

eQTL Fine-Mapping Analysis of Variants Within Alzheimer Disease Loci Across Ancestries in the Alzheimer Disease Genomics Consortium (ADGC)

Michelle Grunin*, Penelope Benchek*, Yeunjoo E Song*, Makaela Mews, Yousef Mustafa, Nicholas A Kushch, Farid Rajabli, Giuseppe Tosto, Brian W Kunkle, Li-San Wang, Lindsay A Farrer, Richard Mayeux, Margaret A Pericak-Vance, Gerard D Schellenberg, Gyungah R Jun, Christiane Reitz, Adam C Naj, William S Bush*, Jonathan L Haines*, ADGC: For full list of affiliations please see abstract

PURPOSE

Fine-mapping of GWAS is critical for determining causative relevance of variants in associated loci. Looking at multiple ancestries to determine which variants are most informative for specific/across ancestries helps clarify pathogenesis and treatment implications.

METHODS

We leveraged ADGC data including Europeans(EUR), Hispanic(HIS), African(AFR) and East Asian(EAA) ancestries(37,382 EUR/8,899 HIS/6,728 AFR/3,232 EAA). We examined GWAS results for 12 AD loci with cross-ancestry information:CR1, BIN1, TREM2, CD2AP, PTK2B, CLU, SHARPIN, MS4A6A, PICALM,ABCA7, LRR4C4 and LHX5-AS1. All variants in these genes were analyzed in 2 fine-mapping models via meSuSie :EUR/HIS/AFR(3-ancestry) and adding EAA comprising less variants(4-ancestry) to determine which ancestries play the largest role in association. Variants with PIP score > 0.5 were included and have results credible in >1 ancestry. The credible variants were examined in 7 eQTL databases: ROSMAP,BrainSeq, Common Mind and gTEX (EUR only) , MAGENTA TensorQTL, MESA, and MetaBrain(multi-ancestry)to determine eQTL involvement. eQTL data was generated from immune cells, whole body systems and brain data.

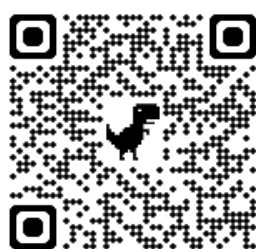
RESULTS

10/36 variants were significant eQTL(P<0.05) in MESA affecting monocyte gene expression incoding areas in only one ancestry, indicating specificity, while 26 were significant in >1 ancestry(3-ancestrymodel). Most significant eQTLs in >1 ancestry were rs1582763, rs17057043, rs28834970, and rs472486(P<1x10-8=multiple ancestries). Multiple variants were significant eQTLs in MAGENTA in >1 ancestry and whole blood data split via CIBERSORTx(P<0.01). In addition, eQTL variants in MAGENTA and CIBERSORTx had significant interaction with AD status(P<0.05). All variants found as eQTL in >2 ancestries were significant eQTLs in 4 ancestries. 19/36 variants having multi-ancestry components(EUR,HIS,AFR) were brain eQTLs(P<0.05) including some splice QTLs (n=4), including hippocampus, cerebellum, cortex, and caudate. 4/19 loci with variants credible in >1 ancestry were brain eQTLs in >1/8 databases(P<0.01). In MetaBrain, the variants were found to regulate 286 genes(MetaBrain P<0.05), with 3 that were significant eQTLs in AFR, EAS, and EUR. 5 variants were significant eQTL in cortex in EUR and AFR only, while 1 variant was a cortex eQTL in EUR and EAS only.

CONCLUSIONS

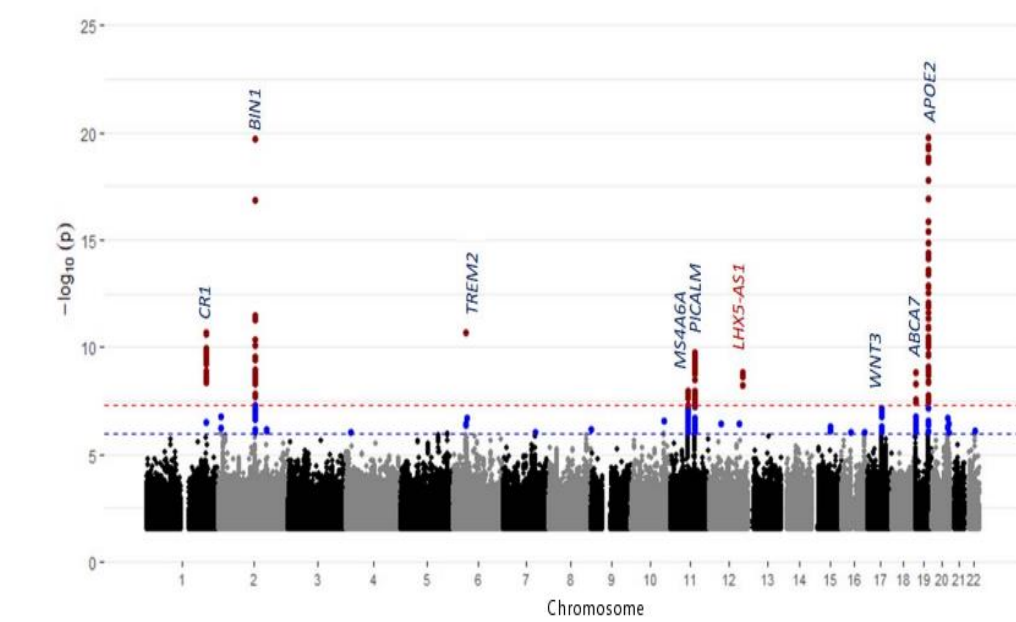
This analysis indicates that ADGC GWAS fine-mapping variants are eQTLs in monocyte and brain tissues across multiple ancestries or ancestry-specific. This indicates important roles in AD pathogenesis. This reemphasizes the role of ancestry-specific information in AD genetic architecture.

Contact:
mag235@case.edu
or
michelle.grunin@gmail.com
or via my website here:

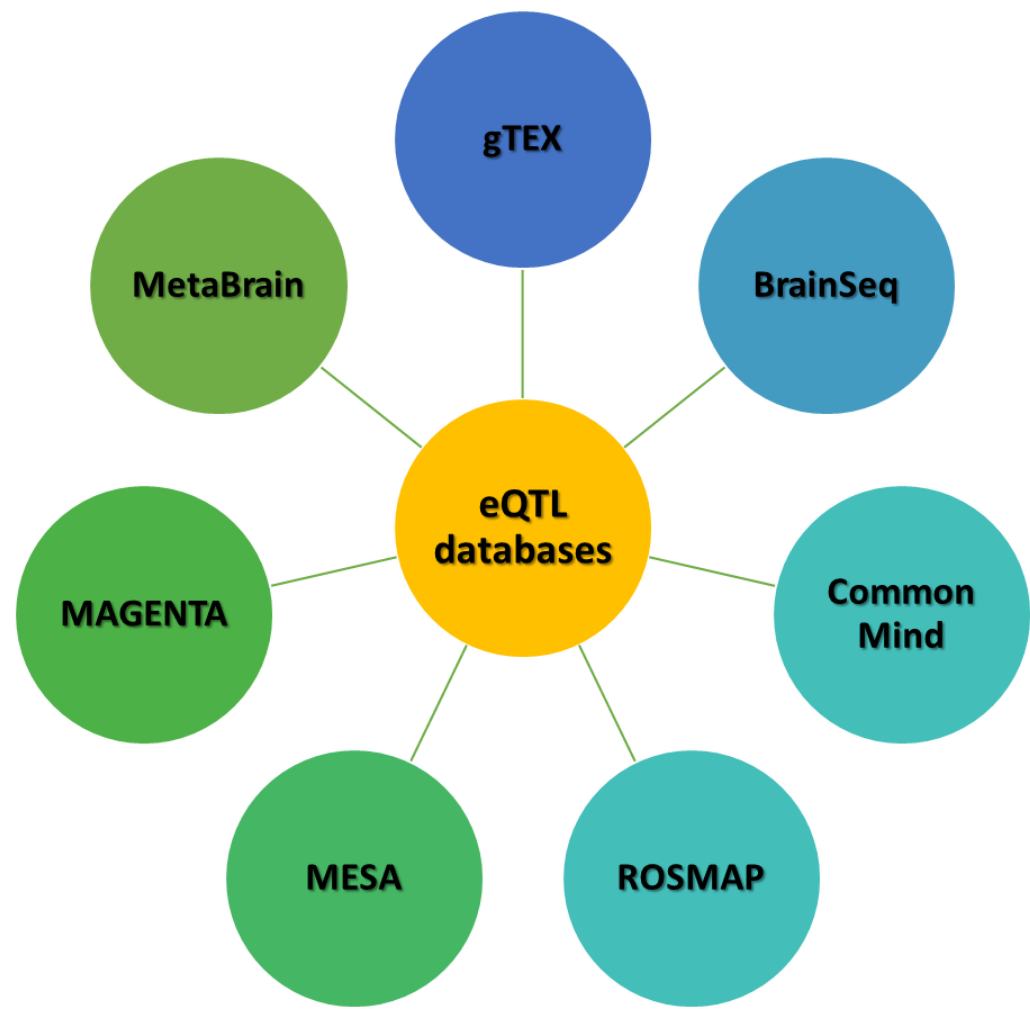
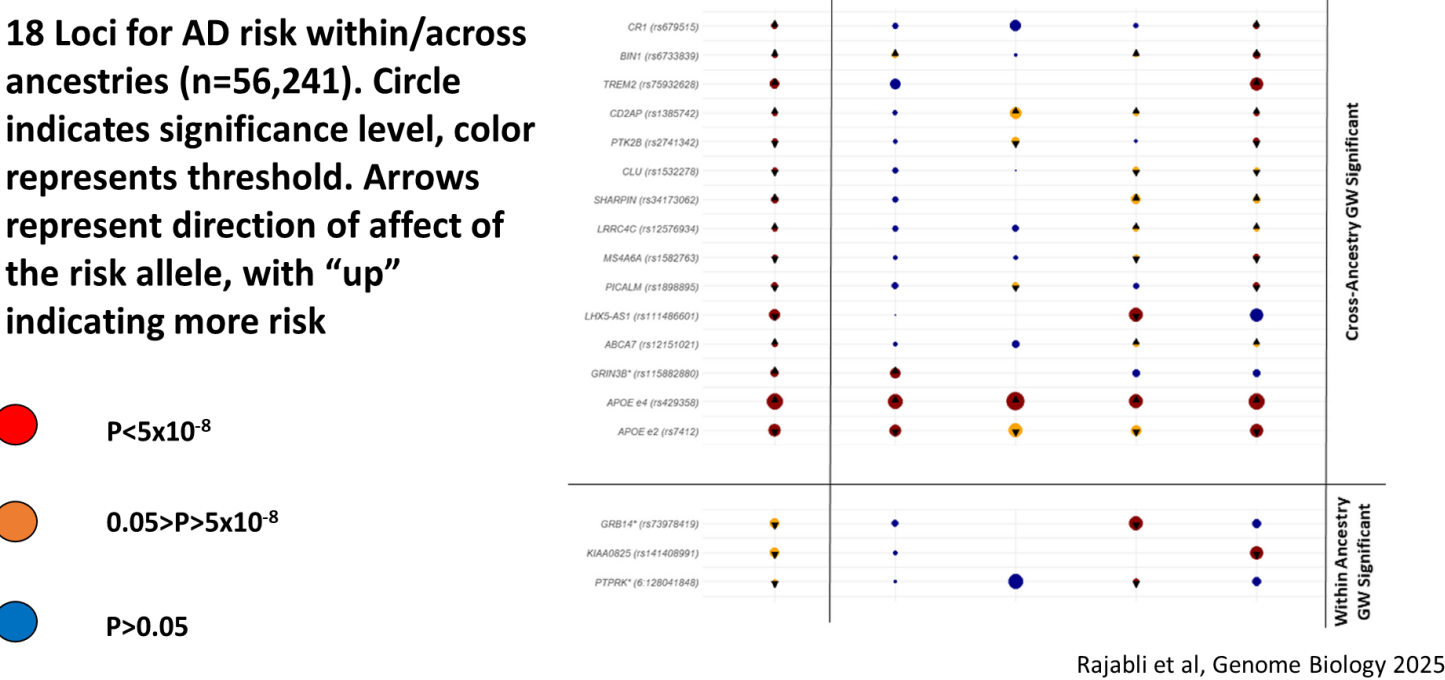


Funding Sources: *Michelle Grunin: BrightFocus Foundation (M2021006F)
Disclosures: None

Largest Multi-Ancestry Analysis of the ADGC



Within Ancestry Analysis: ADGC Multi-Ancestry



MESA eQTL			
Significance by number of *			
(<0.05, 0.01, 0.001)			
	Gene	NHW	AA
rs10779335	CR1	*	-
rs11680911	BIN1	*	*
rs11756893	TREM2	*	-
rs11787077	TREM2	*	-
rs1532276	CLU	*	-
rs1532277	CLU	*	-
rs1582763	MS4A6A	***	*
rs17057043	PTK2B	**	*
rs2281256	TREM2	*	-
rs28834970	PTK2B	**	*
rs472486	PICALM	***	**
rs497816	PICALM	*	*
rs519961	PICALM	*	*

MESA eQTL			
Significance by number of *			
(<0.05, 0.01, 0.001)			
	Gene	NHW	AA
rs526904	PICALM	*	*
rs566975	PICALM	*	*
rs573167	PICALM	*	*
rs586274	PICALM	*	*
rs6987305	PTK2B	*	*
rs73223431	PTK2B	*	*
rs7561528	BIN1	*	*
rs7740963	CD2AP	*	-
rs867230	CLU	*	-
rs9331896	CLU	*	*
rs9369693	CD2AP	*	-
rs9381562	CD2AP	*	*
rs9473117	CD2AP	*	*

Ancestry Specific eQTLs in MESA
9 were significant eQTLs (P<0.05) **in only one ancestry**
Multi-ancestry eQTLs in MESA
26 were significant **in >1 ancestry** (3-ancestry model).
The most significant eQTLs in >1 ancestry were rs1582763, rs17057043, rs28834970, and rs472486 (P<1x10-8)

Examples of eQTLs shared across all ancestries in multi-ancestry eQTL databases:

Variant	Gene	MAGENTA Tensor eQTL			MESA		MetaBrain		
		NHW	CH	AA	NHW	AA	AFR	EAS	NHW
rs28834970	PTK2B	✓✓✓	✓✓	✓✓✓	✓✓	✓	✓	✓	✓
rs1532276	CLU	✓	✓	✓✓	✓	NA	✓		✓
rs4147919	ABCA7	✓✓	✓✓✓	✓✓	NA	NA	✓	✓	✓
rs519961	PICALM	✓✓	✓	✓	✓	✓	✓		✓

P<0.0001 = 3 checkmarks
P<0.001 = 2 checkmarks
P<0.05 = 1 checkmark
NA= Not Present in Dataset
Blank = Not Significant

- 21/40 variants are significant eQTLs in multiple ancestries, in several brain or monocyte studies, rather than being specific to any one specific ancestry.

Examples of eQTLs **specific to specific ancestries** in multi-ancestry eQTL databases:

Variant	Gene	MAGENTA Tensor eQTL			MetaBrain		
		NHW	CH	AA	AFR	EAS	NHW
rs34173062	SHARPIN	✓					✓
rs114812713	TREM2	✓					✓
rs9395283	CD2AP			✓			
rs2070926	CLU	✓✓		✓	✓		✓

P<0.0001 = 3 checkmarks
P<0.001 = 2 checkmarks
P<0.05 = 1 checkmark
NA= Not Present in Dataset
Blank = Not Significant

6/40 variants are significant eQTLs in only a **single ancestry**, and 3/40 are **only in two ancestries**, in several brain or monocyte studies, indicating precision via fine-mapping analysis

eQTL NHW Database Selected				
Variant	Gene	Significant Y/N in gTEX, CommonMind, ROSMAP DLDPFC, BrainSeq	eQTL in BRAIN AREA for Gene	Brain Area
rs10779335	CR1	Y, Y, N, Y	CR1 or CR2	Caudate, Putamen, Nucleus, Frontal Cortex, Amygdala, Hippocampus, Cortex (CR2)
rs867230	CLU	Y, Y, N, N	CLU	Nucleus Accumbens, Basal Ganglia, Cerebral Hemisphere, Frontal Cortex, Putamen
rs4147922	ABCA7	Y, N, Y, Y	ARGHAP45 or POLR2E	Cerebellum, Cerebral Hemisphere
rs73223431	PTK2B	Y, N, N, N	PTK2B, CHRNA2, TRIM35	Cerebellar Hemisphere
rs28834970	PTK2B	Y, N, N, N	PTK2B, CHRNA2, TRIM35	Cerebellar Hemisphere Cortex, Cerebellar Hemisphere
rs4147919	ABCA7	Y, N, N, N	TMEM259	

- Amongst the 40 variants that were significant in fine mapping analysis
- 27 were eQTLs in NHW eQTL databases (P<0.05) in brain tissue including hippocampus, cerebellum, cortex and caudate.
 - 3 variants were eQTL in brain tissue in **more than one database** (P<0.05).
 - Some eQTLs **affect genes that are not the original variant locus**.

MetaBrain Multi-Ancestry eQTL				
SNP	Gene	AFR	EAS	NHW
rs28834970	PTK2B	Yes	Yes	Yes
rs6987305	PTK2B	Yes	Yes	Yes
rs9349416	CD2AP	Yes	No	Yes
rs2070926	CLU	Yes	No	Yes
rs4147919	ABCA7	Yes	Yes	Yes
rs519961	PICALM	Yes	No	Yes
rs867230	CLU	Yes	No	Yes
rs1532276	CLU	Yes	No	Yes
rs4663105	BIN1	No	Yes	Yes

- In the same 40 variant list, they were found to **regulate 286 genes (P<0.05) with 3 variants significant in AFR, EAS, and NHW samples**.
- 5 variants were significant eQTL in cortex in **NHW and AFR only**
1 variant was significant eQTL in cortex in **NHW and EAS only**

Same Variant Regulates Differentially in Different Ancestries

Most Significant Variants:

- rs4147919: which regulated **TMEM259** in cortex in NHW (P=7.98E-18)
- rs6987305: which regulates **TRIM35** in cortex in NHW (P1.47E-14)

rs4147919 regulates different genes in cortex **per ancestry** (P<0.05):

Ancestry	Genes Regulated by rs4147919 eQTL variant				
AFR	REEP6	OR4F17	PRTN3	TCF3	CBARP
EAS	PRSS57	C2CD4C	RPS15	PALM	