



X-linked chondrodysplasia punctate 2 testing: Mutation analysis of *EBP*

Clinical Features:

Patients with X-linked chondrodysplasia punctata (CDPX2) [OMIM #302960], also known as Happle syndrome or Conradi-Hünermann syndrome, have asymmetric shortening of the limbs, scoliosis, and widespread epiphyseal stippling, usually including the vertebral column and tracheal cartilage. Another classic finding includes various skin abnormalities, like erythema and scaling “oat bran” ichthyosis in the newborn period or atrophoderma and ichthyosis in older children. Congenital cataracts, microphthalmia, polydactyly, cleft palate, and visceral abnormalities have also been reported. Intelligence is usually normal. Severity in females varies greatly, from stillborns to females with very mild or unnoticeable symptoms (1).

Suggested minimal clinical criteria include **one or more of the following, along with increased levels of 8(9)-cholestenol:**

- scaling ichthyosis
- atrophoderma
- chondrodysplasia punctata on x-rays in infancy
- cataracts
- alopecia

Molecular and Biochemical Genetics:

Mutations of the *EBP* [OMIM #300205] gene, or emopamil binding protein, have been identified in patients with CDPX2 (2, 3). *EBP* has 4 coding exons, and more than 55 mutations have been identified. No clear genotype-phenotype correlations have been reported, most likely due to random X-inactivation. This sterol- Δ^8 - Δ^7 -isomerase gene is the human homolog of *tattered* (*Td*) in mice. Affected hemizygous *Td* male mice die prenatally, and affected heterozygous *Td* female mice are dwarfed, exhibit hyperkeratotic eruption very early in life that resolves, and have similar biochemical findings as heterozygous *EBP* humans (1).

Patients with CDPX2 have increased tissue or plasma levels of 8(9)-cholestenol and 8-dehydrocholesterol. Sterol analysis of plasma and scales from skin lesions is currently used for diagnosis and is available at the Clinical Mass Spectrometry Laboratory at Kennedy Krieger Institute. This test may also distinguish CDPX2 from CHILD syndrome, a phenotypically similar condition caused by mutations in the *NSDHL* (NADH steroid dehydrogenase-like) gene (1). Unpublished data in Dr. Richard Kelley’s lab shows that approximately 95% of patients with these biochemical findings are found to have a mutation in the *EBP* gene.

Inheritance:

CDPX2 is an X-linked condition that occurs in approximately 1 in 100,000 live births. CDPX2 is hypothesized to be lethal in most males, although a few affected hemizygous males with hypomorphic *EBP* mutations have been reported. Penetrance appears to be 100%, and incidence does not vary between populations. Germline mosaicism and/or somatic mosaicism have been reported (1). Recurrence risk for affected individuals and carrier mothers is 50%.

Test methods:

We offer mutation analysis of all 4 coding exons and intron/exon boundaries of *EBP* 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.

Patients with negative or unknown results can enroll in Dr. Aida Metzberg's research study (aida.metzenberg@csun.edu) at the California State University, Northridge for further studies.

Please, send a completed CDPX2 Clinical Questionnaire and patient consent form with each sample.

This information will be used to aid in interpretation of the test result. With the family's consent, the clinical data form along with the test result will be shared with Dr. Metzberg and entered anonymously into a database for research purposes.

EBP mutation analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$540
CPT codes:	81403 81404
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. Herman GE. Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. Hum Mol Genet 2003; 12 Spec No 1: R75-88.
2. Derry JM, Gormally E, Means GD et al. Mutations in a delta 8-delta 7 sterol isomerase in the tattered mouse and X-linked dominant chondrodysplasia punctata. jderry@immunex.com. Nat Genet 1999; 22: 286-290.
3. Braverman N, Lin P, Moebius FF et al. Mutations in the gene encoding 3 beta-hydroxysteroid-delta 8, delta 7-isomerase cause X-linked dominant Conradi-Hünermann syndrome. Nat Genet 1999; 22: 291-294.

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