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Gaucher Disease

Synonyms: Glucocerebrosidase Deficiency, Glucosylceramidase Deficiency

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Summary

Clinical characteristics

Gaucher disease (GD) encompasses a continuum of clinical findings from a perinatal lethal disorder to an asymptomatic type. The identification of three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular) is useful in determining prognosis and management.

GD type 1 is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease.

GD types 2 and 3 are characterized by the presence of primary neurologic disease; in the past, they were distinguished by age of onset and rate of disease progression, but these distinctions are not absolute.

- Disease with onset before age two years, limited psychomotor development, and a rapidly progressive course with death by age two to four years is classified as GD type 2.
- Individuals with GD type 3 may have onset before age two years, but often have a more slowly progressive course, with survival into the third or fourth decade.

The *perinatal-lethal form* is associated with ichthyosiform or collodion skin abnormalities or with nonimmune hydrops fetalis. The *cardiovascular form* is characterized by calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia. Cardiopulmonary complications have been described with all the clinical subtypes, although varying in frequency and severity.

Diagnosis/testing

The diagnosis of GD relies on demonstration of deficient glucocerebrosidase (glucosylceramidase) enzyme activity in peripheral blood leukocytes or other nucleated cells or by the identification of biallelic pathogenic variants in *GBA*.

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Note: The amino acid numbering for glucocerebrosidase used in this *GeneReview* follows the HGVS-recommended nomenclature, which includes the first 39 amino acids, and differs from the traditional numbering system, which does not include the first 39 amino acids. Using the HGVS-recommended nomenclature, the pathogenic variant p.Asn370Ser is named p.Asn409Ser and the pathogenic variant p.Leu444Pro is named p.Leu483Pro.

Management

Treatment of manifestations: When possible, management by a multidisciplinary team at a Comprehensive Gaucher Center. For persons not receiving enzyme replacement therapy (ERT) or substrate reduction therapy (SRT), symptomatic treatment includes partial or total splenectomy for massive splenomegaly and thrombocytopenia. Supportive care for all affected individuals may include: transfusion of blood products for severe anemia and bleeding; analgesics for bone pain; joint replacement surgery for relief from chronic pain and restoration of function; and anti-bone resorptive agents, calcium, and vitamin D for osteoporosis.

Prevention of primary manifestations: ERT is usually well tolerated and provides sufficient exogenous enzyme to overcome the block in the catabolic pathway, clearing the stored substrate, GL1, and thus reversing hematologic and liver/spleen involvement. Although bone marrow transplantation (BMT) had been undertaken in individuals with severe GD, primarily those with chronic neurologic involvement (GD type 3), this procedure has been largely superseded by ERT or SRT. Miglustat may be indicated in symptomatic individuals with GD type 1 who are not able to receive ERT. Eliglustat has been shown to improve or stabilize key disease features in those naïve to or switched from enzyme replacement therapy.

Prevention of secondary complications: The use of anticoagulants in individuals with severe thrombocytopenia and/or coagulopathy should be discussed with a hematologist to avoid the possibility of excessive bleeding.

Surveillance: Recommendations for comprehensive serial monitoring have been published by the International Collaborative Gaucher Group Registry (ICGG) and other groups.

Agents/circumstances to avoid: Nonsteroidal anti-inflammatory drugs in individuals with moderate to severe thrombocytopenia.

Evaluation of relatives at risk: It is appropriate to offer testing to asymptomatic at-risk relatives so that those with glucocerebrosidase enzyme deficiency or biallelic pathogenic variants can benefit from early diagnosis and treatment if indicated.

Pregnancy management: Pregnancy can exacerbate preexisting symptoms and trigger new features in affected women. Those with severe thrombocytopenia and/or clotting abnormalities are at increased risk for bleeding around the time of delivery. Evaluation by a hematologist prior to delivery is recommended. The lack of studies on the safety of eliglustat use during pregnancy and lactation has led to the recommendation that this medication be avoided during pregnancy, if possible.

Genetic counseling

Gaucher disease (GD) 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. Targeted analysis for pathogenic variants can be used to detect carriers in high-risk populations (e.g., Ashkenazi Jewish persons). Because the carrier frequency for GD in certain populations is high (e.g., 1:18 in individuals of Ashkenazi Jewish heritage) and the p.[Asn409Ser;Asn409Ser] phenotype is variable, individuals who undergo carrier testing may be identified as being homozygous. Prenatal testing for pregnancies at increased risk is possible using molecular genetic testing when both pathogenic variants in a family are known – or assay of glucocerebrosidase enzymatic activity if only one or neither pathogenic variant in the family is known.

GeneReview Scope

Gaucher Disease: Included Phenotypes
• Gaucher disease type 1 • Gaucher disease type 2 (acute) • Gaucher disease type 3 (subacute/chronic) • Gaucher disease, perinatal-lethal form • Gaucher disease, cardiovascular form

Diagnosis

Suggestive Findings

Gaucher disease (GD) encompasses a continuum of clinical findings from a perinatal lethal disorder to an asymptomatic type. GD **should be suspected** in individuals (by age) with the following combinations of central nervous system, bony, hematologic, and other clinical findings.

Table 1. Gaucher Disease: Clinical Subtypes

Age	Subtype	Primary CNS Involvement	Bone Disease [1]	Other
Adult	Type 1	No	Yes	• Splenomegaly • Hepatomegaly • Cytopenia [2] • Pulmonary disease
Infancy - early childhood	Type 2 (acute or infantile)	• Bulbar signs • Pyramidal signs • Cognitive impairment	No	• Hepatomegaly • Splenomegaly • Cytopenia[2] • Pulmonary disease • Dermatologic changes
Childhood	Type 3 (subacute; juvenile)	• Oculomotor apraxia • Seizures • Progressive myoclonic epilepsy	Yes	• Hepatomegaly • Splenomegaly • Cytopenia [2] • Pulmonary disease
Perinatal	Perinatal-lethal form	Pyramidal signs	No	• Ichthyosiform or collodion skin changes • Nonimmune hydrops fetalis
Cardiovascular-predominant variant	Cardiovascular form	Oculomotor apraxia	Yes	• Calcification of mitral & aortic valves • Corneal opacity • Mild splenomegaly

1. Osteopenia, focal lytic or sclerotic lesions, and/or osteonecrosis
2. Anemia, leukopenia, and/or thrombocytopenia

Establishing the Diagnosis

The diagnosis of Gaucher disease (GD) **is established** in a proband by the finding of 0%-15% of normal glucocerebrosidase enzyme activity in peripheral blood leukocytes (or other nucleated cells) or by the identification of biallelic pathogenic variants in *GBA* on molecular genetic testing (see Table 2).

Note: (1) Molecular analysis of *GBA* is complicated by the presence of a highly homologous pseudogene, *GBAP*. (2) The amino acid numbering for glucocerebrosidase used in this *GeneReview* follows the HGVS-recommended nomenclature, which includes the first 39 amino acids, and differs from the traditional numbering system, which

does not include the first 39 amino acids. Using the HGVS-recommended nomenclature, the pathogenic variant p.Asn370Ser is named p.Asn409Ser and the pathogenic variant p.Leu444Pro is named p.Leu483Pro. For a more complete list of pathogenic variants using traditional and standard nomenclature, see Montfort et al [2004].

Molecular testing approaches can include **single-gene testing** or use of a **multigene panel.**

Single-gene testing

- Sequence analysis of *GBA* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- Targeted analysis for pathogenic variants can be performed first, particularly in individuals of Ashkenazi Jewish ancestry.
    - The four most common variants account for approximately 90% of the pathogenic variants in this population:
        - c.84dupG (formerly known as 84GG)
        - c.115+1G>A (formerly known as IVS2+1)
        - p.Asn409Ser (formerly known as p.N370S)
        - p.Leu483Pro (formerly known as p.L444P)
    - In non-Jewish populations, the same four alleles account for approximately 50%-60% of pathogenic variants.

      Note: Non-Jewish individuals with GD tend to be compound heterozygotes with one common and one "rare" pathogenic variant (see Table 3) or a unique pathogenic variant.

A multigene panel that includes *GBA* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) Special consideration for the presence of the highly homologous pseudogene, *GBAP*, must be taken into account. (2) 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. (3) 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 pathogenic variants 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. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis (possibly excluding *GBA*), and/or other non-sequencing-based tests.

Table 2. Molecular Genetic Testing Used in Gaucher Disease

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
GBA	Sequence analysis [3, 4]	~99% [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown; likely <1% [7]

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. Due to the presence of a highly homologous pseudogene (*GBAP*), PCR-based methods must be designed to differentiate *GBA* from the pseudogene.
5. Complex disease-causing alleles derived from *GBA-GBAP* recombinant events, such as the common RecNciI allele, may be detected by sequence analysis.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that rely on hybridization, such as multiplex ligation-dependent probe amplification (MLPA) or gene-targeted microarray designed to detect single-exon deletions or duplications, may not detect deletions or duplications in regions of high homology between *GBA* and *GBAP.* Methods such as quantitative PCR, long-range PCR, and Southern blotting may be used to detect deletion/duplication of *GBA*.
7. Deletions of 3,925 bp of exons 1-2 and 5'UTR (a region unique to *GBA*) and of the whole gene have been reported [Beutler & Gelbart 1994, Cozar et al 2011]

Table 3. Proportion of Individuals with *GBA* Pathogenic Variants Using the Panel of Four Common Variants

Variants [1]	% of Affected Individuals [2, 3]
p.[Asn409Ser]+[Asn409Ser]	29%
p.[Asn409Ser]+[?]	20%
p.[Asn409Ser]+[Leu483Pro]	16%
p.Asn409Ser+c.84dupG	12%
p.[Leu483Pro]+[Leu483Pro] [4]	6%
p.[Leu483Pro]+[?]	3%
p.Asn409Ser+c.115+1G>A	3%

1. Table 5 provides the variant name and nucleotide changes according to current nomenclature guidelines.
2. Based on data from 1,097 individuals in the Gaucher Registry (International Collaborative Gaucher Group [October 1999]). In this population, 94% of individuals had type 1, 1% had type 2, and 5% type 3 (see Clinical Characteristics).
3. GD pathogenic variant detection rates based on sequence analysis available through the ICGG Registry Program (registration required)
4. Recombinant (Rec) alleles (i.e., the RecNciI allele; see Molecular Genetics) contain two to four single-nucleotide variants (including p.Leu483Pro) that arise as a result of gene rearrangements between exons 9 and 10 of the functional gene and pseudogene. Thus, testing for the p.Leu483Pro variant alone does not allow distinction of the isolated p.Leu483Pro allele from Rec alleles, and may lead to an error in genotype designation [Tayebi et al 2003].

Clinical Characteristics

Clinical Description

Gaucher disease (GD) encompasses a spectrum of clinical findings from a perinatal-lethal form to an asymptomatic form. However, for the purposes of determining prognosis and management, the classification of GD by clinical subtype is still useful in describing the wide range of clinical findings and broad variability in presentation. Three major clinical types are delineated by the absence (type 1) or presence (types 2 and 3) of primary central nervous system involvement (see Table 1).

Type 1 GD

Bone disease. Clinical or radiographic evidence of bone disease occurs in 70%-100% of individuals with type 1 GD. Bone disease ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis [Wenstrup et al 2002]. Bone involvement, which may lead to acute or chronic bone pain, pathologic fractures, and subchondral joint collapse with secondary degenerative arthritis, is often the most debilitating aspect of type 1 GD [Pastores et al 2000].

Acute bone pain manifests as "bone crises" or episodes of deep bone pain that are usually confined to one extremity or joint [Cohen 2003] and are often accompanied by fever and leukocytosis but sterile blood culture. The affected region may be swollen and warm to touch; imaging studies may reveal signal abnormalities consistent with localized edema or hemorrhage; x-rays may show periosteal elevation ("pseudo-osteomyelitis") [Pastores & Meere 2005].

Conventional radiographs (x-rays) may reveal undertubulation (Erlenmeyer flask configuration) noted in the distal femur and endosteal scalloping as a sign of bone marrow infiltration. MRI reveals the extent of marrow involvement and the presence of fibrosis and/or infarction. In general, marrow infiltration extends from the axial to the appendicular skeleton, and greater involvement is often seen in the lower extremities and proximal sites of an affected bone. The epiphyses are usually spared, except in advanced cases. Bone densitometry studies enable quantitative assessment of the degree of osteopenia.

Bone disease in GD may not correlate with the severity of hematologic or visceral problems.

Secondary neurologic disease in type 1 GD. Although individuals with type 1 GD do not have primary CNS disease, neurologic complications (spinal cord or nerve root compression) may occur secondary to bone disease (e.g., severe osteoporosis with vertebral compression; emboli following long bone fracture), or coagulopathy (e.g., hematomyelia) [Pastores et al 2003].

The incidence of peripheral neuropathy may be higher than previously recognized [Halperin et al 2007, Capablo et al 2008]. In a two-year prospective study, which enrolled 103 affected individuals, 11 (10.7%) were diagnosed with sensory motor axonal polyneuropathy [Biegstraaten et al 2010].

Hepatosplenomegaly. The spleen is enlarged (i.e., 1,500-3,000 cc in size, compared to 50-200 cc in the average adult) with resultant hypersplenism associated with pancytopenia (i.e., anemia, leukopenia, and thrombocytopenia). Infarction of the spleen can result in acute abdominal pain. Rarely, acute surgical emergencies may arise because of splenic rupture [Stone et al 2000b].

Liver enlargement is common, although cirrhosis and hepatic failure are rare [Ayto et al 2010].

Cytopenias. Cytopenia is almost universal in untreated GD. Anemia, thrombocytopenia, and leukopenia may be present simultaneously or independently [Zimran et al 2005]. The pattern of cytopenia in GD is dependent on spleen status.

Low platelet count may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction. Immune thrombocytopenia has also been reported and should be excluded in individuals with persistent thrombocytopenia despite GD-specific therapy. Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy. The risk for bleeding may be increased in the presence of clotting abnormalities.

Anemia may result from hypersplenism, hemodilution (e.g., pregnancy), iron deficiency or B_{12} deficiency, and, in advanced disease, decreased erythropoiesis as a result of bone marrow failure from Gaucher cell infiltration or medullary infarction.

Leukopenia is rarely severe enough to require intervention. Deficient neutrophil function has been reported.

Coagulation abnormalities. Acquired coagulation factor deficiencies include low-grade disseminated intravascular coagulation and specific inherited coagulation factor deficiencies (e.g., factor XI deficiency among Ashkenazi Jews). An investigation of Egyptian individuals with type 1 GD revealed a wide variety of coagulation factor abnormalities (fibrinogen, factor II, VII, VIII, X, XII) [Deghady et al 2006]. Abnormal platelet aggregation may contribute to bleeding diathesis in the presence of normal platelet counts [Linari & Castaman 2016].

Pulmonary involvement. The following can be observed:

- Interstitial lung disease
- Alveolar/lobar consolidation
- Pulmonary arterial hypertension (PAH); well documented in individuals with liver disease and presumably the result of inability to detoxify gut-derived factors, which somehow adversely affect the pulmonary endothelium with resultant pulmonary hypertension. PAH can also occur in individuals with GD without liver disease [Mistry et al 2002]. In a study of 14 individuals with PAH, median age at GD diagnosis was 36 years (22-63). There was a female preponderance (ratio 5:2), and all individuals in this report had undergone splenectomy (median age 12 years) [Lo et al 2011].

Dyspnea and cyanosis with digital clubbing attributed to hepatopulmonary syndrome have been described in individuals with liver dysfunction, often caused by an intercurrent disease (e.g., viral hepatitis).

Those individuals with type 1 GD without evident lung involvement who limit physical exertion because of easy fatigability may have impaired circulation [Miller et al 2003].

Pregnancy and childbirth. Except in women with significant pulmonary arterial hypertension, pregnancy is not contraindicated in GD (see Pregnancy Management).

In some women the diagnosis of GD is first made in pregnancy because of exacerbation of hematologic features.

Malignancy. Epidemiologic studies have suggested elevated risk of certain malignancies in GD including the following:

- Multiple myeloma [Rosenbloom et al 2005]
- Hepatocellular carcinoma [de Fost et al 2006]
- Non-Hodgkins lymphoma, malignant melanoma, and pancreatic cancer [Landgren et al 2007]

Except in the case of multiple myeloma, other reports have failed to find these associations [Cox et al 2015b]. The basis for increased risk for multiple myeloma remains the subject of investigations [Nair et al 2018].

Immunologic abnormalities. Children or adults may have polyclonal gammopathy [Wine et al 2007]. An increased incidence of monoclonal gammopathy has been reported in adults [Brautbar et al 2004]. Affected individuals also exhibit altered cellular immune profiles with increased peripheral blood NKT lymphocytes and reduced numbers of functionally normal dendritic cells [Lalazar et al 2006, Micheva et al 2006].

Metabolic abnormalities. GD is associated with metabolic abnormalities including high resting energy expenditures (possibly the result of elevated cytokine levels) and low circulating adiponectin and peripheral insulin. The hypermetabolic state is not associated with altered thyroid hormone resistance [Langeveld et al 2007a, Langeveld et al 2007b, Langeveld et al 2008].

Serum concentrations of angiotensin-converting enzyme, tartrate-resistant acid phosphatase, ferritin, chitotriosidase, and PARC/CCL18 are usually elevated. Serum concentrations of total and HDL cholesterol are often low.

Abnormalities in the concentration of certain bone markers have been found in some individuals with GD in serum (e.g., osteocalcin, bone-specific alkaline phosphatase, macrophage inhibitory protein-1 alpha and beta)

and urine (e.g., urinary hydroxyproline, free deoxypyridinoline, calcium); however, the routine utility of these findings in clinical practice is not established [Giuffrida et al 2012, Masi & Brandi 2015].

Psychological complications. Persons with GD exhibit moderate to severe psychological complications including somatic concerns and depressed mood [Packman et al 2006].

Other

- Cholelithiasis occurs in a significant proportion of adults with GD:
  - In a cohort of 417 affected individuals, the prevalence of gallstones (GS) was 32%, and found to be higher in women.
  - Those with GS were more likely to be asplenic ($p<0.0001$) and older ($p<0.0001$); and have higher low-density lipoprotein (LDL) cholesterol concentrations ($p=0.002$) and more severe GD1 disease than those without GS [Taddei et al 2010].
  - Additional risk factors include age, family history of GS, higher body mass index values, disease severity, and splenectomy [Zimmermann et al 2016].
- Cardiac and renal complications are rare.

Type 2 GD / Type 3 GD (Primary Neurologic Disease)

Neurologic disease. Previously, affected individuals were classified into type 2 or type 3 GD based on the age of onset of neurologic signs and symptoms and the rate of disease progression. Children with onset before age two years with a rapidly progressive course, limited psychomotor development, and death by age two to four years were classified as having type 2 GD. Individuals with type 3 GD may have onset before age two years but often have a more slowly progressive course, with life span extending into the third or fourth decade in some cases. However, these distinctions are not absolute and it is increasingly recognized that neuropathic GD represents a phenotypic continuum, ranging from abnormalities of horizontal ocular saccades at the mild end to hydrops fetalis at the severe end [Goker-Alpan et al 2003].

Bulbar signs include stridor, squint, and swallowing difficulty.

Pyramidal signs include opisthotonus, head retroflexion, spasticity, and trismus.

Oculomotor apraxia, saccadic initiation failure, and opticokinetic nystagmus are common [Nagappa et al 2015]. Oculomotor involvement may be found as an isolated sign of neurologic disease in individuals with a chronic progressive course and severe systemic involvement (e.g., massive hepatosplenomegaly).

Generalized tonic-clonic seizures and progressive myoclonic epilepsy have been observed in some individuals [Roshan Lal & Sidransky 2017]. In a study of 122 affected individuals, seizures and myoclonic seizures were reported in 19 (16%) and three (2%) persons, respectively [Tylki-Szymańska et al 2010].

Dementia and ataxia have been observed in the later stages of chronic neurologic disease.

Brain stem auditory evoked response (BAER) testing may reveal abnormal wave forms (III and IV) [Okubo et al 2014]. MRI of the brain may show mild cerebral atrophy. (A normal EEG, BAER, or brain MRI does not exclude neurologic involvement.)

Perinatal-lethal form. The perinatal-lethal form is associated with hepatosplenomegaly, pancytopenia, and microscopic skin changes (i.e., abnormalities in the stratum corneum attributed to altered glucosylceramide-to-ceramide ratio) and may present clinically with ichthyosiform or collodion skin abnormalities or as nonimmune hydrops fetalis [Orvisky et al 2002]. Arthrogryposis and distinctive facial features are seen in 35%-43% [Mignot et al 2003].

Another rare severe variant of GD is associated with hydrocephalus, corneal opacities, deformed toes, gastroesophageal reflux, and fibrous thickening of splenic and hepatic capsules [Stone et al 2000b, Inui et al 2001].

Cardiovascular form. Individuals homozygous for the p.Asp448His allele present with an atypical phenotype dominated by cardiovascular disease with calcification of the mitral and aortic valves [Altunbas et al 2015]. Additional findings include mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia [George et al 2001].

Genotype-Phenotype Correlations

The level of residual glucocerebrosidase enzyme activity as measured in vitro from extracts of nucleated cells does not correlate with disease type or severity.

Genotype-phenotype correlations in GD are imperfect. Significant overlap in the clinical manifestations found between individuals with the various genotypes precludes specific counseling about prognosis in individual cases. At present the factors that influence disease severity or progression within particular genotypes are not known. Discordance in phenotype has been reported even among monozygotic twins [Lachmann et al 2004, Biegstraaten et al 2011].

The following observations apply:

Type 1 GD

- Individuals with at least one p.Asn409Ser allele do not develop primary neurologic disease [Koprivica et al 2000]. However, the presence of an p.Asn409Ser allele does not eliminate the risk for Parkinson disease among individuals with GD.
- In general, individuals who are homozygous for the p.Asn409Ser or p.Arg535His variant tend to have milder disease than those with other genotypes. It is suspected that a significant proportion of Ashkenazi Jewish individuals with this genotype may be asymptomatic and thus do not come to the attention of medical professionals [Bronstein et al 2014]. However, surveillance is critical, as a proportion of these individuals do develop progressive disease [Taddei et al 2009].

Primary neurologic disease (type 2 and type 3 GD)

- Individuals who are homozygous for the p.Leu483Pro variant tend to have severe disease, often with neurologic complications (i.e., types 2 and 3), although several individuals (including adults) with this genotype have had no overt neurologic problems. This variant results in an unstable enzyme with little or no residual activity.
  - In a study of 31 individuals with type 2 GD, p.Leu483Pro accounted for 25 alleles (40%) [Stone et al 2000c]. The p.Leu483Pro variant occurred alone (9 alleles), with the p.Glu365Lys polymorphism (1 allele), and as part of a recombinant allele (15 alleles).
  - In another study, homozygosity for the p.Leu483Pro variant was the most common genotype among individuals with type 3 GD (10/24 individuals, or 42%) [Koprivica et al 2000].
  - In a study of affected individuals of Japanese and Korean ancestry with GD including type 1 disease, p.Leu483Pro accounted for 41% and 20.8% of alleles, respectively. The second most common allele among Japanese was p.Phe252Ile (14%); among Koreans, p.Gly85Glu (13.9%). The absence of p.Asn409Ser among those examined accounted for the higher frequency of the neuropathic subtype when compared to that seen in Western countries [Eto & Ida 1999, Jeong et al 2011].
- In individuals with GD and myoclonic epilepsy, Park et al [2003] identified 14 genotypes (including the variants p.Val433Leu [commonly known as V394L], p.Gly416Ser [commonly known as G377S], and p.Asn227Ser [commonly known as N188S]) previously associated with non-neuronopathic GD, in

combination with the variant p.Leu483Pro and recombinant alleles that have been previously associated with neuropathic GD.
- A second variant, p.His294Gln (commonly known as H255Q) occurring *in cis* with the p.Asp448His variant has been identified among Greek and Albanian individuals. Homozygosity for the p.[Asp448His;His255Gln] allele has been associated with type 2 GD [Michelakakis et al 2006].

Perinatal-lethal form. Genotypic heterogeneity is significant in this rare subset of individuals. The following have been observed:

- Homozygosity for recombinant alleles [Stone et al 2000a]
- The mutated alleles p.Ser235Pro (S196P), p.Arg170Leu (R131L), p.Arg159Trp (R120W), and p.Arg296Gln (R257Q) [Stone et al 2000a]
- Compound heterozygosity for an insertion-type pathogenic variant and the pathogenic missense variant p.Arg159Gln (R120Q), previously reported in an individual with type 1 GD [Felderhoff-Mueser et al 2004]

Cardiovascular form. This phenotype has been described only in individuals who are homozygous for the p.Asp448His (commonly known as D409H) allele. The biochemical basis for the unique clinical features associated with this form is not fully delineated. It should be noted that homozygosity for the p.[Asp448His;p.His294Gln] allele is associated with neuropathic type 2 GD and not the cardiovascular form (see **Primary neurologic disease** above).

c.84dupG and c.115+1G>A

- Despite the observed allele frequencies for the pathogenic variants c.84dupG and c.115+1G>A, no live-born homozygote for either variant has been identified. Thus, it is presumed that these genotypes are lethal.
- Children who are compound heterozygotes (i.e., c.[84dupG]+[115+1G>A]) have a subacute disease course with progressive pulmonary involvement and death in the first to second decade.

Prevalence

A study from Australia reported a disease frequency of 1:57,000 [Meikle et al 1999]; a similar study from the Netherlands reported 1.16:100,000 [Poorthuis et al 1999]. In the Czech Republic, the birth prevalence was reported as 1.13 per 100,000 [Poupetová et al 2010].

A founder effect for specific alleles underlies the observed occurrence of GD in specific populations:

- Ashkenazi Jewish, Spanish, and Portuguese (p.Asn409Ser)
- Swedish (p.Leu483Pro)
- Jenin Arab, Greek, and Albanian (p.Asp448His). Among Greeks and Albanians, p.Asp448His has been found *in cis* with p.His294Gln.

Non-neuropathic GD (type 1) is prevalent in the Ashkenazi Jewish population, with a disease prevalence of 1:855 and an estimated carrier frequency of 1:18.

The prevalence of neuropathic GD (types 2 and 3) varies across ethnic groups but appears to be higher among those who are not of European origin.

Genetically Related (Allelic) Disorders

Parkinsonian features have been reported in a few individuals with type 1 GD; studies suggest a possible cause-and-effect relationship rather than mere coincidence, although the underlying basis remains incompletely understood [Blanz & Saftig 2016, Lopez et al 2016, Aflaki et al 2017]. The following findings suggest that

pathogenic variants in *GBA* and/or alterations in glucosylceramide metabolism may be a risk factor for parkinsonism [Sidransky 2005].

- The precise risk to individuals with Gaucher disease of developing Parkinson disease (PD) is not known, but has been variously estimated at 20- to 30-fold the risk to an individual in the general population [Bultron et al 2010, McNeill et al 2012].
- *GBA* pathogenic variants have been identified in 5%-10% of individuals with PD [Sidransky et al 2009]. PD associated with pathogenic variants in *GBA* (GBA-PD) is clinically, pathologically, and pharmacologically indistinguishable from idiopathic "sporadic" PD, although GBA-PD is associated with slightly earlier onset (~5 years earlier) and more frequent cognitive dysfunction [Neumann et al 2009].
- Family studies suggest that the incidence of parkinsonism may be higher in obligate heterozygotes for GD. Among Ashkenazi Jewish individuals who developed PD, those with GD experienced a younger age at onset than those who were obligate heterozygotes (mean, 54.2 vs 65.2 years, respectively; P = .003). Estimated age-specific risk for PD at 60 and 80 years of age was 4.7% and 9.1% among those with GD, 1.5% and 7.7% among heterozygotes, and 0.7% and 2.1% among non-carriers, respectively [Alcalay et al 2014].

Differential Diagnosis

Saposin C deficiency or prosaposin deficiency (OMIM 610539). Saposin C is a cofactor for glucocerebrosidase in the hydrolysis of GL1. Individuals with saposin C deficiency or prosaposin deficiency may present with symptoms characteristic of severe neuropathic Gaucher disease (GD) (i.e., progressive horizontal ophthalmoplegia, pyramidal and cerebellar signs, myoclonic jerks, and generalized seizures) [Pàmpols et al 1999, Qi & Grabowski 2001] or non-neuronopathic disease [Tylki-Szymańska et al 2007]. These individuals demonstrate GL1 accumulation and visceromegaly but have normal glucocerebrosidase enzyme activity measured in vitro. Saposin C deficiency is caused by biallelic pathogenic variants in *PSAP* and inherited in an autosomal recessive manner.

Lysosomal storage diseases (LSDs). Findings in GD may overlap with some lysosomal storage diseases; however, the distinctive clinical features associated with these lysosomal storage diseases, the availability of biochemical testing in clinical laboratories, and an understanding of their natural history should help distinguish between them.

Hepatosplenomegaly is observed in Niemann-Pick disease types A and B (see Acid Sphingomyelinase Deficiency), Niemann-Pick disease type C, Wolman disease (lysosomal lipase deficiency), the mucopolysaccharidoses (including mucopolysaccharidosis type I and mucopolysaccharidosis type II), and the oligosaccharidoses. The following features are not found in individuals with GD and should direct further investigations to these alternative diagnoses:

- Coarse facial features
- Dysostosis multiplex on skeletal radiographs
- Vacuolated lymphocytes on peripheral blood smear examination
- The presence of a cherry-red spot on fundoscopy
- White matter changes (leukodystrophy) on brain MRI

Gaucher cells. The characteristic storage cells of GD should be distinguished from those found in other storage disorders such as Niemann-Pick disease type C. "Pseudo Gaucher cells," which resemble Gaucher storage cells at the light microscopic but not ultrastructural level, occur in a number of hematologic conditions including myeloproliferative and myelodysplastic disorders.

Legg-Calvé-Perthes disease (OMIM 150600). Osteonecrosis may be a presenting feature of GD, which should be considered in the differential diagnosis of children with suspected Legg-Calvé-Perthes disease [Kenet et al

2003]. A heterozygous pathogenic variant in *COL2A1* causes a subset of cases of Legg-Calvé-Perthes disease inherited in an autosomal dominant manner.

Congenital ichthyoses and collodion skin changes are observed in autosomal recessive congenital ichthyosis.

Hydrops fetalis may be encountered in other LSDs, including GM1 gangliosidosis, sialidosis type 1 (OMIM 256550), Wolman disease, mucopolysaccharidosis type VII (MPS VII; OMIM 253220), mucopolysaccharidosis type IV (MPS IV; see MPS IVA), galactosialidosis (OMIM 256540), Niemann-Pick disease type C, disseminated lipogranulomatosis (Farber disease), infantile free sialic acid storage disease (ISSD), and mucolipidosis II (I-cell disease) [Stone & Sidransky 1999, Kooper et al 2006].

Myoclonic seizures are also observed in hexosaminidase A deficiency, sialidosis type 1, alpha-N-acetylgalactosaminidase deficiency (OMIM 609241), and fucosidosis (OMIM 230000). In addition to the LSDs, several genetic disorders are known to be associated with progressive myoclonic epilepsy (reviewed in de Siqueira [2010]). Lysosome membrane protein 2 (encoded by *SCARB2*) has been shown to facilitate lysosomal targeting for the nascent glucocerebrosidase [Reczek et al 2007]. Biallelic pathogenic variants in *SCARB2* have been associated with action myoclonus-renal failure (OMIM 254900).

Management

Evaluations Following Initial Diagnosis

Factors that may influence the extent of clinical testing at the time of diagnosis:

- Age
- Mode of ascertainment (e.g., family screening vs disease signs and symptoms)
- Presence/absence of primary neurologic involvement

Baseline (pre-treatment) assessments may be useful in selecting treatment modality and regimen (i.e., enzyme dose and frequency of infusion).

The following evaluations may be considered, if they were not performed as part of the diagnostic assessment:

- Hemoglobin concentration and platelet count
- Baseline spleen and liver volumes by MRI
- EKG and echocardiography to identify elevated pulmonary artery pressure
- Plain radiographs of the femur (anterior-posterior view), spine (lateral view), and any symptomatic sites
- Bone age in individuals with growth and pubertal delay
- Consultation with a clinical geneticist

Treatment of Manifestations

Management by a multidisciplinary team with expertise in treating GD is available at Comprehensive Gaucher Centers (see National Gaucher Foundation). Enzyme replacement therapy and substrate reduction therapy are available options for this condition (see Prevention of Primary Manifestations). Clinical management guidelines have been published [Biegstraaten et al 2018].

Although enzyme replacement therapy (ERT) has changed the natural history of GD and eliminated the need for splenectomy in individuals with hypersplenism, persons not receiving ERT and certain other individuals may require symptomatic treatment, including the following:

- **Partial or total splenectomy** for individuals with massive splenomegaly with significant areas of infarction and persistent severe thrombocytopenia with high risk of bleeding

- **Transfusion of blood products** for severe anemia and bleeding. Anemia and clotting problems unresponsive to ERT should prompt investigations for an intercurrent disease process. Evaluation by a hematologist is recommended prior to any major surgical or dental procedures or parturition [Hughes et al 2007].
- **Analgesics for bone pain.** Persistent bone pain in individuals on treatment should prompt evaluations to exclude the possibility of a mechanical problem (e.g., pathologic fracture or joint collapse secondary to osteonecrosis, degenerative arthritis).
- **Joint replacement surgery** for relief from chronic pain and restoration of function (i.e., improved joint range of motion). Bone pain in individuals who have undergone joint replacement may indicate a problem with the prosthesis and the need for surgical revision.
- **Supplemental treatment.** Calcium and vitamin D may benefit individuals with GD and low bone density. Anti-bone-resorbing agents may also be indicated; ideally, evaluations and management should be undertaken in consultation with metabolic bone specialists [Wenstrup et al 2004, Masi & Brandi 2015].

Persons with GD with findings suggestive of multiple myeloma and parkinsonism should be referred to the appropriate specialists.

Prevention of Primary Manifestations

Bone marrow transplantation (BMT) has been largely superseded by enzyme replacement therapy (see Enzyme Replacement Therapy) or substrate reduction therapy (see Substrate Reduction Therapy). Individuals with chronic neurologic GD and progressive disease despite ERT or SRT may be candidates for BMT or a multimodal approach (i.e., combined ERT and BMT or SRT).

Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) is based on the provision of sufficient exogenous enzyme to overcome the block in the catabolic pathway and effect the clearance of the stored substrate, GL1.

- There are three recombinant glucocerebrosidase enzyme preparations currently available: **imiglucerase** (Cerezyme®); **velalglucerase alfa** (VPRIV®); and **taliglucerase alfa** (Elelyso®).
- Regular intravenous infusions of the recombinant enzymes have been demonstrated to be safe and effective in reversing those features resulting from hematologic and visceral (liver/spleen) involvement [Weinreb et al 2002, Zimran et al 2010, Zimran et al 2011, Ben Turkia et al 2013].
- It is likely that end-stage histologic changes (e.g., fibrosis, infarction) influence the response to ERT. Thrombocytopenia may persist in individuals with residual splenomegaly and/or the presence of splenic nodules [Stein et al 2010].
- ERT is well tolerated. Approximately 10%-15% of individuals develop antibodies to infused imiglucerase; whereas antibody formation has been reported in 1% of persons receiving velaglucerase. In most cases these individuals remain asymptomatic [Rosenberg et al 1999, Starzyk et al 2007]. Adverse effects (e.g., pruritus, hives) are relatively well controlled with premedication using antihistamines.
- **Individuals with type 1 GD** report improved health-related quality of life after 24-48 months of ERT [Damiano et al 1998, Masek et al 1999, Weinreb et al 2007].
- After prolonged treatment, ERT reduces the rate of bone loss in a dose-dependent manner [Wenstrup et al 2007], improves bone pain, and reduces bone crises [Charrow et al 2007].
- ERT does not alter the ultimate prognosis of neurologic disease in GD, although treatment of those with GD type 3 can lead to significant improvement in quality of life associated with improvement in systemic manifestations [Sechi et al 2014, Charrow & Scott 2015].
- **Individuals with type 2 GD** and pyramidal tract signs are not likely to respond to ERT or SRT, perhaps because the underlying neuropathology is cell death rather than lysosomal storage of GL1 [Takahashi et al

1998]. These individuals and those with hydrops fetalis are not appropriate candidates for BMT, ERT, or SRT [Campbell et al 2003, Migita et al 2003].

- **Individuals with type 3 GD** appear to derive some benefit from ERT, although long-term prognosis remains to be defined for this heterogeneous group [Vellodi et al 2001, Lee et al 2014]. Onset of progressive myoclonic seizures while on ERT appears to indicate a poor prognosis [Frei & Schiffmann 2002]. Brain stem auditory evoked responses have deteriorated in individuals with type 3 GD on ERT [Campbell et al 2003]. SRT used in combination with ERT for type 3 GD with progressive neurologic disease does not appear to alter ultimate prognosis. Moreover, residual somatic symptoms, including kyphosis and lymphadenopathy, may also be observed [Lee et al 2014]. Long-term data from the ICGG Registry has been published [El-Beshlawy et al 2017].

Consensus recommendations exist for ERT and monitoring of children with type 1 GD [Baldellou et al 2004, Charrow et al 2004, Grabowski et al 2004] (see Published Guidelines / Consensus Statements). The optimal dose and frequency of recombinant enzyme administration is not certain, mostly because of limited information regarding tissue half-life and distribution and the limitations associated with the modalities used for assessing clinical disease course. Intravenously infused enzyme may not reach adequate concentrations in certain body sites (e.g., brain, bones, and lungs). In the majority of individuals, treatment is initiated with a dose of 15-60 units of enzyme per kg of body weight administered intravenously every two weeks. The enzyme dose may be increased or decreased after initiation of treatment and during the maintenance phase, based on response – i.e., hematopoietic reconstitution, reduction of liver and spleen volumes, and stabilization or improvement in skeletal findings [Pastores et al 2004].

Affected individuals may require assistance with insurance-related issues and reimbursement because of the high cost of ERT.

Substrate Reduction Therapy

Substrate reduction therapy (SRT) aims to restore metabolic homeostasis by limiting the amount of substrate precursor synthesized (and eventually subject to catabolism) to a level that can be effectively cleared by the mutated enzyme with residual hydrolytic activity [Dwek et al 2002].

- **Miglustat** is the first oral agent for the treatment of individuals with mild to moderate Gaucher disease for whom ERT is not a therapeutic option (e.g., because of constraints such as allergy, hypersensitivity, or poor venous access). In at least three studies, involving more than 30 individuals with GD type 1, miglustat treatment resulted in a significant decrease in liver and spleen volume after six to 18 months, with clinical improvement noted over 24 months. Bone involvement and platelet and hemoglobin values remained stable or were modestly improved [Cox et al 2000, Elstein et al 2004a, Pastores et al 2005]. An increase in bone density at the lumbar spine and femoral neck was reported to occur as early as six months after the initiation of miglustat monotherapy [Pastores et al 2007]. The most common adverse reactions noted in the clinical trials were weight loss (60% of individuals), and bloating, flatulence, and diarrhea (80%), which resolved or diminished with longer use of the product.
- **Eliglustat,** an alternative inhibitor of glucosylceramide synthetase, has been shown in clinical trials to be a safe and effective treatment for individuals with Gaucher disease type 1 who are not on any therapy as well as those previously treated with ERT [Kamath et al 2014, Cox et al 2015a, Cox et al 2017, Mistry et al 2015]. Longer-term studies provide further support to conclusions derived from the pivotal trials [Cox et al 2015a, Mistry et al 2017]. The experience with once-daily and twice-daily dosing in patients has been found to maintain mean values for hematologic and visceral measures within established therapeutic goals during the double-blind treatment and long-term extension periods. Patients on twice-daily eliglustat showed more stability overall [Charrow et al 2018].

Note: (1) Reported side effects of eliglustat were generally mild. (2) The use of eliglustat requires cytochrome P450 2D6 genotyping and avoidance of drugs that may interact through this metabolic pathway [Balwani et al 2016]. (3) Drug distribution studies indicate that eliglustat, a P-glycoprotein ligand, is not transported across the blood-brain barrier and, thus, not indicated for neuronopathic forms of GD.

Prevention of Secondary Complications

The use of anticoagulants in individuals with severe thrombocytopenia and/or coagulopathy should be discussed with a hematologist to avoid the possibility of excessive bleeding.

Surveillance

Physicians who are the US regional coordinators for the International Collaborative Gaucher Group Registry (ICGG) and other groups have published recommendations for comprehensive serial monitoring of the severity and rate of disease progression [Baldellou et al 2004, Charrow et al 2004, Grabowski et al 2004, Vom Dahl et al 2006]. A European working group has also published a consensus document relating to management goals for individuals with GD1 [Biegstraaten et al 2018]:

- **Medical history** (at least every 6-12 months) including weight loss, fatigue, depression, change in social, domestic, or school- or work-related activities, bleeding from the nose or gums, menorrhagia, shortness of breath, abdominal pain, early satiety as a result of abdominal pressure, joint aches or reduced range of movement, and bone pain
- **Physical examination** (at least every 6-12 months) including heart and lungs, joint range of motion, gait, neurologic status, and evidence of bleeding (bruises, petechiae). In children, attention should be given to growth (height, weight, and head circumference using standardized growth charts) and pubertal changes (using the Tanner staging system). Neurologic evaluation is particularly important in the early detection of type 2 and type 3 disease in children. A severity scoring tool has been developed to evaluate neurologic features of neuronopathic GD [Davies et al 2007].
- **Assessment of hemoglobin concentration and platelet count** (with frequency based on symptoms and treatment status). Hemoglobin, platelet count, and coagulation indices should also be assessed prior to surgical or dental procedures.
- **Other blood tests** at the physician's discretion may include measurement of the following:
  - Serum concentrations of tartrate-resistant acid phosphatase, liver enzymes (aspartate aminotransferanse or alanine amino transferase), iron, ferritin, and vitamins B_{12} and D.
  - Plasma activity of chitotriosidase, a macrophage-derived chitin-fragmenting hydrolase, and plasma concentration of PARC/CCL18. Levels are typically elevated, and are felt to correlate with body-wide burden of disease. An enzyme dose-dependent decrease in plasma chitotriosidase activity has been observed in affected individuals on ERT; however, up to 40% of affected individuals of European origin are homozygous or heterozygous for a common null variant, confounding interpretation of test results [Grace et al 2007].
- **Assessment of spleen and liver volumes** by MRI. Parenchymal abnormalities can be identified as well. In situations in which access to an MRI is problematic, abdominal ultrasonography (US) may be performed. Abdominal US may provide information on organ volume and parenchymal abnormalities and also call attention to the presence of gallstones [Patlas et al 2002]. MRI or US are the preferred modalities in the pediatric population.
- **Screening for pulmonary hypertension.** EKG and echocardiography with Doppler studies to identify elevated pulmonary artery pressure
- **Skeletal assessment**
  - **Plain radiographs** of the femur (anterior-posterior view), spine (lateral view), and any symptomatic sites. Radiographs can reflect the status of both the compact/mineralized compartment and

medullary compartment. In children, particularly those with signs of growth and pubertal delay, x-ray of the left hand and wrist to determine bone age is appropriate.

- **Coronal T_1- and T_2-weighted MR images of the hips to the distal femur.** T_1-weighted MRI is the most sensitive method for following bone marrow infiltration. T_2-weighted MRI is the most sensitive method for detecting active bone infarcts, osteonecrosis, and osteomyelitis [Maas et al 2002b]. The developmental transition from cellular (red) to fatty (yellow) bone marrow, which normally occurs from childhood to early adulthood, may confound interpretation of the extent of long bone infiltration by Gaucher cells (lipid-engorged macrophages) in affected children younger than age 15 years [McHugh et al 2004]. Semiquantitative methods (BMB score and S-MRI score) have been developed to facilitate serial assessments [Robertson et al 2007, Roca et al 2007].
- **Other methods** include dual-energy x-ray absorptiometry (DEXA) to identify osteoporosis and risk for pathologic fractures, technetium Tc-99 sulfur colloid nuclear scanning to assess location and extent of infiltration [Mariani et al 2003], and quantitative chemical-shift MRI or spectroscopy to quantify decrease in bone marrow fat content as a marker of bone marrow infiltration [Maas et al 2002a].

- **Assessment of disease severity.** Two reports have delineated a means for scoring disease severity, incorporating standard assessments of disease severity [Di Rocco et al 2008, Weinreb et al 2010]. With increasing therapeutic options, the ability to benchmark response may inform the modality of choice and selected regimen [Weinreb et al 2008]. A new framework, based on the disease severity scoring system (DS3), has been used to project the long-term health outcomes of individuals with GD1 who are starting treatment [Ganz et al 2017].

Agents/Circumstances to Avoid

Nonsteroidal anti-inflammatory drugs should be avoided in individuals with moderate to severe thrombocytopenia.

Evaluation of Relatives at Risk

It is appropriate to evaluate asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and treatment to reduce morbidity. Evaluations can include:

- Assay of glucocerebrosidase enzyme activity in peripheral blood leukocytes or other nucleated cells;
- Molecular genetic testing if the pathogenic variants in the family are known.

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

Pregnancy Management

Pregnancy may affect the course of GD both by exacerbating preexisting symptoms and by triggering new features such as bone pain. Women with severe thrombocytopenia and/or clotting abnormalities may be at an increased risk for bleeding around the time of delivery [Elstein et al 2004b]; therefore, evaluation by a hematologist prior to delivery is recommended [Hughes et al 2007]. In symptomatic women, treatment should ideally be started prior to conception [Granovsky-Grisaru et al 2011].

Although eliglustat use is not contraindicated during pregnancy and breastfeeding, the lack of controlled studies demonstrating the safety of eliglustat during human pregnancy and lactation has led to a recommendation to avoid this treatment during pregnancy, if possible [Balwani et al 2016, Belmatoug et al 2017].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Substrate reduction therapy. Preclinical studies involving analogs that may be efficacious for primary CNS involvement are ongoing [Larsen et al 2012, Marshall et al 2016].

Chaperone-mediated enzyme enhancement therapy. Pharmacologic chaperones, competitive reversible active site inhibitors, serve as a folding template for the defective enzyme during its transit to the endoplasmic reticulum. Such agents may restore enzyme activity within the lysosome and clear stored substrate. The drug isofagamine, which has been shown to exhibit these properties in studies of cultured fibroblasts in vitro, is currently in clinical trials to establish its safety and efficacy when given to adults with type 1 GD [Steet et al 2007, Mena-Barragán et al 2018].

Ambroxol, a mucolytic agent, is also a potential pharmacologic glucocerebrosidase chaperone [Zimran et al 2013]. An open-label pilot study of high-dose oral ambroxol in combination with ERT in five Japanese affected individuals found that ambroxol had a good safety and tolerability profile. Significantly increased lymphocyte glucocerebrosidase activity and decreased glucosylsphingosine levels in the cerebrospinal fluid were also noted. Myoclonus, seizures, and pupillary light reflex dysfunction markedly improved in all affected individuals. Relief from myoclonus led to impressive recovery of gross motor function in two patients, allowing them to walk again [Narita et al 2016].

Histone deacetylase inhibitors increase the quantity and activity of glucocerebrosidase by limiting the deacetylation of heat shock protein 90. As a consequence, there was less enzyme degradation [Yang et al 2013].

Gene therapy. Gene therapy involves the introduction of *GBA* into hematopoietic stem cells [Enquist et al 2006]. In limited trials, some enzyme has been produced by transduced cells, but enzyme production does not appear to be sustained and therefore does not result in a permanent cure. It is anticipated that transduced cells would not have a proliferative advantage over uncorrected cells. Furthermore, it is unlikely that significant metabolic cross-correction would occur as only small amounts of enzyme are secreted into the circulation.

In a murine model of GD (p.Asp448Val/null) intravenous administration of a recombinant AAV8 serotype vector bearing human glucocerebrosidase resulted in sustained hepatic enzyme secretion, preventing GL-1 accumulation in presymptomatic mice and normalizing GL-1 levels in older mice [McEachern et al 2006]. AVROBIO, a clinical-stage biotechnology company, has announced a planned lentiviral-based gene therapy trial in Gaucher disease, to commence in late 2018 / early 2019.

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

The elevation of the serum concentration of several serologic markers (e.g., D-dimer, CCL18/PARC, CD163) in individuals with GD is considered a possible surrogate indicator of disease burden that could be used in monitoring treatment response [Shitrit et al 2003, Boot et al 2004, Møller et al 2004, Smid et al 2016]. However, the prognostic value of these markers, their role in patient stratification according to clinical disease severity, and determination of the optimum time to initiate therapy are unknown.

Glucosylsphingosine (Lyso-GL1), a deacylated lysolipid, has been found to be massively elevated in the plasma of individuals with GD1 (n-169), with marked reduction observed following treatment with ERT or SRT [Murugesan et al 2016]. Lyso-GL1 levels correlated significantly with plasma chitotriosidase levels, hepatomegaly, splenomegaly, splenectomy, and treatment mode.

Elevation of the protein glycoprotein non-metastatic B, found in brain samples from individuals with type 2 and 3 GD, may be used as a marker to quantify neuropathology in those with GD and as a marker of treatment efficacy once suitable treatments are initiated [Zigdon et al 2015].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Gaucher disease (GD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- In most instances, the parents of a proband are heterozygotes (i.e., carriers of one *GBA* pathogenic variant).
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.
- Because the carrier frequency for GD in certain populations is high (e.g., 1:18 in individuals of Ashkenazi Jewish heritage) and the p.[Asn409Ser]+[Asn409Ser] phenotype is variable, a parent may be found to be homozygous rather than heterozygous.

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

- The offspring of an individual with GD are obligate heterozygotes (carriers) for a pathogenic variant in *GBA*.
- A high carrier rate for GD exists in certain populations, increasing the risk that an affected individual may have a reproductive partner who is heterozygous. In the Ashkenazi Jewish population, for example, one in 18 individuals is a carrier for GD; the offspring of such an individual and a proband are at 50% risk of being affected and 50% risk of being obligate heterozygotes.

Other family members. Each sib of an obligate heterozygote is at a 50% risk of being a carrier of a *GBA* pathogenic variant.

Carrier (Heterozygote) Detection

Biochemical genetic testing. Measurement of glucocerebrosidase enzyme activity in 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.

Molecular genetic testing can be used to identify carriers among at-risk family members once the pathogenic variants have been identified in the family.

Testing for the four common *GBA* alleles (p.Asn409Ser, p.Leu483Pro , c.84dupG, c.115+1G>A) has been included in panels specifically designed for carrier screening in the Ashkenazi Jewish population [Zuckerman et al 2007].

Because the frequency for GD in certain populations is high (e.g., individuals of Ashkenazi Jewish heritage) and the p.[Asn409Ser]+[Asn409Ser] phenotype is variable, individuals who undergo carrier testing may be identified as being homozygous.

Pre-conception testing of the partner of a known carrier or affected individual may be requested, especially in ethnic groups of high prevalence. In this instance targeted analysis for pathogenic variants is insufficient and full sequence analysis should be undertaken.

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

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

Except in families in which a previously affected sib had neurologic disease (i.e., types 2 or 3), it is not possible to be certain of the phenotypic severity in a pregnancy at risk. Individuals with GD with acute neurologic disease (i.e., type 2) tend to have a similar disease course. However, it should be noted that individuals with GD and chronic neurologic involvement (i.e., type 3) could show variable rates of disease progression, even when they are members of the same family.

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 [Beutler 2007, Zuckerman et al 2007].

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.

- **Medline Plus**

  Gaucher Disease

- **National Gaucher Foundation (NGF)**
  2227 Idlewood Road
  Suite 6
  Tucker GA 30084
  Phone: 800-504-3189 (toll-free)
  Fax: 770-934-2911
  Email: ngf@gaucherdisease.org
  www.gaucherdisease.org
- **National Library of Medicine Genetics Home Reference**
  Gaucher disease
- **NCBI Genes and Disease**
  Gaucher disease
- **The Gauchers Association Ltd**
  Evesham House Business Centre
  48/52 Silver Street
  Dursley Gloucestershire GL11 4ND
  United Kingdom
  Phone: +44 1453 549231
  Email: office@gauchers.org.uk
  www.gaucher.org.uk
- **Canadian MPS Society**
  #218-2055 Commercial Drive
  Vancouver British Columbia V5N 0C7
  Canada
  Phone: 800-667-1846; 604-924-5130
  Email: info@mpssociety.ca
  www.mpssociety.ca
- **Center for Jewish Genetics**
  Ben Gurion Way
  30 South Wells Street
  Chicago IL 60606
  Phone: 312-357-4718
  Email: jewishgeneticsctr@juf.org
  www.jewishgenetics.org
- **National Organization for Rare Disorders (NORD)**
  RareCareSM

Phone: 800-999-6673

Patient Assistance Programs

- **Gaucher Network Registry**

  www.gaucherdisease.org/gaucher-network-registry

- **RegistryNXT!**

  Phone: 888-404-4413

  Email: RegistryNXT.helpdesk@us.imshealth.com

  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. Gaucher Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GBA	1q22	Lysosomal acid glucosylceramidase	PD mutation database (GBA) CCHMC - Human Genetics Mutation Database (GBA)	GBA	GBA

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 Gaucher Disease (View All in OMIM)

230800	GAUCHER DISEASE, TYPE I
230900	GAUCHER DISEASE, TYPE II
231000	GAUCHER DISEASE, TYPE III
231005	GAUCHER DISEASE, TYPE IIIC
606463	GLUCOSIDASE, BETA, ACID; GBA
608013	GAUCHER DISEASE, PERINATAL LETHAL

Molecular Genetic Pathogenesis

Gaucher disease (GD) is caused by deficient activity of the lysosomal enzyme glucocerebrosidase and the resultant accumulation of its undegraded substrate, glucosylceramide (GL1) and other glycolipids. The major peripheral substrate source is the breakdown of senescent blood cells and tissue debris; the incompletely metabolized GL1 substrate is stored in cells of monocyte/macrophage lineage of the reticuloendothelial system. In the CNS, GL1 is believed to originate from the turnover of membrane gangliosides, although neuronal cell death may be the basis of neuropathic involvement [Aerts et al 2003].

Gene structure. *GBA* ("glucosidase, beta, acid") comprises 7 kb with 11 exons; the cDNA is approximately 2.5 kb. Two different upstream ATG codons are utilized as translation initiation sites. A highly homologous (96% identity) pseudogene, *GBAP*, (5 kb) is located 16 kb downstream. For a detailed summary of gene and protein information, see Table A, **Gene**.

Note: A related gene, *GBA2* (glucosidase beta (bile acid) 2), encodes a microsomal nonlysosomal glucosylceramidase that catalyzes the conversion of glucosylceramide to free glucose and ceramide and the hydrolysis of bile acid 3-O-glucosides. Pathogenic variants of *GBA2* have been shown to cause an autosomal recessive (AR) form of cerebellar ataxia with spasticity [Hammer et al 2013] and AR hereditary spastic paraplegia 46 (HSP46) [Martin et al 2013].

Pathogenic variants. At least 200 pathogenic variants in *GBA* have been identified; they include missense and nonsense variants, splice junction variants, deletions and insertions of one or more nucleotides, and complex alleles resulting from gene conversion or gene fusion with the downstream pseudogene (see Table A) [Tayebi et al 2003, Rozenberg et al 2006, Alfonso et al 2007].

Approximately 12% of disease-causing alleles are formed by recombination between *GBA* and *GBAP* [Tayebi et al 2003]; the most common recombinant allele, termed RecNciI, is defined by the creation of a *NciI* restriction site [Zimran et al 1990, Tayebi et al 2003].

Historically, *GBA* variants were numbered based on the position in the nucleotide sequence that encodes the mature glucocerebrosidase protein, wherein the first nucleotide of the alanine codon (GCC) was designated as 1. This naming convention is still often used, although it does not comply with current standards of nomenclature (see Table 5).

The variants p.Asn409Ser, c.84dupG, c.115+1G>A, and p.Leu483Pro account for 90% of the mutated alleles in Ashkenazi Jewish individuals with type 1 GD and for 50%-60% of mutated alleles in non-Jewish individuals with type 1 GD. The frequencies of the most common genotypes associated with the p.Asn409Ser allele are listed in Table 4. The frequency of the p.Asn409Ser allele is higher among Iberians (Portuguese: 63%; Spanish: 46%) than among other non-Jewish population groups from Western, Central, and Eastern Europe [Giraldo et al 2000, Alfonso et al 2007]. In contrast, the p.Asn409Ser and c.84dupG alleles have not been identified among Japanese and Chinese individuals with GD. The occurrence of deleterious alleles among the Japanese (e.g., p.Leu483Pro: 41% allele frequency; p.Phe252Ile: 14%) and Chinese (p.Leu483Pro: 54%; RecNciI: 25%) may explain the higher incidence of neuropathic disease in these populations [Wan et al 2006]. Thus, screening restricted to the four "common" pathogenic variants (p.Asn409Ser, c.84dupG, c.115+1G>A, and p.Leu483Pro) does not lead to 100% detection.

Table 4. Frequency of Genotypes Involving at Least One Copy of p.Asn409Ser

Genotype [1]	% of Ashkenazi Jewish Individuals [2]	% of Non-Jewish Individuals [3]
p.[Asn409Ser]+[Asn409Ser]	41%	9%
p.[Asn409Ser]+[Leu483Pro]	3%	19%
p.Asn409Ser+c.84dupG	23%	0%
p.Asn409Ser+c.115+1G>A	6%	2%
p.[Asn409Ser]+[Val433Leu]	8%	0%
p.Asn409Ser+RecNciI [4]	0%	4%

Table does not include all possible genotype permutations and thus frequency figures do not account for 100% of individuals.
1. Table 5 provides the variant names and nucleotide changes corresponding to current nomenclature guidelines.
2. Data derived from Koprivica et al [2000]. In this paper, the p.Arg502Cys variant was identified in nine (14%) of the non-Jewish individuals with type 1 GD, but in only one Ashkenazi Jewish individual with type 1 GD (p.Leu483Pro/p.Arg502Cys). The 55-bp deletion was found in two non-Jewish individuals with type 1 GD (both p.Asn409Ser/del 55bp) and one non-Jewish individual with type 3 GD in whom the second allele remains to be identified.
3. Data derived from Filocamo et al [2002], a study involving 144 unrelated Italian individuals with GD. This study represents the largest single group of non-Jewish individuals examined, with information on genotype rather than individual disease allele frequency.
4. Recombinant allele; see Table 5.

Table 5. *GBA* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Common Variant Name [1]	Predicted Protein Change per HGVS Nomenclature	Reference Sequences
c.84dupG [2]	84GG (84-85insG)	p.Leu29AlafsTer18	NM_000157.3 NP_000148.2
c.115+1G>A [2]	IVS2+1G>A	--	
c.254G>A	G46E	p.Gly85Glu	
c.476G>A	R120Q	p.Arg159Gln	
c.475C>T	R120W	p.Arg159Trp	
c.509G>T	R131L	p.Arg170Leu	
c.680A>G	N188S	p.Asn227Ser	
c.703T>C	S196P	p.Ser235Pro	
c.754T>A	F213I	p.Phe252Ile	
c.882T>G	H255Q	p.His294Gln	
c.887G>A	R257Q	p.Arg296Gln	
c.1093G>A	E326K	p.Glu365Lys	
c.1226A>G	N370S	p.Asn409Ser	
c.1246G>A	G377S	p.Gly416Ser	
c.1263del55	55bp del exon 9	--	
c.1297G>T	V394L	p.Val433Leu	
c.1342G>C	D409H	p.Asp448His	
c.1448T>C	L444P	p.Leu483Pro	
c.1504C>T	R463C	p.Arg502Cys	
c.1604G>A	R486H	p.Arg535His	
(complex allele involving several changes at a specific location) [3]	RecNciI [3]		

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. In the common variant names, amino acid number 1 is the first residue (Ala) of the mature protein. In contrast, the standard naming convention designates amino acid number 1 as the first residue (Met) of the signal sequence.
2. Variants in the signal sequence
3. Recombinant allele derived from a recombination between functional *GBA* and pseudogene *GBAP1*; see also Table 3 [Eyal et al 1990, Tayebi et al 2003].

Normal gene product. Glucocerebrosidase (also known as glucosylceramidase) is a lysosomal membrane-associated glycoprotein. The mature protein is composed of 497 amino acids, with four oligosaccharide chains coupled to specific asparagine residues [van Weely & Aerts 2000]. The three-dimensional conformation of the enzyme is stabilized by the formation of three disulfide bonds. The enzyme is responsible for hydrolyzing glucosylceramide into glucose and ceramide.

Glucocerebrosidase enzyme activity is stimulated by interaction with the lipid phospatidylserine and the protein saposin C. Structural predictions (based on hydrophobic cluster analysis) indicate that the glutamine residues 235 and 340 play key roles in the active site of human glucocerebrosidase [Fabrega et al 2002]. The nascent glucocerebrosidase polypeptide is composed of 536 amino acids, including 39 that encode a signal sequence that

is later cleaved after it directs the polypeptide to transit the endoplasmic reticulum. Two different upstream ATG codons are utilized as translation initiation sites; use of the second ATG translation start leaves a functional signal sequence of 19 amino acid residues. The 497-amino-acid sequence of the mature protein is the same regardless of the translation start codon.

Abnormal gene product. *GBA* pathogenic variants result in mRNA instability and/or loss of protein, or in an enzyme with altered activity and/or conformation [Grabowski & Horowitz 1997].

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Chapter Notes

Revision History

- 21 June 2018 (ma) Comprehensive update posted live

- 26 February 2015 (gp) Revision: eliglustat FDA approved for use in the US
- 19 September 2013 (me) Comprehensive update posted live
- 21 July 2011 (cd) Revision: corrections to mutation nomenclature
- 1 February 2011 (me) Comprehensive update posted live
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- 23 November 2005 (gp) Revision: information on miglustat (Management)
- 2 June 2005 (me) Comprehensive update posted live
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