



GBA Factsheet

Gaucher Disease Type I

CENTOGENE ID	399
Gene(s) name (OMIM®, HGNC)	GBA
Gene OMIM®	606463
Disease OMIM®	230800
Gene location	1q22

INHERITANCE PATTERN

Autosomal recessive

DISEASE SYNONYMS

Glucocerebrosidase Deficiency, Glucosylceramidase Deficiency amyloidosis, familial Amyloid polyneuropathy.

MATERIAL

Minimum DNA (µg)	Minimum EDTA Blood (ml)	Minimum Filtercards (pcs)
2	1	2

TURNAROUND TIME (estimated working days upon sample receipt)

Enzymatic (glucocerebrosidase)	Biomarker LYSO-GB1	Full Gene Sequencing	DEL/DUP Analysis
7	7	15	20

We recommend ordering parallel or reflex testing workflows to shorten the total turnaround time.

Clinical Features

Gaucher disease (GD) includes three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular). GD type 1, the most common form of Gaucher disease, is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disorders.

Patients show highly variable phenotypes. Some might be asymptomatic, while others may manifest painless splenomegaly, thrombocytopenia, anemia or pancytopenia in childhood age. Thrombocytopenia causes bleedings, which may manifest in nosebleed, gum bleeding, and/or hematoma. Patients may also have chronic fatigue, hepatomegaly, bone pain, or pathologic fractures. Clinical or radiographic evidence of bone disease occurs in 70 – 100% of individuals with GD type 1. Bone disease ranges from asymptomatic osteopenia to focal lytic

or sclerotic lesions and osteonecrosis. The most debilitating aspect of type 1 GD is bone pain, pathologic fractures, and subchondral joint collapse with secondary degenerative arthritis.

In GD types 2 and 3 the primary neurologic disease is the hallmark. GD type 2 can affect children before the age of two, with a rapidly progressive course, limited psychomotor development, and death by the age of two to four years. Individuals with GD type 3 usually have a slower progressive course of the disease with a life span extending into the third or fourth decade.

Differential Diagnosis

Findings in GD may partially overlap with lysosomal storage diseases, saposin C deficiency, prosaposin deficiency, hepatomegaly and Legg-Calve-Perthes disease.

Diagnostic Strategy: Biochemistry & Genetics

We offer the following assay selection for diagnosing Gaucher disease:

Biochemistry

- The biomarker Lyso-Gb1: primary screening marker with almost perfect sensitivity and specificity to identify GD patients. Furthermore used to complement a positive enzymatic result or to monitor disease progression and/or treatment efficacy. In case of enzyme replacement therapy (ERT), Lyso-Gb1 has also been demonstrated as an adequate biomarker to help defining individual therapeutic dosage.^{2,3}
- A method using Lyso-Gb1 is covered by US Patent No. 10,859,580, other pending US applications, and pending applications and patents in other jurisdictions.
- Enzymatic quantification (glucocerebrosidase)

Genetics

- Sequence analysis of entire coding and flanking intronic regions of the GBA gene with NGS single gene sequencing.
- If no pathogenic variant is identified, deletion/duplication analysis will be performed using qPCR.

For differential diagnosis we recommend CentoMetabolic® (comprehensive coverage with more than 166 genes) or Whole Genome Sequencing (to detect deep intronic variants and variants involving regulatory regions).

The most common pathogenic variants are c.84dupG (formerly known as 84GG), c.115+1G>A (IVS2+1), p.Asn409Ser (p.N370S), and p.Leu483Pro (p.L444P). Reference sequence: NM_000157.3 (NP_000148.2).

Referral Reasons

The following individuals are candidates for this particular gene testing:

- Individuals with a family history of GD and presentation of the most common symptoms
- Individuals without a positive family history, but with symptoms resembling the disease
- Individuals with a negative but suspected family history, to perform proper genetic counseling (prenatal analyses are recommended in families with affected individuals)

Test Utility

Sequencing and deletion/duplication testing of this gene as well as related genes should be performed in all individuals suspected for this particular phenotype. In parallel, other genes reported to be related with this clinical phenotype should also be analyzed for the presence of mutations, due to the overlap in many clinical features caused by those particular genes. Confirmation of a clinical diagnosis through genetic testing can allow for genetic counseling and may direct medical management.⁴ Genetic counseling can provide a patient and/or family with the natural history of the condition, identify at-risk family members, provide reproductive risks, and allow for appropriate referral for patient support and/or resources.

Treatment

Management by an interdisciplinary team. Treatment usually includes enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). ERT consists of infusions of mannose-terminated glucocerebrosidase, resulting in regression of many visceral manifestations of the disease. Enzyme replacement therapy can be used in most patients with Types 1 and 3 Gaucher disease. Symptomatic treatment includes transfusion of blood products for severe anemia and bleeding, analgesics for bone pain, joint replacement surgery for relief from chronic pain and restoration of function, partial or total splenectomy for massive splenomegaly and thrombocytopenia. Regarding bone disease calcium, anti-bone resorptive agents, and vitamin D for osteoporosis are recommended.¹

REFERENCES

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