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Genetic Testing for Cornelia de Lange Syndrome

Information for Patients and Families

What do I need to know about testing my child for Cornelia de Lange syndrome?

Cornelia de Lange syndrome (CdLS) is caused by a change in someone's DNA. People with CdLS are small for their age, have learning problems and look more like each other than their family members. This blood test may prove that your child has CdLS. However, half of the children with CdLS will have a negative result, so this test will not rule out CdLS. There is also a chance that the test will find something that we do not understand. Thus, we may need to test the child's parents to learn more. This information sheet will provide more details about CdLS and this testing. Please talk to a genetic counselor, if you have more questions about testing.

What is Cornelia de Lange syndrome?

Cornelia de Lange syndrome (CdLS) is a rare genetic condition. As with other syndromes, individuals with CdLS look alike. Common findings in these children include: small size at birth (often under five pounds), slow growth and small stature, and small head size (microcephaly). Typical facial features include thin eyebrows which frequently meet at midline (synophrys), long eyelashes, short upturned nose and thin, downturned lips.

Other frequent findings include extra body hair (hirsutism), small hands and feet, joining of the second and third toes, incurved fifth fingers, indigestion, seizures, heart defects, cleft palate, problems feeding, and learning problems. Limb differences, including missing limbs or portions of limbs, usually fingers, hands or forearms, are also found in some individuals. Not everyone with CdLS has all of the findings or is affected to the same degree.

What causes CdLS?

CdLS is caused by a change (mutation) in the *NIPBL* (Nipped-B-like) gene, *SMC3* (structural maintenance of chromosome 3) gene, *SMC1A* (structural maintenence of chromosomes 1A) gene, *RAD21* gene or the *HDAC8* (histone deacetylase 8) gene. We each have two copies of the *NIPBL, SMC3* and *RAD21* gene. Half the individuals with CdLS have a change in one copy of the *NIPBL* gene that we can find by sequencing (reading the gene). About 5% of individuals have part of the gene missing or doubled. This requires an additional test (deletion/duplication testing). Females have two copies of the *SMC1A* and *HDAC8* gene, and males have one copy. Only 1 in 20 patients with CdLS have a change in one copy of *SMC1A*. Collectively only 1 in 25 patients with CdLS have a change in either the *SMC3*, *RAD21* or *HDAC8* gene. Genes are written instructions to make proteins. When there is a change in the instructions, the protein may not be made or may not work properly. Thus, the smaller amount of good protein from one of these genes causes the features in CdLS. Research continues to look for other causes of CdLS.

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

The first person to be tested in any family would be the individual thought to have CdLS. Testing for mutations in *NIPBL, SMC1A, SMC3, RAD21* or *HDAC8* is complex. It is like reading a very long book and looking for a single spelling mistake. 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 875 in the second paragraph). Once a change is found in the person with CdLS, testing other family members, even during a pregnancy, is easy and fast because we know where to look. Testing is now available at The University of Chicago Genetics Services Laboratory.

Reasons for genetic testing for CdLS:

- confirm the diagnosis
- reassure that other family members are not affected
- provide information and resources for future pregnancies
- provide information during a pregnancy regarding possible CdLS in the baby

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

Finding a change will confirm that the child has CdLS. Once a change has been found in an individual, then other family members may be tested, if they choose to.

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

Not finding a change does not mean that your child does not have CdLS. If your doctor is not sure about the diagnosis, a negative result may lean against it. We are only able to find changes in about 60% of people with CdLS. Researchers are working to improve our testing.

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 CdLS or not. In this situation, we recommend testing parents. If a parent is found to have the same change (and presumably does not have CdLS), then most likely this change is just a normal variant. If it is not found in a parent, it is more likely related to CdLS.

How do I get my child tested?

We recommend that a genetic doctor or genetic counselor help you order the test for your child. If you think your child may have CdLS, you should make an appointment with someone that works in genetics. This can be made through your local physician or hospital. They can order the testing for CdLS. If there are any questions about ordering the testing, please ask them 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 sequencing *NIPBL* is $2100, cost for *NIPBL* deletion/duplication testing is $1000. Cost for *SMC1A* sequencing is $1500, cost for *SMC1A* deletion/duplication testing is $1000. The cost of *SMC3, RAD21* and *HDAC8* sequencing is $2900. All insurance companies are different, but most of them should cover at least part of the cost of testing. You can contact your insurance company to learn more about your coverage prior to testing. You will want to ask your insurance company what your coverage is for the following CPT (Current Procedural Terminology) codes:

- *NIPBL* sequencing: 81407
- *NIPBL* deletion/duplication testing: 81406
- *SMC1A* sequencing: 81406
- *SMC1A* deletion/duplication testing: 81405
- *SMC3, RAD21, HDAC8* sequencing: 81407

Insurance companies use these codes to define the method of testing. In most cases, The University of Chicago will bill your hospital or lab, which will then bill your insurance company. You may receive a bill for any amount not covered by your insurance company, i.e. co-payment, deductible, etc. In some cases, The University of Chicago cannot bill your hospital or lab. In this case, we will need payment from you by check or credit card before testing. You will need to get repaid from your insurance company; The University of Chicago is not responsible for this.

When/how will I get the results?

Testing takes approximately 4 weeks for *NIPBL* sequencing, 4 weeks for deletion/duplication testing, 4 weeks for *SMC1A* testing, and 4 weeks for *SMC3, RAD21* and *HDAC8* sequencing. Your physician will be informed of the results as soon as it is complete. Results will be faxed and mailed to your 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 research studies. Now that some causes of CdLS have been found, we can begin to understand how this change results in the findings in people with CdLS. The University of Chicago and Dr. Ian Krantz's lab at The Children's Hospital of Philadelphia (CHOP) will be working together to compare the results of testing and the features of the patients. Your physician will be asked to fill out a form about your child with the blood sample. This information is used to help with your child's test result. Research studies are available in the laboratory of Dr. Ian Krantz at the Children's Hospital of Philadelphia. Please contact Dr. Krantz (ian2@mail.med.upenn.edu) to obtain more information about participation, if desired.

Additional Resources:

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