

HIDDEN FUNCTIONAL CONNECTIVITY AMONG ALZHEIMER'S RISK GENES REVEALED BY NETWORK BIOLOGY

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01 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide. In 2024, the first genome-wide association study in Argentinian and Chilean populations identified genetic variants associated with AD risk, revealing both shared genetics with European populations as well as presence of novel loci¹.

The study identified five genes expressed in blood: *PLCG2* (immune signaling, known AD-associated gene replicated in Argentinian and Chilean population), *ADAM17* (protein processing, novel association), *TREM2* (microglial receptor, novel association), *RNF138* (protein recycling, novel association, with activity in blood), and *TRIB1* (metabolism regulation, novel association, linked with lipid metabolism). These genes appeared as independent hits on different chromosomes, yet lysosomal functional annotation appeared across multiple genes, suggesting potential shared mechanisms.

02 Challenge

How do these seemingly independent GWAS signals converge in Alzheimer's disease pathology? Understanding whether these variants function through separate pathways or within integrated, interacting network could clarify disease mechanisms and help prioritize potential therapeutic targets.

03 Solution

We analyzed these five AD-associated novel and replicated GWAS genes using Mavatar Discovery Blood related networks (neighbours = 3, distance = 3, gene filter = protein coding genes): A) Blood General: network created based on linear gene correlations from 114,841 blood samples across 1,279 datasets, and B) AI-Blood General: network created using autoencoder-derived from 226,660 features across 1,318 datasets representing both linear and non-linear gene expression relationships. This allowed us to compare how linear correlation versus complex non-linear relationships reveal different aspects of gene connectivity.

06 References

1. Dalmaso, M. C. et al. The first genome-wide association study in the Argentinian and Chilean populations identifies shared genetics with Europeans in Alzheimer's disease. *Alzheimers Dement.* 20, 1298–1308 (2024).

04 Results

The Blood General correlation network (shown in red) revealed bridging relationships connecting the gene clusters. The AI-Blood General autoencoder network (shown in blue) captured additional non-linear relationships. Both approaches demonstrated studied GWAS associations are not truly independent, but rather are a part of a larger connected system.

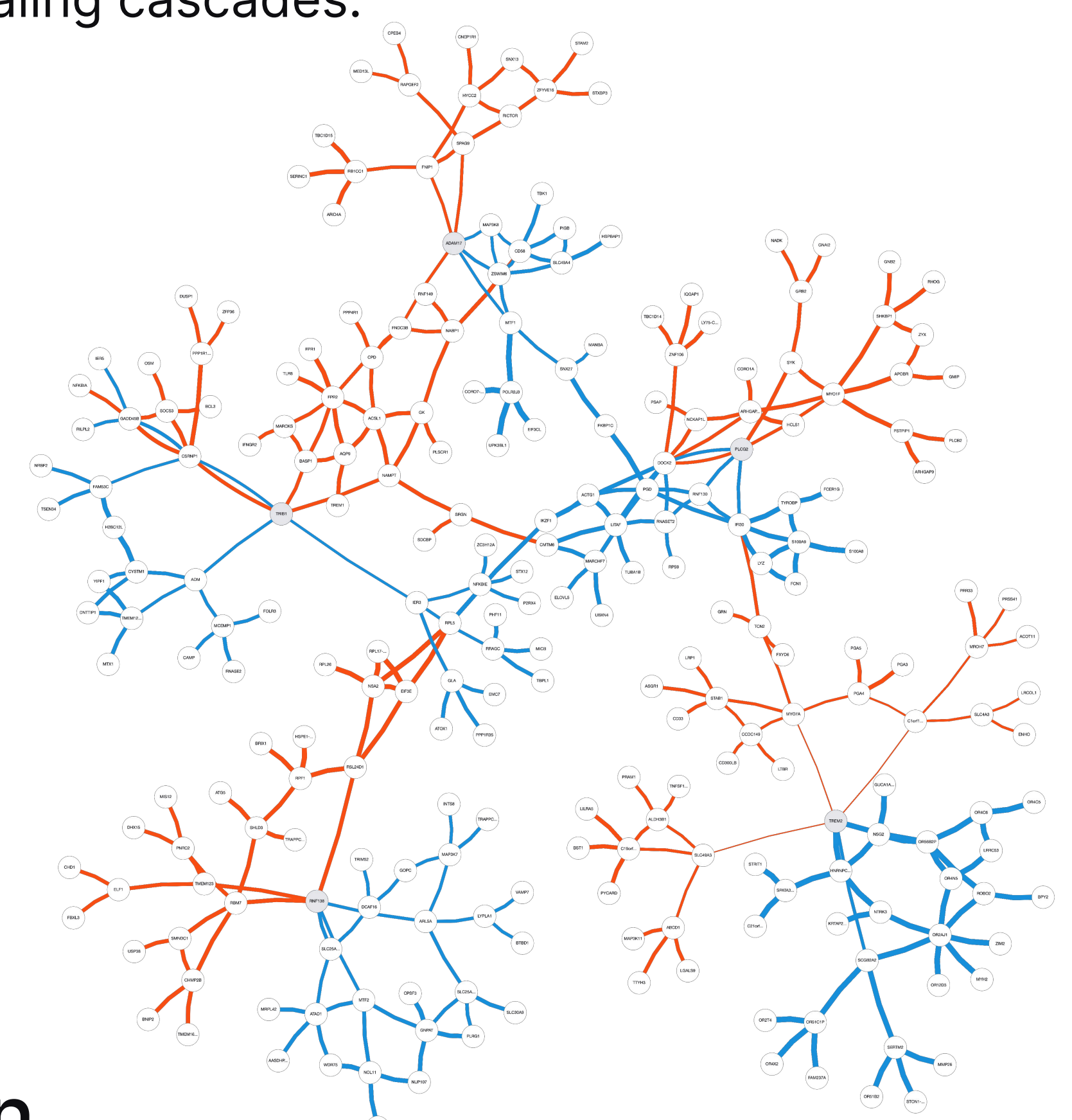
Our functional enrichment analysis revealed in GO Cellular Component important terms such as Lysosomal membrane ($p=4.73e-2$), Lysosomal lumen ($p=2.23e-2$) whereas GO Molecular Function revealed RAGE receptor binding ($p=4.26e-3$) which directly binds amyloid-beta. GO Biological Process showed enriched terms in Positive Regulation Of Tumor Necrosis Factor Production ($p=1.28e-1$), Positive Regulation of Interleukin 6 ($p=9.18e-3$) and Interleukin 10 ($p=7.17e-5$) and Interleukin 8 ($p=8.62e-3$) Production, Microglial cell activation Involved in Immune Response ($p=6.56e-3$), and Response to axon injury ($p=1.49e-2$) and cellular response pathways.

These results independently support GWAS lysosomal annotation through gene co-expression networks, while additionally uncovering coordinated molecular programs involved in immune signaling, lipid metabolism, and neuronal response.

Despite being derived from blood transcriptome data, the network captured CNS-relevant mechanisms including microglial activation, response to axon injury, RAGE-amyloid interactions, and neuroinflammatory signaling cascades.

Figure 1. Gene co-expression network created with Mavatar Discovery 1.6.1 around five GWAS genes.

Nodes represent genes, red edges represent linear co-expression, blue edges represent non-linear co-expression patterns.



05 Conclusion

Using Mavatar Discovery, we demonstrated that five AD GWAS loci from the first Argentinian-Chilean study, previously regarded as independent due to their location on distinct chromosomes, form a connected co-expression module involving lysosomes, protein clearance, and neuroinflammation. By comparing networks representing linear and non-linear gene associations, we revealed hidden functional relationships that conventional analysis missed, confirming shared biological mechanisms between Latin American and European populations. This network biology approach synthesized research across hundreds of studies within minutes, providing unbiased mechanistic insights without requiring coding or generating new experimental data.

OUR FINDINGS HIGHLIGHT

- ✦ Although located on different chromosomes, the five AD GWAS genes form a connected co-expression network, demonstrating biological convergence despite genomic independence.
- 🌀 Network enrichment analysis revealed coordinated involvement in lysosomal function, immune signaling, lipid metabolism, and neuroinflammatory pathways central to Alzheimer's pathology.
- 🔍 AI-derived non-linear networks uncovered hidden gene relationships beyond traditional correlation analysis, providing deeper mechanistic insight without new experimental data.