

2p16.3 (NRXN1) Deletions

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De novo mutations and copy number deletions in NRXN1 (2p16.3) pose a significant risk for schizophrenia (SCZ). It is unclear how NRXN1 deletions impact cortical development in a cell type-specific manner and disease background modulates these phenotypes. Here, we leveraged human pluripotent stem cell-derived forebrain organoid models carrying NRXN1 heterozygous deletions in isogenic and SCZ patient genetic backgrounds and conducted single-cell transcriptomic analysis over the course of brain organoid development from 3 weeks to 3.5 months. Intriguingly, while both deletions similarly impacted molecular pathways associated with ubiquitin-proteasome system, alternative splicing, and synaptic signaling in maturing glutamatergic and GABAergic neurons, SCZ-NRXN1 deletions specifically perturbed developmental trajectories of early neural progenitors and accumulated disease-specific transcriptomic signatures. Using calcium imaging, we found that both deletions led to long-lasting changes in spontaneous and synchronous neuronal networks, implicating synaptic dysfunction. Our study reveals developmental-timing- and cell-type-dependent actions of NRXN1 deletions in unique genetic contexts.