Bridging Transcriptomics and Phenomics in the Analysis of Human Ageing

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Background

- Ageing is a complex trait and a major risk factor of a plethora of human diseases with varying pathologies[1,2]. There is a general consensus that ageing results from the accumulation of "damage".
- Vast research in biogerontology using model organisms has identified highly conserved cellular pathways involved in ageing. But, the genetic factors modulating human ageing may be different from other animals because of differences in evolutionary selection.
- Thus, 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.

Bioinformatics Pipeline

- We analyzed human transcriptomics data from the Genotype-Tissue Expression (GTEx) project to determine genes that are differentially expressed with age 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 and the genes associated with human phenotypes to identify a subset of human traits that are closely connected to ageing.

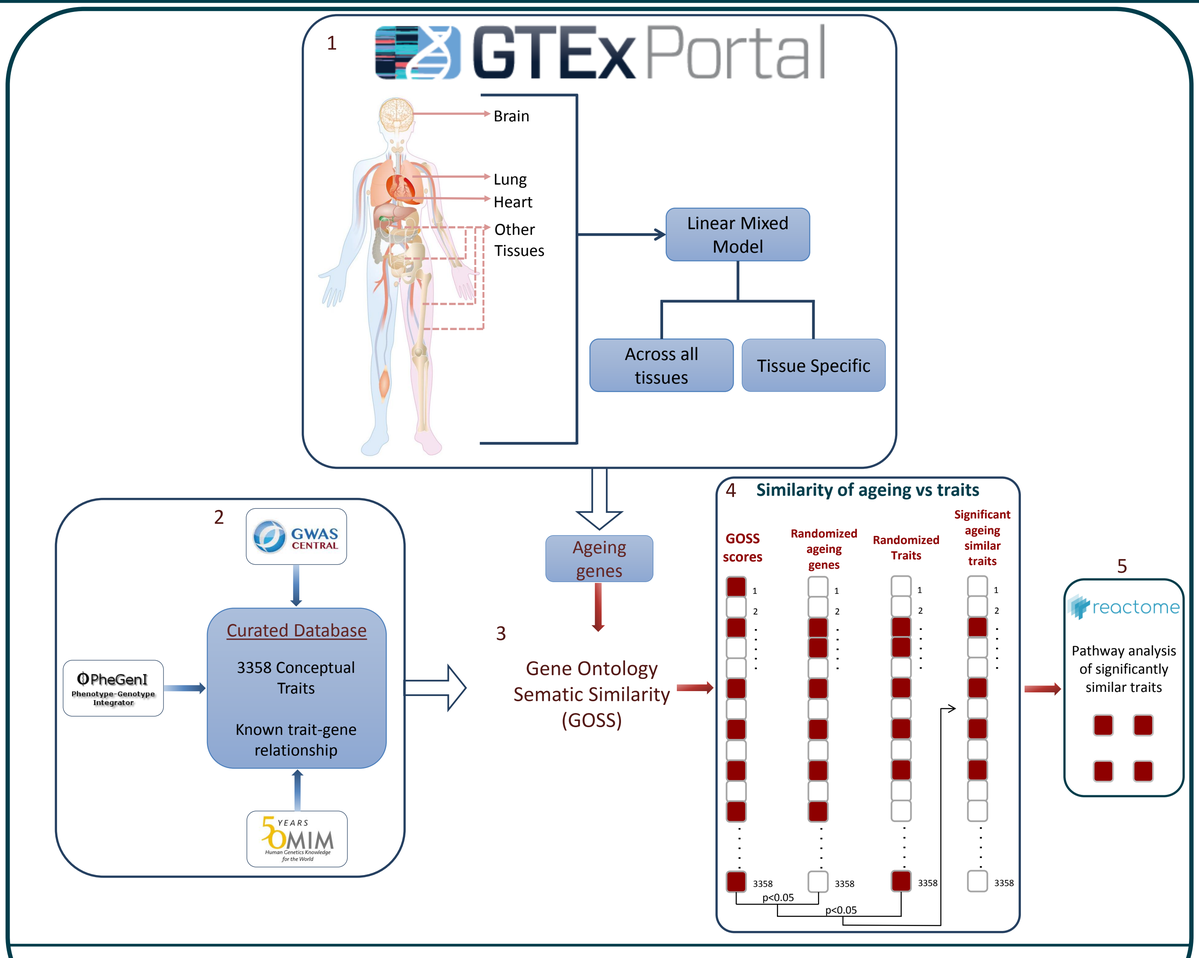

Figure 1: Schematic of the bioinformatics analysis pipeline.

Results

- The enrichment analysis of genes related to these traits pointed to immune system, cellular response to stress, DNA repair mechanisms and signal transduction pathways involved in the insulin receptor signaling cascade, insulin growth factor receptor and other growth factor signaling pathways (e.g. EGFR, VEGF) (see Fig. 2).

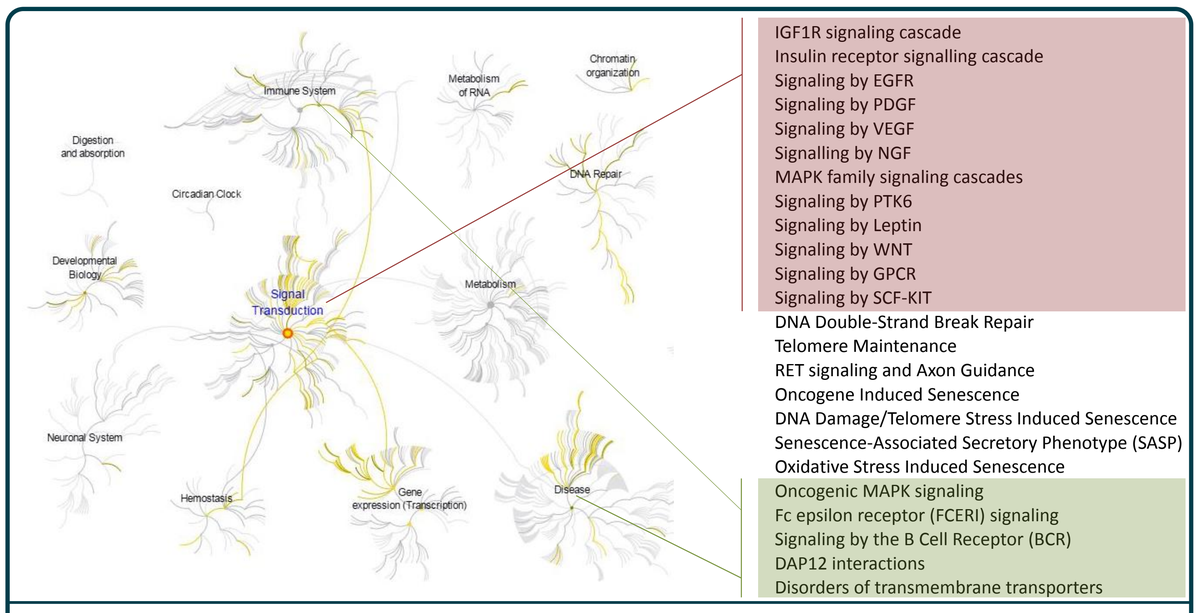

Figure 2: Pathway enrichment analysis of human traits related to ageing genes.

Ageing-similar Human Traits		
3q21q26 syndrome	Diabetes mellitus	Lung cancer
Multiple colorectal Adenomas	Dyserythropoietic anemia	Macular degeneration
Alopecia universalis	Dyskeratosis congenita	Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome
Aortic Aneurysm	Eosinophilia	Melanoma
Atrichia with papular lesions	Progressive myoclonic Epilepsy	MHC class II deficiency
Bare lymphocyte syndrome	Fanconi anemia	Nephropathy due to CFHR5 deficiency
B-cell non-Hodgkin lymphoma	Feingold syndrome	Neuromyotonia and axonal neuropathy
Beckwith-Wiedemann syndrome	Floating-Harbor syndrome	Oculoauricular syndrome
Blood group--Lutheran inhibitor	Focal facial dermal dysplasia	Palmoplantar hyperkeratosis and true hermaphroditism
Early-onset Breast cancer	Fragile X syndrome	Palmoplantar hyperkeratosis with squamous cell carcinoma
Brittle cornea syndrome	Gaucher Disease	Palmoplantar keratoderma
Cardiofaciocutaneous syndrome	Genitopatellar syndrome	Restless legs syndrome
Cerebroretinal microangiopathy	Glioblastoma	Retinitis pigmentosa with or without situs inversus
Charcot-Marie-Tooth disease	Hepatic adenoma	Rheumatoid arthritis
Cleft palate with ankyloglossia	Hypothyroidism	SBBYSS syndrome
COACH syndrome	IMAGE syndrome	Scalp-ear-nipple syndrome
Colorectal adenomatous polyposis	immune system	Sotos syndrome
Corticosteroid-binding globulin deficiency	Insulin Resistance	Spinocerebellar ataxia
Desbuquois dysplasia	Chronic Leukemia	Vitreoretinopathy

Table 1: Ageing-similar human traits (overall)

- Table 1 shows the list of human traits with significantly high GO semantic similarity scores with the ageing genes.
- IGF-IIS pathways also prominently appear among the enriched pathways across tissues, along with upstream growth factor signaling pathways and immune system related pathways.

Summary

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

Acknowledgment

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References

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