

About NGLY1 Deficiency

A handbook for patients, families
and healthcare providers

NGLY1.org



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What is NGLY1 Deficiency?

NGLY1 Deficiency (or N-glycanase 1 Deficiency) is an ultra-rare genetic disorder characterized by movement disorder, global developmental delays, seizures, and lack of tears. It falls within the family of Congenital Disorders of Glycosylation (CDG), being the first known Congenital Disorder of Deglycosylation or CDDG.

As of January 2018, NGLY1.org, a leading patient support and research organization for NGLY1 Deficiency, is aware of 63 patients from a variety of geographic and ethnic backgrounds, with ages ranging from a few months to 22 years. Some symptoms caused by NGLY1 Deficiency are progressive. No cure is currently available.

Introduction

History

NGLY1 Deficiency was first described in a patient in 2012. Almost twenty years earlier in 1993, Japanese researcher Tadashi Suzuki identified the enzyme later identified to be the genetic cause of NGLY1 Deficiency - PNGase (N-Glycanase).

When researchers found NGLY1 mutations in **Bertrand Might in 2012**, they were relatively certain that it was those mutations that caused the symptoms in the then 4-year old. To confirm this they needed to find a second patient with mutations in the NGLY1 gene with similar symptoms. A social media campaign quickly lead to more patients and more than 4 years later, **we are aware of 63 patients worldwide.**

It is crucial for this number to grow, as the community can provide important information and support to every new family, as well as gain more insights into the disease with every new patient.

The NGLY1 community is very fortunate to collaborate with the National Institutes of Health (NIH) in Bethesda, Maryland, USA, where several NGLY1 patients are being seen under two important protocols gaining valuable insights into the characteristic symptoms and natural progression of the disease and laying the groundwork for future therapeutic approaches.



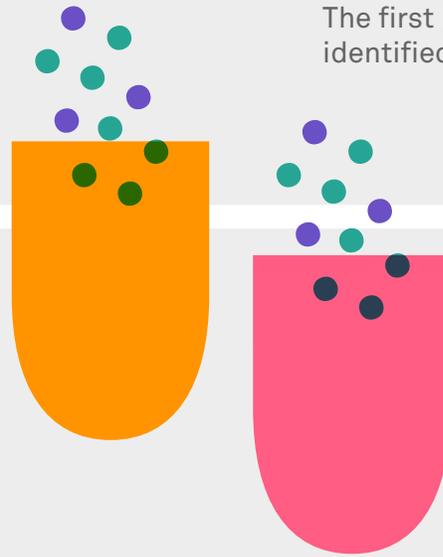
1983

IDENTIFICATION

Identification of gene by Tadashi Suzuki (1993).

FIRST CASE

The first NGLY1 patient identified in 2012.

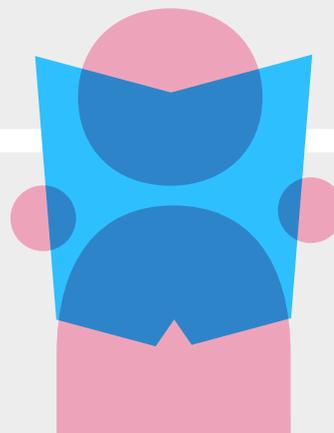


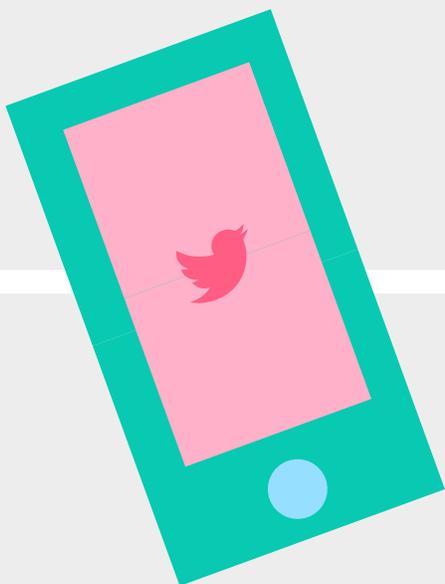
COMMUNITY

Community grows with more than 50 patients diagnosed with NGLY1 (2017).

RESEARCH

Research funded by NGLY1 patient groups accelerate understanding of NGLY1 and possible treatments.





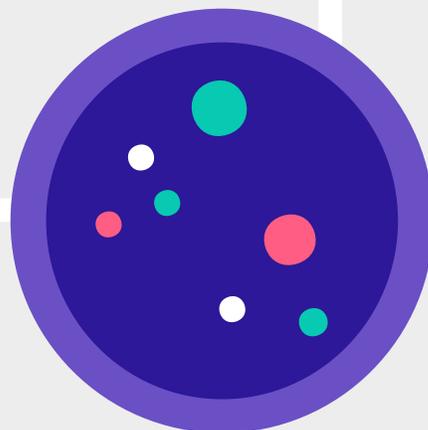
CAMPAIGN

A social media campaign quickly led to finding more NGLY1 Patients worldwide.



NIH CDG PROTOCOL

National Institutes of Health CDG Protocol to study NGLY1 and other Congenital Disorders of Glycosylation.



FUTURE

We are gaining valuable insights symptoms and natural progression of the disease and laying the groundwork for future therapeutic opportunities.

Hope

2018

Genetics

The NGLY1 gene lies on Chromosome 3.

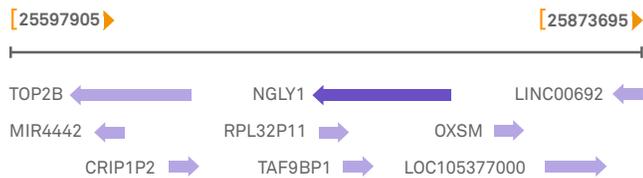
Amongst the known patients, there is a variety of different mutations dispersed along the NGLY1 gene. The most common mutation seen in NGLY1 patients is the nonsense mutation p.R401X, or c. 1201A>T, where a change in one codon signals the cell to prematurely stop building the enzyme N-glycanase.

N-glycanase deficiency is an autosomal-recessive disorder. What does that mean?

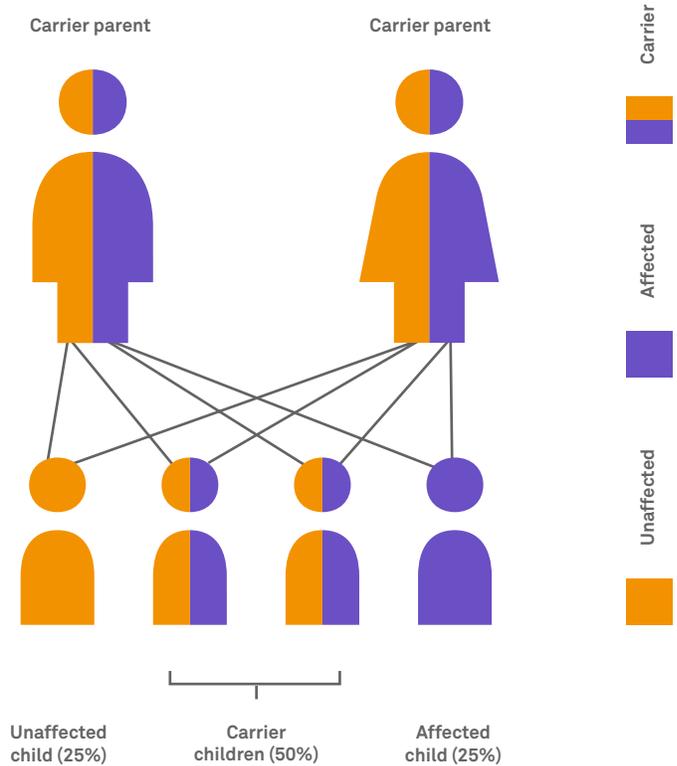
Every person has two copies of the NGLY1 gene. If one of those two copies is a mutation, a person will be a "carrier". Being a carrier is not a problem as the one remaining normal copy of the NGLY1 gene is sufficient to produce enough N-glycanase.

But if two carriers meet and have a child, they stand a 25% chance of producing a child with TWO mutated copies of the gene, hence a child that has the disease. 50% of their offspring will be carriers and the remaining 25% will be unaffected.

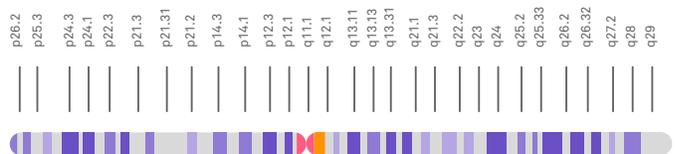
Molecular Location: base pairs 25,718,944 to 25,790,039 on chromosome 3 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



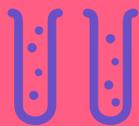
Autosomal Recessive Inheritance Pattern:



Cryogenetic Location: 3p24.2, which is the short (p) arm of chromosome 3 at position 24.2



Most patients with a confirmed diagnosis have had whole genome exome sequencing.



Urine screening is a newer and easier way to diagnose NGLY1, which is why most current patients have been diagnosed by sequencing which until a year ago was the only way to get a diagnosis.

Symptoms

& Diagnosis

Symptoms

The most prevalent symptoms of NGLY1 Deficiency are movement disorder, global developmental delays, seizures, and lack of tears. Patients with NGLY1 Deficiency may also experience:

Physical Symptoms

- **Overall hypotonia/low tone** as well as tightness/contractures in ankles and wrists.
- **Complex hyperkinetic movement disorder** which makes it difficult for the patients to walk, sit, feed themselves etc. More severe when younger.
- **Lack of tears** as most patients have very dry eyes resulting in bad eye infections when not properly taken care of.
- **Smaller head** (microcephaly)
- **Lack of sweat** which makes it difficult for patients to regulate their body temperature in warm weather.
- **Difficulty with swallowing causing aspiration**
- **Small feet and hands**

Clinical Symptoms

- **Liver dysfunction:** Patients present with elevated liver transaminases such as AST, ALT and sometimes AFP. Liver values may trend toward the normal range over time.
- **Low protein in urine and CSF**

Neurologic Symptoms

- **Global developmental delay**
 - Difficulty with or unable to walk
 - Most are non-verbal
 - Test significantly below average on cognitive skills tests
- **Diminished reflexes**
- **Seizures**
 - Common seizure types include sudden jerks or startles (myoclonic), drops (atonic) and staring spells (absence).
 - Seizures are generally multi-focal.
 - Patient EEGs are often described as “abnormal.”
- **Peripheral neuropathy** with additional demyelinative features in some patients
- **Auditory Neuropathy:** Many patients show abnormal findings on auditory brainstem response (ABR). Their ears function normally, but the processing of the sound in the brain is abnormal.
- **Sleep disorders**
 - Many patients show a disturbed sleep pattern, especially at a young age.
 - Apnea: Many have been diagnosed with obstructive and/or central sleep apnea.

Diagnosis

The process of coming to a definitive diagnosis for a child with NGLY1 Deficiency, is a challenging time. Due to the rarity of the disease, and the lack of widespread awareness, it may take longer for medical staff to recognise the tell tale signs of NGLY1 Deficiency.

In the past, NGLY1 Deficiency typically has been diagnosed through:

- Whole Exome Sequencing or Whole Genome Sequencing
- Panel Screen / Exome Slice
- Enzyme Activity Testing
- NEW Urine Biomarker Screen

Strong Indicators of NGLY1 Deficiency:

- **Decreased protein and albumin** in the cerebrospinal fluid (CSF)
- **Elevated oligosaccharides in urine** have recently been discovered as unique biomarkers for NGLY1 Deficiency, offering hope for a much easier and cheaper way to a diagnosis.
- **Developmental delay**
- **Lack of tears** (alacrima or hypolacrima)
- **Abnormal EEG**
- **High liver values in young children**
- **Movement disorder**

Some common differential diagnoses are:

- Mitochondrial Disease
- Congenital Disorders of Glycosylation
- Rett-Syndrome
- Lysosomal Storage Disorders
- Cerebral Palsy

The unique combination of these indicators of NGLY1 Deficiency (ICD E77.8) should prompt doctors to **test for the disease**.



How can NGLY1.org help families?

NGLY1.org can provide free testing for enzymatic activity provided with sufficient evidence of NGLY1 Deficiency. Email info@ngly1.org for more details.



‘Thanks to NGLY1.org and it’s worldwide community, we were finally linked to our forever ‘tribe’ – a carefully woven network of parents, children, researchers, scientists, and doctors all working towards a treatment and cure.’

- Jennifer Leftwich, mom to Gage

Prognosis

With so few patients evaluated so far, it is difficult to give a prognosis especially as the mechanism of harm is not yet fully understood.

From recent NIH research, we know that NGLY1 Deficiency is a progressive disease. Patients appear to lose functions with age (for example: peripheral neuropathy as well as auditory findings deteriorate).

Some symptoms however appear to improve or remain stable over time such as the liver values and the movement disorder.

Most children do not appear to be medically fragile. However, some children have passed away at a young age primarily due to complications following respiratory infections and/or seizure complications.

Children with NGLY1 Deficiency have a relative strength in social skills. They have great difficulty acquiring new skills across many areas, but show good potential and benefit from a variety of inputs.

Several patients can talk or communicate with speech-generating devices, may ambulate with the help of a gait-trainer, and a few are able to do simple reading and math.

Just as with other complex conditions, it is crucial not to underestimate the cognitive abilities of NGLY1 patients and to find ways to work around what might be severe physical, language and sensory challenges.



‘ We are grateful that NGLY1.org helps create awareness of NGLY1 deficiency. This is crucial for growing our community and ultimately for finding a cure! ’

- Christina Rentzmann, Mom to Benno



Patient care

Medical Care

As a caretaker, it is very important to remember that you get all the help you can and take care of yourself first. It is always easier said than done, but so important to ensure continuous high-quality care for our children.

There are **many good days and experiences**. Most families find that the older the children get the easier it becomes to strike a balance between their medical needs, therapies and enjoying time as a family.

Most patients are not medically fragile, but we have seen minor pediatric conditions such as simple infections spiral out of control quickly, which makes it important to take early and decisive action once the patient appears to deteriorate.

Medications NGLY1 patients may take:

(Be sure to check with your doctor before making any changes to your medication regimen)

- **Anti-Seizure:** Levetiracetam (Keppra), Valproic acid (Depakote), Lamotrigine (Lamictal)
- **Eye drops and ointments:** frequently during the day and night
- Reflux
- **Constipation:** Stool softener, enemas
- **Pain:** Ibuprofen, baclofen
- **Sleep:** Melatonin, clonidine
- **Supplements:** Ubiquinol, Levocarnitine, Multivitamin
- Alpha Lipoic Acid
- Botox injections

NGLY1 Deficiency is a progressive condition.

Patients tend to develop new medical concerns over time like sudden aspiration of foods or liquids where swallowing previously was not an issue as well as increasing muscle weakness that makes walking more difficult.

On the other hand, we also find they become more stable, happier and continue to learn new cognitive skills at their own pace as they get older.

Specialist doctors to consult:

An interdisciplinary team will follow the patients over a longer period of time.

- Geneticist
- Developmental pediatrician
- Ophthalmologist
- Pulmonologist
- Sleep specialist
- Neurologist
- Gastroenterologist
- Otolaryngologist (ENT)
- Orthopedist
- Physiatrist
- Audiologist

Therapeutic care

Most children will require at least some equipment. The most common equipment used in for the NGLY1 patients are: Adaptive stroller or wheelchair, therapy chair, stander, walker or gait trainer, bath chair, toilet chair, splints, orthotics, glasses, hearing aids, cooling vest, DMO suits, vibrating vest for airway clearance, electronic communication devices, and special beds.

Many families will at some point choose to modify their houses and cars to make them accessible. Some children will require a G-tube for feeding, a BiPAP at night, and a central line (such as a port) for administering medication. Some kids may qualify for private duty nursing care. Most children also benefit from being seen by a team specialised in assistive technology.

- **Physical therapy:** Working on strength, functional mobility, bone density, preventing contractures and scoliosis.
- **Occupational therapy:** Working on tasks of daily living such as self-feeding, self-care, fine motor tasks as well as sensory regulation.
- **Speech therapy:** Some patients speak, all will benefit from oral-motor exercises that are also crucial for chewing and swallowing as well as sound production. Speech therapists specialised in augmented and alternative communication (AAC) will be able to assist with choosing and setting up a speech generating device.
- **Hearing and vision therapy:** As hearing and vision are most likely affected in most patients, they will benefit from specialized services addressing the question how the environment should be structured so they can maximise their auditory and visual input (like minimising background noise allows people with auditory neuropathy to listen without getting overwhelmed).

The complexity and rareness of this condition poses a challenge for schools. It is important to stress that just because NGLY1 patients may be severely impaired in different ways, it doesn't mean they lack cognitive abilities in the same way. Most will be taught in special education programs with a focus on life skills. They benefit from a small student-teacher ratio and teams experienced with alternate communication systems.

Social skills are a relative strength for NGLY1 patients. They love to connect with other people and can have an amazing sense of humor. Although every patient is different, they all seem to share a love for colorful plastic toys that spin and rattle, balls, the color red and the iPad (watching shows like "Elmo's World" or playing with apps).



Social skills are a relative strength for NGLY1 patients. They love to connect with other people and can have an amazing sense of humor!



Special education and IEP resources are available at [NGLY1.org](https://www.ngly1.org)!



About us

About NGLY1.org

As of January 2018, a leading patient support and research organization for NGLY1 Deficiency, is aware of 63 patients from a variety of geographic and ethnic backgrounds, with ages ranging from a few months to 24 years. Some symptoms caused by NGLY1 Deficiency are progressive. No cure is currently available.

At NGLY1.org we believe that finding treatments and cures for NGLY1 children is Positively Possible®. NGLY1.org is supporting crucial research on a better understanding of NGLY1 Deficiency. NGLY1 Deficiency was only discovered in 2012, but we are hopeful that finding a cure has come within reach.

Programs

Research: Conduct and promote science that may lead to understanding, treatments and cures for N-Glycanase Deficiency including:

- Funding/collaborating with researchers
- Setting up a patient registry
- Biomarker approval
- Mobilize participants for clinical trials/medication studies

Awareness: Educate the scientific, medical and general populations to improve diagnosis, understanding and treatment of N-Glycanase Deficiency.

Support: Provide guidance and community support for families of individuals (mostly children) affected by NGLY1 Deficiency including:

- Bring together the NGLY1 community
- Family conferences with financial support for travel
- Connect families and researchers



Contact us

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Our mission

The mission of NGLY1.org, a 501(c) (3) nonprofit, is to eliminate the challenges of N-Glycanase Deficiency through research, awareness, and support.