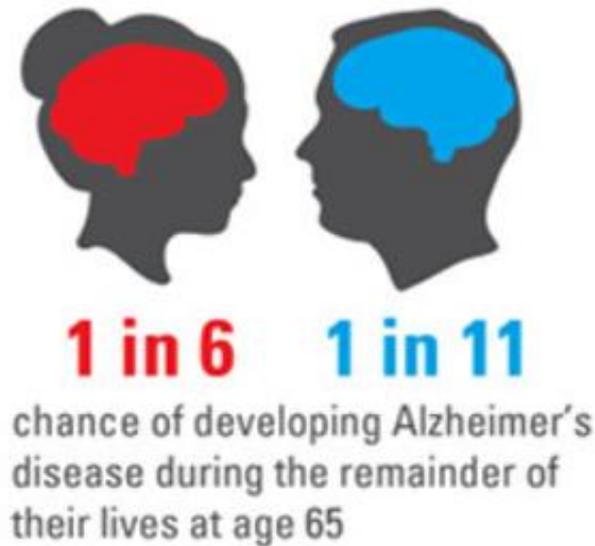# Computational analysis of sex differences
in omics data for Alzheimer's and Parkinson's disease

Enrico Glaab, Luxembourg Centre for Systems Biomedicine

Motivation: Sex differences in Alzheimer's disease (AD)

1 in 6   1 in 11

chance of developing Alzheimer's disease during the remainder of their lives at age 65

- Higher incidence rate among females in the older age groups, also when adjusting for differential survival (Gao et al., 1998)

- Females have more global AD pathology (Barnes et al., 2005), while males suffer a more aggressive disease progression and earlier mortality (Dubal et al., 2020)

- Molecular mechanisms and mediators of these sex differences are unknown

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Motivation: Sex differences in Parkinson's disease (PD)

CREDIT: Armando Barone
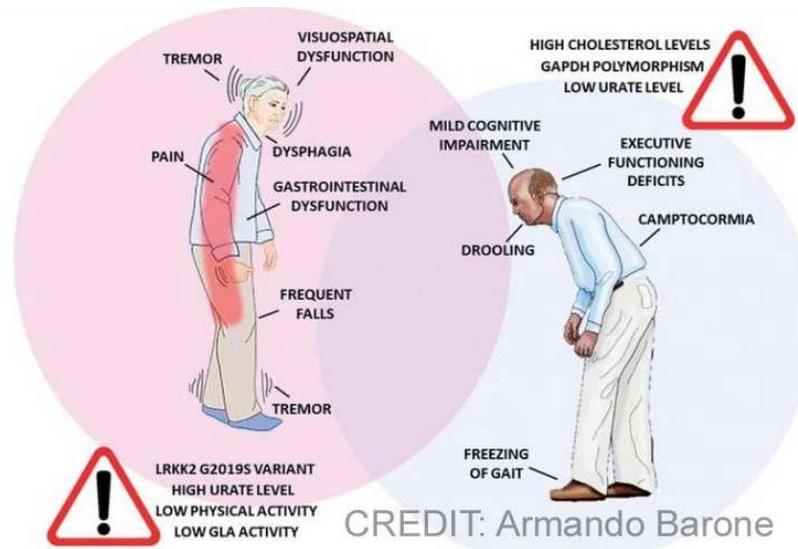
- Higher incidence rate among males for sporadic PD in most studies (Mayeux et al., 1995; Baldereschi et al., 2000, Wooten et al., 2004)

- Females present more often with tremor, associated with milder motor deterioration and striatal degeneration (Haaxma et al., 2007)

- Molecular mechanisms and mediators of these sex differences are unknown

Categorization of sex differences: Disease stage

Sex differences can affect all phases before and during a disease:
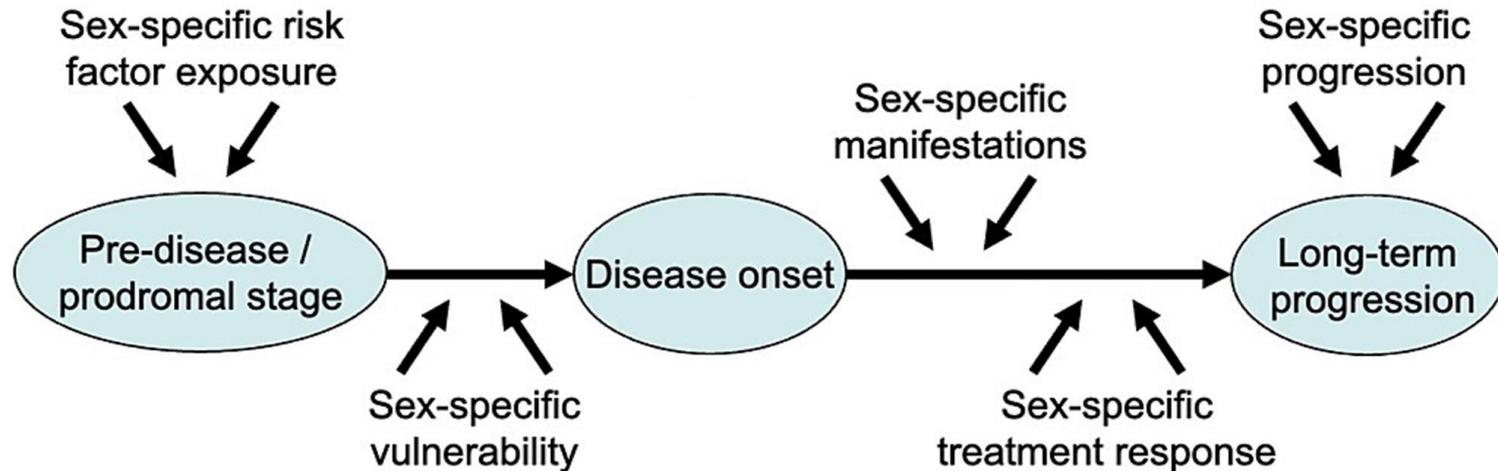
→ Each aspect of sex-specificity in disease risk, pathology, progression and treatment may require dedicated analyses

Loo et al., Brief. Bioinform., 2024

Categorization of sex differences: Molecular pattern

Disease-associated sex differences can be grouped into four patterns of changes:
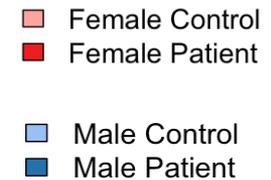
1. Sex-specific changes:

2. Sex-dimorphic changes:

3. Sex-modulated changes:

4. Sex-neutral changes:

Computational omics analysis workflow

Computational Data Pre-processing

- Quality Control & Filtering (depending on omics type)
- Cell Type Annotation Clustering (for single-cell data)

Sex-dependent Analyses

| Gene/protein/metabolite-level analysis | Pathway-level analysis | Gene Regulatory Network Analysis | Cell-Cell Communication |

Types of sex differences identified:

- **Female-specific** — Changes only in females
- **Male-specific** — Changes only in males
- **Sex-dimorphic** — Opposite changes in sexes
- **Sex-modulated** — Diverse magnitude of changes

Sex-dependent Regulatory Networks

Gene1 → Gene2, Gene3, Gene4
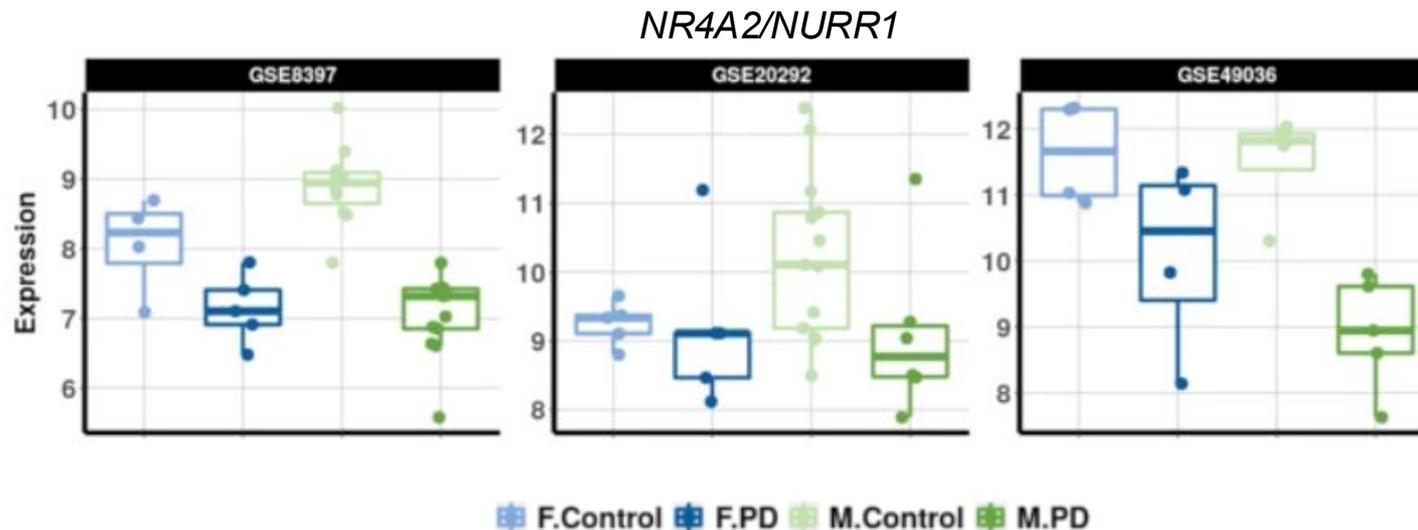
- Key regulator
- Target genes
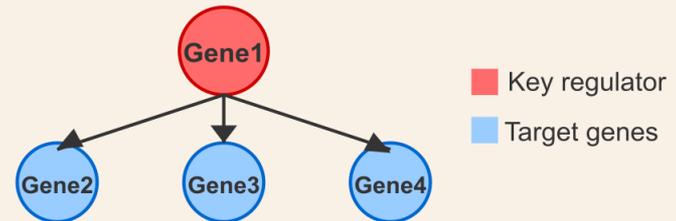
Application to Parkinson's disease: Omics meta-analysis
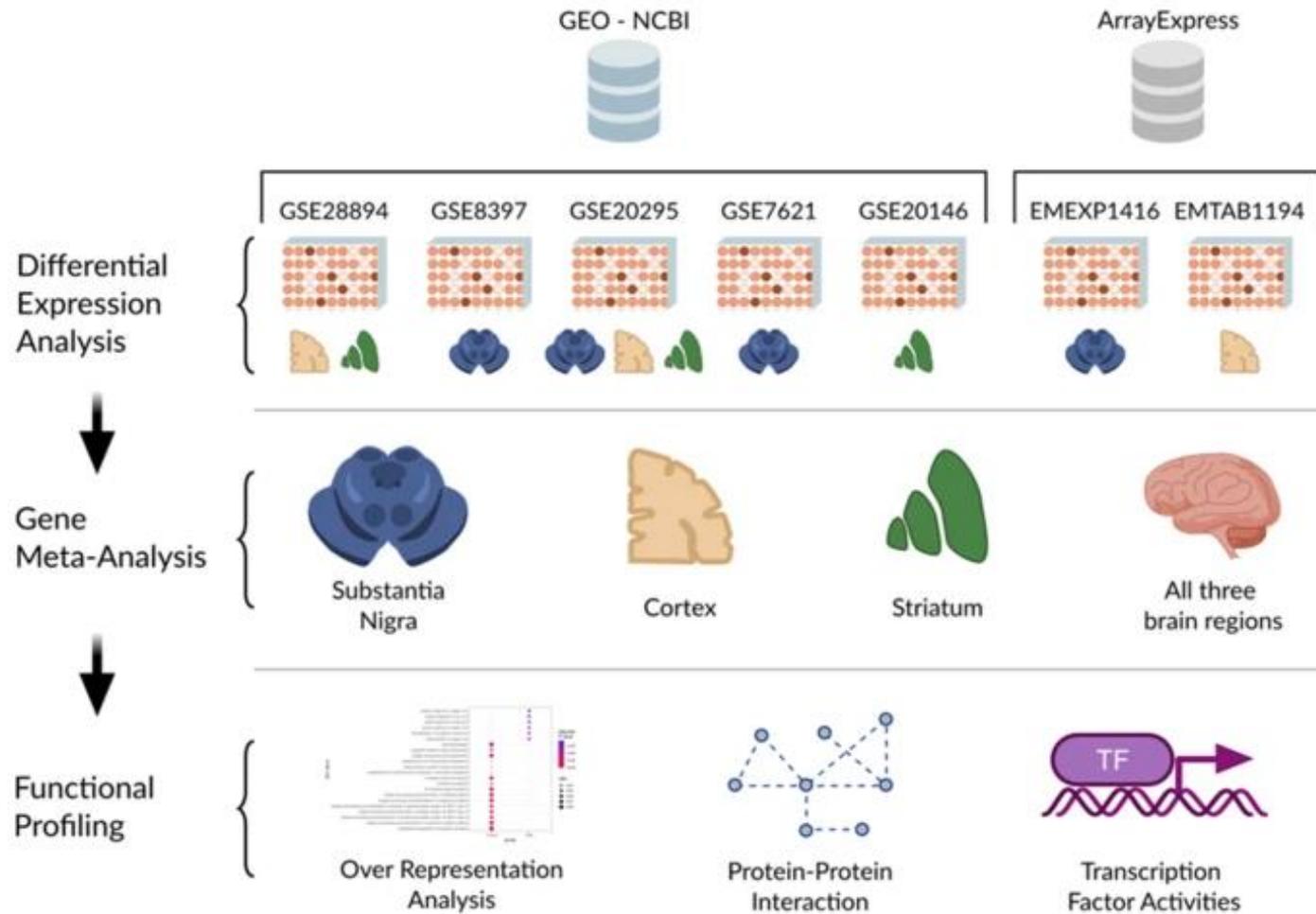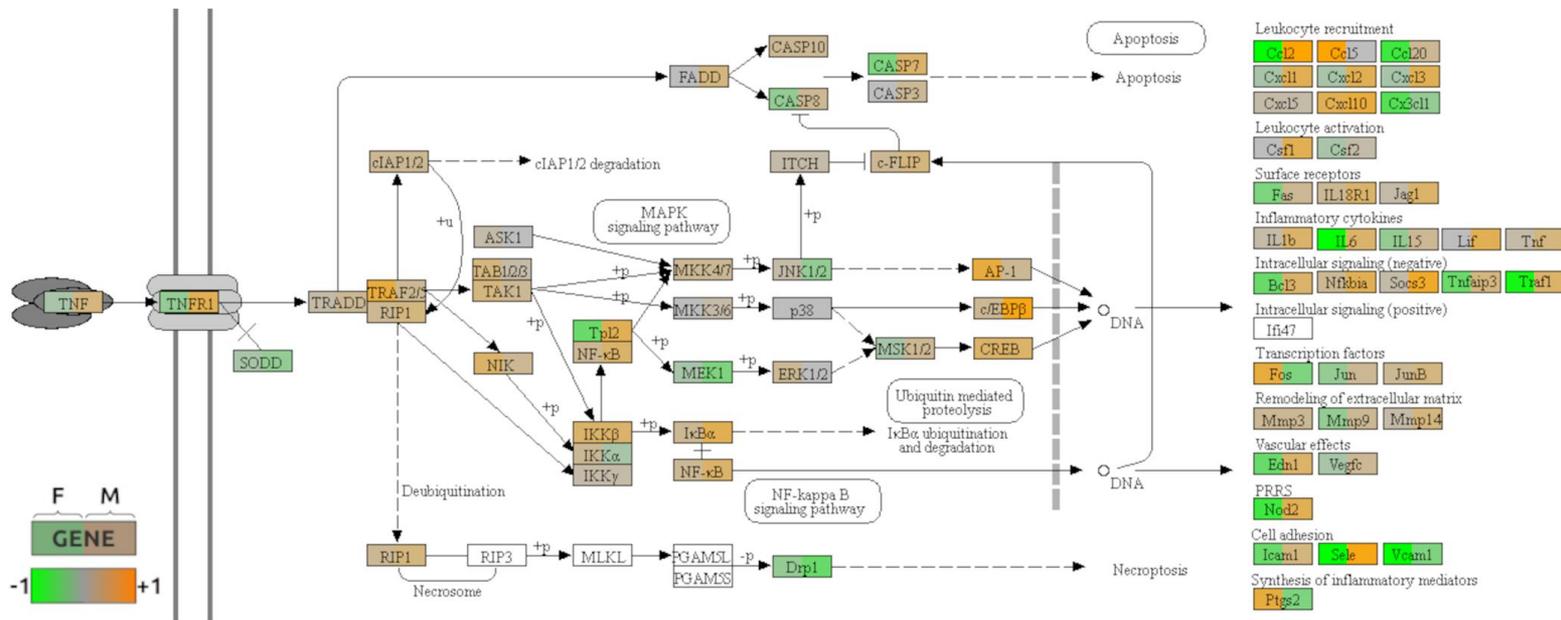
PD transcriptomics: Gene-level analysis

- Several sex-dependent differentially expressed genes (DEGs) identified

- Many top significant genes have well-known functional associations with PD

- Example: *NR4A2* → dopamine metabolism regulator, mutations in familial PD

NR4A2/NURR1

→ sex-modulated expression: significantly stronger changes in males

PD transcriptomics: Pathway analysis

- Enrichment of sex-dependent DEGs in pathways (KEGG, GO, Reactome)

- Main changes in mitochondrial and inflammatory response pathways

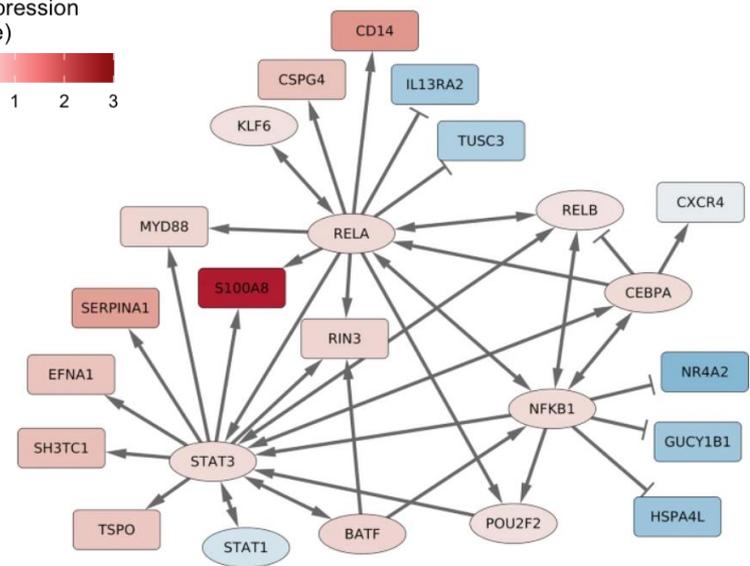- Example: TNF signaling pathway (KEGG)

PD transcriptomics: Regulatory network analysis

- Transcription factors (TFs) with sex-dependent changes & sex differences in their downstream target genes were identified

- Multiple of these TFs are members of the statin or NFκB family (e.g., STAT3)
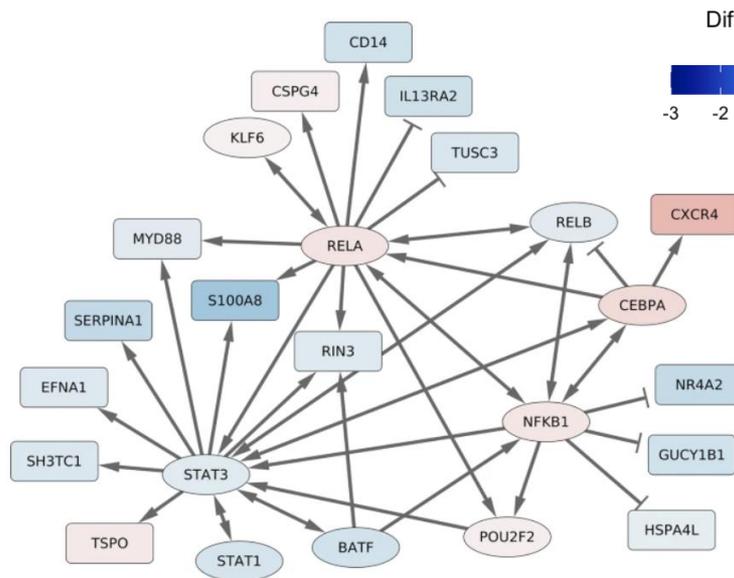
STAT3 network: logFC in males

STAT3 network: logFC in females

Tranchevent et al., npJ Parkinsons Dis., 2024

Alzheimer's disease (AD): Project overview

Step 1: Collect gene expression data from *post-mortem* cortical tissue of AD

patients and two mouse models of early AD-like pathology

Step 2: Compare disease-associated sex-dependent changes in mice & humans

at gene-, pathway- and network-level

Amyloid-beta model (Tg2576, age: 6M)

Tau model (THY-Tau22, age: 7M)

Sex-dependent Analysis

Differential Expression

Pathway Enrichment

Gene Regulatory Network Analysis
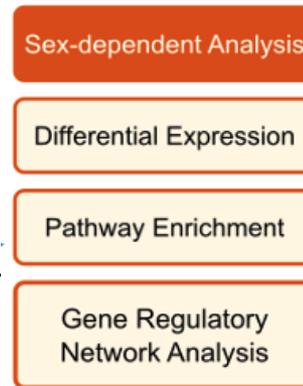
Alzheimer patients

Overlap between disease models and species

Shared sex-dependent DEGs across two mouse models and human AD:
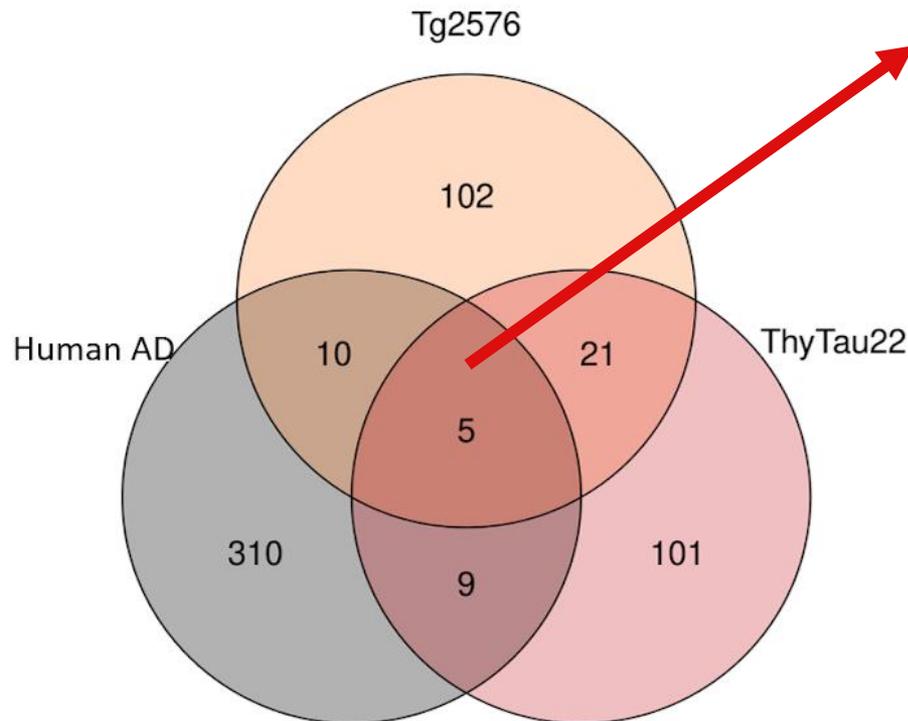
Genes with shared significance:

- *MBP*   (myelin binding protein)

- *PLP1*   (myelin proteolipid protein 1)

- *MALAT1* (lncRNA)

- *HSP90AA1* (heat shock protein)

- *ACTB* (actin beta)

Ali et al., Cell Death Dis., 2024

Sex-dependent pathway alterations

Pathways enriched in sex-specific changes in models of AD-like pathology:
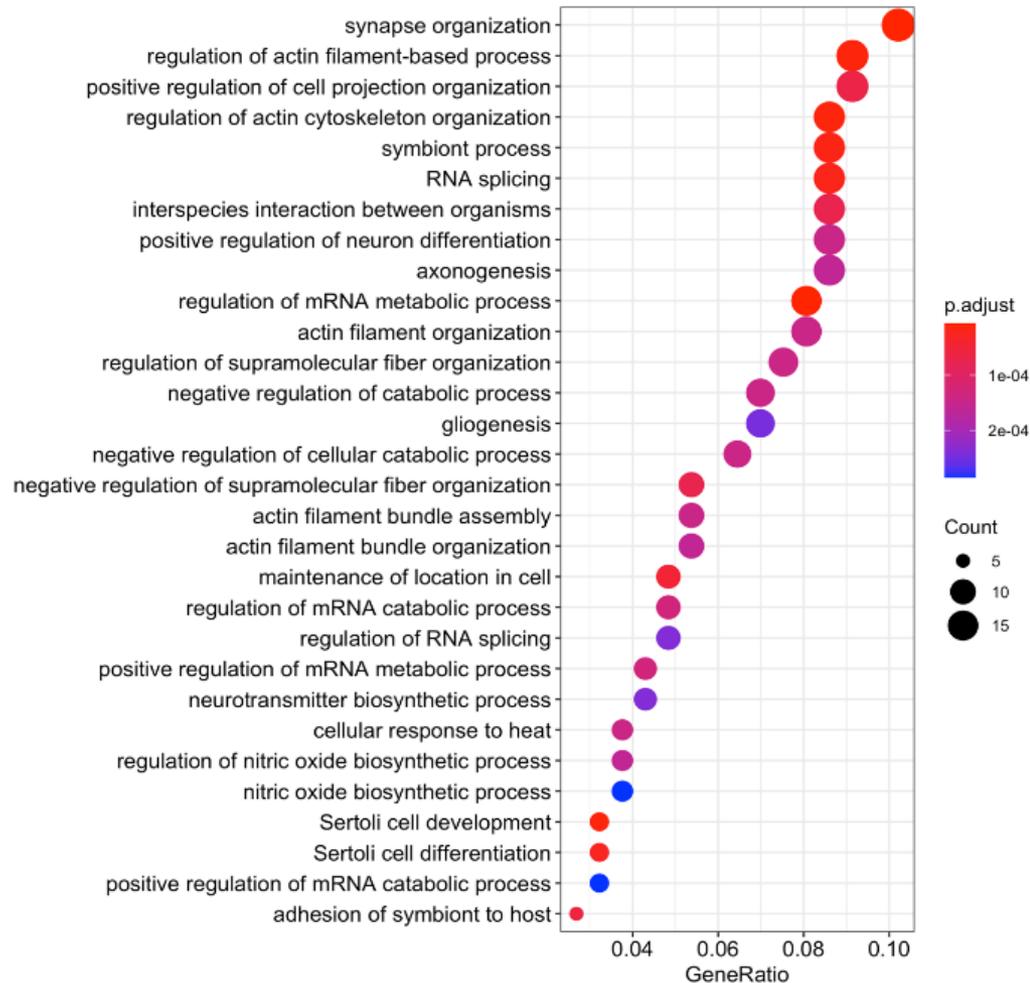
Goal: Find coordinated and consistent activity changes in gene regulatory networks

→ *Egr1* (early growth response 1) identified as key regulator of sex-dependent changes

→ *Egr1* is modulated by 17β-estradiol and upregulates acetylcholine-esterase (Hu et al., 2019)

→ *Egr1* inhibition is protective in the 3xTG model (Qin et al., 2017)
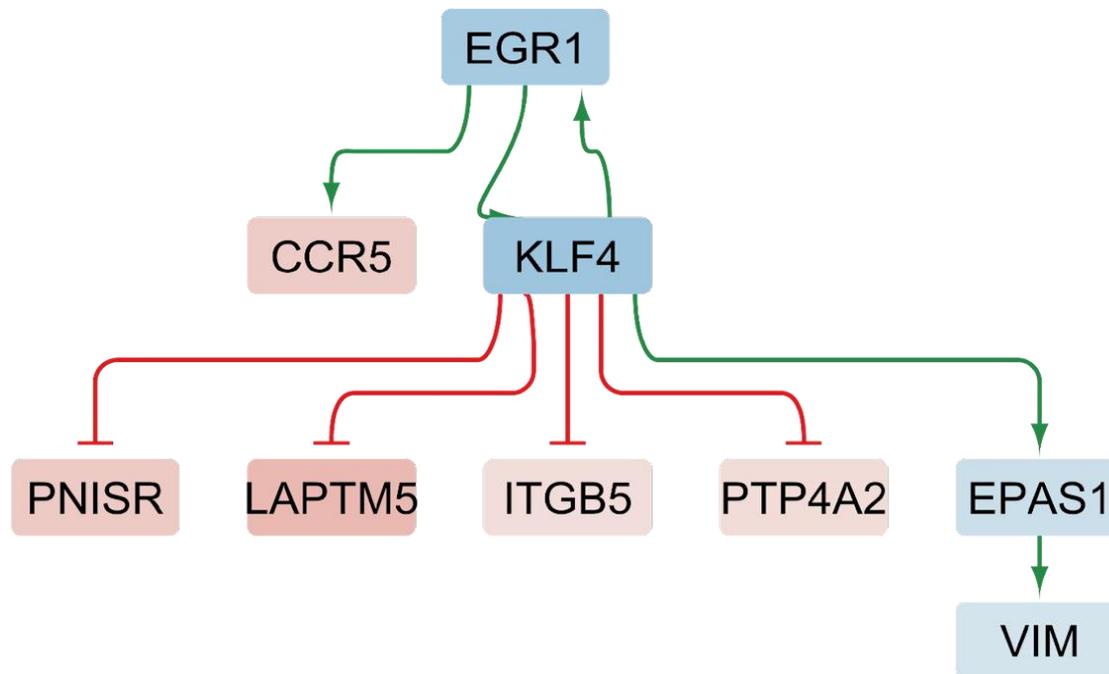
Summary & Conclusion

- Significant disease-associated sex differences in AD and PD for individual genes, pathways and sub-networks

- PD: Main changes in mitochondrial and inflammatory pathways; key transcription factors associated with dopamine metabolism (*NR4A2*) and NF-κB and STAT3 signaling pathways

- AD: Main changes in synapse organization, RNA splicing, and gliogenesis. The key regulatory gene *Egr1* upregulates acetylcholine-esterase, and its inhibition is protective in the 3xTG model.

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Thank you!

- **Biomedical Data Science Group**

- **Collaborators (national & international)**

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