The University of Chicago Genetic Services Laboratories

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Genetic Testing for X-linked chondrodysplasia punctata

Information for Non-genetics Professionals

Clinical Features:

Patients with X-linked chondrodysplasia punctata (CDPX2), 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.

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

Inheritance and Etiology:

CDPX2 is caused by a mutation in the *EBP* (emopamil binding protein) gene on the X chromosome. Patients with CDPX2 also have increased tissue or plasma levels of 8(9)-cholestenol and 8-dehydrocholesterol. This biochemical testing is available at the Clinical Mass Spectrometry Laboratory at Kennedy Krieger Institute and may also distinguish CDPX2 from CHILD syndrome, a similar condition caused by mutations in the *NSDHL* (NADH steroid dehydrogenase-like) gene. Approximately 95% of patients with these biochemical findings are found to have a mutation in the *EBP* gene.

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 males with mild *EBP* mutations have been reported. Most patients with CDPX2 are females. Due to the great variability in symptoms and severity in females, apparently asymptomatic mothers of children with CDPX2 may be carriers. Recurrence risk for affected individuals and carrier parents is 50%.

Genetic Testing:

The first person to be tested in any family would be the individual with features of CDPX2. Testing is performed by direct sequencing of the 4 coding exons of the gene. Once a change is identified in the individual with CDPX2, testing for other family members, or even prenatal testing, can be performed by direct sequencing of the familial mutation, instead of the whole gene. This is rather quick and inexpensive.

Reasons for genetic testing for CDPX2:

- confirm the diagnosis
- offer reassurance that other family members are not affected
- provide accurate information and counseling resources for future pregnancies
- provide accurate information during a pregnancy regarding possible CDPX2 in the fetus

Test ordering and Billing:

Clinical testing for CDPX2 is now available at The University of Chicago Genetics Services Laboratory. A test requisition form, billing form, consent form and clinical data sheet are required for testing. These forms can be found on the lab website (www.dnatesting.uchicago.edu) or by calling the lab. If there are any questions about ordering testing, please contact the lab.

All insurance companies are different, but most of them should cover at least part of the cost of testing. We recommend that a parent or physician's office contact the patient's insurance company with the specific CPT codes (below) to learn more about the specific coverage prior to testing. The University of Chicago will bill the the patient's insurance company, hospital or referring laboratory. The patient may receive a bill for any amount not covered by the insurance company. If the patient does not have medical insurance and we cannot bill their institution, we will require payment from the patient by check or credit card before beginning testing.

EBP sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$540
CPT codes:	81404
Turn-around time:	4 - 6 weeks

EBP deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81403
Turn-around time:	4 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:	81403
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:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Possible Results of Genetic Testing:

- Mutation detected: finding a mutation will confirm a diagnosis of CDPX2. Once a change has been identified in an affected individual then it allows for easy testing of other family members, who may choose to be tested.
- No mutation detected: not finding a mutation does not rule out the diagnosis of CDPX2, but it does make it less likely. If biochemical testing has not been performed, it may give more information about the diagnosis.
- Variant of unknown significance: A small number of patients will be found to have a change in the gene, but we are not sure whether that change causes CDPX2 or not. In this situation, we recommend testing parents for a charge of $390/parent. If a parent is found to have the same change (and presumably does not have CDPX2), then most likely this change is just a normal variant in the population. If it is not found in a parent, it is more likely to be the cause of CDPX2.

Reporting of 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. All abnormal results will be reported by telephone.

Research studies:

The University of Chicago and Dr. Aida Metzenberg's lab at California State University, Northridge will be working together to compare the mutations found by testing and the clinical features of the patients. You will be asked to fill out a clinical data form about each patient and submit it with the blood sample. This information will be used to aid in test interpretation. On the consent form, the patient or their parents can choose to participate in research studies. If they choose so, the clinical data form along with the child's test result will be shared with Dr. Metzenberg and entered anonymously into a database for research purposes. In addition, patients with negative or unknown results can enroll in Dr. Metzenberg's research protocol for further studies. Please contact her (aida.metzenberg@csun.edu) for more information about these research studies.