KrabbeConnect

CONNECTING PATIENTS & RESEARCH

Helping You and Your Family Understand Krabbe Disease

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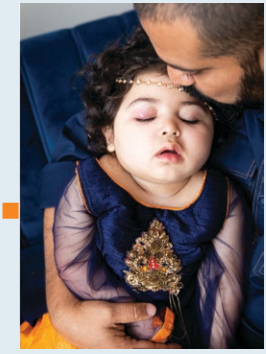
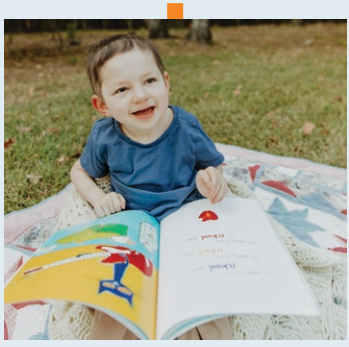




KrabbeConnect
CONNECTING PATIENTS & RESEARCH

Our Mission:

KrabbeConnect bridges science and patient knowledge to improve care and find a cure for Krabbe disease

Our Vision:

A day in which each patient receives an early diagnosis, has access to state-of-the-art care, and lives a life free of Krabbe disease

Your Guide to This Booklet

KrabbeConnect's Story

The concept for KrabbeConnect was born during the 2015 Family Centered-Krabbe Translational Research Network (FC-KTRN) meeting, a collaborative gathering of researchers and families aimed at addressing the uncertainties surrounding Krabbe disease. In 2017, Stacy Pike-Langenfeld approached Anne Rugari to gauge her interest in helping to launch an organization called KrabbeConnect. which was officially incorporated on February 5, 2018.

Since its inception, the Board of Directors has focused on providing essential resources and support to families affected by Krabbe disease. KrabbeConnect aims to amplify the voices and experiences of patients to drive impactful research to #curekrabbe.

Krabbe Disease is a rare genetic disorder

It affects the nervous system, which includes the brain and spinal cord.

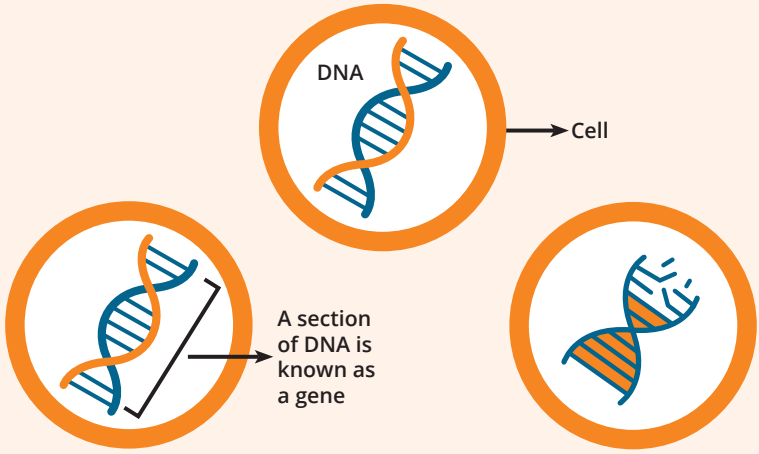
- The disease is a type of leukodystrophy, meaning it mostly damages the white matter in the brain. Leuko = white; Dystrophy = tissue degeneration.
- This happens because your loved-one's body isn't able to produce an important enzyme called galactocerebrosidase **(GALC)**.
- The **GALC** enzyme helps break down certain fats in the brain.

Without GALC, harmful substances build up and damage myelin. Myelin is the protective layer around the nerve cells that helps them work properly.

What Causes Krabbe Disease

What is DNA

Cells make up all parts of the body and perform specific jobs

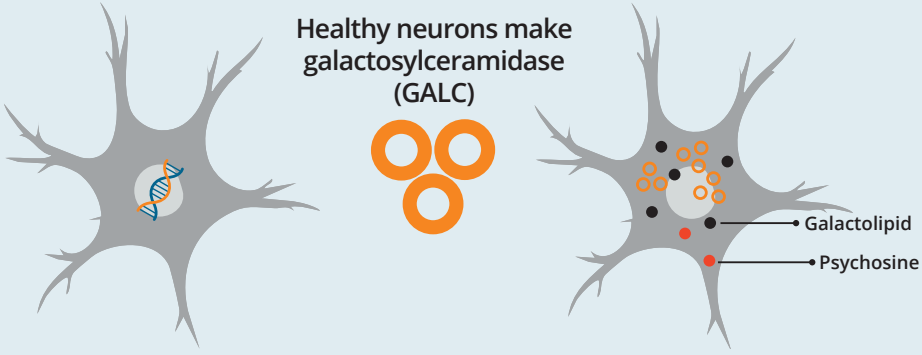


DNA is a genetic manual providing cells instructions

A change in a gene's code is called a genetic varient

Healthy Nerve Cells

Nerve cells, called neurons, send and receive signals from the brain to other parts of the body



Healthy nerve cell (neuron)

GALC is an enzyme that helps neurons function properly

GALC is responsible for breaking down galactolipids and psychosine, substances that become harmful to nerve cells in large amounts.

What Causes Krabbe Disease

In Krabbe disease, a genetic mutation stops neurons from producing GALC

What are the types of Krabbe disease and the signs and symptoms to watch for?

- The signs and symptoms your child may experience will vary because there are different types of Krabbe disease.
- Disease onset is when nerve damage begins and the nerve damage starts to present noticeable symptoms such as vision changes.
- The table on the next page shows the ages of onset in Krabbe disease and the typical symptoms you are seeing or will see at some point as the disease progresses.
    - Infantile Krabbe Disease (IKD) is the most common and most severe form. IKD presents with long and frequent episodes of an abnormal cry ("Krabbe cry") and loss of gained milestones.
    - Late Infantile Krabbe Disease (LIKD) presents with vision disturbances, slurred speech. Abnormal walking (also referred to as "gait").
    - Juvenile Onset Krabbe Disease (JOKD) is when symptoms present between 37 months and 18 years of age
    - Adult Onset Krabbe Disease (AOKD) surfaces later into adulthood and often misdiagnosed with other more common neurodegenerative diseases first.

Types of Krabbe Disease

Early Onset

Infantile (IKD) 0-12 months

Symptoms: Extreme crying, feeding difficulties, poor head control, loss of milestones, fisted hands, and exaggerated startle to noise.

Disease Progression: Progressive neurological decline, seizures, loss of vision, hearing, and body movement.

Late Infantile (LIKD) 13 to 36 months

Symptoms: Loss of acquired milestones, abnormal muscle tone, slow to develop motor skills, and walking abnormalities.

Disease Progression: Similar to IKD but slower progression.

Late Onset

Juvenile Onset (JOKD) >37 mos -18 years

Symptoms: Vision problems, muscle weakness, gait changes, and loss of developmental milestones.

Disease Progression: Variable progression with older patients, slower progression than early onset subtypes.

Adult Onset (AOKD) 18+ years

Symptoms: Gait disturbances, muscle weakness, cognitive regression.

Disease Progression: Variable progression with older patients, slower progression than early onset subtypes.

Life Expectancy

The life expectancy for individuals with Krabbe disease can vary widely. Life expectancy depends on several factors, including the timing of diagnosis, the treatment regimen, the severity of the disease, age at onset, and the presence of any complications or additional health conditions. Your medical team will provide you with the most accurate and up-to-date information on life expectancy.

Inheritance Pattern

Krabbe disease is a genetic disease

This means an individual inherits it from their parents. In order to have Krabbe disease, an individual receives one copy of each non-working GALC gene from each parent.

How is Krabbe disease inherited?

Working GALC Gene

Non-working GALC Gene

One working gene makes enough GALC enzyme to prevent symptoms

Outcome = NO disease

Non-working GALC Gene

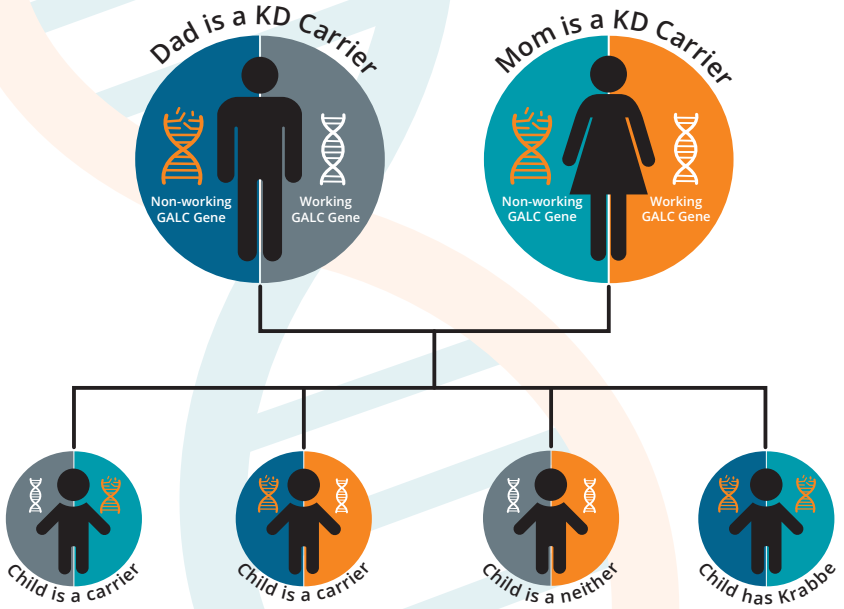
Non-working GALC Gene

No working gene means the body can't make GALC causing symptoms

Outcome = DISEASE

Inheritance Pattern

Krabbe disease is inherited in an autosomal recessive pattern



75% chance each pregnancy will not have Krabbe disease	25% chance each pregnancy will have Krabbe disease

Should my family be tested?

There are genetic counselors who can help you understand the risk in your family.

- They may recommend further genetic testing for you, your partner, or your children.
- There are organizations and programs that provide genetic counseling and genetic testing.

INVITAE

Visit Invitae to learn about genetic testing and counseling

National Society of Genetic Counselors

Visit National Society of Genetic Counselors to talk to a gentic counselor about your family

Patient journey for a loved-one born with Krabbe disease

The Patient Journey Map shown below demonstrates two milestone pathways in Krabbe disease and the steps along the way.

- The symptomatic pathway relates to patients and families who receive a diagnosis with the presentation of clinical symptoms such as severe acid reflux, stiff muscles, seizure, loss of growth milestones, lower limb weakness and more.
- The pre-symptomatic pathway relates to patients identified through newborn screening or those with a prior family history.

Krabbe disease is a challenging condition in both the symptomatic and pre-symptomatic path but support is available at each step along the way.

Patient Journey

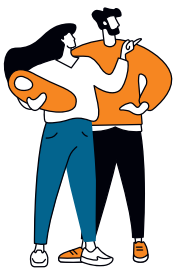
STEP 1
Diagnosis

SYMPTOMATIC PATHWAY

- Patient presents with clinical symptoms
- Lab tests are needed to confirm the diagnosis and the parent's gene mutation/variant for Krabbe disease (genetic test)

PRE-SYMPTOMATIC PATHWAY

- Identified via newborn screening state lab test
- Prior family history of Krabbe disease
- Lab tests are needed to confirm the diagnosis and the parent's gene mutation/variant for Krabbe disease (genetic test)



STEP 2
Connect with a Krabbe Expert

- Determine eligibility for treatment
- Patient undergoes additional testing to determine the type of Krabbe
- Krabbe disease expert and family discuss evaluation results to determine treatment options and management of disease

STEP 3
Disease Management

Supportive Care

- Establish a Primary Care Physician
- Establish a care team and support system
- Inquire with social workers and physicians about funding sources for out- of-pocket medical expenses
- Learn about Krabbe disease from reputable sources
- Stay informed about clinical trials and treatment

Treatment

- A bone marrow or cord blood transplant may stabilize disease progression
- A transplant may improve outcomes in patients if treatment begins before the onset of symptoms
- Clinical trials and new therapies may provide other treatment options.

Monitoring

- Depending on disease type, patients may need to be evaluated routinely for disease progression

How is Krabbe disease diagnosed?

Diagnosing Krabbe disease early is important for families. There are more options for clinical and supportive management of Krabbe disease if diagnosed early (ideally before birth, through NBS, or shortly after symptom onset).

NEWBORN SCREENING TESTS (NBS) are tests that occur shortly after birth to determine if a child has certain health conditions. This blood test can identify Krabbe disease before a child experiences signs and symptoms. NBS for Krabbe disease is available in the United States, however not all states mandate screening for the disease. NBS for Krabbe disease outside of the United States is rare.

AFTER SIGNS AND SYMPTOMS: If a child with Krabbe disease is not diagnosed as a newborn and starts to show signs and symptoms of nervous system damage, doctors will perform blood tests (which may include genetic tests) to confirm the diagnosis.

BEFORE BIRTH: If a doctor suspects that a child could be at risk for Krabbe disease before birth, they can perform genetic tests to see if the child has inherited the disease. This testing does not tell the doctor when a child may start to show signs and symptom.

How is Krabbe Disease Treated?

- Hematopoietic stem cell transplantation (HSCT) emerged in the late 1990s as a potential treatment for Krabbe disease.
- HSCT is a treatment that works best if done before onset of symptoms.
- It uses healthy cells to replace the missing GALC enzyme to ideally slow disease progression, helping loved-ones with Krabbe disease to live longer.
- Early testing such as NBS is important for HSCT to work best.
- Although HSCT is the mainstay treatment for Krabbe disease, ongoing research in gene therapy is showing promising results https://krabbeconnect.org/research-studies-trials/krabbe-clinical-trials/.
- In the US, HSCT has been used in children with Krabbe disease when:
  - Diagnosed with infantile onset in the first 30 days of life.
  - Diagnosed with later-onset types and the symptoms are mild.

Who is the care team?

Geneticist: A doctor/team who helps diagnose the disease, explains how it is inherited and provides advice for families.

Neurologist: A doctor who treats problems with the brain and nerves caused by Krabbe disease.

Hematologist/Transplant: A doctor who will oversee and decide the best options for HSCT.

Developmental Pediatrician: A doctor trained in diagnosing and treating special health needs. They are instrumental in making referrals to specialists.

Gastroenterologist/Dietician: These specialists help with eating problems and ensure the patient is receiving enough nutrition.

Physical, Occupational, and Speech Therapists: These therapists help with moving, talking and swallowing, making it easier for the patient to engage in everyday activities.

Pulmonologist: A doctor who helps with breathing problems that can happen as the disease progresses.

Palliative Care Physician: A physician that manages symptoms like pain, seizures, and feeding issues while supporting the patient and family emotionally. They focus on holistic and compassionate support when coordinating care, guiding treatment decisions, and ensuring comfort.

What else can the care team do for a family and loved-one with Krabbe disease?

- Provide treatment that addresses the underlying cause of the disease
- Offer supportive or palliative care to relieve symptoms
- Provide medications to reduce symptoms such as pain, digestive difficulties and seizures

But what if available treatments are not right for our family due to:

- Religious beliefs
- Insufficient support mechanisms for parents and siblings
- Inability to "relocate" for ~6 months or more to be at a Center of Excellence
- Financial hardship

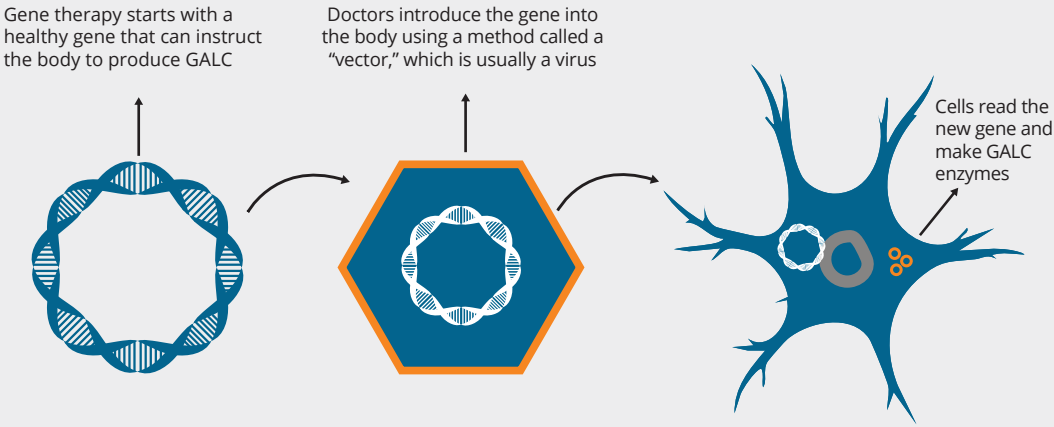
Krabbe disease is a complex condition, and there is no one-size-fits-all approach to managing it. Each family must make decisions based on their values, beliefs, and unique circumstances. If you need additional support, please don't hesitate to reach out to KrabbeConnect. However, please note that KrabbeConnect's goal is to provide unbiased information; the final decision lies with the family and their care team.

With limited treatment options, it is important to consider the role of clinical trials

Clinical trials are essential for making potential treatments available for all types of diseases, including rare ones.

- There are many treatments being studied that could help loved-ones with Krabbe disease - even those who are not eligible for stem cell transplantation.
- The medicines being studied seek to be disease-modifying, meaning they help the body produce enough GALC.
- Your loved-one may be eligible to participate in a clinical trial for Krabbe disease and receive treatment that could help them.
- It is important to learn about the requirements and risks associated with the individual trials being conducted.
- To learn more about Krabbe disease clinical trials, visit **clinicaltrials.gov or KrabbeConnect.org**

The Basics of Gene Therapy and How it Works



Gene therapy is often given to people through different types of injections. Talk to your doctor about the different ways gene therapy may be given to a loved-one with Krabbe disease

Services and Resources Provided by KrabbeConnect

PATIENT SUPPORT TEAM: Connect with an easy-to-talk to parent, sibling, or grandparent who is experienced with the Krabbe disease journey.

PATIENT ASSISTANCE PROGRAM: A program that offers financial support for Krabbe disease families in need.

PARTNER WITH US PROGRAM: A unique program to help families establish a fund, utilizing KrabbeConnect's non-profit platform, to aid advances in research or patient care in Krabbe disease.

PATIENT JOURNEY AND RESOURCE MAPS: Easy to read maps meant to give newly diagnosed families and those working in the medical community the ability to comprehend their treatment options and quickly navigate support resources in a small amount of time.

WEBINARS AND VIDEOS: A program that works to keep patients, caregivers, industry partners, and the medical community informed about Krabbe disease.

NEWBORN SCREENING (NBS): A program that works to inform families about the importance of newborn screening, provides state-by-state Krabbe disease NBS insights, and works to advocate for the inclusion of Krabbe disease screening in worldwide.

#curekrabbe Shop: A program to help spread Krabbe disease awareness by purchasing #curekrabbe apparels and gifts.

Please visit KrabbeConnect.org for more information about any of the above programs.

"We make a living by what we get ... but we make a life by what we give." *Winston Churchill*

KrabbeConnect
CONNECTING PATIENTS & RESEARCH

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Glossary of Terms

A

Autosomal Recessive Disease – A disease that is only developed by a person when they inherit one copy of a mutated gene from each parent.

C

Carrier – An individual with a mutated gene whose child can inherit the mutation. A carrier may or may not show symptoms of the condition associated with the mutation.

Cell - A unit that makes up all living things and body parts. Cells provide structure for the body, take in nutrients from food, and perform tasks that help the body work properly.

Clinical Trial – A study designed to evaluate the safety, effectiveness, and dosing of a new treatment in people.

D

Demyelination – The loss of the protective coating of nerve cells called myelin.

Disease Onset – The first time a disease starts to affect a person's health with signs or symptoms.

DNA - The code that instructs cells how to work. DNA is the hereditary material that is in every cell of the body.

E

Enzyme – A substance in the body that helps bring about chemical reactions.

G

Galactolipids – A cell component comprised of a lipid (fat) and a carbohydrate (sugar) found in the nerve cell membrane.

Galactosylceramidase (GALC) – An enzyme responsible for breaking down a type of waste in cells called galactolipids.

Genes – Sections of DNA that determine specific genetic traits.

Gene Therapy – A medical approach where an individual gene is introduced to the body to correct a genetic disease.

Genetic Disease – A disease caused by one or more genetic mutations.

Glossary of Terms

Genetic Mutation – A change in the code of a specific gene.

H

Hematopoietic Stem Cell Transplant (HSCT) – Introducing a healthy, immature blood cell into the body to replace unhealthy stem cells, allowing healthy cells to form and work properly. There are risks associated with HSCT, and infants with Krabbe disease who benefit from stem cell transplants may still experience disease progression, such as difficulties with speech, walking, and other motor skills.

M

Myelin – A substance that forms a protective layer around nerve cells. Myelin helps signals travel throughout the brain and spinal cord.

N

Neurodegeneration – The loss of the structure and ability of nerves to work.

P

Palliative Care – Specialized medical care for people living with serious illnesses focused on providing the best quality of life (often used interchangeably with supportive care).

Proteins – Particles that play many different important roles in the body. Proteins do most of the work in cells and make up much of the body's tissues and organs.

Psychosine – A galactolipid that is toxic to cells in large amounts. Psychosine builds up in the nervous system if GALC is not present.

S

Supportive Care – The prevention, management, and treatment of disease symptoms, with the goal of improving quality of life, often referred to as palliative care.

Please visit https://krabbeconnect.org/glossary/ for more information about other terms you may want to be aware of when you speak with your care team.