**Definition**

Pompe disease is a genetic disorder caused by mutations in the GAA gene. The GAA gene codes for an enzyme called acid alpha-glucosidase (GAA) which is necessary for the degradation of glycogen in the lysosome. Without this enzyme, glycogen accumulates in cells, particularly in muscles and heart muscle.

**How Inherited**

Pompe disease is inherited in an autosomal recessive pattern. Both parents are carriers and there is a deficiency of the critical enzyme activity. Each parent of a newborn with Pompe disease typically has one functional GAA gene and one non-functional GAA gene. In people with Pompe disease, there is no functional GAA gene.

**Incidence:**

Incidence: The overall incidence of Pompe disease is approximately 1 in 17,000 births. It is panethnic.

**Newborn Screening:**

Screening for Pompe disease is accomplished by analysis of GAA enzyme activity by mass spectrometry. If concentrations are normal, the gene is sequenced. If concentrations are low, the gene is sequenced. Results from partial deficiency may be low in healthy newborns, thus giving a false negative result. Within the GAA gene, at least one pseudodeficiency allele will be indicated on the newborn screen with at least one GAA gene mutation should be assessed with leukocyte GAA enzyme analysis. Babies with two mutations will require an electrophoresis screen with at least one GAA gene mutation.
Pompe disease is a genetic disorder caused by mutations in the GAA gene. It is a progressive metabolic condition that causes muscle weakness. The GAA gene codes for an enzyme called acid alpha-glucosidase (GAA) which is necessary for the degradation of glycogen in the lysosomes. Mutations in GAA result in an accumulation of glycogen in the lysosomes. It is therefore considered a Lysosomal Storage Disorder. Pompe disease is inherited in an autosomal recessive pattern. Normally a person has two functional GAA genes. In people with Pompe disease, both copies of this gene have a mutation and there is a deficiency of the critical enzyme activity. Each parent of a newborn with Pompe disease typically has one functional and one mutated gene and is considered a carrier. When both parents are carriers, the chance of a newborn inheriting two mutated genes is 25%.

Symptoms in carriers

None known.

Symptoms

The symptoms of Pompe disease vary in terms of age of onset and severity, and correspond to the degree of GAA enzyme activity.

First Tier Screening: Newborn Screening

Incidence: The overall incidence of Pompe disease is approximately 1 in 17,000 births. It is panethnic. New York State Method of Screening (First Tier): Screening for Pompe disease is accomplished by analysis of GAA enzyme activity by mass spectrometry. If concentrations are normal, the sample is deemed within acceptable limits. If abnormal, second tier screening is performed.

Second Tier Screening: Sequencing of the GAA Gene

Testing can be affected by: GAA enzyme activity may be low in healthy newborns, thus giving a false positive result. Within the GAA gene, at least one pseudodeficiency allele has been identified which results in lower GAA enzyme activity but no clinical symptoms of Pompe disease.

Interpretation/Reporting of data: Results are reported as within acceptable limits, repeat specimen required or as a referral. Prompt consultations with specialists are required for each referral.

• When two GAA mutations are identified in an infant, it is consistent with a diagnosis of Pompe disease. The baby will be referred to a Metabolic Geneticist at one of the designated Specialty Care Centers.

• When one mutation is identified in an infant, additional testing by a Metabolic Geneticist is needed in order to determine if the baby is affected by Pompe disease or is a carrier. This is because DNA sequence analysis may not detect all possible mutations in the GAA gene. These evaluations include analysis of leukocyte GAA enzyme and creatine kinase (CK). If low GAA activity persists, follow recommendations for reaching a diagnosis (see below). If GAA activity is normal in leukocytes, the baby is a carrier of Pompe disease.

• When no mutation is identified in GAA gene, but one or more variants of uncertain significance or polymorphisms are found, a repeat newborn screen is requested. If low GAA enzyme activity persists, follow recommendations for one mutation (see above).

• When GAA gene sequencing reveals a pseudodeficiency allele only, which results in lower GAA enzyme activity but no clinical symptoms of Pompe disease, this is considered screen negative. The presence of the pseudodeficiency allele will be indicated on the report, but no follow-up testing is recommended.

Referral to Specialty Care Center: Babies with an abnormal newborn screen for Pompe disease with an identified GAA mutation are referred to an Inherited Metabolic Disease Specialty Care Center for a diagnostic evaluation.

Diagnosis

All babies who have a positive Pompe newborn screen with at least one GAA gene mutation should be assessed with leukocyte GAA enzyme analysis, and babies with two mutations will require a cardiac evaluation (echocardiogram and EKG) to look for signs of cardiomyopathy, and also a test for urine tetrasaccharide (Glc4). Babies with a confirmed diagnosis will be referred to Pediatric Cardiology, and may require assessments by Pulmonology, Ophthalmology, Gastroenterology/ Nutrition, Developmental Pediatrics, Audiology,