# Causal network analysis on multi-omics data from Alzheimer's brain reveals strong connection between mitochondria functions and AD outcomes

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## Background

- The "amyloid (Aβ) cascade" hypothesis in Alzheimer's disease (AD) has been the focus of therapeutic efforts.
- Recent clinical trials on antibody drug clearing Aβ plagues in brain show benefits of slowing down cognitive decline but rather modestly.
- Aitia has applied it's causal A.I. platform to build a comprehensive AD model connecting multi-omic and clinical features and utilized it to explore and understand AD biology most impactful on clinical outcomes.

## Methods

- Using the proprietary REFS™ platform [1], Bayesian networks were built using clinical, demographic, and multi-omics data from 273 postmortem brain samples of ROSMAP project [2] (Figure 1 A). *In silico* perturbations were performed for all genes and proteins in the model to assess their causal effects on all other variables (Figure 1 B, C).
- Hierarchical clustering was conducted using causal effects as similarity metrics to identify RNA and protein modules. These modules were annotated using gene ontology (GO) term (Metascape) [3] and their causal relationship with AD outcomes. (Figure 1 D, E, F).
- Module level causal network was built including AD risk factors, RNA modules, protein modules, and AD outcomes. The module level causal effect was defined as total causal effects normalized to module sizes (Figure 1 G).

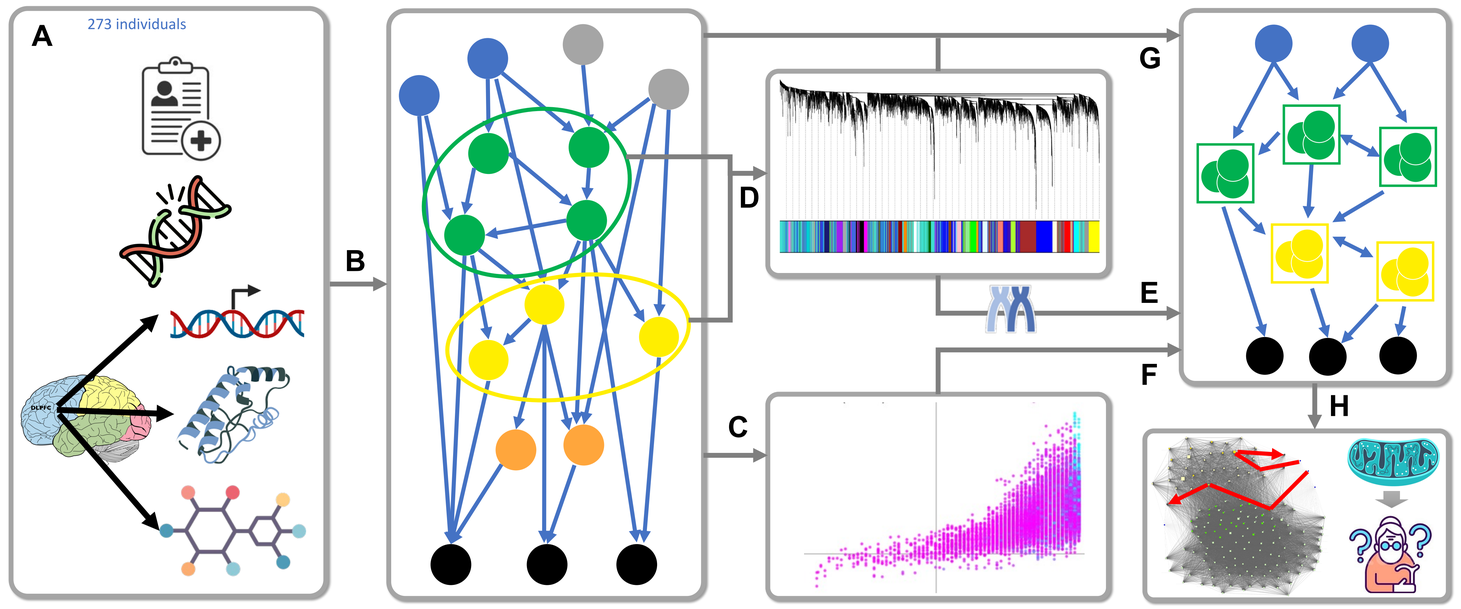


***Figure 1**, General workflow. **A**, Clinical and genomic data from 273 individuals, with transcriptomic, proteomic, and metabolomic data from their postmortem brain tissue (DLPFC) were used in our analysis. **B**, Building causal Bayesian network models among all variables using AITIA's REFS™ platform. **C**, Identify top causal drivers of AD endpoints. **D**, Hierarchical clustering were used to identify RNA and protein modules based on simulated causal relationships respectively. **E**, Annotating RNA and protein modules using Metascape. **F**, Annotating RNA and protein modules using enrichment of AD outcome drivers. **G**, Building module level causal network using AD risk factors, RNA modules, protein modules, and outcomes. **H**, Identifying top paths from risk factors to AD outcomes.*

## Results

- Hierarchical clustering of RNA and protein causal networks identified 119 and 33 modules respectively. Some modules were over-represented with AD outcome drivers (Table 1)

***Table 1**, Modules over-represented by AD drivers*

| # Modules | Over-represented with | | |
|---|---|---|---|
| | Cognition drivers | Pathology drivers | Both |
| RNA | 8 | 8 | 6 |
| Protein | 4 | 1 | 3 |

- Out of modules Over-represented with AD drivers, 3 protein modules (m5, m22, and m25) and 2 RNA modules (m16 and m18) were strongly enriched with genes related to mitochondria functions. (Figure 2).
- 1 Protein module (m3) and 1 RNA module (m8) were enriched in synaptic signaling, a well-known pathway affected in late AD (Figure 3).
- Risk factors were driving cognition (MMSE score) through 3 paths:
  - immune response and supramolecular fiber organization
  - mitochondria function and peptide hormone processing
  - nervous system development regulation
- Risk factors were driving pathological outcomes through 2 paths:
  - monoatomic cation transmembrane transport and nervous system development.
  - mitochondria function, protein transport/catabolism, and neuron projection development.
- Among all RNA and Protein modules, The protein "aerobic respiration" module showed strongest causal effects to Braak staging.

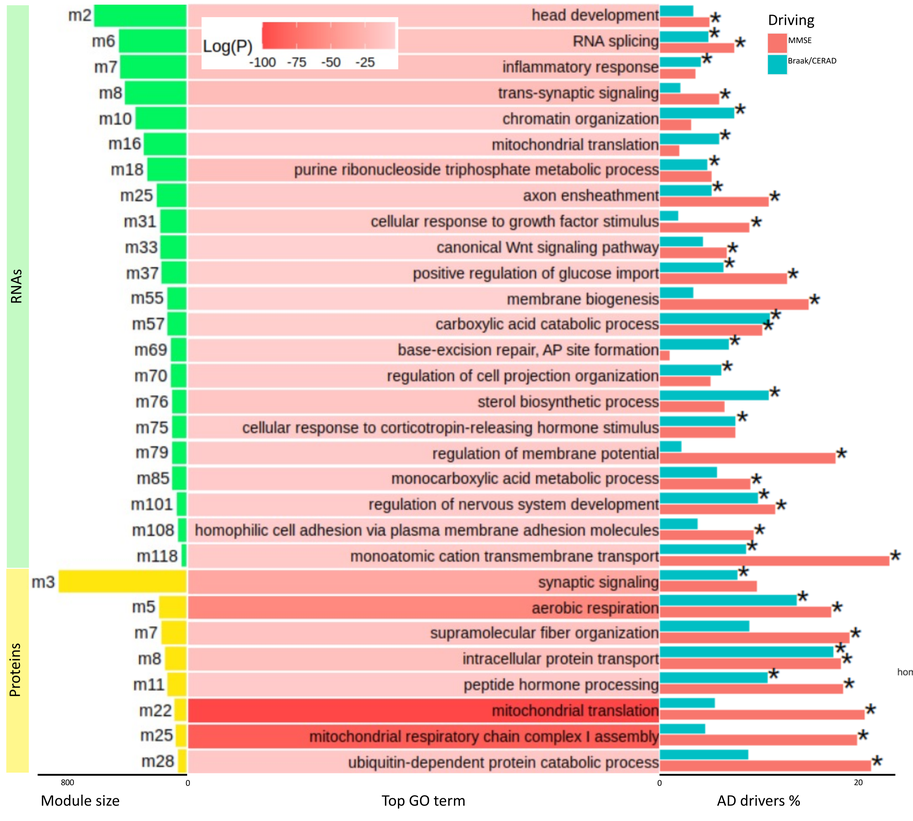


***Figure 2**, 30 RNA and protein modules that are enriched in AD drivers. *: BH adjusted P value < 0.05.*

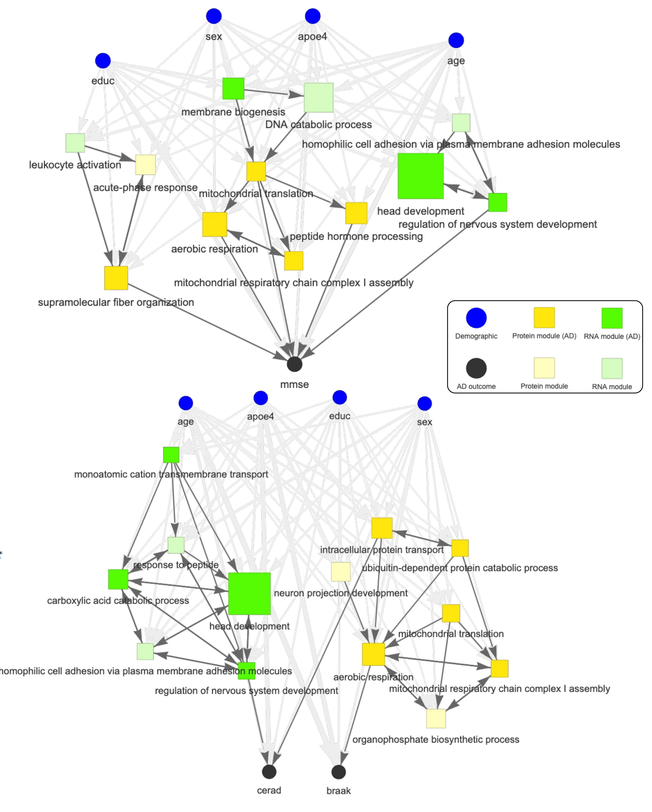


***Figure 4**, Top causal paths from AD risk factors to cognitive (MMSE score) and pathological (CERAD and Braak) endpoints.*

## Conclusions

- The Causal A.I. driven AD brain models revealed strong connection of mitochondria functions with both cognitive ability and AD pathology.
- Protein clusters involved in mitochondria functions and RNA clusters involved in neuron development were causally driving AD outcomes while being driven by well-known AD risk factors. Further investigation of genes in these clusters may reveal novel therapeutic candidates with high impact on clinical outcomes.
- This comprehensive network approach powered by rich multi-omic data could help generate new hypothesis or deepen our understanding on existing hypothesis, such as "mitochondria cascade hypothesis" of AD first proposed two decades ago[4].

## References

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