THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

ARSE mutation analysis for X-linked recessive chondrodysplasia punctata

Clinical Features:

Patients with X-linked recessive chondrodysplasia punctata (CDPX1) [OMIM #302950], also known as brachytelephalangic chondrodysplasia punctata, have asymmetric shortening of the limbs, underdevelopment of the nasal cartilage, scoliosis, malalignment of the spine, short stature and mental retardation. Radiologically, hypoplasia of the bones of the fingers and epiphyseal punctated calcifications of the tubular bones due to abnormal calcium deposition is evident, but disappear within the first years of life with progressive bone development (1, 2). Additional findings include ichthyosis in the newborn period and cataracts. Males are predominantly impacted, with carrier females typically not exhibiting symptoms or radiographic abnormalities. However, CDPX1 has also been reported in females (3).

Molecular and Biochemical Genetics:

The aryl sulfatase E (*ARSE)* gene [OMIM #300180] is a member of the sulfatase family of enzymes located on chromosome Xp22.3 (4). Mutations in the *ARSE* gene have been identified in patients with CDPX1 [2,3]. *ARSE* has 10 coding exons, and missense, nonsense, frameshift and deletion mutations have been reported (5). Mutations in the *ARSE* gene have been identified in 30-75% of patients with CDPX1 (3, 5). In addition to asymptomatic carrier females, asymptomatic and mildly affected males with *ARSE* mutations have also been identified, suggesting incomplete penetrance and significant clinical variability in CDPX1. The clinical presentation of CDPX1 can even vary between affected males within a family. In general, missense mutations in the *ARSE* gene are associated with a mild phenotype, while nonsense mutations and intragenic deletions result in a more severe phenotype (3). Severe phenotypes can also arise from chromosomal rearrangements of the Xp22 region (5).

Patients with CDPX1 exhibit decreased levels of the aryl sulfatase enzyme, which is thought to be involved in cartilage and bone formation, although the exact mechanism remains unclear (6). The ARSE enzyme can also be inhibited by warfarin, and CDPX1 can exhibit a similar phenotype to that manifested in warfarin embryopathy (6).

Inheritance:

CDPX1 is a rare, X-linked recessive condition, occurring in less than 1:1,000,000 live births (1). To date, germline mosaicism has not been reported. As an X-linked recessive condition, the recurrence risk for a carrier female is 50% in a male child.

Test methods:

The University of Chicago Laboratory offers mutation analysis of all 10 coding exons and intron/exon boundaries of *ARSE* by direct sequencing of amplification products in both the forward and reverse directions.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

ARSE mutation analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$900
CPT codes:	81404 81405
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Baitner AC, Maurer SG, Gruen MB et al. The genetic basis of the osteochondrodysplasias. J Pediatr Orthop 2000: 20: 594-605.
2. Franco B, Meroni G, Parenti G et al. A cluster of sulfatase genes on Xp22.3: mutations in chondrodysplasia punctata (CDPX) and implications for warfarin embryopathy. Cell 1995: 81: 15-25.
3. Sheffield LJ, Osborn AH, Hutchison WM et al. Segregation of mutations in arylsulphatase E and correlation with the clinical presentation of chondrodysplasia punctata. J Med Genet 1998: 35: 1004-1008.
4. Franco B, Meroni G, Parenti G et al. A cluster of sulfatase genes on Xp22.3: mutations in chondrodysplasia punctata (CDPX) and implications for warfarin embryopathy. Cell 1995: 81: 15-25.
5. Brunetti-Pierri N, Andreucci MV, Tuzzi R et al. X-linked recessive chondrodysplasia punctata: spectrum of arylsulfatase E gene mutations and expanded clinical variability. American journal of medical genetics 2003: 117: 164-168.
6. Parenti G, Meroni G, Ballabio A. The sulfatase gene family. Current opinion in genetics & development 1997: 7: 386-391.

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