Investigating the relationship of deep brain iron with Alzheimer's disease

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Abstract

Iron is an essential element for normal development and physiology of the brain. While its accumulation increases due to normal aging, dysregulated accumulation or distribution has been found to be associated with neurodegenerative diseases, including Alzheimer's disease (AD). However, the putative genes and pathways associated with brain iron accumulation remain incompletely understood, and whether genetically predicted brain iron accumulation shares genetic factors with increased AD risk has yet to be explored. Here we aim to investigate genetically regulated gene expression patterns and pathways associated with brain iron accumulation, and to explore the shared genetic architectures and shared mechanism with AD.

We have conducted a genome-wide association study (GWAS) for brain iron in six subcortical regions in UK Biobank participants (n= 39,103). We have estimated the brain iron levels in these regions via quantitative susceptibility mapping (QSM) method, which computes spatial distribution of magnetic susceptibility from the signal phase of gradient echo magnetic resonance imaging (MRI) data. We employed bioinformatics methods to explore potential genes and pathways that underlie brain iron accumulation and to identify the shared genetic architecture between brain iron deposition and AD.

We performed a transcriptome-wide association study (TWAS) and identified 398 genes associated with brain iron accumulation (FDR<0.05, COLOC PP4>0.80). Genetic correlation analyses revealed significant positive associations between brain iron and AD risk in the caudate nucleus ($rg = 0.213$, $P = 1.5\times10^{-2}$), and putamen ($rg = 0.1163$, $P = 3.35\times10^{-2}$). Beyond these regional effects, brain iron in all six subcortical regions exhibited significant genetic overlap with AD. Notably, we identified 60 independent pleiotropic loci, of which 8 showed evidence of colocalisation. Key pleiotropic genes (such as *HFE*, *SLC11A2*, *SLC39A8*, *SLC39A12*, *SLC39A13*, *SLC40A1*) are implicated iron transport and regulation.

Overall, our study identifies novel genetic factors underlying brain iron accumulation and provides critical insights into neurobiological mechanisms linking brain iron accumulation with AD. Our findings enhance the understanding of shared genetic architecture and highlight the potential for the use of brain iron measures as biomarkers for neurological disorders.