Pompe Disease: GAA Gene Sequencing

**Test Code:** AN  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81406 x1

### Condition Description

Glycogen storage disease type II (GSD-II) is an autosomal recessive disorder due to a deficiency of the lysosomal enzyme acid alpha-1,4-glucosidase (abbreviated GAA). The function of the GAA enzyme, also known as acid maltase, is to breakdown glycogen in the lysosome. Absent or reduced GAA activity results in accumulation of glycogen within the lysosome, particularly in muscle cells. GSD-II is divided into two forms: an infantile form and a juvenile/adult onset form. In individuals with the infantile form of Pompe disease there is less than 1% of normal enzymatic activity, whereas in the juvenile/adult onset form there is some residual enzymatic activity. In Pompe disease, affected infants are severely hypotonic and have cardiomegaly. In addition, patients may have an enlarged tongue. The disease is usually fatal within the first year of life due to cardiopulmonary failure. The clinical presentation in the infantile/adult onset form (onset after 12 months of age) is much more variable than in the Infantile form of Pompe disease. In this later onset form of the disease, patients generally suffer from slowly progressive proximal muscle weakness with progressive respiratory insufficiency. Unlike the infantile form, in the later onset form there is usually not cardiomegaly or cardiomyopathy.

Mutations in the GAA gene cause deficiency of the GAA enzyme. More than 200 mutations in the GAA gene have been described to date[1]. The most common variant found in GSD II is a change in intron 1, specifically a splice site mutation, that is associated with the late onset form of the disease[2]. The life expectancy of these patients varies considerably, with death ultimately occurring due to respiratory insufficiency. Enzyme replacement therapy for treatment of symptoms of Pompe disease is FDA approved.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

For questions about testing for Pompe disease, call the Emory Genetics Laboratory at (470) 378-2200 or (855) 831-7447. For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.


### References:

1. www2. eur.nl/fgg/ch1/pompe

### Genes

**GAA**

### Indications

- Confirmation of a clinical diagnosis of GSD II
- Prenatal testing for known familial mutations.
- Assessment of carrier status in high risk family members known mutation analysis.

### Methodology

PCR amplification of 20 exons contained in the GAA gene coding region will performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis. Results of molecular analysis must interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Detection

Clinical Sensitivity: In a study by Herman et al. in 29 patients with either infantile of juvenile/adult onset GSD II (58 alleles assessed), 55 pathogenic mutations were identified giving a detection rate of 95%[2]. In a second study by Montalvo et al. investigating only late onset GSD II in 40 Italian patients, 77 mutations were identified giving a detection rate of 96%[3].

Analytical Sensitivity: ~99%

Prevalence: The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of GSD II is not specifically known, but is likely to be rare and may vary by ethnicity.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Specimen Requirements

Submit only 1 of the following specimen types
* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene\textsuperscript{TM} Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Known Mutation Analysis (KM) is available to test family members.
- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.