

Beyond Nearest Genes: Prioritization Across Identified Alzheimer Disease Risk Regions

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Background

Large-scale GWAS have identified many Alzheimer disease and related dementia risk loci, but the causal genes underlying many signals remain unresolved. Traditional nearest-gene annotation can miss biologically relevant genes located elsewhere within the associated chromosomal region.

Objective

To move beyond nearest-gene annotation by defining full Alzheimer disease risk regions and systematically prioritizing protein-coding genes for downstream fine-mapping and functional validation.

Method

Step 1: Paper results

(Bellenguez et al., 2022)

Table 1 had 33 previously known Alzheimer-associated loci & **Table 2** had 42 newly discovered loci. Total of **83 sentinel SNPs (variants)**.

Step 2: Combine variants

Each SNP has a **nearest gene** listed. Removing duplicates → **75 unique nearest-gene regions** (the loci).

Step 3: Define locus boundaries

Defined a **±1 Mb window** around each SNP. Overlapping ±1 Mb windows were **merged into larger regions**.

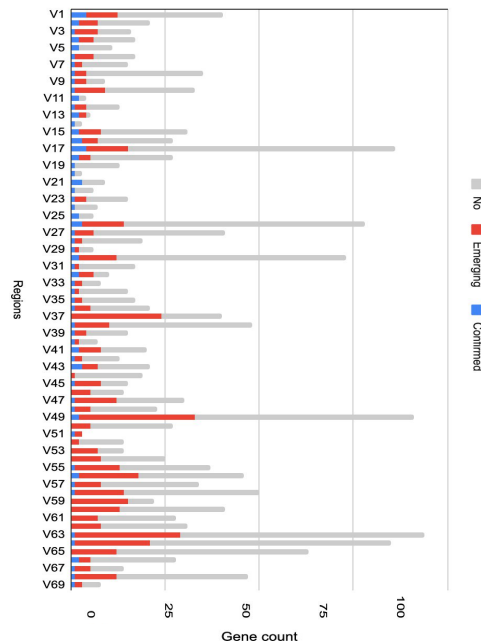
Step 4: Regions

Created individual tabs (V1–V69) regions. Used UCSC Genome Browser to extract the complete set of protein-coding genes within each region.

Step 5: Prioritization

Extracted information (genes, location, tier, evidence, etc) to categorize we utilized **exhaustive manual literature curation** across seven functional domains

Results



85 Confirmed genes with genome-wide association support.
422 Emerging genes supported by functional, transcriptomic, protein-level, eQTL, or pathway evidence.
1,336 genes without sufficient prioritized evidence.

Mechanisms:

Confirmed genes reinforced several major Alzheimer disease mechanisms: Innate immunity and microglial biology, Endosomal and lysosomal trafficking, Lipid metabolism, TNF-α and NF-κB signaling & Synaptic and mitochondrial pathways

Emerging Candidates for Follow-up:

NEU1: lysosomal clearance and amyloid-β accumulation. LRRC4B: synaptic function and cognition, & FIS1: mitochondrial fragmentation and neurodegeneration

Example Functional Hub:

V17 contains both the confirmed immune-related gene HLA-DRB1 and the emerging lysosomal candidate NEU1. This region highlights how Alzheimer disease risk may reflect interactions between immune regulation and lysosomal degradation rather than a single nearest-gene effect.

Conclusion

This regional prioritization framework moves beyond nearest-gene annotation by defining actionable Alzheimer disease risk regions and distinguishing Confirmed genes from Emerging candidates. Next, we will fine-map the 69 regions to identify causal variants and prioritize therapeutic targets for functional validation.

Reference

Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet.* 2022;54(4):412-436.
doi:10.1038/s41588-022-01024-z

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