Cornelia deLange syndrome: Mutations disrupt cellular recycling and cause childhood genetic disease

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Genetics researchers have identified a key gene that, when mutated, causes the rare multisystem disorder Cornelia deLange syndrome (CdLS). By revealing how mutations in the HDAC8 gene disrupt the biology of proteins that control both gene expression and cell division, the research sheds light on this disease, which causes intellectual disability, limb deformations and other disabilities resulting from impairments in early development.

"As we better understand how CdLS operates at the level of cell biology, we will be better able to define strategies for devising treatments for CdLS, and possibly for related disorders," said study leader Matthew A. Deardorff, M.D., Ph.D., a pediatric genetics clinician and scientist at The Children's Hospital of Philadelphia. Deardorff also is in the Perelman School of Medicine at the University of Pennsylvania.

Deardorff and co-corresponding author Katsuhiko Shirahige, Ph.D., of the Research Center for Epigenetic Disease at the University of Tokyo, published their study online today in *Nature*.

The current findings add to previous discoveries by researchers at The Children's Hospital of Philadelphia. A group led by Ian Krantz, M.D., and Laird Jackson, M.D., announced in 2004 that mutations in the NIPBL gene are the primary cause of CdLS, accounting for roughly 60 percent of the "classical" cases of the disease. In 2007, Deardorff joined

them to describe mutations in two additional genes, SMC1A and SMC3. First described in 1933, CdLS affects an estimated 1 in 10,000 children.

The CdLS research team at Children's Hospital has focused on the cohesin complex, a group of proteins that form a bracelet-like structure that encircles pairs of chromosomes, called sister chromatids. "Cohesin has two roles," said Deardorff. "It keeps sister chromatids together during cell division, and it allows normal transcription—the transmission of information from DNA to RNA."

Deardorff added that mutations that perturb normal cohesin function can interfere with normal human development. Such is the case in CdLS, which exemplifies a newly recognized class of diseases called cohesinopathies.

In the current study, the scientists investigated both acetylation—how an acetyl molecule is attached to part of the cohesin complex¬—and deactylation, the removal of that molecule. Normally, deactylation helps recycle cohesin to make it available during successive rounds of cell division. The study team found that mutations in the HDAC8 gene threw off normal cellular recycling of cohesin.

Mutations in the gene cause loss of HDAC8 protein activity, and consequently decrease the amount of "recharged" cohesin available to properly regulate gene transcription. This, in turn, the researchers suggest, impairs normal embryonic development and gives rise to CdLS.

The researchers showed in cell cultures that mutations in HDAC8 lead to a decrease in cohesin binding to genes, similar to that seen for cells deficient in the NIPBL gene. They also identified HDAC8 mutations in approximately 5 percent of patients with CdLS.

Because mothers of children with CdLS may carry mutations in the

HDAC8 gene, identifying these mutations will be very useful in accurately counseling families of their recurrence risk—the likelihood of having a subsequent child with CdLS.

Furthermore, added Deardorff, by providing biological details of the underlying defect in CdLS, the current research suggests future approaches to treating the genetic disease. "By concentrating downstream on the biological pathway in the cohesin cycle rather than focusing on the defective gene, we may be able to eventually screen for small-molecule drugs that could be used to intervene in CdLS."

Deardorff and colleagues will continue investigate CdLS and possible therapies. Last month, the Doris Duke Charitable Foundation chose Deardorff to receive a Clinical Scientist Development Award. This three-year award, totaling $486,000, is directed to further studies of cohesin abnormalities in human disease. Deardorff is a member of Children's Hospital's Center for Cornelia deLange Syndrome and Related Diagnoses, one of the world's leading programs in studying and treating CdLS.

More information: "HDAC8 mutations in Cornelia deLange Syndrome affect the cohesin acetylation cycle," *Nature*, advance online publication Aug. 12, 2012. doi:10.1038/nature11316" target="_blank">dx.doi:10.1038/nature11316

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