COMP Gene Analysis in Multiple Epiphyseal Dypslasia (MED) and Pseudoachondroplasia (PSACH)

Disorder also known as: Multiple Epiphyseal Dysplasia Fairbank or Ribbing Type, EDM1; Spondyloepiphyseal Dysplasia, Pseudoachondroplastic

Clinical Features:
Both MED and PSACH are characterized by short limbed dwarfism, identifiable during childhood, with a normal face and head. Skeletal findings in MED include epiphyseal dysplasia, hip dysplasia and degenerative arthritic changes, brachydactyly with shortened metacarpals and phalanges, and hyperextensible finger joints. Findings in PSACH are typically more severe and include lordosis, kyphosis, and scoliosis as well as other vertebral/spinal anomalies and a waddling gait. In addition, brachydactyly and “telescoping” fingers, ulnar deviation of the wrists; short tubular bones, fragmented epiphyses and irregular mushroomed metaphyses, limited elbow and hip extension, lax ligaments, genu valgum, varum, and recurvatum may be seen. Cervical cord compression myelopathy is a complication of this condition. Clinical diagnosis in these disorders may be difficult due to the absence of characteristic facial features (in contrast to achondroplasia) and the fact that growth retardation may not be apparent until the second year of life. Variant in the COMP gene (cartilage oligomeric matrix protein), a member of the thrombospondin gene family, underly both disorders, as they are allelic. Almost all cases of PSACH are thought to be due to pathogenic variants in COMP, and approximately 80% of classical MED cases are a result of a pathogenic variant in this gene. The COMP gene encompasses 19 exons. Exons 4-19, which encode the EGF-like (type II) repeats, calmodulin-like (type III) repeats, and the C-terminal domain, correspond in sequence and intron location to the thrombospondin genes, while exons 1-3 are unique to COMP.

Inheritance Pattern/Genetics:
Autosomal dominant, with gonadal mosaicism reported in some families

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate

method. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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:

A COMP pathogenic variant has been identified in almost all cases of PSACH and approximately 80% of classical MED cases. All COMP variants reported to date have been found in exons 8-18 and would be detectable with this test.

References:

1. Hecht et al., Nat Genet 10:325-329 (1995).
2. Briggs et al., Nat Genet 10:330-336 (1995).
3. Delot et al., Hum Mol Genet 8(1):123-128 (1999).
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5. Briggs MD and Chapman KL, Hum Mut 19:465-478 (2002).
6. Kennedy et al., Eur J Hum Genet 13:547-55 (2005).
7. Zank et al., Eur J Hum Genet 15:150-4 (2007).
8. Mabuchi et al., Hum Genet 112:84-90 (2003).
9. Kennedy et al., Eur J Hum Genet 13:547-555 (2005).