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Integrated systems approach to identify genetic networks and hubs in Alzheimer's disease

Background

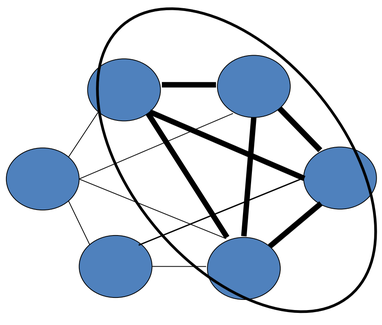
- Network analysis allows for a greater understanding of the interactions of genes in the biological processes that underlie the pathophysiological state of disease
- Allows for identification of sub-networks that are formed of clusters of highly interconnected genes, also known as modules
- Can then identify hub genes which are highly connected within modules and play an important role in preservation of the module.

Objective

- Use network analysis to gain molecular insight into Alzheimer's disease using gene expression data in blood

Methods

- Datasets GSE63060 and GSE63061 from GEO database merged:
  - Microarray dataset
  - Whole blood
  - 245 AD, 142 MCI and 182 HC
- Weighted Gene Correlation Network Analysis (WGCNA) is used to build networks



Modules of highly connected genes are found using hierarchical clustering and an additional *k*-means correction based step

- Preservation of modules between Alzheimer's, MCI and healthy control were identified using NetRep [1]
- Intra modular hubs of high biological relevance are identified using betweenness centrality (BC), closeness centrality, module membership and PageRank.
- The R code used for the novel hub detection test is available at http://tiny.cc/ltbtlz

Modules

We highlight these significant modules:
AD network modules not present in control and MCI networks (1/29)

- Regulation of lipolysis in adipocytes, Neuroactive ligand-receptor interaction, detection of chemical stimulus involved in sensory perception of smell (1076 genes)

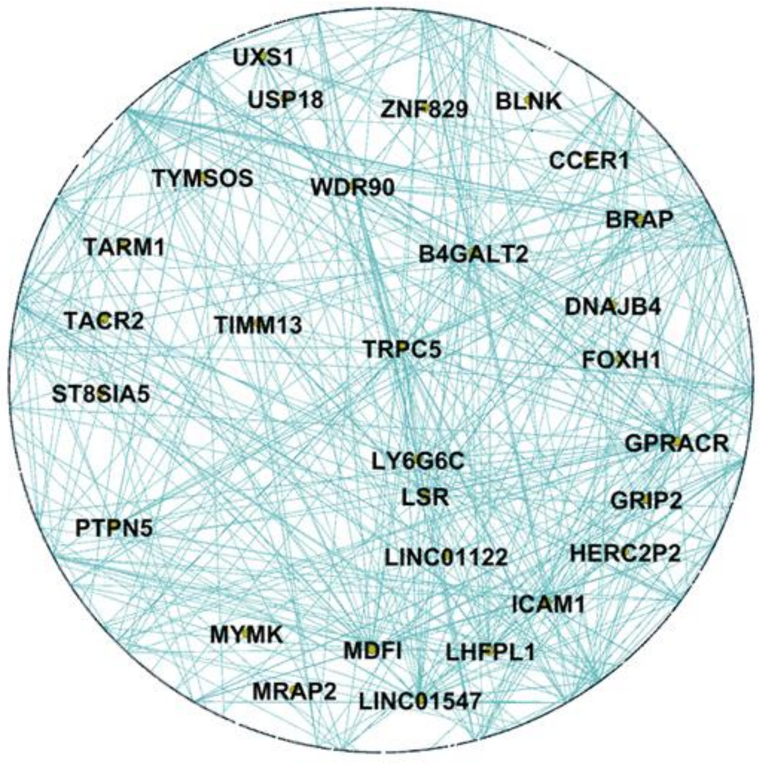
Processes associated with healthy control modules not present in PD network (3/58)

- sensory perception, regulation of potassium ion transmembrane transport (584 genes)
- Peroxisome, amide transport (248 genes)
- Establishment of epithelial cell polarity (187 genes)

Hub genes and Transcription factors

- A permutation test was created to identify the highly connected hub genes:
  - Within the AD module not preserved in MCI associated with olfactory systems, we identified *OR5AS1* which encodes a member of the olfactory receptor family and plays a role in triggering response to smells
- *REST* was identified as a regulator in AD module associated with olfactory systems not preserved in MCI networks.
- A full list of hubs can be found at bit.ly/NetworkAD

Regulation of lipolysis in adipocytes in Alzheimer's disease



- Modules are visualised using Gephi
- Hub genes are shown in the centre of the network
- We highlight the following hub genes:
  - *TRPC5* helps form non-selective Ca2+-permeable channels
  - *BRAP* has been associated with obesity and other metabolic traits, which can play a role in effecting insulin signaling and aging

Conclusion

- We have identified many important processes that are altered in Alzheimer's disease patients or are present in Alzheimer's patients but not in healthy controls
- We show multiple novel genes that play an important role in key processes that are dysregulated in Alzheimer's disease and could present new therapeutic targets
- A full list of significant modules and hub genes can be found at: bit.ly/NetworkAD

[1] Ritchie *et al.* (2016). Cell Systems 3, 71–82

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Athena SWAN Silver Award