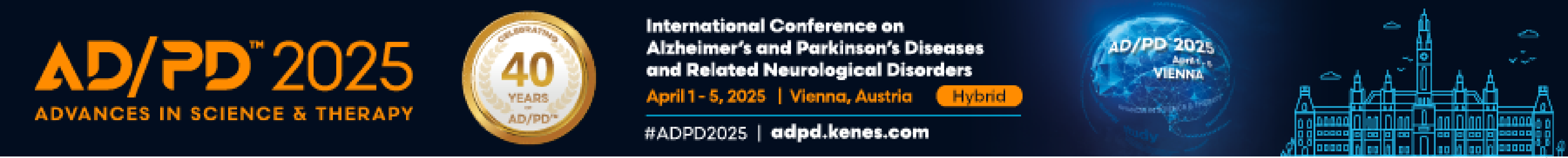

COLUMBIA
TAUB INSTITUTE FOR RESEARCH
ON ALZHEIMER'S DISEASE
AND THE AGING BRAIN

GiusTo Lab

Fine-mapping of Runs of Homozygosity and Their Role in Alzheimer's Disease

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No conflicts of interest to disclose

ROH relevance in Alzheimer's Disease

- Long stretches of homozygous genotypes inherited from a common ancestor reflects regions of the genome under autozygosity
- AD risk may be influenced by rare, recessive variants that are enriched in ROH regions
- Pinpoint specific loci/region within ROHs associated with AD and prioritize regions for rare variant association tests
- Identify homozygous deleterious alleles that would otherwise be missed in GWAS

Material and Methods -1

- Retrieved genotype data of 351 Peruvians from GAPP Study, 823 Mexicans from MHAS Study, and 26,369 individuals from ADSP R5 dataset

Group	Race	Ethnicity	Total number of simples (N)
1	White	Hispanics	2474
2	White	Nonhispanics	17106
5	Asian	Korean (KBASE)	1970
		(GARD)	589

Material and Methods -2

- **Genetic outlier removed**
- ROH are identified using the following params:

```
--homozyg-group
--homozyg-kb 300
--homozyg-window-het 3
--maf 0.01
```

The ROH regions satisfying the following criteria were selected:

- Should be consensus ROH regions
- ROH must be prevalent more than 25% within the group
- ROH length > Median of ROH identified in the group

For downstream analysis

Material and Methods -3

Fine-mapping of ROH

Step 1

For each ROH region, AD association was checked using GLM + StepAIC model

Step 2

Within each significant ROH region, rare SNPs (MAF < 0.01) were followed up by single marker and gene based rare variant anlysis

Step 3

Significant genes were mapped with gene-expression data for regulatory insight

BRAINscape: A Comprehensive Multi-Omics Analysis Tool

- Developed an open-source R package BRAINscape for exploring multi-omics data in Hispanics and Non-Hispanics individuals

- BRAINscape includes eQTL (TensorQTL) and differential expression analysis (DESeq2)

- **Citation:** Ruhela, V., Basilio Cieza Huaman, Zikun Yang, & Giuseppe Tosto. (2025). BRAINscape (0.4.0). Genetics and Genomics (Zenodo). https://doi.org/10.5281/zenodo.14925129

ROH Identification and their ancestry estimation in Peru and MHAS

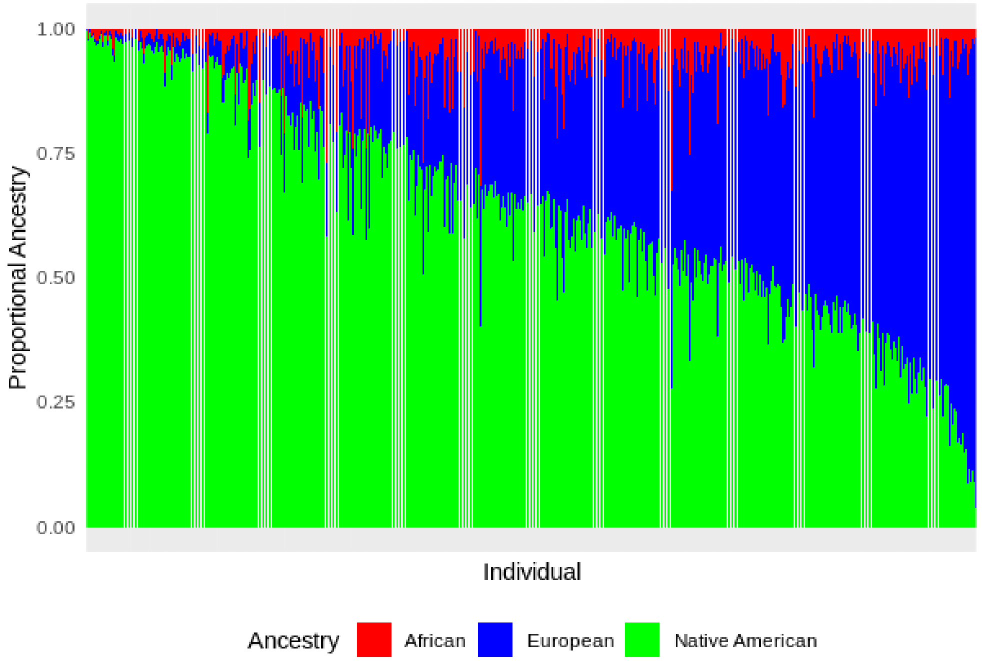
Number of Significantly AD associated ROH regions in Peru and MHAS

Population	Total number of AD associated ROH	Total number of Rare Variants within AD associated ROH
Peru	19	693
MHAS	59	8311

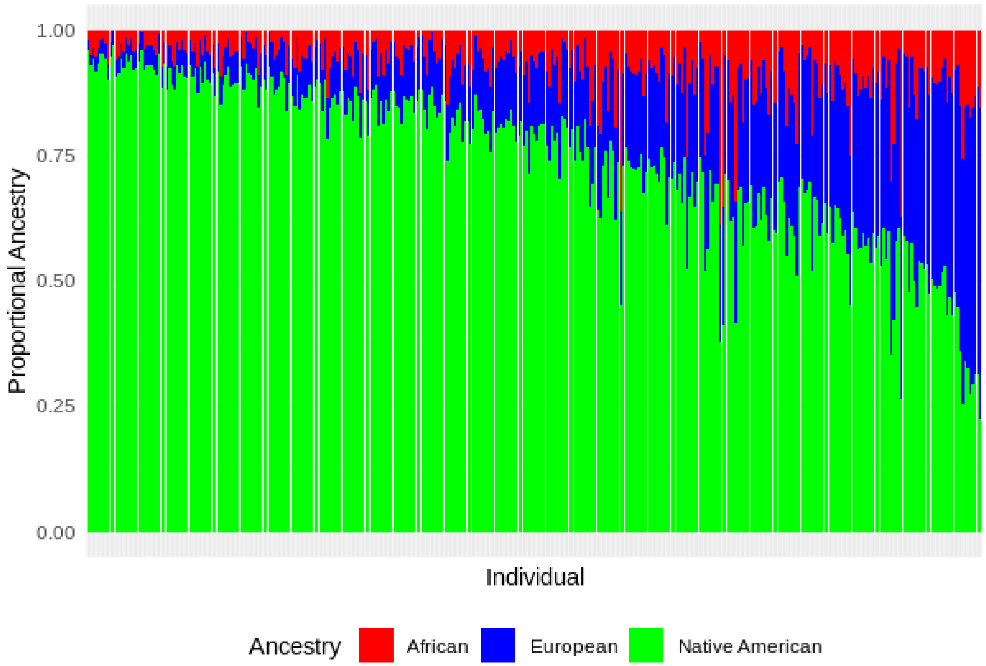
	Ancestry Estimation Analysis	% African Ancestry	% European Ancestry	% Native American Ancestry
Peru	ROH Consensus	7.88	17.47	74.63
	ROH Overlap with MHAS	14.3	32.91	52.77
MHAS	ROH Consensus	6.005	30.88	63.112
	ROH Overlap with Peru	9.75	28.58	61.65

Ancestry Analysis of most prevalent ROH Regions in Peru and MHAS Individuals

MHAS ROH Consensus region Ancestry



Peru ROH Consensus region Ancestry



ROH Overlap across Peru and MHAS Individuals

Chromosome	ROH Start in Peruvians	ROH End in Peruvians	AD Association P.value of ROH in Peruvians	ROH Start in Mexicans	ROH End in Mexicans	AD Association P.value of ROH in Mexicans
chr11	67091366	67162648	0.027	67079036	67101104	0.008
chr11	66712424	66883030	0.04	66812101	66866926	0.002
chr11	66712424	66883030	0.04	66874932	66882056	0.002
chr11	66985343	66996649	0.02	66966090	67035216	0.0002
chr15	43473780	43823394	0.03	43617388	43641743	1.24E-05
chr15	43473780	43823394	0.03	43709894	43722950	1.24E-05
chr15	43473780	43823394	0.03	43798714	43900890	1.24E-05
chr15	43213957	43239213	0.01	43225356	43251546	0.006

Fine-mapping of overlapping ROH region in Peru and MHAS

Meta Analysis for the ROH overlap region in Chr-11 and 15

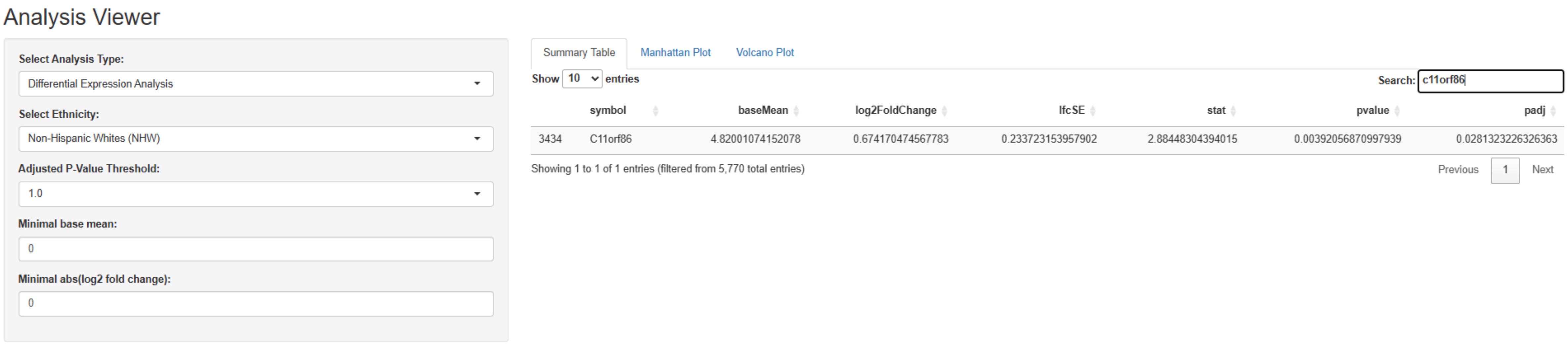
Chromosome	Gene	SKATO P.value
11	C11orf86	0.04

For all chromosomes

MHAS Rare Gene-based Analysis

Chromosome	Gene	SKATO P.value
18	NOL4	0.01
19	LINC01224	0.02
19	ZNF675	0.03
19	ZNF568	0.03
19	ZNF585A	0.04
19	ZNF420	0.05
	Peru Gene-based Analysis	
21	GRIK1-AS2	0.003
	Meta Analysis	
18	NOL4	0.0009
19	ZNF675	0.002
19	IPO5P1	0.03
19	ZNF91	0.03
14	LRRC9	0.04

Differential Expression Analysis of C11orf86 in Non-Hispanics



Analysis Viewer

Select Analysis Type: Differential Expression Analysis

Select Ethnicity: Non-Hispanic Whites (NHW)

Adjusted P-Value Threshold: 1.0

Minimal base mean: 0

Minimal abs(log2 fold change): 0

Show 10 entries

Search: c11orf86

	symbol	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
3434	C11orf86	4.82001074152078	0.674170474567783	0.233723153957902	2.88448304394015	0.00392056870997939	0.0281323226326363

Showing 1 to 1 of 1 entries (filtered from 5,770 total entries)

ADSP R5 Umbrella ROH Fine-mapping

Race	Ethnicity	Total ROH	Prevalent CON ROH	ROH significantly associated with AD
White	Hispanics	112614	3396	60
White	Non-Hispanics	372082	11267	924
Asian	Korean (KBASE + GARD)	131514	5781	109

ADSP R5 Umbrella ROH Fine-mapping (Rare Variants Gene-based Analysis)

Gene	p.val
MHAS	
NOL4	0.01
ZNF675	0.03
ZNF568	0.03
Peru	
GRIK1-AS2	0.003
ADSP Whites (Hispanics)	
MACF1	0.01
ST3GAL2	0.02
NEGR1	0.02
MMP16	0.03
ADSP Whites (Non-Hispanics)	
DPP10	0.01
HEXA	0.007
RIT2	0.02
ADSP Asian (GARD + KBASE)	
NEGR1	0.01
PDE4D	0.03
DPP10	0.03
Meta Analysis	
VPS13B	0.001

Conclusion

- ROH analysis reveals rare, recessive variants missed by traditional GWAS.

- ROH fine-mapping reveals Alzheimer’s-linked regions in Peruvians, Mexicans, and ADSP cohorts.

- Chromosomes 11 and 15 show ancestry-driven homozygous regions tied to AD risk.

- Key genes: MMP16, MACF1, NEGR1, ST3GAL2 (White Hispanics) and DPP10, HEXA, RIT2 (Non-Hispanic Whites).

- Highlights the value of ancestry-informed analysis and ROH fine-mapping in AD research.

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