Genetic Susceptibility of Alzheimer's Disease in African Americans

Risk and Resilience to Alzheimer's Disease in African Americans Conference

Rutgers University
June 20, 2023
Goldie S. Byrd PhD

Presentation

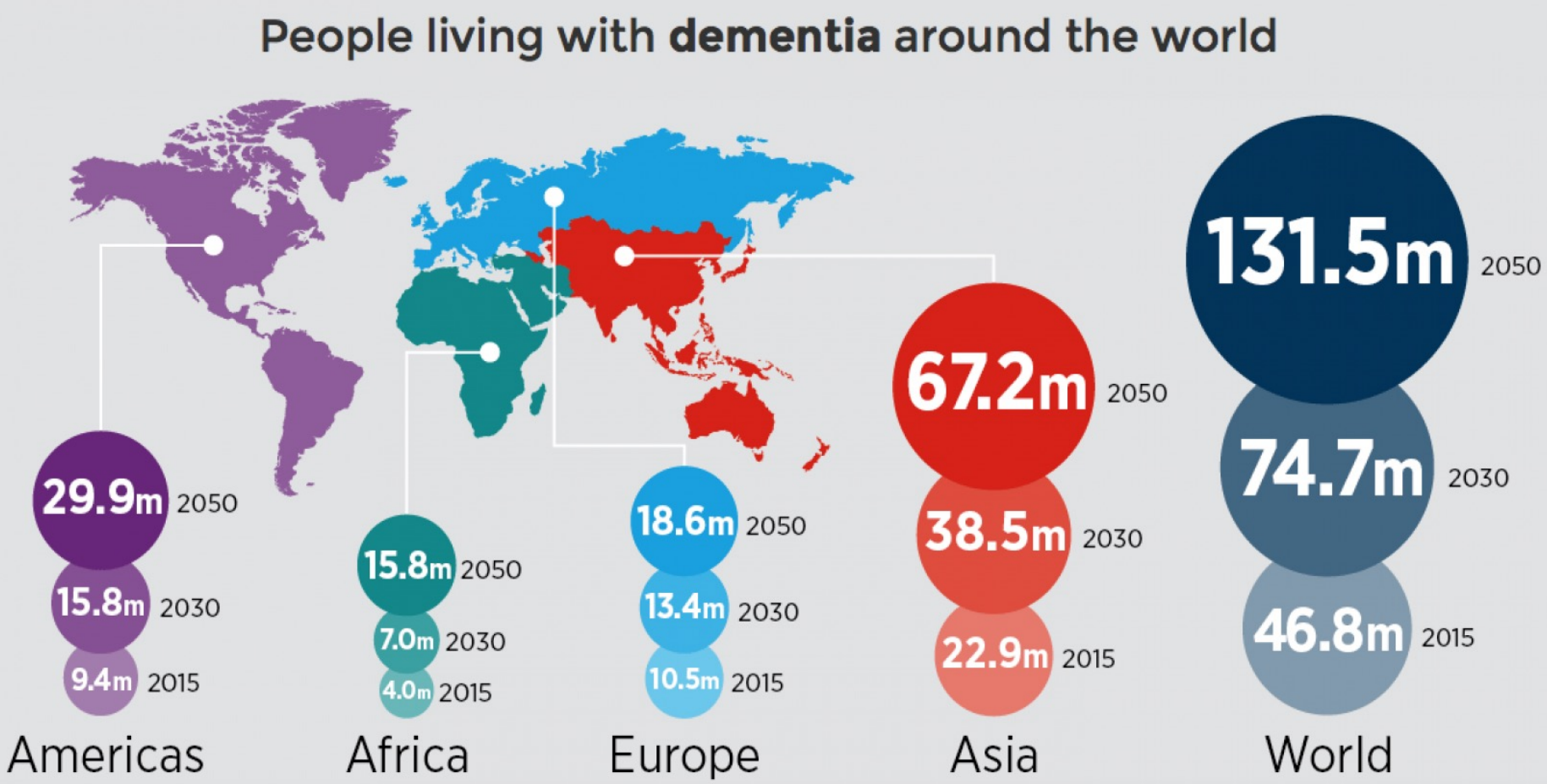
Genetics of AD

Why Study AD Genetics Research in African Americans

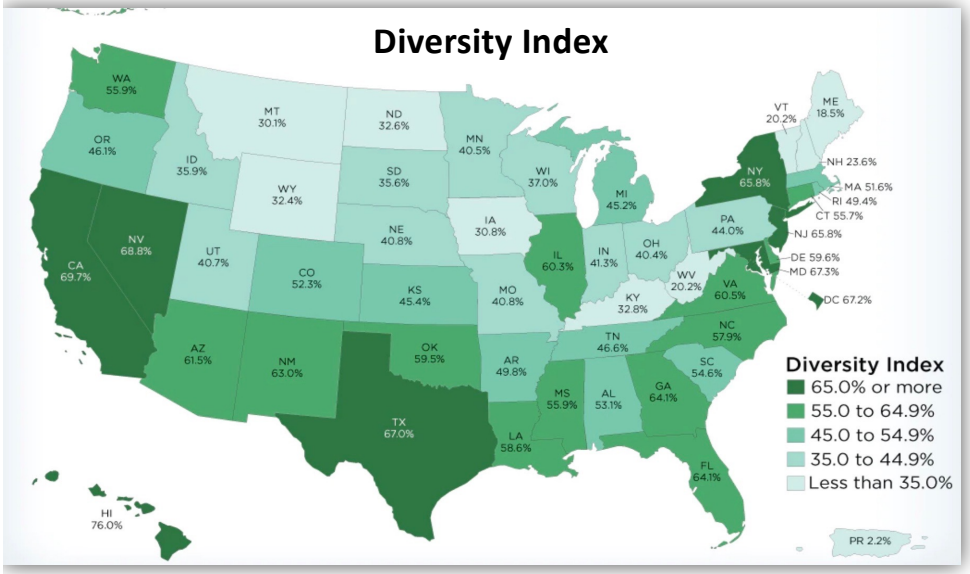
Global and Local Ancestry

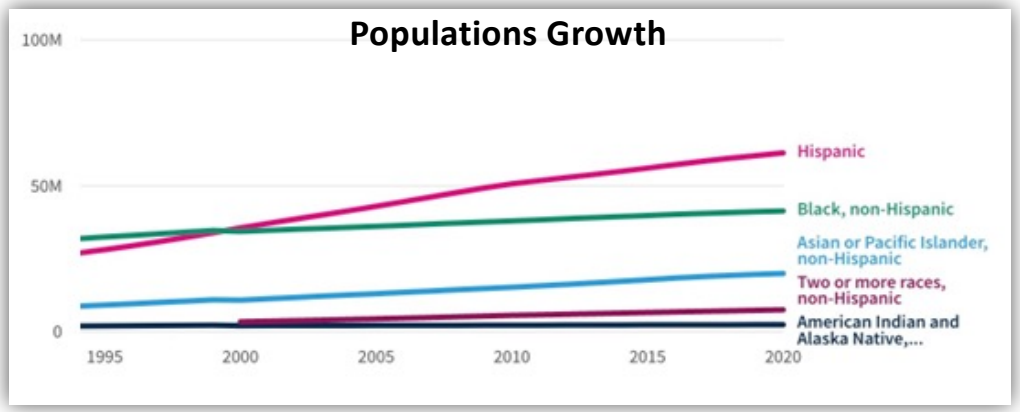
Inclusion
Barriers and Solutions for Genetics Research in African Americans

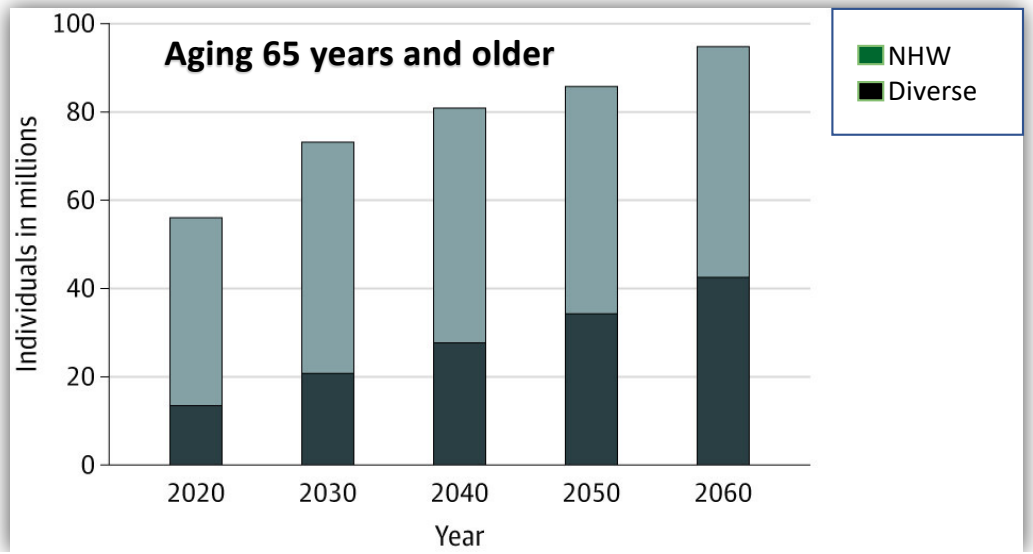
Alzheimer's Disease



US Populations Diversity, Growth and Aging



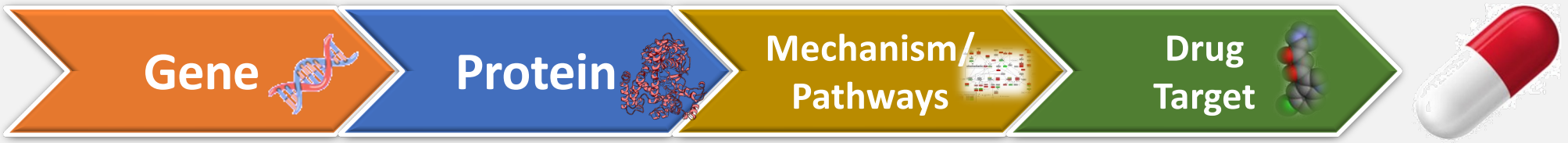




2020 US Census
Kawas CH et al. JAMA 2021

Human Genetics Disease Research Goals

- Study human disease mechanism directly in humans
- Prediction
- Mechanism
- Drug targets



Genetic Studies in Alzheimer's Disease

Why study genes?

- To identify new targets for drug discovery
- Genetics targets are 2X as successful in drug trials versus non-genetic targets.

Why study Diverse Groups

- 25 genetic risk factors for Alzheimer's disease discovered-primarily in individuals of European ancestral descent
- Different ancestral groups have different genetic risk factors
- So that treatments are universally translational

Why Genetic Studies in Alzheimer's Disease: Drug Discovery: Twice as Successful


ANALYSIS

nature genetics

The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

"We estimate that selecting genetically Supported targets could double the success rate in clinical development."


PLOS | GENETICS

RESEARCH ARTICLE

Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval

Emily A. King*, J. Wade Davis, Jacob F. Degner

Department of Computational Genomics, AbbVie, North Chicago, Illinois, United States of America

Late Onset Alzheimer's was not thought to have a genetic component until…

Gene hunters. The Duke team *(left to right)*: Warren Strittmatter, Allen Roses, Guy Salvesen, Ann Saunders, John Gilbert, Margaret Pericak-Vance, Mark Alberts, Elizabeth Corder, and Donald Schmechel.

Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families

E. H. Corder, A. M. Saunders, W. J. Strittmatter, D. E. Schmechel, P. C. Gaskell, G. W. Small, A. D. Roses, J. L. Haines, M. A. Pericak-Vance*

SCIENCE • VOL. 261 • 13 AUGUST 1993

The discovery of *ApoE* as a genetic risk factor in Alzheimer's Disease revolutionized the field of complex disease genetics

Early Findings

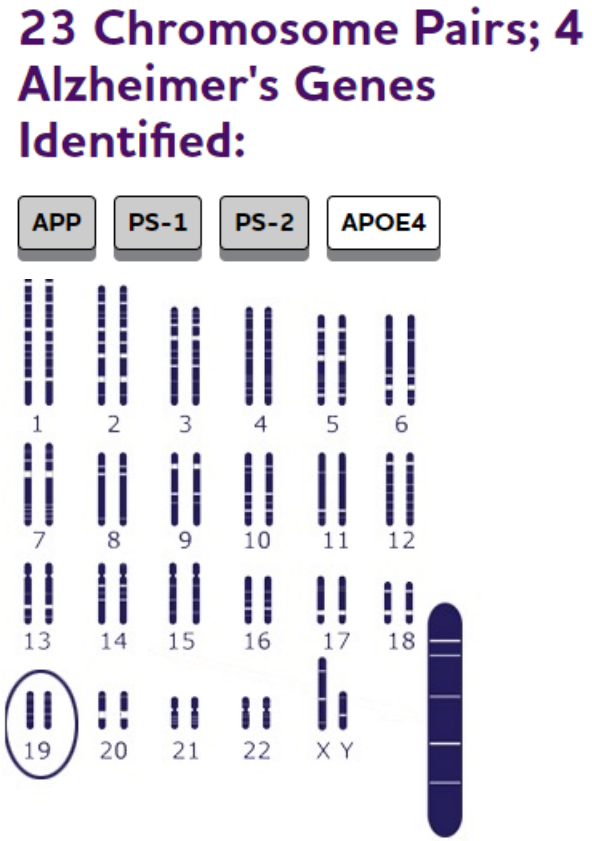
The 23 human chromosome pairs contain all of the 30,000 genes that code the biological blueprint for a human being. This interactive illustration highlights the chromosomes containing each of the three genes that cause familial Alzheimer's and the gene with the greatest impact on Alzheimer's risk.

Familial Alzheimer's (Early Onset) Genes

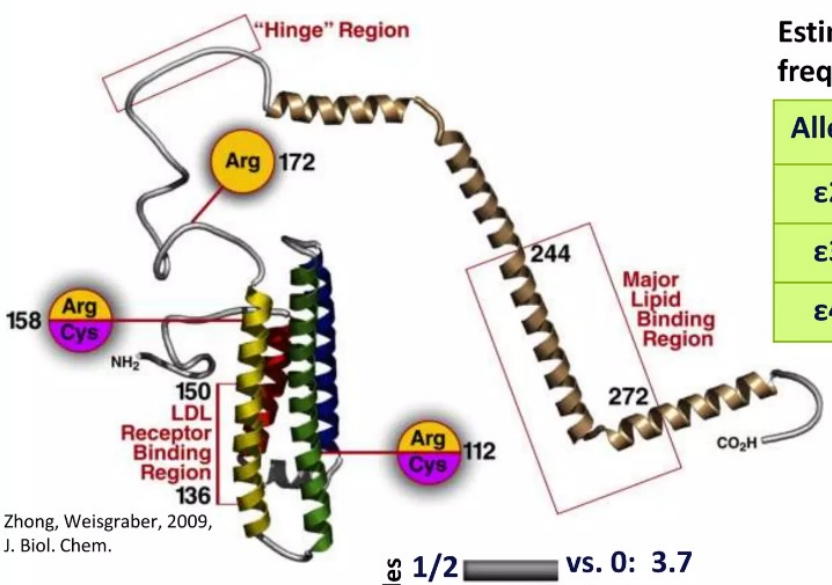
App Chromosome 21 (1987)
Ps-1 Chromosome 14 (1991)
Ps-2 Chromosome 1 (1993)

Sporadic (Late Onset) AD

APOE-4 1993)
Gene with greatest known impact



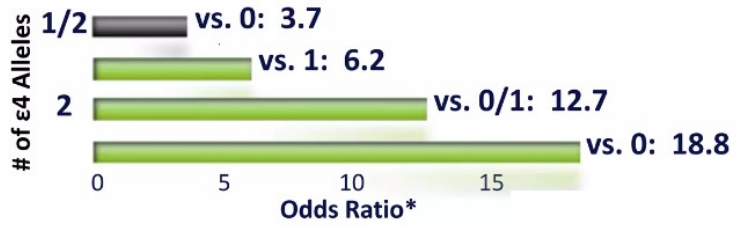
Apolipoprotein E: Genetic Risk



Zhong, Weisgraber, 2009, J. Biol. Chem.

Estimated human genotype frequency of APOE All ethnicities http://www.alzgene.org

Allele	ε2	ε3	ε4
ε2	~1%	~11%	~2%
ε3		~62%	~22%
ε4			~2%
AD:		~43%	~15%



Martins et al., 1995 NeuroReport
Laws et al., 1999 NeuroReport

Why Study Alzheimer's Disease in African Americans

- **African Americans and Hispanic individuals are more likely to develop AD and dementia compared to non-Hispanic White populations**
  - **Greater familial risk for AD**
  - **Limited health care access**
  - **AD patients identified at later stages**
  - **Poorer treatment outcomes**

- **NAPA Act: Presidentially mandated during the Obama Administration with continued bi-partisan congressional support to identify new drug targets**

http://www.socialgradient.org/alzheimers-center-aids-african-americans/

http://www.poststat.net/pwp008/pub.49/issue.350/article.528/

Ancestry and *APOE*

REPORTS

Gene dose of apolipoprotein E type 4
risk of Alzheimer's disease in late on

EH Corder, AM Saunders, WJ Strittmatter, DE Schmechel, PC Gaskell, GW Small, A

Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease

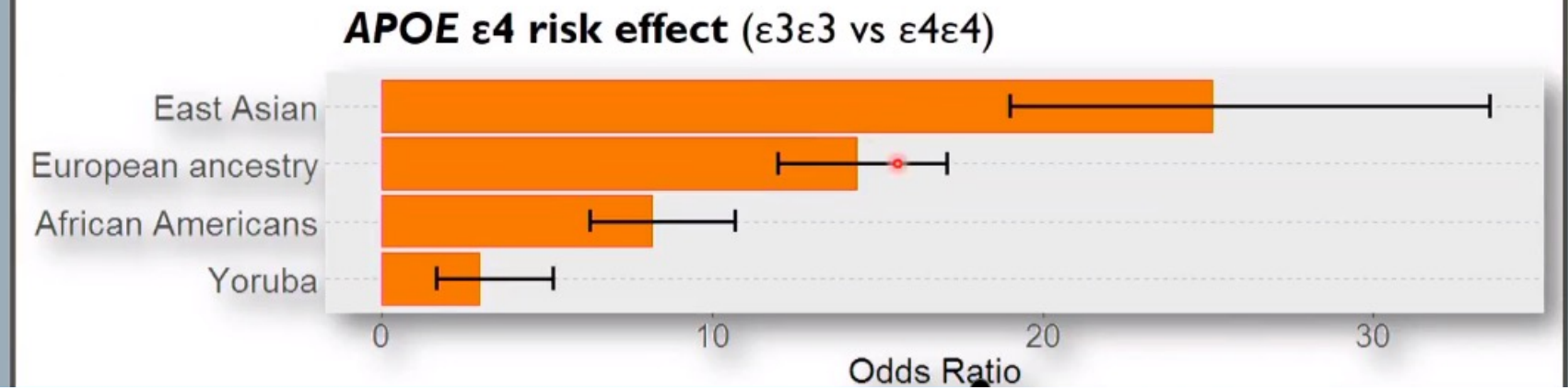
E. H. Corder[1], A. M. Saunders[1], N. J. Risch[1], W. J. Strittmatter[1,2], D. E. Schmechel[1,3,4], P. C. Gaskell, Jr.[1], J. B. Rimmler[1], P. A. Locke[1], P. M. Conneally[4], K. E. Schmader[4,7], G. W. Small[4], A. D. Roses[1,3], J. L. Haines[5] & M. A. Pericak-Vance[1]

Reviews

Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease

A Meta-analysis

Lindsay A. Farrer, PhD; L. Adrienne Cupples, PhD; Jonathan L. Haines, PhD; Bradley Hyman, MD, PhD; Walter A. Kukull, PhD; Richard Mayeux, MD; Richard H. Myers, PhD; Margaret A. Pericak-Vance, PhD; Neil Risch, PhD; Cornelia M. van Duijn, PhD; for the APOE and Alzheimer Disease Meta Analysis Consortium



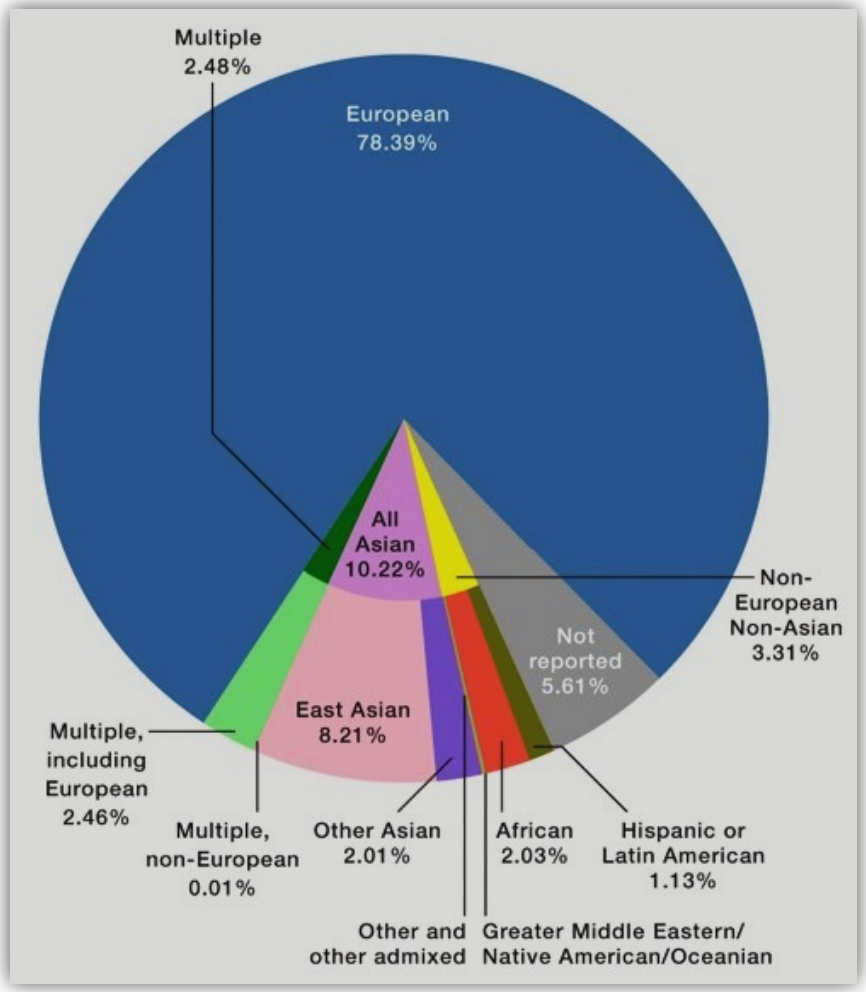
Corder et al. 1993 Science
Corder et al 1994
Farrer et al., 1997 JAMA

Hendrie et al. 2014. Int Psychogeriatr
Choi et al. 2019 J Clin Med
Reitz et al., 2013 JAMA

Why Study African Americans and other Diverse Groups

- The underrepresentation of ancestrally diverse populations in genetic studies:
  - hinders our ability to fully understand the genetic architecture of disease, and
  - intensify health inequalities.
  - reduce the power of risk prediction
- The translation of genetic research into clinical practice may be dangerously incomplete or, worse, mistaken

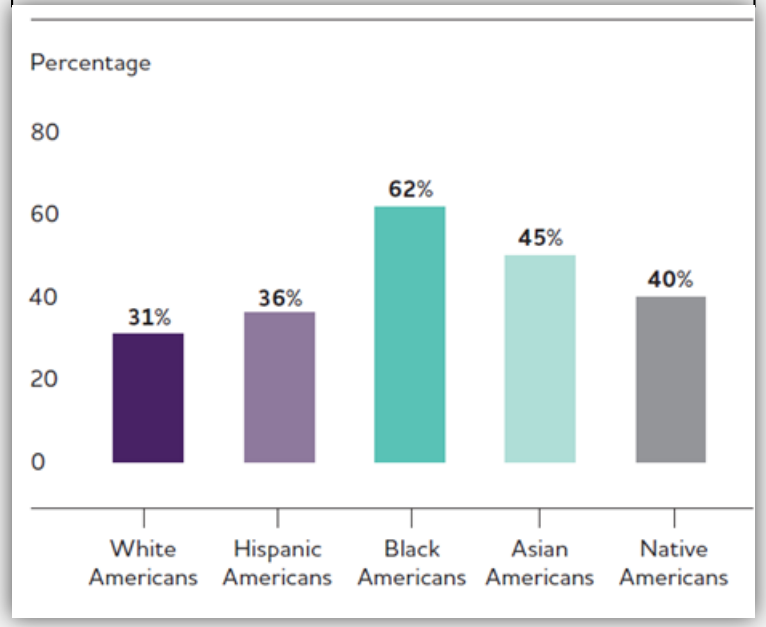
Ancestry category distribution of <u>individuals</u> in study catalog



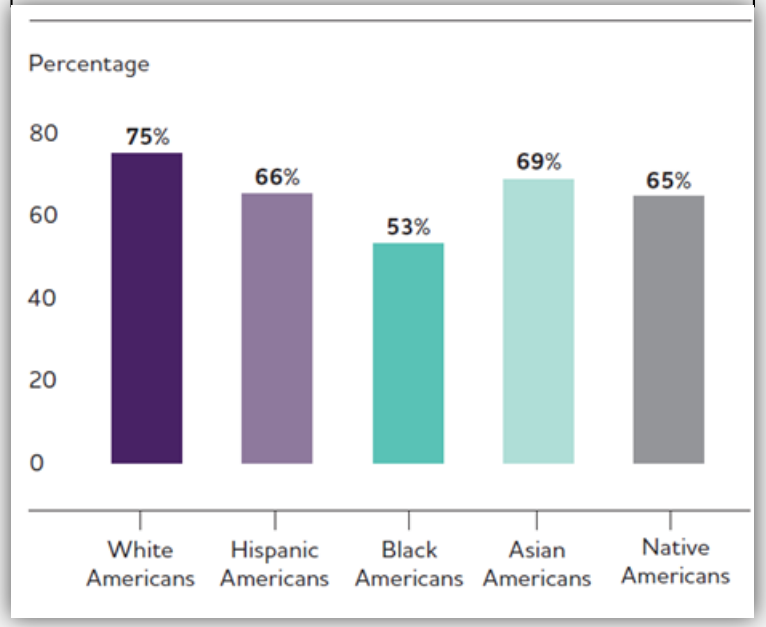
Sirugo, et al, 2019

Current Perspectives on Alzheimer's Research

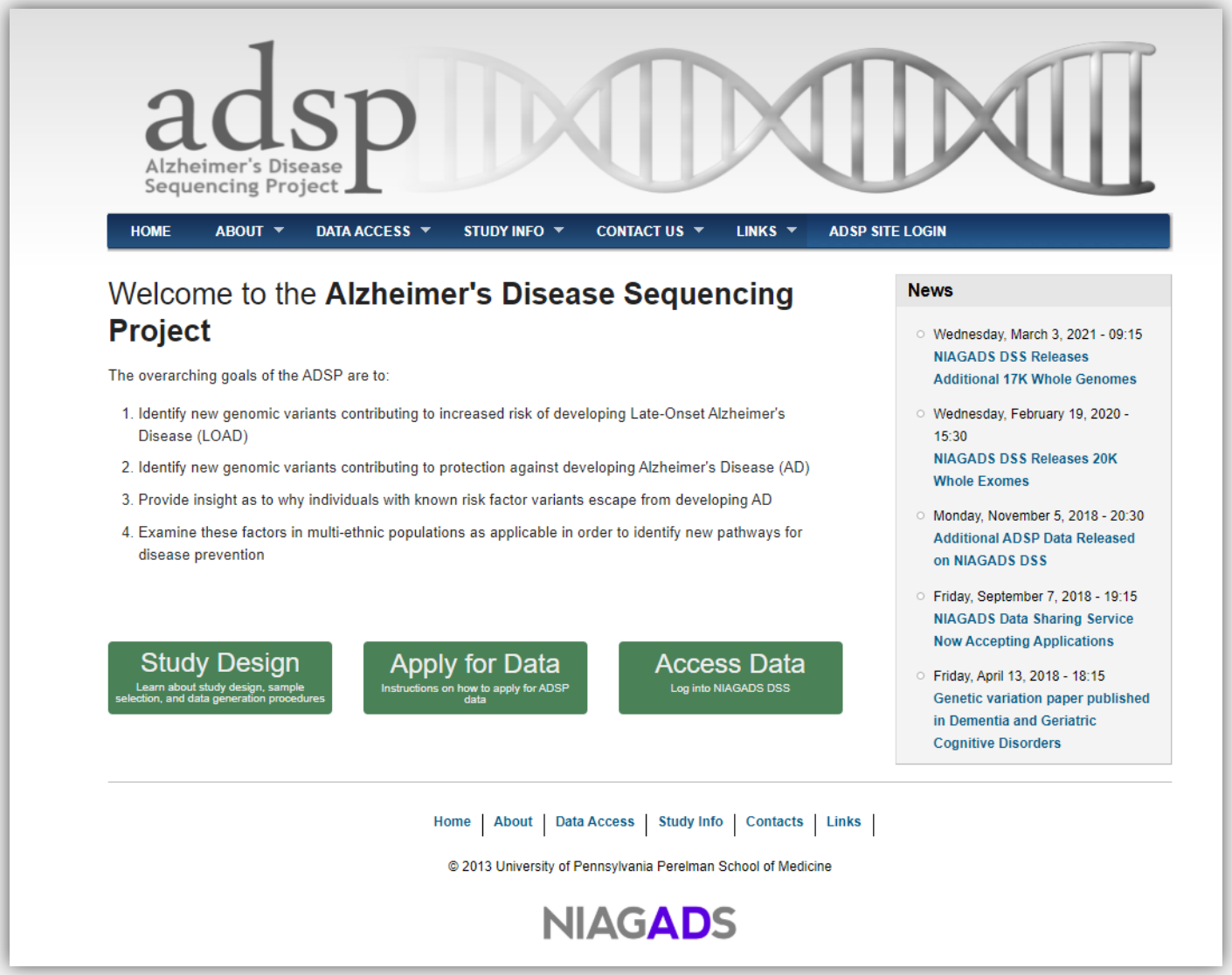
Percentage of US Adults Who Believe Medical Research is Biased Against People of Color



Percentage of US Adults Who Trust an Alzheimer's Cure Will be Shared Equally Regardless of Race, Color or Ethnicity



2021 Alzheimer's Disease Facts and Figures: Special Report on Race, Ethnicity and Alzheimer's in America

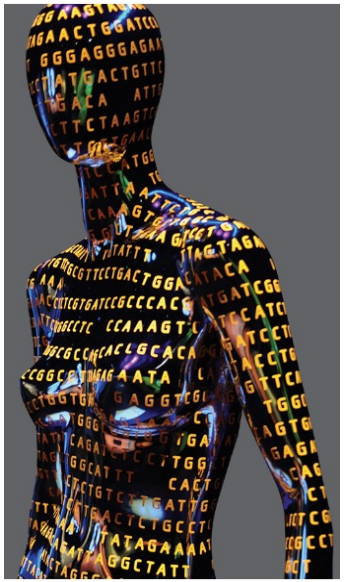


Funded by:
National Institute For Aging

https://www.niagads.org/adsp/content/home

Why are Such Studies Possible?

With the completion of the **Human Genome Project in 2003** and the **International HapMap Project in 2005**, researchers now have a set of research tools that make it possible to find the genetic contributions to common diseases. The tools include computerized databases that contain the reference human genome sequence, a map of human genetic variation and a set of new technologies that can quickly and accurately analyze whole-genome samples for genetic variations that contribute to the onset of a disease. **Genome-wide association** studies involve scanning markers across the genomes of many people to find genetic variations associated with a particular disease.



The National Plan has six ambitious goals to:

Prevent and Effectively Treat Alzheimer's Disease and Related Dementias by 2025

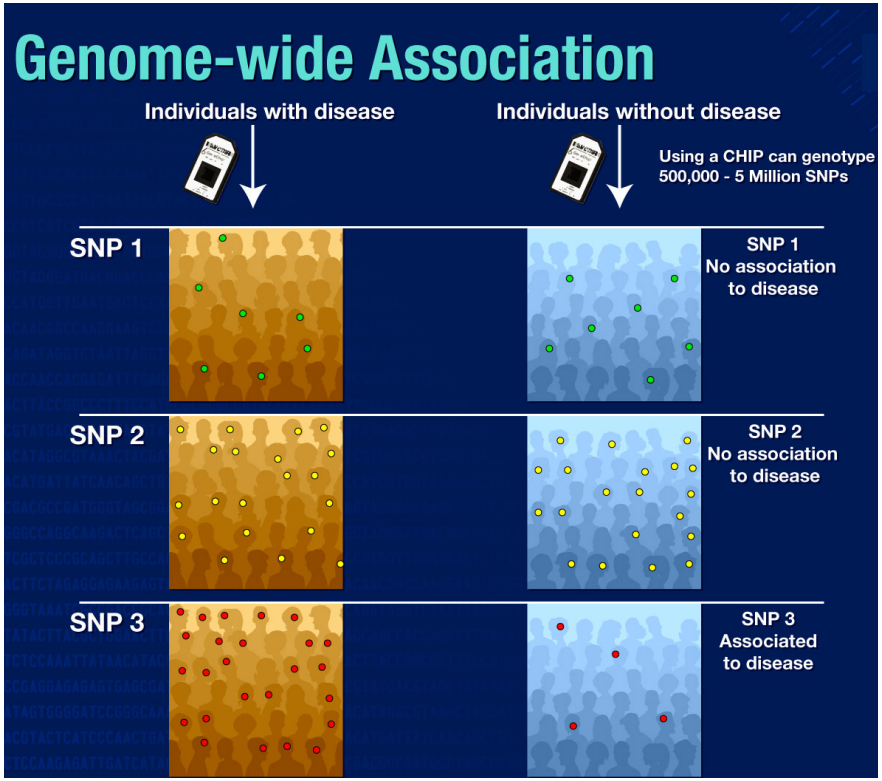
Enhance Care Quality and Efficiency

Expand Supports for People with Alzheimer's Disease and Related Dementias and Their Families

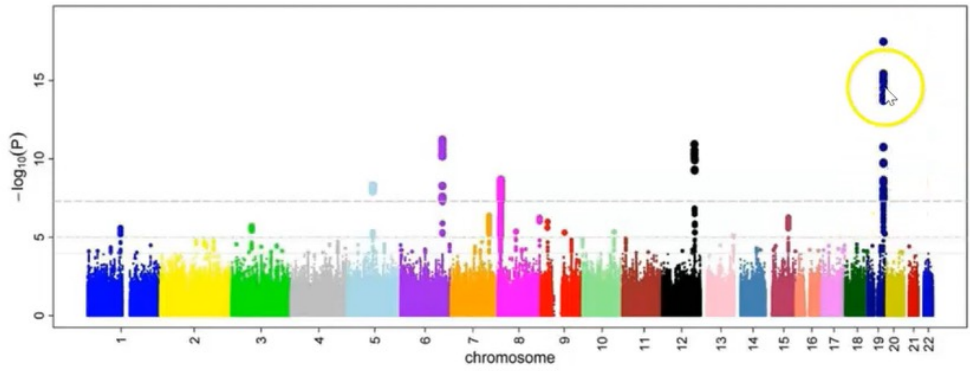
Enhance Public Awareness and Engagement
Improve Data to Track Progress

Accelerate Action to Promote Healthy Aging and Reduce Risk Factors for Alzheimer's Disease and Related Dementias

Identifying Risk Loci



GWAS does not identify a specific gene, but points us to Where to begin looking for a gene involved in disease
ApoE is on *chromosome 19*



A Manhattan plot depicting several strongly associated risk loci

Form Strong Collaborations with Academic Partners

- Partnership began 20 years ago
- No formal involvement of African Americans in Genetics Research
- $50,000 to start entire project
- Grass Roots efforts in NC
- Education, Partnerships with pastors, churches and community centers
- Strong foothold in NC, recruited over 1200 individuals in 5 years.
- Largest collection of African American Multiplex AD families

Goldie S. Byrd PhD

Professor and Director of the Maya Angelou Center for Health Equity at Wake Forest School of Medicine

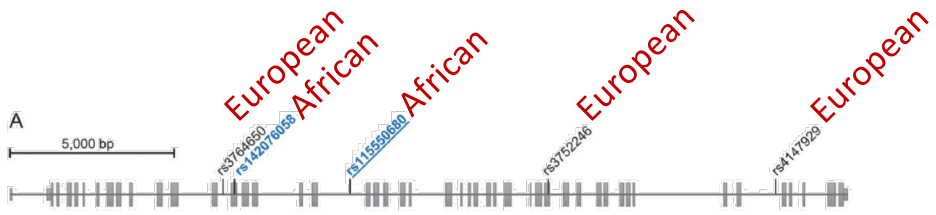
Genetic Distinctions in Alzheimer Disease

Published Data over the past decade supports the need for Diversity in AD Genetics Research

Novel Rare Loci in African American GWAS (Kunkle et al. 2020)

IGFIR: chr15q26
AP15: chr11p12
RBFOX1: chr16p13

***ABCA7* in European and African Ancestries** (Cukier et al. 2016)



Rare variants in AKAP9
African Americans (Logue et al. 2014)
Hispanic families in ADSP (Vardarajan et al. 2016)

- To prevent "genomic" health disparities
- To not miss population specific variants and/or genes

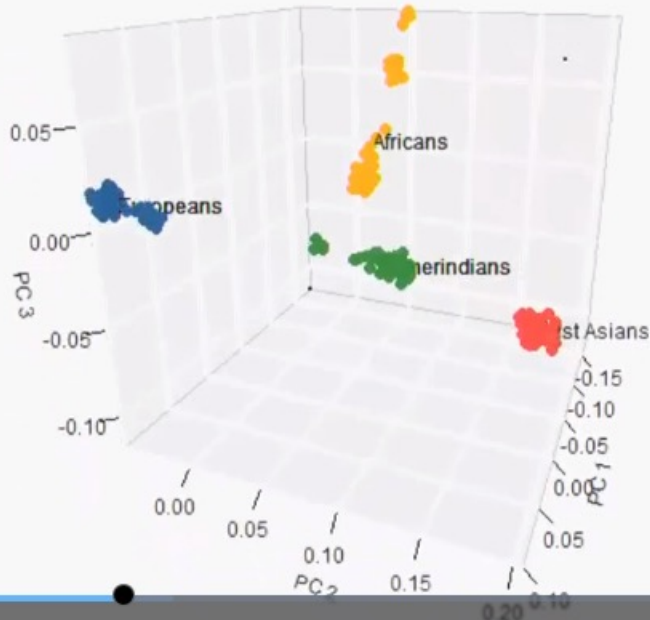
Ancestry and *APOE*

- **Why would *APOE* ε4 have disparate effects across ancestries?**
  - Environmental/exposure effects that vary by population (gene x environment interaction)
  - Population-specific genetic effects that vary by population (gene x gene interaction)

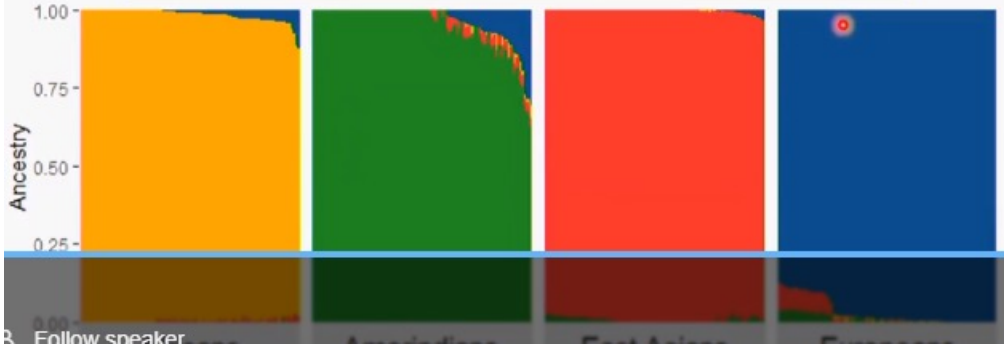
- **Modern genomics methods can explore these hypotheses**
  - Rajabli et al., 2018, *PLoS Genet*
  - Rajabli et al., 2022, *PLoS Genet*

Global Ancestry: Continental Populations

{*Algorithmic ancestry estimation: PCA*}



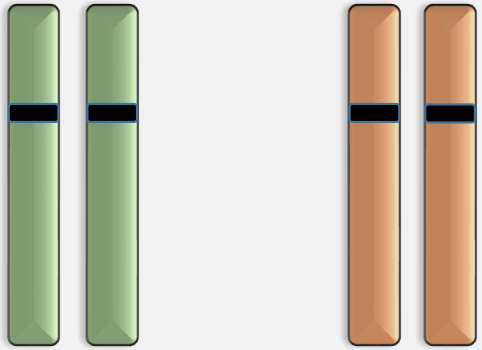
{*Model Based Ancestry Estimation*}



Follow speaker

Admixture – Local Ancestry

Population A

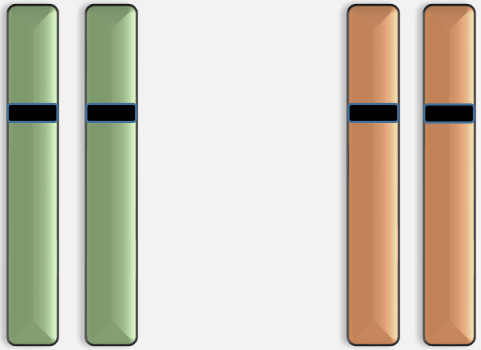


1st Generation

Population B

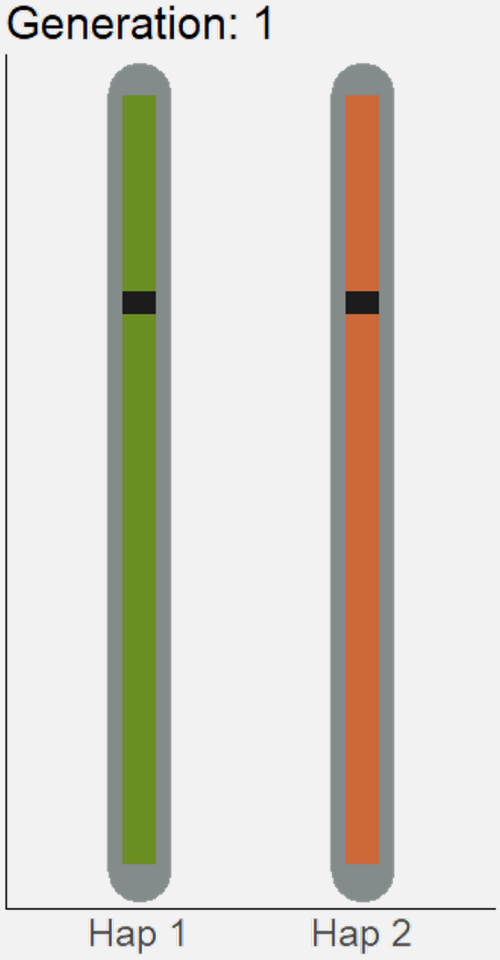
Admixture – Local Ancestry

Population A



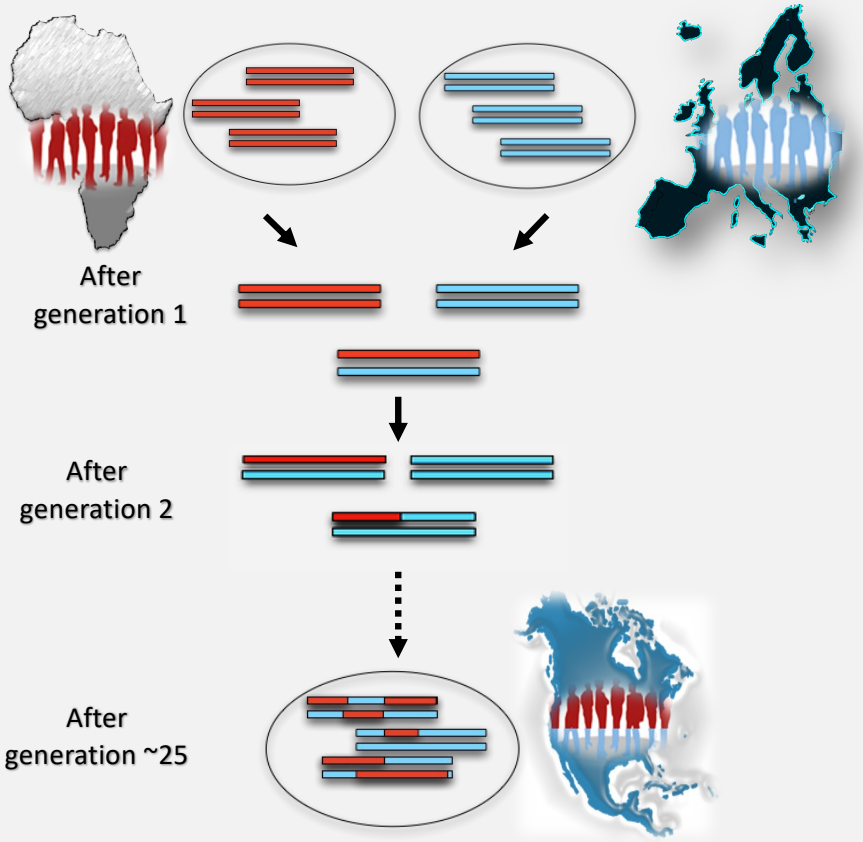
1st Generation

Population B

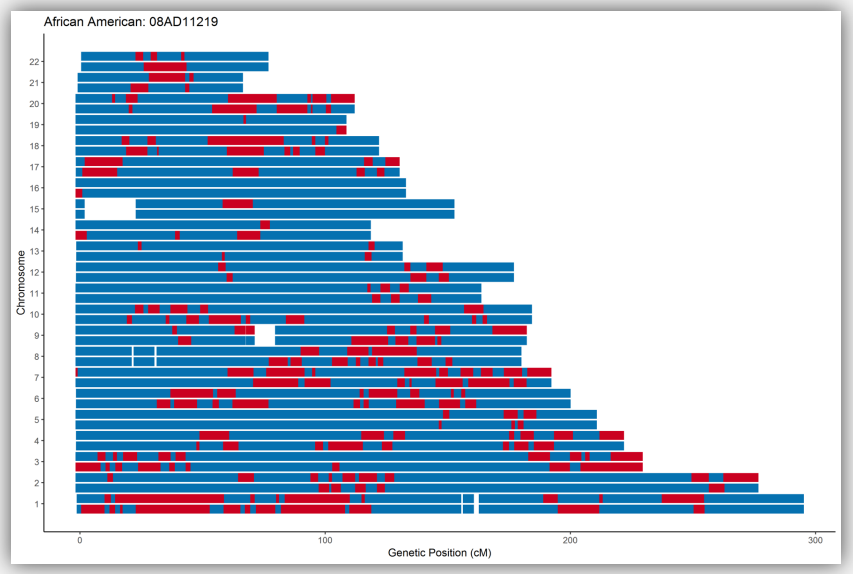


African Americans and Local Ancestry

- AA population is an admixed population

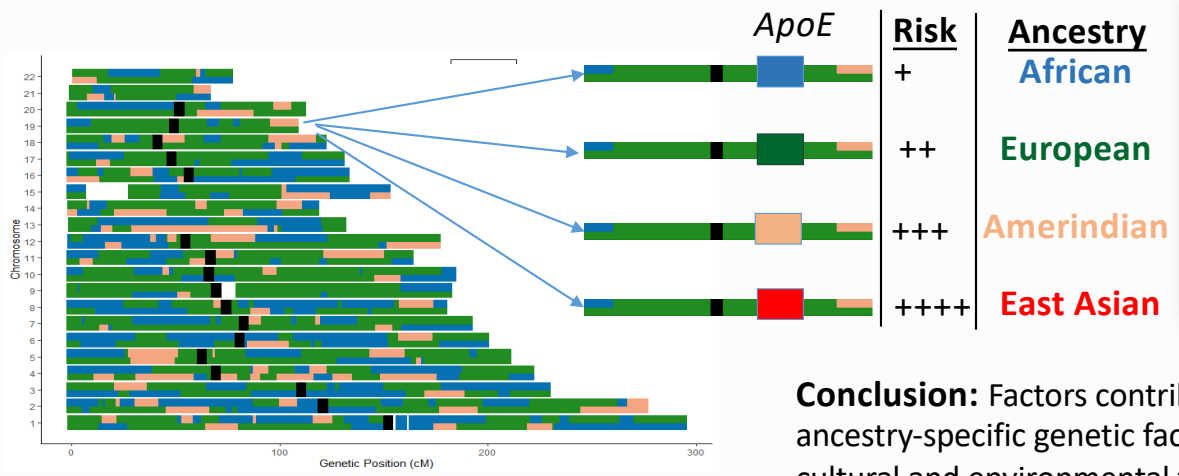


- Local ancestry estimates of a Black American individual



The US Black population is a two-way admixed population with genetic ancestry from African and European ancestors.

Admixture – Local Ancestry – *ApoE*



PLOS GENETICS

RESEARCH ARTICLE

Ancestral origin of *ApoE ε4* Alzheimer disease risk in Puerto Rican and African American populations

Farid Rajabli[1*], Briseida E. Feliciano[2], Katrina Celis[1], Kara L. Hamilton-Nelson[1], Patrice L. Whitehead[1], Larry D. Adams[1], Parker L. Bussies[1], Clara P. Manrique[1], Alejandra Rodriguez[2], Vanessa Rodriguez[1], Takiyah Starks[3], Grace E. Byfield[3], Carolina B. Sierra Lopez[2], Jacob L. McCauley[1], Heriberto Acosta[4], Angel Chinea[2], Brian W. Kunkle[1], Christiane Reitz[5], Lindsay A. Farrer[6], Gerard D. Schellenberg[7], Badri N. Vardarajan[5], Jeffery M. Vance[1,8], Michael L. Cuccaro[1,8], Eden R. Martin[1,8], Jonathan L. Haines[9], Goldie S. Byrd[3], Gary W. Beecham[1,8*], Margaret A. Pericak-Vance[1,8*]

Conclusion: Factors contributing to the lower risk effect in the *ApoE* are due to ancestry-specific genetic factors near *ApoE* rather than non-genetic ethnic, cultural and environmental factors.

ELSEVIER

Alzheimer's & Dementia

Alzheimer's & Dementia 15 (2019) 1524-1532

Featured Article

Local ancestry at *APOE* modifies Alzheimer's disease risk in Caribbean Hispanics

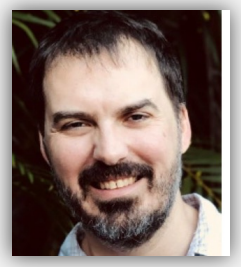
Elizabeth E. Blue[a,*], Andréa R. V. R. Horimoto[b], Shubhabrata Mukherjee[c], Ellen M. Wijsman[a,b,d], Timothy A. Thornton[b,e,**]

Global and local ancestry modulate *APOE* association with Alzheimer's neuropathology and cognitive outcomes in an admixed sample

Michel Satya Naslavsky, Claudia K. Suemoto, Luciano Abreu Brito, Marília Oliveira Scliar, Renata Eloah Ferretti-Rebustini, Roberta Diehl Rodriguez, Renata E. P. Leite, Nathalia Matta Araujo, Victor Borda, Eduardo Tarazona-Santos, Wilson Jacob-Filho, Carlos Pasqualucci, Ricardo Nitrini, Kristine Yaffe, Mayana Zatz, Lea T. Grinberg

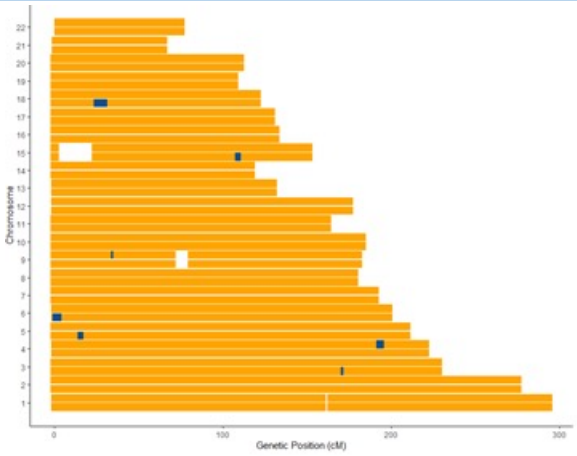
doi: https://doi.org/10.1101/2022.02.02.22270331

Farid Rajabli



Gary Beecham

Ancestry vs. Race



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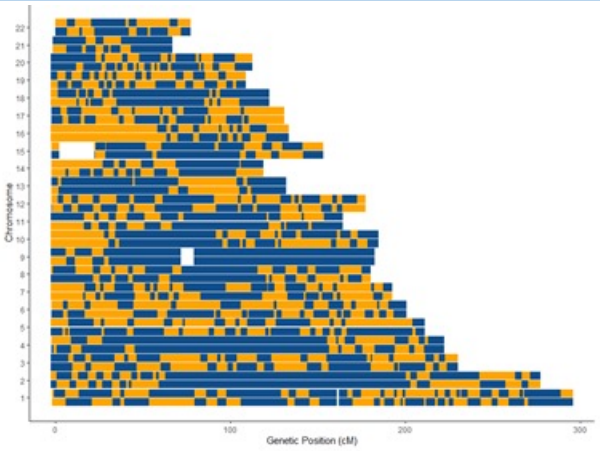
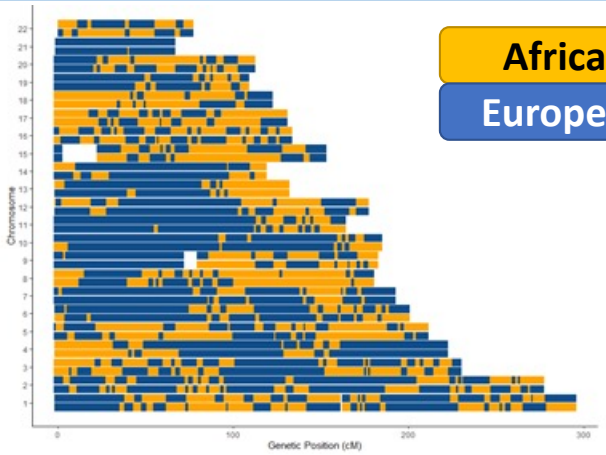


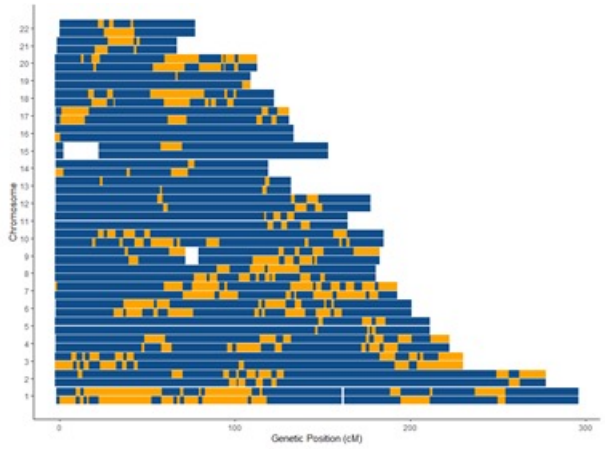
61% 39%



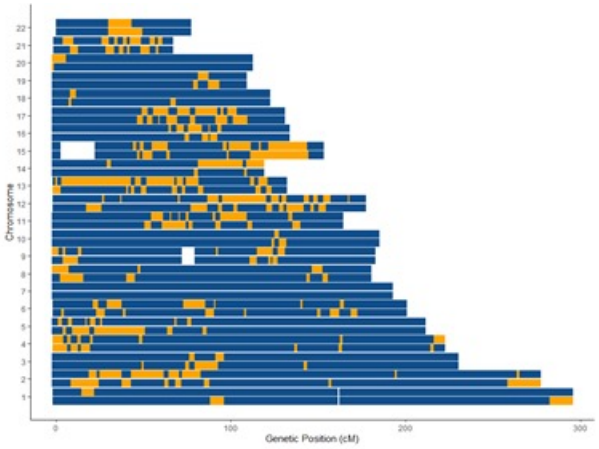
62% 38%

African

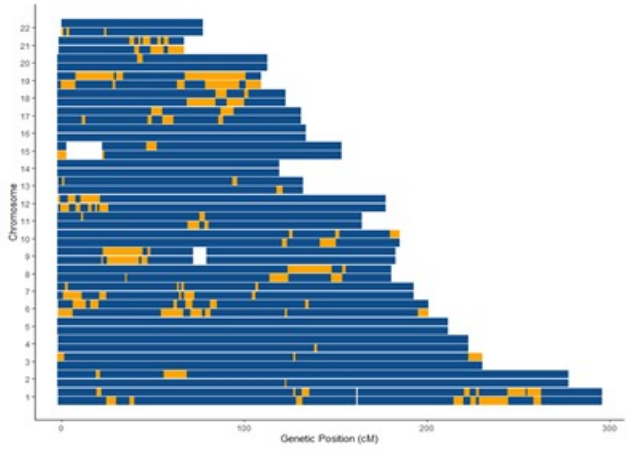
European



82% 18%



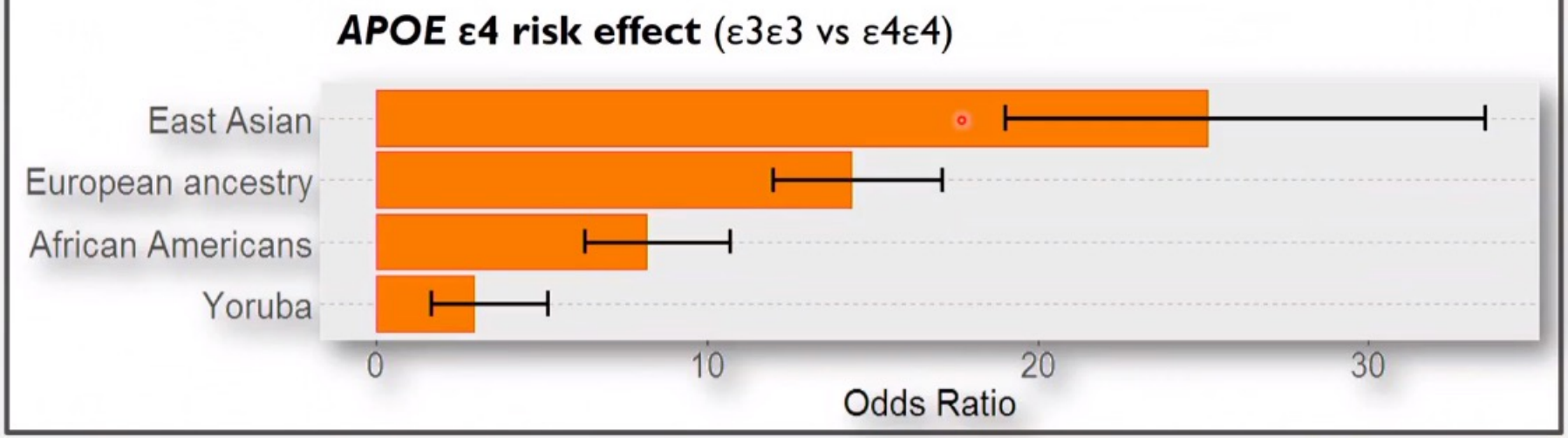
86% 14%



93% 7

Some Recent Studies
Applying Ancestry to Genetic Studies

Back to *APOE*...



Can genetic ancestry methods bring insight into this differential *APOE* effect?

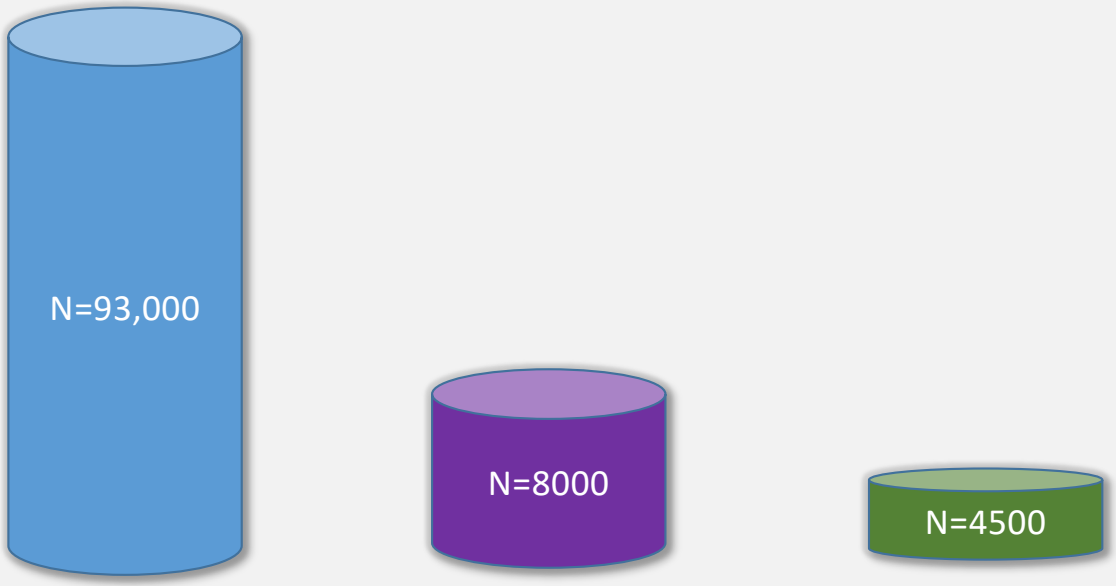
Hendrie et al., 2014, *Int Psychogeriatr*
Choi et al., 2019, *J Clin Med*
Reitz et al., 2013, *JAMA*

Ancestry vs. Race

- Ancestry is biological and is about the history of genetic variation and the origin of one's population
- Race, itself is not biological, but is often self-ascribed or socially-ascribed by others
- As I have shown populations used to live in isolation with each geographic region having its own genetic map (Continental Populations)
- Populations today particularly in the US are admixed (multiple ancestries) with individuals of European, African, Amerindian and Asian ancestry.

Most GWAS for AD have been conducted in individuals of EU descent

Largest AD Genome-wide Association Studies



Europeans

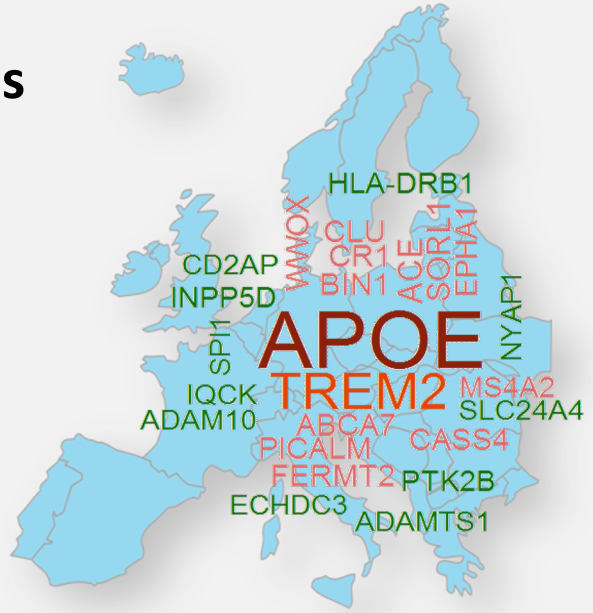
(Kunkle et al. 2019)

African Americans

(Kunkle et al. 2020)

Hispanics

(Tosto et al. 2015)



Inclusion at all Levels

Diversity makes for a rich tapestry,
and we must understand
that all the threads of the tapestry are

EQUAL IN VALUE

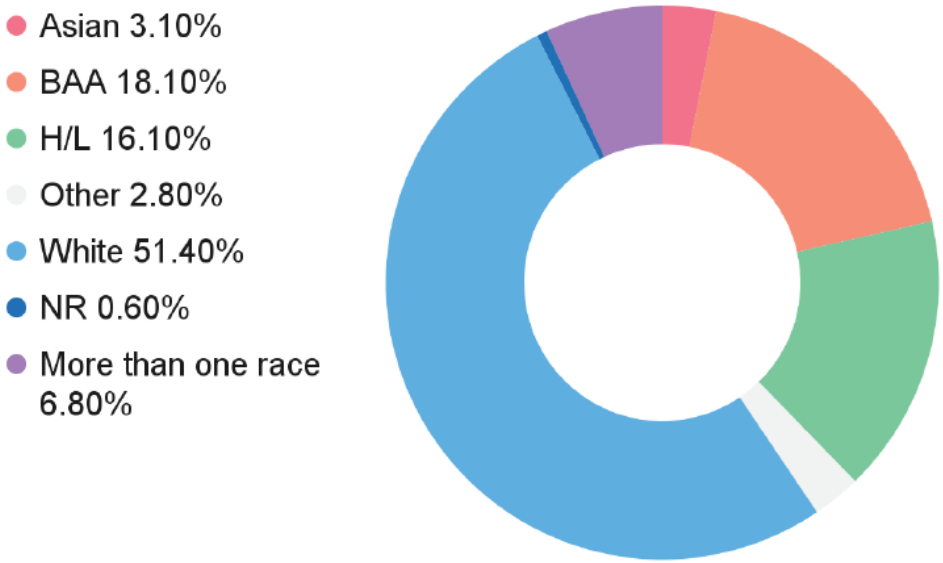
no matter what their color.

- Maya Angelou

- Researchers
- Workforce
- Participants
- Volunteers

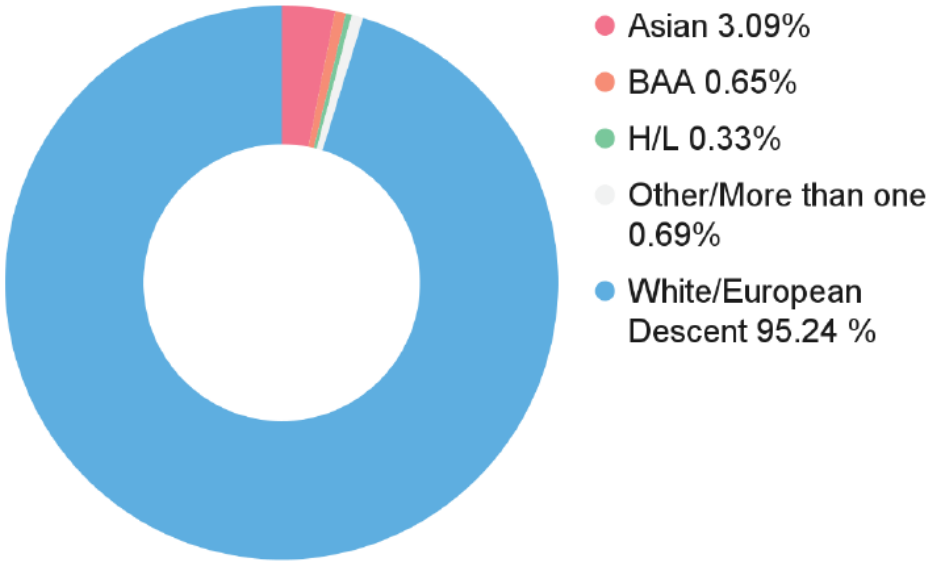
A Transformational Approach to Diversity, Equity and Inclusion in Precision Medicine

All of Us Research Program



Source: *All of Us* Research Program Data Snapshots, Race and Ethnicity (Updated March 3, 2023)

Other Genomic Studies



Source: Global Genome Wide Association Studies (GWAS) (Updated February 3, 2023)

Alzheimer's Disease Sequencing Project (ADSP)*

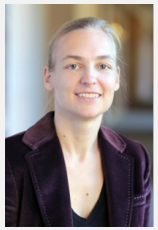
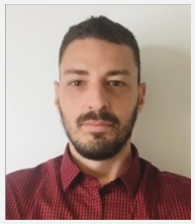
- ADSP https://www.niagads.org/adsp/content/home
  - Sequence over 100,000 individuals from multiple ancestries and ethnic backgrounds
  - 100's of Researchers from around the world are contributing and working together to find new drug targets for therapies
- READD-ADSP part of this larger international ADSP effort
  - Goals:
    - DNA, RNA, Plasma Biomarkers and CVD markers for extensive phenotyping
    - Whole Genome Sequencing

Recruitment and Retention for AD Diversity Genetic Cohorts in the ADSP (READ-ADSP)

University of Miami
Margaret Pericak-Vance
Brian Kunkle
Jeffery Vance


Wake Forest University
Goldie Byrd


Columbia University
Giuseppe Tosto
Christiane Reitz

University of Ibadan
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Case Western Reserve University
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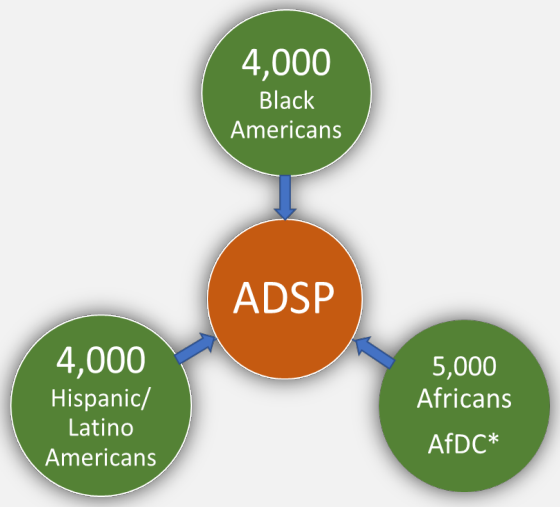
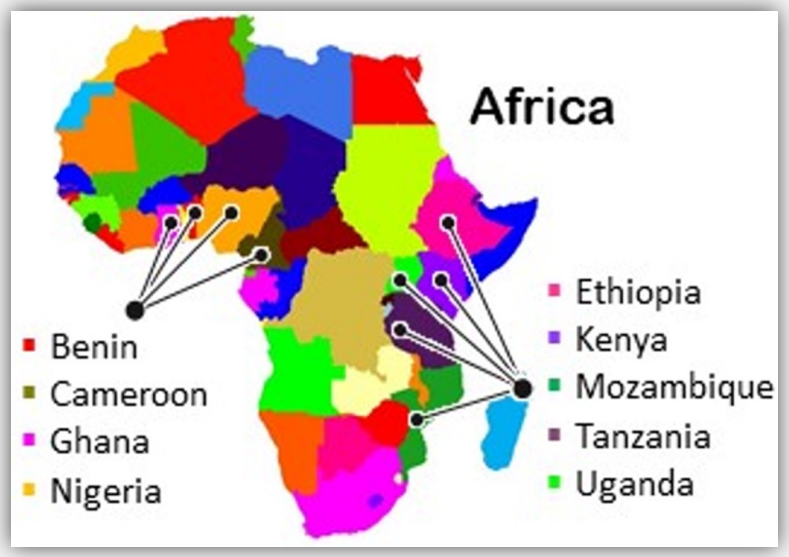
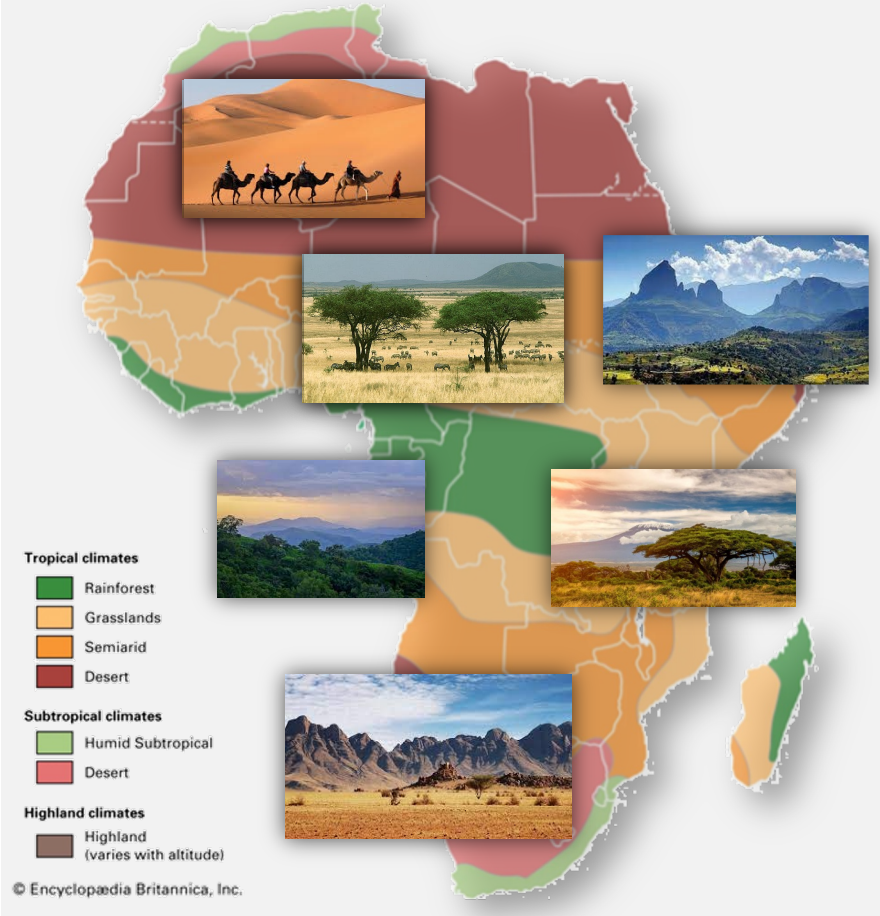


*AfDC; African Dementia Consortium



Diversity: Africa



- Africa is home to ethnic, cultural, linguistic, ancestral, and ecological/environmental diversity
  - 54 Countries
  - ~3,000 different ethnic groups
  - ~2,100 different languages

READ-ADSP GOALS

- DNA, RNA, Plasma Biomarkers and Whole Genome Sequencing
- Social Determinants of Health (SDOH) also influence AD risk, but studies collecting both biological and SDOH data are rare. *Collecting SDOH data provides a basis for the integrative studies of biological and social risks of AD.*

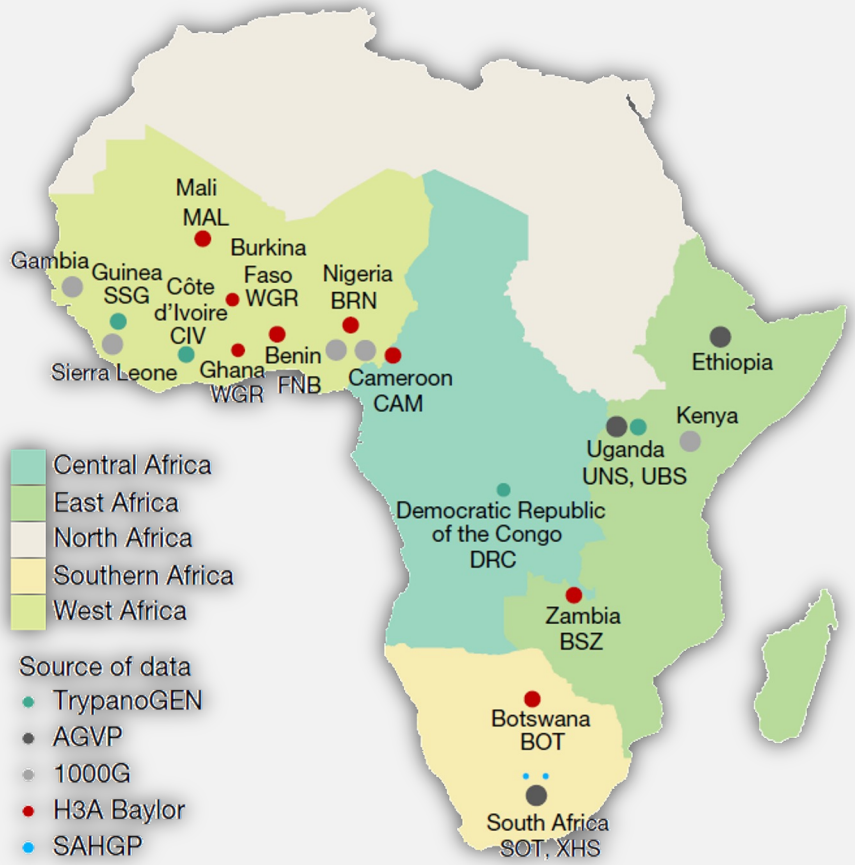
Dr. Farid Rajabli (U of Miami)

Dr. Azizi Seixas. (U of Miami)

www.cdc.gov

Dr. Joshua Akinyemi (Ibadan, Nigeria)

Genetic Diversity: sub-Saharan Africa



Article

High-depth African genomes inform human migration and health

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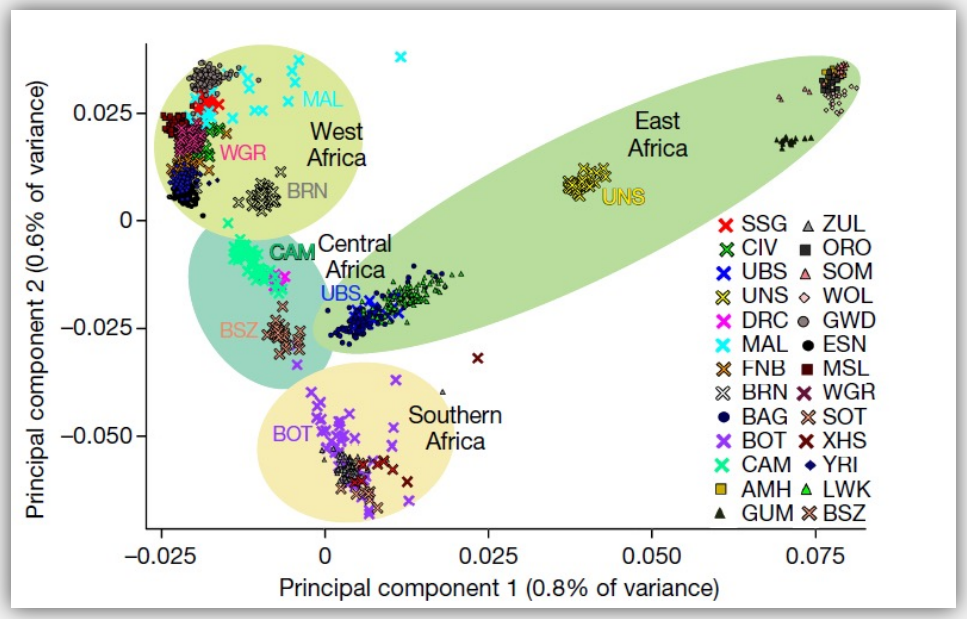
Ananyo Choudhury[1], Shaun Aron[1], Laura R. Botigué[2], Dhriti Sengupta[1], Gerrit Botha[3], Taoufik Bensellak[4], Gordon Wells[4,5,6], Judit Kumuthini[5,6], Daniel Shriner[7], Yasmina J. Fakim[8,9], Anisah W. Ghoorah[8], Eileen Dareng[10,11], Trust Odia[12], Oluwadamilare Falola[13], Ezekiel Adebiyi[12,13], Scott Hazelhurst[1,14], Gaston Mazandu[3], Oscar A. Nyangiri[15], Mamana Mbiyavanga[3], Alia Benkahla[16], Samar K. Kassim[17], Nicola Mulder[3], Sally N. Adebamowo[18,19], Emile R. Chimusa[20], Donna Muzny[21], Ginger Metcalf[21], Richard A. Gibbs[21,22], TrypanoGEN Research Group*, Charles Rotimi[7], Michèle Ramsay[1,23], H3Africa Consortium*, Adebowale A. Adeyemo[7,11], Zané Lombard[24,11] & Neil A. Hanchard[22,11]

Africa, the most genetically diverse continent



Choudhury et al. 2020 *Nature*

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1000's of Research Participants/COAACH Volunteers

Community Partners/Collaborators

University of Miami, Case Western Reserve University and Columbia University

COAACH AAAD Team/Staff and Students

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North Carolina A&T State University,

- Alumni
- Endowment Donors

National Institutes of Health

- NHGRI, NIMHD,NIA

Merck, Inc. & Co,

AARP, Inc.

Alzheimer's Association

Collaborators' Meeting at COAACH at NC A&T to Initiate New Genetics of *Familial* Alzheimer's disease in African Americans