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"Effects of deafness on central neural cell chemistry – a spatial transcriptomic analysis of the auditory cortex and hippocampus in a mouse model of congenital deafness"

Objective: According to the World Health Organization (WHO), approximately 10 million new cases of dementia are diagnosed annually – a number expected to rise with an aging global population. Hearing loss is a significant modifiable risk factor, accounting for an estimated 8% of dementia cases. While clinical interventions such as hearing aids and cochlear implants have been shown to reduce dementia risk, the underlying molecular mechanisms linking auditory deprivation to cognitive decline remain poorly understood. This study investigates how congenital deafness alters gene expression in the auditory cortex and hippocampus – regions critical for auditory processing and memory, thereby trying to elucidate the impact of congenital deafness on gene expression patterns in key brain regions involved in auditory processing and memory. We hypothesize that genes associated with synaptogenesis and neural plasticity in the auditory cortex will be downregulated in congenitally deaf mice compared to wild-type controls and deafness-rescued mice.

Methods: We employed spatial transcriptomics (10x Genomics Visium) to analyze brain tissue from wild-type (WT), USH1C mutant (congenitally deaf), and antisense oligonucleotide (ASO)-treated USH1C mice (hearing-rescued). Brains were perfused with paraformaldehyde (PFA), cryosectioned at 10 µm thickness (bregma +2.8 to +3.2 mm), and processed using the CytAssist-enabled Visium protocol. Following H&E staining, decrosslinking, destaining, and CYTAssist enabled transfer onto Visium Spatial Gene Expression slides (10x Genomics) which automates tissue processing and image capture, spatially barcoded mRNA was captured, reverse-transcribed, pooled, normalized and sequenced on an Illumina NextSeq 2000 platform using a NextSeq 2000 P4 (100 cycles) flowcell according to manufacturer's recommendations. Data was analyzed using the 10xGenomics Space Ranger pipeline.

Possible Results: Cell clusters will be annotated using Allen Brain Atlas markers, and UMAPs generated. We anticipate significant differential gene expression across groups. In USH1C mice, genes associated with synaptic function, plasticity, and neuronal maintenance (e.g., *BDNF*, *SYN1*) are expected to be downregulated, while neuroinflammatory markers (e.g., *GFAP*) may be upregulated. ASO-treated mice are predicted to show partial restoration of these gene expression patterns. Spatial mapping will localize these changes to specific cortical layers and hippocampal subregions.

Conclusion: This study provides a molecular framework for understanding how auditory deprivation may contribute to cognitive decline and dementia risk and aims to provide critical insights into the molecular consequences of congenital deafness on central neural cell chemistry, particularly within brain regions vital for auditory processing and cognition. The findings suggest that congenital deafness induces transcriptional reprogramming in the auditory cortex, marked by reduced plasticity and increased inflammation. Partial reversal following ASO treatment highlights the potential for early intervention. This study underscores the utility of spatial transcriptomics in uncovering region-specific molecular changes underlying sensory deprivation and cognitive vulnerability.