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Regulation of endoderm development by zebrafish Nipbl

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Heterozygous loss of the *Nipped-B-like* gene (*Nipbl*) is the most common cause of Cornelia de Lange Syndrome (CdLS). Although *Nipbl* is a cohesin-associated protein conserved among all eukaryotes, recent studies suggest that it regulates gene expression through mechanisms independent of cohesin's established role in chromatid cohesion. There are 2 *Nipbl* genes in zebrafish, *zNipbl-1* and *zNipbl-2*, and embryos injected with morpholinos targeting either gene (*zNipbl*-morphants) show defects in formation of the gut/visceral organs and heart with a range of severity from looping defects to organs duplication. Such morphants show significant reductions in *sox32*, *sox17* and *foxa2* expressions in endoderm cells, and we found that combined *sox17*/*foxa2*-double morphants exhibited gut bifurcations similar to *zNipbl*-morphants. Interestingly, the degree of *sox17* and *foxa2* suppression in *zNipbl*-morphants was greater than could be explained by the reduction in *sox32* (a known positive regulator of these genes), and the response of these genes to ectopic *sox32* was significantly blunted. These data suggest that *zNipbls* may influence *sox17* and *foxa2* transcription directly. In *zNipbl*-morphants, we also observed abnormal spatial expression of the left–right patterning genes, *lefty2* and *southpaw*, although Kuppfer's vesicle (KV), a critical organ for left–right patterning that depends on *sox32* function, formed normally, implying that *zNipbls* act downstream of KV formation. These results support the idea that *zNipbls* regulate embryonic development through modulating gene expression at multiple levels. Supported by NIH P01-HD052860.

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