



UNIVERSITY OF MIAMI

MILLER SCHOOL OF MEDICINE

HUSSMAN INSTITUTE

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Leveraging African Ancestral Analyses To Unveil Insights Into Alzheimer Disease Mechanisms And Risk Heterogeneity Across All Populations

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Background

- The Recruitment and Retention for Alzheimer's Disease Detailed Genetic Cohorts in the Alzheimer's Disease Sequencing Project (READD-ADSP) DAWN Initiative is creating a resource to increase genetic ancestry representation in Alzheimer disease (AD) studies.
- DAWN has generated whole-genome sequence (WGS) and Global Screening Array v3 (GSA) data from Africa recruited as part of the African Dementia Consortium (AfDC) and self-identified African Americans (AA) and Hispanics/Latinos (HL) residing in the United States (U.S.).
- Populations with substantial African ancestry have the greatest genetic and phenotypic variation and contribute significantly to global population structure. Studying these populations is critical for identifying novel AD risk and protective factors and improving our understanding of the disease in U.S. populations, particularly AA and HL with African ancestry.
- AA and HL have higher AD prevalence in the U.S.; the population of these groups are increasing more quickly than Non-Hispanic Whites and will account for nearly 50% of clinical AD cases by 2060, an increase of 68.5% of the AD burden in the US since 2020.¹
- The objective of this study is to characterize population structure and ancestral heterogeneity across global populations, thereby establishing a robust framework to guide and enhance the discovery of genetic risk and protective factors and their functional characterization underlying AD. These insights will inform the identification of therapeutic targets with the potential to benefit both U.S. and global populations.

Clinical AD Burden in U.S.

2020

70.8%

17.5%

11.7%

Total: 6.07M

Population Growth

2060

50.8%

22.4%

26.9%

Total: 13.85M

Non-Hispanic White

Hispanic/Latino

African American

Prevalence

Clinical AD Prevalence (%)

NHW

HL

AA

Methods

- We studied 2,230 African Americans, 2,134 Hispanics/Latinos and 2,902 Africans passing quality control with GSA data and some additionally with WGS data. To assess population structure and ancestry, we primarily ran 3 analyses on unrelated READD-ADSP DAWN participants:
 - Principal Component Analysis (PCA)**
 - We randomly selected 100 Africans from each country of ascertainment; 100 self-identified African Americans; Up to 100 Hispanics/Latinos from each country of birth with at least 50 participants.
 - For reference data, we included unadmixed populations from the Human Genome Diversity Project (HGDP) and 1000 Genomes Project (TGP) and randomly selected 50 individuals from each sub-population (i.e. GBR, IBS, TSI in Europe).
 - Local Ancestry (LA)**
 - We phased 1,482 African Americans and 1,542 Hispanics/Latinos with WGS data with Beagle 5.5 (27Feb25.75f).
 - We ran 4-way admixture LA using reference populations for African, Amerindian, East Asian and European genomes from HGDP and TGP with RFMix2 (commit: 09599c1).
 - Multidimensional scaling (MDS)**
 - With the LA calls generated, regions of African ancestry were isolated by selecting the single African haplotype in heterozygous individuals, taking the first haplotype in homozygous individuals, and masking genotypes with zero African ancestry to generate pseudo-haplotypes for MDS.

1. Phased Genotypes

1 1 1 0 0 1 1 0 0 0 1 1 0 1 1
1 0 1 1 0 0 1 0 0 1 0 0 1 1 0

2. European-specific Haplotypes

1 1 1 0 0 1 1 0 0 1 1 0
0 1 0 0 0 0 0 0 0 0 1 1 0

2. African-specific Haplotypes

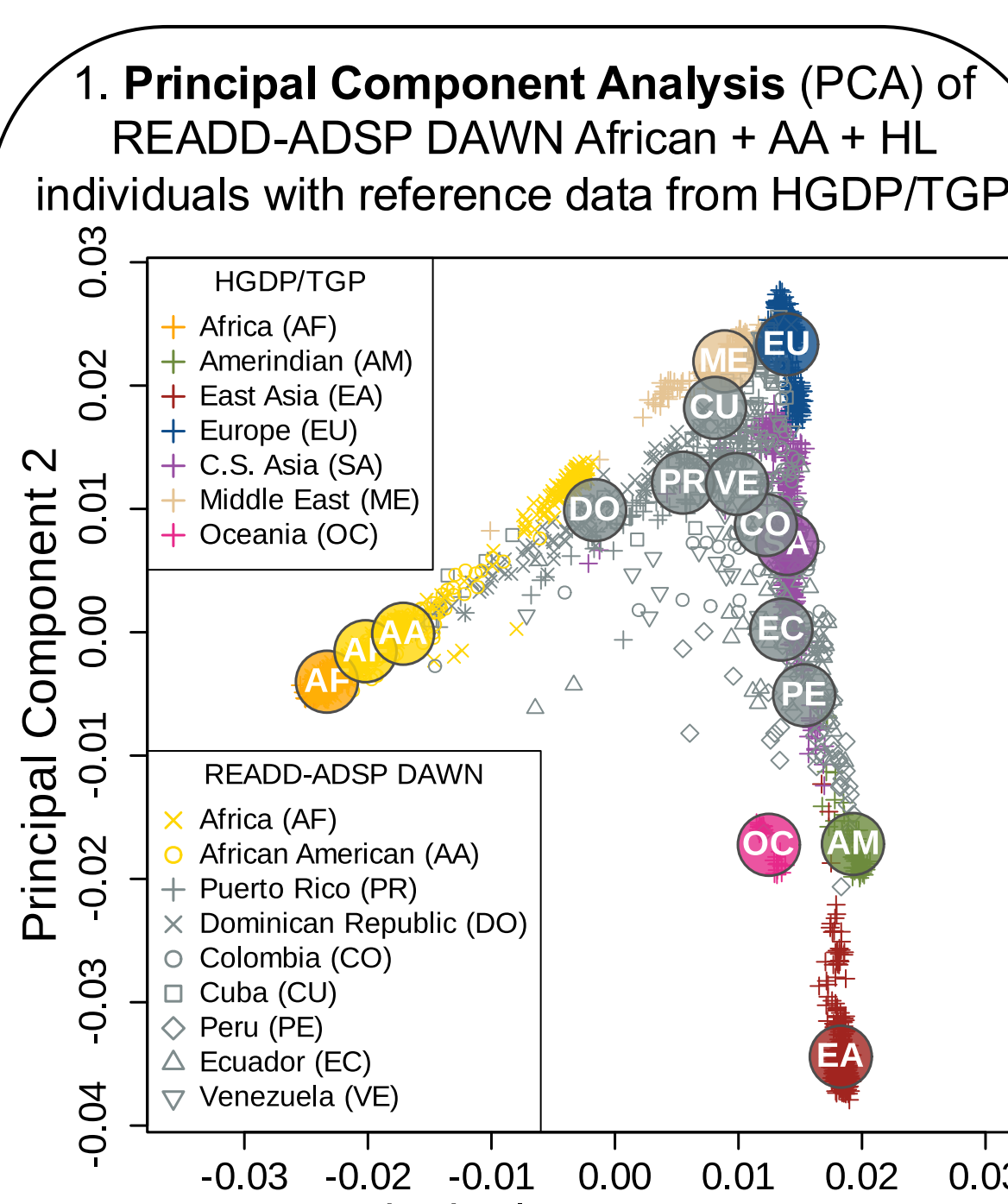
0 0 1 1 1 0 0 1 1 0 0 1 1
1 0 0 1 0 0 1 0 0 1 0

3. African pseudo-haplotype for MDS

1 0 0 1 1 0 0 1 1 0 0 1 1

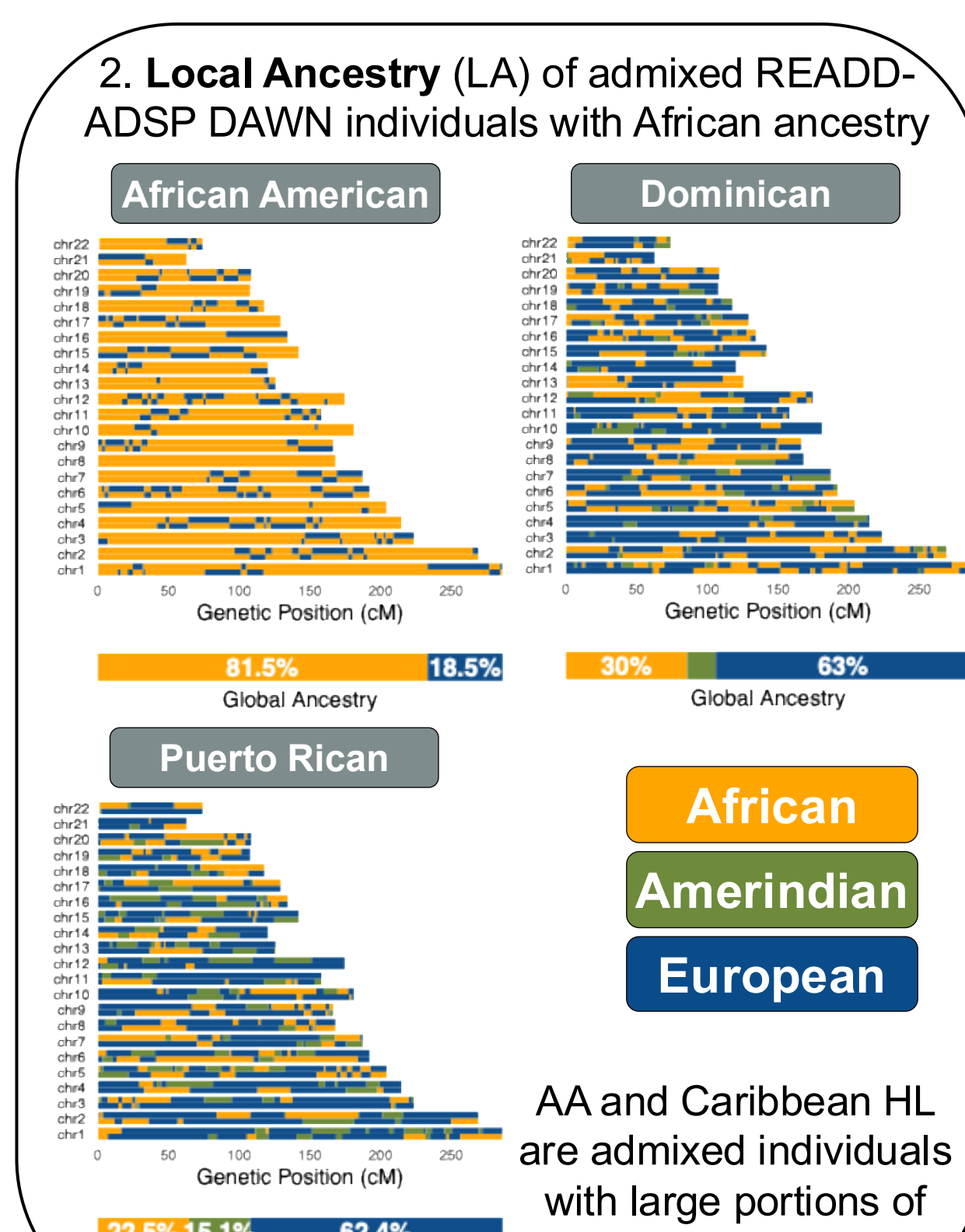
Results

1. Principal Component Analysis (PCA) of READD-ADSP DAWN African + AA + HL individuals with reference data from HGDP/TGP



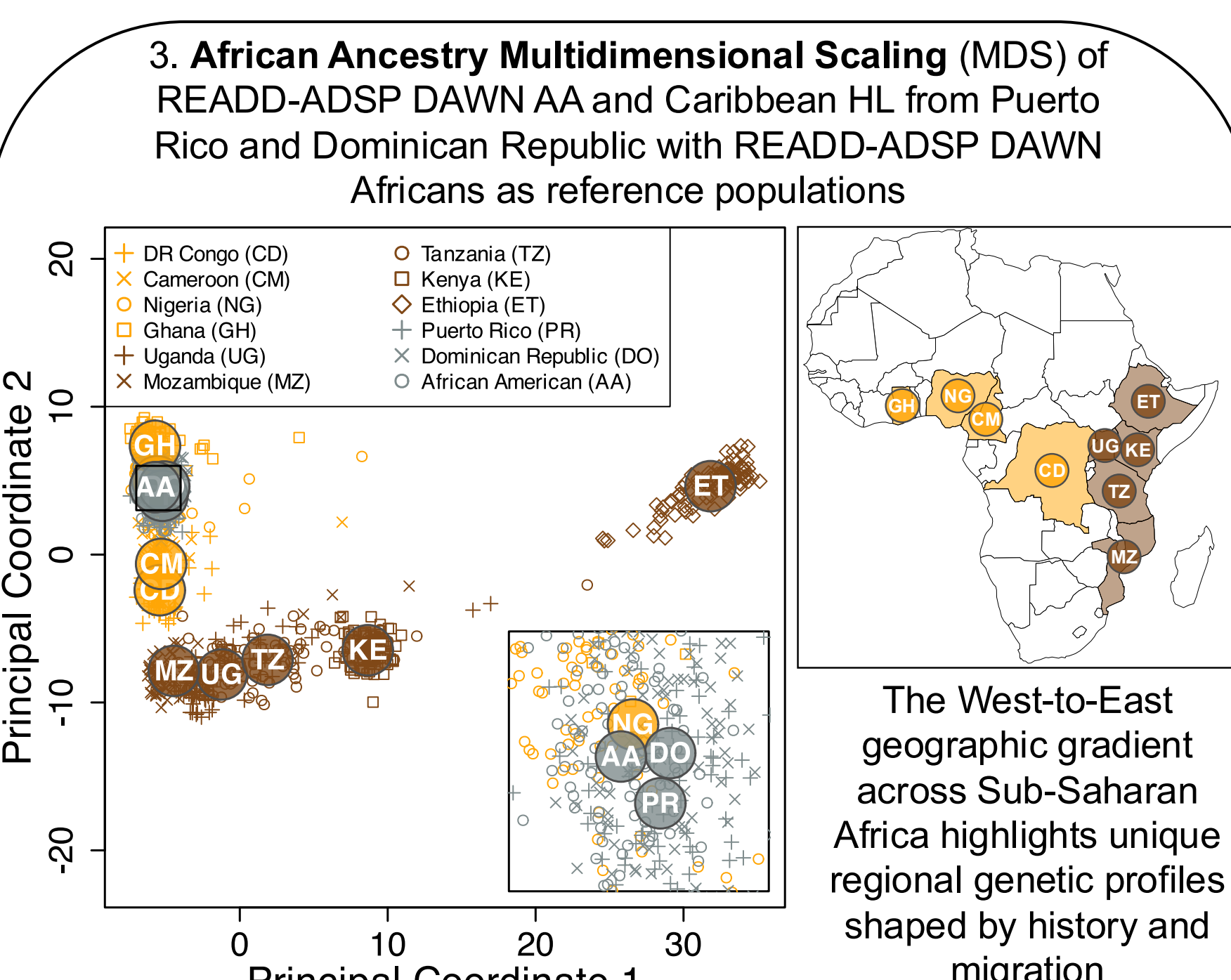
READD-ADSP DAWN includes individuals with different genetic backgrounds from Africa and self-identified AA and HL living in the U.S.

2. Local Ancestry (LA) of admixed READD-ADSP DAWN individuals with African ancestry



AA and Caribbean HL are admixed individuals with large portions of African ancestry

3. African Ancestry Multidimensional Scaling (MDS) of READD-ADSP DAWN AA and Caribbean HL from Puerto Rico and Dominican Republic with READD-ADSP DAWN Africans as reference populations

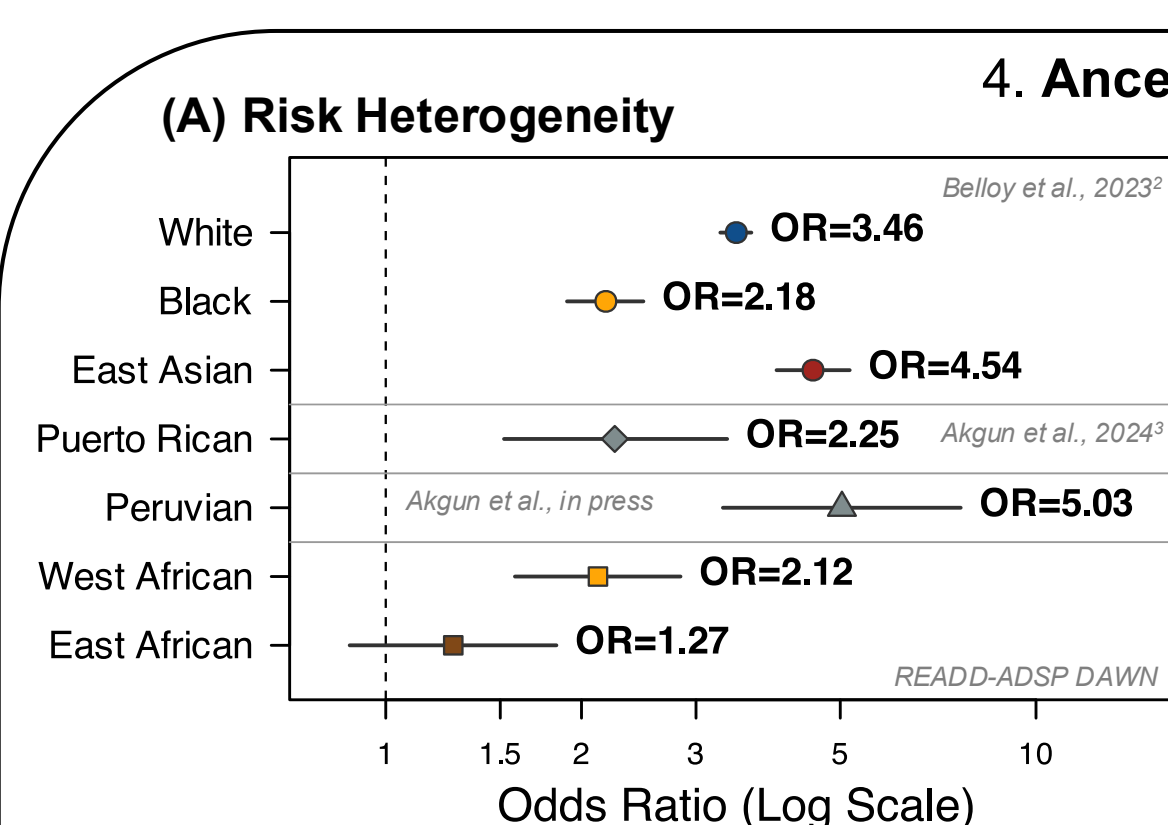


The West-to-East geographic gradient across Sub-Saharan Africa highlights unique regional genetic profiles shaped by history and migration

African ancestry in AA and Caribbean HL clusters most closely to the genetics of present-day West-Central Africans, consistent with known historical migration from Africa to the United States and Caribbean

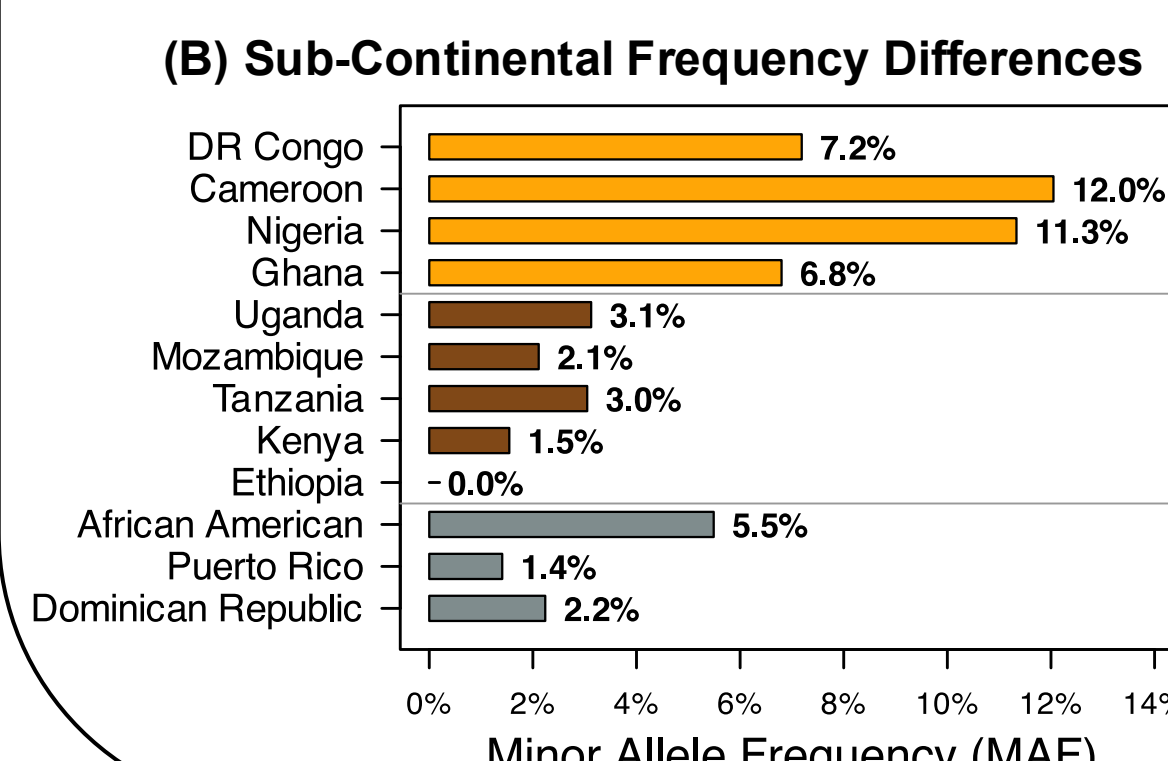
4. Ancestry in Alzheimer Disease (AD) Loci

(A) Risk Heterogeneity



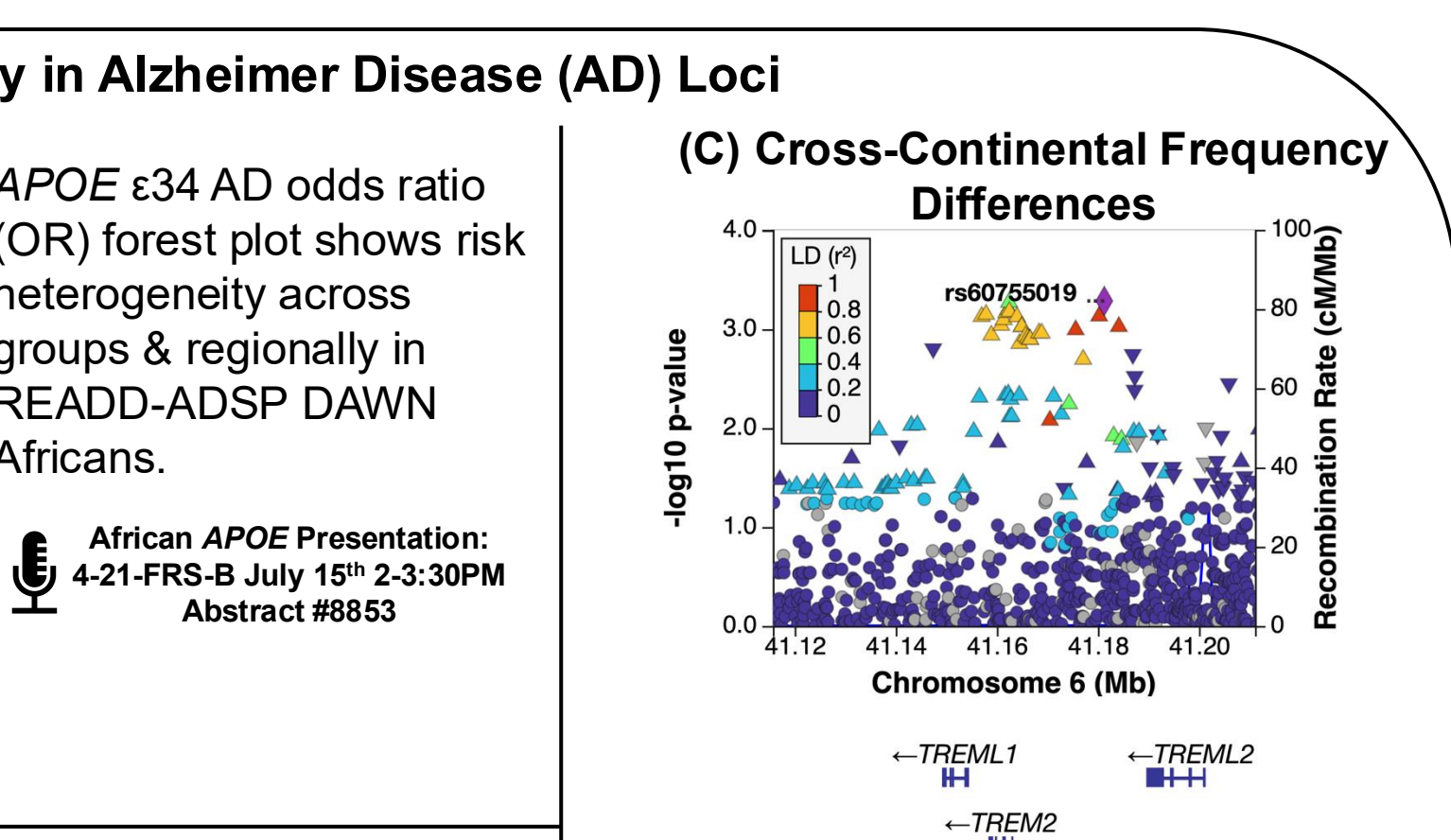
White: OR=3.46
Black: OR=2.18
East Asian: OR=4.54
Puerto Rican: OR=2.25
Peruvian: OR=5.03
West African: OR=2.12
East African: OR=1.27

(B) Sub-Continental Frequency Differences



DR Congo: 7.2%, Cameroon: 12.0%, Nigeria: 11.3%, Ghana: 6.8%, Uganda: 3.1%, Mozambique: 2.1%, Tanzania: 3.0%, Kenya: 1.5%, Ethiopia: 0.0%, African American: 5.5%, Puerto Rico: 1.4%, Dominican Republic: 2.2%

(C) Cross-Continental Frequency Differences



rs60755019; hg38: chr6-41181270_A/G

Study	MAF	OR	P
READD-ADSP DAWN Africans	0.220	1.32	5.19x10 ⁻⁴
Bellenguez et al., 2022 ⁶	0.004	1.55	2.10x10 ⁻⁸

A known AD risk locus in *TREML2* originally identified in Europeans with rare frequency is replicated in READD-ADSP African GWAS with a much higher allele frequency.

African GWAS Presentation: 4-21-FRS-B July 15th 2-3:30PM Abstract #842

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Conclusion

- The DAWN study addresses a critical need in AD research by expanding studies of African ancestry populations to improve our understanding of AD and advance future prevention and treatment strategies.
- AD is a complex phenotype with a multitude of factors influencing clinical outcomes. We describe risk heterogeneity and ancestry-specific loci with substantial impacts on AD pathogenesis.
- African ancestry is a large component in many groups residing in the United States, including African Americans and Caribbean HL. Through MDS analysis,

we show that this African ancestry most closely aligns with the genetic background of West-Central Africans.

- There is substantial sub-continental heterogeneity in Africa that impacts AD through loci such as *APOE* ε4 and the West-Central African derived *ABCA7* 44-bp frameshift deletion.
- The unique regional genetic profiles and admixture dynamics across African Americans, Caribbean HL, and Africans prove that global populations are a requirement for unraveling pathways in AD therapeutic targeting.

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