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The Role of *NIPBL* in Cornelia de Lange Syndrome

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Cornelia de Lange Syndrome (CdLS) is a severe developmental disorder frequently associated with heterozygous loss-of-function *NIPBL* mutations. *NIPBL* loads cohesin onto chromatin. Cohesin mediates sister chromatid cohesion important for mitosis, but is also increasingly being recognized as a regulator of gene expression. In CdLS patient cells and animal models, the presence of multiple gene expression changes with little or no cohesion defect suggests that disruption of gene regulation underlies this disorder. However, the effect of *NIPBL* haploinsufficiency on cohesin binding, and how this relates to the clinical presentation of CdLS, has not been fully investigated. We examined genome-wide cohesin binding and its relationship to gene expression using mouse embryonic fibroblasts (MEFs) from *Nipbl* +/− mice that recapitulate the CdLS phenotype. We found a global decrease in cohesin binding, including those at CTCF sites and repeat regions. Cohesin-bound genes are enriched for H3K4me3 at the promoters and are mostly down-regulated in *Nipbl* mutant MEFs with evidence for reduced promoter-enhancer interaction, suggesting that gene activation is the primary cohesin function sensitive to Nipbl reduction. Over 50% of genes affected in mutant MEFs are cohesin target genes, including those involved in adipogenesis, indicating their direct contributions to the Nipbl haploinsufficiency-induced CdLS phenotype. Interestingly, mutations in several cohesin subunit genes exhibit mild and somewhat distinct phenotypes compared to that of NIPBL haploinsufficiency, raising the possibility that NIPBL may have unique functions independent of cohesin. We will discuss our recent findings that support the notion that the cohesin-independent role of NIPBL also contributes to the CdLS pathogenesis. *This work was supported in part by NIH grants P01-HD052860 and R21 HD062951.*