GALNS Gene Analysis in Morquio Syndrome A (Mucopolysaccharidosis Type IVA)

Clinical Features:

Mucopolysaccharidosis type IVA or Morquio syndrome A is a lysosomal storage disorder characterized by skeletal dysplasia due to excessive storage of keratan sulfate. Affected individuals usually present with unusual skeletal features including short trunk dwarfism, odontoid hypoplasia, pectus carinatum, kyphosis, gibbus, scoliosis, genu valgus, coxa valga, and flaring of the lower ribs.[1] Hypermobile joints and an abnormal gait with a tendency to fall may also be presenting features.[1] Unlike other mucopolysaccharidoses (MPS) intelligence is often preserved. Odontoid hypoplasia is the most serious skeletal finding because, in combination with ligamentous laxity and mucopolysaccharide deposition, it may result in atlantoaxial subluxation, cervical myelopathy or even death.[1] Other possible features include pulmonary compromise, valvular heart disease, hearing loss, hepatomegaly, fine corneal clouding, and widely spaced teeth with abnormally thin enamel with increased risk of caries formation.[1] Patients may also have coarse facial features, although this is usually milder than that seen in MPSI or MPSII.[1] Patients appear healthy at birth with initial symptoms usually presenting by the age of 3 years, at which time the patient is usually evaluated due to the unusual skeletal features. Morquio syndrome A patients exhibit a wide spectrum of clinical symptoms and more mildly affected patients may have a normal quality of life and mild bone and visceral organ involvement.[2] The incidence of Morquio syndrome A has been estimated to be from 1 in 76,000 in Northern Ireland to 1 in 450,000 in Portugal.[1]

Morquio syndrome A is caused by pathogenic variants in the GALNS gene encoding the N-acetylgalactosamine 6-sulfatase (GALNS) enzyme that is involved in the lysosomal degradation of the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate. The phenotype is due to the distribution of keratan sulfate, which is highest in the cartilage and cornea. Deficiency of the GALNS enzyme results in lysosomal storage of undegraded substrates. Affected individuals may have elevated levels of keratan sulfate in plasma and urine with evidence that higher levels correlate with a more severe phenotype.[1] However, keratan sulfate may not be elevated, particularly in patients with attenuated phenotypes or in older patients.[1] The GALNS gene is located on chromosome 16q24.3 and has 14 exons.

Inheritance Pattern/Genetics:

Autosomal Recessive

Test Methods:

Variant analysis of the GALNS 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 GALNS 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:

In a large study that included 227 patients with Morquio syndrome A, analysis of the GALNS gene identified variants on 84% of alleles.[1] In a second study of 55 patients with Morquio syndrome A, analysis of the GALNS gene identified variants on over 90% of alleles.[3]

At this time, more than 150 variants have been identified that occur throughout the GALNS gene.[1] Approximately 70% of variants are missense with nonsense, splice-site, small deletions/insertions and large deletions also described.[1] The most prevalent variant is p.R386C, which was reported on 8.9% of mutant alleles.[1] Several variants are common in specific populations including p.I113F and p.T312S that account for 18% and 14% of British/Irish variants respectively, p.G301C that accounts for approximately 70% of mutant alleles in Colombians, and p.M1?, observed on approximately 27% of alleles in Italian patients.[1] Genotype/phenotype correlations have been reported for certain variants.[1]

References:

1. Tomatsu et al., (2005) Hum Mutat 26:500-512
2. Tomatsu et al., (2004) Hum Mutat 24:187
3. Dung et al., (2013) Mol Genet Metab 110 :129-138