

## **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.<sup>1</sup> Hypermobile joints and an abnormal gait with a tendency to fall may also be presenting features.<sup>1</sup> 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.<sup>1</sup> 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.<sup>1</sup> Patients may also have coarse facial features, although this is usually milder than that seen in MPSI or MPSII.<sup>1</sup> 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.<sup>2</sup> 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.<sup>1</sup>

### **Genetics:**

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.<sup>1</sup> However, keratan sulfate may not be elevated, particularly in patients with attenuated phenotypes or in older patients.<sup>1</sup> The *GALNS* gene is located on chromosome 16q24.3 and has 14 exons.

### **Inheritance Pattern**

Autosomal Recessive

### **Test Methods:**

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *GALNS* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched

targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

### Variant Spectrum:

Variants reported in the *GALNS* gene include missense, nonsense, splice site, small deletions/insertions and large deletions.<sup>1</sup> The most prevalent variant is p.R386C, which was reported on 9% of pathogenic alleles.<sup>1</sup> 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 pathogenic alleles in Colombians, and p.M1?, observed on approximately 27% of alleles in Italian patients.<sup>1</sup> Genotype/phenotype correlations have been reported for certain variants.<sup>1</sup>

### 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