

The University of Chicago Genetic Services Laboratories



5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
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ARSE 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 [2]. 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 [4]. Mutations in the *ARSE* gene have been identified in 30-75% of patients with CDPX1 [3,4]. 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 [4].

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 [5]. The *ARSE* enzyme can also be inhibited by warfarin, and CDPX1 can exhibit a similar phenotype to that manifested in warfarin embryopathy [5].

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:

We offer full gene sequencing of all 10 coding exons and intron/exon boundaries.

Mutation analysis (sequencing)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1500
CPT codes:	83891, 83898 x 4, 83904 x 6, 83912
Turn-around time:	4 - 6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3 - 4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

Soma Das, Ph.D.
Director, Molecular Genetics Laboratory
ABMG Certified Molecular Geneticist

Stuart Schwartz, Ph.D.
Director, Cytogenetics Laboratory
ABMG Certified Cytogeneticist

William B. Dobyns, M.D. and Darrel J. Waggoner, M.D.
Clinical Advisors
ABMG Certified Clinical Geneticists

Melissa Dempsey, M.S.
Certified Genetic Counselor

References:

1. Baitner, A.C., *et al.*, The genetic basis of the osteochondrodysplasias. *J Pediatr Orthop*, 2000. **20**(5):594-605.
2. Franco, B., *et al.*, A cluster of sulfatase genes on Xp22.3: mutations in chondrodysplasia punctata (CDPX) and implications for warfarin embryopathy. *Cell*, 1995. **81**(1):15-25.
3. Sheffield, L.J., *et al.*, Segregation of mutations in arylsulphatase E and correlation with the clinical presentation of chondrodysplasia punctata. *J Med Genet*, 1998. **35**(12):1004-1008.
4. Brunetti-Pierri, N., *et al.*, X-linked recessive chondrodysplasia punctata: spectrum of arylsulphatase E gene mutations and expanded clinical variability. *Am J Med Genet A*, 2003. **117**(2):164-168.
5. Parenti, G., *et al.*, The sulfatase gene family. *Curr Opin Genet Dev*, 1997. **7**(3):386-391.

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