GENEReviews

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Krabbe Disease

[*GALC Deficiency, Galactocerebrosidase Deficiency, Galactosylceramidase Deficiency, Globoid Cell Leukodystrophy*]

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Summary

Disease characteristics. Krabbe disease is characterized by infantile-onset progressive neurologic deterioration and death before age two years (85%-90% of individuals) or by onset between age six months and the fifth decade with slower disease progression (10%-15%). Children with the infantile form appear to be normal for the first few months of life but show extreme irritability, spasticity, and developmental delay before age six months; psychomotor regression progresses to a decerebrate state with no voluntary movement. In the late-onset forms, individuals can be clinically normal until weakness, vision loss, and intellectual regression become evident. The clinical course is variable even within the same family.

Diagnosis/testing. In almost all individuals with Krabbe disease, galactocerebrosidase (GALC) enzyme activity is deficient (0%-5% of normal activity) in leukocytes isolated from whole heparinized blood or in cultured skin fibroblasts. Testing is most reliable when conducted in a laboratory with demonstrated experience in this assay. Carrier testing by measurement of GALC enzyme activity in leukocytes or in cultured skin fibroblasts is unreliable because of the wide range of enzymatic activities observed in carriers and non-carriers. Molecular genetic testing of *GALC* may be used for carrier detection in at-risk relatives if the disease-causing alleles have been identified in the family .

Management. *Treatment of manifestations:* supportive care to control irritability and spasticity in children with infantile-onset Krabbe disease in Stage II or III. *Prevention of primary manifestations:* Hematopoietic stem cell transplantation (HSCT) in presymptomatic infants and older individuals with mild symptoms may improve and preserve cognitive function, but peripheral nervous system function may deteriorate. Significant clinical variability in late-onset forms makes evaluation of treatment effectiveness difficult. *Testing of relatives at risk:* Testing at-risk infants can reduce morbidity and mortality through early diagnosis and HSCT using umbilical cord blood.

Genetic counseling. Krabbe disease is inherited in an autosomal recessive manner. If both parents are carriers, each child 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. Each healthy sib of a proband has a 2/3 chance of being a carrier. For genetic counseling purposes, a carrier frequency of one in 150 may be used for the general population. Prenatal diagnosis is possible either by measurement of GALC enzyme activity (ideally, GALC enzyme activity should be measured in both parents before prenatal testing is undertaken) or by molecular genetic testing if both disease-causing alleles in an affected family member are known.

Diagnosis

Clinical Diagnosis

Individuals with the infantile form of Krabbe disease present with the following:

- Irritability
- Muscle hypertonicity
- Progressive neurologic deterioration
- Peripheral neuropathy
- Evidence of white matter disease on neuroimaging
- Elevation of cerebrospinal fluid (CSF) protein concentration

While most individuals have the infantile form, older individuals ranging in age from six months to the fifth decade have also been diagnosed with galactocerebrosidase deficiency. They usually present with weakness and vision loss and may experience intellectual regression.

Neuroimaging. Progressive, diffuse, and symmetrical cerebral atrophy is observed by neuroimaging.

In the early stage of the disease, CT can be normal; diffuse cerebral atrophy involving both gray and white matter develops later. Diffuse hypodensity of the white matter may be present, particularly in the parieto-occipital region. These findings are nonspecific and are observed in many diseases of white matter.

In general, MRI detects demyelination in the brain stem and cerebellum more clearly than CT at the early stage of the disease; however, some infants have had deceptively normal MRIs when CT had already revealed symmetric hyperdensity involving the cerebellum, thalami, caudate, corona radiata, and brain stem.

Individuals with Krabbe disease who have severe demyelination show high-intensity lesions on T2-weighted images with a loss of diffusional anisotropy and relatively high signal on diffusion-weighted images. Calculation of the T2 value in the central white matter provides objective judgment for demyelinating diseases. It is progressively prolonged in the occipital deep white matter and posterior part of the central semiovale in individuals with late-onset Krabbe disease.

Testing

For laboratories offering biochemical testing, see Testing.

Galactocerebrosidase (GALC) enzyme activity

- **Symptomatic individuals** The accurate measurement of GALC enzyme activity requires use of the radiolabeled natural substrate galactosylceramide (gal-cer). This in vitro assay, available in specialized clinical laboratories, utilizes a synthetic buffer and detergent mixture. All individuals with Krabbe disease have very low GALC enzyme activity (0%-5% of normal activity) in leukocytes isolated from whole, heparinized blood and cultured skin fibroblasts. This test is most reliable when conducted in a laboratory with demonstrated experience in performing the assay.

  Note: The finding of GALC enzyme activity that is 8%-20% of normal in a healthy individual, in an individual with neurologic disease that is not typical of any form of Krabbe disease, or in an individual identified by newborn screening presents a

diagnostic problem and requires additional study. In most instances, such individuals have multiple copies of known polymorphisms in both *GALC* alleles. However, some individuals with enzyme activity in this range may have a disease-causing mutation on one allele and multiple polymorphic changes on the other allele, and thus may be carriers of Krabbe disease.

- **Carrier testing.** Carrier testing by measurement of GALC enzyme activity in leukocytes or cultured skin fibroblasts is unreliable because of the wide range of enzymatic activities observed in carriers and non-carriers. The presence of polymorphisms in the coding region of the *GALC* gene results in amino acid changes that affect GALC enzyme activity but that do not result in clinical disease when inherited in the homozygous state or, as far as is known, when inherited together with a disease-causing mutation.

  Note: Although the finding of low GALC enzyme activity in one or both healthy parents of an affected child makes prenatal testing using enzyme activity more difficult, it is accurate when performed in an experienced laboratory.

- **Newborn screening.** With improvements in treatment options for presymptomatic individuals, efforts to develop newborn screening methods are under investigation. A method utilizing dried blood spots and tandem mass spectrometry to measure GALC enzyme activity has been published [Li, Brockman et al 2004; Li, Scott et al 2004]. In August 2006 New York State instituted newborn screening for Krabbe disease, and several individuals were identified as being at risk for developing Krabbe disease in their lifetime. The identification of these individuals permitted umbilical cord transplantation in two of the individuals within the first month of life, although one subsequently died of complications. The other high-risk individuals have mutations suggesting later onset and are being carefully monitored.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *GALC* is the most common gene known to be associated with Krabbe disease.

Clinical uses

- Carrier testing in families with known mutations
- Prenatal diagnosis (molecular analysis is not required for accurate prenatal diagnosis)
- Preimplantation genetic diagnosis

Clinical testing

- **Targeted mutation analysis**
  - **Infantile Krabbe disease.** One mutation (a 30-kb deletion) accounts for approximately 45% of the mutant alleles in individuals of European ancestry [Rafi et al 1995, Luzi et al 1995] and 35% of the mutant alleles in individuals of Mexican heritage. This large deletion results in the classic infantile form in the homozygous state or when heterozygous with another mutation associated with severe disease.
  - **Late-onset Krabbe disease.** The 809G>A mutation is often found in individuals with the late-onset form of Krabbe disease. One copy of this mutation, even when present with the 30-kb deletion in the second allele, always results in late-onset Krabbe disease.

- **Sequence analysis.** It is possible to sequence the entire coding region, intron-exon boundaries, and 5'-untranslated region of the *GALC* gene and identify essentially 100% of the disease-causing mutations and polymorphisms.
- **Deletion/duplication analysis.** Deletions involving single exons and multiple exons have been detected.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Krabbe Disease

Test Method	Mutations Detected	Mutation Detection Rate	Test Availabilty
Targeted mutation analysis	*GALC* 30-kb deletion	Infantile Krabbe disease: varies by ethnicity	Clinical Testing
	GALC 809G>A mutation	Late-onset Krabbe disease: approximately 50% have one copy of the mutation	
Sequence analysis	*GALC* sequence variants	~100%	
Deletion/duplication analysis [1]	Exonic, multi-exonic and whole-gene deletions/duplications of GALC	Unknown	

1. Testing that detects deletions/duplications not readily detectable by sequence analysis of genomic DNA; a variety of methods may be used such as quantitative PCR, real-time PCR, multiplex ligation dependent probe amplification (MLPA), or array CGH (see Testing).

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

- Measurement of GALC enzyme activity in leukocytes or another tissue to establish the diagnosis
- Molecular genetic analysis of the proband to identify both disease-causing alleles to aid in carrier detection in at-risk family members and possibly for prenatal diagnosis

Genetically Related (Allelic) Disorders

All individuals with a deficiency of GALC enzyme activity have symptoms consistent with some type of leukodystrophy.

Clinical Description

Natural History

Approximately 85%-90% of individuals with Krabbe disease have the infantile form presenting with extreme irritability, spasticity, and developmental delay before age six months. The remaining 10%-15% have onset between age six months and the fifth decade.

Infantile form. The infantile form has three stages:

- **Stage I** is characterized by irritability, stiffness, arrest of motor and mental development, and episodes of temperature elevation without infection, possibly caused by involvement of the hypothalamus. The child, apparently normal for the first few months after birth, becomes hypersensitive to auditory, tactile, or visual stimuli and begins to cry frequently without apparent cause. Many infants keep their fists tightly clenched throughout their lives. Slight retardation or regression of psychomotor development as well as vomiting and other feeding difficulties may result in progressive loss of weight leading to emaciation. In some infants, peripheral neuropathy is a presenting feature with no other neurologic symptoms appreciated for

several months [Korn-Lubetzki et al 2003]. Seizures may occur as an initial clinical symptom. Infantile spasms rarely occur. The CSF protein concentration is already increased at this stage.

- **Stage II** is characterized by rapid and severe motor and mental deterioration. There is marked hypertonicity with extended and crossed legs, flexed arms, and a backward-bent head. Tendon reflexes are hyperactive. Minor tonic or clonic seizures occur. Optic atrophy and sluggish pupillary reactions to light are common. Clinical examination does not always reveal peripheral neuropathy, especially in the early stages when symptoms and signs of central nervous system involvement are overwhelming.
- **Stage III,** sometimes reached within a few weeks or months, is the "burnt out" stage. The infant is blind and decerebrate with no voluntary movement. The infant has no contact with his/her surroundings.

The average age of death in children with the infantile form is 13 months; however, some succumb by age eight months from infections and respiratory failure, while others live for two or more years. Even with the best care, it is difficult to extend the life of a severely affected child.

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

One infant, diagnosed with Krabbe disease 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. These findings suggest that careful examination could reveal clinical manifestations of Krabbe disease in an affected infant earlier than the reported age of onset.

Late-onset forms. Individuals with late-onset forms can be clinically normal until almost any age when symptoms of weakness, vision loss, and intellectual regression become evident. The clinical course of older individuals is variable. Individuals with the late-infantile or juvenile form who present after age one year may have nonspecific findings related to walking difficulties, vision loss, and loss of developmental milestones. These individuals regress at an unpredictable rate, but all become severely incapacitated and die two to seven years after diagnosis.

Loonen et al (1985) identified late-infantile (early-childhood) and juvenile (late-childhood) forms in 18 individuals.

In the late-infantile group (onset age six months to three years), irritability, psychomotor regression, stiffness, ataxia, and loss of vision were the most common initial symptoms. In most cases the course was progressive and resulted in death approximately two years after onset.

In the juvenile group (onset age three to eight years), children developed loss of vision together with hemiparesis, ataxia, and psychomotor regression. Most children with the juvenile form showed an initial rapid deterioration followed by a more gradual progression lasting for years. None died during the follow-up period that ranged from ten months to seven years.

Some individuals with onset in adolescence and adulthood present with loss of manual dexterity, burning paresthesia 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].

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 symptoms began after age 20 years [Kolodny et al 1991, Satoh et al 1997, Wenger 2003]. An example of the former is an individual reported by Kolodny et al (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].

The phenotypes can differ considerably between individuals with later-onset forms, including siblings, who have the same *GALC* genotype. Findings in two sisters illustrate this point. At age 28 years, sister 1 had been considered normal until a few years previously when she experienced lower-extremity paresis with episodes of tripping and clumsiness when walking. Heel cord lengthening was performed, but spastic paresis continued with clumsy gait and difficulty rising from a squatting or sitting position. Ten years earlier, nerve conduction studies had shown slowing in motor and sensory fibers. She had no obvious intellectual impairment, was married, and at age 38 years, had a child and continued to work part-time. Sister 2 had been considered normal until age four to five years, when she developed progressive weakness in all extremities. She experienced rapid mental deterioration and seizures. At age 36 years, she was significantly mentally retarded and wheelchair bound, although she could function in a sheltered environment.

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.

EMG and NCV. Motor nerve conduction velocities (NCVs) are consistently low. NCV studies have been reported to be normal in some adults with an enzymatically confirmed diagnosis.

Visual and auditory evoked responses, NCV, and EEG are all more frequently and more severely abnormal in individuals with early-infantile onset [Husain et al 2004].

MRI. In general, in the early stage of Krabbe disease MRI detects demyelination in the brain stem and cerebellum more clearly than CT, but some infants have a deceptively normal MRI.

In some cases, CT reveals symmetric hyperdensity involving the cerebellum, thalami, caudate, corona radiata, and brain stem.

On MRI the T1 value is decreased, with normal or slightly decreased T2 in white matter of the centrum semiovale.

T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI showed symmetric high intensity of the pyramidal tract and optic radiation in an adult whose initial clinical manifestations occurred at age 60 years. The T2 value is progressively prolonged in the occipital deep white matter and posterior part of central semiovale in late-onset disease. MRI is also useful for differentiation between dysmyelination and demyelination. Individuals with Krabbe disease with severe demyelination showed high-intensity lesions on T2-weighted images, with a loss of diffusional anisotropy and relatively high signal intensity on diffusion-weighted images.

MRS. Magnetic resonance spectroscopy can also be used to document the demyelination, gliosis, and axonal loss in white matter of individuals with typical and atypical Krabbe disease.

Genotype-Phenotype Correlations

GALC Enzyme Activity —No consistent correlation has been observed between age of onset and residual GALC enzyme activity measured in leukocytes or cultured skin fibroblasts.

Occasionally, some individuals with Krabbe disease have slightly higher than expected GALC enzyme activity. Because the active enzyme consists of a large aggregate containing multiple copies of the 30-kd and 50-kd subunits derived from the same precursor and because many individuals are compound heterozygotes, it is difficult to place much significance on the detection of a small amount of residual enzyme activity.

***GALC* Mutations —Infantile form.** The common 30-kb deletion results in the classic infantile form in the homozygous state or when heterozygous with another mutation associated with severe disease. Three other mutations associated with the infantile phenotype make up another 15% of the mutant alleles in individuals of European ancestry [Kleijer et al 1997, Wenger et al 1997]. Except for the 809G>A mutation, all disease-causing mutations listed in Table 3 result in the infantile phenotype when homozygous or compound heterozygous with each other.

Late-onset forms. Many individuals with late-onset disease are compound heterozygotes, having one copy of the 809G>A mutation and one copy of the common 30-kb deletion. Although having one copy of the 809G>A allele always results in a milder phenotype, it is not possible to predict the clinical course, as illustrated by the two sisters described in Clinical Description. Five additional families with multiple affected members with the 30-kb del/809G>A genotype have significant intra- and interfamilial clinical variability [Wenger, personal observation].

Only one individual of Japanese heritage with adult-onset disease is known to be homozygous for the 809G>A mutation. One individual with adult-onset disease had a complex genotype with three mutations on one allele and two on the other [Luzi et al 1996]. Other mutations have been described [Kukita et al 1997].

Prevalence

Krabbe disease occurs in approximately one in 100,000 births in the United States and Europe.

The carrier frequency in individuals with no family history is about one in 150.

The disease is pan ethnic; however, no cases have been identified in individuals of Jewish ancestry. A very high incidence of the disease is found in a Druze community in Northern Israel and two Moslem Arab villages located near Jerusalem, where the carrier rate is estimated to be one in six.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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. Differentiation of Krabbe disease from other degenerative diseases is often

difficult. Individuals of any age with progressive deterioriation of the central or peripheral nervous systems should be tested for Krabbe disease.

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 cases) with onset between age one and two years; juvenile MLD (~20%-30%) with onset between age four years and sexual maturity (12-14 years); and adult MLD (~15%-20%) with onset after sexual maturity. All individuals eventually lose motor and intellectual functions. The disease course may be from three to ten or more years in the late infantile-onset form and up to 20 years or more in the juvenile- and adult-onset forms. Death most commonly results from pneumonia or other infection.

MLD is suggested by arylsulfatase A enzyme activity in leukocytes that is less than 10% of normal controls. Because of the high frequency of the so-called pseudodeficiency (Pd) allele, additional studies in all individuals with low arylsulfatase activity are required. The diagnosis of MLD is confirmed by one or more of the following additional tests: molecular genetic testing of the *ARSA* gene, urinary excretion of sulfatides, and/or finding of metachromatic lipid deposits in nervous system tissue. Several individuals with Krabbe disease who were also homozygous for the Pd allele had low arylsulfatase A activity [Wenger, unpublished].

GM1 gangliosidosis. The GM1 gangliosidoses, including Morquio syndrome type B, result from defects in acid β-galactosidase. They are clinically variable, ranging from newborns with nonimmune fetal hydrops to adults with varying degrees of neurologic involvement. In addition to psychomotor retardation, young individuals usually have coarse facial features and hepatosplenomegaly, neither of which is found in individuals with Krabbe disease. Skeletal involvement is variable. Some individuals primarily have dysostosis multiplex with no neurologic involvement, and others have only neurologic problems, such as dysarthria, and mild vertebral changes. Low-acid β-galactosidase enzyme activity in both leukocytes and plasma establishes the diagnosis of GM1 gangliosidosis and Morquio syndrome type B and differentiates them from galactosialidosis, a disorder in which β-galactosidase enzyme activity is low in leukocytes only.

GM2 gangliosidosis. The GM2 gangliosidoses are a group of neurodegenerative disorders caused by the intralysosomal storage of the specific glycosphingolipid GM2 ganglioside. Tay-Sachs disease, the prototype GM2 gangliosidosis, is characterized by loss of motor skills beginning between age 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.

The diagnosis of hexosaminidase A deficiency relies upon the demonstration of absent to near-absent beta-hexosaminidase A (HEX A) enzymatic activity in the serum or white blood cells of a symptomatic individual in the presence of normal or elevated activity of the beta-hexosaminidase B (HEX B) isoenzyme. Mutation analysis of the *HEXA* gene is used primarily for genetic counseling purposes 1) to distinguish pseudodeficiency alleles from disease-causing alleles in individuals with apparent deficiency of HEX A enzymatic activity identified

in population screening programs and 2) to identify specific disease-causing alleles in affected individuals.

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. The finding of elevated N-acetylaspartic acid concentration in urine confirms the diagnosis of Canavan disease.

Saposin A deficiency. An infant with abnormal myelination resembling Krabbe disease was found to have a mutation in the saposin A region of the prosaposin *(PSAP*) gene [Spiegel et al 2005]. This heat-stable protein interacts with the enzyme GALC to catalyze the hydrolysis of the natural lipid substrates. The infant with mutations in the saposin A region of the *PSAP* gene had low GALC enzyme activity when measured in leukocytes, but not in cultured skin fibroblasts.

X-Linked

X-linked adrenoleukodystrophy (X-ALD) affects the nervous system white matter and the adrenal cortex. Three main phenotypes are seen in males: (1) The childhood cerebral form 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. (2) Adrenomyeloneuropathy (AMN) manifests most commonly in the late twenties as progressive paraparesis, sphincter disturbances, and varying degrees of distal sensory loss. (3) "Addison disease only" presents with primary adrenocortical insufficiency between age two years and adulthood and most commonly by age 7.5 years; some degree of neurologic disability (most commonly AMN) usually develops later.

Approximately 20% of carrier females develop neurologic manifestations that resemble adrenomyeloneuropathy, but have later onset (age 35 years or later) and milder disease than do affected males.

The plasma concentration of very-long-chain fatty acids (VLCFA) is elevated in more than 99% of males with X-ALD of all ages regardless of the presence or absence of symptoms. The assay has a sensitivity of approximately 85% in female carriers.

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. Molecular genetic testing of the *PLP1* gene is diagnostic.

Autosomal Dominant

Alexander disease is a disorder of cortical white matter. Although two forms are common, infantile (80% of affected individuals) and juvenile (~14%), neonatal and adult forms are also recognized. The infantile form presents in the first two years of life typically with megalencephaly, seizures, progressive psychomotor retardation with loss of developmental milestones, and quadriparesis. 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 megalencephaly, bulbar/pseudobulbar signs including speech abnormalities, swallowing difficulties, frequent vomiting, lower-limb spasticity, poor coordination (ataxia), gradual loss of intellectual function, and seizures.

Diagnostic criteria based on MRI findings include extensive white matter involvement with frontal preponderance, periventricular rim of low T2 and high T1 signal intensity, and mild signal changes and swelling in the basal ganglia, thalamus, and brain stem [van der Knaap et al 2001]. *GFAP*, which encodes glial fibrillary acidic protein, is the only gene currently known to be associated with Alexander disease. Molecular genetic testing detects mutations in more than 90% of affected individuals.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Krabbe disease:

- Neurologic examination
- EEG
- Brain MRI and MRS

Treatment of Manifestations

Treatment of individuals with infantile-onset Krabbe disease who are diagnosed in Stage II or III is limited to supportive care to control irritability and spasticity.

Prevention of Primary Manifestations

Hematopoietic stem cell transplantation (HSCT) in presymptomatic infants [Escolar et al 2005] and older individuals with mild symptoms [Krivit et al 1998] provides a benefit over symptomatic treatment only. Treated individuals show improved and preserved cognitive function; however, many show progressive deterioration of peripheral nervous system findings.

The availability of suitable donors has changed considerably with the use of umbilical cord blood for HSCT.

The identification of newborns with the potential to develop Krabbe disease by newborn screening (presently in place in New York State) facilitates the initiation of treatment before neurologic damage has occurred. Concerns remain regarding the age at which to start treatment, prediction of clinical course without treatment, and long-term consequences of treatment.

Given the significant clinical variability among individuals with late-onset forms (even those with the same genotype), evaluation of treatment effectiveness is difficult.

Testing of Relatives at Risk

If the disease has been identified in an affected family member, it is appropriate to test at-risk infants so that morbidity and mortality can be reduced by early diagnosis and treatment with HSCT using umbilical cord blood [Escolar et al 2005].

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

Therapies Under Investigation

Studies using the well-characterized animal models to investigate other treatment options including gene therapy, enzyme replacement therapy, neural stem cell transplantation, substrate reduction therapy, and chemical chaperone therapy are being conducted. However, at this time HSCT is the most effective method of therapy in the mouse models of Krabbe disease. None of these other methods are ready for human trials.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

In utero HSCT in fetuses predicted to be affected with Krabbe disease has been tried three times with little success [Bambach et al 1997].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 child are obligate heterozygotes and therefore each carry one mutant allele.
- While each parent carries one normal and one mutated *GALC* allele, the measured GALC enzyme activity can range widely in carriers because of polymorphisms in the normal copy of the gene. Although some parents have quite low GALC enzyme activity measured in vitro, none have had clinical disease.

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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.

Offspring of a proband with adult-onset Krabbe disease. The offspring of an individual with adult-onset Krabbe disease are obligate heterozygotes (carriers) for a disease-causing mutation in the *GALC* gene.

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.

Carrier Detection

At-risk family members

- As the contribution of each allele is additive, when the GALC enzyme activity of both parents is known, it is usually possible to accurately determine carrier status of the sibs of an affected individual by measurement of GALC enzyme activity. When the enzyme activity of the parents is not known or if the individual is not an at-risk sib, carrier testing using GALC enzyme activity is not reliable.
- When the *GALC* disease-causing mutations have been identified in the proband, accurate carrier detection of at-risk family members is possible using molecular genetic testing.

Reproductive partners of at-risk family members. No reliable carrier detection exists for individuals who do not have a family history of Krabbe disease. The carrier frequency in the general population is about one in 150.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Biochemical genetic testing. Prenatal testing is available for at-risk couples who have had an affected child. Ideally, GALC enzyme activity should be measured in both parents before prenatal testing is undertaken. GALC enzyme activity can be measured directly using either fetal cells obtained by chorionic villus sampling at approximately ten to 12 weeks' gestation, cultured cells from CVS, or cultured amniotic fluid cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation. Measurement of GALC enzyme activity for prenatal testing is reliable, and molecular genetic testing is not necessary. It is essential that there be no maternal contamination in the sample used for prenatal analysis.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is also possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed. It is essential that there be no maternal contamination in the sample used for prenatal analysis.

Carrier status documented in only one parent. When one parent is a known heterozygote and the reproductive partner has inconclusive enzymatic activity and no disease-causing *GALC* mutation has been found on DNA analysis, or when the mother is a known heterozygote and the father is unknown and/or unavailable for testing, options for prenatal testing can be explored in the context of formal genetic counseling.

Preimplantation diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. However, it should be noted that this procedure is not routine, and errors have occurred in the prediction of a child free of Krabbe disease. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Krabbe Disease

Gene Symbol	Chromosomal Locus	Protein Name
GALC	14q31	Galactocerebrosidase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Krabbe Disease

245200	KRABBE DISEASE
606890	GALACTOSYLCERAMIDASE; GALC

Table C. Genomic Databases for Krabbe Disease

Gene Symbol	Locus Specific	Entrez Gene	HGMD
GALC	GALC	2581 (MIM No. 245200)	GALC

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The normal gene is about 57 kb long with 17 exons that code for 669 amino acids. The 5' flanking region of the gene is GC rich and contains one potential YY1 element and one potential SP1 binding site. The strongest promoter activity is -176 to -24 upstream of the initiation codon. Inhibitory sequences are immediately upstream of the promoter region and within intron 1 [Luzi et al 1997] (see Table 2).

Table 2. Most Common Polymorphisms in the *GALC* Gene

Nucleotide Change [1]	Amino Acid Change	Percent of All Alleles
502C>T	p.R168C	4%-5%
694G>A	p.D232N	8%-10%
1637T>C	p.I546T	30%-40%
502C>T + 1637T>C [2]	p.R168C + p.I546T	<2%

1. Complementary DNA nucleotide number
2. The two mutations on the same allele

Pathologic allelic variants: Nearly 70 mutations, including polymorphisms, have been identified (summarized in Wenger et al 2001). The more common mutations that have occurred

in the heterozygous state in more than one unrelated individual and in the homozygous state are given in Table 3.

Table 3. Most Common Disease-Causing Mutations in *GALC* in Individuals with European Ancestry

Percent of Mutant Alleles	Nucleotide Change [1]	Comments
40%-50%	30-kb deletion	
5%-8%	1538C>T	
5%-8%	1652A>C	
2%-5%	1424delA	
1%-2%	809G>A	One copy of the allele will result in late-onset disease
32%-47%		Other mutant alleles

1. Complementary DNA nucleotide number

Mutations occur in every one of the 17 exons. Missense mutations causing the infantile form of Krabbe disease are found in both subunits, although more seem to be found in the coding region for the 30-kd subunit.

The 30-kb deletion, which always occurs with the 501C>T (R168C) polymorphism, makes up approximately 45% of mutant alleles in the population with European ancestry. The 30-kb deletion, starting within the large intron 10 and continuing beyond the end of the gene, probably originated in Sweden and spread throughout Europe, including Spain. This mutation makes up approximately 35% of the mutant alleles in individuals of Mexican heritage and results in the classic infantile form when found homozygous or heterozygous with another severe mutation. Three other mutations associated with the infantile phenotype make up another 15% of the mutant alleles in individuals with European ancestry [Kleijer et al 1997, Wenger et al 1997].

One mutation, G>A at position 809 (based on cDNA sequence counting from the A of the initiation sequence), resulting in G>D substitution at amino acid position 270, always results in the later-onset form of Krabbe disease. One copy of this mutation, even when present with the 30-kb deletion in the second allele, results in late-onset Krabbe disease. All alleles with the 809G>A mutation (except the adult Japanese individual in whom it was not mentioned [Kukita et al 1997]) have the 1637T>C (p.I546T) polymorphism. It is possible that the 809G>A mutation would not be disease causing if the normal isoleucine residue were present.

A number of small deletions and insertions result in a frame shift and premature termination. Even missense mutations very near the 3' end of the coding region that result in amino acid changes near the carboxyl end of the 30-kd subunit result in clinical disease [Rafi et al 1996, Jardim et al 1999]. Both subunits are needed for activity, and it is difficult to predict the clinical presentation from the location or type of missense mutation.

Other unique mutations occur within certain ethnic groups [Fu et al 1999]. Unique point mutations resulting in infantile Krabbe disease have been identified in two isolates in the Middle East [Rafi et al 1996]. The Druze in Northern Israel and a Moslem Arab village near Jerusalem each has its own unique missense mutation near the 3' end of the gene. For members of these villages, identification of affected individuals, carrier testing, and prenatal diagnosis can be done by molecular genetic analysis.

Normal gene product: The 80-kd precursor contains six potential glycosylation sites and is proteolytically cut into the active 50-kd and 30-kd subunits. These subunits are not active individually, and galactocerebrosidase (GALC) enzyme activity cannot be generated by mixing together the two subunits. The subunits aggregate into a very high molecular-weight complex

that is very hydrophobic. Normally only a very small amount of GALC protein is made in all cell types; however, it appears to be stable and to work efficiently on the natural substrates.

Abnormal gene product: It appears that most disease-causing missense mutations result in the production of protein that is unstable and rapidly degraded. All small and large deletions result either in frame shifts and premature stop codons or in deletion of a significant portion of the gene. The polymorphic missense mutations result in protein that is less active than protein coded for by the most common allele. This reduced activity may result from changes in secondary structure of the mature enzyme or protein instability. While these effects are measurable in vitro, it is not known what effects the changes have in vivo, especially in the peripheral and central nervous systems.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Hunter's Hope Foundation
6368 West Quaker Street
Orchard Park NY 14127
Phone: 877-984-4673 (toll-free); 716-667-1200
Fax: 716-667-1212
Email: info@huntershope.org
www.huntershope.org

National Library of Medicine Genetics Home Reference
Krabbe disease

Canadian MPS Society
PO Box 30034
RPO Parkgate North Vancouver
British Columbia
Canada V7H 2Y8
Phone: 800-667-1846; 604-924-5130
www.mpssociety.ca

United Leukodystrophy Foundation (ULF)
2304 Highland Drive
Sycamore IL 60178
Phone: 800-728-5483; 815-895-3211
Fax: 815-895-2432
Email: office@ulf.org
www.ulf.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Suggested Readings

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Chapter Notes

Author Notes

Since 1969 Dr. Wenger has been doing research on certain lysosomal storage diseases, primarily Krabbe disease, and in 1973 the diagnostic laboratory was started. Since then, about 40,000 individuals have been screened for lysosomal diseases in his laboratory.

Author History

Stephanie Coppola, BS; Jefferson Medical College (2004-2006)
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Revision History

- 5 August 2008 (cd) Revision: deletion/duplication analysis available clinically for *GALC*
- 3 January 2007 (me) Comprehensive update posted to live Web site
- 27 September 2004 (me) Comprehensive update posted to live Web site
- 25 November 2002 (me) Comprehensive update posted to live Web site
- 19 June 2000 (me) Review posted to live Web site
- February 2000 (dw) Original submission