



## NGLY1-Related Congenital Disorder of Deglycosylation

Synonyms: *NGLY1*-CDDG, *NGLY1* Deficiency, *NGLY1*-Related Disorder

Christina Lam, MD, FACMG,<sup>1</sup> Lynne Wolfe, MS, CRNP,<sup>2</sup> Anna Need, PhD,<sup>3</sup> Vandana Shashi, MD,<sup>4</sup> and Gregory Enns, MD, FACMG<sup>5</sup>

Created: February 8, 2018.

### Summary

#### Clinical characteristics

Individuals with *NGLY1*-related congenital disorder of deglycosylation (*NGLY1*-CDDG) typically display a clinical tetrad of developmental delay / intellectual disability in the mild to profound range, hypo- or alacrima, elevated liver transaminases that may spontaneously resolve in childhood, and a complex hyperkinetic movement disorder that can include choreiform, athetoid, dystonic, myoclonic, action tremor, and dysmetric movements. About half of affected individuals will develop clinical seizures. Other findings may include obstructive and/or central sleep apnea, oral motor defects that affect feeding ability, auditory neuropathy, constipation, scoliosis, and peripheral neuropathy.

#### Diagnosis/testing

The diagnosis of *NGLY1*-CDDG is established in a proband by the identification of biallelic pathogenic variants in *NGLY1* on molecular genetic testing. Typical serum screening tests for congenital disorders of glycosylation (i.e., analysis of serum transferrin glycoforms, N and O glycan profiling) will NOT reliably detect *NGLY1*-CDDG.

#### Management

*Treatment of manifestations:* Lubricating eye drops and/or bland ointments for hypolacrima; feeding therapy and/or supplemental tube feeding for those with oromotor deficits and feeding difficulties; adequate access to water and a cool environment (including a cooling vest for those who live in hot climates) for hypohydrosis; vitamin D supplementation for those with vitamin D deficiency; evaluation by a developmental pediatrician and supportive therapies for developmental and cognitive issues; standard treatment for hearing loss, sleep apnea,

**Author Affiliations:** 1 University of Washington Seattle Children's Hospital Seattle, Washington; Email: [ctlam2@uw.edu](mailto:ctlam2@uw.edu). 2 National Institutes of Health Bethesda, Maryland; Email: [wolfela@mail.nih.gov](mailto:wolfela@mail.nih.gov). 3 Imperial College London London, United Kingdom; Email: [a.need@imperial.ac.uk](mailto:a.need@imperial.ac.uk). 4 Duke University Durham, North Carolina; Email: [vandana.shashi@duke.edu](mailto:vandana.shashi@duke.edu). 5 Stanford University Stanford, California; Email: [genns@stanford.edu](mailto:genns@stanford.edu).

constipation, scoliosis, and seizure disorder; consideration of referral to a hematologist for abnormal hematologic studies; consideration of referral to a gastroenterologist for elevated liver transaminases.

*Surveillance:* Annual follow up by a pediatrician/internist, rehabilitation medicine specialist, ophthalmologist, neurologist, and nutritionist is recommended. Periodic evaluation by a developmental pediatrician, gastroenterologist/hepatologist, and audiologist should be considered.

*Agents/circumstances to avoid:* Hot environment in those with hypohydrosis.

## Genetic counseling

NGLY1-CDDG is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

## Diagnosis

Formal diagnostic criteria have not been established.

## Suggestive Findings

NGLY1-related congenital disorder of deglycosylation (NGLY1-CDDG) **should be suspected** in individuals with the following clinical features and supportive laboratory findings.

**Clinical features** include:

- Developmental delay / intellectual disability, most often in the severe to profound range
- Hyperkinetic movement disorder
- Hypo- or alacrima

**Supportive laboratory findings** include elevated ALT and AST during early childhood that spontaneously normalize.

Note: Typical serum screening tests for congenital disorders of glycosylation (i.e., analysis of serum transferrin glycoforms, N and O glycan profiling) will NOT reliably detect NGLY1-CDDG (see Clinical Description, **Biochemical**).

## Establishing the Diagnosis

The diagnosis of NGLY1-CDDG **is established** in a proband by the identification of biallelic pathogenic variants in *NGLY1* on molecular genetic testing (see Table 1).

## Recommended Testing

**A multigene panel** that includes *NGLY1* and other genes of interest (see Differential Diagnosis) is recommended (see Table 1). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Testing to Consider

**Comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if the phenotype alone is insufficient to support gene-targeted testing.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Single-gene testing.** Sequence analysis of *NGLY1* followed by gene-targeted deletion/duplication analysis (if no pathogenic variant is found) may be considered in a proband with features that are highly suggestive of NGLY1-CDDG. However, because many of the clinical features overlap with those of other intellectual disability / developmental delay syndromes, a multigene panel or comprehensive genomic testing are typically used in lieu of single-gene testing.

**Table 1.** Molecular Genetic Testing Used in *NGLY1*-Related Congenital Disorder of Deglycosylation

Gene <sup>1</sup>	Method	Proportion of Probands with Pathogenic Variants <sup>2</sup> Detectable by Method
<i>NGLY1</i>	Sequence analysis <sup>3</sup>	46/46
	Gene-targeted deletion/duplication analysis <sup>4</sup>	Unknown <sup>5</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. No data on detection rate of gene-targeted deletion/duplication analysis are available.

## Clinical Characteristics

### Clinical Description

*NGLY1*-related congenital disorder of deglycosylation (NGLY1-CDDG) is a multisystemic neurodevelopmental disorder in which individuals most commonly exhibit a tetrad of developmental delay / intellectual disability, hyperkinetic movement disorder, hypolacrimalia, and elevated transaminases during early childhood [Need et al 2012, Enns et al 2014, Heeley & Shinawi 2015, Caglayan et al 2015, Lam et al 2017]. Diagnosis has been achieved at ages ranging from three months to 20 years, mostly through broad molecular testing, such as exome analysis. While most individuals with NGLY1-CDDG survive into early adulthood, with a relatively stable clinical course [Enns et al 2014, Lam et al 2017], death during infancy from unclear causes has been reported. In addition, an affected child died following an infection complicated by uncontrolled seizure activity [Enns et al 2014], and an affected adolescent died from respiratory failure during a respiratory infection [Caglayan et al 2015]. Since so few cases have been identified, understanding of the clinical phenotypic spectrum and natural history continues to evolve.

**Growth.** In approximately half of individuals with NGLY1-CDDG birth weight is below the tenth centile, while the majority of birth lengths and birth head circumferences are appropriate for gestational age [Lam et al 2017].

Despite a robust appetite, individuals with *NGLY1*-CDDG develop failure to thrive with weight affected more than length/height. Acquired microcephaly has also been noted in some [Lam et al 2017].

**Development.** Developmental delay and/or intellectual disability is seen universally in individuals with *NGLY1*-CDDG. Severity of delay is broad and ranges from individuals having an IQ below average (70s) to individuals with profound intellectual disability. The majority of individuals are nonverbal or can only use single words or phrase speech. Despite lack of verbal communication, they use and benefit from alternate forms of augmentative communication tools, such as switch boards or electronic tablet-based tools. Affected individuals have a consistent developmental profile on the Vineland Adaptive Behavior Scales, Second Edition, in which individuals have relatively strong socialization skills, followed by communication skills, followed by weaknesses in motor skills with fine motor worse than gross motor skills, reflected in low daily living skills [Lam et al 2017].

**Neurologic.** Approximately half of affected individuals develop clinical seizures. While most develop myoclonic seizures, documented seizure types also include infantile spasms and atonic, tonic, absence, and gelastic seizures. Age of onset ranges from two months to ten years. In some individuals seizures have been intractable, while in others seizures have been controlled with levetiracetam or valproic acid [Lam et al 2017]. Compared to individuals with seizures of different etiologies, those with *NGLY1*-CDDG have not been more severely affected by any specific antiepileptic medication.

In addition, individuals with *NGLY1*-CDDG universally exhibit a complex hyperkinetic movement disorder that can include choreiform, athetoid, dystonic, myoclonic, action tremor, and dysmetric movements [Lam et al 2017].

Further findings may include the following:

- CSF laboratory results typically demonstrate:
  - Low total protein (from 8 affected individuals, mean protein level was 11 mg/dL, standard error of the mean [SEM] 1) and albumin (from 9 affected individuals, mean 9 mg/dL, SEM 1);
  - Low CSF/serum albumin ratios (from 9 affected individuals, mean ratio was 3, SEM 1);
  - Low CSF 5-hydroxyindolacetic acid, homovanillic acid, and tetrahydrobiopterin levels, especially in older individuals [Enns et al 2014, Lam et al 2017].
- Brain MRI can show:
  - Delayed myelination during early childhood (ages 0-5), but not in older individuals;
  - Progressive cerebral and occasional cerebellar atrophy, which correlates with worsening function. In 10/11 affected individuals imaged cerebral volume loss was found; in 4/11 cerebellar volume loss was also seen [Lam et al 2017].
- Brain MRS can be significant for:
  - Lower N-acetylaspartylglutamate and N-acetylaspartate levels compared to normal;
  - Higher choline and myo-inositol levels, becoming more prominent with increasing age, worsening function, and lower brain volume [Lam et al 2017].
- Nerve conduction studies most often demonstrate an axonal sensorimotor polyneuropathy with additional demyelinating features that are length dependent and appear progressive. Neuropathy has been documented in all nerves tested including the median, ulnar, radial, peroneal, tibial, and sural nerves. Individual testing typically reveals more severe neuropathy in the lower (compared to upper) extremities, with lower amplitudes and slower conduction.
- Needle electromyogram may show neurogenic findings with varying degrees of acute and chronic changes.
- QSWEAT testing can show absent sweat response, more frequently in the lower extremities than in the forearm, suggesting a length-dependent neuropathy [Lam et al 2017].

**Ophthalmologic.** Most affected individuals, with the exception of the youngest reported person, have evidence of hypo- or alacrimal. Corneal findings include neovascularization, pannus formation, and scarring secondary to hypolacrimal. Lagophthalmus, ptosis, exotropia and/or esotropia, optic nerve pallor or atrophy, retinal pigmentary changes including pigmentary granularity and pigmentary retinopathy, and cone dystrophy have been observed in individuals with NGLY1-CDDG [Lam et al 2017].

**Audiologic.** Tympanometry and behavioral hearing thresholds were normal in the individuals who could tolerate and cooperate with these exams. There is a consistent profile on auditory brain stem evoked response showing dyssynchronous and/or absent transmission through the auditory brain stem and/or eighth nerve in most individuals that appears to worsen with age [Lam et al 2017].

**Cardiac.** Echocardiogram is normal, and electrocardiogram shows heart rates in the low 100s with a minority of affected individuals with a QTcB >440 ms, but a normal QTcF.

Note: The QTcB is the standard clinical correction of the QT interval using Bazett's formula, calculated as QT interval divided by square root of the RR interval. The QtcF is the alternative correction based on Fridericia's formula, which is defined as the QT interval divided by the cube root of the RR interval. The QTcB is believed to overestimate the QT prolongation at higher heart rates, and the QTcF may underestimate the QT prolongation at slower heart rates [FDA 2005].

**Sleep.** Approximately half of tested individuals with NGLY1-CDDG have also been documented to have mild-to-profound obstructive and/or central sleep apnea [Lam et al 2017].

**Feeding.** Oral motor defects, including premature spillage, pharyngeal swallow response delays, poor oral bolus formation, weakness of the lips and tongue, dystonic movements of the tongue, and persistent oral reflexes of suckling and suck/swallow are seen in the majority of affected individuals. However, these findings typically do not prohibit oral feeding in the majority of individuals. Enteral feeds have been helpful with nutritional management, although this decision is made on a case-by-case basis [Lam et al 2017].

**Gastrointestinal.** The majority of affected individuals have some degree of constipation [Enns et al 2014].

Transaminases (AST and ALT):

- Are typically elevated and range from just slightly above the upper limit of normal to >1,000 U/L in the first two years of life;
- Usually normalize by age four years without any specific intervention.

Note: In the few liver biopsies performed, findings have been normal or consistent with microvesicular steatosis, ductular proliferation, focal microvacuolation, and micronodular cirrhosis with bands of fibrosis with regenerative nodules.

Total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels are low in about one third of tested individuals, but particle numbers and sizes of HDL, LDL, and VLDL are normal [Lam et al 2017].

Abdominal ultrasound findings can include splenomegaly, steatosis, coarse or inhomogeneous liver texture, and hepatomegaly.

Fibroscan scores show evidence of liver fibrosis in a few affected individuals [Lam et al 2017].

**Hematologic.** Coagulation studies in some individuals can be significant for low protein C, factor II, factor IX, factor XI, and fibrinogen levels. However, significant bleeding or clotting episodes have not yet been reported. Complete blood count is generally unremarkable [Lam et al 2017].

**Immunologic.** Affected individuals typically are reported to have fewer infections than their peers, with the exception of a few individuals with recurrent, more severe, respiratory infections. Antibody titers indicate that

individuals with *NGLY1*-CDDG appear to respond typically to vaccinations, with the exception of rubella and rubeola vaccinations for which titers exhibited out-of-range elevations or were negative (for rubeola) in a majority of tested individuals [Lam et al 2017].

**Musculoskeletal** findings include delayed bone age despite a normal endocrine evaluation, low bone density in several individuals with a history of recurrent fractures, joint hypermobility, coxa valga, scoliosis, dislocations or subluxations of the hip or shoulder joints, and sclerosis of the phalanges or tarsal bones [Lam et al 2017]. These findings were present even in affected individuals who were ambulatory.

**Biochemical** findings include the following:

- Carbohydrate-deficient transferrin analysis in blood may show small elevations in mono- and a-oligosaccharides and tri-sialo-oligosaccharides, but not to the levels typically seen in *PMM2*-CDG.
- O-glycan profiling is normal.
- Urine quantitative mucopolysaccharides can be elevated, but with a normal pattern.
- Free and total carnitine, uric acid, white blood cell CoQ<sub>10</sub>, plasma amino acids, and urine organic acids are essentially normal.
- Lactate was normal in the majority of affected individuals, but can be mild to moderately elevated (~5 mmol/L) especially in younger affected individuals.
- Lactate to pyruvate ratio is typically normal.
- Urine amino acids can show generalized aminoaciduria, especially in older individuals [Lam et al 2017].
- On liver biopsy, abnormal cristae and mitochondrial proliferation was noted in one individual, while depleted cristae and mitochondrial DNA depletion was seen in another individual [Kong et al 2018].
- On quadriceps muscle biopsy mitochondrial proliferation and mitochondrial DNA depletion was noted in one affected individual [Kong et al 2018].

## Genotype-Phenotype Correlations

The most common pathogenic variant is c.1201A>T (p.Arg401Ter), accounting for approximately one third of pathogenic alleles. Affected individuals harboring at least one copy of this pathogenic variant tend to have a more severe clinical course with higher scores on the Nijmegen Pediatric CDG Severity scale [Lam et al 2017].

A sib pair with the cryptic pathogenic c.930C>T splice site variant (predicted as a silent p.Gly310=) and a p.Gln208Ter nonsense variant exhibited relatively mild impairment in all domains [Lam et al 2017].

## Nomenclature

*NGLY1*-CDDG was previously referred to as congenital disorder of glycosylation type Iv (CDG-Iv).

*NGLY1*-CDDG is the first primary defect of N-linked *deglycosylation* shown to cause human disease. Following the established nomenclature for congenital disorders of glycosylation, where disorders are formally named with the involved gene (not italicized) followed by -CDG (e.g., *PMM2*-CDG) [Jaeken et al 2009], the authors propose that this disorder and future disorders of N-linked deglycosylation follow a similar format, except using CDDG instead of CDG.

## Prevalence

A total of 18 individuals from 14 families have been described in the literature [Need et al 2012, Enns et al 2014, Caglayan et al 2015, Heeley & Shinawi 2015, Bosch et al 2016, Lam et al 2017]. However, according to a database maintained by [NGLY1.org](http://NGLY1.org), biallelic pathogenic variants in *NGLY1* coupled with suggestive clinical phenotype have been identified in 46 individuals worldwide. Most of the reported affected individuals have been of northern European background, but this is likely due to ascertainment bias rather than a true increased

prevalence in that population. Although not yet reported in the literature, individuals with African and non-white Hispanic background have been confirmed to have NGLY1-CDDG [Lam & Wolfe, personal observation].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *NGLY1*.

## Differential Diagnosis

The tetrad of developmental delay / cognitive impairment, hyperkinetic movement disorder, hypo/alacrima, and elevated transaminases during early childhood is pathognomonic of NGLY1-CDDG [Need et al 2012, Enns et al 2014, Caglayan et al 2015, Heeley & Shinawi 2015, Lam et al 2017]. However, other multisystemic disorders and conditions that feature variable neurologic phenotypes, including seizures, chorea, athetosis, **dystonia**, myoclonus, tremors, **ataxia**, and dysmetria, are in the differential diagnosis.

**Table 2.** Disorders to Consider in the Differential Diagnosis of *NGLY1*-Related Congenital Disorder of Deglycosylation

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Congenital disorders of glycosylation (CDGs) (see <a href="#">Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview</a> .)	See footnote 1.	AR XL	<ul style="list-style-type: none"> <li>Intrauterine growth restriction</li> <li>DD / cognitive impairment</li> <li>Neurologic dysfunction</li> <li>Liver disease <sup>2</sup></li> </ul>	In persons w/NGLY1-CDDG: <ul style="list-style-type: none"> <li>No apparent lipodystrophy or significant cardiac manifestations <sup>3</sup></li> <li>Nonspecific brain imaging findings, but usually relatively mild abnormalities <sup>4</sup></li> </ul>
Mitochondrial disorders	>250 genes <sup>5</sup>	AR AD Maternal	<ul style="list-style-type: none"> <li>Multisystem involvement</li> <li>Pigmentary retinopathy <sup>6</sup></li> </ul> In some w/NGLY1-CDDG: <ul style="list-style-type: none"> <li>Mild biochemical evidence of mt impairment, especially transient or mildly ↑ blood lactate levels</li> <li>Nonspecific electron transport chain abnormalities in skin fibroblasts, muscle, &amp; liver, &amp; mildly abnormal mt morphology on electron microscopy <sup>3, 6</sup></li> </ul>	Persons w/NGLY1-CDDG: <ul style="list-style-type: none"> <li>Do not typically have episodes of metabolic decompensation or clinical presentations assoc w/ classic mt disorder phenotypes.</li> <li>Have normal CSF lactate levels. <sup>6</sup></li> </ul>
Neurotransmitter disorders (involving metabolic pathways related to monoamine & amino acid metabolism; e.g., <a href="#">GTPCH1-deficient dopa-responsive dystonia</a> , <a href="#">tyrosine hydroxylase deficiency</a> ,	See footnote 8.	See footnote 8.	On CSF analysis: <ul style="list-style-type: none"> <li>Various combinations of abnormal levels of HVA, 5-HIAA, &amp; biopterin metabolites in neurotransmitter disorders <sup>9, 10</sup></li> </ul>	In persons w/NGLY1-CDDG: <ul style="list-style-type: none"> <li>Oculogyric crises not reported</li> <li>No diurnal fluctuation of symptoms</li> <li>Peripheral neuropathy common</li> </ul>



Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
aromatic L-amino acid decarboxylase deficiency			<ul style="list-style-type: none"> <li>In some cases, ↓ HVA, 5-HIAA, &amp; tetrahydrobiopterin in NGLY1-CDDG; such findings appear to correlate w/degree of brain atrophy. <sup>11</sup></li> </ul>	<p>In persons w/neurotransmitter disorders:</p> <ul style="list-style-type: none"> <li>Alacrima/hypolacrima &amp; liver dysfunction not typically seen</li> </ul>
Secondary abnormalities in neurotransmitter metabolites	See footnote 8.	See footnote 8.	<ul style="list-style-type: none"> <li>↓ HVA may be present in hypoxic-ischemic encephalopathy, CNS infections, &amp; some genetic disorders. <sup>10</sup></li> <li>↓ HVA &amp; 5-HIAA may occur in hypoxic-ischemic encephalopathy, congenital infections, &amp; some genetic disorders. <sup>12</sup></li> </ul>	<p>In GTP cyclohydrolase 1-deficient dopa-responsive dystonia:</p> <ul style="list-style-type: none"> <li>Intellectual &amp; cognitive function typically normal</li> </ul>
<i>MECP2</i> -related disorders	<i>MECP2</i>	XL	<p>Cognitive impairment, seizures, ataxia, tremors, &amp; acquired microcephaly:</p> <ul style="list-style-type: none"> <li>Are common features in <i>MECP2</i>-related disorders;</li> <li>May also be seen in NGLY1-CDDG.</li> </ul>	<ul style="list-style-type: none"> <li><i>MECP2</i>-related disorders are classically assoc w/a period of normal development, followed by stagnation &amp; relatively rapid regression in females.</li> <li>Persons w/NGLY1-CDDG have neither a period of normal development nor such rapid developmental regression.</li> </ul>
Creatine deficiency syndromes	<i>GAMT</i> <i>GATM</i> SLC6A8	AR XL	Like NGLY1-CDDG, disorders of creatine synthesis may be assoc w/DD & cognitive impairment, movement disorders, seizures, & behavior abnormalities.	Alacrima & liver disease are not seen in disorders of creatine synthesis.
Triple-A syndrome (OMIM 231550)	AAAS	AR	<ul style="list-style-type: none"> <li>Alacrima</li> <li>Mild dementia</li> <li>Cerebellar ataxia <sup>13</sup></li> </ul>	<ul style="list-style-type: none"> <li>Triple A syndrome does not feature choreoathetosis.</li> <li>Adrenal insufficiency is not a prominent feature of NGLY1-CDDG.</li> <li>Persons with Triple A syndrome may have anisocoria.</li> </ul>
Alacrima, achalasia, and mental retardation syndrome (AAMR) (OMIM 615510)	<i>GMPPA</i>	AR	<ul style="list-style-type: none"> <li>Alacrima</li> <li>ID</li> <li>Variable hypotonia</li> <li>Ataxia</li> <li>Spasticity</li> <li>Hearing impairment <sup>14</sup></li> </ul>	<p>AAMR:</p> <ul style="list-style-type: none"> <li>Does not feature choreoathetosis.</li> <li>May feature anisocoria.</li> </ul>



Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Hereditary sensory and autonomic neuropathy (HSAN)	See footnote 15.	See footnote 16.	Alacrima may also be present in some forms of HSAN incl <a href="#">familial dysautonomia</a> (FD) & HSAN type VI (OMIM 614653) <sup>15</sup>	<ul style="list-style-type: none"> <li>• FD &amp; HSAN type VI do not feature choreoathetosis.</li> <li>• Persons w/HSAN usually have normal cognitive function.</li> </ul>

5-HIAA = 5-hydroxyindoleacetic acid; AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DD = developmental delay; HVA = homovanillic acid; ID = intellectual disability; MOI = mode of inheritance; mt = mitochondrial; XL = X-linked

1. See OMIM Phenotypic Series: [Congenital Disorders of Glycosylation, Type I](#) and [Congenital Disorders of Glycosylation, Type II](#) to view genes associated with these phenotypes.
2. Freeze et al [2012]
3. Enns et al [2014]
4. Some individuals with *NGLY1*-CDDG have cerebral and cerebellar atrophy, but the cerebellar atrophy is not typically as severe as in the CDGs [Lam et al 2017].
5. Alston et al [2017]
6. Lam et al [2017], Kong et al [2018]
7. Neurotransmitter disorders are associated with a wide spectrum of neurologic abnormalities including seizures, choreoathetosis, dystonia, hypotonia, oculogyric crises, and psychiatric disease [Pons 2009, Marecos et al 2014, Ng et al 2015].
8. For more information, see hyperlinked *GeneReviews*, OMIM entries, and/or citations.
9. Pons [2009], Ng et al [2015]
10. Genetic disorders that may be associated with low HVA include [mitochondrial disorders](#), [glycine encephalopathy](#), [Aicardi-Goutières syndrome](#), Rett syndrome (see [MECP2 Disorders](#)), [myotonic dystrophy type 1](#), and vanishing white matter disease (see [Childhood Ataxia with Central Nervous System Hypomyelination/Vanishing White Matter](#)).
11. Enns et al [2014], Lam et al [2017]
12. Genetic disorders that may be associated with low HVA and 5-HIAA include [mitochondrial disease](#), [Niemann-Pick disease type C](#), [Alexander disease](#), [glycine encephalopathy](#), [pontocerebellar hypoplasia type 2](#) (see [TSEN54-Related Pontocerebellar Hypoplasia](#)), Rett syndrome (see [MECP2 Disorders](#)), [Smith-Lemli-Opitz syndrome](#), [urea cycle disorders](#) [Molero-Luis et al 2013, Ng et al 2015].
13. Tullio-Pelet et al [2000], Handschug et al [2001]
14. Koehler et al [2013]
15. Anderson et al [2001], Edvardson et al [2012]
16. See OMIM Phenotypic Series: [Hereditary Sensory and Autonomic Neuropathy](#) to view genes and modes of inheritance associated with these phenotypes.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NGLY1*-related congenital disorder of deglycosylation (*NGLY1*-CDDG), the evaluations summarized in Table 3 (if not performed as part of the initial evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of *NGLY1*-CDDG

System/Concern	Evaluation	Comment
<b>Eyes</b>	Ophthalmologic eval for hypolacrima & retinal disease	
<b>ENT/Mouth</b>	Auditory brain stem evoked potentials	
<b>Respiratory</b>	Sleep study	If review of systems reveals snoring or symptoms concerning for sleep apnea

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
<b>Gastrointestinal</b>	Nutrition eval to optimize intake	Feeding & swallowing eval if indicated
	<ul style="list-style-type: none"> <li>• Transaminase levels</li> <li>• Eval for constipation</li> </ul>	Consultation w/gastroenterologist or hepatologist as needed
<b>Musculoskeletal</b>	Radiologic & orthopedic assessment incl DXA scan	To evaluate bone health & help manage scoliosis, coxa valga, &/or contractures
<b>Skin</b>	QSWEAT analysis to evaluate for hypohydrosis	
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>• Neurologic &amp; neurodevelopmental eval of cognitive abilities</li> <li>• Nerve conduction study</li> </ul>	
<b>Endocrinologic</b>	Vitamin D level	To assess for vitamin D deficiency
<b>Hematologic/Lymphatic</b>	Protein C; factor II, IX, XI; fibrinogen levels	Consultation w/hematologist if abnormal
<b>Miscellaneous/Other</b>	Speech & language eval	Referral to speech therapist if indicated
	Rehabilitation team eval	Referral for OT &/or PT if indicated
	Consultation w/clinical geneticist &/or genetic counselor	

DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

## Treatment of Manifestations

Treatment and quality of life can be optimized when care is provided by specialists in biochemical genetics, neurology, developmental pediatrics, ophthalmology, gastroenterology, orthopedics, and rehabilitation medicine who are knowledgeable about NGLY1-CDDG.

Table 4. Treatment of Manifestations in Individuals with NGLY1-CDDG

Manifestation/Concern	Treatment	Considerations/Other
<b>Hypolacrima</b>	Lubricating eye drops &/or bland ointments	
<b>Hearing loss</b>	Standard treatment	See <a href="#">Hereditary Hearing Loss and Deafness Overview</a> .
<b>Sleep apnea</b>	Routine management	
<b>Oromotor deficits leading to feeding problems</b>	Feeding therapy; supplemental tube feeding if indicated	Referral to gastroenterologist
<b>Constipation</b>	Standard management	Referral to gastroenterologist if refractory to typical medical management
<b>Abnormal hematologic &amp;/or gastroenterologic labs</b>	Follow up w/hematologist & gastroenterologist	
<b>Scoliosis &amp; osteopenia</b>	Routine management	
<b>Hypohydrosis</b>	Adequate access to water & cool environment (AC, wet T-shirt, &/or spray bottle of water)	Cooling vests may be helpful in hot climates.
<b>Seizures</b>	Standard treatment	Referral to neurologist for those w/refractory or severe seizures
<b>Vitamin D deficiency</b>	Supplemental vitamin D	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
<b>Any condition requiring surgical intervention</b>	Surgery best performed in centers w/surgeons & anesthesiologists experienced in care of those w/ metabolic disorders & special needs	

AC = air conditioning

## Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

**Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

### Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

**All ages.** Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

## Motor Dysfunction

### Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including dystonia, consider involving appropriate specialists to aid in management of baclofen, Botox<sup>®</sup>, anti-parkinsonian medications, or orthopedic procedures.

**Fine motor dysfunction.** Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

**Oral motor dysfunction.** Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

**Communication issues.** Consider evaluation for alternative means of communication (e.g., [augmentative and alternative communication](#) [AAC]) for individuals who have expressive language difficulties.

## Surveillance

In the absence of formal surveillance guidelines, the authors recommend the following:

- Annual follow up by:
  - Pediatrician or internist
  - Physical medicine and rehabilitation medicine
  - Ophthalmology
  - Neurology
  - Nutrition
- Follow up as recommended by:
  - Developmental pediatrician
  - Gastroenterologist/hepatologist
  - Audiologist
  - Clinical or biochemical geneticist

## Agents/Circumstances to Avoid

Hot environment should be avoided by those with hypohydrosis.

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

No FDA-approved treatments for NGLY1-CDDG exist.

Enzyme replacement therapy is currently being evaluated in the pre-clinical arena.

Pre-clinical screens for endo-beta-N-acetylglucosaminidase (ENGase) inhibitors are underway [Bi et al 2017].

Large-scale compound screens on model organisms and cell lines are being evaluated.

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*NGLY1*-related congenital disorder of deglycosylation (*NGLY1*-CDDG) is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *NGLY1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with *NGLY1*-CDDG are obligate heterozygotes (carriers) for a pathogenic variant in *NGLY1*.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a *NGLY1* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *NGLY1* pathogenic variants in the family.

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *NGLY1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Grace Science Foundation**  
**Phone:** 650-746-4591  
**Email:** [info@gracescience.org](mailto:info@gracescience.org)  
[www.gracescience.org](http://www.gracescience.org)
- **CDG CARE (Community Alliance and Resource Exchange)**  
**Phone:** 866-295-7910  
**Email:** [info@cdgcare.com](mailto:info@cdgcare.com)  
[cdgcare.org](http://cdgcare.org)

## Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

**Table A.** NGLY1-Related Congenital Disorder of Deglycosylation: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
<i>NGLY1</i>	3p24.2	Peptide-N(4)-(N-acetyl-beta-glucosaminyl)asparagine amidase	NGLY1	NGLY1

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for NGLY1-Related Congenital Disorder of Deglycosylation ([View All in OMIM](#))

610661	N-GLYCANASE 1; NGLY1
615273	CONGENITAL DISORDER OF DEGLYCOSYLATION 1; CDDG1

**Gene structure.** *NGLY1* is located on chromosome 3:25,718,944-25,790,039 on the reverse strand (GRCh38/hg19). The canonic transcript of *NGLY1*, [NM\\_018297.3](#) (ENST00000280700.9), has 12 exons, spans 2,473 bp, and encodes 654 amino acids. There are three protein coding transcript variants; the clinical relevance of these variants is unknown [Suzuki 2016]. See Table A, **Gene** for a detailed summary of gene and protein information.

**Pathogenic variants.** A number of loss-of-function pathogenic variants in *NGLY1* have been reported, including nonsense, missense, frameshift, and splice site variants. These occur all through the gene, with no obvious hot spots. The p.Arg401Ter nonsense variant is the most common, and since most of the individuals diagnosed with NGLY1-CDDG are of northern European background, this variant may have originated in northern Europe [Enns et al 2014].

**Table 5.** NGLY1 Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.622C>T	p.Gln208Ter	NM_018297.3 NP_060767.2
c.930C>T	p.Gly310= (splice site)	
c.1201A>T	p.Arg401Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

**Normal gene product.** N-glycanase contains 654 amino acids. Functional domains include:

- Amino acids 26-102: peptide:N-glycanase/UBA or UBX-containing proteins (PUB) domain
- Amino acids 269-354: catalytic transglutaminase domain
- Amino acids 457-651: PAW (present in PNGase and other worm proteins) domain

N-glycanase catalyzes the deglycosylation of misfolded glycoproteins as part of the endoplasmic reticulum-associated degradation (ERAD) process [Suzuki 2016]. This enzyme is highly conserved in eukaryotes down to yeast, although the yeast homolog is expressed in both the cytoplasm and nucleus [Suzuki et al 2000].

**Abnormal gene product.** The exact pathogenesis of the NGLY1-CDDG is unclear. Loss of N-glycanase is associated with dysregulation of the ERAD process [Enns et al 2014]. One hypothesis is that loss of N-glycanase and ERAD dysregulation results in endo-beta-N-acetylglucosaminidase (ENGase) to act on the unfolded glycoproteins, resulting in N-GlcNAc protein aggregation in the cytoplasm.

If the formation/aggregation of N-GlcNAc proteins is shown to be related to the symptoms/signs of NGLY1-CDDG, inhibition of ENGase activity may be a therapeutic target [Huang et al 2015]. Additionally, deglycosylation of certain glycoproteins may be necessary for their activation and may contribute to the pathogenesis of NGLY1-CDDG [Lehrbach & Ruvkun 2016].

## References

### Literature Cited

- Alston CL, Rocha MC, Lax NZ, Turnbull DM, Taylor RW. The genetics and pathology of mitochondrial disease. *J Pathol.* 2017;241:236-50. PubMed PMID: 27659608.
- Anderson SL, Coli R, Daly IW, Kichula EA, Rork MJ, Volpi SA, Ekstein J, Rubin BY. Familial dysautonomia is caused by mutations of the IKAP gene. *Am J Hum Genet.* 2001;68:753-8. PubMed PMID: 11179021.
- Bi Y, Might M, Vankayalapati H, Kuberan B. Repurposing of Proton Pump Inhibitors as first identified small molecule inhibitors of endo-β-N-acetylglucosaminidase (ENGase) for the treatment of NGLY1 deficiency, a rare genetic disease. *Bioorg Med Chem Lett.* 2017;27:2962-6. PubMed PMID: 28512024.
- Bosch DG, Boonstra FN, de Leeuw N, Pfundt R, Nillesen WM, de Ligt J, Gilissen C, Jhangiani S, Lupski JR, Cremers FP, de Vries BB. Novel genetic causes for cerebral visual impairment. *Eur J Hum Genet.* 2016;24:660-5. PubMed PMID: 26350515.
- Caglayan AO, Comu S, Baranoski JF, Parman Y, Kaymakcalan H, Akgumus GT, Caglar C, Dolen D, Erson-Omay EZ, Harmanci AS, Mishra-Gorur K, Freeze HH, Yasuno K, Bilguvar K, Gunel M. NGLY1 mutation causes neuromotor impairment, intellectual disability, and neuropathy. *Eur J Med Genet.* 2015;58:39-43. PubMed PMID: 25220016.
- Edvardson S, Cinnamon Y, Jalas C, Shaag A, Maayan C, Axelrod FB, Elpeleg O. Hereditary sensory autonomic neuropathy caused by a mutation in dystonin. *Ann Neurol.* 2012;71:569-72. PubMed PMID: 22522446.



- Enns GM, Shashi V, Bainbridge M, Gambello MJ, Zahir FR, Bast T, Crimian R, Schoch K, Platt J, Cox R, Bernstein JA, Scavina M, Walter RS, Bibb A, Jones M, Hegde M, Graham BH, Need AC, Oviedo A, Schaaf CP, Boyle S, Butte AJ, Chen R, Chen R, Clark MJ, Haraksingh R; FORGE Canada Consortium; Cowan TM, He P, Langlois S, Zoghbi HY, Snyder M, Gibbs RA, Freeze HH, Goldstein DB. Mutations in NGLY1 cause an inherited disorder of the endoplasmic reticulum-associated degradation pathway. *Genet Med*. 2014;16:751-8. PubMed PMID: 24651605.
- FDA. International Conference on Harmonisation; guidance on E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. *Fed Regist*. 2005;70:61134-5. PubMed PMID: 16237860.
- Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurology of inherited glycosylation disorders. *Lancet Neurol*. 2012;11:453-66. PubMed PMID: 22516080.
- Handschug K, Sperling S, Yoon SJ, Hennig S, Clark AJ, Huebner A. Triple A syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. *Hum Mol Genet*. 2001;10:283-90. PubMed PMID: 11159947.
- Heeley J, Shinawi M. Multi-systemic involvement in NGLY1-related disorder caused by two novel mutations. *Am J Med Genet A*. 2015;167A:816-20. PubMed PMID: 25707956.
- Huang C, Harada Y, Hosomi A, Masahara-Negishi Y, Seino J, Fujihira H, Funakoshi Y, Suzuki T, Dohmae N. Endo-beta-N-acetylglucosaminidase forms N-GlcNAc protein aggregates during ER-associated degradation in Ngly1-defective cells. *Proc Natl Acad Sci U S A*. 2015;112:1398-403. PubMed PMID: 25605922.
- Jaeken J, Hennes T, Matthijs G, Freeze HH. CDG nomenclature: time for a change! *Biochim Biophys Acta*. 2009;1792:825-6. PubMed PMID: 19765534.
- Koehler K, Malik M, Mahmood S, Giesselmann S, Beetz C, Hennings JC, Huebner AK, Grahn A, Reunert J, Nurnberg G, Thiele H, Altmuller J, Nurnberg P, Mumtaz R, Babovic-Vuksanovic D, Basel-Vanagaite L, Borck G, Bramswig J, Muhlenberg R, Sarda P, Sikiric A, Anyane-Yeboah K, Zeharia A, Ahmad A, Coubes C, Wada Y, Marquardt T, Vanderschaeghe D, Van Schaftingen E, Kurth I, Huebner A, Hubner CA. Mutations in GMPPA cause a glycosylation disorder characterized by intellectual disability and autonomic dysfunction. *Am J Hum Genet*. 2013;93:727-34. PubMed PMID: 24035193.
- Kong J, Peng M, Ostrovsky J, Kwon YJ, Oretsky O, McCormick EM, He M, Argon Y, Falk MJ. Mitochondrial function requires NGLY1. *Mitochondrion*. 2018; 38: 6-16. PubMed PMID: 28750948.
- Lam C, Ferreira C, Krasnewich D, Toro C, Latham L, Zein WM, Lehky T, Brewer C, Baker EH, Thurm A, Farmer CA, Rosenzweig SD, Lyons JJ, Schreiber JM, Gropman A, Lingala S, Ghany MG, Solomon B, Macnamara E, Davids M, Stratakis CA, Kimonis V, Gahl WA, Wolfe L. Prospective phenotyping of NGLY1-CDDG, the first congenital disorder of deglycosylation. *Genet Med*. 2017;19:160-8. PubMed PMID: 27388694.
- Lehrbach NJ, Ruvkun G. Proteasome dysfunction triggers activation of SKN-1A/Nrf1 by the aspartic protease DDI-1. *Elife*. 2016;5: e17721. PubMed PMID: 27528192.
- Marecos C, Ng J, Kurian MA. What is new for monoamine neurotransmitter disorders? *J Inher Metab Dis*. 2014;37:619-26. PubMed PMID: 24696406.
- Molero-Luis M, Serrano M, Ormazabal A, Perez-Duenas B, Garcia-Cazorla A, Pons R, Artuch R. Homovanillic acid in cerebrospinal fluid of 1388 children with neurological disorders. *Dev Med Child Neurol*. 2013;55:559-66. PubMed PMID: 23480488.
- Need AC, Shashi V, Hitomi Y, Schoch K, Shianna KV, McDonald MT, Meisler MH, Goldstein DB. Clinical application of exome sequencing in undiagnosed genetic conditions. *J Med Genet*. 2012;49:353-61. PubMed PMID: 22581936.
- Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders--clinical advances and future perspectives. *Nat Rev Neurol*. 2015;11:567-84. PubMed PMID: 26392380.

- Pons R. The phenotypic spectrum of paediatric neurotransmitter diseases and infantile parkinsonism. *J Inherit Metab Dis.* 2009;32:321-32. PubMed PMID: 19107571.
- Suzuki T, Park H, Hollingsworth NM, Sternglanz R, Lennarz WJ. PNG1, a yeast gene encoding a highly conserved peptide:N-glycanase. *J. Cell Biol.* 2000;149:1039-52 PubMed PMID: 10831608.
- Suzuki T. Catabolism of N-glycoproteins in mammalian cells: molecular mechanisms and genetic disorders related to the processes. *Mol Aspects Med.* 2016;51:89-103. PubMed PMID: 27237602.
- Tullio-Pelet A, Salomon R, Hadj-Rabia S, Mugnier C, de Laet MH, Chaouachi B, Bakiri F, Brottier P, Cattolico L, Penet C, Begeot M, Naville D, Nicolino M, Chaussain JL, Weissenbach J, Munnich A, Lyonnet S. Mutant WD-repeat protein in triple-A syndrome. *Nat Genet.* 2000;26:332-5. PubMed PMID: 11062474.

## Chapter Notes

### Author Notes

The Medical Genetics Branch of the National Human Genome Research Institute continues to study the natural history of patients with NGLY1-CDDG. Careful phenotyping facilitates the characterization of disease progression necessary to evaluate the efficacy of therapeutic interventions.

### Acknowledgments

Dr Matthew Might and Mrs Cristina Might ([www.ngly1.org](http://www.ngly1.org)) provided prevalence and genotype information included in this *GeneReview*.

### Revision History

- 8 February 2018 (ma) Review posted live
- 29 November 2016 (cl) Original submission

## License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: [admasst@uw.edu](mailto:admasst@uw.edu).