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The Role of Gene-Environment Interactions in Neural Tube Defect Risk

Congenital malformations, including those of the central nervous system (CNS), are among the most common causes of childhood death and loss of pregnancy worldwide. During early embryonic development, the precursor to the CNS – the neuroectoderm - is shaped into a hollow neural tube that will give rise to the brain and spinal cord. This shaping is driven by highly conserved morphogenetic cell movements that extend the head-to-tail axis and ensures proper closure of the developing neural tube. Disruptions in these cell movements by environmental and/or genetic factors results in improper morphogenesis and consequently, neural tube defects (NTDs), conditions characterized by the improper/failed closure of the neural tube. Mutations in developmental signaling pathways such as Planar Cell Polarity and Nodal are known to disrupt neural tube development; however, genetics alone are insufficient to explain the etiology of most NTDs. Exposure to environmental toxicants in utero are correlated with increased NTD risk, but how these factors interact with known risk genes remains poorly understood.

Zebrafish with mutations in Nodal signaling components exhibit open neural tubes with a wide range of phenotypic severity, providing an experimentally and genetically tractable model of NTDs. Using this model, our lab is working to identify modifier genes and environmental exposures that interact with Nodal signaling during early neuroectoderm development to confer enhanced risk of NTDs.