AGS/NIA R13 Bench-to-Bedside Conference Series
Stress Tests and Biomarkers of Resilience

Integrative omics Predicting Resilience

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No disclosures
Integration of genomics can help to

1) identify those at risk, promoting disease prevention strategies;
2) diagnose disease at earlier stages where better control or even mitigation of disease is possible;
3) predict disease severity allowing for early intervention and optimal, effective management; and
4) select the most efficacious treatment.
The promise of the Polygenic Risk Score (PRS)

PRS delivers on the scientific promise of using genetics in predicting disease/health outcomes in a translational framework that is equitable across populations.

CHALLENGES
- Robust genetic evidence
- Sample size
- Heterogeneity*
- Diversity*
- Translational value
  - Dx risk
  - Dx severity
  - Dx trajectory
  - Dx pathophysiology*
- Transferability
- Representation
Genomics $\rightarrow$ Phenotype: far greater than genetics in a silo
Multi-omics ➔ Phenotype
Context matters: gene * environment interactions

https://www.nature.com/articles/ejhg2008106
Multi-omics ➔ Phenotype: The promise beyond the Polygenic Risk Score (PRS)

Integrative omics approaches to clinical translation: PRS + MRS

“Methylation risk scores significantly outperform the baseline and PRS models “

Multi-omics → Phenotype: The promise beyond the Polygenic Risk Score (PRS)
Genetics for Aging: much broader in scope than the genetics of a single biomarker or hallmark or age-related disease.
Genetics for Aging: much broader in scope than germline variation.

Hallmarks of Aging

- Altered intercellular communication
- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Mitochondrial dysfunction
- Deregulated nutrient sensing
- Loss of proteostasis
- Cellular senescence

The Dynamic Genome

- Telomere length
  - Telomere attrition
  - Hematopoietic stem cell sample
    - Passenger mutation
    - Driver mutation
    - Clonal expansion
  - Prevalence
- Clonal hematopoiesis
- Mitochondrial DNA
  - Heteroplasmy
  - Copy number
Genetics for Aging: much broader in scope than germline variation and connectivity is high.

**Hallmarks of Aging**

- Altered intercellular communication
- Stem cell exhaustion
- Cellular senescence
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- Deregulated nutrient sensing
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- Telomere attrition
- Loss of proteostasis
- Genomic instability

**A lens on telomere biology**

- p53-p21
- Crisis, telomeric fusion
- Sirt1, p53/PGC-1α/β
- Senscence
- Genomic instability
- Mitochondrial dysfunction
- Stem cell exhaustion
- Deregulated nutrient sensing
- cGAS/STING YAP1
- Inflammation
- Loss of proteostasis
- Epigenetic regulation
- Sirt1
- Sirt1-7

Genetics for Aging: much broader in scope than germline variation and connectivity is high.

Evaluating genomic signatures of aging in brain tissue as it relates to Alzheimer’s disease

Megon T. Lynch, Margaret A. Todd, Jose W. Faraji, Eugene Yang, Peter Alberdi, Phillip L. De Jager, Francine Grodstein, David A. Bennett & Rockel A. Mathis

Telomere length (TL), epigenetic age acceleration, and mitochondrial DNA copy number (mtDNAcopy) decline are established hallmarks of aging. Each has been individually associated with Alzheimer’s dementia, cognitive function, and pathology Alzheimer’s disease status. Epigenetic age and mtDNAcopy have been studied in brain tissue directly, but prior work on TL in brain is limited to small sample sizes and most studies have examined brain tissue (39). Importantly, TL, epigenetic age acceleration, and mtDNA copy number all show an association with cognition in a non-demented prefrontal cortex (uTOCP) tissue from N=187 participants of the Religious Order Study (ROS) or the Rush Memory and Aging Project (RAMAP). TL and mtDNAcopy were estimated from whole genome sequencing (WGS) data and cortical clock age was computed on 1047 CpG sites. We examined dementia, MCI, and level of end-stage cognition, pathologic AB, and three quantitative AD traits, as well as measures of other neurodegenerative diseases and cerebrovascular disease (CVS). We previously showed that mtDNAcopy from uTOCP brain tissue was associated with clinical and pathologic features of AD; here, we show that these associations are independent of TL. We found TL to be associated with Aβ-amyloid burden (beta = -0.35, p = 0.03), hippocampal atrophy (beta = -0.5, p = 0.001) and clinical measures of AD. The strongest associations with pathologic measures of AD were with cortical clock and there were associations of mtDNAcopy with global AD pathology and tau burden. Of the other pathologic traits, mtDNAcopy was associated with hippocampal volume, neurofibrillary tangles in CA1 and cortical clock was associated with amyloid burden. Multimodal age acceleration, accelerated aging on both mtDNAcopy and cortical clock, had greater effect size than single measure alone. These findings highlight for the first time that age acceleration determined on multiple genomic measures, mtDNAcopy and cortical clock may have a larger effect on AD/AU disorders related disorders (ADRD) pathogenesis than single measures.
Summary & Challenges

1) **When/where to measure?**

- Perinatal
- Infancy (0-12 months)
- Toddlerhood (1-3 years)
- Childhood (4-9 years)
- Early Adolescence (10-13 years)
- Middle Adolescence (14-17 years)
- Young Adulthood (18-21 years)
- Adulthood (>21 years)

Study of first 1000 days

Study of early childhood

Adolescent to adult transition

2) **What to measure?**

- Analytical validity: Accuracy and reliability of a test to measure a specific biomarker.
- Clinical validity: The accuracy of how well a test detects or predicts clinical diagnosis or outcome.
- Clinical utility: The likelihood the test is to inform clinical decisions and improve outcome.

3) **How to integrate?**

- Analytical sensitivity: How often is the test positive when the biomarker is present?
- Analytical specificity: How often is the test negative when the biomarker is not present?
- Robustness: Repeatability and reproducibility of the assay within and across laboratories.
- Limits of detection: Lowest level of reliable detection of transcripts.
- Stability: Collection, handling, transport of sample and impact on robustness.
- Gold standards: Reference sets for assessing sensitivity and specificity.

4) **Evaluating readiness?**

- Appropriate intervention: Assessment of test impact on patient care, publishing of clinical trials.
- Quality assurance: Quality control measures for tests, reagents and/or facilities.
- Economics: Financial costs and economic benefits associated with test.
- Education: Educational materials and informed consent requirements.
- ELSI: Assessment of ethical, legal and societal implications that arise in the context of the test.
References