SickKids | Genome Diagnostics

Gaucher Disease

Gaucher disease (GD), the most common lipid-storage disorder, has a clinical spectrum ranging from perinatal lethality to asymptomatic. The most common symptoms of Gaucher disease are enlargement of the liver and spleen, anemia, reduced platelets (resulting in easy bruising and long clotting times), bone pain and osteoporosis. There are three clinical forms of Gaucher disease: Type 1 has physical symptoms without neurological involvement, Type 2 is characterized by severe neurological symptoms, and is usually fatal during the first three years of life, Type 3 has mild neurological symptoms which appear later in childhood and progress more slowly than the neurological symptoms of Type 2.

Genetics

Gaucher disease is an autosomal recessive disorder caused by mutations in the *β*-glucosidase (*GBA)* gene, located on chromosome 1 (1p21-p23). The incidence of GD is ~1:60,000 in the general population and 1:1000 in the Ashkenazi Jewish population. Four mutations account for ~90% of disease causing alleles in the Ashkenazi Jewish population and 50-60% in non-Jewish populations. Non-Jewish individuals with Gaucher disease tend to be compound heterozygotes with one 'rare' mutation, four of which are tested in this panel and one common mutation. The identification of mutations cannot conclusively differentiate between Gaucher disease type I, II and III. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

Confirming a diagnosis

To confirm a diagnosis of Gaucher disease an assay for glucosylceramidase enzyme activity in leukocytes or other nucleated cells should be done as a confirmatory diagnostic test. Molecular genetic testing should not be used in place of biochemical testing.

Test Methods

Direct Mutation Analysis: Samples are analyzed for the four common mutations in the *GBA* gene: 84dupG, N370S, IVS2(+1)G>A & L444P. Five other 'rare' mutations, Δ55bp, V394L, D409H, R496H, N370T are also examined.

- The nomenclature used for reporting the eight mutations in the *GBA* gene uses common nomenclature rather than standardized nomenclature.

Test sensitivity

- In the Ashkenazi Jewish population approximately 90% of patients will have a mutation detectable by this panel, whereas 50-60% in the non-Jewish population

Who Should be Tested?

- Individuals with low *b*-glucosidase enzyme activity, to identify the underlying *GBA* mutation
- Individuals at elevated risk of being carriers of Gaucher disease

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

Reason for referral	*GBA* gene mutations	Explanation
Carrier testing	None detected	This individual is unlikely to be a carrier of ***Gaucher disease***.
Carrier testing	One mutation detected	This individual is a carrier of ***Gaucher disease***, and may transmit a mutation to offspring.
Diagnosis	None detected	This result does not support a diagnosis of ***Gaucher disease***.
Diagnosis	One mutation detected	This result is unable to confirm a diagnosis of ***Gaucher disease***.
Diagnosis	Two mutations detected	This result confirms a diagnosis of ***Gaucher disease***.

For More Information

National Gaucher Foundation of Canada: *http://www.gaucher.org/*

Online Mendelian Inheritance in Man (OMIM) http://www.ncbi.nlm.gov/omim

230800 (Type 1)

230900 (Type 2)

231000 (Type 3)

GeneTests online clinical information resource - http://www.genetests.org/profiles/gaucher

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1.Current molecular testing will not detect all possible mutations in these genes. A negative result does not rule out the possibility that the individual carries a rare mutation not included in the assay.

2.We strongly recommend that biochemical analysis be done on these patients as it can be a useful complement to molecular testing.

3.Test results should be interpreted in the context of clinical findings, family history, ethnic background and other laboratory data.

4.This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.