Decoding ASXL3: A Novel Predictor of the Spectrum, Onset, and Treatment for Neurodevelopmental Disorders

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Neurodevelopmental disorders (NDDs) affect over 300 million people globally. In previous research, we identified ASXL3 as a biomarker for NDDs, but our understanding of how the clinical severity spectrum of NDDs arises remained unknown. Here, we uncover that ASXL3 functions as a dosage-sensitive regulator of neurogenesis, offering new insight into NDD pathogenesis. Using CRISPR-Cas9-engineered ASXL3 +/+, +/-, and -/- human embryonic stem cells, we show that loss of ASXL3 leads to a stepwise accumulation of ubiquitinated histone H2A (H2Aub) at NDD-linked genes. This chromatin change partially represses neurogenic transcription in ASXL3+/- and fully blocks it in ASXL3-/-, providing the novel mechanistic explanation for the ASXL3-linked NDD severity spectrum. By analyzing fetal single-cell RNA-seq data, we found ASXL3 expression begins at 13 weeks of gestation, defining the earliest window for non-invasive prenatal diagnosis (NIPT). We further show that FGF2 treatment restores lost neurons in ASXL3+/- and -/- brain organoids. FGF2 was effective when applied during neurogenesis (97% recovery of lost neurons), before neurogenesis (95% recovery with no unregulated proliferation), even after neuronal specification (92%), highlighting a broad therapeutic window. To enable clinical use, we designed a patent-pending drug capsule and delivery mechanism, including a ligand-functionalized nanocarrier, for targeted delivery in utero and in vivo. Together, our findings identify ASXL3 dosage as a central mechanism driving NDD variability and introduce the first combined diagnostic and therapeutic platform for early intervention.

Awards Won: