Multiple Loci Influencing Hippocampal Degeneration Identified by Genome Scan

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No Disclosures

The Endophenotype Advantage

- APOE + 10 GWAS loci account for ~ 35% of genetic variance for AD
- Where is the "missing heritability?"

  Answer: Small(er) effect loci, rare variants, structural variants, gene-gene & gene-environment interactions

  ➔Requires extremely large samples to address
- AD complex phenotype
- Endophenotypes (MRI, cognitive, biomarker) can increase signal-to-noise ratio

Study Populations for MRI Trait GWAS

Multi Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study

- Caucasian and African American families containing primarily discordant sib pairs
- Cross-sectional, single time-point
- Semi-quantitative MRI measures of neurodegeneration (HV, TCV) and cerebrovascular disease (WMH) included in study

Alzheimer's Disease Neuroimaging Initiative (ADNI)

- Unrelated subjects
- Quantitative volumetric measures
- Baseline + Longitudinal follow-up

AD	:	MCI	:	CON
1	:	2	:	1

Subject Characteristics

	PHASE ONE (Genome Wide)		
	ADNI		
Class	AD	MCI	CON
Sample Size	168	336	188
Age (S.D.)	75.4 (7.6)	75.2 (7.1)	75.0 (4.9)
Freq APOE ε4	0.420	0.342	0.144

Subject Characteristics

	PHASE ONE (Genome Wide)				
	ADNI			MIRAGE Caucasian	
Class	AD	MCI	CON	AD	CON
Sample Size	168	336	188	454	537
Age (S.D.)	75.4 (7.6)	75.2 (7.1)	75.0 (4.9)	73.2 (8.3)	69.0 (8.7)
Freq APOE ε4	0.420	0.342	0.144	0.291	0.194

Subject Characteristics

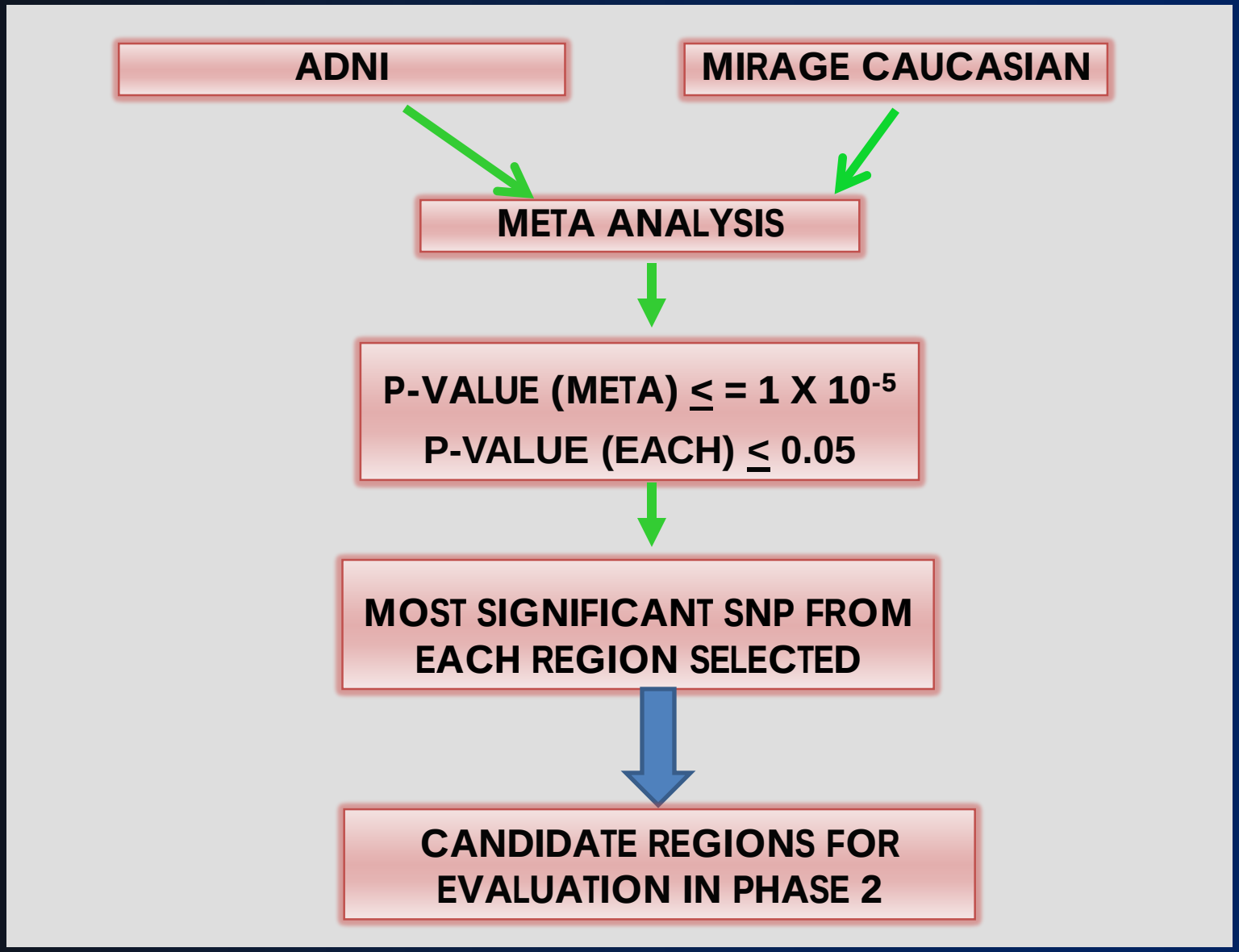
	PHASE ONE (Genome Wide)					PHASE TWO (Regions)	
	ADNI			MIRAGE Caucasian		MIRAGE African American	
Class	AD	MCI	CON	AD	CON	AD	CON
Sample Size	168	336	188	454	537	188	231
Age (S.D.)	75.4 (7.6)	75.2 (7.1)	75.0 (4.9)	73.2 (8.3)	69.0 (8.7)	74.7 (9.4)	68.4 (10.2)
Freq APOE ε4	0.420	0.342	0.144	0.291	0.194	0.335	0.205

ADNI Subjects With MRI Trait Data by Visit

VISIT	MRI Trait		
	HV	TCV	WMH
Baseline	688	688	692
6 months	---	---	631
12 months	591	591	592
18 months	---	---	253
24 months	---	---	472
36 months	---	---	264
48 months	---	---	33
Non scheduled visit	---	---	64

HV = hippocampal volume
TCV = total cerebral volume
WMH = white matter hyperintensities

Phase 1: GWAS in Two Caucasian datasets



Data Analysis

Illumina Infinium Chip	ADNI	MIRAGE
Human 610-Quad BeadChip	Y	Y
HUmanCNV370-Duo		Y

Genotype Imputation

MaCH; HapMap 2 and 3 reference SNP panels

Quality Control

Excluded SNPs: MAF < 3%, not in HWE ($p<10^{-6}$), $r^2<0.8$

Association Testing – GEE

familial correlation (MIRAGE)

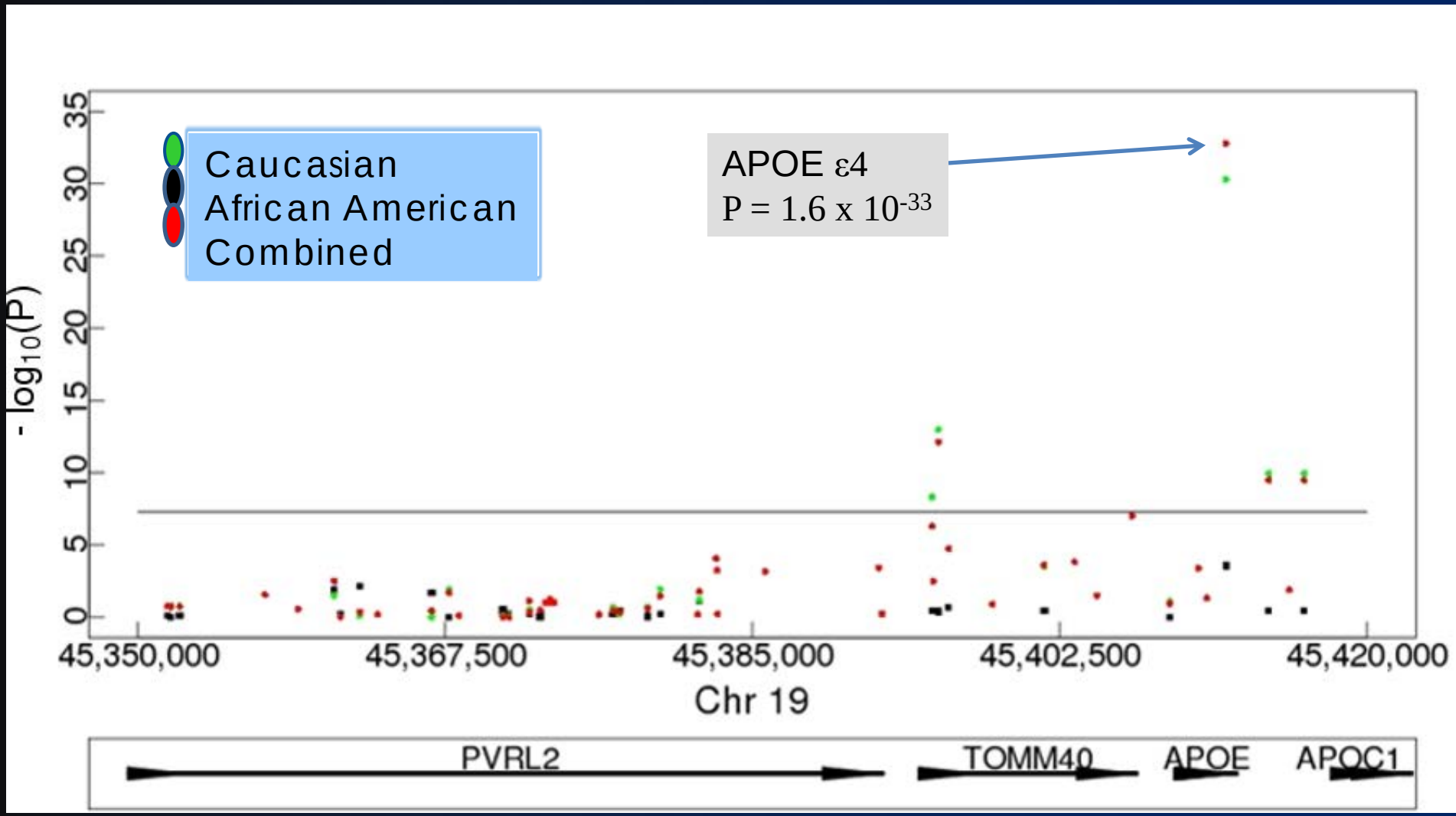
repeated measures (ADNI)

GWAS (Phase 1) Regions of Interest

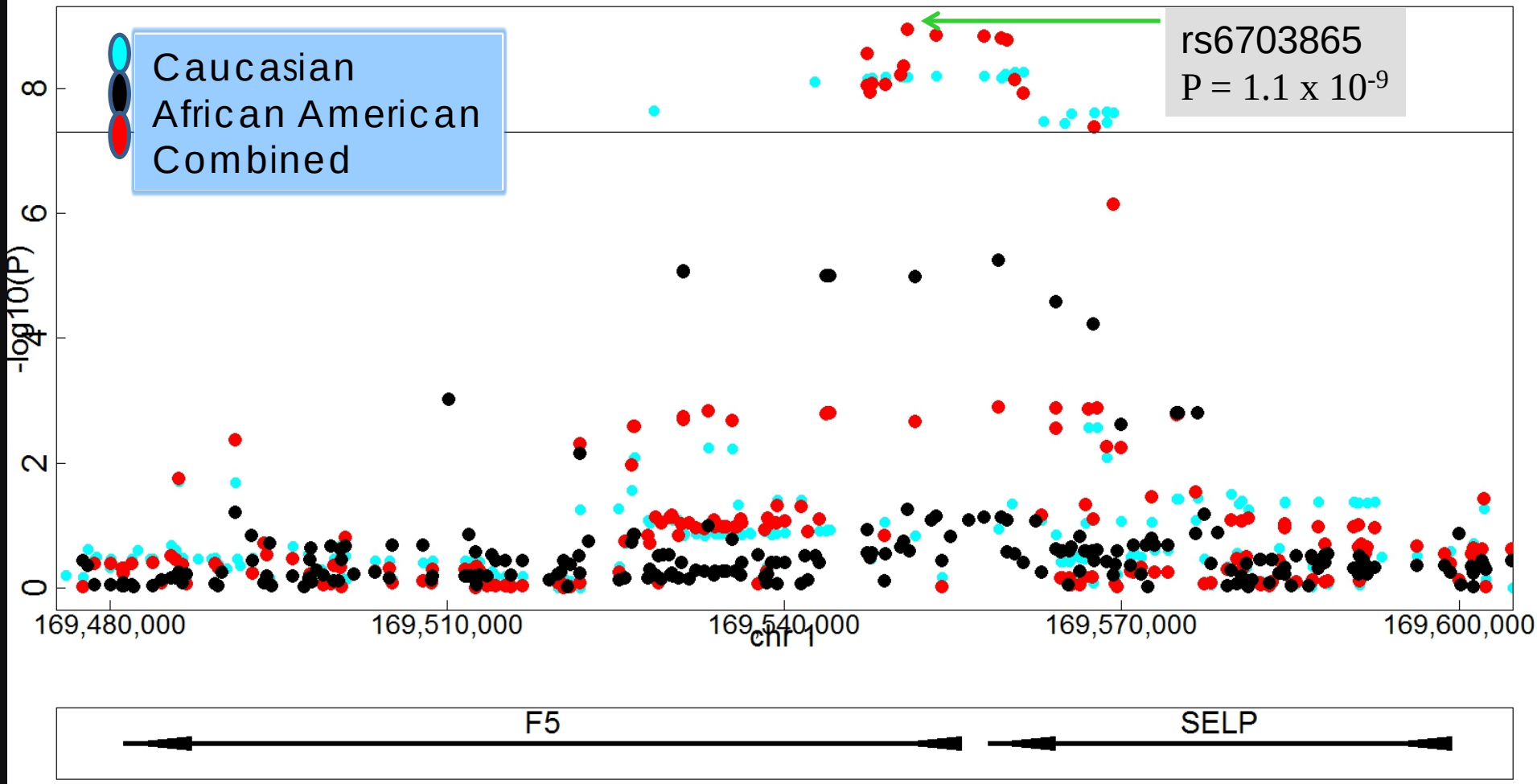
Trait	Number
Hippocampal Volume	14
Total Cerebral Volume	3
White Matter Hyperintensities	5

ROI's Tested in African Americans in Phase 2

Hippocampal Volume



Hippocampal Volume



Other Notable Results – HV

LHFP	ADNI	MIRAGE Cauc.	META WHITE	MIRAGE Afr.Am	META ALL	Dir of Effect
rs9315702	8.8×10^{-4}	9.9×10^{-5}	4.8×10^{-7}	1.1×10^{-2}	1.5×10^{-8}	---
rs7996238	1.8×10^{-1}	6.8×10^{-3}	5.3×10^{-3}	6.1×10^{-3}	2.8×10^{-4}	---

PICALM	ADNI	MIRAGE Cauc.	META WHITE	MIRAGE Afr.Am	META ALL	Dir of Effect
rs596864	4.7×10^{-3}	2.0×10^{-4}	4.8×10^{-6}	6.0×10^{-1}	1.0×10^{-5}	---
rs17148741	2.9×10^{-1}	3.1×10^{-1}	1.4×10^{-1}	9.4×10^{-5}	8.6×10^{-1}	+++

Other Notable Results

Hippo. Vol. GCFC2	ADNI	MIRAGE Cauc.	META WHITE	MIRAGE Afr.Am	META ALL	Dir of Effect
rs2298948	4.2×10^{-4}	2.8×10^{-3}	3.9×10^{-6}	2.0×10^{-3}	4.9×10^{-8}	---

Cerebral Vol SYNPR	ADNI	MIRAGE Cauc.	META WHITE	MIRAGE Afr.Am	META ALL	Dir of Effect
rs935753	1.3×10^{-2}	5.5×10^{-1}	1.3×10^{-1}	7.1×10^{-5}	2.1×10^{-1}	-++
rs11708252	5.5×10^{-5}	1.7×10^{-2}	4.0×10^{-6}	5.2×10^{-1}	1.2×10^{-3}	--+

White Matter Hyperintens.	ADNI	MIRAGE Cauc.	META WHITE	MIRAGE Afr.Am	META ALL	Dir of Effect
APOE	1.4×10^{-1}	5.6×10^{-3}	9.2×10^{-1}	9.0×10^{-1}	9.5×10^{-1}	-+-

Hippocampal Volume Genes

Factor V

- essential co-factor of blood coagulation cascade
- Leiden variant associated with risk of vascular dementia and perhaps AD in Rotterdam Study

P-Selectin

- Granule membrane protein that mediates interaction of activated endothelial cells or platelets with leukocytes
- Stellos et al. *J Cereb Blood Flow Metab* 2010
  - Higher levels – AD fast cognitive decline
  - Lower levels – AD slow cognitive decline

Cerebral Volume Genes

Synaptoporin

- Membrane protein of synaptic vesicles involved in uptake storing, docking and regulating release of neurotransmitters
- Highly conserved protein
- Two splice variants
- Expressed only in brain

Summary and Conclusions

- In a biracial sample with multiple ascertainment schemes, identified genome significant association of HV with *APOE, F5/SELP, LHFP* and *GCFC2*.
  - All supported by evidence in 3 datasets
  - *GCFC2* result less certain since evidence with only one SNP
  - GW significance with endophenotypes obtained in sample of 2,100
    ➔ ~ 10 times smaller sample than needed for GWAS of AD risk
- Strong evidence for association of TCV with *SYNPR* in whites and African Americans
- Except *GCFC2*, different SNPs in same gene associated in whites and African Americans
  - Allelic heterogeneity
  - Population differences in linkage disequilibrium structure

Summary & Conclusions

- No evidence for association of WMH with *APOE*
  - Consistent with hypothesis that APOE mechanisms of action is through neurodegenerative pathway (e.g., amyloid-β recycling)
- No evidence for association of HV with rs7294919 (between *HRK* and *FBXW8*), *MSRB3*, or *WIFI* as reported in much larger GWAS (Bis et al & Stein et al, *Nature Genetics* 44, 2012)
  - False negative results due to lower power
  - Genes influencing hippocampal changes concomitant with AD are different from those associated with normal aging
- Full details: Melville et al, *Ann Neurol*, *72: 65-75*

Who did the work and supported it

Boston University

Scott Melville
Jacki Buros
Tony Parrado
Badri Vardarajan
Mark Logue
Gyungah Jun
Kathy Lunetta
Clint Baldwin

Indiana University

Andrew Saykin
Li Shen
Shannon Risacher
Sungeun Kim

Charles DeCarli
MIRAGE Investigators
ADNI Investigators

NIA (R01-AG09029, R01-AG025259, P30-AG13846, P30-AG010129 and K01 AG030514) and the Dana Foundation; ADNI supported by U01 AG024904 and RC2 AG036535 (PI: Michael Weiner)

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Ultimate Goal