Alzheimer's Disease-associated *circHomer1* can inhibit the expression of long *APP* and *MAPT* mRNA isoforms in the frontal cortex via competing for binding to HuD.

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Circular RNAs (circRNAs) are a novel category of non-coding RNAs derived from the back-splicing and covalent joining of exons or introns. Recent studies have suggested that circRNAs are preferentially generated from synaptic plasticity-related genes and are particularly enriched in the brain. Although some circRNAs have been found to sequester microRNAs and others to associate with RNA-binding proteins (RBPs), the mechanism of action of most circRNAs remains poorly understood. Moreover, little is known about the potential involvement of circRNAs in Alzheimer's disease (AD). Using circRNA-specific quantification, we had previously found that *circHomer1*, a neuronal-enriched circRNA derived from Homer protein homolog 1 (*HOMER1*) capable of regulating cognitive function, is significantly downregulated postmortem brains of patients with AD and robustly associated with clinical dementia ratings and AD-associated neuropathology. Here we show that *in vivo* knockdown (KD) of *circHomer1* in mouse frontal cortex results in a significant upregulation of long Amyloid precursor protein (*APP*) and microtubule-associated protein tau (*MAPT*) mRNA isoforms, of which accumulation of their respective encoded proteins are the pathological hallmark of AD. Furthermore, we show that *circHomer1* is predicted to directly bind to both of these mRNA isoforms, potentially competing for binding with ELAV-like protein 4 (*ELAVL4* or HuD), an RBP associated with AD and known to both bind to *circHomer1* and associate with the long *APP* mRNAs, to promote their stability. Lastly, we demonstrate that *circHomer1* is reduced in iPSC-derived neurons from subjects with AD and in the cortex of the 5xFAD model of AD. Ongoing experiments are aimed at further investigating the role of *circHomer1* in *APP* and *MAPT* gene regulation and AD-associated pathogenesis and examining the effects of different drugs on brain *circHomer1* expression. Taken together, our work introduces novel molecular networks with potential importance for AD.