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

Background

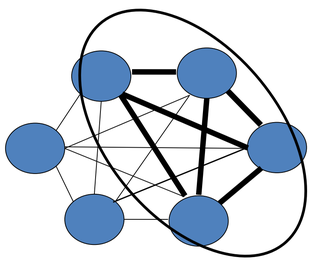
- Network analysis allows for a greater understanding of the interactions of genes in the biological processes that underlie the pathophysiological state of disease
- Primarily it allows for identification of sub-networks that are formed of clusters of highly interconnected genes, also known as modules, and 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

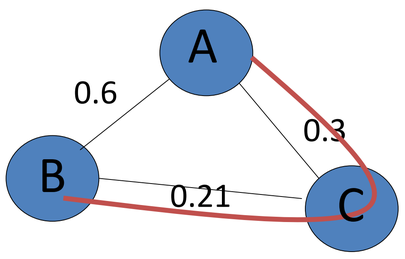
Method

- GSE99039
  - Microarray dataset
  - Idiopathic Parkinson's
  - Whole blood
  - 204 disease and 231 healthy control
- weighted gene correlation network analysis (WGCNA) is used to build networks



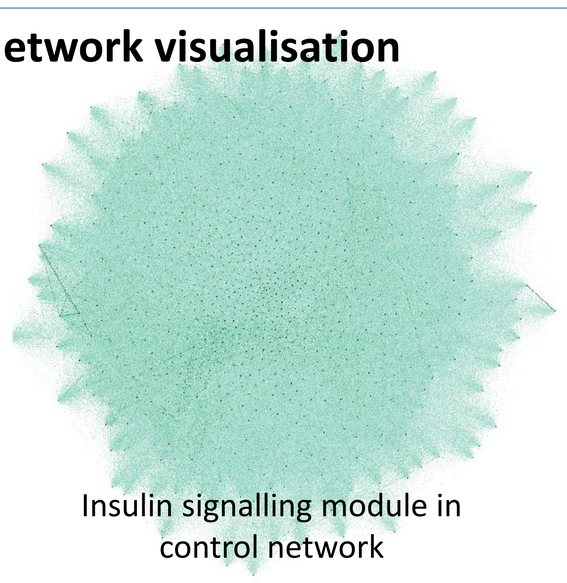
Modules of highly connected genes are found using hierarchical clustering and an additional K-means correction based step

- Preservation of modules between Parkinson's and healthy control were identified using NetRep [2]
- Intra modular hubs of high biological relevance are identified using betweenness centrality (BC)
  - BC of a node is the number of shortest paths between every two other nodes in the module that pass through that node

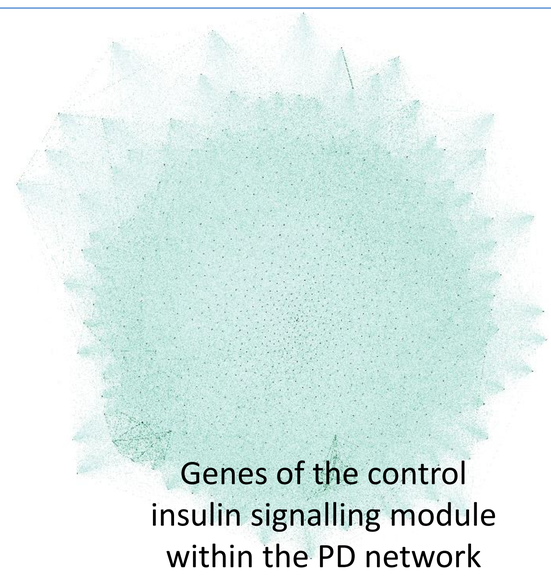


Red line indicates an example of a shortest path through the network between node A and B, which passes through node C. Here, C has a high betweenness centrality

Network visualisation



Insulin signalling module in control network



Genes of the control insulin signalling module within the PD network

Modules not preserved between control and PD have reduced connections between nodes

The darker the connection between nodes the stronger it is

Modules

PD network modules not preserved in control network

- fungal virulence and N-glycosylation pathways (601 genes)
- Methyltransferase activity - 345 genes
- Retinoic acid (RA) metabolism (1899 genes)
- cell death and RNA viral replication (270 genes)
- RNA polymerase II recruitment to insulin promoting regions for signaling cascade (268 genes)
- Blood clotting (147 genes)
- Mitochondrial metabolism (523 genes)
- Proliferation and migration of cells (907 genes)
- G-protein coupled acetylcholine receptor (1897 genes)

Control network modules not preserved in PD network

- insulin signalling (865 genes)
- ion channels (2965 genes)

Hub genes

- Initially, some hub genes are clear within modules:
- RPS4Y1 (normalised BC of 0.489) in PD Cell death and RNA viral replication module
  - previously shown to be candidate gene for PD in blood studies [2]
- USP3-AS1 (normalised BC of 0.330) in PD RNA polymerase II recruitment to insulin promoting regions module
  - Encodes the USP3 antisense RNA 1 long non-coding RNA
- MTPN (normalised BC of 0.186) in PD Blood clotting module
  - Encodes myotrophin protein involved in regulating growth of cardiomyocytes
- PDAP1 (normalised BC of 0.180) in control mitochondrial metabolism module
  - PDAP1 modulates the mitogenic activity of PDGF ligands, which play a role in PD [3]
- CPM (normalised BC of 0.173) in control insulin module
  - Expression associated with monocyte to macrophage differentiation [4]

Conclusion

- Here we have implemented WGCNA to give insight into the underlying genetic interactions in PD and highlight highly connected genes
- We show multiple novel genes that regulate and play an important role in key processes that are dysregulated in Parkinson's disease and could present new therapeutic targets.
- We look to expand on these initial hub genes to identify less obvious hub genes and important gene to gene connections within modules

References
[1] Ritchie *et al*. (2016) *Cell systems*, 3(1): 71-82. [2] Sun *et al*. (2014). *Neuro Endocrinol Lett*., 35(5):398-404.
[3] Sharma *et al*. (2016) *Int J Biochem Cell Biol.* 78:194-205 [4] Lauterbach and Wunderlich (2017) 469(3): 385–396.

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Athena SWAN Silver Award