

## 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 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 tested for 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.

Clinical 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 in an older child with CdLS), or in individuals who are less typical. On page 8 is a fact sheet on the new gene, *HDAC8*, along with additional information on testing.

