Integrative Network Modeling of Cognitive Resilience to Alzheimer's Disease (R01AG057907)

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Rationale

- No effective method is available for preventing and/or treating this devastating disease.

- However, certain individuals of the elder population (≥ 85 years) remain cognitively intact, including some with substantial plaques and neurofibrillary tangle burdens, the two pathological hallmarks for fully symptomatic AD.

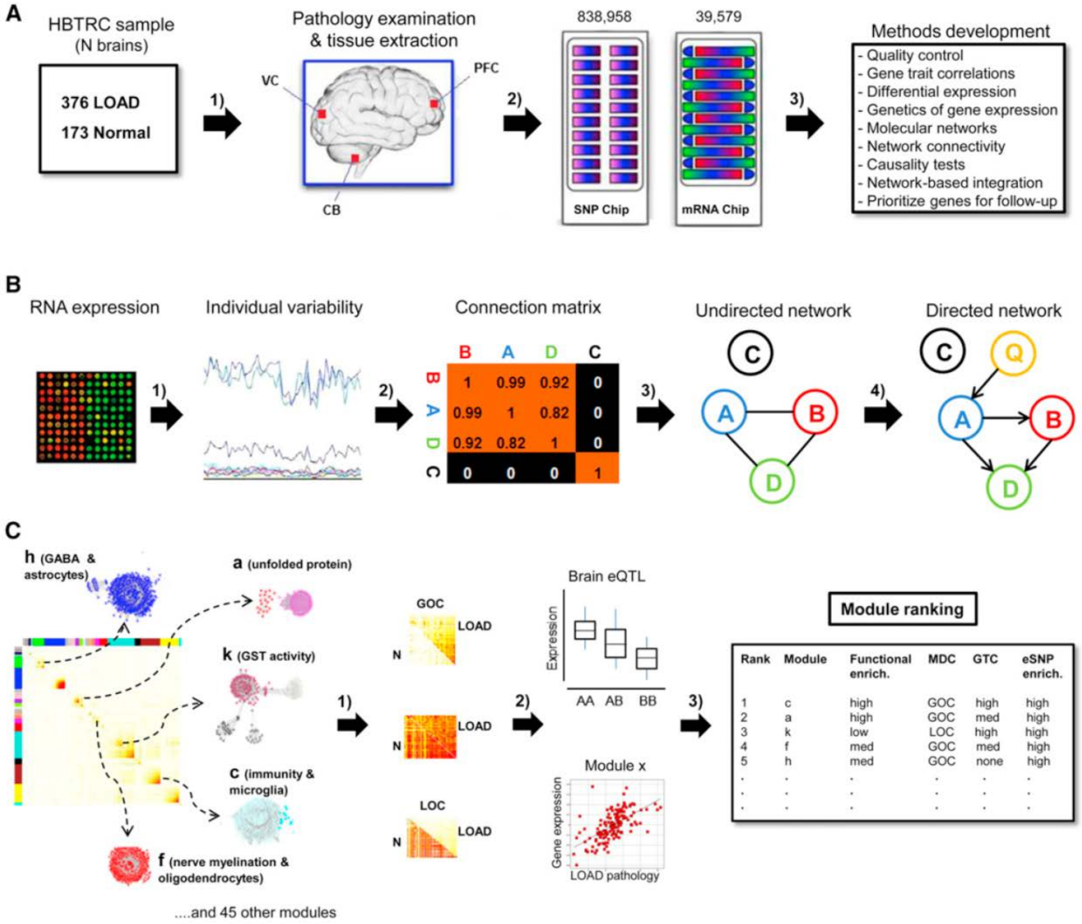
- The mechanisms of cognitive resilience and protection against AD in these elderly persons remain elusive.

Overall Goals

This grant aims to systematically develop and validate molecular network models underlying cognitive resilience to AD risk.

- Generate and analyze an AD-resilient dataset comprised of matched genetic, transcriptomic and proteomic data from a large number of **very old and AD-resilient human brains**
- Build network models of cognitive resilience to AD
- Extensively validate network drivers using *C. elegans* and mouse models.

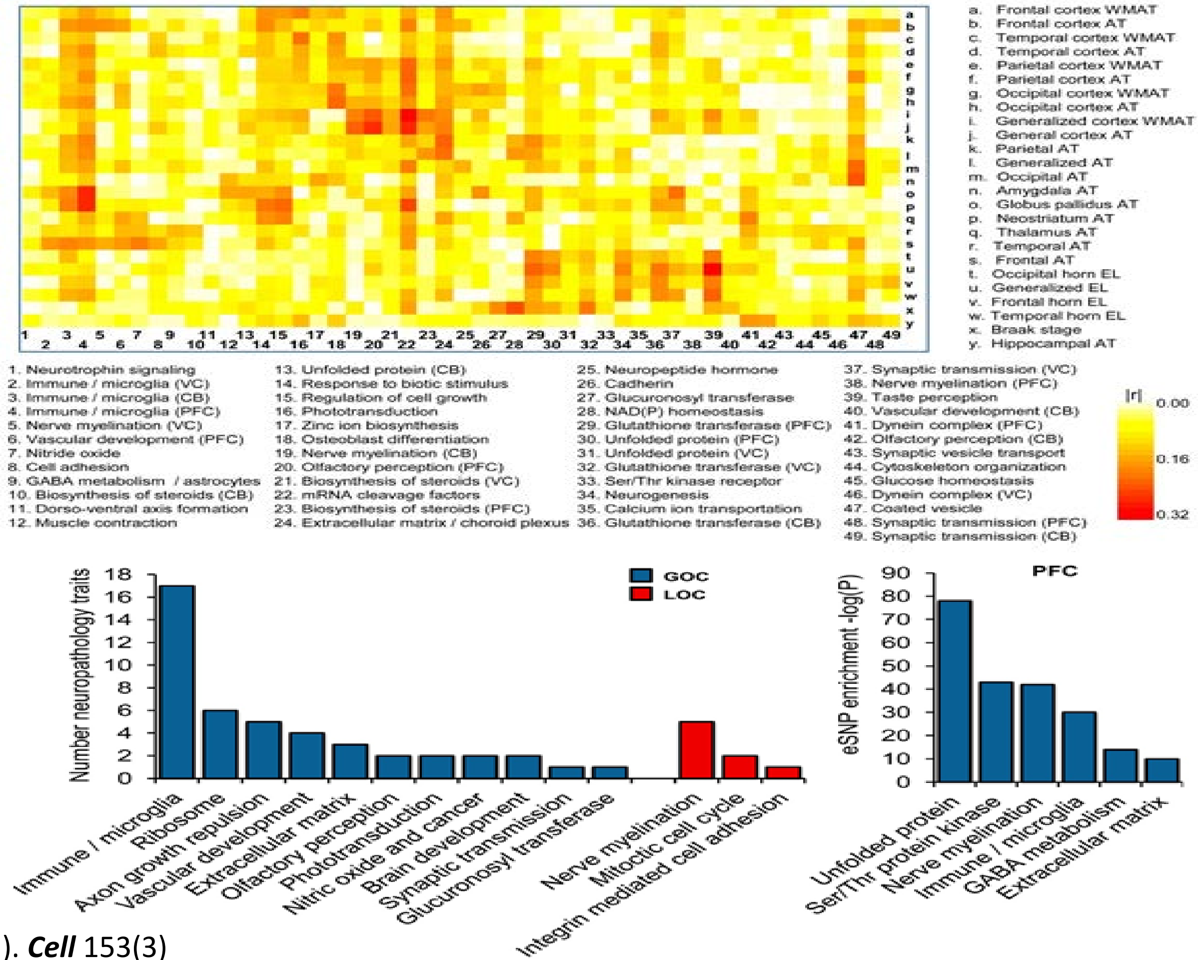
Overview of HBBAD Cohort and Analysis Flow



subset	samples
Alzh_PFC	310
Alzh_CR	263
Alzh_VC	190
Norm_PFC	153
Norm_CR	128
Norm_VC	121

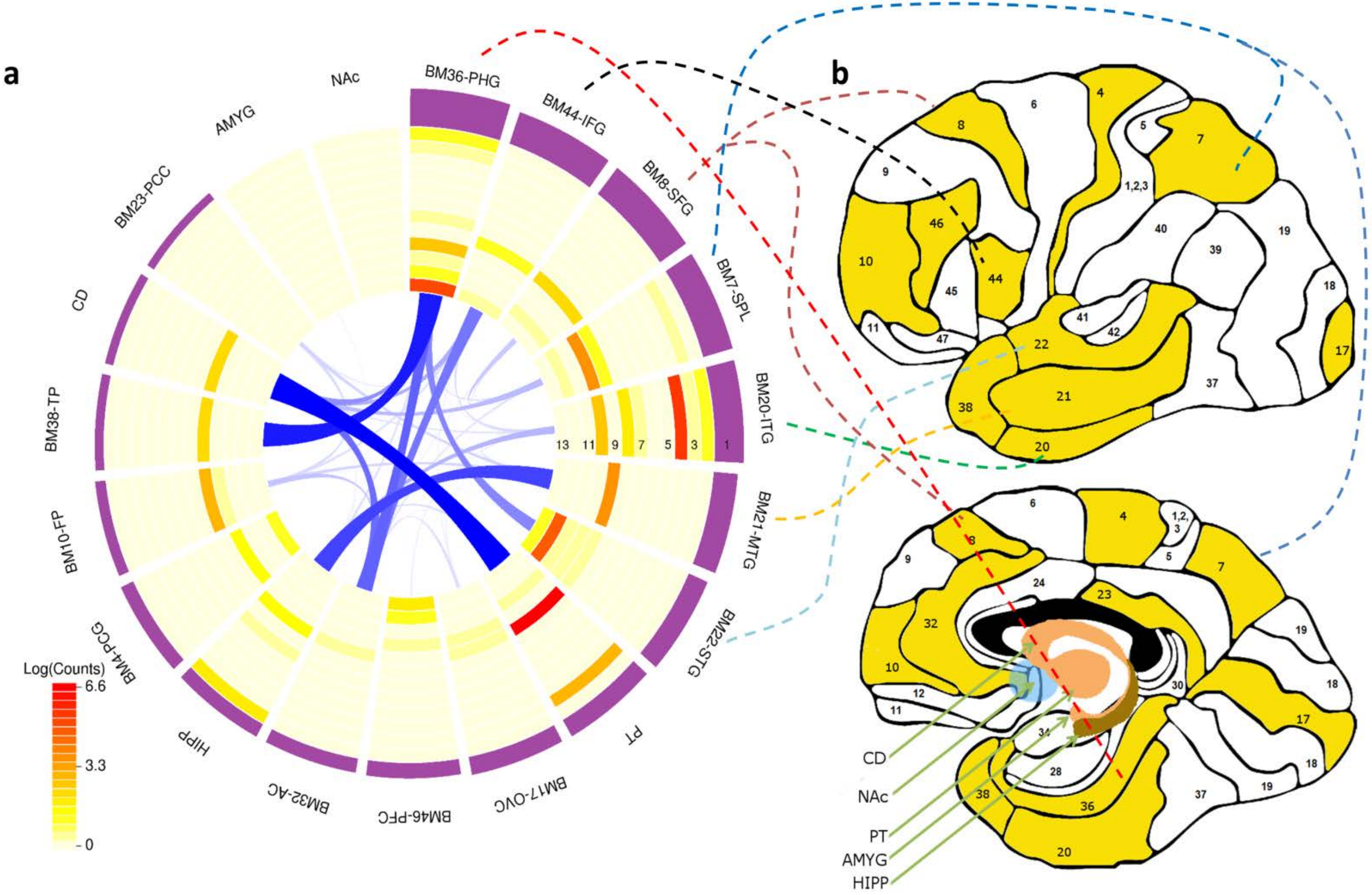
Zhang B et al. (2013). ***Cell*** 153(3)

Gene Modules Associated with AD Pathology



Zhang B et al. (2013). ***Cell*** 153(3)

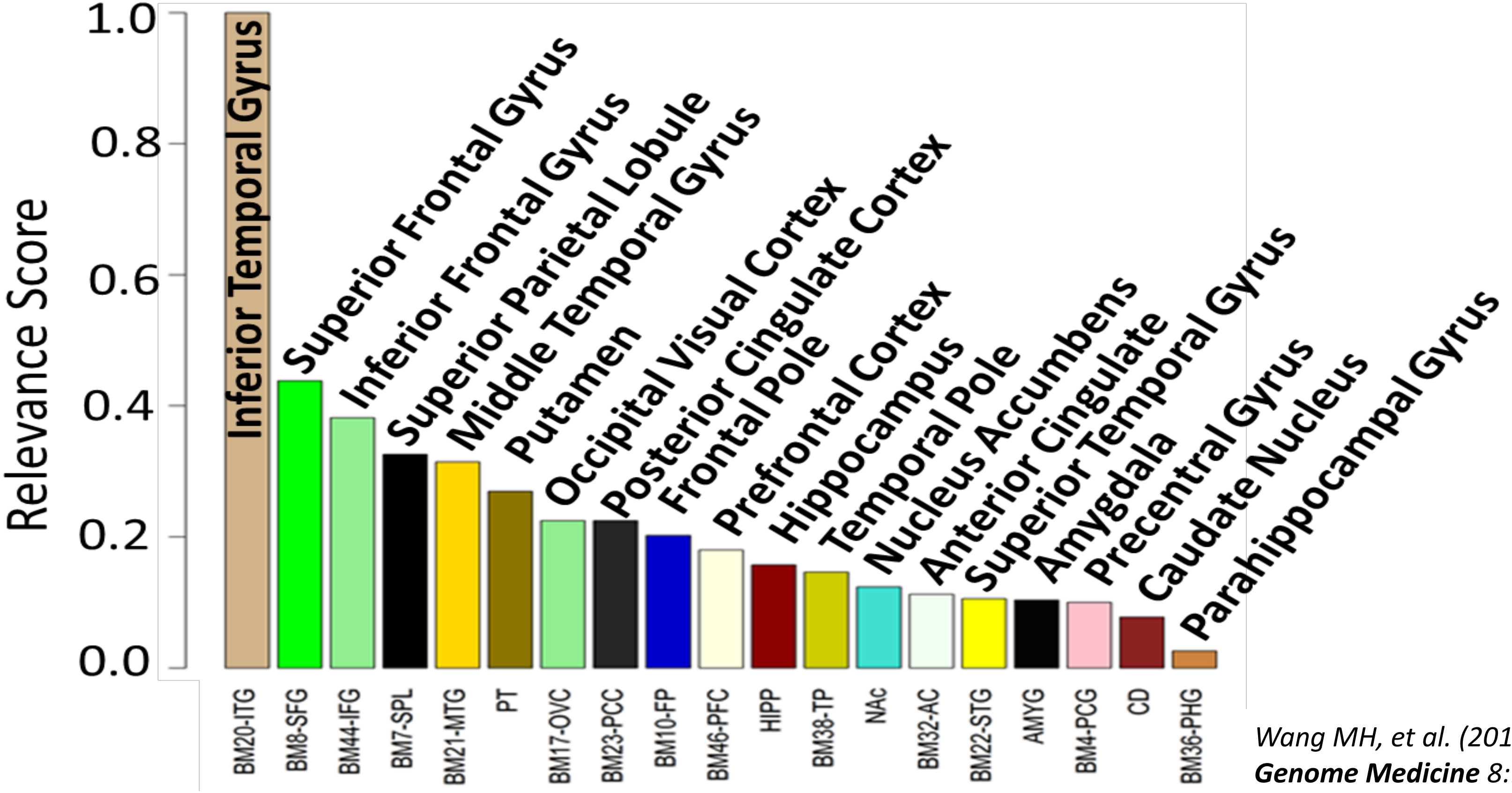
Brain regions rank-ordered by the relevance to AD pathology



Region	Full Nmae
BM10-FP	Frontal Pole
BM17-OVC	Occipital Visual Cortex
BM20-ITG	Inferior Temporal Gyrus
BM21-MTG	Middle Temporal Gyrus
BM22-STG	Superior Temporal Gyrus
BM23-PCC	Posterior Cingulate Cortex
BM32-AC	Anterior Cingulate
BM36-PHG	Parahippocampal Gyrus
BM38-TP	Temporal Pole
BM4-PCG	Precentral Gyrus
BM44-IFG	Inferior Frontal Gyrus
BM46-PFC	Dorsolateral Prefrontal Cortex
BM7-SPL	Superior Parietal Lobule
BM8-FC	Prefrontal Cortex
BMa-AMYG	Amygdala
BMb-CD	Caudate Nucleus
BMc-HIPP	Hippocampus
BMd-NAc	Nucleus Accumbens
Bme-PT	Putamen

Wang MH, et al. Genome Medicine 8:104

Selective Myelination Vulnerability of 19 Brain Regions to AD



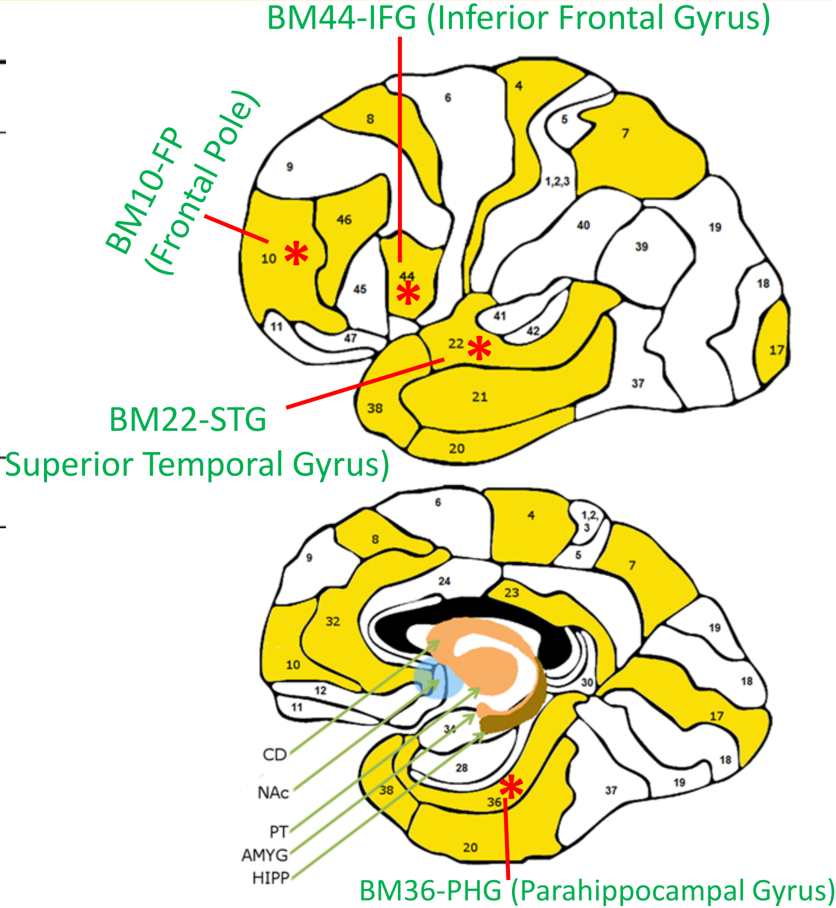
Wang MH, et al. (2016)
***Genome Medicine** 8:104;*

The Mount Sinai Cohort of Large-scale Genomic, Transcriptomic and Proteomic Data in Alzheimer's Disease

Demographic characteristics of MSBB AD samples

CDR	N (Sex F/M)	Mean PMI	CDR	Mean Age	Mean Cortical Plaque Density
0	44 (32/12)	590.8	0	82.4	2.06
0.5	47 (24/23)	603.2	0.5	81.7	3.19
1	38 (26/12)	418.6	1	84.9	6.27
2	49 (31/18)	460.3	2	86.5	8.96
3	78 (56/22)	385.2	3	86.4	9.79
4	47 (30/17)	392.8	4	87.6	10.64
5	61 (39/22)	368.3	5	82.3	18.59
All	364 (238/126)	445	2.4	84.7	9.11

- Transcriptomics (RNA-seq) – 4 brain regions
- Proteomics (BM10, BM36 ongoing)
- Whole Exome Sequencing
- Whole Genome Sequencing



Wang MH et al. *Nature Scientific Data* (in press)

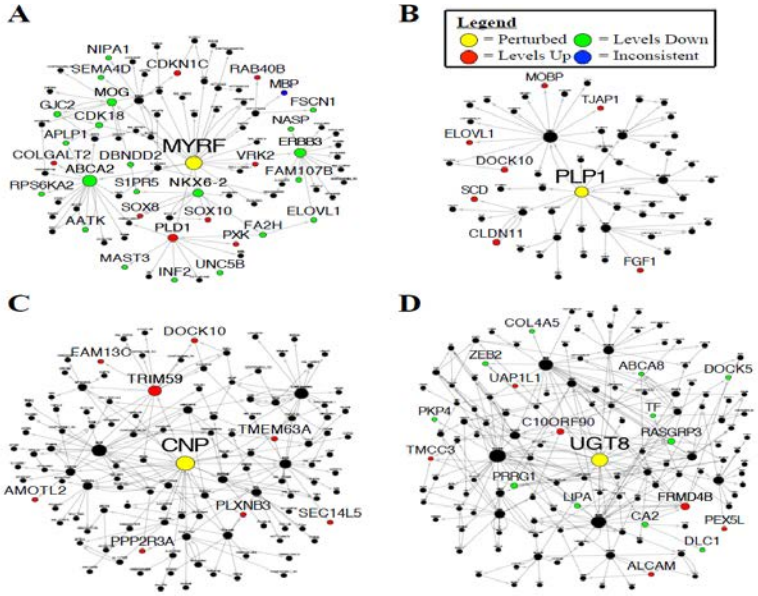
McKenzie *et al. Molecular Neurodegeneration* (2017) 12:82
DOI 10.1186/s13024-017-0219-3

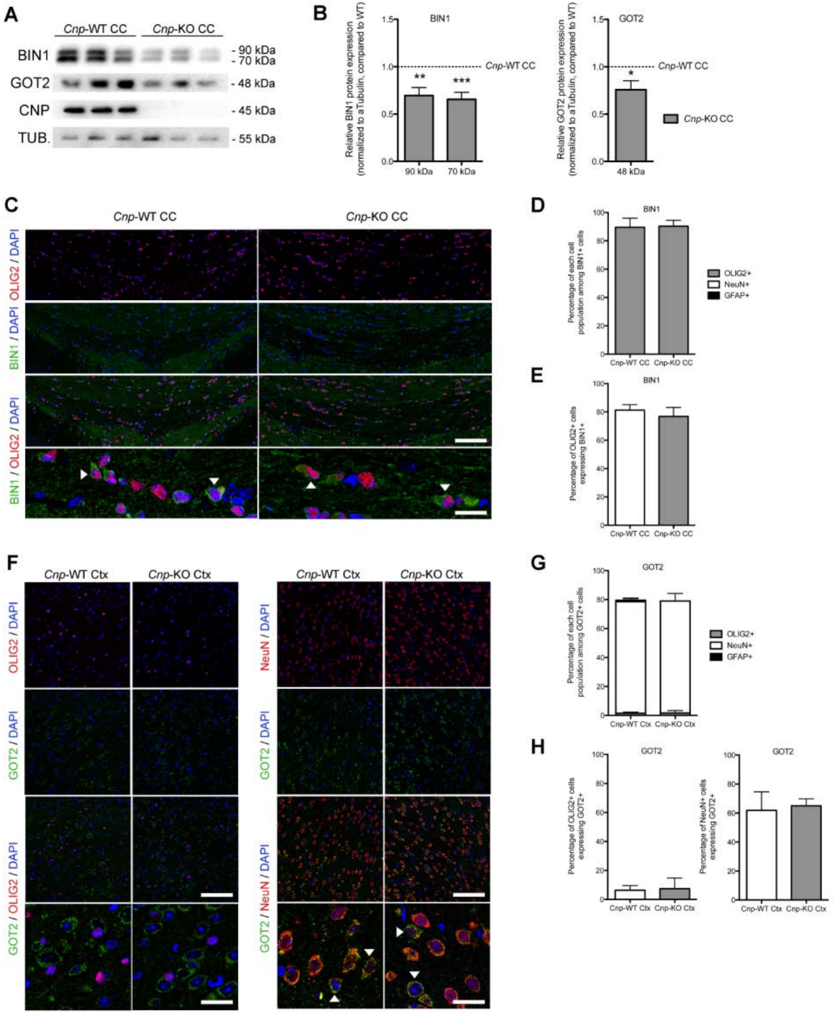
Molecular Neurodegeneration

RESEARCH ARTICLE **Open Access**

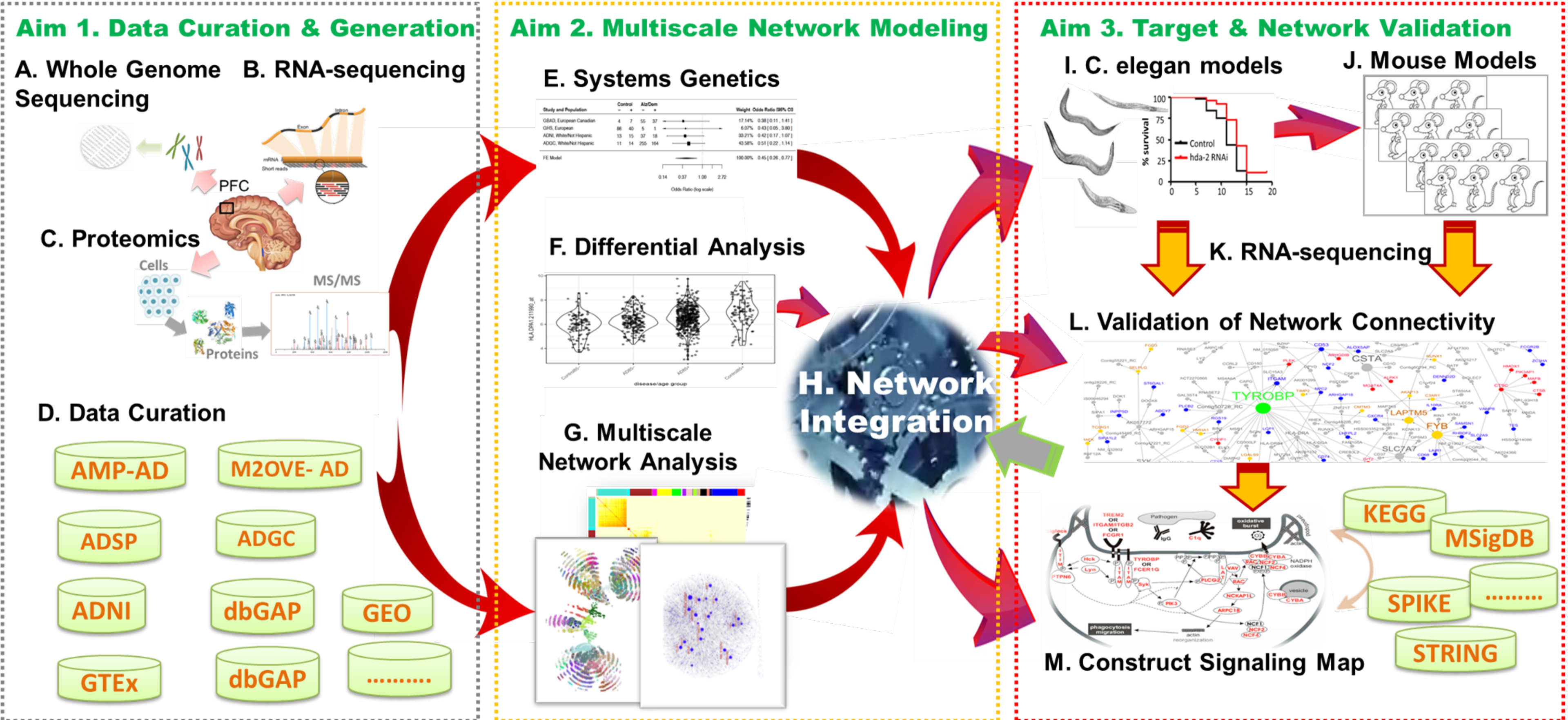
Multiscale network modeling of oligodendrocytes reveals molecular components of myelin dysregulation in Alzheimer's disease

Andrew T. McKenzie[1,2,3], Sarah Moyon[4,13], Minghui Wang[1,2], Igor Katsyv[1,2,3], Won-Min Song[1,2], Xianxiao Zhou[1,2], Eric B. Dammer[5], Duc M. Duong[6,7], Joshua Aaker[8], Yongzhong Zhao[1,2], Noam Beckmann[1,2], Pei Wang[1,2], Jun Zhu[1,2], James J. Lah[9,10], Nicholas T. Seyfried[6,7,9], Allan I. Levey[9,10], Pavel Katsel[11], Vahram Haroutunian[2,11,12], Eric E. Schadt[1,2], Brian Popko[8], Patrizia Casaccia[2,4,13*] and Bin Zhang[1,2*]





Approaches



Aim 1. Data Curation & Generation

A. Whole Genome Sequencing

B. RNA-sequencing

C. Proteomics

D. Data Curation

AMP-AD

M2OVE- AD

ADSP

ADGC

ADNI

dbGAP

GEO

GTEx

dbGAP

……….

Aim 2. Multiscale Network Modeling

E. Systems Genetics

F. Differential Analysis

G. Multiscale Network Analysis

H. Network Integration

Aim 3. Target & Network Validation

I. C. elegan models

J. Mouse Models

K. RNA-sequencing

L. Validation of Network Connectivity

M. Construct Signaling Map

KEGG

MSigDB

SPIKE

……….

STRING

Subgroups of Interest

- OONL (oldest/old normal): Very old (age of death (AoD) ≥ 85) AD-resilient
- YONL (young/old normal): Young (AoD < 85) healthy
- OOAD (oldest/old AD): (AoD ≥85) AD
- YOAD (young/old AD): Young (AoD < 85) AD.

Data Generation (Prefrontal Cortex)

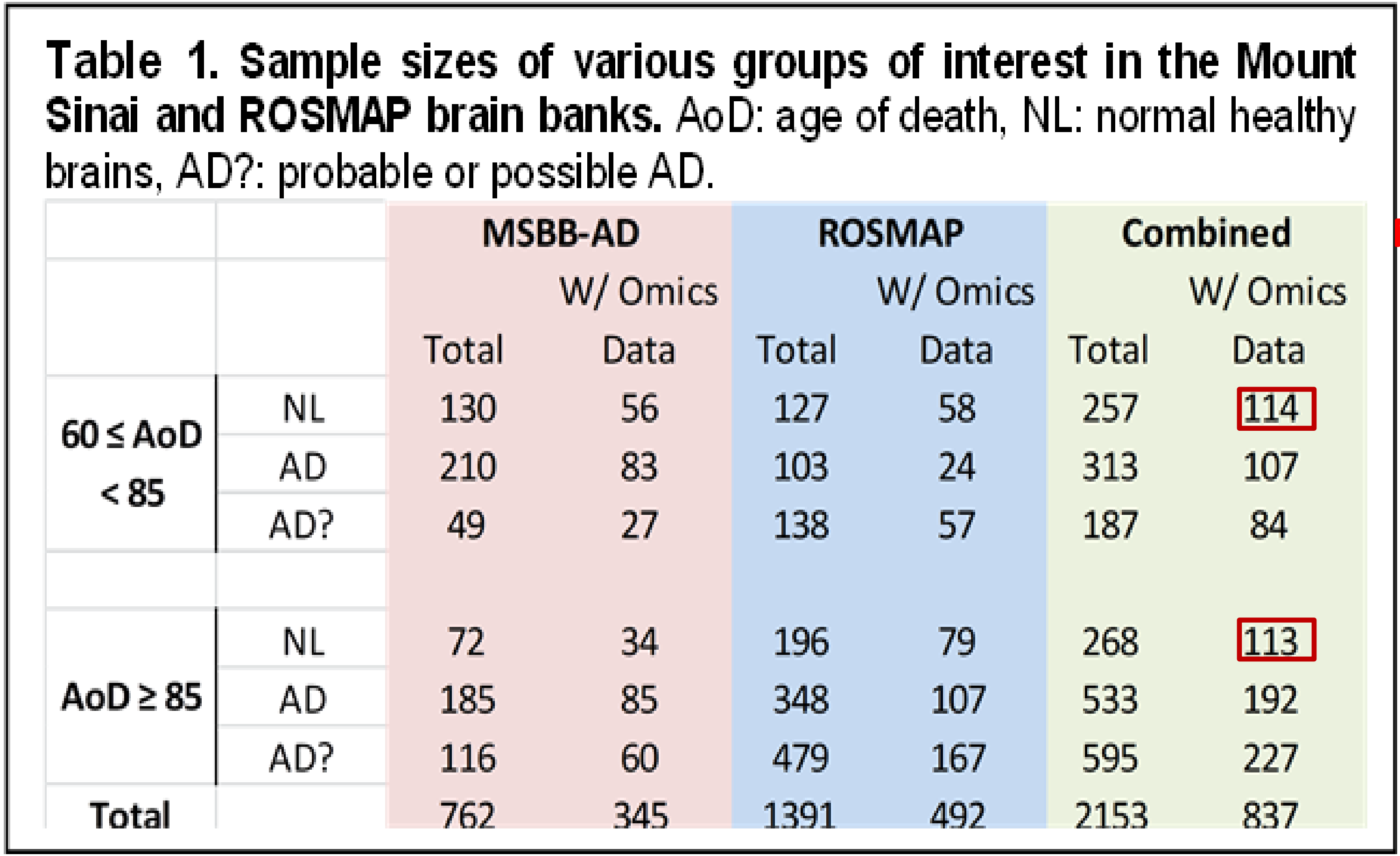
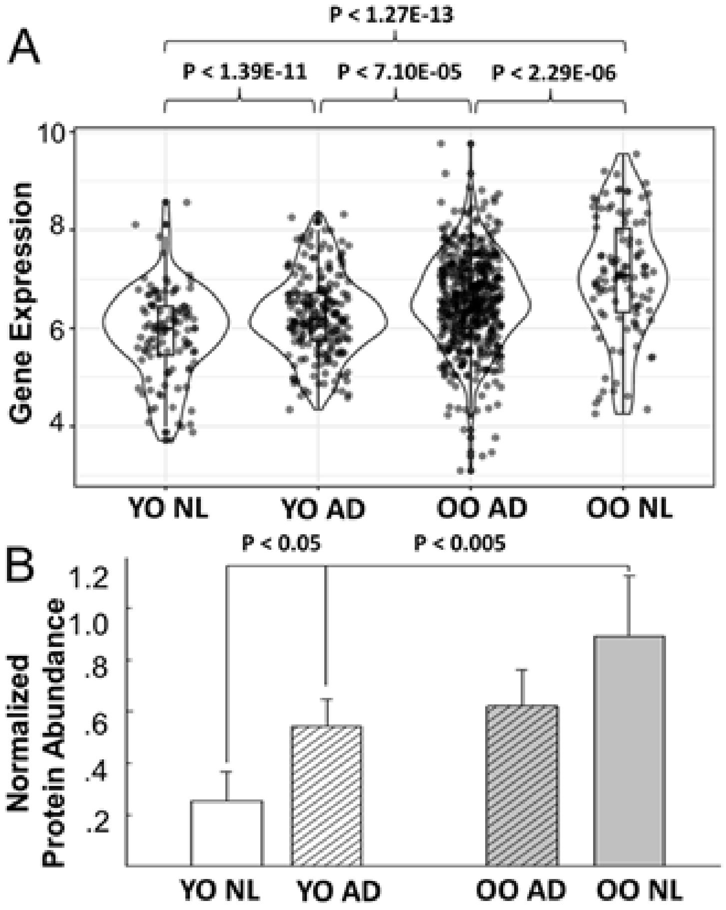


Table 1. Sample sizes of various groups of interest in the Mount Sinai and ROSMAP brain banks. AoD: age of death, NL: normal healthy brains, AD?: probable or possible AD.

		MSBB-AD		ROSMAP		Combined	
			W/ Omics		W/ Omics		W/ Omics
		Total	Data	Total	Data	Total	Data
60 ≤ AoD < 85	NL	130	56	127	58	257	114
	AD	210	83	103	24	313	107
	AD?	49	27	138	57	187	84
AoD ≥ 85	NL	72	34	196	79	268	113
	AD	185	85	348	107	533	192
	AD?	116	60	479	167	595	227
Total		762	345	1391	492	2153	837

New	Total
113	227
	107
137	250
	192

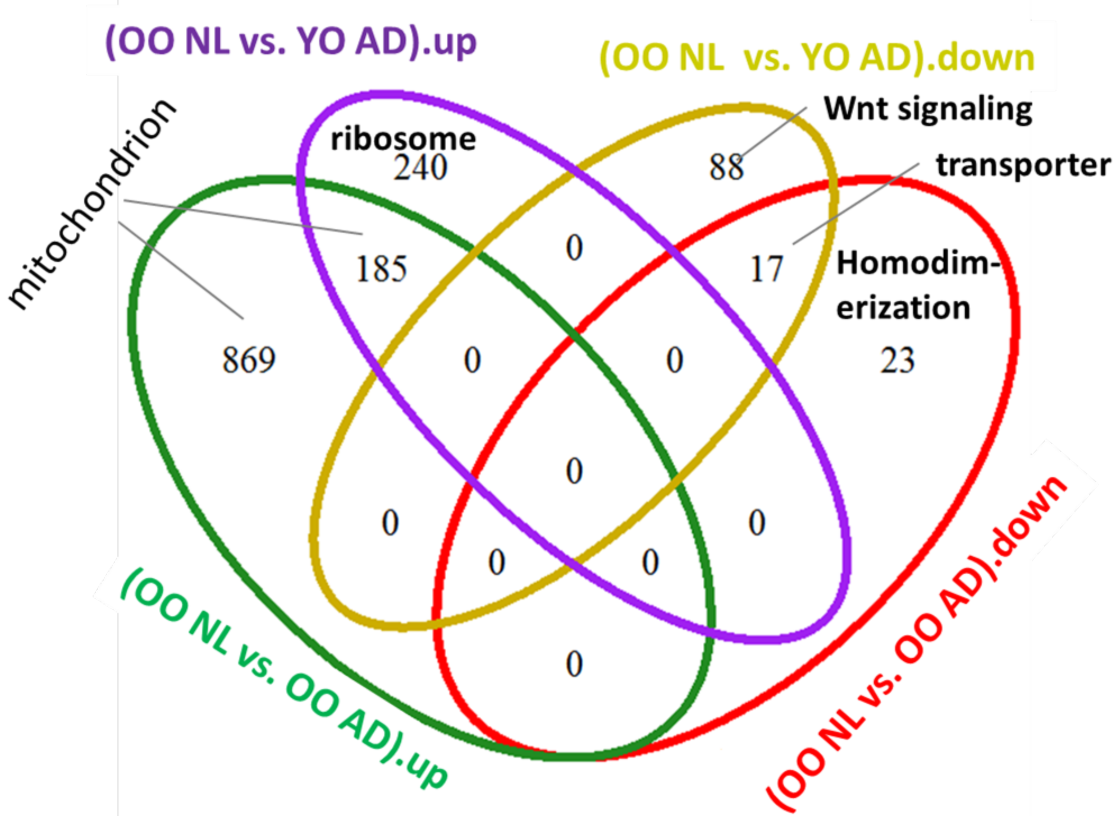
Differential Analysis of the MSBB-AD Data



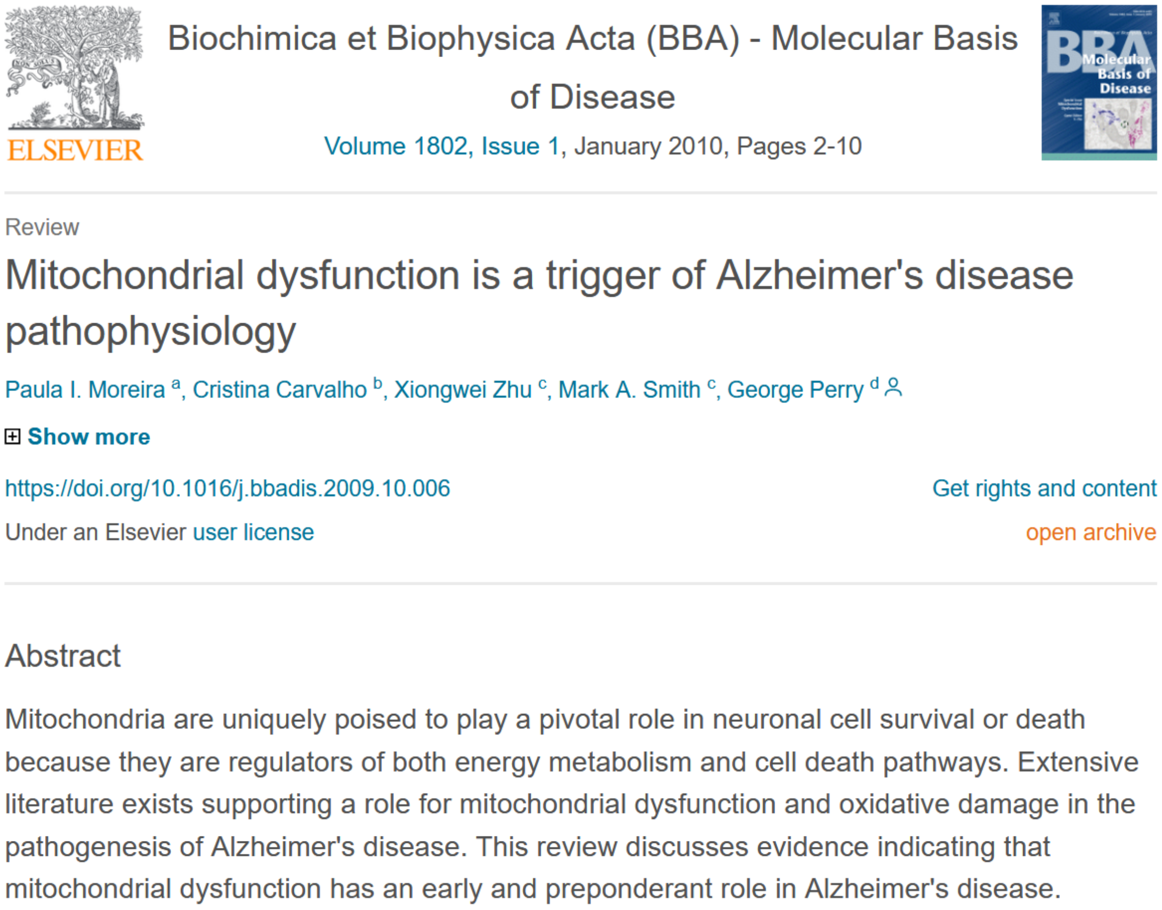
A) Trend analysis identified ***HLA-DPA1*** with the most significant up-regulation trend.

B) Expression of ***HLA-DPA1*** protein in the temporal cortex of young-old and oldest-old persons with and without dementia.

Differential Analysis of the ROSMAP Data



Differential Analysis of the ROSMAP Data



ELSEVIER

Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease

Volume 1802, Issue 1, January 2010, Pages 2-10

Review

Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology

Paula I. Moreira [a], Cristina Carvalho [b], Xiongwei Zhu [c], Mark A. Smith [c], George Perry [d]

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https://doi.org/10.1016/j.bbadis.2009.10.006

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Abstract

Mitochondria are uniquely poised to play a pivotal role in neuronal cell survival or death because they are regulators of both energy metabolism and cell death pathways. Extensive literature exists supporting a role for mitochondrial dysfunction and oxidative damage in the pathogenesis of Alzheimer's disease. This review discusses evidence indicating that mitochondrial dysfunction has an early and preponderant role in Alzheimer's disease.

Summary & Future Work

- The framework of multiscale network modeling of AD has been extensively validated.
- Preliminary analysis of three large transcriptomic datasets identified novel subnetworks and key regulators of resilience to AD.
- RNA-sequencing and proteomic profiling of a large number of AD-resilient and contrast groups are undergoing.
- **Future work**
    - Integrate multi-Omics data into high-resolution network models of resilience to AD
    - Screen a large number of candidate drivers *in vivo*

Team for the AMP-AD U01 Grant

Icahn School of Medicine
at Mount Sinai

- **Genomics, Informatics, Networks**
  - Bin Zhang, Eric Schadt, Jun Zhu, **Minghui Wang**, Zhidong Tu, Joel Dudley, Won-min Song
- **Tissue collection and profiling**
  - Vahram Haroutunian
- **Clinical, experimental validation**
  - Sam Gandy, Michelle Ehrlich, Joe Buxbaum, Stephen Salton, Mary Sano, Charles Mobbs (C. elegans), **Kristen Brennand** and **Aiqun Li** (stem cells)

National Center
for Geriatrics and Gerontology

- **Fly models**
  - Koichi Iijima

NYSCF The New York Stem Cell Foundation
Accelerating Cures Through Stem Cell Research

- **High throughput stem cell production and differentiation**
  - Scott Noggle
  - Valentina Fossati

Sage
BIONETWORKS

- **Data hosting, sharing, competitions**
  - Lara Mangravite
  - Mette Peters
  - Ben Logsdon

Team for the Resilience R01 Grant

Icahn School of Medicine at Mount Sinai

Data Integration

- **Bin Zhang (contact PI)**
- Minghui Wang
- Ali Sharma
- Erming Wang
- Chen Ming
- Ryan Neff
- Shuyu Dan Li
- Rong Chen
- Zhidong Tu
- Li Chen
- Lei Guo

in vivo Validations

- **Michelle Ehrlich (M-PI)**
- Sam Gandy
- Charles Mobbs
- Mickael Audrain
- Tomas Fanytza
- Ben Shackleton

Data Generation

- **Vahram Haroutunian (M-PI)**
- Pavel Katsel

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CHICAGO 1972

Sample Preparation & Data QC

- **Chris Gaiteri**
- David A Bennett
- Ryan Johnson
- Gregory Klein

BRIGHAM YOUNG UNIVERSITY
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BYU
1875
PROVO, UTAH

Genetics of Resilience

- **John Kauwe**

St. Jude Children's Research Hospital

Proteomics

- **Junmin Peng**
- Kaiwen Yu
- Boer Xie

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Turning Discovery Into Health

AMP-AD Consortium

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M^{2}OVE-AD Consortium

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