An update on the genetic causes of CdLS
By Antonie Kline, M.D., CdLS Foundation Medical Director

In 2004, the news that “the” Cornelia de Lange Syndrome (CdLS) gene had been discovered was very much welcomed, following years of searching and many families donating blood samples towards this cause.

Now, eight years later, the picture seems much more confusing. Despite the knowledge of the most recently reported fourth CdLS gene (HDAC8) and another closely related gene (RAD21), the percentage of people with CdLS having detectable changes (mutations) on testing remains under 70 percent, and the diagnosis is still made clinically. You may ask, “How can this be?”

We now know that CdLS is caused by changes in genes related to the formation and function of the protein cohesin, which is actually a protein complex made up of many sub-parts. Cohesin itself is extremely important, not only in the developing embryo and fetus, but also in all humans after delivery, both in cell division and repair and in gene regulation. Cohesin is loaded onto half of the each chromosome, or sister chromatids, prior to cell division, via a loading protein, coded for by the gene NIPBL, which was the first gene discovered and the most commonly detected (in about 60 percent of all individuals with CdLS).

Core components of the cohesin ring, formed around the sister chromatids, are coded for by the genes SMC1A and SMC3, accounting for five percent and less than one percent respectively, of the mutations detected in all individuals. Two more recently discovered genes also involved in the cohesin complex are RAD21 and HDAC8, again each accounting for less than one percent and five percent respectively in all individuals with CdLS.

RAD21 is also a core component of the cohesin ring and HDAC8 helps stabilize the cohesin complex. As more genes related to CdLS are detected, we will gain a better understanding of cohesin, how it works and how it affects pathways in the cell.

If functioning improperly, many important cell functions cannot be carried out. If unable to function at all, the individual cannot survive. It is likely that the most severe mutations are not viable at birth, but rather are lost prenatally. Less severe mutations cause delayed or abnormal function of cohesin.

Not all clinical gene testing for CdLS is available commercially. A clinical diagnosis by a geneticist familiar with the features and range of variability of CdLS is usually enough to confirm this condition.

Testing is recommended for individuals whose parents may wish to undergo prenatal diagnosis for future pregnancies by testing for a specific mutation (possible only if the mutation can be detected on an older child with CdLS), or on individuals who are less typical. As the studies continue, further details and information will be available and able to be relayed to the families.

To follow is a fact sheet on the new gene, HDAC8, along with additional information on testing.
HDAC8 FAQ Sheet

In July 2012, the fourth “CdLS gene”—HDAC8—was announced. Many parents and professionals have questions about this latest finding and what it means.

HDAC8 is an X-linked gene, meaning it is located on the X chromosome. The X and Y chromosomes are the sex chromosomes that determine whether an individual will be a boy or girl. Typically, a female has two Xs (XX) and a male has an X and Y (XY).

Individuals with CdLS who have the gene change in HDAC8 make up just a small portion of all people with CdLS.

Sara Noon, a genetic counselor at the Children’s Hospital of Philadelphia (CHOP) answers some common questions below.

Q: Does the child have to be tested for the previous genes first before being tested for this gene?

A: Currently, testing for HDAC8 is only available on a research basis at CHOP. Research enrollment is offered to individuals with CdLS or a CdLS-like phenotype that have had clinical testing of NIPBL and SMC1A and no mutations were identified. Submission of relevant clinical information, photographs, and consent forms are required.

Q: Should mothers be tested?

A: If a child has an identified mutation in the HDAC8 gene, the mutation could have occurred as a new (de novo) mutation in that individual or it could have been inherited from a parent. Since women have two copies of the X chromosome, mothers can be carriers for an HDAC8 mutation. When a mother is a carrier for an HDAC8 mutation, one copy of her X chromosome has the HDAC8 mutation and the other copy does not. Unaffected mothers who are carriers typically do not show any signs or symptoms of this disorder because the copy of the X chromosome without the mutation can compensate for the copy with the mutation.

Once an HDAC8 mutation is identified in a child, it is helpful to test the mother to determine her carrier status. Determining the carrier status of the mother can help identify whether the mutation in the child was a new mutation or inherited. It can also provide useful information about risk to siblings and future pregnancies.

Q: If the mother is carrying the mutation, what are the chances it will be passed to another child?

A: If the mother is a carrier for the mutation, overall she has a 50% chance of transmitting the mutation in each pregnancy. Males who inherit the mutation will be affected and females who inherit the mutation will be carriers and are usually not affected*. Therefore, when a mother is a carrier she has a 25% chance to have a son who is affected, a 25% chance to have a son who is not affected, a 25% chance to have a daughter who is a carrier, and a 25% chance to have a daughter who is neither a carrier nor affected.

Note: In the absence of identifying a mutation in the mother, the possibility of germline mosaicism cannot be excluded. Germline mosaicism refers to when the mutation is present in the parents’ egg or sperm cells.
It is possible for female carriers of an HDAC8 mutation to be affected and present with either mild features or a more classically defined CdLS presentation. This is due to an effect called skewed x-inactivation.

**Q:** What is the cost for testing for each of the genes? Is the Children’s Hospital of Philadelphia the only place that tests for this new gene?

**A:** Clinical testing for NIBPL and SMC1A is offered at the University of Chicago. Costs and turnaround time are as follows:

- NIPBL sequencing (6 - 8 weeks) $2,650
- NIPBL deletion/duplication testing (4 weeks) $500
- SMC1A sequencing (4 - 6 weeks) $2,025
- SMC1A deletion/duplication testing (4 - 6 weeks) $1,000

As stated earlier in this FAQ, testing for HDAC8 is available through a research study at CHOP. CHOP does not charge a fee for individuals to be a part of the study. Since it is a research lab and not a clinical lab, there is no guarantee of a turnaround time for results. It could take up to one year for results to be returned. Once testing for HDAC8 is available clinically this site will be updated.

**Q:** Will insurance cover testing?

**A:** Some insurance companies will cover genetic testing; however, how much is covered depends on each individual's insurance provider and particular plan.

**For more information about testing:**

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