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Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview

Synonyms: Carbohydrate-Deficient Glycoprotein Syndromes, CDG Syndromes

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Summary

Many human disorders of glycosylation pathways have now been identified; they include defects in synthetic pathways for N-linked oligosaccharides, O-linked oligosaccharides, shared substrates, glycophosphatidylinositol (GPI) anchors, and dolichols. This overview will focus on disorders of the N-linked glycan synthetic pathway and some disorders that overlap this metabolic network (multiple-pathway disorders).

The goals of this overview on congenital disorders of glycosylation are the following:

Goal 1

Describe the clinical characteristics of congenital disorders of N-linked glycosylation.

Goal 2

Review the causes of congenital disorders of N-linked glycosylation.

Goal 3

Provide an evaluation strategy to identify the genetic cause of congenital disorders of glycosylation in a proband.

Goal 4

Inform (when possible) management.

Goal 5

Inform genetic counseling of family members of a proband with congenital disorders of N-linked glycosylation.

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Clinical Characteristics of Congenital Disorders of Glycosylation

Congenital disorders of N-linked glycosylation (CDG-N-linked) pathway – for the purposes of this *GeneReview* – refers to disorders of the N-linked glycan synthetic pathway and some disorders that overlap this metabolic network – referred to here as multiple-pathway disorders.

CDG-N-linked are a group of disorders caused by the defective synthesis of N-linked oligosaccharides, sugars linked together in a specific pattern and attached to proteins and lipids (N-linked glycans link to the amide group of asparagine via an N-acetylglucosamine residue) [Jaeken & Matthijs 2001, Grünewald et al 2002, Freeze 2006, Grünewald 2007].

Clinical Manifestations

Almost all types of congenital disorders of glycosylation (CDG) present in infancy. Because of the important biologic functions of the oligosaccharides in both glycoproteins and glycolipids, incorrect synthesis of these compounds results in broad multisystem clinical manifestations [Varki 1993] that may include one or more of the following: failure to thrive, developmental delay, hepatopathy, hypotonia/neurologic abnormalities, hypoglycemia, protein-losing enteropathy, eye abnormalities, immunologic findings, skin abnormalities, and skeletal findings [Rymen & Jaeken 2014]. It is becoming increasingly clear that the clinical spectrum can involve individual or multiple organ systems and may or may not affect neurodevelopment. CDG is increasingly being considered in the differential diagnosis for varied symptoms across multiple age groups and clinical specialties.

For many types of CDG, the phenotype is not completely known because only a few affected individuals have been reported.

Note: In 2009 the nomenclature for all types of CDG was changed to include the official gene symbol (not italicized) followed by "-CDG." If the type has a known letter name, it is added in parentheses as shown for CDG type 1a; new nomenclature: PMM2-CDG (*CDG-Ia*) [Jaeken et al 2009a].

CDG N-Linked

PMM2-CDG (*CDG-Ia*). The typical clinical course of PMM2-CDG *(CDG-Ia)* has been divided into an infantile multisystem stage, late-infantile and childhood ataxia-intellectual disability stage, and adult stable disability stage; see PMM2-CDG (*CDG-Ia*). The phenotypic spectrum includes hydrops fetalis at the severe end [van de Kamp et al 2007] and a mild neurologic phenotype in adults with multisystemic involvement at the mild end [Barone et al 2007, Coman et al 2007].

The infantile multisystem stage, the most commonly seen stage, is characterized by failure to thrive, inverted nipples, abnormal subcutaneous fat distribution, and cerebellar hypoplasia, in combination with facial dysmorphism and developmental delay.

Neuroimaging may demonstrate the following:

- An enlarged cisterna magna and superior cerebellar cistern in late infancy to early childhood

  In 13 affected individuals, the extent of cerebellar involvement on brain imaging correlated with functional and cognitive assessments [Serrano et al 2015].
- Occasionally both infratentorial and supratentorial changes compatible with atrophy
- Dandy-Walker malformations and small white matter cysts
- Myelination that varies from normal to insufficient or delayed maturation

- Areas of ischemia or edema followed by focal necrosis in those who have had a recent stroke-like episode [Ishikawa et al 2009]

MPI-CDG (*CDG-Ib*). Cyclic vomiting, profound hypoglycemia, failure to thrive, liver fibrosis, and protein-losing enteropathy, occasionally associated with coagulation disturbances without neurologic involvement, are characteristic [de Koning et al 1998, Jaeken et al 1998, Niehues et al 1998, Babovic-Vuksanovic et al 1999, de Lonlay et al 1999, Adamowicz et al 2000, de Lonlay & Seta 2009]. The clinical course is variable even within families.

ALG6-CDG (*CDG-Ic*) is now considered to be a common type of CDG [Jaeken et al 2015]. The characteristic clinical phenotype of ALG6-CDG (*CDG-Ic*) (previously carbohydrate-deficient glycoprotein syndrome type V) includes hypotonia, developmental delay, ataxia and epilepsy [Morava et al 2016].

- The clinical presentation may be milder than in PMM2-CDG (*CDG-Ia*); stroke-like episodes and peripheral neuropathy have not been reported.
- Rare features have included brachydactyly, deep vein thrombosis, pseudotumor cerebri with normal brain MRI, pubertal abnormalities including hyperandrogenism with virilization, and retinal degeneration [Sun et al 2005, Kahook et al 2006, Miller et al 2011].

ALG3-CDG (*CDG-Id*). A total of 11 affected individuals have been described; features include severe neurologic involvement, microcephaly, seizures, dysmorphic facial features, skeletal anomalies (arthrogryposis multiplex congenita, chondrodysplasia punctata), and eye anomalies (cataract, corneal opacities, iris coloboma) [Lepais et al 2015].

DPM1-CDG (*CDG-Ie*). Features may include severe developmental delay, microcephaly, seizures, ataxia, peripheral neuropathy, eye abnormalities (retinopathy, nystagmus, strabismus), and severe gastrointestinal involvement [Dancourt et al 2006, Bursle et al 2017]. One infant presented with congenital muscular dystrophy similar to that seen in the dystroglycanopathies [Yang et al 2013].

MPDU1-CDG (*CDG-If*). Five individuals had severe developmental delay, generalized scaly, erythematous skin, and attacks of hypertonia [Jaeken et al 2000, Kranz et al 2001, Schenk et al 2001].

ALG12-CDG (*CDG-Ig*). Features may include generalized hypotonia, feeding difficulties, moderate to severe developmental delay, progressive microcephaly, seizures, dysmorphic facial features, frequent upper respiratory tract infections, hypogonadism with or without hypospadias, impaired immunity with decreased immunoglobulin levels, cardiac anomalies, and decreased coagulation factors [Chantret et al 2002, Grubenmann et al 2002, Thiel et al 2002, Zdebska et al 2003, Di Rocco et al 2005, Eklund et al 2005a, Eklund et al 2005b, Kranz et al 2007a].

ALG8-CDG (*CDG-Ih*) is characterized by severe multisystem involvement with seizures, distinctive facial features, protein-losing enteropathy, and hematopoietic issues (anemia, thrombocytopenia, decreased levels of factor XI, protein C, and antithrombin III) [Chantret et al 2003, Schollen et al 2004a, Eklund et al 2005b, Höck et al 2015].

A pair of sibs who had a milder presentation with pseudo-gynecomastia, hypotonia, intellectual disability, and ataxia were described [Stölting et al 2009].

ALG2-CDG (*CDG-Ii*). An individual age six years had bilateral iris colobomas, unilateral cataract, infantile spasms beginning at age four months, and severe developmental delay; coagulation factors were abnormal [Thiel et al 2003].

DPAGT1-CDG (*CDG-Ij*) is characterized by hypotonia, intractable seizures, developmental delay, skeletal anomalies, and microcephaly [Carrera et al 2012, Timal et al 2012, Würde et al 2012].

ALG1-CDG (*CDG-Ik*). The phenotypic spectrum ranges from mild intellectual disability to death in the first few weeks of life [Ng et al 2016]. Features may include severe developmental delay, rapidly progressive microcephaly, hypotonia, early-onset seizures, severe coagulation defects, immunodeficiency, nephrotic syndrome, liver dysfunction, and cardiomyopathy [Schwarz et al 2004, Dupré et al 2010].

ALG9-CDG (*CDG-IL*). Features may include microcephaly, hypotonia, developmental delay, seizures, hepatomegaly, pericardial effusion, renal cysts, and skeletal dysplasia. Brain MRI may demonstrate cerebral atrophy and delayed myelination [Frank et al 2004, Weinstein et al 2005, AlSubhi et al 2016].

DOLK-CDG (*CDG-Im*). Dilated cardiomyopathy in combination with a muscular dystrophy phenotype [Lefeber et al 2011], a purely neurologic phenotype [Helander et al 2013], and a severe fatal multiple system syndrome have been described [Lieu et al 2013]. Features may include hypotonia, ichthyosis, seizures, and progressive microcephaly.

RFT1-CDG (*CDG-In*). Common features include severe developmental delay, hypotonia, visual disturbances, seizures, feeding difficulties, sensorineural hearing loss, inverted nipples, and microcephaly [Jaeken et al 2009b, Vleugels et al 2009]. Two adult sibs had severe cognitive impairment and controlled seizures; neither had visual impairment [Ondruskova et al 2012].

DPM3-CDG (*CDG-Io*). A single described individual diagnosed at age 27 years had a low normal IQ and mild muscle weakness. She presented initially at age 11 years with mild muscle weakness and waddling gait. She had dilated cardiomyopathy without signs of cardiac muscle hypertrophy at age 20 years followed by a stroke-like episode at age 21 years [Lefeber et al 2009].

ALG11-CDG (*CDG-Ip*). Features include developmental delay, strabismus, and seizures [Thiel et al 2012]. One infant developed an unusual fat pattern around age six months [Rind et al 2010]; she had persistent vomiting and gastric bleeding and died at age two years.

SRD5A3-CDG (*CDG-Iq*). Common features including congenital eye malformations (ocular coloboma, optic nerve hypoplasia, and variable degree of visual loss), nystagmus, hypotonia, developmental delay/intellectual disability, and cerebellar ataxia. Less commonly affected individuals have dermatologic complications and/or congenital heart defects [Cantagrel et al 2010, Morava et al 2010].

Note: Biallelic pathogenic variants in *SRD5A3* have also been identified in people with Kahrizi syndrome, an allelic disorder characterized by coloboma, cataract, kyphosis, and intellectual disability [Kahrizi et al 2011].

DDOST-CDG (*CDG-Ir*). A single child was described, presenting with failure to thrive, developmental delay, hypotonia, strabismus and hepatic dysfunction. At three years the child walked but continued to have fine motor delays and minimal speech development. Brain MRI showed dysmyelination [Jones et al 2012].

MAGT1-CDG was reported in a family with two girls with mild cognitive impairment and two boys with more severe cognitive involvement. The mother is reported to have mild cognitive impairment [Molinari et al 2008].

TUSC3-CDG has been described in 12 individuals (including 2 French sibs and 3 Iranian sibs) with nonsyndromic moderate-to-severe cognitive impairment and normal brain MRI [Garshasbi et al 2011].

ALG13-CDG was described in one child with microcephaly, hepatomegaly, edema of the extremities, intractable seizures, recurrent infections and increased bleeding tendency who died at age one year [Timal et al 2012].

PGM1-CDG. Features may include dilated cardiomyopathy, chronic hepatitis, fatigue, and Pierre Robin sequence with cleft palate [Timal et al 2012].

Note: Biallelic pathogenic variants in *PGM1* have also been described in an individual with a clinical diagnosis of glycogen storage disease type 14 with recurrent rhabdomyolysis [Stojkovic et al 2009].

STT3A-CDG (*CDG-Iw*). Two sibs have been described with microcephaly, cognitive impairment, failure to thrive, seizures, and cerebellar atrophy [Shrimal et al 2013].

STT3B-CDG (*CDG-Ix*). A single individual with microcephaly, severe developmental delay, failure to thrive, seizure disorder, and liver and genitourinary abnormalities has been described [Shrimal et al 2013].

SSR4-CDG (*CDG-Iy*) is an X-linked disorder in which males have microcephaly, cognitive impairment, and seizure disorder. Other features may include feeding issues with oral aversion, failure to thrive, and distinctive facial features. Less commonly, skeletal, hematologic, cardiac, and renal abnormalities have been described [Ng et al 2015].

MGAT2-CDG (*CDG-IIa*). Individuals have facial dysmorphism, stereotypic hand movements, seizures, and varying degrees of developmental delay, but no peripheral neuropathy or cerebellar hypoplasia. A bleeding disorder is caused by diminished platelet aggregation [Van Geet et al 2001].

MOGS-CDG (*CDG-IIb*). Findings include distinctive facial features, generalized hypotonia, cognitive impairment, seizures, abnormal brain imaging, hearing loss, and recurrent infections along with hypogammaglobulinemia [Sadat et al 2014]. One infant also had hypoplastic genitalia, feeding difficulties, hypoventilation, and generalized edema [De Praeter et al 2000].

SLC35C1-CDG (*CDG-IIc*). Severe growth and developmental delay, microcephaly, hypotonia, distinctive facial l features, and recurrent bacterial infections with persistent, highly elevated peripheral blood leukocyte count are characteristic [Etzioni et al 2002].

B4GALT1-CDG (*CDG-IId*). Mild developmental delay, Dandy-Walker malformation, progressive hydrocephalus, coagulation abnormalities, and elevated serum creatine kinase concentration have been observed [Peters et al 2002].

SLC35A2-CDG is an X-linked disorder leading to severe early-onset encephalopathy [Kodera et al 2013].

GMPPA-CDG was identified in several individuals with cognitive impairment and autonomic dysfunction including achalasia and alacrima. Gait abnormalities were also seen [Koehler et al 2013].

Multiple-Pathway Disorders

COG7-CDG (*CDG-IIe*). Features include dysmorphic facies with a small mouth (although one had full lips), micro- and retrognathia, short neck, wrinkled and loose skin, adducted thumbs, overlapping long fingers, hypotonia, hepatosplenomegaly and progressive jaundice, seizures, and early death [Wu et al 2004, Spaapen et al 2005, Morava et al 2007, Ng et al 2007].

SLC35A1-CDG (*CDG-IIf*). One affected infant presented at age four months with macrothrombocytopenia, neutropenia, and immunodeficiency, and died at age 37 months of complications from bone marrow transplantation [Martinez-Duncker et al 2005].

COG1-CDG (*CDG-IIg*). An affected infant presented in the first month of life with feeding difficulties, failure to thrive, and hypotonia. She had mild developmental delays, rhizomelic short stature, and progressive microcephaly with slight cerebral and cerebellar atrophy on brain MRI, as well as cardiac abnormalities and hepatosplenomegaly [Foulquier et al 2006].

COG2-CDG. A single individual was described with acquired microcephaly, cognitive impairment, seizures and liver dysfunction [Kodera et al 2015].

COG8-CDG (*CDG-IIh*). Two affected infants with severe developmental delay, hypotonia, seizures, esotropia, failure to thrive, and progressive microcephaly were reported [Foulquier et al 2007, Kranz et al 2007b].

COG5-CDG (*CDG-IIi*). Features may include peripheral neuropathy, hepatic dysfunction, and mild cognitive impairment, although more severe cognitive impairment with blindness and deafness has also been described [Paesold-Burda et al 2009, Rymen et al 2012].

COG4-CDG (*CDG-IIj*). Features include severe cognitive impairment, seizures, hypotonia, liver cirrhosis, recurrent infections and early death. Less common features may include microcephaly, ataxia, and brisk uncoordinated movements [Reynders et al 2009, Ng et al 2011].

TMEM165-CDG (*CDGIIk*). Sibs with a skeletal dysplasia affecting the epiphyses, metaphyses, and diaphyse were described. Additional features included abnormal white matter and pituitary hypoplasia on brain MRI [Foulquier et al 2012].

COG6-CDG (*CDG-IIL*). Features include microcephaly, cognitive impairment, seizures, liver abnormalities, recurrent infections, and ectodermal involvement with hypohidrosis and hyperkeratosis [Lübbehusen et al 2010, Rymen & Jaeken 2014].

DHDDS-CDG. Features may include microcephaly, severe developmental delay, liver and renal dysfunction, and severe seizures or retinitis pigmentosa as an isolated finding [Willer et al 2012, Sabry et al 2016].

DPM2-CDG. Failure to thrive, developmental delay, osteopenia, hypotonia, liver dysfunction, increased creatine kinase, and early death have been observed [Barone et al 2012].

MAN1B1-CDG is characterized by nonsyndromic intellectual disability [Rafiq et al 2011].

PGM3-CDG. Eight individuals with severe atopic dermatitis, recurrent infections due to immunodeficiency, and renal involvement have been described [Zhang et al 2014].

Causes of Congenital Disorders of Glycosylation

Forty-two different enzymes in the N-linked oligosaccharide synthetic pathway or interactive pathways are currently recognized to be deficient in each of the types of CDG-N-linked or among the multiple-pathway disorders (see Table 1).

Table 1. Molecular Genetics of Congenital Disorders of Glycosylation

CDG Type [1]	# of Cases Reported [2]	Gene [3]	Protein [3]	MOI
CDG-N-linked				
PMM2-CDG (*CDG-Ia*)	700 [4]	*PMM2*	Phosphomannomutase 2	AR
MPI-CDG (*CDG-Ib*)	20	*MPI*	Mannose-6-phosphate isomerase	AR
ALG6-CDG (*CDG-Ic*)	89	*ALG6*	Dolichyl pyrophosphate Man(9)GlcNAc(2)-PP-Dol alpha-1,3-glucosyltransferase	AR
ALG3-CDG (*CDG-Id*)	11	*ALG3*	Dol-P-Man:Man(5)GlcNAc(2)-PP-Dol alpha-1,3-mannosyltransferase	AR
DPM1-CDG (*CDG-Ie*)	9	*DPM1*	Dolichol-phosphate mannosyltransferase subunit 1	AR
MPDU1-CDG (*CDG-If*)	5	*MPDU1*	Mannose-P-dolichol utilization defect 1 protein	AR
ALG12-CDG (*CDG-Ig*)	7	*ALG12*	Dol-P-Man:Man(7)GlcNAc(2)-PP-Dol alpha-1,6-mannosyltransferase	AR
ALG8-CDG (*CDG-Ih*)	5	*ALG8*	Probable dolichyl pyrophosphate Glc1Man9GlcNAc2 alpha-1,3-glucosyltransferase	AR
ALG2-CDG (*CDG-Ii*)	≤2	*ALG2*	Alpha-1,3/1,6-mannosyltransferase ALG2	AR

Table 1. continued from previous page.

CDG Type [1]	# of Cases Reported [2]	Gene [3]	Protein [3]	MOI
DPAGT1-CDG (*CDG-Ij*)	5	*DPAGT1*	UDP-N-acetylglucosamine--dolichyl-phosphate N-acetylglucosaminephosphotransferase	AR
ALG1-CDG (*CDG-Ik*)	57	*ALG1* (*HMT-1*)	Chitobiosyldiphosphodolichol beta-mannosyltransferase	AR
ALG9-CDG (*CDG-IL*)	≤2	*ALG9*	Alpha-1,2-mannosyltransferase ALG9	AR
DOLK-CDG (*CDG-Im*)	≤2	*DOLK (DK1)*	Dolichol kinase	AR
RFT1-CDG (*CDG-In*)	6	*RFT1*	Protein RFT1 homolog	AR
DPM3-CDG (*CDG-Io*)	≤2	*DPM3*	Dolichol-phosphate mannosyltransferase subunit 3	AR
ALG11-CDG (*CDG-Ip*)	4	*ALG11*	GDP-Man:Man(3)GlcNAc(2)-PP-Dol alpha-1,2-mannosyltransferase	AR
SRD5A3-CDG (*CDG-Iq*)	15	*SRD5A3*	Polyprenol reductase	AR
DDOST-CDG (*CDG-Ir*)	1	*DDOST*	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	AR
MAGT1-CDG	4	*MAGT1*	Magnesium transporter protein 1	XL
TUSC3-CDG	12	*TUSC3*	Tumor suppressor candidate 3	AR
ALG13-CDG	1	*ALG13*	Putative bifunctional UDP-N-acetylglucosamine transferase and deubiquitinase ALG13	XL
PGM1-CDG	2	*PGM1*	Phosphoglucomutase-1	AR
MGAT2-CDG (*CDG-IIa*)	4	*MGAT2*	Alpha-1,6-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltransferase	AR
STT3A-CDG, STT3B-CDG	2	*STT3A, STT3B*	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3A/STT3B	AR
SSR4-CDG	<2	*SSR4*	Translocon-associated protein subunit delta	XL
MOGS-CDG (*CDG-IIb*)	≤2	*MOGS (GCS1)*	Mannosyl-oligosaccharide glucosidase	AR
SLC35C1-CDG (*CDG-IIc*)	≤2	*SLC35C1*	GDP-fucose transporter 1	AR
B4GALT1-CDG (*CDG-IId*)	≤2	*B4GALT1*	Beta-1,4-galactosyltransferase 1	AR
SLC35A2-CDG	<2	SLC35A2	UDP-galactose translocator	XL
GMPPA-CDG	<2	*GMPPA*	Mannose-1-phosphate guanyltransferase alpha	AR
Multiple-pathway disorders				
COG7-CDG (*CDG-IIe*)	≤2	*COG7*	Conserved oligomeric Golgi complex subunit 7	AR
SLC35A1-CDG (*CDG-IIf*)	≤2	*SLC35A1*	CMP-sialic acid transporter	AR
COG1-CDG (*CDG-IIg*)	≤2	*COG1*	Conserved oligomeric Golgi complex subunit 1	AR
COG2-CDG	1	*COG2*	Conserved oligomeric Golgi complex subunit 2	AR
COG8-CDG (*CDG-IIh*)	≤2	*COG8*	Conserved oligomeric Golgi complex subunit 8	AR
COG5-CDG (*CDG-IIi*)	7	*COG5*	Conserved oligomeric Golgi complex subunit 5	AR

Table 1. continued from previous page.

CDG Type [1]	# of Cases Reported [2]	Gene [3]	Protein [3]	MOI
COG4-CDG (*CDG-IIj*)	≤2	*COG4*	Conserved oligomeric Golgi complex subunit 4	AR
TMEM165-CDG (*CDG-IIk*)	5	*TMEM165*	Transmembrane protein 165	AR
COG6-CDG (*CDG-IIL*)	17	*COG6*	Conserved oligomeric Golgi complex subunit 6	AR
DPM2-CDG	<2	*DPM2*	Dolichol phosphate-mannose biosynthesis regulatory protein	AR
DHDDS-CDG	<2	*DHDDS*	Dehydrodolichyl diphosphate syntase complex subunit DHDDS	AR
MAN1B1-CDG	<2	*MAN1B1*	Endoplasmic reticulum mannosyl-oligosaccharide 1,2-alpha-mannosidase	AR
PGM3-CDG	8	*PGM3*	Phosphoglucomutase 3	AR

AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked inheritance

1. The nomenclature used for CDG types includes a Roman numeral, I or II, and a letter (a-z) [Aebi et al 1999]. The Roman numeral is based on transferrin oligosaccharide analytic pattern: Type I and Type II. Letters are assigned in chronologic order of the date of publication of discovery.

2. Proportion of CDG types as reported in Jaeken [2010]

3. Data are compiled from the following standard references: gene from HGNC; protein from UniProt.

4. The prevalence of PMM2-CDG (*CDG-1a*) may be as high as 1:20,000 [Jaeken & Matthijs 2001]. The expected carrier frequency of *PMM2* pathogenic variants in the Danish population is 1:60-1:79 [Matthijs et al 2000].

Evaluation Strategy

The diagnostic test for all N-linked types of CDG is analysis of serum transferrin glycoforms, also called "transferrin isoforms analysis" or "carbohydrate-deficient transferrin analysis." This diagnostic test is performed by isoelectric focusing (IEF) or by capillary electrophoresis, GC/MS, CE-ESI-MS, or MALDI-MS to determine the number and presence of incomplete sialylated N-linked oligosaccharide residues linked to serum transferrin [Jaeken & Carchon 2001, Marklová & Albahri 2007, Sanz-Nebot et al 2007].

Results of such testing may reveal the following:

- **Normal transferrin isoform pattern.** Two biantennary glycans linked to asparagine with four sialic acid residues
- **Type I transferrin isoform pattern.** Decrease of tetrasialotransferrin and increased asialotransferrin and disialotransferrin. The pattern indicates defects in the earliest synthetic steps of the N-linked oligosaccharide synthetic pathway.
- **Type II transferrin isoform pattern.** Increased trisialo- and monosialo- fractions, most likely because of the incorporation of truncated or monoantennary sugar chains, defects in the terminal portion of the pathway [Jaeken & Matthijs 2001].

Note: (1) The diagnostic validity of analysis of serum transferrin glycoforms before age three weeks is controversial [Clayton et al 1992, Stibler & Skovby 1994]. (2) The use of Guthrie cards with whole blood samples is not suggested; however, the use of Guthrie cards with blotted serum yields accurate results [Carchon et al 2006]. (3) Rarely, individuals with the diagnosis of PMM enzyme deficiency with normal transferrin glycosylation have been reported [Fletcher et al 2000, Marquardt & Denecke 2003, Hahn et al 2006]. (4) Results are expected to be normal in MOGS-CDG (*CDG-IIb*) and SLC35C1-CDG (*CDG-IIc*). (5) The possibility that an abnormal transferrin glycoform analysis is the result of a transferrin protein variant can be confirmed with a glycoform analysis of a serum sample from the parents.

Molecular Genetic Testing

The type of CDG is established in a proband by the identification of biallelic pathogenic (or likely pathogenic) variants (or a hemizygous pathogenic variant in a male with an X-linked CGD) in one of the 44 known CDG-associated genes (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

If previous biochemical testing is not diagnostic for or suggestive of a particular CDG, molecular testing approaches most often involve use of a **multigene panel** or **more comprehensive genomic testing**.

Note: Single-gene testing, such as sequencing of *PMM2*, *MP1*, and a few other genes, is available for individuals with abnormal transferrin results and a strong clinical suspicion for a specific CGD subtype.

A multigene panel that includes some or all of the 44 genes discussed in this *GeneReview* may be considered. 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.

More comprehensive genomic testing including exome sequencing and genome sequencing may be considered if the phenotype alone is insufficient to support gene-targeted testing or if use of a multigene panel that includes some or all of the genes listed in Table 1 fails to confirm a diagnosis in an individual with abnormal serum transferrin and clinical features of CDG. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic, particularly when the proband is male and deletion or duplication of an X-linked gene could explain the clinical features.

Management

Treatment of Manifestations

For all congenital disorders of N-linked glycosylation and most multiple-pathway disorders except MPI-CDG (*CDG-Ib*)

- **Failure to thrive.** Infants and children can be fed any type of formula for maximal caloric intake. They can tolerate carbohydrates, fats, and protein. Early in life, children may do better on elemental formulas. Their

feeding may be advanced based on their oral motor function. Some children require placement of a nasogastric tube or gastrostomy tube for nutritional support until oral motor skills improve.

- **Oral motor dysfunction with persistent vomiting.** Thickening of feeds, maintenance of an upright position after eating, and antacids can be helpful for children with gastroesophageal reflux and/or persistent vomiting. Consultation with a gastroenterologist and nutritionist is often necessary. Children with a gastrostomy tube should be encouraged to eat by mouth if the risk of aspiration is low. Continued speech and oral motor therapy aids transition to oral feeds and encourages speech when the child is developmentally ready.
- **Developmental delay.** Occupational therapy, physical therapy, and speech therapy should be instituted. As the developmental gap widens between children with CDG and their unaffected peers, parents, educators, and therapists need continued counseling and support.
- **"Infantile catastrophic phase."** Very rarely, infants may have a complicated early course presenting with infection, seizure, or hypoalbuminemia with third spacing that may progress to anasarca. Some children are responsive to aggressive albumin replacement with Lasix®; others may have a more refractory course. Symptomatic treatment in a pediatric tertiary care center is recommended. Parents should also be advised that some infants with PMM2-CDG (*CDG-Ia*) never experience a hospital visit while others may require frequent hospitalizations.
- **Strabismus.** Consultation with a pediatric ophthalmologist early in life is important so that potential eye abnormalities can be diagnosed and therapies that preserve vision (glasses, patching, or surgery) can be instituted as needed.
- **Hypothyroidism.** Although children with CDG are usually chemically euthyroid [Martin & Freeze 2003], thyroid function tests are frequently abnormal. However, free thyroxine analyzed by equilibrium dialysis, the most accurate method, has been reported as normal in seven individuals with CDG. Diagnosis of hypothyroidism and L-thyroxine supplementation should be reserved for those children and adults with elevated TSH and low free thyroxine measured by equilibrium dialysis.
- **Renal issues.** Bilateral hyperechoic kidneys are often seen on ultrasound in children with PMM2-CDG (*CDG-Ia*). Enlarged kidneys, renal cysts, and congenital nephrotic syndrome have been reported in individuals with PMM2-CDG (*CDG-Ia*) and other forms of CDG.
    - Baseline renal ultrasound should be performed on all affected children at the time of diagnosis [Grünewald 2009, Sinha et al 2009].
    - While proteinuria in affected children is extremely rare, routine urinalysis to evaluate for proteinuria is recommended after diagnosis. Follow-up urinalysis should be considered in the first three years of life or if clinical signs indicate.
- **Stroke-like episodes.** Supportive therapy includes intravenous hydration, maintenance of normal blood glucose, and physical therapy during the recovery period.
- **Coagulopathy.** Low levels of coagulation factors, both pro- and anticoagulant, rarely cause clinical problems in daily activities but must be addressed when an individual with CDG undergoes surgery. Consultation with a hematologist is recommended to document the pro- and anti- clotting factor levels and coagulation status. Discussion of the coagulation status and management issues with the surgeon is important. When necessary, infusion of fresh frozen plasma corrects the factor deficiency and clinical bleeding. The potential for imbalance of the level of both pro- and anticoagulant factors may lead to either bleeding or thrombosis. Care givers, especially of older affected individuals, should be taught the signs of deep venous thrombosis, which can occasionally be mistaken for injury from trauma in individuals with intellectual and communication disabilities.
- **Immunologic status.** Most individuals affected with CDGs have functional immune systems; however, children with rare types of N-linked CDG have recurrent or unexpectedly severe infections and should be evaluated by an immunologist. Unless otherwise indicated, full pediatric vaccinations are recommended for affected children and adults.

Additional management issues of adults with CDG

- **Orthopedic issues — thorax shortening, scoliosis/kyphosis.** Management involves appropriate orthopedic and physical medicine management, well-supported wheel chairs, appropriate transfer devices for the home, and physical therapy. Occasionally, surgical treatment of spinal curvature by an experienced team is warranted.
- **Independent living issues.** Young adults with CDG and their parents need to address issues of independent living. Aggressive education in functional life skills and/or vocational training help the transition when schooling is completed. Independence in self-care and the activities of daily living should be encouraged. Support and resources for parents of a disabled adult are important aspects of management.
- **Deep venous thrombosis (DVT).** DVT has been reported in several adults with PMM2-CDG (*CDG-Ia*) and MPI-CDG (*CDG-Ib*) and should be kept in mind in the management of all individuals with CDG. Rapid diagnosis and treatment of DVT are essential to minimize the risk of pulmonary emboli; sedentary affected adults and children are at increased risk for DVT.

Prevention of Primary Manifestations

MPI-CDG (*CDG-Ib*), characterized by hepatic-intestinal disease, is the most common type of CDG for which therapy exists. Because so few individuals have been treated and the natural history of this disorder is variable, careful monitoring and discussion among physicians treating these individuals are warranted [Jaeken et al 1998, Niehues et al 1998, de Lonlay et al 1999, Hendriksz et al 2001, de Lonlay & Seta 2009]:

- In the first reported case, mannose normalized hypoproteinemia and coagulation defects and rapidly improved the protein-losing enteropathy and hypoglycemia [Harms et al 2002]. One gram of mannose per kg body weight was given per day, divided into five oral doses.
- In two children with MPI-CDG (*CDG-Ib*) treated from infancy with mannose, protein-losing enteropathy and vomiting improved significantly; however, the two children were recently reported to have progressive liver fibrosis [Mention et al 2008].
- Recurrent episodes of thromboembolism and consumptive coagulopathy did not recur in an individual with MPI-CDG (*CDG-Ib*) treated with mannose [Tamminga et al 2008].
- For some individuals with MPI-CDG (*CDG-Ib*), heparin therapy can be an alternative to mannose in the treatment of the enteropathy [de Lonlay & Seta 2009].
- A woman age 28 years with MPI-CDG (*CDG-Ib*) developed progressive liver fibrosis despite mannose treatment and heparin therapy and had a successful liver transplant with resolution of her symptoms for at least two years post transplant [Janssen et al 2014].

Prevention of Secondary Complications

Because infants with CDG have more limited reserves than their peers, parents should have a low threshold for evaluation by a physician for prolonged fever, vomiting, or diarrhea. Aggressive intervention with antipyretics, antibiotics (if warranted), and hydration may prevent stroke-like episodes, seizures in children with potentially lower seizure threshold as well as the morbidity associated with the "infantile catastrophic phase."

Surveillance

Annual

- Assessment by a physician with attention to overall health and possible need for referral for speech, occupational, and physical therapy
- Eye examination

- Liver function tests; thyroid panel; serum concentrations of the clotting factors protein C, protein S, factor IX, and antithrombin III

Other

- Periodic assessment of bleeding and clotting parameters by a hematologist
- Follow up with an orthopedist when scoliosis becomes evident

Agents/Circumstances to Avoid

Acetominophen and other agents metabolized by the liver should be used with caution.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from prompt initiation of treatment (in the treatable forms of N-linked CDG) and those who require developmental monitoring and medical management.

Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Serum transferrin analysis if the pathogenic variant(s) in the family are not known and transferrin was abnormal in the proband.

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

Therapies Under Investigation

In one individual with SLC35C1-CDG (*CDG-IIc*), fucose improved the fucosylation of glycoproteins and reduced recurrent infections [Marquardt et al 1999].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to 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

Most congenital disorders of N-linked glycosylation and multiple pathway (CDG-N-linked) are inherited in an autosomal recessive manner. MGAT1-CDG, ALG13-CDG, SLC35A2-CDG, and SSR4-CDG are inherited in an X-linked manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one 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. See, however, Related Genetic Counseling Issues, **Increased recurrence risk for PMM2-CDG (*CDG-Ia*)**.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Adults with CDG – except for those with MPI-CDG (*CDG-Ib*) – have not been reported to reproduce. (One woman with MPI-CDG (*CDG-Ib*) had a child without complications.)
- The offspring of an individual with MPI-CDG (*CDG-Ib*) are obligate heterozygotes (carriers).

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the CDG-N-linked-related pathogenic variants in the family.

X-linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of a male with MAGT1-CDG, ALG13-CDG, SLC35A2-CDG, or SSR4-CDG will not have the disorder nor will he be hemizygous for the pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier. The proportion of affected males representing simplex cases is unknown.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers. There have not been any reported cases of a heterozygous female (carrier) being affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. To date it is unknown whether affected males can reproduce.

Carrier detection. Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the CDG-N-linked-related pathogenic variant has been identified in the proband.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Increased recurrence risk for PMM2-CDG (*CDG-Ia*). Studies of the outcomes of prenatal testing suggest that the percentage of affected fetuses is higher than predicted by Mendel's second law. The risk to sibs of a proband is estimated to be closer to 1/3 than to the expected 1/4. This finding of an apparent increased recurrence risk as a result of transmission ratio distortion continues to be validated [Schollen et al 2004b].

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 affected, 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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in the family, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for a congenital disorder of N-linked glycosylation or multiple pathway are possible.

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.

- **CDG CARE (Community Alliance and Resource Exchange)**
  Phone: 866-295-7910
  Email: info@cdgcare.com
  cdgcare.org
- **Foundation Glycosylation (FoG)**
  Canada
  www.thefog.ca
- **Portuguese Association CDG and other Rare Metabolic Diseases (APCDG-DMR)**
  Portugal
  www.apcdg.com
- **Practical Guide to CDG**
  Practical Guide to CDG

Chapter Notes

Author Notes

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