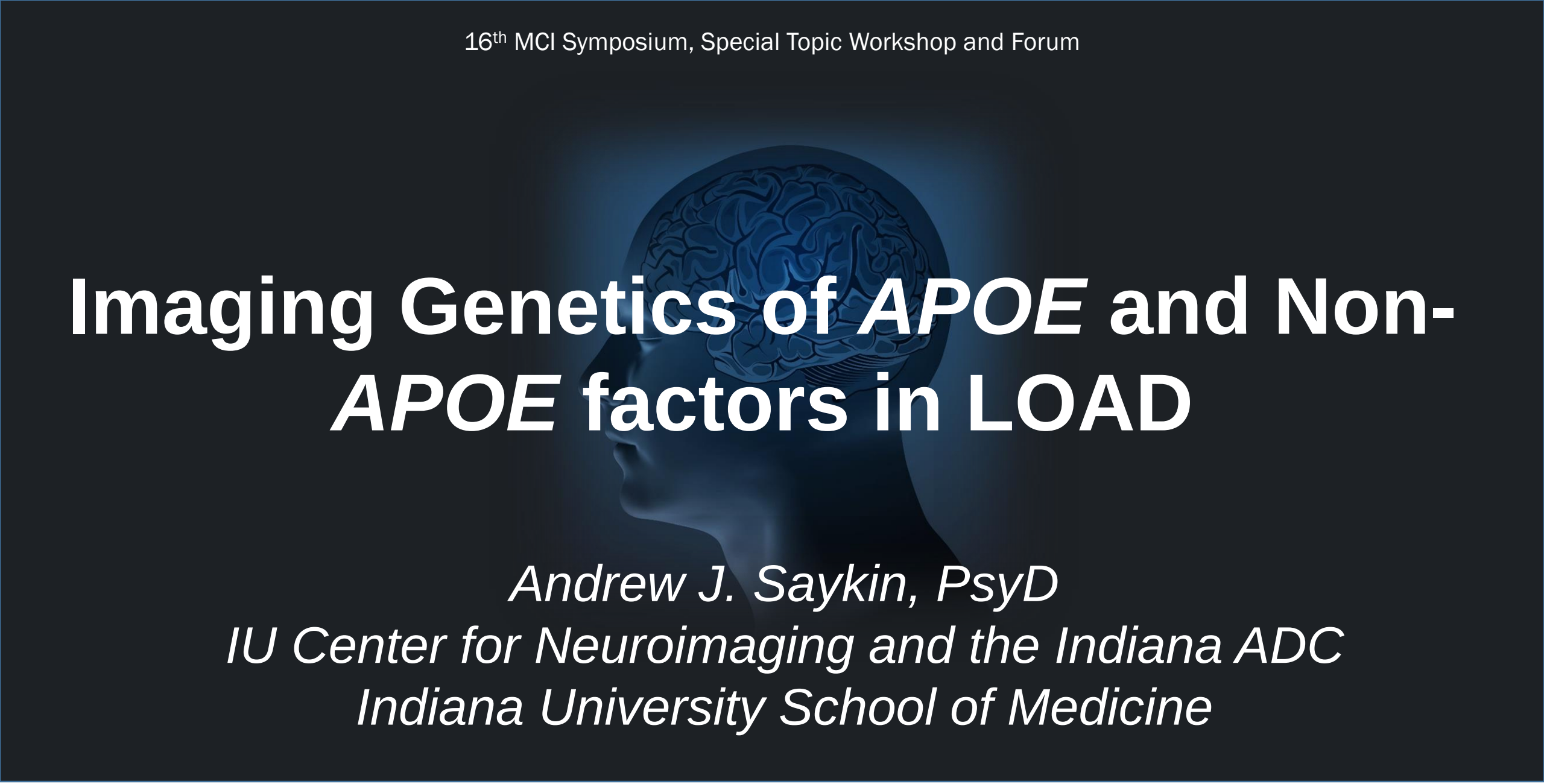


Imaging Genetics of *APOE* and Non-*APOE* factors in LOAD

Andrew J. Saykin, PsyD
IU Center for Neuroimaging and the Indiana ADC
Indiana University School of Medicine

DISCLOSURES

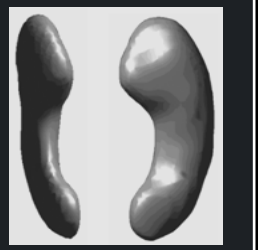
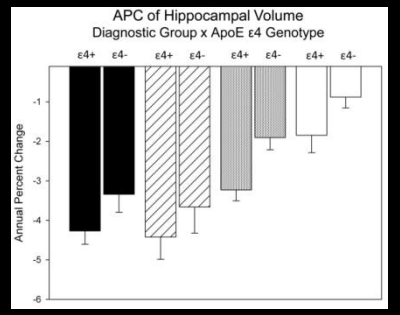
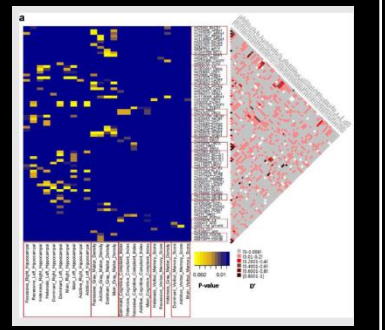
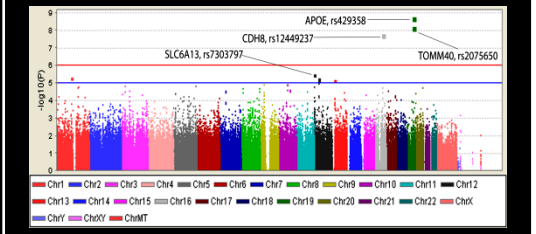
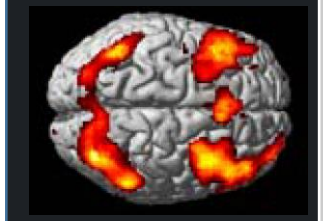
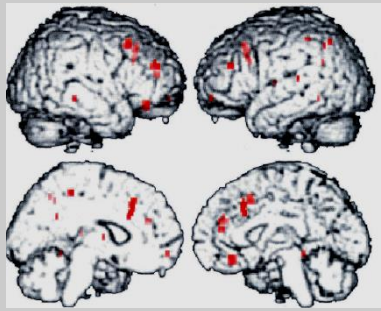
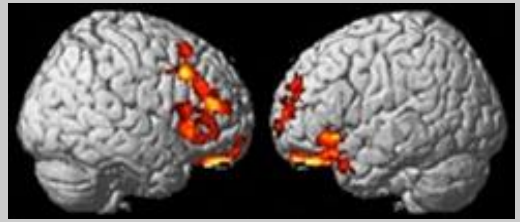
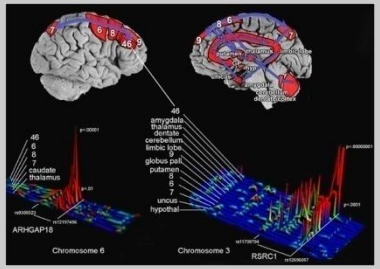
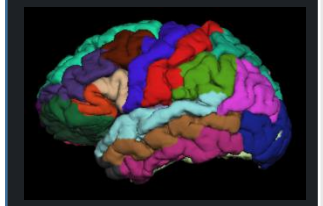
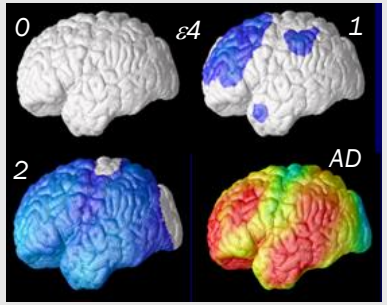
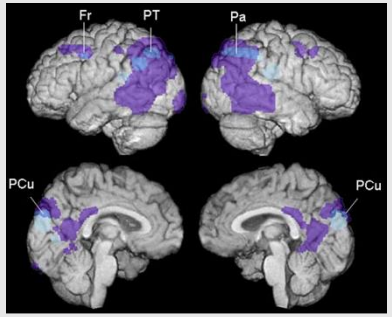
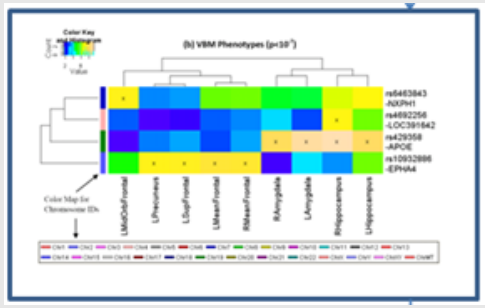
Disclosures

- Eli Lilly (Collaborative Grant), Arkley BioTek (SBIR), Avid Radiopharmaceuticals, Bayer
- Editor-in-Chief, *Brain Imaging and Behavior,* a Springer Nature journal

Grant Support

- National Institute on Aging – P30 AG10133 (IADC)
  - ADNI: U01 AG024904 & RC2 AG036535; Indiana: R01 AG19771
  - U01 AG032984, U24 AG21886, P30 AG010129, K01 AG030514
- National Institute of Biomedical Imaging and Bioengineering
- National Library of Medicine: R01 LM011360 and K99/R00 LM011384
- National Science Foundation: IIS-1117335
- Foundation for the NIH (ADNI-1 GWAS, WGS, AMP-AD)
  - Anonymous Foundation (Challenge Grant), Gene Network Sciences, Merck, Pfizer
  - ADNI methylation project (AbbVie, Biogen and J&J, in-kind support)
- Alzheimer's Association & Brin Wojcicki Foundation – Whole Genome Sequencing
- IUSM Strategic Research Initiative (SRI), Indiana Spinal Cord & Brain Injury Research Fund, CTSI

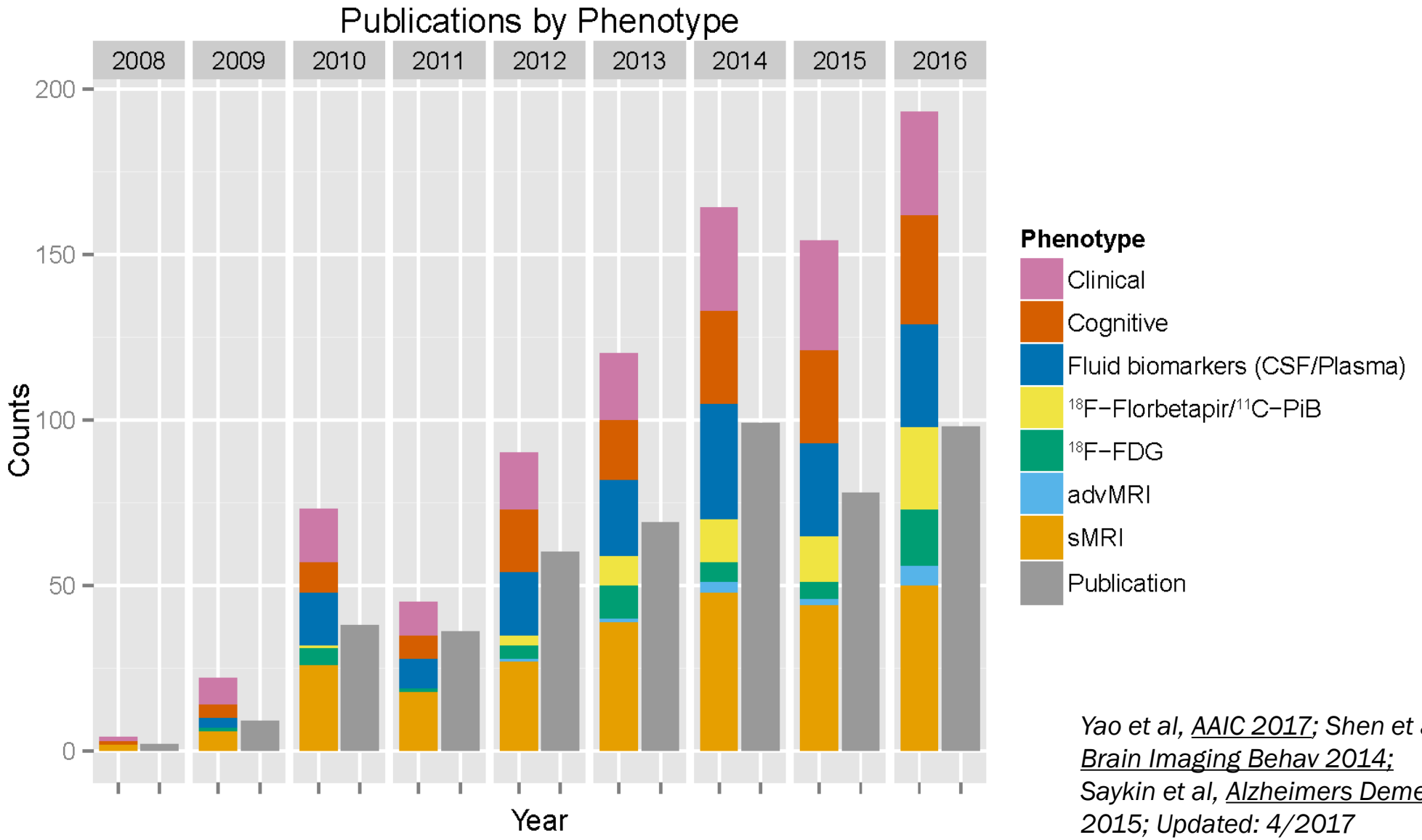
Brain-Genome Association Strategies: First Decade

	Candidate Gene/SNP	Biological Pathway	Genome-wide Analysis
ROI		 *Risacher et al 2010*	*Sloan et al 2010* 	 *Potkin et al 2009; Saykin et al 2010*
Circuit		 *Egan et al 2001 COMT*	 *Swaminathan et al 2010 PiB ROIs & amyloid pathway*	 *Potkin et al 2009 Mol Psych schizophrenia study*
Whole Brain		 *Reiman et al PNAS 2009; Also Ho et al 2010 FTO*	 *Reiman et al 2008 cholesterol pathway genes*	 *Shen et al 2010 ROIs; Stein et al 2010 voxels*

Saykin, 2011

Genetics studies Using ADNI Endophenotypes:

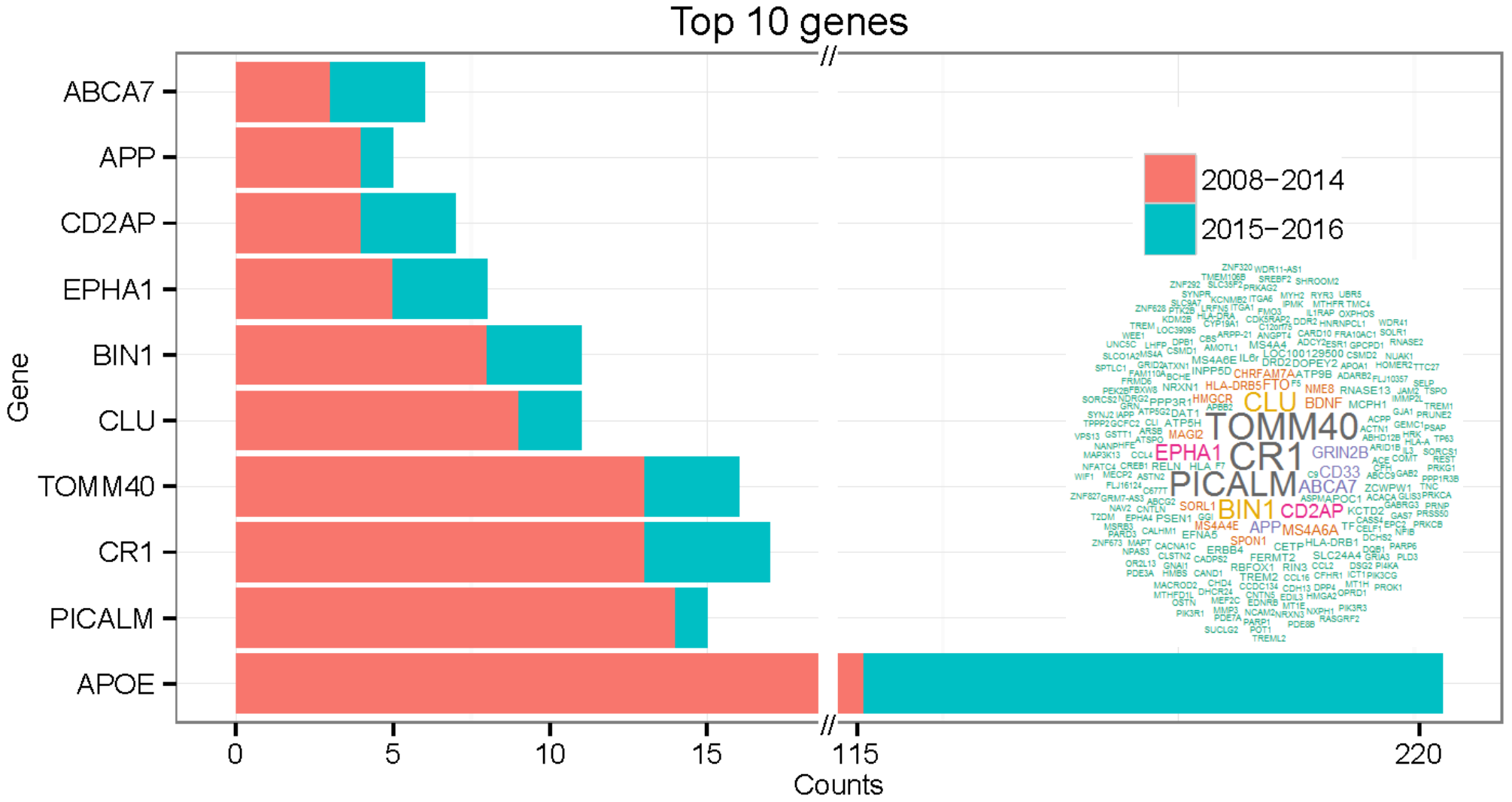
Publications Using ADNI Genetic Data (2008–2016)



Year	Pubs
2008	2
2009	9
2010	38
2011	36
2012	60
2013	69
2014	99
2015	78
2016	98

Yao et al, AAIC 2017; Shen et al, Brain Imaging Behav 2014; Saykin et al, Alzheimers Dement 2015; Updated: 4/2017

Most frequently reported genes in manuscripts using ADNI genetic data (2008–2016)



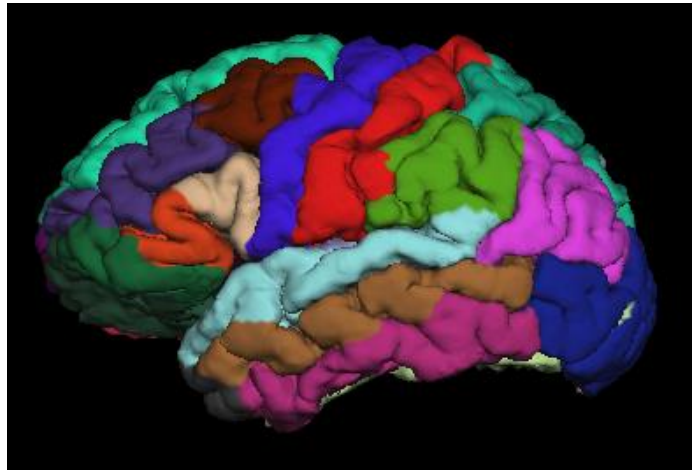
Yao et al, AAIC 2017;

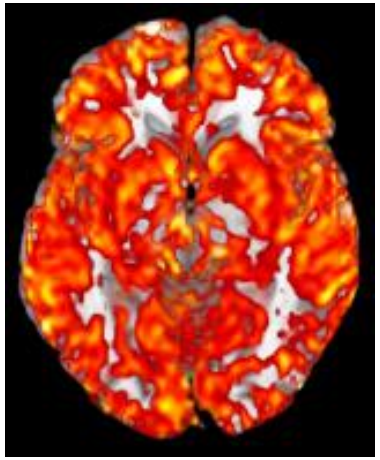
Shen et al, Brain Imaging Bhav 2014; Saykin et al, Alzheimers Dement 2015

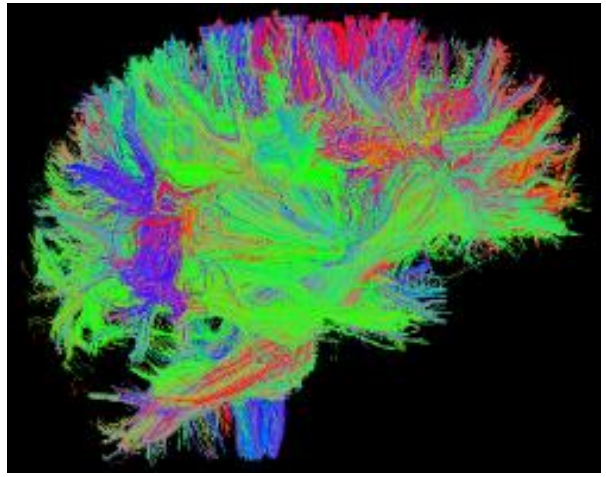
Updated: 4/2017

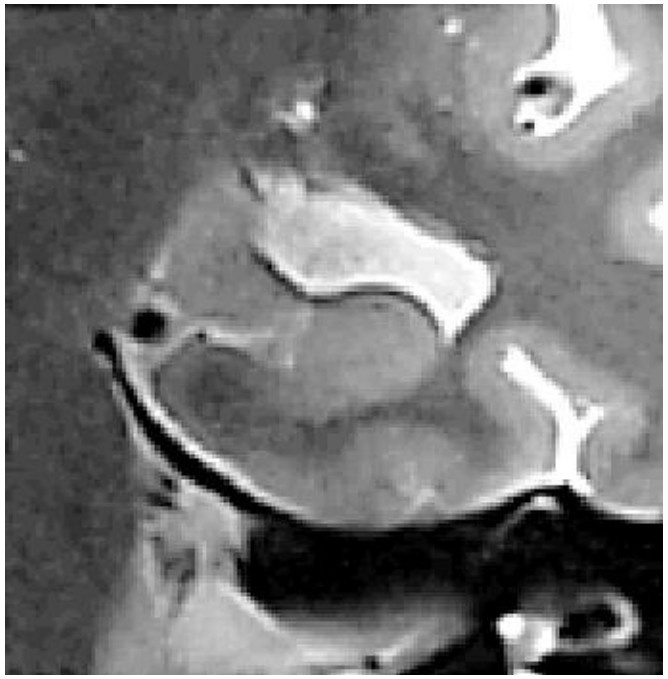
Multimodal MR Phenotypes

- MPRAGE, 3D FLAIR, SWI
- High Res. Hippocampal Sequence
- Diffusion MR (DTI and NODDI)
- fMRI: Resting State & Task-based BOLD
- Arterial Spin Labeled Perfusion





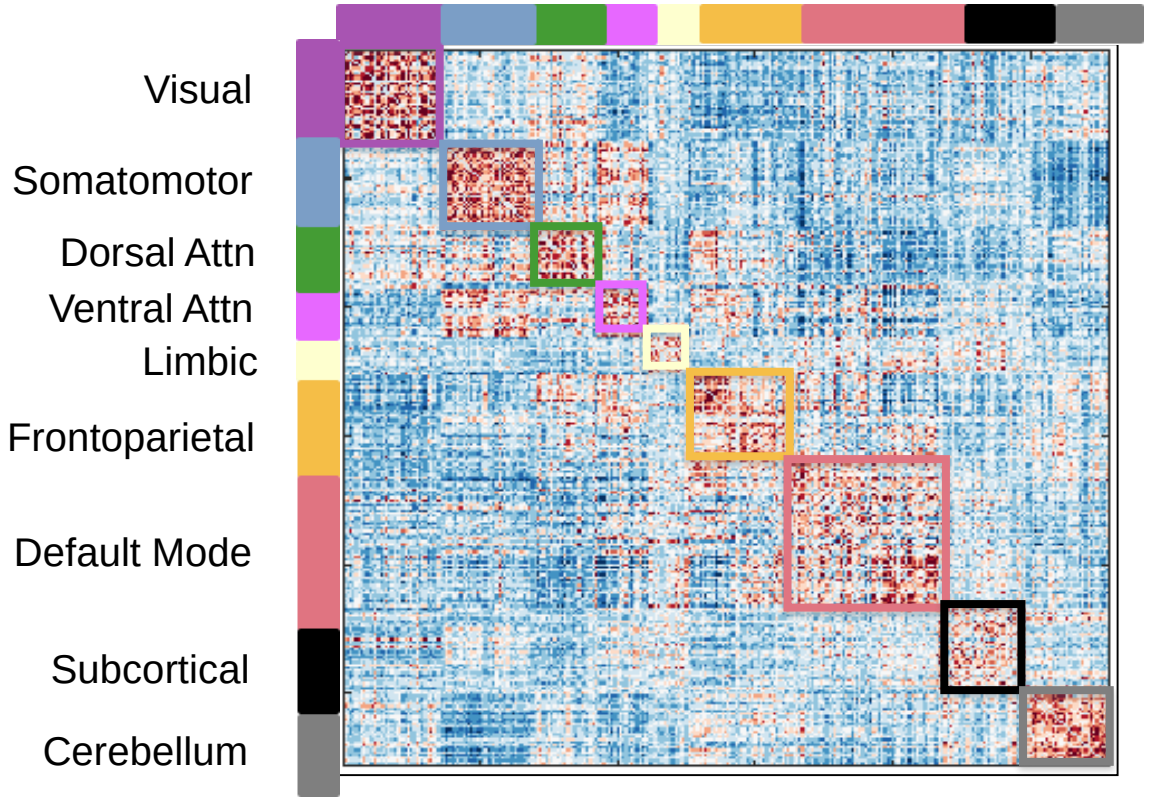




NODDI: neurite orientation dispersion and density

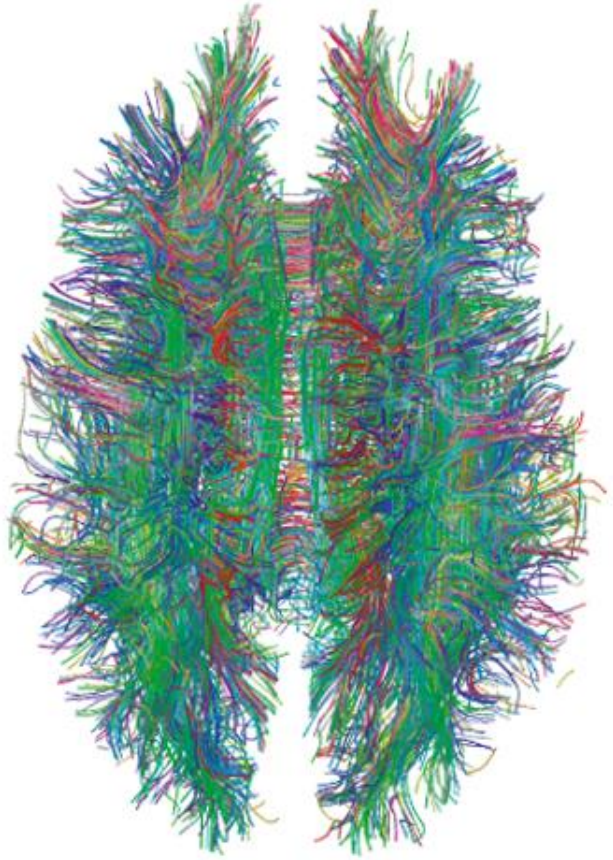
Connectome as Endophenotype

Resting State Networks



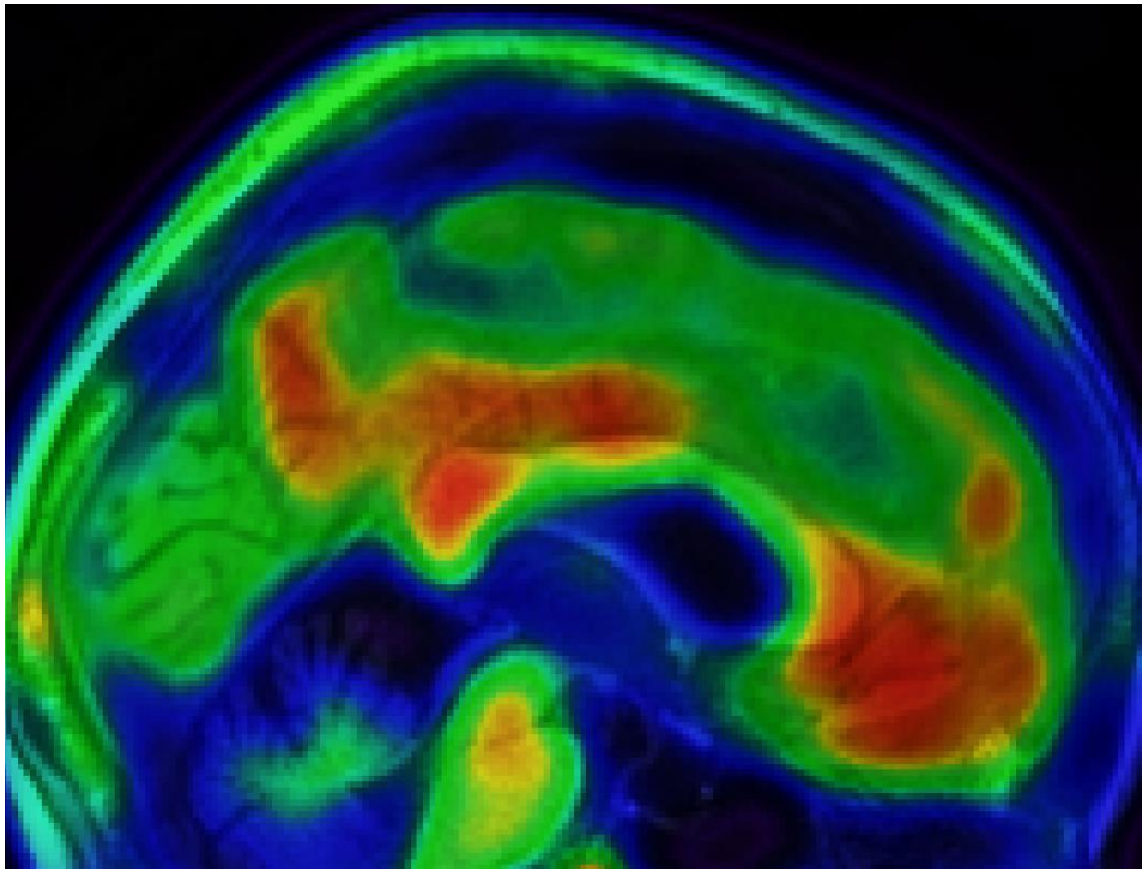
Contreras et al. (2017) *Alz & Dementia*

Structural Connectome

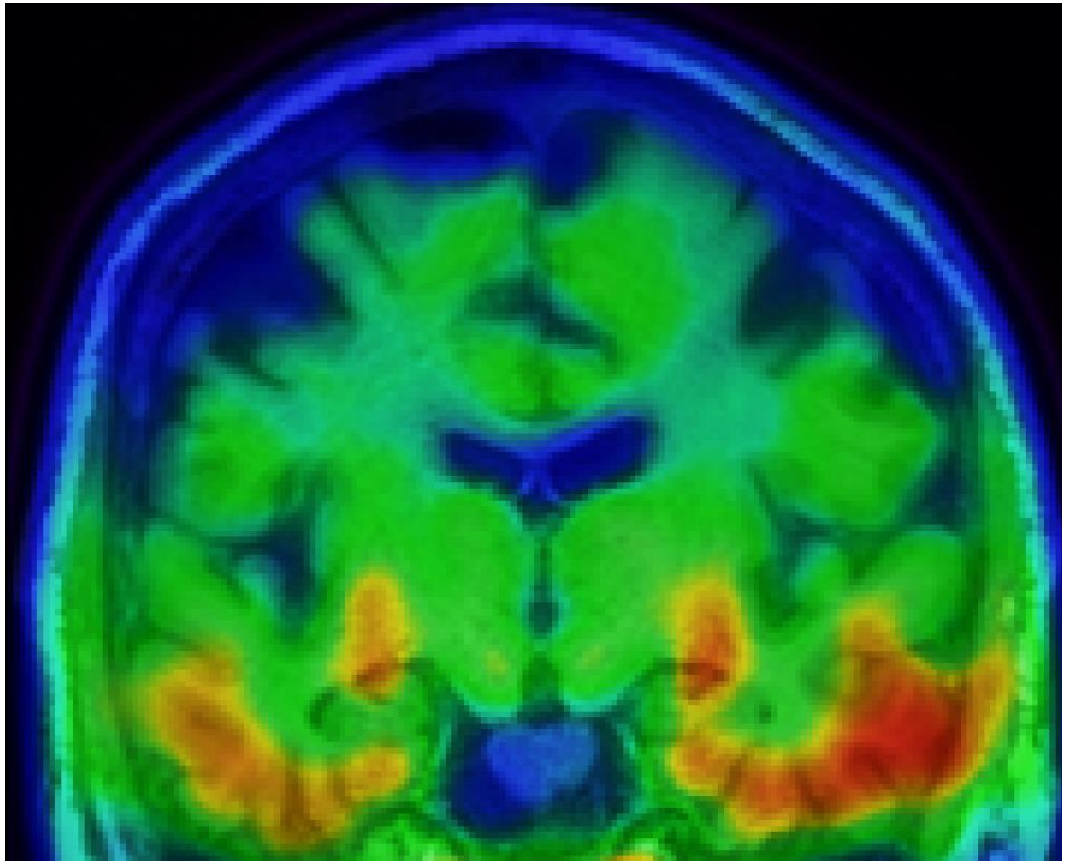


Gigandet, Hagmann et al (2008)

Molecular Imaging Phenotypes



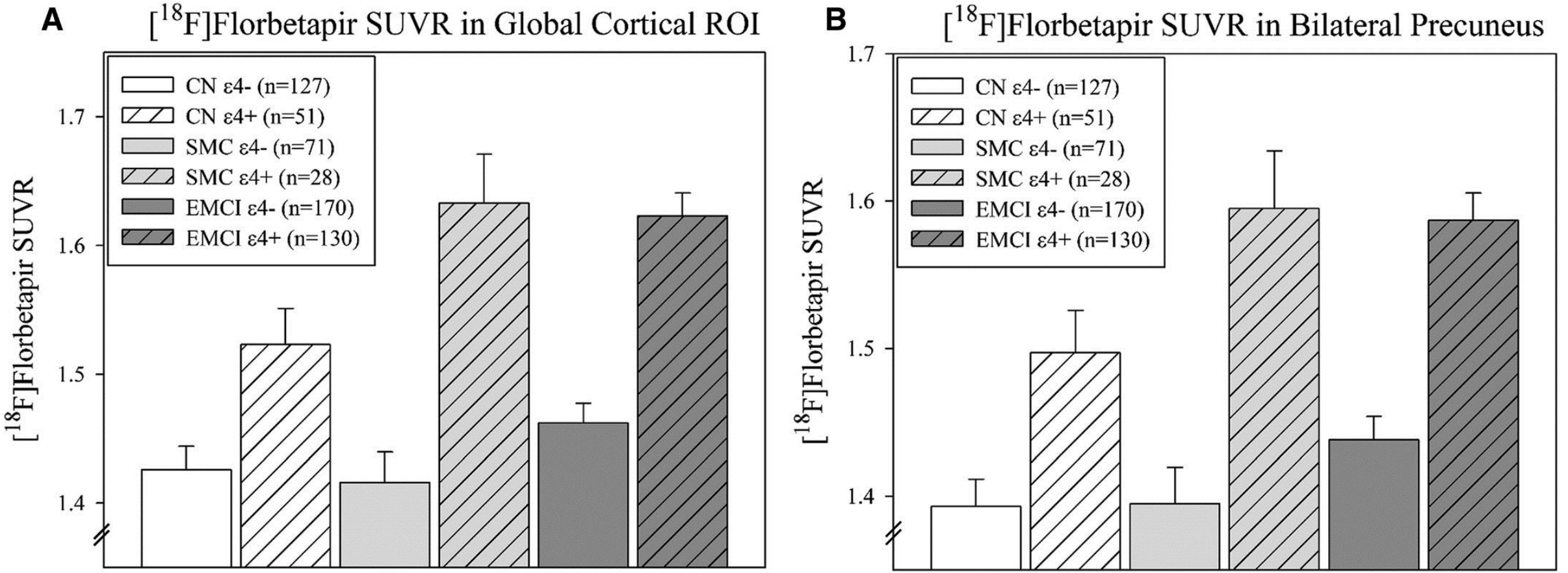
Amyloid PET [^{18}F]Florbetapir



Tau PET [^{18}F]AV-1451

Indiana ADC

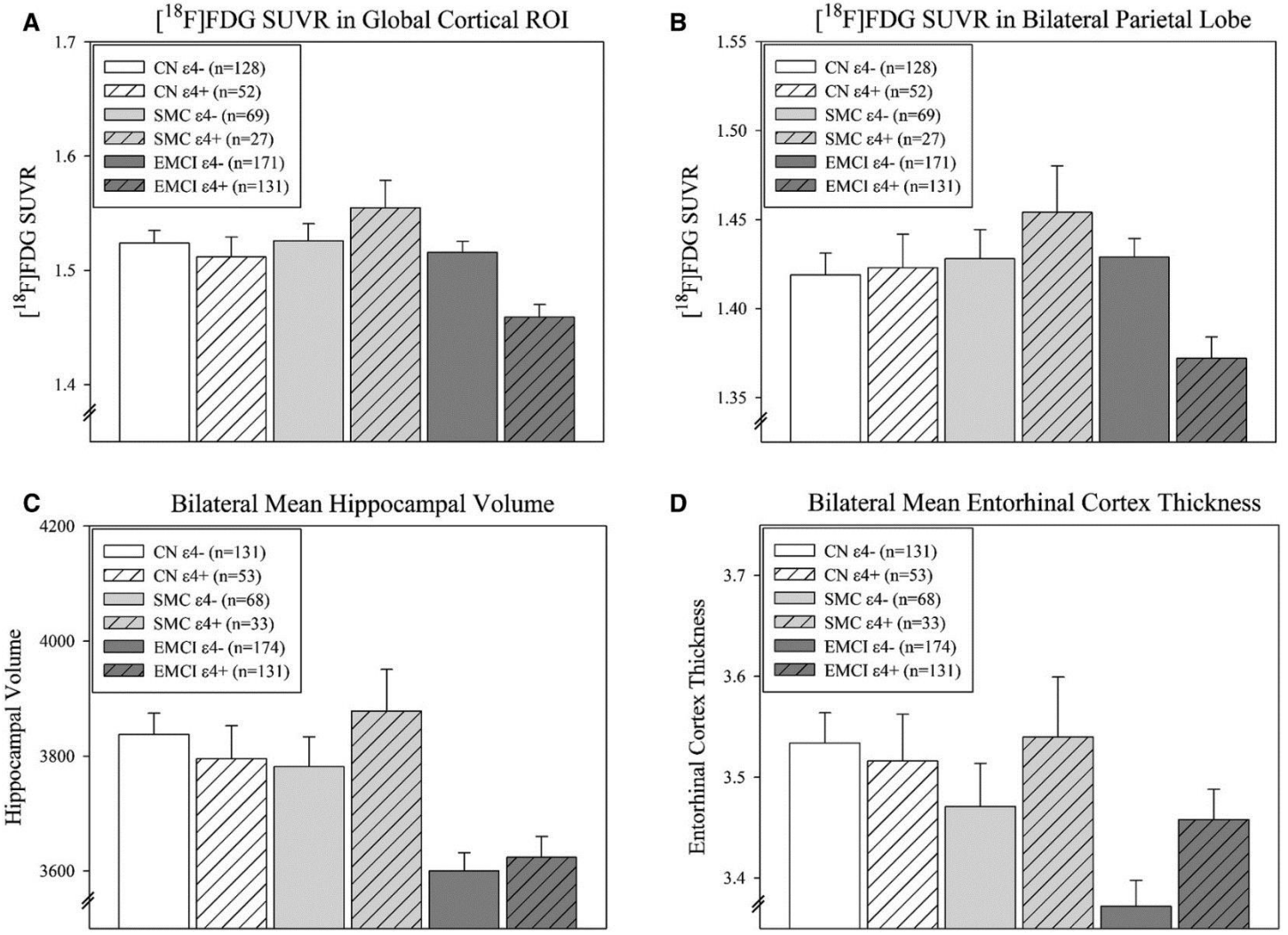
APOE ε4 Status and Early Stage Amyloid Deposition on PET



Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

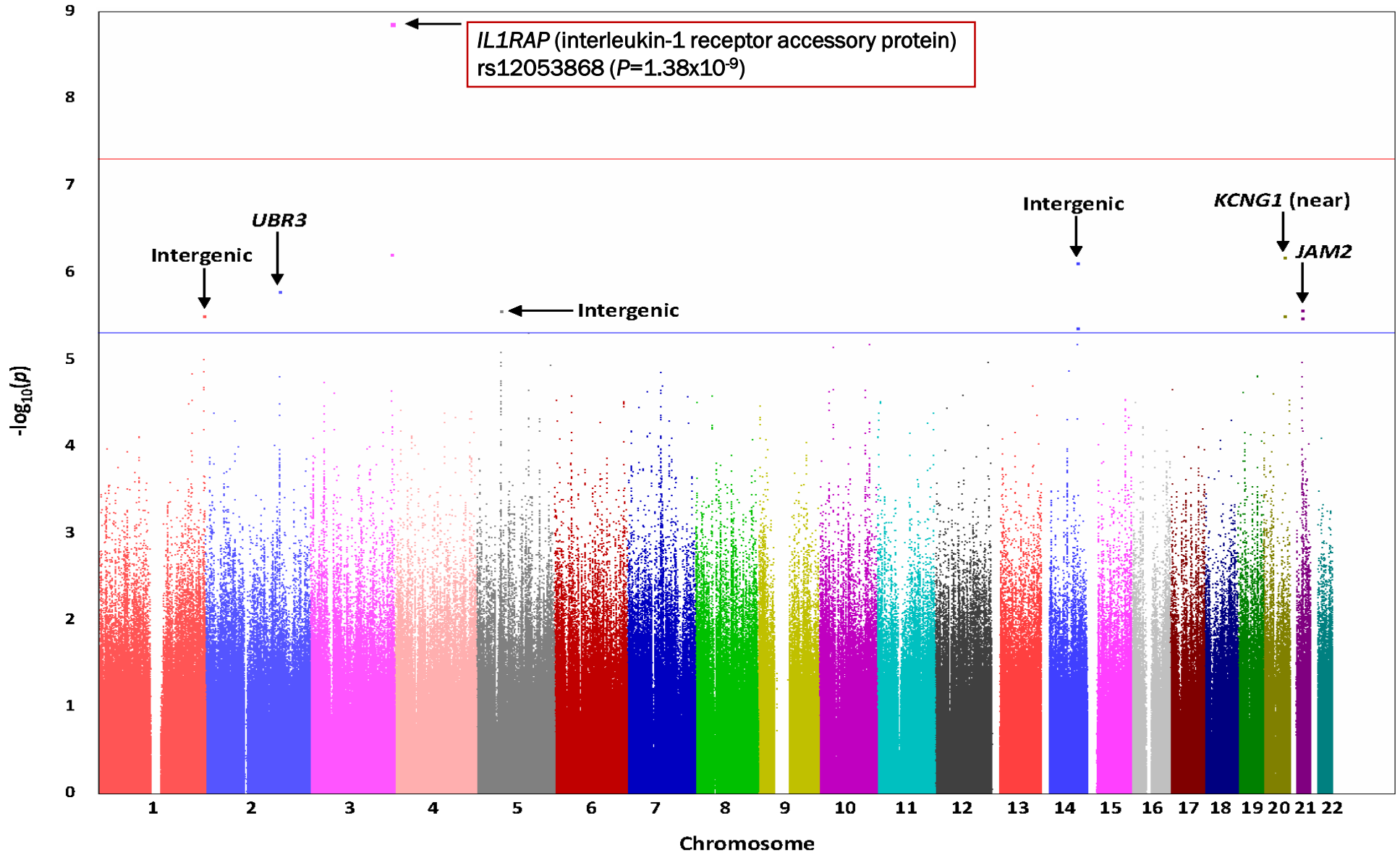
APOE ε4 Status: Early Stage Atrophy and Glucose Metabolism



Risacher et al. Alzheimer's & Dementia (2015): DOI: (10.1016/j.jalz.2015.03.003)

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

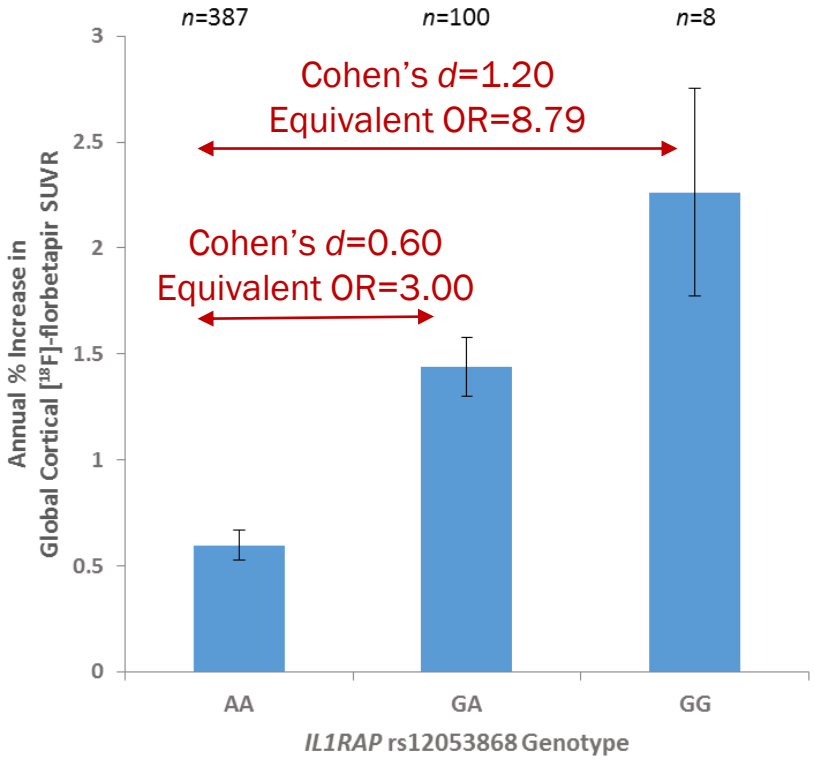
GWAS of Longitudinal Amyloid PET: IL1RAP Example



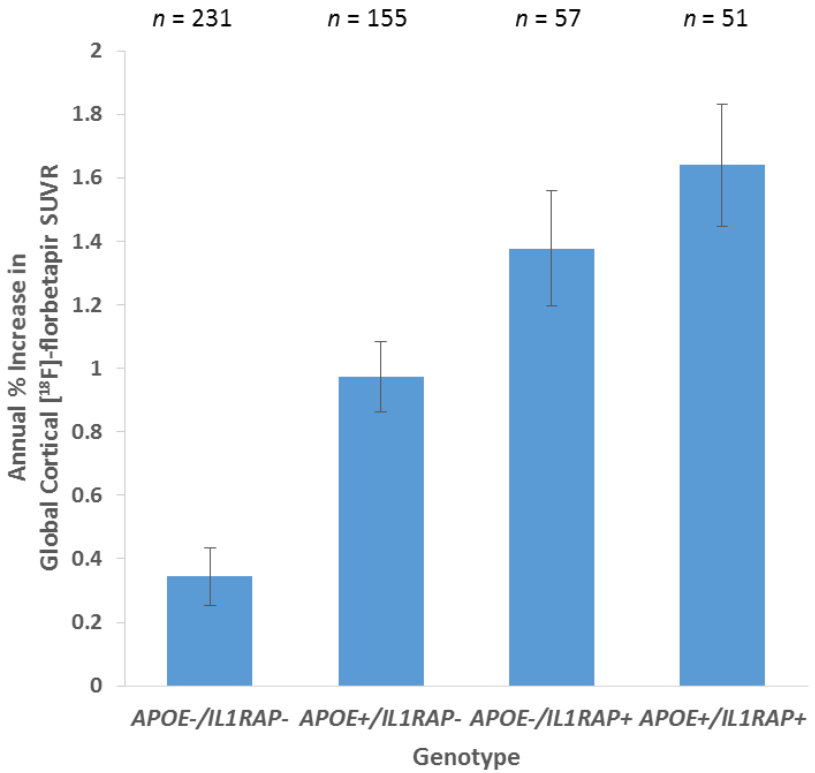
Ramanan et al, BRAIN, 2015 Oct;138 (Pt 10):3076-3088.

Combined Effects of *IL1RAP* rs12053868 and *APOE*

IL1RAP rs12053868-G is associated with higher rates of amyloid accumulation



IL1RAP rs12053868-G and *APOE* ε4 exert independent, additive effects



-*IL1RAP* (7.1%) + *APOE* ε4 (3.4%) explain 10.5% of the phenotypic variance (age and gender explain 0.9%)

-*IL1RAP* association remains genome-wide significant (P=5.80x10^{-9}) with additional covariates of *APOE* ε4 status, baseline diagnosis, education, baseline amyloid burden and its square, and PCA eigenvectors

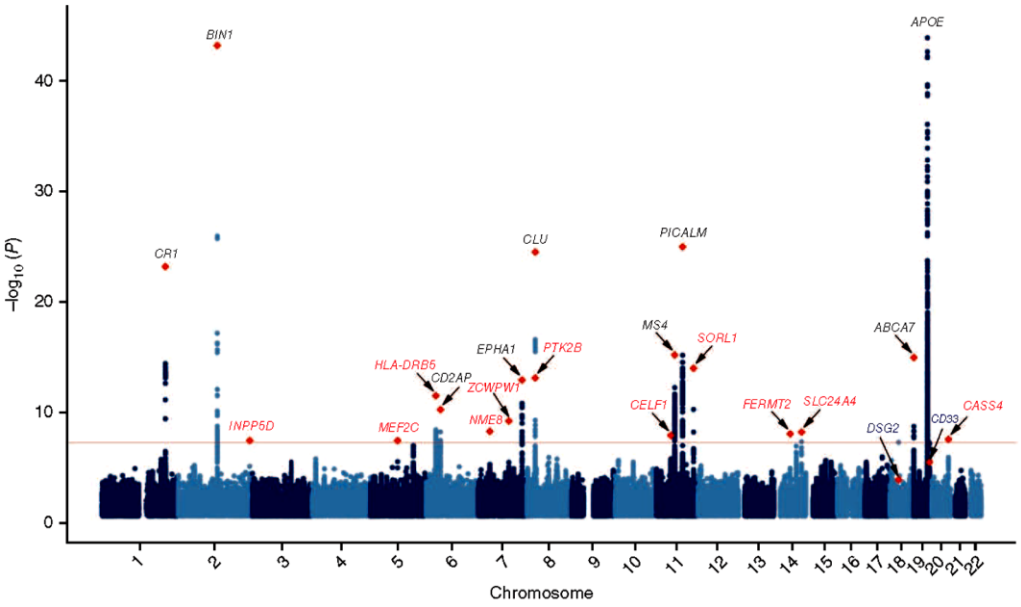
Ramanan et al, BRAIN, 2015 Oct;138(Pt 10):3076-3088.

IGAP – Top AD Candidates: Imaging Associations

LETTERS

nature genetics

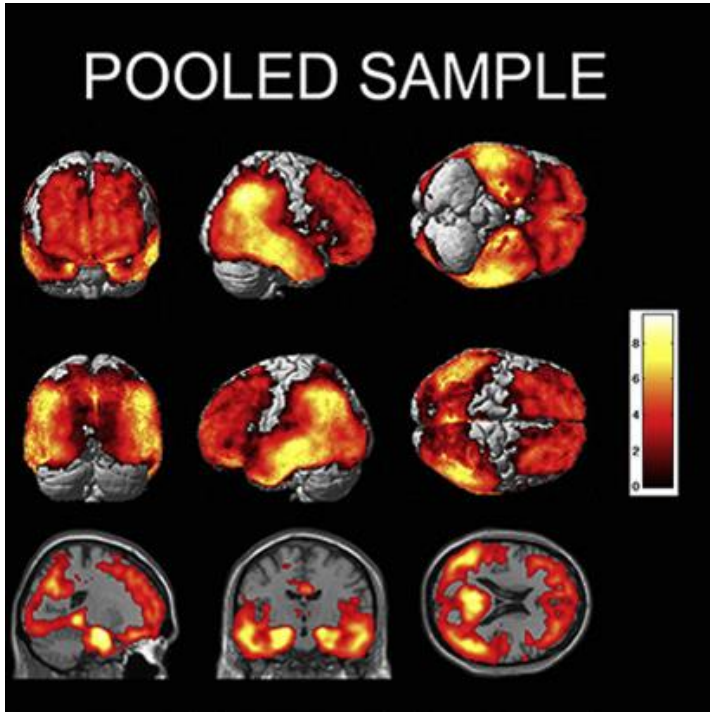
Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease

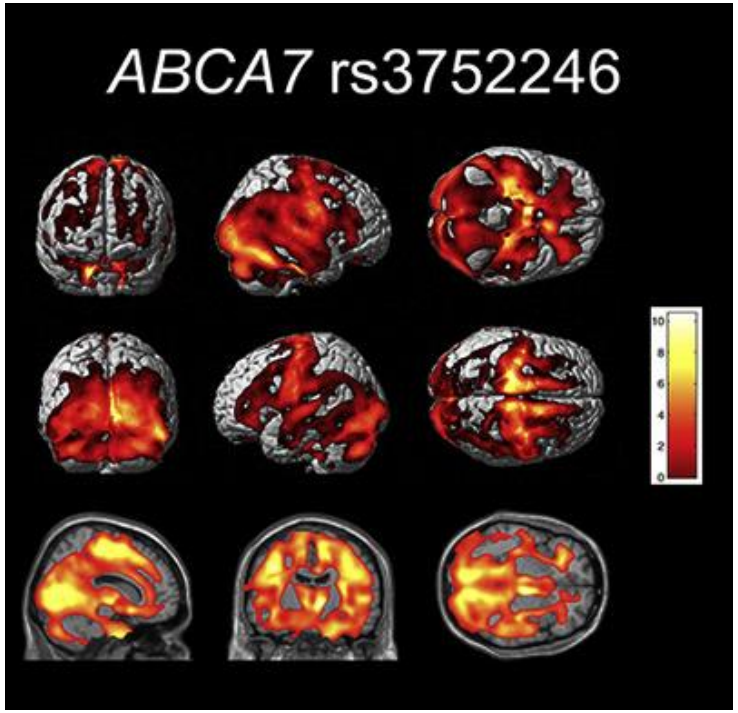


Lambert et al Nature Genetics (2013)

APOE effect: Multivariate analysis of 27 variants in the pooled ADNI sample

Disease stage specific effects in ADNI: *ABCA7* association in AD group only





Stage et al (2016) *Alz & Dem: DADM*

ENIGMA Consortium

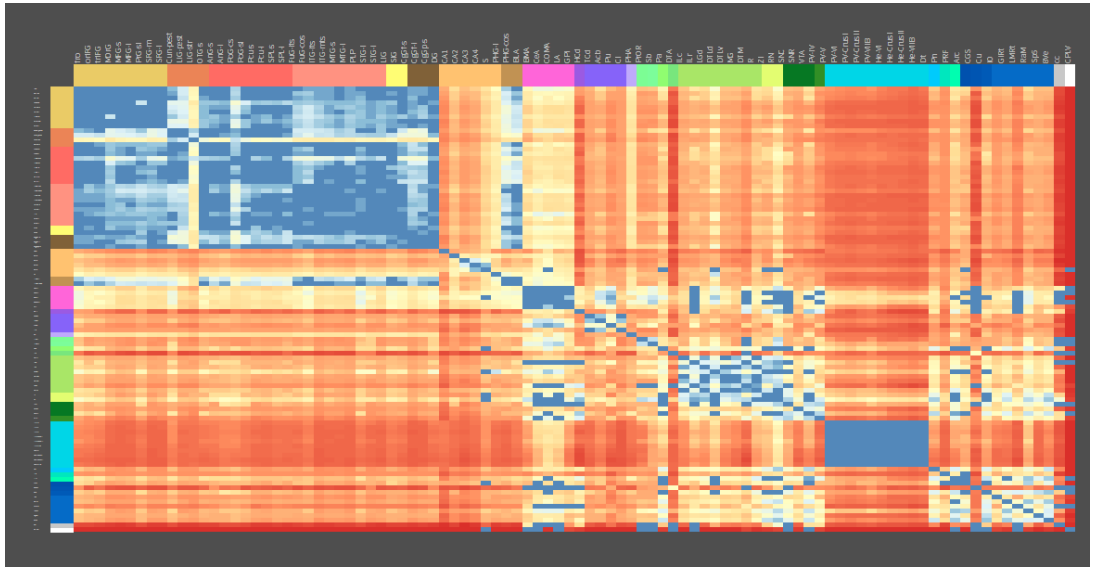
Paul Thompson et al (http://enigma.ini.usc.edu/)

Selected studies & data sets:

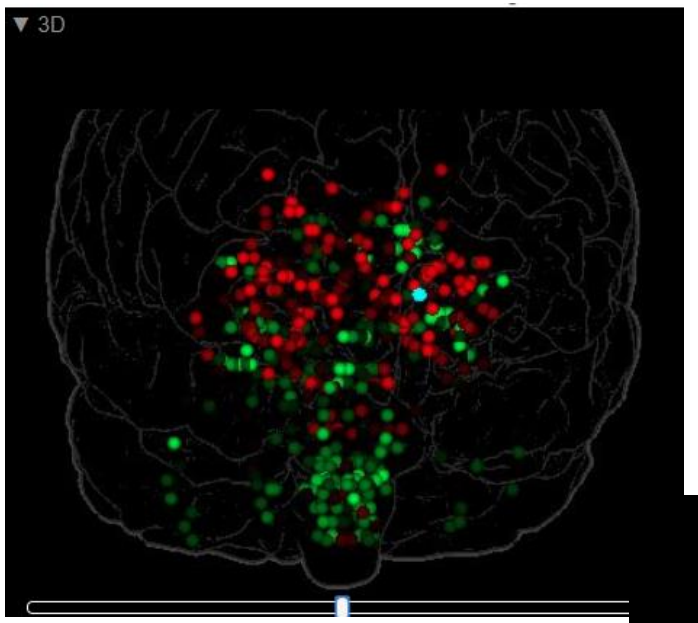
- GWAS of subcortical volumes (ENIGMA2) (Hibar et al., *Nature*, 2015)
- GWAS of intracranial volume (Adams et al., *Nature Neuroscience*, 2016) from the ENIGMA-CHARGE collaboration
- GWAS of hippocampal volume (Hibar et al., *Nature Communications*, 2017) from the ENIGMA-CHARGE collaboration

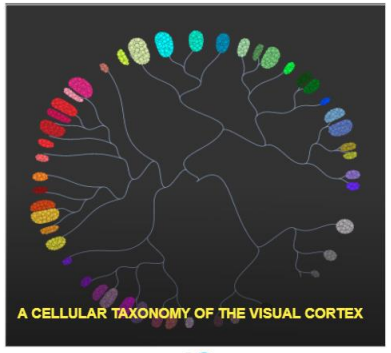
Allen Atlas: 3D Gene Expression Mapping

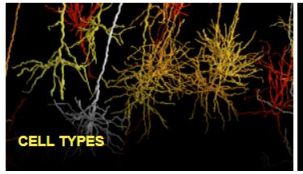
Genetic architecture of the human brain

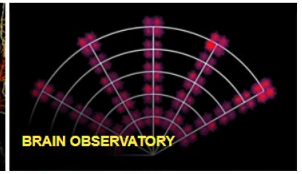


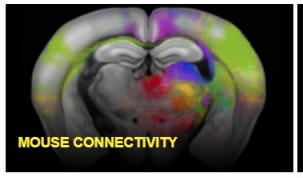
Example of APOE expression





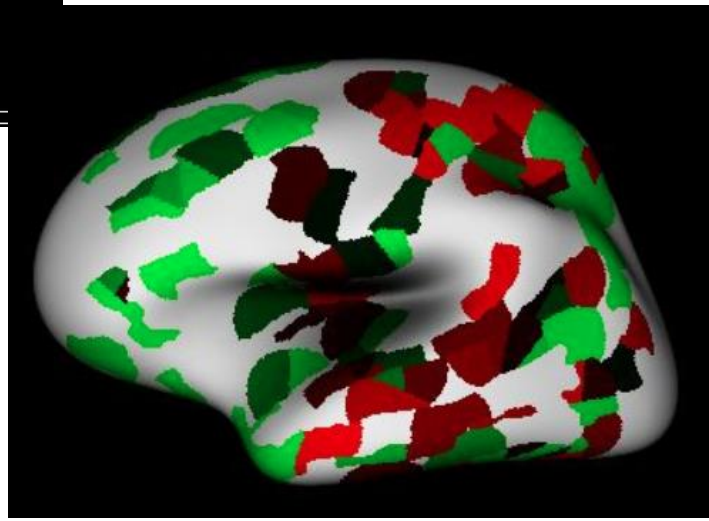






http://www.brain-map.org/

Example of ABCA7 expression --->



Working Toward a Systems Biology of AD

Transcriptome**
RNA sequence and expression

Proteome*
Protein expression, structure, and function

Metabolome*,†
Metabolite / enzyme profile

Epigenome†
DNA methylation and histone modification

Genome*,**
DNA sequence and variation

Molecular Networks/Pathways

Interactome†
Interaction (e.g., gene-gene, gene-protein)

Exposome*,**
Environment, life style, diet, drug, age

Perturbed biochemical networks/pathways

Brain structure & function*,**
Structural and functional brain imaging

Healthy vs Disordered Brains‡

Healthy Brain AD Brain Healthy Brain AD Brain

PiB PET

Structure Function Connectivity

Connectome**
Anatomical and functional brain connectivity

Systems Biology Approach

*: ADNI-1
**: ADNI-GO/2

Image sources
†: upload.wikimedia.org.
‡: www.uphs.upenn.edu

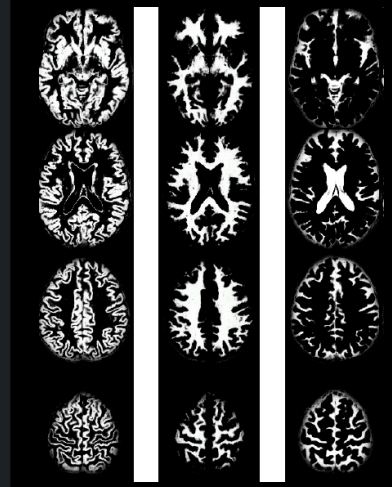
ADNI

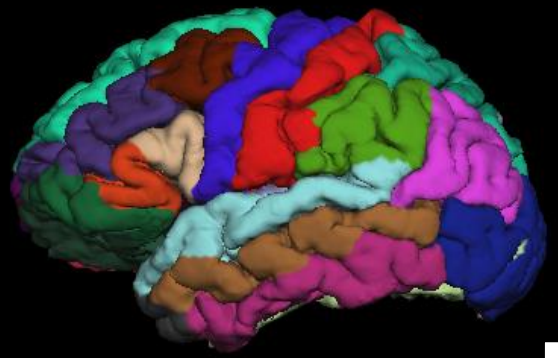
Neuroscience Center

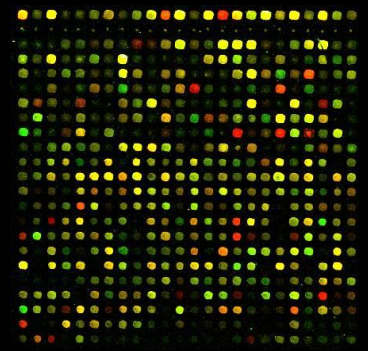
Saykin et al Alzheimer's & Dementia 11 (2015) 792-814

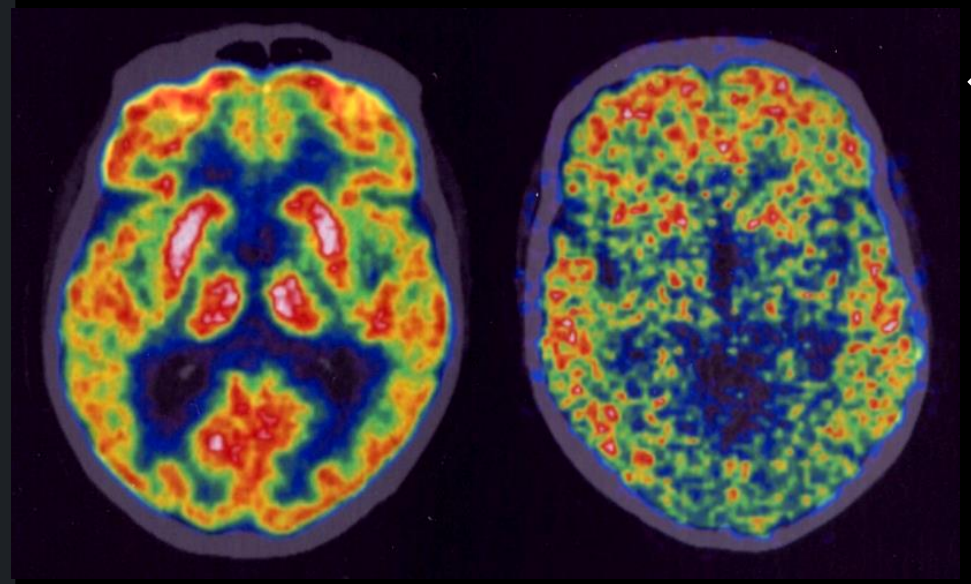
INDIANA UNIVERSITY SCHOOL OF MEDICINE

Relating Imaging Phenotypes, Genes & Clinical Information is a BIG DATA Challenge

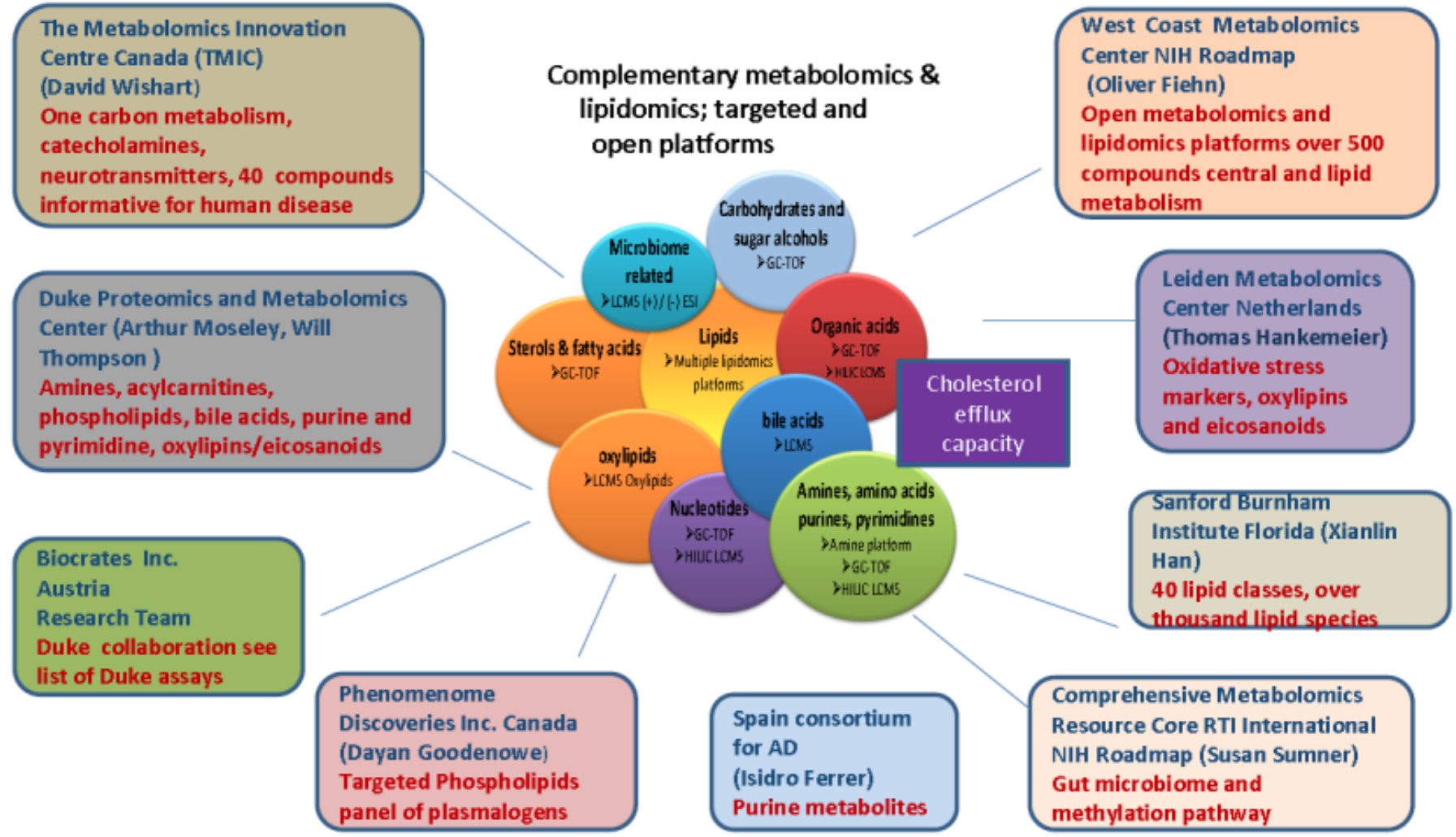








AD Metabolomics Consortium (ADMC)



PI: Rima Kaddurah-Daouk, Duke University

https://sites.duke.edu/adnimetab/about-us/participating-centers/

Defining Metabolomic Networks in AD

ELSEVIER

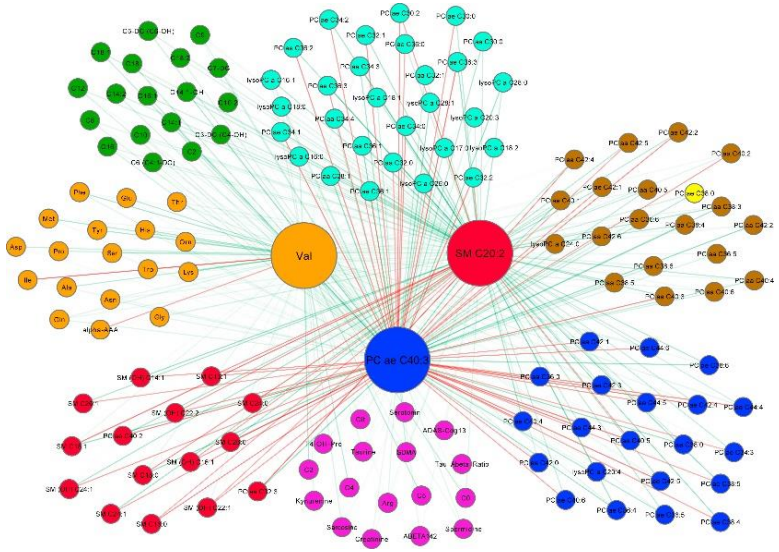
Alzheimer's & Dementia ■ (2017) 1-20

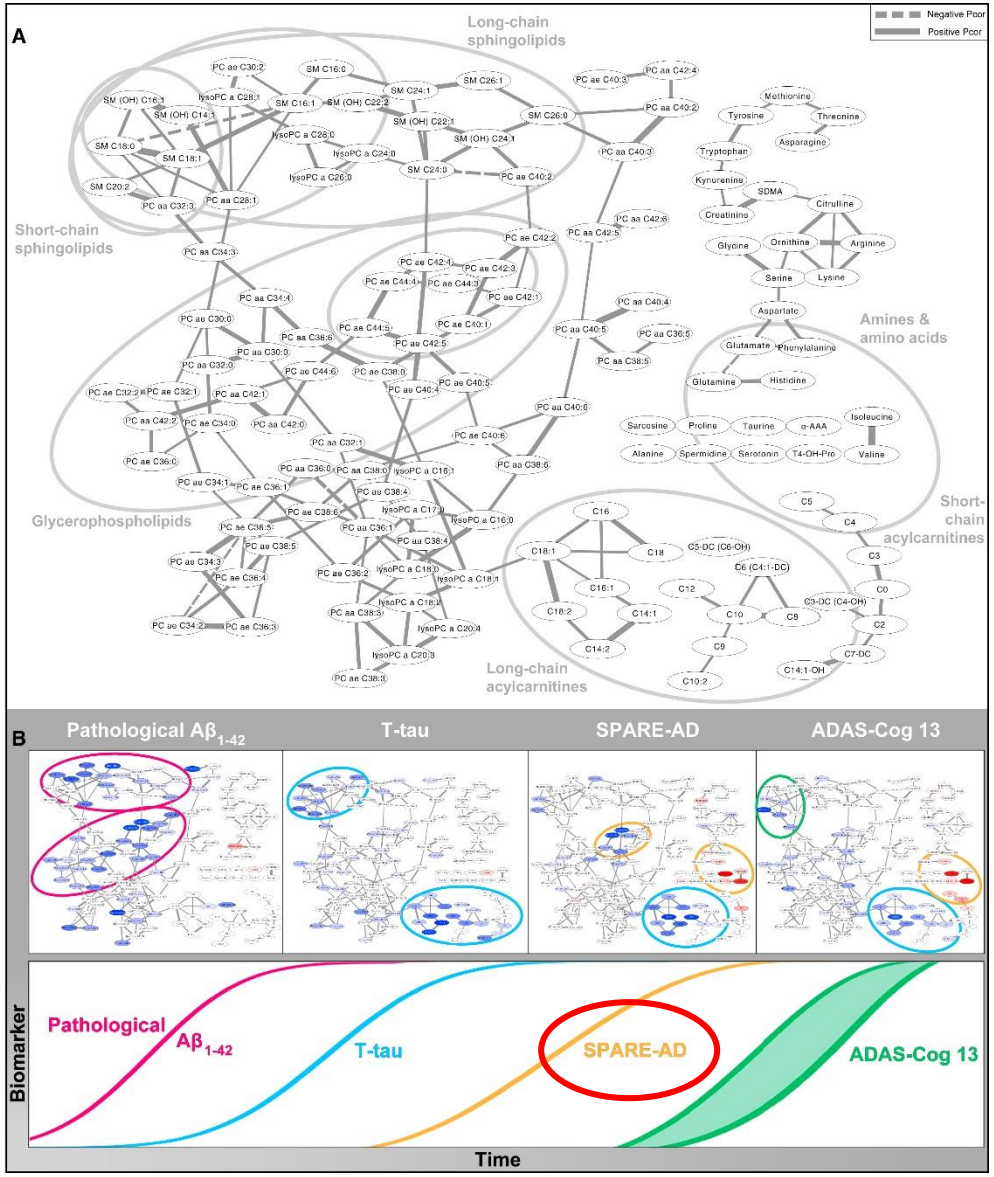
Alzheimer's & Dementia

Featured Article

Metabolic network failures in Alzheimer's disease—A biochemical road map

Jon B. Toledo[a,b,**], Matthias Arnold[c], Gabi Kastenmüller[c,d], Rui Chang[e], Rebecca A. Baillie[f], Xianlin Han[g], Madhav Thambisetty[h], Jessica D. Tenenbaum[j], Karsten Suhre[c,k], J. Will Thompson[l], Lisa St. John-Williams[l], Siamak MahmoudianDehkordi[m], Daniel M. Rotroff[m], John R. Jack[m], Alison Motsinger-Reif[m], Shannon L. Risacher[n,o], Colette Blach[i,j], Joseph E. Lucas[p], Tyler Massaro[p], Gregory Louie[q,r], Hongjie Zhu[q,r], Guido Dallmann[s], Kristaps Klavins[s], Therese Koal[s], Sungeun Kim[n,o], Kwangsik Nho[n,o], Li Shen[n,o], Ramon Casanova[h], Sudhir Varma[h], Cristina Legido-Quigley[t], M. Arthur Moseley[l], Kuixi Zhu[e], Marc Y. R. Henrion[e], Sven J. van der Lee[u], Amy C. Harms[v], Ayse Demirkan[u], Thomas Hankemeier[u,v], Cornelia M. van Duijn[u,v], John Q. Trojanowski[a], Leslie M. Shaw[a], Andrew J. Saykin[n,o], Michael W. Weiner[w], P. Murali Doraiswamy[q,r], Rima Kaddurah-Daouk[q,r,x,*], for the Alzheimer's Disease Neuroimaging Initiative and the Alzheimer Disease Metabolomics Consortium[1]





Path from genetic signal to targeted therapeutics

Understand biological pathway

Identify biomarkers

Discover loci/genes robustly associated with relevant trait	Identify causal gene underpinning pathogenesis	Understand underlying mechanism	Develop therapeutic hypothesis	Identify patients most likely to benefit
Common variant associations	Mapping / Sequencing	Gene-centric phenome scans	Molecular pharmacology	Biomarker development
Rare variant associations	Tissue expression	iPSC and related	Assay development	Molecular epidemiology
Monogenic disorders	eQTL, pQTL, mQTL	In-vitro functional assessment	Cell-based perturbation	Clinical trial samples
Family-based	Pathway analysis	Gene editing	Mechanistic models	Clinical imaging

Target discovery and qualification → Understanding disease biology → Stratification & enrichment

Saykin et al, Alzheimer's & Dementia 11 (2015) 792-814

Molecular Validation & Therapeutics: New Models

Model Organism Development and Evaluation for Late-onset Alzheimer's Disease (MODEL-AD)

Contact PI: Bruce Lamb

ADNI contributes target nominations & characterization
MODEL-AD is creating organisms based on ADNI reports

INDIANA UNIVERSITY

The Jackson Laboratory
Leading the search for tomorrow's cures

Sage BIONETWORKS

Website: https://Model-AD.org

Contact: ModelAD@iupui.edu

Data: https://www.synapse.org/#!Synapse:syn2580853/wiki/409840

Thanks to IADC, IU Neuroscience, ADNI & AMP-AD

Indiana Alzheimer Disease Center

Directions & Challenges in Imaging Genomics

- Structural, functional & molecular imaging as endophenotypes
  - Connectome as QTL
- Integration of polygenic scoring approaches with endophenotypes
- Epigenetic changes and longitudinal studies
- Network approaches to multi-layered -omics and imaging data
- Connecting peripheral metabolic changes in targeted biochemical pathways to brain structure and function
- Use of imaging genetics and related phenotypes to enrich clinical trials
- Resolving heterogeneity by integrating genetics, other –omics and imaging biomarker profiles → precision medicine of AD & related disorders
- Target discovery and validation, informing model system development and assessment of therapeutic strategies