Leids Universitair Medisch Centrum

FOS Molecular Data Science 2020

Aging -

a multi-dimensional process:

translation from human to models

Vered Raz
Human Genetics
Leiden University Medical centre

Schedule

When	What: Animal models on ageing	Who	Where
13.30-14.00	Lecture: aging process and models	Vered Raz	
14.00-15.30	Self Study: Mouse model of Ageing	You	
15.30-17.00	Mouse model of Ageing: Presentation and Discussion	You	

Definitions:

- A multifactorial process
- Aging
- Models: human, animals or cellular

What is a multifactorial process?

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- **Spatial**
  - Systemic: all tissues are involved
    vs
  - A tissue-specific involvement
- **Temporal (time-dependent)**
  - Age of onset
  - An age-associated pattern
  - Progression: linear or non-linear
- **Molecular (regulators vs. signatures)**
  - Key regulators vs. multiple regulators
  - Key cellular processes vs. multiple processes

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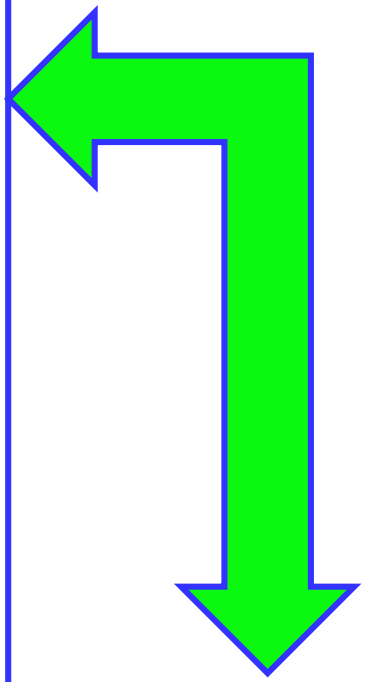

Prediction models

Aging – definition(s)

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Evolutionary biology:
1. An age-dependent or age-progressive **decline in intrinsic physiological function**, leading to an increase in age-specific mortality rate and a decrease in age-specific **reproductive rate**.
2. an age-progressive loss or de-tuning of **fitness (natural section)** or the *state of adaptation*.

Britannica:
Progressive physiological changes in an organism that lead to a **decline** of **biological functions** and of the organism's ability to adapt to metabolic stress (senescence).

Senescence: A biological process of growing older in a deleterious (harmful) sense.

Medical: The process of becoming older, a process that is genetically determined and environmentally modulated leading to an increase in disease risk.

WHO:
Biological: a process that is genetically determined and environmentally modulated.
Social: life transitions (causes and/or triggers)

Aging in human

Evolutionary biology:
1. An age-dependent or age-progressive **decline in intrinsic physiological function**, leading to a decrease in social function and overall activity.
2. an age-progressive loss or de-tuning *adaptation.*

Britannica:
Progressive physiological changes in an organism that lead to a **decline** of **biological functions** and of the organism's ability to adapt to metabolic stress (senescence).

Senescence: A biological process of growing older in a deleterious (harmful?) sense.

Medical: The process of becoming older, a process that is genetically determined and environmentally modulated leading to **an increase in disease risk**. **– what about the elderly who are are active and healthy?**

WHO:
Biological: a process that is epi-genetically determined and environmentally modulated.
Social: life transitions (causes and/or triggers)

Aging- a multifactorial biological process

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Onset

When onset start?
Diagnosis (Biomarkers?)

How to study?
- Chronological age?
- Molecular age?
- Metabolic age?

progression

- Cellular degeneration
- Tissue degeneration
- Organ function
- Tissue and organ communication

Aging- a multifactorial biological process

Aging: An increase in disease risk

Aging-associated chronic disorders in the general population

Adult-onset hereditary disorders

Healthy

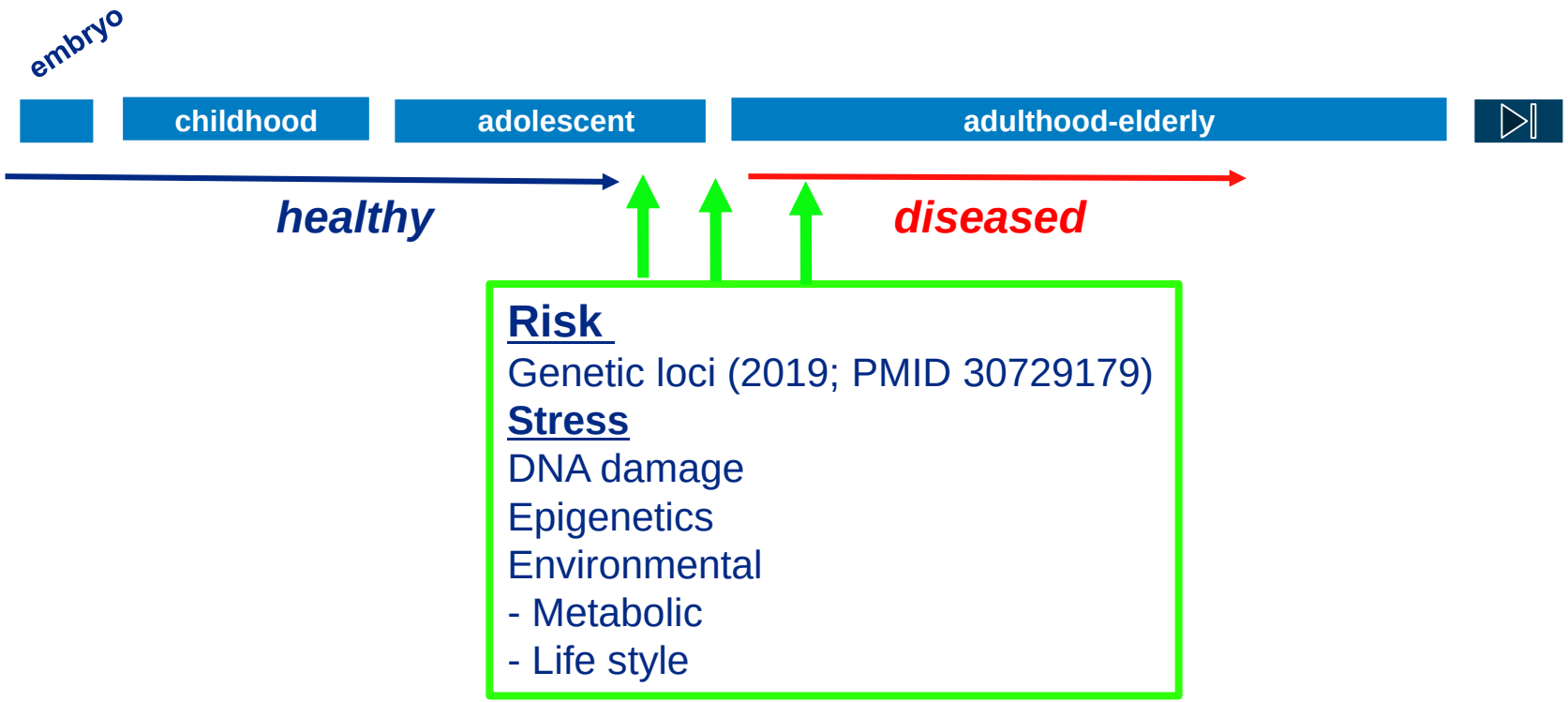
Aging-associated disorders

Hereditable

Mutations: germline

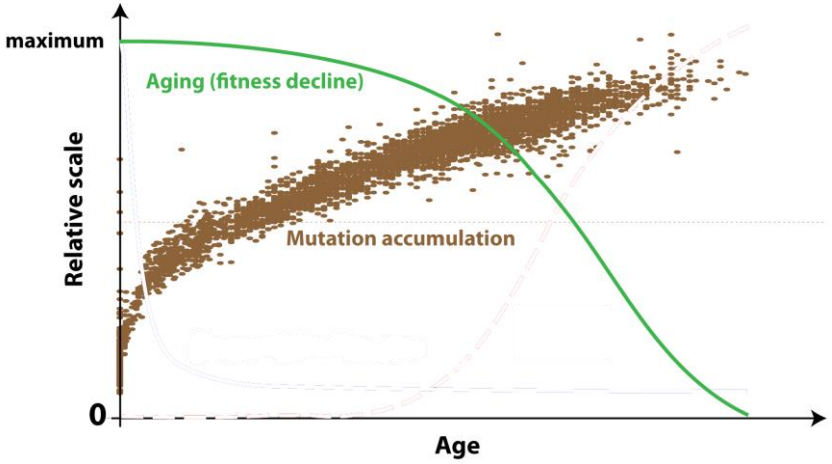
Non-Hereditable

Spontaneous
- de novo
- sporadic



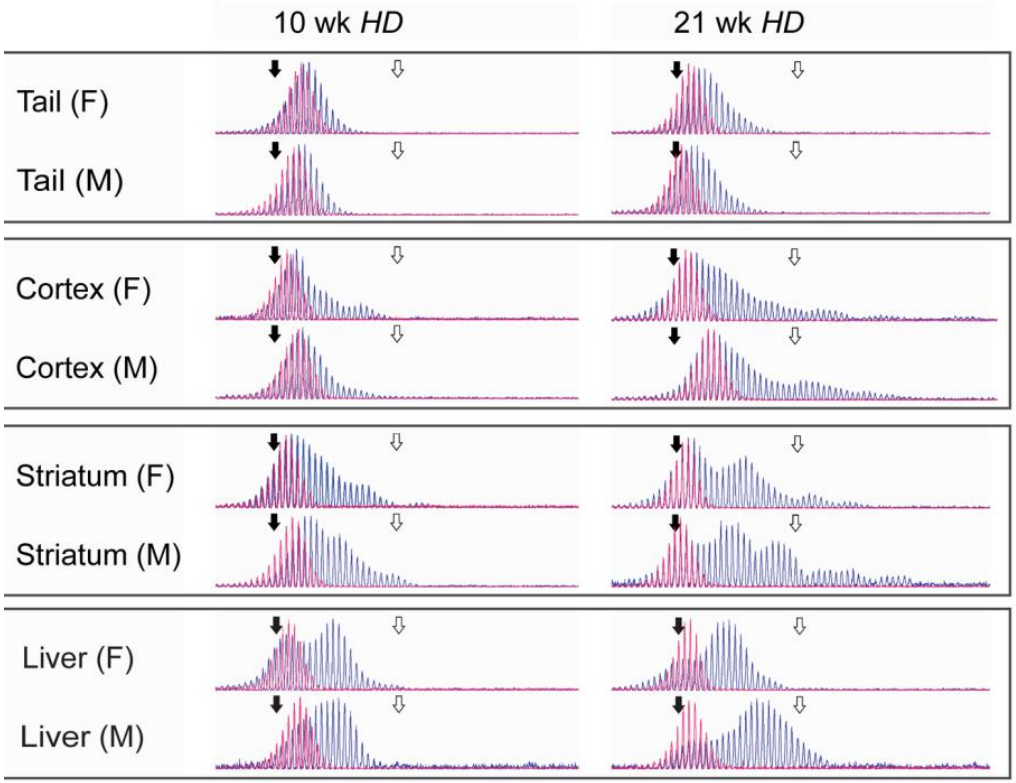
An Age-associated genomic instability

DNA damage



Modified from
Andrii I. Rozhok & James DeGregori

Age-associated somatic instability



Møllersen et al., PLoS Genet 2010

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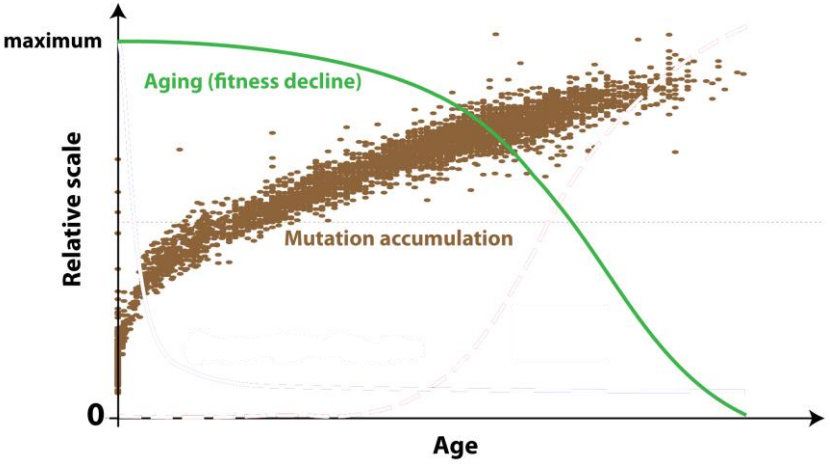

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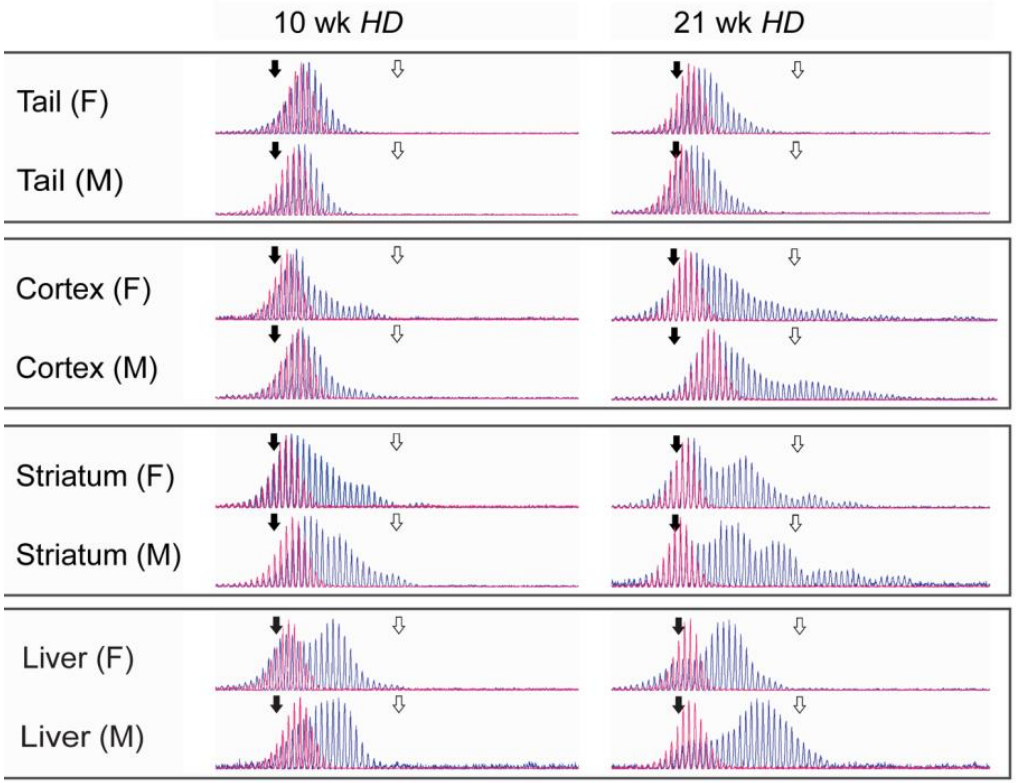


Tissue-specific somatic instability

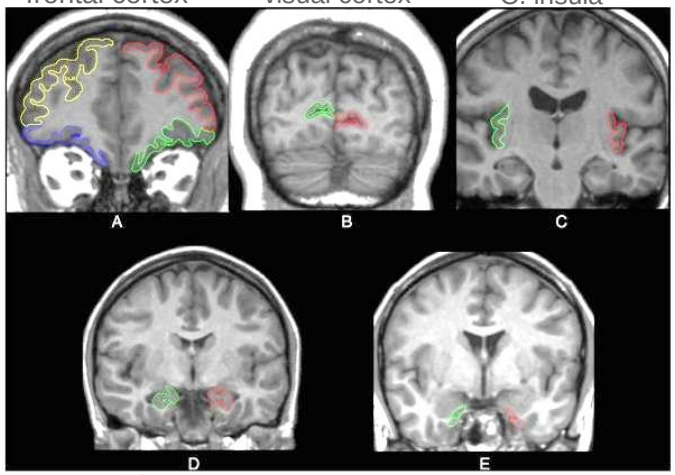
Møllersen et al., PLoS Genet 2010

Tissue specific age-associated changes

A. Lateral and orbito-frontal cortex

B. primary visual cortex

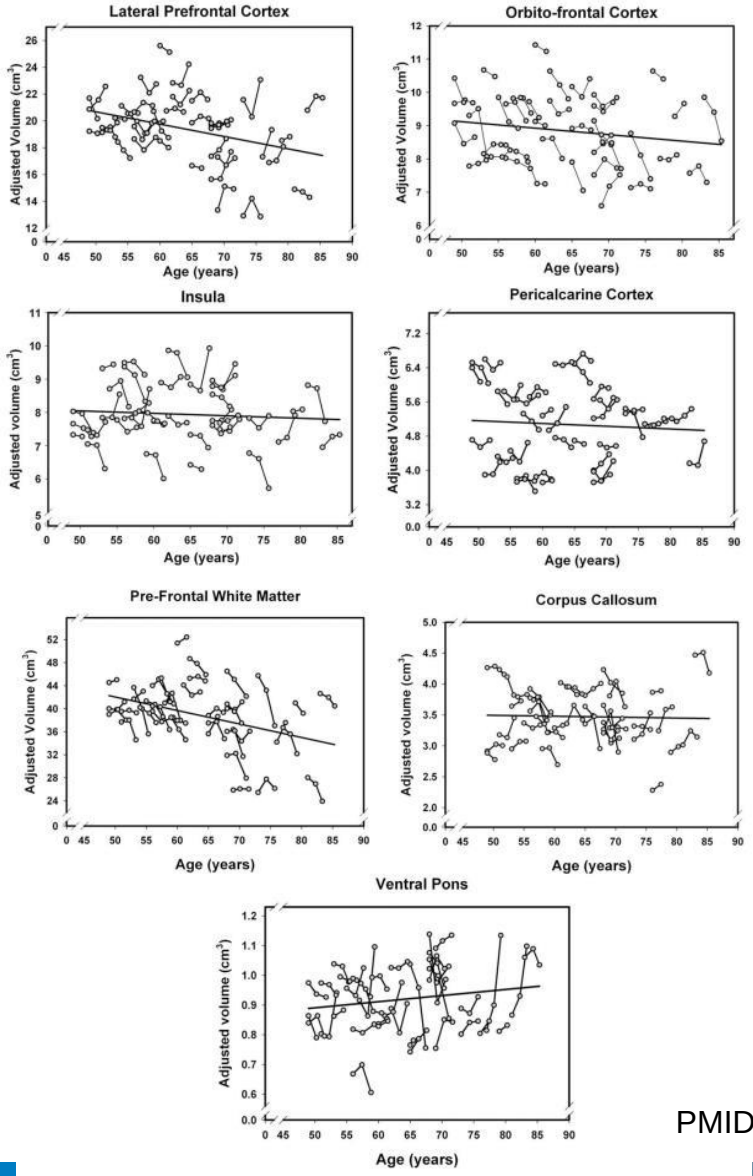
C. insula



D. hippocampus

E. entorhinal cortex

Study design:
Healthy individuals
Longitudinal MRI scan (2-3 per subject)
Age-range: (48-87)



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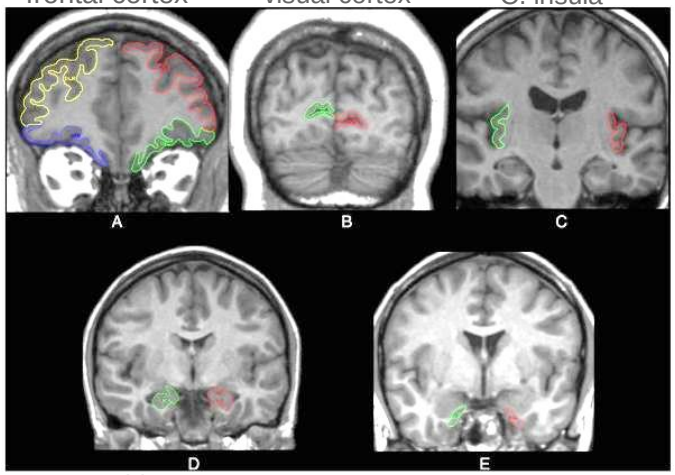

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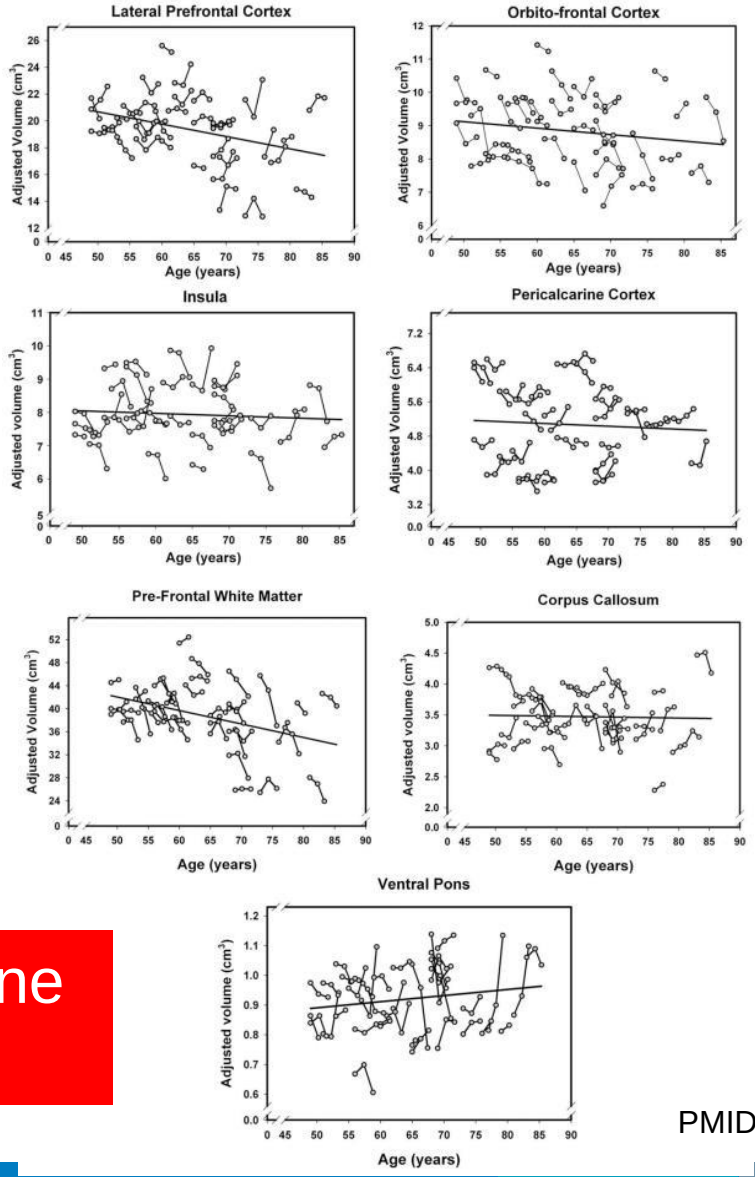

Study design:
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A tissue-specific functional decline within the humn brain

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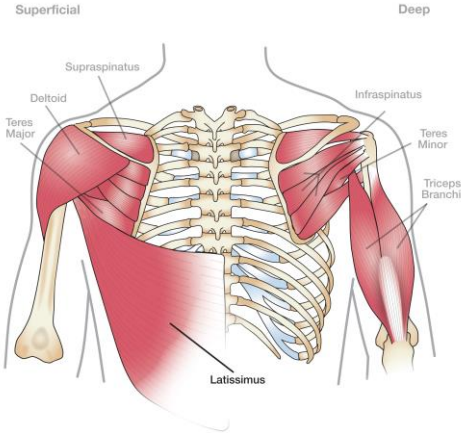
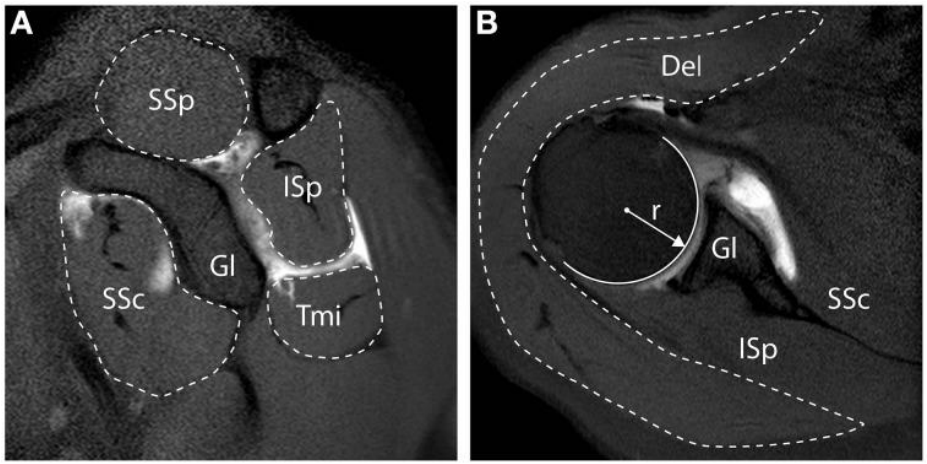
Age-associated shoulder diseases





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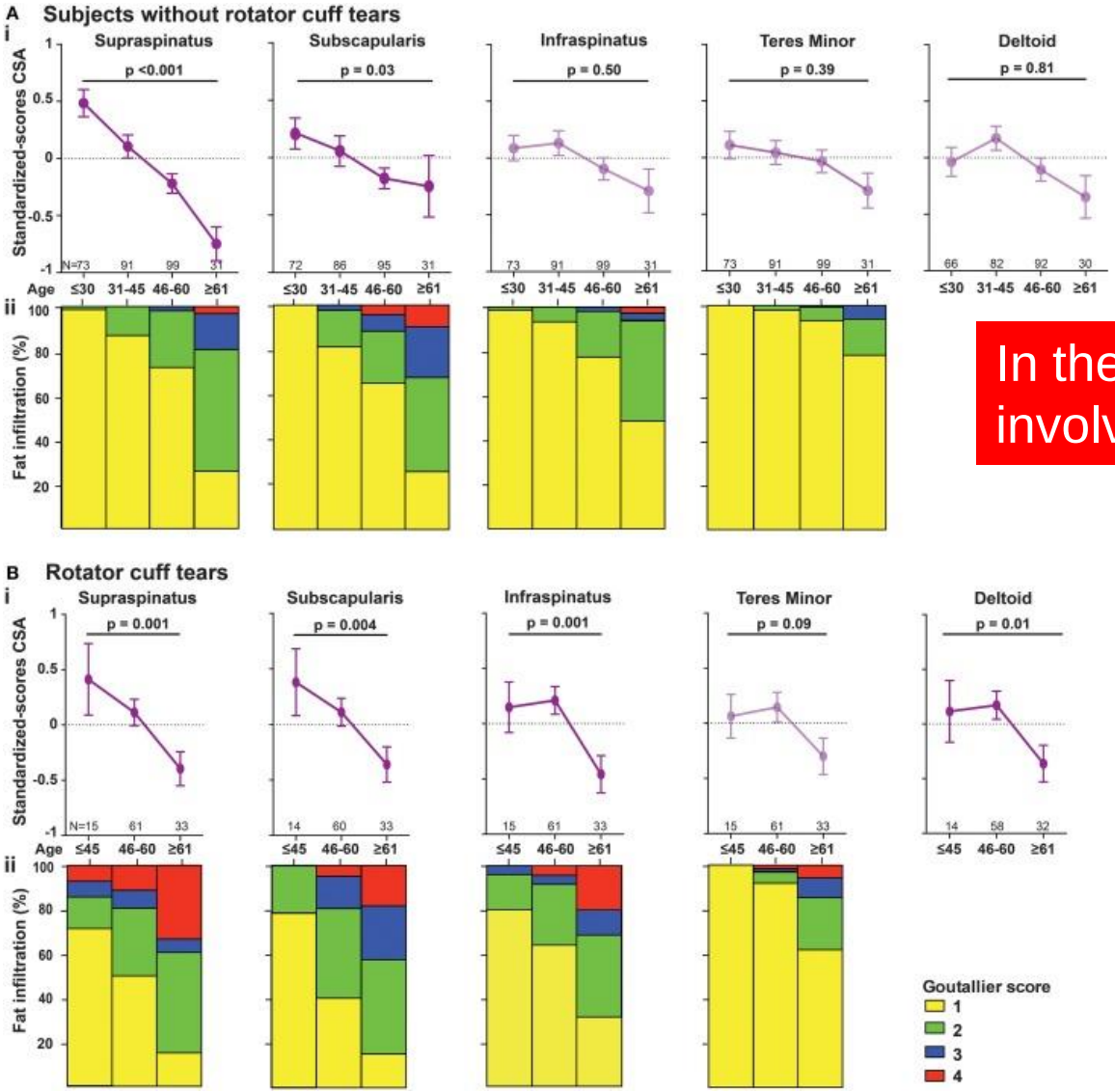
Progression of RC tear is age-associated



In the shoulder joint, muscle involvement is age-associated

PMID: 26733863

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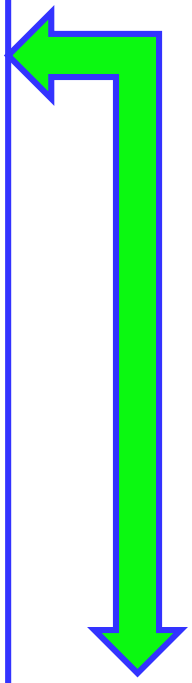


Prediction models

Assessment of aging using molecular data system

Large dataset (omics) - statistics

The *globaltest*: determine whether a global expression pattern of all genes or a group of genes is significantly related to a feature, such as disease, clinical feature, biological pathway or physiological condition.

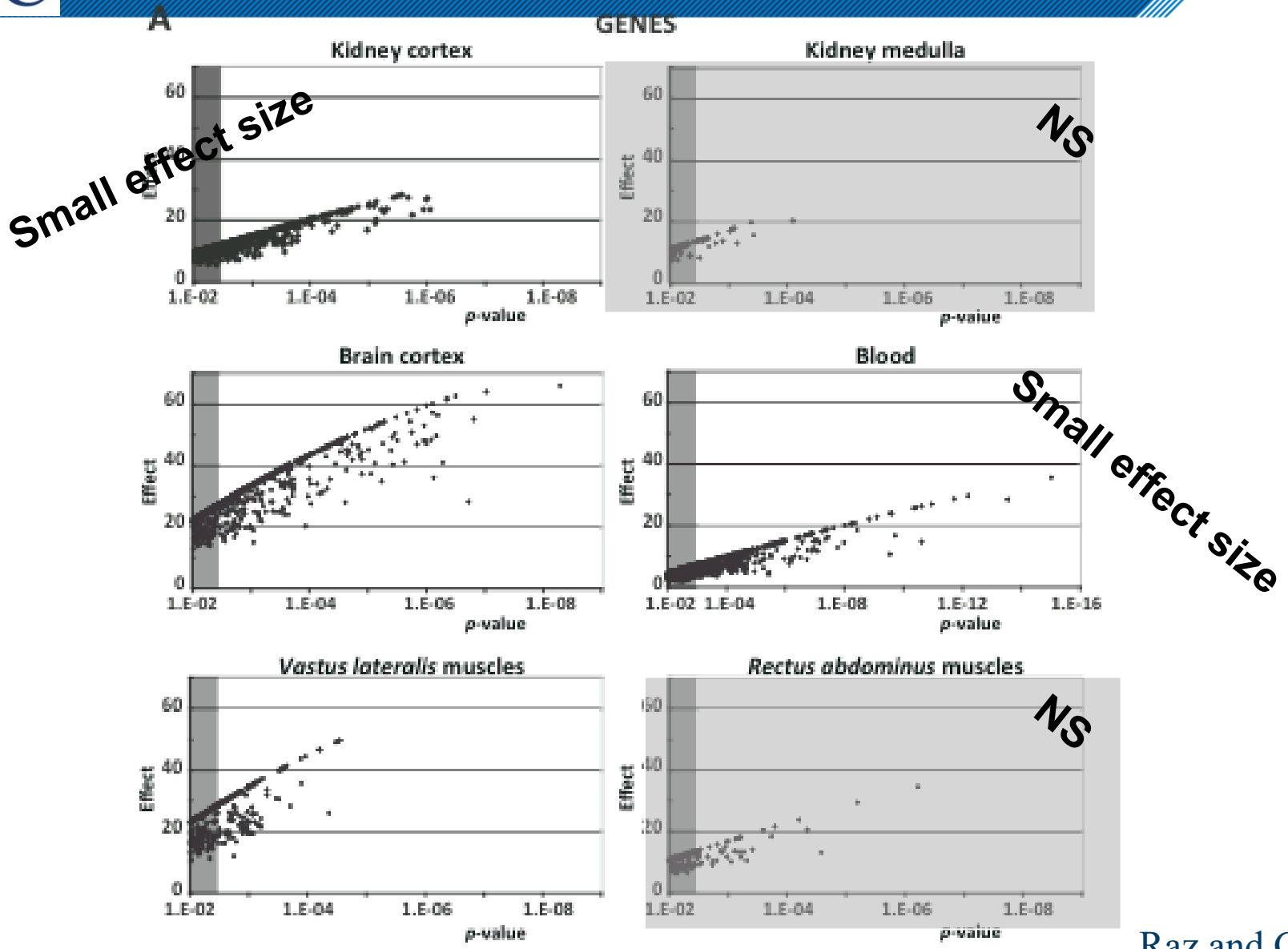
J. Goeman

Age-associated expression profiles in human organs

The *globaltest in cross-sectional RNA microarray*

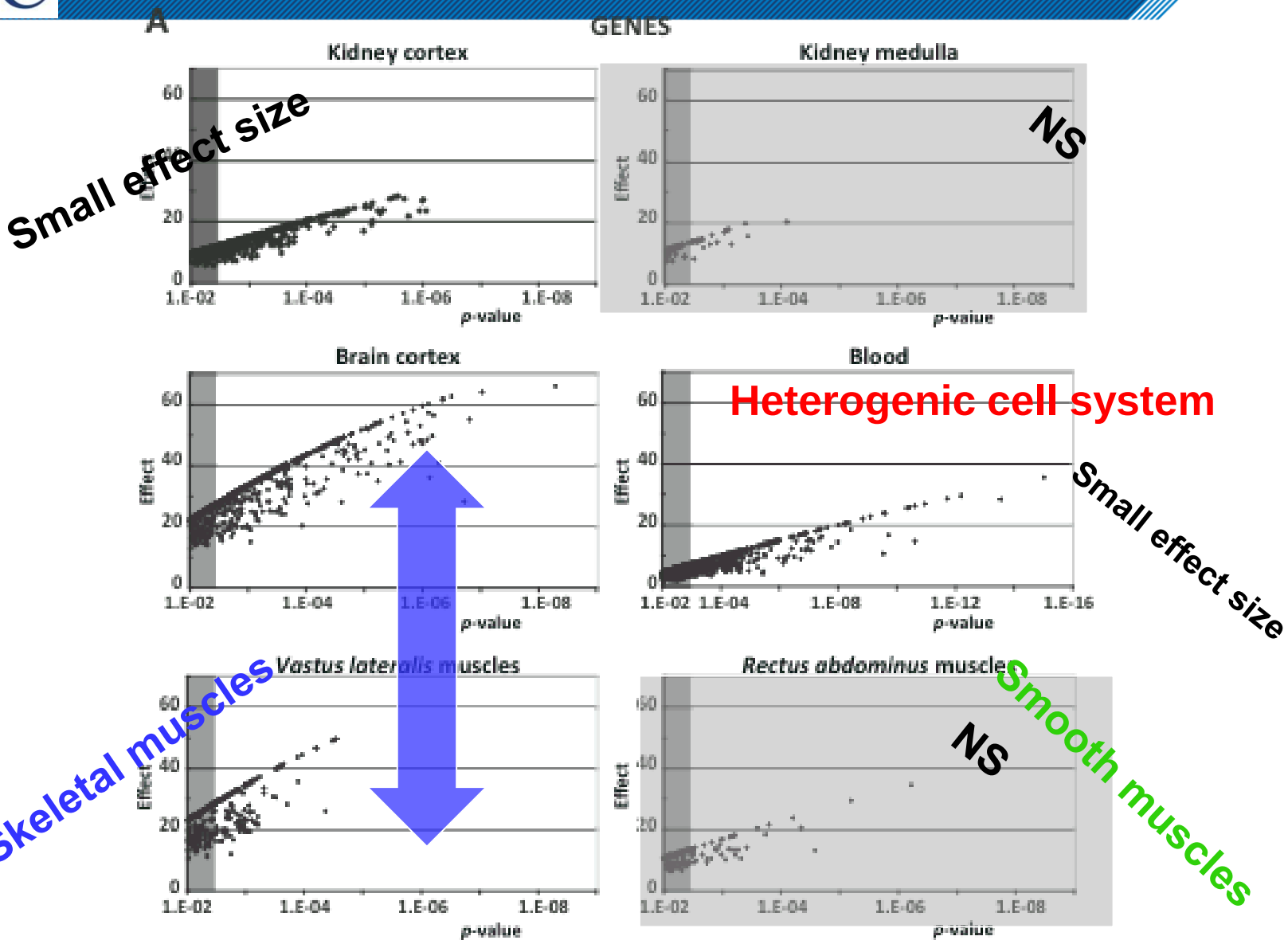
Tissue	Nr of samples	Age range	*P*-value	Effect size: *Statistics*	Effect size: *Expected*	SD	% age-regulated genes*	% age-regulated KEGG pathways
Whole blood	150	42-102	**0.001**	1.28	0.68	0.10	22.0	69.4
Kidney cortex	70	27-92	**0.002**	4.25	1.42	0.59	13.3	69.0
Brain cortex	30	26-106	**0.004**	8.96	3.57	1.35	23.5	58.2
Vastus lateralis muscles	29	35-89	**0.015**	5.52	3.70	0.68	11.7	52.3
Kidney medulla	60	29-92	0.150	2.27	1.72	0.57	5.5	7.0
Rectus abdominis muscles	62	24-83	0.247	2.00	1.67	0.78	5.9	5.3

Globaltest analysis in Aging datasets



Raz and Goeman

Globaltest analysis in Aging datasets



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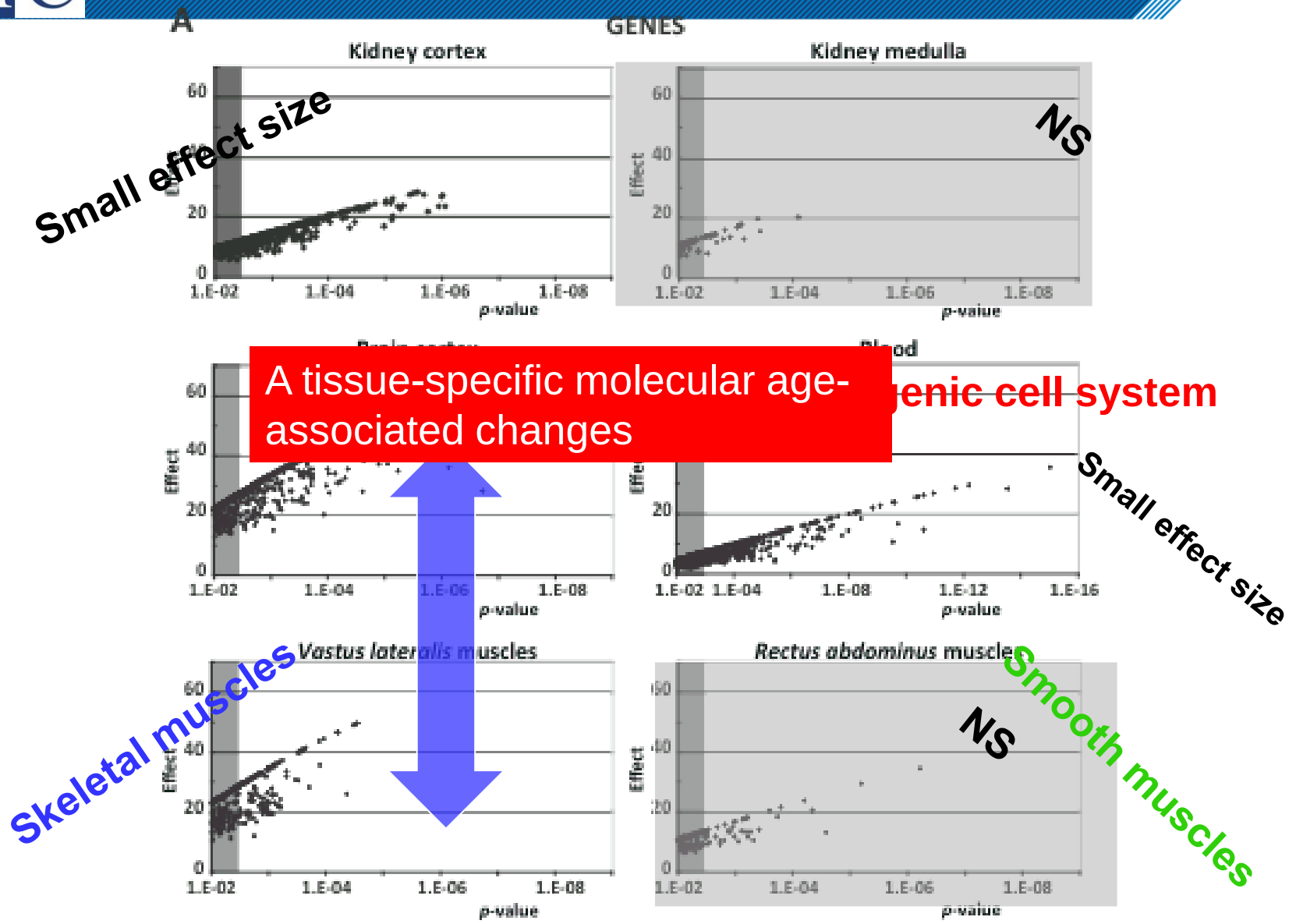

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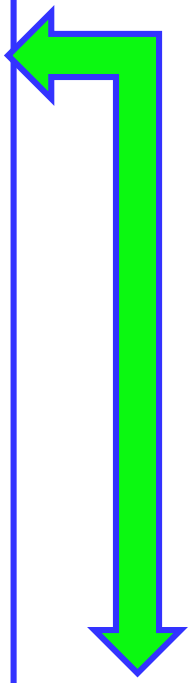
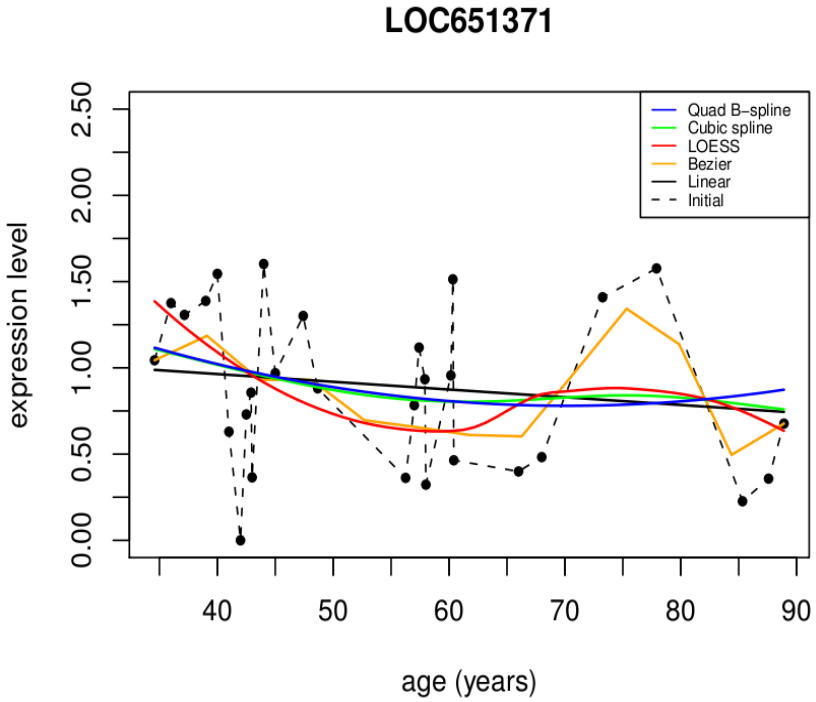
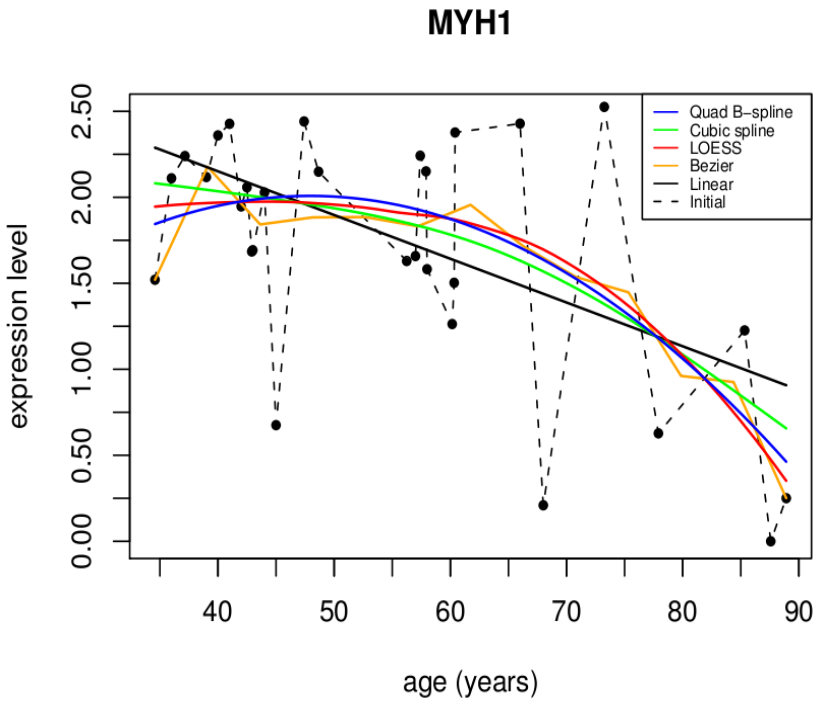


Prediction models

Age-associated temporal changes: which model is the best?



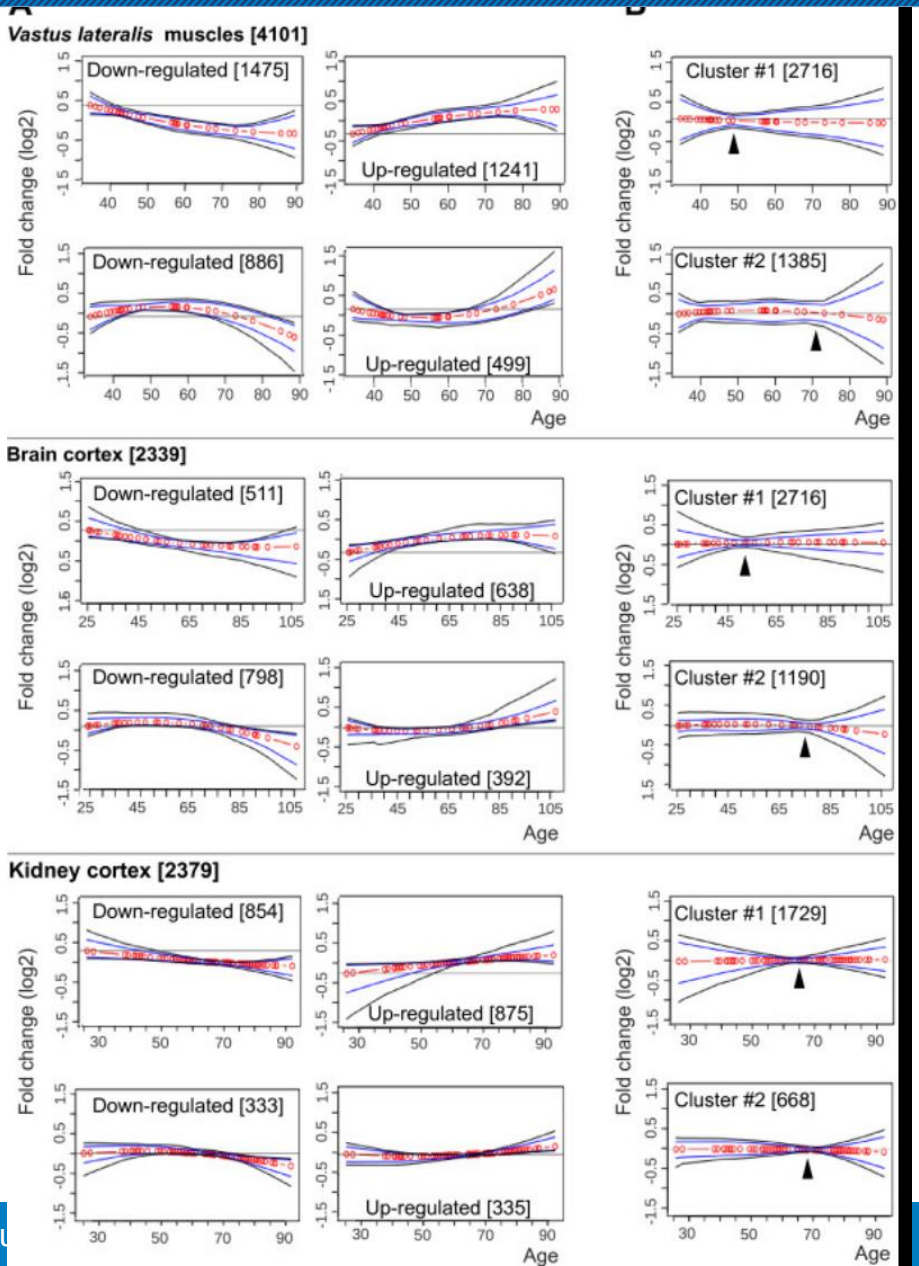


Average correlation		
Comparison	Fitted	Residuals
Cubic spline - Quadratic B-spline	0.951	0.998
Quadratic B-spline - LOESS	0.885	0.994
LOESS - Cubic spline	0.965	0.996
Linear - Quadratic B-spline	0.701	0.983
Average covariance		
Comparison	Fitted	Residuals
Cubic spline - Quadratic B-spline	0.015	0.173
Quadratic B-spline - LOESS	0.017	0.171
LOESS - Cubic spline	0.016	0.170
Linear - Quadratic B-spline	0.010	0.179

Regression models: which to use in aging studies?

PMID: 24524210

Age-associated temporal changes
A bio-statistical approach



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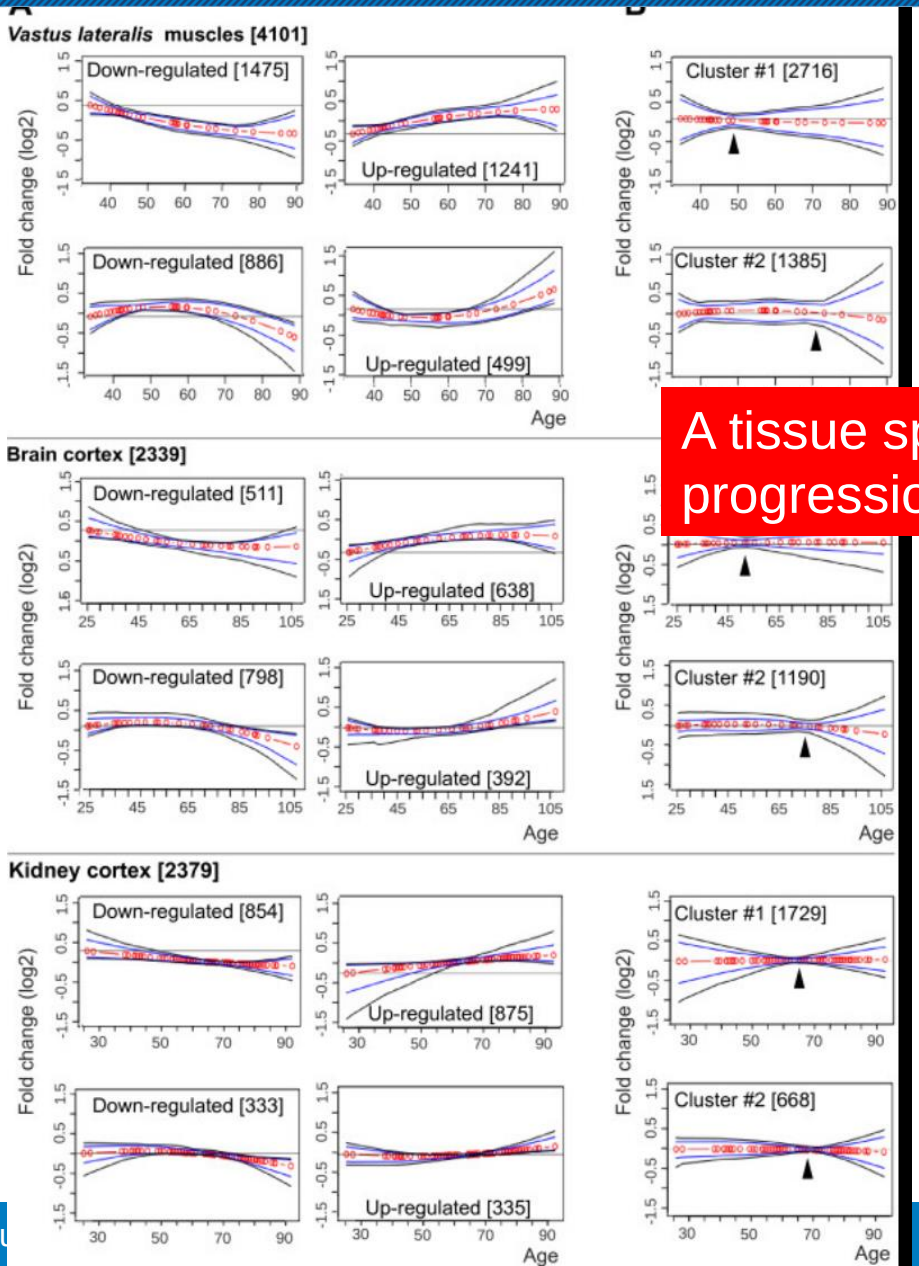
Age-associated temporal changes
A bio-statistical approach



A tissue specific progression

PMID: 24524210

What is a multifactorial process?

- **Spatial (RNA expression profiles)**
  - all tissues or
  - Tissue specific involvement
- **Temporal**
  - Age of onset (??)
  - Tissue specific age-associated pattern
- **Molecular**
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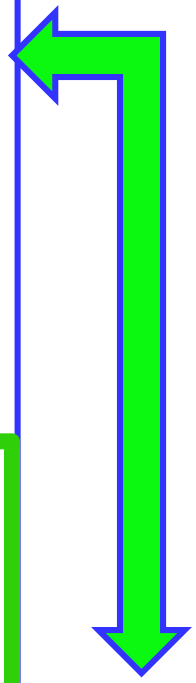


Prediction models

Molecular examples:

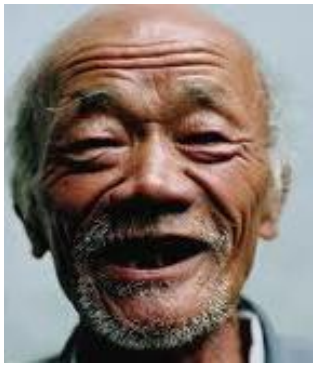
Key regulators vs. multiple regulators

Key cellular processes vs. multiple processes

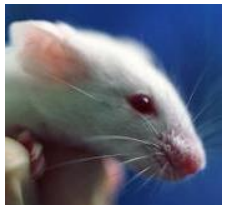
Aging – model organisms

adulthood

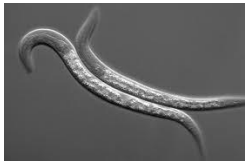
Human



Years

mouse 

Months

worm 

Days

Time scale

The choice of the model system

Which model to choose?

Every group gets a different an aging-related assignment:

- Describe the ageing-associated condition (problem): consider tissue specificity, age of onset, progression.
- Discuss potential models for the condition and the tools to develop potential option(s) to study it in order to develop therapy.

Aim: to find the fastest and least expensive path to develop a therapy

Aid: Attached literature

Conditions:

- Sarcopenia :reduced muscle function: muscle weakness and atrophy
- Dementia: reduced cognitive capacity with age
- Autoimmune disorders: reduced ability to distinguish self from nonself (identification of foreign antigens
- Arthrosis: Degeneration of connective tissues

literature:

- Sarcopenia :reduced muscle function: muscle weakness and atrophy
10.1016/j.ijcard.2017.03.152
https://www.sciencedirect.com/science/article/pii/S0142961215002483

- Dementia: reduced cognitive capacity with age
https://doi.org/10.1016/j.neubiorev.2020.02.012
10.1016/j.brainres.2019.146427

- Autoimmune (blistering) disorders: reduced ability to distinguish self from nonself (identification of foreign antigens
https://onlinelibrary.wiley.com/doi/full/10.1111/exd.13415

- Arthrosis: Degeneration of connective tissues
- https://www.sciencedirect.com/science/article/abs/pii/S0014299150026642