



Genetics of dementia in a Turkish cohort

Understudied populations contribute to our understanding of disease genetics

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Acknowledgements

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RCCN Travel Award

Sponsor: Prof. Henry Paulson, MADRC

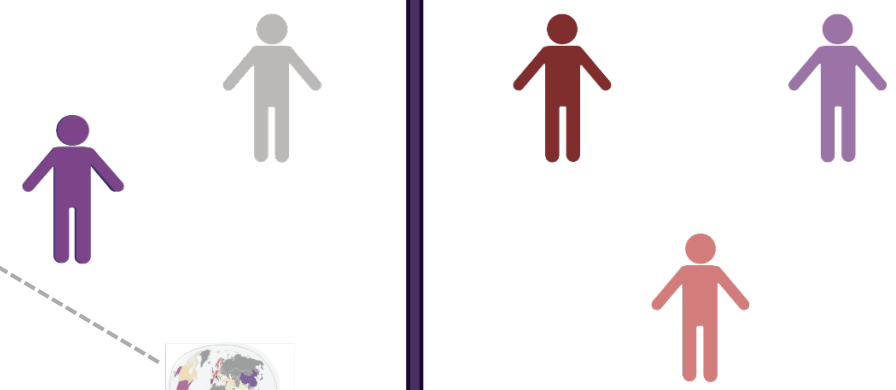
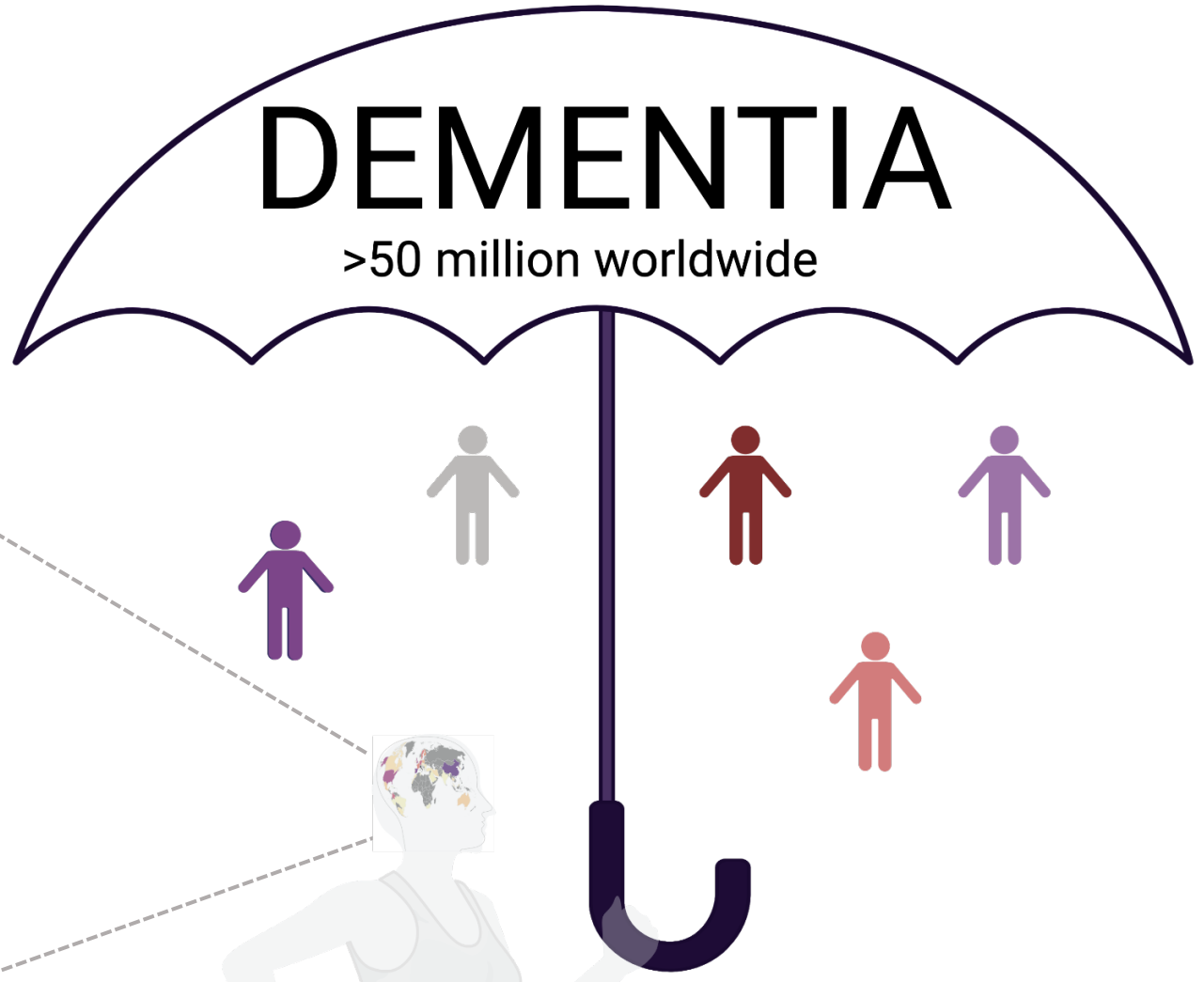
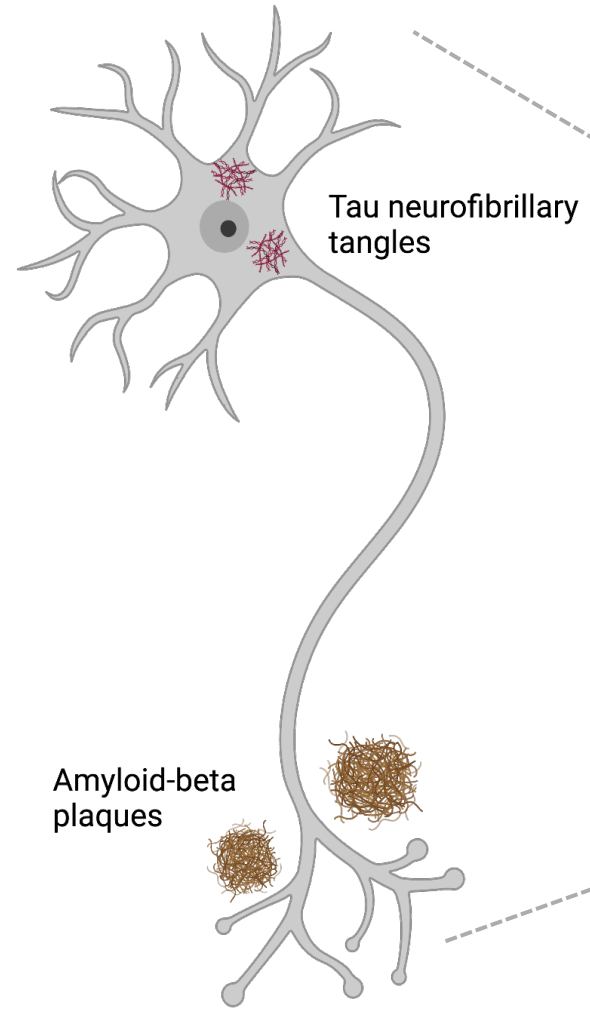
RCCN Planning Committee

Workshop Attendees

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DEMENTIA

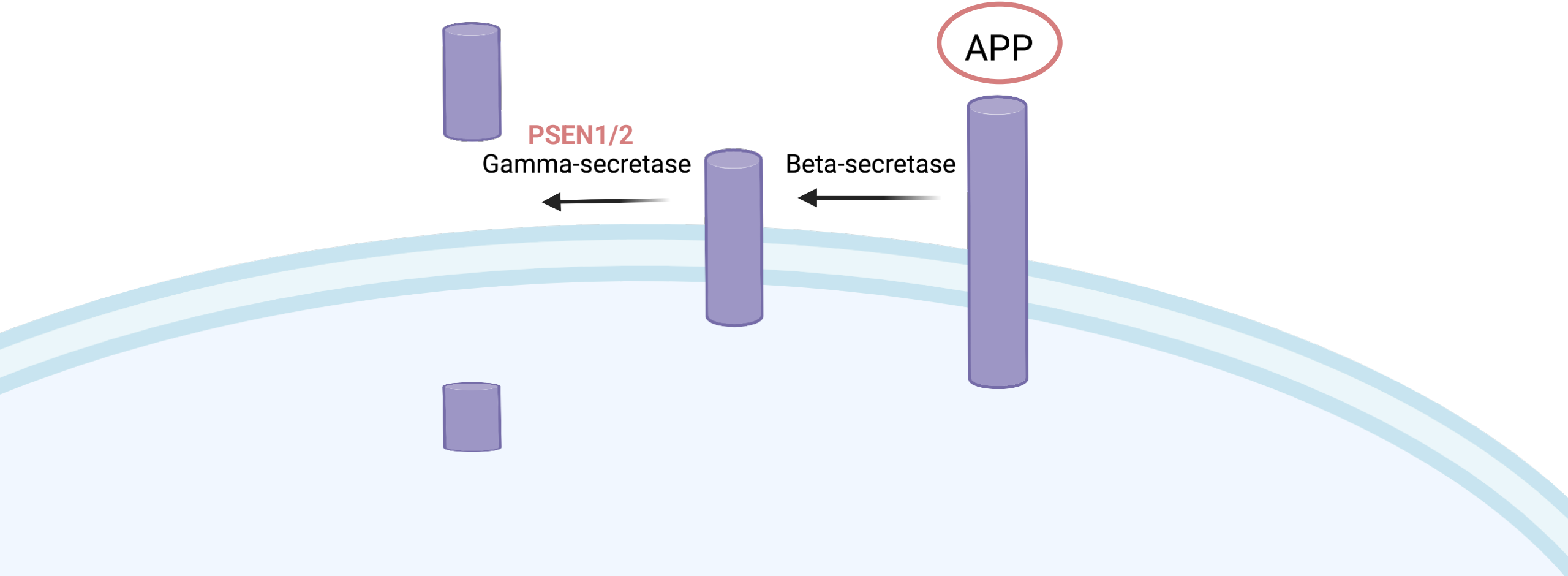
>50 million worldwide



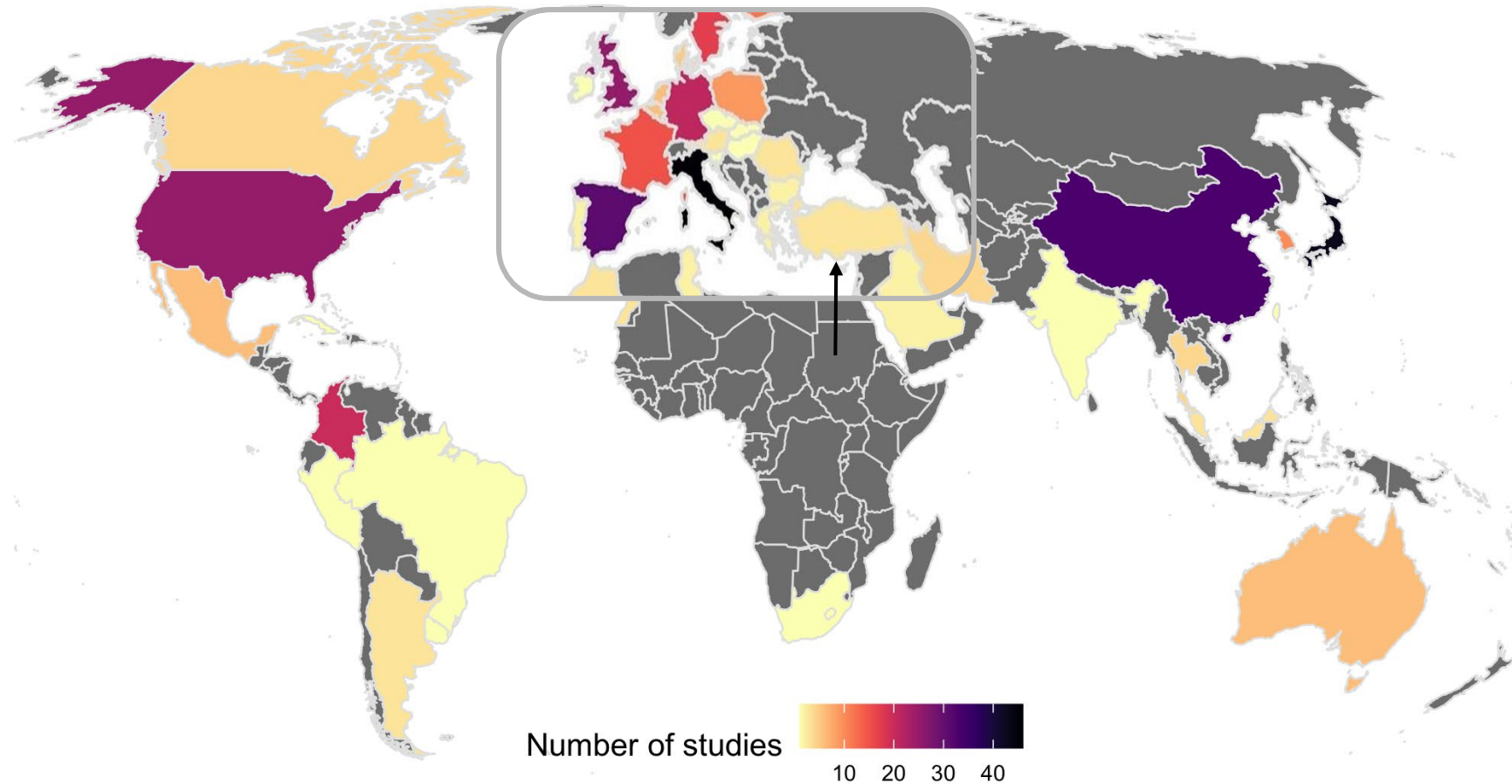
Alzheimer's disease

APP and PSENs in Alzheimer's disease

Amyloid-beta



Identifying understudied populations in AD genetics

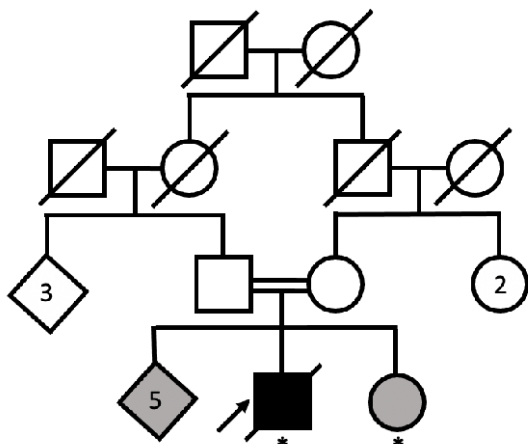


World map with number of studies reporting variants in *APP*, *PSEN1* or *PSEN2* in patients per country.

(Dehghani *et al.*, 2021; *Brain*)

Growing consanguineous Turkish dementia cohort

>400 families



Diagnoses including:

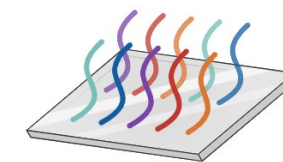
- Alzheimer's disease,
- Frontotemporal dementia,
- Mild cognitive impairment



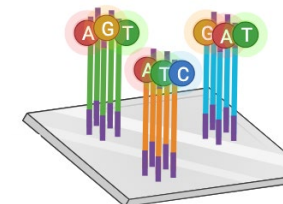
google.com/maps

Methods:

Whole genome genotyping



Whole exome sequencing



External data: GME Variome & TR Variome

> [Nat Genet.](#) 2016 Sep;48(9):1071-6. doi: 10.1038/ng.3592. Epub 2016 Jul 18.

Characterization of Greater Middle Eastern genetic variation for enhanced disease gene discovery

[Eric M Scott](#)^{1 2 3}, [Anason Halees](#)⁴, [Yuval Itan](#)⁵, [Emily G Spencer](#)^{1 2 3}, [Yupeng He](#)^{1 2 3}, [Mostafa Abdellateef Azab](#)^{1 2 3}, [Stacey B Gabriel](#)⁶, [Aziz Belkadi](#)^{7 8}, [Bertrand Boisson](#)^{5 7 8}, [Laurent Abel](#)^{5 7 8}, [Andrew G Clark](#)⁹, [Greater Middle East Variome Consortium](#); [Fowzan S Alkuraya](#)^{10 11}, [Jean-Laurent Casanova](#)^{1 5 7 8 12}, [Joseph G Gleeson](#)^{1 2 3}

Collaborators, Affiliations: [+ expand](#)

PMID: 27428751 PMCID: [PMC5019950](#) DOI: [10.1038/ng.3592](#)



[Free PMC article](#)

> [Proc Natl Acad Sci U S A.](#) 2021 Sep 7;118(36):e2026076118. doi: 10.1073/pnas.2026076118.

The genetic structure of the Turkish population reveals high levels of variation and admixture

[M Ece Kars](#)¹, [A Nazlı Başak](#)², [O Emre Onat](#)¹, [Kaya Bilguvar](#)³, [Jungmin Choi](#)^{3 4}, [Yuval Itan](#)^{5 6}, [Caner Çağlar](#)⁷, [Robin Palvadeau](#)², [Jean-Laurent Casanova](#)^{8 9 10 11 12}, [David N Cooper](#)¹³, [Peter D Stenson](#)¹³, [Alper Yavuz](#)¹⁴, [Hakan Buluş](#)¹⁵, [Murat Günel](#)^{3 16}, [Jeffrey M Friedman](#)^{7 12}, [Tayfun Özçelik](#)^{17 18 19}

Affiliations [+ expand](#)

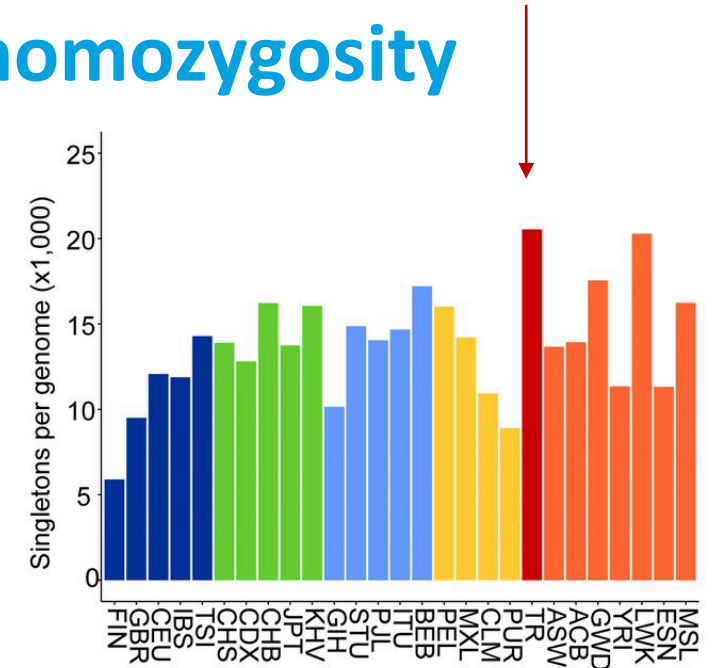
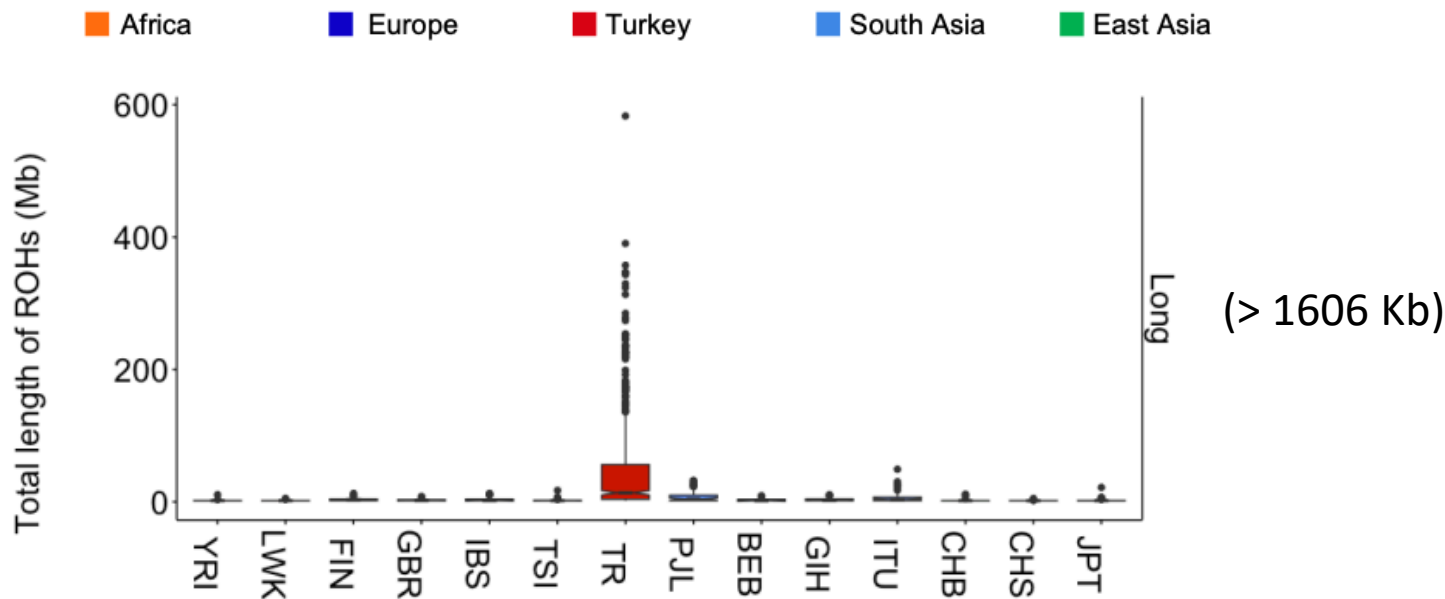
PMID: 34426522 PMCID: [PMC8433500](#) (available on 2022-02-23)

DOI: [10.1073/pnas.2026076118](#)



Genetic characterization

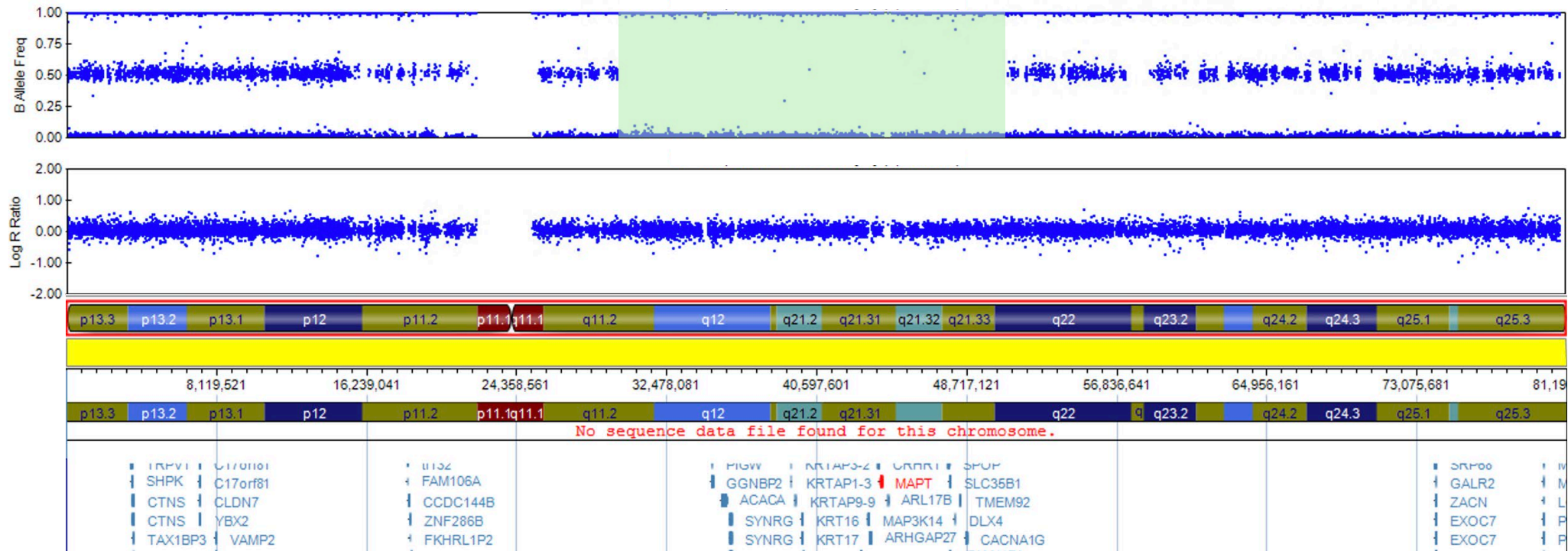
1. Rare variant analyses utilizing regions of homozygosity
2. Copy number variant analyses



Turkish (and Luhya in Webuye, Kenya) populations have a higher number of singletons compared to other 1K genomes populations

(Kars *et al.*, 2021; *PNAS*)

Rare variants in extended ROHs: *MAPT*

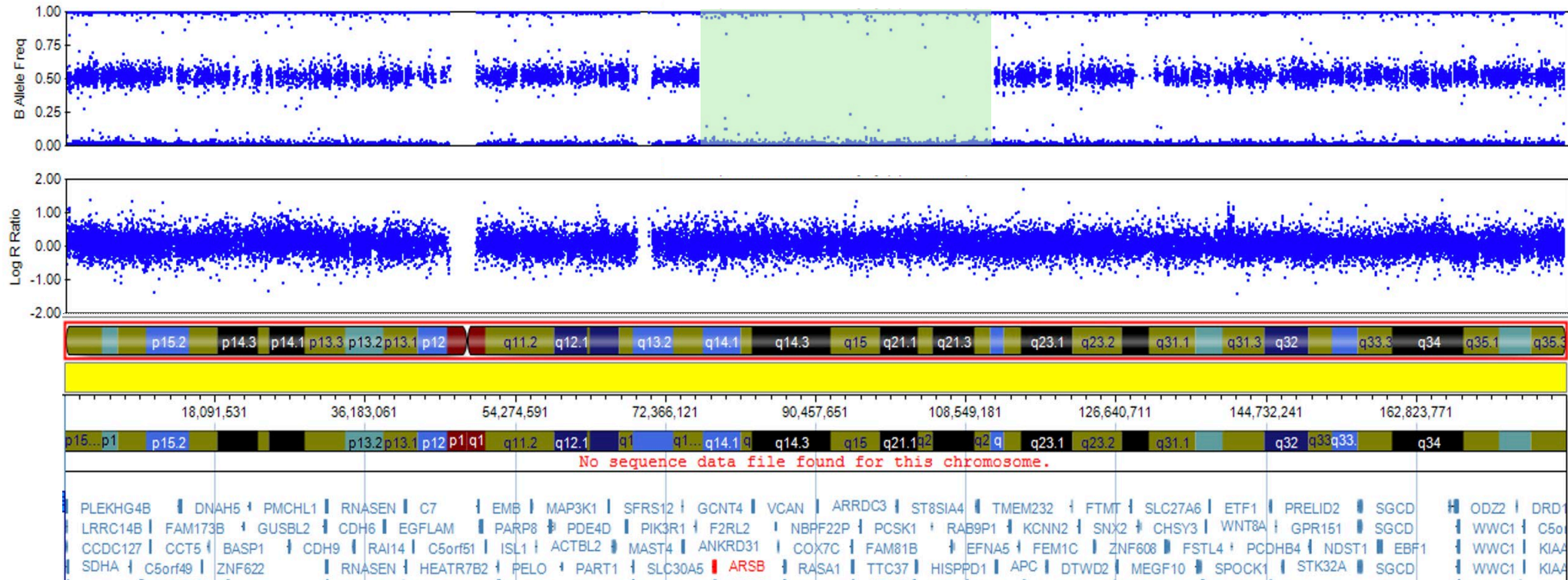


SNP zygosity across chromosome 17 with the ROH encompassing *MAPT* highlighted in green

Homozygous *MAPT* p.Pro605Leu in FTD case with age at onset 34 years.

(Presented at AAIC 2021)

Rare variants in extended ROHs: *ARSB*



SNP zygosity across chromosome 5 with the ROH encompassing *ARSB* highlighted in green

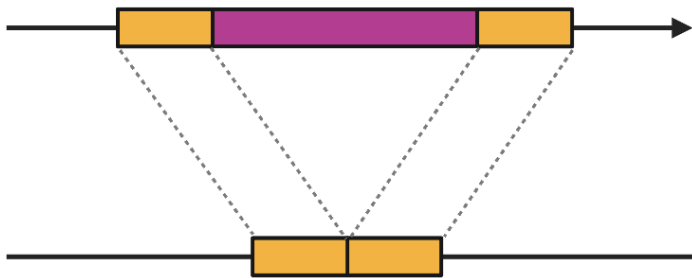
Homozygous *ARSB* p.Arg152Trp in probable Alzheimer's disease

Pathogenic for mucopolysaccharidosis, a lysosomal storage disorder (Szpiech *et al.*, 2013; *Am J Hum Genet*)

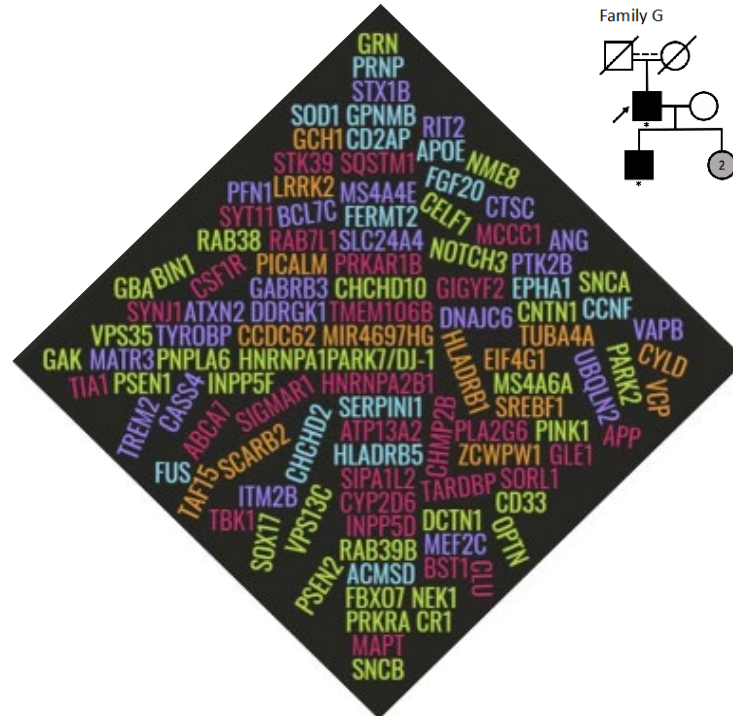
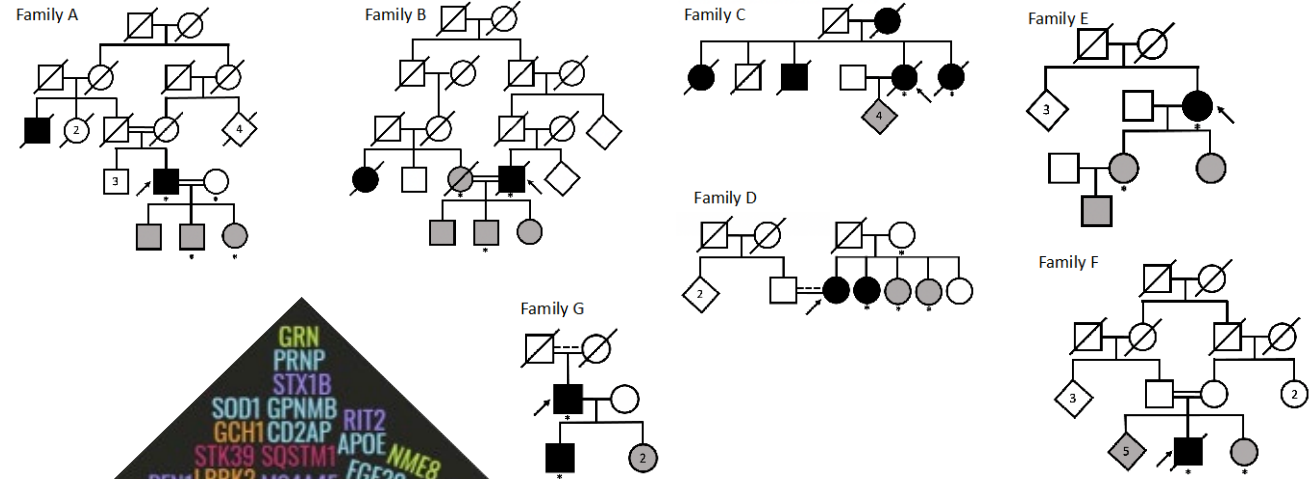
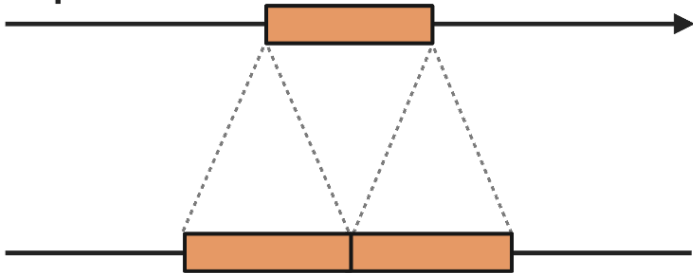
(Presented at AAIC 2021)

Copy number variation

Deletion



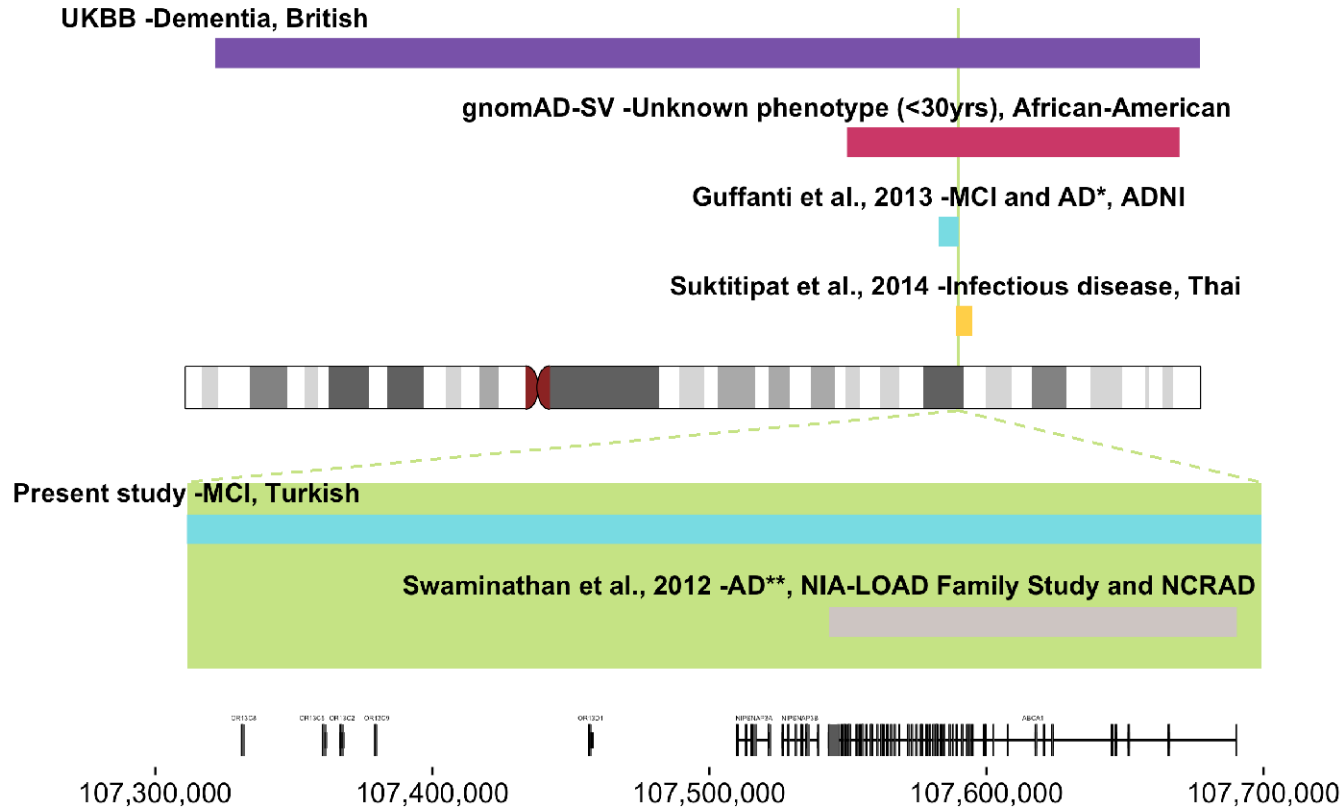
Duplication



1- Genome-wide scan for segregation of CNVs

2- CNVs overlapping genes implicated in neurodegenerative diseases

Deletions spanning *ABCA1*



ABCA1

→ Cholesterol transporter from the ATP-binding cassette transporter superfamily

→ In a recent AD GWAS, rs1800978 in *ABCA1* was identified as the lead SNP in a novel genome-wide significant locus (Bellenguez *et al.*, 2022; Nat. Genet.)

*This CNV region encompasses heterozygous deletions reported in 1 MCI patient and 4 AD patients. **This CNV was reported in 3 AD patients.

(Dehghani *et al.*, 2021; *Human Genomics*)

Gaps and Opportunities

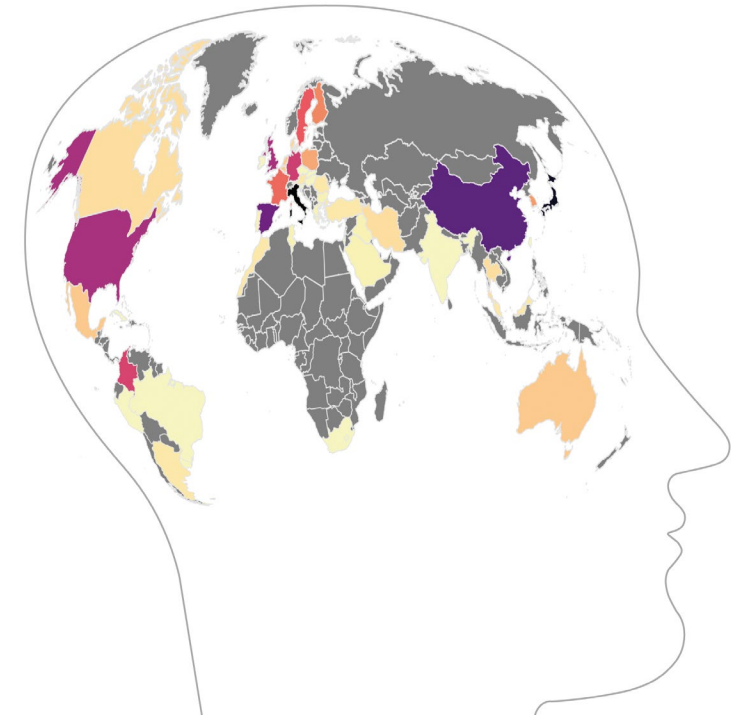
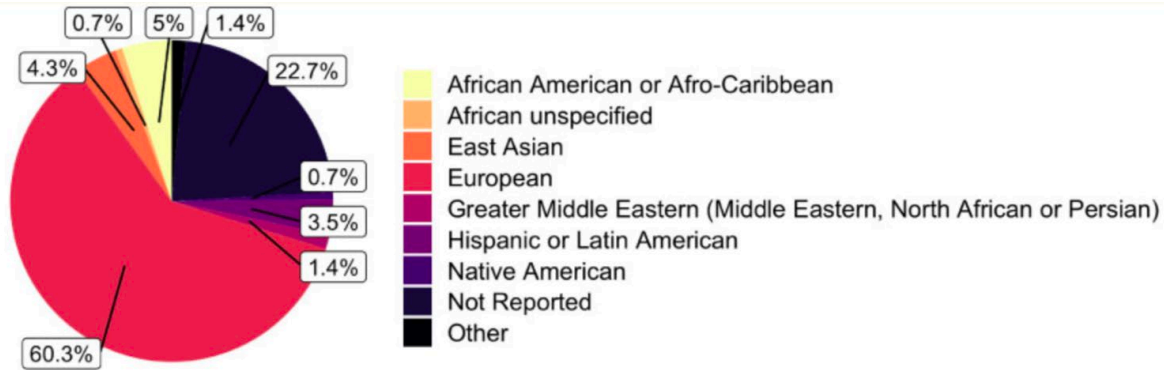


Table 1 Table of novel SNPs that were initially identified by reaching genome-wide significance in GWAS performed in understudied populations

Chromosome	SNP-effect allele	Nearest gene	Population	Source
3	rs7431992-A	<i>CACNA2D3</i>	Caribbean Hispanics	Tosto et al. ⁷
5	rs75002042-A	<i>FBXL7</i>	Caribbean Hispanics	Tosto et al. ⁷
7	rs112404845-T	<i>COBL</i>	African American	Mez et al. ⁸
13	rs16961023-G	<i>SLC10A2</i>	African American	Mez et al. ⁸
19	rs11553053-T	<i>HMHA1</i>	African American	Reitz et al. ⁹

Since these associations were reported, there have been no further reports of associations between Alzheimer's disease and *FBXL7*, *COBL*, *SLC10A2* or *HMHA1*.

- Continuing to establish and grow cohorts from understudied populations
- Utilizing collaborative funding opportunities, community partnerships
- Mitigate health inequities (representation of World populations in genetic studies), to avoid health disparities (development & implementation of clinical genetic risk assessment)