EXT1 and EXT2 Gene Analysis in Hereditary Multiple Exostoses (HME)

Disorder also known as: Multiple osteochondromatosis; hereditary multiple osteochondromata; multiple cartilaginous exostoses; diaphyseal aclasis; HME

Clinical Features:
Individuals with hereditary multiple exostoses (HME) often develop benign cartilage-capped tumors (exostoses) at the ends of the long bones or the surface of flat bones. Exostoses develop prior to skeletal maturity only. Bony deformity, bowing of the long bones, limited range of motion, and premature osteoarthrosis may be associated with HME. Exostoses also may cause complications by putting pressure on nearby tissues, nerves or blood vessels. A rare but severe risk in patients with multiple exostoses is the development of malignant chondrosarcoma, which occurs in 1-5% of patients.3 Pathogenic variants in the EXT1 gene seem to be associated with a more severe disease and higher risk of developing chondrosarcoma than EXT2 gene variants.4

Inheritance Pattern/Genetics:
Autosomal dominant. About 10% of individuals with HME have a negative family history, which may be due to a de novo variant or reduced penetrance of a variant in a parent. The literature suggests that disease penetrance is high (95%) and that most non-expressing carriers are female.

There is genetic heterogeneity in HME, and three chromosomal loci are known to be associated with this condition. GeneDx offers sequence analysis for the EXT1 gene on 8q24 and the EXT2 gene on 11p11-p12. A possible third gene on chromosome 19p is thought to account for a small number of cases but has not yet been identified.

Most pathogenic variants (90%) in the EXT1 and EXT2 genes are frameshift, splice site, or nonsense variants that cause nonsense-mediated mRNA decay or premature truncation of the corresponding exostosin protein. Missense variants have also been reported. Studies have shown that gross deletions of the EXT1 gene were observed in 5-9% of patients with HME, while deletions of the EXT2 gene were observed in up to 3% of patients.3,7 All pathogenic variants are expected to result in loss of function of the tumor suppressor gene.

Test Methods:
Variant analysis for the EXT1 and EXT2 genes is offered as a tiered or concurrent test. Tier 1 analysis for HME includes full gene sequencing of the EXT1 gene and deletion/duplication testing for both the EXT1 and EXT2 genes. Using genomic DNA obtained from the submitted
specimen, bi-directional sequence of all 11 coding exons of the EXT1 gene is obtained and analyzed. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons in both the EXT1 and EXT2 genes. Tier 2 analysis for HME includes sequence analysis of the coding region of the EXT2 gene. Tier 1 and Tier 2 testing can be ordered sequentially or simultaneously. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

Test Sensitivity:
Approximately 70-95% of affected individuals with HME are found to have a pathogenic variant in the EXT1 or EXT2 genes.\textsuperscript{1,5-8} EXT1 variants account for approximately 56-78% of the variants identified and EXT2 variants account for approximately 21-44% of the variants identified, according to reviews.\textsuperscript{1,3,5-7} The sequencing method employed by GeneDx is highly likely to identify an EXT1 or EXT2 variant, if it exists. HME can also be associated with contiguous deletion syndromes or partial gene deletions of one or more exons, which are not detected with our sequencing methods. However, partial or whole gene deletions will be identified by ExonArrayDx analysis.

References: