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# PMM2-CDG

## Synonyms: *CDG-Ia*, Congenital Disorder of Glycosylation Type 1a (CDG1a), Phosphomannomutase 2 Deficiency

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# Summary

## Clinical characteristics

PMM2-CDG, the most common of a group of disorders of abnormal glycosylation of N-linked oligosaccharides, is divided into three clinical stages: infantile multisystem, late-infantile and childhood ataxia–intellectual disability, and adult stable disability. The clinical manifestations and course are highly variable, ranging from infants who die in the first year of life to mildly affected adults. Clinical findings tend to be similar in sibs.

- In the infantile multisystem presentation, infants show axial hypotonia, hyporeflexia, esotropia, and developmental delay. Feeding issues, vomiting, faltering growth, and developmental delay are frequently seen. Subcutaneous fat may be excessive over the buttocks and suprapubic region. Two distinct clinical courses are observed: (1) a nonfatal neurologic course with faltering growth, strabismus, developmental delay, cerebellar hypoplasia, and hepatopathy in infancy followed by neuropathy and retinitis pigmentosa in the first or second decade; and (2) a more severe neurologic-multivisceral course with approximately 20% mortality in the first year of life.
- The late-infantile and childhood ataxia–intellectual disability stage, which begins 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 seizures, stroke-like episodes or transient unilateral loss of function, coagulopathy, retinitis pigmentosa, joint contractures, and skeletal deformities.
- In the adult stable disability stage, intellectual ability is stable; peripheral neuropathy is variable, progressive retinitis pigmentosa and myopia are seen, thoracic and spinal deformities with osteoporosis worsen, and premature aging is observed; females may lack secondary sexual development and males may exhibit decreased testicular volume. Hypogonadotropic hypogonadism and coagulopathy may occur. The risk for deep venous thrombosis is increased.

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## Diagnosis/testing

The diagnosis of PMM2-CDG is established in a proband with type I transferrin isoform analysis and identification of either biallelic pathogenic variants in *PMM2* on molecular genetic testing or (if results of molecular genetic testing are uncertain) low levels of phosphomannomutase (PMM) enzyme activity.

## Management

*Treatment of manifestations:* Symptomatic treatment for severe infantile phase in a pediatric tertiary care center. Optimal routine care in infants and children should maximize caloric intake including: use of a nasogastric tube or gastrostomy tube, anti-gastroesophageal reflux measures, speech and oral motor therapy to aid transition to oral feeds. Standard treatment for seizures; occupational therapy, physical therapy, and speech therapy for developmental delay. In all affected individuals care should include standard treatment of ocular and vision issues and cardiac issues; treatment of bleeding disorders and/or coagulopathy per hematologist with consultation with surgeon prior to surgeries; hydration for stroke-like episodes with physical therapy, occupational therapy, and speech therapy during the recovery period; standard management of deep venous thrombosis (DVT) with education regarding risk of DVT; treatment of hypothyroidism, hypoglycemia, and other endocrinopathies per endocrinologist. Multicystic kidneys are managed conservatively; standard treatments for other renal issues; counseling regarding avoidance of fracture; orthopedic intervention for scoliosis; rehabilitation medicine services including wheelchairs, transfer devices, physical therapy, and educational adaptation as needed; management of immune dysfunction per immunologist; education for life skills, vocational training, independent self-care, and activities of daily living; parental support for long-term care planning.

*Surveillance:* At each visit assess growth, nutritional status, safety of oral intake, seizures, and developmental progress; ophthalmology evaluations every one to two years; cardiology assessment as needed; annual AST, ALT, and albumin until normalization; liver ultrasound every three to five years; measure TSH, free T4, and glucose every one to two years; assess gonadal function at pubertal age as recommended by endocrinologist; blood pressure, urine dipstick for proteinuria, and serum creatinine every one to two years or as needed; assessment for osteopenia every one to two years; orthopedic assessment if scoliosis becomes evident; complete blood count and differential every one to two years; annual assessment of bleeding and clotting parameters by a hematologist including prothrombin time, protein C, protein S, antithrombin III, factor IX, and factor XI.

*Agents/circumstances to avoid:* Cautious use of acetaminophen and other agents metabolized by the liver if significant liver insufficiency is present.

## Genetic counseling

PMM2-CDG is inherited in an autosomal recessive manner. At conception, the theoretic 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. Carrier testing for at-risk family members and prenatal testing for a pregnancy at increased risk are possible if both *PMM2* pathogenic variants in the family have been identified.

# Diagnosis

PMM2-CDG is the most common of a group of disorders of abnormal glycosylation of N-linked oligosaccharides.

## Suggestive Findings

PMM2-CDG **should be suspected** in a **child**, **adolescent/adult**, or **fetus** with the following findings.

**In a child.** Developmental delay and hypotonia in combination with any of the following:

**Clinical findings**

- Faltering growth
- 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
- Recurrent infections with concerns about immunologic dysfunction and vaccine non-responsiveness
- Osteopenia, scoliosis
- Cerebellar hypoplasia/atrophy and small brain stem and additional characteristic findings on brain MRI (See Clinical Description.)

**Laboratory findings**

- Hepatic dysfunction (elevated transaminases)
- Coagulopathy with abnormal prothrombin time, low serum concentration of factors IX and XI, antithrombin III, protein C, and/or protein S
- Occasional hypoglycemia seen in infants, with some due to hyperinsulinemia
- Possible hypothyroidism reflected by elevated TSH; however, thyroxine levels, performed by equilibrium dialysis, are the most reliable marker for thyroid function.
- Osteopenia frequently with normal calcium, magnesium, and phosphate levels
- Proteinuria and aminoaciduria with elevated creatinine reported in some individuals

**In an adolescent or adult.** Any of the following:

**Clinical findings**

- Cerebellar dysfunction (ataxia, dysarthria, dysmetria) and characteristic findings on brain MRI (See Clinical Description.)
- Non-progressive cognitive impairment
- Seizures
- Stroke-like episodes
- Peripheral neuropathy with or without muscle wasting
- Absent or atypical secondary sexual development in females, small testes in males
- Retinitis pigmentosa and myopia
- Progressive scoliosis with truncal shortening
- Joint contractures

**Laboratory findings**

- Elevated liver function tests (transaminases)
- Low serum concentration of factors IX and XI, antithrombin III, protein C, and/or protein S
- Gonadal dysfunction in most but not all adult females with varying levels of FSH, LH, and estradiol. Most males have normal pubescence but may have low testosterone and sex hormone-binding globulin.

**In a fetus.** Nonimmune hydrops fetalis [van de Kamp et al 2007, Léticée et al 2010]

## Establishing the Diagnosis

The diagnosis of PMM2-CDG **is established** in a proband with suggestive findings and most often a type I transferrin isoform pattern and either biallelic pathogenic (or likely pathogenic) variants in *PMM2* identified on molecular genetic testing (see Table 1) or (if results of molecular genetic testing are uncertain) low levels of phosphomannomutase 2 (PMM2) enzyme activity.

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 section is understood to include any likely pathogenic variants. (2) Identification of biallelic *PMM2* variants of uncertain significance (or of one known *PMM2* pathogenic variant and one *PMM2* variant of uncertain significance) does not establish or rule out the diagnosis.

**Diagnostic type I transferrin isoform pattern** on analysis of serum transferrin glycoforms (also called "transferrin isoforms analysis" or "carbohydrate-deficient transferrin analysis"). The analysis, based on isoform analysis historically by isoelectric focusing (IEF) or other currently used methods (capillary electrophoresis, GC/MS, CE-ESI-MS, MALDI-MS), determines the number and structure of sialylated N-linked oligosaccharide residues linked to serum transferrin [Marklová & Albahri 2007, Sanz-Nebot et al 2007].

Possible results of such testing include:

- **Normal transferrin isoform pattern.** Two biantennary glycans linked to asparagine with four sialic acid residues
- **Type I transferrin isoform pattern.** Decreased tetra-sialotransferrin and increased asialo-transferrin and di-sialotransferrin. The pattern indicates defects in the earliest synthetic steps of the N-linked oligosaccharide synthetic pathway.
- **Type II transferrin isoform pattern.** Increased tri-sialotransferrins and/or mono-sialotransferrins. The pattern indicates defects in the later parts of the N-linked glycan pathway.

Note: (1) There are significant concerns about the diagnostic validity of analysis of serum transferrin glycoforms before age three weeks [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 clinical features of PMM2-CDG, PMM2 enzyme deficiency, and a normal transferrin isoform pattern have been reported [Hahn et al 2006]. (4) Historically the possibility that an abnormal transferrin glycoform analysis is due to PMM2-CDG can be confirmed with a glycoform analysis of a serum sample from the parents or by a neuraminidase treatment followed by IEF and electrospray ionization time-of-flight mass spectrometry (ESI-TOF MS) [Park et al 2014, Zühlsdorf et al 2015]. (5) In adults with milder forms of PMM2-CDG, serum transferrin glycoforms can be mildly abnormal or near normal [Wolthuis et al 2014]. (6) Type I transferrin isoform patterns can also be seen in individuals with untreated galactosemia or fructosemia, liver disease, severe infections, and chronic inflammatory disease.

**Molecular genetic testing approaches** can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with neurologic and/or multiorgan dysfunction are more likely to be diagnosed using genomic testing (see Option 2).

## Option 1

**Single-gene testing.** Sequence analysis of *PMM2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Three pathogenic variants are common in individuals of European ancestry and may be included on carrier screening panels:

- The pathogenic variant p.Arg141His is found in the compound heterozygous state in approximately 40% of individuals; it is never found in the homozygous state.
- The pathogenic variant p.Phe119Leu is frequently found in northern Europe, where the genotype [p.Arg141His]+[p.Phe119Leu] makes up a majority of all pathogenic variants [Jaeken & Matthijs 2001].
- The pathogenic variants p.Val231Met and p.Pro113Leu are common all over Europe.

**A multigene panel** that includes *PMM2* and other genes of interest (see Differential Diagnosis) may be considered 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. 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*. (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.

## Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by neurologic and/or multiorgan dysfunction **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

**Table 1.** Molecular Genetic Testing Used in PMM2-CDG

| Gene [1] | Method | Proportion of Pathogenic Variants [2] Detectable by Method [3] |
|---|---|---|
| *PMM2* | Sequence analysis [4] | >99% [5] |
| | Gene-targeted deletion/duplication analysis [6] | <1% [7] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* In individuals with either an abnormal transferrin isoform pattern on analysis of serum transferrin glycoforms or enzymatically confirmed phosphomannomutase 2 deficiency [Jaeken et al 2014] (full text)
*4.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*5.* Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
*6.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*7.* Reported deletions include a 28-kb deletion that includes exon 8 [Schollen et al 2007] and complete exon 8 deletion caused by an Alu retrotransposition [Haeuptle & Hennet 2009, Pérez et al 2011, Jaeken et al 2014].

**PMM2 enzyme activity.** In infants presenting with a severe/classic clinical picture of PMM2-CDG, PMM2 enzyme activity in fibroblasts and leukocytes is typically 0% to 10% of normal [Van Schaftingen & Jaeken 1995, Carchon et al 1999, Jaeken & Carchon 2001]. If measurement of enzyme activity is used to verify the diagnosis, use of leukocytes is preferable given that intermediate enzyme activity values (including values in the normal range) in fibroblasts have been reported in affected individuals [Grünewald 2009].

# Clinical Characteristics

## Clinical Description

Some features of PMM2-CDG are usually present in infancy, but may be too subtle to recognize and thus not come to medical attention. The clinical course varies by severity and includes the following typical presentations and stages: hydrops fetalis at the severe end, infantile multisystem presentation, late-infantile and childhood ataxia–intellectual disability stage, and an adult stable disability stage [Schiff et al 2017, Altassan et al 2019].

**Table 2.** PMM2-CDG: Frequency of Select Features

| Feature | Infantile Multisystem Presentation | Late-Infantile & Childhood Ataxia-ID Stage | Adult Stable Disability Stage | Comment |
|---|---|---|---|---|
| **Hypotonia** | Common | Common | Common | Both truncal & axial |
| **Faltering growth** | Common | Common | NA | Often due to feeding issues &/or vomiting |
| **Developmental delay** | Common | Common | NA | Adults have stable intellectual & motor involvement. |
| **Intellectual disability** | NA | Common | Common | |
| **Ocular features** | Common | Common | Common | Esotropia, strabismus in infants, retinitis pigmentosa, myopia. Cataracts may develop in adults. |
| **Hyporeflexia** | Common | Common | Common | |
| **Seizures** | Reported | Reported | Reported | Typically responsive to medication |

*Table 2. continued from previous page.*

| Feature | Infantile Multisystem Presentation | Late-Infantile & Childhood Ataxia-ID Stage | Adult Stable Disability Stage | Comment |
|---|---|---|---|---|
| **Ataxia** | NA | Common | Common | |
| **Stroke-like episodes** | Not reported | Reported | Not seen | Can present before age 2 yrs; not reported in adulthood |
| **Peripheral neuropathy** | Not reported | Common | Common | Observed at end of 1st decade |
| **Abnormal subcutaneous fat distribution** | Common | Common until early childhood, then disappears | Rare | Buttocks, suprapubic region, labia majora in females, & inverted nipples; may disappear w/age |
| **Characteristic facial features** | Common | Common | Coarse facies reported | Changes w/age |
| **Endocrine dysfunction** | Reported | Reported | Reported | Hypoglycemia & hypothyroidism reported in infants. Hypogonadotropic hypogonadism reported in adults |
| **Osteopenia** | Reported | Common | Common | |
| **Cardiac manifestations** | Common | Rare | Rare | Pericardial effusions seen in infancy, cardiomyopathy & structural heart defects reported but rare |
| **Liver manifestations** | Common | Common | Common | ↑ transaminases; may return to normal w/age |
| **Renal manifestations** | Reported | Reported | Reported | Multicystic kidneys w/normal function seen in children; proteinuria & aminoaciduria w/ nephropathy rarely reported |
| **Immunologic** | Rare | Rare | Rare | Recurrent infections consistent w/immunologic dysfunction & minimal response to vaccines |
| **Characteristic features on neuroimaging** | Common | Common | Common | Cerebellar atrophy on MRI |
| **Coagulopathy** | Common | Common | Common | Both pro- & anticoagulation factors are diminished; risk of bleeding life long, risk of DVT ↑ in adulthood |

ID = intellectual disability; NA = not applicable

## Nonimmune Hydrops Fetalis (NIHF)

NIHF has been reported in 12 individuals along with antenatal complications of hydropic placenta and polyhydramnios. All individuals who have presented with antenatal/neonatal hydrops fetalis died by age three months.

## Infantile Multisystem Presentation

An early-onset infantile multisystem presentation is characterized by feeding issues and faltering growth, developmental delay, seizures, ocular manifestations, dysmorphic features, and multivisceral involvement. There is variability in presentation, with some children showing only faltering growth and developmental delay and never requiring hospitalization. Strabismus and cerebellar hypoplasia are absent in some individuals.

Rarely, infants have a complicated early-infantile course presenting with fever, infection or seizure, and clinical deterioration that leads to hypoalbuminemia and third spacing with progression to anasarca. Approximately 20% of affected infants die within the first year of life with a severe neurologic-multivisceral course. Infants with

this more severe course may have faltering growth, vomiting, intractable hypoalbuminemia, anasarca, pericardial effusion, renal hyperechogenicity, renal cysts, nephrotic syndrome, hepatic fibrosis, and multiorgan failure [de Lonlay et al 2001, Marquardt & Denecke 2003, Schiff et al 2017, Altassan et al 2019].

**Feeding/growth.** Feeding issues and vomiting may cause faltering growth. Growth is significantly impaired [Kjaergaard et al 2002].

**Neurologic.** Infants show hypotonia, hyporeflexia, and developmental delay. They continue to gain developmental skills throughout their lives. Seizures, which are usually responsive to anti-seizure medication, are common in early childhood. In one study of 23 affected individuals who had seizures, the mean age of the first seizure was 17 months (range: 3-53 months) [Pérez-Dueñas et al 2009].

**Ophthalmologic features** are frequent and can involve both the structural components (development of the lens and retina) as well as ocular mobility and intraocular pressure [Morava et al 2009, Thompson et al 2013]. Commonly reported ophthalmologic features include esotropia, strabismus, retinitis pigmentosa, abnormal eye movements, and myopia [Schiff et al 2017, Altassan et al 2019].

**Dysmorphic features.** Reported facial features include prominent forehead, long face, almond-shaped palpebral fissure, short nose, long philtrum, thin vermilion of the upper lip, and large protruding ears. An unusual distribution of subcutaneous fat over the buttocks and the suprapubic region may be observed. In girls, subcutaneous fat distribution of the labia majora is involved as well. Inverted nipples are common. The inverted nipples and abnormal fat pads typically disappear with age.

**Cardiac.** Congenital cardiac anomalies or hypertrophic cardiomyopathy with transient myocardial ischemia have been reported but are rare [Marquardt et al 2002, Romano et al 2009, Altassan et al 2019]. 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 individuals and may be fatal [Truin et al 2008].

**Liver function.** Transaminases (AST and ALT) begin to rise in the first year of life and in young children may be in the range of 1,000 to 1,500 U/L without clinical sequelae. Typically, AST and ALT levels return to normal by age three to five years in children with PMM2-CDG and remain normal throughout their lives with occasional mild elevations during intercurrent illnesses [Starosta et al 2021]. Hypoalbuminemia can also be seen. Affected children do not need a liver biopsy unless warranted by additional clinical evidence. Liver biopsy can demonstrate steatosis and lamellar inclusions in macrophages and in hepatocyte lysosomes but not in Kupffer cell lysosomes [Jaeken & Matthijs 2001, Starosta et al 2021].

**Hematologic.** Coagulopathy with decreased serum concentrations of coagulation factors as well as antithrombin III, protein C, and protein S may be present.

**Endocrine.** In general, children with PMM2-CDG are chemically euthyroid [Miller & Freeze 2003]. Note that measurement of thyroid-binding globulin may be low and thyroid-stimulating hormone (TSH) may be transiently high. Free T4 should also be measured by equilibrium dialysis, the most accurate method, as clinically relevant hypothyroidism in PMM2-CDG is rare [Mohamed et al 2012]. Diagnosis of hypothyroidism and L-thyroxine supplementation should be reserved for those children and adults with elevated TSH and low free T4 measured by equilibrium dialysis.

Hypoglycemia is reported in infancy with 40% due to hyperinsulinemia [Altassan et al 2019].

**Renal.** Nephrotic syndrome is rare but has been reported [Sinha et al 2009]. Renal ultrasound examination in eight infants and children with PMM2-CDG showed no changes in the two individuals with only neurologic involvement and increased cortical echogenicity and/or small pyramids that may or may not have been hyperechoic in the six affected children with multivisceral involvement [Hertz-Pannier et al 2006].

**Musculoskeletal.** Osteopenia, while present from infancy, does not appear to significantly increase the risk of fractures. Osteopenia continues throughout life. If fracture occurs, healing appears to be normal.

**Immunologic**. Recent reports of immune dysfunction in some individuals with PMM2-CDG has prompted the recommendation that baseline tests at the time of diagnosis should include leukocyte count and immunoglobulin levels [Altassan et al 2019, Francisco et al 2020].

## Late-Infantile and Childhood Ataxia–Intellectual Disability Stage

The onset of late-infantile and childhood ataxia–intellectual disability stage occurs between ages three and ten years. Children continue to gain developmental skills with a course characterized by hypotonia and ataxia. Language and motor development are delayed and walking without support is rarely achieved [Jaeken & Matthijs 2001]. IQ typically ranges from 40 to 70. Individuals with borderline intellectual function and normal development have been described [Giurgea et al 2005, Pancho et al 2005, Barone et al 2007]. The children usually are extroverted and cheerful. Seizures may occur; they are usually responsive to anti-seizure medication.

Affected individuals may have stroke-like episodes or transient unilateral loss of function sometimes associated with fever, seizure, dehydration, or trauma in childhood or adulthood. Recovery may occur over a few hours to several months. Persistent neurologic deficits after a stroke-like episode occasionally occur but are rare. The etiology of these stroke-like episodes has not been fully elucidated [Altassan et al 2019].

Kyphoscoliosis, thoracic deformities, and thoracic shortening may also occur in older children but are more typically seen in adolescents and affected adults. One child with PMM2-CDG had skeletal dysplasia, characterized by platyspondyly affecting all the vertebrae and severe spinal cord compression at the level of the craniocervical junction [Schade van Westrum et al 2006] leading to the recommendation in affected children of cervical spine x-rays in neutral, flexion, and extension to assess for atlantoaxial instability.

Intracranial hemorrhage, while not common, has been described [Stefanits et al 2014].

A progressive peripheral neuropathy may begin in this age range.

Retinitis pigmentosa due to a progressive photoreceptor degeneration [Thompson et al 2013], myopia [Jensen et al 2003], cataract [Morava et al 2009], and joint contractures may also occur but are more typically seen in affected adults.

## Adult Stable Disability Stage

Adults with PMM2-CDG typically demonstrate stable rather than progressive intellectual disability. Some adults have normal cognitive abilities while most have IQs in the 40-70 range.

Additional neurologic features include variable progressive peripheral neuropathy and cerebellar ataxia [Schoffer et al 2006, Barone et al 2007]. Other cerebellar signs include dysarthria and dysmetria. Most adults are not ambulatory but are socially engaged with supported employment and living settings.

Progression of thoracic and spinal deformities can result in severe kyphoscoliosis and shortening and widening of the ribcage. Osteopenia and osteoporosis are common in adults [Monin et al 2014].

Women can lack secondary sexual development as a result of hypogonadotropic hypogonadism [Miller & Freeze 2003, Altassan et al 2019]. In some females, laparoscopy and ultrasound examination have revealed absent ovaries. Most males virilize normally at puberty but may exhibit decreased testicular volume.

Other endocrine dysfunction includes hyperprolactinemia, insulin resistance, and rarely hyperinsulinemic hypoglycemia [Miller & Freeze 2003, Shanti et al 2009]. Incorrect glycosylation affecting IGFBP3 function and an acid-labile subunit in the IGF pathway can lead to short stature [Miller et al 2009].

While low levels of coagulation factors (both pro- and anticoagulant) rarely cause clinical issues in daily activities, these factors must be assessed if an individual with PMM2-CDG undergoes surgery or an invasive procedure. These studies should include prothrombin time, fibrinogen, factor IX, factor XI, antithrombin, and protein C and protein S. Imbalances of pro- and anticoagulant factors may lead to either bleeding or thrombosis. Deep venous thrombosis (DVT) has been reported in adults and children with PMM2-CDG [Krasnewich et al 2007]. Risk is increased in those who are sedentary [Altassan et al 2019]. Family and caregivers should be taught the signs of DVTs, which can be missed in an individual with communication challenges and ataxia, who may have frequent bumps and bruises.

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

**Neuroimaging.** An enlarged cisterna magna and superior cerebellar cistern are 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 brain CT examinations performed on three children with PMM2-CDG 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, appeared 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, cerebellar atrophy did not appear to progress. Development of the supratentorial structures was normal.

## Pathophysiology

PMM2-CDG is caused by deficiency of phosphomannomutase 2 (PMM2) 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]. Because of the important biologic functions of the oligosaccharides in both glycoproteins and glycolipids, incorrect synthesis of these compounds results in embryologic developmental differences and postnatal multisystem clinical manifestations [Varki 1993, Freeze 2006] (see Figure 1).

## Genotype-Phenotype Correlations

Some genotype-phenotype correlations have been proposed, although recognition that there is significant phenotypic variability even with the same genotype is prudent.

- C-terminal pathogenic variants, 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 PMM2-CDG, was studied in Scandinavia [Kjaergaard et al 2001]. Individuals presented with severe feeding issues, severe failure to thrive, severe hypotonia, developmental delay 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. Homozygosity or compound heterozygosity for pathogenic variants with virtually no residual activity (e.g., p.Arg141His) is likely incompatible with life [Matthijs et al 2000].
- 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, age ten years, was severely affected.

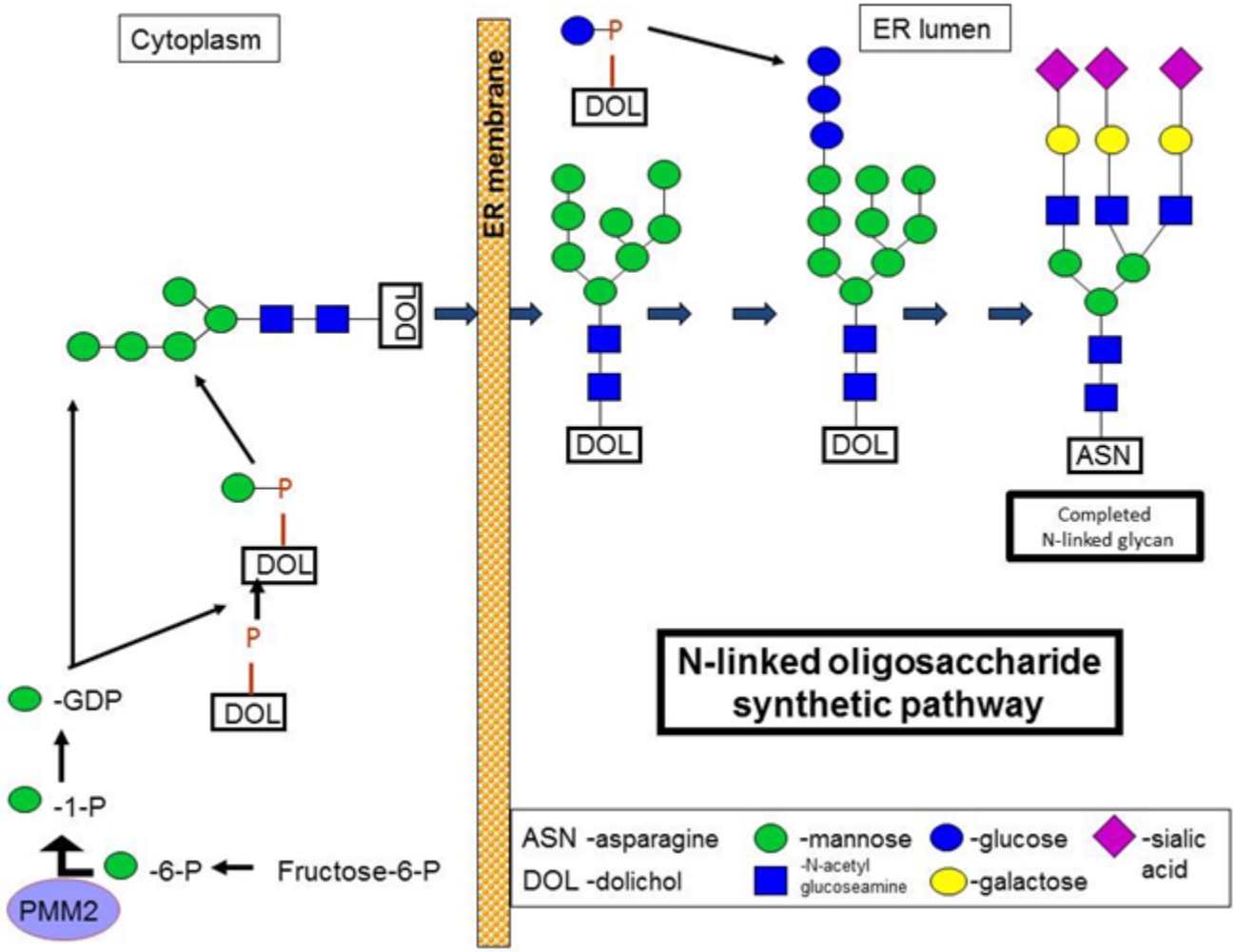


**Figure 1.** N-linked glycans are synthesized by adding individual charged sugars in a specific order to the growing multi-sugar structure, or oligosaccharide. Phosphomannomutase 2 (PMM2) is required for synthesis of one of these charged sugars, mannose-1-phosphate (man-1-P) from mannose-6-phosphate (man-6-P). Without adequate pools of man-1-P (as a result of decreased activity of PMM2), synthesis of complete N-linked glycans will be affected. The early steps of this complex multistep pathway occur in the endoplasmic reticulum, followed by completion of the synthesis after the growing structure is transferred to the Golgi.

- 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 appeared to be associated with a milder phenotype without pericardial effusions, coagulation defects, or nutritional disturbances. Some individuals were able to walk independently.
- The pathogenic variant p.Leu32Arg, which is particularly frequent in Italy, is associated with a milder phenotype with preserved ambulation and mild cognitive impairment despite cerebellar hypoplasia on brain MRI [Barone et al 2015].

**Modifiers.** A relatively common mild *ALG6* variant (p.Phe304Ser) in combination with biallelic *PMM2* pathogenic variants may exacerbate the clinical severity in PMM2-CDG; however, this information cannot currently be used to predict clinical outcome [Westphal et al 2002, Bortot et al 2013].

## Nomenclature

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 follows in parenthesis; thus the new nomenclature for this disorder is PMM2-CDG [Jaeken et al 2009].

PMM2-CDG was previously referred to as CDG-1a; carbohydrate-deficient glycoprotein syndrome, type 1a (CDGS1a); and Jaeken syndrome.

## Prevalence

PMM2-CDG is the most common form of congenital disorders of glycosylation. The prevalence could be as high as 1:20,000 [Jaeken & Matthijs 2001].

The expected carrier frequency for a *PMM2* pathogenic variant in the Danish population is 1:60 to 1:79 [Matthijs et al 2000].

# Genetically Related (Allelic) Disorders

A child with biallelic *PMM2* pathogenic variants [c.167G>T];[c.422G>A] presented in infancy with congenital hyperinsulinemic hypoglycemia and prenatally detected bilateral polycystic kidneys. At age six years she has normal growth and development and is a rare example of a clinical presentation of PMM2-CDG without neurologic involvement [Cabezas et al 2017, Soares et al 2020].

# Differential Diagnosis

**Early infantile presentation (in those infants who have not yet had an MRI).** Many metabolic and genetic disorders that present in infancy share at least some of the clinical features of PMM2-CDG. Metabolic disorders in the differential diagnosis of hypotonia, developmental delay, and growth deficiency are summarized in Table 3a.

**Table 3a.** Metabolic Disorders to Consider in the Differential Diagnosis of PMM2-CDG in Infants Who Have Not Yet Had an MRI

| Genes | DiffDx Disorder | Overlapping Clinical Features | Distinguishing Features |
|---|---|---|---|
| >175 genes | Other CDGs [1] & CDDGs (See CDG-N-Linked & Multiple Pathway Overview & NGLY1-CDDG.) | • IUGR<br>• DD/ID<br>• Neurologic dysfunction<br>• Liver disease<br>• Can have abnormal transferrin glycoform analysis | • Can be indistinguishable<br>• PMM2 enzyme activity is abnormal only in PMM2-CDG. |
| >300 genes | Mitochondrial disorders | • Multisystem involvement<br>• Pigmentary retinopathy<br>• Movement disorder | Persons w/PMM2-CDG:<br>• Do not typically have episodes of metabolic decompensation or clinical presentations assoc w/classic mt disorder phenotypes;<br>• Do not typically have significantly ↑ acidemia if not assoc w/hypoperfusion;<br>• Have abnormal transferrin glycoform analysis & deficient PMM2 activity. |

*Table 3a. continued from previous page.*

| Genes | DiffDx Disorder | Overlapping Clinical Features | Distinguishing Features |
|---|---|---|---|
| >20 genes | Peroxisomal biogenesis defects (See Zellweger Spectrum Disorder.) | • Multisystem involvement<br>• DD/ID<br>• Neurologic dysfunction<br>• Liver disease | Persons w/PMM2-CDG do not have abnormal very long chain fatty acids. |
| >20 genes | Urea cycle disorders / organic acidemias (See Propionic Acidemia, Glutaric Acidemia Type 1, Isolated Methylmalonic Acidemia, & Disorders of Intracellular Cobalamin Metabolism.) | • Hypotonia<br>• Growth deficiency<br>• Feeding intolerance<br>• DD/ID<br>• Spasticity | Persons w/PMM2-CDG:<br>• Do not typically have episodes of metabolic decompensation;<br>• Do not have hyperammonemia;<br>• Have abnormal transferrin glycoform analysis & deficient PMM2 activity. |

CDDG = congenital disorder of deglycosylation; CDG = congenital disorder of glycosylation; CDG-N-linked = congenital disorders of N-linked glycosylation; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; IUGR = intrauterine growth restriction; mt = mitochondrial; NGLY1-CDDG = *NGLY1*-related congenital disorder of deglycosylation
*1.* See OMIM Phenotypic Series: Congenital Disorders of Glycosylation, Type I and Congenital Disorders of Glycosylation, Type II to view genes associated with these phenotypes.

**Disorders with overlapping MRI findings.** See Table 3b.

**Table 3b.** Metabolic Disorders with Overlapping MRI Findings in the Differential Diagnosis of PMM2-CDG

| Gene | Disorder [1] | MRI Findings | Clinical Features |
|---|---|---|---|
| *ABHD12* | PHARC syndrome (OMIM 612674) | Cerebellar atrophy | Neurodegeneration, hearing loss, ataxia, retinitis pigmentosa, cataracts |
| *ALDH18A1* | Delta-1-pyrroline-5-carboxylate synthetase deficiency [2] | Cerebellar atrophy | Faltering growth, hypotonia, DD, cognitive impairment, cutis laxa, joint hyperlaxity, short stature, microcephaly, cataracts |
| *ALDH5A1* | Succinic semialdehyde dehydrogenase deficiency | Cerebellar atrophy, abnormalities of myelination, hyperintensity of $T_1$-weighted signals in the globus pallidus | DD, hypotonia, hyporeflexia, ataxia, epilepsy |
| *FA2H* | Fatty acid hydroxylase-associated neurodegeneration | Profound pontocerebellar atrophy, confluent periventricular white matter abnormalities, iron accumulation | Progressive spastic paraparesis & dysmetria; cognitive decline, optic atrophy, xeroderma |
| *GCDH* | Glutaric acidemia type 1 | Cerebellar atrophy, progressive disturbance of myelination, cortical atrophy, signal changes &/or atrophy of the basal ganglia; striatal injury spreading in a dorsoventral direction | Progressive dystonic cerebral palsy; acute brain injury assoc w/infections; choreoathetosis |
| *L2HGDH* | L-2-hydroxyglutaric aciduria (OMIM 236792) | Cerebellar atrophy, leukoencephalopathy, ↑ signal density of dentate nuclei & globi pallidi on $T_2$-weighted images, variety of neurologic malignancies | Seizures, progressive ataxia, spasticity, ID, DD |
| *MVK* | Mevalonate kinase deficiency (OMIM 610377) | Cerebellar atrophy | ID, ataxia, hypotonia, faltering growth, dysmorphic features, autoinflammation |

*Table 3b. continued from previous page.*

| Gene | Disorder [1] | MRI Findings | Clinical Features |
|---|---|---|---|
| *PLA2G6* | Infantile neuroaxonal dystrophy, NBIA (See *PLA2G6*-Associated Neurodegeneration.) | Cerebellar atrophy, signal hyperintensity in the cerebellar cortex, hypointensities in the globus pallidus & substantial nigra | Progressive motor & cognitive deterioration, cerebellar ataxia, hypotonia, visual disturbances, progression to spastic tetraplegia; chronic denervation |
| *SLC39A8* | SLC39A8 deficiency | Cerebellar atrophy | Hypotonia, DD, recurrent infections, cranial synostosis, hypsarrhythmia, disproportionate dwarfism |
| See footnote 3. | Leigh syndrome (See Mitochondrial Disorders Overview & Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview.) | Cerebellar atrophy, leukoencephalopathy w/brain stem & spinal cord involvement, $T_2$-weighted hyperintense lesions in putamina, globi pallidi, caudate, & brain stem | Progressive neurologic & motor decline |

DD = developmental delay; ID = intellectual disability; NBIA = neurodegeneration with brain iron accumulation; PHARC = *p*olyneuropathy, *h*earing loss, *a*taxia, *r*etinitis pigmentosa, and *c*ataract

*1.* With the exception of delta-1-pyrroline-5-carboxylate synthetase deficiency (which can be inherited in either an autosomal dominant and autosomal recessive manner) and Leigh syndrome (which can be inherited in an autosomal recessive, autosomal dominant, X-linked, or maternal manner), the disorders in Table 3b are inherited in an autosomal recessive manner.

*2.* Marco-Marín et al [2020]

*3.* Many genes (nuclear and mitochondrial) are known to be associated with Leigh syndrome.

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PMM2-CDG, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended [Grünewald 2009, Schiff et al 2017, Altassan et al 2019].

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with PMM2-CDG

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Gastrointestinal/ Nutrition** | Gastroenterology / nutrition / feeding team eval | • To incl eval of growth, aspiration risk, & nutritional status<br>• Consider eval for gastrostomy tube placement in infants w/dysphagia &/or aspiration risk. |
| **Neurologic** | • Neurologic eval<br>• Assess for ataxia, dysmetria, dysarthria.<br>• Administer clinical ataxia scale (e.g., ICARS). | • Consider baseline neuroimaging.<br>• Baseline EEG if seizures are a concern<br>• Nerve conduction studies in older affected persons |

*Table 4. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Development** | Developmental assessment | To incl:<br>• Motor, adaptive, cognitive, & speech-language eval<br>• Eval for early intervention / special education |
| | PT/OT assessment | • In infants: gross motor & fine motor skills<br>• In older children / adults assess mobility, ADL, & need for adaptive devices. |
| | Speech therapy assessment | • In infants, eval to assess suck & swallow<br>• In older children / adults assess communication both oral & w/adaptive devices to optimize care & independence. |
| **Eyes** | Ophthalmologic eval | To assess:<br>• Vision<br>• Ocular mobility<br>• Structural anomalies of the lens & retina<br>• Intraocular pressure |
| **Cardiac** | Echocardiogram, EKG & chest x-ray to evaluate for cardiac anomalies, hypertrophic cardiomyopathy, & pericardial effusions | |
| **Liver function** | • Measurement of ALT, AST, serum albumin concentration<br>• Liver ultrasound | |
| **Hematologic** | • Complete blood count<br>• Assessment of bleeding & clotting parameters by hematologist incl prothrombin time, protein C, protein S, antithrombin III, factor IX, & factor XI | If prothrombin time is prolonged incl: factor II, factor V, factor VII & factor X. |
| **Endocrine** | • Height assessment<br>• TSH, thyroid binding globulin & free T4<br>• Calcium, magnesium, & phosphorus<br>• Glucose | In those w/hypoglycemia: further workup should incl: plasma insulin, cortisol, growth hormone, lactic acid, ammonia beta-hydroxybutyrate, free fatty acids, & urinary ketones |
| | Assess gonadal function at pubertal age including tanner stage, growth velocity, bone age, FSH, LH, estradiol in females and testosterone & sex hormone binding globulin in males | |
| **Renal** | • Blood pressure<br>• Serum creatinine<br>• Urinalysis to evaluate for proteinuria & aminoaciduria<br>• Renal ultrasound exam to evaluate for microcysts | |
| **Musculoskeletal** | • Orthopedics / physical medicine & rehab / PT & OT assessment for contractures & skeletal deformities<br>• C-spine radiographs in neutral, extension, & flexion to assess for atlantoaxial instability<br>• Assessment for kyphoscoliosis starting at adolescence<br>• DXA scan starting in adolescence | |

*Table 4. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Immunology** | • Leukocyte count & immunoglobulin levels<br>• Antibody titer testing after vaccinations | |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & their families re nature, MOI, & implications of PMM2-CDG to facilitate medical & personal decision making |
| **Family support & resources** | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral. | |

ADL = activities of daily living; ALT = alanine transaminase AST = aspartate transaminase; DXA = dual-energy x-ray absorptiometry; ICARS = International Cooperative Ataxia Rating Scale; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; T4 = thyroxine; TSH = thyroid-stimulating hormone

*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

**Table 5.** Treatment of Manifestations in Individuals with PMM2-CDG

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Severe infantile phase** | • Symptomatic treatment in a pediatric tertiary care center is recommended.<br>• Some children are responsive to aggressive albumin replacement w/furosemide; others may have a more refractory course. | • Because infants w/PMM2-CDG have less physiologic reserve than peers, parents should have a low threshold for eval by physician for prolonged fever, vomiting, or diarrhea.<br>• Aggressive intervention w/antipyretics & antibiotics if warranted & hydration may improve morbidity assoc w/severe infantile phase.<br>• Parents should also be advised that some infants w/PMM2-CDG never experience a hospital visit, while others may require frequent hospitalizations. |
| **Faltering growth, oral motor dysfunction, persistent vomiting, GER** | • Consultation w/gastroenterologist & nutritionist<br>• In infants, any type of formula or breast milk fortification for maximal caloric intake<br>• Nasogastric tube or gastrostomy tube for nutritional support if needed until oral motor skills improve<br>• Thickening of infant feeds<br>• Maintenance of upright position after eating; antacids<br>• Speech therapy / oral motor therapy to aid transition to oral feeds | • Carbohydrates, fats, & protein are tolerated.<br>• Early in life, children may do better on elemental formulas.<br>• Children w/gastrostomy tube should be encouraged to eat by mouth if risk of aspiration is low. |
| **Seizures** | Standardized treatment w/ASM by experienced neurologist | • Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.<br>• Education of parents/caregivers [1] |

*Table 5. continued from previous page.*

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Stroke-like episodes** | Supportive therapy incl:<br>• Hydration by IV if necessary<br>• PT, OT, & speech therapies during recovery period | While ASMs & anticoagulants have been tried there is no evidence that either prevent stroke-like episodes. |
| **Developmental delay** | • Referral to an early intervention program for PT, OT, & speech therapy<br>• Referral to a developmental pediatrician to monitor progress & facilitate ongoing developmental services. | As the developmental gap widens between children w/PMM2-CDG & unaffected peers, parents need continued counseling & support. |
| **Strabismus** | Intervention by a pediatric ophthalmologist early in life is important to preserve vision through glasses, patching, or surgery. | |
| **Visual acuity, retinitis pigmentosa, & other eye issues** | Treatment per ophthalmologist | No PMM2-CDG specific treatments for ophthalmologic manifestations in PMM2-CDG |
| **Cardiac manifestations incl pericardial effusion & (rarely) cardiomyopathy** | Many pericardial effusions resolve w/o intervention. | No PMM2-CDG-specific treatments for cardiac manifestations |
| **Coagulopathy** | • Consultation w/hematologist (to document coagulation status & factor levels)<br>• Discussion w/surgeon & hematologist prior to surgery<br>• When necessary, infusion of fresh frozen plasma corrects the factor deficiency & clinical bleeding. | Low levels of coagulation factors, both pro- & anticoagulant, rarely cause clinical issues in daily activities. However, reports of both hemorrhagic & thrombotic events justify vigilance by caregivers. |
| | Rapid diagnosis & treatment of DVT are essential to minimize risk of pulmonary emboli. | Caregivers (esp of older affected persons) should be taught signs of DVT. |
| **Hypothyroidism & other endocrinopathy** | Treatment per endocrinologist | |
| **Renal** | Multicystic kidneys can be managed conservatively; no PMM2-CDG-specific management of renal dysfunction | |
| **Orthopedic issues – osteopenia, thorax shortening, scoliosis/ kyphosis** | • Counseling regarding avoidance of fractures<br>• Management per orthopedic & physical medicine, well-supported wheelchairs, appropriate transfer devices for the home, & PT.<br>• Occasionally, surgical treatment of kyphoscoliosis is warranted. | |
| **Immune dysfunction** | • Treatment per immunologist<br>• Consider post vaccination titers to establish vaccine responsiveness. | |

*Table 5. continued from previous page.*

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Family support & resources** | • Aggressive education throughout school years in functional life skills &/or vocational training helps the transition when schooling is completed.<br>• Independence in self-care & ADL should be encouraged.<br>• Address issues of independent living w/young adults & parents.<br>• Support & resources for parents of a disabled adult<br>• Support caregiver understanding of need for long-term care plans & successor caregivers for affected older adults. | |

Schiff et al [2017], Altassan et al [2019]
ADL = activities of daily living; ASM = anti-seizure medication; DVT = deep venous thrombosis; GER = gastroesophageal reflux; OT = occupational therapy; PT = physical therapy
*1.* Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

## Surveillance

**Table 6.** Recommended Surveillance for Individuals with PMM2-CDG

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Feeding/Growth** | • Measurement of growth parameters<br>• Eval of nutritional status & safety of oral intake | At each visit |
| **Neurology** | • Monitor those w/seizures as clinically indicated.<br>• Assess for new manifestations incl seizures, changes in tone, movement disorders. | |
| **Development** | Monitor developmental progress & educational needs. | |
| **Eyes** | Ophthalmology exam | Every 1-2 yrs &/or as needed |
| **Cardiovascular** | Cardiology assessment | As needed |
| **Liver** | AST, ALT, & albumin | • Annually until normalization<br>• Those w/chronic ↑ of transaminases, at risk for fibrosis, may need noninvasive elastography. |
| | Liver ultrasound | Every 3-5 yrs |
| **Endocrine** | • Height assessment<br>• TSH & free T4<br>• Glucose<br>• Calcium, magnesium, phosphate | Every 1-2 yrs &/or as needed |
| | Assess gonadal function at pubertal age incl Tanner stage, growth velocity, bone age, FSH, LH, estradiol in females & testosterone & sex hormone-binding globulin in males | As recommended by endocrinologist |
| **Renal** | • Blood pressure<br>• Urine dipstick for proteinuria<br>• Serum creatinine | Every 1-2 yrs &/or as needed |
| | Multicystic kidneys can be followed conservatively. | |

*Table 6. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Musculoskeletal** | Monitor for osteopenia/osteoporosis | Every 1-2 yrs &/or as needed |
| | DXA scan | Every 3-5 yrs starting in adolescence |
| | Orthopedist assessment when scoliosis becomes evident | |
| **Immunology** | Complete blood count & differential | Every 1-2 yrs |
| **Hematologic** | Assessment of bleeding & clotting parameters by hematologist incl prothrombin time, protein C, protein S, antithrombin III, factor IX, & factor XI | • Annually &/or as needed<br>• Consultation at time of surgery<br>• If prothrombin time is prolonged, factors II, V, VII, VIII & X should be measured. |

Altassan et al [2019]
ALT = alanine transaminase AST = aspartate transaminase; DXA = dual-energy x-ray absorptiometry; T4 = thyroxine; TSH = thyroid-stimulating hormone

## Agents/Circumstances to Avoid

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

## Evaluation of Relatives at Risk

Newborns at risk should have molecular testing for the familial *PMM2* pathogenic variants.

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

## Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

# 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

PMM2-CDG is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are typically heterozygotes (i.e., carriers of one *PMM2* pathogenic variant).
- Accurate recurrence risk counseling relies on carrier testing of both parents to determine if both are heterozygous for a *PMM2* variant. If carrier testing detects the variant in only one parent:
  - And the child appears to have homozygous *PMM2* pathogenic variants, possible explanations include a large deletion on one allele (if not previously tested for) and uniparental isodisomy for

chromosome 16. (Uniparental isodisomy was reported in a proband with PMM2-CDG [Vaes et al 2020].)
    - And the child has compound heterozygous *PMM2* pathogenic variants, the child may theoretically have one inherited variant and one *de novo* pathogenic variant. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- If both parents are known to be heterozygous for a *PMM2* pathogenic variant, the theoretic risks to sibs of an affected individual at conception 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 [Schollen et al 2004]. (See Related Genetic Counseling Issues, **Increased recurrence risk for PMM2-CDG**.)
- If the proband has PMM2-CDG as the result of uniparental isodisomy for chromosome 16 and only one parent is heterozygous for a *PMM2* pathogenic variant, the theoretic risks to sibs of an affected individual at conception are a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier. (The risk to the sibs of being affected with *PMM2*-CDG is not increased over that of the general population.)
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Adults with PMM2-CDG are not known to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a *PMM2* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PMM2* pathogenic variants in the family.

## 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.** 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 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 at risk of being heterozygotes (i.e., carriers of one *PMM2* pathogenic variant).

**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

**High a priori risk.** Once the *PMM2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for PMM2-CDG are possible.

**Low a priori risk.** *PMM2* molecular testing should be considered in nonimmune hydrops fetalis [van de Kamp et al 2007].

Note: Transferrin isoform analysis on fetal serum is an unreliable diagnostic test. PMM2 enzyme activity may also be falsely low in poorly growing amniocytes or chorionic villi.

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

# Resources

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

- **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
- **Directory of CDG Patient Advocacy Groups and Local Patient Representatives**
  www.apcdg.com/cdg-patient-groups

# Molecular Genetics

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

**Table A.** PMM2-CDG: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PMM2* | 16p13.2 | Phosphomannomutase 2 | PMM2 database | PMM2 | PMM2 |

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

**Table B.** OMIM Entries for PMM2-CDG (View All in OMIM)

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

## Molecular Pathogenesis

*PMM2* encodes phosphomannomutase 2 (PMM2), an enzyme specifically involved in the conversion of mannose-6-phosphate to mannose-1-phosphate, which is then further converted to GDP-mannose. GDP-mannose is the activated mannose used in the biosynthesis of N-linked glycoproteins.

Deficient PMM2 causes hypoglycosylation by lowering the intracellular mannose-1-phosphate pool, leading to deficiency of GDP-mannose, and thus deficient lipid-linked oligosaccharide synthesis. With deficiency of lipid-linked oligosaccharides, glycosylation of proteins at the asparagine residue becomes deficient, leading to dysfunction of these underglycosylated proteins.

**Mechanism of disease causation.** Loss of function

***PMM2*-specific laboratory technical considerations.** A processed pseudogene, *PMM2P1*, has been identified on chromosome 18 [Schollen et al 1998].

**Table 7.** Notable *PMM2* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| NM_000303.2 NP_000294.1 | c.95T>G | p.Leu32Arg | Common pathogenic variant in Italy, assoc w/a milder phenotype w/preserved ambulation & mild cognitive impairment despite cerebellar hypoplasia on brain MRI [Barone et al 2015] |
| | c.338C>T | p.Pro113Leu | Common pathogenic variant in European populations |
| | c.357C>A | p.Phe119Leu | 2nd most common pathogenic variant in northern European populations; together w/p.Arg141His, accounts for 88% of all pathogenic variants in the Danish population [Kjaergaard et al 1998] |
| | c.395T>C | p.Ile132Thr | Milder phenotype when present w/p.Arg141His [de Lonlay et al 2001] |
| | c.415G>A | p.Glu139Lys | Milder phenotype when present w/p.Arg141His [de Lonlay et al 2001] |
| | c.422G>A | p.Arg141His | Most common pathogenic variant in northern European populations; together w/p.Phe119Leu, accounts for 88% of all pathogenic variants in the Danish population [Kjaergaard et al 1998, Schollen et al 2000] |
| | c.563A>G | p.Asp188Gly | Severe phenotype when present w/p.Arg141His [Matthijs et al 1998] |
| | c.653A>T | p.His218Leu | May be assoc w/a milder phenotype [Matthijs et al 1999, Tayebi et al 2002] |
| | c.677C>G | p.Thr226Ser | Milder phenotype when present w/p.Arg141His [de Lonlay et al 2001] |

*Table 7. continued from previous page.*

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| | c.691G>A | p.Val231Met | Assoc w/high early mortality & severe multiorgan insufficiency [Barone et al 2015] |
| | c.710C>T | p.Thr237Met | May be assoc w/a milder phenotype [Matthijs et al 1999, Tayebi et al 2002, Altassan et al 2019] |
| | c.722G>C | p.Cys241Ser | May be assoc w/a milder phenotype [Matthijs et al 1999, Tayebi et al 2002] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

# Chapter Notes

## Author Notes

Christina Lam is a board-certified clinical geneticist and medical biochemical geneticist. After completion of her pediatrics and genetics residency at UCLA and her medical biochemical genetics and clinical research fellowship at the National Institutes of Health, she joined the faculty at the University of Washington in Seattle, Washington, practicing medical biochemical genetics mostly at Seattle Children's Hospital. She received her MD from the David Geffen School of Medicine at UCLA in 2007. She is currently an Assistant Professor of Pediatrics at the University of Washington.

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 where she saw children with developmental delay and congenital disorders of glycosylation. In 2009 she moved to the National Institute of General Medical Sciences where she is a Program Director in the Division of Genetics.

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## Author History

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