> 1:138,000 infantile onset 1:57,000 adult onset	Ausems et al [1999], Poorthuis et al [1999]
US	1:40,000 combined	Martiniuk et al [1998]
South China/Taiwan	1:50,000	Lin et al [1987]



Table 4. continued from previous page.

Population	Incidence	Reference
European descent	1:100,000 infantile onset 1:60,000 late onset	Martiniuk et al [1998]
Australia	1:145,000	Meikle et al [1999]
Portugal	1:600,000	Pinto et al [2004]

1. Combined = all Pompe disease phenotypes

## Genetically Related (Allelic) Disorders

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

## Differential Diagnosis

### Infantile-Onset Pompe Disease (IOPD)

Disorders to be considered in the differential diagnosis:

- **Spinal muscular atrophy 1** (Werdnig-Hoffman disease, SMA I) is characterized by hypotonia, feeding difficulties, progressive proximal muscle weakness, and areflexia; no cardiac involvement. SMA I is caused by biallelic pathogenic variants in *SMN1*. Inheritance is autosomal recessive. Lack of cardiomegaly should help distinguish SMA1 from IOPD.
- **Danon disease** is characterized by hypotonia, hypertrophic cardiomyopathy, and myopathy as a result of excessive glycogen storage; it is caused by a hemizygous pathogenic *LAMP2* variant in males and a heterozygous pathogenic *LAMP2* variant in females [Arad et al 2005]. Inheritance is X-linked. Males are more severely affected than females, and the typical age of presentation with cardiomyopathy and weakness is in mid adolescence, although a few with infantile onset have been reported. In addition, intellectual disability may be present, which is unusual in Pompe disease.
- **Carnitine uptake disorder** (OMIM 212140) is characterized by muscle weakness and cardiomyopathy without elevated serum CK concentration; it is caused by biallelic pathogenic variants in *SLC22A5*. Inheritance is autosomal recessive. Phenotypes vary widely, including asymptomatic women ascertained through newborn screening of their newborns. Acutely symptomatic infants may have encephalopathy or coma, which is unusual in Pompe disease.
- **Glycogen storage disease type IIIa** (debrancher deficiency) is characterized by hypotonia, cardiomegaly, muscle weakness, and elevated serum concentration of creatine kinase with more dramatic liver involvement than typically seen in Pompe disease. It is caused by biallelic pathogenic variants in *AGL*. Inheritance is autosomal recessive.
- **Glycogen storage disease type IV** (branching enzyme deficiency) is characterized by hypotonia, cardiomegaly, muscle weakness, and elevated serum concentration of creatine kinase with more dramatic liver involvement than typically seen in Pompe disease (similar to GSD IIIa). It is caused by biallelic pathogenic variants in *GBE1*. Inheritance is autosomal recessive.
- **Hypertrophic cardiomyopathy** is characterized by biventricular hypertrophy without hypotonia or pronounced muscle weakness. See [Hypertrophic Cardiomyopathy Overview](#).
- **Myocarditis** is characterized by inflammation of the myocardium leading to cardiomegaly without hypotonia or muscle weakness.
- **Mitochondrial/respiratory chain disorders** show wide variation in clinical presentation, and may include hypotonia, respiratory failure, cardiomyopathy, hepatomegaly, seizures, deafness, and elevated serum

concentration of creatine kinase. They are often distinguishable from Pompe disease by the absence of hypotonia and presence of cognitive involvement. See [Mitochondrial Disorders Overview](#).

## Late-Onset Pompe Disease (LOPD)

The early involvement of the respiratory muscles is often useful in distinguishing juvenile-onset Pompe disease from many neuromuscular disorders.

Disorders to be considered in the differential diagnosis:

- **Limb-girdle muscular dystrophy.** Progressive muscle weakness is seen in the legs, pelvis, and shoulders; with sparing of the truncal muscles. Inheritance is autosomal recessive, or less commonly autosomal dominant.
- **Duchenne-Becker muscular dystrophy.** Progressive proximal muscle weakness, respiratory insufficiency, and difficulty ambulating are seen; the disorder primarily affects males. It is caused by a hemizygous *DMD* pathogenic variant in males. Inheritance is X-linked.
- **Polymyositis** is characterized by progressive, symmetric, unexplained muscle weakness.
- **Glycogen storage disease type V** (McArdle disease; muscle glycogen phosphorylase deficiency). Elevated serum concentration of creatine kinase and muscle cramping with exertion. Biallelic pathogenic variants in *PYGM* are causative. Inheritance is autosomal recessive.
- **Glycogen storage disease type VI.** Hypotonia, hepatomegaly, muscle weakness, and elevated serum concentration of creatine kinase are seen. Biallelic pathogenic variants in *PYGL* are causative. Inheritance is autosomal recessive.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Pompe disease, [guidelines](#) have been published for the initial evaluation of individuals with:

- Infantile-onset Pompe disease (IOPD) [American College of Medical Genetics expert panel; see Kishnani et al 2006b];
- Late-onset Pompe disease (LOPD) [Cupler et al 2012].

#### Chest radiography

- **IOPD.** Nearly all affected infants have cardiomegaly on chest x-ray [van den Hout et al 2003]. Further, evaluation of apparent lung volume reduction, areas of atelectasis, and any pulmonary fluid may be helpful in directing other therapies.
- **LOPD.** Baseline radiographic evaluation of the lungs and heart silhouette is indicated but only rarely reveals cardiomegaly.

#### Electrocardiography (EKG)

- **IOPD.** The majority of affected infants have left ventricular hypertrophy and many have biventricular hypertrophy [van den Hout et al 2003].
- **LOPD.** Based on findings of significant conduction abnormalities in four of 131 adults with LOPD, Sacconi et al [2014] recommended Holter monitoring at initial evaluation.

#### Echocardiography

- **IOPD.** Typically echocardiography demonstrates hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction in the early phases of the disease process. In later stages, dilated cardiomyopathy may be seen.
- **LOPD.** Echocardiographic assessment for dilatation of the ascending thoracic aorta has been recommended [El-Gharbawy et al 2011].

### **Pulmonary**

- **IOPD.** Most infants have varying degrees of respiratory insufficiency. Respiratory status should be established with regard to cough, presence of wheezing or labored breathing, and/or feeding difficulties. Diaphragmatic weakness caused by excessive glycogen deposits results in mild to moderate reduction of vital capacity; however, objective assessment of pulmonary functions in infants is difficult at best. Most infants display respiratory difficulty with feeds or sleep disturbance [Kravitz et al 2005].
- **LOPD.** Affected individuals should be evaluated for cough, wheezing, dyspnea, energy level, exercise tolerance, and fatigability. Formal pulmonary function tests show pulmonary insufficiency. An attempt to assess ventilatory capacity in the supine position can detect early ventilatory insufficiency. Pulse oximetry, respiratory rate, and venous bicarbonate and/or pCO<sub>2</sub> should be obtained to assess for alveolar hypoventilation [van der Beek et al 2011, Cupler et al 2012].

### **Nutrition/feeding**

- **IOPD.** Affected individuals should be evaluated for possible feeding difficulties (e.g., facial hypotonia, macroglossia, tongue weakness, and/or poor oromotor skills) [Jones et al 2010, van Gelder et al 2012]. Assessment of growth (i.e., height, weight, head circumference), energy intake, and feeding (including video swallow study) is appropriate. All infants should be evaluated for gastroesophageal reflux disease.
- **LOPD.** Assessment of nutritional status as baseline is recommended. Assessment of swallowing difficulty by video swallow study may identify barriers to adequate nutrition and risk for aspiration. Gastrointestinal symptoms similar to those reported in individuals with irritable bowel syndrome may be underreported in this population and may undermine quality of life.

### **Audiologic – IOPD**

- Baseline hearing evaluation including tympanometry is appropriate. See [Genetic Hearing Loss Overview](#) for a discussion of age-related methods of hearing evaluation.
- Sensorineural hearing loss is now documented in children with IOPD, and hearing aids may be of benefit [van Capelle et al 2010].

### **Disability inventory – IOPD and LOPD**

- All affected individuals should undergo assessment of motor skills and overall functioning to guide subsequent therapies and monitor progression of the disease.
- Assessment of risk for falls is recommended.

**Other.** Consultation with a clinical geneticist and/or genetic counselor is recommended.

## **Treatment of Manifestations**

**Guidelines** for the management of IOPD have been put forth by an expert panel from the American College of Medical Genetics [Kishnani et al 2006b]:

- **Cardiomyopathy.** Medical intervention needs to be individualized as use of standard drugs may be contraindicated in certain stages of the disease process (see Agents/Circumstances to Avoid) [Kishnani et al 2006b].
- **Arteriopathy.** Treatment does not differ from that in the general population.
- **Conduction disturbances.** Individuals with hypertrophic cardiomyopathy are at high risk for tachyarrhythmia and sudden death [Tabarki et al 2002]; 24-hour Holter monitoring is useful in characterizing the type and severity of rhythm disturbance. Management includes avoidance of stress, infection, fever, dehydration, and anesthesia. Medical therapy, if indicated, often necessitates a careful balance of ventricular function and should be undertaken by a cardiologist familiar with Pompe disease.
- **Muscle weakness.** Physical therapy is appropriate to maintain range of motion and assist in ambulation. Proximal motor weakness can result in contractures of the pelvic girdle in infants and children, necessitating aggressive management including surgery [Case et al 2012].  
Scoliosis is frequent, particularly in individuals with infantile- or childhood-onset disease [Roberts et al 2011].
- **Difficulty with communication** is common, and speech therapy as well as the use of augmented communication devices may be helpful.
- **Nutrition/feeding.** Infants may need specialized diets and maximal nutrition, with some requiring gastric feedings.  
Persons with LOPD may also develop feeding concerns and are often managed on a soft diet, with a few requiring gastric or jejunal feedings.
- **Respiratory insufficiency.** Respiratory support including CPAP and BiPAP may be required. Inspiratory/expiratory training has improved respiratory muscle strength in adults with LOPD [Jones et al 2011].  
Macroglossia and severe respiratory insufficiency in the infantile form may necessitate tracheostomy.

## Prevention of Primary Manifestations

### CRIM Status

Although enzyme replacement therapy (ERT) should be initiated as soon as the diagnosis of IOPD or symptomatic Pompe disease is established, it may be appropriate to determine cross-reactive immunologic material (CRIM) status prior to initiating ERT, as individuals who do not produce cross-reactive immunologic material (i.e., who are CRIM-negative) generally develop high titer anti-rhGAA antibodies during ERT and require modified therapy protocols using immunomodulation early in the treatment course, optimally before the first infusion [Winchester et al 2008, Kishnani et al 2010, Messinger et al 2012]. Multiple immunomodulation protocols are in use, most of which use rituximab with additional drugs (including mycophenylate mofetil, methotrexate, and sirolimus) [Messinger et al 2012, Elder et al 2013].

Geographic areas in which CRIM-negative status is common include the US and the Middle East [Messinger et al 2012].

Two ways to determine the CRIM status of an individual with Pompe disease are:

- Acid alpha-glucosidase protein quantitation performed by an antibody-based method in cultured fibroblasts;
- Molecular genetic testing to determine if the pathogenic variants result in total absence of enzyme activity (i.e., are CRIM-negative) [Bali et al 2012].

## Enzyme Replacement Therapy (ERT)

Myozyme<sup>®</sup> (alglucosidase alfa) was approved by the FDA in 2006 for IOPD infantile-onset Pompe disease.

Lumizyme<sup>®</sup> was approved by the FDA in 2010 for use in individuals older than age eight years with LOPD. Age restrictions on Lumizyme were removed in 2014.

Myozyme<sup>®</sup> and Lumizyme<sup>®</sup> are administered by slow IV infusion at 20-40 mg/kg/dose every two weeks. Many individuals are now treated with the higher dose.

## Complications of ERT

**Infusion-associated reactions.** In clinical studies, infusion reactions were observed in half of those treated with Myozyme<sup>®</sup>.

The majority of treated children developed IgG antibodies to Myozyme<sup>®</sup> within the first three months of treatment. Infusion reactions appear to be more common in individuals with IgG antibodies. Some affected individuals with high sustained IgG titers may have a poor clinical response to treatment (see Establishing the Diagnosis, **Acid alpha-glucosidase protein quantitation**).

Development of IgE antibodies is less common but may be associated with anaphylaxis requiring life support measures.

Most infusion-associated reactions can be modified by slowing the rate of infusion or administration of antipyretics, antihistamines, or glucocorticoids. For these reasons – and because many individuals with IOPD have preexisting compromise of respiratory and cardiac function – initiation of therapy in centers equipped to provide emergency care is recommended.

**Other.** Children with IOPD may have difficulty with anesthesia for procedures related to placement of devices for venous access.

## Prognosis

**IOPD.** The rationale for newborn screening (NBS) is that cardiac status and motor development in infants with IOPD treated early with enzyme replacement therapy (ERT) are better than in controls [Chien et al 2009]; initiation of ERT before age two weeks is associated with significantly improved gross motor function at age 12 months [Yang et al 2016]. Long-term follow-up data are not yet available on this cohort.

In those in whom ERT was initiated before age six months and before the need for ventilatory assistance, a majority had improved survival, improved ventilator-independent survival, reduced cardiac mass, and significantly improved acquisition of motor skills compared to an untreated cohort.

Longer-term survivors who underwent early ERT may show sustained improvement in cardiac and motor function [Prater et al 2012]. ERT reduces cardiac mass to varying degrees and improves the ejection fraction, although there may be a transient decrease in the ejection fraction after the first several weeks of ERT [Levine et al 2008]. ERT results in an increase of the PR interval and a decrease in the left ventricular voltage [Ansong et al 2006].

While the long-term prognosis is as yet unknown, available studies suggest better cognitive outcomes than had been predicted. Of note, assessment of cognitive abilities is difficult in children younger than age five years with IOPD; typical assessment tools frequently underestimate the cognitive abilities of these children [Kishnani et al 2009, Nicolino et al 2009, Ebbink et al 2012]. Estimates of cognitive abilities at age 24 months using the Bayley scales showed preservation of cognitive abilities in infants ascertained by NBS and treated early with ERT [Lai et al 2016].

Pivotal trials of ERT on IOPD show convincing delay in the onset of dependence on ventilator support, but most affected individuals who are ventilator dependent remain so. This finding is consistent with experimental evidence demonstrating relative resistance of skeletal muscle (especially type II fibers) to effective glycogen depletion with administered alpha glucosidase. Predictors of a poor response to ERT include increase in muscle glycogen during therapy, high IgG titers to alpha glucosidase, and CRIM negativity.

**LOPD.** The major morbidities are motor disability and respiratory insufficiency. In a randomized double-blind placebo-controlled study of 90 affected individuals age eight years and older who were ambulatory and free of invasive ventilatory support at baseline, those receiving the active agent had better preservation of motor function and forced vital capacity at the 78th week evaluation point [van der Ploeg et al 2010]. Similar findings were demonstrated in an open-label trial [Strothotte et al 2010].

Quality of life, assessed with the Rand Corporation 36-Item Short Form Survey Instrument ([SF-36](#)), had declined in adults with LOPD before initiation of ERT and improved in the first two years of ERT [Güngör et al 2016].

Note: Although the timing of initiation of ERT in infants predicted to have LOPD who have been ascertained by newborn screening is not well established, the Taiwan group uses clinical severity to identify those for whom ERT is warranted before age three years [Chien et al 2015].

## Prevention of Secondary Complications

Infections need to be aggressively managed.

Immunizations need to be kept current.

Affected individuals and household members should receive annual influenza vaccinations.

Respiratory syncytial virus (RSV) prophylaxis (palivizumab) should be administered in the first two years of life.

Anesthesia should be used only when absolutely necessary because reduced cardiovascular return and underlying respiratory insufficiency pose significant risks.

## Surveillance

Close follow up is indicated. Management and surveillance [guidelines](#) have been proposed by the ACMG Work Group on Management of Pompe Disease [Kishnani et al 2006b]. Given the wide age range in individuals with LOPD, most of the recommendations can be applied to both IOPD and LOPD.

- Twice-yearly clinical review of development, clinical status, growth, and use of adaptive equipment
- Assessment of respiratory status with each visit with regard to cough, difficulty breathing, wheezing, fatigability, and exercise tolerance:
  - Chest x-rays at regular intervals
  - Pulmonary function tests; yearly or more frequently as indicated
  - Periodic sleep evaluation, which may include regular capnography and pulse oximetry
- Monitoring of overall musculoskeletal and functional status to guide therapies aimed at preventing or minimizing physical impairment and its complications. This may include assessment for scoliosis and bone densitometry.
- Regular nutritional and feeding assessment
- At least annual kidney function studies to monitor for secondary complications related to cardiac and/or pulmonary impairment as well as medication effects



- Annual cardiology evaluation in those with LOPD and as needed for those with IOPD:
  - Periodic echocardiography. Aortic dilatation has been detected by echocardiography in late-onset Pompe disease [El-Gharbawy et al 2011].
  - 24-hour ambulatory EKG (Holter monitoring) at regular intervals [Cook et al 2006]. Sacconi et al [2014] noted that enzyme replacement therapy did not prevent development of significant conduction abnormalities in four of 131 adults with LOPD.
  - Screening for cerebral arteriopathy with aneurysmal dilatation and rupture leading to cerebral infarcts (strokes) and death, which have also been reported [Laforêt et al 2008, Sacconi et al 2010]. Screening strategies for these findings are being developed, but care teams should have a high index of suspicion for cerebral arteriopathy if an individual with late-onset Pompe disease develops unexplained stroke-like symptoms [Sacconi et al 2010].

Note: Individuals with LOPD may not be able to tolerate supine positioning in an MRI scanner due to diaphragmatic weakness.

- Annual hearing evaluation

## Agents/Circumstances to Avoid

Use of standard drugs for treatment of cardiac manifestations may be contraindicated in certain stages of the disease. The use of digoxin, ionotropes, diuretics, and afterload-reducing agents may worsen left ventricular outflow obstruction, although they may be indicated in later stages of the disease.

Hypotension and volume depletion should be avoided.

Exposure to infectious agents is to be avoided.

## Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic sibs of a proband so that morbidity and mortality can be reduced by early diagnosis and treatment with ERT.

Evaluations can include:

- Molecular genetic testing if the *GAA* pathogenic variants in the family are known.
- Testing of *GAA* enzyme activity if the *GAA* pathogenic variants in the family are not known.

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

## Pregnancy Management

Most individuals with infantile-onset Pompe disease (IOPD) have not reproduced.

Many adults with late-onset Pompe disease (LOPD) have reproduced. At least one woman treated with ERT during pregnancy and lactation with no adverse effects on the fetus has been reported [de Vries et al 2011]. As would be expected in a woman with a myopathy and respiratory insufficiency, the growing fetus may pose additional complications to the mother's health. Close respiratory and cardiac surveillance should be initiated in consultation with maternal fetal medicine specialists.

## Therapies Under Investigation

Gene therapy to correct the underlying enzyme defect is under investigation [Raben et al 2002, DeRuisseau et al 2009, Mah et al 2010]. A Phase I/II trial to investigate the ability of AAV-alpha glucosidase to improve

ventilation reported outcomes of children with IOPD treated with ERT. In this trial of phrenic nerve injected AAV-alpha glucosidase and ventilatory training, the rate of ventilatory decline was attenuated in a subset of children, particularly those who were not already dependent on ventilatory assistance full time at the time of intervention [Smith et al 2017].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Other

Experience with bone marrow transplantation in both humans and cattle with acid alpha-glucosidase deficiency is limited; to date, such treatment is not considered successful [Hirschhorn & Reuser 2001].

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Pompe disease is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- In most instances, the parents of an affected child are heterozygotes (i.e., carriers of one GAA pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing 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.
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

### Offspring of a proband

- Survivors with treated infantile-onset Pompe disease (IOPD) are just now attaining reproductive age.
- The offspring of an individual with Pompe disease are obligate heterozygotes (carriers) for a pathogenic variant in GAA.

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

## Carrier (Heterozygote) Detection

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

**Biochemical genetic testing.** Measurement of acid alpha-glucosidase enzyme activity in skin fibroblasts, muscle, or peripheral blood leukocytes is **unreliable** for carrier determination because of significant overlap in residual enzyme activity levels between obligate carriers and the general (non-carrier) population.

## 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.

**Concordance/discordance of phenotype in family members.** Sib pair concordance in IOPD is high in children with null pathogenic variants [Hirschhorn & Reuser 2001]. Age and severity of manifestations in LOPD may vary between affected family members.

### 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.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the GAA pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

**Biochemical genetic testing.** Prenatal testing is possible by measuring GAA enzyme activity in uncultured chorionic villi or amniocytes; however, molecular genetic testing is the preferred method if the familial pathogenic variants are known.

## 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](#).*

- **Acid Maltase Deficiency Association (AMDA)**  
**Phone:** 210-494-6144  
**Email:** [info@amda-pompe.org](mailto:info@amda-pompe.org)  
[www.amda-pompe.org](http://www.amda-pompe.org)
- **Association for Glycogen Storage Disease**  
[www.agsdus.org](http://www.agsdus.org)
- **MedlinePlus**  
[Pompe disease](#)
- **Muscular Dystrophy Association (MDA) - USA**

**Phone:** 833-275-6321

[www.mda.org](http://www.mda.org)

- **Newborn Screening in Your State**

Health Resources & Services Administration

[www.newbornscreening.hrsa.gov/your-state](http://www.newbornscreening.hrsa.gov/your-state)

- **RegistryNXT!**

**Phone:** 888-404-4413

**Email:** RegistryNXTHelpDesk@noflhealth.com

[www.registrynxt.com](http://www.registrynxt.com)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.** Pompe Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">GAA</a>	<a href="#">17q25.3</a>	<a href="#">Lysosomal alpha-glucosidase</a>	<a href="#">Glucosidase, alpha, acid (Pompe disease) (GAA) @ LOVD</a> <a href="#">CCHMC - Human Genetics Mutation Database (GAA)</a>	<a href="#">GAA</a>	<a href="#">GAA</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Pompe Disease ([View All in OMIM](#))

<a href="#">232300</a>	GLYCOGEN STORAGE DISEASE II; GSD2
<a href="#">606800</a>	GLUCOSIDASE, ALPHA, ACID; GAA

**Gene structure.** *GAA* is approximately 20 kb in length and contains 20 exons. The cDNA is more than 3.6 kb in length with 2859 nucleotides of coding sequence.

**Benign variants.** Two benign variants (and the "normal" variant) are responsible for the three known alloenzymes (GAA1, GAA2, and GAA4).

A pseudodeficiency allele c.1726 G>A (p.Gly576Ser), which interferes with enzyme activity toward artificial substrates, is relatively common in Asian as well as other populations studied as part of newborn screening programs [Labrousse et al 2010, Hopkins et al 2015, Lin et al 2017]. Of note: Additional pseudodeficiency alleles are likely to be discovered through newborn screening.

**Pathogenic variants.** More than 150 pathogenic variants in *GAA* have been identified in individuals with Pompe disease. See Table A.

Pathogenic nonsense variants, large and small gene rearrangements, and splicing variants have been observed. Many pathogenic variants are potentially specific to families, geographic regions, or ethnicities.

Combinations of pathogenic variants that result in complete absence of GAA enzyme activity are seen more commonly in infantile-onset Pompe disease (IOPD), whereas combinations of pathogenic variants that result in partial enzyme activity typically are seen more commonly in late-onset Pompe disease (LOPD).

**Table 5.** GAA Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
<b>Pseudodeficiency</b>	c.1726G>A	p.Gly576Ser	NM_000152.5 NP_000143.2
<b>Pathogenic</b>	c.-32-13T>G (IVS1-13T>G <sup>1</sup> )	--	NM_000152.5
	c.525delT	p.Glu176ArgfsTer45	NM_000152.5 NP_000143.2
	c.1935C>A	p.Asp645Glu	
	c.2481+110_2646+39del538 (Exon 18 del)	p.Gly828_Asn882del	
	c.2560C>T	p.Arg854Ter	

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** GAA is a lysosomal enzyme that catalyzes  $\alpha$ -1,4- and  $\alpha$ -1,6-glucosidic linkages at acid pH. There are seven glycosylation sites. The immature protein consists of 952 amino acids with a predicted non-glycosylated weight of 105 kd. The mature enzyme exists in either 76-kd or 70-kd form as a monomer.

**Abnormal gene product.** GAA pathogenic variants result in mRNA instability and/or severely truncated acid alpha-glucosidase or an enzyme with markedly decreased activity.

## Chapter Notes

### Author Notes

**Web:** [STAR Center for Lysosomal Diseases](#)

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### Revision History

- 2 November 2023 (aa) Revision: nomenclature updated for variants c.-32-13T>G and c.2481+110\_2646+39del538
- 11 May 2017 (bp) Comprehensive update posted live
- 9 May 2013 (me) Comprehensive update posted live
- 12 August 2010 (me) Comprehensive update posted live
- 31 August 2007 (me) Review posted live
- 8 January 2007 (bt) Original submission

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