



Krabbe Disease

Synonyms: Galactocerebrosidase Deficiency, GALC Deficiency, Globoid Cell Leukodystrophy

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Summary

Clinical characteristics

Krabbe disease comprises a spectrum ranging from infantile-onset disease (i.e., onset of extreme irritability, spasticity, and developmental delay before age 12 months) to later-onset disease (i.e., onset of manifestations after age 12 months and as late as the seventh decade). Although historically 85%-90% of symptomatic individuals with Krabbe disease diagnosed by enzyme activity alone have infantile-onset Krabbe disease and 10%-15% have later-onset Krabbe disease, the experience with newborn screening (NBS) suggests that the proportion of individuals with possible later-onset Krabbe disease is higher than previously thought. Infantile-onset Krabbe disease is characterized by normal development in the first few months followed by rapid severe neurologic deterioration; the average age of death is 24 months (range 8 months to 9 years). Later-onset Krabbe disease is much more variable in its presentation and disease course.

Diagnosis/testing

The two diagnostic scenarios are the following:

- Scenario 1. The diagnosis of Krabbe disease, suspected in a symptomatic proband based on clinical findings (by age) and other supportive laboratory, neuroimaging, and electrophysiologic findings, is established by detection of deficient GALC enzyme activity in leukocytes. Abnormal results require follow-up molecular genetic testing of *GALC*; elevated psychosine levels can also help establish the diagnosis.
- Scenario 2. In an asymptomatic newborn with low GALC enzyme activity on dried blood spot specimens on NBS urgent time-critical measurement of blood psychosine levels and *GALC* molecular genetic testing is necessary to identify – before age 14 days – those newborns with evidence of infantile-onset Krabbe disease who are candidates for early treatment with hematopoietic stem cell transplantation (HSCT).

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Management

Treatment of manifestations: Treatment of a child who is symptomatic before age six months is supportive and focused on increasing the quality of life and avoiding complications. For older individuals, treatment with HSCT is individualized based on disease burden and manifestations.

Prevention of primary manifestations: Consensus guidelines recommend that asymptomatic newborns identified by either prenatal/neonatal evaluation because of a positive family history of Krabbe disease or an abnormal NBS result undergo additional testing to identify those with infantile-onset Krabbe disease. Those with laboratory findings consistent with infantile-onset Krabbe disease are candidates for HSCT before age 30 days.

Surveillance: Monitor symptomatic individuals with Krabbe disease for development of: hydrocephalus, swallowing difficulties and chronic microaspiration, scoliosis, hip subluxation, and osteopenia, decreased vision, and corneal ulcerations.

Agents/circumstances to avoid: Atypical antipsychotics and multiple medications for seizures can cause over-sedation (affecting cognition, respiratory drive, and rate of neurologic decline). Routine childhood vaccinations can accelerate disease progression.

Evaluation of relatives at risk: Couples who have had one child with molecularly confirmed infantile-onset Krabbe disease may choose prenatal molecular genetic testing in subsequent pregnancies so that newborns with biallelic *GALC* pathogenic variants can be promptly tested and – if appropriate -- referred for HSCT.

Genetic counseling

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

Diagnosis

Krabbe disease (also known as galactocerebrosidase [*GALC*] deficiency) has two major phenotypes that constitute a continuum:

- Infantile-onset Krabbe disease (onset <12 months), characterized by progressive neurologic deterioration in infancy and death before age two years (85%-90% of affected individuals)
- Later-onset Krabbe disease (onset >12 months), with slower disease progression (10%-15%)

Suggestive Findings

The two different scenarios in which Krabbe disease could be suspected in a proband:

- **Scenario 1.** A symptomatic individual
- **Scenario 2.** An asymptomatic newborn with a positive result on NBS

Scenario 1

Krabbe disease **should be suspected** in a **symptomatic proband** based on **clinical findings** (by age) and other supportive **laboratory, neuroimaging, and electrophysiologic findings**.

Clinical findings

Age <12 months (infantile-onset Krabbe disease)

- Excessive crying to extreme irritability
- Feeding difficulties, gastroesophageal reflux disease
- Spasticity of lower extremities and fisting, with axial hypotonia
- Loss of acquired milestones (smiling, cooing, and head control)
- Staring episodes
- Peripheral neuropathy

Age >12 months (later-onset Krabbe disease)

- Slow development of motor milestones or loss of milestones (e.g., sitting without support, walking), slurred speech
- Spasticity of extremities with truncal hypotonia
- Vision loss, esotropia
- Seizures
- Peripheral neuropathy

Other supportive findings

- Increased cerebrospinal fluid (CSF) protein concentration. Ranges vary by age and laboratory, normal infant range reported at 48-72 mg/dL [Shah et al 2011]. Adult range: 18-58 mg/dL.
Note: CSF protein concentration is already increased in Stage I infantile-onset Krabbe disease (see Clinical Description).
- MRI (infantile-onset Krabbe disease) observed within the first few months of age
- Abnormal brain MRI, consistent with demyelination. T₂-weighted images show involvement of periventricular white matter, deep gray matter, and centrum semiovale as well as enhancement of cranial nerves. **Subcortical U-fibers** may be spared until late in the disease course [Gupta et al 2014].
- Abnormal spine MRI (enhancement of spinal nerve roots)
- Abnormal electrophysiologic studies (nerve conduction velocity, brain stem auditory evoked response, visual evoked potentials)

Scenario 2

Krabbe disease **should be suspected in an asymptomatic newborn** with a **positive result on NBS**.

Currently, seven states (Illinois, Kentucky, Missouri, New York, Ohio, Pennsylvania, and Tennessee) perform NBS for GALC deficiency using dried blood spots. While the approaches to testing and cut-off values indicating a positive newborn screen vary by state, all results suggesting GALC deficiency require immediate follow-up studies (see Establishing the Diagnosis, Scenario 2).

Establishing the Diagnosis

Scenario 1

The testing required to establish the diagnosis Krabbe disease in a symptomatic proband. In individuals with some or all of the suggestive findings of infantile-onset Krabbe disease or later-onset Krabbe disease, the diagnosis is established by detection of deficient GALC enzyme activity in leukocytes. Abnormal results require follow-up molecular genetic testing of *GALC*. For children with infantile-onset Krabbe disease, elevated psychosine levels in dried blood spot specimens confirm the diagnosis; however, in individuals who have later-onset Krabbe disease or have progressed to the later stages of the infantile form of disease, it is not yet known if psychosine concentrations are consistently elevated.

Galactocerebrosidase (GALC) enzyme activity is measured in leukocytes isolated from whole heparinized blood or cultured skin fibroblasts. The substrate used (i.e., radiometric substrate, fluorescent substrate, or mass spectrometry substrate) depends on the laboratory.

- Very low GALC enzyme activity (0%-5% of normal activity) is observed in all individuals with Krabbe disease who are symptomatic. Note: Low GALC activity can result from pseudodeficiency alleles (benign *GALC* variants that reduce enzyme activity in vitro but do not cause disease), carrier status for a *GALC* pathogenic variant, or saposin A deficiency (see Molecular Genetics).
- If GALC enzyme activity in leukocytes is completely normal, no additional biochemical testing is required to exclude Krabbe disease. However, if psychosine was elevated in such cases, a diagnosis of saposin A deficiency should be considered.

Psychosine concentration

- **Infantile-onset Krabbe disease.** Very elevated concentrations of psychosine (usually >10 nmol/L) are strongly supportive of early symptomatic Krabbe disease [Turgeon et al 2015, Escolar et al 2017, Minter Baerg et al 2018]. Note that psychosine concentrations may drop significantly in the later stages of infantile-onset Krabbe disease and that psychosine may also be elevated in individuals with saposin A deficiency.
- **Later-onset Krabbe disease.** Psychosine concentrations may not be markedly elevated and may depend on how long the patient has been symptomatic [Escolar et al 2017].

Molecular testing involves single-gene testing. Sequence analysis of *GALC* and targeted analysis for the common *GALC* 30-kilobase deletion (30kb del) is performed [Luzi et al 1995, Rafi et al 1995]. Gene-targeted deletion/duplication analysis should also be performed, at least when the suspicion of Krabbe disease is high and only one *GALC* pathogenic variant has been detected by sequence analysis. See Table 1.

Table 1. Molecular Genetic Testing Used in Krabbe Disease (Galactosylcerebrosidase Deficiency)

Gene ¹	Method	Proportion of Probands with Pathogenic Variants ² Detectable by Method
<i>GALC</i>	Sequence analysis ³	55%-65% ⁴
	Targeted analysis for 30kb del	35%-45% ⁵
	Gene-targeted deletion/duplication analysis ⁶	See footnote 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. 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. Wenger et al [2013], Orsini et al [2016]

5. This large deletion accounts for approximately 35% of the pathogenic variants in individuals with Krabbe disease of Mexican heritage [D.Wenger, personal experience] and 45% of the pathogenic variants in individuals with Krabbe disease of European ancestry [Luzi et al 1995, Rafi et al 1995].

6. 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.

7. Deletions involving single exons and multiple exons, other than the common 30-kb deletion, are rare but have been reported [Wenger et al 2001, Tanner et al 2012].

Scenario 2

The testing required to establish the diagnosis Krabbe disease in an asymptomatic infant identified on NBS. Presumptive positive newborn screening results for Krabbe disease must be followed up urgently with time-critical biochemical and molecular genetic studies to identify those newborns with biochemical and molecular

genetic evidence of infantile-onset Krabbe disease before age 14 days who are candidates for early treatment with hematopoietic stem cell transplantation (HSCT) (see Management, Prevention of Primary Manifestations) [Wasserstein et al 2016, Kwon et al 2018].

Note that regardless of the method used to assay GALC enzyme activity, low GALC activity in dried blood spots and/or leukocytes in asymptomatic newborns is not sufficiently specific to diagnose Krabbe disease, let alone to distinguish between infantile-onset and later-onset Krabbe disease. In addition to certain environmental factors, low GALC activity can result from pseudodeficiency alleles (benign *GALC* variants that reduce enzyme activity in vitro but do not cause disease), heterozygosity (i.e., carrier state) for one *GALC* pathogenic variant, and *GALC* variants observed in later-onset Krabbe disease.

- **The first step in testing an asymptomatic newborn with low GALC enzyme activity identified on NBS.** Measurement of concentration of psychosine in the blood (either a punch from the original NBS dried blood spot specimen or a subsequent sample). Very elevated concentration of psychosine (>10 nmol/L) appears to be specific for severe infantile Krabbe disease [Turgeon et al 2015, Escolar et al 2017, Minter Baerg et al 2018] and warrants next-step testing [Kwon et al 2018].
- **Testing for an asymptomatic newborn with low GALC enzyme activity and very elevated concentration of psychosine identified on NBS**
 - Sequence analysis of *GALC* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants
 - Gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications including the common 30kb deletion (Table 1).

Note: (1) The common 30-kb deletion may be tested for by allele-specific or breakpoint PCR as part of the first-tier sequencing assay [Luzi et al 1995, Rafi et al 1995]. (2) The necessary turn-around time for sequencing and deletion/duplication analysis in this scenario is shorter than routinely offered for diagnostic purposes; therefore, specific arrangements need to be made to ensure expedited testing.

Identification of biallelic *GALC* pathogenic variants known to be associated with infantile-onset Krabbe disease or classified as pathogenic or likely pathogenic further confirms the diagnosis of infantile-onset Krabbe disease [Orsini et al 2016].

Of note, the vast majority of infants identified through the New York State NBS program who have low GALC enzyme activity and two presumptive pathogenic *GALC* variants do not have signs or symptoms of infantile-onset disease [Wasserstein et al 2016] and thus are considered to be at risk for later-onset Krabbe disease. A revised definition of risk for infantile-onset Krabbe disease based on results of psychosine concentration and *GALC* molecular genetic testing that is under review is expected to significantly decrease the proportion of infants designated as at risk for infantile-onset Krabbe disease identified by NBS [Author, personal communication].

Clinical Characteristics

Clinical Description

Historically, 85%-90% of symptomatic individuals with Krabbe disease diagnosed by enzyme activity alone had infantile-onset Krabbe disease (i.e., onset of extreme irritability, spasticity, and developmental delay before age 12 months) and 10%-15% had later-onset Krabbe disease (i.e., onset of manifestations after age 12 months and as late as the seventh decade). In contrast, the vast majority of infants identified through the New York State newborn screening (NBS) program who have low GALC enzyme activity and two presumptive pathogenic *GALC* variants do not have signs or symptoms of infantile-onset disease [Wasserstein et al 2016]; thus, it is likely

that the proportion of individuals with later-onset Krabbe disease is higher than previously thought [Author, personal communication].

Infantile-Onset Krabbe Disease

Infantile-onset Krabbe disease typically has four stages:

- **Stage I.** The infant, apparently normal for the first few months after birth, begins to cry frequently without apparent cause. Many keep their hands tightly fisted. Feeding difficulties and gastroesophageal reflux may result in progressive weight loss leading to emaciation. In some infants, peripheral neuropathy is a presenting feature with no other neurologic features appreciated for several months [Korn-Lubetzki et al 2003].
- **Stage II** is characterized by rapid severe neurologic deterioration with decorticate posturing (marked hypertonicity with extended and crossed legs, flexed arms, and trunk hyperextension [opisthotonus]). Tendon reflexes are absent. Staring episodes and minor muscle spasms occur. Optic atrophy and sluggish pupillary reactions to light are common.
- **Stage III** is characterized by poor control of temperature and heart rate, as well as blindness, deafness, and seizures.
- **Stage IV** is characterized by very low muscle tone and absence of voluntary movement.

The average age of death in children with infantile-onset Krabbe disease is 24 months; however, some succumb by age eight months from infections and respiratory failure, while others live up to age nine years.

Symptoms and signs are confined to the nervous system. No visceromegaly is present. Head size may be large or small; hydrocephalus with increased intracranial pressure has been observed. Macular cherry-red spots were described in one individual.

One infant, diagnosed with GALC deficiency *in utero*, had normal psychomotor development for the first two months of life but lost deep tendon reflexes by age five weeks, had markedly reduced nerve conduction velocities at age seven weeks, and developed neck muscle weakness at age three months [Lieberman et al 1980]. These findings suggest that detailed examination could reveal clinical manifestations of infantile-onset Krabbe disease earlier than the reported age of onset.

Some infants with a positive NBS (and subsequently confirmed to have infantile-onset Krabbe disease) had at least one of the following in the first weeks of life: clonus in the lower extremities, difficulty feeding, abnormal nerve conduction velocity, elevated CSF protein, abnormal brain MRI.

Later-Onset Krabbe Disease

Children with onset between ages 12 months and three years can be clinically normal until they manifest gait changes, hemiplegia/diplegia, visual impairment, febrile seizures, and/or tremors. Because myelination occurs very rapidly between birth and age two years, symptoms develop more rapidly at this age than after age two years.

Children with disease onset between ages 24 months and four years can initially manifest loss of milestones and vision (including rapid loss of vision) or gait changes and seizures.

Although disease progression is variable, children who develop symptoms between ages nine months and four years may have rapid worsening of symptoms shortly after presentation. In most instances death occurs approximately four to six years after onset [M Escolar, personal communication].

Initial manifestations in children older than age six years may be behavioral difficulties (attention-deficit/hyperactivity disorder and mood disorders) followed by motor difficulty. They often decline rapidly soon after disease onset [Fiumara et al 2011].

Some individuals with onset in adolescence and adulthood present with loss of manual dexterity, burning paresthesias in their extremities, and weakness without intellectual deterioration; others become bedridden and continue to deteriorate mentally and physically [Kolodny et al 1991, Satoh et al 1997, Jardim et al 1999, Wenger 2003]. Presenting manifestations in adult-onset disease can also include unilateral upper-limb weakness and lower-limb hypoesthesia [Debs et al 2013]. Disease progression is generally slower in the adult-onset disease than in adolescent-onset disease.

The adult-onset group includes individuals in whom the diagnosis was first made in adulthood (because the subtle symptoms present earlier in life did not prompt biochemical testing) as well as individuals considered completely normal until manifestations began after age 20 years [Kolodny et al 1991, Satoh et al 1997, Wenger 2003]. An example of the former is a woman reported by Kolodny et al [1991] (case 15) who had been "shaky" in childhood, walked slowly with a stiff and wide-based gait, and had progressive, generalized neurologic deterioration after age 40 years. She died of pneumonia at age 73 years. An example of the latter is a woman who developed slowly progressive spastic paraparesis at age 38 years. Demyelination identified on MRI was confined to the corticospinal tract [Satoh et al 1997].

Peripheral neuropathy is less common in later-onset disease (affecting about half of affected individuals) than in infantile-onset disease (affecting nearly all affected individuals) [Husain et al 2004, Siddiqi et al 2006, Debs et al 2013].

Survival varies widely among persons with later-onset disease; the median age is eight years after symptom onset [Bascou et al 2018].

Neurophysiologic findings in later-onset Krabbe disease include the following:

- **Electroencephalogram (EEG).** While normal in the initial stages, the EEG gradually becomes abnormal. Background activity becomes slow and disorganized, with changes that may be asymmetric.
- **Cerebrospinal fluid protein levels** can vary widely but are always elevated in the infantile-onset disease.
- **Electrophysiologic studies.** Although motor nerve conduction velocities are generally low, they are normal in some adults with an enzymatically confirmed diagnosis.

MRI. In general, brain MRI detects demyelination in the brain stem and cerebellum more clearly than CT in the early stage of later-onset Krabbe disease; however, some infants younger than age six months have a deceptively normal MRI because of the low contrast between gray and white matter in this period of brain development. Of note, scoring of atrophy of the midbrain assists in evaluating general disease progression [Zuccoli et al 2015].

Diffusion tensor imaging (DTI) of the brain. DTI is the preferred imaging modality for evaluating asymptomatic infants with Krabbe disease detected by NBS [Gupta et al 2014] (see Management, Prevention of Primary Manifestations).

Genotype-Phenotype Correlations

Infantile-onset Krabbe disease results from severe loss of galactocerebrosidase activity due to:

- Homozygosity for the common *GALC* 30-kb deletion;
- Compound heterozygosity for either the common *GALC* 30-kb deletion and a severe *GALC* pathogenic variant (most frequently nonsense or frameshift variants, but also some missense variants) or two severe pathogenic variants [Tappino et al 2010].

Later-onset Krabbe disease. The following genotypes have been observed in individuals with later-onset disease:

- p.Gly286Asp+30kb del [Furuya et al 1997, De Gasperi et al 1999]
- p.Gly286Asp+p.Pro318Arg [Tappino et al 2010]

- p.Gly286Asp + another severe allele
- p.Thr112Ala+p.Asp187Val [Luzi et al 1996]
- p.Leu634Ser + another severe allele or homozygous p.Leu634Ser [Hossain et al 2014, Zhang et al 2018]

The p.Gly57Ser variant, a founder variant common in Catania, Italy, is associated with late-onset Krabbe disease in both the homozygous and compound heterozygous states [Lissens et al 2007].

Note that although p.Gly286Asp has been observed in individuals with a milder phenotype, to date it is not possible to predict the clinical course in a given individual.

Nomenclature

The protein encoded by *GALC* is termed galactocerebrosidase in UniProt, the standard reference for *GeneReviews* (see Table A). Because additional terms for this protein are used in the published literature, Krabbe disease may also be referred to as:

- Galactosylceramidase deficiency
- Galactosylcerebrosidase deficiency
- β -galactocerebrosidase deficiency

Prevalence

Krabbe disease occurs in approximately one in 250,000 births in the United States [Barczykowski et al 2012] and approximately one in 100,000 births in Europe [Wenger et al 2013]; with the median prevalence varying widely between countries [Tappino et al 2010].

A very high incidence of Krabbe disease is found in a Druze community in northern Israel and two Muslim Arab villages located near Jerusalem where the carrier rate is estimated at one in six [Rafi et al 1996].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Although a history of normal development for the first few months after birth followed by psychomotor deterioration differentiates Krabbe disease from non-progressive CNS disorders of congenital or perinatal origin, it is nonetheless often difficult to differentiate Krabbe disease from other degenerative diseases. Individuals of any age with progressive deterioration of the central or peripheral nervous system should be evaluated for galactocerebrosidase (*GALC*) deficiency.

The following disorders, ordered by mode of inheritance, should be considered in the differential diagnosis.

Autosomal Recessive

Arylsulfatase A deficiency (metachromatic leukodystrophy, MLD) is characterized by three clinical subtypes that can closely resemble late-onset Krabbe disease:

- Late-infantile MLD (50%-60% of individuals) with onset between age one and three years
- Juvenile MLD (~20%-30%) with onset between age four years and sexual maturity (12-14 years)
- Adult MLD (~15%-20%) with onset after sexual maturity

Biallelic pathogenic variants in *ARSA* are causative.

Hexosaminidase A deficiency results in a group of neurodegenerative disorders caused by the intralysosomal storage of the specific glycosphingolipid, GM2 ganglioside. Tay-Sachs disease, the prototype hexosaminidase A deficiency, is characterized by loss of motor skills beginning between ages three and six months with progressive evidence of neurodegeneration, including seizures, macular cherry-red spots, and blindness. Total incapacitation and death usually occur before age four years. The juvenile, chronic, and adult-onset variants of hexosaminidase A deficiency have later onset, slower progression, and more variable neurologic findings, including progressive dystonia, spinocerebellar degeneration, motor neuron disease, and in some individuals with adult-onset disease, a bipolar form of psychosis. Biallelic pathogenic variants in *HEXA* are causative.

Canavan disease. Neonatal/infantile (severe) Canavan disease is characterized by evidence of developmental delays by age three to five months with severe hypotonia and failure to achieve independent sitting, ambulation, or speech. Hypotonia evolves into spasticity and assistance with feeding becomes necessary. Life expectancy is usually into the second decade. Most individuals with Canavan disease have macrocephaly, which is a variable finding in individuals with Krabbe disease. MRI shows prominent involvement of subcortical white matter. Biallelic pathogenic variants in *ASPA* are causative.

Saposin A deficiency (OMIM 611722). An infant from a consanguineous union who demonstrated abnormal myelination resembling Krabbe disease was found to be homozygous for a pathogenic variant in the saposin A region of *PSAP*, which codes prosaposin, a heat-stable protein that interacts with the GALC enzyme to catalyze the hydrolysis of the natural lipid substrates [Spiegel et al 2005]. Saposin A deficiency may also be associated with reduced GALC enzyme activity and elevated psychosine concentrations. Biallelic pathogenic variants in *PSAP* are causative.

X-Linked

X-linked adrenoleukodystrophy (X-ALD) affects the nervous system white matter and the adrenal cortex. The childhood cerebral form of X-ALD is in the differential diagnosis of Krabbe disease. It manifests most commonly between age four and eight years. It initially resembles attention deficit disorder; progressive impairment of cognition, behavior, vision, hearing, and motor function follow the initial symptoms and often lead to total disability within two years. A hemizygous *ABCD1* pathogenic variant is causative.

Pelizaeus-Merzbacher disease (PMD) is part of the phenotypic spectrum of *PLP1*-related disorders of central nervous system myelin formation. The phenotypes that can be observed in males with this disorder range from PMD to spastic paraplegia 2 (SPG2); a wide range of phenotypes can be observed in members of the same family. PMD typically manifests in infancy or early childhood with nystagmus, hypotonia, and cognitive impairment and progresses to severe spasticity and ataxia. Life span is shortened. A hemizygous *PLP1* pathogenic variant is causative.

Autosomal Dominant

Alexander disease is a progressive disorder of cerebral white matter that predominantly affects infants and children and has variable life expectancy. The later-onset forms present with a slower clinical course. The infantile form comprises about 42% of affected individuals, the juvenile form about 22%, and the adult form about 33%. A neonatal form is also recognized. The neonatal form leads to severe disability or death within two years. The infantile form presents in the first two years of life typically with progressive psychomotor retardation with loss of developmental milestones, megalencephaly, frontal bossing, and seizures. Affected individuals survive a few weeks to several years. The juvenile form usually presents between age four and ten years, occasionally in the mid-teens. Survival is variable, ranging from the early teens to the 20s-30s. Affected individuals can present with bulbar/pseudobulbar signs, poor coordination (ataxia), gradual loss of intellectual function, seizures, normocephaly or megalencephaly, and breathing problems. A heterozygous pathogenic variant in *GFAP* is causative.

Autosomal dominant leukodystrophy with dysautonomia is a slowly progressive disorder of central nervous system white matter characterized by onset of autonomic dysfunction in the fourth to fifth decade, followed in months to years by pyramidal and cerebellar involvement. Autonomic dysfunction can include bladder dysfunction, constipation, postural hypotension, feeding difficulties, erectile dysfunction, and (less often) impaired sweating. Pyramidal signs are often more prominent in the lower extremities (i.e., spastic weakness, hypertonia, clonus, brisk deep tendon reflexes, and bilateral Babinski signs). Cerebellar signs typically appear at the same time as the pyramidal signs and can include gait ataxia, dysdiadochokinesia, intention tremor, dysmetria, and nystagmus. Although cognitive function is usually preserved or only mildly impaired early in the disease course, dementia and psychiatric manifestations can occur as late manifestations. Affected individuals may survive for decades after onset. Either an *LMNB1* duplication or (more rarely) a large heterozygous deletion upstream of the *LMNB1* promoter is causative.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of a **symptomatic individual diagnosed with Krabbe disease** (i.e., Scenario 1), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neurologic and developmental examination
- Brain stem auditory evoked response to assess hearing and auditory neuropathy
- Brain MRI (DTI preferred) to understand disease progression and anticipate care needs (e.g., atrophy of brain stem is likely associated with apnea and temperature instability).
- Nerve conduction velocity to help understand the peripheral nerve involvement and development of muscle weakness
- Visual evoked potential to help understand the best approach to visual and developmental therapy
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Symptomatic individual. For a child younger than age six months who is in Stage II or III of infantile-onset Krabbe disease (see Clinical Description), treatment is supportive and focused on increasing the quality of life and avoiding complications (Table 2) [Escolar et al 2016].

Table 2. Treatment of Manifestations in Individuals with Krabbe Disease Who Have NOT Undergone Hematopoietic Stem Cell Transplantation (HSCT)

System/Concern	Manifestation	Treatment
Gastrointestinal	Vomiting & gastroesophageal reflux disease (GERD)	<ul style="list-style-type: none"> • Maintenance of upright positioning during & after feeding • Consideration of proton pump inhibitors in those age >1 yr • Nissen fundoplication w/gastrostomy tube (G-tube) placement.
	Dysphagia	<ul style="list-style-type: none"> • Modifying texture & thickness of foods using commercial thickening agents can help w/swallowing difficulties. • Swallowing ability may be improved by providing tiny tastes of food or juice several times per day in non-feeders. • Consideration of nasogastric tube or gastric tube placement
	Constipation	<ul style="list-style-type: none"> • Maintain appropriate fluid intake. • Consideration of osmotic laxatives &/or use of stimulant medication in those w/refractory constipation

Table 2. continued from previous page.

System/Concern	Manifestation	Treatment
Neurologic	Spasticity	<ul style="list-style-type: none"> • Baclofen & clonazepam may improve global spasticity • Botox injections at specific sites may be considered; spasticity typically decreases for 3-5 mos after each injection.
	Neuropathic pain; seizures	<ul style="list-style-type: none"> • Standard anti-seizure medications; monotherapy is preferred, if possible. • Gabapentin may decrease neuropathic pain & can be used for control of seizures in some.
Musculoskeletal	Contractures	<ul style="list-style-type: none"> • Positioning devices (wedges, rolls, and cushions) to decrease spasticity & prevent contractures • Physical therapy
Respiratory	Excessive airway secretions	<ul style="list-style-type: none"> • Chest physiotherapy • Postural drainage • Suctioning device
Genitourinary	Urinary tract infections	<ul style="list-style-type: none"> • Bladder massage (Crede maneuver) to encourage complete bladder emptying • Intermittent catheterization
Eyes	Delayed pupillary response, difficulty w/upward gaze & palpebral weakness	
	Corneal ulcers	<ul style="list-style-type: none"> • Dark glasses to help reduce photophobia • Eye lubricants or protective ointments
Dental	Delayed dentition	

Table adapted from Escolar et al [2016]

Older individuals with mild manifestations. Treatment (based on standard practice) is tailored to the manifestations in each individual.

Prevention of Primary Manifestations

Escolar et al [2005] reported that all 11 asymptomatic newborns (diagnosed prenatally or shortly after birth because of a family history of Krabbe disease) who underwent HSCT between ages 12 and 44 days had stable engraftment of donor hematopoietic stem cells that provided a long-term source of GALC enzyme. Follow up over four months to six years has thus far revealed that while most children had normal cognitive ability and receptive language, they eventually developed speech and motor difficulties (including spasticity).

Wasserstein et al [2016] reported outcomes for five infants from four families detected by the New York State newborn screening program. Two of the five were sibs. All but the first-born in the sib pair underwent HSCT between days 24 and 41 of life. Outcomes for the four who underwent HSCT were not ideal, likely due to disease severity at the time of the transplantation. More recently, several newborns identified through other state newborn screening programs have had more positive outcomes [Orsini, personal observation].

Wright et al [2017] reported a 15-year study of outcomes for 18 individuals presumed to have a form of infantile-onset Krabbe disease who underwent HSCT in the first seven weeks of life. Following early HSCT, the long-term outcome of motor function reflected the severity of corticospinal tract involvement at birth. Peripheral nerve disease progressed with time, causing severe muscular atrophy and scoliosis. Compared to children not treated as babies, those treated early with HSCT can live relatively normal lives with variable motor disabilities until the teen years when the disease may progress. Mortality was 25%, slightly less than general mortality for non-malignant diseases. Outcomes following HSCT vary widely: some individuals live completely normal lives, whereas others are disabled (ranging from reliance on walkers for mobility to quadriplegia). The outcomes

depend on how early disease is detected, the severity of disease, and progression of the disease prior to treatment.

Asymptomatic newborns with infantile-onset Krabbe disease. Consensus guidelines recommend that asymptomatic newborns identified by either prenatal/neonatal evaluation because of a positive family history of Krabbe disease (see Evaluation of Relatives at Risk) or an abnormal newborn screening result undergo additional testing to identify those with infantile-onset Krabbe disease (see Establishing the Diagnosis, Scenario 2). Those with laboratory findings consistent with infantile-onset Krabbe disease are thus candidates for HSCT before age 14 days [Kwon et al 2018].

Asymptomatic newborns with abnormal newborn screening results presumed to be at risk for later-onset Krabbe disease. No guidelines have been published for monitoring these at-risk individuals and to date there are no validated markers that can predict later disease onset [Wasserstein et al 2016].

Symptomatic individuals with later-onset Krabbe disease. The manifestations of Krabbe disease progress more slowly; thus, individuals with later-onset Krabbe disease diagnosed early enough in the disease course may benefit from HSCT. In a single report by Laule et al [2018] treatment was found to arrest demyelination and axonal loss.

Prevention of Secondary Complications

Symptomatic individuals with Krabbe disease

- Physical therapy can improve strength, mobility, flexibility, and function.
- Erythromycin may be useful as a prophylactic antibiotic and may also improve gastrointestinal motility.
- Annual influenza vaccination is recommended [Anderson et al 2014], although other routine vaccinations are typically avoided (see Agents/Circumstances to Avoid).

Surveillance

Symptomatic individuals with Krabbe disease

Monitor for development of:

- Hydrocephalus and need for VP shunt
- Scoliosis, hip subluxation, and osteopenia (via dual-energy x-ray absorptiometry [DXA] scan)
- Decreased vision and corneal ulcerations
- Swallowing difficulties and chronic microaspiration (via modified barium swallow)

Agents/Circumstances to Avoid

Symptomatic individuals with Krabbe disease

- Atypical antipsychotics and multiple medications for seizures [Author, personal experience], which can: overly sedate patients, further affecting cognition; affect respiratory drive; and accelerate the neurodegenerative cascade
- Routine childhood vaccinations, including live virus vaccines, as the resulting immune response may accelerate disease progression [Escolar et al 2016]
- Prolonged indwelling catheters for urinary retention due to the high risk of infection

Evaluation of Relatives at Risk

Couples who have had one child with molecularly confirmed infantile-onset Krabbe disease may choose prenatal molecular genetic testing in subsequent pregnancies so that newborns with biallelic *GALC* pathogenic

variants can be promptly tested (see Establishing the Diagnosis, Scenario 2) and – if appropriate – referred for HSCT (see Prevention of Primary Manifestations).

Note that because of intrafamilial variability, sibs of an individual with later-onset Krabbe disease may develop the disease at a much earlier age.

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

Therapies Under Investigation

Studies are being conducted using well-characterized animal models to investigate other treatment options including enzyme replacement therapy, neural stem cell transplantation, substrate reduction therapy, and chemical chaperone therapy. To date experimental "combination therapies" (HSCT together with gene therapy) in the GALC-deficient murine model have demonstrated the potential to further advance treatment of GALC deficiency by synergistically increasing the life span of the treated mice [Reddy et al 2013, Rafi et al 2015, Ungari et al 2015].

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. Note: There may not be clinical trials for this disorder.

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

Krabbe disease is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *GALC* 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 (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband with later-onset Krabbe disease. The offspring of an individual with later-onset Krabbe disease are obligate heterozygotes (carriers) for a *GALC* pathogenic variant.

Other family members. Each sib of the proband's parents (aunts and uncles of the proband) and each grandparent is at a 50% risk of being a carrier of a *GALC* pathogenic variant.

Carrier Detection

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

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/preimplantation genetic 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).

Prenatal Testing and Preimplantation Genetic Testing

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

Biochemical genetic testing. Prenatal testing by *GALC* enzyme testing is not offered in the United States.

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](#).

- **National Library of Medicine Genetics Home Reference**
[Krabbe disease](#)
- **Newborn Screening in Your State**
Health Resources & Services Administration
www.newbornscreening.hrsa.gov/your-state
- **Partners for Krabbe Research**
www.krabbes.org
- **The Legacy of Angels Foundation**
PO Box 1014
Prior Lake MN 55372
Email: info@tloaf.org
[Krabbe Disease](#)
- **United Leukodystrophy Foundation**
Phone: 800-SAV-LIVE; 815-748-3211
Email: office@ulf.org

www.ulf.org

- **Myelin Disorders Bioregistry Project**
Phone: 215-590-1719
Email: sherbinio@chop.edu
[Myelin Disorders Bioregistry Project](#)

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. Krabbe Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GALC	14q31.3	Galactocerebrosidase	GALC database BIPMed SNP Array - GALC	GALC	GALC

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 Krabbe Disease ([View All in OMIM](#))

245200	KRABBE DISEASE; KRB
606890	GALACTOSYLCERAMIDASE; GALC

Gene structure. *GALC* is approximately 57 kb in length with 17 exons that code for a 685-amino-acid precursor protein that is processed – after cleavage of the 16-amino-acid signal peptide – into a protein of 669 amino acids. Historical nomenclature numbered amino acids beginning at -16; therefore, codon numbers in older references [Wenger et al 1997] may differ from current standard nomenclature by 16 amino acids.

Benign variants. Three common *GALC* variants (p.Arg184Cys, p.Asp248Asn, and p.Ile562Thr) attenuate *GALC* enzyme activity [Saavedra-Matiz et al 2016]. Although not disease-causing, their presence complicates the interpretation of the clinical significance of low enzyme activity. However, p.Ile562Thr [legacy: p.Ile546Thr] has been shown to be disease causing when *in cis* with another mild pathogenic variant, e.g. p.Thr112Ala [legacy: p.Thr96Ala] [Wenger et al 2014, Saavedra-Matiz et al 2016]. Furthermore, other non-disease-causing variants reduce *in vitro* enzyme activity measurements detected by newborn screening in asymptomatic individuals.

Pathogenic variants. More than 200 pathogenic variants including nonsense, frameshift, splice site, and missense variants have been identified. It is often not possible to predict the clinical presentation from the location or type of variant.

The 30-kb deletion, the most common pathogenic variant, which begins within the large intron 10 and extends beyond the end of the gene, accounts for approximately 45% of pathogenic variants in persons of European ancestry. This deletion comprises a significant proportion of pathogenic variants in individuals of Mexican, Pakistani, and Indian heritage. When in the homozygous state or in the compound heterozygous state with another severe pathogenic variant this deletion results in infantile-onset Krabbe disease. Thus far, all individuals with Krabbe disease identified through newborn screening have a least one copy of the deletion.

Several other pathogenic variants associated with infantile-onset Krabbe disease (p.Thr529Met, p.Tyr567Ser, and c.1472delA) make up another 15% of the abnormal alleles in individuals of European ancestry [Kleijer et al 1997, Wenger et al 1997].

A 7.4-kb deletion has also been observed in multiple patients.

The pathogenic variant p.Gly286Asp results in the later-onset form of GALC deficiency, even when present with the 30-kb deletion as the second allele.

A founder variant common in Catania, Italy, p.Gly57Ser, is associated with later-onset Krabbe disease in both the homozygous and compound heterozygous states [Lissens et al 2007]. In general the genotypes of individuals with Krabbe disease are complex, with combinations of benign variants and pathogenic variants.

When variants of unknown significance are identified, elevated psychosine (within reference range for infantile-onset Krabbe disease) and low GALC activity are suggestive findings of infantile-onset Krabbe disease.

A more complete catalog of reported *GALC* variants is available in Wenger et al [2013].

Table 3. Common *GALC* Polymorphisms and Pathogenic Variants

Variant Classification	DNA Nucleotide Change (Alias ¹)	Predicted Protein Change (Alias ¹)	Reference Sequences
Benign	c.550C>T	p.Arg184Cys (p.Arg168Cys)	NM_000153.3 NP_000144.2
	c.742G>A	p.Asp248Asn (p.Asp232Asn)	
	c.1685T>C	p.Ile562Thr (p.Ile546Thr)	
Pathogenic	(30-kb deletion) ²	--	
	c.169G>A (121G>A)	p.Gly57Ser (Gly41Ser)	
	c.334A>G (286A>G)	p.Thr112Ala (Thr96Ala)	
	c.560A>T (512A>T)	p.Asp187Val (Asp171Val)	
	c.857G>A (809G>A)	p.Gly286Asp ³ (Gly270Asp)	
	c.953C>T (944C>T)	p.Pro318Arg (p.Gly302Arg)	
	c.1472delA (1424delA)	p.Lys491ArgfsTer62	
	c.1586C>T (1538C>T)	p.Thr529Met (Thr513Met)	
	c.1700A>C (1652A>C)	p.Tyr567Ser (Tyr551Ser)	
c.1901T>C (1853T>C)	p.Leu634Ser ⁴ (Leu618Ser)		

See [Quick Reference](#) for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org).

1. Historical variant designations that do not conform to current naming conventions. In this instance, the variant designations conform to the cDNA reference sequence in the HGMD database (see Table A) and some publications.

2. Begins in intron 10 and deletes the remainder of the gene and additional contiguous sequences

3. One copy of this allele together with another pathogenic variant results in late-onset disease.

4. One copy of this allele together with another severe allele in the homozygous state is associated with late-onset disease [Hossain et al 2014, Zhang et al 2018].

Normal gene product. The 80-kd precursor protein contains six potential glycosylation sites and is proteolytically cut into the active 50-kd and 30-kd subunits. These subunits are not active individually, but aggregate into a very high hydrophobic molecular-weight complex.

Abnormal gene product. Loss or significant reduction of galactosylceramidase function results in Krabbe disease.

Chapter Notes

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- 11 October 2018 (bp) Comprehensive update posted live
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- 25 November 2002 (me) Comprehensive update posted live
- 19 June 2000 (me) Review posted live
- February 2000 (dw) Original submission

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