



Bioinformatics Analysis for Understanding the Biology of Aging

Chemical and Biological Systems Engineering Laboratory

Sudharshan Ravi^{1,2} and Rudiyanto Gunawan^{1,2,3}

¹Institute of Chemical and Bioengineering, ETH Zurich, Switzerland

²Swiss Institute of Bioinformatics, Lausanne, Switzerland

³Department of Chemical and Biological Engineering, University of Buffalo, NY, USA

Sunday, October 28, 2018

4:24 PM

Westin Convention Center – Butler

DCHAB

Departement Chemie und
Angewandte Biowissenschaften

ICB

Institute for Chemical
and Bioengineering



Swiss Institute of
Bioinformatics



University at Buffalo

The State University of New York

18AIChE
Annual Meeting, Pittsburgh, PA

Sudharshan Ravi | 28-Oct-18 | 1



Motivation

→ Aging is a systems disease

- Aging is a complex, multifactorial process.
- Unprecedented advances in aging research shows hallmarks of aging.



The Hallmarks of Aging, *Cell*, 153, 2013



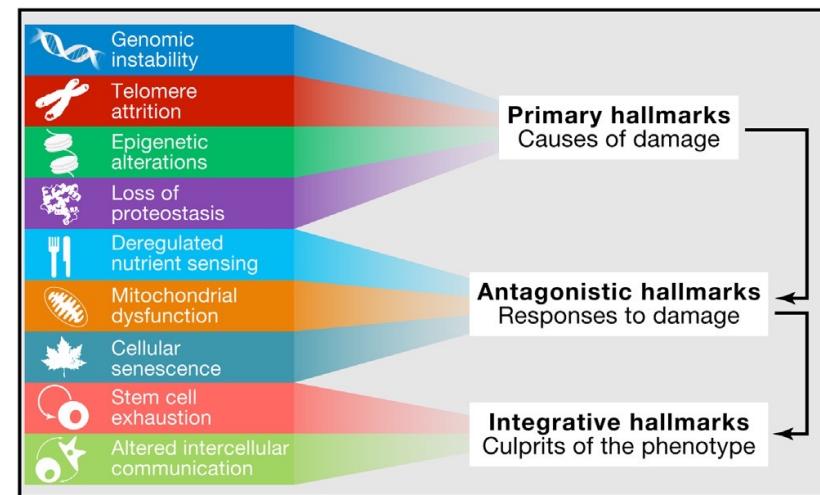
Motivation

→ Aging is a systems disease

- Aging is a complex, multifactorial process.
- Unprecedented advances in aging research shows hallmarks of aging.

→ Etiology of aging in humans is not completely understood

- The timing of alterations in biological processes contributing to aging process in humans is hazy.
- Identifying the dynamics of age-associated changes may provide targets to delay the onset of age related diseases.



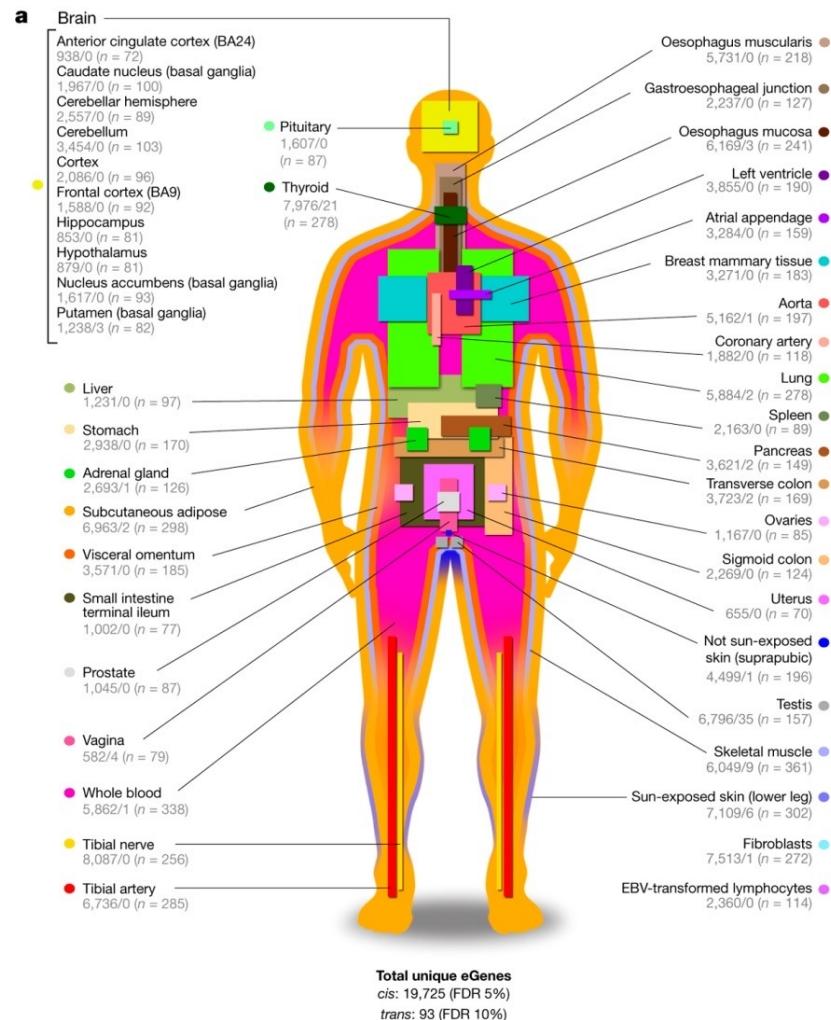
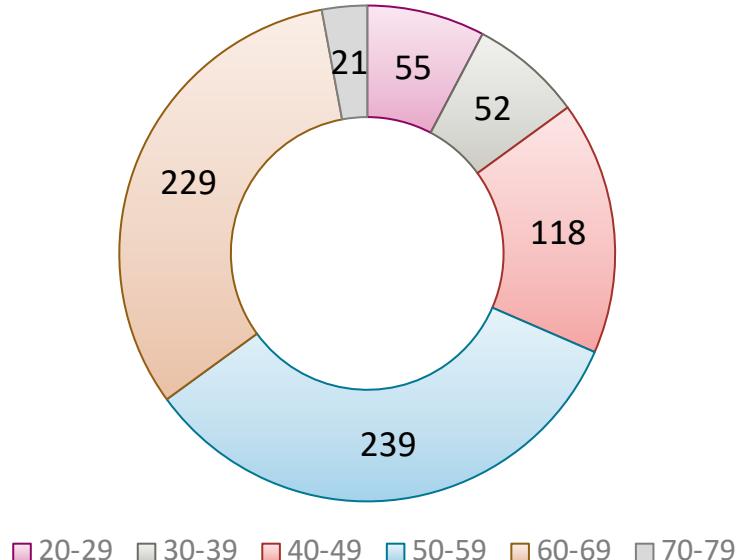
The Hallmarks of Aging, *Cell*, 153, 2013



GTEx Consortium

Characterize expression variation across individuals (714) and tissues (53)

Subjects age groups



A Battle *et al.* *Nature* **550**, 204–213 (2017)



Objectives

➡ What are the human gene expression signatures of cellular aging?

- Age-associated changes in gene expression are indicators of declining cellular functions.

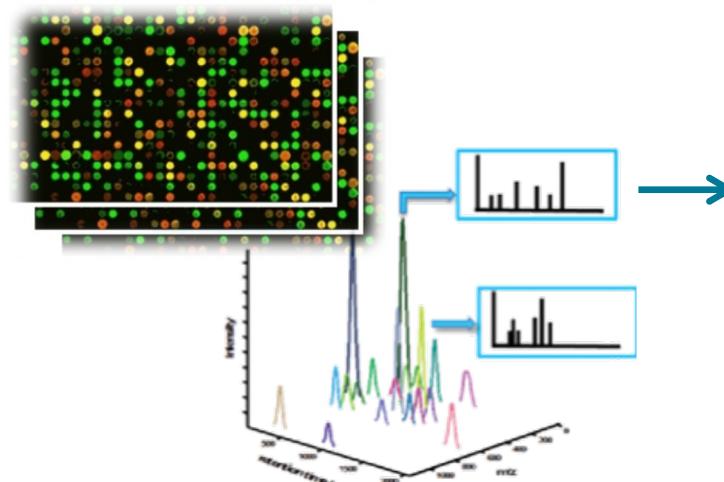
➡ When do we see these variations in mRNA levels?

- Identifying the mechanisms of temporal gene expression changes could explain the transcriptional roadmap of events during the aging process.



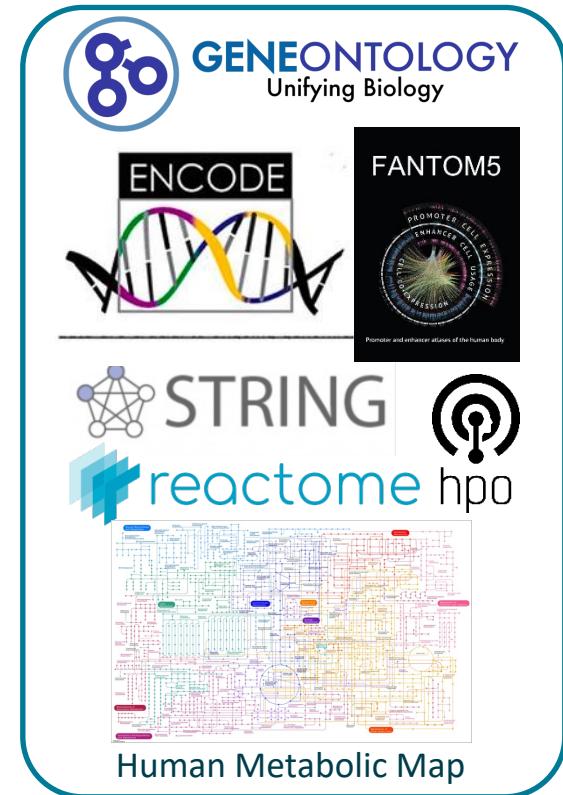


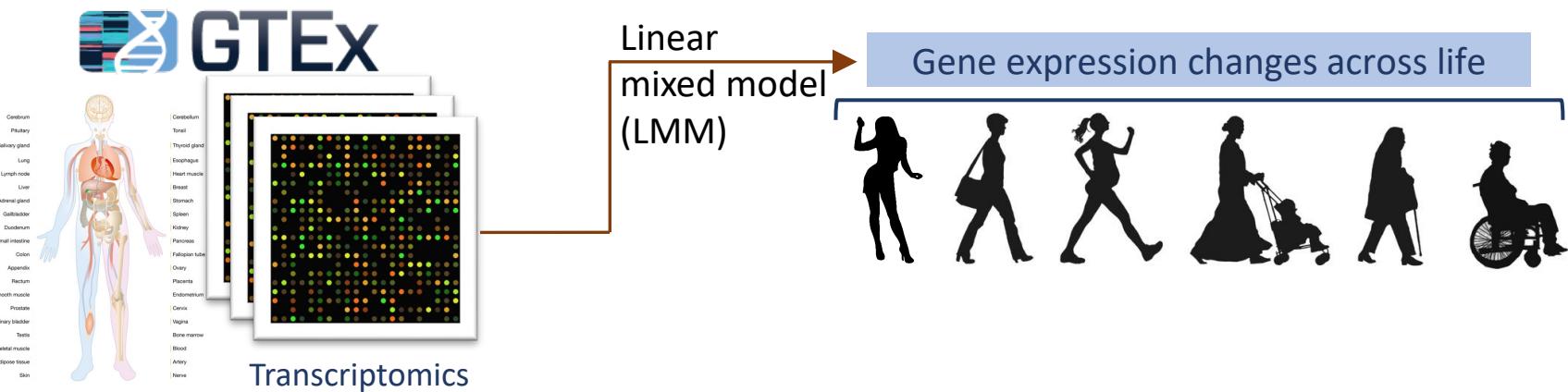
Objectives

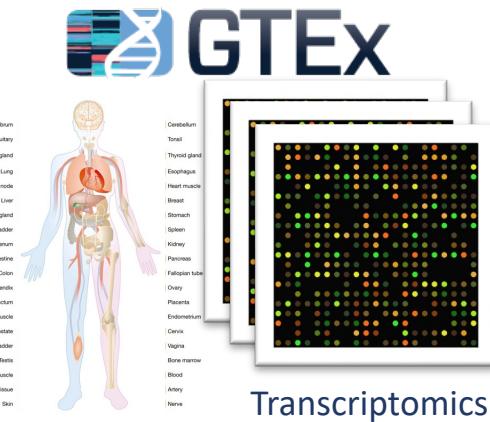


Biological Insights
(genes, proteins, pathways)

Ontologies and Atlases







Linear
mixed model
(LMM)

Gene expression changes across life



$$Y_{ijk} = \beta_i + \alpha_{ij} T_j + \gamma_{ik} Sex_k + \varepsilon_i Age_k + b_k + e_{ijk}$$

Y_{ijk} gene expression of gene i in tissue j from the subject k

β_i Regression intercept of gene i in tissue j

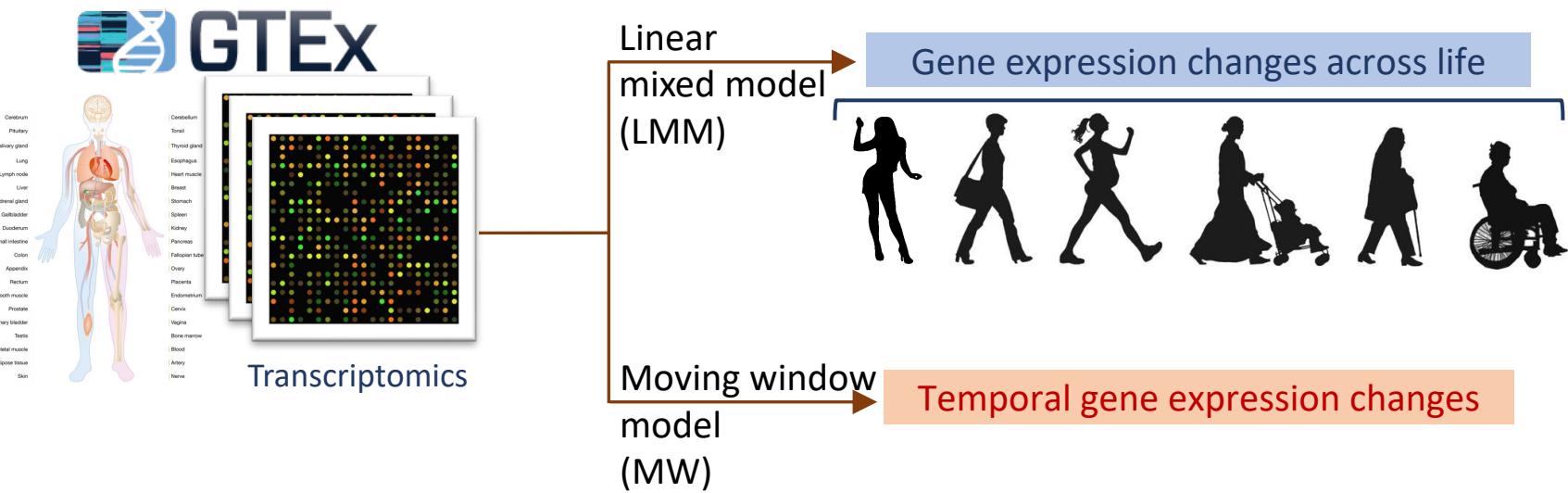
Age_k Effect of the factor – Age **FIXED EFFECT**

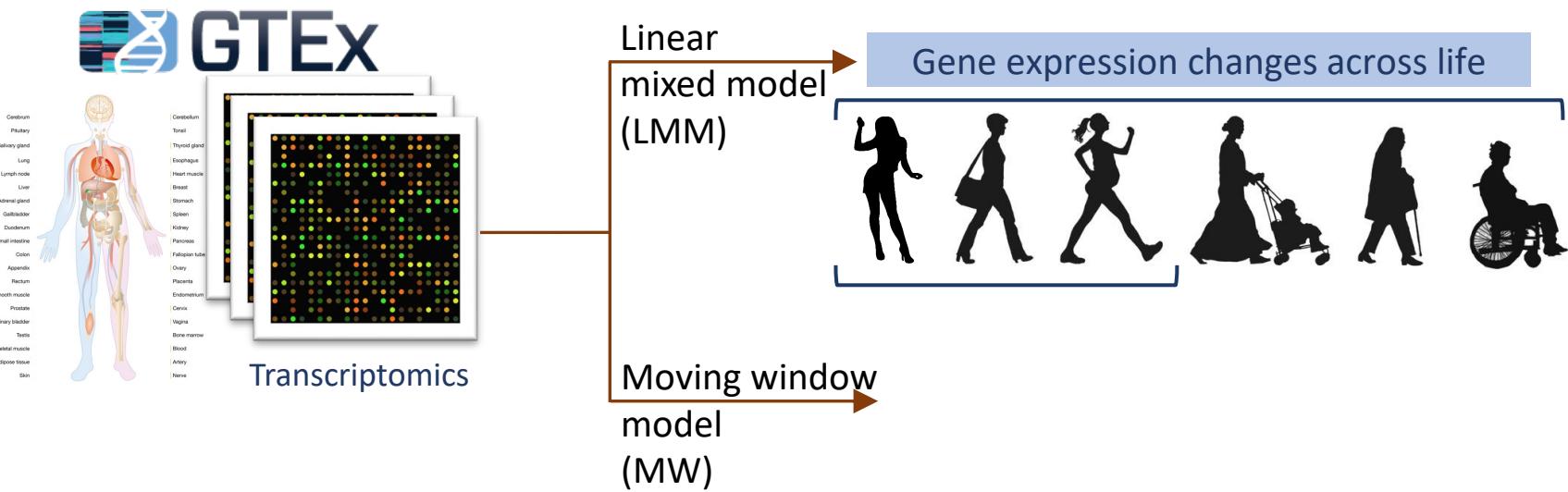
Sex_k Effect of the factor – Sex **FIXED EFFECT**

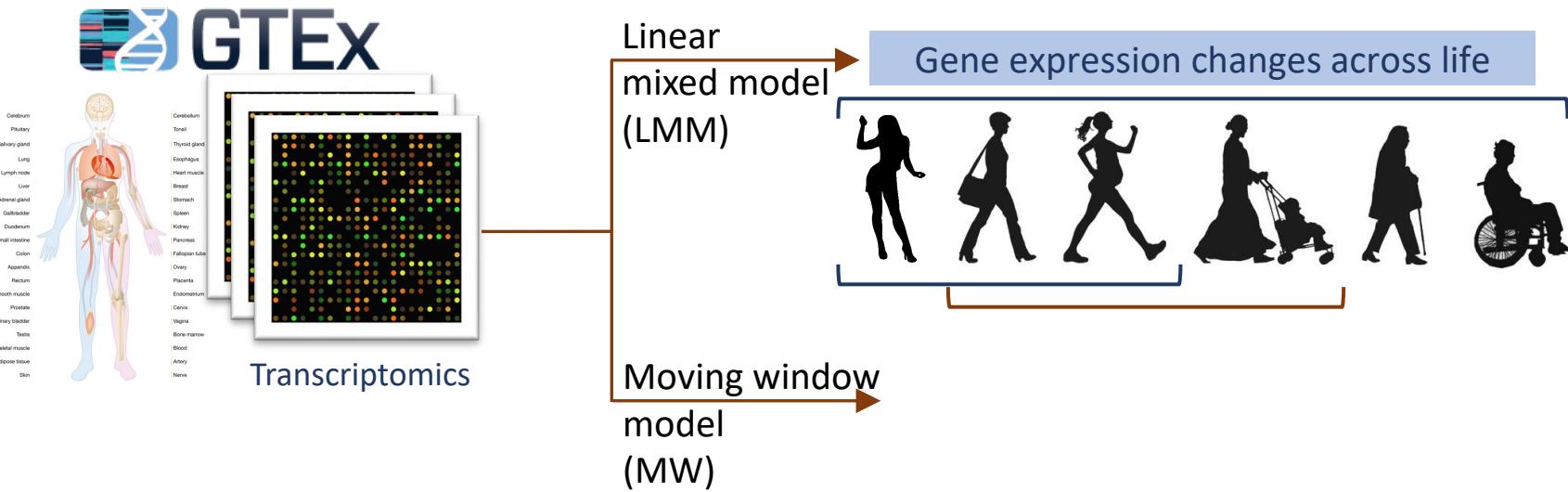
T_i Tissue effect **FIXED EFFECT**

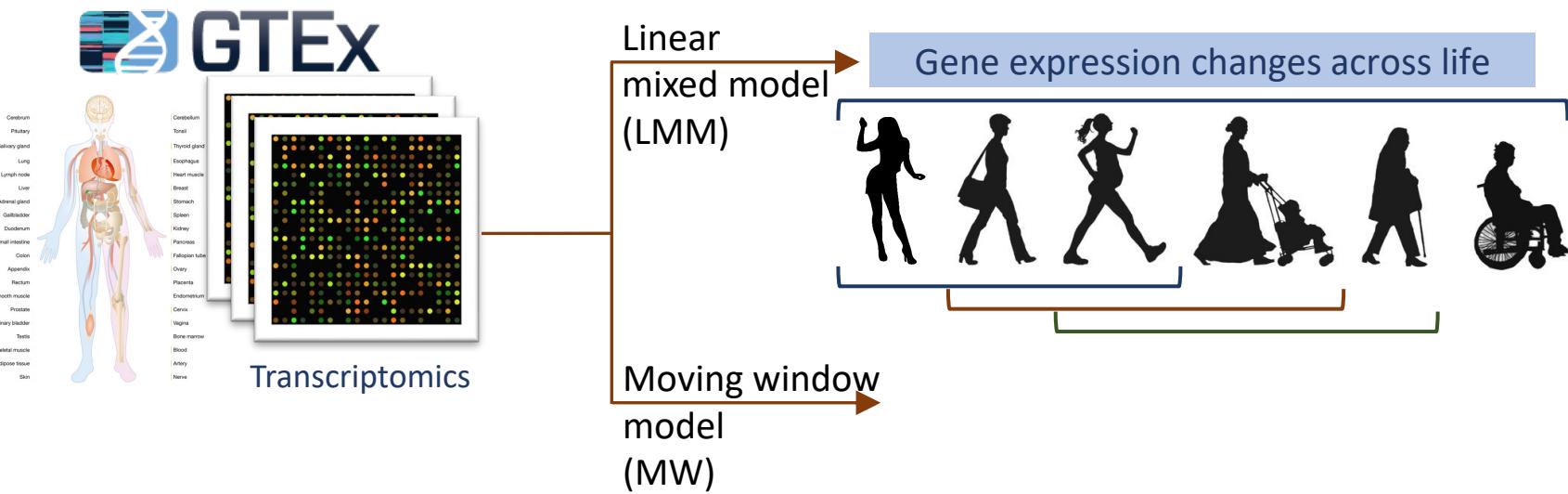
b_k Individual effects **RANDOM EFFECTS**

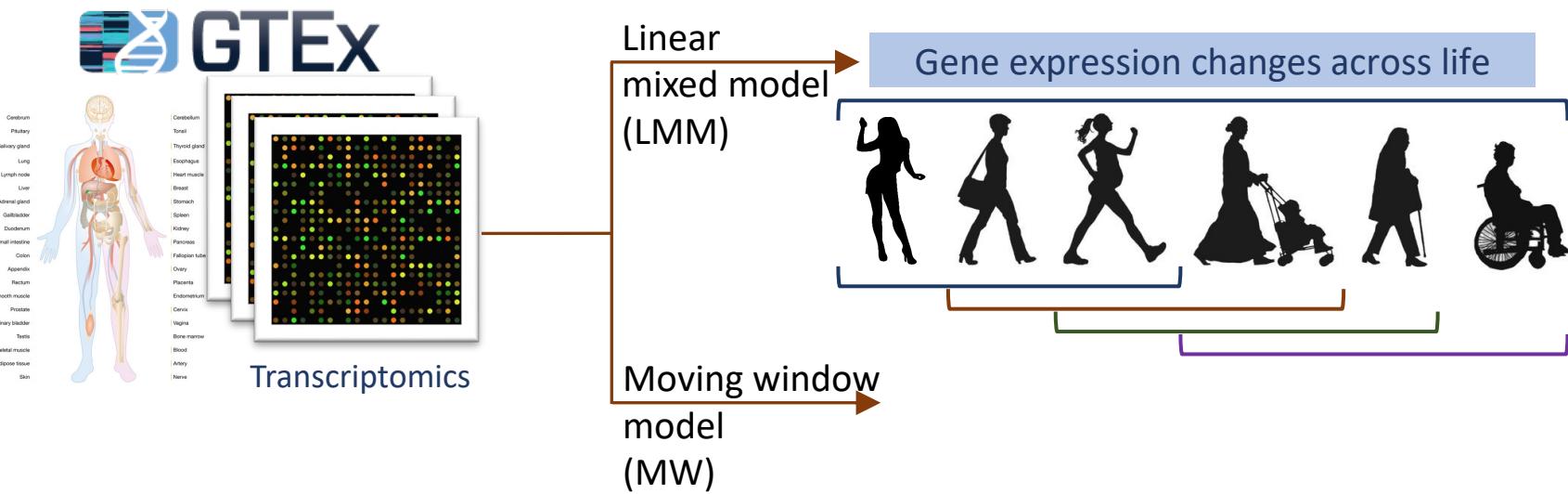
e_{ijk} Errors **RANDOM ERRORS**

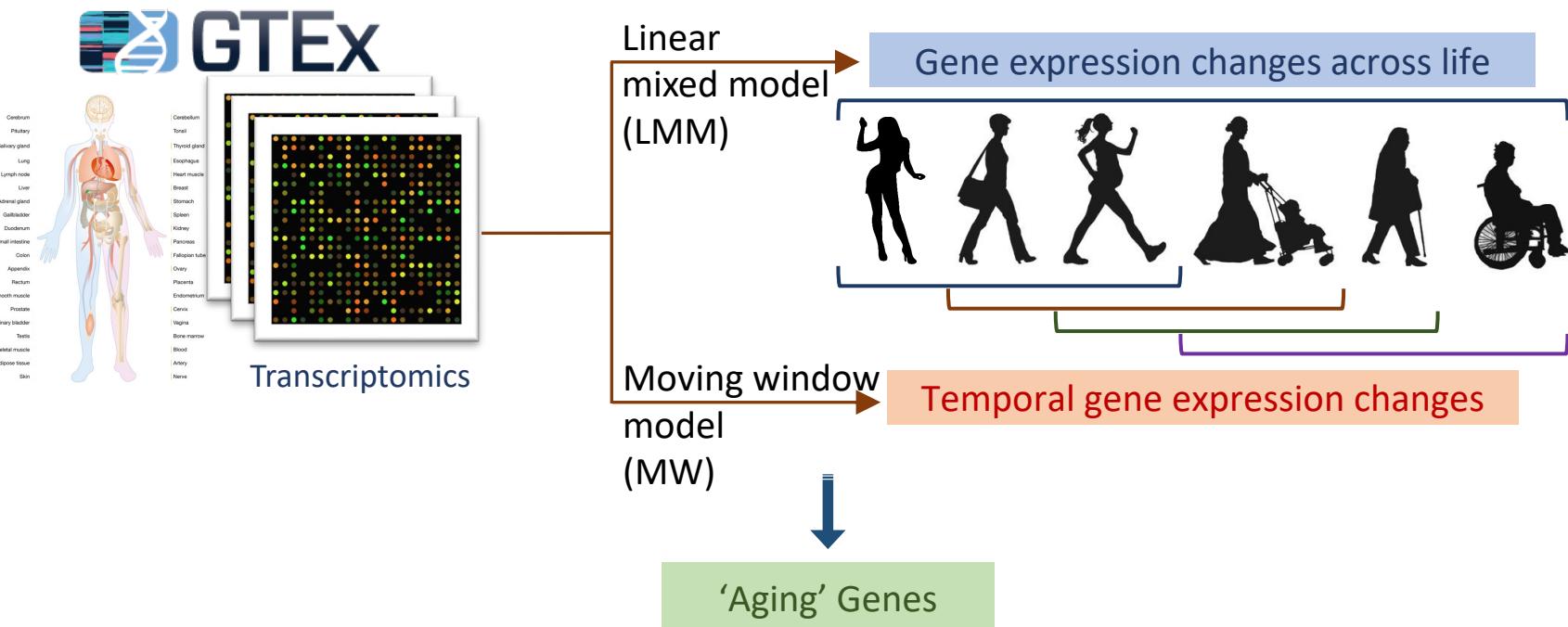


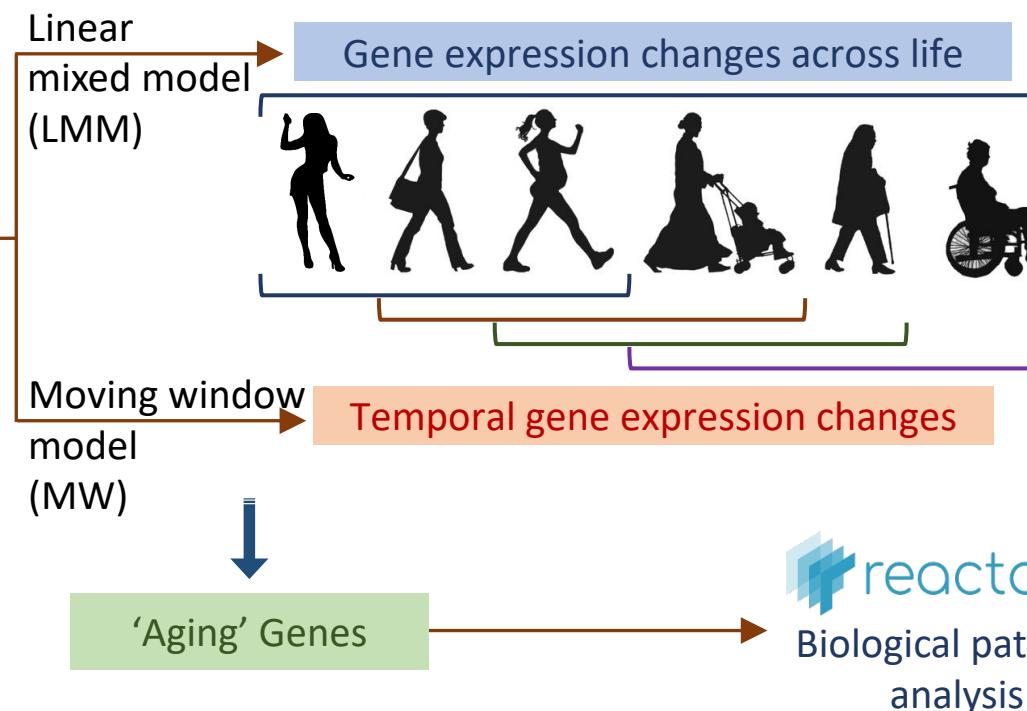
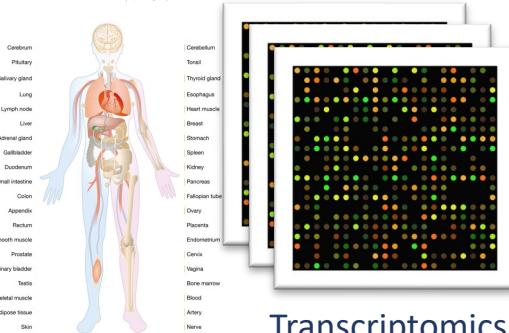


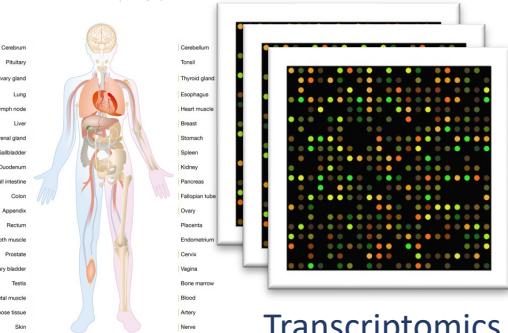












Linear
mixed model
(LMM)

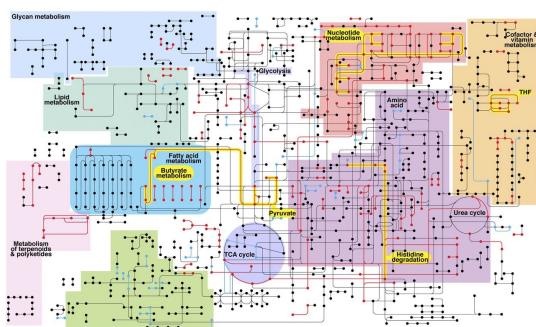
Gene expression changes across life



Moving window
model
(MW)

Temporal gene expression changes

'Aging' Genes

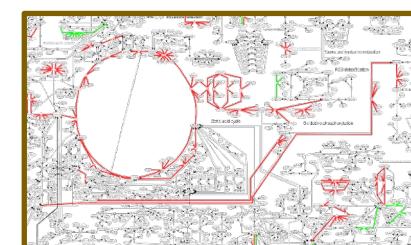


Human Genome scale metabolic network (GSMN)

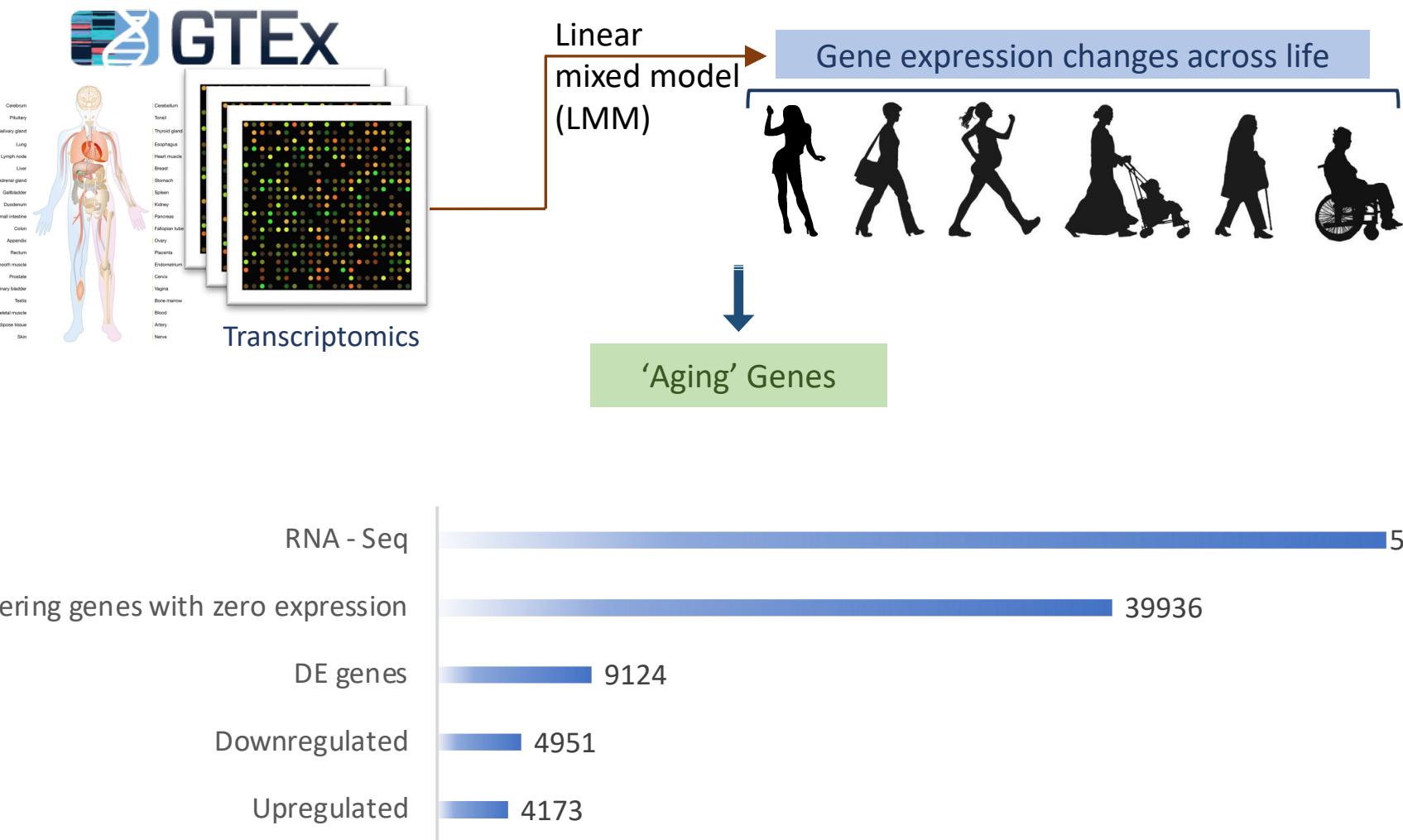


Mapping of 'aging' genes on GSMN

reactome
Biological pathway analysis



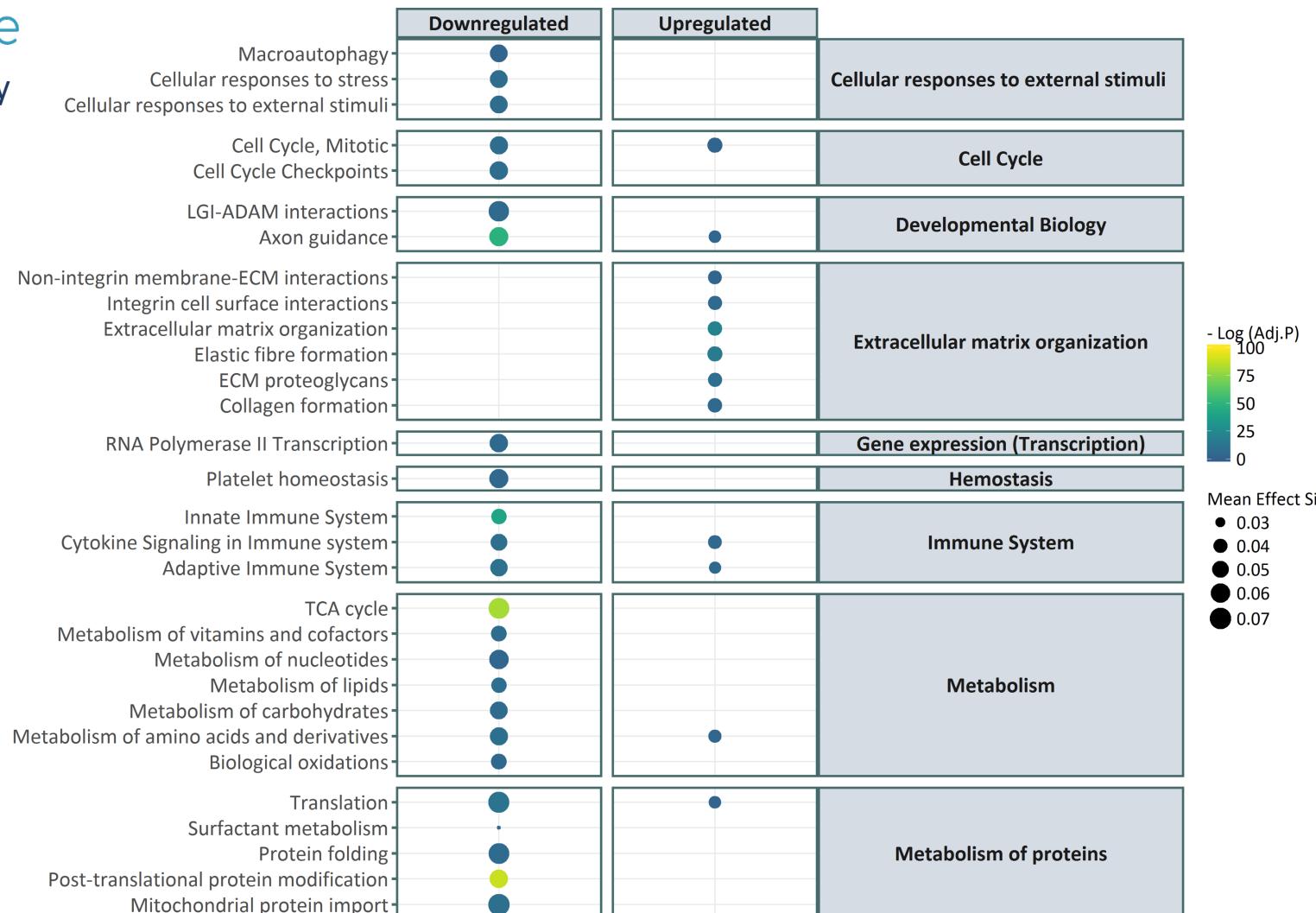
Metabolic pathway enrichment analysis





Overall hallmarks of transcriptome changes

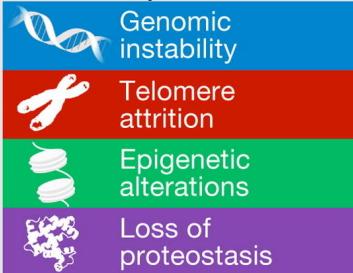
reactome
Biological pathway analysis



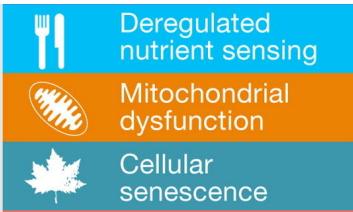


Overall hallmarks of transcriptome changes

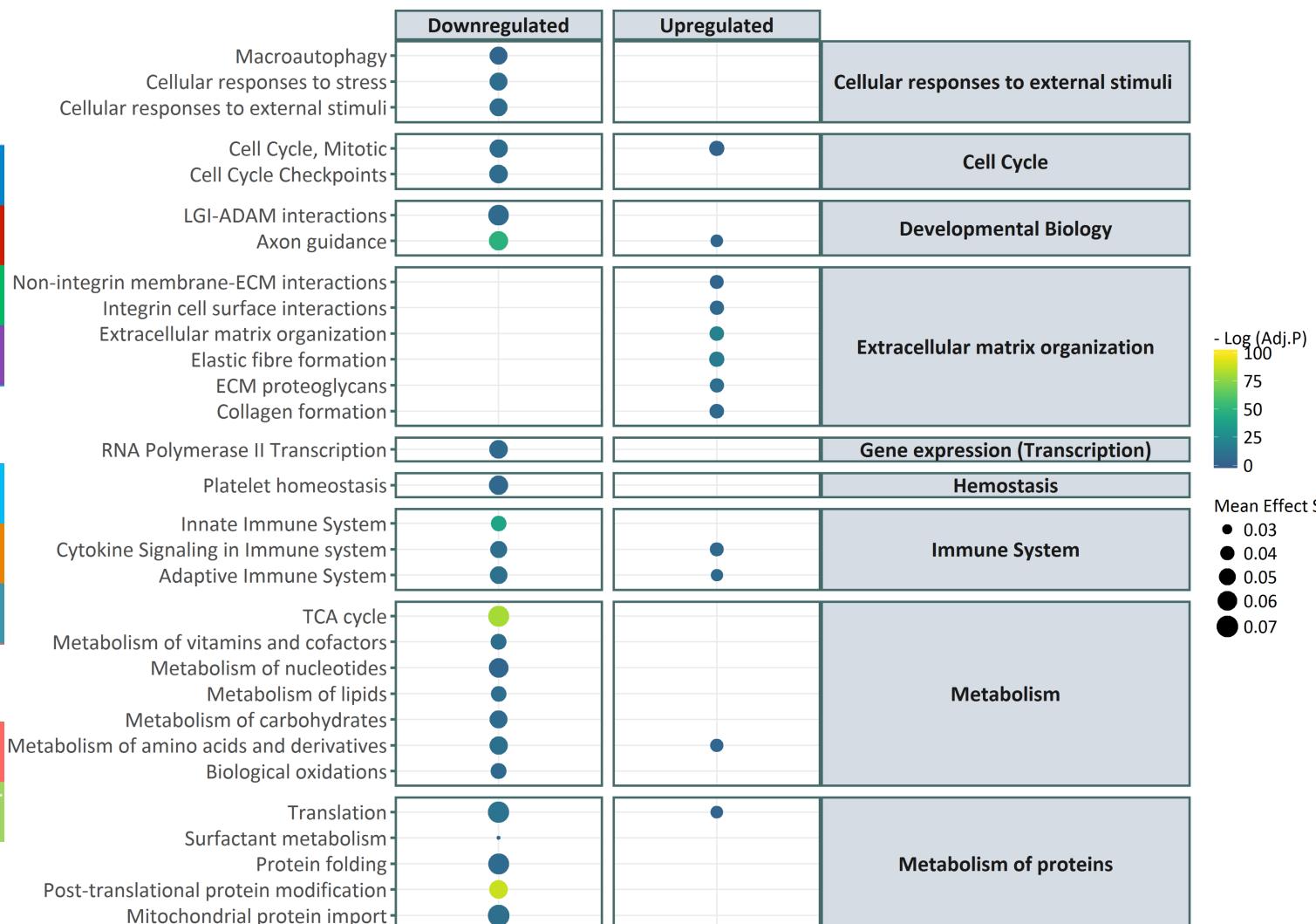
Primary Hallmarks



Antagonistic Hallmarks



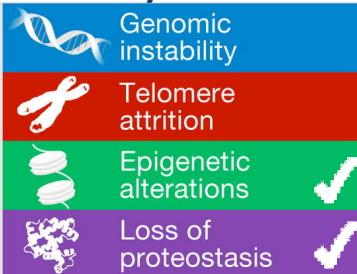
Integrative Hallmarks



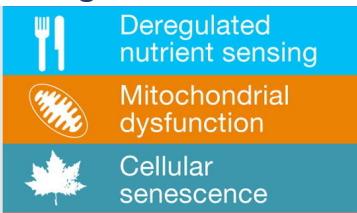


Overall hallmarks of transcriptome changes

Primary Hallmarks



Antagonistic Hallmarks



Integrative Hallmarks





Overall hallmarks of transcriptome changes

Primary Hallmarks

	Genomic instability
	Telomere attrition
	Epigenetic alterations
	Loss of proteostasis

Antagonistic Hallmarks

	Deregulated nutrient sensing
	Mitochondrial dysfunction
	Cellular senescence

Integrative Hallmarks

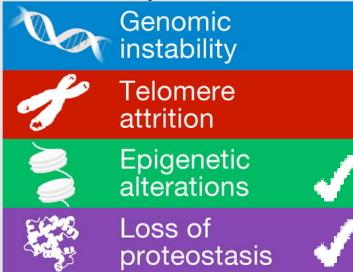
	Stem cell exhaustion
	Altered intercellular communication



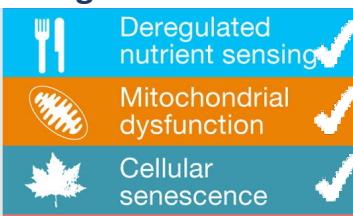


Overall hallmarks of transcriptome changes

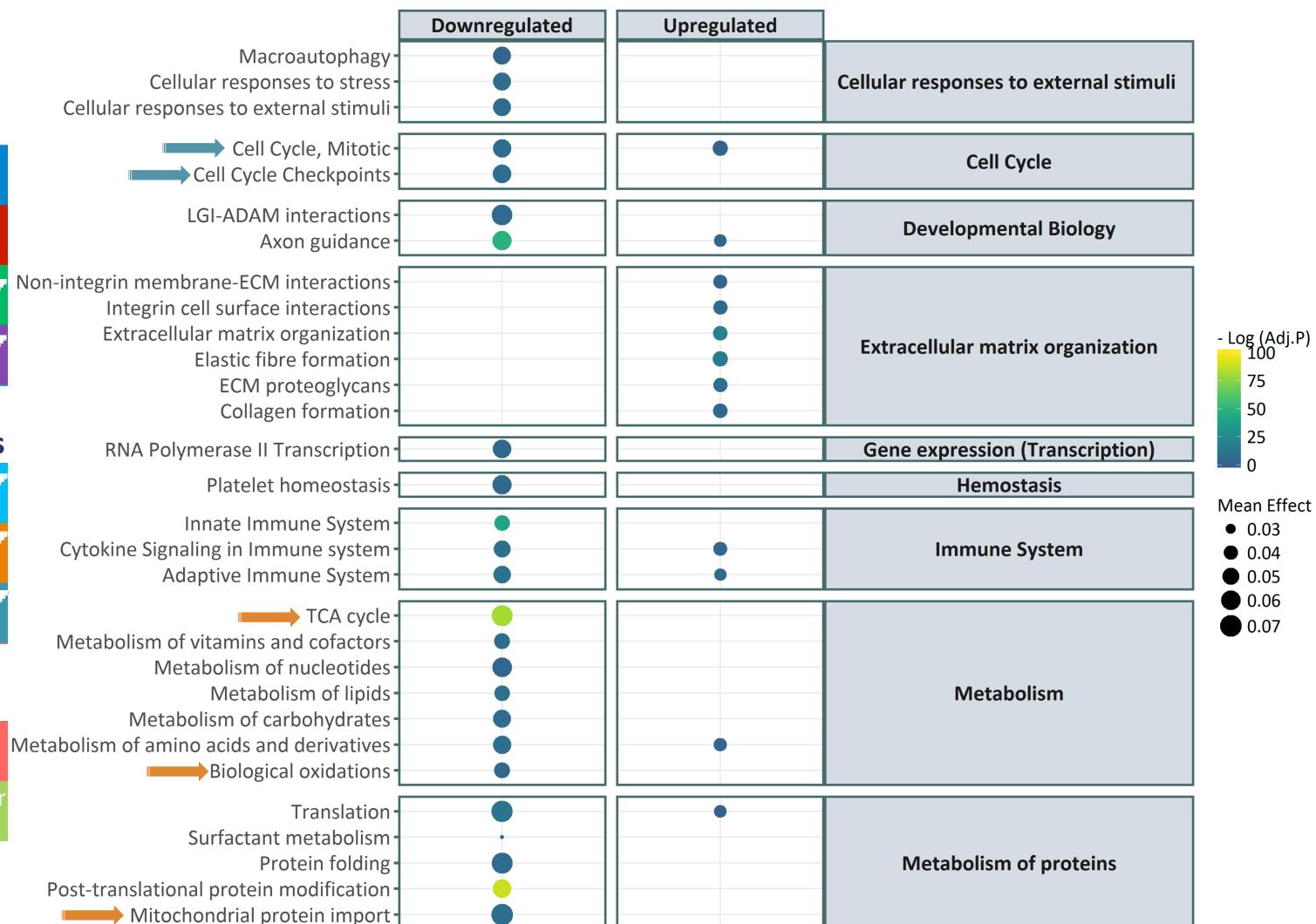
Primary Hallmarks



Antagonistic Hallmarks



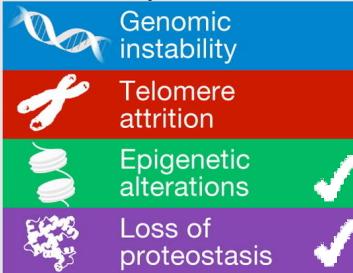
Integrative Hallmarks



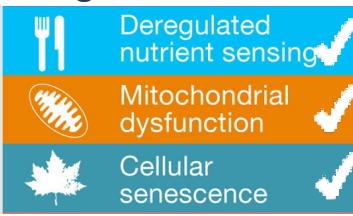


Overall hallmarks of transcriptome changes

Primary Hallmarks



Antagonistic Hallmarks



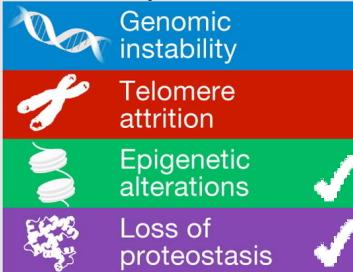
Integrative Hallmarks



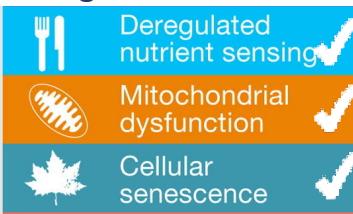


Overall hallmarks of transcriptome changes

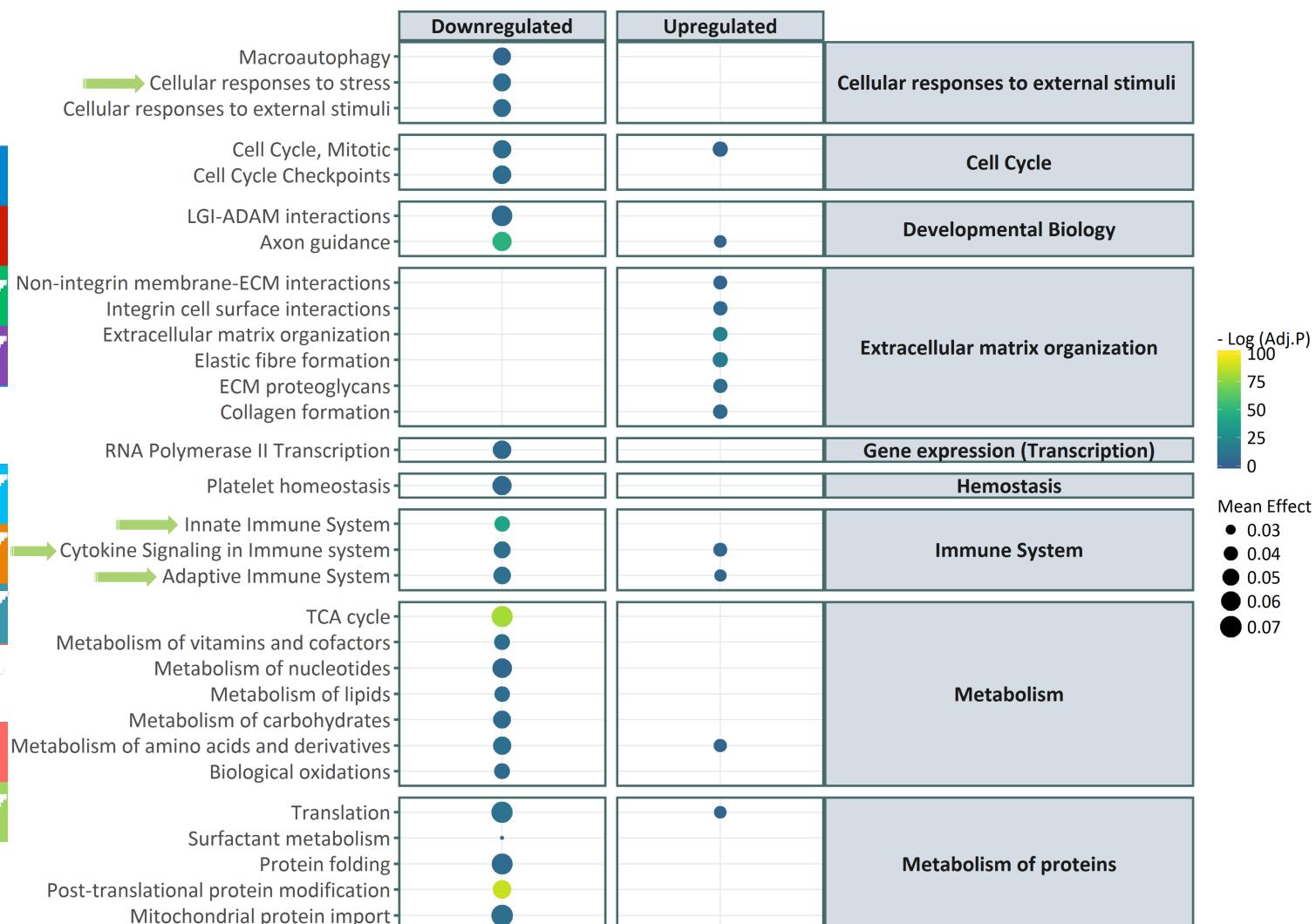
Primary Hallmarks



Antagonistic Hallmarks



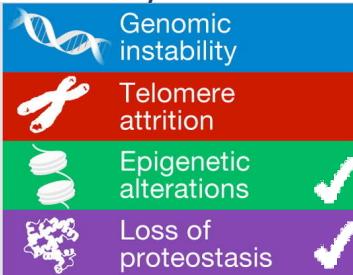
Integrative Hallmarks



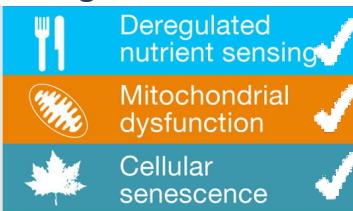


Overall hallmarks of transcriptome changes

Primary Hallmarks



Antagonistic Hallmarks

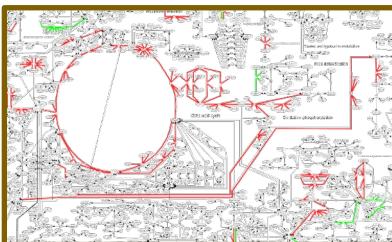


Integrative Hallmarks





Overall hallmarks of transcriptome changes



Metabolic pathway enrichment analysis

Androgen and estrogen synthesis and metabolism

Inositol phosphate metabolism

Nucleotide interconversion

Miscellaneous

Tryptophan metabolism

Arachidonic acid metabolism

Citric acid cycle

Protein degradation

Eicosanoid metabolism

NAD metabolism

Valine, leucine, and isoleucine metabolism

Transport, mitochondrial

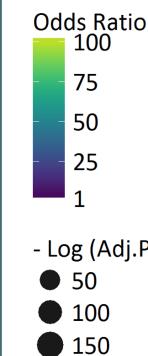
Bile acid synthesis

Transport, peroxisomal

Vitamin B6 metabolism

Xenobiotics metabolism

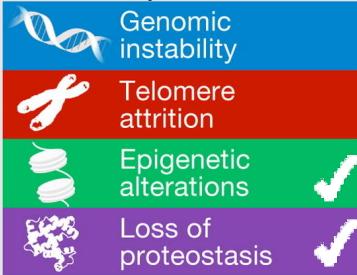
Leukotriene metabolism



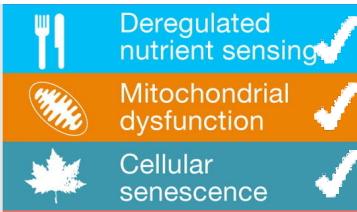


Overall hallmarks of transcriptome changes

Primary Hallmarks



Antagonistic Hallmarks



Integrative Hallmarks





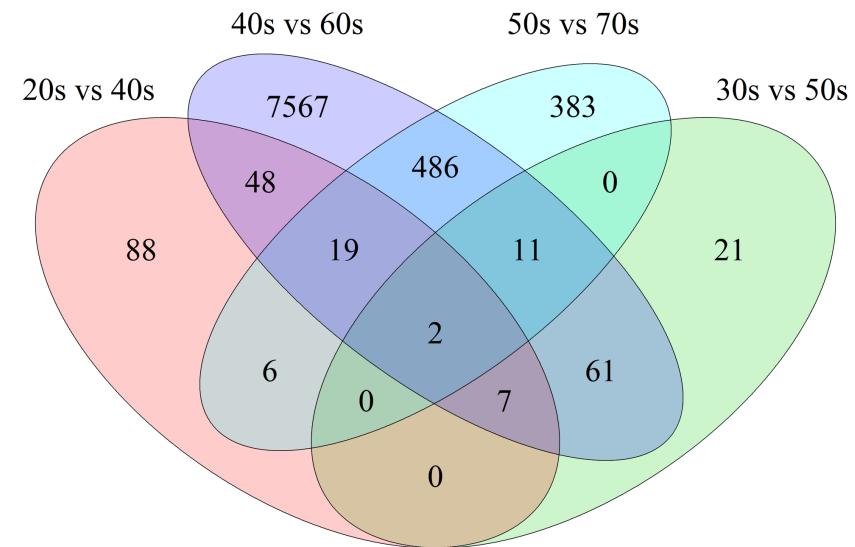
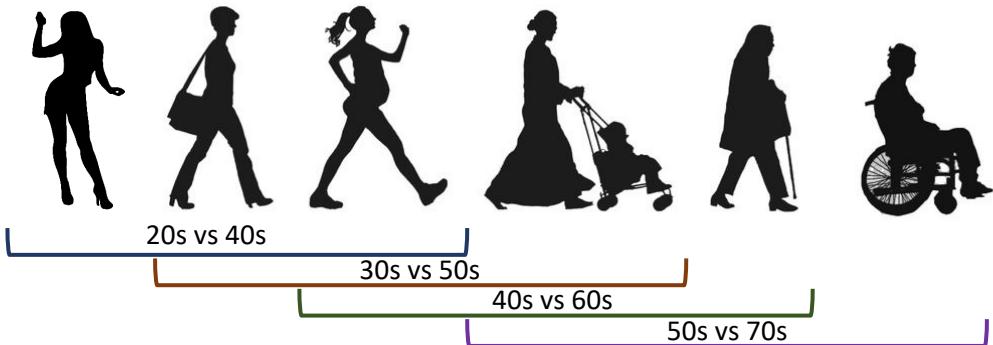
Overall hallmarks of transcriptome changes

- Gene expression signatures in human aging are associated with the known hallmarks of aging (evolutionary conserved pathways).
- Gene expression changes in human aging indicate cellular energetic crisis and issues in precursors and amino acid metabolism.



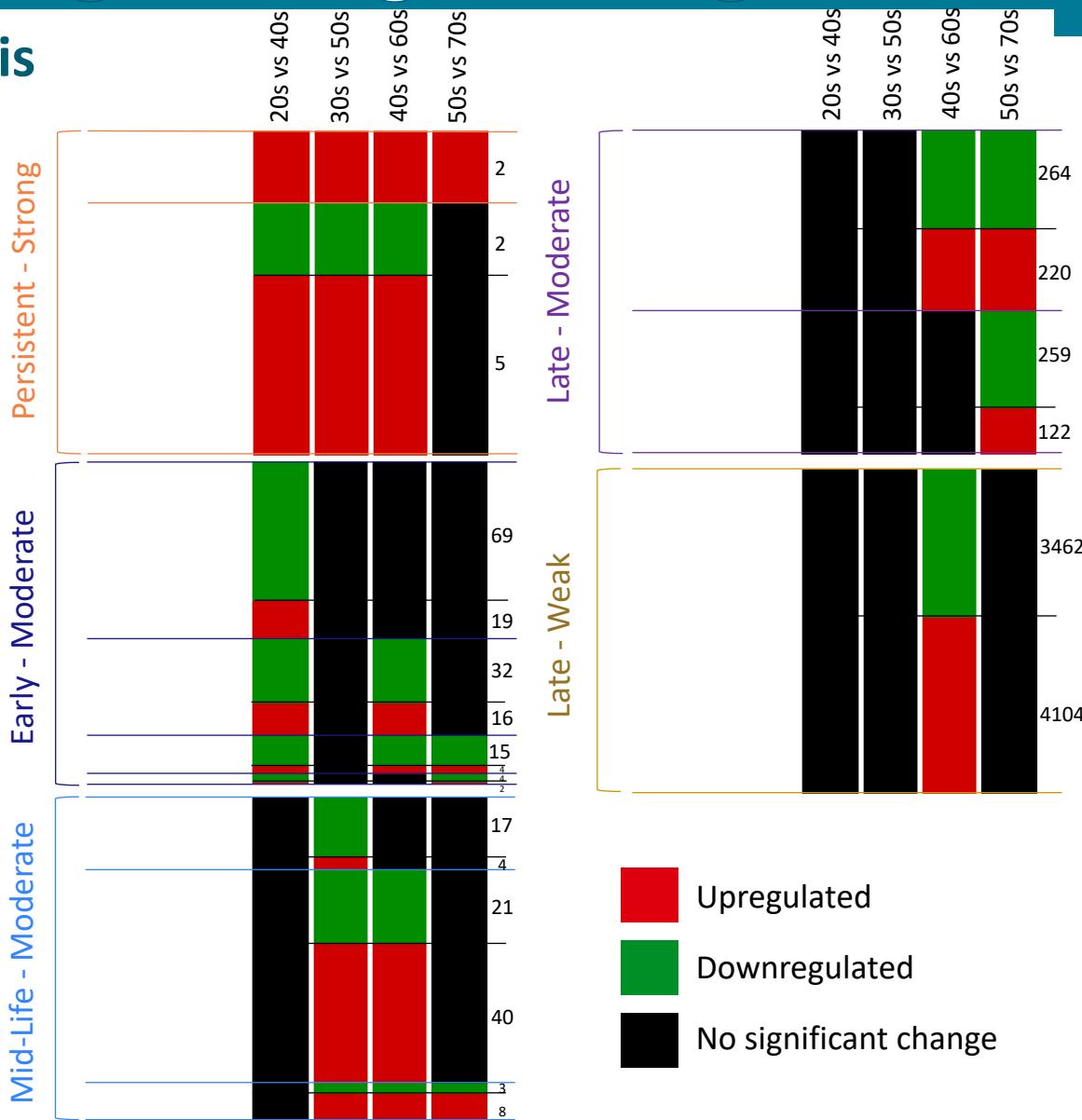
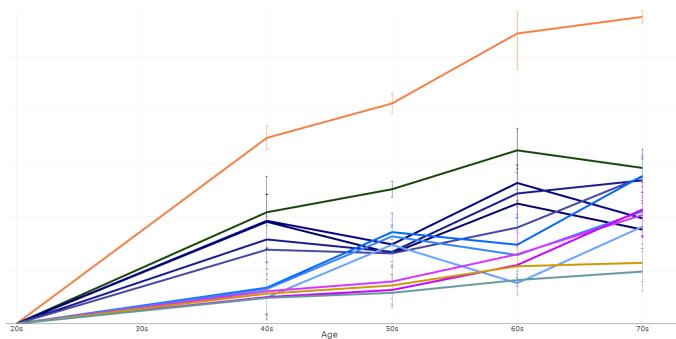
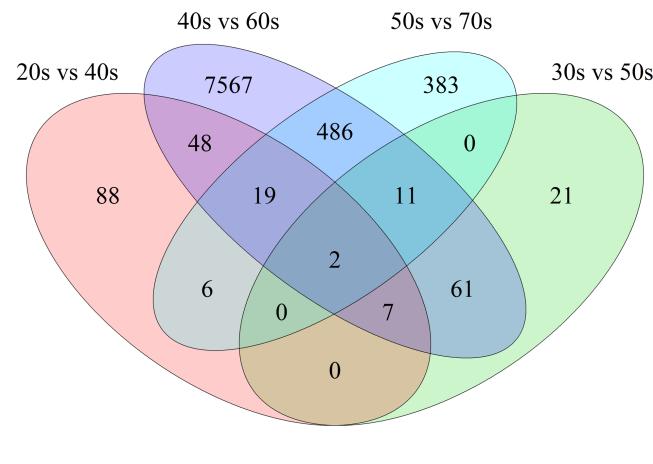
Moving Window Analysis

Temporal gene expression changes



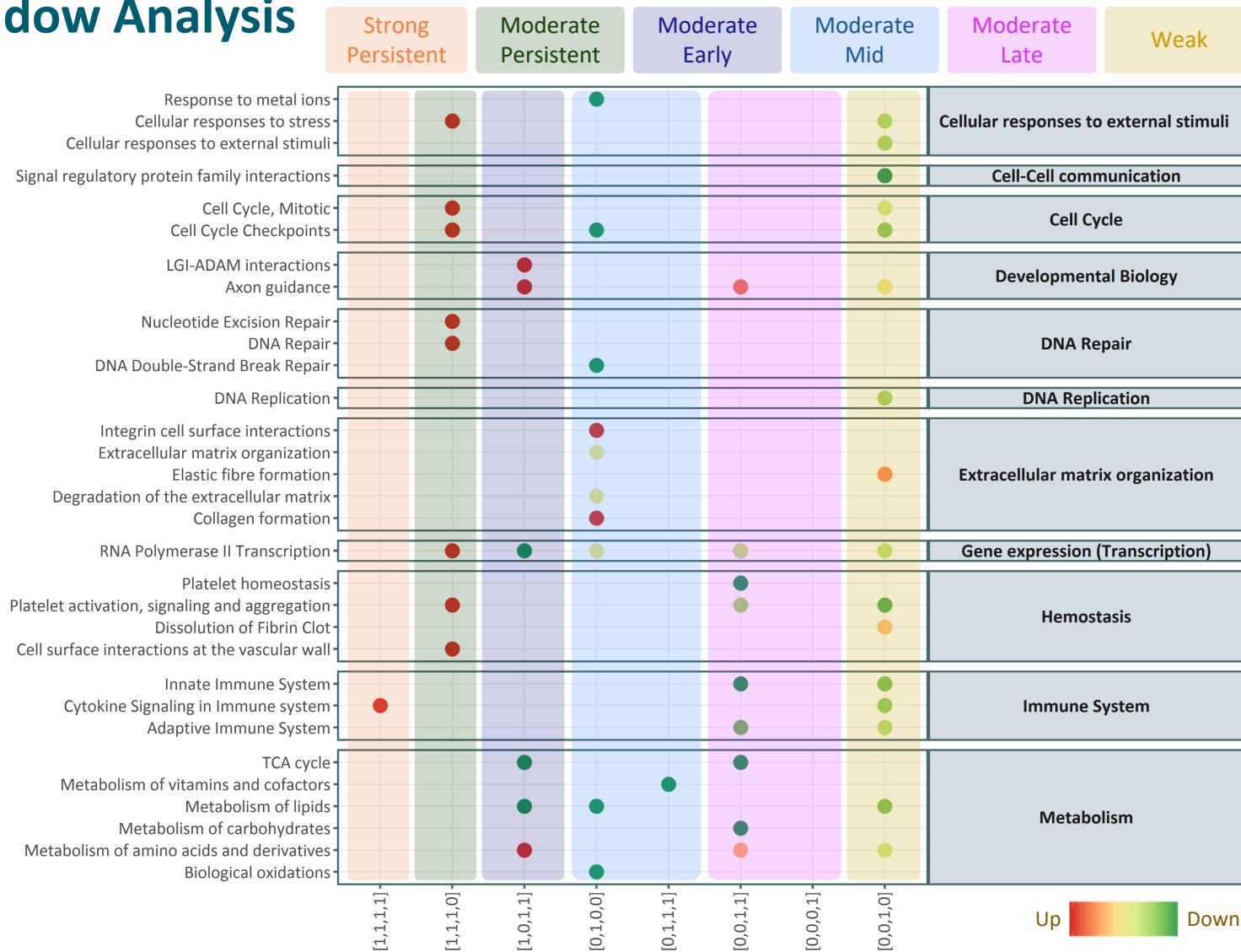


Moving Window Analysis





Moving Window Analysis





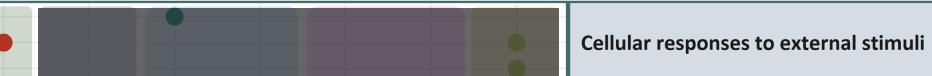
Moving Window Analysis

- Regulation of cell cycle / senescence
- DNA damage repair
- Proinflammatory cytokines

GAS6;CDKN2A

Response to metal ions
Cellular responses to stress
Cellular responses to external stimuli

Strong Persistent
Moderate Persistent

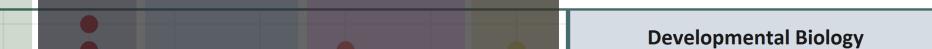


DDB2

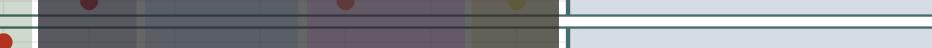
Cell Cycle, Mitotic
Cell Cycle Checkpoints



LGI-ADAM interactions
Axon guidance



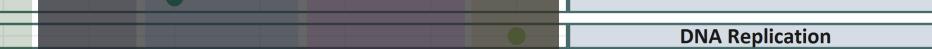
Nucleotide Excision Repair
DNA Repair



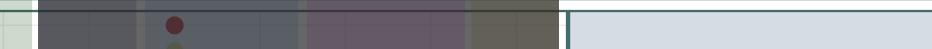
DNA Double-Strand Break Repair
DNA Replication



Integrin cell surface interactions
Extracellular matrix organization



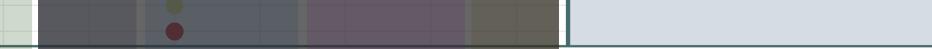
Elastic fibre formation
Degradation of the extracellular matrix



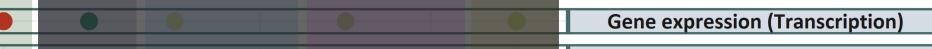
Collagen formation
RNA Polymerase II Transcription



Platelet homeostasis
Platelet activation, signaling and aggregation

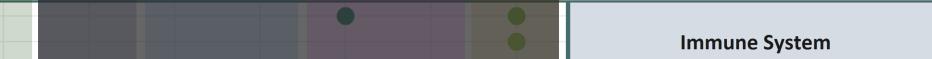


Dissolution of Fibrin Clot
Cell surface interactions at the vascular wall

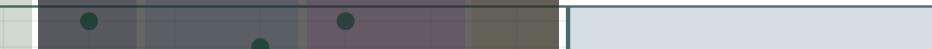


EDA2R

Innate Immune System
Cytokine Signaling in Immune system
Adaptive Immune System



TCA cycle
Metabolism of vitamins and cofactors



Metabolism of lipids
Metabolism of carbohydrates



Metabolism of amino acids and derivatives
Biological oxidations

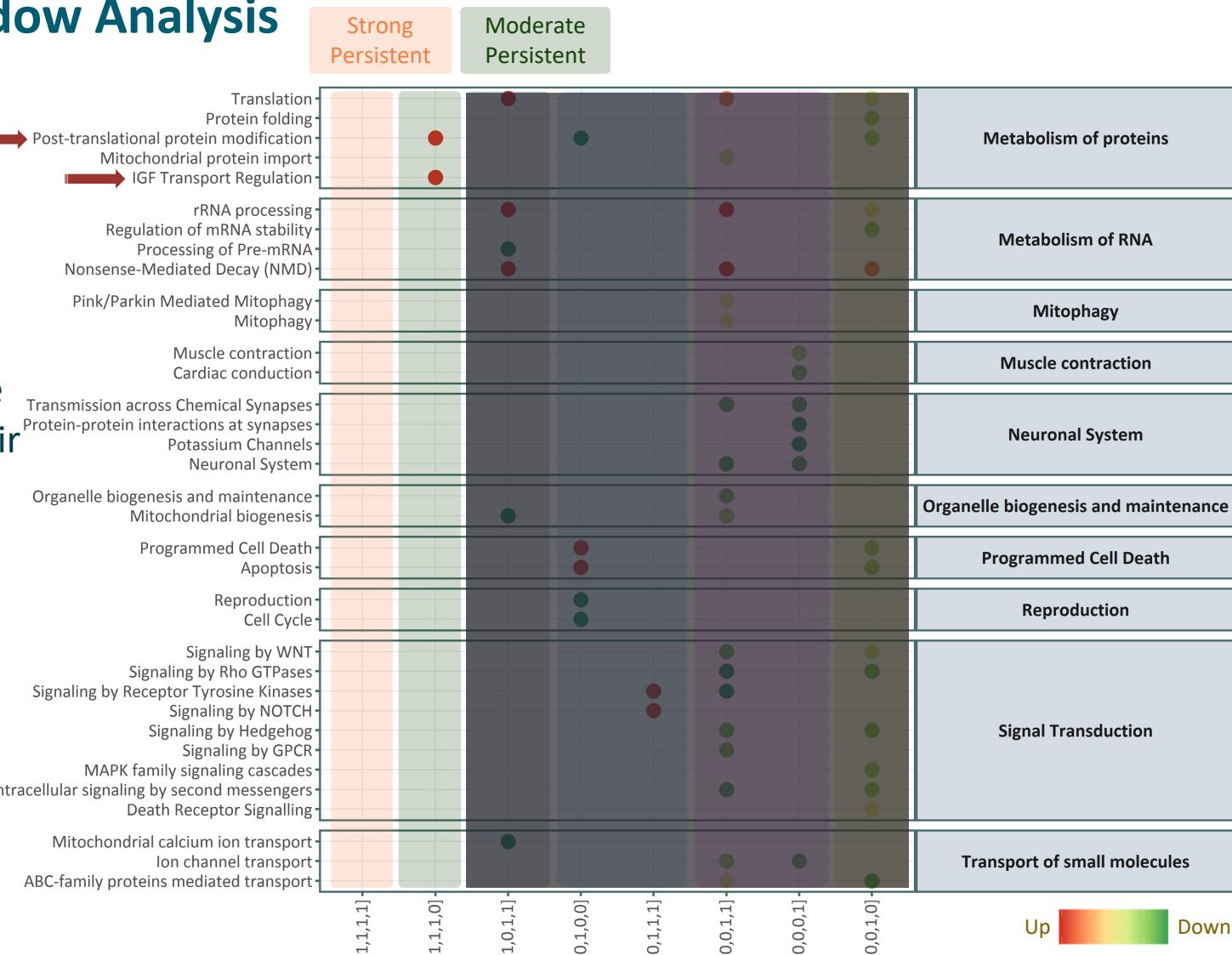




Moving Window Analysis

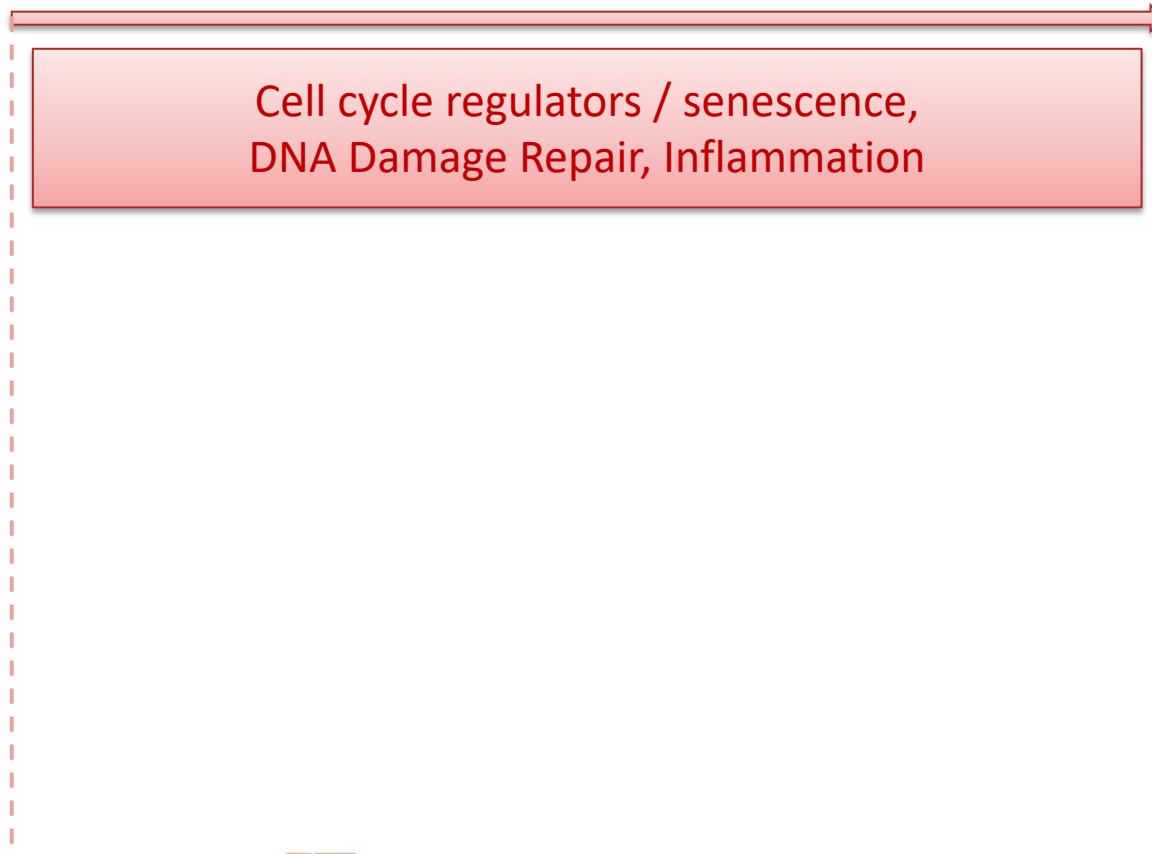
GAS6;CDKN2A

- Regulation of cell cycle / senescence
- DNA damage repair
- Proinflammatory cytokines





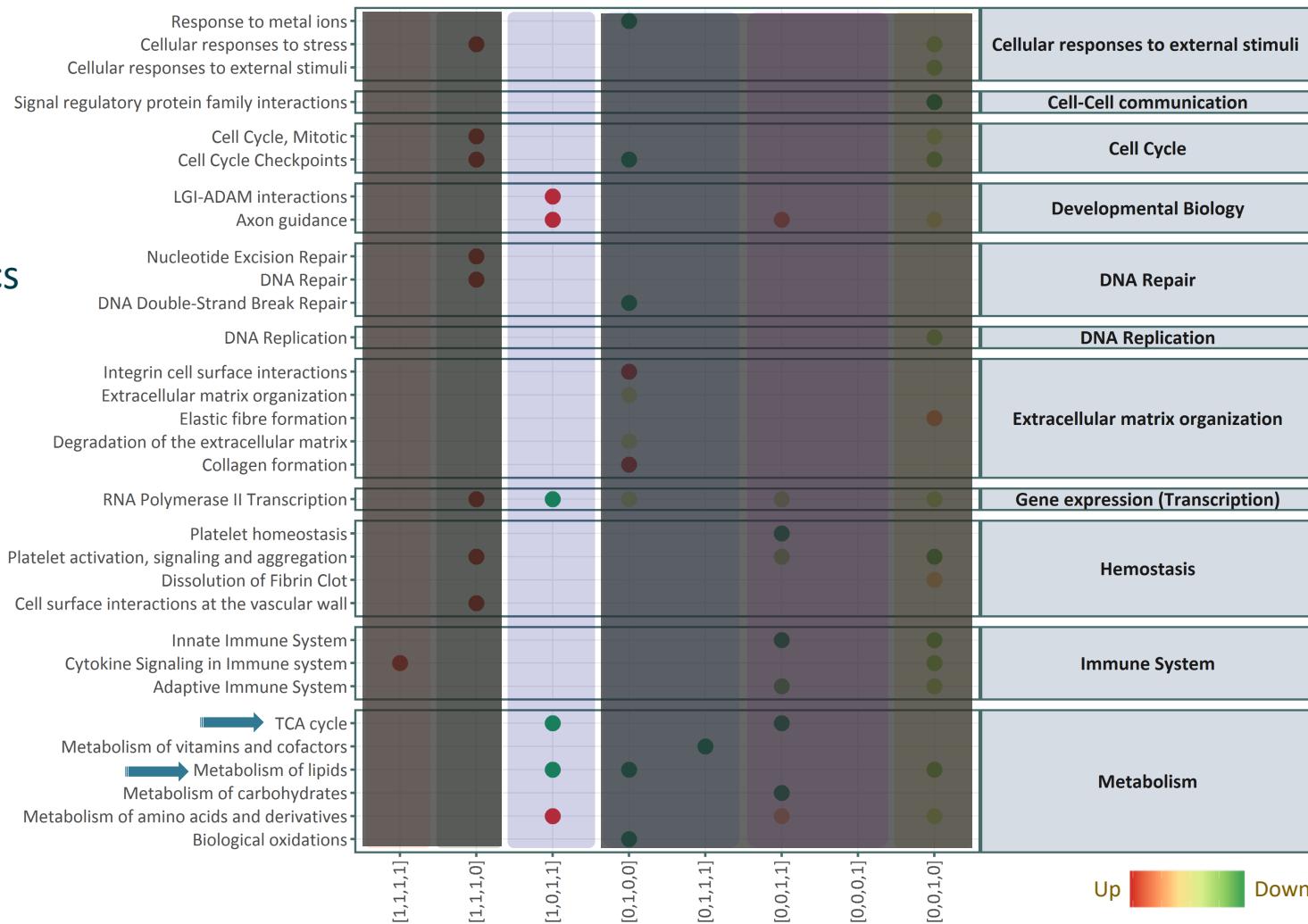
Moving Window Analysis





Moving Window Analysis

Moderate
Early



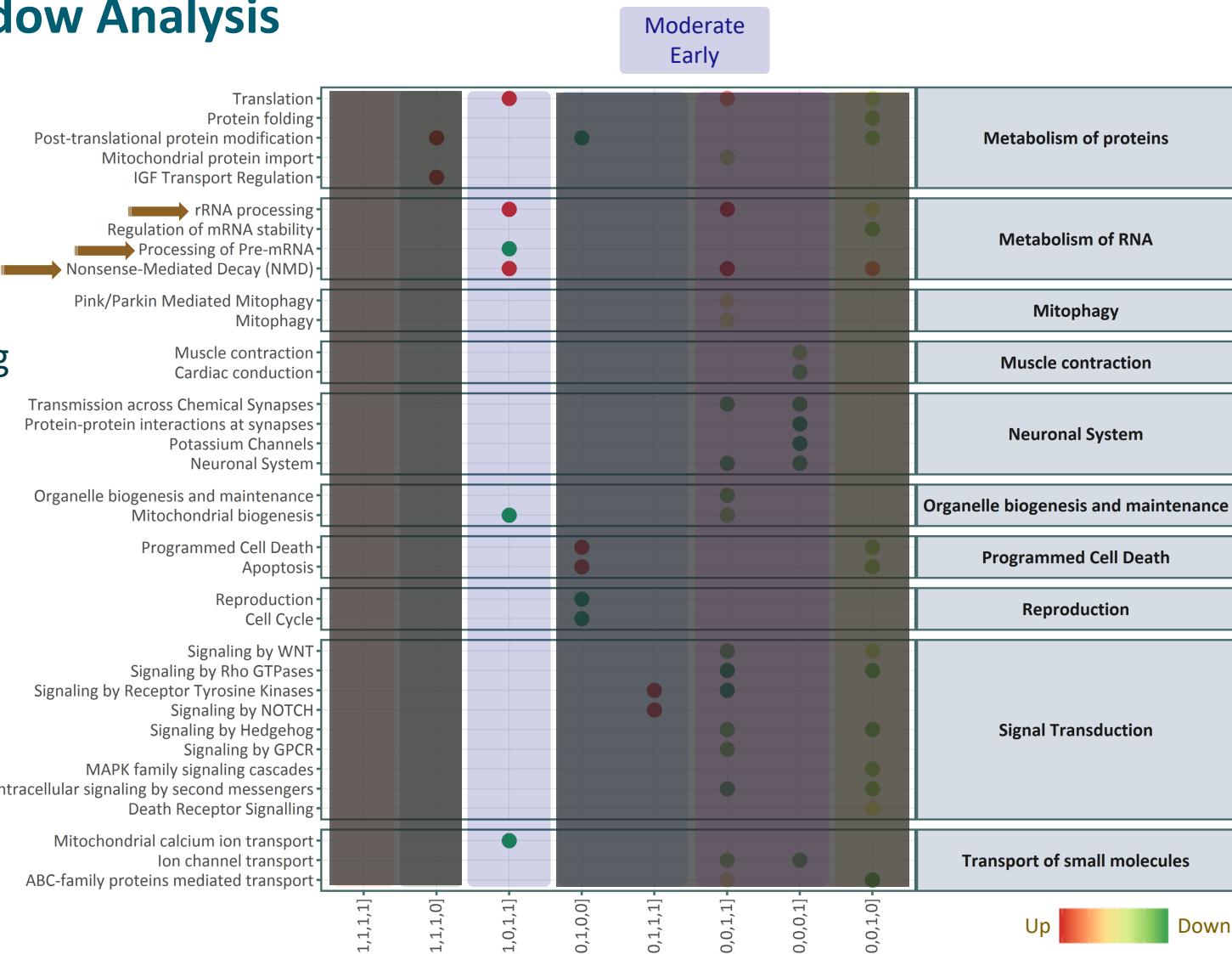
CYCS; CS; COX5A



Moving Window Analysis

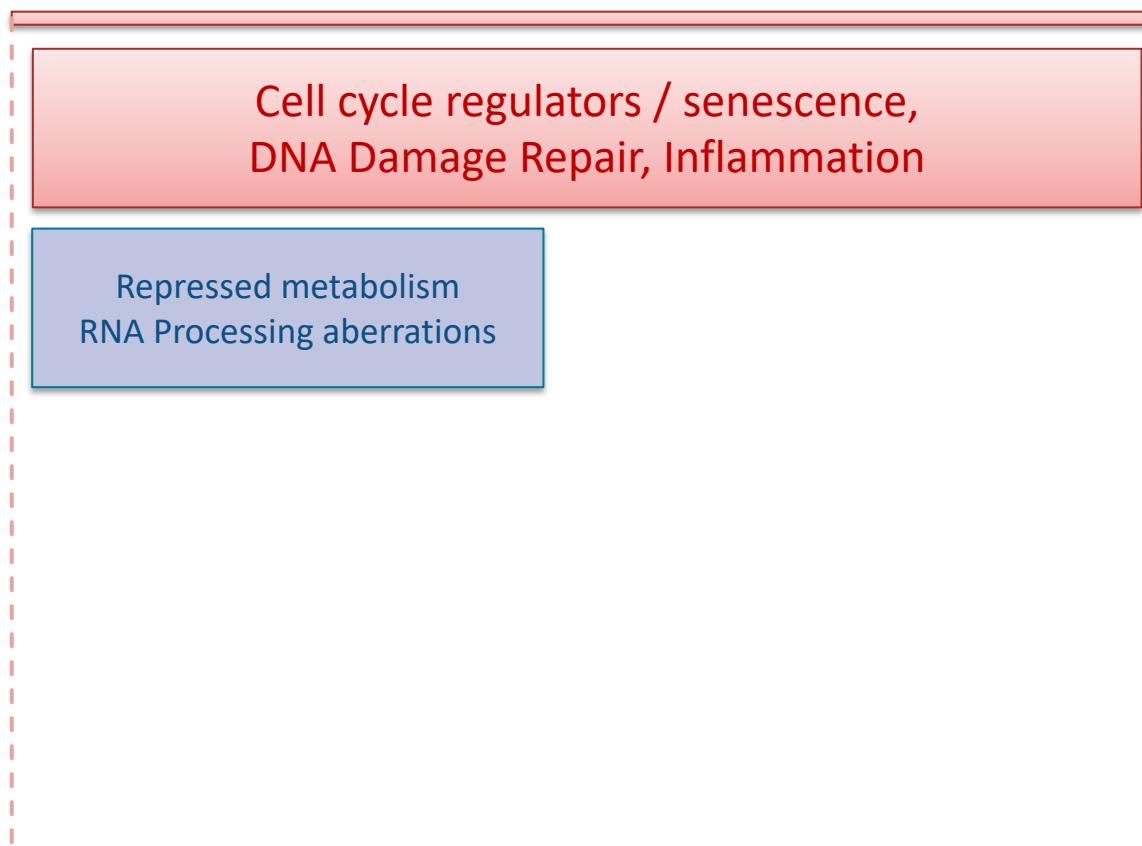
hPSO4;SF3B4

Issues with splicing





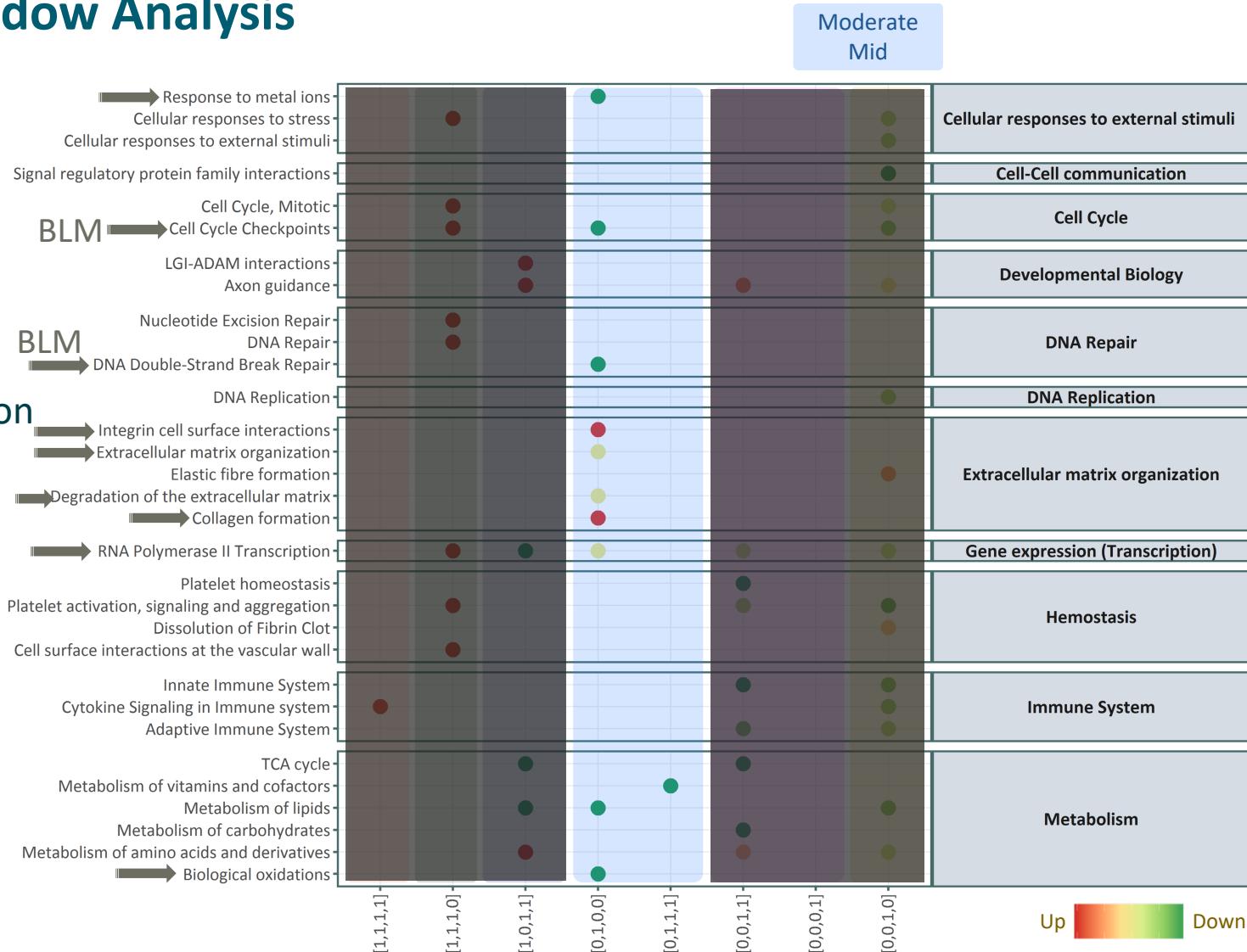
Moving Window Analysis





Moving Window Analysis

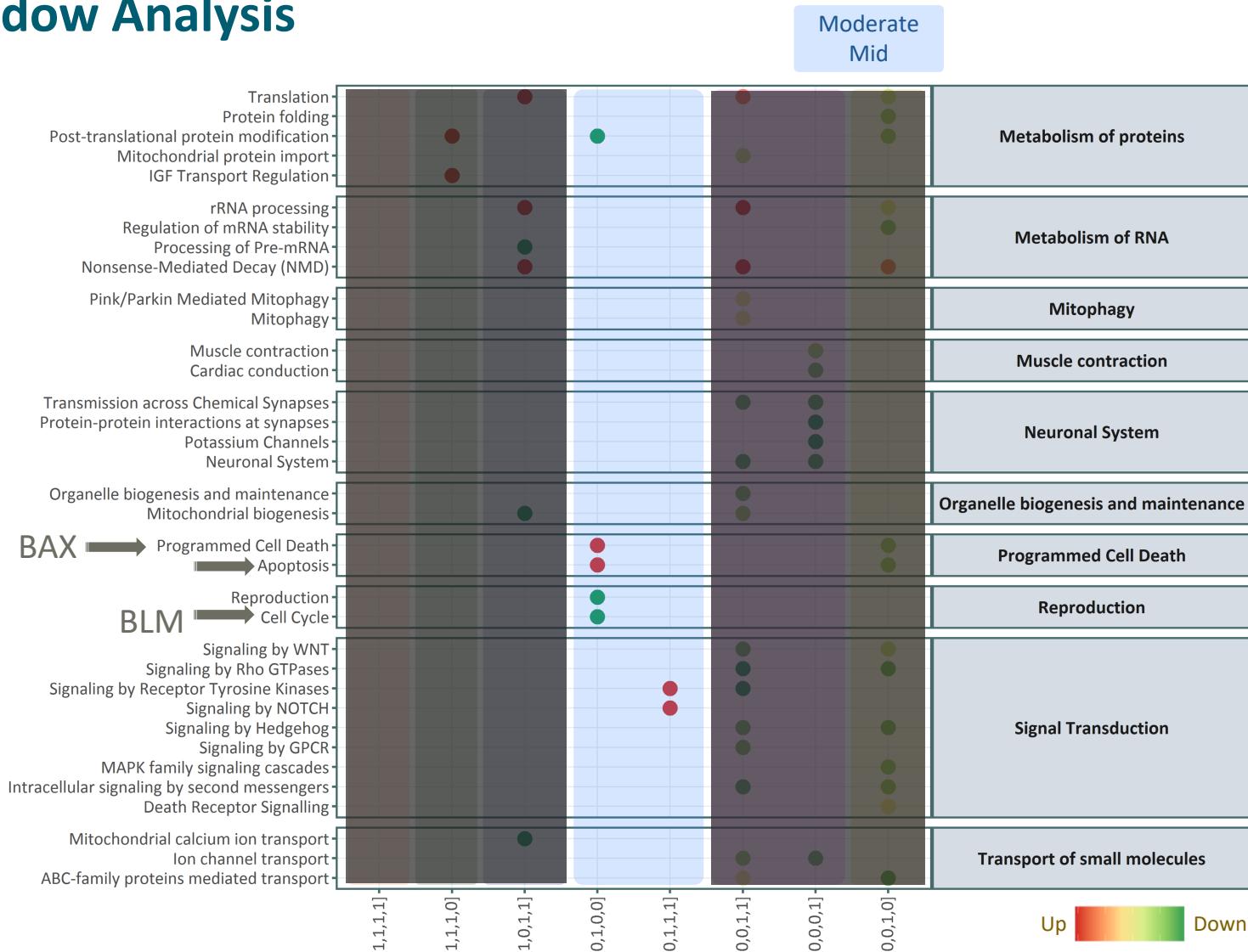
- ECM crisis
- MMP dysregulation
- BLM Repression





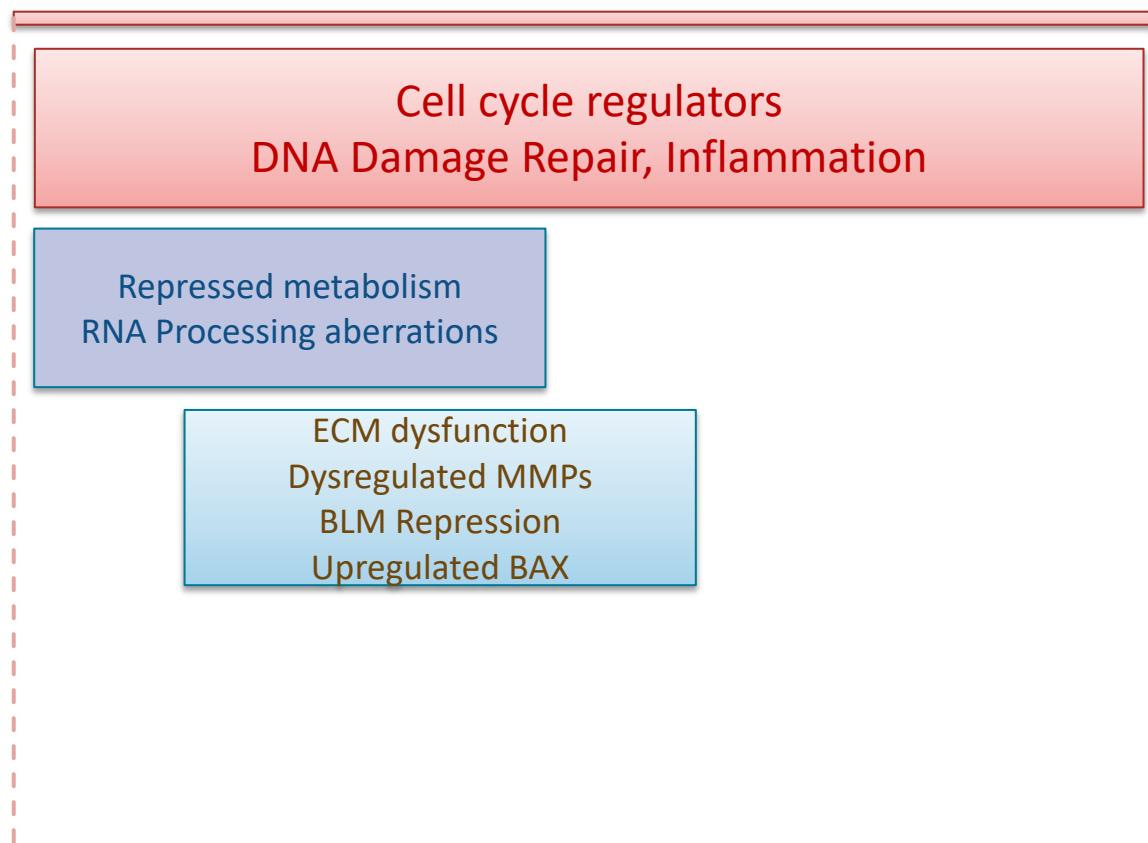
Moving Window Analysis

- BLM Repression
- BAX Upregulation





Moving Window Analysis





Moving Window Analysis

▪ Repressed energetics

▪ Declining immune response

Moderate Late





Moving Window Analysis

Moderate
Late

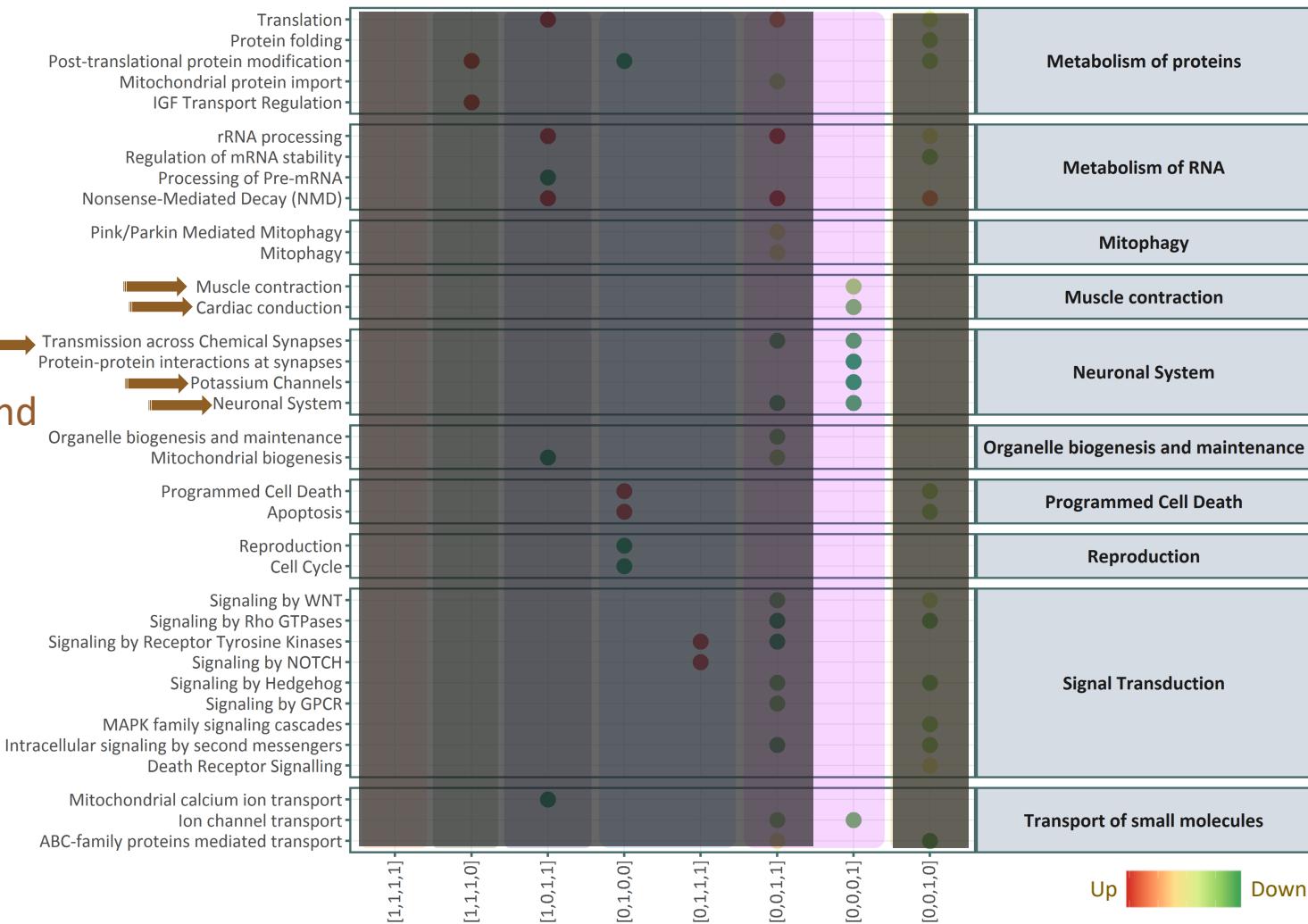
- Mitochondrial dysfunction
- Upregulated NMD
- Aberrant nutrient sensing





Moving Window Analysis

Moderate
Late

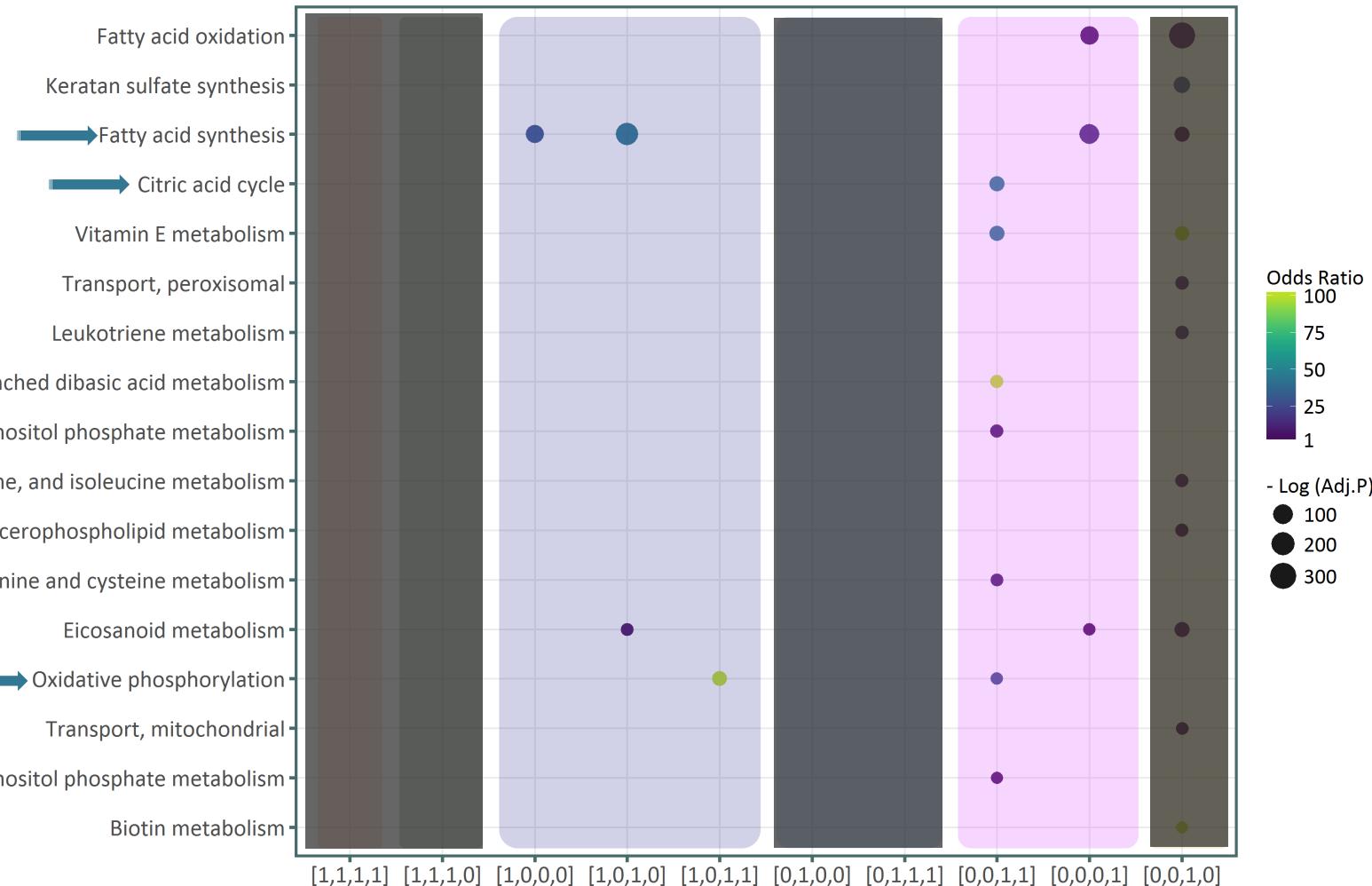


- Motor function and cognitive decline



Moving Window Analysis

Downregulated genes



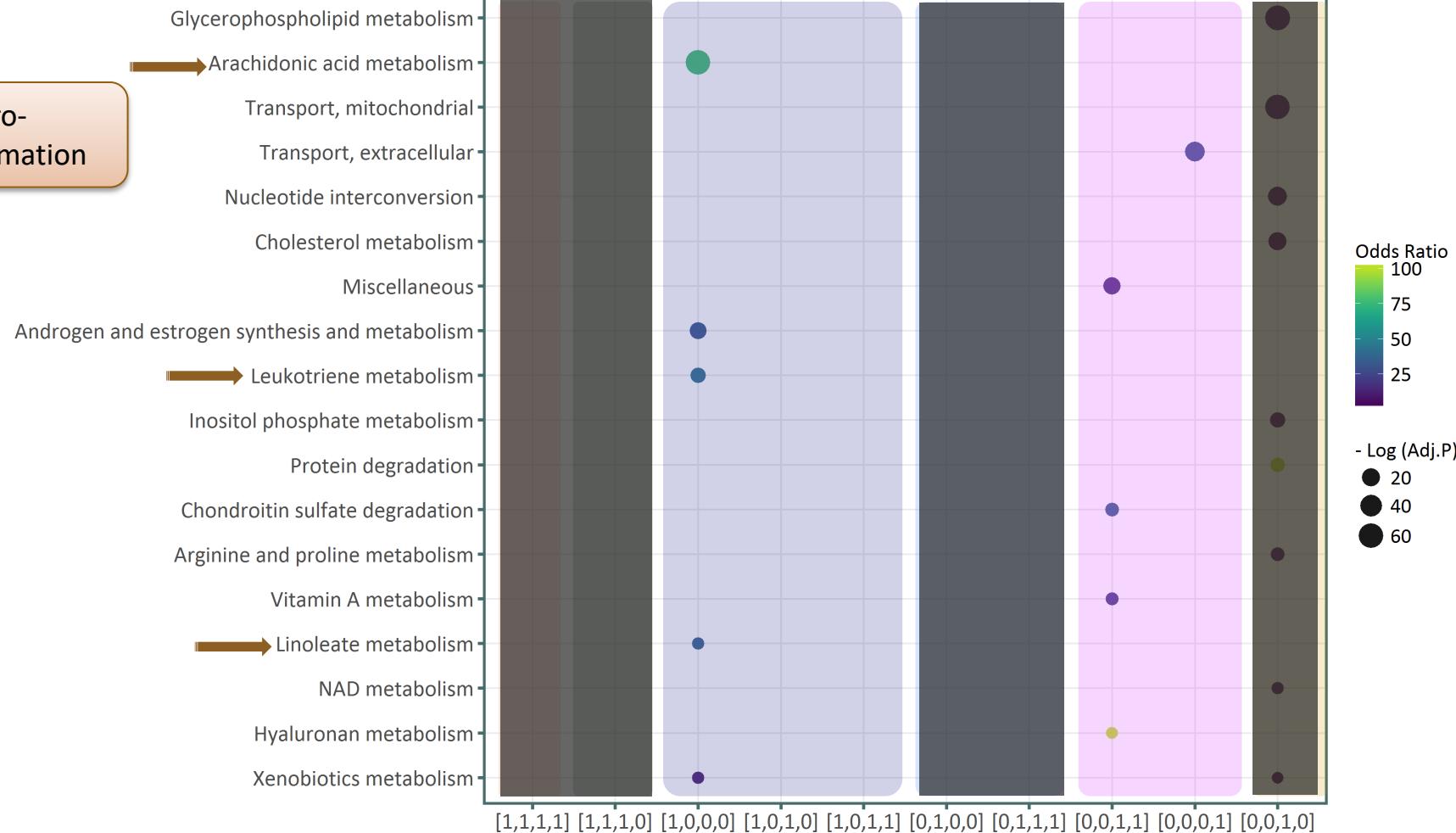


Moving Window Analysis

Upregulated genes

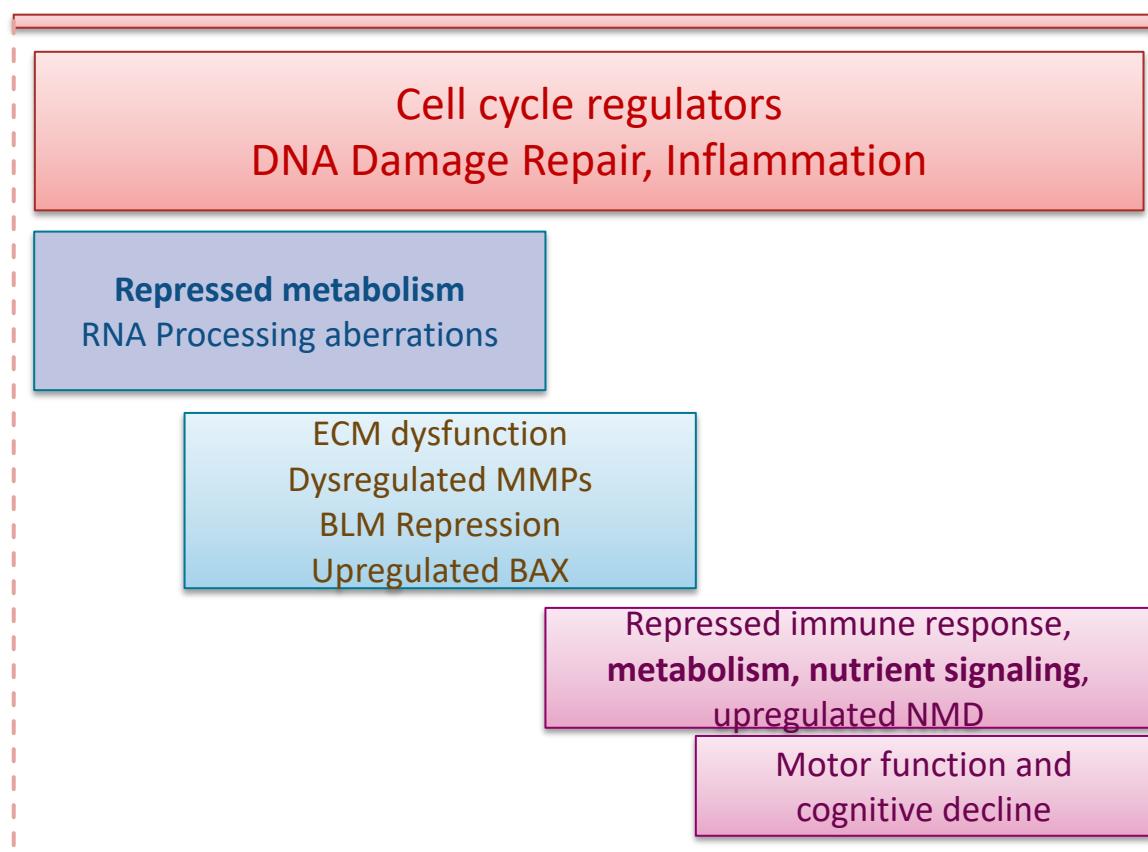
Pro-

Inflammation





Transcriptional signatures of human aging



Thank You for your attention!

