In a rare disorder, a familiar protein disrupts gene function

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As reported this week in the open-access journal *PLoS Biology*, an international team of scientists studying a rare genetic disease has discovered that a bundle of proteins already known to be important for keeping chromosomes together also plays an important role in regulating gene expression in humans. In addition to shedding light on the biological roles of these proteins, the research may lead to the development of better diagnostic tools for Cornelia de Lange syndrome (CdLS), a multisystem developmental disease.

Ian D. Krantz, of The Children's Hospital of Philadelphia, and colleagues investigated cohesin, a protein complex consisting of at least four proteins that form a ring that encircles chromosomes during cell division. Cohesin's long-established "canonical" role is to control chromatids—the long strands that chromosomes form during DNA replication. However, one open question in biology has been, "What does cohesin do when cells are not dividing?" The paper from Krantz's team provides part of the answer, as the first study in human cells to identify genes that are dysregulated when cohesin doesn't work properly. Cohesin's role in dysregulating gene expression has attracted considerable scientific interest with a recent discovery that it may also be implicated in cancer.

Using DNA microarrays, Krantz and colleagues did a genome-wide analysis of mutant cell lines from 16 patients with severe CdLS. All the cells had mutations in the NIPBL gene, which plays a role in moving cohesin onto and off chromosomes, or in genes encoding components of

the cohesin complex itself. The study team identified hundreds of genes that were dysregulated in patient samples compared to samples from healthy individuals, and also detected specific gene expression profiles that are unique to CdLS patients. Importantly, said Krantz, the expression levels of dysregulated genes corresponded to the severity of the disease.

"We found that gene expression is exquisitely regulated by cohesin and the NIBPL gene," said Krantz. "The gene expression patterns we found have great potential to be used in a diagnostic tool for Cornelia de Lange syndrome." He added that gene profiling arrays have the potential to be developed as single-platform tools to diagnose, from a patient's blood sample, not only CdLS, but also a variety of other developmental disorders.

More information: Liu J, Zhang Z, Bando M, Itoh T, Deardorff MA, et al. (2009) Transcriptional Dysregulation in NIPBL and Cohesin Mutant Human Cells. PLoS Biol 7(5):e1000119. doi:10.1371/journal.pbio.1000119, biology.plosjournals.org/perls … journal.pbio.1000119

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