

Differentially Expressed Circular RNAs Across Eight Human Reward-Related Brain Regions

Circular RNAs (circRNAs) are covalently closed, single-stranded RNAs produced primarily by back-splicing of pre-mRNAs. They are highly abundant in the brain and implicated in neuronal differentiation, synaptic plasticity, and long-term memory. Here, we investigated brain region-specific circRNA expression in alcohol use disorder (AUD). Total RNA from eight reward-related brain regions (amygdala, caudate nucleus, cerebellum, hippocampus, nucleus accumbens, prefrontal cortex, putamen, and ventral tegmental area) was profiled by RNA-seq in 12 individuals with AUD and 12 matched controls of European ancestry (sex-balanced groups). CircRNA transcriptomes were processed with DDC and differential expression was tested using limma-voom. Using $P < 0.05$ and absolute fold-change > 2 , we identified region-specific differentially expressed (DE) circRNAs: amygdala (7), caudate nucleus (13), cerebellum (10), hippocampus (9), nucleus accumbens (9), prefrontal cortex (18), putamen (16), and ventral tegmental area (10). DE circRNAs were mapped to host mRNAs and tested for pathway enrichment by gene set enrichment analysis. Enriched pathways included cytokine-cytokine receptor interaction and axon guidance (amygdala); Notch signaling, neuroactive ligand-receptor interaction, cytokine signaling, and tight junctions (caudate); WNT signaling, tight junctions, and JAK-STAT signaling (cerebellum); endocytosis, axon guidance, cytokine signaling, Alzheimer's disease pathways, Notch signaling, and adherens junctions (hippocampus); gap junctions, chemokine signaling, and Alzheimer's disease pathways (nucleus accumbens); endocytosis, WNT and neurotrophin signaling, and Alzheimer's disease pathways (prefrontal cortex); neuroactive ligand-receptor interaction and axon guidance (putamen); and long-term potentiation, JAK-STAT signaling, chemokine signaling, and focal adhesion (ventral tegmental area). Together, these results indicate widespread, region-specific circRNA dysregulation in reward-related brain regions in AUD. The mapped host-gene pathways suggest that altered circRNA expression may contribute to inflammation, synaptic and neuroplastic changes, and neurodegenerative-related processes associated with AUD. Further functional studies are warranted to determine the mechanistic roles of candidate circRNAs in AUD pathophysiology and their potential as biomarkers or therapeutic targets.

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