

CdLS Genetic Information

The Children's Hospital of Philadelphia (Research Study)

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In 2004, researchers at The Children's Hospital of Philadelphia and the University of Newcastle upon Tyne, identified a gene (named *NIPBL*) on chromosome 5 that causes Cornelia de Lange Syndrome, or CdLS, when it is mutated or changed. Since then, two additional genes have been found (named *SMC1A* and *SMC3*) that cause CdLS when changed and there are likely others.

Researchers hope to gain a better understanding of why CdLS varies so widely from one individual to another and what can be done to improve the quality of life for people with the syndrome. As research continues and additional information is learned about the genes, the CdLS Foundation will continue to update our publications and web site at www.CdLSusa.org. Please contact us at **1-800-753-2357** if you have any questions regarding these discoveries.

Why it is important to have found the CdLS genes:

- To confirm the diagnosis
- To understand the diagnosis of CdLS, improve existing therapies, and design new medical therapies
- To understand the role these gene changes play in development
- To offer reassurance, through genetic testing, that other family members are not affected
- To provide accurate information and counseling resources for future pregnancies
- To generate broad interest about the syndrome in the medical/scientific research community

Frequently Asked Questions

Will all people who have the diagnosis of CdLS have one of these genes?

All people have two copies of these genes. CdLS occurs when one of those copies has a change, or mutation, that causes it not to function properly. Currently, we are able to find a change in one of these genes in approximately 60% of individuals with CdLS. A higher percentage may be identifiable as testing procedures become more sophisticated.

How do you know that these genes actually cause CdLS?

Gene changes (called mutations) have been found in many individuals with CdLS that are not present in their parents, meaning that a new change developed in those individuals resulting in CdLS. In a few rare families who have more than one child with CdLS, each of the children with CdLS has had the same mutation, which has not been found in any unaffected family members. Additionally, we have also identified mildly affected families in which a mother or father has passed the gene change on to their children; all individuals with the gene change have CdLS, whereas all family members without the gene change do not. We are able to tell by the type of change in the gene how it will affect the protein for which it codes; in all cases, the changes result in a very abnormal protein or in a protein that is not made.

Is it important to confirm the diagnosis of CdLS?

The diagnosis of CdLS is still primarily a clinical diagnosis based on observable signs and symptoms. A change in the gene may help to clarify some questionable diagnoses, however we must remember that as of now we have not found a change in these genes in all individuals who have a diagnosis of CdLS. This leads us to believe that a person with CdLS could have a change in these genes, or possibly a different gene, that we cannot find at this time.

Is there a test for CdLS available now?

Now that these genes have been found, there is much more work to be done. At present, the lab at The Children's Hospital of Philadelphia (CHOP) continues to work with the blood samples that have been given to Drs. Laird Jackson, Ian Krantz, and Antonie Kline by families in the past. They are also accepting new samples from individuals and families with CdLS. The testing at CHOP is done on a research basis.

Dr. Soma Das at the University of Chicago has established testing in the Molecular Diagnostic Laboratory that she directs for the two most common genes (*NIPBL* and *SMC1A*) that cause CdLS on a clinical basis .

Please contact the CdLS Foundation for more information at 1-800-753-2357 or info@CdLSusa.org.

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 with CdLS. Testing for changes (mutations) in CdLS genes is complicated by the fact that the identified genes are very large. We use the analogy of reading a very long book (e.g. War and Peace) 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 875 in the second paragraph). So once a change is identified in the individual with CdLS, testing for other family members, or even prenatal testing, is relatively easy and fast since we know exactly where to look.

What does a positive test mean for my child, our family?

A positive test will confirm a diagnosis of CdLS, however not finding a change does not rule out the diagnosis. Once a change has been identified in an affected individual, it allows for easy testing of other family members who may choose to be tested.

What does a negative test mean for my child, our family?

In some cases where the diagnosis is doubtful, it may contribute additional evidence against the diagnosis, however we know that even in individuals with classic features of CdLS we are only able to identify mutations in approximately 60% at this time.

If I previously donated blood will I be contacted and told the findings?

In order to participate in testing through Dr. Krantz's lab at The Children's Hospital of Philadelphia, you will need to sign a consent form since testing is presently being offered on a research basis only. As part of the consent form, you must indicate whether or not you want to know the results of the study. If you consent to know the results, they will be reported back to you. Since the study is a research study and not being performed in a clinical lab, it is mandated that any changes identified must be reconfirmed on a second sample before they can be reported. Unfortunately, this means that a second blood sample is needed from the individual with CdLS to confirm the finding. This is an important step for quality assurance and for reporting such critical information back to a family.

Testing at the University of Chicago is done on a clinical basis. This means that only one blood sample is required, results are always reported to the ordering physician within a given amount of time, and a fee is required (which may be covered by your insurance company). These results can be used for carrier testing or prenatal testing for other family members. Previous samples sent to Dr. Krantz's lab are not used at the University of Chicago for clinical testing. Interesting findings from the clinical testing at the University of Chicago may be shared with Dr. Krantz's lab for research purposes.

What are the long-term implications of this discovery?

Now that the basic cause of CdLS has been discovered, we can begin to understand how these changes result in the clinical differences seen in affected individuals. By studying how this occurs we will be able to understand the clinical problems that individuals with CdLS face on a very basic level. With time, we hope this will result in better care for affected individuals. The identification of CdLS genes has inspired other researchers to get involved in studying CdLS, which can only help speed progress in caring for individuals with CdLS.