GLB1 Gene Analysis in GM1-Gangliosidosis and Morquio B Disease (Mucopolysaccharidosis Type IVB)

Clinical Features:

GM1-gangliosidosis and Morquio B disease are rare lysosomal storage disorders caused by deficiency of the β-galactosidase enzyme. GM1-gangliosidosis is a neurodegenerative condition with a phenotypic spectrum that has been classified into three main clinical forms based on onset age and severity. The type I (infantile) form is the most common and severe form with rapidly progressive central nervous system involvement and hypotonia by 6 months of age, visceromegaly, cherry-red spot, white matter abnormalities, coarse facial features and dysostosis multiplex.[1] Type I patients have also been reported with macrocephaly or, less frequently, microcephaly[1] and cardiomyopathy has also been reported in some type I patients.[2, 3] Death usually occurs within the first few years.[3] Type II (late infantile/juvenile) patients usually present between 7 months and 3 years of age with slowly progressive neurological signs including psychomotor delay, hypotonia, locomotor problems, strabismus, muscle weakness, seizures, lethargy and white matter abnormalities. Other characteristic features are dysostosis multiplex, terminal bronchopneumonia[1] and dysmorphic features and skeletal changes that are usually less severe than in type I patients.[1] Type III (adult) patients have the mildest form with onset between 3 and 30 years with cerebellar dysfunction, dystonia, slurred speech, short stature and mild vertebral deformities.[1] Patients with features that overlap the different types of GM1-gangliosidosis have been described.[1] Morquio B disease is a mucopolysaccharidosis characterized by skeletal changes, corneal clouding and impaired cardiac function but no primary nervous system involvement.[1] Patients with phenotypes that are intermediate between GM1-gangliosidosis and Morquio B have also been reported.[1] The incidence of GM1-gangliosidosis is approximately 1 in 100,000 to 1 in 200,000 live births, while the incidence of Morquio B varies greatly from 1 in 75,000 births in Northern Ireland to 1 in 640,000 in Western Australia.[1]

Genetics:

G M1-gangliosidosis and Morquio B have an autosomal recessive pattern of inheritance. GM1-gangliosidosis and Morquio B are caused by pathogenic variants in the GLB1 gene that encodes lysosomal β-galactosidase that cleaves the β-galactose moiety from different substrates such as ganglioside GM1, keratan sulfate or glycopeptides. In patients with GM1-gangliosidosis, β-Gal deficiency results in the accumulation of GM1 ganglioside in nervous tissues and accumulation of glycosaminoglycans and glycopeptides in visceral and skeletal tissues, while in Morquio B patients the enzyme deficiency results in the accumulation of keratan sulfate in bone, cartilage and cornea and the excretion of elevated amounts of keratan sulfate in the urine. The GLB1 gene is located on chromosome 3p21.33 and has 16 exons. GLB1 gives rise to two alternatively spliced mRNAs, a major transcript coding for β-Gal and a

minor transcript that encodes elastin-binding protein (EBP) that is localized to the cell membrane and is involved in the assembly of elastin fibers. It has been proposed that variant(s) that occur in the region of the GLB1 gene encoding both the β-Gal and EBP proteins may contribute to the occurrence of particular clinical phenotypes such as cardiac features.[3,4,5]

Test Methods:

Variant analysis of the GLB1 gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the GLB1 gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:

Sequence analysis is expected to identify a variant on greater than 95% of GLB1 alleles in patients with GM1-gangliosidosis and Morquio B with reduced or absent β-Gal activity.[1,2,4,5,6,7]

Variant Spectrum:

More than 150 variants have been identified in the GLB1 gene that occur throughout the gene and include missense, nonsense, splicing, small deletions/insertions and a large deletion of exon 5.[2,5] Most variants are private; however, common variants exist in certain populations such as p.R59H that is associated with type I GM-gangliosidosis in patients of Gypsy and Spanish origin.[2,5] Genotype/phenotype correlations exist for other variants including p.I51T and p.R201H that are associated with type III (adult) GM1-gangliosidosis, p.R201C associated with type II (late infantile/juvenile) GM1-gangliosidosis and p.W273L associated with Morquio B disease.[6, 7, 8, 9]

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