Hereditary Multiple Exostoses Panel

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

Panel Gene List: *EXT1, EXT2, PTPN11*

Clinical Features:
Individuals with hereditary multiple exostoses (HME) often develop benign cartilage-capped tumors (exostoses or osteochondromas) at the ends of the long bones or the surface of flat bones.[1] The majority of exostoses develop prior to skeletal maturity, however, a small percentage of cases (0.5-2%) develop tumors in adulthood.[2] 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.[1,2] A rare but severe risk in patients with multiple exostoses is the development of malignant chondrosarcoma, which occurs in 1-5% of patients.[1,3] 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]

Individuals with metachondromatosis develop both osteochrondormas and intraosseuous enchondromas. These osteochondromas tend to occur in the digits and point toward the nearby joint. They generally do not cause shortening or bowing of the long bone, joint deformity, or subluxation, and spontaneously regress in adulthood.[5,6] Rare cases of tibia and finger deformity, soft tissue calcifications, and chondrosarcoma have been reported.[6] Pathogenic variants in the *PTPN11* gene are associated with metachondromatosis.

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 (95-100%) and that most non-expressing carriers are female.[1,2]

Three chromosomal loci are associated with osteochondromas. GeneDx offers sequence analysis for the *EXT1* gene on 8q24, *EXT2* gene on 11p11-p12, and *PTPN11* gene on 12q24. Another possible 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.

Most pathogenic variants (65%) in the *PTPN11* gene related to metachondromatosis are frameshift, nonsense, deletion, and splice-site variants leading to haploinsufficiency or loss of function of the corresponding SHP2 protein.[6]

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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 reference sequences 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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.

Test Sensitivity:

Approximately 70-95% of affected individuals with HME are found to have a pathogenic variant in the *EXT1* or *EXT2* genes.[7-11] Approximately 65% of individuals with metachondromatosis are found to have a pathogenic variant in the *PTPN11* gene.[5,6]

References:

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