

ADNI - Alzheimer's Disease Neuroimaging Initiative

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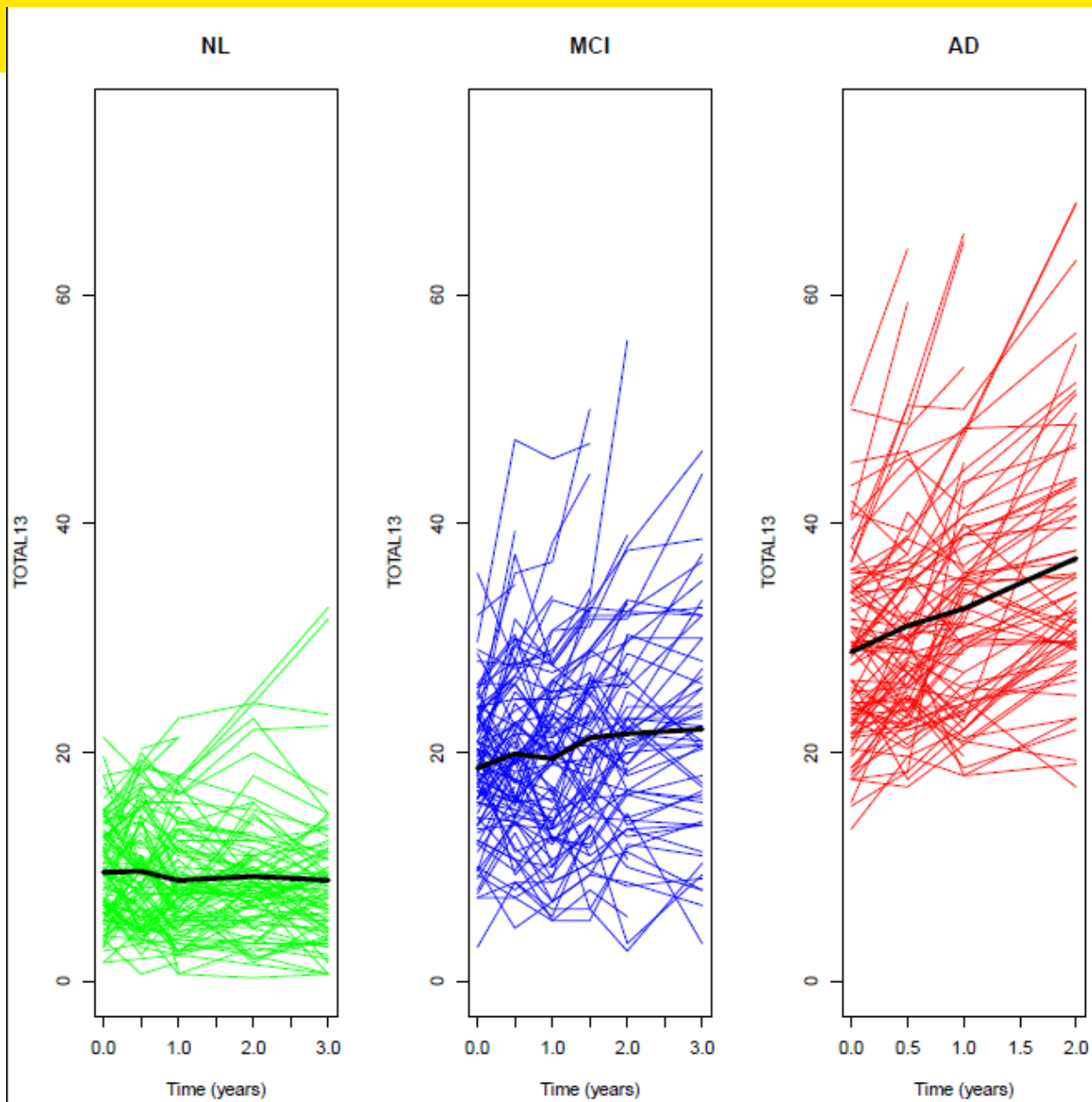
Laurel Beckett UC Davis

**Relevant Disclosures: ADNI PET Core member; ADNI Genetic Core co-head; ADNI Systems Biology Core member; grant and data analysis support for ADNI via ATRI and UCSF
Selected and possibly idiosyncratic view**

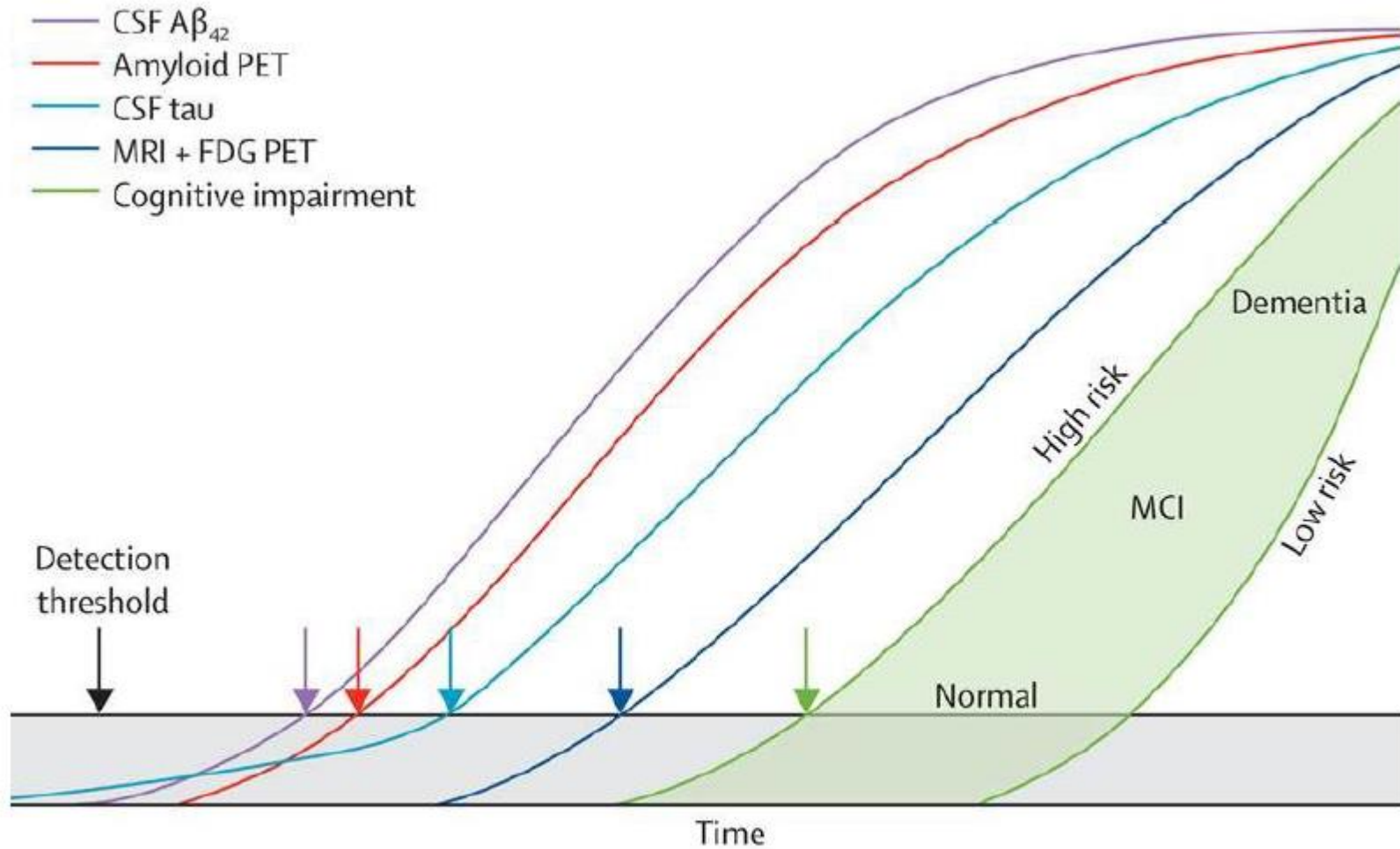
ADNI - Alzheimer's Disease Neuroimaging Initiative

- Large public-private partnership (Weiner, UCSF, PI)
- Over 57 sites in the US and Canada – Goals:
 - Identify optimal methods to measure the progression of MCI and early AD
 - Aid in the development of new treatments and monitor their effectiveness
 - Shorten the time and cost of clinical trials
- Characterize the entire spectrum of Alzheimer's disease, including pre-clinical stages
- Provide Data to help develop most effective clinical trial scenarios
- Currently clinical/neuropsych, structural MRI data, amyloid PET and CSF biomarkers on over 1000 people.
- New data on tau PET, expanded MRI, internet assessments
- Structured prospective observational study

Change in ADAS-Cog



Hypothetical Model of Onset of AD



Jack CR Jr, et al. Update on hypothetical model of Alzheimer's disease. *Lancet Neurology* (2013); 12:207-216

ADNI Study Designs Phases

ADNI-1: 200 Healthy; 400 MCI; and 200 mild AD

ADNI-GO (2009-2011)

- Added early-MCI group (n=200)

- Collect (FDG and amyloid PET), MRI, LP on everyone

ADNI-2 (2011-2016)

- Enrolled new Normals (n=150), early MCI (n=150), MCI (n=150), AD (n=200)

- Later added small group of Normals with memory complaints (Significant Memory Concern)

- Added experimental MRI sequences (fMRI, DTI, ASL)

ADNI-3 (2017-)

- Adding computerized cognitive instrument (CogState)

- Adding tau-PET imaging

- Everyone will get ASL, fMRI, DTI

Currently Available Data without Embargo

- Diagnosis and Diagnostic Changes
- Medical History
- Cognitive and functional testing scores
- Genetics
 - ApoE4 status
 - GWAS and methylation
 - Whole genome sequencing
- Fluid markers
 - CSF A β , tau
 - CSF Proteomics (ADNI-1)
 - Metabolomics

Assumptions/Limitations of ADNI

- Participants meant to reflect a clinical trial population
Not population based
- Participants have limited comorbidities
Those with cortical strokes, heart failure, substance abuse, cancer, other major pre-existing conditions excluded
- Age range of ADNI participants (55-90)
May be difficult to detect earliest stages of disease
- Depends on Deliberately Collected Data for this purpose with Extended Standardization and Training

Categories of Key Findings of ADNI

- Over 900 publications using ADNI data
- Relationships between biomarkers and clinical progression
- Patterns of neurodegeneration in disease progression
- Development of novel biomarkers
- Diagnostic accuracy – changed diagnostic criteria
- Identification of novel AD risk alleles
- Improvement of clinical trial efficiency

Data Science Methods using ADNI

- Imaging-based classifiers (features, ROIs)
- Multimodal classifiers
- Composite cognitive function outcome measures
- Prediction of cognitive decline and disease progression utilizing data from multiple modalities
- Statistical methods for GWAS (including imaging genetics) analysis
- Models establishing “order” of biomarker abnormalities
- New models using Systems Biology and Network Analysis to go beyond GWAS

ADNI Data Access & Resources

Data Access with No Embargo

All data publicly available (upon approval of data access)

<http://adni.loni.usc.edu/data-samples/access-data/>

Resources

<http://adni.loni.usc.edu/>

<http://adni-info.org/>

ADNI Ask the Experts/Experts Knowledge Base

<http://adni.loni.usc.edu/data-samples/access-data/>

ADNI FAQ pages and training slides <http://ADNI google group>

<https://groups.google.com/d/forum/adni-data>

Downloads As of July 2014 there have been over 5.6 million downloads of image data (now 15 million) , 322,940 downloads of clinical data, and 5,867 downloads of genetic data by 3,234 separate downloaders

ADNI related studies

- World-wide ADNI
 - European-ADNI
 - Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing (AIBL)
 - Japan ADNI
 - Taiwan
 - Korea
 - China
 - Argentina
- DOD-ADNI (AD biomarkers in Vietnam Veterans with TBI, PTSD, both, or neither)

New focus on early disease

- Placing the Jack model for classic AD on scale of severity and on time scale relative to diagnosis (Donohue 2014)
- Showing heterogeneity in patterns of trajectories: it's not all "amyloid first" (Filshtein, AAIC 2016)
- Earliest signs of problems in everyday function perceived by patients, before informants
- Looking deeper at amyloid+ NL as possible target for early-phase trials.

Predictors of change in ADAS-Cog in MCI (n=312)

MCI	Correlation	p.value							
FDG-R-UCB	-0.30	0.00	■						
Entr thk	-0.26	0.00	■	■					
CSF tau	0.22	0.00	■	■	■				
AV45-R-UCB	0.20	0.00	■	■	■	■			
CSF abeta	-0.18	0.00		■		■	■		
CSF ptau	0.16	0.00					■		
Hpc Vol	-0.13	0.03						■	
Ventricles	0.12	0.03						■	
Entr vol	-0.09	0.12							■
Whole brain	0.01	0.88							■

- Many baseline markers correlated with increase in ADAS-Cog.
- The same top 4 as for conversion to AD.
- Measures sharing colored bar are not different by multiple comparisons.

Predictors of conversion from MCI to AD within 24 m

Marker	EffectSize			
FDG-R-UCB	1.21	Blue		
CSF tau	1.07	Blue		
AV45-R-UCB	1.03	Blue		
Entr thk	1.01	Blue		
Hpc vol	0.92	Blue	Orange	
CSF pTau	0.89	Blue	Orange	
CSF abeta	0.87	Blue	Orange	
Entr vol	0.72	Blue	Orange	Purple
Ventricles	0.41	Blue	Orange	Purple
Whole brain	0.26		Orange	Purple
W mat hyp	0.26			Purple

Measures with highest effect size for predicting conversion are at top.

Effect size: how many SD separate the means for converters and non-converters.

Measures sharing colored bar are not significantly different by multiple comparisons.

Methods: Harvey et al. (2016)

Promising biomarkers for prediction in MCI

- Baseline means for converters and non-converters and also correlate ($|r| \geq 0.2$) with ADAS-COG change:
 - FDG-PET average across regions of interest (Jagust, UCB)
 - CSF tau
 - AV45 region of interest (Jagust, UCB)
 - Entorhinal thickness
- These markers, singly or in combination, could be used to improve clinical trial design by:
 - Inclusion of people more likely to convert,
 - Exclusion of people more likely to stay stable, or
 - Stratifying by risk group.

Assessing biomarkers in NL is harder

- Prediction of short-term conversion to MCI is much weaker than MCI to AD.
- Short-term change in ADAS-COG is smaller and more variable, so harder to predict.
- Data-driven will see what does change, and look for key subgroups.

Validating change in markers: correlation with ADAS-Cog change in NL

NL	Correlation	p.value					
Hpc vol	-0.18	0.03					
AV45-R-UCB	-0.11	0.18					
Entr thk chg	-0.08	0.31					
Ventricles	0.08	0.32					
Whole brain	-0.08	0.36					
Entr vol	-0.05	0.58					
TBM	0.04	0.67					

- Decrease in hippocampal volume correlated with increase in ADAS-Cog.
- No other association is significant.
- Measures sharing colored bar are not different by multiple comparisons.

Signal-to-noise properties of 1-year change in NL

Normal	samplesize	1	2	3	4	5
WMHYPrate	5,669	Blue				
MMSCORErate	5,111	Blue	Red	Orange		
cdrsumrate	4,501	Blue		Orange		
AV45rate	4,233	Blue		Orange		
etrtrate	3,225	Blue	Red	Orange		
TOTAL13rate	3,170	Blue	Red	Orange		
Etrtrate	1,636	Blue		Orange		
Hpcvrate	1,320	Blue		Orange	Green	
wbrainrate	600				Green	Purple
TBMrate	453				Green	Purple
ventriclesrate	325					Purple

- Sample size required for 1-yr trial in NL to detect 25% reduction in change.
- Best precision (smallest sample size) at bottom.
- Measures sharing colored bar are not significantly different by multiple comparisons.

Potential biomarkers in amyloid+ NL

NL AMY+	mean	sd	sample size				
Ent Vol	-21.6	97.3	5,106				
RAVLT	1.5	4.8	2,394				
AV45-UCB	0.019	0.054	2,104				
ADAS-COG	-0.61	1.55	1,637				
Ent thk	-0.052	0.076	541				
TBM	-0.005	0.006	410				
Wh Brain	-6733	7696	329				
Hpc vol	-57.0	53.3	219				
Ventricles	844	618	135				

NL AMY+	Correl	p.val				
Ventricles	0.21	0.11				
Entr thk ch	-0.20	0.12				
Hpc vol	-0.17	0.19				
Wh brain	-0.10	0.44				
Entr vol	-0.08	0.53				
AV45-UCB	-0.04	0.75				
TBM	-0.02	0.85				

- Analysis in 44 NL who were amyloid+.
- Signal-to-noise ratio for 2-year change (top table) is 1+ for ventricles, HCV.
- Change in ventricles, HCV, ER thickness, may correlate with ADAS-COG change (bottom table).
- Suggests there could be brain changes in this group that are relevant and consistent.

Hypothetical trial design in amyloid+ NL

We hope in ADNI3 to identify specific brain changes in high-risk subgroups that are:

- Relevant potential targets

- With signal-to-noise ratios for change at least 1

- Correlated with clinical change.

Consider a possible Phase II trial, with such a marker as an outcome: (One-sided, level 0.05 trial, with 80% power)

- A 50% or greater reduction in change required sample $n=25$ and would be evidence worth further study.

- A 25% or greater reduction in change required sample $n=99$ and might evidence worth further study.

Data Science Methods using ADNI

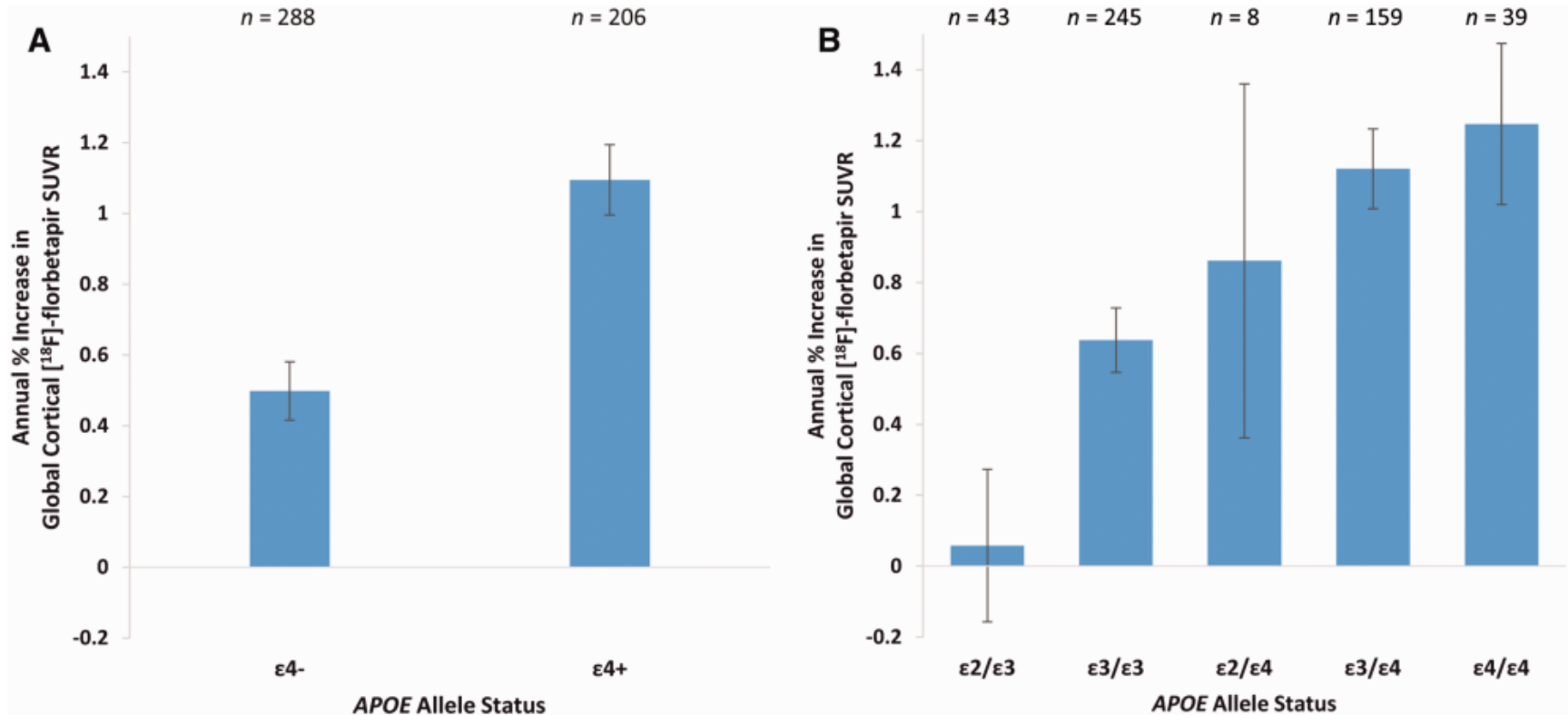
- Imaging-based classifiers (features, ROIs)
- Multimodal classifiers
- Composite cognitive function outcome measures
- Selection of features most “AD-like”
- Prediction of cognitive decline and disease progression utilizing data from multiple modalities
- Statistical methods for GWAS (including imaging genetics)
- Models establishing “order” of biomarker abnormalities
- ADNI has been a model for data sharing without embargo

Effect Size Comparisons in Clinical and Potential Biomarker Surrogate By Stage

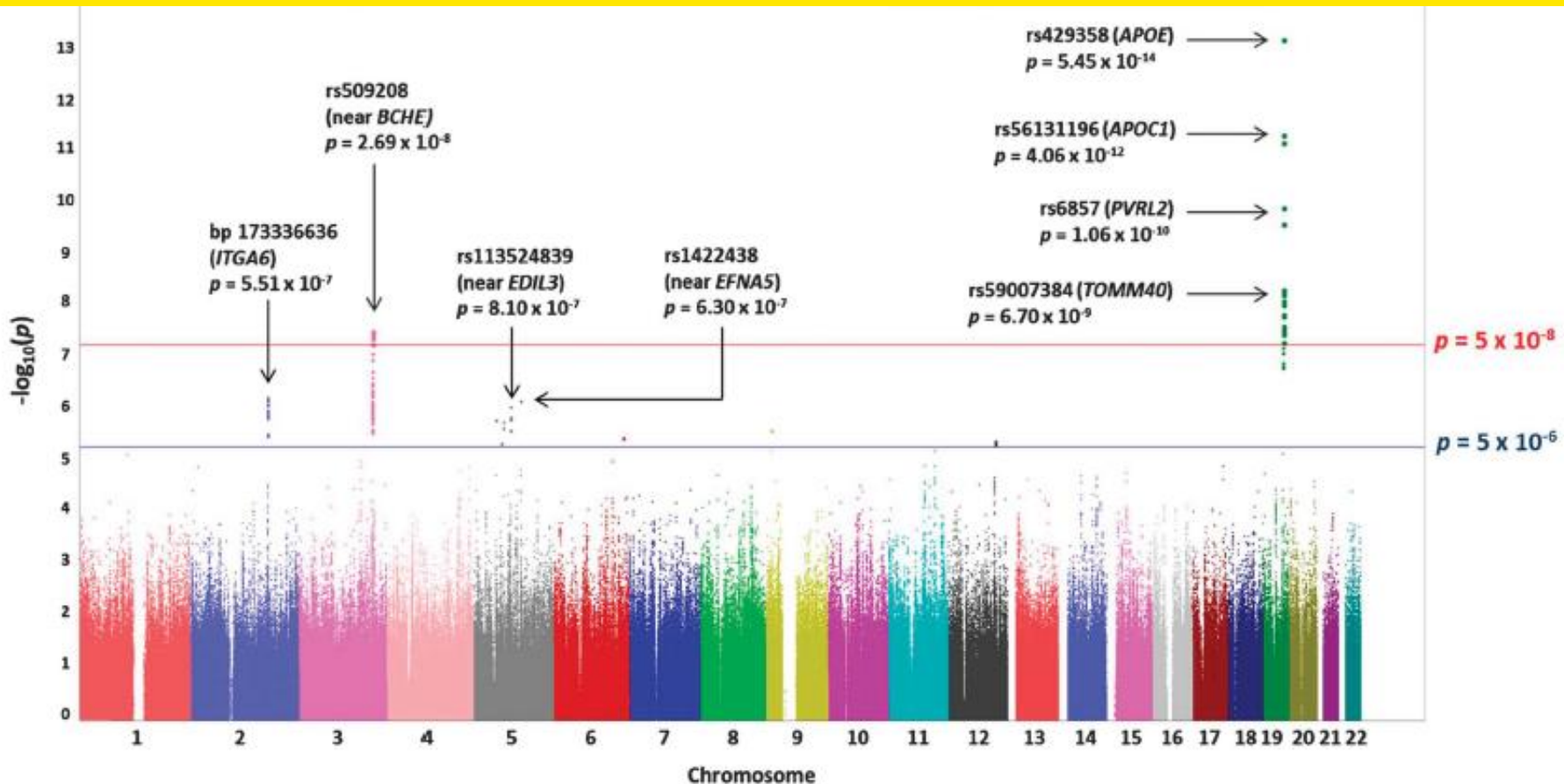
	MCI to AD	24 month change in MCI	Amyloid + normal 24 month change
FDG PET	1.21	-0.50, -0.50	-0.25, -0.33
CSF tau	1.07	0.27	0.38
PET amyloid	1.03	0.25	0.67
Ventricular size	0.41	1.21, 0.99	1.37, 2.71; 1.32
ADAS-cog		0.56, 0.50	0.39, 0.30; 0.36

GWAS of longitudinal amyloid accumulation on ^{18}F -florbetapir PET in AD

Effect of the APOE locus on 2-year change in cortical amyloid PET burden



GWAS of longitudinal amyloid accumulation on ¹⁸F-florbetapir PET in Alzheimer's disease

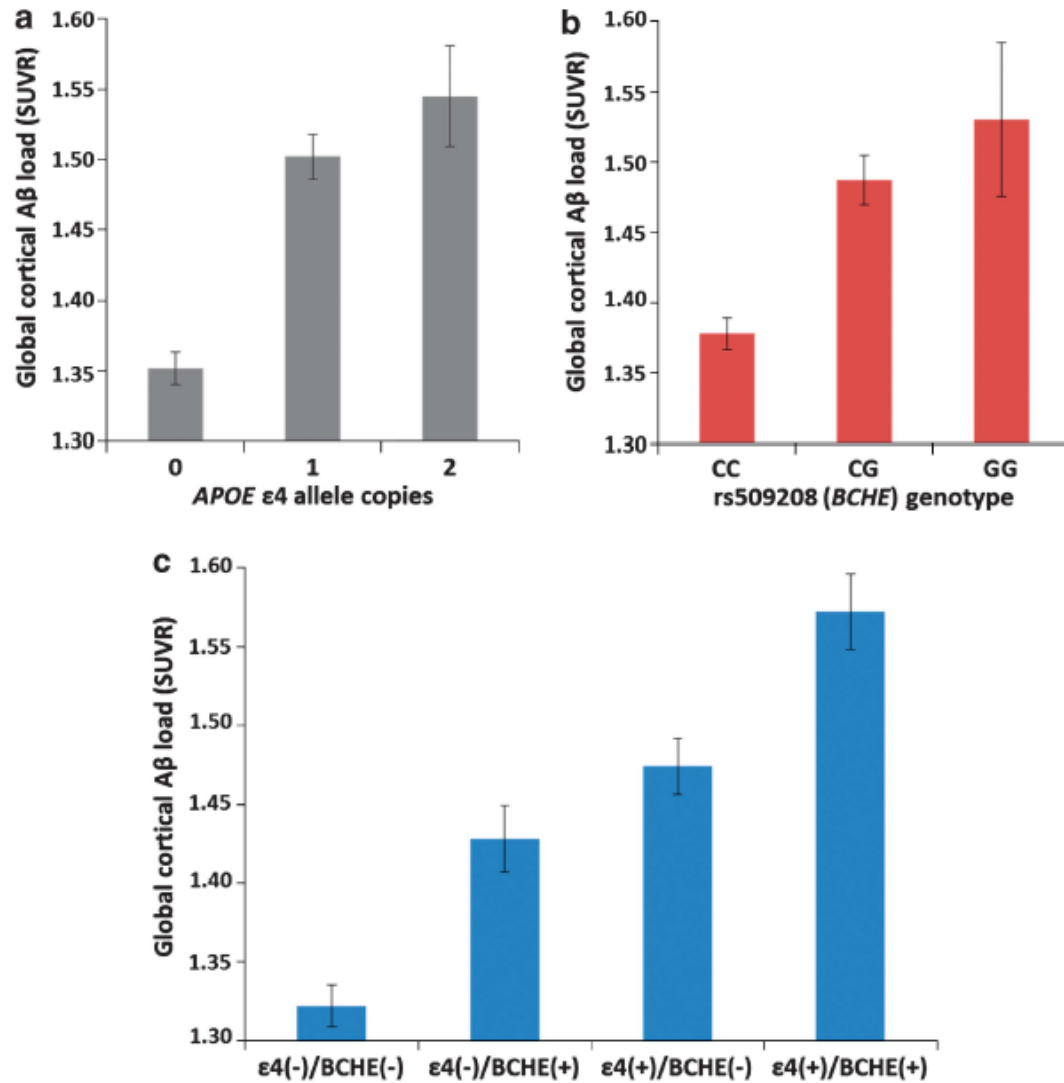


Manhattan plot of observed \log_{10} P-values from the GWAS of cortical Ab load. More than six million SNPs were tested for association to global cortical Ab burden.

APOE and BCHE as modulators of cerebral amyloid deposition: a florbetapir PET genome-wide association study. VK Ramanan et al. *Molecular Psychiatry* (2014) 19, 351–357

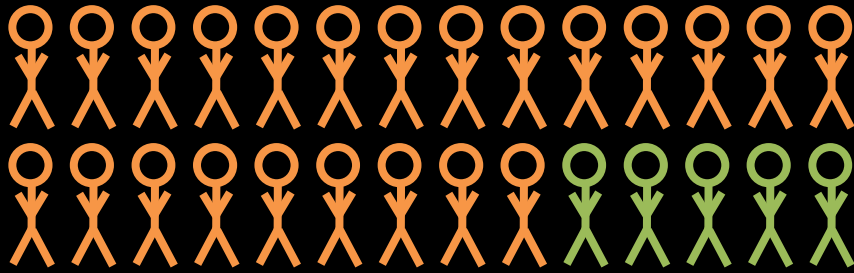
Additional Identification of IL1RAP (microglia) CR1, CLU, and PICALM

APOE & BCHE as modulators of cerebral amyloid deposition

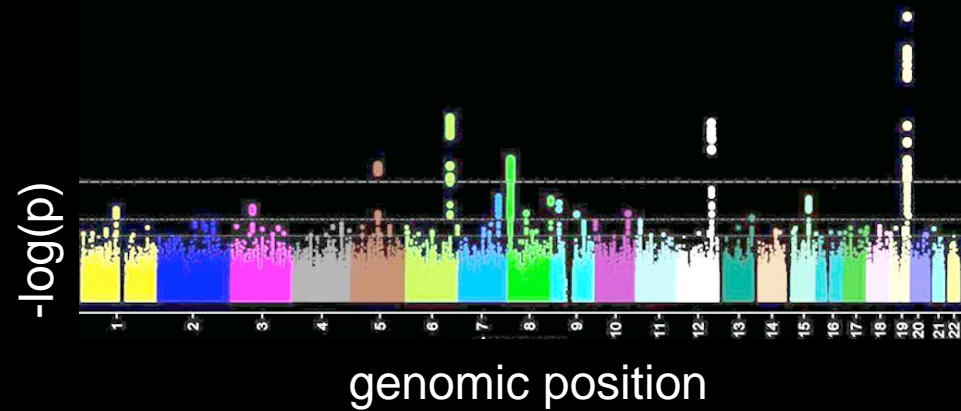
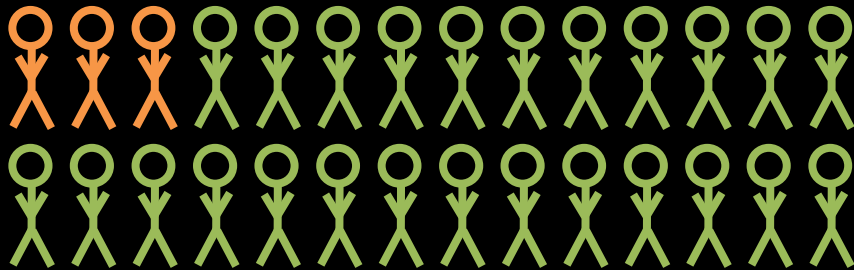


Genome-wide Association Study

Cases



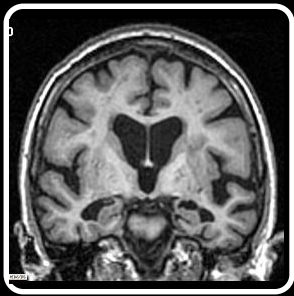
Controls



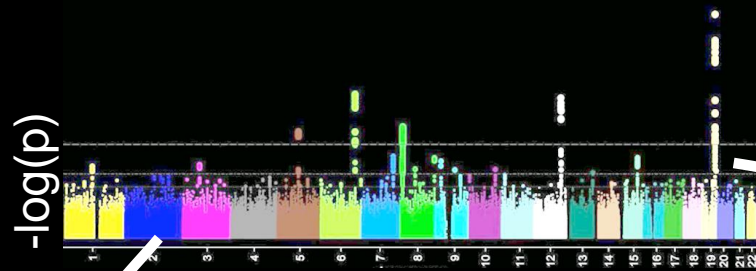
Low statistical strength

- low frequency mutations
- small effect sizes
- epistasis

ADNI NetWAS

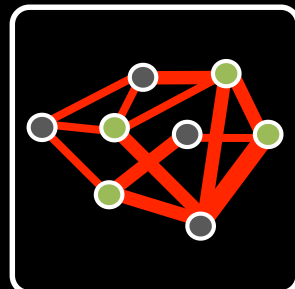


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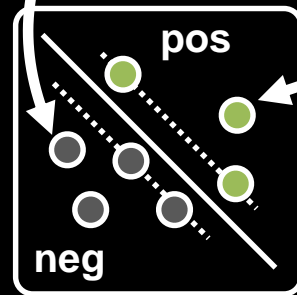


Neuroimaging Data

Genetic Data



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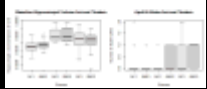


MYO1B	myosin 1B	■
MYO1F	myosin 1F	■
PLEC	plectin	■
MYO1A	myosin 1A	■
KIRREL2	kin of IRRE like 2 (Drosophila)	■
KIRREL3	kin of IRRE like 3 (Drosophila)	■
FRK	Fyn-related kinase	■
ADAM15	ADAM metalloproteinase domain 15	■
PRKD2	protein kinase D2	■

Hippocampus Network

SVM

Tissue-specific NetWAS Genes



IIGC 2017 Abstract

Network-based Genome Wide Study of Hippocampal Imaging Phenotype in Alzheimer's Disease to Identify Functional Interaction Modules

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Conclusions

- Identification of individuals most at risk (particularly in early stages of disease)
- Methods for linking high-dimensional data
- Methods for evaluating biomarker performance
- Improved outcome & choice in outcome measures
- Methods for establishing order of development of biomarker abnormalities
- Big Data? 1000 subjects & millions of observations

Conclusion

- These data driven approaches are prospective, involved standardized as opposed to non standardized data collection.
- Successful public-private partnership
- Pre-competative collaboration with Pharma, NIH and academia