"Genetics of Alzheimer's Disease in Minoritized Populations"

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10/17/2022
Human Genetics Disease Research Goals

- Study human disease mechanism directly in humans
- Prediction
- Mechanism
- Drug targets
Genetic Studies in Alzheimer Disease

Why study genes?
To identify new targets for drug discovery
Genetic targets are 2X as successful in drug trials versus non-genetic targets.

Why study Diverse Groups
More than 30 genetic risk factors for AD discovered—primarily in individuals of European ancestral descent
Different ancestral groups have different genetic risk factors
So that treatments are universally translational
- Black Americans and Hispanic Americans are more likely to develop AD and dementia compared to non-Hispanic white (European) Americans

- Greater familial risk for AD
- Limited health care access
- AD patients identified at later stages
- Poorer treatment outcomes

http://www.socialgradient.org/alzheimers-center-aids-african-americans/
http://www.poststat.net/pwp008/pub.49/issue.350/article.528/
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
AD GWAS studies
Europeans: N~93,000 (Kunkle et al. 2019)
African Americans: N~8,000 (Kunkle et al. 2020)
Hispanics: N~4,500 (Tosto et al., 2015)
Alzheimer Disease

People living with dementia around the world

- Americas: 29.9m (2015), 15.8m (2030), 9.4m (2050)
- Africa: 15.8m (2015), 7.0m (2030)
- Europe: 18.6m (2015), 13.4m (2030), 10.5m (2050)
- Asia: 38.5m (2015), 22.9m (2030)
- World: 131.5m (2050), 74.7m (2030), 46.8m (2015)
Aging Population 65 yrs and older in the US

From Kawas CH et al
JAMA 78(6): 650, 2021
Admixture happens when individuals from two or more genetically distinct populations are interbreeding.
Average Ancestral Proportions in Hispanic Populations and African Americans

- African American
  - African: 80%
  - European: 20%
- Cuban American
  - African: 20%
  - European: 72%
- Dominican
  - African: 40%
  - European: 40%
  - East Asian: 10%
- Mexican American
  - African: 56%
  - European: 40%
  - Native American: 4%
- Peruvian
  - African: 2%
  - European: 22%
  - Native American: 73%
- Puerto Rican
  - African: 15%
  - European: 63%

Legend:
- Orange: African
- Blue: European
- Red: East Asian
- Green: Native American
The US Black population is a two-way admixed population with genetic ancestry from African and European ancestors.
Local Ancestry in Puerto Ricans

Puerto Rican 1
- African: 99.7%
- European: 39%
- Amerindian: 4%

Puerto Rican 2
- African: 39%
- European: 57%
- Amerindian: 13%

Puerto Rican 3
- African: 13%
- European: 84%
- Amerindian: 3%
Race versus Ancestry

• 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.
Ancestry versus Race

<table>
<thead>
<tr>
<th>African</th>
<th>European</th>
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<tr>
<td>99%</td>
<td>18%</td>
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<tr>
<td>61%</td>
<td>39%</td>
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<tr>
<td>62%</td>
<td>38%</td>
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<tr>
<td>82%</td>
<td>18%</td>
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<tr>
<td>86%</td>
<td>14%</td>
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<tr>
<td>93%</td>
<td>7%</td>
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Ancestral origin of ApoE ε4 Alzheimer disease risk in Puerto Rican and African American populations


Plos Genetics 2018

Ancestry
- African
- European
- Amerindian
- Asian

ApoE  
Risk  
- +  
- ++  
- +++  
- ++++

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.
The Risk to Develop Alzheimer Disease (AD) for ApoEe4/4 carriers (compared to ApoEe3/3 carriers) is different across ancestral groups

Odds Ratios:

2 = twice the risk
3 = three times the risk
Etc.

Asian (Japanese)
Amerindians
Europeans
Americans with African Ancestry
Africans
Increased \textit{APOE} €4 expression is associated with the difference in Alzheimer's disease risk from diverse ancestral backgrounds


First published: 01 February 2021 | https://doi.org/10.1002/alz.12287

Anthony J. Griswold, Katrina Celis, Juan I. Young, and Jeffery M. Vance contributed equally to this study.
The Caribbean-Hispanic Alzheimer’s Brain Transcriptome Reveals Ancestry-Specific Disease Mechanisms – *in press*
• **ABCA7**: ATP-binding cassette, sub-family A (ABC1), member 7
  - ABC transporters are a large gene superfamily involved in the movement of molecules across cellular membranes

• Two distinct studies identified single nucleotide polymorphisms (SNPs) in *ABCA7* significantly associated with AD risk

• Both studies were performed with large cohorts of AD patients and controls with European ancestry (non-Hispanic white/NWH).

Risk Prediction may not be accurate

Polygenic risk score bell curve
Critical variants may be missed

- Low frequency variants/variants absent in European populations may be missed
- Rare variants are more likely to be population specific

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

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

**Novel Rare Loci in African American GWAS**
(Kunkle et al. 2020)
- *IGFIR*: chr15q26
- *AP15*: chr11p12
- *RBFOX1*: chr16p13
1. Genetic risk factors for AD can be different depending on your ancestral background.

2. The mechanisms (pathways) between ancestries appear to be similar, but some pathways may be more important in some ancestries than others.

3. \textit{ABCA7} is a much stronger risk factor for AD in African Ancestry than European.

4. \textit{ApoE4} is a much weaker risk factor for AD in African Ancestry than European.

5. The ancestry your patient inherited their \textit{ApoE4} allele from determines their risk for AD from \textit{ApoE4}.

6. Different ancestral risks suggest different therapies maybe needed for different ancestries.
Some Recent Studies
Applying Ancestry to Genetic Studies.
Admixture mapping identifies novel Alzheimer disease risk regions in African Americans.

Farid Rajabli1, Giuseppe Tosto2, Kara L. Hamilton-Nelson1, Brian W. Kunkle1, Badri N. Vardarajan2, Adam Naj3, Patrice G. Whitehead1, Olivia K. Gardner1, William S. Bush4, Sanjeev Sariya2, Richard P. Mayeux2, Lindsay A. Farrer5, Michael L. Cuccaro1,6, Jeffrey M. Vance1,6, Anthony J. Griswold1,6, Gerard D. Schellenberg3, Jonathan L. Haines4, Goldie S. Byrd7, Christiane Reitz2, Gary W. Beecham1,6, Margaret A. Pericak-Vance1,6, Eden R. Martin1,6, for the Alzheimer’s Disease Genetics Consortium (ADGC), Collaboration on Alzheimer’s Disease Research (CADRE) and Alzheimer’s Disease Sequencing Project (ADSP) (IN PRESS, ALZ DIS & DEMENTIA)
Why Admixture Mapping?

- The admixture mapping has a lower multiple testing burden than SNP-based GWAS studies
- Identifies wide genomic regions that might harbor multiple risk loci
Admixed Population X

- Ancestry A
- Ancestry B

Admixture Mapping

Risk locus; $MAF_B \gg MAF_A$
Admixture Mapping Results

Fine-Mapping

(i) Ancestry-aware regression analysis

(ii) Differential Gene-expression Analysis

Significant differential gene-expression results of peripheral blood and post-mortem brain tissues studies

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>GENE NAME</th>
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<tbody>
<tr>
<td>Chr.17p13.2</td>
<td>GP1BA</td>
</tr>
<tr>
<td></td>
<td>SLC25A11</td>
</tr>
<tr>
<td></td>
<td>MINK1</td>
</tr>
<tr>
<td>Chr. 18q21.33</td>
<td>BCL2</td>
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(*) Griswold et al, 2019; ROSMAP, MSBB, Mayo
We identified two novel genome-wide significant admixture mapping signals in AA population:

- on chromosomes 17p13.2 and 18q21.33

Our study *generalized* the European genetic AD risk locus (17p13.2) to the AA population.

Our ancestry-aware analysis showed that AA individuals have a lower risk of AD if they inherited African ancestry at the 17p13.2 locus.

Our fine-mapping revealed several interesting candidate genes, some of which were implicated to contribute to AD risk such as *SLC25A11*, *MINK1* and *BCL2*.
IDENTIFYING THE APOE PROTECTIVE EFFECT

A locus at 19q13.31 significantly reduces the ApoE ε4 risk for Alzheimer’s Disease in African Ancestry  

*PLOS GENETICS, 2022*)
Identifying the Protective effect of the African genome for ApoE4

Risk for AD from ApoE4

- Autopsy studies in different LA
- Sequence differences in LA region
- Inducible Pluripotent Stem Cell studies
  - Single nuclei RNAseq, ATACseq, HiC
  - Interaction with ApoE4 and differences in function due to sequence
  - African and European LA
  - CRISPR

Potential Protective Variant RF1AG059018-Vance

Due to local ancestry surrounding ApoE
This study identified a new African ancestry-specific haplotype that reduces the AD risk effect of APOE ε4 homozygotes in African ancestry by approximately 75%.

- 2 mB from ApoE and lack of known AD genes surrounding rs10423769 suggests novel mechanism of protection
- Located in area of high segmental DNA duplications
- Rs10423769 is a splicing qTL for TMEM145, expressed in brain, highest in cerebellum
Welcome to the Alzheimer’s Disease Sequencing Project

The overarching goals of the ADSP are to:

1. Identify new genomic variants contributing to increased risk of developing Late-Onset Alzheimer’s Disease (LOAD)
2. Identify new genomic variants contributing to protection against developing Alzheimer’s Disease (AD)
3. Provide insight as to why individuals with known risk factor variants escape from developing AD
4. Examine those factors in multi-ethnic populations as applicable in order to identify new pathways for disease prevention

News

- Wednesday, March 3, 2021 - 09:15
  NIAGADS DSS Releases
  Additional 17K Whole Genomes

- Wednesday, February 19, 2020 - 15:30
  NIAGADS DSS Releases 26K Whole Exomes

- Monday, November 5, 2018 - 20:30
  Additional ADSP Data Released on NIAGADS DSS

- Friday, September 7, 2018 - 19:15
  NIAGADS Data Sharing Service
  Now Accepting Applications

- Friday, April 13, 2018 - 18:15
  Genetic variation paper published in Dementia and Geriatric Cognitive Disorders

Funded by: National Institute For Aging

https://www.niagads.org/adsp/content/home
Alzheimer’s Disease
Sequencing Project Follow-up Study (ADSP-FUS)*

Global Effort to Generate Whole Genome Sequencing in Alzheimer’s Disease

Identify new genomic variants contributing to increased risk of developing and protection against Alzheimer's Disease (AD)

Examine these factors in multi-ethnic populations as applicable in order to identify new pathways for disease prevention

*https://www.niagads.org/adsp/content/home
ADSP and Affiliates Currently Funded WGS by Ancestry/ethnicity (thru 2023)

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<tr>
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<th>Non-Hispanic White</th>
<th>Black/African American</th>
<th>Hispanic/Latino</th>
<th>Asian</th>
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<tbody>
<tr>
<td>Cases</td>
<td>11,088</td>
<td>2,717</td>
<td>3,986</td>
<td>2,358</td>
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<tr>
<td>Unaffected</td>
<td>20,714</td>
<td>5,610</td>
<td>7,400</td>
<td>5,073</td>
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<tr>
<td>ADRD/MCI</td>
<td>4,030</td>
<td>379</td>
<td>2,190</td>
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WGS Sample Size Target
GCAD RELEASE 3 AND 4:
INCREASING ANCESTRAL/ETHNIC DIVERSITY

European, 17,887
Hispanic/Latino, 10,546
African, 5,057
Asian, 2,760
Other, 64

WGS by Ancestry/Ethnicity

r3 (17k) release 2021

European, 11,138
Hispanic/Latino, 3,338
African, 3,063
Other, 64

r4 (36k) initial release Fall 2022

European, 17,887
Hispanic/Latino, 10,546
African, 5,057
Asian, 2,760
Other, 64
Recruitment and Retention for AD Diversity Genetic Cohorts in the ADSP (REAAD-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
  - Rufus Akinyemi
  - Adesola Ogunniyi

- Case Western Reserve University
  - Jonathan Haines
  - Will Bush

![Diagram showing recruitment and retention for AD diversity genetic cohorts in the ADSP (REAAD-ADSP)]

- **4,000 Black Americans**
- **4,000 Hispanic/Latino Americans**
- **5,000 Africans AfDC***

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*AfDC; African Dementia Consortium*
• DNA, RNA, Plasma Biomarkers and CVD markers and extensive phenotyping
• 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.
ADSP FOREIGN COHORTS

• Gwangju Alzheimer’s & Related Dementias (GARD) Study – Korea
  • PI: Lindsay Farrer (Boston University)
  • Korea site PI: Kunho Lee (Chosun University)

• Aspirin in Reducing Events in the Elderly (ASPREE) Trial cohort – Australia
  • PI: Paul Lacaze (Monash University)

• Interaction between SARS-CoV-2 Infection and Ancestral genomic Variations in the Risk of Alzheimer’s Disease and Related Disorders (ISAVRAD) - Argentina
  • PI: Gabriel De Erausquin (UT San Antonio)

• Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD) – India
  • PI: Jincook Li (University of Southern California)
Asian Cohort for Alzheimer’s Disease

- **R56 phase:** 1,000 Chinese in US and Canada, additional pilots for Vietnamese and Korean Americans at two sites
- Eventually 5,000 participants in 5 years: Chinese / Korean / Vietnamese Ancestry in US and Canada
- Culturally appropriate recruitment and assessment
- DNA for genetics and plasma for blood-based biomarkers
ACAD Strategy

• 3-Part Data Collection Packet based on NACC UDS; translated into Chinese, Vietnamese, Korean
• Translated validated cognitive test instruments
• Training/outreach material and REDCap data capture
• Recruitment started in September 2021; >1000 signed up, ~500 completed assessment
• Community-Based Participatory Research (CBPR)
• Interdisciplinary team/international collaboration
Studies in Amerindian populations in South America

Enrollment
- 1,700 dementia cases and 1,850 healthy controls
- 7 sites in Peru
- 1 site in Bolivia

Principal Investigators

Giuseppe Tosto
Columbia University

Mario Cornejo-Olivas
San Marcos Foundation and Instituto Nacional de Ciencias Neurologicas (NRC)

Eden R. Martin
University of Miami

Nilton Custodio
Instituto Peruano de Neurociencias

Margaret Pericak-Vance
University of Miami
International Expansion: ADSP and Collaborators
Genetic risk factors for AD can be different depending on your ancestral background.

The mechanisms (pathways) between ancestries appear to be similar, but some genes/pathways may be more important in some ancestries than others.

Investigating the relationship between genetic ancestry, SDOH and disease may inform precision medicine initiatives, risk assessment, and development of ancestry-specific therapeutics and prevention strategies.

ADSP FUS focused on increasing Asian, African and Hispanic/Latino Ancestry Participants.

Critical need to significantly increase diversity in genomic analyses to truly achieve the ability to conduct cross-ancestry comparisons and clarify differences in genetic etiology and potential molecular therapeutic targets.
# Acknowledgments

## Members of the Alzheimer’s Disease Sequencing Project (ADSP) Follow-Up Study Implementation Team

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<tr>
<th>University of Miami</th>
<th>Columbia University</th>
<th>NCRAD</th>
<th>USUHS</th>
<th>University of Pennsylvania</th>
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Thanks to all the researchers and collaborators who have contributed cohorts and to all the patients who have participated in the studies.

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[Logos for NIH, CHARGE Consortium, and ADGC]