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Congenital Disorder of Glycosylation Type 1a

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Summary

Disease characteristics. Congenital disorder of glycosylation type 1a (CDG-1a), the most common of a group of disorders of abnormal glycosylation of N-linked oligosaccharides, is divided into three stages: infantile multisystem, late-infantile and childhood ataxia-mental retardation, and adult stable disability. The three stages notwithstanding, clinical presentation and course are highly variable, ranging from infants who die in the first year of life to mildly involved adults. Clinical presentations tend to be similar in siblings. In the **infantile multisystem stage**, infants show axial hypotonia, hyporeflexia, esotropia, and developmental delay; feeding problems, vomiting, and diarrhea with failure to thrive; and impaired growth. Subcutaneous fat may be excessive over the buttocks and suprapubic region. Two distinct clinical presentations are observed: (1) a non-fatal neurologic form with strabismus, psychomotor retardation, and cerebellar hypoplasia in infancy followed by neuropathy and retinitis pigmentosa in the first or second decade and (2) a neurologic-multivisceral form with approximately 20% mortality in the first year of life. The **late-infantile and childhood ataxia-mental retardation stage**, with onset between ages three and ten years, is characterized by hypotonia, ataxia, severely delayed language and motor development, inability to walk, and IQ of 40 to 70; other findings include stroke-like episodes or transient unilateral loss of function, retinitis pigmentosa, joint contractures, and skeletal deformities. In the **adult stable disability stage**, mental ability is stable; peripheral neuropathy is variable, thoracic and spinal deformities progress, and premature aging is observed; females lack secondary sexual development and males may exhibit decreased testicular volume. Hyperglycemia-induced growth hormone release, hyperprolactinemia, insulin resistance, and coagulopathy may occur.

Diagnosis/testing. CDG-1a is diagnosed by clinical features, neuroimaging, and transferrin isoform analysis to determine the number of sialylated N-linked oligosaccharide residues linked to serum transferrin. Characteristic findings are decreased tetrasialotransferrin and increased asialotransferrin and disialotransferrin. *PMM2* is the only gene associated with CDG-1a. Sequence analysis of *PMM2* detects mutations in up to 100% of individuals in whom CDG-1a has been enzymatically confirmed in research studies.

Management. *Treatment of manifestations:* maximal caloric intake including use of a nasogastric tube or gastrostomy tube; anti-gastroesophageal reflux measures; occupational therapy, physical therapy, and speech therapy for developmental delay; hydration and physical therapy for stroke-like episodes; orthopedic intervention for scoliosis; rehabilitation medicine

services including wheel chairs, transfer devices, and physical therapy as needed. *Prevention of secondary complications:* attention to coagulation status before surgery because of increased risk of bleeding and/or deep venous thrombosis. *Agents/circumstances to avoid:* cautious use of acetaminophen and other agents metabolized by the liver.

Genetic counseling. CDG-1a is inherited in an autosomal recessive manner. At conception, the theoretical risks to sibs of an affected individual are a 25% risk of being affected, a 50% risk of being an asymptomatic carrier, and a 25% risk of being unaffected and not a carrier; however, based on outcomes of at-risk pregnancies, the risk of having an affected child is closer to 1/3 rather than the expected 1/4. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk for CDG-1a is possible when both disease-causing mutations in the family have been identified.

Diagnosis

Clinical Diagnosis

Congenital disorder of glycosylation type 1a (CDG-1a) is the most common of a group of disorders of abnormal glycosylation of N-linked oligosaccharides. The presentation of this disorder is highly variable; therefore, the diagnosis should be considered in a child with developmental delay and hypotonia in combination with any of the following findings:

- Failure to thrive
- Hepatic dysfunction (elevated transaminases)
- Coagulopathy with low serum concentration of factors IX and XI, antithrombin, protein C, and/or protein S
- Hypothyroidism, hypogonadism
- Esotropia
- Pericardial effusion
- Abnormal subcutaneous fat pattern including increased suprapubic fat pad, skin dimpling, and inverted nipples or subcutaneous fat pads having a toughened, puffy, or uneven consistency
- Seizures
- Stroke-like episodes
- Osteopenia, scoliosis
- Cerebellar hypoplasia/atrophy and small brain stem [Aronica et al 2005]

The diagnosis of CDG-1a should be considered in adolescents or adults with suggestive histories and any of the following findings:

- Cerebellar dysfunction (ataxia, dysarthria, dysmetria)
- Non-progressive cognitive impairment
- Stroke-like episodes
- Peripheral neuropathy with or without muscle wasting
- Absent puberty in females, small testes in males
- Retinitis pigmentosa
- Progressive scoliosis with truncal shortening

- Joint contractures

Neuroimaging. An enlarged cisterna magna and superior cerebellar cistern is observed in late infancy to early childhood. Occasionally, both infratentorial and supratentorial changes compatible with atrophy are present. Dandy-Walker malformations and small white matter cysts have been reported [Peters et al 2002].

Myelination varies from normal to delayed or insufficient [Holzbach et al 1995].

Serial CTs performed on three children with CDG-1a revealed that enlargement of the spaces between the folia of the cerebellar hemispheres, especially from the anterior to the posterior aspect, as well as atrophy of the anterior vermis, seemed to progress until around age five years [Akaboshi et al 1995]. Progression of cerebellar atrophy on MRI after age five years is variable. After age nine years, progression of the cerebellar atrophy was not evident. Development of the supratentorial structures was normal.

Testing

CDG-1a is caused by deficiency of phosphomannomutase (PMM) enzyme activity resulting in 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, Grunewald et al 2002].

Analysis of serum transferrin glycoforms (also called "transferrin isoforms analysis" or "carbohydrate-deficient transferrin analysis"). The diagnostic test for CDG-1a is isoelectric focusing (IEF) or other isoform analysis (i.e., performed by capillary electrophoresis, GC/MS, CE-ESI-MS, MALDI-MS) to determine the number of sialylated N-linked oligosaccharide residues linked to serum transferrin [Jaeken & Carchon 2001, Marklova & Albahri 2007, Sanz-Nebot et al 2007]. Such testing is clinically available.

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.** Decreased 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 trisialotransferrins and/or monosialotransferrins. The pattern indicates defects in the later parts of the N-linked glycan pathway.

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) Individuals with the clinical diagnosis of CDG-1a and biochemical diagnosis of PMM enzyme deficiency with normal transferrin glycosylation have been reported [Fletcher et al 2000, Marquardt & Denecke 2003, Hann et al 2006]. (4) It is possible that an abnormal transferrin IEF pattern is the result of a transferrin protein variant, which can be clarified with IEF of a serum sample from the parents.

Phosphomannomutase (PMM) enzyme activity. In individuals presenting with a severe/classic clinical picture of CDG-1a, PMM enzyme activity in fibroblasts and leukocytes is

typically 0% to 10% of normal [Van Schaftingen & Jaeken 1995, Carchon et al 1999, Jaeken & Carchon 2001]. In the US, enzyme testing for CDG-1a is available on a research basis only.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *PMM2* is the only gene associated with congenital disorder of glycosylation type 1a (CDG-1a).

Clinical testing

- **Sequence analysis**
  - In individuals with enzymatically proven CDG-1a, the mutation detection rate in *PMM2* is as high as 100%.
  - The p.Arg141His mutation is found in the compound heterozygous state in approximately 40% of individuals; it is never found in the homozygous state.
  - The mutation p.Phe119Leu is frequently found in northern Europe, where the genotype [p.Arg141His]+[p.Phe119Leu] makes up approximately 72% of all mutations [Jaeken & Matthijs 2001].
  - The mutations p.Val231Met and p.Pro113Leu are common all over Europe.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Congenital Disorder of Glycosylation Type 1a

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]		Test Availability
			Two Mutations	One Mutation	
PMM2	Sequence analysis	Sequence variants	95%	98%	Clinical Testing

1. Individuals with enzymatically confirmed diagnosis [G Matthijs, personal communication]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirmation of the diagnosis in a proband requires molecular genetic testing following the finding of a type I transferrin isoform pattern.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *PMM2*.

Clinical Description

Natural History

The typical clinical course of congenital disorder of glycosylation type 1a (CDG-1a) has been divided into an infantile multisystem stage, late-infantile and childhood ataxia-mental retardation stage, and adult stable disability stage. Recent reports have widened the phenotypic spectrum to include 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].

Infantile multisystem stage. Historically, CDG-1a was characterized by cerebellar hypoplasia, facial dysmorphism, psychomotor retardation, and abnormal subcutaneous fat distribution; however, the clinical phenotype continues to broaden.

Infants show axial hypotonia, hyporeflexia, esotropia, and developmental delay. Feeding problems, vomiting, and diarrhea may cause severe failure to thrive. Growth is significantly impaired [Kjaergaard et al 2002]. Although distinctive facies (high nasal bridge and prominent jaw) and large ears have been reported in the northern European population, these features have not been emphasized in reports of US individuals [Krasnewich & Gahl 1997, Enns et al 2002]. An unusual distribution of subcutaneous fat over the buttocks and the suprapubic region may be observed. In girls, the labia majora are involved as well. Inverted nipples are common.

In one large study, two distinct clinical presentations were observed [de Lonlay et al 2001]:

- A purely neurologic form with strabismus, psychomotor retardation, and cerebellar hypoplasia early on, and neuropathy and retinitis pigmentosa in the first or second decade. This form was not fatal.
- A neurologic-multivisceral form in which manifestations occur early in life. All organs with the exception of the lungs can be involved. Hepatic fibrosis and renal hyperechogenicity are consistent. Some infants have hepatopathy, pericardial effusion, nephrotic syndrome, renal cysts, and multiorgan failure. Approximately 20% of the infants die within the first year of life from failure to thrive, hypoalbuminemia, and aspiration pneumonia in what is called the "infantile catastrophic phase" characterized by intractable hypoalbuminemia, anasarca, and respiratory distress [de Lonlay et al 2001, Marquardt & Denecke 2003]. Strabismus and cerebellar hypoplasia are occasionally absent.

Note: The relatively specific findings of CDG-1a, including dysmorphic features, inverted nipples, and abnormal fat pads, are occasionally absent in both forms.

Congenital cardiac anomalies, hypertrophic cardiomyopathy with transient myocardial ischemia, or cardiac effusions have been reported but are rare [Kristiansson et al 1998, Marquardt et al 2002]. Pericardial effusions are typically without clinical sequelae and usually disappear in a year or two; however, persistent pericardial effusions have been seen in a few more medically involved cases [Krasnewich, personal communication].

Liver function measurements begin to rise in the first year of life. Transaminases (AST and ALT) in young children may be in the range of 1000 to 1500 without clinical sequelae. Typically, the ALT and AST return to normal by age three to five years in children with CDG-1a and remain normal throughout their lives. These children do not need a liver biopsy unless

warranted by additional clinical evidence. Liver biopsy can demonstrate lamellar inclusions in macrophages and in hepatocyte lysosomes but not in Kupffer cell lysosomes [Jaeken & Matthijs 2001].

In general, children with CDG-1a are chemically euthyroid [Miller & Freeze 2003].

Seizures, which are usually responsive to antiepileptic drugs, may occur in the second or third year.

Renal ultrasound examinations in eight infants and children with CDG-1a showed no changes in the two with the neurologic form and increased cortical echogenicity and/or small pyramids that may or may not have been hyperechoic in the six with the multivisceral form [Hertz-Pannier et al 2006].

Siblings with CDG-1a have been reported with immunologic dysfunction/diminished chemotaxis of neutrophils and poor immune response to vaccinations [Blank et al 2006].

One child with CDG-1a and a skeletal dysplasia, characterized by flattening of all vertebrae (platyspondyly), had severe spinal cord compression at the level of the craniocervical junction [Schade van Westrum et al 2006].

Late-infantile and childhood ataxia-mental retardation stage occurs between ages three and ten years. Children have a more static course characterized by hypotonia and ataxia. Language and motor development are severely delayed and walking without support is rarely achieved [Jaeken & Matthijs 2001]. IQ ranges from 40 to 70. The children usually are extroverted and cheerful. Seizures may occur; they are usually responsive to antiepileptic drugs.

In this stage and in adulthood, affected individuals may have stroke-like episodes or transient unilateral loss of function sometimes associated with fever, seizure, dehydration, or trauma. Recovery may occur over a few weeks to several months. Persistent neurologic deficits after a stroke-like episode occasionally occur but are rare. A progressive peripheral neuropathy may begin in this age range.

Retinitis pigmentosa, myopia [Jensen et al 2003], joint contractures, and skeletal deformities may also occur.

Adult stable disability stage. Adults with CDG-1a typically demonstrate stable rather than progressive mental retardation and variable peripheral neuropathy. Progression of thoracic and spinal deformities can result in severe kyphoscoliosis.

Previously undiagnosed adults are now being recognized because of multisystem involvement and cerebellar ataxia [Schoffer et al 2006, Barone et al 2007]. Additionally the mild end of the adult phenotypic spectrum has expanded to include normal cognitive abilities; in three affected sibs, all had multisystem involvement, one with significant cognitive impairment and two with normal cognition [Stibler et al 1994, Jaeken & Matthijs 2001, Coman et al 2007, Krasnewich et al 2007].

Women lack secondary sexual development as a result of hypogonadotrophic hypogonadism [De Zegher & Jaeken 1995, Kristiansson et al 1995, Miller & Freeze 2003]. In some females, laparoscopy and ultrasound examination have revealed absent ovaries. Males virilize normally at puberty but may exhibit decreased testicular volume.

Other endocrine dysfunction includes hyperglycemia-induced growth hormone release, hyperprolactinemia, and insulin resistance [Miller & Freeze 2003].

Coagulopathy with decreased serum concentrations of factors IV, IX, and XI, antithrombin III, protein C, and protein S may be present. Deep venous thrombosis in adults has been reported [Krasnewich et al 2007].

Renal microcysts may be identified on renal ultrasound examination but renal function is typically preserved throughout adulthood [Strom et al 1993].

Pathophysiology. Because of the important biologic functions of the oligosaccharides in both glycoproteins and glycolipids, incorrect synthesis of these compounds results in multisystemic clinical manifestations [Varki 1993, Freeze 2006].

Genotype-Phenotype Correlations

Lack of correlation between genotype and phenotype in CDG-1a has been reported [Erlandson et al 2001, Jaeken & Matthijs 2001, Westphal et al 2001]. In general, individuals with all genotypes show the basic signs of the disorder; i.e., developmental delay, cerebellar atrophy, peripheral neuropathy, stroke-like episodes or comatose episodes, epilepsy, retinal pigmentary degeneration, strabismus, skeletal abnormalities, and hepatopathy. However, the extent of the non-neurologic findings varies depending on the genotype:

- C-terminal mutations, including p.His218Leu, p.Thr237Met, and p.Cys241Ser, may be associated with a milder phenotype [Matthijs et al 1999, Tayebi et al 2002].
- The phenotypic spectrum of the [p.Arg141His]+[p.Phe119Leu] genotype, the most prevalent genotype in CDG-1a, was studied in Scandinavia [Kjaergaard et al 2001]. Individuals with the [p.Arg141His]+[p.Phe119Leu] genotype probably represent the severe end of the clinical spectrum of CDG-1a. Presentation was uniformly early with severe feeding problems, severe failure to thrive, severe hypotonia, developmental delay obvious before age six months, and hepatic dysfunction. Asymptomatic pericardial effusions were common in the first year of life. The functional outcome in ambulation and speech was variable.
- A severe phenotype presenting with a high mortality rate was observed with the [p.Asp188Gly]+[p.Arg141His] genotype: in the study by Matthijs et al [1998], four of five children with this genotype died before age two years. The remaining child, aged ten years, was severely affected.
- de Lonlay et al [2001] reported several compound heterozygous genotypes (including [p.Arg141His]+[p.Thr226Ser], [p.Arg141His]+[p.Ile132Thr], and [p.Arg141His]+[p.Glu139Lys]) that appear to be associated with a milder phenotype termed the "neurologic form" without pericardial effusions, coagulation defects, or nutritional disturbances. Some individuals are able to walk independently.
- The p.Val231Met mutation is associated with high early mortality and severe multi-organ insufficiency.
- Homozygosity or compound heterozygosity for severe mutations with virtually no residual activity, such as p.Arg141His, is likely incompatible with life [Matthijs et al 2000].

Prevalence

CDG-1a is the most common form of the congenital disorders of glycosylation reported to date, with more than 700 affected individuals worldwide. The prevalence could be as high as 1:20,000 [Jaeken & Matthijs 2001].

The expected carrier frequency of *PMM2* mutations in the Danish population is one in 60 to one in 79 [Matthijs et al 2000].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Any child with evidence of coagulopathy, hepatopathy, elevated TSH, or cerebellar hypoplasia **and** the triad of hypotonia, developmental delay, and failure to thrive should be evaluated for congenital disorder of glycosylation type 1a (CDG-1a).

Other genetic disorders to consider in the differential diagnosis

- Prader-Willi syndrome

Congenital muscular dystrophies including Fukuyama congenital muscular dystrophy (FCMD) caused by mutations in *FCMD*, muscle-eye-brain (MEB) disease caused by mutations in *POMGNT1* [Yoshida et al 2001, Martin & Freeze 2003] and Walker-Warburg syndrome, caused by mutations in *POMT1* (see Congenital Muscular Dystrophies Overview)

- Congenital myopathies (e.g., X-linked myotubular myopathy, multiminicore myopathy)

Many metabolic and genetic disorders that present in infancy share at least some of the clinical features of CDG-1a. The following metabolic disorders are in the differential diagnosis of hypotonia, developmental delay, and failure to thrive:

- Mitochondrial disorders (see Mitochondrial Disorders Overview)
- Peroxisome biogenesis disorders, Zellweger syndrome spectrum

Urea cycle defects (see Urea Cycle Disorders Overview)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with congenital disorder of glycosylation type 1a (CDG-1a), the following evaluations are recommended [Jaeken & Carchon 2001, Jaeken & Matthijs 2001, Grunewald et al 2002, Kjaergaard et al 2002, Miller & Freeze 2003]:

- Liver function tests
- Measurement of serum albumin concentration
- Thyroid function tests to evaluate for decreased thyroid binding globulin, elevated serum concentration of TSH, and low serum concentration of free T4
- Coagulation studies including protein C, protein S, antithrombin III, and factor IX
- Urinalysis to evaluate for proteinuria
- Measurement of serum concentration of gonadotropins in adolescent and adult women to look for evidence of hypogonadotrophic hypogonadism
- Echocardiogram to evaluate for pericardial effusions
- Renal ultrasound examination to evaluate for microcysts

Treatment of Manifestations

Failure to thrive. Infants and children can be nourished with 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 help children who experience 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 therapy and oral motor therapy aid transition to oral feeds and encourage 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-1a and their unaffected peers, parents need continued counseling and support.

"Infantile catastrophic phase." Symptomatic treatment may change the clinical course. Parents should also be advised that some infants with CDG-1a never experience a hospital visit while others may require frequent hospitalizations.

Strabismus. Intervention by a pediatric ophthalmologist early in life is important to preserve vision through glasses, patching, or surgery.

Hypothyroidism. Thyroid function tests are frequently abnormal in children with CDG-1a. However, free thyroxine analyzed by equilibrium dialysis, the most accurate method, has been reported as normal in seven individuals with CDG-1a. 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.

Stroke-like episodes. Supportive therapy includes hydration by IV if necessary and physical therapy during the recovery period.

Coagulopathy. Low levels of coagulation factors rarely cause clinical problems in daily activities but must be acknowledged if an individual with CDG-1a undergoes surgery. Consultation with a hematologist (to document the coagulation status and factor levels) and discussion with the surgeon are 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 anti-coagulant factors may lead to either bleeding or thrombosis. Parents, especially of older affected individuals, should be taught the signs of deep venous thrombosis.

Additional management issues of adults with CDG-1a

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 is warranted.

Independent living issues. Young adults with CDG-1a and their parents need to address issues of independent living. Aggressive education throughout the school years in functional life skills and/or vocational training helps 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 an important part of management.

Prevention of Secondary Complications

Because infants with CDG-1a have less physiologic reserve 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 the morbidity associated with the "infantile catastrophic phase."

Although only one case of skeletal dysplasia in CDG-1a has been reported, plain spine films assessing cervical spine anomalies may be useful [Schade van Westrum et al 2006].

Surveillance

Annual

- Assessment by a physician with attention to overall health and referral for speech therapy, occupational therapy, and physical therapy
- Eye examination
- Liver function tests, thyroid panel, 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

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

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may

face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Congenital disorder of glycosylation type 1a (CDG-1a) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of the proband are obligate heterozygotes and therefore each carry one mutant allele.
- Carriers are asymptomatic.

Sibs of a proband

- At conception, the theoretical risks to sibs of an affected individual are a 25% risk of being affected, a 50% risk of being an asymptomatic carrier, and a 25% risk of being unaffected and not a carrier. However, based on outcomes of at-risk pregnancies, the risk of having an affected child is closer to 1/3 than to the expected 1/4.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Adults with CDG-1a have not been reported to reproduce.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis after the *PMM2* disease-causing mutations have been identified in the family.

Related Genetic Counseling Issues

Increased recurrence risk for CDG-1a. 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 caused by transmission ratio distortion continues to be validated [Schollen et al 2004].

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 at risk of being carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

High a priori risk. Prenatal diagnosis for pregnancies at increased risk for CDG-1a is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both *PMM2* disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Low a priori risk. CDG-1a should be considered in non-immune hydrops fetalis. Transferrin isoform analysis on fetal serum is an unreliable diagnostic test. PMM enzyme activity may also be falsely low in poor-growing amniocytes or chorionic villi. Molecular genetic testing for *PMM2* mutations can be considered [van de Kamp 2007].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Congenital Disorder of Glycosylation 1a

Gene Symbol	Chromosomal Locus	Protein Name
PMM2	16p13.3-p13.2	Phosphomannomutase 2

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Congenital Disorder of Glycosylation 1a

212065	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Ia; CDG1A
601785	PHOSPHOMANNOMUTASE 2; PMM2

Table C. Genomic Databases for Congenital Disorder of Glycosylation 1a

Gene Symbol	Entrez Gene	HGMD
PMM2	5373 (MIM No. 601785)	PMM2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants. The normal *PMM2* gene is 51.49 kb with eight exons and codes for a transcript length of 2290 bp. Northern blot analysis shows the highest expression of *PMM2* in the pancreas and liver with weak expression in brain, in contrast to *PMM1,* which is highly expressed in brain. A processed pseudogene, *PMM2P1*, has been identified on chromosome 18 [Schollen et al 1998].

Pathologic allelic variants. See Table 2. Approximately 90 mutations are listed in the Euroglycan Mutation Database (www.euroglycanet.org) [de Lonlay et al 2001,Jaeken & Matthijs 2001,Westphal et al 2001]. These data are collated from six research and diagnostic laboratories [Matthijs et al 2000]. There are numerous missense/nonsense mutations, as well as some nucleotide substitutions, small deletions, small insertion/deletions, and one report of a complex rearrangement. Recently, splice site variants, truncating mutations, and intronic

branch site mutations have also been reported [Vuillaumier-Barrot et al 2006,Schollen et al 2007].

The p.Arg141His mutation is the most common; p.Phe119Leu is the second most common. Kjaergaard et al [1998] reported that these two mutations together accounted for 88% of all mutations in the Danish population.

Table 2. *PMM2* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.338C>T	p.Pro113Leu	NM_000303.2 NP_000294.1
c.357C>A	p.Phe119Leu	
c.395T>C	p.Ile132Thr	
c.415 G>A	p.Glu139Lys	
c.422G>A	p.Arg141His	
c.563A>G	p.Asp188Gly	
c.653A>T	p.His218Leu	
c.677C>G	p.Thr226Ser	
c.691G>A	p.Val231Met	
c.710C>T	p.Thr237Met	
c.722G>C	p.Cys241Ser	

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

Normal gene product. The product of *PMM2* is a 246-amino acid protein with an approximate molecular weight of 28.1 kd. Phosphomannomutase 2 is an enzyme required for the synthesis of GDP-mannose specifically involved in the conversion of mannose-6-phosphate to mannose-1-phosphate, which is then transformed to GDP-mannose, a precursor of mannose for the biosynthesis of N-glycoproteins.

Abnormal gene product. The abnormal phosphomannomutase 2 protein causes hypoglycosylation by lowering the intracellular mannose-1-phosphate pool, producing dysfunctional proteins leading to deficient synthesis of GDP-mannose and incorrect N-linked oligosaccharide synthesis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The CDG Family Network Foundation
P.O. Box 860847
Plano, TX 75074
Phone: 800-250-5273
Email: cdgaware@aol.com
www.cdgs.com

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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