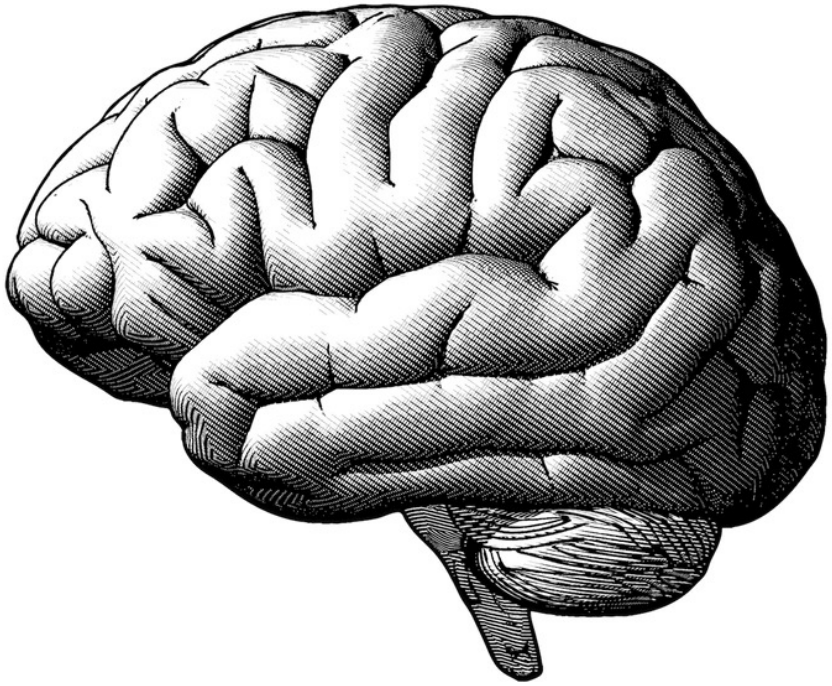

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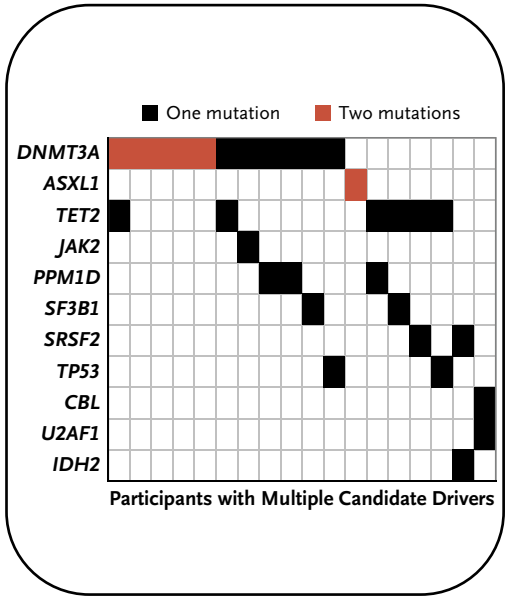
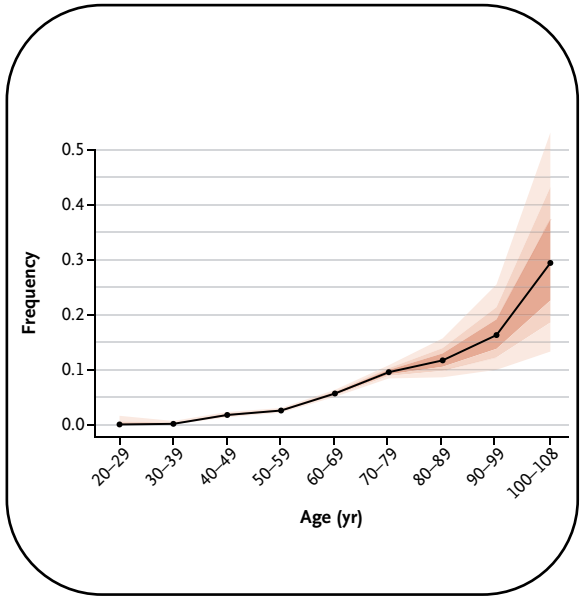
ADRC meeting Oct. 21, 2022

SOMATIC MUTATION PROFILING AND PATHOGENESIS IN ALZHEIMER'S DISEASE BY SINGLE-NEURON GENOME SEQUENCING

Somatic Mutation in Non-Neoplastic Tissues

Blood

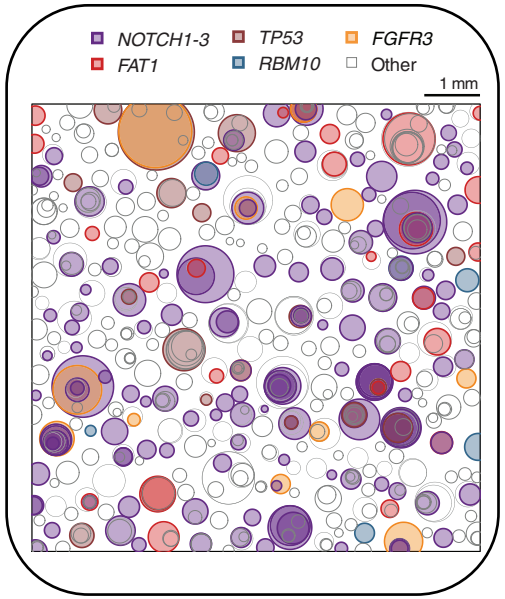




Genovese *et al*. (2014)
NEJM PMID 25426838

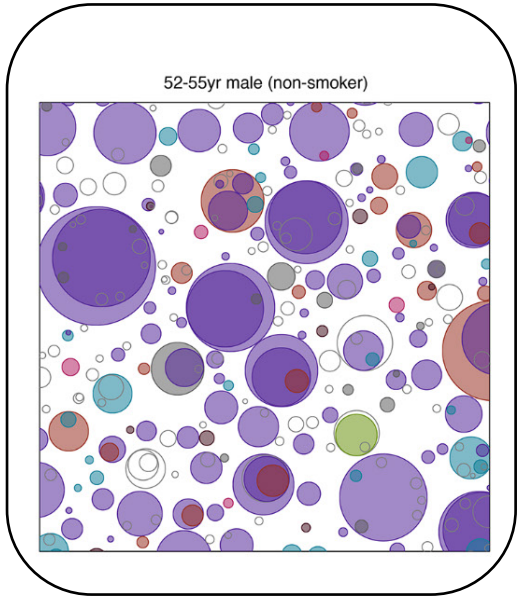
Jaiswal *et al*. (2014)
NEJM PMID 25426837

Skin



Martincorena *et al*. (2015)
Science PMID 25999502

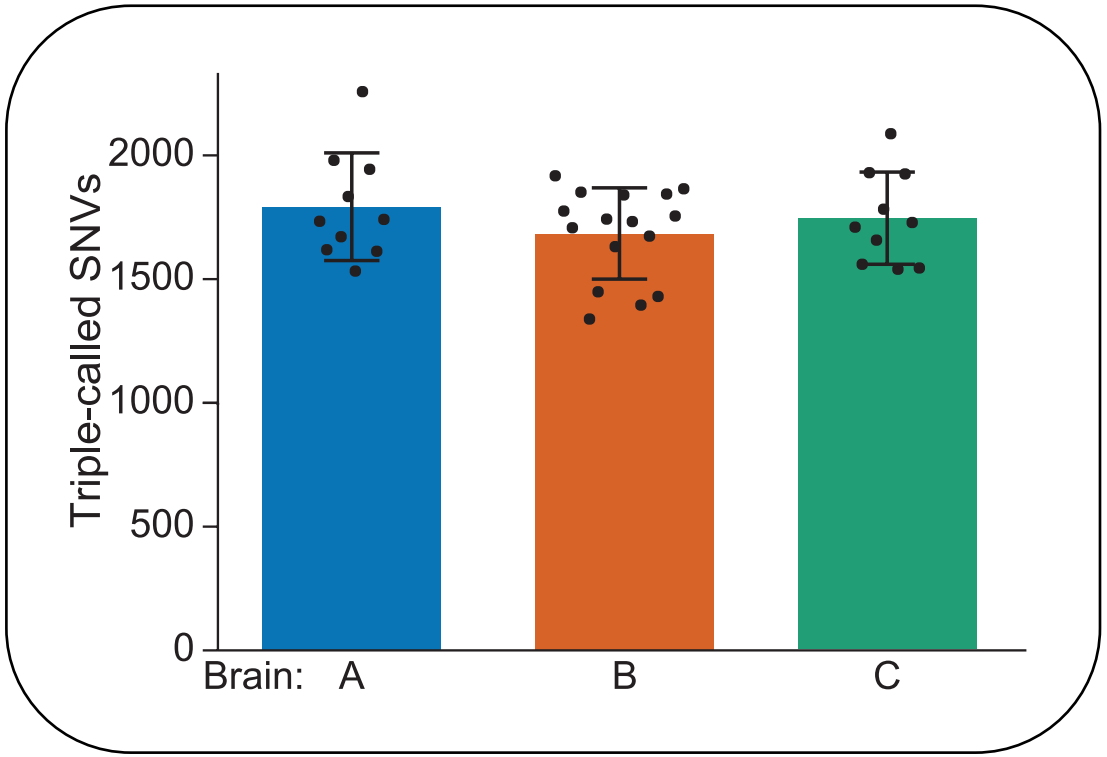
Esophagus



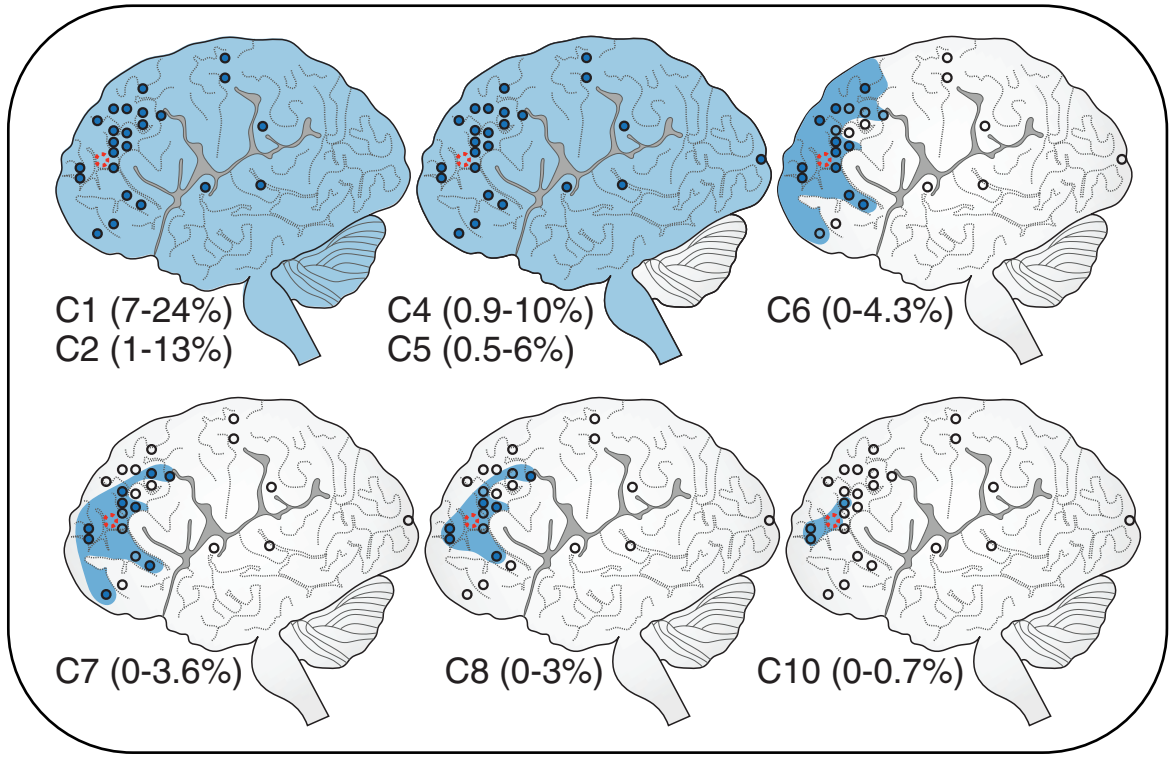
Martincorena *et al*. (2018)
Science PMID 30337457

Somatic Mutations in Neurons

SNV in Human Neurons



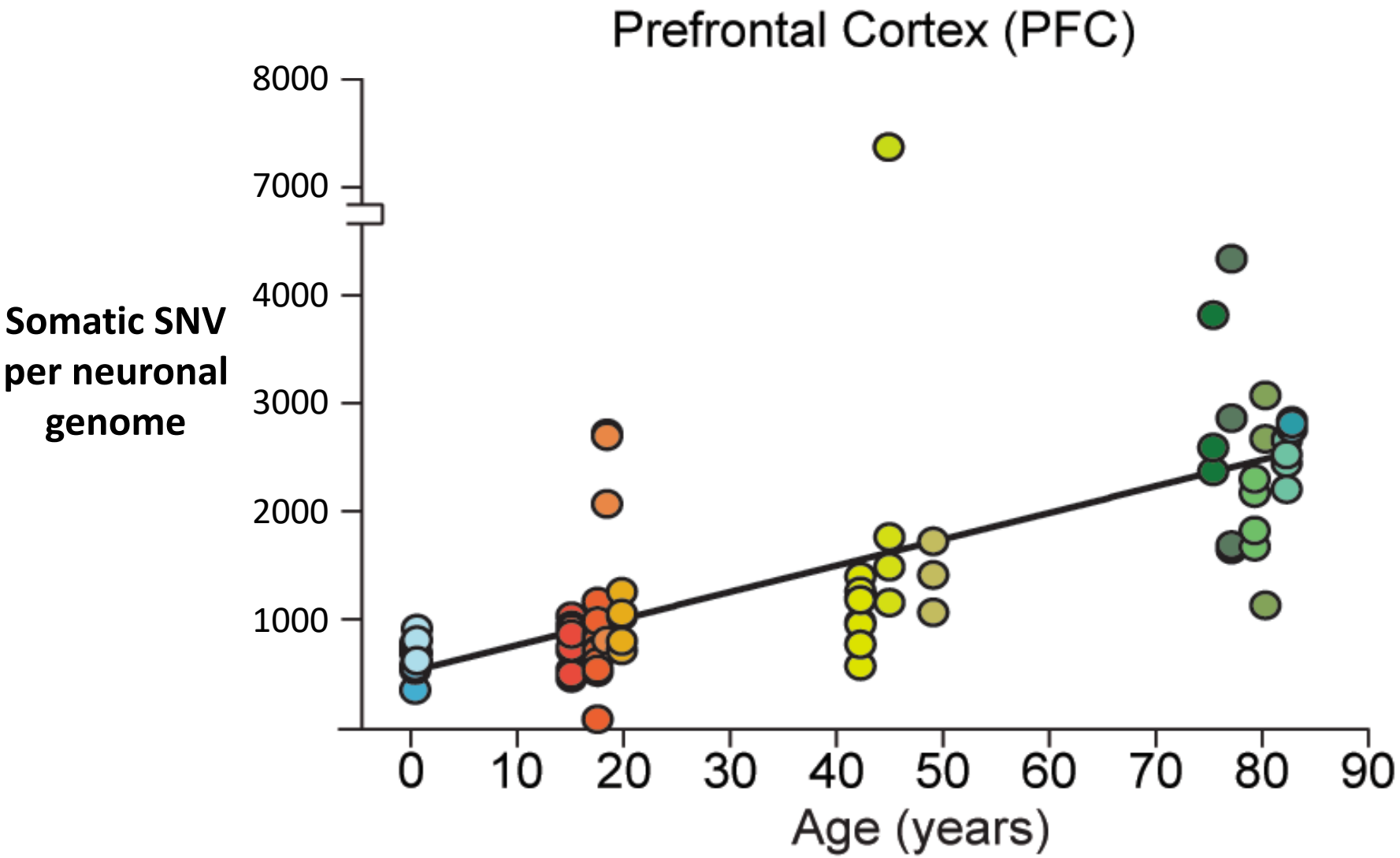
Clonal SNV Show Developmental History



Lodato *et al*. (2015) *Science* PMID 26430121

Hazen *et al*. (2016) *Neuron* PMID 26948891

Neuronal Somatic SNV Increase with Age

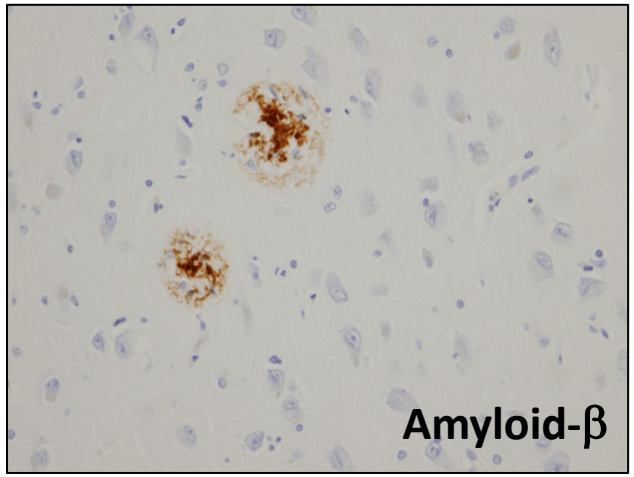


~20 somatic SNVs / year increase

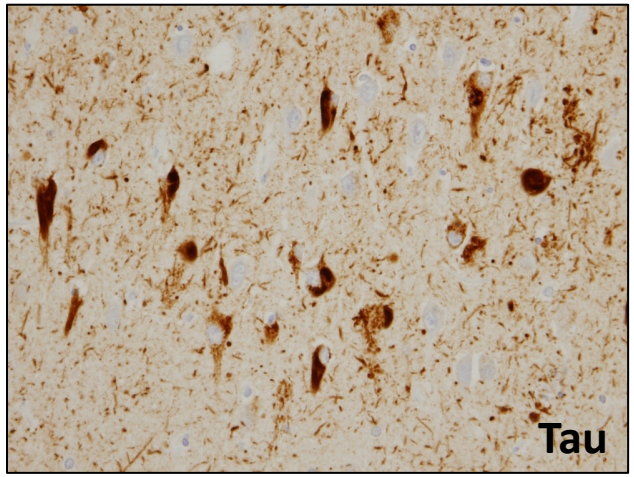
Lodato *et al*. (2018) *Science* 29217584
Luquette, Miller, Zhou *et al*. (2022) *Nature Genetics*
Xing *et al*. (2021) *PNAS* PMID 33593904
Abascal *et al*. (2021) *Nature* PMID 33911282

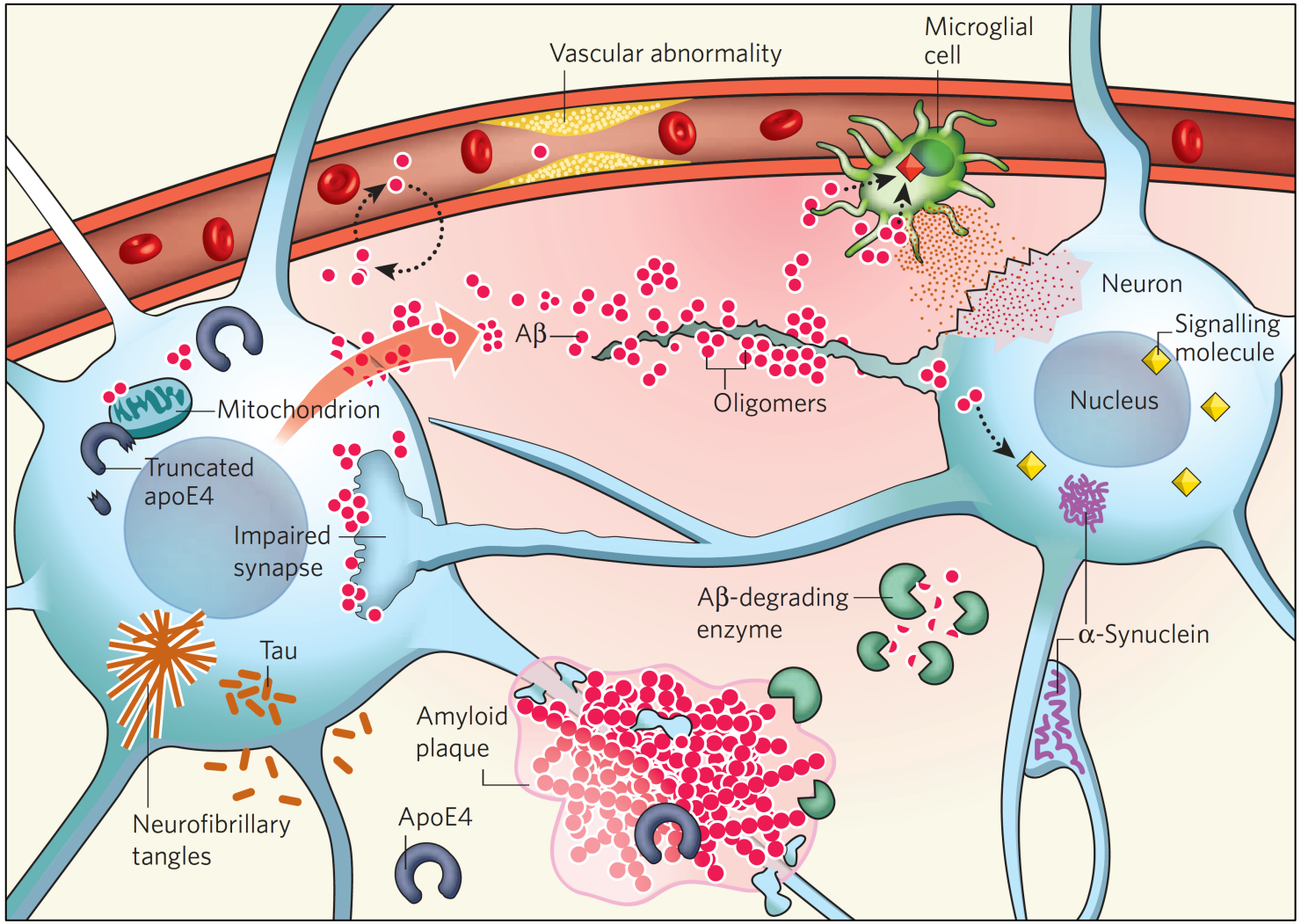
Alzheimer's Disease

Amyloid Plaques



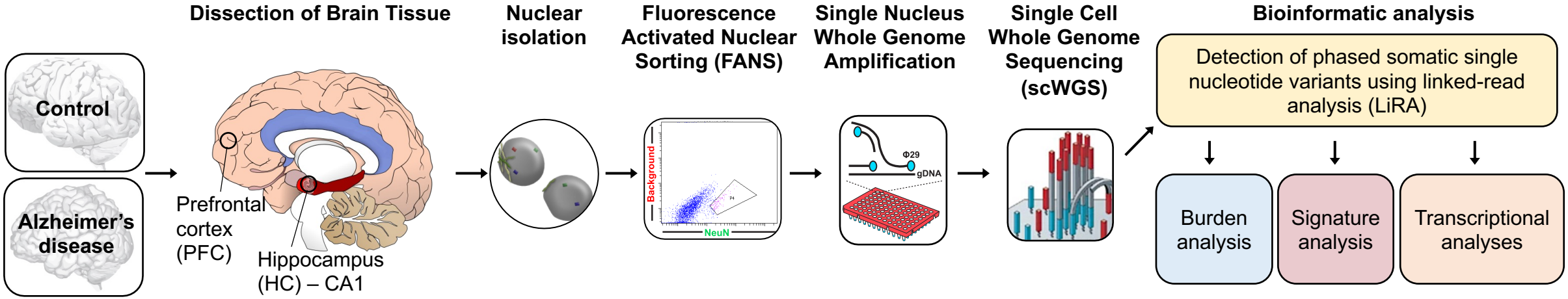
Neurofibrillary Tangles



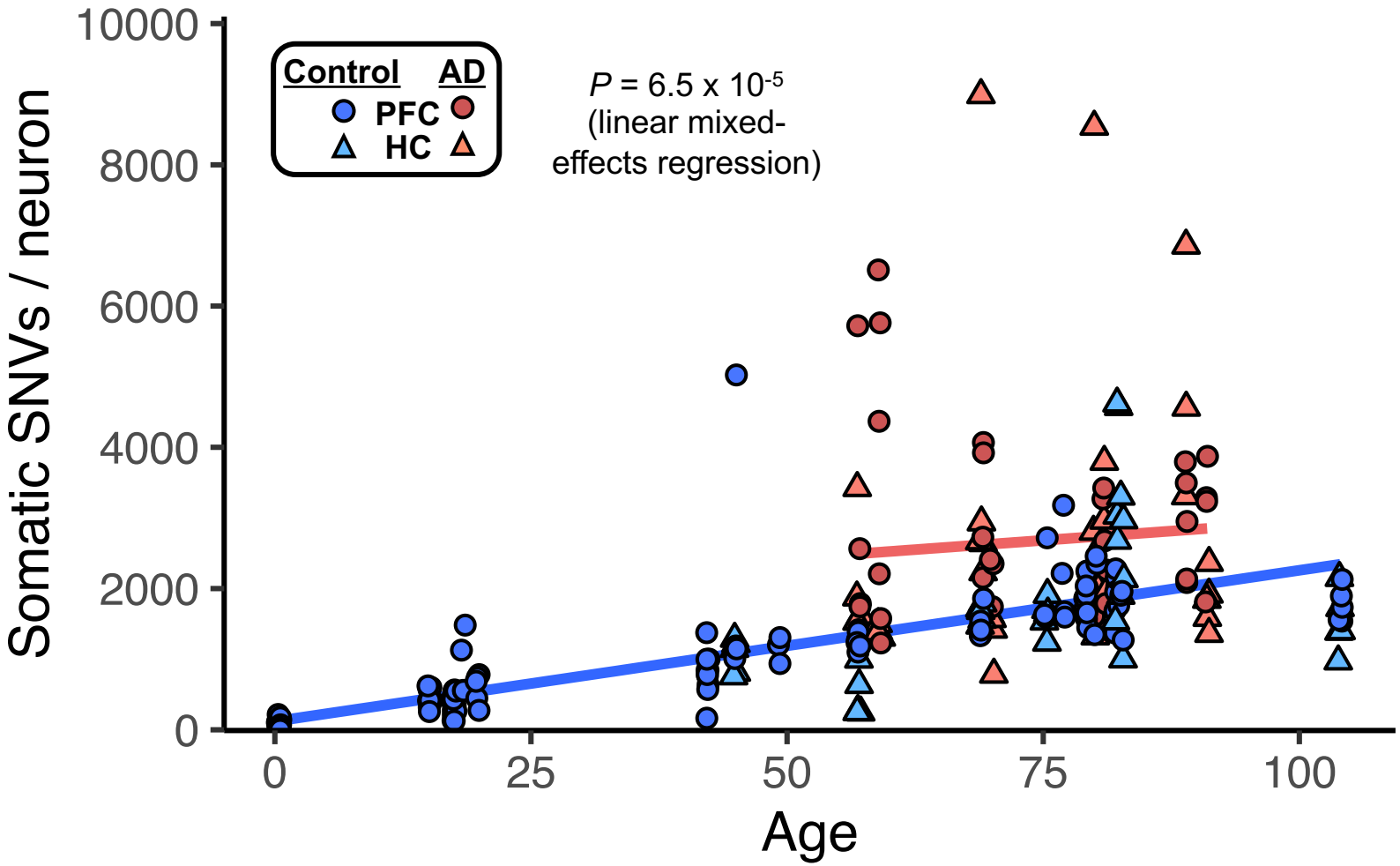


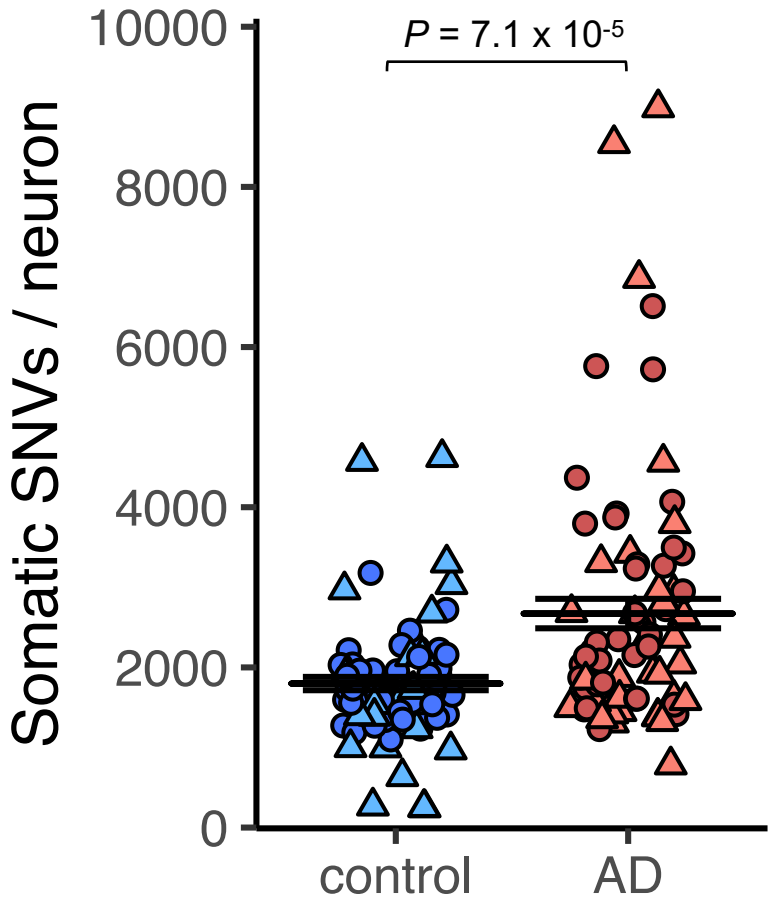
Mucke (2009) *Nature* 461: 895-897

Single-Cell Whole-Genome Sequencing



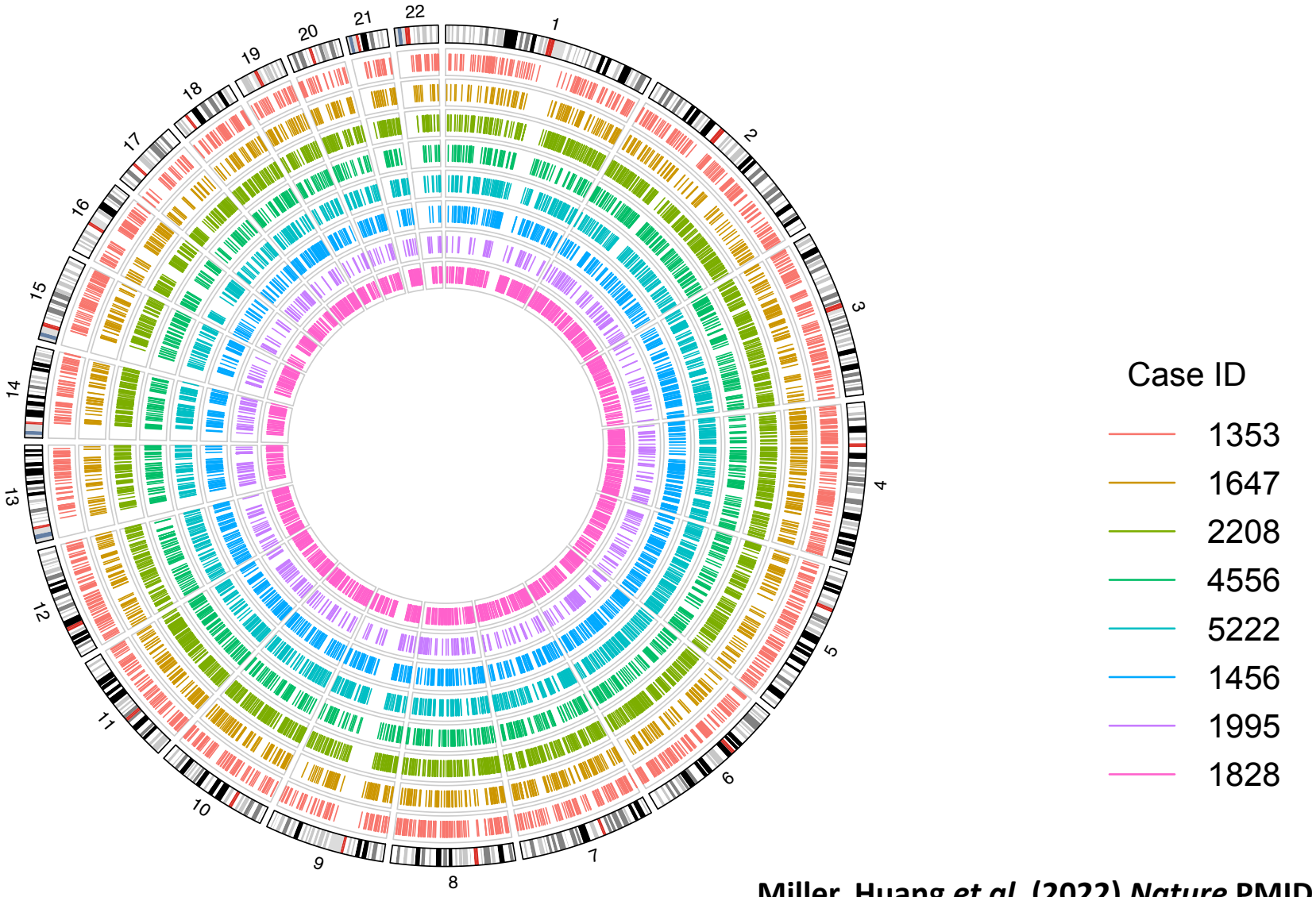
Somatic SNV in Alzheimer's Disease Neurons





Miller, Huang *et al*. (2022) *Nature* PMID 35444284

Somatic SNV in Alzheimer's Disease: Distribution Across the Genome

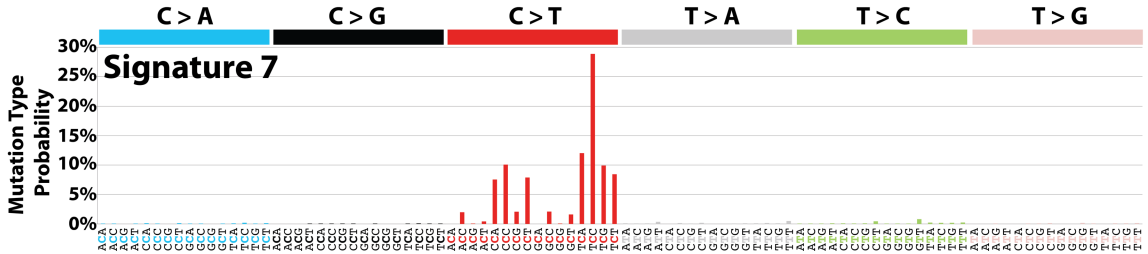


Miller, Huang *et al*. (2022) *Nature* PMID 35444284

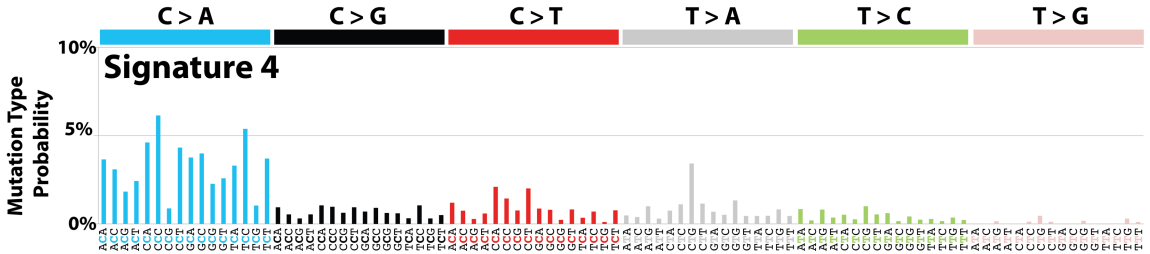
Mutational Signatures and Mutagens

Mutational signature analysis of human cancers

Melanoma



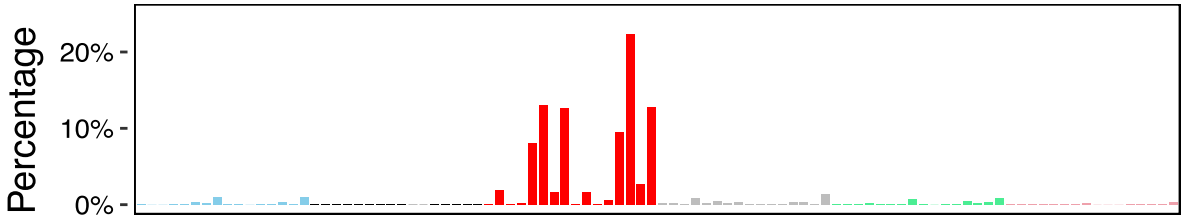
Lung carcinomas



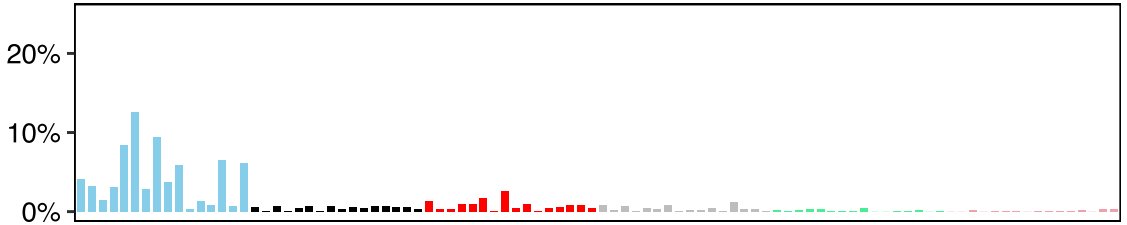
Alexandrov *et al*. (2013) *Nature 23945592*

Mutations observed following exposure of cultured cells

Simulated solar radiation

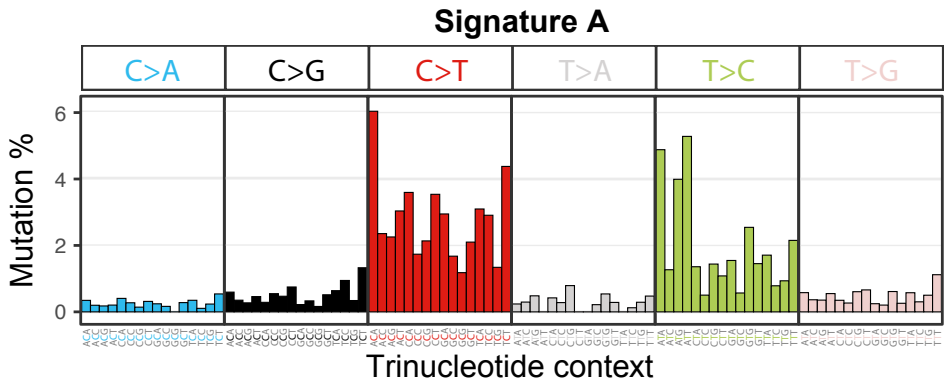


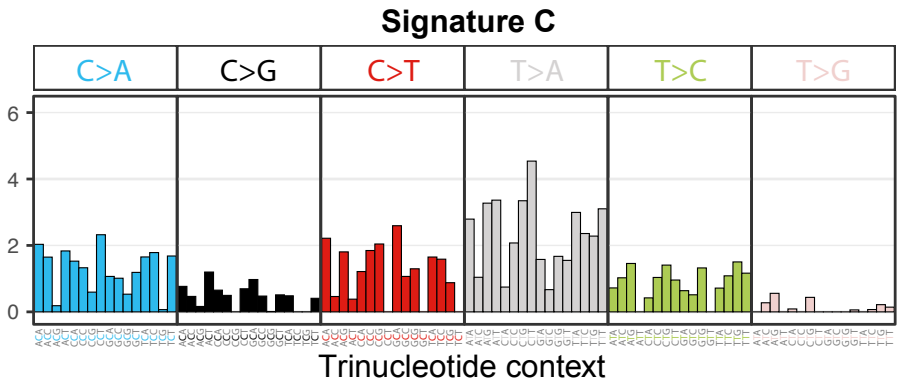
Benzo-a-pyrene (PAH in tobacco smoke)

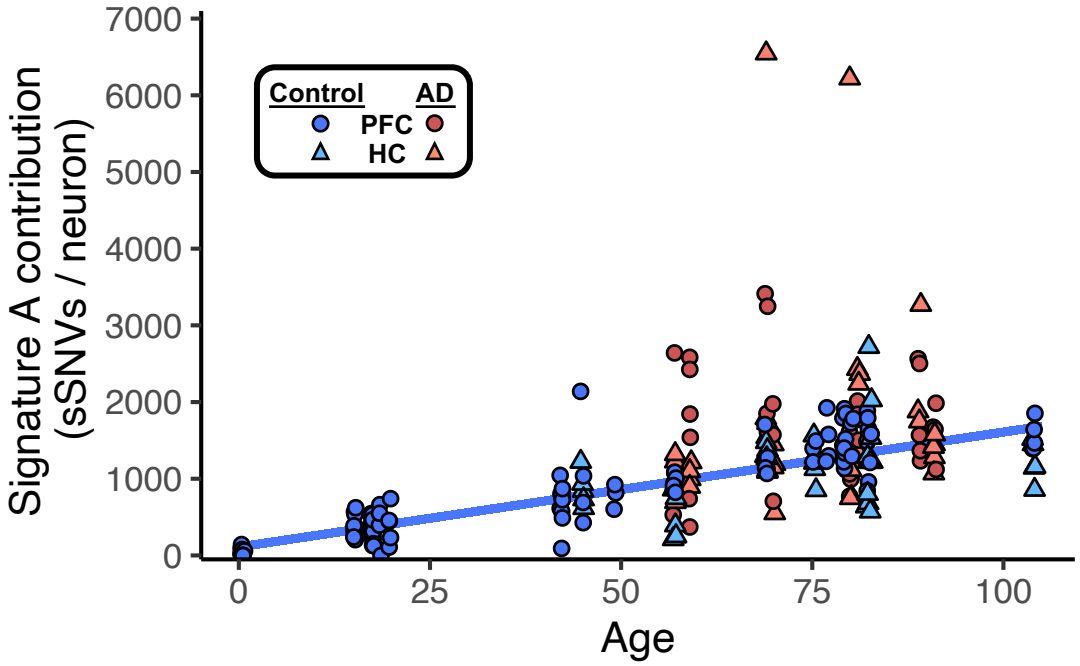


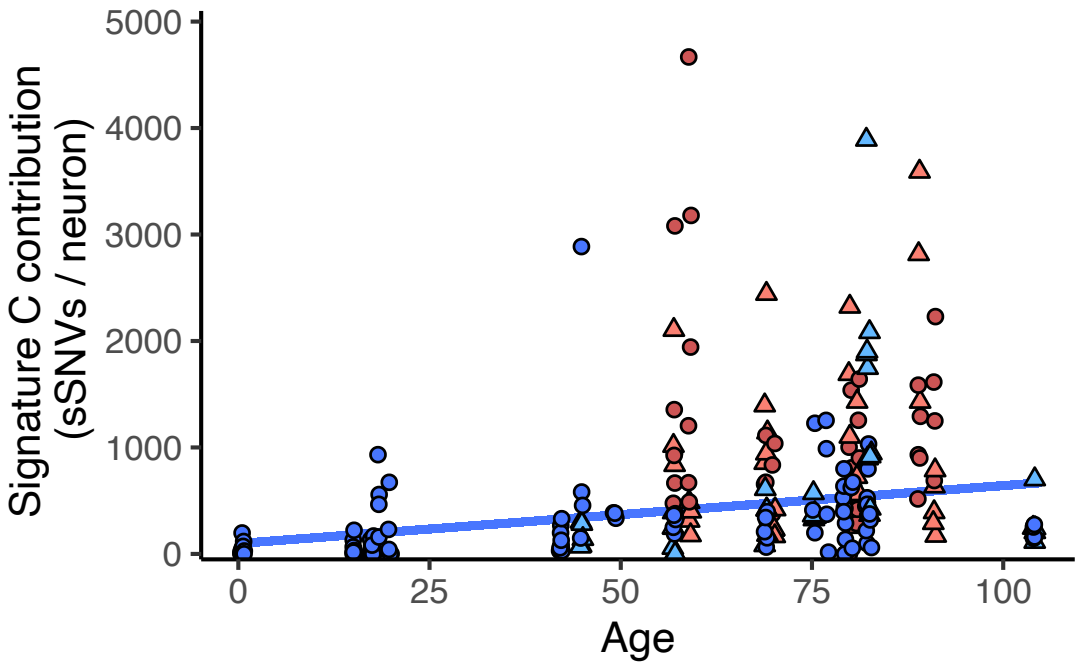
Kucab *et al*. (2019) *Cell* 30982602

Mutational Signature Analysis in AD Neurons



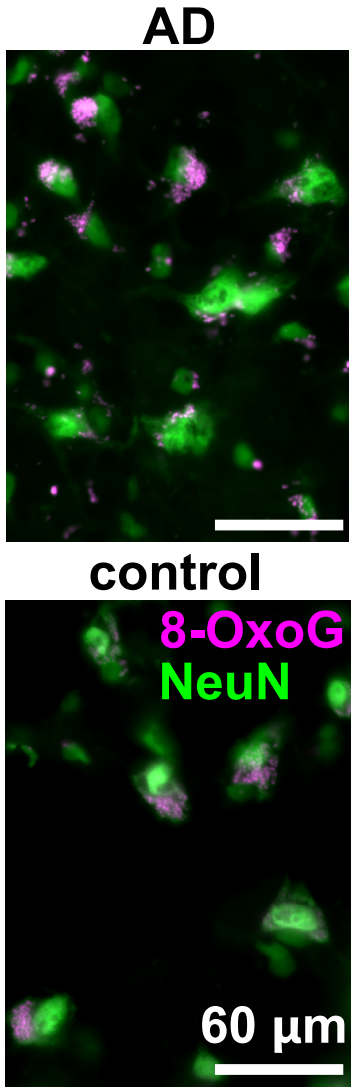


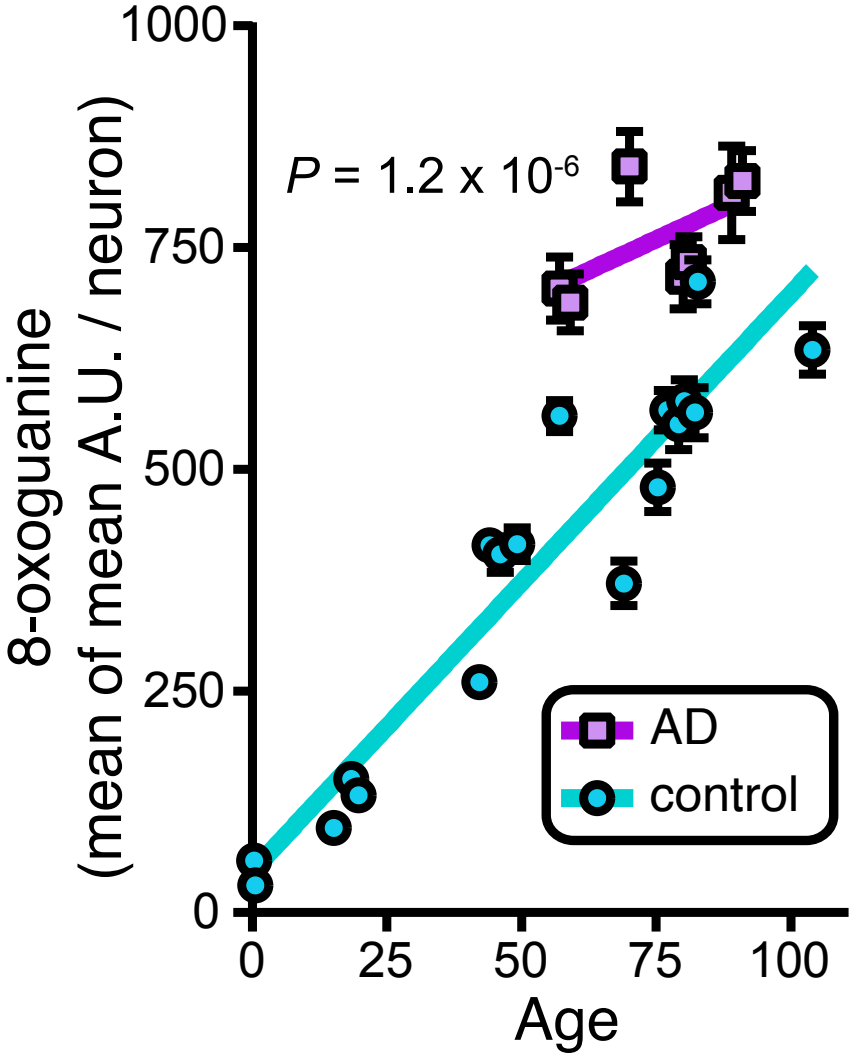




Miller, Huang *et al*. (2022) *Nature* PMID 35444284

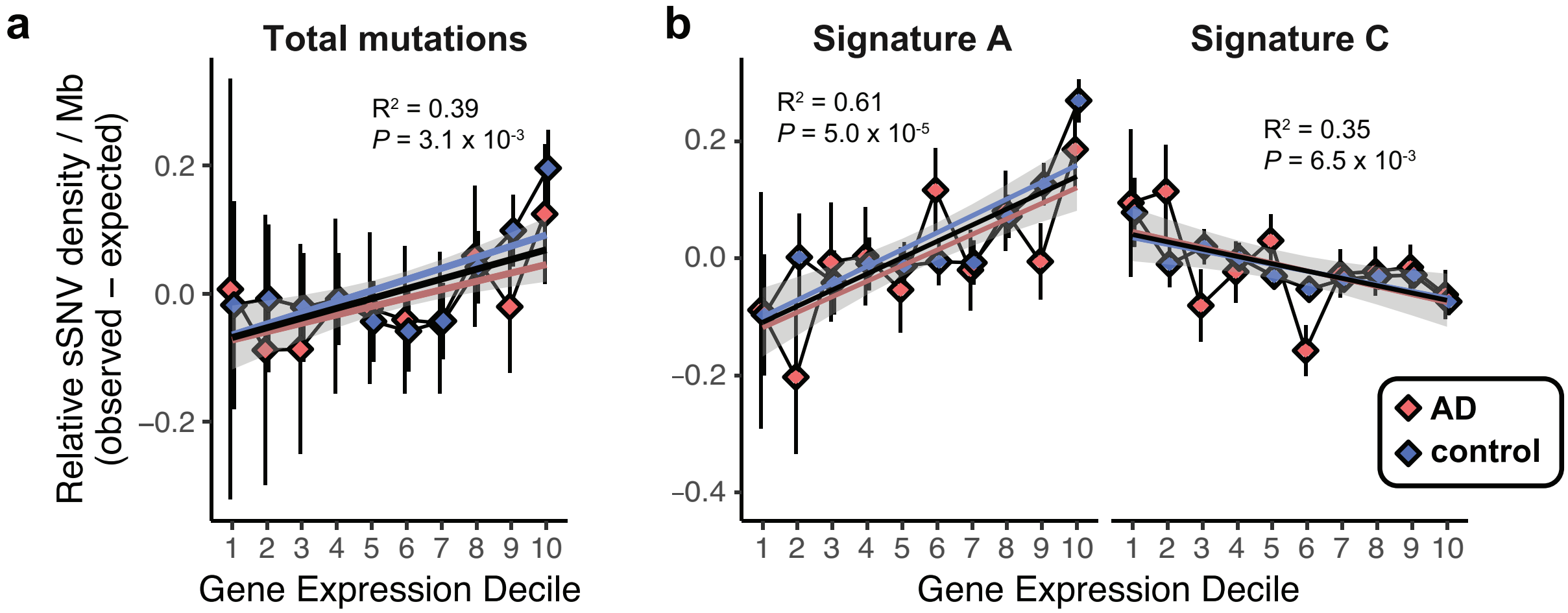
DNA Oxidation in Individual Neurons in AD





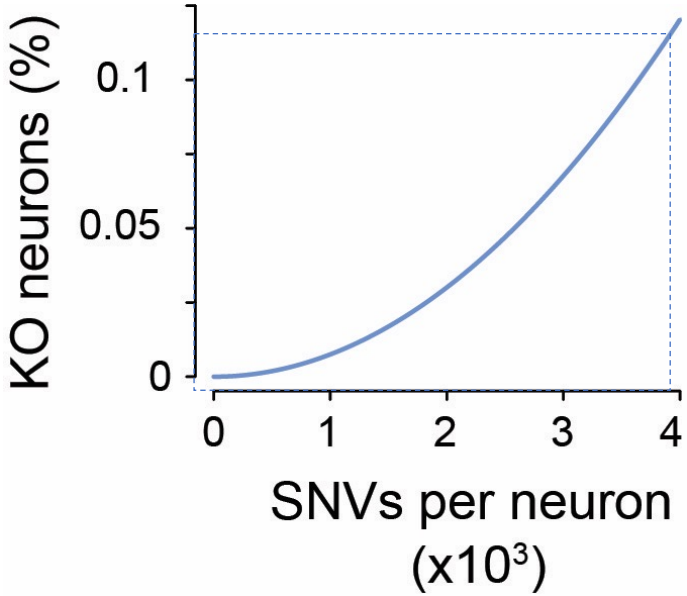
Miller, Huang *et al*. (2022) *Nature* PMID 35444284

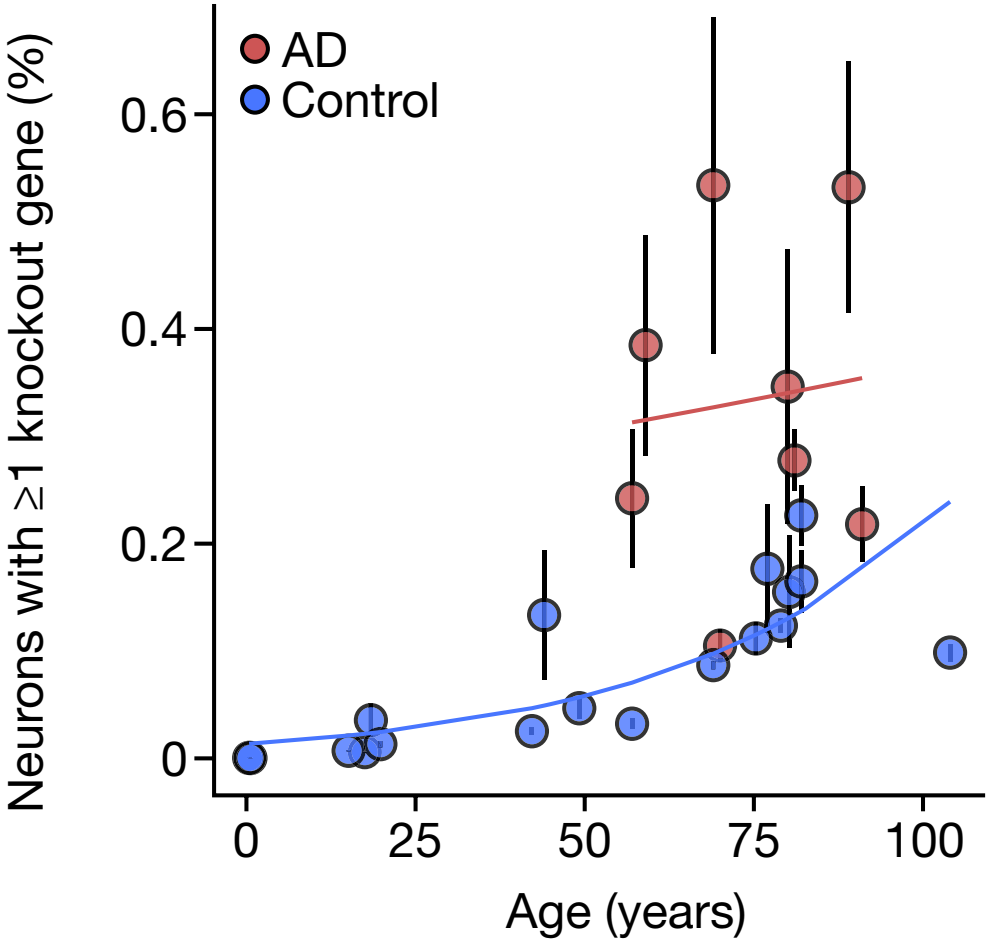
AD Somatic SNV Distribution by Gene Expression



Miller, Huang *et al*. (2022) *Nature* PMID 35444284

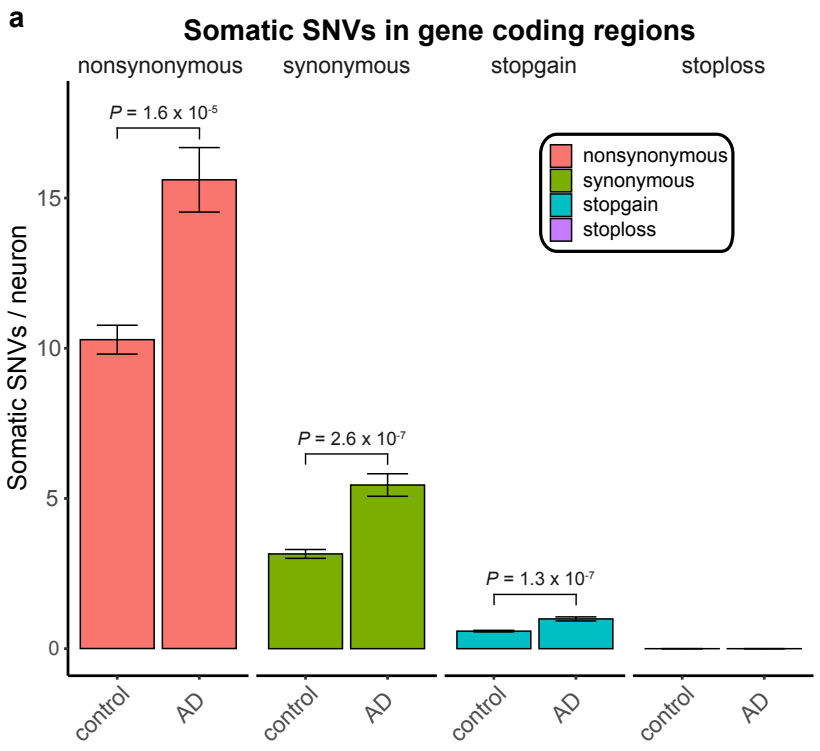
Potential Effect of Somatic SNVs on Neurons: Gene Inactivation

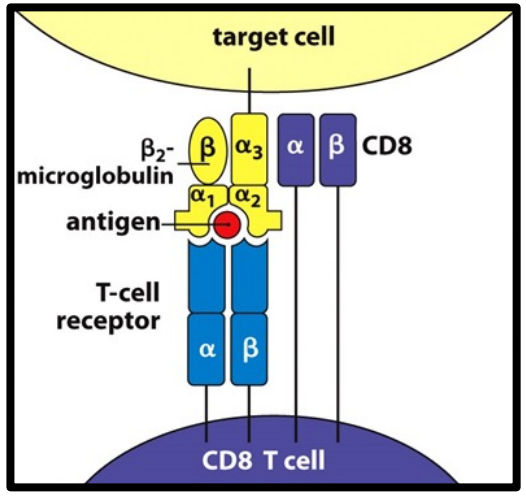




Miller, Huang *et al*. (2022) *Nature* PMID 35444284

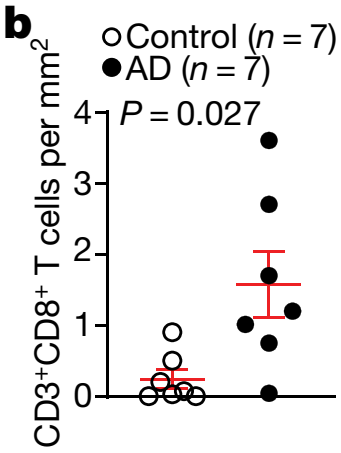
Somatic SNV in AD: Potential Neoantigens

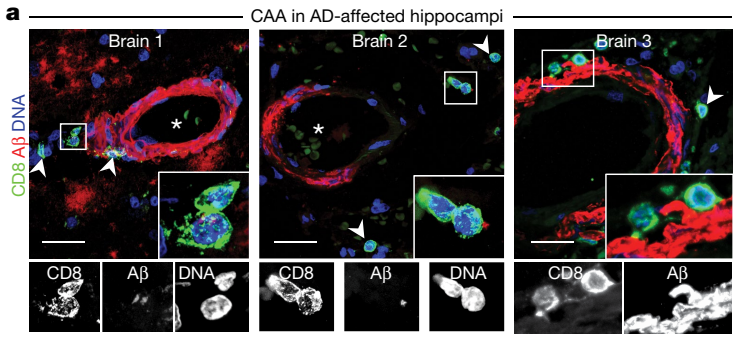




Article

Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease

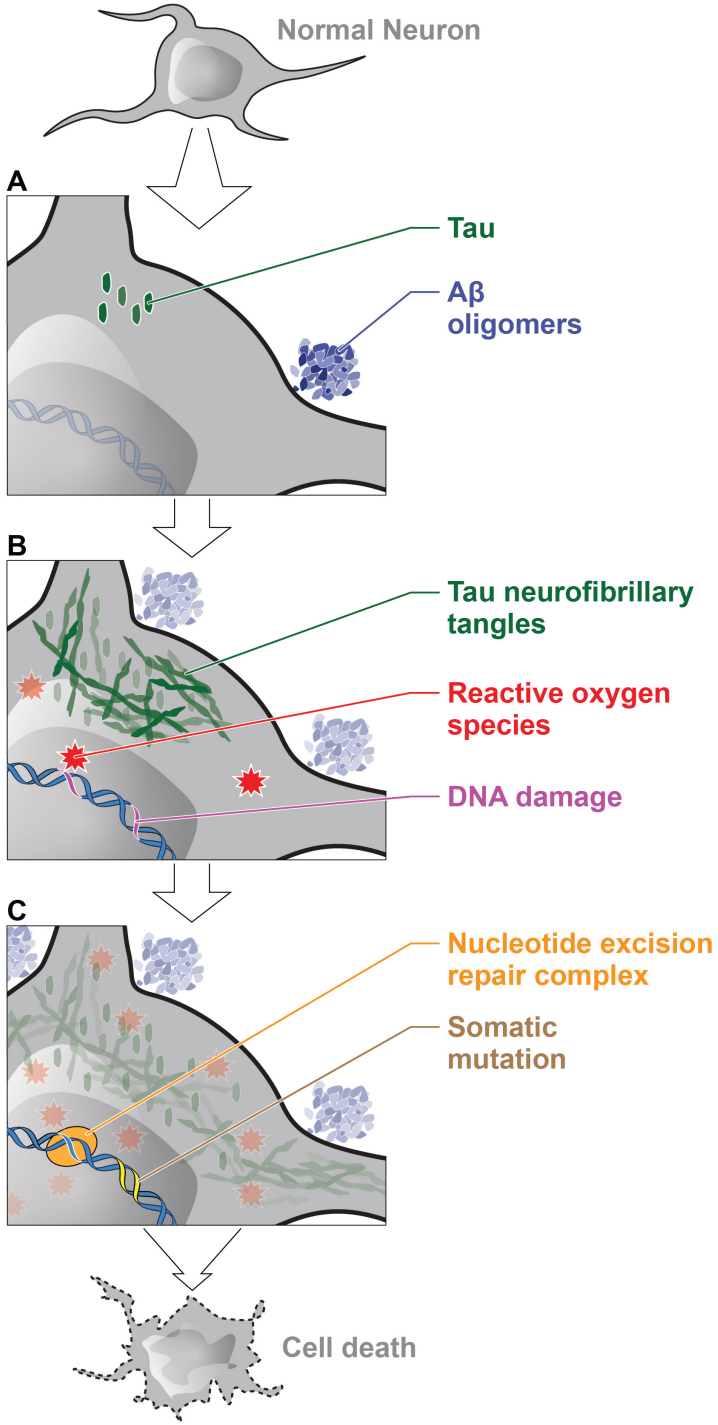




Miller, Huang *et al*. (2022) *Nature* PMID 35444284

Gate *et al*. (2020) *Nature* PMID 31915375

Somatic Mutations in Alzheimer's Disease Pathogenesis



Miller, Huang *et al*. (2022) *Nature* PMID 35444284

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Jay West

NIH National Institute on Aging
NIH NIA K08 Career Development Award

BRIGHAM HEALTH BWH Program for Interdisciplinary Neuroscience
Pilot Award

BrightFocus™ Foundation
Postdoctoral Fellowship

DORIS DUKE CHARITABLE FOUNDATION
Clinical Scientist Development Award

BWH
Startup funding

NIH National Institute of Mental Health

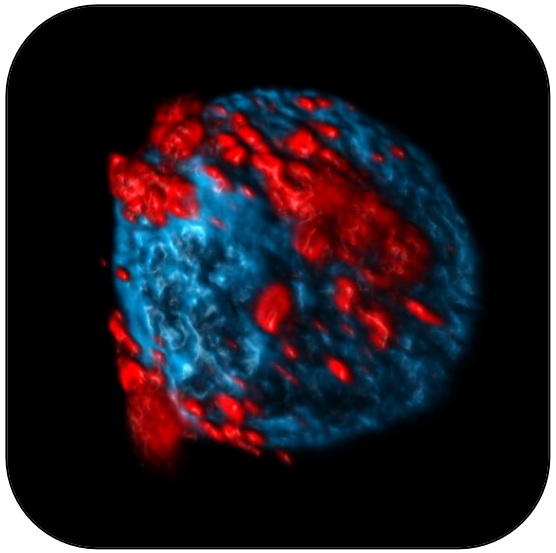
F/PRIME

hhmi Howard Hughes Medical Institute

Brigham and Women's Hospital
Founding Member, Mass General Brigham

Miller lab

HARVARD MEDICAL SCHOOL



Seeking talented scientists to work with us on single-cell and somatic mutation biology in neurodegenerative diseases:

- **Postdoctoral Fellows**
- **Graduate Students**

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