Spatial Multi-Omics Reveals Mutation Class–Specific Neurodevelopmental Perturbations in 8p Syndrome

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ABSTRACT

Chromosome 8p is highly susceptible to structural variation, and individuals with 8p syndrome present with a diverse spectrum of clinical phenotypes, including developmental delay, intellectual disability, autism spectrum disorder, and epilepsy. Despite its clinical relevance, the underlying biological mechanisms remain poorly understood—particularly how different types of 8p mutations, such as deletions and inversion duplication deletions, contribute to divergent outcomes. To address this gap, we leveraged AVITI24™, a spatially resolved multi-omic platform that integrates high-dimensional morphology, targeted transcriptomics, and multiplex protein profiling. This approach enables simultaneous measurement of RNA, protein, and cellular architecture within the same neural tissue context. We applied AVITI24™ to iPSC-derived neuronal progenitor cells from individuals harboring diverse 8p rearrangements as well as matched familial controls. We found that 8p deletions were associated with reduced expression of genes linked to cytoskeletal regulation and organization while inverted duplication deletions were associated with changes in genes related to cell proliferation and lineage specification. Morphological profiling revealed shared features related to cytoskeleton organization as well as mutation class specific changes. These results support the hypothesis that different classes of 8p structural variation produce non-overlapping, yet convergent, disruptions to neurodevelopmental programs and displays the power of multi-omic profiling for uncovering new disease biology.

Introduction

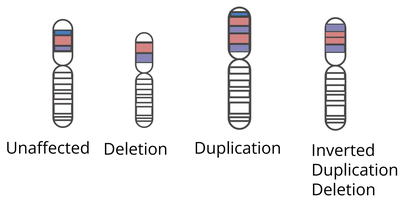

Figure 1. Chromosomal abnormalities in the short arm of chromosome 8.

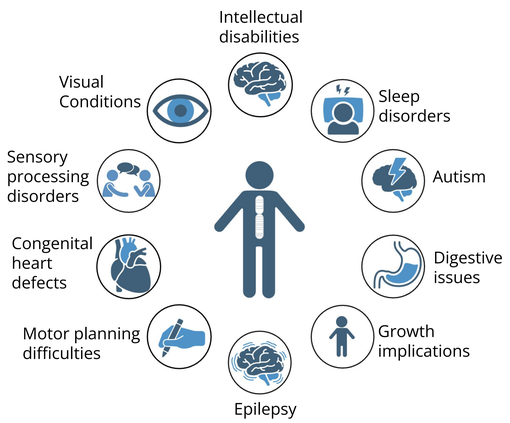

Figure 2. 8p syndrome results in a wide range of symptoms.

METHODS

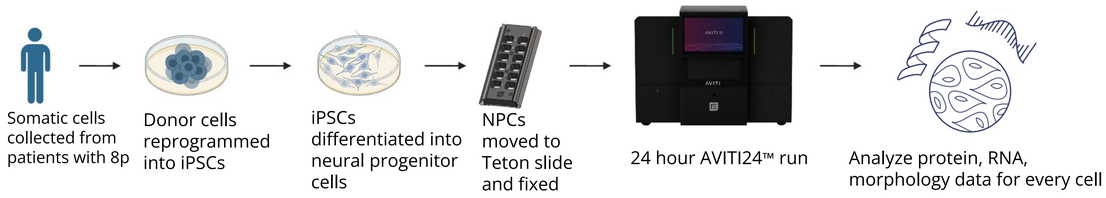

Figure 3. Somatic cells from donors were collected, reprogrammed into iPSCs and differentiated into neural progenitor cells. NPCs were transferred to Teton slide, cultured for one day and then fixed. Slides were run on the AVITI24™ for RNA, protein and morphology data collection.

Results

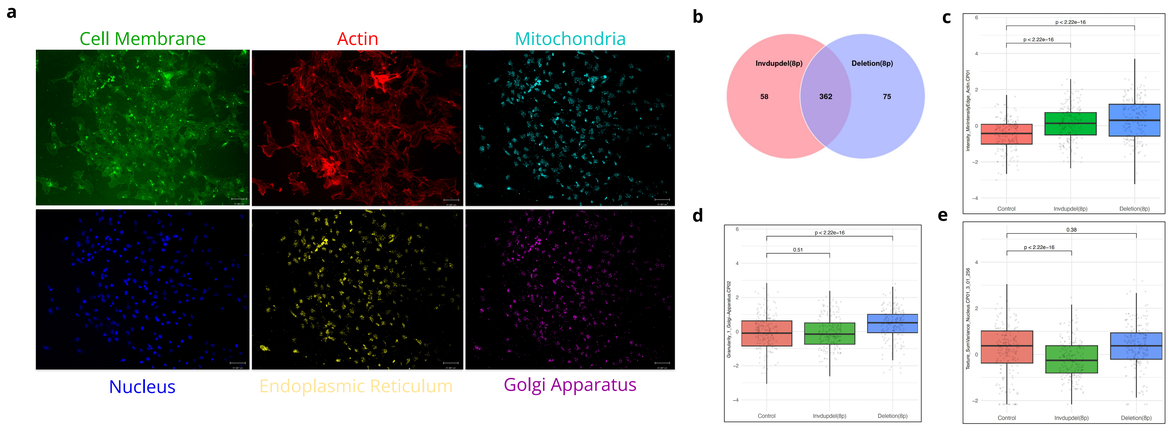

Figure 4. Impact of 8p mutations on cell morphology. a) representative images of cellular stains from AVITI24™ Cell Painting platform. **b**) venn diagram of morphology features impacted by deletion and indeldup mutations on 8p (FDR < 0.05) **c**) Example morphology trait (Intensity_MinIntensityEdge_Action.CP01) that is altered by both chr8p mutations. **d**) Example morphology trait (Granularity_1_Golgi-apparatus.CP01) that is altered by chr8p deletions but not invdupdel. **e**) Example morphology trait (Texture_SumVariance_Nucleus.CP01_3_01_256) that is altered by chr8p invdupdels but not deletions.

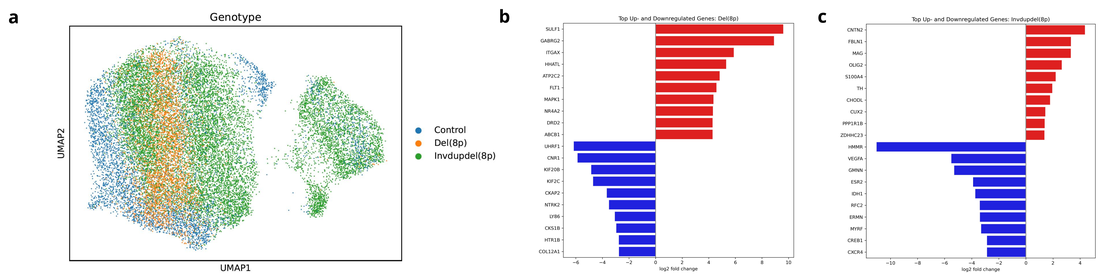

Figure 5. Impact of 8p mutations on gene expression. a) UMAP embeddings based on RNA counts for deletion, indeldup, and control NPCs. **b**) Top 10 upregulated and downregulated genes from deletion vs control comparison. **c**) Top 10 upregulated and downregulated genes from invdupdel vs control comparison.

Results

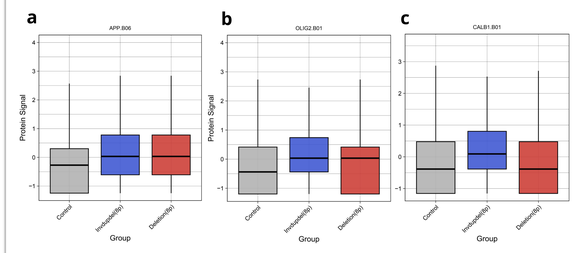

Figure 6. Impact of 8p mutations on protein expression. a & b) Example protein signals (APP, OLIG2) that are altered by both chr8p mutations. **c**) Example protein signal (CALB1) that is altered by chr8p invdupdels but not deletions.

Conclusion

Here, we utilized the AVITI24™ multi-omic platform to profile iPSC-derived neural progenitor cells from individuals with diverse structural variation on chr8p as well as matched controls. The platform enabled us to identify disease and mutation specific phenotypes across many levels of analysis including RNA, protein, and cell morphology.

We observed many morphology features related to actin cytoskeleton organization that are disrupted in both deletion and invdupdel carriers, but interestingly observed some mutation-specific signatures including degraded Golgi in deletion samples and changes to nuclear morphology in invdupdels.

We also observed upregulated OLIG2 gene/ protein expression in invdupdels and increased OLIG2 protein expression in deletions. Additionally, we saw upregulated protein expression for APP across both chr8p types. We also saw invdupdel specific changes in protein related to calcium binding and lineage specification. Interestingly, we did not observe any mutation-specific protein changes in deletions compared to control.

All figures created in BioRender. Thanks to the Project 8p Foundation!