Transcriptomic signatures of brain regional vulnerability to Parkinson's disease

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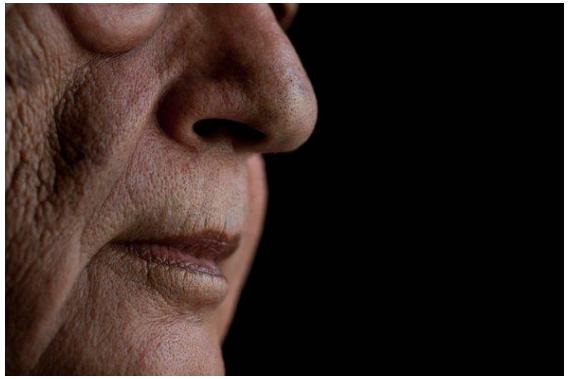
TU Delft

Parkinson's disease (PD) progression

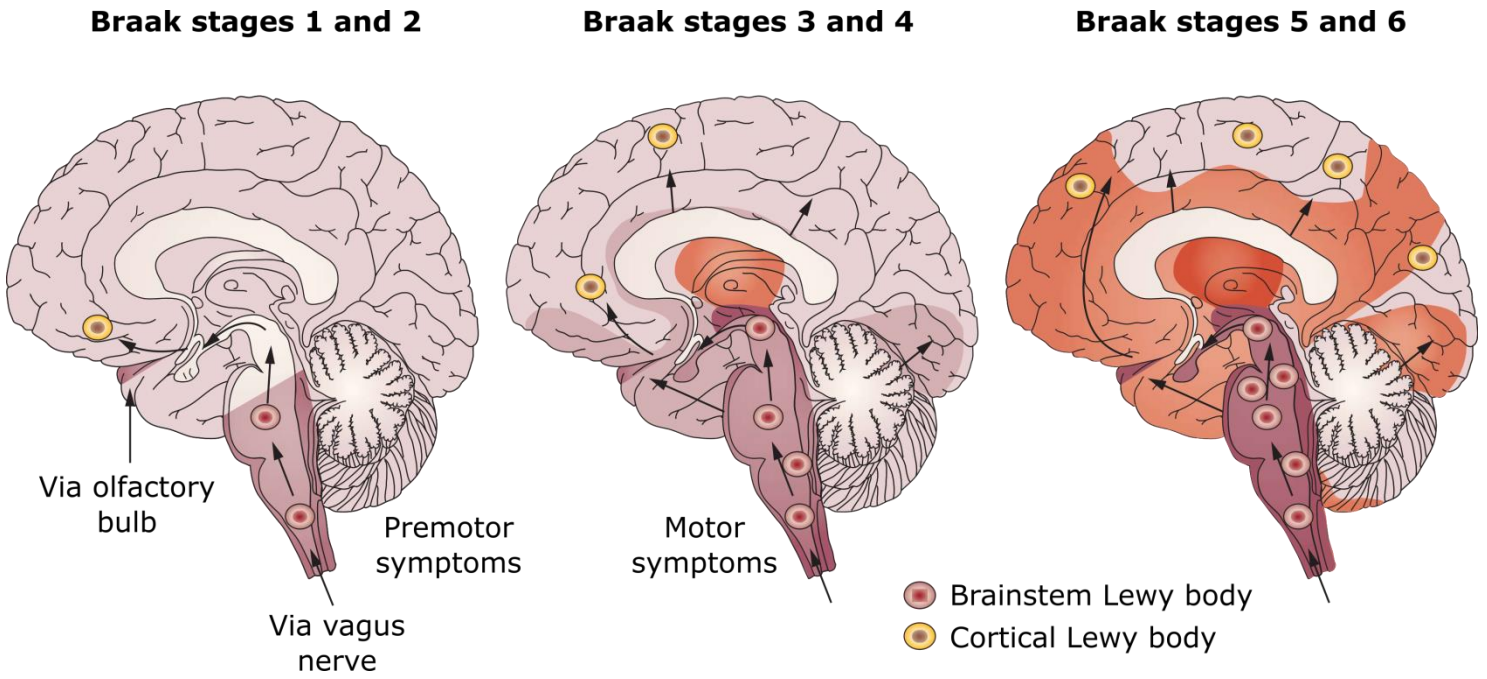


Loss of smell
Little or no facial expression
Tremor

Bradykinesia
Rigidity

Cognitive impairment
Dementia

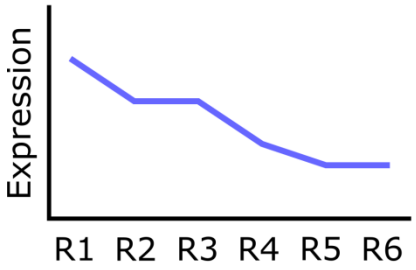
Progressive pathology described by Braak

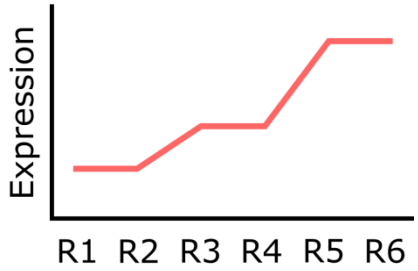


R. L. Doty, 2012

Hypothesis

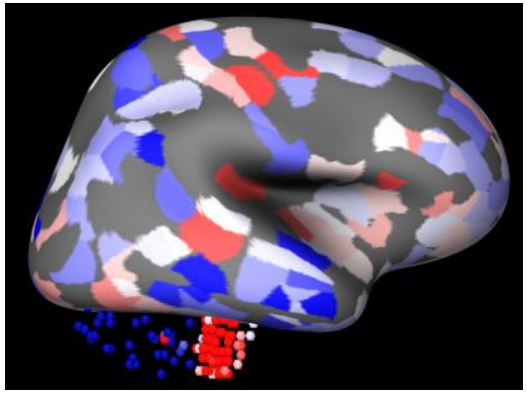
- Spatial gene expression patterns
- Correlation with regions involved in Braak stages

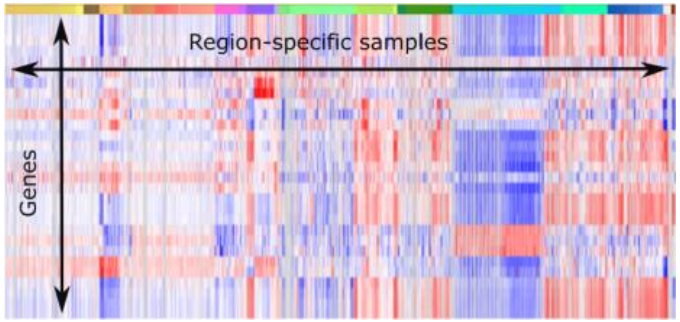




Allen Human Brain Atlas (AHBA)

- Genome-wide microarray data of the healthy brain (20,017 genes)
- 6 Adult donors (5 males & 1 female, mean age 42, range 24-57 years)
- 3,702 Samples (363-946 per donor)
- Samples: MNI coordinates, anatomical annotation





Regions of interest (ROIs)

Brain regions involved in Braak stages

Myelencephalon (**R1**, N=279)

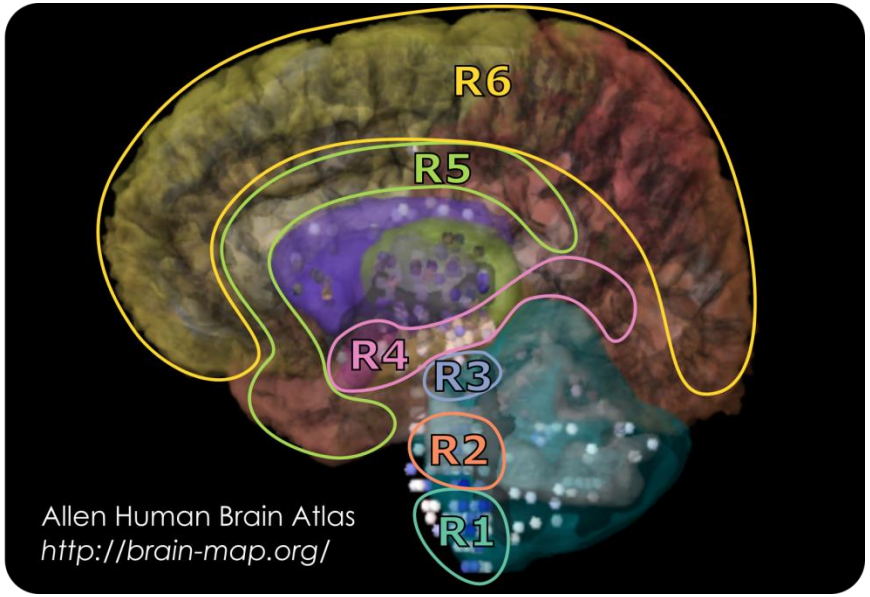
Pontine tegmentum (**R2**, N=414)

Substantia nigra, basal nucleus of Meynert, CA2 field (**R3**, N=89)

Amygdala, occipito-temporal gyrus (**R4**, N=107)

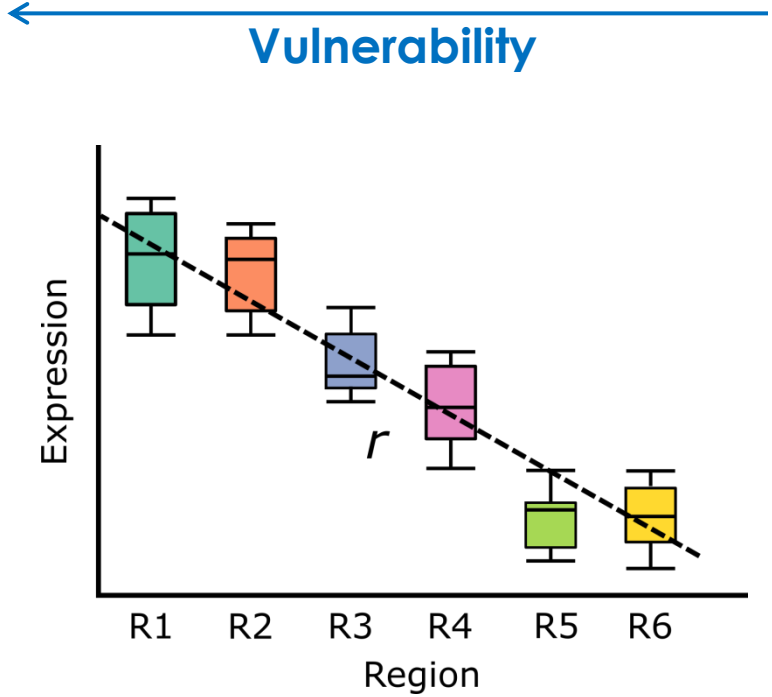
Cingulate gyrus, temporal lobe (**R5**, N=618)

Frontal lobe, parietal lobe (**R6**, N=827)



Correlation with Braak stages

Gene expression for one gene and one donor

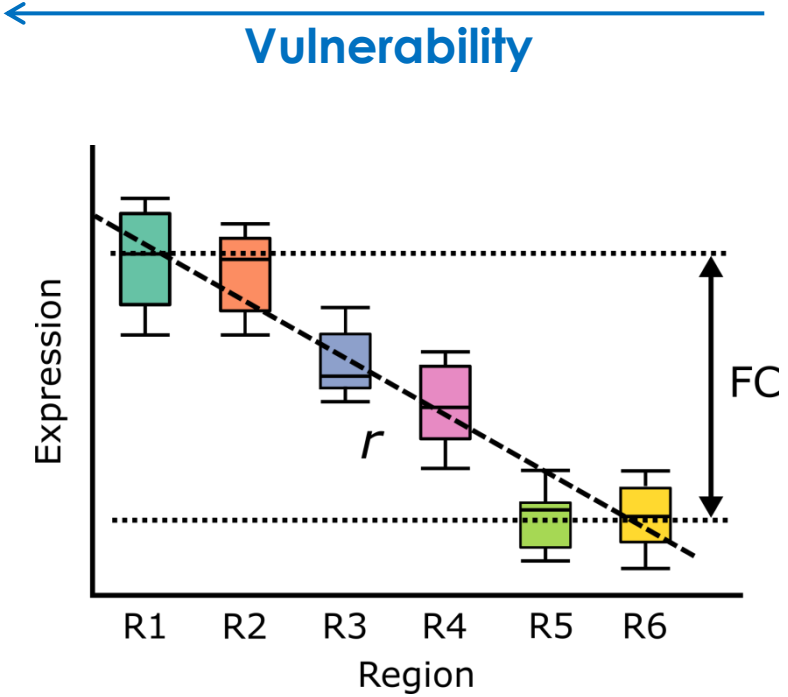


Correlation between gene expression and Braak stage labels

Fold-change (FC) between R1 and R6

Gene expression for one gene and one donor

Differential gene expression analysis

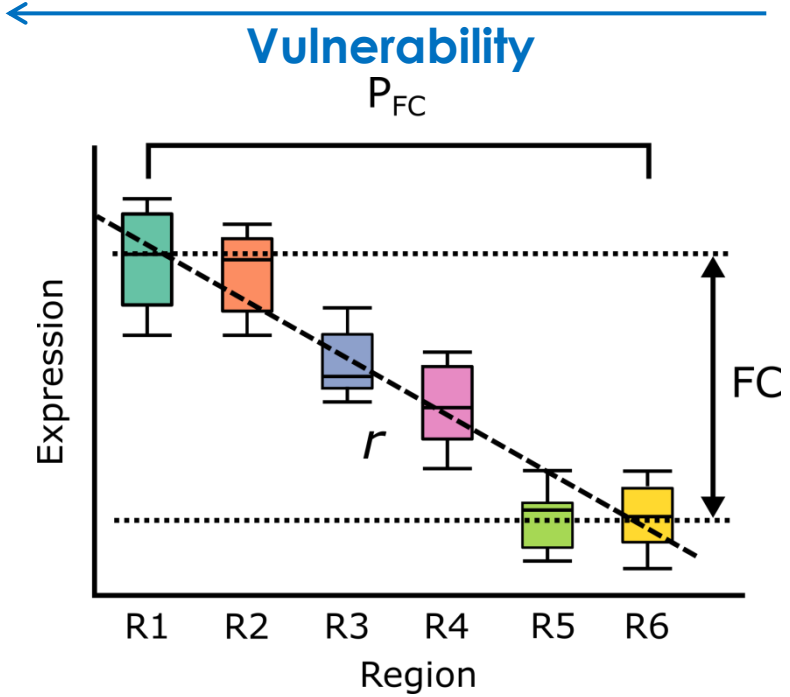


P-value of fold-change (P_{FC})

Gene expression for one gene and one donor

Differential gene expression analysis

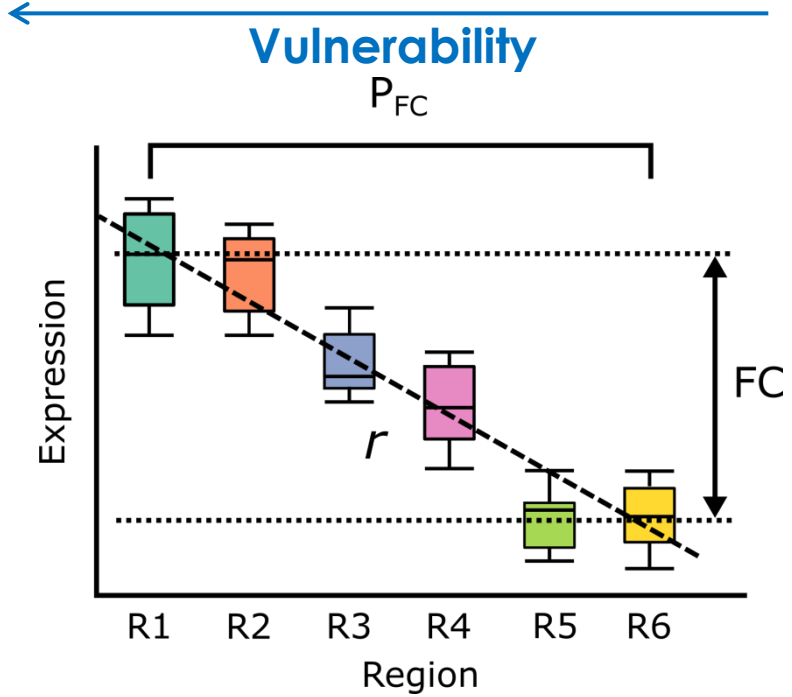
- T-test
- *P*-value corrected for multiple testing



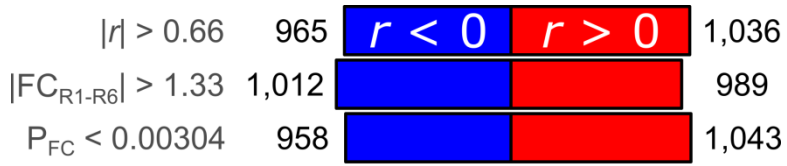
Select genes with 3 criteria

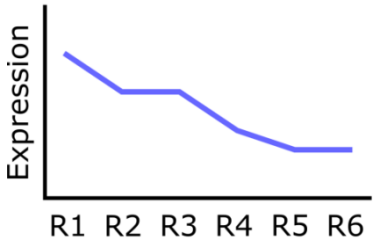
Gene expression for one gene and one donor

1. Correlation *r* with Braak stages
2. FC between R1 and R6
3. P-value of FC



Braak stage-related genes (BRGs)





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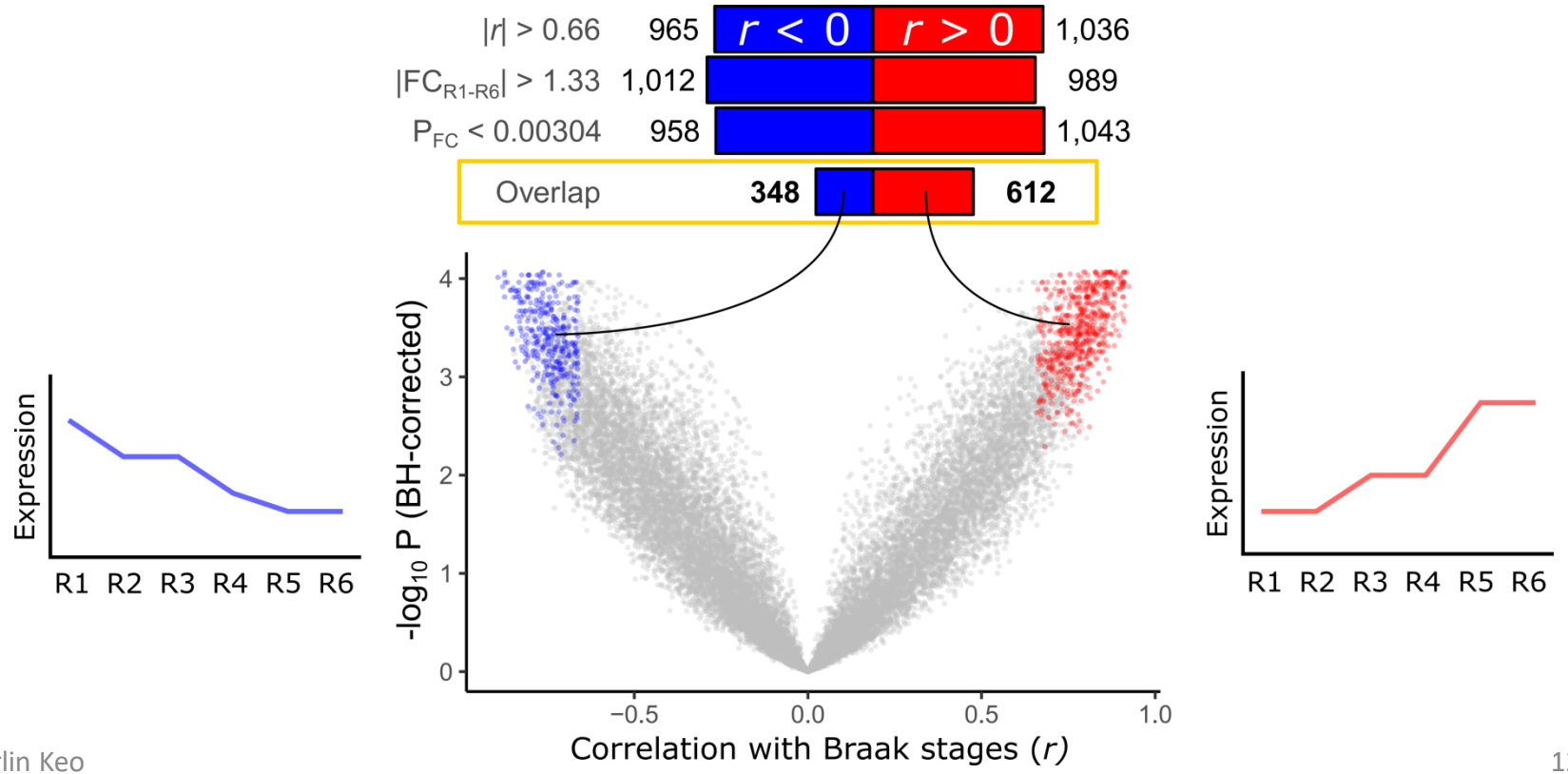
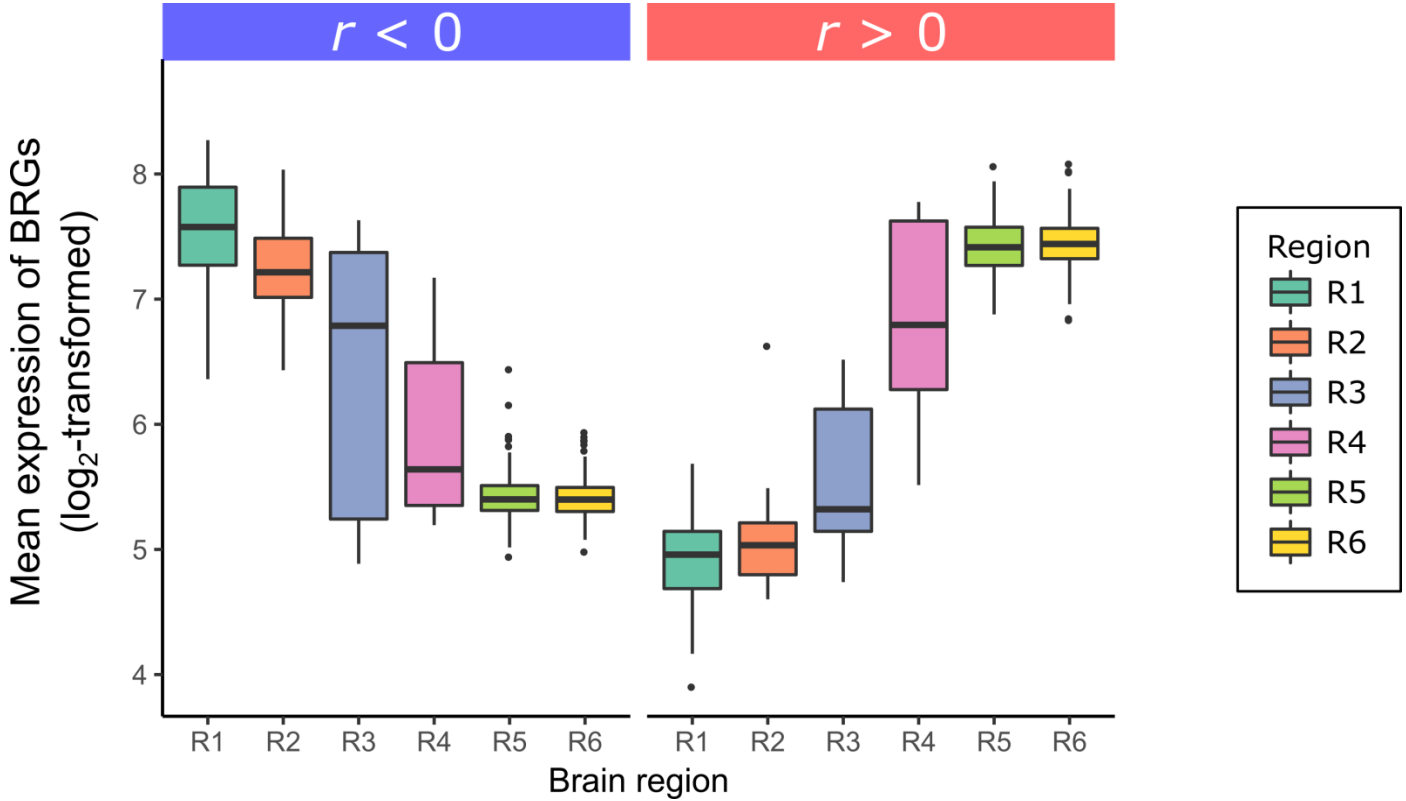
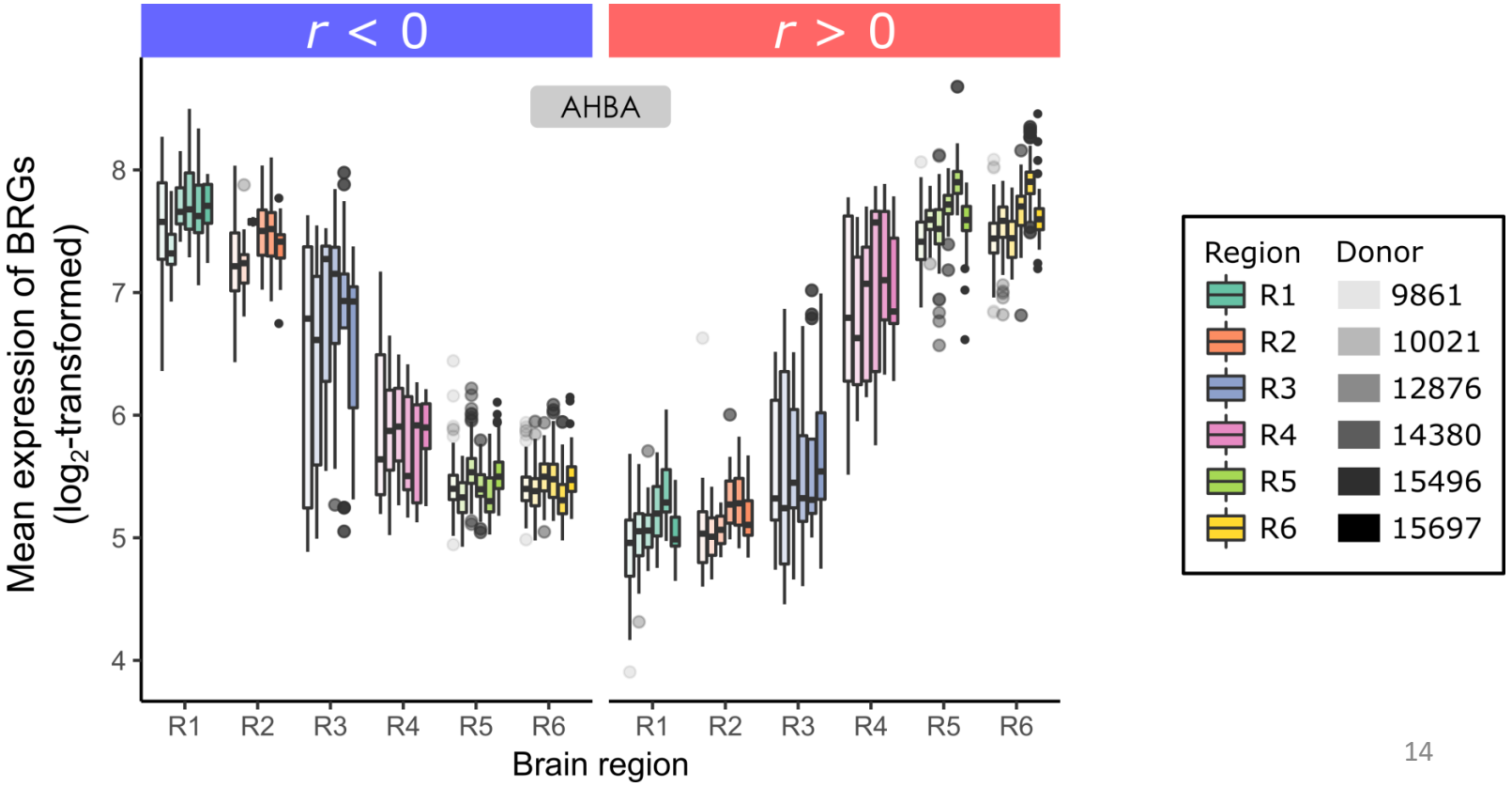


Mean expression across BRGs for one donor



Replicated across donors

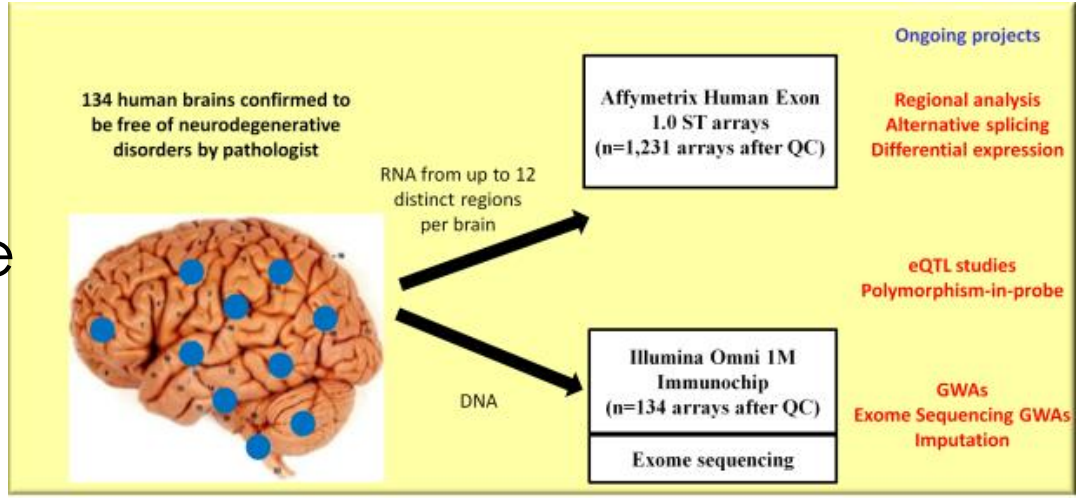


Validation in non-neurological brains

UK Brain Expression Consortium (UKBEC)

- Microarray data
- 134 Brain donors mean age 59, range 16-102 years)

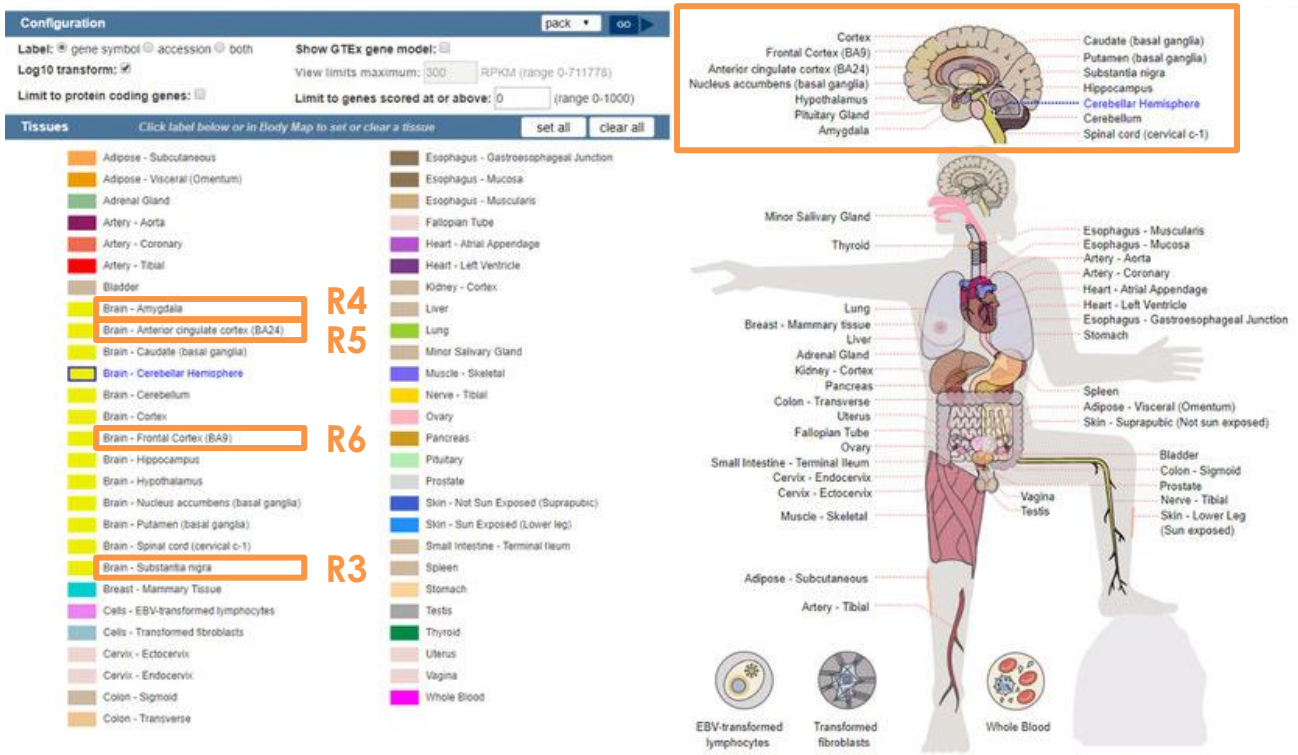
http://www.braineac.org/



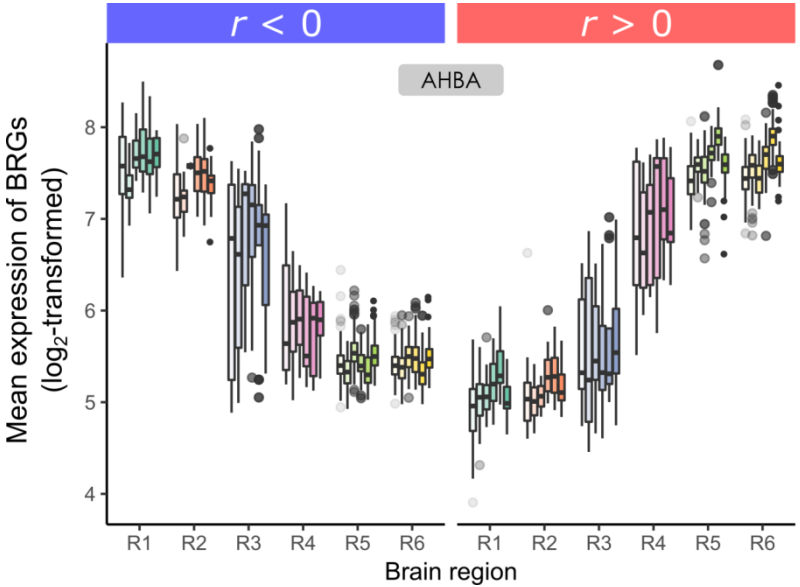
Genotype-Tissue Expression (GTEx) project

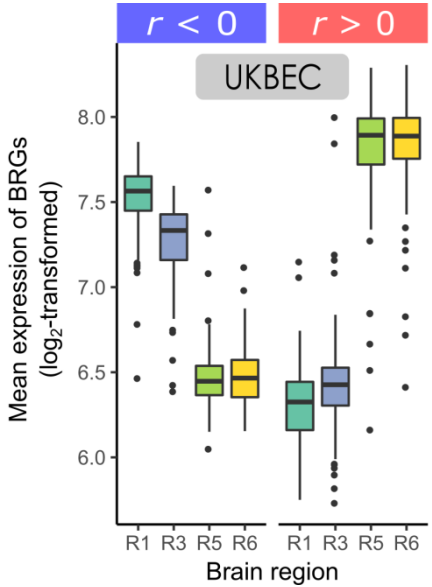
- RNA-seq data
- 751 donors
- Range 20-79y
- 88-129 samples

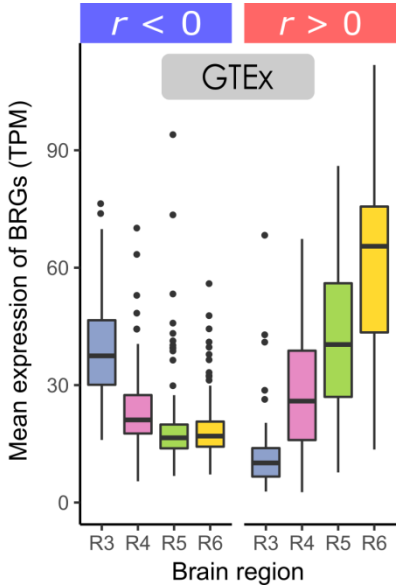
https://gtexportal.org/



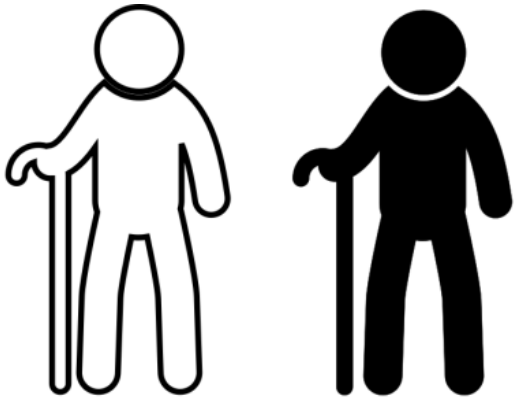
BRGs: Replication in UKBEC & GTEx

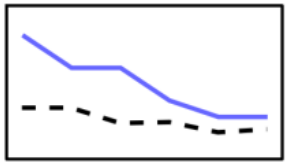


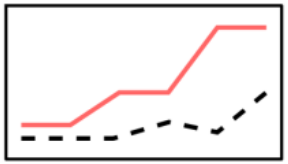




Validation in PD brains







Microarray dataset of PD brains

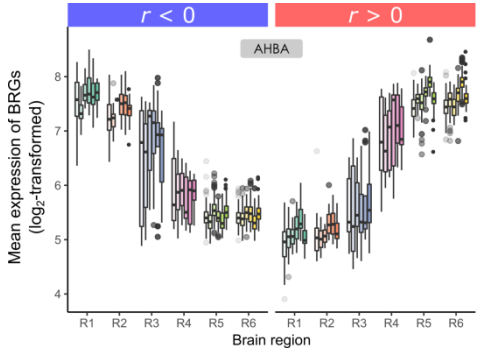
- Data from PD- and, iLBD patients, and age-matched non-demented controls
- Samples taken from the medulla oblongata **(R1)**, locus ceruleus **(R2)**, and substantia nigra **(R3)**

PD

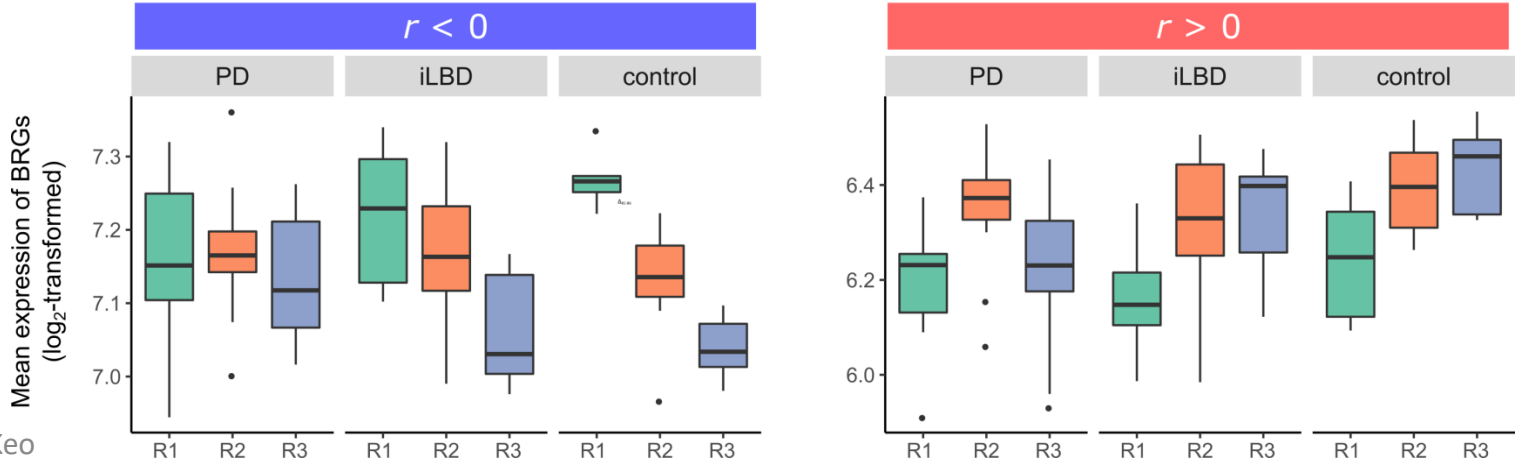
iLBD

Control

BRGs: Replication in PD brains

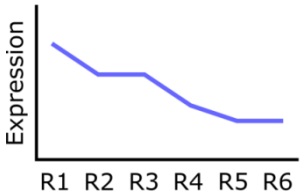


PD microarrray dataset

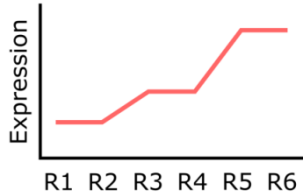


BRGs: PD-variant associated genes

Negative correlated BRGs



Positive correlated BRGs



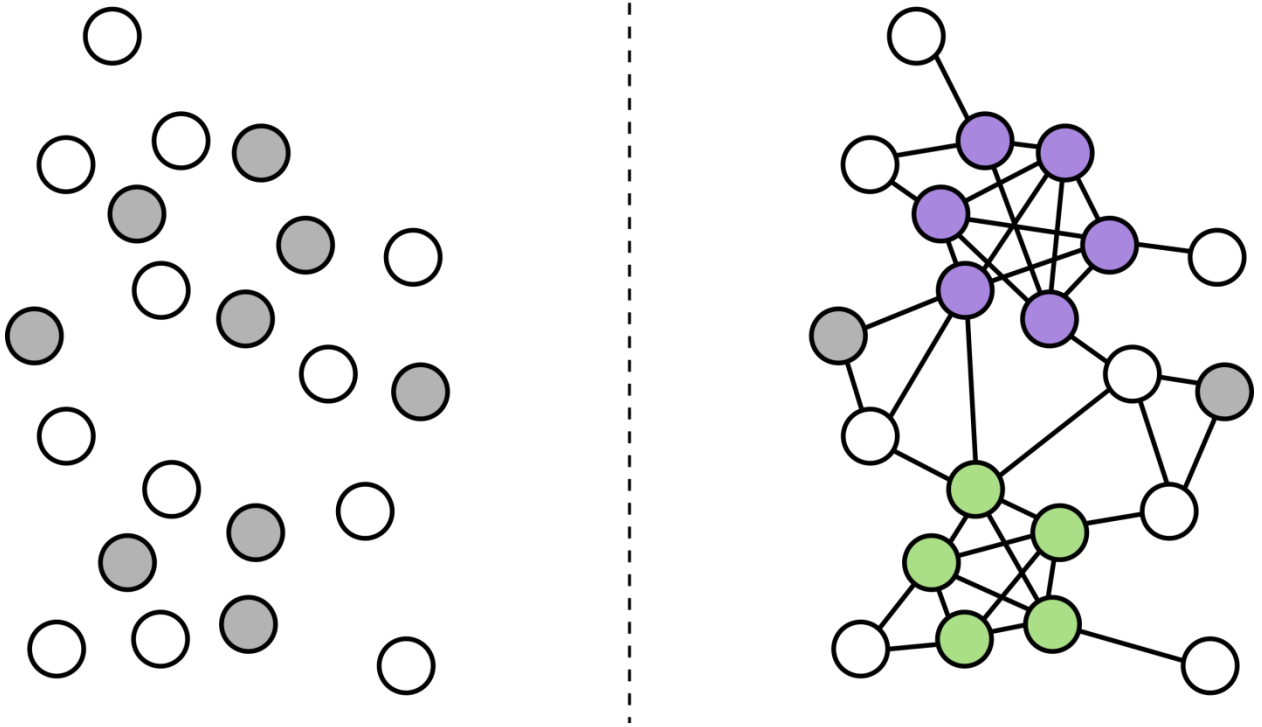
Gene	Braak correlation	Fold-change	P-value (BH-corrected)	Reference
SCARB2	-0.78	-1.44	1.7E-03	Nalls et al. 2014
ELOVL7	-0.67	-1.35	1.4 E-03	Chang et al. 2017
SH3GL2	0.70	1.40	2.3E-03	Chang et al. 2017
SNCA	0.70	1.75	4.3E-04	Bonifati et al. 2014, Chang et al. 2017, Nalls et al. 2014
BAP1	0.77	1.99	1.6E-03	Chang et al. 2017
ZNF184	0.81	2.34	2.9E-03	Chang et al. 2017

Summary so far…

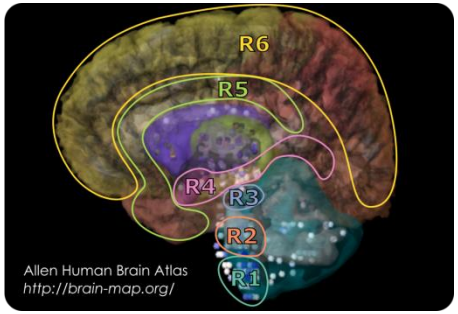
- AHBA to identify Braak stage-related genes (BRGs)
- Expression patterns are replicated in non-neurological brains, and diminished in PD brains
- BRGs include known genetic risk factors for PD

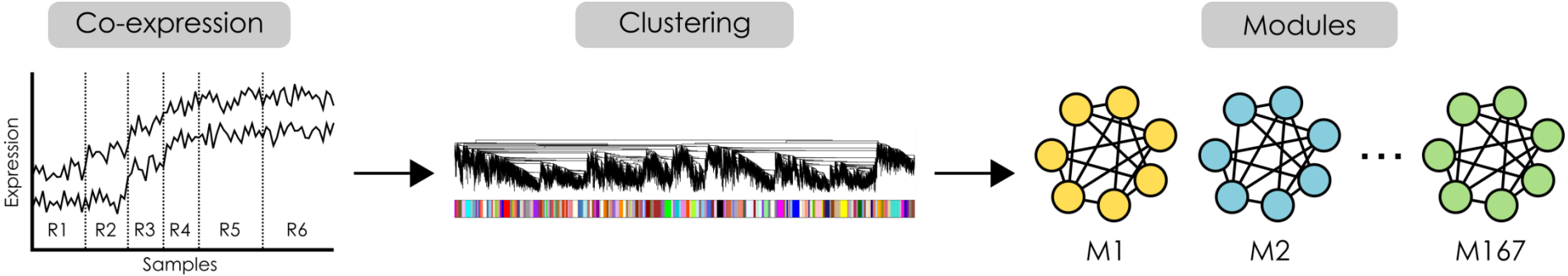
- BRGs may influence vulnerability at regional level as well as between PD patients and controls

Single genes -> groups of genes (modules)



Clustering 20,017 genes

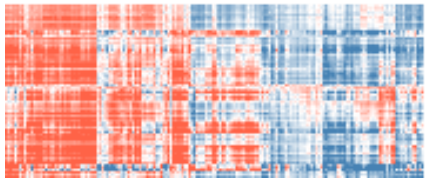




Module -> module expression

One module

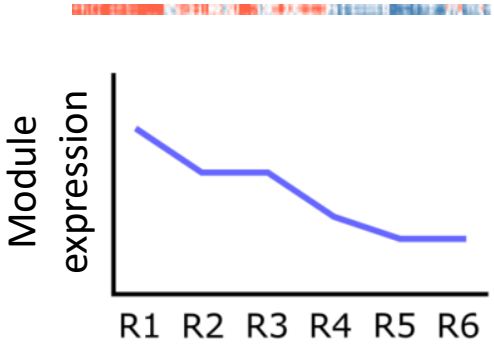
Genes



Samples (ROIs)

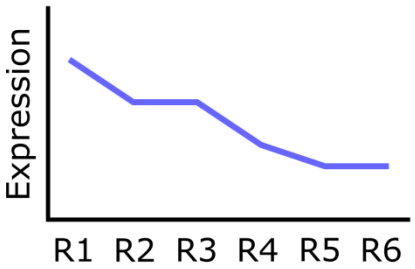
PCA

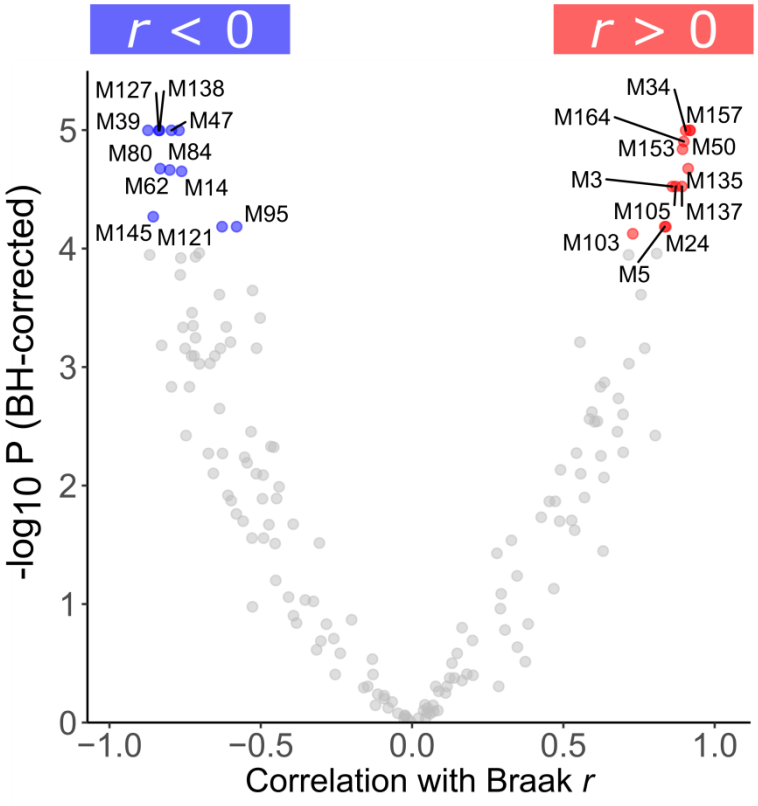
Eigengene expression

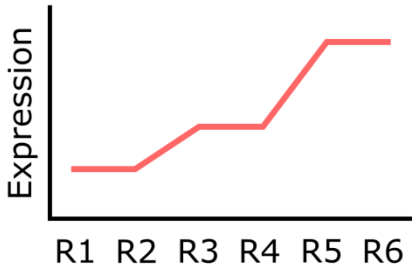


Braak co-expression modules

Corrected *P*-value for testing multiple modules







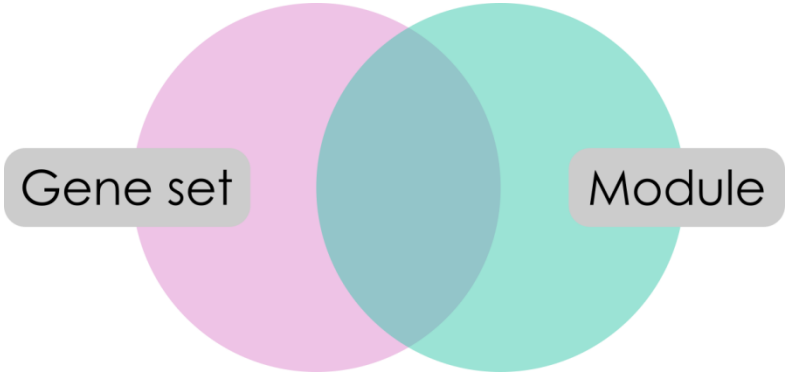
Modules enriched for specific genes

Biological functions

Diseases

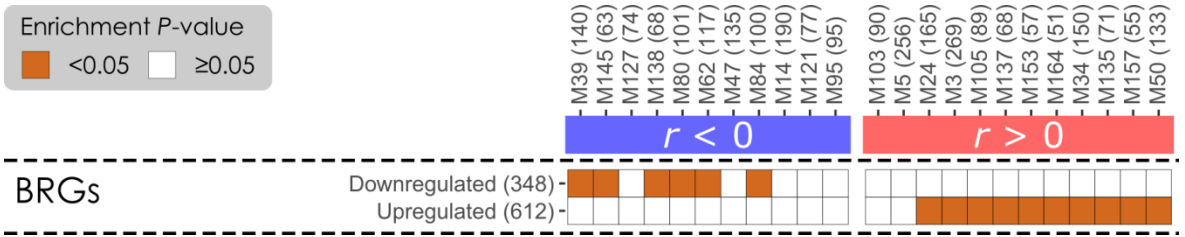
Cell-types

BRGs

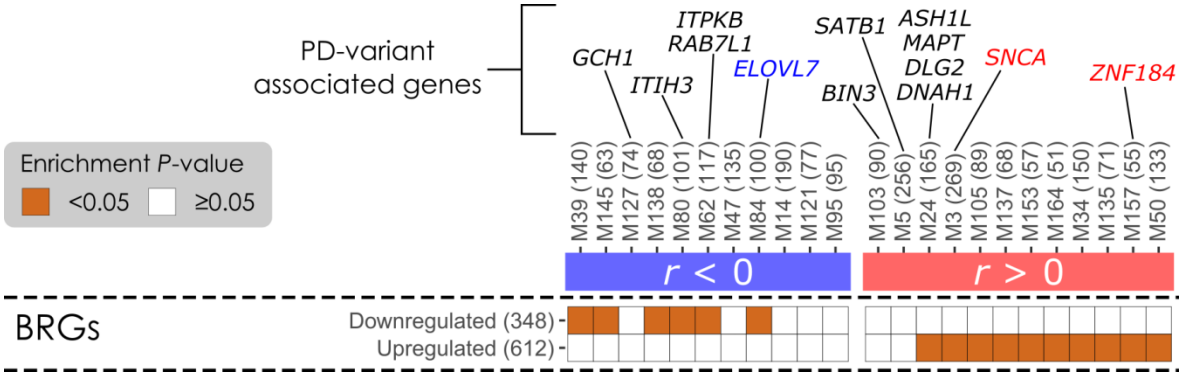


Co-expression modules

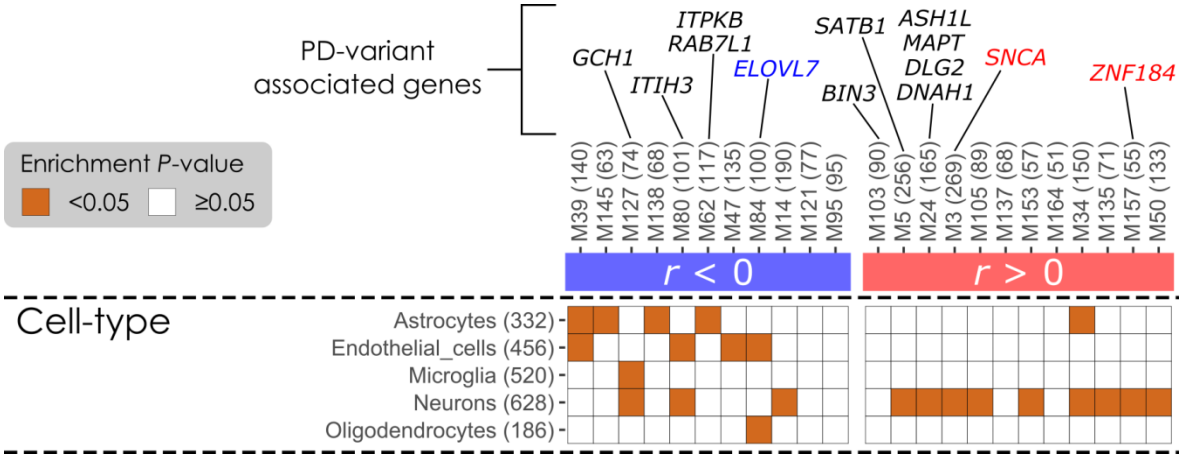
Module enrichment: BRGs



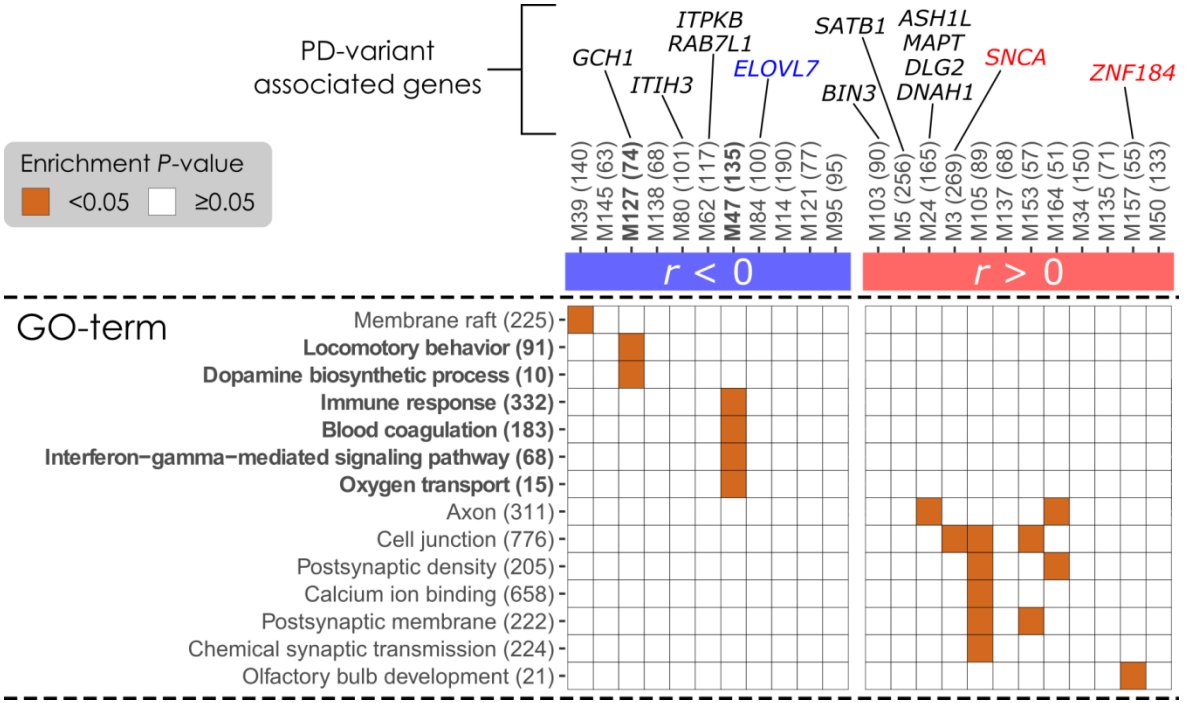
Module enrichment: BRGs



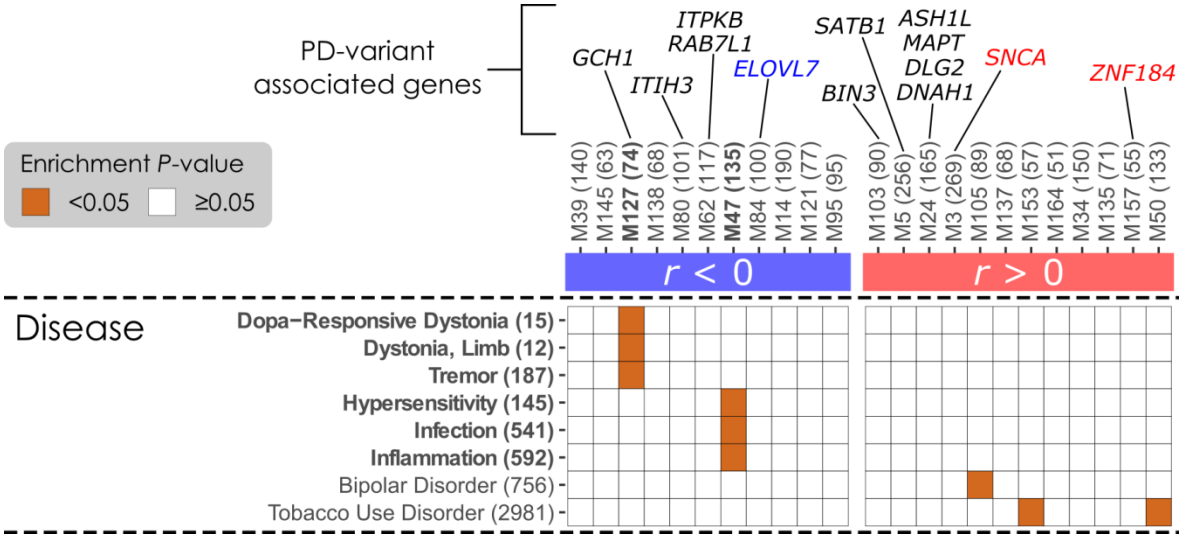
Module enrichment: Cell-types



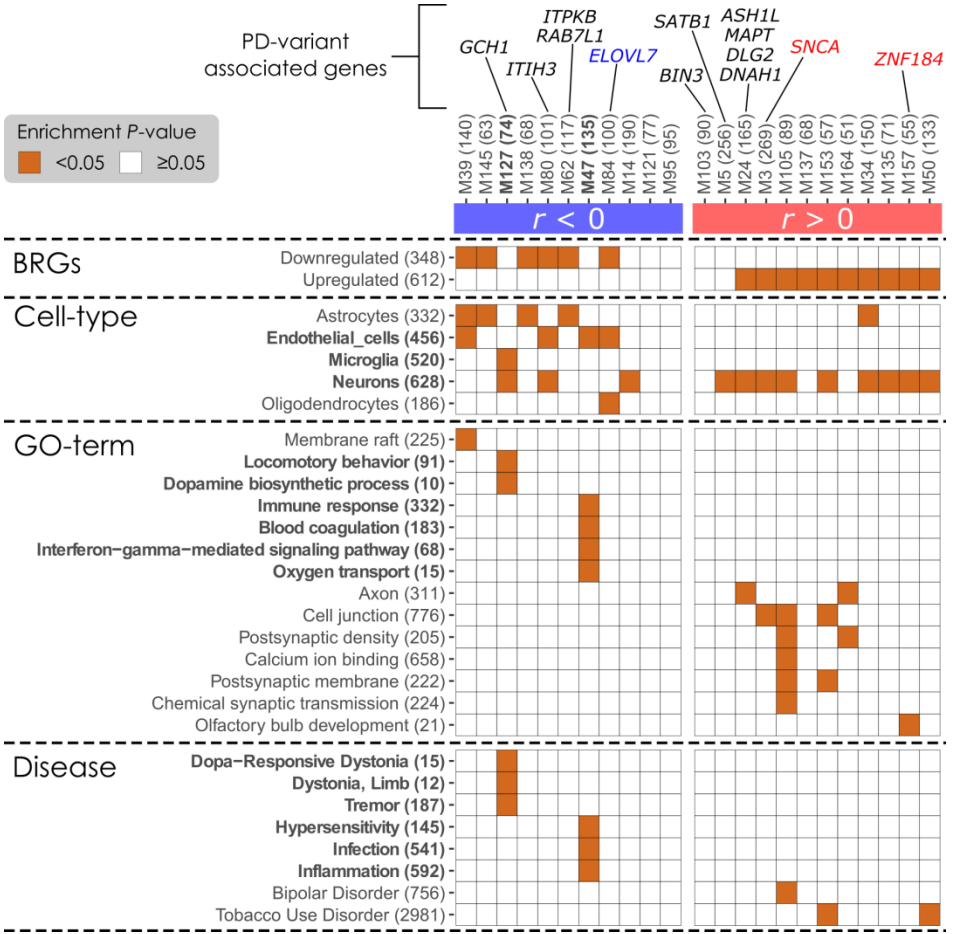
Module enrichment: GO-terms



Module enrichment: Diseases



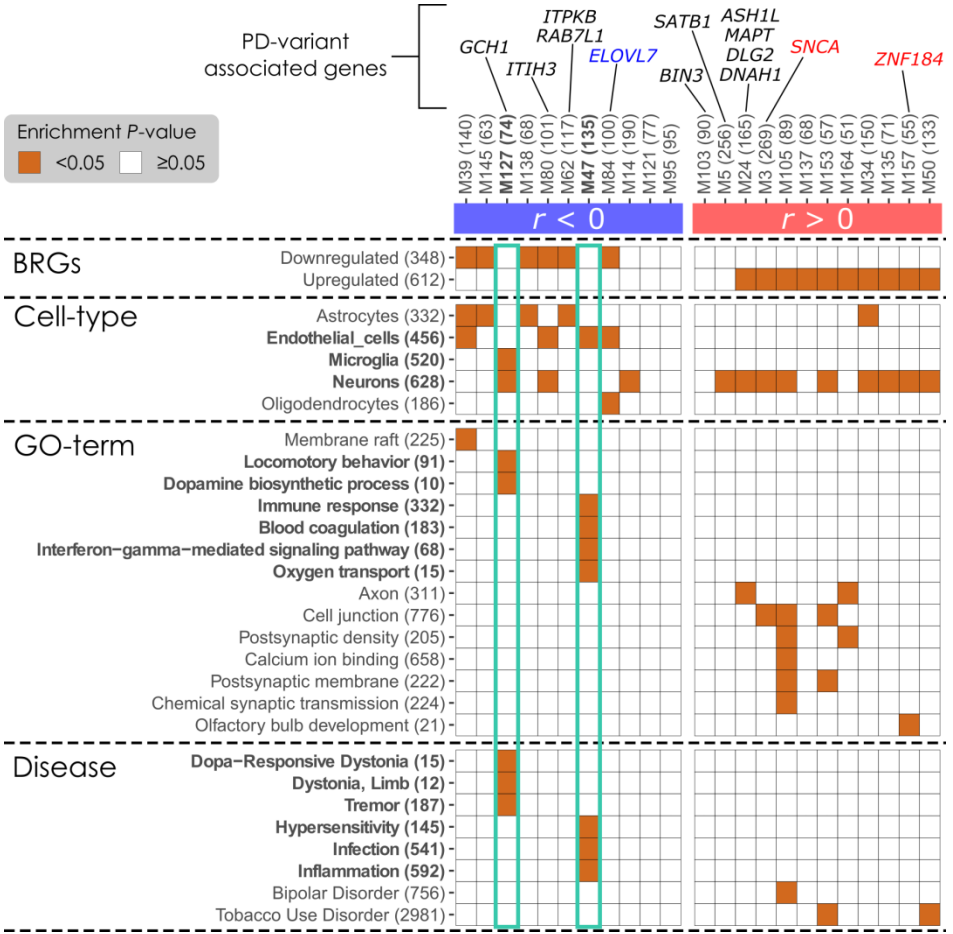
Module enrichment



Zoom in on module

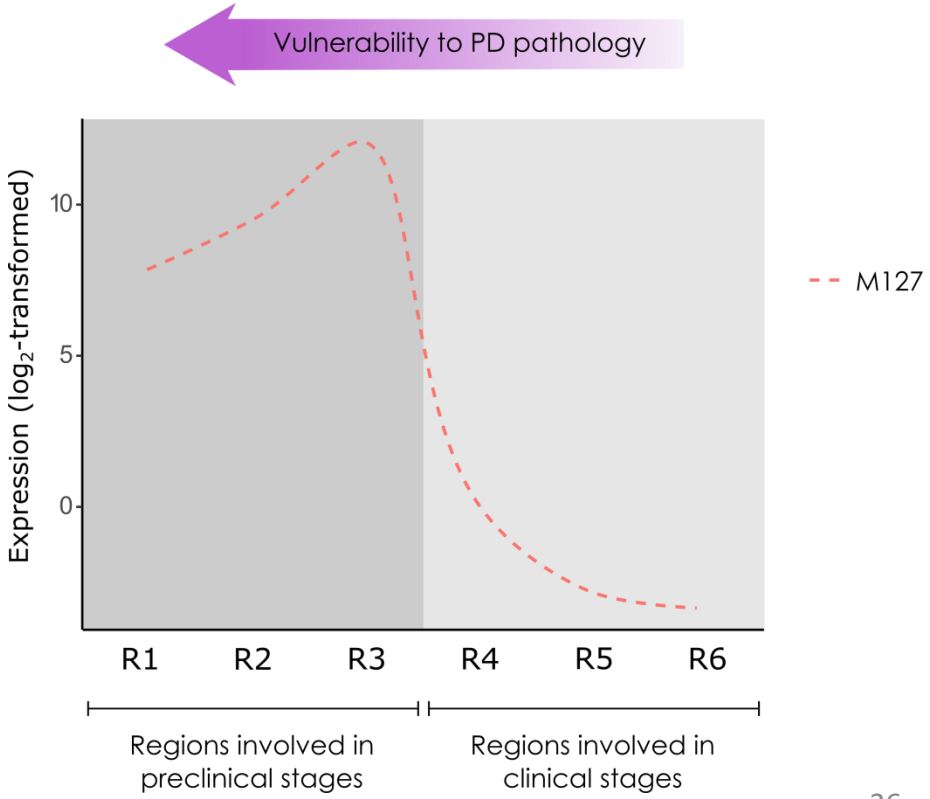
M127: Dopamine synthesis

M47: Blood oxygen transport



Expression patterns of dopaminergic genes

- M127: co-expression module involved in **dopamine biosynthetic process**



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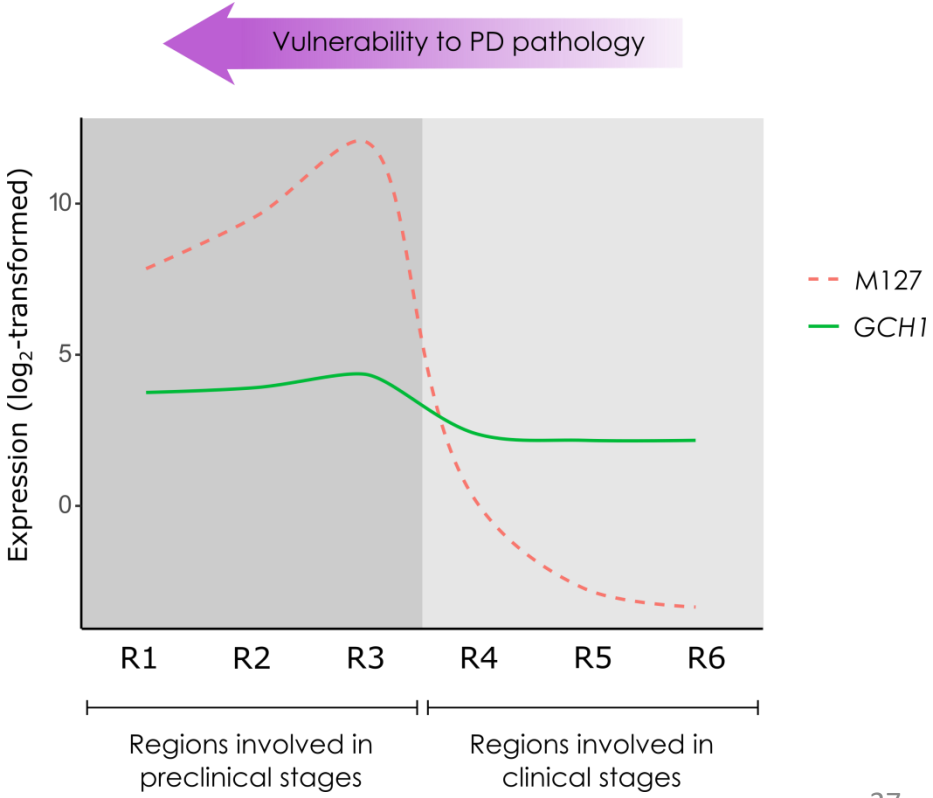
- *GCH1*: together with *TH* required for **production of dopamine**



Expression patterns of dopaminergic genes

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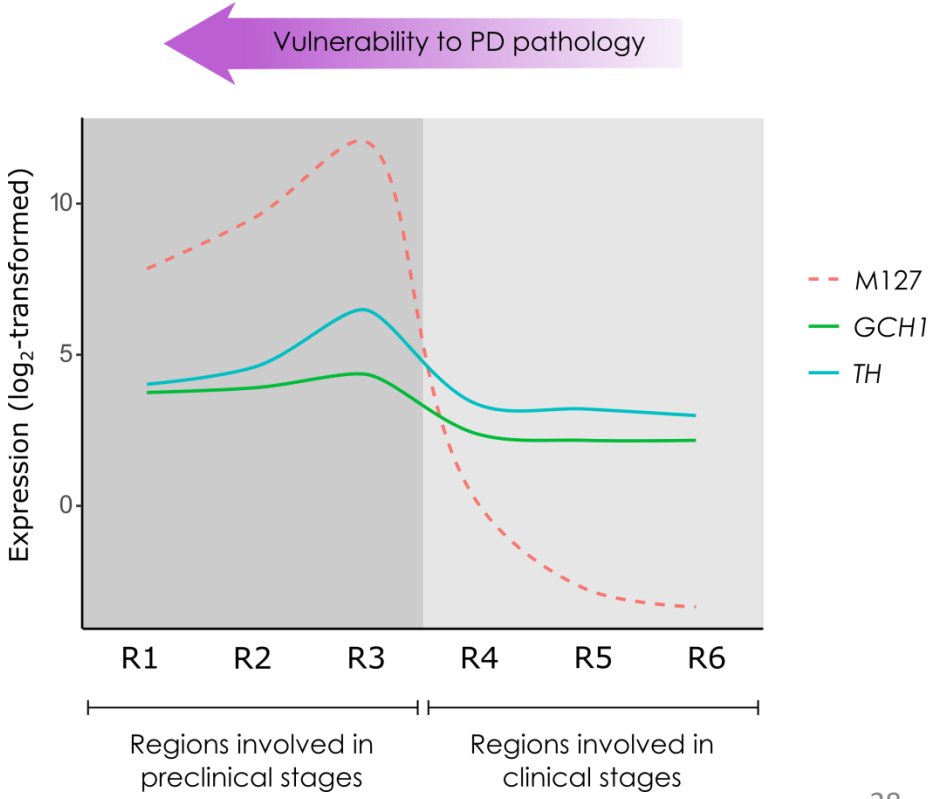

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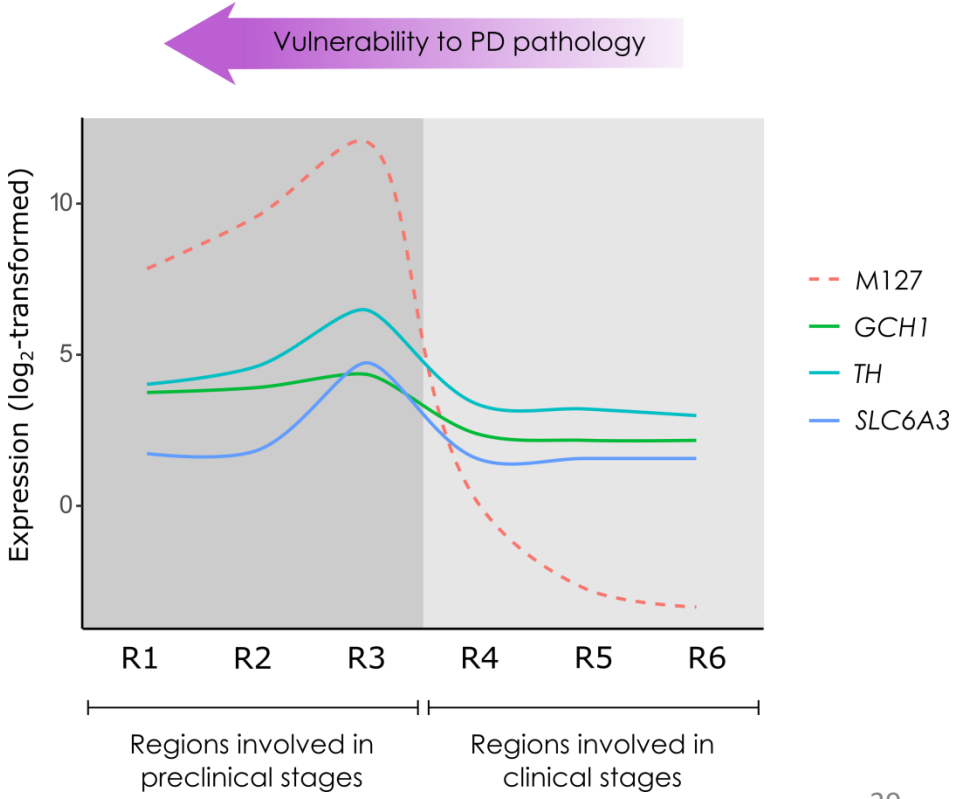
- *SLC6A3/DAT*: **transports dopamine** from the synaptic cleft back to the cytosol



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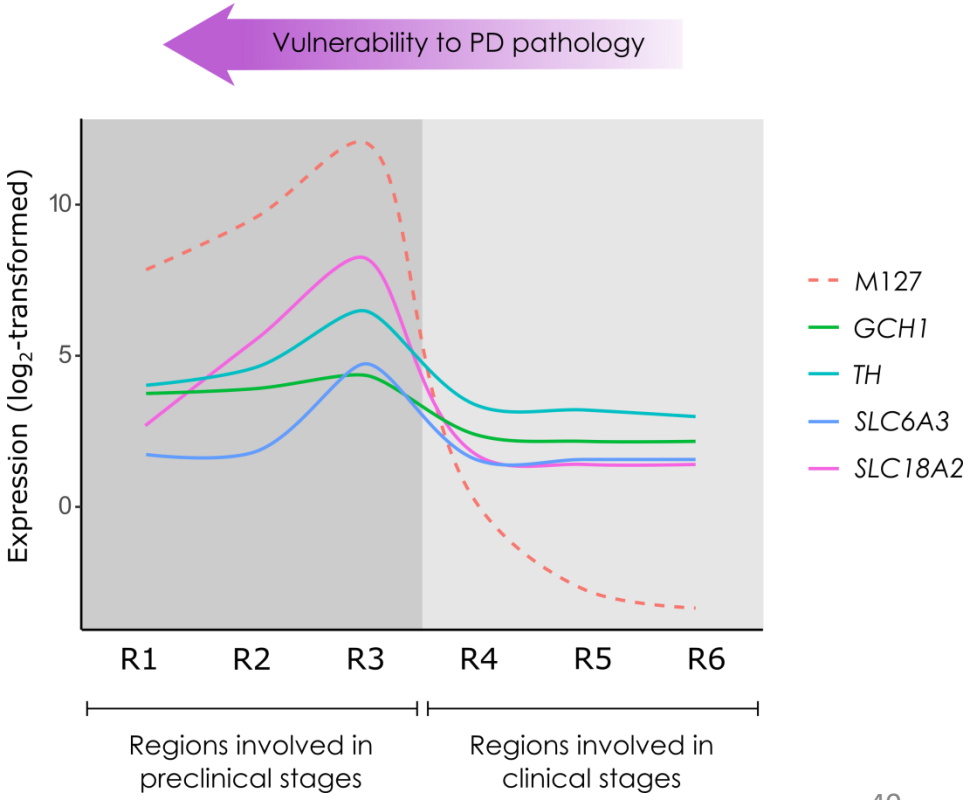
- *SLC18A2/VMAT2*: **stores dopamine** into synaptic vesicles.



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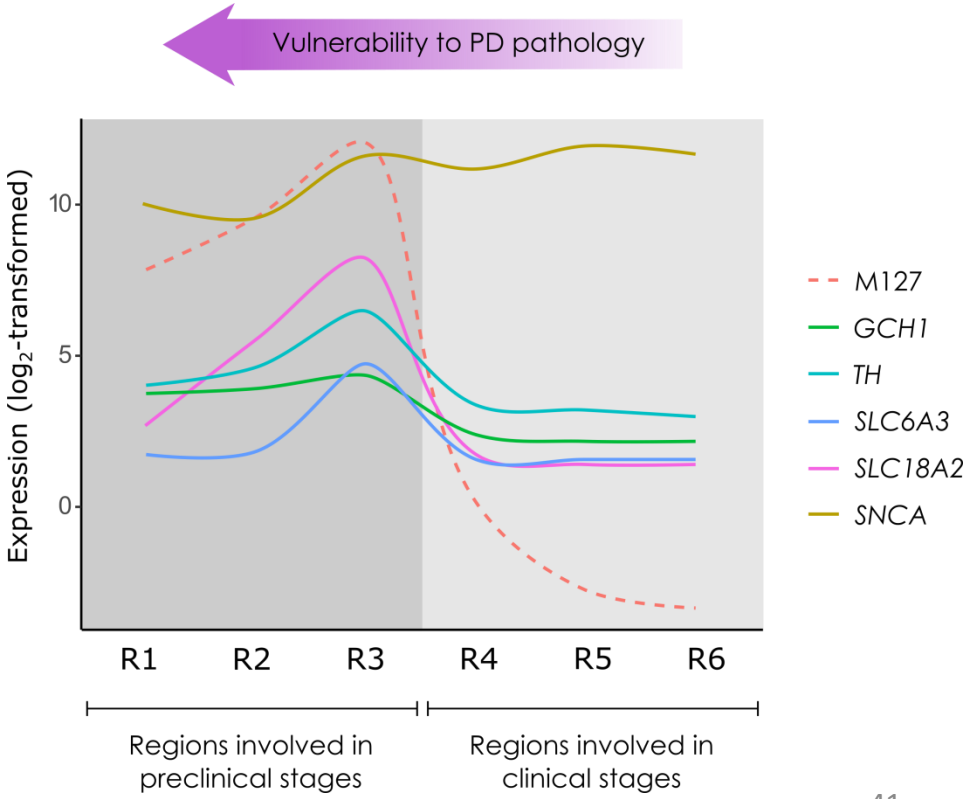
- *TH*: catalyzes tyrosine to the **dopamine precursor of L-DOPA**,
- *SLC6A3/DAT*: **transports dopamine** from the synaptic cleft back to the cytosol
- *SLC18A2/VMAT2*: **stores dopamine** into synaptic vesicles.
- *SNCA*: responsible for **dopamine release/dopamine homeostasis**



Take-home message

- We found genes and modules with expression patterns that correlated with Braak staging
- We found associations with known pathways and reveal spatial information
- Gene (co-)expression patterns need further validation in lab experiments

Summary

- Modules implicated in the dopaminergic and blood oxygen pathways related to Braak staging
- Found risk factors associated with PD

- BRGs and modules remain differentially expressed after correcting for cell-type abundance

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Braak stage-related gene *ADCY1*

AHBA