Jack Kelly (jack.kelly@postgrad.plymouth.ac.uk) and Xinzhong Li
Plymouth University Peninsula Schools of Medicine and Dentistry

Cross-talk between Parkinson and Alzheimer's disease

Introduction

It is widely accepted that Alzheimer's disease (AD) and Parkinson's disease (PD) are different types of disease, however there is increasing evidence that they share several common pathological and physiological characteristics [1].

There is evidence that molecular pathways, including mitochondrial dysfunction, oxidative stress and inflammation are involved in the pathogenesis of both AD and PD and in neurons and oligodendrocytes of AD and PD patients there has been found a co-occurrence of tau and α-synuclein pathology which can seed the aggregation of one another, though the underlying mechanisms of these have not been entirely explained [2].

Objective

- Identify similar differentially expressed genes and pathways between AD and PD
- Identify unique differentially expressed genes and pathways between AD and PD

Method

- ArrayExpress and GEO were searched using the keywords "Parkinson AND array AND Substantia Nigra" and literature search of pubmed to find any additional datasets
- Excluded any studies that used patients with familial Parkinson's, used cell lines, had samples exposed to drugs, in vitro studies and repeated data
- A meta-analysis approach is used to identify differentially expressed genes (DEGs) then ingenuity pathway analysis (IPA) is used to find enriched pathways and protein-protein interaction networks are analysed.
- This is compared to results of meta-analysis of 450 late onset AD (LOAD) frontal cortexes and 212 controls done using a similar methodology [3].

Results

- Meta-analysis was performed on 7 studies including 69 PD Substantia Nigra (SN) and 57 controls data.

Number of differentially expressed genes found in PD and AD

AD up	1358
AD down	1766
Total	3124

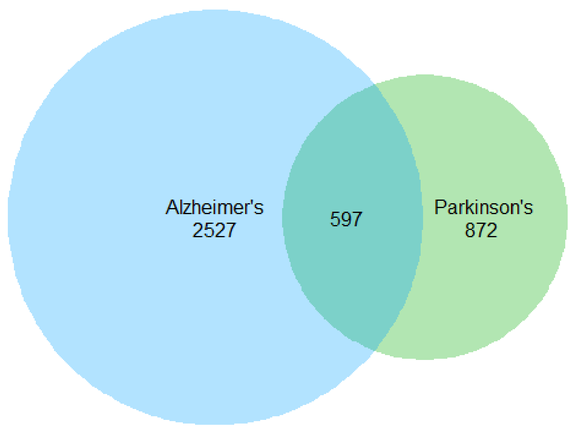
PD up	359
PD down	1110
Total	1469

- Around 40% of DEGs in PD are also DEGs in LOAD, and around 20% of the DEGs in AD are in PD.

Top 10 most significant differentially expressed genes. Genes in red are differentially expressed in both PD and AD

PD	AD
YWHAZ	NEUROD6
DCLK1	ZCCHC17
SNCA	PPEF1
PAIP1	C1QA
CDH8	MANBAL
ATP6V1D	BDNF
FRRS1L	CRH
RGS4	ITPKB
OPA1	FAM211A
ENSA	FKBP5

Number of genes in common between AD and PD



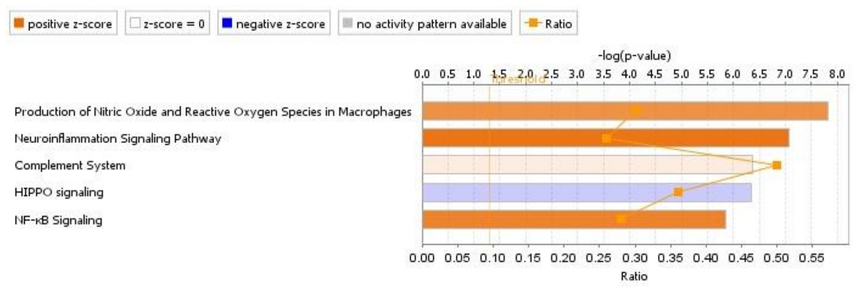
- The association between the number of the genes shared between PD and AD that are up or down regulated is statistically significant (two tailed Fisher's exact test <0.0001)

The regulation of differentially expressed genes in common between AD and PD

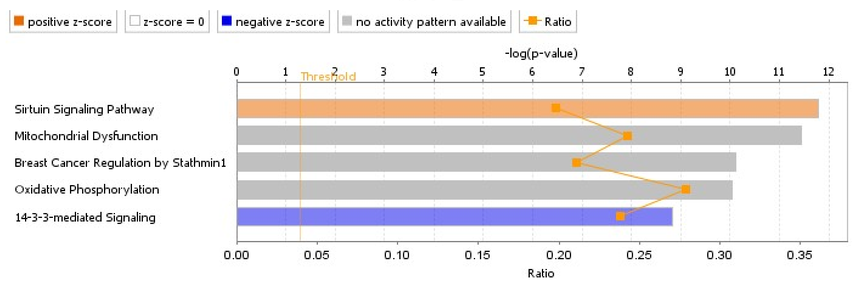
	PD up	PD down	Total
AD up	**139**	**3**	142
AD down	**1**	**454**	455
Total	14	457	597

- IPA identified 213 effected pathways in PD and 192 pathways in AD, with 114 shared between the two.

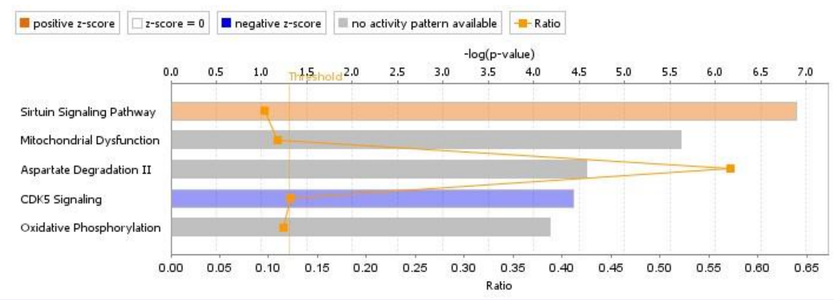
Top canonical pathways for DEGs unique to AD



Top canonical pathways for DEGs unique to PD



Top canonical pathways of DEGs found in AD and PD



Conclusion

- There are significantly more DEGs in LOAD than in PD, suggesting the **brain of LOAD patients is more severely effected**
- Previous studies have supported that most DEGs in different brain areas and blood of PD patients are down-regulated and most DEGs shared between AD and PD are down-regulated.
- 14-3-3ζ (**YWHAZ**) can bind tau and prevent phosphorylation and has been shown to interact with α-synuclein in a similar way [4]
  - 14-3-3ζ is a potential CSF biomarker for Creutzfeldt-Jakob disease and could be valuable in AD and PD
- Downregulation of ***SNCA*** which encodes α-synuclein is downregulated in both perhaps indicating a role of α-synuclein in LOAD
  - SNCA transcripts degrade faster in PD brain than in control ().
- Shared **mitochondrial dysfunction** and **oxidative stress** are confirmed in this study
- The **Sirtuin pathway** has been implicated in modulation of mitochondrial pathways and some proteins in the pathway have potential in reducing α-synuclein inclusions and blocks tau pol- ubiquitination and tau turnover as well as enhancing transcription of *PGC-1α* gene.
  - *PGC-1α* has been identified as a potential therapeutic target in PD, and should be further investigated in AD.[6]
- Many pathways of the shared genes pathways between AD and PD were key pathways found in PD, suggesting that underlying mechanisms of PD are shared with AD, though AD has a more complex interaction of pathways
- Pathways and genes shared between AD and PD were often linked with interactions to tau and α-synuclein

References:
[1] Wang, Q. *et al.* (2017). *Journal of Alzheimer's Disease*, 56(4): pp.1525-1539.
[2] Toledo, J.B. *et al.* (2013). *Acta Neuropathologica,* 126(5): pp.683-697.
[3] Li, X. *et al*. (2015). *Scientific Reports,* 5: 12393
[4] Wang X. *et al*. (2018). *Toxicological Sciences,* (published online ahead of print)
[5] Dumitriu *et al*. (2012). *Parkinson's Disease*, Article 614212
[6] Zheng *et al*. (2010). *Science Translational Medicine*, 2(52):52ra73