



The University of Chicago Genetic Services Laboratories

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Genetic Testing for X-linked chondrodysplasia punctata

Information for Patients and Families

What is X-linked chondrodysplasia punctata?

X-linked chondrodysplasia punctata (CDPX2), also known as Happle syndrome or Conradi-Hünemann syndrome, is a genetic condition that occurs in approximately 1 in 100,000 females and 1 in 1,000,000 males. As in other syndromes, individuals with CDPX2 have a collection of characteristic features and strongly resemble one another. The term "chondrodysplasia punctata" describes the unusual, "dotlike" (punctate) pattern within the growing ends of long bones or the vertebrae that can be seen on X-rays. These changes in the bone can cause curving of the spine (scoliosis), uneven growth of the limbs, and short stature. Other common findings in patients with CDPX2 include skin abnormalities and cataracts. Skin problems can include sparse, coarse scalp hair and abnormal thickening, dryness, or scaling of the skin ("ichthyosis"), which usually resolves after the first few months of life. Individuals can also have malformations of the heart or kidneys, learning delays, or seizures. There is a lot of variability in the features of individuals with CDPX2. Not everyone with this condition has all of the features or is affected to the same degree of severity.

What causes CDPX2?

CDPX2 is caused by a mutation or change in the *EBP* (emopamil binding protein) gene on the X chromosome. Females have two X chromosomes, whereas males have one X and one Y chromosome. Females with CDPX2 have one changed copy of the *EBP* gene and one normal copy that can compensate for the weakness of the changed gene. Genes are the written instructions to make proteins or enzymes. When there is a change in the instructions, the enzyme may not be made or may not work properly. The *EBP* gene makes an enzyme that is important in a pathway that forms cholesterol. Thus, the decreased amount of this enzyme leads to an accumulation of the precursors to cholesterol and causes the features in CDPX2. Because males with CDPX2-causing mutations of *EBP* have no normal copy of the *EBP* gene, they do not survive to birth unless the mutation in *EBP* is a very mild one.

Can my child be tested? Can I be tested? Can my family members be tested?

Because there are several genetic disorders that resemble CDPX2, we recommend biochemical testing of the individual with signs of CDPX2 at the Kennedy Krieger Institute to confirm the clinical diagnosis before doing genetic testing. At least one other disorder of sterol metabolism that sometimes resembles CDPX2, "NSDHL deficiency" or CHILD syndrome, can often be identified by the same biochemical testing undertaken to make the diagnosis of CDPX2. The first person to be tested in any family should be the individual suspected to have CDPX2. After genetic testing confirms the biochemical findings, the same genetic analysis can then be offered for accurate testing of other family members. Testing for changes (mutations) in the gene is like reading a book and looking for a single typographical error. You may read the whole book and miss the "typo," however when you do find it, then it is easy to test other family members (i.e. you know that the change is on page 250 in the second paragraph). So once a change is identified in the individual with CDPX2, testing other family members, or even prenatal testing, is relatively easy and fast since we know exactly where to look. Genetic testing for CDPX2 is now available clinically at The University of Chicago Genetics Services Laboratory.

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

What does it mean for my child if they find a mutation? What does it mean for our family?

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.

What does it mean for my child if they don't find a mutation?

Not finding a mutation does not rule out the diagnosis of CDPX2. In cases where the diagnosis is doubtful, a negative result may lean against the diagnosis. Research is ongoing to improve testing methods and look for other causes of CDPX2 or similar conditions. Please contact Aida Metzenberg (aida.metzenberg@csun.edu; phone: 818-677-3355) for more information about these research studies.

What does it mean for my child if they find a 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. 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.

How do I get my child tested?

We recommend that a geneticist or genetic counselor be involved in helping you order the test for your child. If you suspect that your child has CDPX2, you should arrange for an evaluation by a genetics specialist. Arrangements can usually be made through your local physician, hospital, or university medical center. This genetics specialist can order the biochemical and/or genetic testing for CDPX2 for confirmation of the diagnosis. If there are any questions about ordering the testing, please ask the physician or genetic counselor to contact The University of Chicago Genetics Services Laboratory. A blood sample is required for testing.

How much does the testing cost and will my child's health insurance cover it?

Cost for *EBP* sequencing is \$540, cost for deletion/duplication testing is \$1000. All insurance companies are different, but most of them should cover at least part of the cost of testing. We recommend that you contact your insurance company to learn more about your specific coverage prior to testing. You will want to ask your insurance company what your coverage is for the following CPT (Current Procedural Terminology) codes: 81404 for sequencing, and 81403 for deletion/duplication analysis. Insurance companies use these codes to define the method of testing. The University of Chicago or your hospital or referring laboratory will bill your child's insurance company. You may receive a bill for any amount not covered by your insurance company, i.e. copayment, deductible, etc. If you do not have private medical insurance, we will require payment from you by check or credit card before beginning testing.

When/how will I get the results?

Testing takes approximately 4-6 weeks. Your physician will be informed of the results as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the physician.

If my child's testing is done through The University of Chicago, can we still participate in research studies?

Yes, your child can participate in current research studies. Now we can begin to understand how changes in the gene cause the clinical differences seen in affected individuals. 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 with the clinical features of the patients. Your physician will be asked to submit a clinical data form about your child with the blood sample. This information is used to aid in interpretation of your child's test result. You will also be asked to sign a consent form for testing. If you indicate on this form your desire to participate in the research studies, the clinical data form along with your child's test result will be shared with Dr. Metzenberg and entered anonymously into a database for research purposes.