Multiple Epiphyseal Dysplasia Panel, 6 Genes

Indications for Ordering

Confirm clinical diagnosis of multiple epiphyseal dysplasia (MED)

Test Description

- Targeted capture of all coding exons and exon/intron junctions followed by massively parallel sequencing
- Sanger sequencing to confirm all significant variants
- Deletion/duplication analysis by a tiled custom comparative genomic hybridization (CGH) array

Tests to Consider

Primary tests

Multiple Epiphyseal Dysplasia Panel, Sequencing and Deletion/Duplication, 6 Genes 2008840
- Preferred panel for individuals with clinical phenotype of MED

Multiple Epiphyseal Dysplasia Sequencing, 6 Genes 2008837
- Acceptable test for individuals with clinical phenotype of MED

Multiple Epiphyseal Dysplasia Deletion/Duplication, 6 Genes 2008834
- Order if clinical suspicion is high and sequencing did not detect a pathogenic variant

Related test

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence

- Dominant MED – ≥1/10,000
- Recessive MED – 1/20,000

Symptoms

Heterogeneous group of skeletal dysplasias
- Delayed and irregular enchondral ossification of epiphyses and physes
- Premature osteoarthritis
- Abnormal gait
- Joint stiffness and pain
- Hip degeneration
- Leg positional abnormalities
- Finger hyperextensibility, clinodactyly, brachydactyly
- Myopathy
- Mildly short stature
- Cleft palate
- Scoliosis

Genetics

Genes – *COL9A1, COL9A2, COL9A3, COMP, MATN3*, and *SLC26A2*
- See table for more information about genes

Penetrance

Intrafamilial variability

Inheritance

- Autosomal dominant
  - *COL9A1*
  - *COL9A2*
  - *COL9A3*
  - *COMP*
  - *MATN3*
- Autosomal recessive
  - *SLC26A2*

Variants

- Most variants causative for MED are detectable by sequence analysis
- Variants in multiple genes for MED appear to cause overlapping phenotypes
- Other genetic and/or environmental factors may influence severity of clinical phenotype

Test Interpretation

Clinical sensitivity/specificity

- Dominant MED – ~87%
- Recessive MED – 100%

Results

- Positive
  - One pathogenic variant in the *COL9A1, COL9A2, COL9A3*, *COMP,* or *MATN3* gene was detected
    - Confirms diagnosis and etiology of MED
  - Two pathogenic variants on opposite chromosomes in the *SLC26A2* gene were detected
    - Confirms the diagnosis and etiology of MED
  - One pathogenic variant in the *SLC26A2* gene was detected
    - Predicts carrier status
- Negative
  - No pathogenic variant was detected
    - Reduces, but does not exclude, a diagnosis of MED
- Inconclusive
  - Variants of unknown clinical significance may be identified in any of the six genes analyzed

Limitations

- Deep intronic or regulatory region variants will not be evaluated
- Only the 6 genes listed in the table below are tested
- Not analyzed
  - Large deletions or duplications in exons 1, 2, and 4 of the *COMP* gene
  - Large deletions or duplications in exons 1 and 2 of the *COL9A3* gene
  - Large deletions or duplications in exon 1 of the *MATN3* gene
- Copy-number variants <1 kb may not be detected
- Diagnostic errors can occur due to rare sequence variation

Gene Symbol	Gene Name	NM #	OMIM #	Condition	Inh	Incidence	Variants Detected by Sequencing or Del/Dup Analysis	Other Conditions Due to Variants in the Same Gene
COL9A1	collagen, type IX, alpha 1	001851	120210	Epiphyseal dysplasia, multiple 6 (EDM6)	AD	~1/10,000	Rare	Stickler syndrome, type IV (STL4)
COL9A2	collagen type IX, alpha 2	001852	120260	Epiphyseal dysplasia, multiple 2 (EDM2)	AD		~2-11% depending on ethnicity	Stickler syndrome, type V (STL5)
COL9A3	collagen, type IX, alpha 3	001853	120270	Epiphyseal dysplasia, multiple 3 (EDM3)	AD		~2-5% depending on ethnicity	
COMP	cartilage oligomeric matrix protein	000095	600310	Epiphyseal dysplasia, multiple 1	AD		~37-87% depending on ethnicity	pseudoachondroplasia
MATN3	matrilin 3	002381	602109	Epiphyseal dysplasia, multiple 5 (EDM5)	AD		10-55% depending on ethnicity	spondyloepimetaphyseal dysplasia (SEMD)
SLC26A2	solute carrier family 26 (sulphate transporter, member 2	000112	606718	Epiphyseal dysplasia, multiple 4	AR	~1/20,000	100% for AR MED	achondrogenesis Ib, atelosteogenesis II, diastrophic dysplasia

Inh = inheritance; AD = autosomal dominant; AR = autosomal recessive