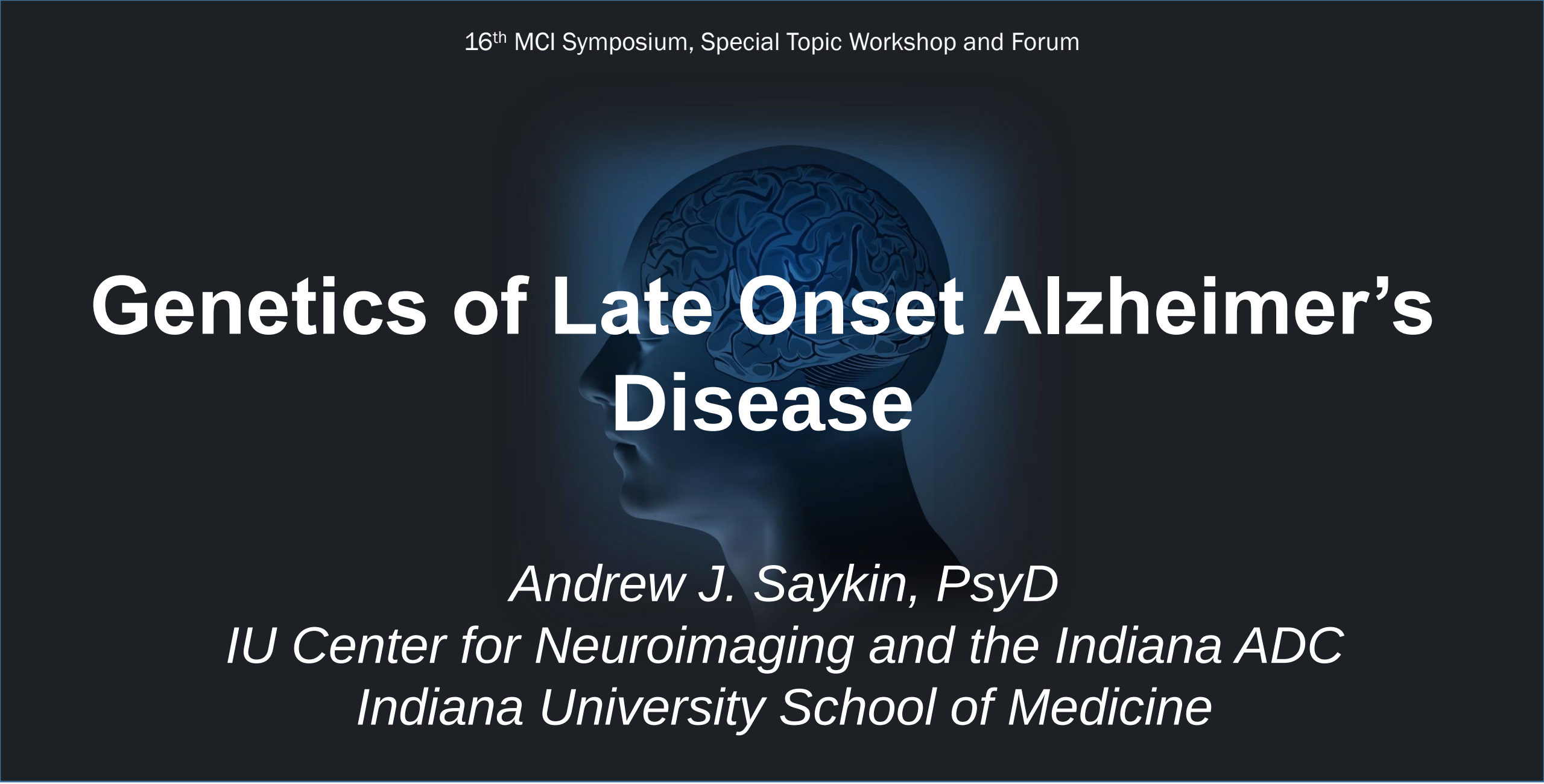

Genetics of Late Onset Alzheimer's Disease

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

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- 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
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  - 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

Genetics is One Piece of the AD Puzzle

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*

Model Systems

Amyloid PET/CSF

Tau PET/CSF

Structure (MRI)

Function (MRI)

Connectome

Vascular function & disease (MRI)

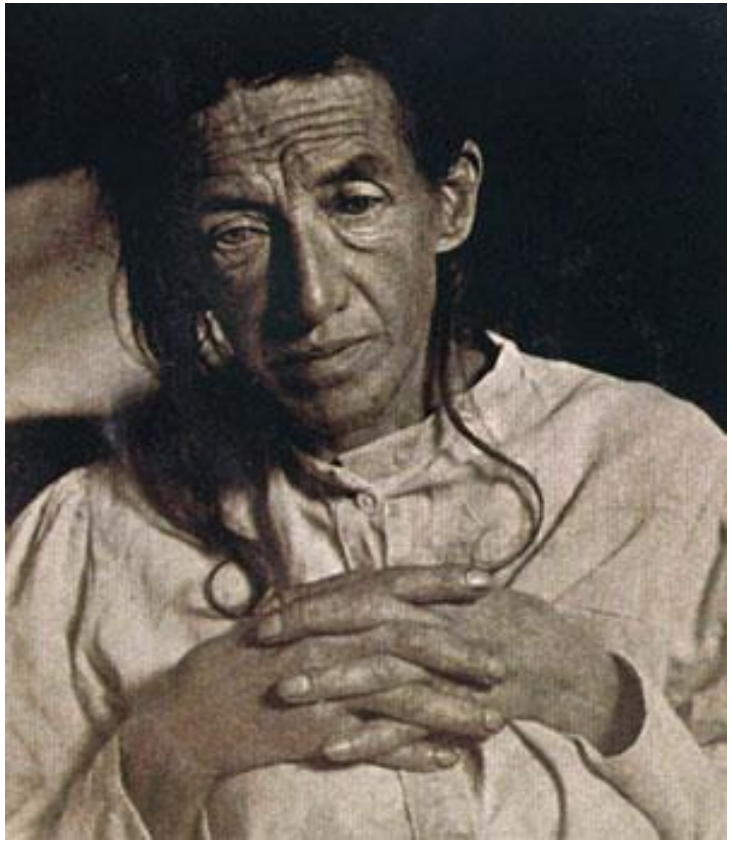
Immune System, Inflammation & Oxidative Stress

Metabolism & Mitochondria

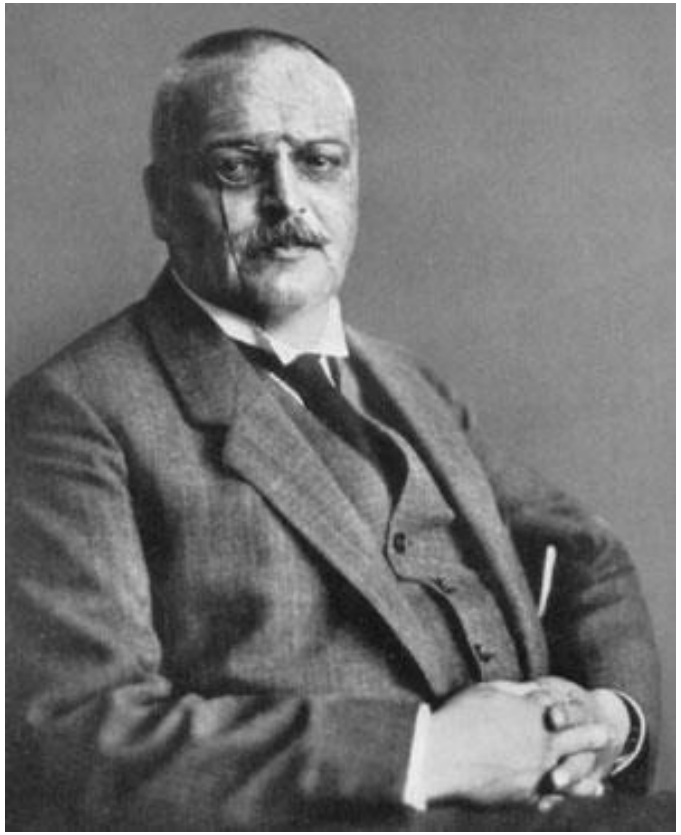
Complex Landscape of Alzheimer's Disease

Saykin 2017

The first patient diagnosed had early onset AD



Auguste Deter - taken in 1906, shortly before her death at age 55, during her stay at Frankfurt's City Mental Institution



Alois Alzheimer (1864-1915)
Published case report on Auguste D in 1907 describing plaques and tangles

Major Alzheimer Candidate Genes - 1990's

Early Onset AD Genes

Late Onset AD Genes

Accounts for ~60-80% of risk
APOE accounts for up to 50%
Up to ~30% remains to be found

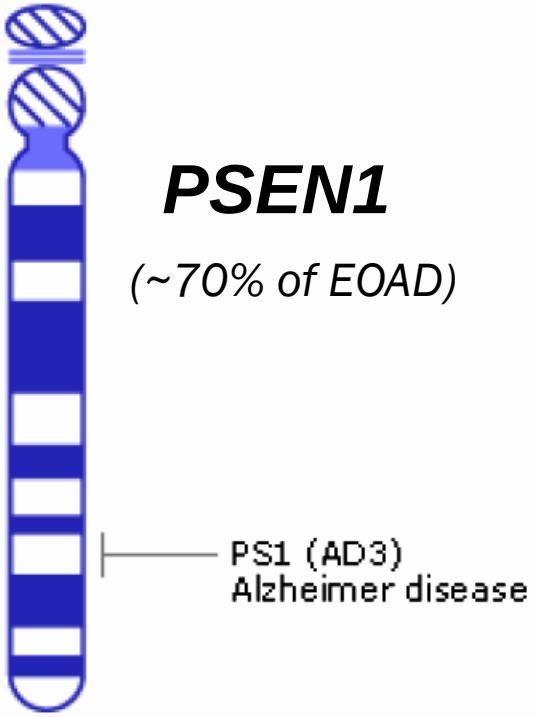
PSEN2

(<5% of EOAD)

Chromosome 1

PSEN1

(~70% of EOAD)

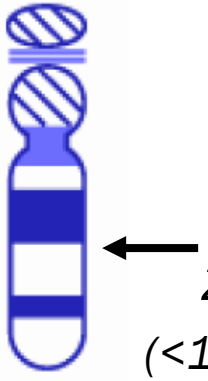


Chromosome 14

APP

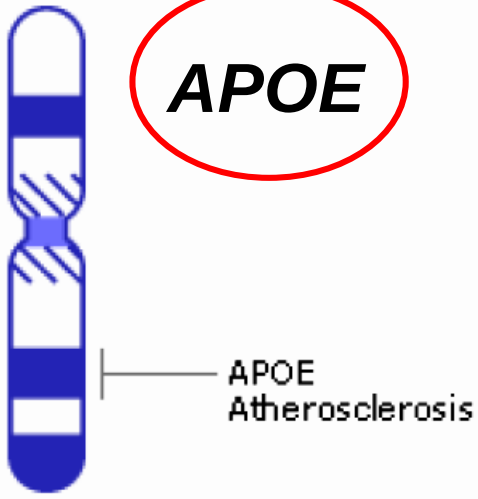
21q21.3

(<10% of EOAD)



Chromosome 21

APOE



Chromosome 19

Insights from Autosomal Dominant AD: The DIAN Consortium

Bateman et al, NEJM (2012)

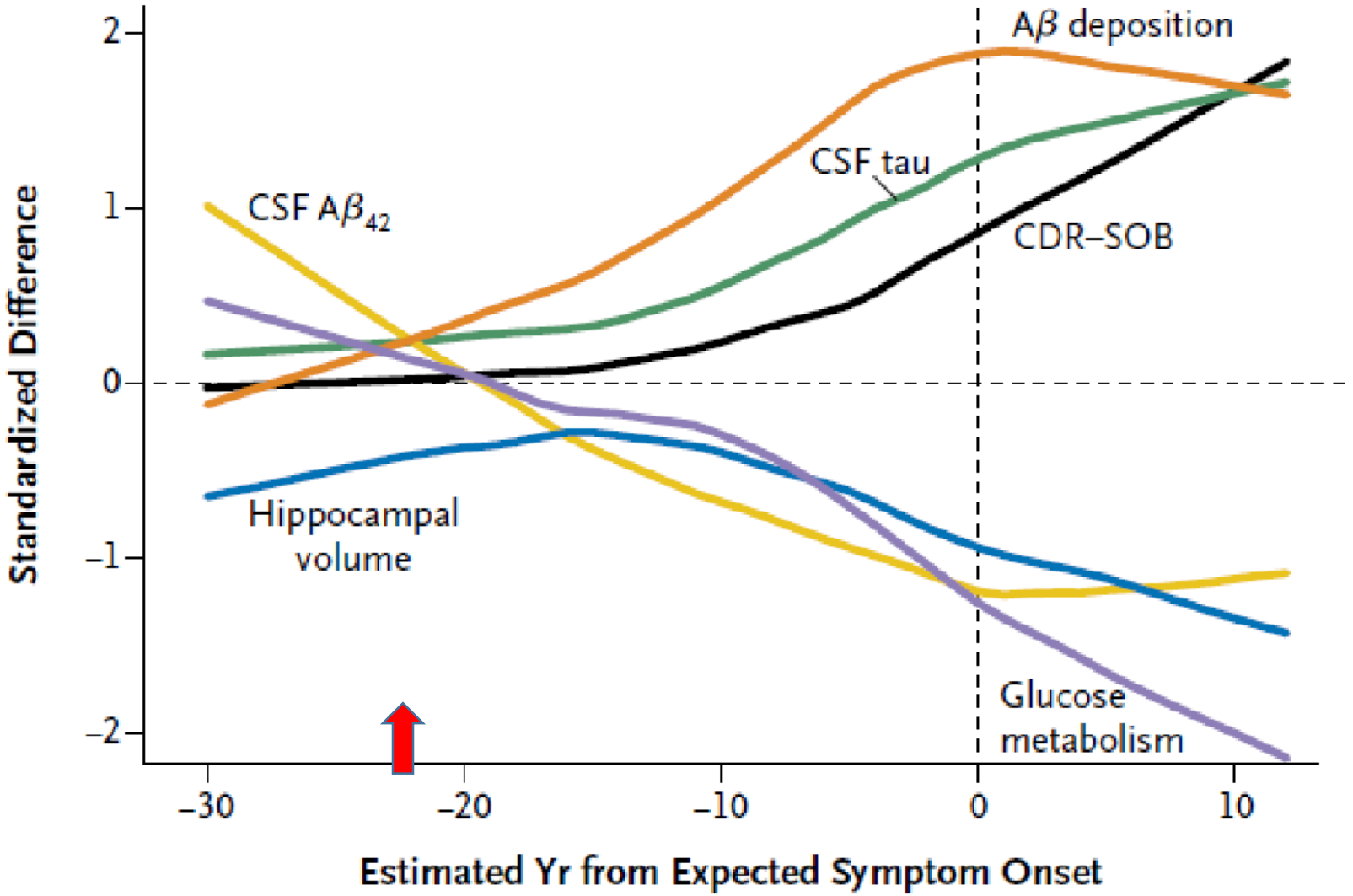
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xiany Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., An Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringma Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Sal and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

Biomarker evidence that AD begins ~20 years prior to diagnosis

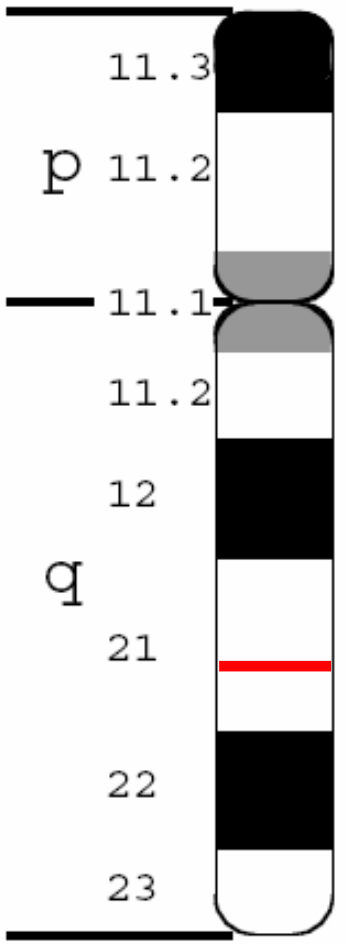


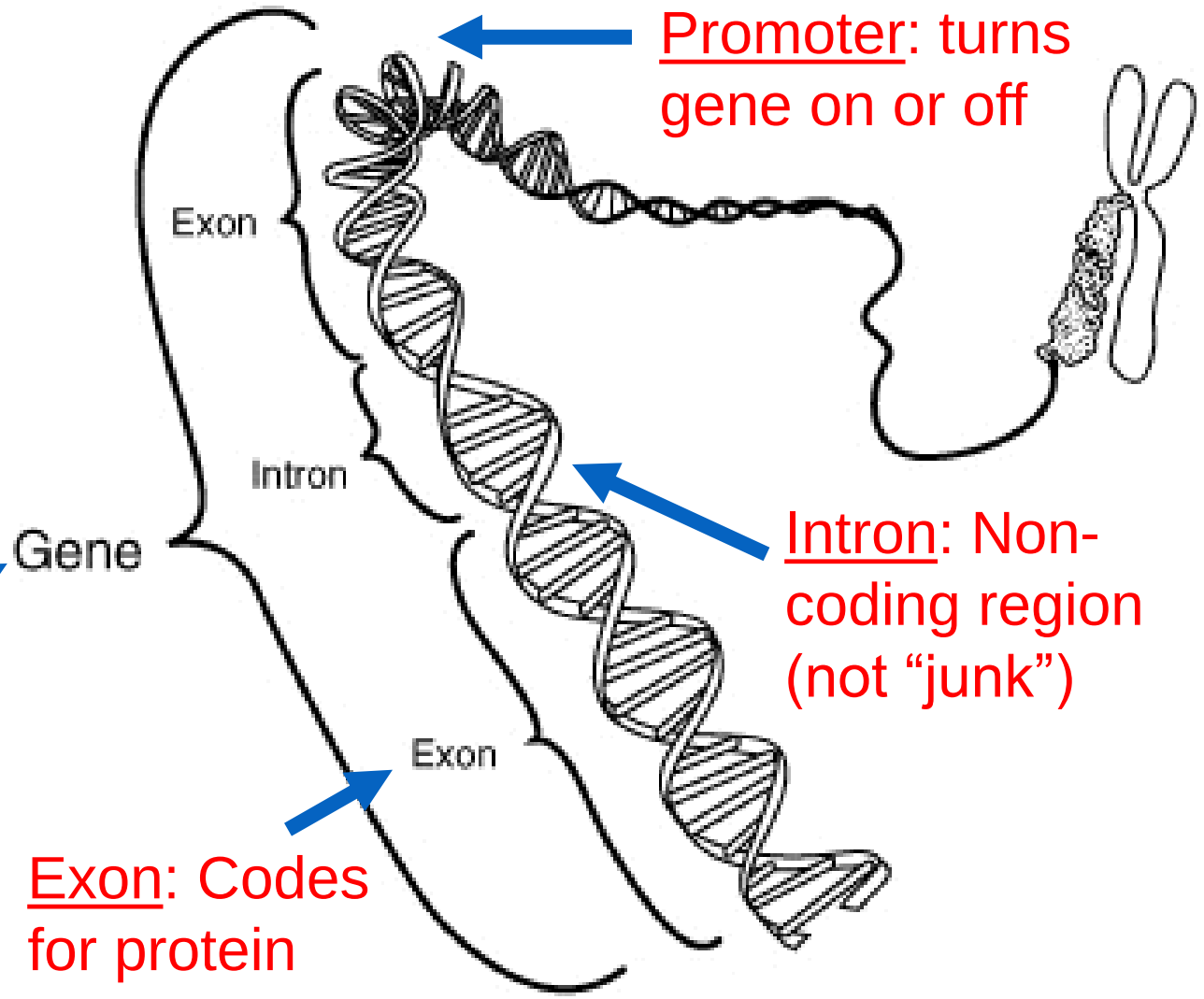
Sporadic Early Onset AD: LEADS

- About 5% of AD has early onset defined as before age 65
- Less than 10% of these patients have mutations in known AD genes
- Longitudinal Early-onset Alzheimer's Disease Study (LEADS) is a new NIA sponsored consortium of 16 institutions that will begin investigating non-familial EOAD in 2018 using cognitive testing, biomarkers, neuroimaging and gene sequencing
- Investigators
  - Liana Apostolova MD, Indiana University
  - Maria Carrillo PhD, Alzheimer's Association
  - Brad Dickerson MD, Harvard University
  - Gil Rabinovici MD, UCSF

http://news.medicine.iu.edu/releases/2017/10/early-onset-alzheimers.shtml

“Genetics 101”
Chromosome (DNA) -> Gene -> Regions -> Bases



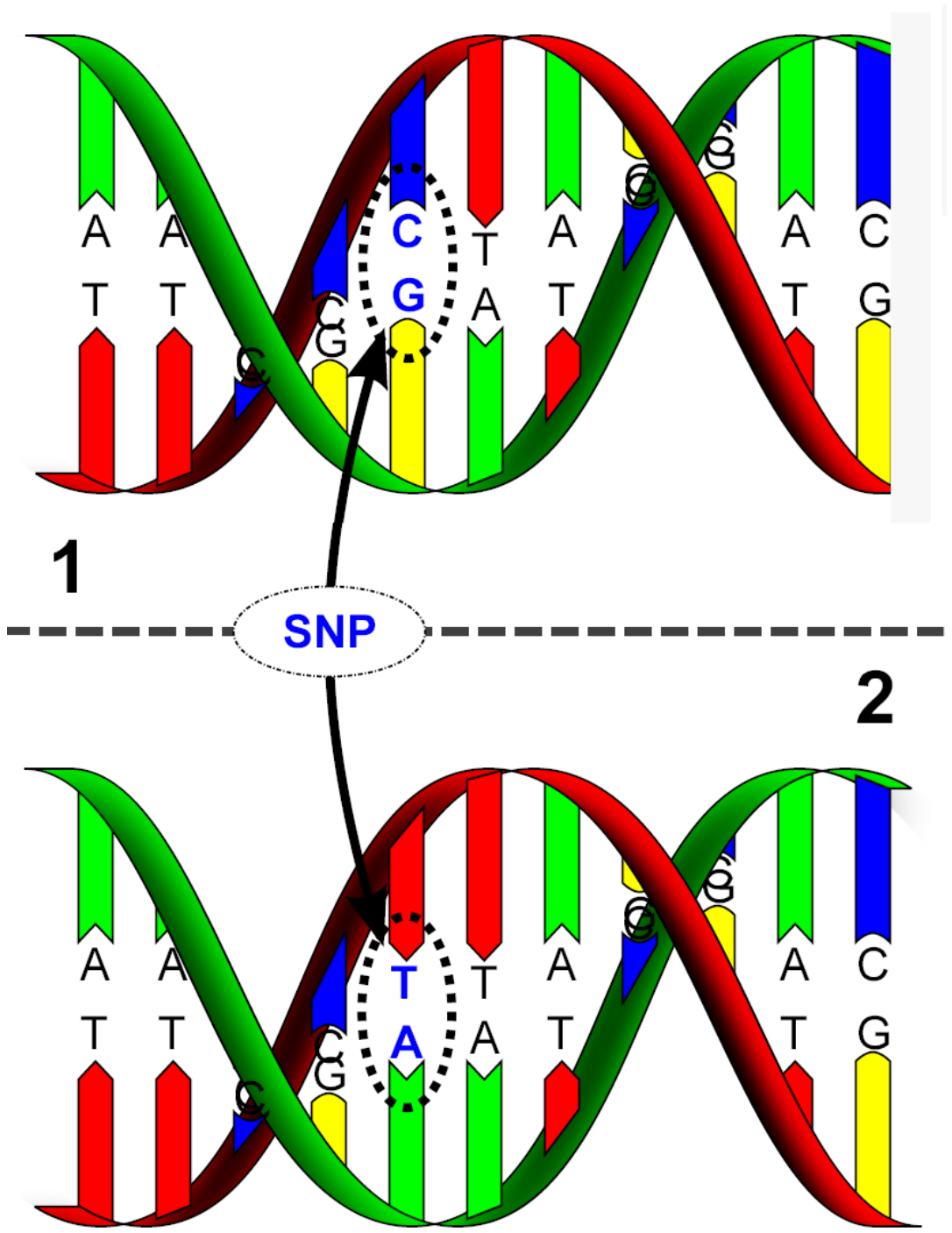


Promoter: turns gene on or off

Intron: Non-coding region (not “junk”)

Exon: Codes for protein

Single Nucleotide Polymorphism (SNP)



Base pairs

⬇

Codon

⬇

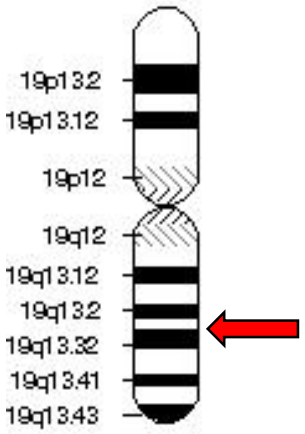
Amino acid

⬇

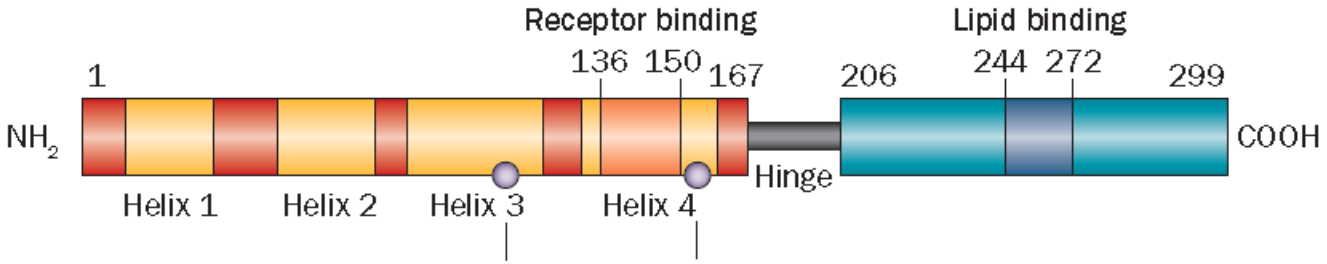
Protein

Source: Wikimedia.org

APOE Genotype & Sporadic AD Risk



Chr. 19q13.2



	Isoform-specific amino acid difference		Allele frequency (%)	
	112	158	General	AD
Apo-E2	Cys	Cys	8.4	3.9
Apo-E3	Cys	Arg	77.9	59.4
Apo-E4	Arg	Arg	13.7	36.7

SNP: rs429358 rs7412

ApoE protein

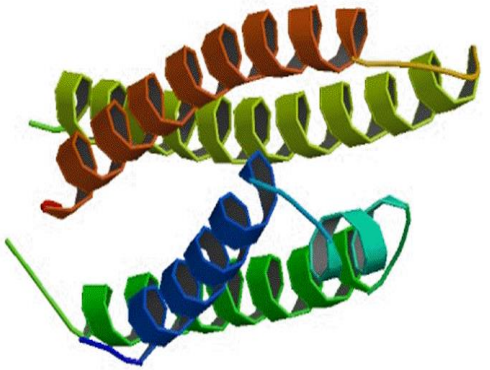


Table 1 | The effect of *APOE* ε4 on AD frequency and age at onset[7]

Characteristic	*APOE* ε4 noncarrier	*APOE* ε4 heterozygous	*APOE* ε4 homozygous
AD frequency (%)	20	47	91
Mean age of clinical onset (years)	84	76	68

Abbreviations: AD, Alzheimer disease; *APOE* ε4, ε4 allele of the apolipoprotein E gene.

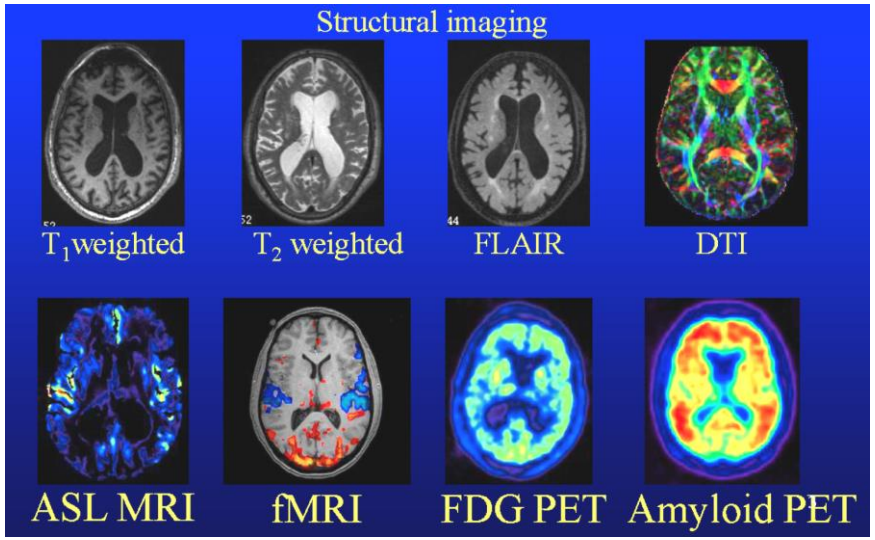
Liu et al, Nature Reviews Neurology, 9:106-118, Feb 2013

Alzheimer's Disease Neuroimaging Initiative (ADNI)

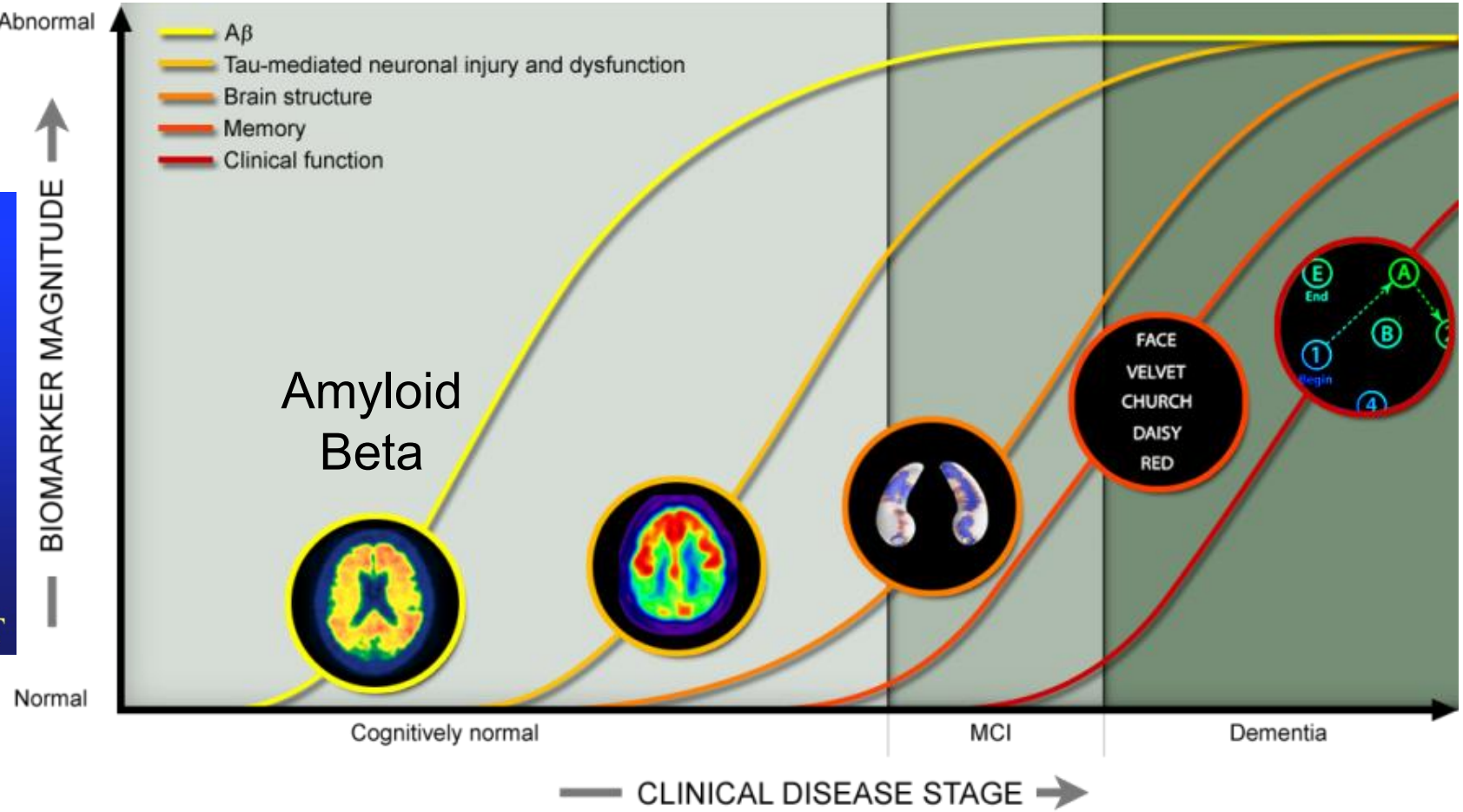
LOAD Biomarkers: Temporal ordering and time-dependent roles

ADNI-3

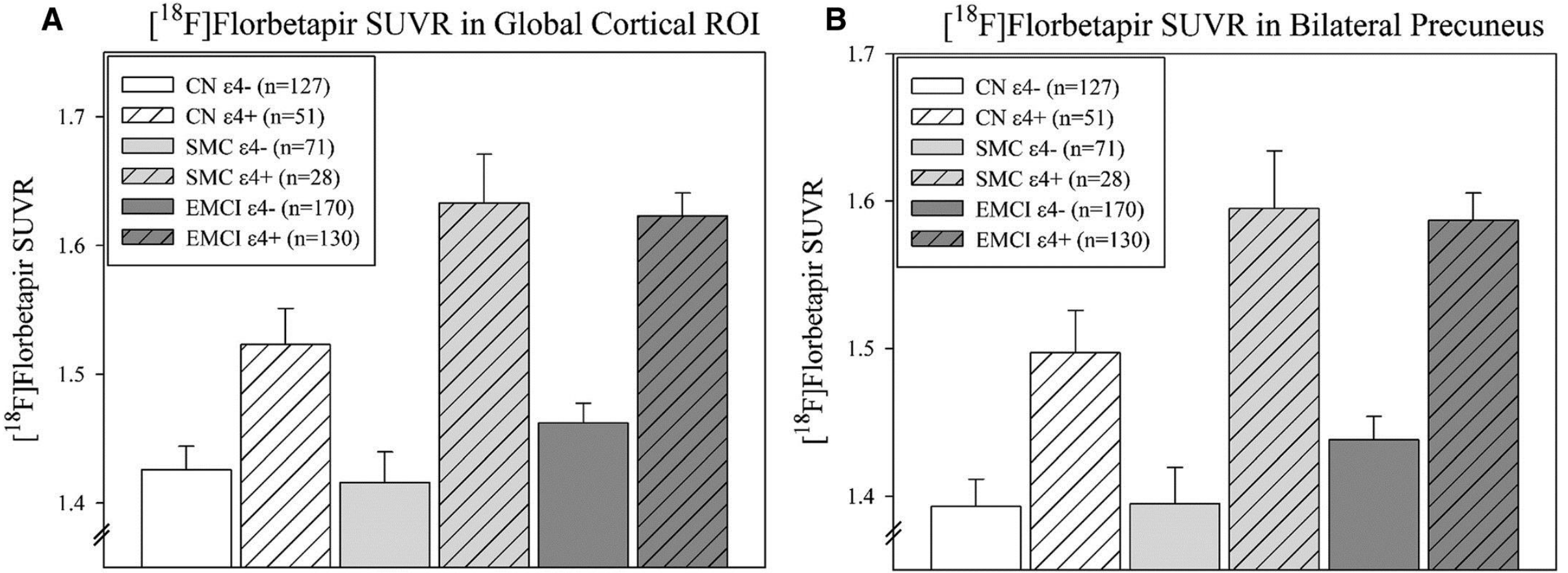
ADNI



Imaging Modalities



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)

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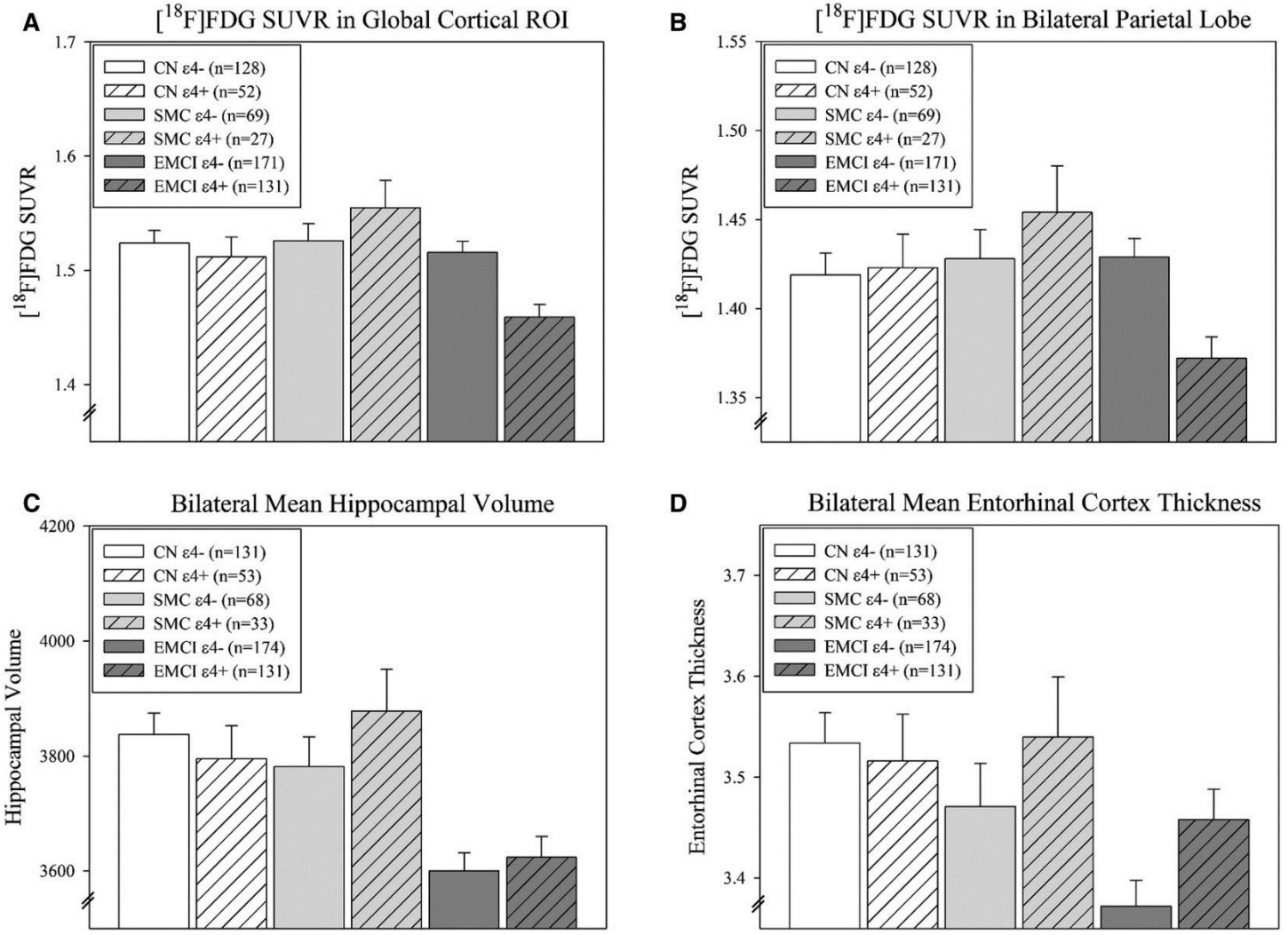
APOE ε4 Status: Early Stage Atrophy and Glucose Metabolism



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

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IGAP Meta-Analysis: Now a "Top 20+" LOAD Genes (2013)

Lambert et al Nature Genetics (2013)* LETTERS

nature genetics

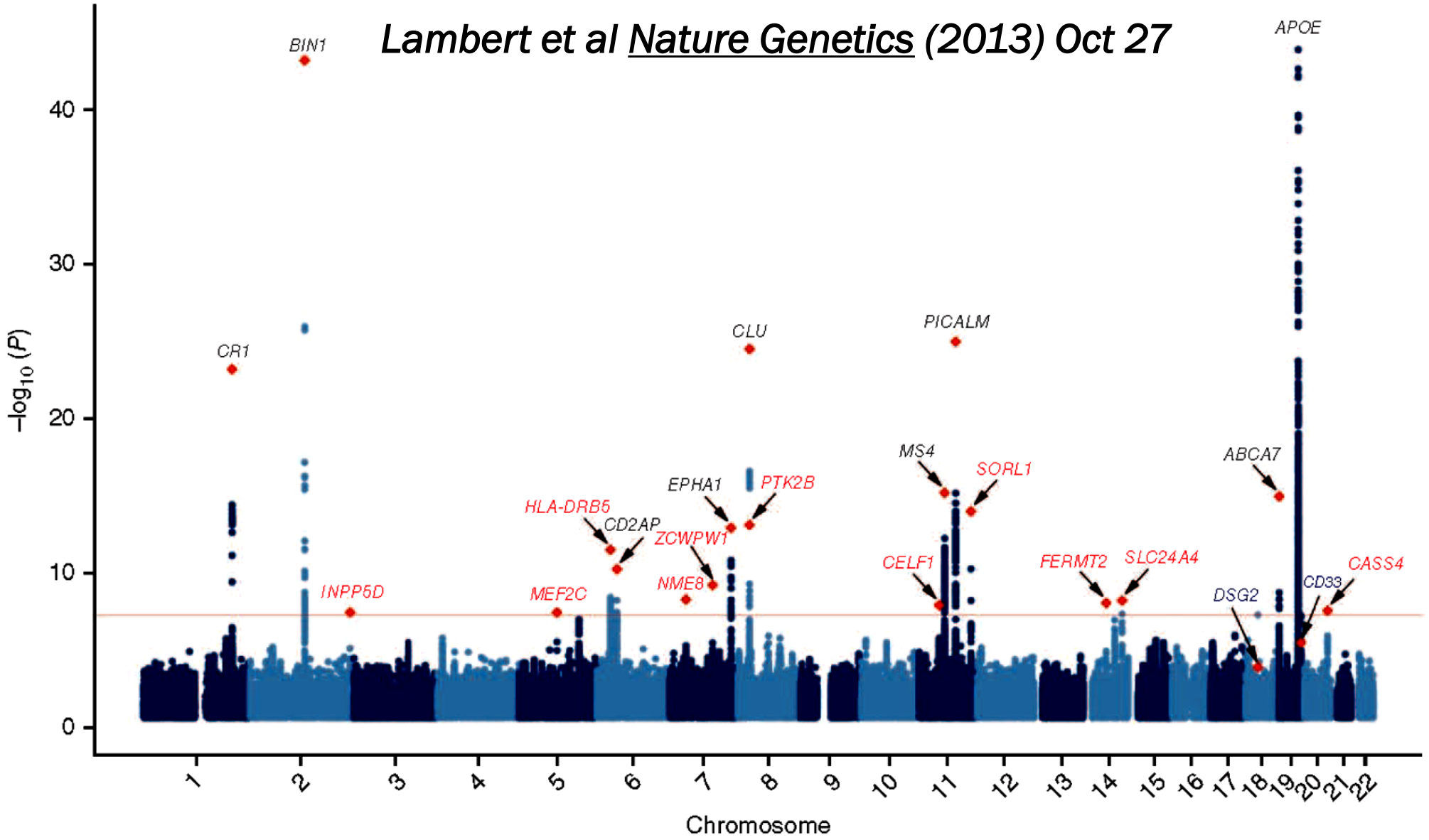
Largest AD GWAS

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

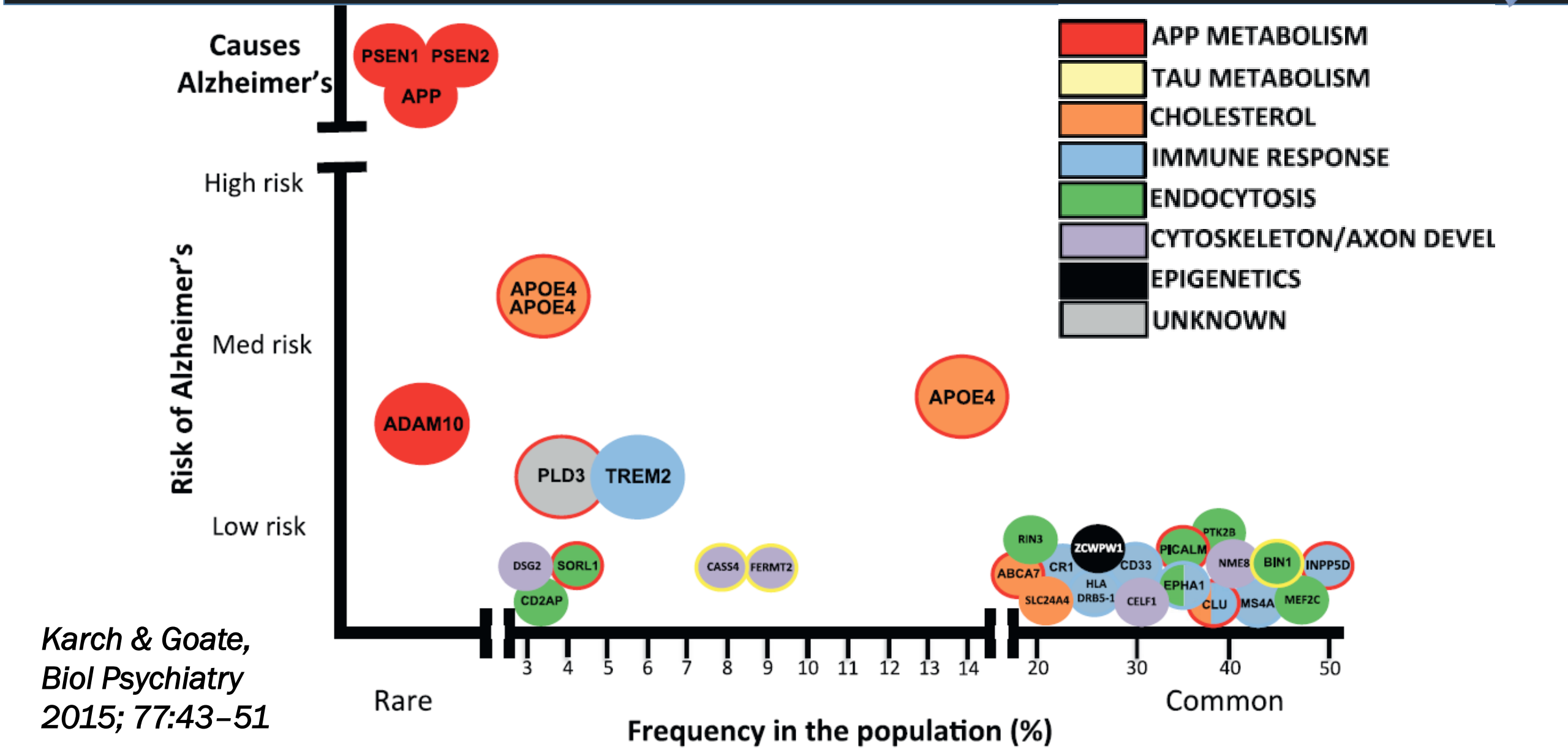
Eleven susceptibility loci for late-onset Alzheimer's disease (LOAD) were identified by previous studies; however, a large portion of the genetic risk for this disease remains unexplained. We conducted a large, two-stage meta-analysis of genome-wide association studies (GWAS) in individuals of European ancestry. In stage 1, we used genotyped and imputed data (7,055,881 SNPs) to perform meta-analysis on 4 previously published GWAS data sets consisting of 17,008 Alzheimer's disease cases and 37,154 controls. In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. In addition to the *APOE* locus (encoding apolipoprotein E), 19 loci reached genome-wide significance ($P < 5 \times 10^{-8}$) in the combined stage 1 and stage 2 analysis, of which 11 are newly associated with Alzheimer's disease.

"In addition to the *APOE* locus, 14 genomic regions had associations that reached genome-wide significance. 9 had been previously identified by GWAS as genetic susceptibility factors, and 5 (HLA-DRB5–HLA-DRB1, PTK2B, SORL1, SLC24A4-RIN3 and DSG2) represent newly associated loci."

IGAP Meta-Analysis: Top 20 AD Genes



Genetic Risk for AD: Pathogenic Mechanisms



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

Next Generation Sequencing
Enables search for novel rare variants

Human Genome: 3 Billion Bases

- Illumina HiSeq Platform
  - Whole Exome Sequencing (WES)
  - Whole Genome Sequencing (WGS)
  - RNA Sequencing (RNA-seq / miRNA-seq)

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

TREM2 and Neurodegenerative Disease

LETTER

doi:10.1038/nature12825

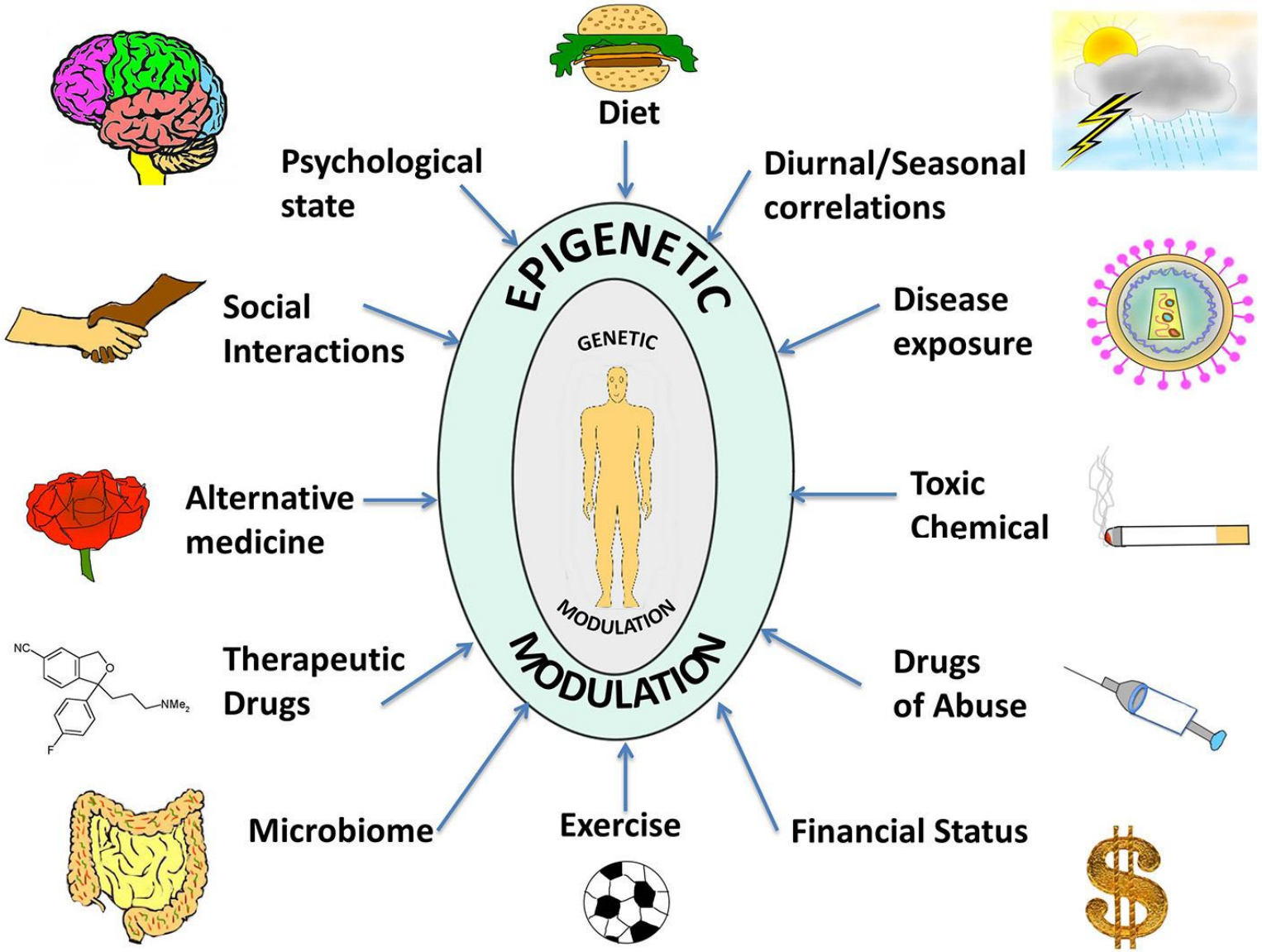
Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease

Carlos Cruchaga[1,2], Celeste M. Karch[1,2]*, Sheng Chih Jin[1]*, Bruno A. Benitez[1], Yefei Cai[1], Rita Guerreiro[3,4], Oscar Harari[1], Joanne Norton[1], John Budde[1], Sarah Bertelsen[1], Amanda T. Jeng[1], Breanna Cooper[1], Tara Skorupa[1], David Carrell[1], Denise Levitch[1], Simon Hsu[1], Jiyoon Choi[1], Mina Ryten[3], UK Brain Expression Consortium (UKBEC)†, Celeste Sassi[3,4], Jose Bras[3], J. Raphael Gibbs[3,4], Dena G. Hernandez[3,4], Michelle K. Lupton[5,6], John Powell[5], Paola Forabosco[7], Perry G. Ridge[8], Christopher D. Corcoran[9,10], JoAnn T. Tschanz[10,11], Maria C. Norton[10,11,12], Ronald G. Munger[12,13], Cameron Schmutz[8], Maegan Leary[8], F. Yesim Demirci[14], Mikhil N. Bamne[14], Xingbin Wang[14], Oscar L. Lopez[15,16], Mary Ganguli[17], Christopher Medway[18], James Turton[18], Jenny Lord[18], Anne Braae[18], Imelda Barber[18], Kristelle Brown[18], The Alzheimer's Research UK (ARUK) Consortium†, Pau Pastor[19,20,21], Oswaldo Lorenzo-Betancor[19], Zoran Brkanac[22], Erick Scott[23], Eric Topol[23], Kevin Morgan[18], Ekaterina Rogaeva[24], Andrew B. Singleton[4], John Hardy[3], M. Ilyas Kamboh[14,15,16], Peter St George-Hyslop[24,25], Nigel Cairns[2,26], John C. Morris[26,27,28], John S. K. Kauwe[8] & Alison M. Goate[1,2,27,28,29]

Polygenic Scores: Combined Effects of Genes

- 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.
- *Tan C.H., et al. Polygenic hazard scores in preclinical Alzheimer disease. Ann Neurol. 2017, 82(3):484-488.*

Gene x Environment Interaction: Epigenetics



Kanherkar et al. (2014), Frontiers in Cell Dev Biol

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

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Path from genetic signal to targeted therapeutics

Understand biological pathway

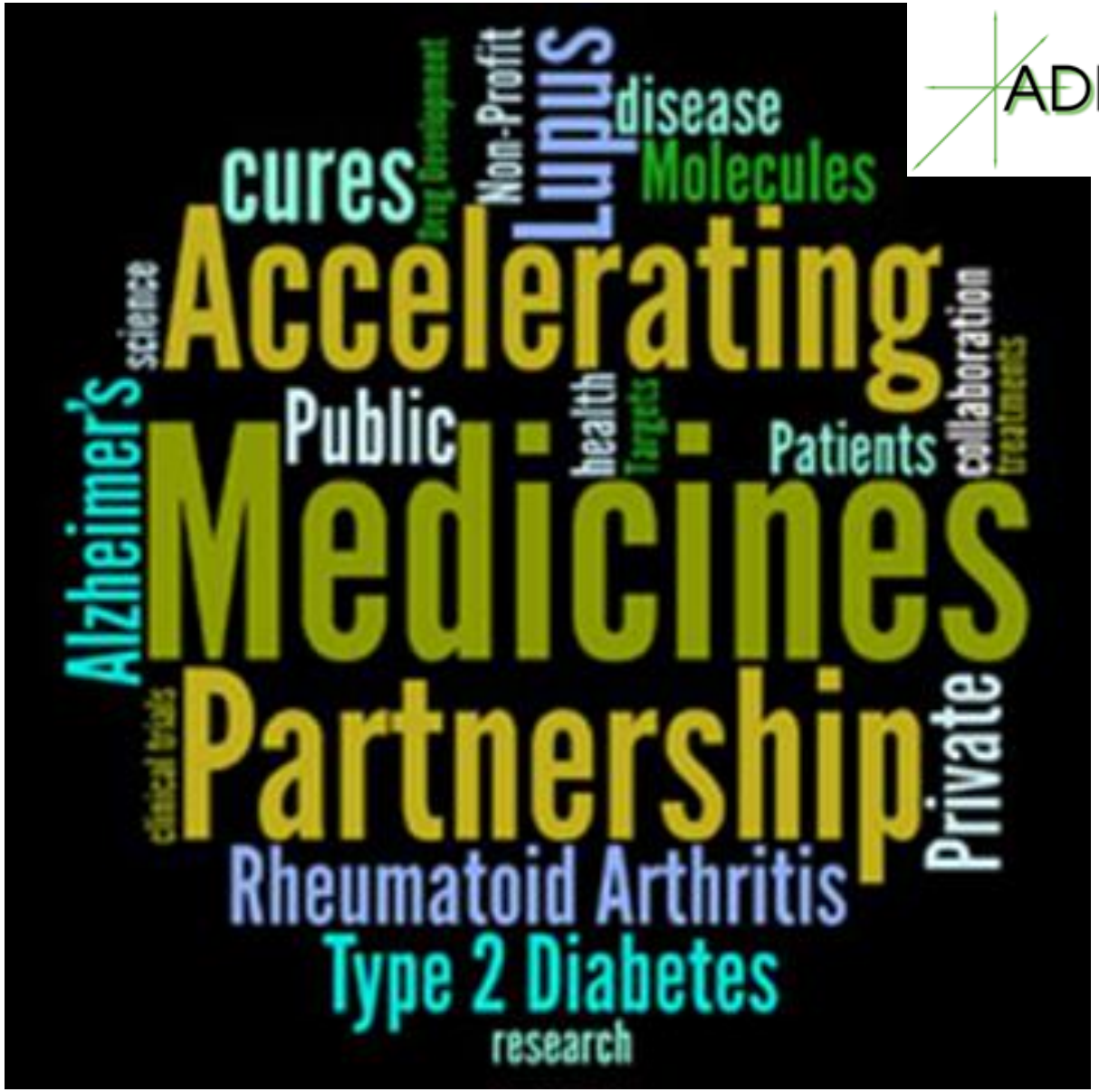
Identify biomarkers

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

Toward a Precision Medicine of AD



ADNI

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

Indiana ADC, IU Neuroscience, ADNI & AMP-AD

ADNI

Indiana University Center for Neuroimaging CfN

INDIANA UNIVERSITY NETWORK SCIENCE INSTITUTE

INDIANACTSI Clinical and Translational Sciences Institute

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Indiana Alzheimer Disease Center

Conclusions

- The genetic architecture of AD differs for familial early onset AD and LOAD
- For LOAD we have gone from only *APOE* to over 25 promising candidate genes
- Next generation sequencing is identifying novel rare variants associated with AD
- Major pathways implicated by genome-wide findings include brain lipids and cholesterol processing and the innate immune system
- Genetic variation can be studied in case/control or biomarker phenotype designs
- Polygenic scores combining gene effects are promising for risk prediction
- The systems biology of AD is a work in progress but will be important for understanding and treating this complex disease
- Longitudinal studies of epigenetic changes such as methylation are needed
- An important goal is to understand heterogeneity by integrating genetics,–omics and imaging/biomarker profiles → precision medicine of AD & related disorders
- Target discovery and validation, informing model system development and assessment of therapeutic strategies are all important directions