Bioinformatics Analysis of Human Ageing From Transcriptomics to Phenomics

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Background

- Ageing is a major risk factor of a plethora of human diseases such as cancer, cardiovascular and neurodegenerative diseases[1,2]. Thus, a better understanding of the biology of ageing has the potential to prevent or delay the on-set of age-related diseases.
- There is a general consensus that ageing results from the accumulation of "damage", but the specific molecular damages are still debated.
- The identification of specific molecular pathways and biological processes that are dysregulated during ageing and that are also relevant in human diseases and traits, may lead to a better understanding of the biology of human ageing.

Age-related changes

- We analyzed human transcriptomics data from the Genotype-Tissue Expression (GTEx) project to elucidate age-related gene expression changes using a linear mixed effect model[3] (see Fig. 1).

$$y_{ijk} = t_i + g_j + b_k + e_{ijk}$$

- Here, y_{ijk} represents the *ijk*-th logarithmic gene expression (RNA – Seq) in the t_i tissue, at the g_j factor, e.g. age, and in the b_k individual. The variable *e* denotes the random error.
- A human phenotype – gene association dataset was manually curated from GWAS database and Mendelian mutations, comprising 3358 conceptual entities or traits and 7257 genes.
- Gene Ontology (GO) semantic similarity scores based on GO biological processes were calculated between the ageing genes (see Fig. 2) and the genes associated with human phenotypes to identify a subset of human traits that are closely connected to ageing.

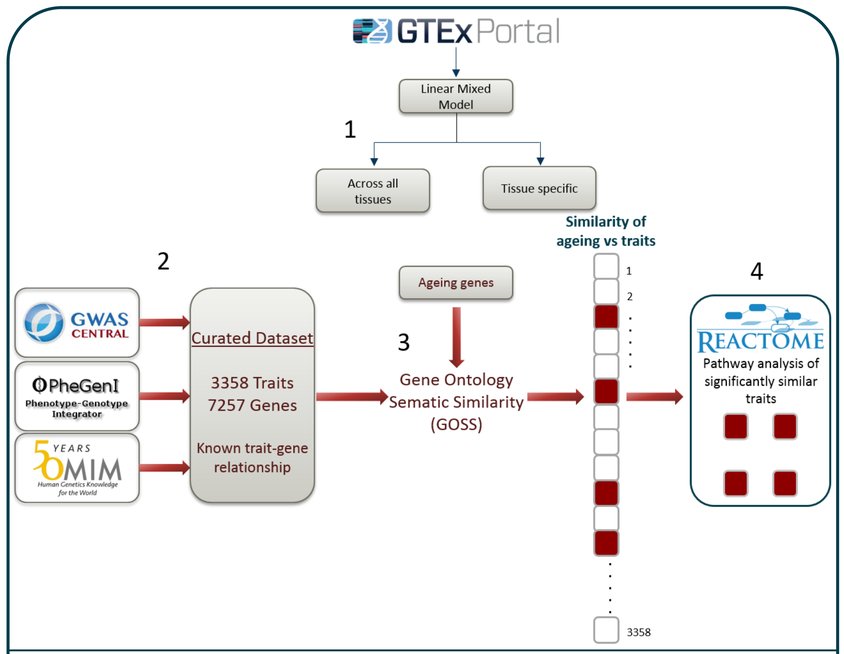
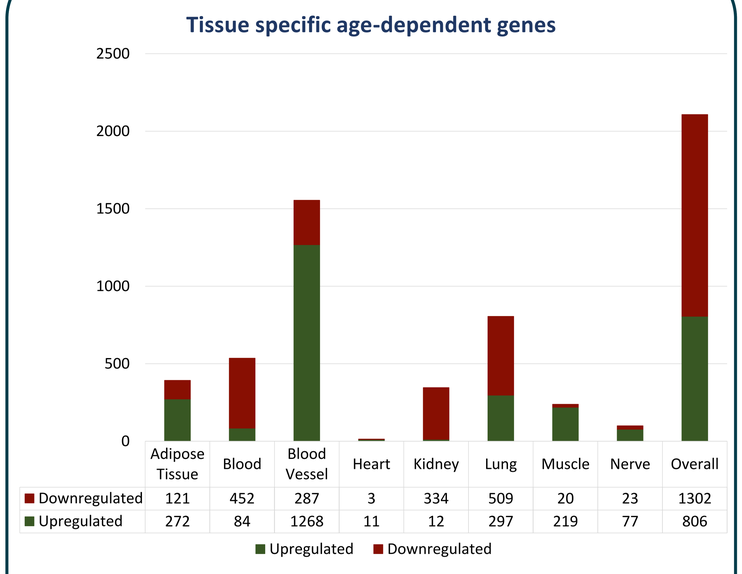


Figure 1: Schematic of the bioinformatics analysis pipeline.

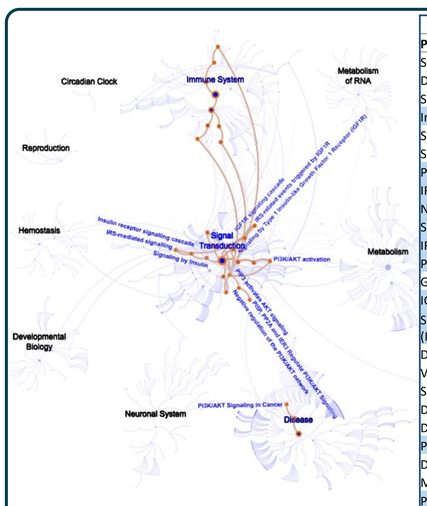


	Adipose Tissue	Blood	Blood Vessel	Heart	Kidney	Lung	Muscle	Nerve	Overall
Downregulated	121	452	287	3	334	509	20	23	1302
Upregulated	272	84	1268	11	12	297	219	77	806

Figure 2: Tissue specific age-dependent genes

Ageing Alterations

- A Reactome pathway enrichment analysis showed that genes from ageing-similar human traits were enriched for the Insulin growth factor (IGF) signaling (IIS) pathways (see Fig 3).



Reactome Pathway Enrichment Analysis	
Pathway name	**FDR**
Signaling by Interleukins	3.75E-12
Diseases of signal transduction	1.72E-10
Signaling by SCF-KIT	2.59E-10
Insulin receptor signalling cascade	3.04E-10
Signaling by VEGF	3.04E-10
Signaling by EGFR	3.04E-10
PIP3 activates AKT signaling	3.04E-10
IRS-mediated signalling	3.04E-10
Negative regulation of the PI3K/AKT network	3.04E-10
Signaling by Insulin receptor	3.05E-10
IRS-related events triggered by IGF1R	3.05E-10
PI3K/AKT activation	3.05E-10
GAB1 signalosome	3.05E-10
IGF1R signaling cascade	3.05E-10
Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	3.19E-10
Downstream signal transduction	3.90E-10
VEGFA-VEGFR2 Pathway	4.34E-10
Signaling by PDGF	4.34E-10
DAP12 signaling	4.34E-10
Downstream signaling events of B Cell Receptor (BCR)	6.34E-10
PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	6.34E-10
DAP12 interactions	9.63E-10
MAPK1/MAPK3 signaling	1.22E-09
PI3K/AKT Signaling in Cancer	1.22E-09

Figure 3: Pathway enrichment analysis of human traits related to ageing genes.

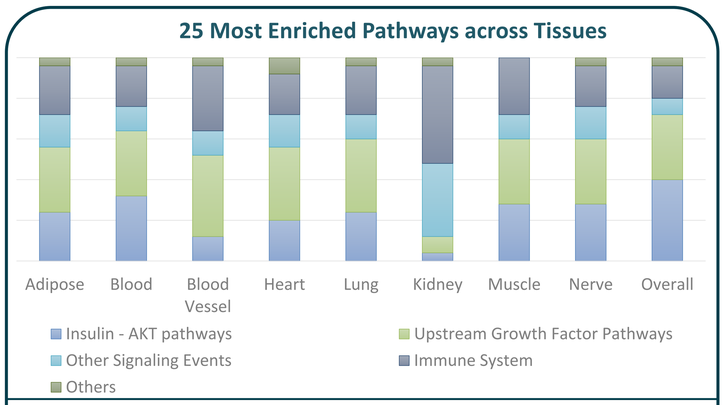


Figure 4: Reactome enrichment analysis across tissues

- Figure 4 shows the composition of the top 25 enriched pathways from the tissue-specific analysis.
- IGF-IIS pathways again prominently appear among the top 25 enriched pathways across all tissues, along with upstream growth factor signaling pathways that act via P13K signaling cascade and immune system related pathways.
- Table 1 shows the list of ageing-similar human traits.

Ageing-Similar Human Traits		
Acampomelic campomelic dysplasia	Crohn disease-associated growth failure	Susceptibility to cerebral malaria
Adenocarcinoma of lung	Autosomal recessive cutis laxa	Martsolf syndrome
Abdominal aortic aneurysm	Transient neonatal cyanosis	Mast syndrome
Aplastic anemia	Digenic deafness	Microvascular complications of diabetes
Type 5D distal arthrogryposis	Permanent neonatal diabetes mellitus	Muscular dystrophy
Lethal arthrogryposis with anterior horn cell disease	Ehlers-Danlos syndrome, type VIIC	Somatic myelofibrosis
Ataxia-telangiectasia	Gastric cancer risk after H. pylori infection	Myocardial infarction
Atrichia with papular lesions	Glioma	Nanophthalmos
Basal cell carcinoma	Hepatocellular cancer	Postmenopausal Osteoporosis
Basal ganglia calcification	Histiocytosis-lymphadenopathy plus syndrome	Ovarian cancer
Budd-Chiari syndrome	Resistance to HIV-1	Piebaldism
Campomelic dysplasia with autosomal sex reversal	Susceptibility to intracranial hemorrhage in brain cerebrovascular malformations	Proliferative vasculopathy and hydraencephaly-hydrocephaly syndrome
CARASIL syndrome	Susceptibility to Kaposi sarcoma	Primary pulmonary hypertension
Cardiovascular function	Lymphangioleiomyomatosis	Systemic juvenile rheumatoid arthritis
Colorectal cancer	Somatic B-cell non-Hodgkin Lymphoma	Saethre-Chotzen syndrome
Cowden syndrome	Mantle cell Lymphoma	Squamous cell carcinoma
Somatic T-cell prolymphocytic leukemia	Follicular thyroid carcinoma	Autosomal dominant woolly hair

Table 1: Ageing-similar human traits

Summary and Outlook

- Age-related changes in human transcriptomics are closely linked to human phenotypes that are related to alterations in nutrition signaling pathways (insulin, growth factor) and immune system response.
- Direct GO enrichment analysis of the ageing genes produced starkly different results, indicating a major role of mitochondria, inflammatory response and oxidative stress[4].
- Overall, our analysis pointed to the dysregulation of signaling pathways as a possible driver of human age-related phenotypes.

Acknowledgement

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References

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