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Modeling Early Developmental Defects in Cornelia de Lange Syndrome Using the Zebrafish

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Heterozygous loss of Nipped-B-like (NIPBL) is the most common cause of Cornelia de Lange Syndrome (CdLS). Nipbl has a highly conserved role in loading cohesin onto chromosomes, but recent studies suggest it also exerts genome-wide effects on gene expression. Recent studies of *Nipbl*+/− mice, which display CdLS-like phenotypes without chromosome cohesion defects (abstract by Calof et al., this meeting), suggest that CdLS results from dysregulated gene regulation. However, the precise targets of *Nipbl* and the mechanism(s) by which it regulates gene expression remain unclear. We sought to investigate these questions using the zebrafish (*Danio rerio*), a vertebrate that offers many advantages over the mouse in terms of ease and speed of genetic manipulation and ability to observe early developmental events. Zebrafish has two genes, *zNipbl-1* and *zNipbl-2*, with >70% amino acid identity to mammalian *Nipbl*; both are expressed maternally and ubiquitously in early embryos. Knock-down of either *zNipbl* using antisense morpholino oligonucleotides (MOs), led to gross morphological defects by 12 hr post-fertilization (hpf), which were more severe when both transcripts were knocked down together. Immunoblotting using antibodies generated against sequences from each zNipbl protein revealed isoform-specific knockdown by each MO. Gene expression profiling and quantitative RT-PCR at gastrulation stages (6–9 hpf) revealed a variety of gene expression changes in embryos treated with one or more MO (''morphants''). Among such changes, we observed the significant upregulation of a set of maternal transcripts that are normally degraded at the onset of zygotic transcription (~4 hpf) and not expressed zygotically; this upregulation appears to reflect impaired or delayed silencing of zygotic expression. Many of these genes were also upregulated by knockdown of *Smc3*, which encodes a cohesin subunit also implicated in CdLS. Among genes that were down-regulated in *zNipbl* morphants, several are involved in the early specification of endoderm, and some morphants went on to display, during later stages, heart and gut defects associated with endoderm deficiency. Such defects may share etiologic features with the heart and gut abnormalities frequently observed in CdLS.

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