GM1 Gangliosidosis Test

The Blueprint Genetics GM1 Gangliosidosis Test is a sequencing analysis of GLB1 gene.

The GM1 Gangliosidosis Test provides a high quality read-out of all exons of GLB1 gene. Our OS-Seq™ technology provides high coverage clinical grade sequencing and enables reliable diagnostics for patients with significantly lower costs and faster turnaround time (basic service TAT 21 days and express service TAT 7-10 days). The GM1 Gangliosidosis Test has undergone rigorous validation process during its evolution at Blueprint Genetics. Our unique sequencing technology combined with in-house built bioinformatics pipeline with GM1 Gangliosidosis mutation and knowledge database, together with our experienced team of geneticists and clinicians, enables efficient diagnostics for GM1 Gangliosidosis patients. Our variant classification schemes and clinical interpretation processes have been developed and validated with thousands of patients with hereditary cardiovascular disease. Blueprint Genetics publically shares all classified variants to improve future diagnostics (ClinVar; http://www.ncbi.nlm.nih.gov/clinvar/). Our mission is to improve the quality of diagnostics and management of GM1 Gangliosidosis patients and their families.

Genes Covered by Panel

The test covers the sequencing of GLB1 gene. All protein coding exons and exon-intron boundaries are covered. Sequencing is also targeted to other regions with reported pathogenic or likely pathogenic mutations.

Description of Test

Blueprint Genetics offers the GM1 Gangliosidosis Test that covers all protein coding exons, exon-intron boundaries and known mutations outside the exon or exon-intron boundaries of the GLB1 gene.

Coverage

In our latest validation of the GM1 Gangliosidosis Test, median sequencing depth in the target region was 313x on a nucleotide level and 100.00% of the nucleotides had at least 15x coverage.

Analytical validity

Analytical validation is a continuous process at Blueprint Genetics. Our mission is to improve the quality of the sequencing process and our standardized validation process follows each modification. In our latest validation the GM1 Gangliosidosis Test had sensitivity of 0.991 and specificity of 1.000 to detect single nucleotide polymorphisms. Our panel had also good performance to detect insertions and deletions. Sensitivity was 1.000 for both indels ranged 1-5 bp and 6-19 bp. This panel has not been validated to identify larger deletions, insertions or complex rearrangements.

Diagnostic yield

Blueprint Genetics provides genetic diagnostics for hundreds of hospitals and clinics around the world. The diagnostic yield varies substantially between hospitals and countries. Diagnostic yield with GM1 Gangliosidosis Test cannot be reliably estimated as the number of patients analyzed, to date, is not high enough. Please review our variant interpretation strategy here.
Bioinformatics

We have developed a unique GM1 Gangliosidosis sequence analyzer and interpretation pipeline. In the core of our bioinformatics lies our in-house created and curated GM1 Gangliosidosis mutation database, which is a synthesis of original publications on GM1 Gangliosidosis and existing mutation databases. The analysis pipeline includes rigorous quality control steps to ensure validity and consistency of results, and incorporates gene variability data from thousands of publicly available human reference sequences in order to eliminate false positive findings and deliver data of the highest relevance. Reference databases currently used are 1000 Genomes (http://www.1000genomes.org), NHLBI GO Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS), Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org). In addition, we apply the following in silico variant prediction tools in our analyses: SIFT (http://sift.jcvi.org), Polyphen (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster (http://www.mutationtaster.org).

Through our online ordering and statement system, Nucleus, the customer can access specific details of the analysis of the patient. This includes coverage and quality specifications and other information on the analysis. This represents our mission to build fully transparent diagnostics where customer has easy access to the details of the analysis.

Clinical Interpretation

In addition to our cutting-edge proprietary sequencing technology and bioinformatics pipeline, BpG also provides the customers with the best-informed clinical statement on the market. Clinical interpretation requires fundamental clinical and genetic understanding on hereditary cardiovascular diseases. At Blueprint Genetics our geneticists and clinicians, who together, evaluate the results from the sequence analysis pipeline in the context of phenotype information provided in the requisition form, prepare the clinical statement. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals, even without training in genetics.

Variants reported in the statement are always classified using the Blueprint Genetics Classification Scheme modified from the ACMG guidelines (Richards et al. 2015), which has been developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our laboratory. Variant classification forms the cornerstone of clinical interpretation and following patient management decisions. Our statement also provides allele frequencies in existing databases and in silico predictions. We also provide PubMed IDs to the articles or submission numbers to public databases that have been used in the interpretation of the detected variants. In our conclusion, we summarize all the existing information and provide our rationale for the classification of the variant.

A final component of the analysis is the Sanger confirmation of variants classified as likely pathogenic or pathogenic. This does not only bring confidence to the results obtained by our NGS solution but establishes the mutation specific test for family members. Sanger sequencing is also used occasionally with other variants reported in the statement. In the case of variant of unknown significance (VUS) we do not recommend risk stratification based on the genetic finding. Furthermore, in the case VUS we do not recommend use of genetic information in patient management or genetic counseling. For some cases Blueprint Genetics offers a special service to investigate the role of identified VUS.

We constantly follow the development on the field of GM1 gangliosidosis and adapt new relevant information and findings to our diagnostics. Relevant novel discoveries can be rapidly translated and adopted into our diagnostics without delay. These processes ensure that our diagnostic panels and clinical statements remain the most up-to-date and relevant on the market.

Sample Requirements

- 3ml of EDTA blood
- Purified DNA 10μg
- Saliva (Oragene DNA OG-500 or OGD-500 kit, DNA Genotek)

Details for sample preparations and sending are found here.

About the Disorder

GM1 gangliosidosis is an inherited disorder that progressively destroys neurons at central and peripheral nervous system. Some researchers classify this condition into three major types based on the age at which signs and symptoms first appear. Although the three types have marked differences in severity, their clinical features can overlap significantly thus some researchers believe that GM1 gangliosidosis represents a continuous disease spectrum instead of three distinct types. GM1 gangliosidosis is autosomal recessive disease caused by mutations in the GLB1 gene. The GLB1 gene provides instructions for
making an enzyme called beta-galactosidase, which has important role in lysosomes to break GM1 ganglioside and thus belongs to lysosomal storage disorders. Reduced activity of beta-galactosidase leads to accumulation of GM1 ganglioside at toxic levels in many tissues and organs eventually causing destruction of nerve cells in the brain, causing many of the signs and symptoms of GM1 gangliosidosis. Severity of the disease is related to the level of beta-galactosidase activity.

In infantile (or type I) form of the disorder child typically appear normal until their development slows and muscles weakness arise. Affected infants eventually lose their previously acquired skills and may develop an exaggerated startle reaction to loud noises. Hepatomegaly develop often by 6 months and splenomegaly later, skeletal abnormalities, flexion contractures, seizures, profound intellectual disability, and corneal clouding are manifested with progressing infantile disease. Loss of vision occurs along rod dystrophy and cherry-red spots characteristic for the disease are identified in half in an eye examination. In some cases, affected individuals have distinctive coarse face with epicanthus, frontal bossing, wide nasal bridge, facial edema, long upper lip, microretrognathia, macroglossia, gingival hypertrophy. Substantial numbers of patients suffer from dilated cardiomyopathy. Children may be deaf and blind by age 1 and often die by age 3 for cardiomyopathy or pneumonia. Type II GM1 gangliosidosis consists of two intermediate forms, late infantile and juvenile forms. They have normal early development, but begin to develop signs and symptoms at the age of 18 months (late infantile form) or 5 years (juvenile form). Individuals with type II disease experience developmental regression slower than type I and usually do not have cherry-red spots, distinctive facial features, or enlarged organs. GM1 gangliosidosis type III represents the mildest end of the disease spectrum. The age becoming symptomatic varies in GM1 gangliosidosis type III, although most affected individuals develop signs and symptoms such as dystonia in their teens.

The incidence of GM1 gangliosidosis is approximately 1 in 100,000-200,000 individuals. Type I is reported more frequently than the other forms of this condition. Most individuals with type III are of Japanese descent.

There are more than 150 different GLB1 mutations described in literature that are quite equally distributed along all exons of the gene. Only a few complex mutations such exon size deletions or duplications have been identified.

**References**
