U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Sparks SE, Krasnewich DM. Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview. 2005 Aug 15 [Updated 2017 Jan 12]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview

Synonyms: Carbohydrate-Deficient Glycoprotein Syndromes, CDG Syndromes

Susan E Sparks, MD, PhD[1] and Donna M Krasnewich, MD, PhD[2]

Created: August 15, 2005; Updated: January 12, 2017.

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.

Author Affiliations: 1 Sanofi Genzyme, Cambridge, Massachusetts; Email: susan.sparks@genzyme.com. 2 National Institutes of Health, Bethesda, Maryland; Email: dkras@mail.nih.gov.

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].

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 was found to have 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].

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

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 variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both 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

References

Literature Cited

Adamowicz M, Matthijs G, Van Schaftingen E, Jaeken J, Rokicki D, Pronicki M. New case of phosphomannose isomerase deficiency (CDG Ib). J Inherit Metab Dis. 2000;23 Suppl 1:184.

Aebi M, Helenius A, Schenk B, Barone R, Fiumara A, Berger EG, Hennet T, Imbach T, Stutz A, Bjursell C, Uller A, Wahlström JG, Briones P, Cardo E, Clayton P, Winchester B, Cormier-Dalre V, de Lonlay P, Cuer M, Dupré T, Seta N, de Koning T, Dorland L, de Loos F, Kupers L, et al. Carbohydrate-deficient glycoprotein syndromes become congenital disorders of glycosylation: an updated nomenclature for CDG. First International Workshop on CDGS. Glycoconj J. 1999;16:669–71. PubMed PMID: 11003549.

AlSubhi S, AlHashem A, AlAzami A, et al. Further delineation of the Alg9-CDG phenotype. JIMD Rep. 2016;27:107–12. PubMed PMID: 26453364.

Babovic-Vuksanovic D, Patterson MC, Schwenk WF, O'Brien JF, Vockley J, Freeze HH, Mehta DP, Michels VV. Severe hypoglycemia as a presenting symptom of carbohydrate-deficient glycoprotein syndrome. J Pediatr. 1999;135:775–81. PubMed PMID: 10586187.

Barone R, Sturiale L, Fiumara A, Uziel G, Garozzo D, Jaeken J. Borderline mental development in a congenital disorder of glycosylation (CDG) type Ia patient with multisystemic involvement (intermediate phenotype). J Inherit Metab Dis. 2007;30:107. PubMed PMID: 17186415.

Barone R, Aiello C, Race V, Morava E, Foulquier F, Riemersma M, Passarelli C, Concolino D, Carella M, Santorelli F, Vleugels W, Mercuri E, Garozzo D, Sturiale L, Messina S, Jaeken J, Fiumara A, Wevers RA, Bertini E, Matthijs G, Lefeber DJ. DPM2-CDG: A muscular dystrophy-dystroglycanopathy syndrome with severe epilepsy. Ann Neurol. 2012;72:550–8. PubMed PMID: 23109149.

Bursle C, Brown D, Cardinal J, Connor F, Calvert S, Coman D. DMP1-CDG (CDG1e) with significant gastrointestinal manifestations; phenotype and genotype expansion. JIMD Rep. 2017;34:27–32. PubMed PMID: 27481510.

Cantagrel V, Lefeber DJ, Ng BG, Guan Z, Silhavy JL, Bielas SL, Lehle L, Hombauer H, Adamowicz M, Swiezewska E, De Brouwer AP, Blümel P, Sykut-Cegielska J, Houliston S, Swistun D, Ali BR, Dobyns WB, Babovic-Vuksanovic D, van Bokhoven H, Wevers RA, Raetz CR, Freeze HH, Morava E, Al-Gazali L, Gleeson JG. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. Cell. 2010;142:203–17. PubMed PMID: 20637498.

Carchon HA, Nsibu Ndosimao C, Van Aerschot S, Jaeken J. Use of serum on Guthrie cards in screening for congenital disorders of glycosylation. Clin Chem. 2006;52:774–5. PubMed PMID: 16595835.

Carrera IA, Matthijs G, Perez B, Cerda CP. DPAGT1-CDG: Report of a patient with fetal hypokinesia phenotype. Am J Med Genet A. 2012;158A:2027–30. PubMed PMID: 22786653.

Chantret I, Dancourt J, Dupre T, Delenda C, Bucher S, Vuillaumier-Barrot S, Ogier de Baulny H, Peletan C, Danos O, Seta N, Durand G, Oriol R, Codogno P, Moore SE. A deficiency in dolichyl-P-glucose:Glc1Man9GlcNAc2-PP-dolichyl alpha3-glucosyltransferase defines a new subtype of congenital disorders of glycosylation. J Biol Chem. 2003;278:9962–71. PubMed PMID: 12480927.

Chantret I, Dupre T, Delenda C, Bucher S, Dancourt J, Barnier A, Charollais A, Heron D, Bader-Meunier B, Danos O, Seta N, Durand G, Oriol R, Codogno P, Moore SE. Congenital disorders of glycosylation type Ig is defined by a deficiency in dolichyl-P-mannose:Man7GlcNAc2-PP-dolichyl mannosyltransferase. J Biol Chem. 2002;277:25815–22. PubMed PMID: 11983712.

Clayton PT, Winchester BG, Keir G. Hypertrophic obstructive cardiomyopathy in a neonate with the carbohydrate-deficient glycoprotein syndrome. J Inherit Metab Dis. 1992;15:857–61. PubMed PMID: 1293380.

Coman D, McGill J, MacDonald R, Morris D, Klingberg S, Jaeken J, Appleton D. Congenital disorder of glycosylation type 1a: Three siblings with a mild neurological phenotype. J Clin Neurosci. 2007;14:668–72. PubMed PMID: 17451957.

Dancourt J, Vuillaumier-Barrot S, de Baulny HO, Sfaello I, Barnier A, le Bizec C, Dupre T, Durand G, Seta N, Moore SE. A new intronic mutation in the DPM1 gene is associated with a milder form of CDG Ie in two French siblings. Pediatr Res. 2006;59:835–9. PubMed PMID: 16641202.

de Koning TJ, Dorland L, van Diggelen OP, Boonman AM, de Jong GJ, van Noort WL, De Schryver J, Duran M, van den Berg IE, Gerwig GJ, Berger R, Poll-The BT. A novel disorder of N-glycosylation due to phosphomannose isomerase deficiency. Biochem Biophys Res Commun. 1998;245:38–42. PubMed PMID: 9535779.

de Lonlay P, Cuer M, Vuillaumier-Barrot S, Beaune G, Castelnau P, Kretz M, Durand G, Saudubray JM, Seta N. Hyperinsulinemic hypoglycemia as a presenting sign in phosphomannose isomerase deficiency: A new

manifestation of carbohydrate-deficient glycoprotein syndrome treatable with mannose. J Pediatr. 1999;135:379–83. PubMed PMID: 10484808.

de Lonlay P, Seta N. The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of mannose treatment for CDG-Ib. Biochim Biophys Acta. 2009;1792:841–3. PubMed PMID: 19101627.

De Praeter CM, Gerwig GJ, Bause E, Nuytinck LK, Vliegenthart JF, Breuer W, Kamerling JP, Espeel MF, Martin JJ, De Paepe AM, Chan NW, Dacremont GA, Van Coster RN. A novel disorder caused by defective biosynthesis of N-linked oligosaccharides due to glucosidase I deficiency. Am J Hum Genet. 2000;66:1744–56. PubMed PMID: 10788335.

Di Rocco M, Hennet T, Grubenmann CE, Pagliardini S, Allegri AE, Frank CG, Aebi M, Vignola S, Jaeken J. Congenital disorder of glycosylation (CDG) Ig: report on a patient and review of the literature. J Inherit Metab Dis. 2005;28:1162–4. PubMed PMID: 16435218.

Dupré T, Vuillaumier-Barrot S, Chantret I, Yayé HS, Le Bizec C, Afenjar A, Altuzarra C, Barnérias C, Burglen L, de Lonlay P, Feillet F, Napuri S, Seta N, Moore SE. Guanosine diphosphate-mannose:GlcNAc2-PP-dolichol mannosyltransferase deficiency (congenital disorders of glycosylation type Ik): five new patients and seven novel mutations. J Med Genet. 2010;47:729–35. PubMed PMID: 20679665.

Eklund EA, Newell JW, Sun L, Seo NS, Alper G, Willert J, Freeze HH. Molecular and clinical description of the first US patients with congenital disorder of glycosylation Ig. Mol Genet Metab. 2005a;84:25–31. PubMed PMID: 15639192.

Eklund EA, Sun L, Westphal V, Northrop JL, Freeze HH, Scaglia F. Congenital disorder of glycosylation (CDG)-Ih patient with a severe hepato-intestinal phenotype and evolving central nervous system pathology. J Pediatr. 2005b;147:847–50. PubMed PMID: 16356445.

Etzioni A, Sturla L, Antonellis A, Green ED, Gershoni-Baruch R, Berninsone PM, Hirschberg CB, Tonetti M. Leukocyte adhesion deficiency (LAD) type II/carbohydrate deficient glycoprotein (CDG) IIc founder effect and genotype/phenotype correlation. Am J Med Genet. 2002;110:131–5. PubMed PMID: 12116250.

Fletcher JM, Matthijs G, Jaeken J, Van Schaftingen E, Nelson PV. Carbohydrate-deficient glycoprotein syndrome: beyond the screen. J Inherit Metab Dis. 2000;23:396–8. PubMed PMID: 10896303.

Foulquier F, Amyere M, Jaeken J, Zeevaert R, Schollen E, Race V, Bammens R, Morelle W, Rosnoblet C, Legrand D, Demaegd D, Buist N, Cheillan D, Guffon N, Morsomme P, Annaert W, Freeze HH, Van Schaftingen E, Vikkula M, Matthijs G. TMEM165 deficiency causes a congenital disorder of glycosylation. Am J Hum Genet. 2012;91:15–26. PubMed PMID: 22683087.

Foulquier F, Ungar D, Reynders E, Zeevaert R, Mills P, Garcia-Silva MT, Briones P, Winchester B, Morelle W, Krieger M, Annaert W, Matthijs G. A new inborn error of glycosylation due to a Cog8 deficiency reveals a critical role for the Cog1-Cog8 interaction in COG complex formation. Hum Mol Genet. 2007;16:717–30. PubMed PMID: 17220172.

Foulquier F, Vasile E, Schollen E, Callewaert N, Raemaekers T, Quelhas D, Jaeken J, Mills P, Winchester B, Krieger M, Annaert W, Matthijs G. Conserved oligomeric Golgi complex subunit 1 deficiency reveals a previously uncharacterized congenital disorder of glycosylation type II. Proc Nat Acad Sci USA. 2006;103:3764–9. PubMed PMID: 16537452.

Frank CG, Grubenmann CE, Eyaid W, Berger EG, Aebi M, Hennet T. Identification and functional analysis of a defect in the human ALG9 gene: definition of congenital disorder of glycosylation type IL. Am J Hum Genet. 2004;75:146–50. PubMed PMID: 15148656.

Freeze HH. Genetic defects in the human glycome. Nat Rev Genet. 2006;7:537–51. PubMed PMID: 16755287.

Garshasbi M, Kahrizi K, Hosseini M, Nouri Vahid L, Falah M, Hemmati S, Hu H, Tzschach A, Ropers HH, Najmabadi H, Kuss AW. A novel nonsense mutation in TUSC3 is responsible for non-syndromic autosomal

recessive mental retardation in a consanguineous Iranian family. Am J Med Genet. 2011;155A:1976–80. PubMed PMID: 21739581.

Grubenmann CE, Frank CG, Kjaergaard S, Berger EG, Aebi M, Hennet T. ALG12 mannosyltransferase defect in congenital disorder of glycosylation type lg. Hum Mol Genet. 2002;11:2331–9. PubMed PMID: 12217961.

Grünewald S. Congenital disorders of glycosylation: rapidly enlarging group of (neuro)metabolic disorders. Early Hum Dev. 2007;83:825–30. PubMed PMID: 17959325.

Grünewald S. The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia). Biochim Biophys Acta. 2009;1792:827–34. PubMed PMID: 19272306.

Grünewald S, Matthijs G, Jaeken J. Congenital disorders of glycosylation: a review. Pediatr Res. 2002;52:618–24. PubMed PMID: 12409504.

Hahn SH, Minnich SJ, O'Brien JF. Stabilization of hypoglycosylation in a patient with congenital disorder of glycosylation type Ia. J Inherit Metab Dis. 2006;29:235–7. PubMed PMID: 16601903.

Harms HK, Zimmer KP, Kurnik K, Bertele-Harms RM, Weidinger S, Reiter K. Oral mannose therapy persistently corrects the severe clinical symptoms and biochemical abnormalities of phosphomannose isomerase deficiency. Acta Paediatr. 2002;91:1065–72. PubMed PMID: 12434892.

Helander A, Stödberg T, Jaeken J, Matthijs G, Eriksson M, Eggertsen G. Dolichol kinase deficiency (DOLK-CDG) with a purely neurological presentation caused by a novel mutation. Mol Genet Metab. 2013;110:342–4. PubMed PMID: 23890587.

Hendriksz CJ, McClean P, Henderson MJ, Keir DG, Worthington VC, Imtiaz F, Schollen E, Matthijs G, Winchester BG. Successful treatment of carbohydrate deficient glycoprotein syndrome type 1b with oral mannose. Arch Dis Child. 2001;85:339–40. PubMed PMID: 11567948.

Höck M, Wegleiter K, Ralser E, Kiechl-Kohlendorfer U, Scholl-Bürgi S, Fauth C, Steichen E, Pichler K, Lefeber DJ, Matthjis G, Keldermans L, Maurer K, Zschocke J, Karall D. ALG8-CDG: novel patients and review of the literature. Orphanet J Rare Dis. 2015;10:73. PubMed PMID: 26066342.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Ishikawa N, Tajima G, Ono H, Kobayashi M. Different neuroradiological findings during two stroke-like episodes in a patient with congenital disorder of glycosylation type Ia. Brain Dev. 2009;31:240–3. PubMed PMID: 18485644.

Jaeken J. Congenital disorders of glycosylation. Ann N Y Acad Sci. 2010;1214:190–198. PubMed PMID: 21175687.

Jaeken J, Carchon H. Congenital disorders of glycosylation: the rapidly growing tip of the iceberg. Curr Opin Neurol. 2001;14:811–5. PubMed PMID: 11723393.

Jaeken J, Hennet T, Matthijs G, Freeze H. CDG nomenclature: Time for a Change! Biochim Biophys Acta. 2009a;1792:825–6. PubMed PMID: 19765534.

Jaeken J, Imbach T, et al. A newly recognized glycosylation defect with psychomotor retardation, ichthyosis and dwarfism. J Inherit Metab Dis. 2000;23 Suppl 1:186.

Jaeken J, Lefeber D, Matthijs G. Clinical utility gene card for: ALG6 defective congenital disorder of glycosylation. Eur J Hum Genet. 2015 Feb;23(2)

Jaeken J, Matthijs G. Congenital disorders of glycosylation. Annu Rev Genomics Hum Genet. 2001;2:129–51. PubMed PMID: 11701646.

Jaeken J, Matthijs G, Saudubray JM, Dionisi-Vici C, Bertini E, de Lonlay P, Henri H, Carchon H, Schollen E, Van Schaftingen E. Phosphomannose isomerase deficiency: a carbohydrate-deficient glycoprotein syndrome with hepatic-intestinal presentation. Am J Hum Genet. 1998;62:1535–9. PubMed PMID: 9585601.

Jaeken J, Vleugels W, Régal L, Corchia C, Goemans N, Haeuptle MA, Foulquier F, Hennet T, Matthijs G, Dionisi-Vici C. RFT1-CDG: Deafness as a novel feature of congenital disorders of glycosylation. J Inherit Metab Dis. 2009b;32 Suppl 1:S335–8. PubMed PMID: 19856127.

Janssen MC, de Kleine RH, van den Berg AP, Heijdra Y, van Scherpenzeel M, Lefeber D, Morava E. Successful liver transplantation and long term follow-up in a patient with MPI-CDG. Pediatrics. 2014;134:e279–83. PubMed PMID: 24982104.

Jones MA, Ng BG, Bhide S, Chin E, Rhodenizer D, He P, Losfeld ME, He M, Raymond K, Berry G, Freeze HH, Hegde MR. DDOST mutations identified by whole-exome sequencing are implicated in congenital disorders of glycosylation. Am J Hum Genet. 2012;90:363–8. PubMed PMID: 22305527.

Kahook MY, Mandava N, Bateman JB, Thomas JA. Glycosylation type Ic disorder: idiopathic intracranial hypertension and retinal degeneration. Br J Ophthalmol. 2006;90:115–6. PubMed PMID: 16361681.

Kahrizi K, Hu CH, Garshasbi M, Abedini SS, Ghadami S, Kariminejad R, Ullmann R, Chen W, Ropers HH, Kuss AW, Najmabadi H, Tzschach A. Next generation sequencing in a family with autosomal recessive Kahrizi syndrome (OMIM 612713) reveals a homozygous frameshift mutation in SRD5A3. Eur J Hum Genet. 2011;19:115–7. PubMed PMID: 20700148.

Kodera H, Ando N, Yuasa I, Wada Y, Tsurusaki Y, Nakashima M, Miyake N, Saitoh S, Matsumoto N, Saitsu H. Mutations in COG2 encoding a subunit of the conserved oligomeric golgi complex cause a congenital disorder of glycosylation. Clin Genet. 2015;87:455–60. PubMed PMID: 24784932.

Kodera H, Nakamura K, Osaka H, Maegaki Y, Haginoya K, Mizumoto S, Kato M, Okamoto N, Iai M, Kondo Y, Nishiyama K, Tsurusaki Y, Nakashima M, Miyake N, Hayasaka K, Sugahara K, Yuasa I, Wada Y, Matsumoto N, Saitsu H. De novo mutations in SLC35A2 encoding a UDP-galactose transporter cause early-onset epileptic encephalopathy. Hum Mutat. 2013;34:1708–14. PubMed PMID: 24115232.

Koehler K, Malik M, Mahmood S, Gießelmann S, Beetz C, Hennings JC, Huebner AK, Grahn A, Reunert J, Nürnberg G, Thiele H, Altmüller J, Nürnberg P, Mumtaz R, Babovic-Vuksanovic D, Basel-Vanagaite L, Borck G, Brämswig J, Mühlenberg R, Sarda P, Sikiric A, Anyane-Yeboa K, Zeharia A, Ahmad A, Coubes C, Wada Y, Marquardt T, Vanderschaeghe D, Van Schaftingen E, Kurth I, Huebner A, Hübner 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.

Kranz C, Basinger AA, Güçsavaş-Calikoğlu M, Sun L, Powell CM, Henderson FW, Aylsworth AS, Freeze HH. Expanding spectrum of congenital disorder of glycosylation Ig (CDG-Ig): sibs with a unique skeletal dysplasia, hypogammaglobulinemia, cardiomyopathy, genital malformations, and early lethality. Am J Med Genet A. 2007a;143A:1371–8. PubMed PMID: 17506107.

Kranz C, Denecke J, Lehrman MA, Ray S, Kienz P, Kreissel G, Sagi D, Peter-Katalinic J, Freeze HH, Schmid T, Jackowski-Dohrmann S, Harms E, Marquardt T. A mutation in the human MPDU1 gene causes congenital disorder of glycosylation type If (CDG-If). J Clin Invest. 2001;108:1613–9. PubMed PMID: 11733556.

Kranz C, Jungeblut C, Denecke J, Erlekotte A, Sohlbach C, Debus V, Kehl HG, Harms E, Reith A, Reichel S, Grobe H, Hammersen G, Schwarzer U, Marquardt T. A defect in dolichol phosphate biosynthesis causes a new inherited disorder with death in early infancy. Am J Hum Genet. 2007b;80:433–40. PubMed PMID: 17273964.

Lefeber DJ, de Brouwer AP, Morava E, Riemersma M, Schuurs-Hoeijmakers JH, Absmanner B, Verrijp K, van den Akker WM, Huijben K, Steenbergen G, van Reeuwijk J, Jozwiak A, Zucker N, Lorber A, Lammens M, Knopf C, van Bokhoven H, Grünewald S, Lehle L, Kapusta L, Mandel H, Wevers RA. Autosomal recessive dilated cardiomyopathy due to DOLK mutations results from abnormal dystroglycan O-mannosylation. PLoS Genet. 2011;7:e1002427. PubMed PMID: 22242004.

Lefeber DJ, Schonberger J, Morave E, Guillard M, Huyben KM, Verrijp J, Grafakou O, Evangeliou A, Preijers FW, Manta P, Yildiz J, Grunewald S, et al. Deficiency of Dol-P-Man synthase subunit DPM3 bridges the

congenital disorders of glycosylation with the dystroglycanopathies. Am J Hum Genet. 2009;85:76–86. PubMed PMID: 19576565.

Lepais L, Cheillan D, Frachon SC, Hays S, Matthijs G, Panagiotakaki E, Abel C, Edery P, Rossi M. ALG3-CDG: Report of two siblings with antenatal features carrying homozygous p.Gly96Arg mutation. Am J Med Genet A. 2015;167A:2748–54. PubMed PMID: 26126960.

Lieu MT, Ng BG, Rush JS, Wood T, Basehore MJ, Hegde M, Chang RC, Abdenur JE, Freeze HH, Wang RY. Severe, fatal multisystem manifestations in a patient with dolichol kinase-congenital disorder of glycosylation. Mol Genet Metab. 2013;110:484–9. PubMed PMID: 24144945.

Lübbehusen J, Thiel C, Rind N, Ungar D, Prinsen BH, de Koning TJ, van Hasselt PM, Körner C. Fatal outcome due to deficiency of subunit 6 of the conserved oligomeric Golgi complex leading to a new type of congenital disorders of glycosylation. Hum Mol Genet. 2010;19:3623–33. PubMed PMID: 20605848.

Marklová E, Albahri Z. Screening and diagnosis of congenital disorders of glycosylation. Clin Chim Acta. 2007;385:6–20. PubMed PMID: 17716641.

Marquardt T, Denecke J. Congenital disorders of glycosylation: review of their molecular bases, clinical presentations and specific therapies. Eur J Pediatr. 2003;162:359–79. PubMed PMID: 12756558.

Marquardt T, Luhn K, Srikrishna G, Freeze HH, Harms E, Vestweber D. Correction of leukocyte adhesion deficiency type II with oral fucose. Blood. 1999;94:3976–85. PubMed PMID: 10590041.

Martin PT, Freeze HH. Glycobiology of neuromuscular disorders. Glycobiology. 2003;13:67R–75R.

Martinez-Duncker I, Dupré T, Piller V, Piller F, Candelier JJ, Trichet C, Tchernia G, Oriol R, Mollicone R. Genetic complementation reveals a novel human congenital disorder of glycosylation of type II, due to inactivation of the Golgi CMP-sialic acid transporter. Blood. 2005;105:2671–6. PubMed PMID: 15576474.

Matthijs G, Schollen E, Bjursell C, Erlandson A, Freeze H, Imtiaz F, Kjaergaard S, Martinsson T, Schwartz M, Seta N, Vuillaumier-Barrot S, Westphal V, Winchester B. Mutations in PMM2 that cause congenital disorders of glycosylation, type Ia (CDG-Ia). Hum Mutat. 2000;16:386–94. PubMed PMID: 11058895.

Mention K, Lacaille F, Valayannopoulos V, Romano S, Kuster A, Cretz M, Zaidan H, Galmiche L, Jaubert F, de Keyzer Y, Seta N, de Lonlay P. Development of liver disease despite mannose treatment in two patients with CDG-Ib. Mol Genet Metab. 2008;93:40–3. PubMed PMID: 17945525.

Miller BS, Freeze HH, Hoffmann GF, Sarafoglou K. Pubertal development in ALG6 deficiency (congenital disorder of glycosylation type Ic). Mol Genet Metab. 2011;103:101–3. PubMed PMID: 21334936.

Molinari F, Foulquier F, Tarpey PS, Morelle W, Boissel S, Teague J, Edkins S, Futreal PA, Stratton MR, Turner G, Matthijs G, Gecz J, Munnich A, Colleaux L. Oligosaccharyltransferase-subunit mutations in nonsyndromic mental retardation. Am. J. Hum. Genet. 2008;82:1150–7. PubMed PMID: 18455129.

Morava E, Tiemes V, Thiel C, Seta N, de Lonlay P, de Klerk H, Mulder M, Rubio-Gozalbo E, Visser G, van Hasselt P, Horovitz DD, de Souza CF, Schwartz IV, Green A, Al-Owain M, Uziel G, Sigaudy S, Chabrol B, van Spronsen FJ, Steinert M, Komini E, Wurm D, Bevot A, Ayadi A, Huijben K, Dercksen M, Witters P, Jaeken J, Matthijs G, Lefeber DJ, Wevers RA. ALG6-CDG: a recognizable phenotype with epilepsy, proximal muscle weakness, ataxia and behavioral and limb anomalies. J Inherit Metab Dis. 2016;39:713–23. PubMed PMID: 27287710.

Morava E, Wevers RA, Cantagrel V, Hoefsloot LH, Al-Gazali L, Schoots J, van Rooij A, Huijben K, van Ravenswaaij-Arts CM, Jongmans MC, Sykut-Cegielska J, Hoffmann GF, Bluemel P, Adamowicz M, van Reeuwijk J, Ng BG, Bergman JE, van Bokhoven H, Körner C, Babovic-Vuksanovic D, Willemsen MA, Gleeson JG, Lehle L, de Brouwer AP, Lefeber DJ. A novel cerebello-ocular syndrome with abnormal glycosylation due to abnormalities in dolichol metabolism. Brain. 2010;133:3210–20. PubMed PMID: 20852264.

Morava E, Zeevaert R, Korsch E, Huijben K, Wopereis S, Matthijs G, Keymolen K, Lefeber DJ, De Meirleir L, Wevers RA. A common mutation in the COG7 gene with a consistent phenotype including microcephaly, adducted thumbs, growth retardation, VSD and episodes of hyperthermia. Eur J Hum Genet. 2007;15:638–45. PubMed PMID: 17356545.

Ng BG, Shiryaev SA, Rymen D, Eklund EA, et al. ALG1-CDG: Clinical and Molecular Characterization of 39 Unreported Patients. Hum Mutat. 2016;37:653–60. PubMed PMID: 26931382.

Ng BG, Raymond K, Kircher M, Buckingham KJ, et al. Expanding the molecular and clinical phenotype of SSR4-CDG. Hum Mutat. 2015;36:1048–51. PubMed PMID: 26264460.

Ng BG, Sharma V, Sun L, Loh E, Hong W, Tay SK, Freeze HH. Identification of the first COG-CDG patient of Indian origin. Mol Genet Metab. 2011;102:364–7. PubMed PMID: 21185756.

Ng BG, Kranz C, Hagebeuk EE, Duran M, Abeling NG, Wuyts B, Ungar D, Lupashin V, Hartdorff CM, Poll-The BT, Freeze HH. Molecular and clinical characterization of a Moroccan Cog7 deficient patient. Mol Genet Metab. 2007;91:201–4. PubMed PMID: 17395513.

Niehues R, Hasilik M, Alton G, Korner C, Schiebe-Sukumar M, Koch HG, Zimmer KP, Wu R, Harms E, Reiter K, von Figura K, Freeze HH, Harms HK, Marquardt T. Carbohydrate-deficient glycoprotein syndrome type Ib. Phosphomannose isomerase deficiency and mannose therapy. J Clin Invest. 1998;101:1414–20. PubMed PMID: 9525984.

Ondruskova N, Vesela K, Hansikova H, Magner M, Zeman J, Honzik T. RFT1-CDG in adult siblings with novel mutations. Mol Genet Metab. 2012;107:760–2. PubMed PMID: 23111317.

Paesold-Burda P, Maag C, Troxler H, Foulquier F, Kleinert P, Schnabel S, Baumgartner M, Hennet T. Deficiency in COG5 causes a moderate form of congenital disorders of glycosylation. Hum Mol Genet. 2009;18:4350–6. PubMed PMID: 19690088.

Peters V, Penzien JM, Reiter G, Korner C, Hackler R, Assmann B, Fang J, Schaefer JR, Hoffmann GF, Heidemann PH. Congenital disorder of glycosylation IId (CDG-IId) -- a new entity: clinical presentation with Dandy-Walker malformation and myopathy. Neuropediatrics. 2002;33:27–32. PubMed PMID: 11930273.

Rafiq MA, Kuss AW, Puettmann L, Noor A, Ramiah A, Ali G, Hu H, Kerio NA, Xiang Y, Garshasbi M, Khan MA, Ishak GE, Weksberg R, Ullmann R, Tzschach A, Kahrizi K, Mahmood K, Naeem F, Ayub M, Moremen KW, Vincent JB, Ropers HH, Ansar M, Najmabadi H. Mutations in the alpha 1,2-mannosidase gene, MAN1B1, cause autosomal-recessive intellectual disability. Am J Hum Genet. 2011;89:176–82. PubMed PMID: 21763484.

Reynders E, Foulquier F, Teles EL, Quelhas D, Morelle W, Rabouille C, Annaert W, Matthijs G. Golgi function and dysfunction in the first COG4-deficient CDG type II patient. Hum Molec Genet. 2009;18:3244–56. PubMed PMID: 19494034.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Rind N, Schmeiser V, Thiel C, Absmanner B, Lübbehusen J, Hocks J, Apeshiotis N, Wilichowski E, Lehle L, Körner C. A severe human metabolic disease caused by deficiency of the endoplasmatic mannosyltransferase hALG11 leads to congenital disorder of glycosylation-Ip. Hum Mol Genet. 2010;19:1413–24. PubMed PMID: 20080937.

Rymen D, Jaeken J. Skin manifestations in CDG. J Inherit Metab Dis. 2014;37:699–708. PubMed PMID: 24554337.

Rymen D, Keldermans L, Race V, Régal L, Deconinck N, Dionisi-Vici C, Fung CW, Sturiale L, Rosnoblet C, Foulquier F, Matthijs G, Jaeken J. COG5-CDG: expanding the clinical spectrum. Orphanet J Rare Dis. 2012;7:94. PubMed PMID: 23228021.

Sabry S, Vuillaumier-Barrot S, Mintet E, Fasseu M, Valayannopoulos V, Héron D, Dorison N, Mignot C, Seta N, Chantret I, Dupré T, Moore SE. A case of fatal Type I congenital disorders of glycosylation (CDG I) associated with low dehydrodolichol diphosphate synthase (DHDDS) activity. Orphanet J Rare Dis. 2016;11:84. PubMed PMID: 27343064.

Sadat MA, Moir S, Chun TW, Lusso P, Kaplan G, et al. Glycosylation, hypogammaglobulinemia, and resistance to viral infections. N Engl J Med. 2014;370(17):1615–25. PubMed PMID: 24716661.

Sanz-Nebot V, Balaguer E, Benavente F, Neusub C, Barbosa J. Characterization of transferrin glycoforms in human serum by CE-UV and CE-ESI-MS. Electrophoresis. 2007;28:1949–57. PubMed PMID: 17523137.

Schenk B, Imbach T, Frank CG, Grubenmann CE, Raymond GV, Hurvitz H, Korn-Lubetzki I, Revel-Vik S, Raas-Rotschild A, Luder AS, Jaeken J, Berger EG, Matthijs G, Hennet T, Aebi M. MPDU1 mutations underlie a novel human congenital disorder of glycosylation, designated type If. J Clin Invest. 2001;108:1687–95. PubMed PMID: 11733564.

Schollen E, Frank CG, Keldermans L, Reyntjens R, Grubenmann CE, Clayton PT, Winchester BG, Smeitink J, Wevers RA, Aebi M, Hennet T, Matthijs G. Clinical and molecular features of three patients with congenital disorders of glycosylation type Ih (CDG-Ih) (ALG8 deficiency). J Med Genet. 2004a;41:550–6. PubMed PMID: 15235028.

Schollen E, Kjaergaard S, Martinsson T, Vuillaumier-Barrot S, Dunoe M, Keldermans L, Seta N, Matthijs G. Increased recurrence risk in congenital disorders of glycosylation type Ia (CDG-Ia) due to a transmission ratio distortion. J Med Genet. 2004b;41:877–80. PubMed PMID: 15520415.

Schwarz M, Thiel C, Lübbehusen J, Dorland B, de Koning T, von Figura K, Lehle L, Körner C. Deficiency of GDP-Man:GlcNAc2-PP-dolichol mannosyltransferase causes congenital disorder of glycosylation type Ik. Am J Hum Genet. 2004;74:472–81. PubMed PMID: 14973778.

Serrano M, de Diego V, Muchart J, Cuadras D, et al. Phosphomannomutase deficiency (PMM2-CDG): ataxia and cerebellar assessment. Orphanet J Rare Dis. 2015;10:138. PubMed PMID: 26502900.

Sinha MD, Horsfield C, Komaromy D, Booth C, Champion M. Congenital disorders of glycosylation: a rare cause of nephrotic syndrome. Nephrol Dial Transplant. 2009;24:2591–4. PubMed PMID: 19474279.

Shrimal S, Ng BG, Losfeld ME, Gilmore R, Freeze HH. Mutations in STT3A and STT3B cause two congenital disorders of glycosylation. Hum Mol Genet. 2013;22:4638–45. PubMed PMID: 23842455.

Spaapen LJM, Bakker JA, van der Meer SB, Sijstermans HJ, Steet RA, Wevers RA, Jaeken J. Clinical and biochemical presentation of siblings with COG-7 deficiency, a lethal multiple O- and N-glycosylation disorder. J Inherit Metab Dis. 2005;28:707–14. PubMed PMID: 16151902.

Stibler H, Skovby F. Failure to diagnose carbohydrate-deficient glycoprotein syndrome prenatally. Pediatr Neurol. 1994;11:71. PubMed PMID: 7527215.

Stojkovic T, Vissing J, Petit F, Piraud M, Orngreen MC, Andersen G, Claeys KG, Wary C, Hogrel J-Y, Laforet P. Muscle glycogenosis due to phosphoglucomutase 1 deficiency. New Eng J Med. 2009;361:425–7. (Letter). PubMed PMID: 19625727.

Stölting T, Omran H, Erlekotte A, Denecke J, Reunert J, Marquardt T. Novel ALG8 mutations expand the clinical spectrum of congenital disorder of glycosylation type Ih. Mol Genet Metab. 2009;98:305–9. PubMed PMID: 19648040.

Sun L, Eklund EA, Van Hove JL, Freeze HH, Thomas JA. Clinical and molecular characterization of the first adult congenital disorder of glycosylation (CDG) type Ic patient. Am J Med Genet A. 2005;137:22–6. PubMed PMID: 16007612.

Tamminga RY, Lefeber DJ, Kamps WA, van Spronsen FJ. Recurrent thrombo-embolism in a child with a congenital disorder of glycosylation (CDG) type Ib and treatment with mannose. Pediatr Hematol Oncol. 2008;25:762–8. PubMed PMID: 19065443.

Thiel C, Schwarz M, Hasilik M, Grieben U, Hanefeld F, Lehle L, von Figura K, Körner C. Deficiency of dolichyl-P-Man:Man7GlcNAc2-PP-dolichyl mannosyltransferase causes congenital disorder of glycosylation type Ig. Biochem J. 2002;367:195–201. PubMed PMID: 12093361.

Thiel C, Schwarz M, Peng J, Grzmil M, Hasilik M, Braulke T, Kohlschutter A, von Figura K, Lehle L, Korner C. A new type of congenital disorders of glycosylation (CDG-Ii) provides new insights into the early steps of dolichol-linked oligosaccharide biosynthesis. J Biol Chem. 2003;278:22498–505. PubMed PMID: 12684507.

Thiel C, Rind N, Popovici D, Hoffmann GF, Hanson K, Conway RL, Adamski CR, Butler E, Scanlon R, Lambert M, Apeshiotis N, Thiels C, Matthijs G, Korner C. Improved diagnostics lead to identification of three new patients with congenital disorder of glycosylation-Ip. Hum Mutat. 2012;33:485–7. PubMed PMID: 22213132.

Timal S, Hoischen A, Lehle L, Adamowicz M, Huijben K, Sykut-Cegielska J, Paprocka J, Jamroz E, van Spronsen FJ, Korner C, Gilissen C, Rodenburg RJ, Eidhof I, Van den Heuvel L, Thiel C, Wevers RA, Morava E, Veltman J, Lefeber DJ. Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. Hum Mol Genet. 2012;21:4151–61. PubMed PMID: 22492991.

van de Kamp JM, Lefeber DJ, Ruijter GJ, Steggerda SJ, den Hollander NS, Willems SM, Matthijs G, Poorthuis BJ, Wevers RA. Congenital disorders of glycosylation type Ia presenting with hydrops fetalis. J Med Genet. 2007;44:277–80. PubMed PMID: 17158594.

Van Geet C, Jaeken J, Freson K, Lenaerts T, Arnout J, Vermylen J, Hoylaerts MF. Congenital disorders of glycosylation type Ia and IIa are associated with different primary haemostatic complications. J Inherit Metab Dis. 2001;24:477–92. PubMed PMID: 11596651.

Varki A. Biological roles of oligosaccharides: all of the theories are correct. Glycobiology. 1993;3:97–130. PubMed PMID: 8490246.

Vleugels W, Haeuptle MA, Ng BG, Michalski JC, Battini R, Dionisi-Vici C, Ludman MD, Jaeken J, Foulquier F, Freeze HH, Matthijs G, Hennet T. RFT1 deficiency in three novel CDG patients. Hum Mutat. 2009;30:1428–34. PubMed PMID: 19701946.

Weinstein M, Schollen E, Matthijs G, Neupert C, Hennet T, Grubenmann CE, Frank CG, Aebi M, Clarke JT, Griffiths A, Seargeant L, Poplawski N. CDG-IL: an infant with a novel mutation in the ALG9 gene and additional phenotypic features. Am J Med Genet A. 2005;136:194–7. PubMed PMID: 15945070.

Willer T, Lee H, Lommel M, Yoshida-Moriguchi T, de Bernabe DB, Venzke D, Cirak S, Schachter H, Vajsar J, Voit T, Muntoni F, Loder AS, Dobyns WB, Winder TL, Strahl S, Mathews KD, Nelson SF, Moore SA, Campbell KP. ISPD loss-of-function mutations disrupt dystroglycan O-mannosylation and cause Walker-Warburg syndrome. Nat Genet. 2012;44:575. PubMed PMID: 22522420.

Wu X, Steet RA, Bohorov O, Bakker J, Newell J, Krieger M, Spaapen L, Kornfeld S, Freeze HH. Mutation of the COG complex subunit gene COG7 causes a lethal congenital disorder. Nat Med. 2004;10:518–23. PubMed PMID: 15107842.

Würde AE, Reunert J, Rust S, Hertzberg C, Haverkämper S, Nürnberg G, Nürnberg P, Lehle L, Rossi R, Marquardt T. Congenital disorder of glycosylation type Ij (CDG-Ij, DPAGT1-CDG): extending the clinical and molecular spectrum of a rare disease. Mol Genet Metab. 2012;105:634–41. PubMed PMID: 22304930.

Yang AC, Ng BG, Moore SA, Rush J, Waechter CJ, Raymond KM, Willer T, Campbell KP, Freeze HH, Mehta L. Congenital disorder of glycosylation due to DPM1 mutations presenting with a dystroglycanopathy-type congenital muscular dystrophy. Mol Genet Metab. 2013;110:345–51. PubMed PMID: 23856421.

Zdebska E, Bader-Meunier B, Schischmanoff PO, Dupré T, Seta N, Tchernia G, Kościelak J, Delaunay J. Abnormal glycosylation of red cell membrane band 3 in the congenital disorder of glycosylation Ig. Pediatr Res. 2003;54:224–9. PubMed PMID: 12736397.

Zhang Y, Yu X, Ichikawa M, Lyons JJ, Datta S, Lamborn IT, et al. Autosomal recessive phosphoglucomutase 3 (PGM3) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity, and neurocognitive impairment. J Allergy Clin Immunol. 2014;133:1400–9. PubMed PMID: 24589341.

Chapter Notes

Author Notes

Susan Sparks is a board-certified pediatrician, clinical geneticist, and clinical biochemical geneticist. She is currently a medical director at Sanofi Genzyme. After completion of her genetics and biochemical genetics fellowship at the National Institutes of Health, she held faculty positions at Children's National Medical Center in Washington, DC, and Levine Children's Hospital at Carolinas Medical Center in Charlotte, NC. She received her MD and PhD in molecular biology and pharmacology from the Chicago Medical School in 1997 and 1999, respectively.

Donna Krasnewich is a board-certified clinical biochemical geneticist and pediatrician. She trained at Wayne State University School of Medicine in Detroit, Michigan, and received her MD and PhD in pharmacology in 1986. After completing her fellowship in genetics at the National Institutes of Health (NIH), she joined the faculty of the National Human Genome Research Institutes (NHGRI) at NIH and was the Deputy Clinical Director of NHGRI. She is currently a Program Director at NIH in the National Institute of General Medical Sciences and continues her interest in children with developmental delay and congenital disorders of glycosylation.

Revision History

- 12 January 2017 (ma) Comprehensive update posted live
- 30 January 2014 (cd) Revision: scope of the overview changed to N-linked glycosylation
- 8 November 2012 (cd) Revision: molecular testing for mutations in *TMEM165* and *PGM1* available clinically
- 9 August 2012 (cd) Revision: SRD5A3-CDG (CDG-Iq), DDOST-CDG (CDG-Ir), TUSC3-CDG, and congenital disorders of glycosylation multigene panels now listed in the GeneTests™ Laboratory Directory; CDG types and associated references added
- 11 August 2011 (cd) Revision: clinical testing available for MAGT1-CDG.
- 21 April 2011 (me) Comprehensive update posted live
- 1 September 2009 (cd) Revision: sequence analysis available clinically for CDG-Io
- 18 December 2008 (cd) Revision: sequence analysis available clinically for CDG-Im, -In, -Ic, -Id, and -If
- 23 June 2008 (me) Comprehensive update posted live
- 15 August 2005 (me) Overview posted live
- 27 February 2004 (dk) Original submission

License