GM1 Gangliosidosis

Disease information for patients and families

PassageBio

Understanding GM1 Gangliosidosis

A rare, inherited disease that causes a variety of symptoms

GM1 gangliosidosis is a genetic disorder that occurs when a person has very low amounts of a vital enzyme, β-galactosidase (referred to as β-gal). This enzyme affects nerve cells (called neurons) in the brain and spinal cord, components of the central nervous system (CNS). This results in a number of symptoms that may lead parents to believe that their child needs medical attention.

The earlier signs and symptoms of GM1 gangliosidosis include:

- Poor feeding/ appetite
- Difficulty sitting up and crawling
- Difficulty swallowing
- Seizures
- Failure to thrive
- Poor muscle strength
- Difficulty breathing
- Non-responsiveness

GM1 gangliosidosis is most common and severe in babies younger than 1 year old. It is also important to understand that anyone born with GM1 gangliosidosis has low amounts of β-gal, even if symptoms do not appear until later in childhood.

GM1 gangliosidosis is estimated to affect 1 in 100,000 to 200,000 babies born worldwide

Understanding the Different Types of GM1 Gangliosidosis

The disease is more common in infants and toddlers, but it can affect people of all ages

GM1 gangliosidosis impacts people differently based on the age at which symptoms appear and how severe they are.

- The severity of GM1 gangliosidosis is generally determined by how much of the β-gal enzyme is active within the cell
- There is usually less β-gal activity in the youngest patients, which means they generally will have a more severe form of the disease

Types of GM1 Gangliosidosis

Early onset infantile (Type 1)

- The most common, severe, and progressive form of the disease
- Symptoms appear by 6 months of age
  - Include limpness (called “hypotonia”), delays in development, feeding difficulties, and skeletal abnormalities
- Damage to the CNS occurs rapidly, with the inability of muscles to relax, deafness, and blindness often seen by 1 year of age

Late onset infantile (Type 2a)

- Symptoms occur between 6 months and 2 years of age
  - Include seizures, a lag in motor and learning skills, failing to meet developmental milestones, and/or losing of milestones that have been achieved
- Overall, symptoms are similar to those of Early Onset Infantile GM1 gangliosidosis, but disease progression is slower

Juvenile (Type 2b)

- Symptoms appear from 2 to 5 years of age
  - May include abnormalities in movement, a change in the ability to speak clearly, and abnormal eye movements

Adult (Type 3)

- Symptoms may appear at 5 years of age or older, although they may appear in the 20s and 30s
  - Often include weakness in the arms and legs that progresses over time, leading to the inability to walk without assistance and slurred speech

Understanding What Causes GM1 Gangliosidosis

The disease is referred to as a “lysosomal storage disorder”

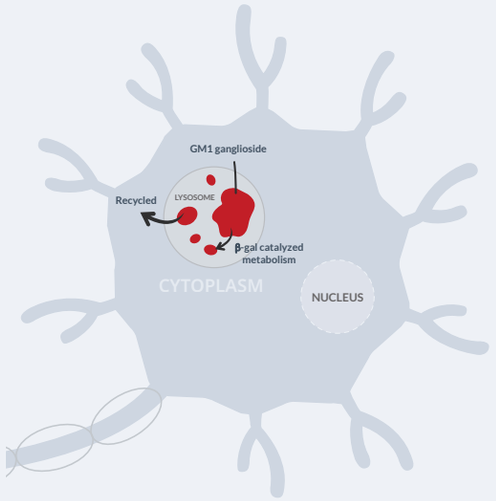
GM1 gangliosidosis, like other diseases in this group of disorders, involves small compartments within cells, ie, nerves, liver, heart, etc. (called lysosomes). Lysosomes contain various enzymes that break down (or metabolize) larger molecules into smaller components for reuse or recycling elsewhere in the cell. This avoids the buildup of too many of these components within the cell.

In GM1 gangliosidosis, the function of lysosomes is disrupted by genetic mutations

The galactosidase beta 1 (*GLB1*) gene provides the cells of the nervous system with instructions on how to make the enzyme β-gal.

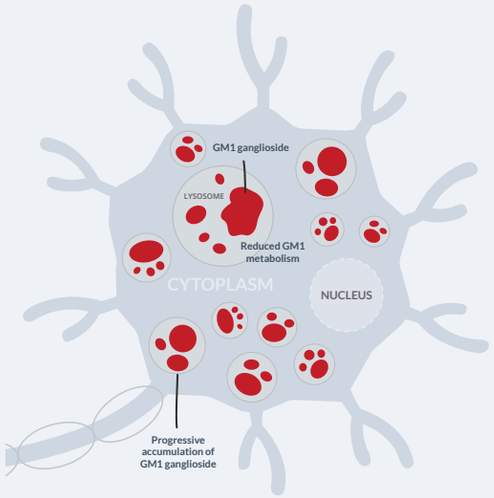
- The body needs β-gal to process a key fatty acid (or lipid) known as GM1 ganglioside
- Without enough of the β-gal enzyme, GM1 ganglioside builds up to harmful levels within the lysosomes in the nerve cells and other body tissues
- Accumulation of lipids within the lysosomes ultimately destroys nerve function
- Lack of β-gal can also lead to buildup of other damaging substances in the eyes, heart, bones, liver, and spleen

Lysosomal accumulation of GM1 gangliosides in the CNS



Healthy nerve cell with normal function

In patients with healthy *GLB1* genes, there is enough β-gal enzyme to metabolize GM1 ganglioside and keep them at normal levels so the neurons can function properly.



GM1 gangliosidosis nerve cell with harmful buildup

In patients with *GLB1* gene mutations, GM1 ganglioside builds up over time to harmful levels. This results in the death of the cell, which leads to the decline of nerve function and the onset of disease symptoms.

Understanding Who Is at Risk of GM1 Gangliosidosis

The disease is passed down from parents to their children

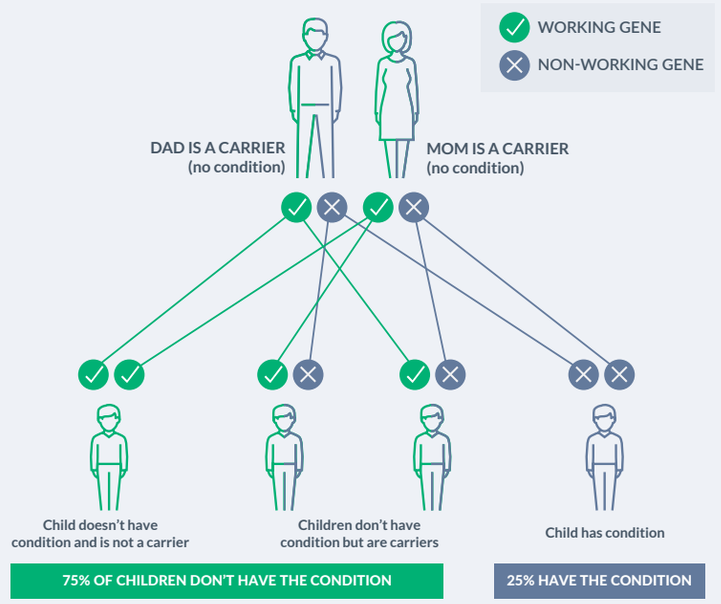
Every person has two copies of the *GLB1* gene. If one of those two copies is a mutation, the person is a "carrier" of GM1 gangliosidosis.

In a carrier, the one remaining normal copy of the *GLB1* gene is sufficient to produce enough β-gal for normal functioning. This means the carrier may not have the symptoms of the disease.

But if both parents are carriers there is a...

- 25% chance for the child to receive two functioning copies of the healthy gene and not have GM1
- 50% chance for the child to be a carrier but not have GM1
- 25% chance for the child to receive TWO mutated copies of the *GLB1* gene, which means the child would have GM1

How GM1 gangliosidosis is inherited from parents



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Understanding How GM1 Gangliosidosis Is Diagnosed

Early diagnosis is critical due to rapid nervous system progression

The presence of GM1 gangliosidosis symptoms indicates that there is ongoing, progressive disease activity. This is why early diagnosis is so important, especially for patients with the more progressive infantile types of the disease.

Signs that may lead to a diagnosis of infantile forms of GM1 gangliosidosis

The process often begins when parents or physicians notice symptoms that are commonly associated with the disease, such as poor muscle strength, limpness, the inability to sit up and crawl, poor feeding and failure to thrive, and the presence of a “cherry red spot” in the back of the eye that is seen during an eye exam.

Signs that may lead to a diagnosis of juvenile or adult GM1 gangliosidosis

GM1 gangliosidosis should be considered when there is new or worsening muscle weakness, slurred speech, lack of balance or coordination, other movement disorders, and/or a reduced ability to learn or comprehend.

Tests Used in Diagnosing GM1 Gangliosidosis

If a doctor suspects that a patient has GM1 gangliosidosis, he or she has a number of tests that can be used to confirm a diagnosis.

Various forms of imaging

- Neuroimaging to visualize the nervous system structure and function
- Other imaging techniques, including X-rays, abdominal ultrasound, and echocardiogram

Blood tests

- Used to evaluate patient's level of β-gal activity

Genetic testing

- Used for determining if there are mutations in the *GLB1* gene

Once a doctor confirms a diagnosis of GM1 gangliosidosis, care then occurs with an interdisciplinary team of specialists who will follow the patient over a longer period of time.

Specialists involved in the care of a patient with GM1 gangliosidosis

- Neurologist
- Developmental pediatrician
- Gastroenterologist
- Cardiologist
- Physiatrist/Physical therapist
- Geneticist or metabolic specialist
- Ophthalmologist
- Pulmonologist
- Orthopedist
- Audiologist/Ear, nose, and throat specialist

How GM1 gangliosidosis is managed once diagnosis is confirmed

Currently, there are no approved disease-modifying treatments available for GM1 gangliosidosis.

- Patients are managed with symptomatic and supportive care
- Early diagnosis is critical due to the rapid neurodegeneration caused by this disease

Resources for Families and Patients

Advocacy organizations

Cure GM1 Foundation

A nonprofit patient advocacy group that provides support and resources for families caring for a child with GM1 gangliosidosis.

National Tay-Sachs & Allied Diseases Association (NTSAD)

A nonprofit patient advocacy group that is focused on research, forging collaboration, fostering community, and supporting families.

Passage Bio Is Committed to Transforming Lives

Patients drive every decision we make, from which therapies to pursue to how we will pursue them. We focus on developing effective treatments that are desperately needed for CNS disorders, like GM1 gangliosidosis.

We believe that collaboration is important. We are committed to working with patient advocacy groups that are also committed to transforming lives.

For more information about Passage Bio and our work to develop an effective treatment for GM1 gangliosidosis, please visit us at ***PassageBio.com***.

If identified quickly, patients with GM1 gangliosidosis may be eligible for clinical trials, so early diagnosis is critical.

If you would like more information, please talk with a healthcare professional or send inquiries to Passage Bio at *patientservices@passagebio.com*.

One Commerce Square
2005 Market Street, 39th Floor
Philadelphia, PA 19103
www.passagebio.com

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