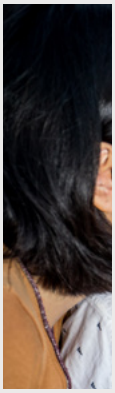
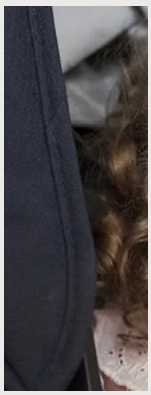
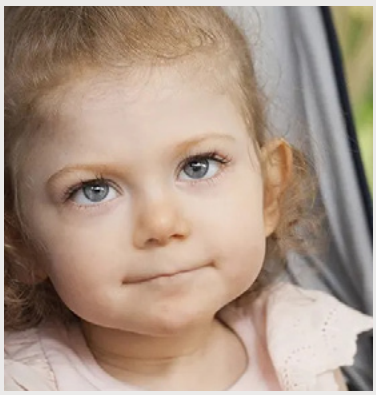
grace science foundation

NGLY1 DEFICIENCY



A guide for patients, families, and caregivers





Welcome

Dear Member of the NGLY1 Deficiency Community,

You are likely reading this booklet because NGLY1 Deficiency has touched your life. If you are uncertain what a diagnosis of NGLY1 Deficiency means, we hope this guide will give you some answers.

Inside you'll find information about the cause, symptoms, diagnosis, and management of NGLY1 Deficiency. We also provide resources to help on your journey, as well as updates on the progress toward potential therapies.

This guide was written by a team of NGLY1 Deficiency experts, including physicians, scientists, genetic counselors, and patient advocates associated with Grace Science Foundation, a nonprofit research and patient advocacy organization founded in 2014 to understand and cure NGLY1 Deficiency as well as to promote community development. We are in contact with over 70 families (representing 24 different countries) with a confirmed diagnosis of NGLY1 Deficiency.

For more information about our global community, please visit **gracescience.org** or contact us at **info@gracescience.org** or **650-746-4591**.

Sincerely,
Kristen & Matt Wilsey
Co-Founders,
Grace Science Foundation

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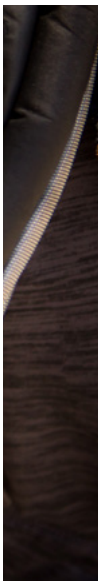
Introduction to NGLY1 Deficiency



What is NGLY1 Deficiency?

Condition Overview

NGLY1 Deficiency (pronounced N-*Gly*-One) is an ultra-rare, neurodevelopmental disorder caused by mutations in the *NGLY1* gene. Symptoms typically present in infancy and affect multiple systems in the body. Individuals are diagnosed through a combination of genetic (DNA) testing and clinical evaluation. Characteristic features of NGLY1 Deficiency include, but are not limited to:

- Global developmental delay and / or intellectual disability
- Involuntary movements (hyperkinetic movement disorder)
- Poor tear production (alacrima)
- Signs of liver dysfunction (elevated transaminases)
- Nerve damage (peripheral neuropathy)

Specific symptoms and their severity may differ between individuals with this condition, and disease progression varies.

While the expected lifespan is unknown, the oldest patient known to Grace Science Foundation is 40 years old. As of May 2022, over 100 cases have been identified worldwide through Grace Science Foundation and scientific publications.

Individuals with NGLY1 Deficiency have relatively strong social skills and have been described as having happy demeanors and a love of listening to music. Because there is currently no cure for NGLY1 Deficiency, care focuses on managing symptoms and supportive therapies to help individuals reach their full potential.

Grace Science Foundation is funding researchers throughout the world to better understand the disease and find possible treatments. A gene therapy for NGLY1 Deficiency is in development by Grace Science, LLC (gracescience.com), a biotechnology company founded in 2017.

What causes NGLY1 Deficiency?

An Introduction to the Genetics of NGLY1 Deficiency

NGLY1 Deficiency is caused by changes, or mutations, in the *NGLY1* gene. NGLY1 is one of roughly 20,000 genes found in the cells of the human body.

Genes contain the instructions for making our bodies develop and function, and are passed down from parent to child. Each of us has two copies of almost every gene — one inherited from our biological mother and one from our biological father.

NGLY1 Deficiency occurs when an individual inherits one mutation in the *NGLY1* gene from each parent, meaning both copies of their *NGLY1* gene carry a mutation. This pattern is called autosomal recessive inheritance.

What Does it Mean to be a Carrier of NGLY1 Deficiency?

- Being a carrier of NGLY1 Deficiency means that an individual has ("carries") a mutation in one of their two *NGLY1* genes.
- Carriers do not show symptoms of NGLY1 Deficiency.
- Grace Science Foundation can provide resources about genetic counseling and testing for family members who want to know if they are carriers for NGLY1 Deficiency (carrier screening).

What Does that Mean for Parents Who are Both Carriers?

- There is a **1 in 4 (25%)** chance of having an unaffected child who is not a carrier of NGLY1 Deficiency.
- There is a **2 in 4 (50%)** chance of having an unaffected child who is a carrier of NGLY1 Deficiency.
- There is a **1 in 4 (25%)** chance of having a child affected by NGLY1 Deficiency.

Autosomal Recessive Inheritance

Diagram shows the possible outcomes when both parents carry an *NGLY1* mutation. There is a 25% chance of having an unaffected child with two normal *NGLY1* genes (left), a 50% chance of having an unaffected child who also is an *NGLY1* carrier (middle), and a 25% chance of having an affected child with two mutations in *NGLY1* (right).

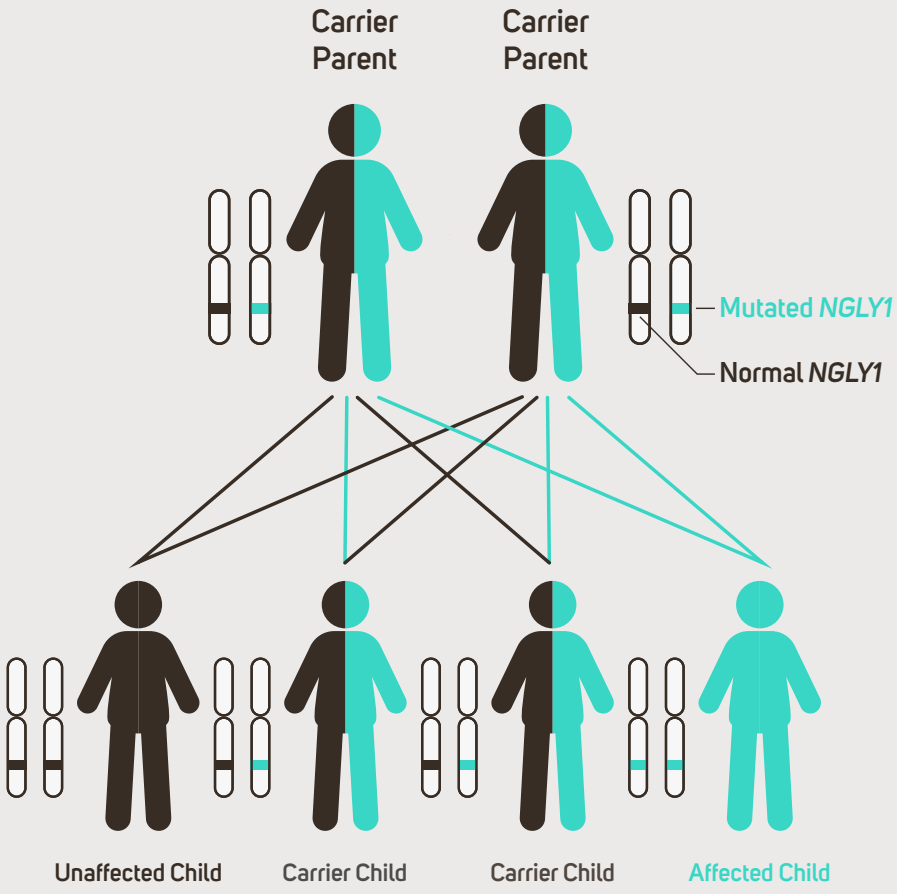


Figure 1. Autosomal Recessive Inheritance

What Does the *NGLY1* Gene Do?

Most genes provide instructions for creating proteins that play a critical role in many functions of the body. The *NGLY1* gene encodes the **N-glycanase 1** protein ("NGLY1" comes from **N-gly**canase **1**).

The **N-glycanase 1** protein removes sugars (glycans) from other proteins. It removes the sugar from abnormal (misfolded) proteins that need to be broken down and recycled by the cell. **N-glycanase 1** also removes the sugar from a specific protein called Nrf1 involved in a cell's response to stress.

N-glycanase 1 may also have other biological purposes that have not yet been identified. The exact manner in which its absence or loss of function causes the symptoms of NGLY1 Deficiency is not fully understood.

While **N-glycanase 1** is responsible for removing sugars from other proteins (**deglycosylation**), there are hundreds of genes that provide instructions for the opposite process, attaching sugars to proteins (**glycosylation**). Mutations in any one of these genes cause congenital disorders of glycosylation (CDG). For this reason, NGLY1 Deficiency should not be confused with a CDG.

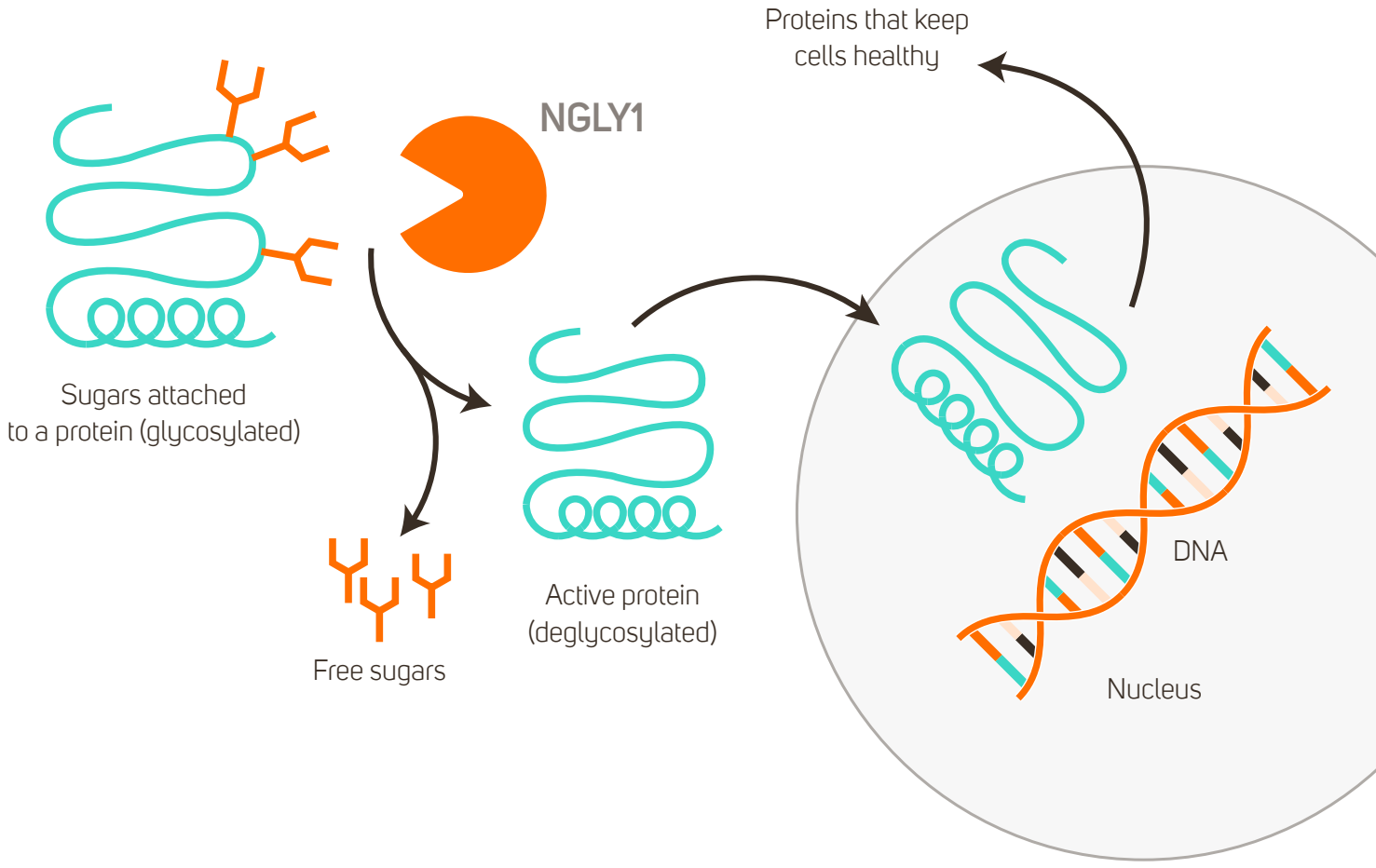


Figure 2. The N-glycanase 1 enzyme removes sugars from other proteins

Symptoms & Diagnosis

What does NGLY1 Deficiency look like?

Signs and Symptoms

NGLY1 Deficiency is a multisystemic disease that primarily affects the brain, nerves, muscles, digestive tract, liver, and eyes.

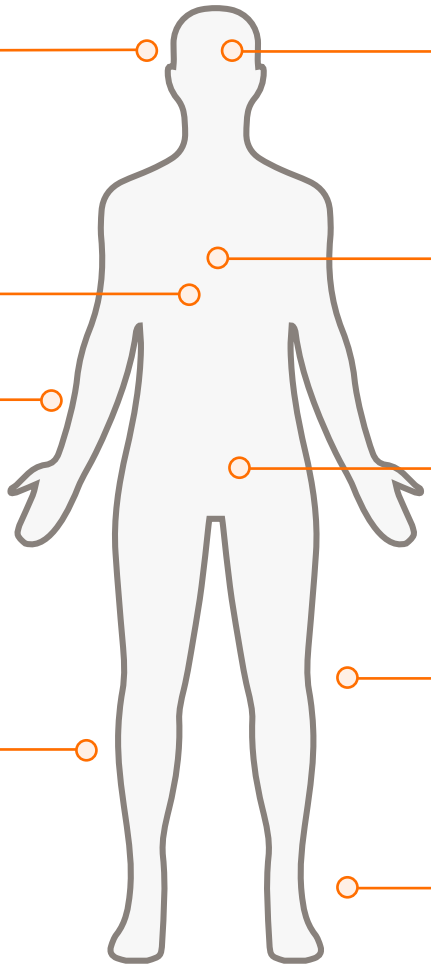
Symptoms and their severity vary between patients, but the most common symptoms are explained in the diagram below.

Global developmental delay and/or intellectual disability
- delays in reaching cognitive and motor milestones like learning to talk and walk

Elevated liver enzymes (*transaminitis*)
- a sign of liver dysfunction

Seizures
- seizure types include sudden, jerky spasms (*myoclonic seizures*), staring spells (*absence seizures*), sudden loss of muscle strength called drop episodes (*atonic seizures*), or other seizure types

Movement disorder
- unusual movements that may be described as jerky, involuntary movements (*hyperkinetic*), poor muscle control (*ataxia*), tremors, or repetitive muscle contractions (*dystonia*)



Lack of tears (*alacrima*) or poor tear production (*hypoalacrima*)
- chronically dry eyes that can lead to vision impairment over time if untreated

Feeding difficulties and severe constipation
- difficulty swallowing (*dysphagia*), challenges getting adequate nutrition and maintaining a healthy gut

Difficulty maintaining weight (*failure to thrive*)
- many patients struggle to maintain weight after middle childhood (*roughly after age 11*)

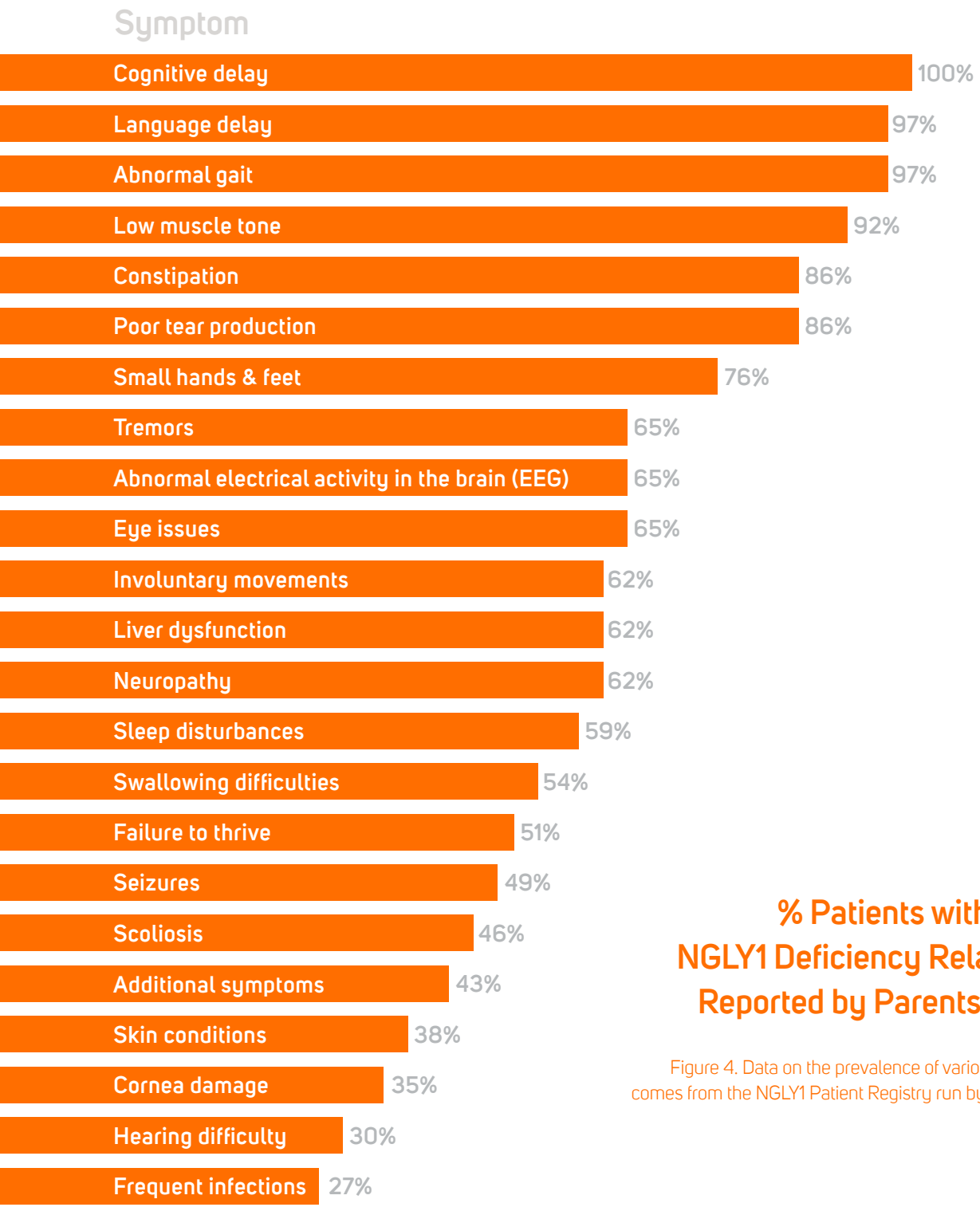
Low muscle tone (*hypotonia*)
- lack of tension in muscles that is needed to maintain position; described as "floppy," because limbs and head may appear limp

Damage to nerves (*peripheral neuropathy*)
- decreased ankle reflexes, numbness or weakness

Figure 3. Diagram of important NGLY1 symptoms to know

Which Symptoms are Most Common?

The Grace Science Foundation collects data on NGLY1 patient symptoms. The diagram below highlights the percentage of patients surveyed (N = 37) with various NGLY1 Deficiency symptoms.



% Patients with various NGLY1 Deficiency Related Symptoms Reported by Parents or Caregivers

Figure 4. Data on the prevalence of various NGLY1-related symptoms comes from the NGLY1 Patient Registry run by the Grace Science Foundation

How is NGLY1 Deficiency diagnosed?

When making a diagnosis, doctors assess a patient's symptoms, genetic testing results, and other clinical tests, such as laboratory results.

Types of Genetic Testing

A definitive diagnosis is made through molecular genetic (DNA) testing. The genetic test is ordered by a doctor, who may order a gene panel, whole exome sequencing (WES), or whole genome sequencing (WGS). Each of these tests reads through parts (gene panel & WES) or all (WGS) of an individual's genetic code to detect changes.

Interpreting Changes in the Genetic Code

Genes are made of a long code of DNA bases (A, T, C, & G) arranged in a specific order.

Most changes in DNA, or variants, do not cause disease. As an analogy, consider the word "gray," which can also be spelled "grey" — though different, the meaning of the word remains the same. Similarly, variants that do not alter the function of the gene reflect the normal human variation that makes each person unique.

Understanding Mutations

However, some variants are like a spelling error that disrupts the meaning of a word. For example, "griy" no longer holds the same meaning as "gray." These harmful changes in DNA that cause disease are called mutations. Currently, approximately 60 unique mutations in the *NGLY1* gene have been detected in patients with NGLY1 Deficiency.

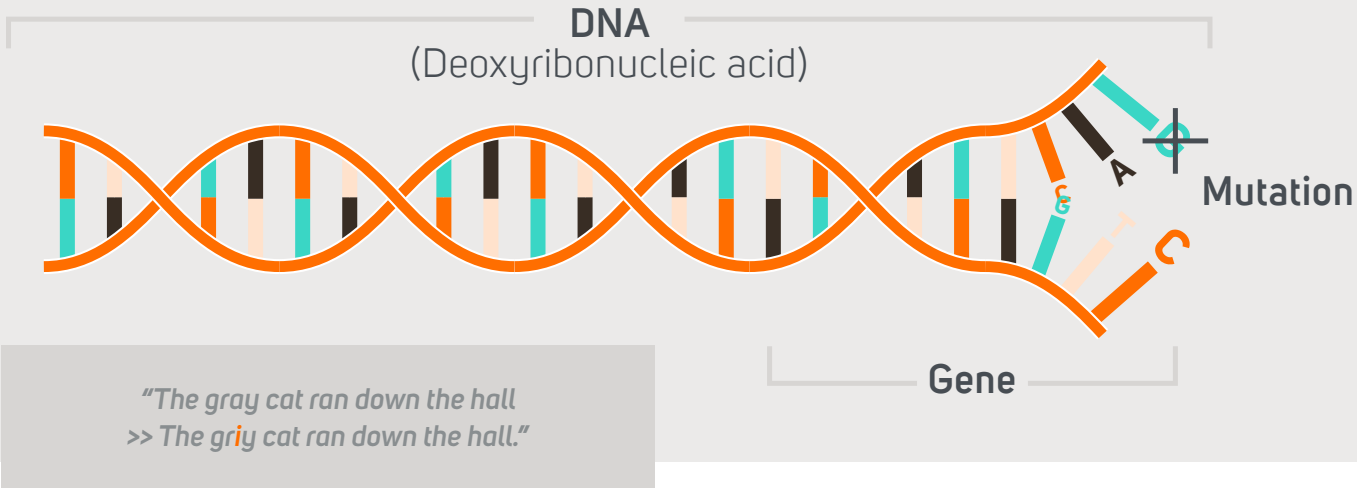


Figure 5. Similar to how a spelling error can disrupt the meaning of a word, a mutation in the DNA code can disrupt the function of a gene

Common Challenges to Confirming a Diagnosis of NGLY1 Deficiency

Variants of uncertain significance (VUS)

If a variant in the *NGLY1* gene is found that has not been detected in another patient before, it can be unclear whether it causes disease. These changes in DNA are called a variant of uncertain significance (VUS).

Only one copy of the *NGLY1* gene has a mutation

Sometimes, a mutation in only one copy of the *NGLY1* gene is detected. This may occur because technology is not able to detect a mutation in the second copy or the patient really only has one *NGLY1* gene that has a mutation.

Unclear inheritance pattern

If the biological parents have not had genetic testing, it is more challenging to know whether one mutation was inherited from the biological mother and one mutation was inherited from the biological father.

Additional Steps if You Do NOT Have a Confirmed Ddiagnosis

Genetic testing for family members

Testing biological parents in addition to the patient ("trio testing") can be an important step to interpreting the inheritance pattern and any variant of uncertain significance.

Biomarker testing

Doctors can also measure biomarkers, which are molecules in the body that can indicate disease. For example, elevated blood sugar is a biomarker for diabetes. Patients with NGLY1 Deficiency may have elevated aspartylglucosamine (GNA), a small protein-sugar fragment. When the N-glycanase 1 protein is missing or not working correctly, GNA can be detected in the blood. Elevated GNA alone is not enough to confirm a diagnosis of NGLY1 Deficiency, but in combination with genetic testing and the presence of suggestive symptoms, it can provide support for this diagnosis.

Contact us at **info@gracescience.org** for more information on a screening test that can detect GNA in patient samples.

Current Management & Future Therapies

What care do patients with NGLY1 Deficiency typically need?

There is currently no approved treatment or cure for NGLY1 Deficiency. Care focuses on managing individual symptoms, specialized therapy plans, and improving quality of life.

Because the presence and severity of symptoms varies among patients with NGLY1 Deficiency, they might not need all of the care mentioned below, or they might have additional care needs.

Keep in mind that while doctors are experts in particular areas of care, a parent or caregiver is an expert on their child. If a new or changing symptom is identified, always let your care team know.

Specialist Care

Because NGLY1 Deficiency affects many systems in the body, patients often need a large team of clinicians.

Physicians

Neurologists
manage issues related to the brain and nerves, such as movement disorder symptoms and seizures.

Gastroenterologists
assist with feeding difficulties, nutrition, and constipation.

Orthopedists
help treat skeletal differences such as scoliosis or joint contractures.

Medical geneticists
evaluate and treat conditions with genetic causes.

Ophthalmologists
treat eye complications.

Endocrinologists
specialize in health problems due to body's hormones.

Otolaryngologists (ENT)
aid in swallowing difficulties.

Hepatologists
attend to issues involving the liver.

Pulmonologists
ease issues related to lungs or breathing.

Sleep specialists
regulate sleep patterns.

Below is a list of the types of specialists and healthcare providers commonly seen and what they do:

Therapists, Counselors, and other Healthcare Providers

Genetic counselors
interpret the meaning of genetic information for patients and families and provide support to improve the lives of people impacted by genetic conditions.

Medical social workers
help navigate the healthcare system and provide support for coping with the emotional and physical demands of caregiving.

Speech-language pathologists
improve communication, either verbally or with augmentative and alternative communication (AAC) tools.

Occupational therapists
build skills for daily living such as self-feeding and self-care.

Physical therapists
instruct movements to build strength and functional mobility.

Audiologists
evaluate hearing difficulties.

Respite Caregivers
give the primary caregivers a short break.

Therapies are important for helping patients reach their full potential and improve their quality of life. Families have reported physical therapy and hippotherapy (a specialized form of physical, occupational, and speech therapy using horses) have been particularly helpful.

Everyday Care

Children with NGLY1 Deficiency learn new skills at their own pace. While some learn to communicate verbally, many rely on alternative methods. Some children will walk independently, but many will need assistance either from caregivers or mobility devices.

Children with NGLY1 Deficiency require full-time care for all aspects of daily living including mobility, communication, feeding, and toileting.

Daily care routines may also include administering:

- Daily eye drops and ointments for lack of tear production
- Stool softeners and laxatives for constipation
- Supplements or over-the-counter vitamins
- Symptom-specific medications, such as anti epileptic drugs for seizures–*Contact us for a list of medications other families have tried and scientific paper(s) that could be shared with your care team*

There are many specialized tools that can make daily living easier, including:

- Splints, orthotics, or ankle foot orthoses (AFOs)
- Mobility devices such as standers, walkers, gait trainers, adaptive strollers, or wheelchairs–*An orthopedist, physical therapist, and / or occupational therapist can help to evaluate which device might work best*
- Augmentative and Alternative Communication (AAC) devices–*A speech & language pathologist can explain different types of devices and how to use them*
- Bath chairs and toilet chairs
- Adaptive utensils and feeding tools
- If needed, glasses, hearing aids, cooling vest (for temperature regulation), custom orthotic suits (for scoliosis), vibrating vest (for airway clearance)

All information, content, and material provided in this document is for informational purposes only and is not intended to serve as a substitute for the consultation, diagnosis, and/or medical treatment of a qualified physician or healthcare provider. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition.

School and Education

Children with NGLY1 Deficiency need an individualized education plan (IEP) to ensure the educational setting meets their needs.

While children with NGLY1 Deficiency will need extra support, there are still options to attend school in a variety of educational settings including:

- Public Schools
- Specialized Schools
- Adult Vocational Training
- Residential Care Centers

Possible Medical Procedures

Doctors may recommend certain procedures over time such as:

- Botox injections for muscle spasms or hypertonia (botox injections are very common in the calf muscles)
- Casting for joint contractures (tightening of the muscles, tendons, and ligaments around a joint that limits its ability to move)
- Surgeries for specific symptoms, such as spinal fusion surgery for scoliosis, heel cord lengthening surgery for mobility, or feeding tube placement for difficulty feeding

What therapies are on the horizon?

Gene Therapy

Gene therapy has been used to treat several genetic disorders with encouraging results and is a promising type of treatment being investigated for NGLY1 Deficiency. The basic goal of a gene therapy is to deliver a healthy copy of the gene causing disease. For NGLY1 Deficiency, that means delivering a healthy *NGLY1* gene.

A gene therapy can be delivered to the body either directly into the blood or directly into the fluid that circulates through the brain and spinal cord (the central nervous system, or CNS). Because NGLY1 Deficiency primarily causes neuromuscular symptoms, targeting the central nervous system is expected to provide the most benefit.

An investigational NGLY1 gene therapy is currently in the drug development stage at Grace Science, LLC. Results from non-clinical studies in the animal model of disease have been encouraging. Clinical trial planning is ongoing and projected to begin early 2023.

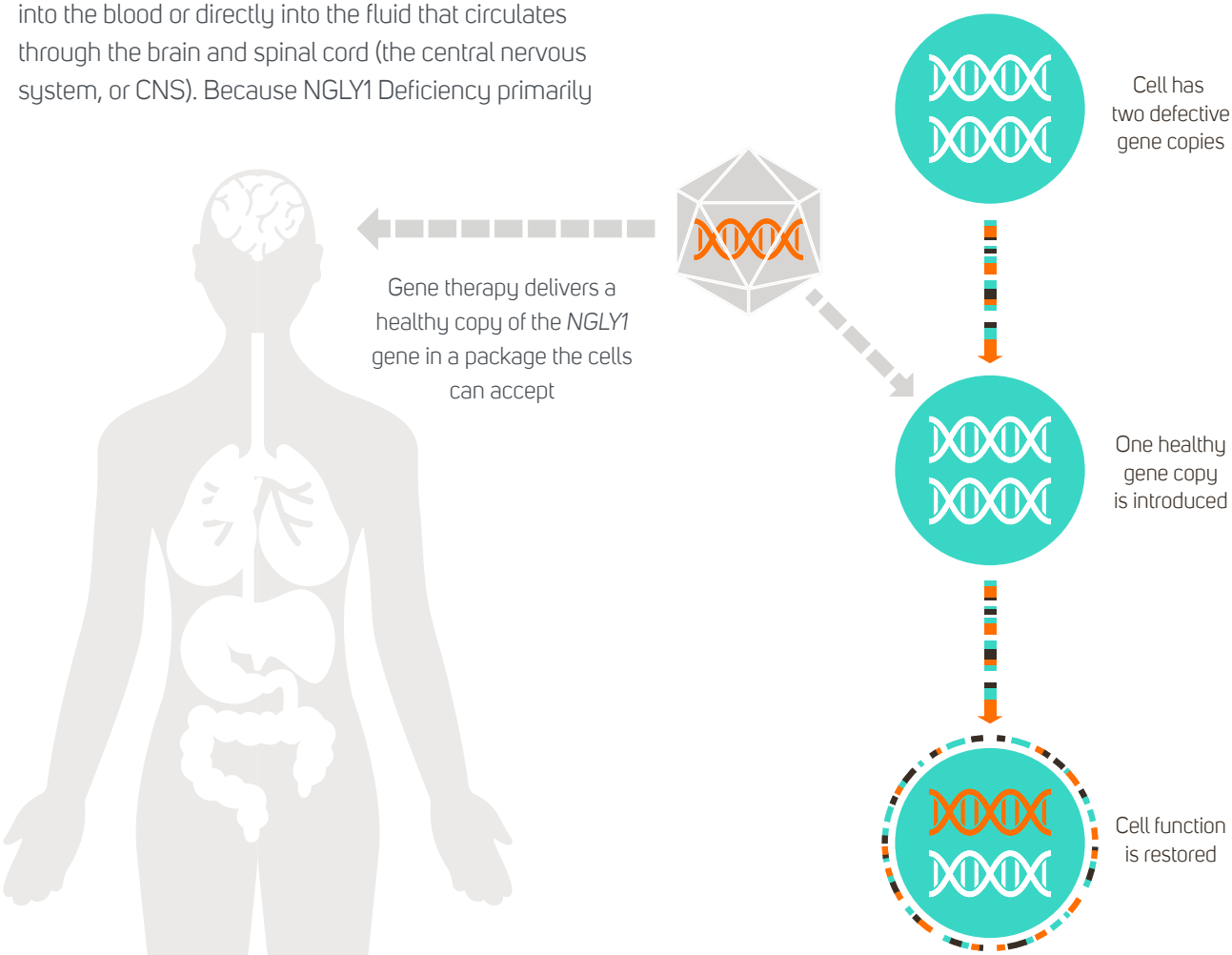
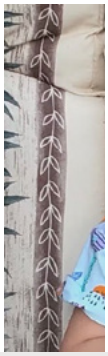


Figure 6. Gene Therapy aims to deliver a healthy copy of the *NGLY1* gene to cells that lack functional *NGLY1*

Resources for Families



What options exist for family planning?

Decisions about family planning are challenging for families affected by inherited conditions such as NGLY1 Deficiency. Some families find comfort in knowing there are multiple options available.

When planning for another child

In vitro fertilization (IVF) with preimplantation genetic testing (PGT-M)—Fertilization occurs in a lab where the embryo can be tested for the presence of NGLY1 mutations before being transferred to the uterus. PGT-M was formerly referred to as PGD (Preimplantation Genetic Diagnosis)

Adoption—Some families may want to consider adopting a child who needs a home.

If already pregnant

Prenatal genetic testing—A small amount of amniotic fluid can be taken from the mother's womb—a procedure called an amniocentesis — and tested to see if the fetus inherited mutations in both copies of the *NGLY1* gene. This information has helped existing NGLY1 Deficiency families prepare for having a child with special medical needs. It can also inform a family's decision to continue the pregnancy.

No testing—If someone does become pregnant, testing may not be the right choice for every family. They may continue the pregnancy regardless of prenatal test results or not want to know that information.

A preconception or prenatal genetic counselor can help facilitate discussions around family planning in the context of inherited conditions.

*The National Society of Genetic Counselors offers a **'Find a Genetic Counselor'** tool on its website. This can help people find a genetic counselor within the United States and Canada.*

What types of resources are available?

Being a caregiver for a child with complex medical needs poses unforeseen challenges and develops unrivaled resilience. You are not alone. There are many resources available to help families impacted by NGLY1 Deficiency.

Community Support

A dedicated, private family email group and a private Facebook group for parents of children confirmed to have NGLY1 Deficiency provide spaces for parents to pose questions, learn from each other's experience, and get support

Research Opportunities

Grace Science Foundation offers opportunities to contribute to research by:

- Hosting a patient registry to collect, store, and analyze information about as many NGLY1 Deficiency patients as possible.
- Maintaining a biorepository of patient samples for use in research.

Educational Materials

Informational webinars for parents and caregivers of individuals confirmed to have NGLY1 Deficiency are hosted by Grace Science Foundation every other month.

Additionally, Grace Science Foundation compiles and maintains a list that includes over-the-counter supplements and vitamins, eye treatments, and communication devices recommended by clinical experts in NGLY1 Deficiency.

Lastly, Grace Science Foundation has hosted Scientific and Family Conferences. We hope to see you at a future conference.

Visit **gracescience.org** or contact **info@gracescience.org** to learn more about the process to get connected with the NGLY1 Deficiency community and educational materials.

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Let's Stay Connected!

Grace Science Foundation is dedicated to finding a cure for NGLY1 Deficiency, as well as supporting families with this condition.

Submit questions, requests, or feedback here:
info@gracescience.org

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