Age-Related Molecular Networks Underlying Resilience to AD

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AGE IS THE #1 RISK FACTOR FOR LOAD

Alzheimer’s is a disease, and is not a normal part of the aging process.

Normal Aging vs. Pathological Aging

Risk for Alzheimer's disease increases exponentially with age.
After age 65, the risk of doubles every 5 years.

After age 85, the risk reaches nearly one-third.

Age-related biological changes (rather than time itself) likely predisposes to AD pathology.
Shared predisposing factors
IS SLOWER BIOLOGICAL AGING LINKED TO DECREASED AD RISK?

We don’t all age in the same way or at the same rate. Can heterogeneity in aging account for differences in AD risk?

Quantifying “biological aging”
Measure numerous age-related molecular changes to predict a person’s biological age.
QUANTIFYING “BIOLOGICAL AGING”

DNA Methylation & Age
Chronological age has been shown to correspond with distinct changes in DNA methylation (DNAm) at specific CpG sites.

“EPIGENETIC AGE”

**Horvath:** Weighted average of 353 CpGs.
Horvath (2013) Genome Biology

**Hannum:** Weighted average of 71 CpGs.
Hannum et al. (2013) Molecular Cell

**Levine:** Weighted average of 513 CpGs.
EPIGENETIC CLOCKS
Horvath, Hannum, & Levine

<table>
<thead>
<tr>
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<th>Levine DNAm Age</th>
<th>Horvath DNAm Age</th>
<th>Hannum DNAm Age</th>
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<tr>
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<tr>
<td>Hannum DNAm Age</td>
<td>0.482</td>
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</table>

Only moderate correlations between the three clocks after adjusting for chronological age.

The clocks are not using the same CpGs.

They appear to be capture different phenomena.
Horvath et al. DNA methylation-based biomarkers and the epigenetic clock theory of ageing.

What are the different phenomena being captured?
METHYLATION MODULES

Hypomethylation

Hypermethylation

[Graph depicting dynamic tree cut with labels for 'WholeBlood', 'FCTX', 'DLPFCX', 'Colon', 'HUVEC', 'Breast', 'Skin', 'Kidney', with color bars indicating hypomethylation and hypermethylation]
METHYLATION MODULES

Positive Age Correlation

Negative Age Correlation
EPIGENETIC DRIFT (ENTROPY)

Divergence of the epigenome as a function of age due to stochastic changes. With increased entropy, methylation state becomes less predictable across the population of cells, (tends towards 50%).

1. Repeat Consensus WGCNA for HUVEC, fetal DLPFC, and age correlations.

2. Calculate Mahalanobis Distance (MD) for each module, using HUVEC as the reference. Represents dysregulation/entropy.

3. Test whether MD is associated with aging and AD neuropathology.
PRELIMINARY RESULTS USING ROS-MAP DATA

Nine Modules Identified

bicor=0.86, p=8.2e-199

bicor=0.37, p=1e-24
PRELIMINARY RESULTS USING ROS

AMP-AD Knowledge Portal

**NIA-Reagan**
- p = 2.4e-07

- High
- Intermediate
- Low
- No AD

**CERAD**
- p = 2e-06

- Definite
- Possible
- Probable
- No AD

**Braak Staging**
- p = 2e-06

- 0-2
- 3-4
- 5-6

**Cognitive Dx**
- p = 0.00067

- NCI/MCI
- AD
# Preliminary Results Using ROS-Map Data

<table>
<thead>
<tr>
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<th>Standardized Beta Coefficient</th>
<th>P-value</th>
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<td>NFT</td>
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<td>Tangle Density</td>
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<td>Neuritic Plaques</td>
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<td>Diffuse Plaques</td>
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<td>Amyloid Load</td>
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<td>6.6E-4</td>
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</table>
MOVING FORWARD
Generating New Data from ROS-MAP Samples

Oversampling of APOE e4+:  
- 232 heterozygous (68% AD),  
- 18 homozygous (89% AD)  
- 100 e4- (55% AD)

Multiple Brain Regions  
- Compare samples from three regions  
  - Superior temporal cortex (BA22)  
  - Prefrontal cortex (BA10)  
  - Cerebellum

Integromics Networks  
- Identify hubs, pathways, and potential drug targets  
- Explore relationship between changes at epigenomic, transcriptomic, proteomic, and phenotypic levels.