Research Article

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The Role of Genetic Mutations in NGLY1 Gene on the NGLY1 Deficiency Syndrome

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Summary

NGLY1 deficiency is a rare disorder that can affect multiple body systems. Affected individuals may have failure to reach developmental milestones, intellectual disability, movement disorders, seizures, liver disease, and an inability to produce tears when crying (alcryma) or rarely produce tears. The specific symptoms and severity of the disorder can vary significantly among affected individuals. Additional symptoms may develop in some children. NGLY1 deficiency is caused by a disease-causing variant (mutation) in the NGLY1 gene. This variant is inherited in an autosomal recessive pattern. As of April 2021, fewer than 100 people have been identified with NGLY1 deficiency. Affected infants often have reduced muscle tone (hypotonia), in which the child is described as being excessively "floppy". About half of all infants are born with low birth weight and, despite a normal appetite, many infants will fail to gain weight or grow for their age and sex (growth failure). Some infants have difficulty swallowing and are at risk of food or liquids going down the wrong tube and ending up in the lungs (aspiration). Constipation may also occur. In some infants, head circumference, which is normal at birth, may be smaller than expected with age (acquired microcephaly). NGLY1 deficiency syndrome is caused by mutations in the NGLY1 gene, which is located on the short arm of chromosome 3 at 3p24.2. Genes provide instructions for making proteins that play an important role in many body functions. When a mutation occurs in a gene, the protein product may be defective, ineffective, absent, or overproduced. Depending on the function of the specific protein, this can affect many organs in the body, including the brain.

Keywords: NGLY1 gene, Genetic Disorder, Mutation, Hypotonia.

Overview of NGLY1 Deficiency Syndrome

NGLY1 deficiency is a rare disorder that can affect multiple body systems. Affected individuals may have failure to reach developmental milestones, intellectual disability, movement disorders, seizures, liver disease, and an inability to produce tears when crying (alcryma) or rarely produce tears. The specific symptoms and severity of the disorder can vary significantly among affected individuals. Additional symptoms may develop in some children. NGLY1 deficiency is caused by a disease-causing variant (mutation) in the NGLY1 gene. This variant is inherited in an autosomal recessive pattern. As of April 2021, fewer than 100 people have been identified with NGLY1 deficiency. It is possible that only severely affected children have been diagnosed, and descriptions of the disorder reflect how severely affected these individuals are. This is because children with the condition are more likely to be referred to specialists, receive genetic testing, and receive a diagnosis. Some researchers believe that people with milder forms of NGLY1 deficiency are more likely to have it.[1]

Clinical Signs and Symptoms of NGLY1 Deficiency Syndrome

Although researchers have been able to establish a clear syndrome with characteristic or "core" symptoms, much of the disorder is not fully understood. Several factors, including the small number of cases identified, the lack of

large clinical studies, and the possibility that other genes may influence the disorder, prevent doctors from developing a complete picture of the associated symptoms and prognosis. As researchers learn more about the disorder, the potential spectrum or specific pattern of symptoms will become clearer. Therefore, it is important to note that each child is unique and that an individual child may not have all of the symptoms listed below.[1]

Figure 1: Images of children with NGLY1 deficiency syndrome with dysmorphic face.[1]

Affected infants often have reduced muscle tone (hypotonia), in which the child is described as being excessively "floppy". About half of all infants are born with low birth weight and, despite a normal appetite, many infants will fail to gain weight or grow for their age and sex (growth failure). Some infants have difficulty swallowing and are at risk of food or liquids going down the wrong tube and ending up in the lungs (aspiration). Constipation may also occur. In some infants, head circumference, which is normal at birth, may be smaller than expected with age (acquired microcephaly). Most affected infants and children may not produce tears or produce few tears when crying (alacrima). This can lead to complications including inflammation of the eyelids (blepharitis), eye infections, irritation and open sores on the cornea, the clear layer on top of the eye (corneal ulcer). The eyes may not be aligned properly and may point in different directions (strabismus). In a small number of children, there was a loss of the main nerve that carries sensory input to the brain to form an image (optic atrophy) and pigmentary changes in the membrane at the back of the eye (retina) and abnormalities of certain cells of the retina called cone cells (cone dystrophy). Visual impairment has also been described in some children. Neurodevelopmental symptoms are common in NGLY1 deficiency, including delays in reaching developmental milestones such as sitting, crawling, or walking. As children get older, they may have difficulty walking independently or may not be able to walk at all. There may be delays in speech development, and children are often unable to speak or can only speak a few words. Intellectual disability is common and can range from children with a below-average IQ score to significant intellectual disability. Most affected children may have a complex movement disorder that includes abnormal tremors and increased and sometimes uncontrollable muscle spasms (hyperkinesis). Specific movement abnormalities include choreoathetosis, action tremor, myoclonic movements, dystonic movements, and dysmetria. Choreoathetosis is characterized by irregular, rapid, and jerky movements that may occur with slow, jerky movements. Other types of abnormal movements can occur, including mild tremors when trying to perform a task (action tremor), jerking or jerking movements (myoclonic movements), involuntary muscle contractions that force the body into abnormal and sometimes painful movements or positions (dystonic). Movements and lack of coordination and precision in voluntary movements (dysmetria), which means that affected individuals under- or overreach when trying to grasp an object, or stumble when walking.[1,2]

Some children may have elevated levels of certain liver enzymes, which usually indicate liver dysfunction or damage. Mild scarring (fibrosis) of the liver can develop. One person had acute liver failure that resolved. Most often, liver enzyme levels improve as the child gets older. Sometimes, the liver may be larger than normal (hepatomegaly). Some children have had various types of seizures. The age of onset of seizures varies from 2 months to 10 years. Sometimes the seizures respond to medications, and sometimes they continue despite drug treatment (intractable seizures). Various skeletal problems have been reported, including small hands or feet, frequent fractures, a hip defect that causes the thighbone to angle toward the body (coxa valga), and an abnormal sideways curvature of the spine (scoliosis). Joints that are loose and have a greater range of motion than normal (hypermobility) and partial or complete dislocation (subluxation) of some joints, such as the hip or shoulder.[1,2]

A small number of affected children are prone to frequent and severe respiratory infections. However, most children are no different or have fewer infections than affected children. Some affected people develop peripheral neuropathy, a condition that occurs when the nerves that carry messages from the brain and spinal cord to the rest of the body are damaged. Affected people may experience tingling, burning, numbness, and shooting pain. As it progresses, peripheral neuropathy can lead to ulcers or infections in the feet, weakness and balance, and walking problems that do not improve.[1,2]

Some children experience hearing loss. The ears function normally, but the way the brain processes sound is abnormal (auditory neuropathy). Additional symptoms can include an abnormally large spleen (splenomegaly), repeated temporary pauses in breathing during sleep (sleep apnea), sleep pattern disturbances, decreased reflexes, or an inability or reduced ability to sweat. This may make it difficult for affected individuals to regulate their body temperature (causing them to overheat) during hot months. Adrenal insufficiency has been reported in NGLY1 deficiency. The adrenal glands, which are located in the kidney, make hormones. In adrenal insufficiency, the adrenal glands cannot make enough hormones to respond to stress, regulate blood pressure, and regulate sexual development. This can lead to serious illness, especially during times of stress, such as during an infection.[1,2]

Etiology of NGLY1 Deficiency Syndrome

NGLY1 deficiency syndrome is caused by mutations in the NGLY1 gene, which is located on the short arm of chromosome 3 at 3p24.2. Genes provide instructions for making proteins that play an important role in many body functions. When a mutation occurs in a gene, the protein product may be defective, ineffective, absent, or overproduced. Depending on the function of the specific protein, this can affect many organs in the body, including the brain.[1,3]

Researchers have found that the NGLY1 gene produces a specialized protein (enzyme) called N-glycanase, which helps remove and recycle damaged proteins in the body. This enzyme is involved in a process called deglycosylation, in which sugar molecules called sugar chains or glycans are removed from proteins. This step is essential for breaking down damaged or misfolded (misfolded) proteins so that their components can be recycled. Some researchers believe that these misfolded proteins accumulate in certain tissues of the body. This enzyme is also important in activating some proteins that need their glycans removed at the right time to function properly. Due to mutations in the NGLY1 gene, affected individuals do not make sufficient levels or produce an ineffective form of N-glycanase and cannot properly remove sugar chains from proteins. N-glycanase is also important in regulating some aspects of DNA reading (DNA transcription). The exact way in which the lack of N-glycanase protein ultimately causes the symptoms of the disorder is not yet fully understood.[1,3]

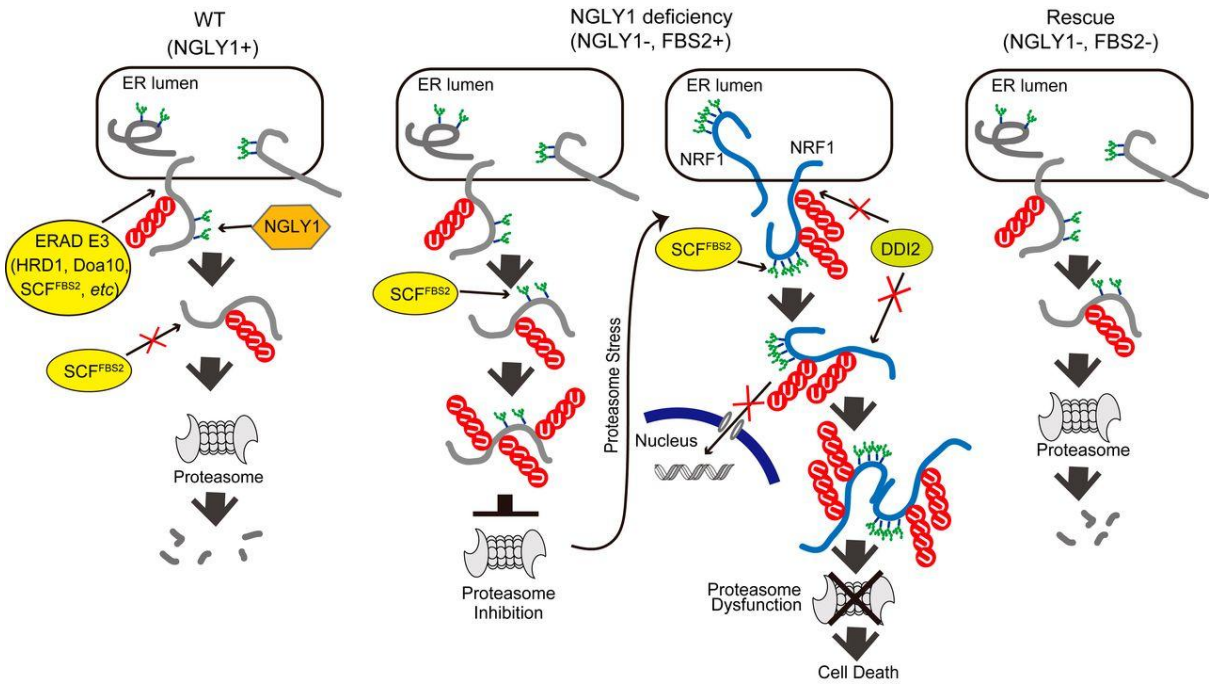

Figure 2: Schematic of the molecular mechanism in NGLY1 deficiency syndrome.[1]

Genetic diseases are determined by the combination of genes for a particular trait that are on chromosomes received from both parents. NGLY1 deficiency is inherited in an autosomal recessive pattern. Recessive genetic disorders occur when a person inherits the same abnormal gene for a trait from each parent. If a person receives one normal gene and one gene for the disease, the person will be a carrier of the disease, but will usually not show symptoms. The risk that both

carrier parents will pass on both defective genes and have an affected child is 25 percent with each pregnancy. The risk of having a child who is a carrier like the parent is 50 percent with each pregnancy. The chance that a child will receive normal genes from both parents and be genetically normal for that particular trait is 25 percent. This risk is the same for males and females.[1,4]

Frequency of NGLY1 Deficiency Syndrome

NGLY1 deficiency is an extremely rare disorder that was first reported in the medical literature in 2012. According to the NGLY1 Foundation, as of April 2021, approximately 75 people worldwide have been identified with the disorder. Rare diseases such as NGLY1 deficiency are often undiagnosed or misdiagnosed, making it difficult to determine the true prevalence in the general population.[1,4]

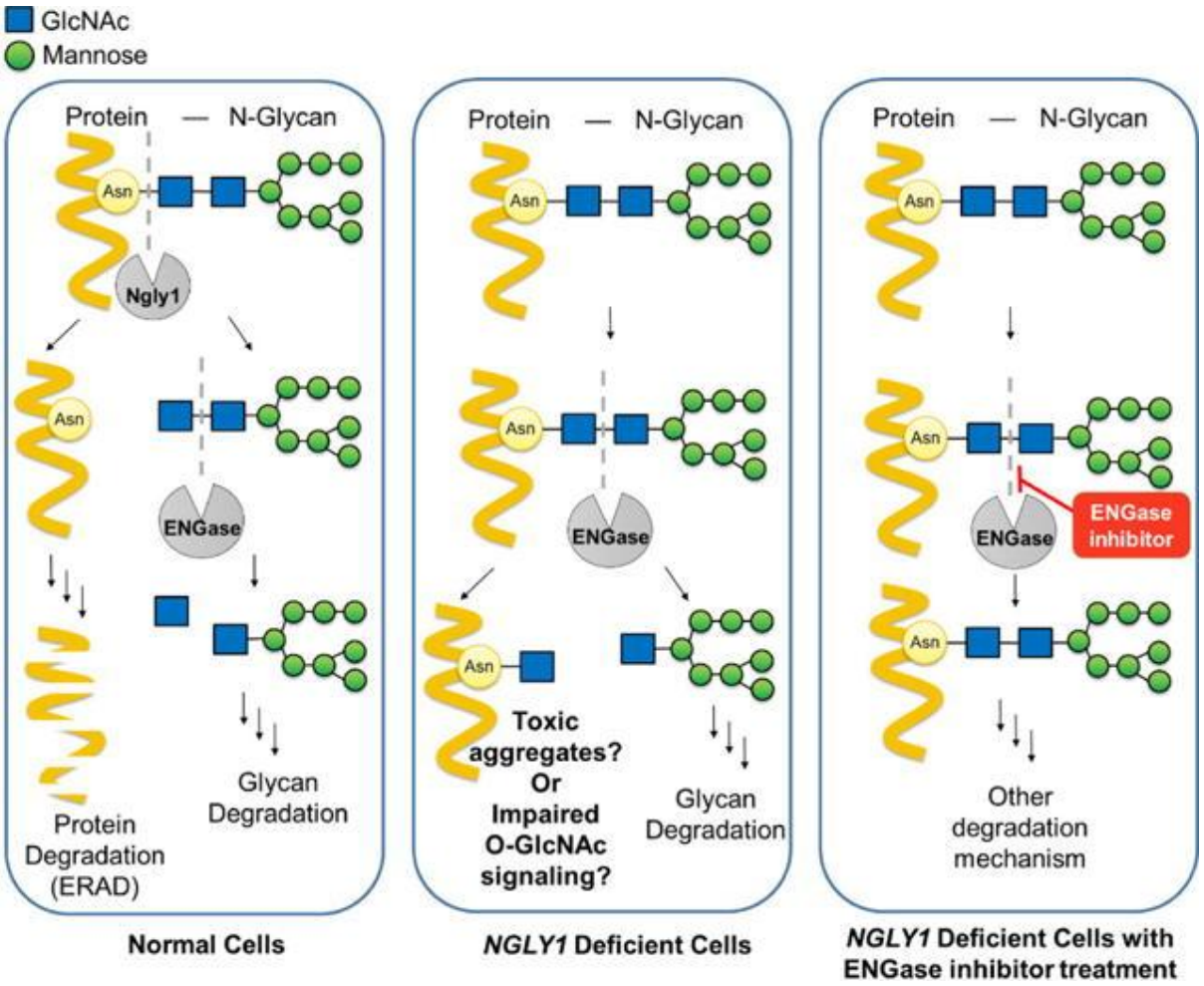

Figure 3: Schematic of the mechanism of cells containing altered (deficient) NGLY1 protein versus normal cells.[1]

Disorders Associated with NGLY1 Deficiency Syndrome

The symptoms of the following disorders can be similar to those of NGLY1 deficiency. Comparison may be helpful for differential diagnosis:

Congenital disorders of glycosylation (CDG) is an umbrella term for a rapidly expanding group of rare genetic and metabolic disorders that are caused by defects in the complex biochemical process known as glycosylation. Glycosylation is the process by which sugar "trees" (glycans) are created, modified, and chemically attached to specific proteins or fats (lipids). When these sugar molecules are attached to proteins, they form glycoproteins. When they are attached to lipids, they form glycolipids. Glycoproteins and glycolipids have numerous important functions in all tissues and organs. Glycosylation involves many different genes that code for different proteins, such as enzymes. A deficiency or absence of one of these enzymes can lead to a variety of symptoms that potentially affect multiple systems. CDG can affect any part of the body and there is often a significant neurological component. CDG can be associated with a wide range of symptoms, and the severity can range from mild to severe, disabling, or life-threatening. CDG usually becomes apparent in infancy. An individual's CDG is caused by a mutation in a specific gene. Most CDG is inherited as an autosomal recessive condition. CDG was first reported in the medical literature in 1980 by Dr. Jaak Jaeken and colleagues. Over 100 different forms of CDG have been identified in the years since. Several different names have been used to describe these disorders, including carbohydrate-deficiency glycoprotein syndromes. Recently, Jaeken and colleagues have proposed a classification system that names each subtype by the official abbreviation of its defective gene, followed by a hyphen and

CDG. For example, congenital disorder of glycosylation type α1 is now known as PMM2-CDG. PMM2 is the defective gene that causes this CDG subtype.[1,5]

Mitochondrial diseases are a group of rare genetic disorders. Found by the hundreds in nearly every cell in the body, mitochondria are often described as the powerhouses of the cell. They produce most of the cell's energy through the enzymes of the respiratory chain (complexes I-V), which convert electrons derived from sugars and fats into ATP, the cell's energy store. The genetic blueprint for essential components of the respiratory chain is mitochondrial DNA (mtDNA). Disorders caused by mitochondrial dysfunction, often respiratory chain defects, are called mitochondrial diseases. Because energy is essential for many tissue functions, mitochondrial diseases commonly affect multiple organs of the body.[1,5]

There are other neurodevelopmental disorders that can have symptoms that overlap with those associated with NGLY1 deficiency. These disorders include inherited sensory and autonomic neuropathies. Rett syndrome; MECP2 duplication syndrome; Triple-A syndrome; creatine deficiency syndromes including creatine transporter deficiency, guanidinostate methyltransferase deficiency, and L-arginine:glycine amidinotransferase deficiency; and neurotransmitter deficiencies such as Segawa syndrome and tyrosine hydroxylase deficiency. Neurotransmitters are chemicals that transmit nerve impulses from one nerve cell (neuron) to another, amplifying them and enabling nerve cells to communicate with each other.[1,5]

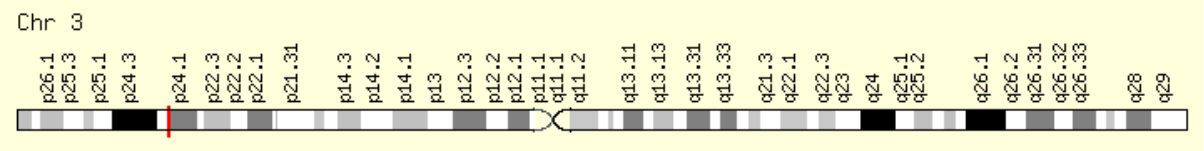

Figure 4: Schematic of the physical map of chromosome number 3, where the NGLY1 gene is located on the short arm of this chromosome as 3p24.2.1

Diagnosis of NGLY1 Deficiency Syndrome

The diagnosis of NGLY1 deficiency is based on the identification of characteristic symptoms, a careful patient history, a thorough clinical evaluation, and a variety of specialized tests. There are no formal diagnostic criteria for the disorder. A combination of characteristic symptoms, including developmental delay, alacrity, hyperkinetic movement disorders, and liver disease, may necessitate testing for the disorder.[1,6]

Most people are diagnosed with molecular genetics (DNA) testing. Molecular genetic testing can identify mutations in the NGLY1 gene that cause NGLY1 deficiency, but it is only available as a diagnostic service in specialized laboratories.[1,6]

If molecular genetic testing identifies variants in the NGLY1 gene that have not been seen before, further testing is needed to confirm the diagnosis. Sometimes, the research test requires a small sample of skin tissue, obtained by cutting a small piece of skin (a skin biopsy), which is then examined under a microscope.[1,6]

Liver chemistry tests can show elevated levels of certain liver enzymes, aspartate transaminase (AST) and alanine transaminase (ALT), in the blood. Sometimes, there is an increase in alpha-fetoprotein (AFP). Elevations of these liver enzymes can occur in a variety of diseases and are not diagnostic of NGLY1 deficiency by themselves. Levels of these enzymes return to normal in children with age, and this test is not useful for older children.[1,6]

Researchers have discovered that urine tests from affected people may show abnormalities in certain long sugar chains called oligosaccharides. Blood spot tests have also shown elevated levels of a specific sugar bound to a protein called aspartylglucosamine.[1,6]

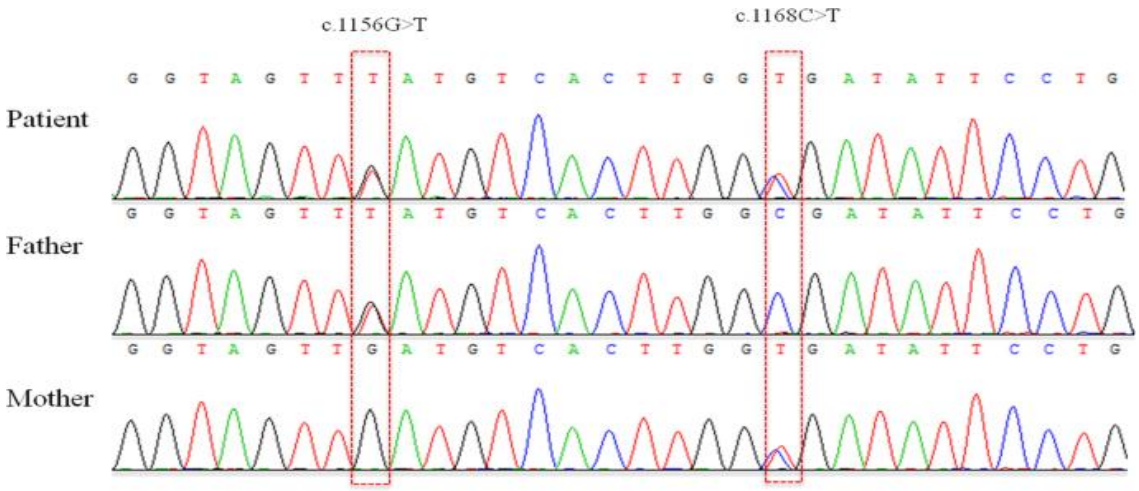

Figure 5: Schematic of a nucleotide mutation example in the NGLY1 gene.[1]

Treatment Pathways for NGLY1 Deficiency Syndrome

Treatment of NGLY1 deficiency is directed at the specific symptoms that are evident in each individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, doctors who specialize in diagnosing and treating disorders of the brain, nerves, and nervous system in children (pediatric neurologists), neurologists, doctors who specialize in diagnosing and treating eye disorders (ophthalmologists), doctors who specialize in diagnosing and treating disorders of the digestive tract (gastroenterologist), doctors who specialize in diagnosing and treating liver disorders (hepatologists), doctors who specialize in diagnosing and treating skeletal disorders (orthopedicians), doctors who specialize in diagnosing and treating genetic disorders (medical geneticists), speech pathologists, psychologists, and other healthcare professionals may need to plan a systematic and comprehensive treatment plan. Psychosocial support for the entire family is also essential. Genetic counseling may be helpful for affected individuals and their families.[1,7]

There is no standard treatment protocol or guideline for affected individuals. Due to the rarity of the condition, there are no treatment trials that have been tested on large groups of patients. Various treatments have been reported in the medical literature as part of single case reports or small patient series. Therapeutic trials would be very useful to determine the long-term safety and effectiveness of specific drugs and treatments for people with NGLY1 deficiency.[1,7]

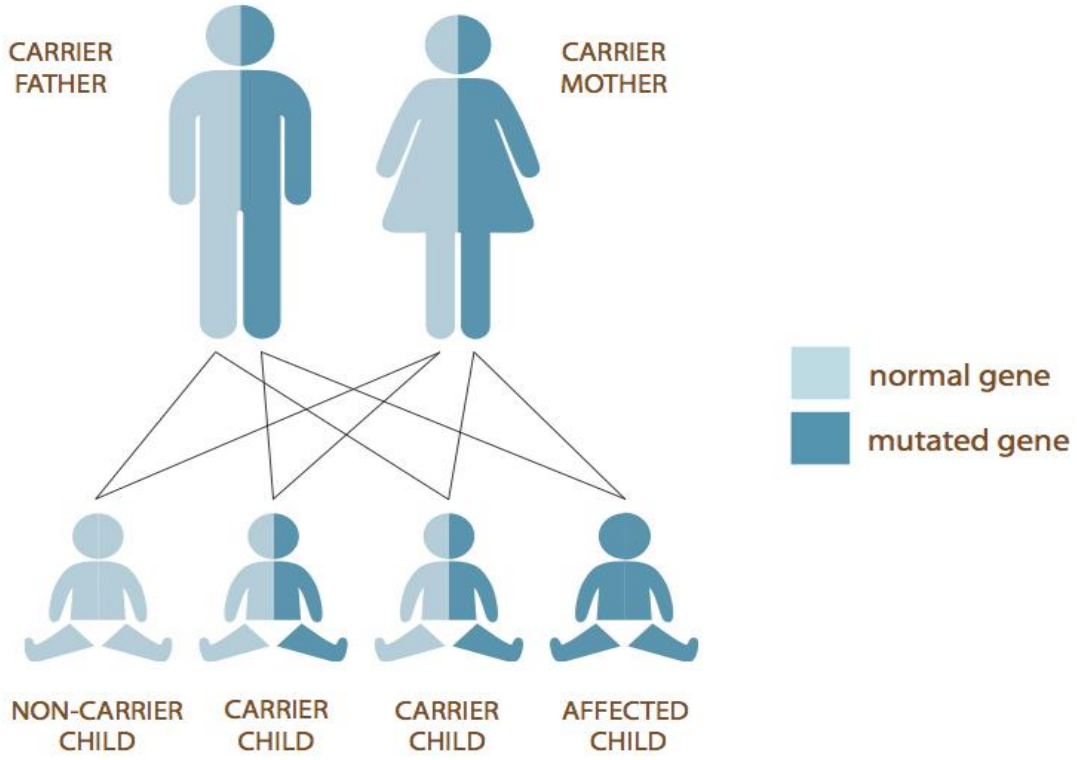

Figure 6: Schematic of the autosomal recessive inheritance pattern that NGLY1 deficiency syndrome follows.[1]

Infants with NGLY1 deficiency should be evaluated for feeding problems and treated with standard procedures if necessary. This may include the placement of a feeding tube. A feeding tube may be passed through the nose and into the stomach through the esophagus, or it may be inserted directly into the stomach through a small surgical hole in the abdominal wall. The feeding tube ensures that the affected person receives adequate nutrients.[1,8]

Poor or no tear production may be treated with lubricating eye drops or gentle ointments. Anti-seizure medications called antiepileptics may be tried. Sometimes, these medications are effective, but sometimes seizures continue (intractable seizures). Braces and other orthotics can help children walk. Some children need a wheelchair.[1,8]

People who are unable to sweat may need water to stay hydrated, especially when they are engaged in physical activity. Things like cooling vests or access to cool environments (such as those with air conditioning or other cooling methods) are also helpful.[1,8]

Affected children may benefit from occupational, physical, and speech therapy. Hydrotherapy and music therapy have also been helpful for some affected children. Augmentative and assistive communication devices can help children express their thoughts, wants, needs, and ideas. Additional medical, social, or vocational services, including specialized education programs, may be necessary. Many of the symptoms associated with NGLY1 deficiency, including constipation, scoliosis, sleep apnea, and hearing loss, respond to standard or routine treatment options. Researchers will soon be investigating whether supplementation with specific sugars improves tear production. Additional trials based on these discoveries in laboratory models of the disease may soon be conducted.[1,9,10,11,12,13]

Discussion

Although researchers have been able to establish a clear syndrome with characteristic or "core" symptoms, much of the disorder is not fully understood. Several factors, including the small number of cases identified, the lack of large clinical studies, and the possibility that other genes may influence the disorder, prevent doctors from developing a complete picture of the associated symptoms and prognosis. As researchers learn more about the disorder, the potential spectrum or specific pattern of symptoms will become clearer. Some children may have elevated levels of certain liver enzymes, which usually indicate liver dysfunction or damage. Mild scarring (fibrosis) of the liver can develop. One person had acute liver failure that resolved. Most often, liver enzyme levels improve as the child gets older. Sometimes, the liver may be larger than normal (hepatomegaly). Some children have had various types of seizures. The age of onset of seizures varies from 2 months to 10 years. Sometimes the seizures respond to medications, and sometimes they continue despite drug treatment (intractable seizures). Researchers have found that the NGLY1 gene produces a specialized protein (enzyme) called N-glycanase, which helps remove and recycle damaged proteins in the body. This enzyme is involved in a process called deglycosylation, in which sugar molecules called sugar chains or glycans are removed from proteins. This step is essential for breaking down damaged or misfolded (misfolded) proteins so that their components can be recycled. Some researchers believe that these misfolded proteins accumulate in certain tissues of the body. This enzyme is also important in activating some proteins that need their glycans removed at the right time to function properly. Treatment of NGLY1 deficiency is directed at the specific symptoms that are evident in each individual. Treatment may require the coordinated efforts of a team of specialists. There is no standard treatment protocol or guideline for affected individuals. Due to the rarity of the condition, there are no treatment trials that have been tested on large groups of patients. Various treatments have been reported in the medical literature as part of single case reports or small patient series. Therapeutic trials would be very useful to determine the long-term safety and effectiveness of specific drugs and treatments for people with NGLY1 deficiency.[1-13]

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