Genetic Heterogeneity of Clinically Defined AD

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Indiana ADC

ADC Clinical Core Leaders Meeting

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SCHOOL OF **MEDICINE**

Disclosures & Acknowledgements

Disclosures

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The Indiana Neurorepository Project

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Overview

- Dimensions of Heterogeneity
- Genes and gene pathways
  - Impact on risk/protective factors
  - Influence on age of onset
- Cognitive subtypes and trajectories
- Signal or noise? Can we model heterogeneity?
- Implications

High Dimensionality Landscape

Subjective Cognitive Decline

Informant Perception

Cognitive Performance

Social Networks

Lifestyle & environment

- Cognitive stimulation, diet, exercise, sleep

Biomarkers

- *CSF, blood, others*
- *Multi-omics*

Genomics

- DNA, mRNA, miRNA

- Epigenetics

Amyloid - PET/CSF

Tau - PET/CSF

MRI - structure

MRI - function

Connectome

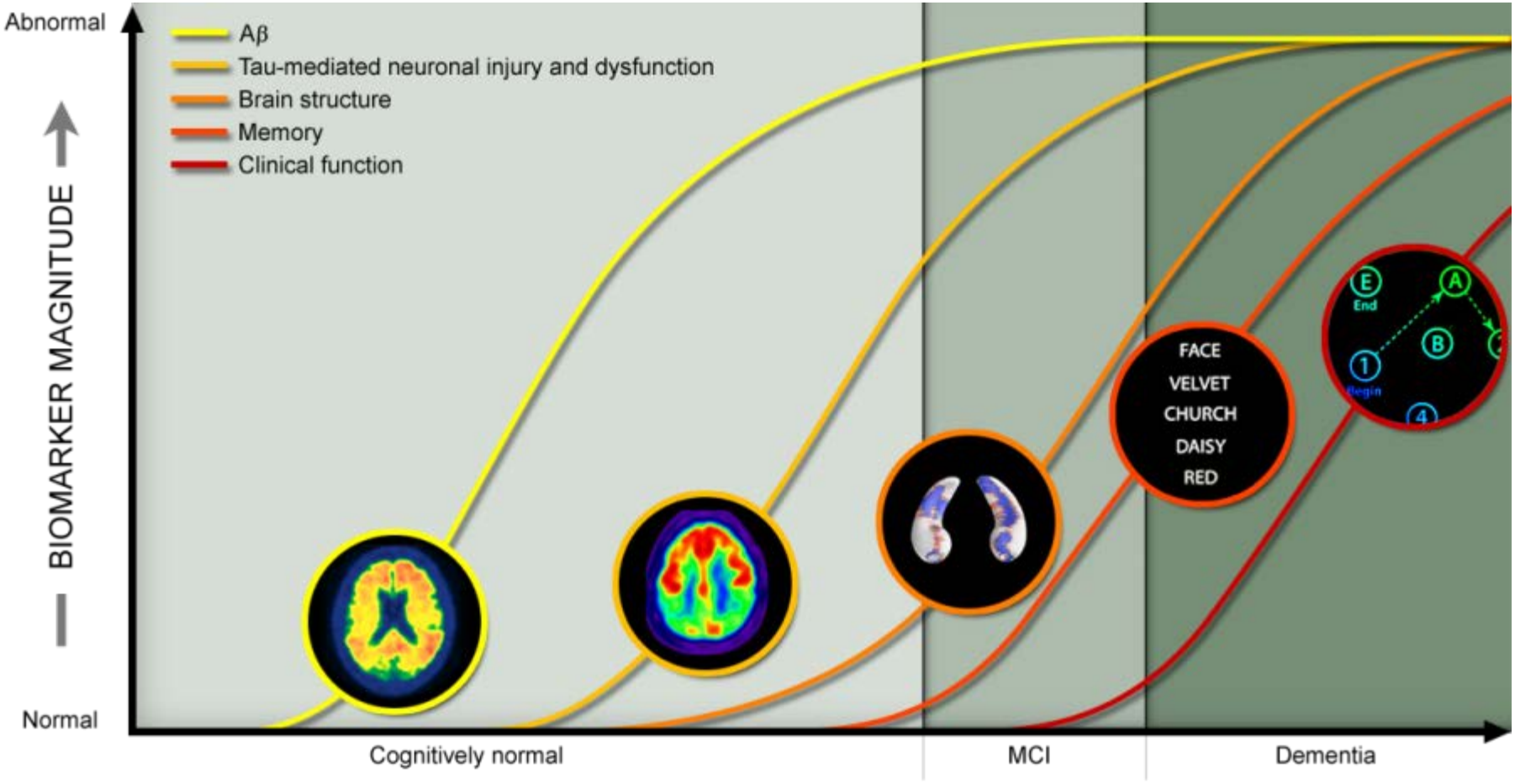
Vascular function & CVD burden

Immune System, Inflammation & Oxidative Stress

Metabolism & Mitochondria

Saykin 2017

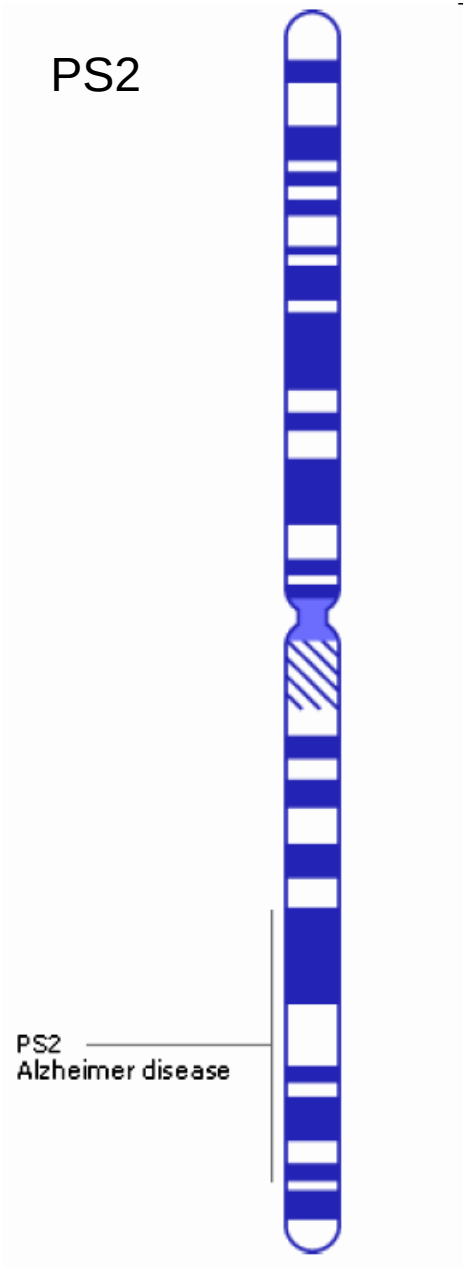
Dynamic Aspects: Temporal Heterogeneity



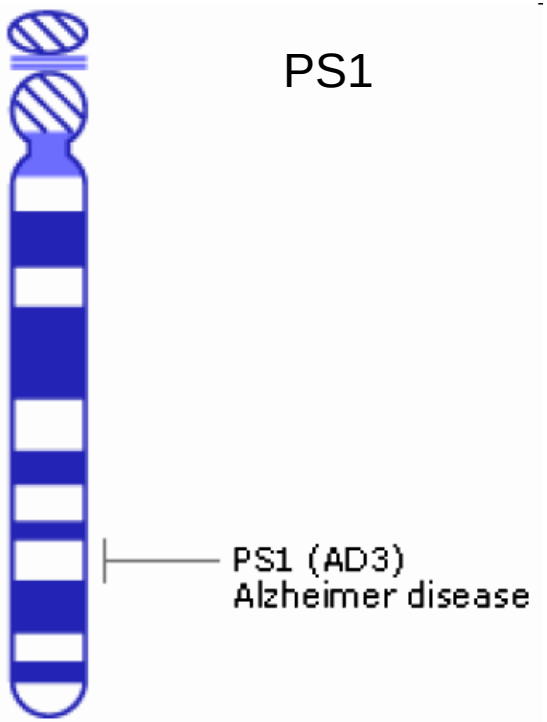
http://adni.loni.usc.edu/study-design/background-rationale/

Heritability

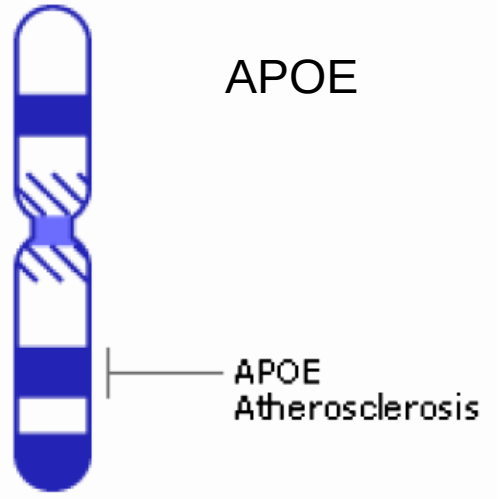
LOAD: genetic factors account for ~60-80% of risk (Gatz et al 2006); APOE accounts for up to 50% (Ashford & Mortimer 2002); so up to 30% remains to be found.



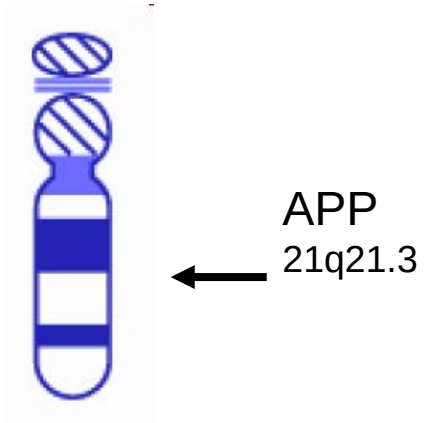
Chromosome 1



Chromosome 14

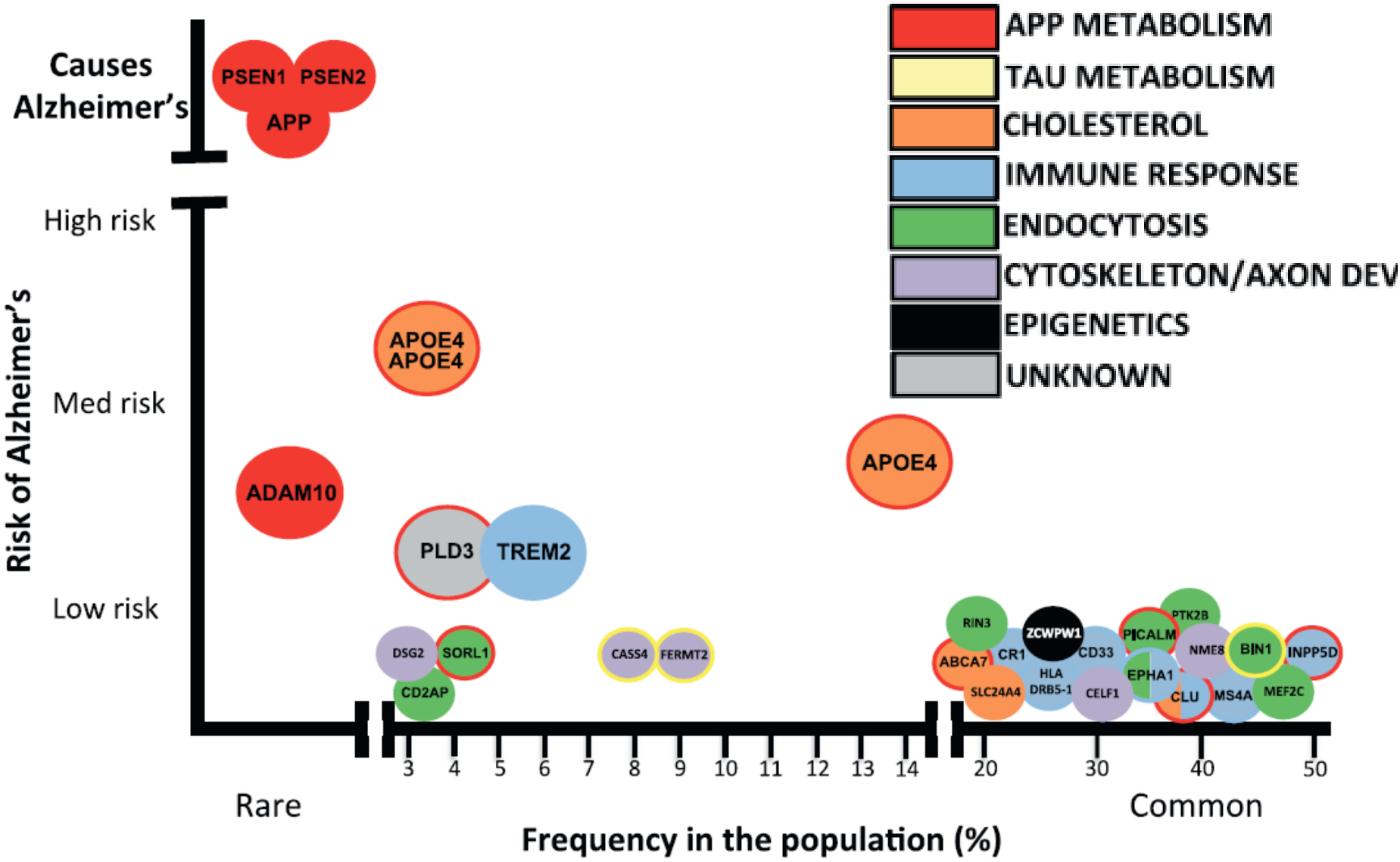


Chromosome 19



Chromosome 21

Genetic Risk for AD: Many Pathways



C. Karch & A. Goate, Biol Psychiatry 2015; 77:43–51

AD Cognitive Subtypes: Studies by Many Groups

ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-11

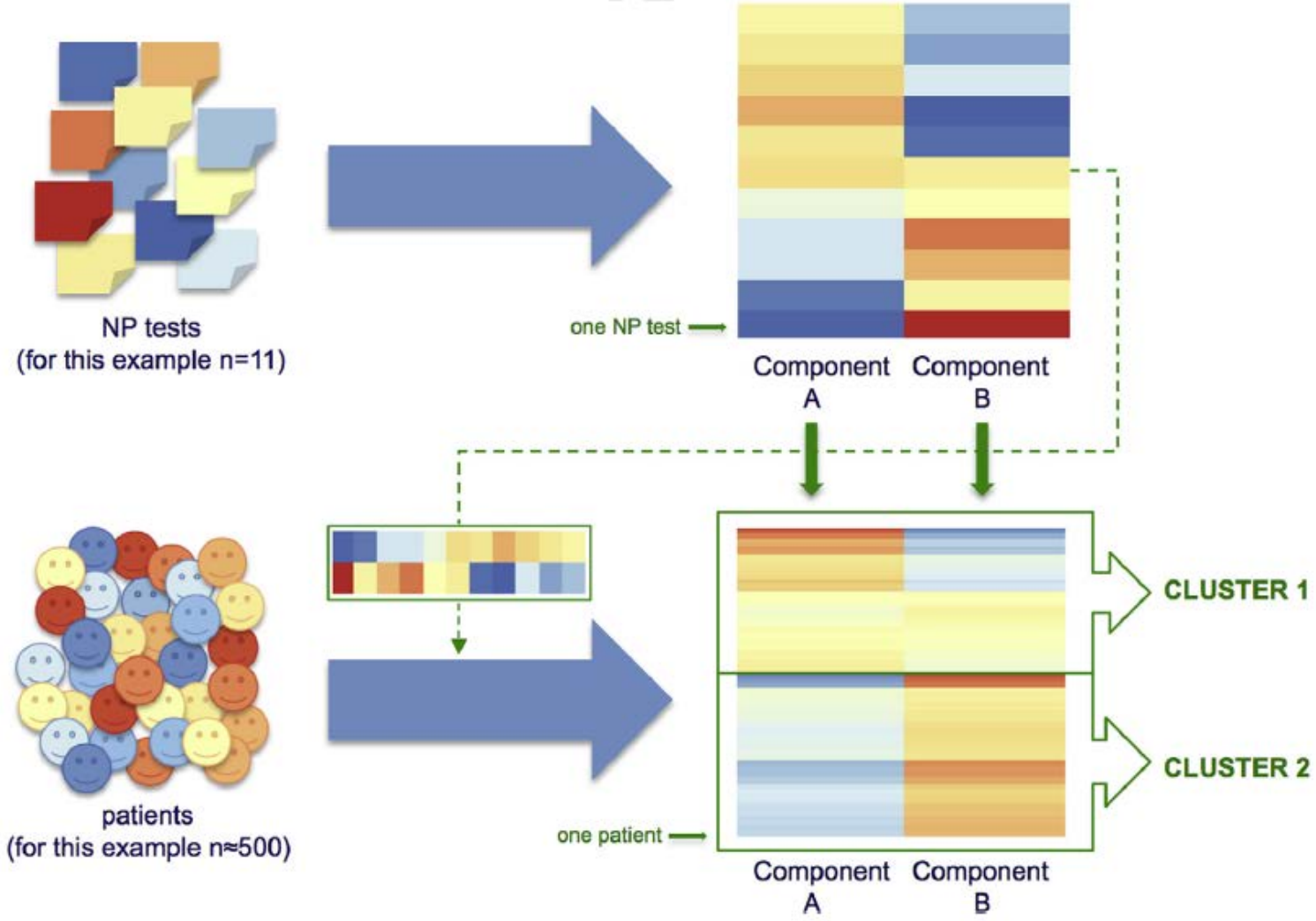
Alzheimer's & Dementia

Featured Article

Cognitive subtypes of probable Alzheimer's disease robustly identified in four cohorts

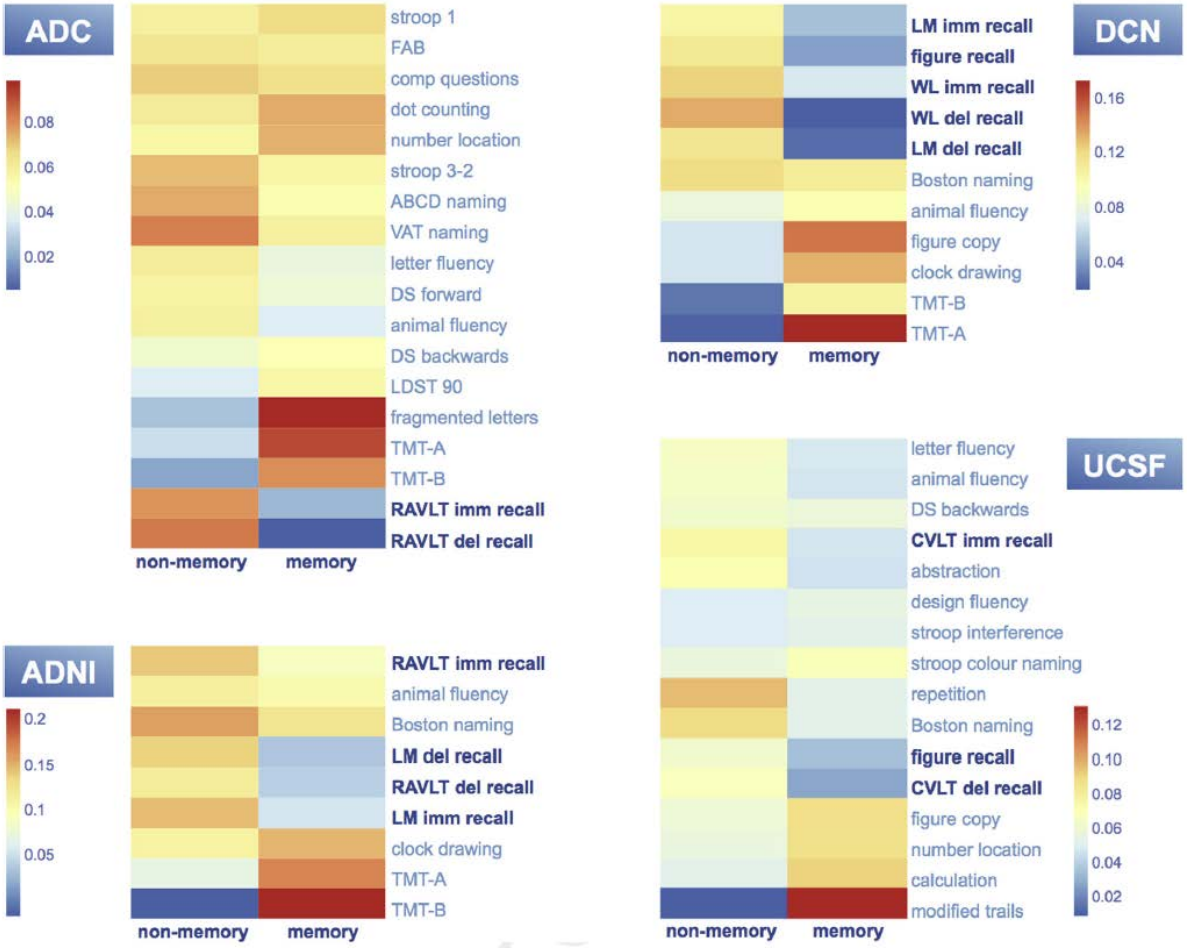
Nienke M. E. Scheltens[a,*], Betty M. Tijms[a], Teddy Koene[b], Frederik Barkhof[c,d,e], Charlotte E. Teunissen[f], Steffen Wolfsgruber[g,h], Michael Wagner[g,h], Johannes Kornhuber[i], Oliver Peters[j], Brendan I. Cohn-Sheehy[k], Gil D. Rabinovici[k], Bruce L. Miller[k], Joel H. Kramer[k], Philip Scheltens[a], Wiesje M. van der Flier[a,l], Alzheimer's Disease Neuroimaging Initiative[l], German Dementia Competence Network, University of California San Francisco Memory and Aging Center, and Amsterdam Dementia Cohort

Cognitive Subtypes



N. Scheltens et al Alz & Dem 4/2017

Multiple tests and cohorts



N. Scheltens et al Alz & Dem 4/2017

Genetic architecture of memory and executive functioning in AD

EPAD:GRF
Executive Prominent AD:
Genetics and Risk Factors

Brain Imaging and Behavior (2012) 6:649–660
DOI 10.1007/s11682-012-9207-y

ADNI: FRIDAY HARBOR 2011 WORKSHOP SPECIAL ISSUE

Dysexecutive and amnesic AD subtypes defined by single indicator and modern psychometric approaches: relationships with SNPs in ADNI

Shubhabrata Mukherjee · Emily Trittschuh · Laura E. Gibbons · R. Scott Mackin · Andrew Saykin · Paul K. Crane · for the Alzheimer's Disease Neuroimaging Initiative

(P Crane R01 AG 042437)

Neurobiology of Aging 41 (2016) 115–121

Contents lists available at ScienceDirect

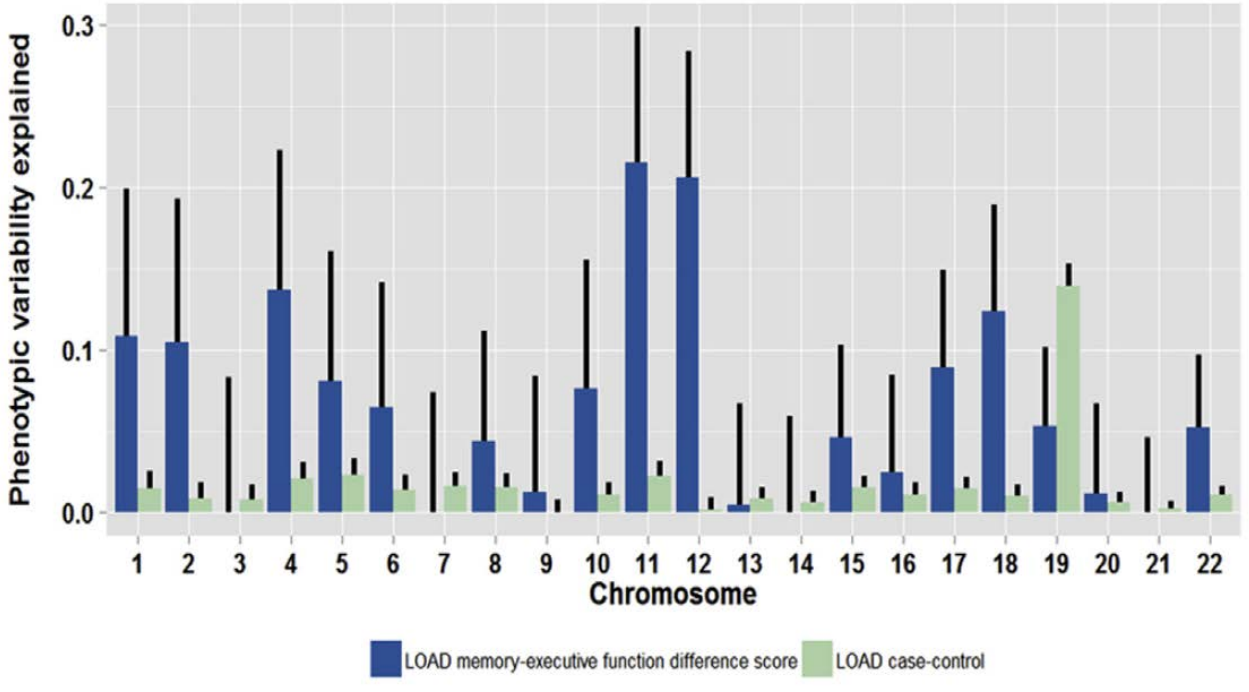
Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

The executive prominent/memory prominent spectrum in Alzheimer's disease is highly heritable

Jesse Mez [a], Shubhabrata Mukherjee [b], Timothy Thornton [c], David W. Fardo [d], Emily Trittschuh [e], Sheila Sutti [f], Richard Sherva [g], John S. Kauwe [h], Adam C. Naj [i], Gary W. Beecham [j], Alden Gross [k], Andrew J. Saykin [l], Robert C. Green [f], Paul K. Crane [b,*], for Executive Prominent Alzheimer's Disease: Genetics and Risk Factors (EPAD:GRF), the Alzheimer's Disease Neuroimaging Initiative (ADNI1) [1], and the Alzheimer's Disease Genetics Consortium (ADGC)

Subtypes are Heritable (0.68)



Dynamic Aspects: Cognitive Trajectory

ELSEVIER

Alzheimer's & Dementia ■ (2013) 1–8

Alzheimer's & Dementia

Genome-wide association study of the rate of cognitive decline in Alzheimer's disease

Richard Sherva[a], Yorghos Tripodis[b], David A. Bennett[c], Lori B. Chibnik[d,e,f], Paul K. Crane[g], Philip L. de Jager[d,e,f], Lindsay A. Farrer[a,b,h], Andrew J. Saykin[i], Joshua M. Shulman[j], Robert C. Green[k,*], The GENAROADS Consortium, and The Alzheimer's Disease Neuroimaging Initiative

Genetics of Resilience

Brain Imaging and Behavior
DOI 10.1007/s11682-013-9259-7

ORIGINAL RESEARCH

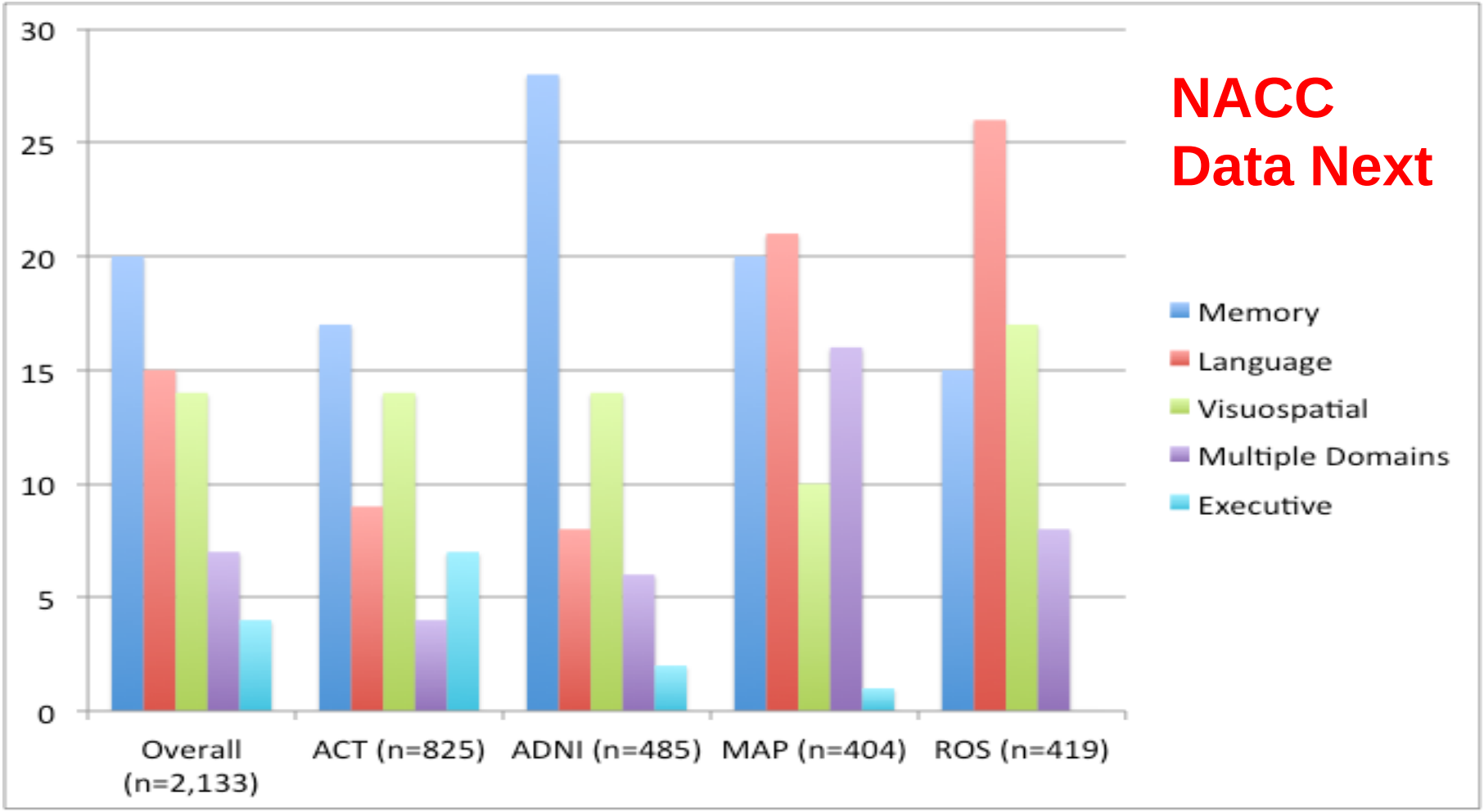
Gene-based GWAS and biological pathway analysis of the resilience of executive functioning

Shubhabrata Mukherjee · Sungeun Kim · Vijay K. Ramanan · Laura E. Gibbons · Kwangsik Nho · M. Maria Glymour · Nilüfer Ertekin-Taner · Thomas J. Montine · Andrew J. Saykin · Paul K. Crane · for the Alzheimer's Disease Neuroimaging Initiative

Searching for protective factors

Pathway (gene set) name	Set size[a]	Uncorrected *P*-value
Dendritic/Neuron spine	151 (131)	1.27×10^{-12}
Presynaptic membrane	47 (42)	8.68×10^{-11}
Postsynaptic density/ Dendritic spine head	111 (100)	2.00×10^{-10}
Calcium ion transmembrane transporter activity	109 (104)	3.75×10^{-10}
Ras guanyl-nucleotide exchange factor activity	93 (86)	4.67×10^{-10}
Rho guanyl-nucleotide exchange factor activity	75 (68)	9.33×10^{-10}
Calmodulin binding	161 (150)	1.11×10^{-9}
Calcium channel activity	92 (89)	1.89×10^{-9}
Guanyl-nucleotide exchange factor activity	167 (151)	2.91×10^{-9}
Cell adhesion molecule binding	52 (46)	5.06×10^{-9}
Synaptic membrane	204 (179)	9.49×10^{-9}
Divalent inorganic cation transmembrane transporter activity	129 (120)	3.21×10^{-8}
Transmembrane receptor protein tyrosine phosphatase activity	18 (18)	3.53×10^{-8}
Regulation of phospholipase C activity	65 (61)	5.22×10^{-8}
Voltage-gated ion channel activity	177 (156)	5.41×10^{-8}
Positive regulation of phospholipase C activity	64 (60)	5.54×10^{-8}
Chloride channel activity	72 (60)	8.36×10^{-8}
Axon part	121 (106)	8.48×10^{-8}
Synapse organization	83 (71)	1.03×10^{-7}
cAMP metabolic process	32 (30)	1.38×10^{-7}

Cognitively-defined subgroups
(P Crane R01 AG 042437)



- Memory most common overall, followed by language
- Isolated substantial language deficits quite marked in MAP and especially ROS
- Too few with isolated substantial executive functioning deficits for genetic analyses
- Multiple domains more common in MAP (especially) and ROS than in ADNI or ACT
  - Likely heterogeneous; ignoring for genetic analyses

APOE: Proportion with ≥1 ε4 alleles

Study	Overall	None	Memory	Language	Visuospatial	Multiple	Executive	Total n	p
ACT	34	35	47	25	30	31	20	711	0.005
ADNI	64	66	74	55	55	46	58	485	0.021
MAP	34	33	45	26	24	40	33	386	0.10
ROS	36	34	47	42	38	36	29	393	0.15
Total	42	42	56	31	38	39	27	1975	<0.001

lower by 10%	
lower by 5%	p>0.05
within 5%	p<0.05
higher by 5%	p<0.01
higher by 10%	p<0.0025

Paul Crane et al, unpublished data

Genetics of Subtypes: IGAP SNP Results

Gene	MAF	OR	ACT	ROS/MAP	ADNI	Meta	P(Meta)	P(Hetero)
*SORL1**	0.04	1.30						
BIN1	0.41	1.22						
CR1	0.20	1.18						
*CLU**	0.38	1.16						
ABCA7	0.19	1.15						
*PICALM**	0.36	1.15						
FERMT2	0.09	1.14						
*CASS4**	0.08	1.14						
*MS4A6A**	0.40	1.11						
*EPHA1**	0.34	1.11						
HLA-DRB5-HLA-DRB1	0.28	1.11						
PTK2B	0.37	1.10						
CD2AP	0.27	1.10						
*ZCWPW1**	0.29	1.10						
*SLC24A4-RIN3**	0.22	1.10						
INPP5D	0.49	1.08						
CELF1	0.32	1.08						
NME8	0.37	1.08						
*MEF2C**	0.41	1.08						
*CD33**	0.31	1.06						
		Case						
		Control						

OR <	OR >
0.80	1.25
0.67	1.50
0.57	1.75
0.50	2.00

p(meta)	p(het)
0.05	0.05
0.01	0.01
0.0025	0.0025

Paul Crane et al, unpublished data

No domain with prominent deficits

Gene	MAF	OR	ACT	ROS/MAP	ADNI	Meta	P(Meta)	P(Het)
*SORL1**	0.04	1.30	0.97	1.38	-	1.11	0.60	0.40
BIN1	0.41	1.22	1.25	1.03	1.17	1.16	0.042	0.56
CR1	0.2	1.18	1.12	1.36	1.06	1.18	0.058	0.47
*CLU**	0.38	1.16	0.89	1.28	1.18	1.14	0.084	0.15
ABCA7	0.19	1.15	1.20	1.40	1.31	1.28	0.004	0.76
*PICALM**	0.36	1.15	1.11	1.32	1.06	1.16	0.031	0.40
FERMT2	0.09	1.14	1.04	1.02	1.19	1.08	0.51	0.83
*CASS4**	0.08	1.14	1.10	0.99	1.40	1.16	0.22	0.48
*MS4A6A**	0.4	1.11	1.07	1.11	1.16	1.11	0.13	0.89
*EPHA1**	0.34	1.11	0.98	0.94	1.05	0.99	0.87	0.83
HLA-DRB5-HLA-DRB1	0.28	1.11	0.90	1.20	-	1.05	0.61	0.10
PTK2B	0.37	1.10	1.28	0.98	0.85	1.03	0.64	0.042
CD2AP	0.27	1.10	1.11	1.07	1.26	1.14	0.08	0.66
*ZCWPW1**	0.29	1.10	1.01	1.30	1.19	1.15	0.058	0.32
*SLC24A4-RIN3**	0.22	1.10	1.32	1.08	1.13	1.18	0.042	0.54
INPP5D	0.49	1.08	1.06	1.02	1.21	1.09	0.19	0.57
CELF1	0.32	1.08	1.09	1.11	0.94	1.05	0.47	0.59
NME8	0.37	1.08	0.88	0.89	0.94	0.90	0.11	0.91
*MEF2C**	0.41	1.08	1.20	1.30	1.11	1.20	0.010	0.68
*CD33**	0.31	1.06	1.27	0.96	1.07	1.09	0.22	0.23
		Case	223	227	246	696		
		Control	1407	887	331	2625		

OR <	OR >
0.80	1.25
0.67	1.50
0.57	1.75
0.50	2.00

p(meta)	p(het)
0.05	0.05
0.01	0.01
0.0025	0.0025

Paul Crane et al, unpublished data

Isolated substantial memory deficits

Gene	MAF	OR	ACT	ROS/MAP	ADNI	Meta	P(Meta)	P(Hetero)
*SORL1**	0.04	1.30	2.27	0.94	-	1.17	0.59	0.20
BIN1	0.41	1.22	1.05	1.29	0.84	0.99	0.93	0.17
CR1	0.20	1.18	1.56	1.16	1.45	1.36	0.005	0.53
*CLU**	0.38	1.16	0.97	1.12	1.07	1.07	0.48	0.90
ABCA7	0.19	1.15	1.16	0.98	1.27	1.17	0.17	0.70
*PICALM**	0.36	1.15	1.38	1.20	1.35	1.31	0.003	0.80
FERMT2	0.09	1.14	1.41	1.36	1.69	1.49	0.003	0.77
*CASS4**	0.08	1.14	1.24	1.02	2.15	1.44	0.024	0.12
*MS4A6A**	0.40	1.11	1.34	0.91	1.49	1.21	0.028	0.033
*EPHA1**	0.34	1.11	1.39	1.15	1.00	1.13	0.22	0.38
HLA-DRB5-HLA-DRB1	0.28	1.11	0.93	1.10	-	1.03	0.84	0.49
PTK2B	0.37	1.10	1.18	0.98	0.95	1.02	0.80	0.58
CD2AP	0.27	1.10	1.06	0.99	1.16	1.08	0.46	0.78
*ZCWPW1**	0.29	1.10	1.63	1.24	1.33	1.37	0.001	0.55
*SLC24A4-RIN3**	0.22	1.10	1.27	1.04	1.03	1.10	0.36	0.68
INPP5D	0.49	1.08	1.12	1.11	1.30	1.19	0.040	0.66
CELF1	0.32	1.08	1.01	1.10	1.05	1.06	0.55	0.94
NME8	0.37	1.08	1.12	1.04	0.91	1.01	0.90	0.62
*MEF2C**	0.41	1.08	1.42	1.54	1.15	1.32	0.003	0.39
*CD33**	0.31	1.06	1.02	1.06	1.15	1.08	0.39	0.87
		Case	82	112	179	373		
		Control	1407	887	331	2625		

OR <	OR >
0.80	1.25
0.67	1.50
0.57	1.75
0.50	2.00

p(meta)	p(het)
0.05	0.05
0.01	0.01
0.0025	0.0025

Paul Crane et al, unpublished data

Isolated substantial language impairment

Gene	MAF	OR	ACT	ROS/MAP	ADNI	Meta	P(Meta)	P(Het)
*SORL1**	0.04	1.30	0.66	0.88	-	0.82	0.43	0.64
BIN1	0.41	1.22	0.90	1.03	1.00	0.99	0.95	0.91
CR1	0.2	1.18	1.47	1.53	1.63	1.54	<0.001	0.97
*CLU**	0.38	1.16	0.94	0.87	1.54	0.99	0.89	0.09
ABCA7	0.19	1.15	1.00	1.07	0.93	1.01	0.92	0.93
*PICALM**	0.36	1.15	1.18	1.13	0.86	1.07	0.51	0.52
FERMT2	0.09	1.14	1.27	0.99	1.35	1.10	0.58	0.72
*CASS4**	0.08	1.14	1.02	1.03	1.14	1.05	0.77	0.97
*MS4A6A**	0.4	1.11	1.17	0.93	1.00	0.99	0.90	0.69
*EPHA1**	0.34	1.11	0.81	0.97	0.81	0.89	0.29	0.72
HLA-DRB5-HLA-DRB1	0.28	1.11	0.65	0.88	-	0.83	0.14	0.35
PTK2B	0.37	1.10	1.46	1.11	0.97	1.13	0.25	0.44
CD2AP	0.27	1.10	2.16	1.10	1.38	1.42	0.001	0.022
*ZCWPW1**	0.29	1.10	0.64	1.04	0.81	0.89	0.29	0.21
*SLC24A4-RIN3**	0.22	1.10	1.00	0.86	1.35	0.96	0.71	0.33
INPP5D	0.49	1.08	1.09	0.83	1.47	0.99	0.95	0.06
CELF1	0.32	1.08	0.84	1.08	0.96	1.01	0.92	0.66
NME8	0.37	1.08	0.79	1.08	0.72	0.94	0.54	0.21
*MEF2C**	0.41	1.08	1.15	1.03	1.33	1.11	0.33	0.67
*CD33**	0.31	1.06	0.90	1.20	1.02	1.10	0.35	0.54
		Case	41	163	48	252		
		Control	1407	887	331	2625		

OR <	OR >
0.80	1.25
0.67	1.50
0.57	1.75
0.50	2.00

p(meta)	p(het)
0.05	0.05
0.01	0.01
0.0025	0.0025

Paul Crane et al, unpublished data

Isolated substantial visuospatial impairment

Gene	MAF	OR	ACT	ROS/MAP	ADNI	Meta	P(Meta)	P(Het)
*SORL1**	0.04	1.3	1.79	1.06	-	1.25	0.52	0.47
BIN1	0.41	1.22	1.24	1.26	1.03	1.14	0.23	0.69
CR1	0.2	1.18	1.55	1.18	1.84	1.45	0.002	0.29
*CLU**	0.38	1.16	0.66	0.80	1.18	0.87	0.21	0.13
ABCA7	0.19	1.15	1.30	0.74	1.21	1.12	0.43	0.34
*PICALM**	0.36	1.15	0.92	1.34	1.20	1.16	0.14	0.32
FERMT2	0.09	1.14	1.55	0.59	0.72	0.89	0.53	0.09
*CASS4**	0.08	1.14	1.60	0.67	1.06	0.95	0.77	0.11
*MS4A6A**	0.4	1.11	1.04	1.16	1.18	1.13	0.24	0.88
*EPHA1**	0.34	1.11	0.83	1.08	0.81	0.87	0.20	0.56
HLA-DRB5-HLA-DRB1	0.28	1.11	1.01	1.14	-	1.09	0.54	0.65
PTK2B	0.37	1.1	0.84	0.97	1.04	0.96	0.67	0.73
CD2AP	0.27	1.1	1.38	1.20	1.41	1.32	0.012	0.79
*ZCWPW1**	0.29	1.1	0.99	0.87	1.63	1.07	0.58	0.08
*SLC24A4-RIN3**	0.22	1.1	1.33	0.82	0.85	0.93	0.54	0.24
INPP5D	0.49	1.08	1.04	1.21	0.89	1.04	0.70	0.47
CELF1	0.32	1.08	0.77	0.91	0.85	0.85	0.14	0.84
NME8	0.37	1.08	1.35	1.18	1.12	1.20	0.08	0.78
*MEF2C**	0.41	1.08	1.21	1.78	1.04	1.28	0.031	0.13
*CD33**	0.31	1.06	1.29	1.27	1.32	1.29	0.020	0.99
		Case	61	88	84	233		
		Control	1407	887	331	2625		

OR <	OR >
0.80	1.25
0.67	1.50
0.57	1.75
0.50	2.00

p(meta)	p(het)
0.05	0.05
0.01	0.01
0.0025	0.0025

Paul Crane et al, unpublished data

Summary of genetic results (meta-analysis)

Gene	MAF	OR	No Domain	Memory	Visuospatial	Language
*SORL1**	0.04	1.30	1.11	1.17	1.25	0.82
BIN1	0.41	1.22	**1.16**	0.99	1.14	0.99
CR1	0.20	1.18	1.18	**1.36**	**1.45**	**1.54**
*CLU**	0.38	1.16	1.14	1.07	0.87	0.99
ABCA7	0.19	1.15	**1.28**	1.17	1.12	1.01
*PICALM**	0.36	1.15	**1.16**	**1.31**	1.16	1.07
FERMT2	0.09	1.14	1.08	**1.49**	0.89	1.10
*CASS4**	0.08	1.14	1.16	**1.44**	0.95	1.05
*MS4A6A**	0.40	1.11	1.11	**1.21***	1.13	0.99
*EPHA1**	0.34	1.11	0.99	1.13	0.87	0.89
HLA-DRB5-HLA-DRB1	0.28	1.11	1.05	1.03	1.09	0.83
PTK2B	0.37	1.10	1.03	1.02	0.96	1.13
CD2AP	0.27	1.10	1.14	1.08	**1.32**	**1.42***
*ZCWPW1**	0.29	1.10	1.15	**1.37**	1.07	0.89
*SLC24A4-RIN3**	0.22	1.10	**1.18**	1.10	0.93	0.96
INPP5D	0.49	1.08	1.09	**1.19**	1.04	0.99
CELF1	0.32	1.08	1.05	1.06	0.85	1.01
NME8	0.37	1.08	0.90	1.01	1.20	0.94
*MEF2C**	0.41	1.08	**1.20**	**1.32**	**1.28**	1.11
*CD33**	0.31	1.06	1.09	1.08	**1.29**	1.10
		Case	696	373	233	252
		Control	2625	2625	2625	2625

OR <	OR >
0.80	1.25
0.67	1.50
0.57	1.75
0.50	2.00

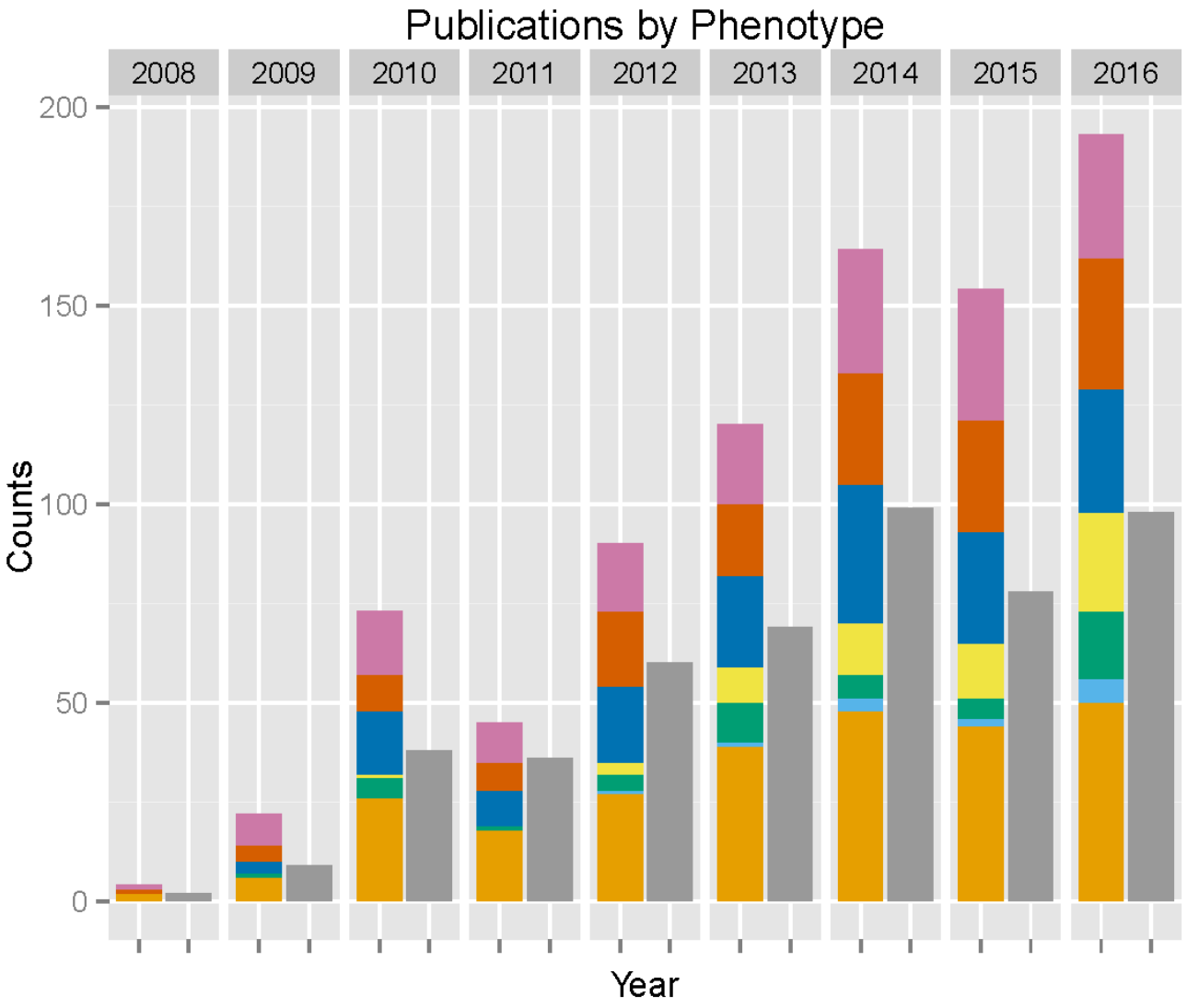
p>0.05
p<0.05
p<0.01
p<0.0025

* Het p<0.05

Paul Crane et al, unpublished data

More Heterogeneity: Genetics of Quantitative 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

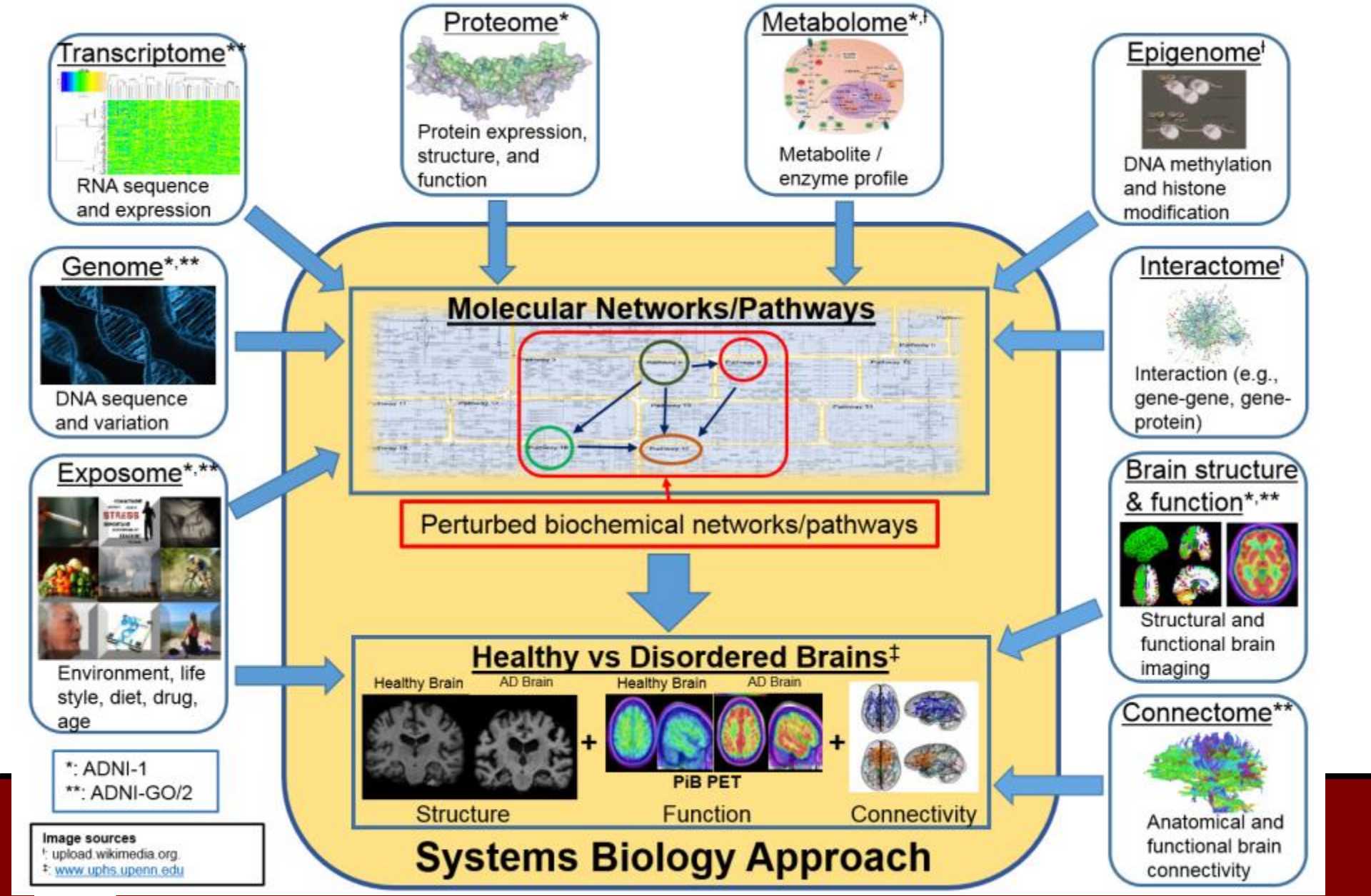
Shen et al, Brain Imaging Behav 2014; Yao et al, AAIC 2015 & AAIC 2016 & AAIC 2017; Saykin et al, Alzheimers Dement 2015

Updated: 4/2017

Role for Polygenic Risk Scores

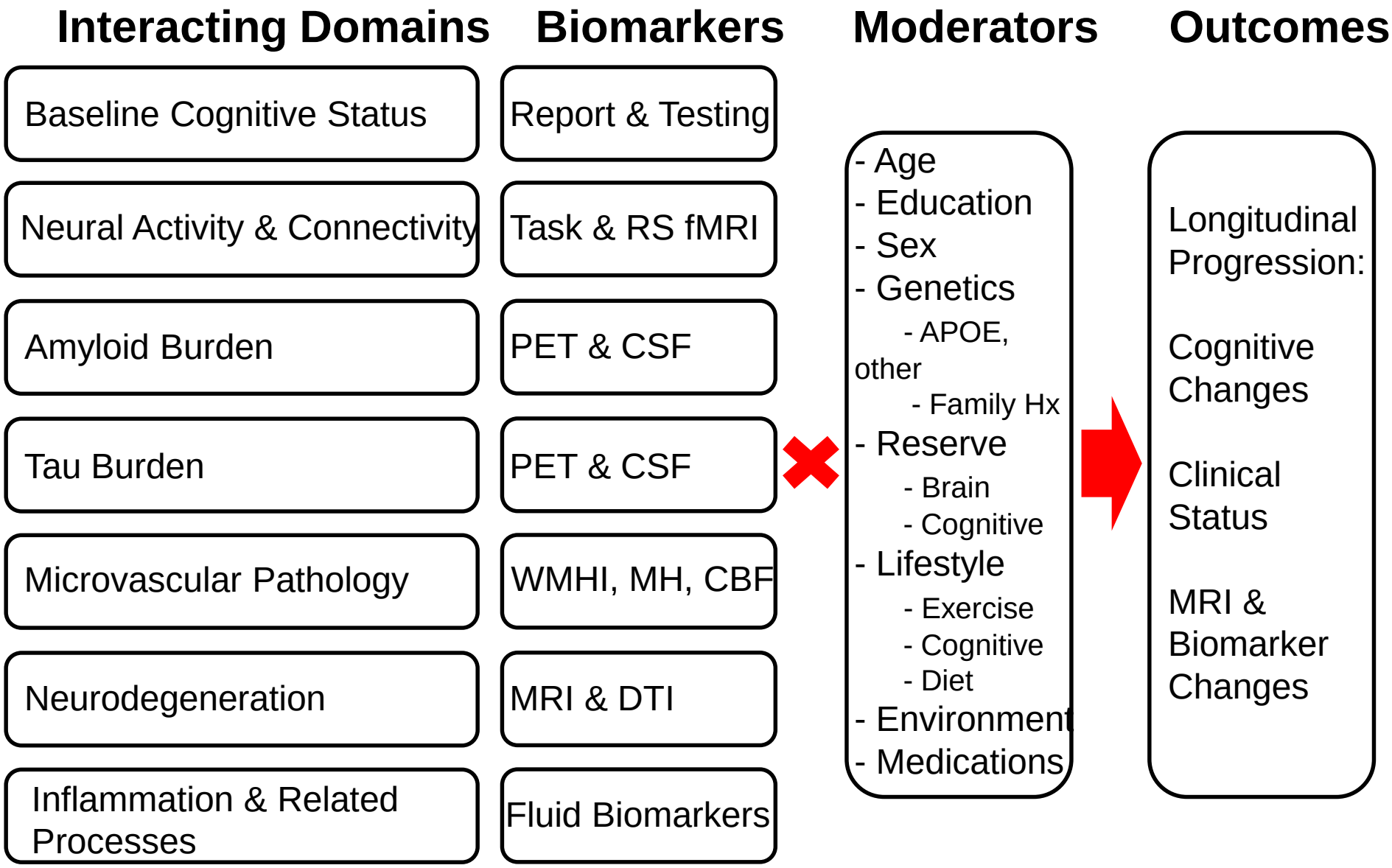
- Mormino, E.C., et al., *Polygenic risk of Alzheimer disease is associated with early- and late-life processes.* Neurology, 2016. **87**(5): p. 481-8.
- Hohman, T.J., et al., *Discovery of gene-gene interactions across multiple independent data sets of late onset Alzheimer disease from the Alzheimer Disease Genetics Consortium.* Neurobiol Aging, 2016. **38**: p. 141-50.
- Gaiteri, C., et al., *Genetic variants in Alzheimer disease - molecular and brain network approaches.* Nat Rev Neurol, 2016. **12**(7): p. 413-27.
- Yokoyama, J.S., et al., *Decision tree analysis of genetic risk for clinically heterogeneous Alzheimer's disease.* BMC Neurol, 2015. **15**: p. 47.
- Martiskainen, H., et al., *Effects of Alzheimer's disease-associated risk loci on cerebrospinal fluid biomarkers and disease progression: a polygenic risk score approach.* J Alzheimers Dis, 2015. **43**(2): p. 565-73.
- Escott-Price, V., et al., *Common polygenic variation enhances risk prediction for Alzheimer's disease.* Brain, 2015. **138**(Pt 12): p. 3673-84.
- Desikan, R.S., et al., *Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score.* PLoS Med, 2017. **14**(3): p. e1002258.

Working toward a Systems Biology of AD



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

From Noise to Signal: Modeling Heterogeneity

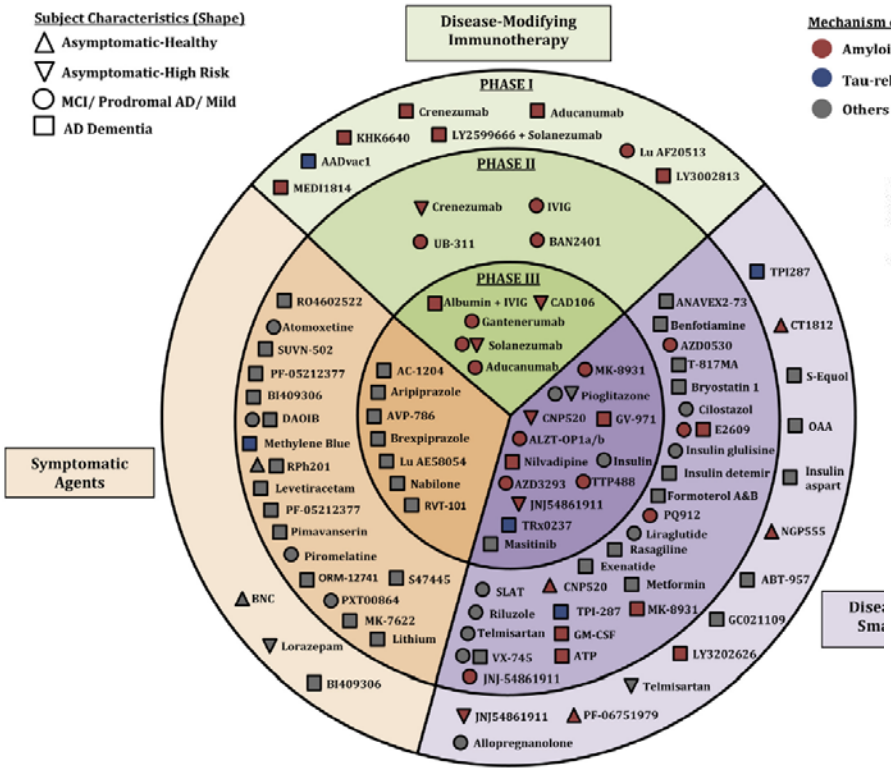


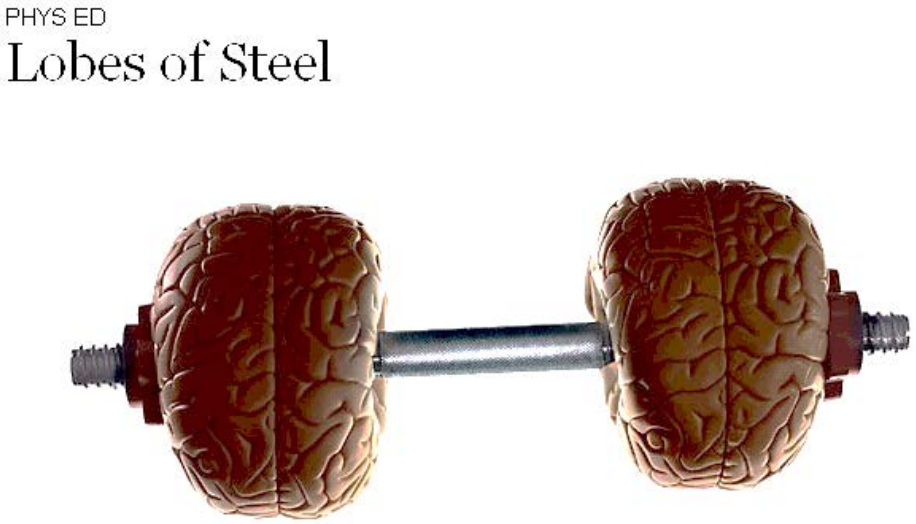
** WMHI: white matter hyperintensities; MH: microhemorrhages; CBF: cerebral blood flow*

Saykin, unpublished

- CMS coverage for amyloid imaging with Evidence Development
- Trial sponsored by the Alzheimer's Association
- Managed by the American College of Radiology (ACR) and American College of Radiology Imaging Network (ACRIN)
- 18,500 patients with cognitive impairment & unclear diagnosis
- **IU site (Apostolova)**
- **Genetics add-on study led by IU (Foroud & Saykin)**
  - **Remote consent and saliva kits for DNA (NCRAD) & Analyses (Imaging Genomics Lab)**

Relevance for Interventions





Cummings et al, Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 222-232

Summary & Discussion

- Heterogeneity is multidimensional with several axes – clinical, neuropathological & genetic
- Memory prominent – *APOE+* canonical AD pathology
- Heterogeneity is dynamic – time is another dimension
  - Phenotypes; gene expression, epigenetic modifications, etc.
- Hopefully we can turn “noise” into signal -> modeling
  - Understand fundamental disease mechanisms and
  - Tailor therapeutics with real “precision”
- How can the ADCs best contribute to resolving issues of heterogeneity?