Association of Common and Rare Variants with Alzheimer's Disease in 16,905 Individuals with Whole-Genome Sequence (WGS) Data from the Alzheimer's Disease Sequencing Project (ADSP)

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Contacts:
wan-ping.lee@pennmedicine.upenn.edu
gpeloso@bu.edu

Wan-Ping Lee[1,2], Seung Hoan Choi[3], Collaboration on Alzheimer's Disease Research (CADRE), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), Gerard D Schellenberg[1,2], Anita L Destefano[3,4], Jonathan L Haines[5,6], Gina M Peloso[3]

[1]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, PA, USA; [2]Penn Neurodegeneration Genomics Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; [3]Department of Biostatistics, Boston University School of Public Health, MA, USA; [4]Department of Neurology, School of Medicine, Boston University, MA, USA; [5]Department of Population and Quantitative Health Sciences, School of Medicine, Case Western Reserve University, OH, USA; [6]Cleveland Institute for Computational Biology, School of Medicine, Case Western Reserve University, OH, USA

ABSTRACT: We examined the association between AD and common variants as well as aggregates of rare coding and noncoding variants in 13,371 individuals of diverse ancestry with WGS data from ADSP, including 6,519 AD cases and 6,852 controls (African Americans: 1,137 cases and 1,707 controls; Hispanics: 1,021 cases and 1,988 controls; Non-Hispanic Whites: 4,230 cases and 3,109 controls).

In addition to *APOE*, we identified variants near or in *CR1*, *BIN1*, and *LINC00320* associated with AD. We also observed a haplotype on chromosome 14 spanning multiple genes, including *PSEN1*, associated with AD in a Hispanic subgroup. Rare coding and noncoding variant aggregates in this region are also associated with AD.

Finally, we observed suggestive aggregates of coding rare variants in *ABCA7*, including frameshift deletions, in the non-Hispanic White subgroup (p=5.35x10-6), and rare noncoding variants in the promoter of *TOMM40* associated with AD, distinct from *APOE* using the pooled samples (p=7.21x10-8). Taken together, the findings from our study suggest that WGS has the potential to identify rare and novel genetic loci.

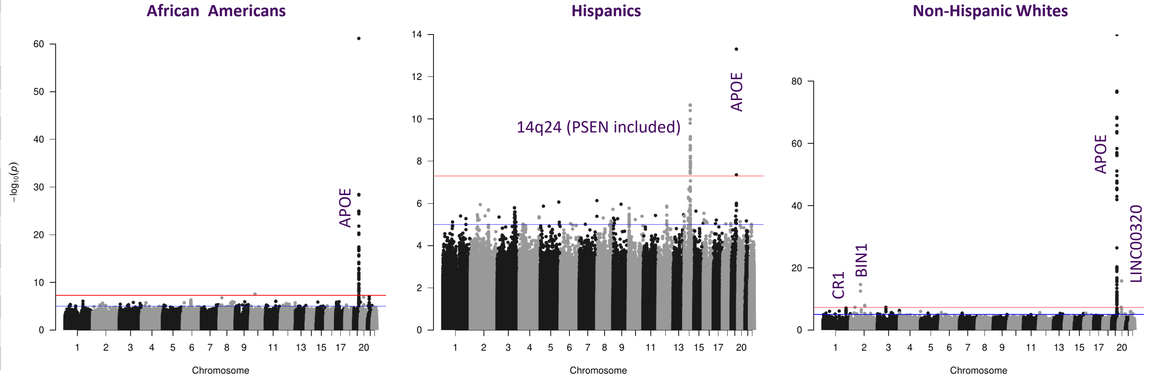
Significant single variants associated with AD

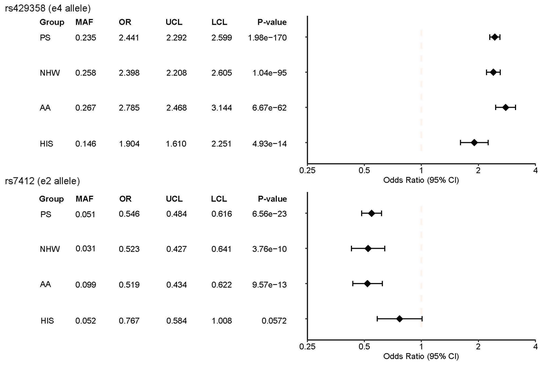
Variants*	Gene	RSID	Group	MAF	beta	p-value**
1-207510847-T-G	CR1	rs12037841	NHW	0.201	-0.236	$7.79x10^{-08}$
2-127133851-A-C	BIN1	rs4663105	PS	0.470	0.150	$3.20x10^{-09}$
			NHW	0.427	0.200	$1.17x10^{-08}$
14-73615125-C-T	(various)	rs9671262	HIS	0.005	2.955	$2.21x10^{-11}$
19-44908684-T-C	APOE	rs429358	PS	0.230	0.89	$1.98x10^{-170}$
			AA	0.267	1.024	$6.67x10^{-62}$
			HIS	0.145	0.644	$4.93x10^{-14}$
			NHW	0.258	0.875	$1.04x10^{-95}$
21-20730315-G-A	LINC00320	rs144204759	AA	0.018	1.225	$1.85x10^{-09}$

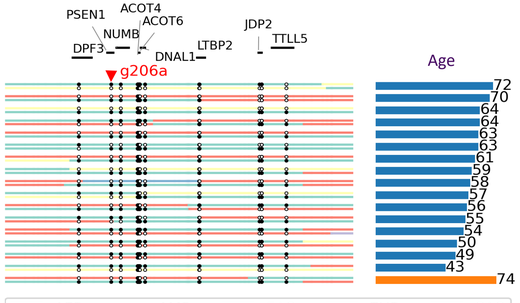
*Coordinates in GRCh38; **Where more than one was significant for a linked gene, the most significant p-value, either with or without APOE adjustment, is reported for each gene; NHW, non-Hispanic White; PS, pooled samples; HIS, hispanic; AA, African American

Aggregates of rare variants in noncoding sets with AD

Group	Gene name	Chr	Category	# variants	STAAR-O p-value*
PS	TOMM40	19	Promoter (DHS)	134	$7.21x10^{-08}$
PS	ELMSAN1	14	Enhancer (DHS)	1133	$1.81x10^{-09}$
PS	EIF2B2	14	Enhancer (DHS)	1240	$3.18x10^{-08}$
PS	MIR4505	14	ncRNA	7	$2.40x10^{-11}$
HIS	PTGR2	14	Promoter (CAGE and DHS)	7	$8.85x10^{-12}$
HIS	ELMSAN1	14	Enhancer (DHS)	366	$3.11x10^{-11}$
HIS	PTGR2	14	Enhancer (CAGE)	153	$5.89x10^{-11}$
HIS	ACOT6	14	Enhancer (DHS)	33	$4.23x10^{-10}$
HIS	ELMSAN1	14	Promoter (DHS)	55	$8.84x10^{-10}$
HIS	ACOT4	14	Promoter (CAGE)	6	$9.29x10^{-10}$
HIS	ACOT4	14	Enhancer (CAGE)	9	$9.79x10^{-10}$







Local ancestry analysis of G206A (in *PSEN1*) carriers to indicate that mutations in 14q24 are based on a founder event of an African.