From GWAS to Function: Prioritizing Genes in Neurodegenerative Brain Disease Risk Loci through Cell-type-specific Transcript eQTL Mapping

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Neurodegenerative brain diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), sporadic Creutzfeldt-Jakob disease (sCJD), and frontotemporal lobar degeneration (FTLD) impose a substantial burden on individuals and their families. While genome-wide association studies (GWAS) have identified numerous disease-associated variants, most lie in non-coding regions, making their functional relevance unclear. For my thesis, I aim to prioritize genes near lead variants associated with various neurodegenerative brain diseases making use of expression quantitative trait loci (eQTLs), which are variants that influence the expression of nearby genes—potentially mediating phenotypic effects.

I started by analysing genotyping array data (Illumina Infinium™ Global Screening Array-24 v3.0) from individuals with and without AD. Following stringent quality control and genotype imputation via the TOPMed R3 reference panel, I extracted genetic data for the GWAS lead variants of the previously mentioned neurodegenerative brain diseases. I then integrated these genotypes with long-read single-nucleus RNA-sequencing data from human brain tissues to perform transcript-level cell-type-specific eQTL (transcript-ct-eQTL) mapping.

The transcript-ct-eQTL mapping showed potential cell-type-specific regulatory effects of the GWAS lead variants of the five diseases. One example is the FTLD- and AD-associated lead variant rs5848, which showed a significant association ($P = 0.001$) with expression of the ENST00000587109 transcript of the GRN gene in GABAergic neurons.

This integrative approach prioritizes genes through transcript-ct-eQTL mapping to shed light on the functional implications of disease-associated genetic variants on brain transcript diversity, not only for AD but for other neurodegenerative brain diseases as well.