Mitochondrial CHCHD10 Reverses Neuronal DNA Methylation Deficits and Attenuates Tau Pathology in Alzheimer's Disease

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Mitochondrial dysfunction is increasingly recognized as a contributing factor in neurodegenerative diseases, including Alzheimer's disease (AD). CHCHD10, a mitochondrial intermembrane protein, plays a key role in mitochondrial cristae organization, dynamics, and oxidative phosphorylation. CHCHD10 variants have been linked to elevated reactive oxygen species, TDP-43-associated pathology, and multiple neurodegenerative conditions. The role of CHCHD10 in AD pathology remains largely unknown. In this study, we investigated the epigenetic impact of CHCHD10 in AD, focusing on DNA methylation alterations in patients' fibroblast-converted neurons. Using an overexpression model, we observed significant changes in methylation patterns in AD neurons, including a reversal of disease-associated hypomethylation by upregulation of CHCHD10. Through gene set enrichment analyses, we discovered many enriched pathways and phenotypes associated with methylation reversals, including those associated with ubiquitination, cysteine-associated enzyme activity, increased inflammatory response, and abnormal enzyme/coenzyme activity. Using brain-associated disorder eQTL data, we discovered a negative linear relationship between the methylation differential percentage and beta score for individual genes. Expanding on this, many areas of heightened colocalization between eQTL and AD-associated GWAS datasets were discovered to have methylation reversals. One gene of interest, KATNAL2, exhibited demethylation in AD neurons, which was re-methylated upon CHCHD10 overexpression. Functional assays confirmed that KATNAL2 expression modulates tau pathology and that CHCHD10 overexpression attenuates the deleterious effects. These findings suggest a neuroprotective role for CHCHD10 through epigenetic regulation in AD.

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