Gene Network Analysis Reveals Functional Drivers of Age-Associated Disorders

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Background

Old age is characterized by an increase in morbidity, most notably in chronic conditions such as cancer and heart disease. While many of these disorders have robust genetic and environmental associations, the strongest predictive factor for nearly all of them is age itself. This serves as the thrust behind the "Geroscience Hypothesis," which posits that because aging physiology plays a major role in most chronic diseases, therapies that directly target drivers of aging could dramatically enhance quality of life.[1] However, the precise identification of these factors, along with their relative contributions toward distinct disease states, remains elusive. We hypothesize that drivers of aging can be inferred using network analysis, as upstream factors responsible for coordinated patterns of age-dependent gene expression.

Linear Regression and Differential Expression Analysis

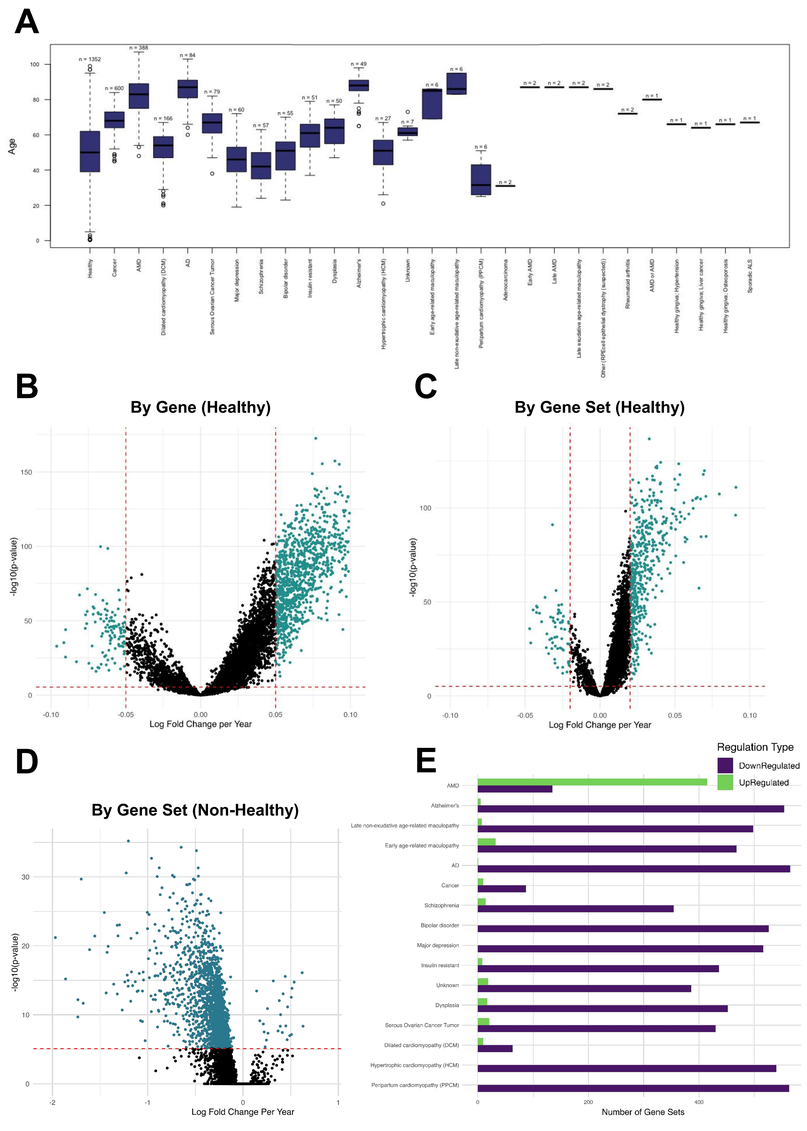

Figure 1. Age-associated gene expression changes differ across disease states. (A) Summary of 3060 human tissue donors by age and health status.[2] **(B)** Linear regression coefficients and corresponding p-values for age-dependent change in gene expression. **(C)** Corresponding linear regression data for average expression of MSigDB gene sets.[3] **(D)** Differential gene set expression in diseased tissues relative to healthy ones. **(E).** Number of up- and down- regulated age-associated gene sets by disease type.

Identification of Co-Regulatory Interactions

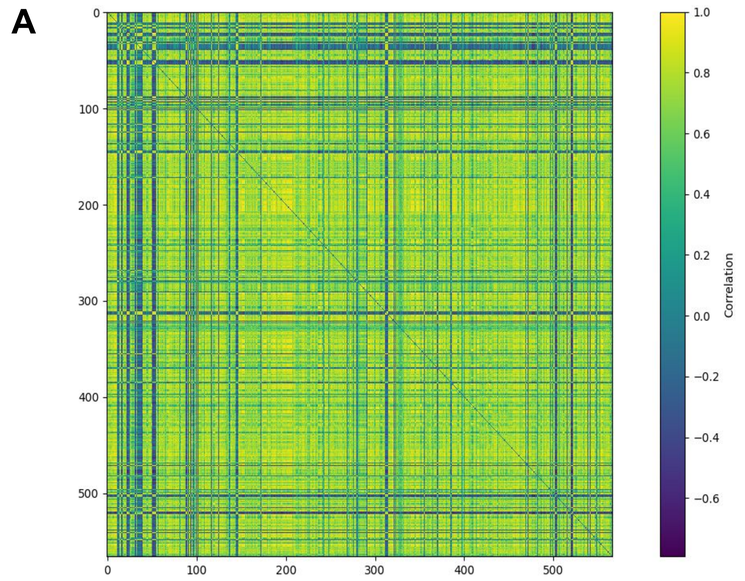

Figure 2. Gene set correlation matrix. Pearson correlation coefficients (PCCs) were calculated from each pairwise combination of 566 age-associated gene sets across all healthy patients. Network edges, representing co-regulatory interactions, were implemented when |PCC| > 0.8.

Network Construction and HTML Functionality

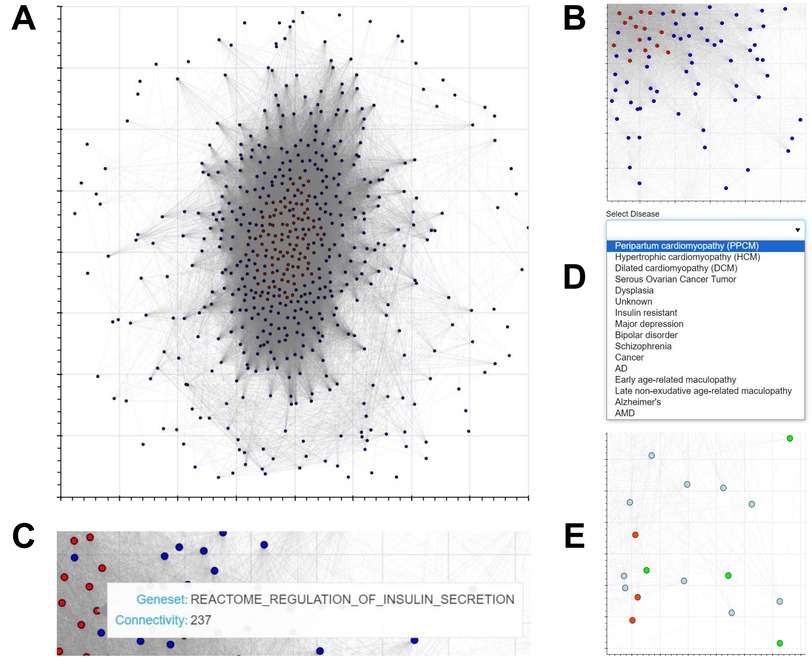

Figure 3. An interactive network of age-associated gene sets. (A) Overall network view. **(B)** Critical nodes (red) represent the 100 most interconnected gene sets. **(C)** Hovering over a node allows users to see its name and connectivity. **(D-E)** Users can select different age-associated disorders from a search bar. Node color indicates whether a given gene set's expression increases (red), decreases (green), or remains the same (light blue) relative to healthy tissue.

Annotation of Functional Drivers

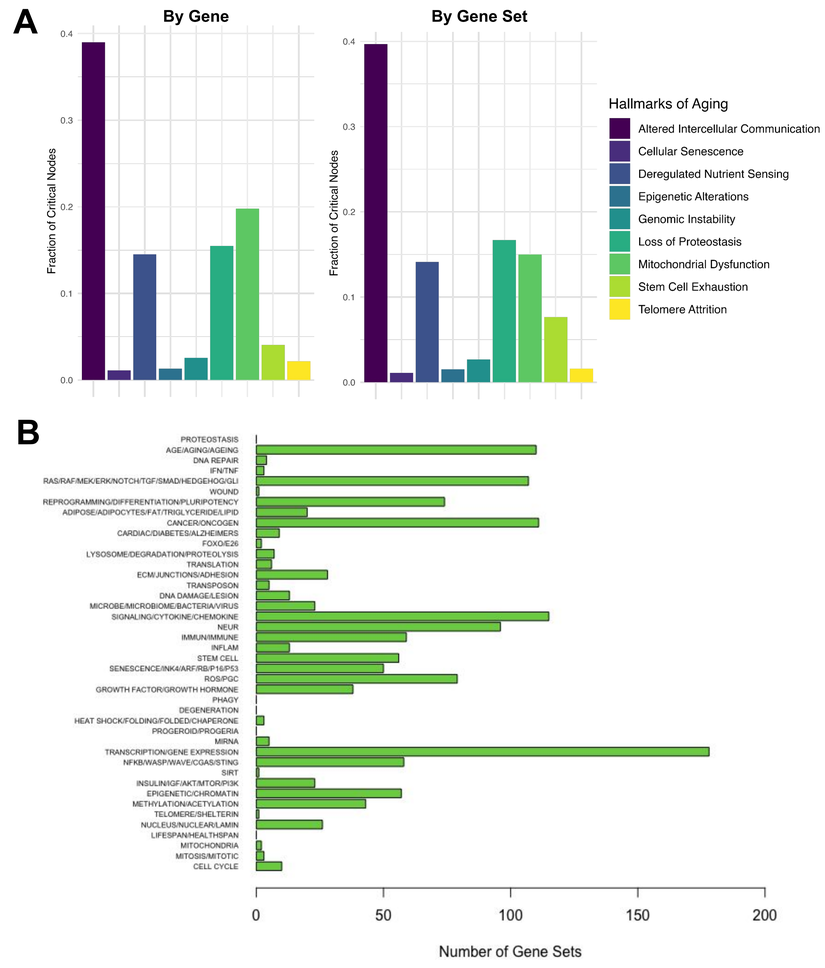

Figure 4. Network outputs align with well-characterized age-associated pathways. (A). Correspondence of critical nodes to classic hallmarks of aging[4] for genes (left) and gene sets (right). Hallmarks of aging were assigned based on literature annotations.[5] **(B)** Enrichment of known age-associated pathways within regression-derived network inputs. Relevant gene sets were selected based on string comprehension within their MSigDB summaries.

Conclusions / Future Directions

Conclusions:

- Gene expression changes with age across a diverse array of human tissues
- Different age-associated disorders exhibit distinct expression profiles
- Network-derived gene sets overlap substantially with known hallmarks of aging

Future Directions:

- Expand hallmark of aging annotations to individual disease states
- Use deep learning to assess co-regulation in a more nuanced way
- Develop an improved model to describe non-linear changes in age-associated expression

References:

1. Sierra et al. (2021). *J Am Geriatr Soc.* 10.1111/jgs.17301
2. Shokhirev and Johnson (2020). *Aging Cell.* 10.1111/acel.13280
3. Liberzon et al. (2015). *Cell Systems*. 10.1016/j.cels.2015.12.004
4. López-Otín et al. (2013). *Cell*. 10.1016/j.cell.2013.05.039
5. Holzscheck et al. (2020). *Aging*. 10.18632/aging.103499

Check out our network!