Decoding Common and Rare Variant Associations in Alzheimer's Disease Using Deep Learning

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Interpreting the role of genetic variants in Alzheimer's disease (AD) is challenging due to limited functional specificity across brain cell types. To address this, we developed deep learning models trained on human microglia RNA-seq data to predict the regulatory impact of non-coding variants on splicing and gene expression. We introduced the Splicing Modifier Score (SMS) to improve fine-mapped splicing QTL (sQTL) prediction, validated using *isoMiGA*, a long-read isoform atlas of human microglia that identified over 35,000 novel context-specific isoforms. To enhance rare variant interpretation, we also developed *Gruyere*, a Bayesian framework that learns trait-specific weights across functional annotations. Applied to whole-genome sequencing data from the Alzheimer's Disease Sequencing Project (7,966 cases, 13,412 controls), Gruyere uncovered 10 novel AD-associated loci, including *TREM2*, not identified by other rare variant tests. Our deep learning models achieved high predictive accuracy for splicing in microglia (PR-AUC = 0.853), and delta scores effectively prioritized fine-mapped sQTLs (ROC-AUC = 0.656). Several fine-mapped variants were functionally validated using MPRA in iPSC-derived microglia. Integration with MiGA's long-read splicing QTL map revealed that key AD loci—including *CD33*, *PLCG2*, *PILRA*, and *MS4A6A*—are likely mediated through isoform-level regulation. Together, these results establish a framework for brain cell type–specific functional variant interpretation and provide a powerful approach for identifying novel regulatory mechanisms for AD.

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