GWAS and Candidate Studies of MRI and Amyloid PET Phenotypes for Alzheimer's Disease

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ADC Director Meeting, Boston, October 6, 2012

Acknowledgements & Disclosures

- **National Institute on Aging**
  - ADNI U01 AG024904 & RC2 AG036535
  - R01 AG19771 & P30 AG10133
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- Foundation for the NIH
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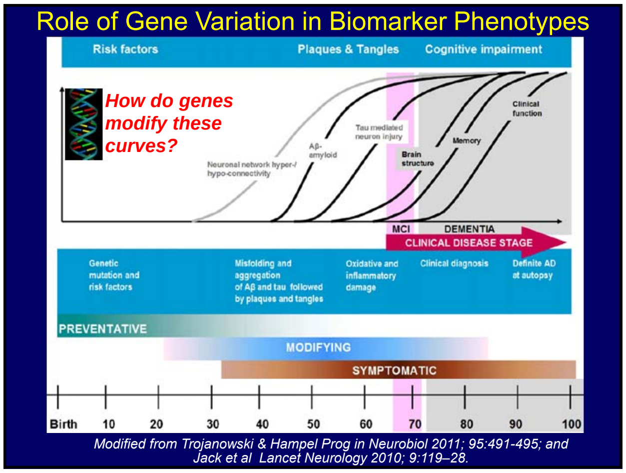
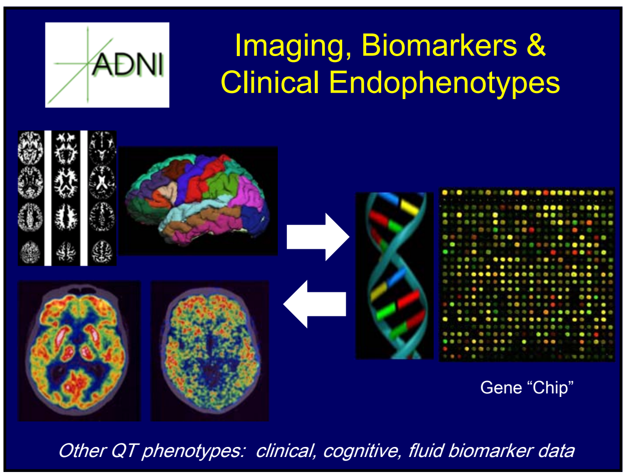
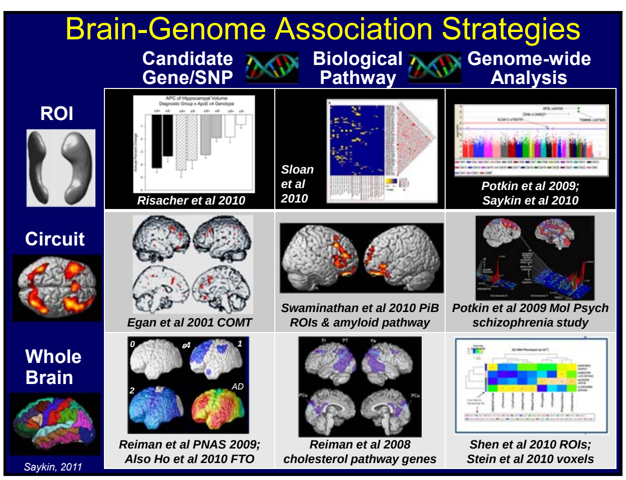
  - Gene Network Sciences, Merck, Pfizer (DNA ext.)
- Alzheimer's Association & Brin Wojcicki Foundation
  - Sequencing of ADNI-GO/2
- Saykin disclosures for related work:
  - Siemens Healthcare, Welch-Allyn, Eli Lilly

Overview

- Neuroimaging as an endophenotype
  - Enhanced statistical power and proximity to biology
- Methodological issues in mapping between quantitative biomarker phenotypes and genetic data
- Emerging findings, challenges & future directions:
  - Genome-wide whole brain analysis – MRI phenotypes
  - Candidate gene and pathway-based analyses
    - Example: PiB PET
  - New Florbetapir PET GWAS
  - Ongoing work and new directions
    - Exome and Whole Genome Sequencing


Role of Gene Variation in Biomarker Phenotypes
Risk factors
Plaques & Tangles
Cognitive impairment
How do genes modify these curves?
Clinical function
Tau mediated neuron injury
Memory
Aβ-amyloid
Brain structure
Neuronal network hyper-/ hypo-connectivity
MCI
DEMENTIA
CLINICAL DISEASE STAGE
Genetic mutation and risk factors
Misfolding and aggregation of Aβ and tau followed by plaques and tangles
Oxidative and inflammatory damage
Clinical diagnosis
Definite AD at autopsy
PREVENTATIVE
MODIFYING
SYMPTOMATIC
Birth 10 20 30 40 50 60 70 80 90 100
Modified from Trojanowski & Hampel Prog in Neurobiol 2011; 95:491-495; and Jack et al Lancet Neurology 2010; 9:119–28.


ADNI
Imaging, Biomarkers & Clinical Endophenotypes
Gene "Chip"
Other QT phenotypes: clinical, cognitive, fluid biomarker data


Brain-Genome Association Strategies
Candidate Gene/SNP
Biological Pathway
Genome-wide Analysis
ROI
Circuit
Whole Brain
Risacher et al 2010
Sloan et al 2010
Potkin et al 2009; Saykin et al 2010
Egan et al 2001 COMT
Swaminathan et al 2010 PiB ROIs & amyloid pathway
Potkin et al 2009 Mol Psych schizophrenia study
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

Whole Brain & Genome-wide Analysis

ROI-based

NeuroImage

Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: A study of the ADNI cohort

Shen et al NeuroImage 53 (2010) 1051–1063

Voxel-based

NeuroImage

Voxelwise genome-wide association study (vGWAS)

Stein et al NeuroImage 53 (2010) 1160–1174

New GWAS Loci for Brain Structure

Nature Genetics, April 15, 2012


Hippocampal Volume: 12q14 & 12q24

Intracranial Volume (ICV): 6q22, 12q14/15, & 12q24, 17q21

Stein et al, n=21,151 — *ENIGMA Consortium including ADNI*
Identification of common variants associated with human hippocampal and intracranial volumes

Bis et al, n=9,232 — *CHARGE Consortium; also ENIGMA/ADNI*
Common variants at 12q14 and 12q24 are associated with hippocampal volume

Ikram et al, n=8,175 — *CHARGE Consortium; also EGC*
Common variants at 6q22 and 17q21 are associated with intracranial volume

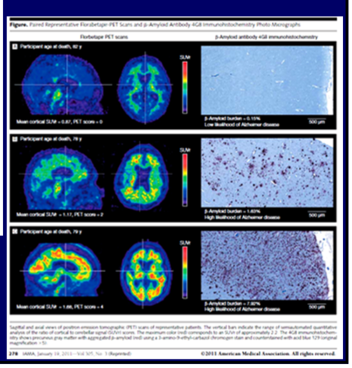
Taal et al, n=10,768 — *EGC Consortium; also CHARGE*
Common variants at 12q15 and 12q24 are associated with infant head circumference

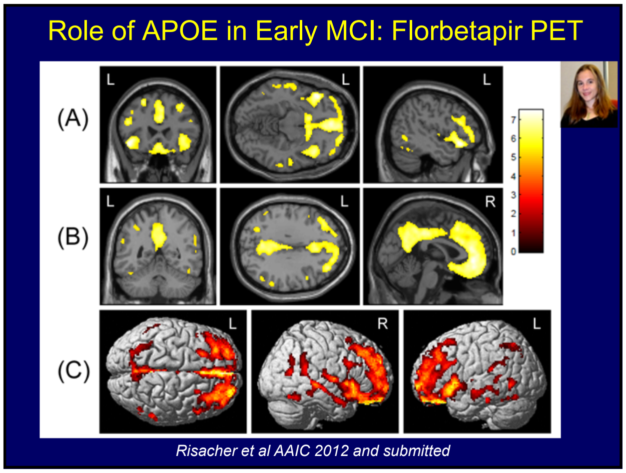
[18F]Florbetapir PET as Intermediate Phenotype: Neuropathological Validated for Imaging Amyloid

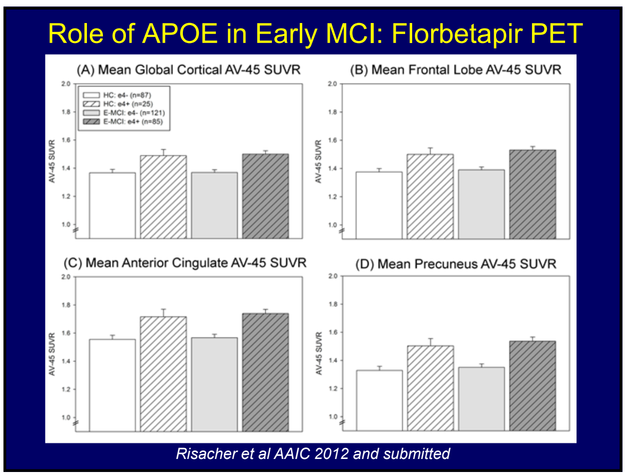
Use of Florbetapir-PET for Imaging β-Amyloid Pathology

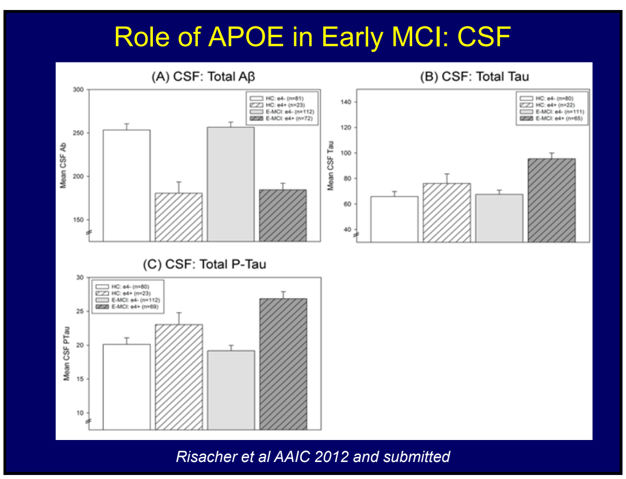
JAMA Jan 19, 2011

FDA approval in 2012

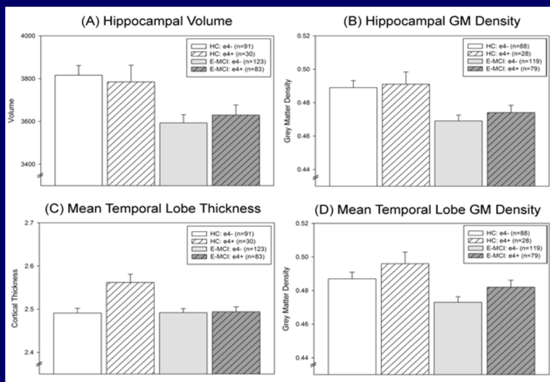



Role of APOE in Early MCI: Florbetapir PET
(A)
(B)
(C)
L
R
Risacher et al AAIC 2012 and submitted


Role of APOE in Early MCI: Florbetapir PET
(A) Mean Global Cortical AV-45 SUVR
(B) Mean Frontal Lobe AV-45 SUVR
(C) Mean Anterior Cingulate AV-45 SUVR
(D) Mean Precuneus AV-45 SUVR
HC: e4- (n=87)
HC: e4+ (n=25)
E-MCI: e4- (n=121)
E-MCI: e4+ (n=85)
AV-45 SUVR
Risacher et al AAIC 2012 and submitted

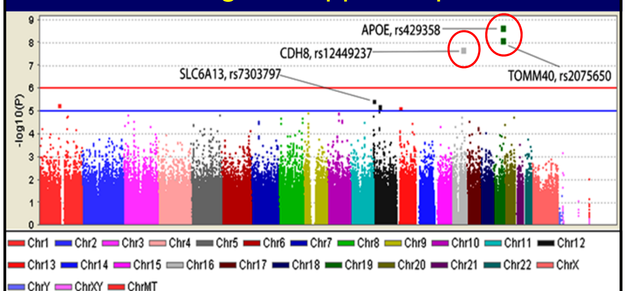

Role of APOE in Early MCI: CSF
(A) CSF: Total Aβ
HC: e4- (n=81)
HC: e4+ (n=23)
E-MCI: e4- (n=112)
E-MCI: e4+ (n=72)
Mean CSF Ab
(B) CSF: Total Tau
HC: e4- (n=80)
HC: e4+ (n=22)
E-MCI: e4- (n=111)
E-MCI: e4+ (n=65)
Mean CSF Tau
(C) CSF: Total P-Tau
HC: e4- (n=80)
HC: e4+ (n=23)
E-MCI: e4- (n=112)
E-MCI: e4+ (n=69)
Mean CSF PTau
Risacher et al AAIC 2012 and submitted

Role of APOE in Early MCI: Structure



Risacher et al AAIC 2012 and submitted

Longitudinal GWAS on Adjusted Annual Percent Change in Hippocampal Volume



APOE (Chr 19): rs429358 is the epsilon 4 allele marker
TOMM40 (Chr 19): translocase of outer mitochondrial membrane 40 homolog (LD with APOE)
CADH8 (Chr 16): cadherin 8, type 2; synaptic adhesion, axonal growth/guidance (no data in AD)

Saykin et al Alzheimer's & Dementia (2010); 6:265–273

Increasing Focus on Biological Pathways

Review

Trends in Genetics July 2012, Vol. 28, No. 7

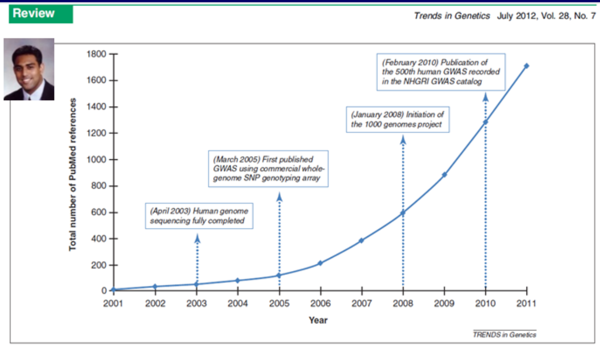


Figure 1. PubMed citations for 'pathway analysis' from 2001 to 2011. The use of pathway analysis has grown exponentially in the past 3–5 years. This explosion in use has followed major developments (shown in boxes) in characterizing the human genome and in performing genome-wide studies of complex diseases and traits. Data points represent the total number of references displayed through a PubMed search for 'pathway analysis', using date limits of January 1, 2001 and December 31 of the calendar year denoted on the x-axis. Abbreviations: GWAS, genome-wide association study; NHGRI, National Human Genome Research Institute; SNP, single nucleotide polymorphism.

Ramanan et al, Trends in Genetics, July 2012, Vol. 28, No. 7

DOI 10.1007/s11682-011-9136-1

ORIGINAL RESEARCH

Amyloid pathway-based candidate gene analysis of [11C]PiB-PET in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort

Shanker Swaminathan · Li Shen · Shannon L. Risacher · Karmen K. Yoder · John D. West · Sungeun Kim · Kwangsik Nho · Tatiana Foroud · Mark Inlow · Steven G. Potkin · Matthew J. Huentelman · David W. Craig · William J. Jagust · Robert A. Koeppe · Chester A. Mathis · Clifford R. Jack Jr. · Michael W. Weiner · Andrew J. Saykin · the Alzheimer's Disease Neuroimaging Initiative (ADNI)

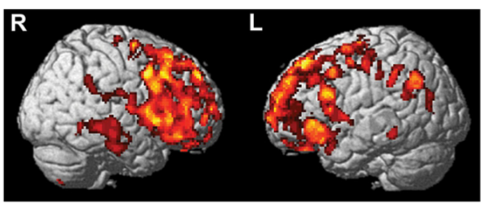
Abstract Amyloid imaging with [^{11}C]Pittsburgh Compound-B (PiB) provides *in vivo* data on plaque deposition in those with, or at risk for, Alzheimer's disease (AD). We performed a gene-based association analysis of 15 quality-controlled amyloid-pathway associated candidate genes in 103 Alzheimer's Disease Neuroimaging Initiative participants. The mean normalized PiB uptake value across four brain regions known to have amyloid deposition in AD was used as a quantitative phenotype. The minor allele of an intronic SNP within *DHCR24* was identified and associated with a lower average PiB uptake. Further investigation at whole-brain voxel-wise level indicated that non-carriers of the minor allele had higher PiB uptake in frontal regions compared to carriers. *DHCR24* has been previously shown to confer

Swaminathan et al, Brain Imaging & Behavior (2012)

Amyloid Gene Pathway PET Study: [11C]PiB

DHCR24 (seladin - selective AD indicator – cholesterol synthesis pathway)

Brain Imaging and Behavior



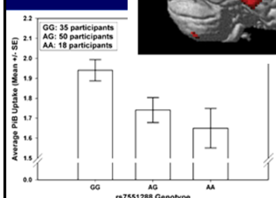


Fig. 2 Comparison of average PiB uptake from four brain regions in the three genotype groups (GG, AG and AA) of rs7551288. 'A' represents the minor allele and 'G' represents the major allele of this SNP

Swaminathan et al, Brain Imaging & Behavior (2012)

DOI 10.1007/s11682-011-9136-1

Fig. 3 Visualization of the results of statistical parametric mapping analysis. The regions with significantly (uncorrected $p<0.005$, cluster size=50 voxels) increased PiB uptake in 35 participants with the GG genotype group compared to 50 participants with the AG and 18 participants with the AA genotype groups are shown in color. The red-to-yellow scale indicates increasing statistical significance of differences in PiB uptake

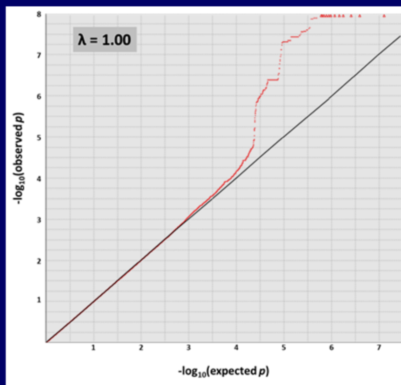
[^{18}F]Florbetapir GWAS Sample (ADNI-GO/2, N=555)

	HC (n=179)	EMCI (n=190)	LMCI (n=115)	AD (n=71)
Age (years)	76·68 (6·25)	71·04 (7·41)	75·61 (8·14)	75·87 (8·15)
Gender (women, %)	87 (49%)	83 (44%)	41 (36%)	27 (38%)
Education (years)	16·27 (2·72)	15·89 (2·65)	16·11 (2·90)	16·04 (2·87)
APOE ε4 allele (present, %)	41 (23%)	77 (41%)	49 (43%)	45 (64%)
CDR-SOB	0·07 (0·29)	1·22 (0·73)	1·73 (1·18)	5·63 (2·70)
Mini Mental Status Examination	29·07 (1·25)	28·39 (1·52)	27·74 (1·84)	21·68 (4·24)
Logical Memory Immediate Recall (WMS-R)	14·94 (3·36)	10·93 (2·81)	8·74 (4·35)	4·20 (3·10)
Logical Memory Delayed Recall (WMS-R)	14·08 (3·64)	8·87 (1·73)	6·13 (4·38)	1·67 (2·50)

Data are number (%) or mean (SD). CDR-SOB = Clinical Dementia Rating-Sum of Boxes. WMS-R = Wechsler Memory Scale-Revised. PET = positron emission tomography.

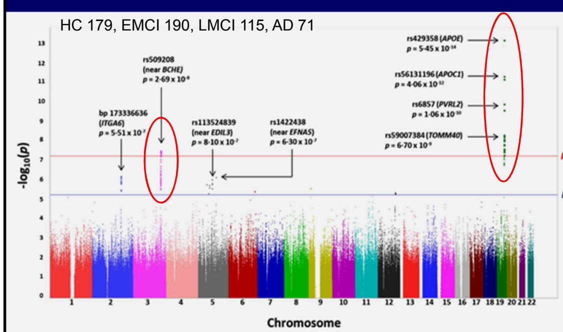
Ramanan et al, submitted

Florbetapir GWAS Q-Q Plot



Ramanan et al, submitted

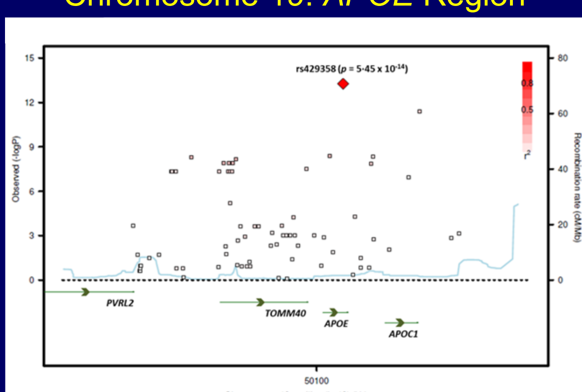
GWAS of [18F]Florbetapir PET Amyloid Burden



Two significant loci explain 15% of variance in cortical Aβ levels
(*APOE:* 10.7%; *BCHE*: 4.3%)

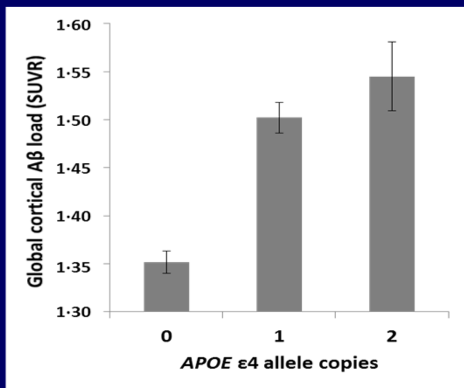
Ramanan et al, submitted

Chromosome 19: *APOE* Region



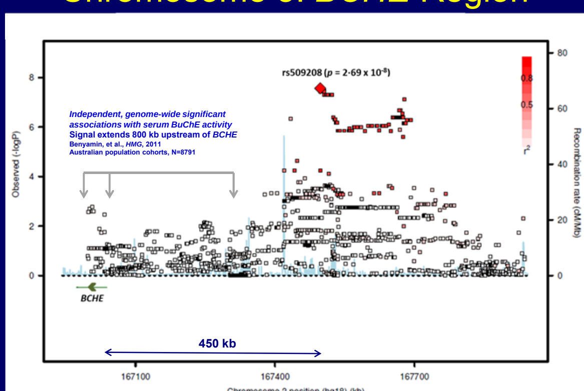
Ramanan et al, submitted

Influence of *APOE*



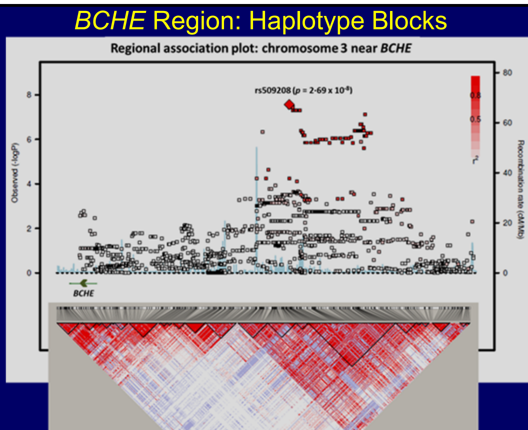
Ramanan et al, submitted

Chromosome 3: *BCHE* Region



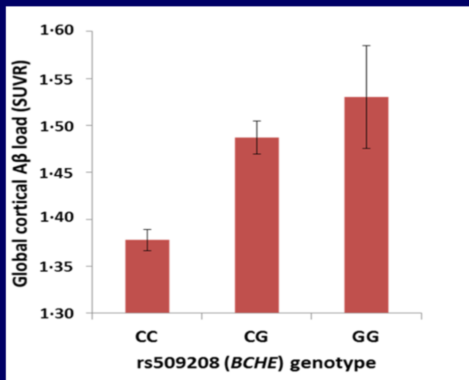
Ramanan et al, submitted

BCHE Region: Haplotype Blocks



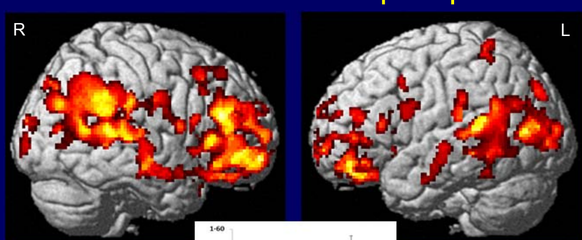
Ramanan et al, submitted

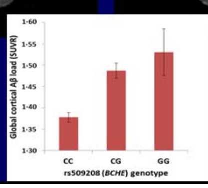
Influence of *BCHE*



Ramanan et al, submitted

Topography of rs509208 (*BCHE*) Influence on Florbetapir Uptake





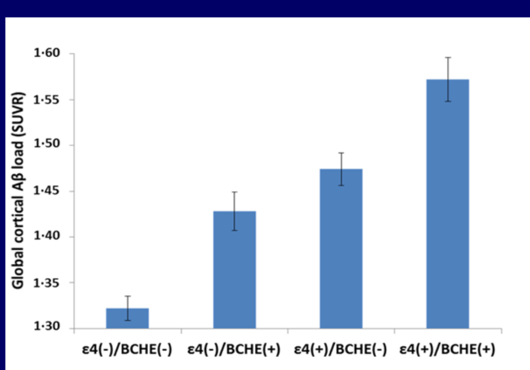
<u>Covariates</u>:
age, sex, diagnosis and APOE ε4 status

p <.05, FWE corrected

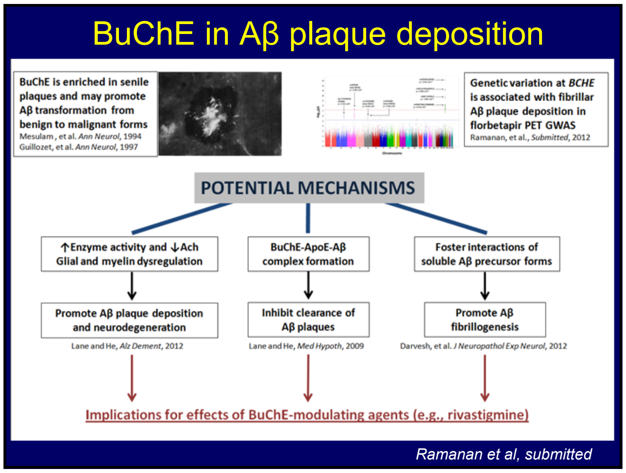
ADNI, N=555

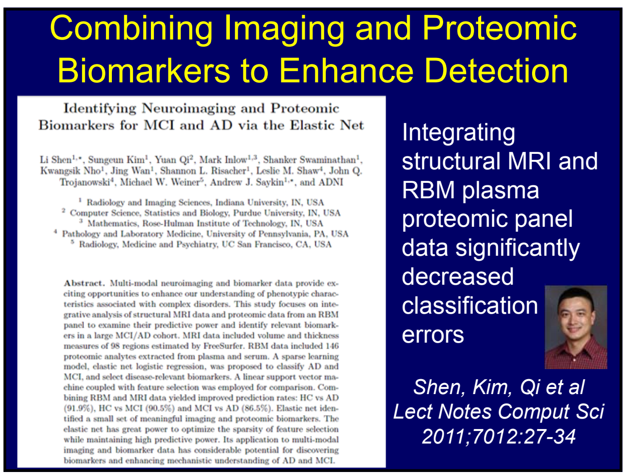
Ramanan et al, submitted

Additive Effects of *APOE* and *BCHE*



Ramanan et al, submitted


BuChE in Aβ plaque deposition
BuChE is enriched in senile plaques and may promote Aβ transformation from benign to malignant forms
Mesulam, et al. Ann Neurol, 1994
Guillozet, et al. Ann Neurol, 1997
Genetic variation at BCHE is associated with fibrillar Aβ plaque deposition in florbetapir PET GWAS
Ramanan, et al., Submitted, 2012
POTENTIAL MECHANISMS
↑Enzyme activity and ↓Ach
Glial and myelin dysregulation
BuChE-ApoE-Aβ complex formation
Foster interactions of soluble Aβ precursor forms
Promote Aβ plaque deposition and neurodegeneration
Lane and He, Alz Dement, 2012
Inhibit clearance of Aβ plaques
Lane and He, Med Hypoth, 2009
Promote Aβ fibrillogenesis
Darvesh, et al. J Neuropathol Exp Neurol, 2012
Implications for effects of BuChE-modulating agents (e.g., rivastigmine)
Ramanan et al, submitted


Combining Imaging and Proteomic Biomarkers to Enhance Detection
Identifying Neuroimaging and Proteomic Biomarkers for MCI and AD via the Elastic Net
Li Shen[1,*], Sungeun Kim[1], Yuan Qi[2], Mark Inlow[1,3], Shanker Swaminathan[1], Kwangsik Nho[1], Jing Wan[1], Shannon L. Risacher[1], Leslie M. Shaw[4], John Q. Trojanowski[4], Michael W. Weiner[5], Andrew J. Saykin[1,*], and ADNI
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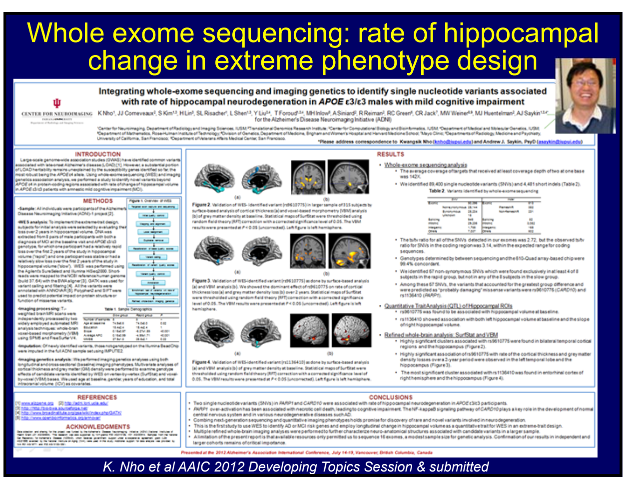
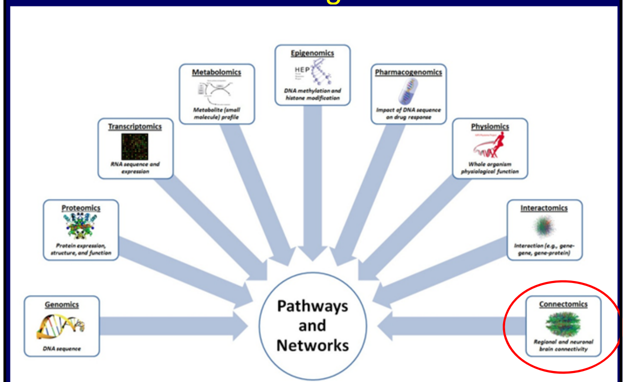
[3] Mathematics, Rose-Hulman Institute of Technology, IN, USA
[4] Pathology and Laboratory Medicine, University of Pennsylvania, PA, USA
[5] Radiology, Medicine and Psychiatry, UC San Francisco, CA, USA
Abstract. Multi-modal neuroimaging and biomarker data provide exciting opportunities to enhance our understanding of phenotypic characteristics associated with complex disorders. This study focuses on integrative analysis of structural MRI data and proteomic data from an RBM panel to examine their predictive power and identify relevant biomarkers in a large MCI/AD cohort. MRI data included volume and thickness measures of 98 regions estimated by FreeSurfer. RBM data included 146 proteomic analytes extracted from plasma and serum. A sparse learning model, elastic net logistic regression, was proposed to classify AD and MCI, and select disease-relevant biomarkers. A linear support vector machine coupled with feature selection was employed for comparison. Combining RBM and MRI data yielded improved prediction rates: HC vs AD (91.9%), HC vs MCI (90.5%) and MCI vs AD (86.5%). Elastic net identified a small set of meaningful imaging and proteomic biomarkers. The elastic net has great power to optimize the sparsity of feature selection while maintaining high predictive power. Its application to multi-modal imaging and biomarker data has considerable potential for discovering biomarkers and enhancing mechanistic understanding of AD and MCI.
Integrating structural MRI and RBM plasma proteomic panel data significantly decreased classification errors
Shen, Kim, Qi et al
Lect Notes Comput Sci
2011;7012:27-34


Whole exome sequencing: rate of hippocampal change in extreme phenotype design
Integrating whole-exome sequencing and imaging genetics to identify single nucleotide variants associated with rate of hippocampal neurodegeneration in APOE ε3/ε3 males with mild cognitive impairment
INTRODUCTION
METHODS
RESULTS
REFERENCES
ACKNOWLEDGEMENTS
CONCLUSIONS
K. Nho et al AAIC 2012 Developing Topics Session & submitted

Future: Convergent "-Omics"



Ramanan et al, Trends in Genetics, July 2012, Vol. 28, No. 7:
dx.doi.org/10.1016/j.tig.2012.03.004

ADNI Genotyping Working Groups

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