UCSF Weill Institute for Neurosciences

Memory and Aging Center

Beyond *APOE*: Advances in Alzheimer's genetics research

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Neurogenetics in Aging

UCSF Weill Institute for Neurosciences
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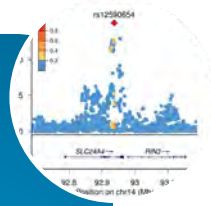
How does genomic variation contribute to brain structure and function in healthy aging and neurodegenerative disease in diverse populations?

biological understanding & biomarker discovery

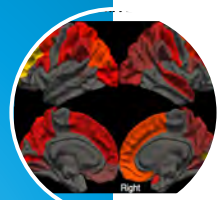


genomics

Rare variants in the neuronal ceroid lipofuscinosis gene *MFSD8* are candidate risk factors for frontotemporal dementia

transcriptomics

Single-cell RNA-seq reveals alterations in peripheral *CX3CR1* and nonclassical monocytes in familial tauopathy



neuroimaging

Radiogenomics of *C9orf72* Expansion Carriers Reveals Global Transposable Element Derepression and Enables Prediction of Thalamic Atrophy and Clinical Impairment

Genetics Mini-Lesson

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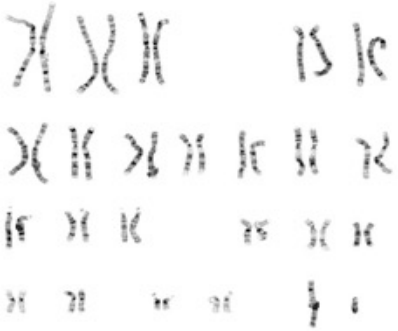
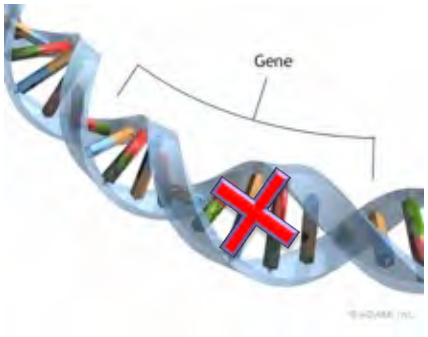
Genome: the 'cookbook' of a human kitchen

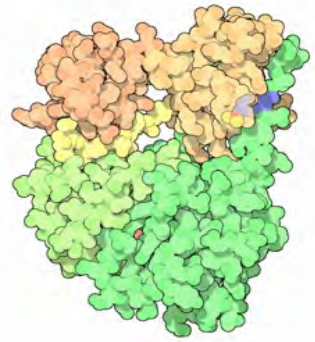
genome



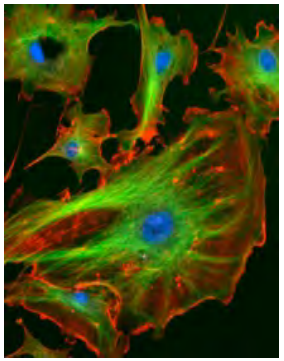
gene



protein



cell



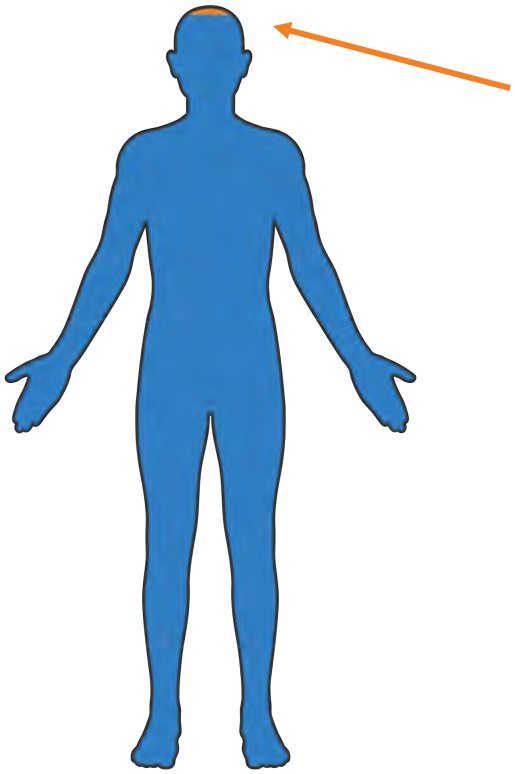
Cookbook

Recipe

Salad Dressing

Mediterranean Salad

Humans are 99.6% **genetically identical*!**



Only 0.4% of the remaining genetic variation accounts for:

- Differences in **visual appearance** (hair, eye color)
- Increased risk for **disease**
- Increased **health** & **longevity**
- Altered **response to medication**

*to the human reference genome

https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation

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Single Nucleotide Polymorphisms (SNPs)

- SNPs are differences between individuals **at a single position** in their DNA sequence
- Usually, each position only has 2 possibility, or **alleles**

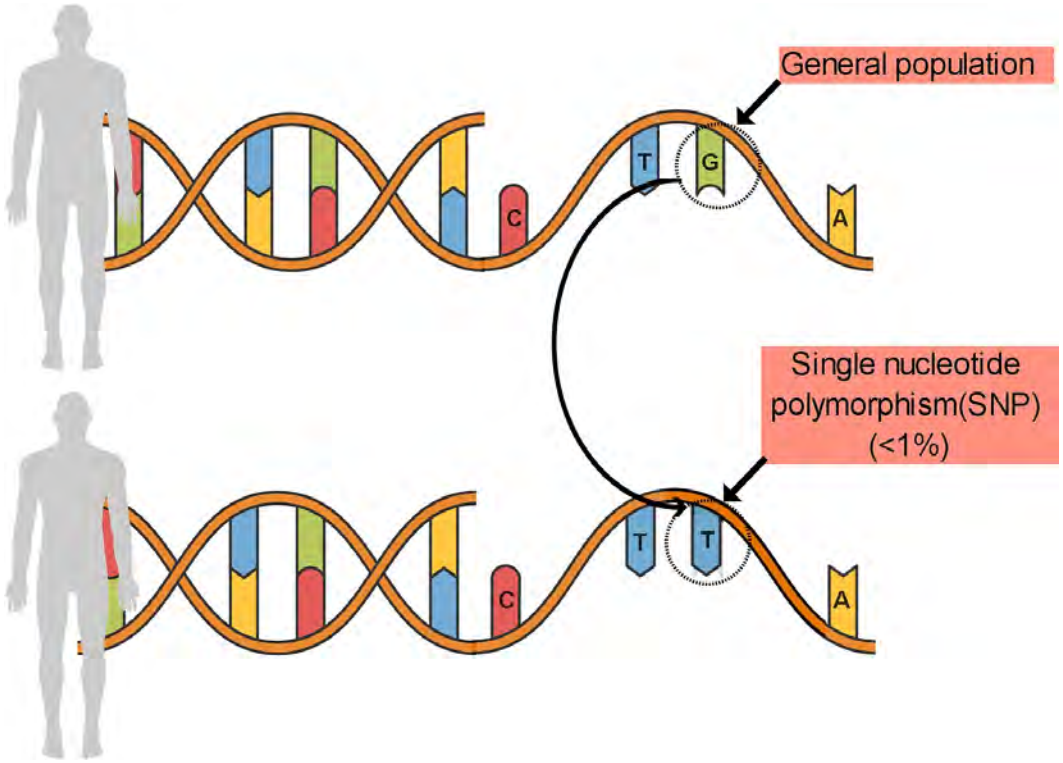

Figure: Lima, L.S., Galiciolli, M.E.A., Pereira, M.E. *et al.* Modification by genetic polymorphism of lead-induced IQ alteration: a systematic review. *Environ Sci Pollut Res* **29**, 43435–43447 (2022). https://doi.org/10.1007/s11356-022-19981-7

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Most human genetic variation is harmless

- Harmless SNPs result in normal protein expression
- Certain **SNP mutations can disrupt protein formation,** resulting in altered, non-functional, or toxic proteins that <u>contribute to disease</u>

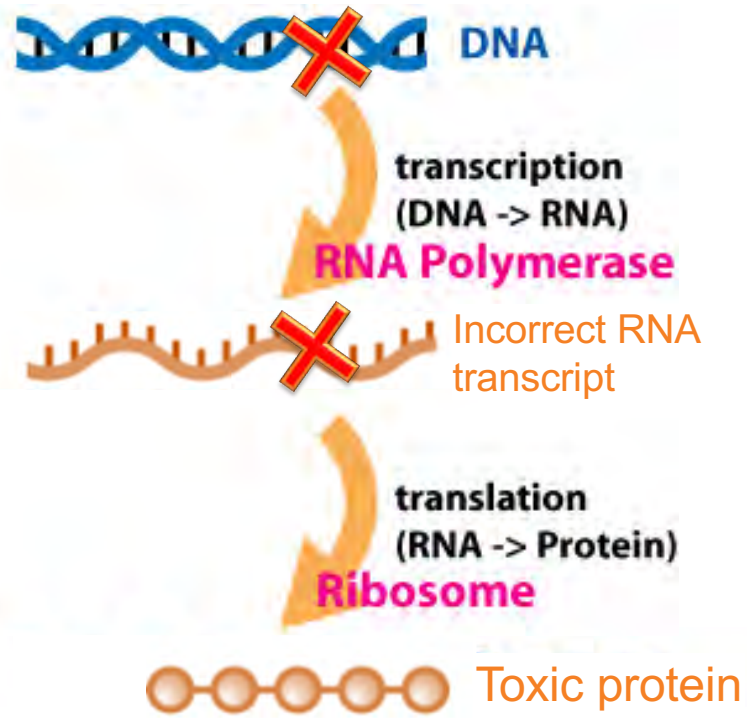
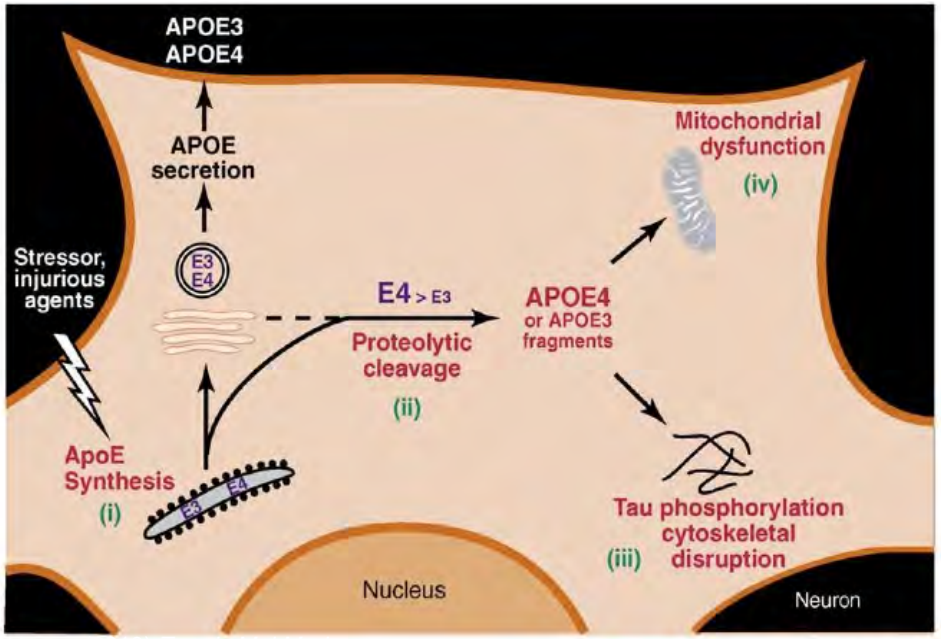


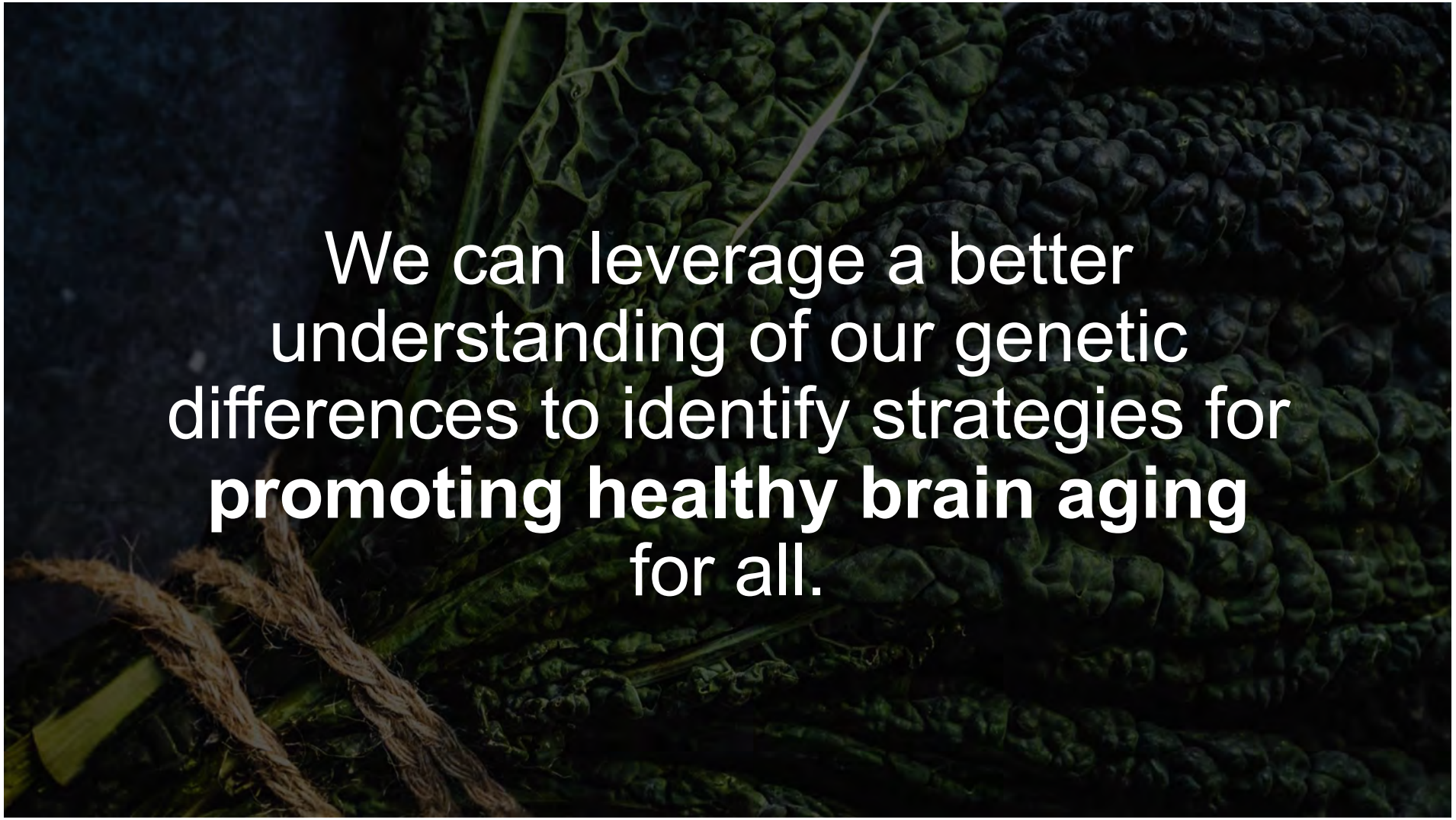
Figure: https://www.fightingblindness.ca/resources/genetic-testing-for-inherited-retinal-diseases/

Why is studying genetic variation important?

- Gives insight into **disease biology**
- Identifies new targets for **disease intervention**
- Provides early marker of **disease risk**



Huang (2010) *Trends Mol Med*


We can leverage a better
understanding of our genetic
differences to identify strategies for
promoting healthy brain aging
for all.

Genetics of Alzheimer's disease: beyond *APOE*

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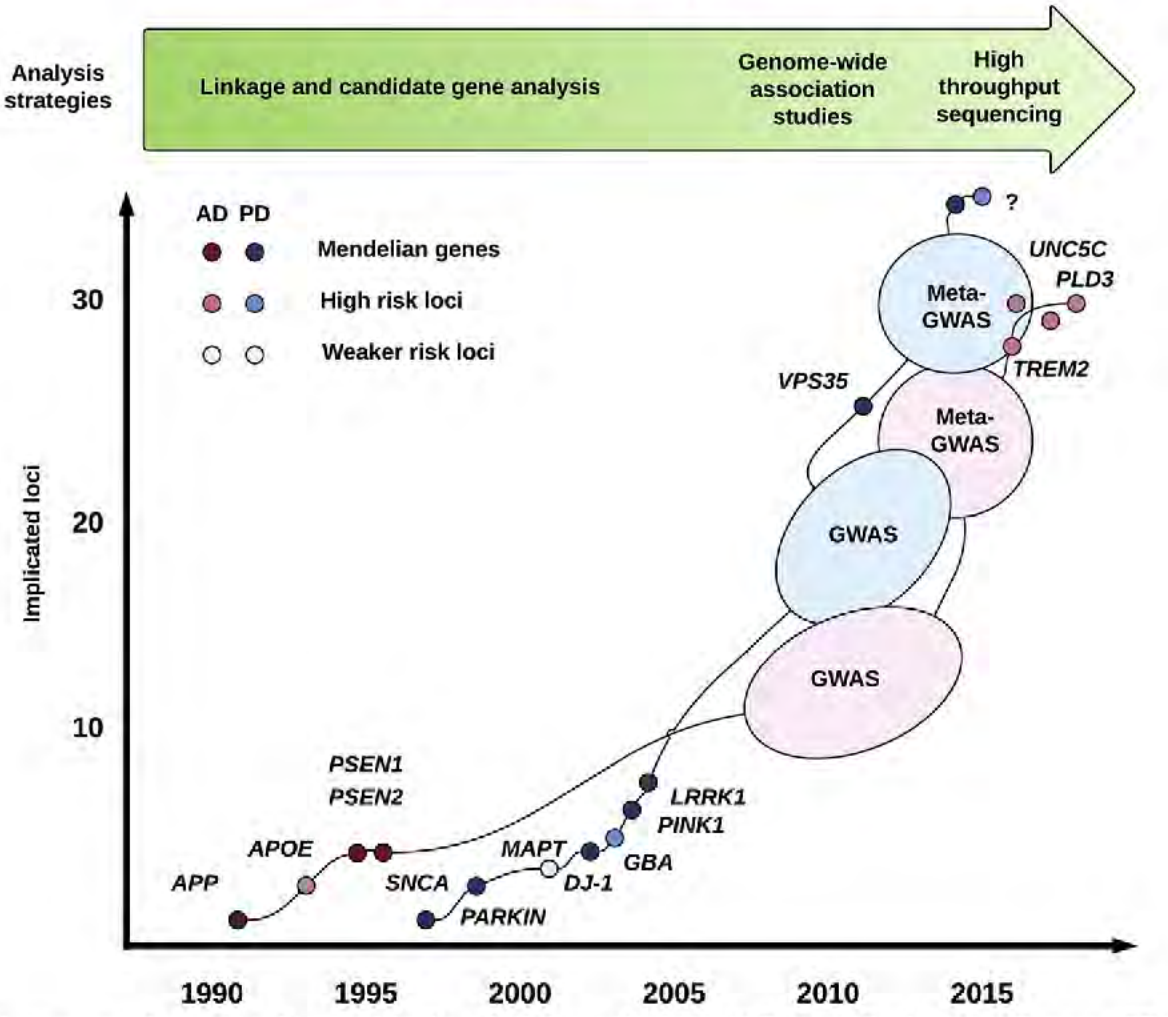
A Brief History

- Disease-causing **familial variants** discovered first (*APP, PSEN1/2*), along with **risk gene *APOE***
- Followed by the discovery of additional genes (***MAPT, TREM2***)
- New discoveries being driven by genome-wide association studies (GWAS) and big datasets



Pihlstrom et al, 2017 *Handbook of Clinical Neurology*

Newer discoveries in AD genetics leverage studies of large cohorts

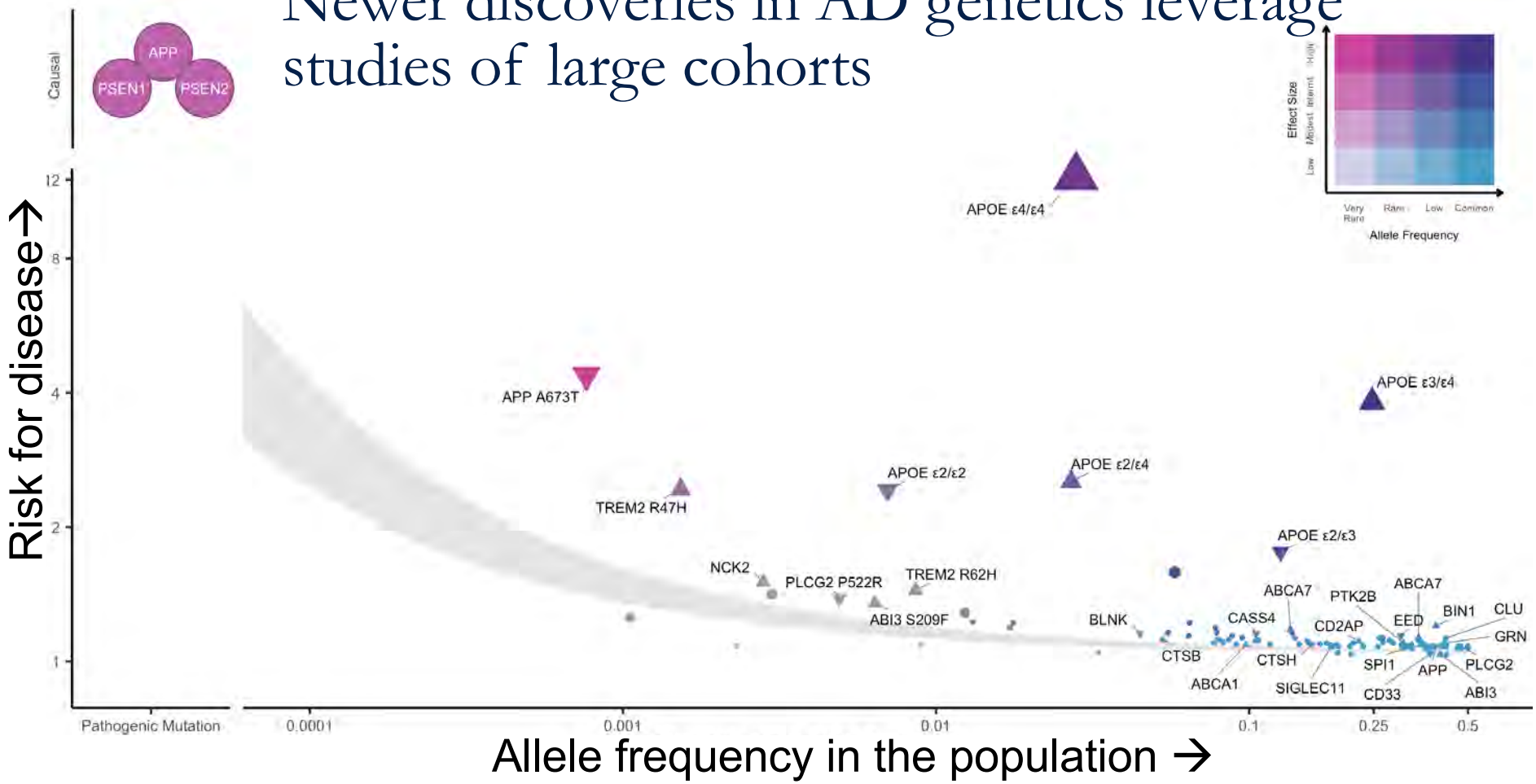


Figure by Shea Andrews: https://github.com/sjfandrews/ADGenetics (2022)

New insights into the genetic etiology of Alzheimer's disease and related dementias

nature genetics

Bellenguez et al, 2022.

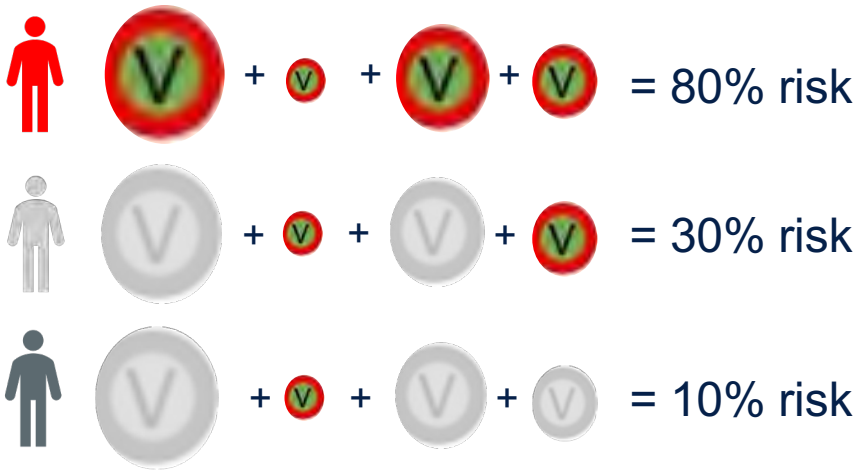
- Early 2022 GWAS performed on 111,326 clinically diagnosed and proxy AD cases*, 677,663 controls
- Found 75 risk SNPs, 45 new at the time of analysis
- Highlighted microglia implication
- Built a new genetic risk score improving AD prediction

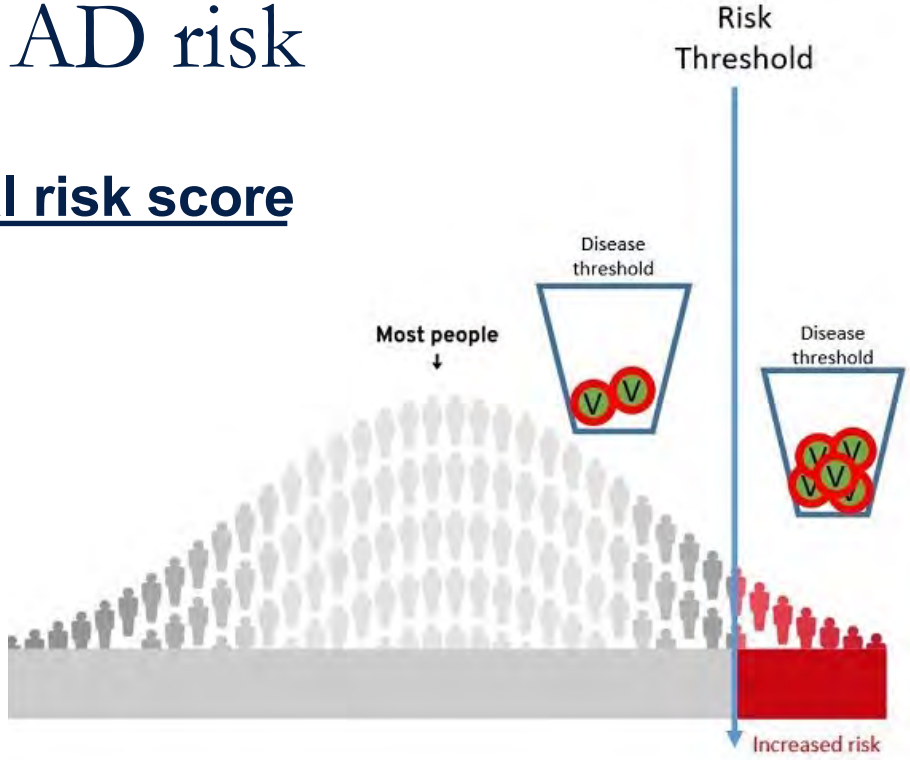
*All cases were of European ancestry

Genetic risk scores across ancestral populations

Goal: combine all known genetic variants (V) to predict individualized AD risk

Sum of V * effect size **= individual risk score**





https://www.mayo.edu/research/emerge-genome-informed-risk-assessment/risk-assessment/polygenic-risk-scores

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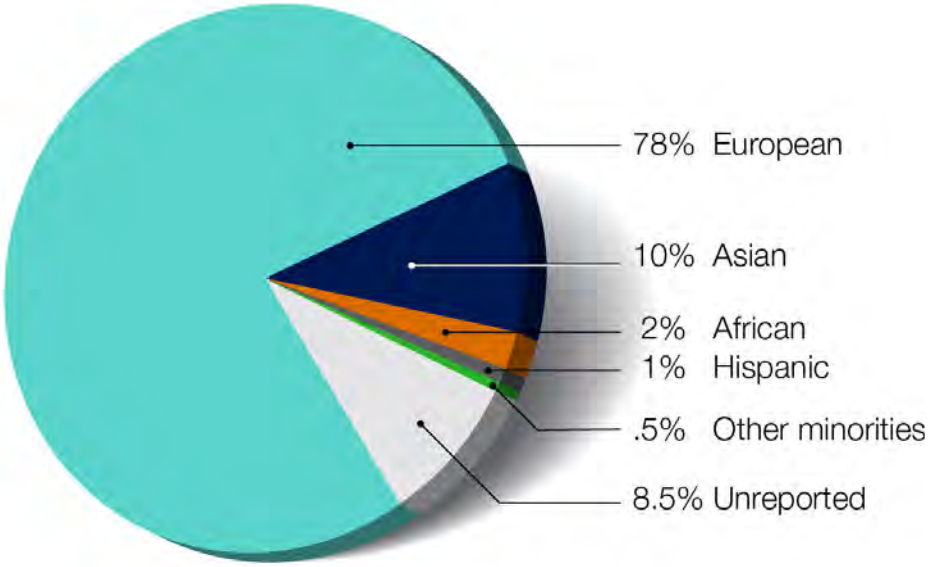
Challenge: most genomes available for research are from individuals with European ancestry

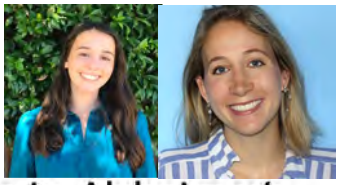
- Solution #1: Develop **methodological approaches** to improve accuracy of PRS in non-EUR ancestries

- Solution #2: Design studies that **increase representation** of global populations in genomics research



https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

Solution #1:



Julie Lake

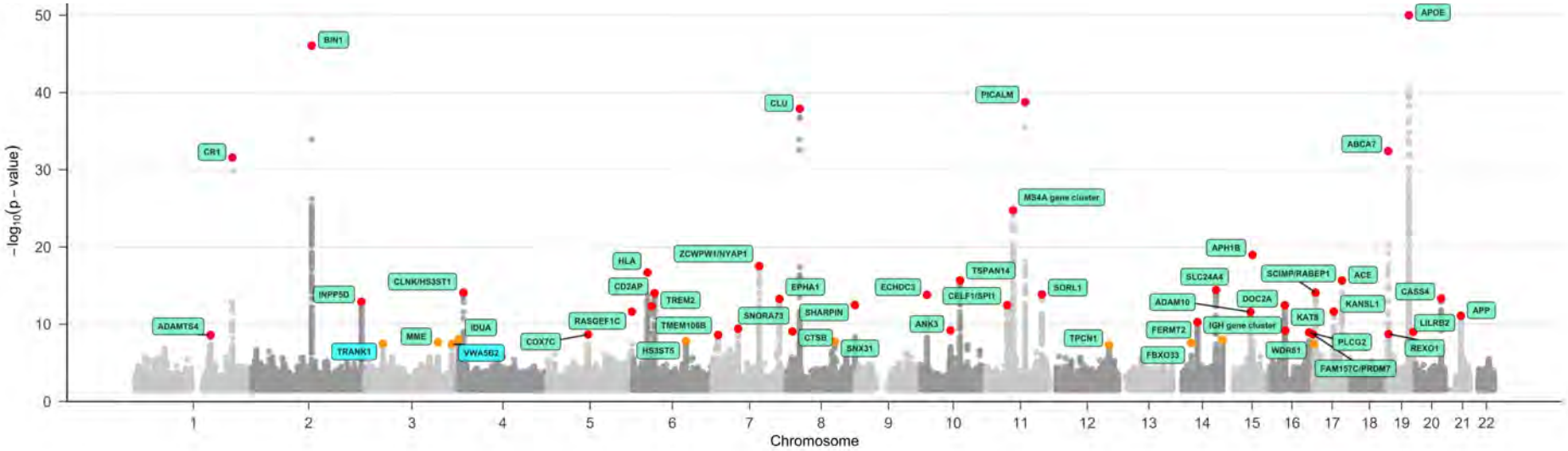
Caroline Warly Solsberg

We can leverage genomic diversity across populations to enhance gene discovery

ARTICLE OPEN

Multi-ancestry meta-analysis and fine-mapping in Alzheimer's disease

Julie Lake[1,21], Caroline Warly Solsberg[2,3,4,21], Jonggeol Jeffrey Kim[1,5], Juliana Acosta-Uribe[6,7], Mary B. Makarious[1,8,9], Zizheng Li[2,3], Kristin Levine[10,11], Peter Heutink[12], Chelsea X. Alvarado[1,10,11], Dan Vitale[1,10,11], Sarang Kang[13,14], Jungsoo Gim[13,14,15], Kun Ho Lee[13,14,15,16], Stefanie D. Pina-Escudero[2,3,4], Luigi Ferrucci[17], Andrew B. Singleton[1,11], Cornelis Blauwendraat[11,18], Mike A. Nalls[1,10,11], Jennifer S. Yokoyama[2,3,4,19,21] and Hampton L. Leonard[1,10,11,20,21]



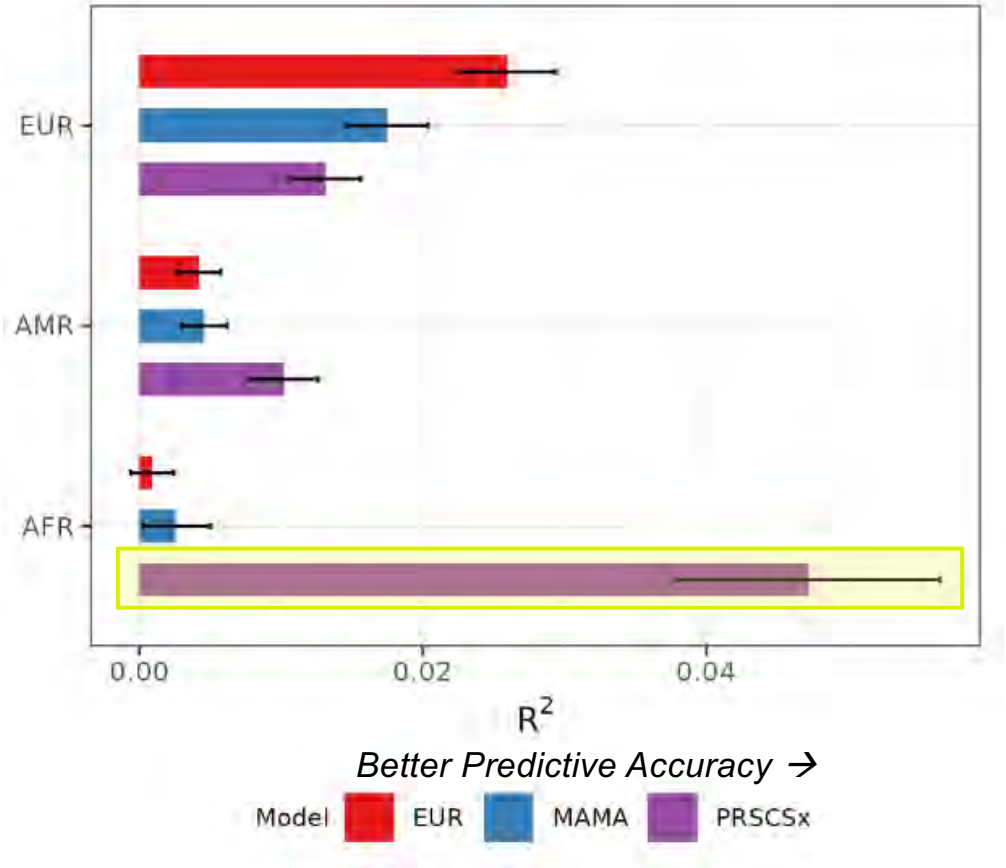
Two novel loci identified on chr 3

Limited to MAF > 0.01 in at least <u>three</u> datasets, reducing tests to P=5e-08

Solution #1:

Cross-Ancestry Polygenic Risk Scores Enhance Alzheimer's Disease Risk Prediction in Multiethnic Cohorts

Preprint on medRxiv. Posted October 7, 2025.



- Single-ancestry PRS is most accurate in European populations
- Improved cross-ancestry methods for generating PRS (**PRSCSx**) improved risk predictions for non-European populations

Meri Okorie

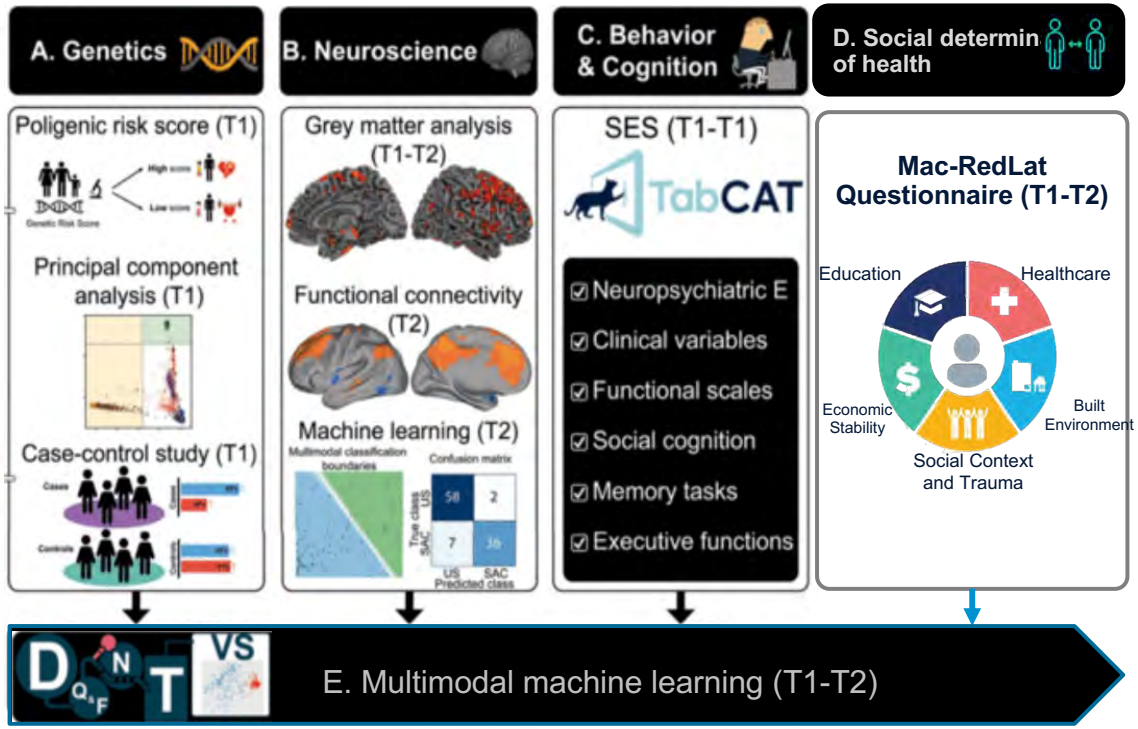
Shea Andrews

Chi Udeh-Momoh

Solution #2:

US-South American Initiative For Genetic-Neural-Behavioral Interactions In Human Neurodegenerative Research

Total:
4,200
participants

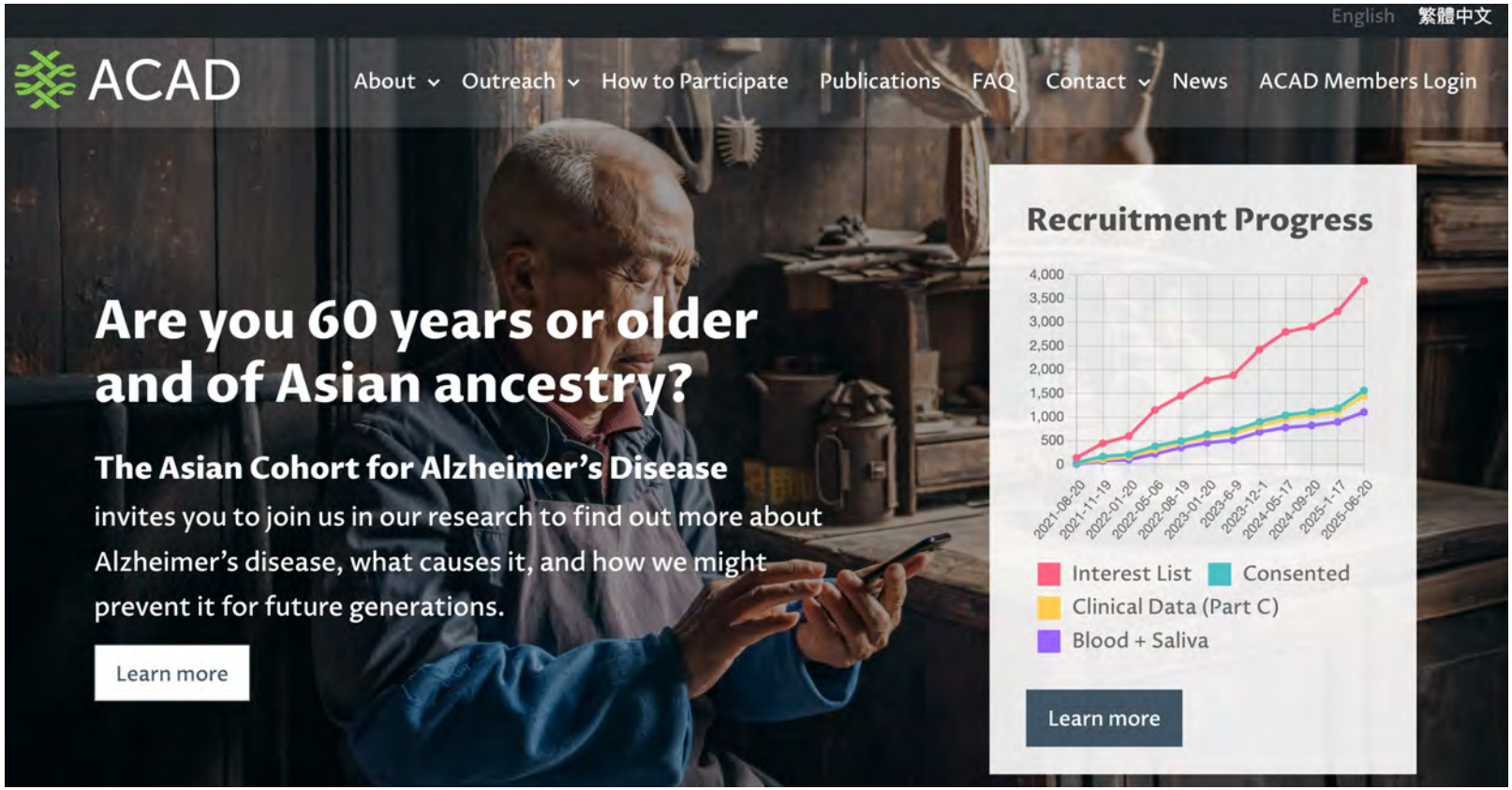


ReD-Lat
Multi-Partner Consortium to Expand Dementia Research in Latin America

Project Directors: Agustin Ibañez & Bruce Miller

NIH NIA · alzheimer's association · Tau Consortium · Global Brain Health Institute · UCSF

Solution #2: Asian Cohort for Alzheimer's Disease



https://acadstudy.org/contact-us/

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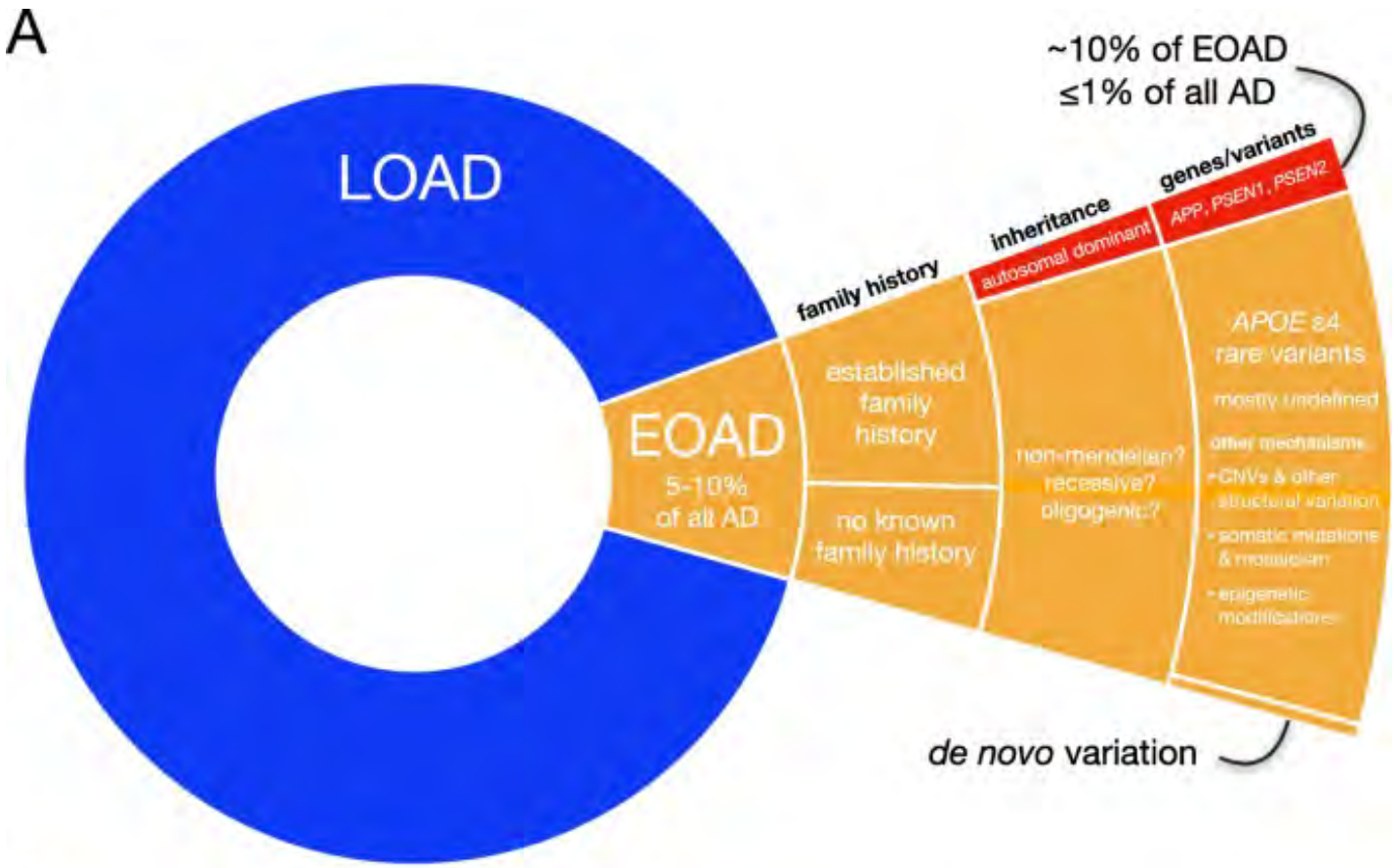
Gene expression in the blood as a biomarker of early-onset AD

What do we mean when we say early-onset AD (EOAD)?

- EOAD *is not* synonymous with autosomal dominant (mendelian) AD
- EOAD *is* AD with symptom onset before age 65 (age 60 in some studies)
- age cutoff is arbitrary, but individuals w/ EOAD are more likely to:
  - have an aggressive clinical course
  - have an atypical (non-amnestic) clinical presentation
  - experience delays in diagnosis
  - be excluded from clinical trials

Most cases of EOAD are *not* familial!

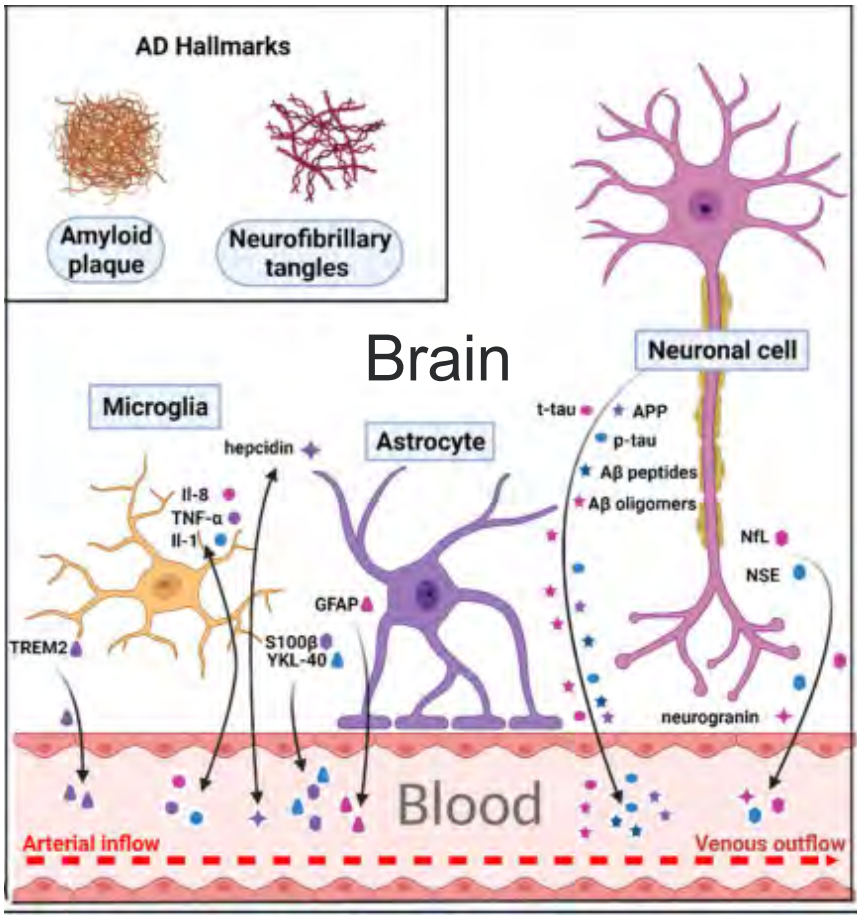


Most genetic contributions to EOAD remain to be discovered!

Sirkis et al., Dissecting the clinical heterogeneity of early-onset Alzheimer's disease. *Molecular Psychiatry*, 2022.

Why do we care about blood in Alzheimer's disease?

- Blood contains peripheral immune cells (PBMCs)
- Blood-brain barrier (BBB) interaction
- Blood is accessible, easy, and cheap to collect



Delaby C, Hirtz C, Lehmann S. Overview of the blood biomarkers in Alzheimer's disease: Promises and challenges. Rev Neurol (Paris). 2023 Mar;179(3):161-172.

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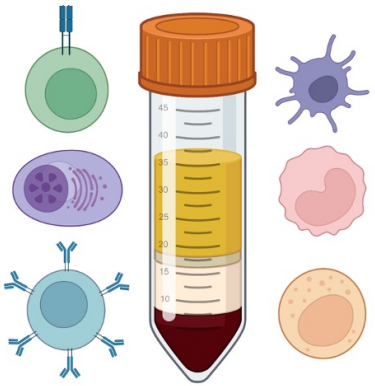
Our Goal: leverage gene expression in blood immune cells to enable discovery in EOAD.



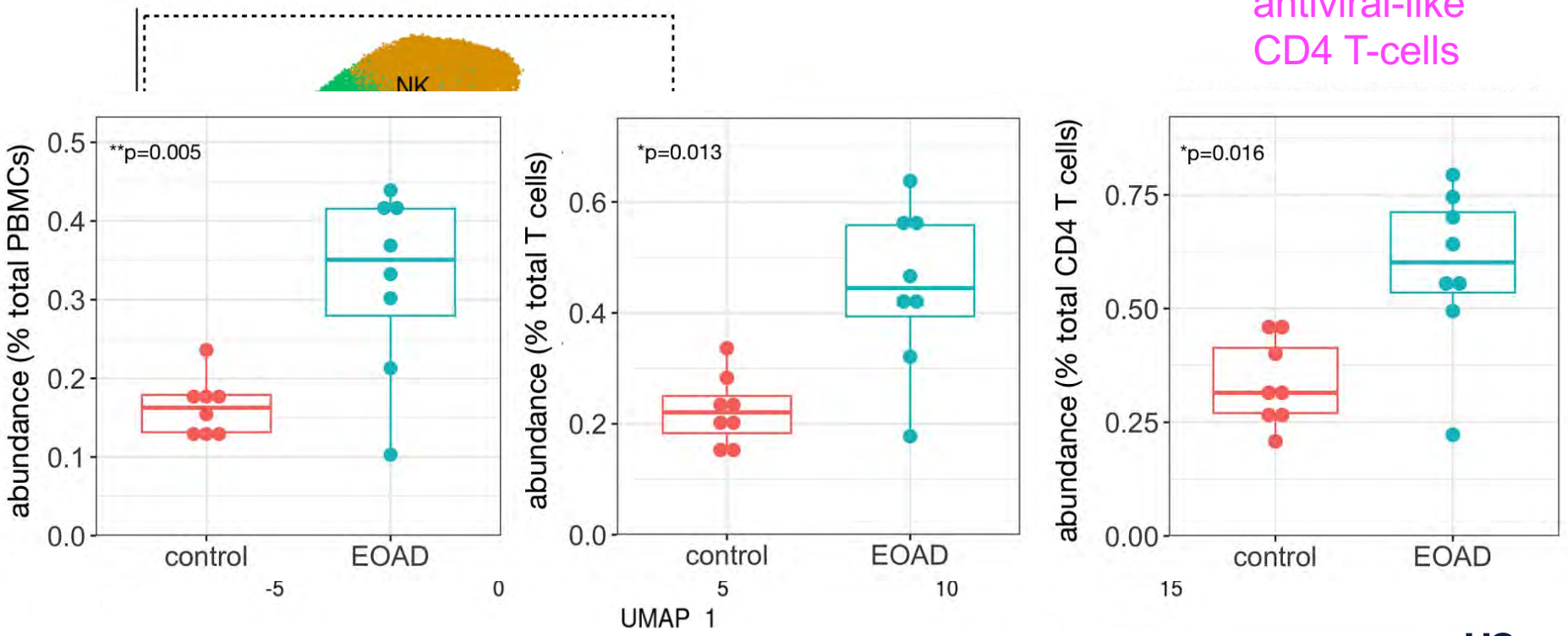
Respond to disease?

Mirror brain myeloid cells?

Can we use these cells to learn about disease biology?

Expansion of antiviral-like CD4 T-cells in EOAD

antiviral-like
CD4 T-cells



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Conclusion:

Blood-based transcriptomics may serve as a disease-specific biomarker of brain-relevant biology and provide new avenues to explore in EOAD

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Open for Submissions

For articles submitted in 2024, *npj Dementia* has **APC waivers** available that can be allocated upon acceptance on an ad-hoc basis. For additional information contact the Managing Editor.

Aims & Scope

npj Dementia considers all aspects of research that advances the field towards effective disease interventions. In addition to its focus on common forms of neurodegenerative dementias, npj Dementia highlights rare, atypical, and early-onset dementias as a means to uncover unifying and novel mechanisms of disease.