

### What is congenital disorder of glycosylation type 1a?

Congenital disorder of glycosylation type 1a is an inherited disease characterized by variable developmental delays and muscle and bone problems that change with age. Individuals with congenital disorder of glycosylation type 1a have defects in the enzyme phosphomannomutase 2. This enzyme is important in the cellular process of attaching sugars to proteins (glycosylation). The symptoms of congenital disorder of glycosylation type 1a are due to abnormalities in the glycosylation process, which leads to a wide variety of symptoms throughout the body.<sup>1</sup>

### What are the symptoms of congenital disorder of glycosylation type 1a and what treatment is available?

The symptoms of congenital disorder of glycosylation type 1a change as a person ages. Most individuals are diagnosed in infancy, but a small number of babies have been found to have hydrops fetalis (abnormal buildup of fluid in the body) detected by prenatal ultrasound.<sup>2</sup> The course of disease is divided into three stages based on age and symptoms.

Symptoms in the “infantile, multi-system stage” may include<sup>1,3</sup>:

- Hypotonia (low muscle tone)
- Feeding problems
- Vomiting and diarrhea
- Seizures
- Unusual fat distribution (more than usual on buttocks and pelvic area) and inverted nipples
- Strabismus (“crossed eyes” or “lazy eyes”)
- Variable growth and developmental delays
- Distinctive facial features
- Liver complications
- Osteopenia (low bone mineral density)
- Death in the first year of life for 20% of individuals

Typically, between 3 and 10 years of age a more static phase of disease begins. Symptoms of this “late-infantile and childhood ataxia-intellectual disability stage” may include<sup>3</sup>:

- Persistence of strabismus, osteopenia, developmental delays (which may include mental retardation), and muscle weakness
- Ataxia (difficulty coordinating movements)
- Stroke-like episodes
- Bone abnormalities
- Joint contractures (tightening of the muscles or tendons preventing full extension)
- Retinitis pigmentosa (vision disorder that may lead to blindness)

Around adolescence or by adulthood, the “adult stable disability stage” begins with symptoms that may include<sup>3</sup>:

- Persistence of previous symptoms
- Variable intellectual ability
- Peripheral neuropathy (pain and/or numbness in the hands and feet)
- Scoliosis and/or kyphoscoliosis (abnormal curvatures of the spine)
- Hypothyroidism
- Insulin resistance
- Premature aging

- Absent puberty for females
- Small testes in males

There is no cure for congenital disorder of glycosylation type 1a, and treatments are aimed at managing and monitoring symptoms. Maximal caloric intake is recommended by supplements or feeding tubes, if necessary. Various early intervention therapies (occupational, speech, physical) are available to address developmental delays. Supportive aids and rehabilitative services may be needed. It is suggested that acetaminophen and other medications broken down by the liver should be avoided.<sup>3</sup>

### How is congenital disorder of glycosylation type 1a inherited?

Congenital disorder of glycosylation type 1a is an autosomal recessive disease caused by mutations in the *PMM2* gene.<sup>1</sup> An individual who inherits one copy of a *PMM2* gene mutation is a carrier and is not expected to have related health problems. An individual who inherits two *PMM2* mutations, one from each parent, is expected to be affected with congenital disorder of glycosylation type 1a.

If both members of a couple are carriers of a mutation in the *PMM2* gene, the risk for an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

### Who is at risk for congenital disorder of glycosylation type 1a?

Congenital disorder of glycosylation type 1a can occur in individuals of all races and ethnicities. The prevalence of affected individuals of European ancestry may be as high as 1 in 20,000 with a calculated carrier frequency of approximately 1 in 71.<sup>3</sup>

Having a relative who is a carrier or who is affected can increase an individual's risk to be a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

### What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

### What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

### Where can I get more information?

Genetics Home Reference: <http://ghr.nlm.nih.gov/condition/pmm2-congenital-disorder-of-glycosylation>

National Organization for Rare Disorders: <http://rarediseases.org/rare-diseases/pmm2-cdg/>

### References

1. Congenital disorder of glycosylation type 1a and PMM2. *Genetics Home Reference*. Available at <http://ghr.nlm.nih.gov/condition/congenital-disorder-of-glycosylation-type-1a>. Accessed: March 16, 2012.
2. van de Kamp J *et al*. Congenital disorder of glycosylation type 1a presenting with hydrops fetalis. *J Med Genet* 2007; 44:277–280.
3. Sparks S and Krasnewich D. PMM2-CDG (CDG-1a). *GeneReviews*. Available at <http://www.ncbi.nlm.nih.gov/books/NBK1110/> Accessed: March 16, 2012.
4. Schollen E *et al*. Lack of Hardy-Weinberg equilibrium for the most prevalent PMM2 mutation in CDG-1a (congenital disorders of glycosylation type 1a) *Eur J Hum Genet* 2000; 8:367-371.