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

Background

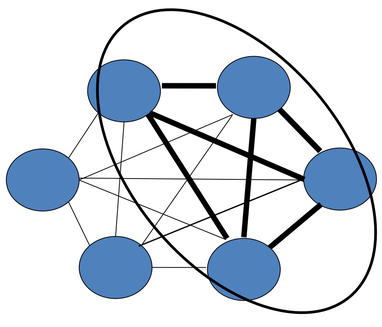
- Network analysis allows for a greater understanding of the interactions of genes in the biological processes that underlie the pathophysiological state of disease
- Allows for identification of sub-networks that are formed of clusters of highly interconnected genes, also known as modules
- Can then 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 Parkinson's disease using gene expression data in blood

Method

- Dataset GSE99039 from GEO database:
  - Microarray dataset
  - Idiopathic Parkinson's
  - Whole blood
  - 204 disease and 231 healthy control
- 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 Parkinson's 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.

Modules

We highlight these significant modules:

PD network modules not present in control network (14/54)

- Infection (92 genes)
- Natural killer cell mediated cytotoxicity (150 genes)
- Insulin resistance (351 genes)
- Response to misfolded proteins (150 genes)
- Clathrin-dependent endocytosis (310 genes)
- B cell activation(95 genes)

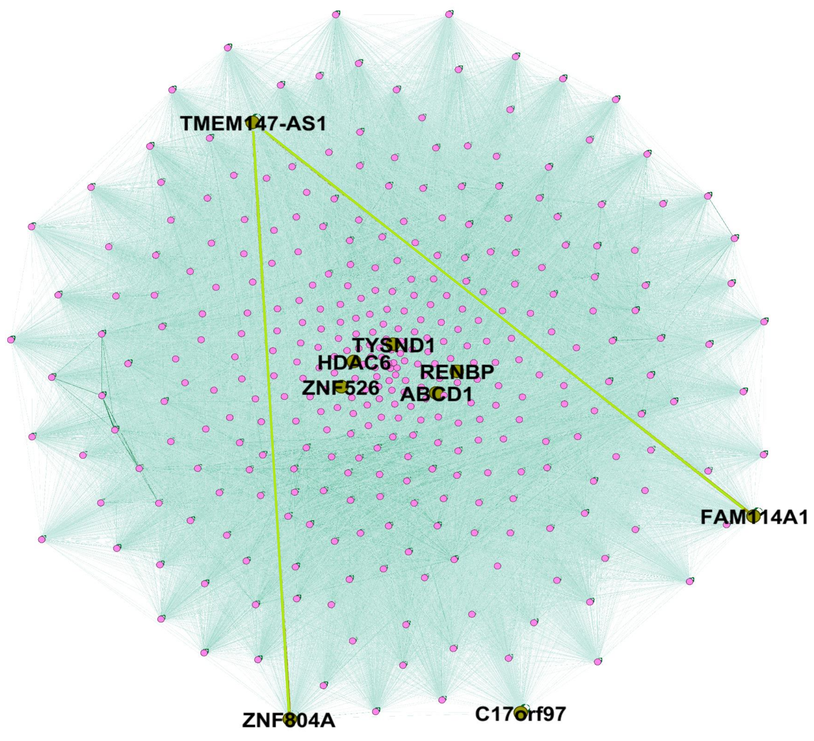
Processes associated with healthy control modules not present in PD network (4/25)

- Hedgehog signalling pathway (1992 genes)
- Antigen processing and presentation (606 genes)

Hub genes

- A permutation test was created to identify the highly connected hub genes:
  - Hub genes in the infection module (*CTSL, HERC5*) have been implicated in infection previously, but are novel Parkinson's genes
  - The hub gene *SNRNP70* in response to misfolded protein module has been correlated with amyloid-β and tau [2]
  - *C15orf48* and *UBL7* are the top hub genes for Clathrin-dependent endocytosis module
- A full list of hubs can be found at bit.ly/NetworkPD

Insulin Resistance in Parkinson's disease



- Modules are visualised using Gephi
- Hub genes are highlighted:
  - *HDAC6* has been shown to be a regulator of glucose metabolism [3]
  - *FAM114A1* has been associated with insulin resistance [4]
- Many of these hub genes (e.g. *RENBP, HDAC6, FAM114A1*) have been associated with insulin resistance previously, however are novel to Parkinson's disease

Conclusion

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

[1] Ritchie *et al*., 2016. *Cell Systems*, 3(1): 71-82. [2] Hales *et al*., 2016. *Proteomics*, 16(23): 3042-53
[3] Winkler *et al*., 2012. *Diabetes*, 61(2): 513-523. [4] Xie *et al*., 2016. *Obestity,* 24(7): 1506-14

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Athena SWAN Silver Award