Molecular signature linking Alzheimer's Disease and Epilepsy

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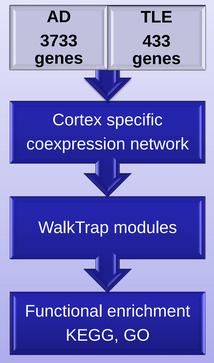
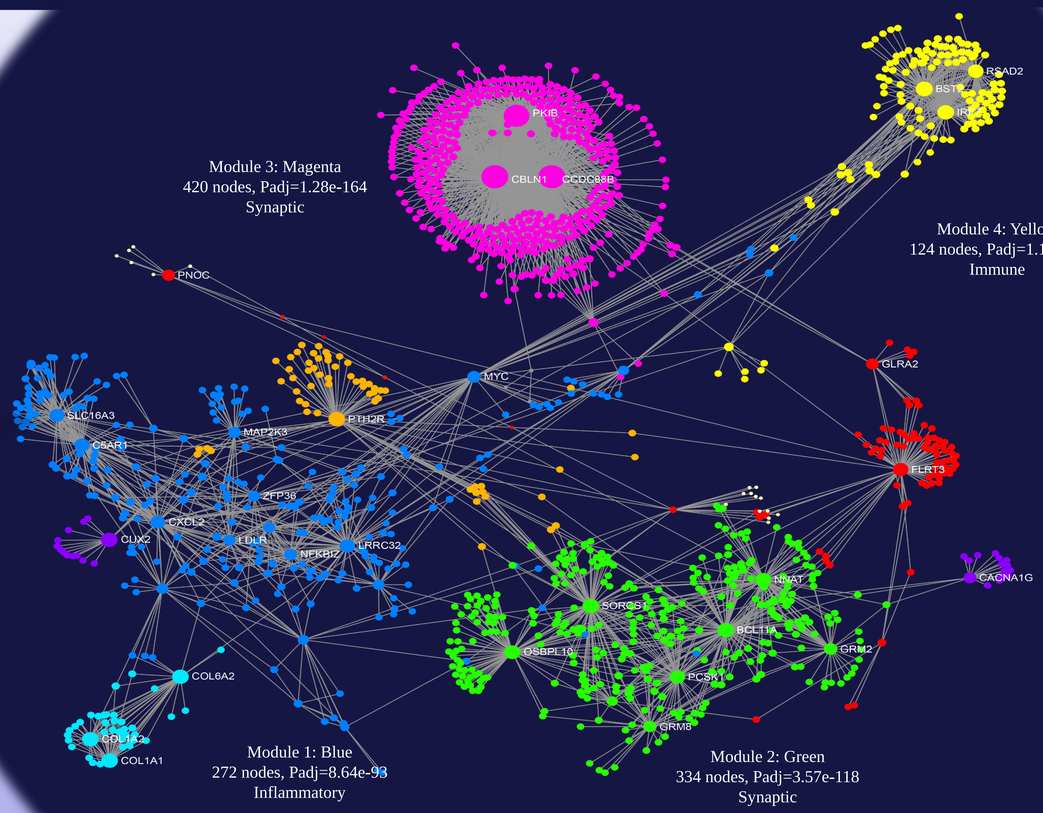
Introduction

- Alzheimer's disease (AD) is a neurodegenerative disease affecting 50 million people worldwide
- Increased prevalence of seizures in AD patients[1]
- Hypothesis: Commonly dysregulated genes and pathways lead to neurodegeneration and seizures
- Data: microarray dataset of AD brain tissue (HBTRC)[2], 443 epileptogenic genes from Johnson et al. linked to temporal lobe epilepsy[3]

Methods

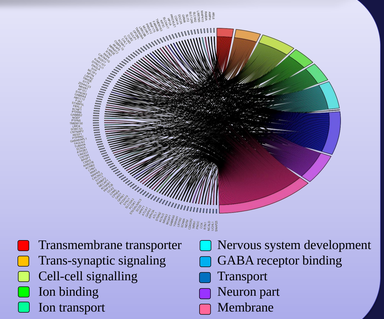


Cortex-specific gene coexpression networks for AD and TLE were created using the TCSBN Database[4]. These networks were then intersected into a final network representing AD and TLE. Strong enrichment in immune (modules 1,4,6) and synaptic pathways (modules 2,3,5) was detected.



Synaptic dysfunction

The gene set in module 2 shows enrichment in GABAergic synaptic processes, neuro-transmitter transport and synaptic signalling.

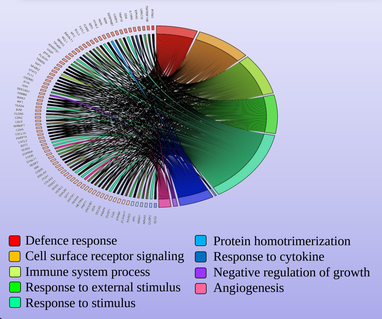


Hubs

Hub genes of each network are determined by degree centrality. These hubs likely have protein-protein interactions with a large group of genes and may act as regulators.

Network	Genes	Degree
AD	PGM2L1	379
	GABBR2	371
	DLGAP1	301
TLE	GRM4	370
	CBLN1	368
	PKIB	361
AD+TLE	CBLN1	210
	PKIB	203
	CCDC88B	202

Inflammation



This chord diagram depicts the significant GO terms after hierarchical reduction of overlapping terms in Module 1. Enrichment in KEGG immune pathways and multiple inflammatory cascades such as TNFa and MAPK were detected.

Network Graph

AD+TLE network is an intersection of cortex-specific gene coexpression networks of Alzheimer's Disease and temporal lobe epilepsy. The nodes represent genes and edges are determined by Pearson correlation coefficients of the expression pattern of genes. Larger nodes are those of at least 20 degree centrality. The WalkTrap algorithm[5] identified 11 communities called modules shown in various colours in the graph. These modules represent a group of genes that are likely working together and belong to similar biological pathways.

Conclusions

- There is dysregulation in synaptic transmission processes and strong enrichment in inflammatory pathways in both Alzheimer's disease and temporal lobe epilepsy.
- Network abnormalities and seizures in AD may be associated to dysregulation in the GABAergic systems and inflammatory cytokines
- Studies with rodents that model both AD and TLE pathology are recommended to validate the gene signature of epileptic AD brain in order to develop more targeted therapies for the relevant patient group