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CTCF knockout in zebrafish induces alterations in regulatory landscapes and developmental gene expression

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CTCF is an 11-zinc-finger DNA-binding protein that acts as a transcriptional repressor and insulator as well as an architectural protein required for 3D genome folding. CTCF mediates long-range chromatin looping and is enriched at the boundaries of topologically associating domains, which are sub-megabase chromatin structures that are believed to facilitate enhancer-promoter interactions within regulatory landscapes. Although CTCF is essential for cycling cells and developing embryos, its in vitro removal has only modest effects over gene expression, challenging the concept that CTCF-mediated chromatin interactions and topologically associated domains are a fundamental requirement for gene regulation. Here we link the loss of chromatin structure and gene regulation in an in vivo model and during animal development. We generated a ctcf knockout mutant in zebrafish that allows us to monitor the effect of CTCF loss of function during embryo patterning and organogenesis. CTCF absence leads to loss of chromatin structure in zebrafish embryos and affects the expression of thousands of genes, including many developmental genes. In addition, chromatin accessibility, both at CTCF binding sites and cis-regulatory elements, is severely compromised in ctcf mutants. Probing chromatin interactions from developmental genes at high resolution, we further demonstrate that promoters fail to fully establish long-range contacts with their associated regulatory landscapes, leading to altered gene expression patterns and disruption of developmental programs. Our results demonstrate that CTCF and topologically associating domains are essential to regulate gene expression during embryonic development, providing the structural basis for the establishment of developmental gene regulatory landscapes.