ARSE Gene Analysis in X-Linked Recessive Chondrodysplasia Punctata (CDPX1)

Disorder also known as: CPXR, Brachytelephalangic chondrodysplasia punctata

Clinical Features:
X-linked recessive chondrodysplasia punctata (CDPX1) is characterized by abnormal cartilage and bone development, including nasomaxillary hypoplasia, absence of the anterior nasal spine, hypoplasia of distal phalanges (brachytelephalangy), stippled epiphyses on X-ray (chondrodysplasia punctata) especially in the hands and feet, hearing loss and short stature. CDPX1 has variable expression. Less severely affected individuals have normal intellect, minimal morbidity and may achieve normal stature in adulthood. More severe cases may involve marked nasal hypoplasia requiring choanal stents, punctuate calcifications involving the tracheobronchial tree and leading to airway complications, as well as abnormal ossification of the cervical vertebrae resulting in cervical spine stenosis and instability, requiring close follow-up, surgical interventions and early lethality in some cases. Cardiac defects, mental retardation and seizure disorders have also been described.

Inheritance Pattern/Genetics:
X-linked recessive

Test Methods:
Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of the 11 exons of the ARSE gene is analyzed to evaluate for a variant in this gene. In females, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently with sequencing 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:
Several studies have shown the sensitivity of full gene sequencing in affected males to be up to 60-75%. Due to the limitations of sequence analysis, the sensitivity of our testing is slightly reduced in female index cases as deletions spanning one or more exons, which have been shown to occur in up to 15% of cases, may not be detected in females. ARSE gene deletions are suspected in males based on failed amplification of either the entire gene or specific exonic fragments. In females, where sequencing cannot detect large deletions, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is included to evaluate for a deletion or

duplication of one or more exons of this gene. Carrier testing in female relatives of an ARSE gene deletion can be performed using this or other quantitative deletion testing method.

References:

1. Brunetti-Pierri, N. et al. (2003) X-Linked Recessive Chondrodysplasia Punctata: Spectrum of Arylsulfatase E Gene Mutations and Expanded Clinical Variability Am J Med Genet 117A:164-168.
2. Sheffield, L.J. et al. (1998) Segregation of mutations in arylsulphatase E and correlation with the clinical presentation of chodrodysplasia punctata J Med Genet 35:1004-1008.
3. Franco B. et al. (1995) A Cluster of Sulfatase Genes on Xp22.3: Mutations in Chondrodysplasia Punctata(CDPX) and Implications for Warafin Embryopathy Cell 81:15-25.