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

*Also known as:* Multiple Epiphyseal Dysplasia Fairbank or Ribbing Type, EDM1; Spondyloepiphyseal Dysplasia, Pseudoachondroplastic

**Mendelian Inheritance in Man Number:** 132400 (MED); 177170 (PSACH); 600310 (COMP)

**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. Mutation 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 mutation in COMP, and approximately 80% of classical MED cases are a result of a mutation 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:**
Autosomal dominant, with gonadal mosaicism reported in some families

**Reasons for referral:**
1. Confirmation of a clinical diagnosis
2. Identification of patients at risk for early onset arthritic changes
3. Genetic counseling
4. Prenatal diagnosis in families with known mutation

**Test method:**
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 mutation, complete sequence analysis of the remaining 7 exons (rest of gene) can be accomplished upon request. If no mutation 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. Mutations 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 mutation has been identified in almost all cases of PSACH and approximately 80% of classical MED cases. All COMP mutations 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).

Mutation spectrum:
Many of the mutations in the COMP gene affect conserved residues among the eight calmodulin-like repeats of the gene product. The GAC repeat sequence in exon 13 (alternatively called “exon 17B” in some previous reports) is a hotspot for mutations in the gene. Additional genotype-phenotype correlations suggest mutations affecting the sixth, seventh and eighth calmodulin-like repeats typically produce a severe PSACH phenotype, whereas mutations in the fourth and fifth repeats result in MED. Mutations elsewhere in the gene cause milder PSACH or MED phenotypes, with the majority of in-frame deletions, insertions or indels causing PSACH. Rarely, large deletions of one or more exons of the COMP gene have been reported.

Specimen Requirements and Shipping/Handling:
- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes** CANNOT be accepted for this test.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the COMP gene, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

Required Forms:
Sample Submission (Requisition) Form – complete both sides
Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Multiple Epiphyseal Dysplasia” and “Pseudoachondroplasia” pages on our website: www.genedx.com