Bohring-Opitz Syndrome (BOS)

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ASXL1 (additional sex combs-like 1) plays key roles in epigenetic regulation of early developmental gene expression. De novo protein-truncating mutations in ASXL1 cause Bohring-Opitz syndrome (BOS; OMIM #605039), a rare neurodevelopmental condition characterized by severe intellectual disabilities, distinctive facial features, hypertrichosis, increased risk of Wilms tumor, and variable congenital anomalies, including heart defects and severe skeletal defects giving rise to a typical BOS posture. These BOS-causing ASXL1 variants are also high-prevalence somatic driver mutations in acute myeloid leukemia. We used primary cells from individuals with BOS (n = 18) and controls (n = 49) to dissect gene regulatory changes caused by ASXL1 mutations using comprehensive multiomics assays for chromatin accessibility (ATAC-seq), DNA methylation, histone methylation binding, and transcriptome in peripheral blood and skin fibroblasts. Our data show that regardless of cell type, ASXL1 mutations drive strong cross-tissue effects that disrupt multiple layers of the epigenome. The data showed a broad activation of canonical Wnt signaling at the transcriptional and protein levels and upregulation of VANGL2, which encodes a planar cell polarity pathway protein that acts through noncanonical Wnt signaling to direct tissue patterning and cell migration. This multiomics approach identifies the core impact of ASXL1 mutations and therapeutic targets for BOS and myeloid leukemias.