COMP Gene Analysis in Multiple Epiphyseal Dysplasia (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 obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of exons 8-19 of the COMP gene is analyzed. In cases where the analysis of these hotspot regions does not identify a variant, complete sequence analysis of the remaining 7 exons (rest of gene) can be accomplished upon request. If no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or 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:
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. Large deletions of one or more exons would be detectable by targeted array CGH analysis with exon-level resolution (ExonArrayDx).

References: