

Localised genetic overlap between Alzheimer’s disease and schizophrenia implicates oligodendrocyte-specific regulation of *ADAM10* in both disorders

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Introduction

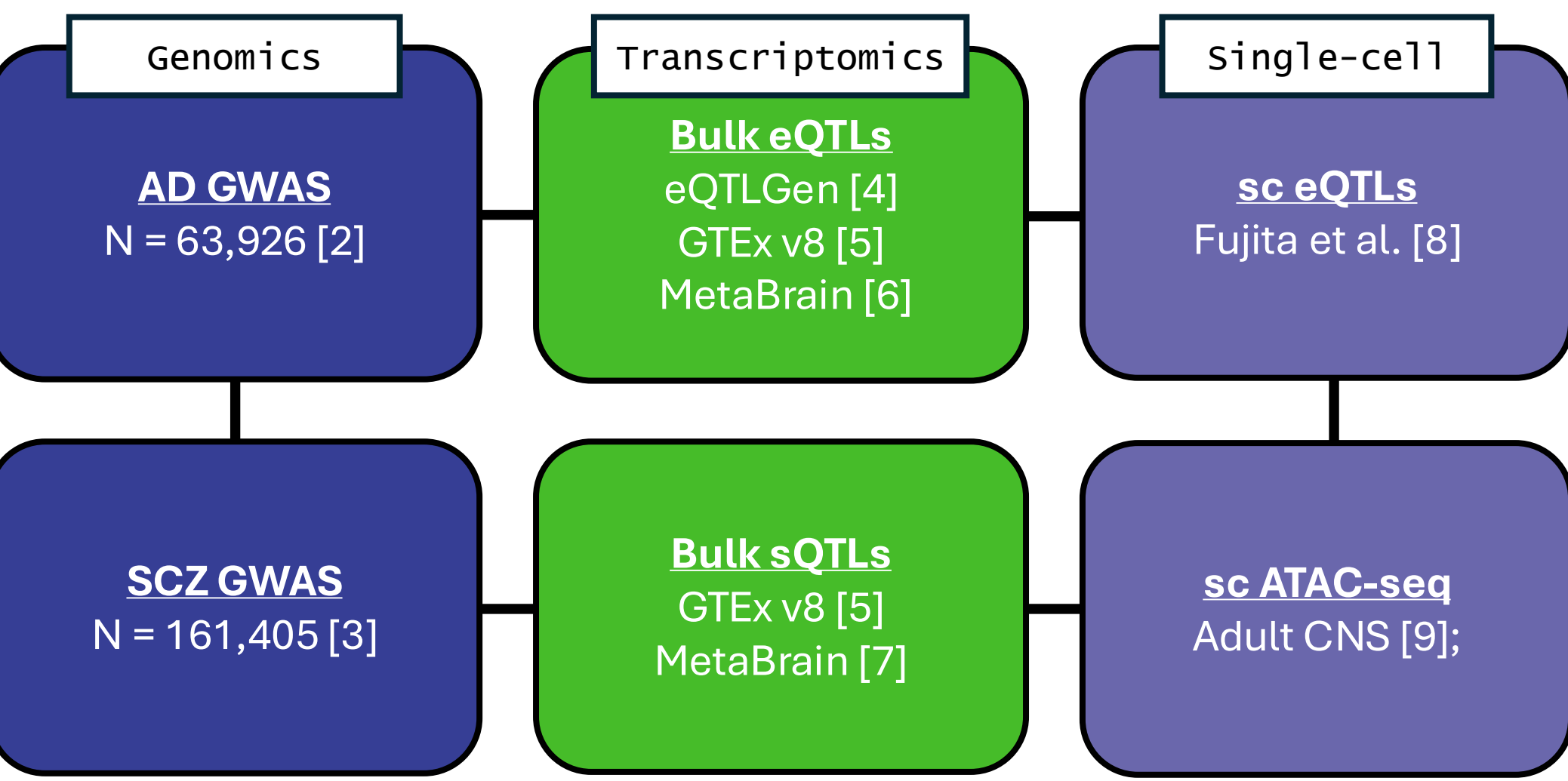
Background

Psychotic symptoms, including hallucinations and delusions, occur in **up to 60%** of individuals with Alzheimer’s disease (AD) [1] and are associated with more severe cognitive decline and **poorer prognosis**. These symptoms **overlap** with those observed in schizophrenia (SCZ), raising the possibility of **shared biological mechanisms** between the disorders. We therefore investigated the **shared genetic architecture** of AD and SCZ using disease-specific genome wide association studies (GWASs), bulk quantitative trait loci (QTL) and **single-cell** datasets.

Objectives

- ⇒ Identify **loci** underlying **shared risk** between AD and SCZ.
- ⇒ Identify shared candidate **causal variants** and **target genes**.
- ⇒ Characterise **regulatory mechanisms** underlying shared risk.
- ⇒ Identify the **cell types** implicated in shared genetic liability.

Multi-Omics Datasets



RESEARCH HIGHLIGHTS

- Multiple lines of evidence converged on *ADAM10* as the strongest shared AD-SCZ locus.
- AD and SCZ risk alleles were associated with reduced *ADAM10* expression in mature oligodendrocytes.
- rs653765 and rs1427281 were prioritised as candidate regulatory variants underlying the shared signal.



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Methods

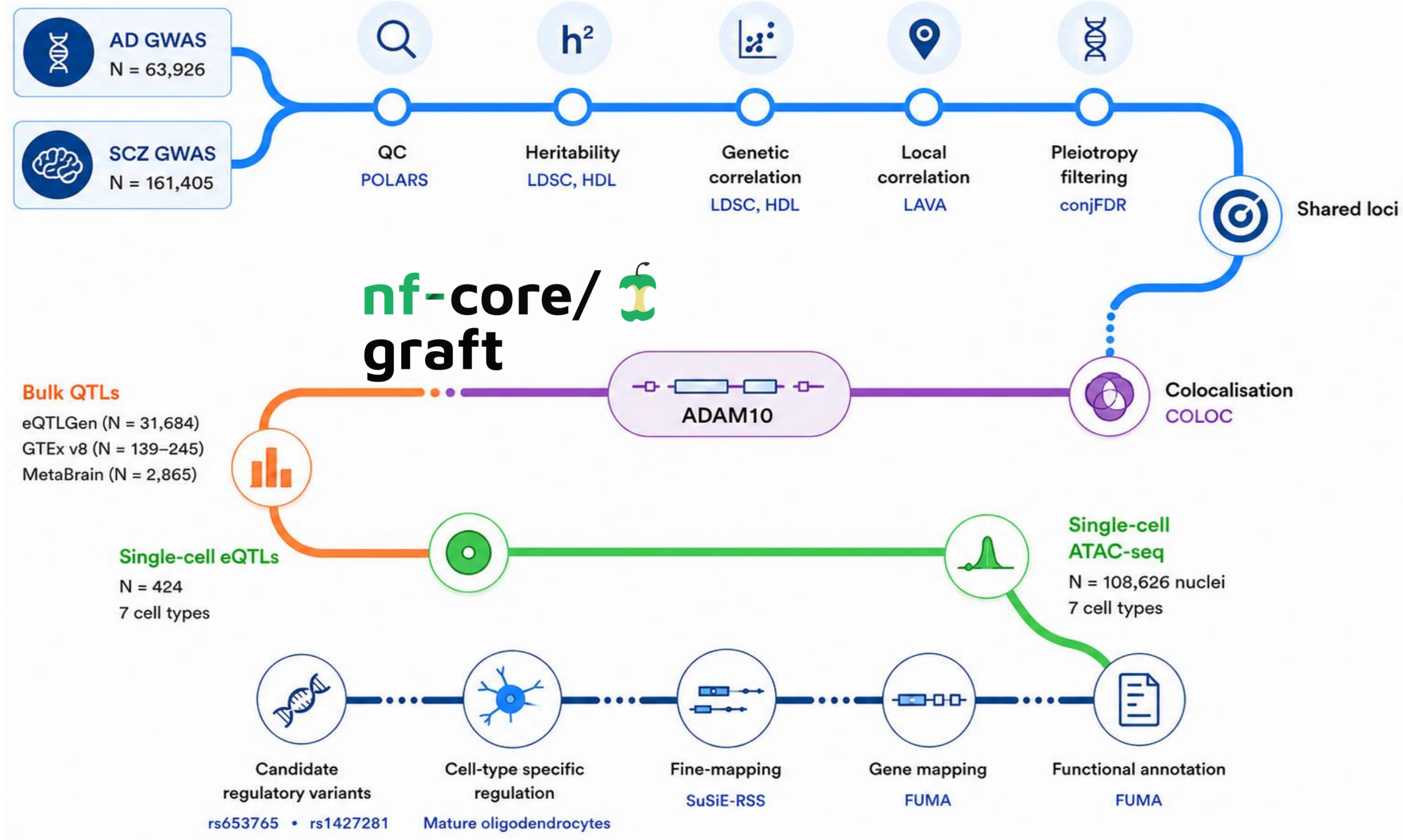


Figure 1: *nf-core/graft* pipeline for exploring the shared genetic components between AD and SCZ.

AD and SCZ GWAS were used to assess shared **genetic architecture** (Figure 1). **Shared loci** were identified, tested for evidence of a common **causal variant**, and fine-mapped to prioritise candidate causal variants. Bulk and single-cell **QTL datasets** were used to identify the **genes** driving shared genetic risk. Prioritised variants at those genes were then mapped onto single-cell ATAC-seq data to identify **regulatory variants** and their relevant cell types.

Results

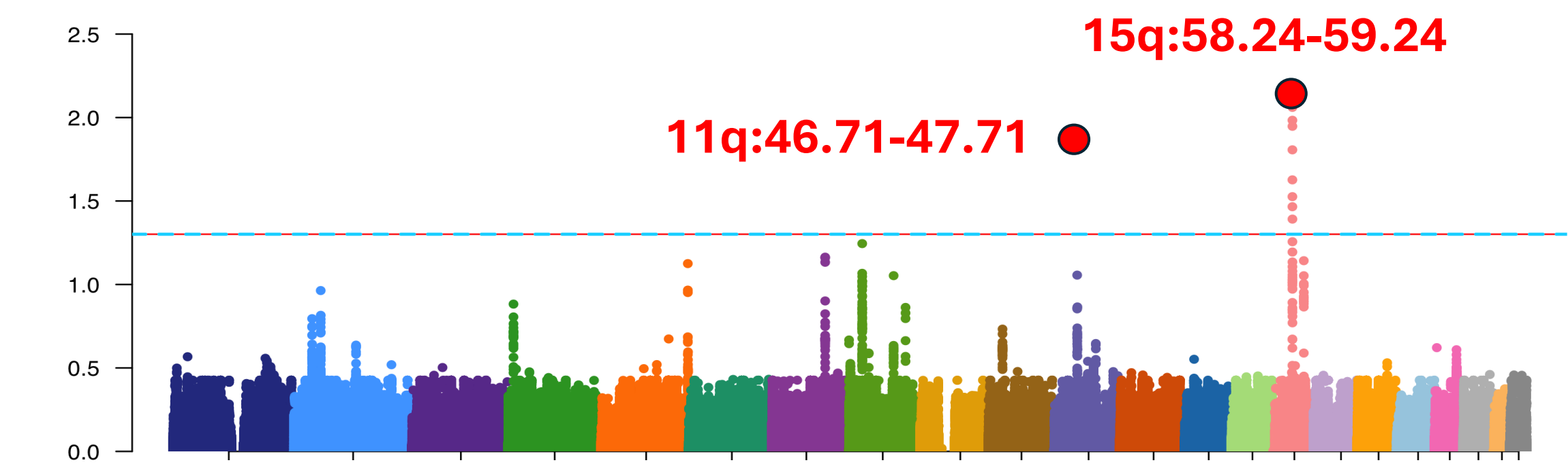


Figure 2: AD-SCZ conjFDR Manhattan plot (x-axis: chromosome number; y-axis: $-\log_{10}(\text{conjFDR})$).

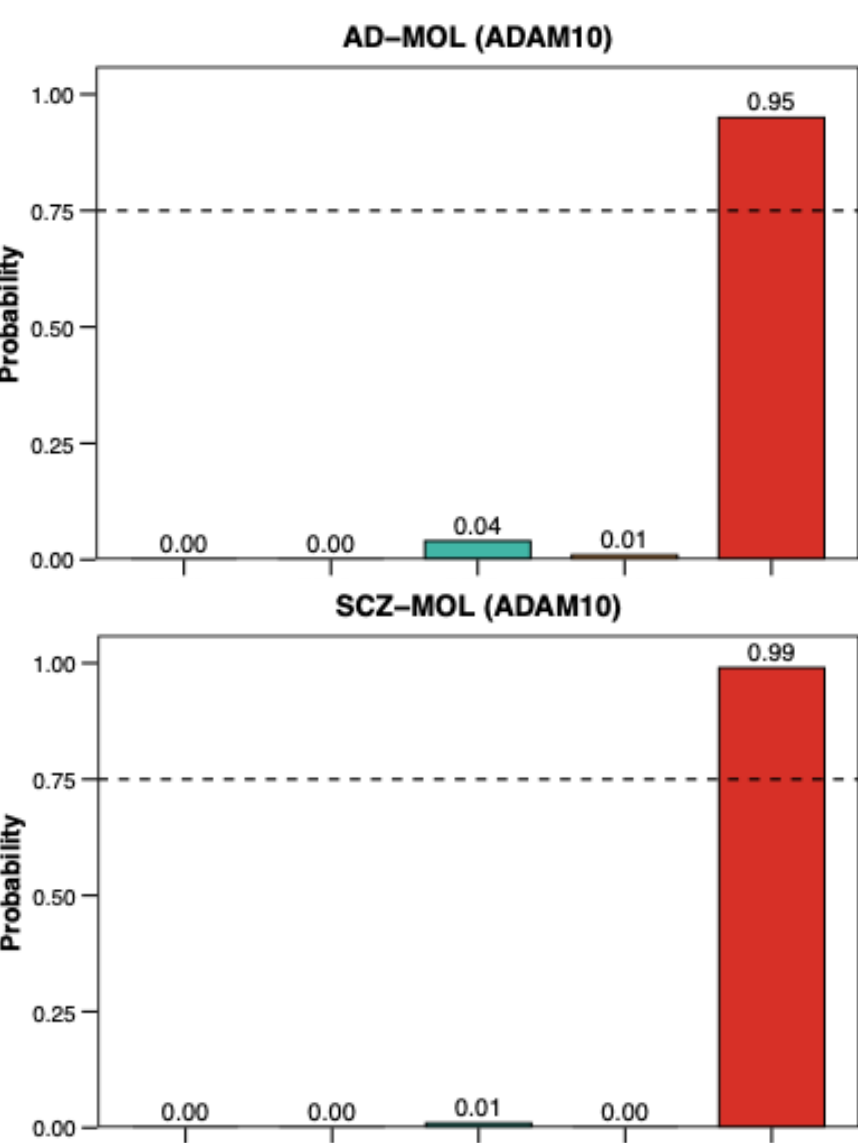
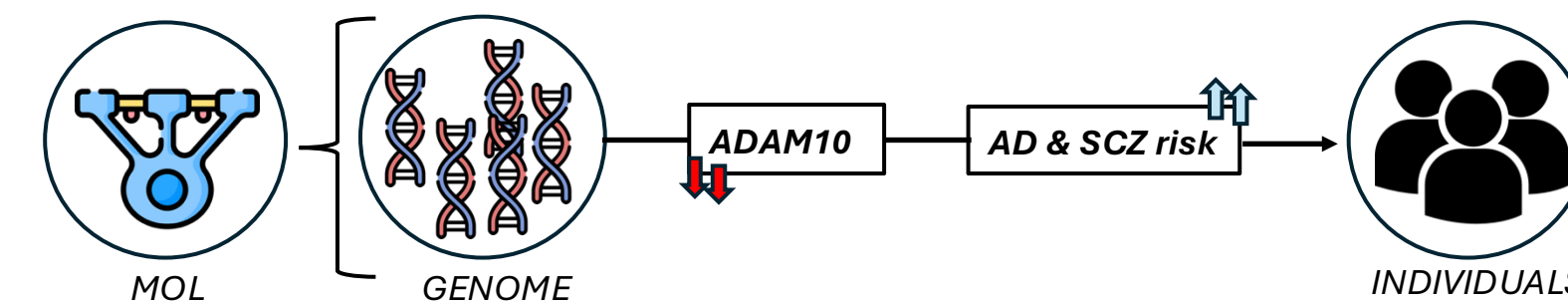


Figure 3: (A) GWAS-QTL coloc for AD-MOL. (B) GWAS-QTL coloc for SCZ-MOL.



Results (cont.)

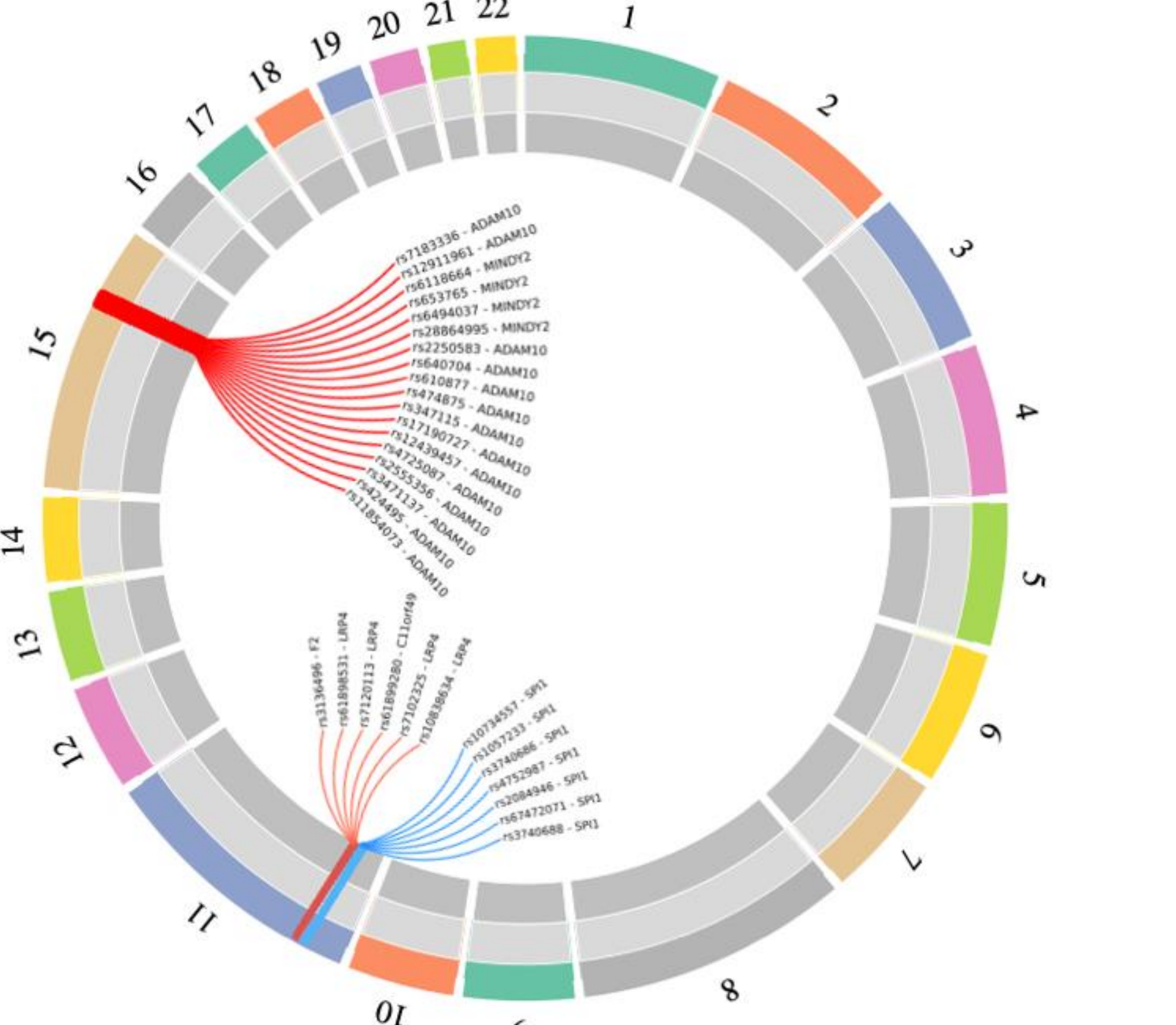


Figure 4: Candidate causal variants for two key loci.

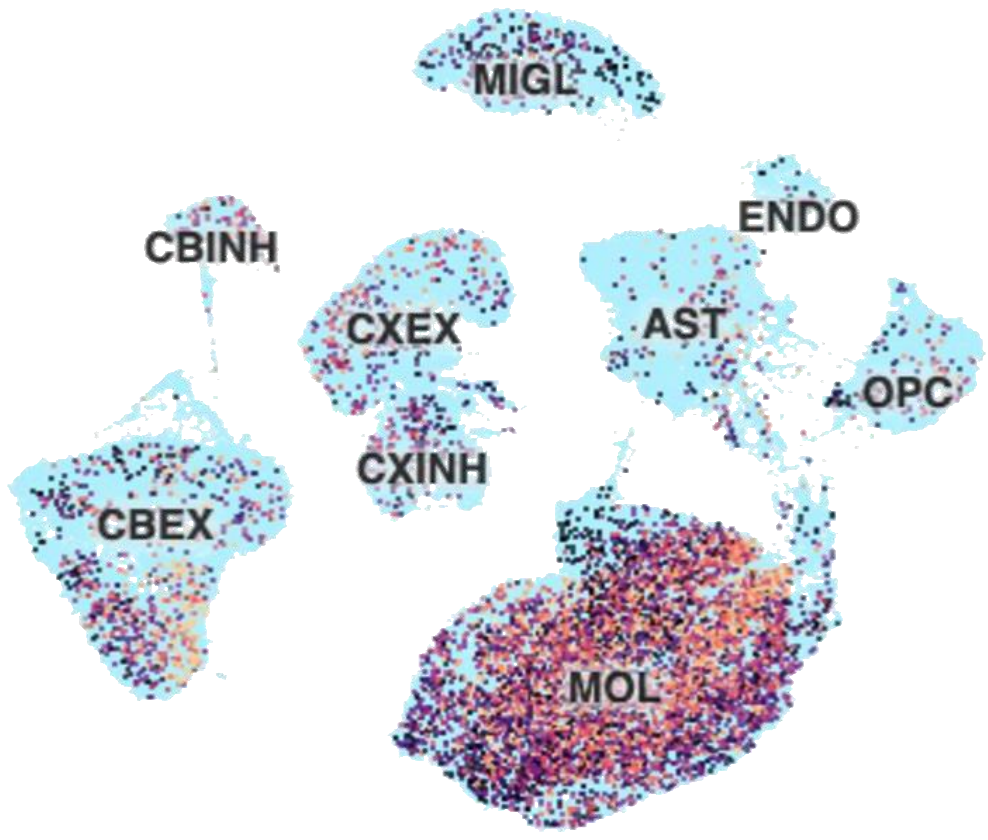


Figure 5: UMAP for sc-ATAC-seq pseudobulk enrichment of *ADAM10*

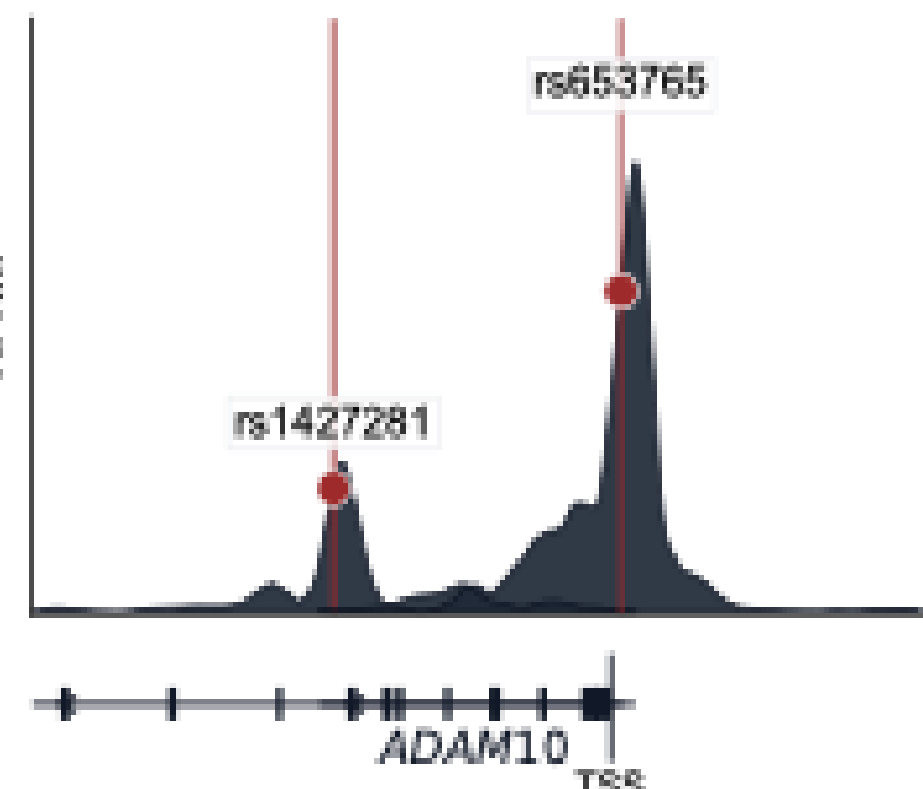


Figure 6: Open chromatin peaks around *ADAM10* gene for two key variants in MOL

18 shared variants (Figure 4) were prioritised in chr15, of which **~80%** were non-coding and most mapped within *ADAM10*. Two variants, **rs653765** and **rs1427281**, were also prioritised by MOL fine-mapping. Single-cell ATAC-seq demonstrated that both variants overlap **accessible chromatin enriched** in MOL, with rs653765 localising to the *ADAM10* **promoter** and rs1427281 mapping to a **putative enhancer** element (Figures 5-6).

Conclusion

Genetic overlap between AD and SCZ appears to be **locus-specific**. *ADAM10* emerged as the most robustly supported **shared** locus, with evidence for a non-coding **regulatory** mechanism in **mature oligodendrocytes**. **rs653765** and **rs1427281** were prioritised as candidate regulatory variants. Our findings implicate *ADAM10*-related oligodendrocyte and **myelination biology** in both disorders.