Common Genetic Variation Underlying Alzheimer's Disease and Related MRI and Cognitive Endophenotypes

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National Institute on Aging

National Heart Lung and Blood Institute

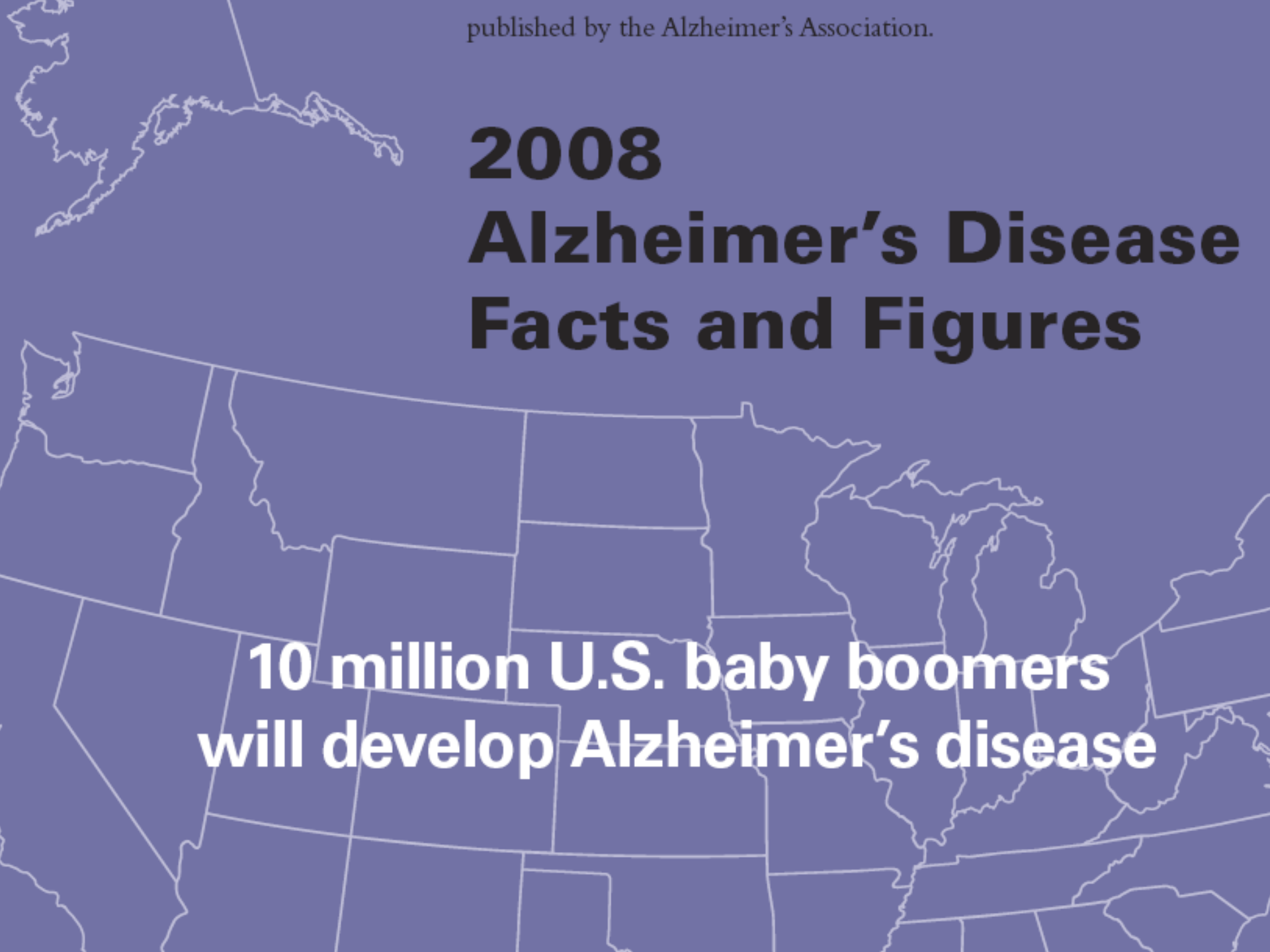
National Institute of Neurological Disorders and Stroke

Framingham Heart Study — Three Generations of Dedication — 1948 1971 2002

Boston University

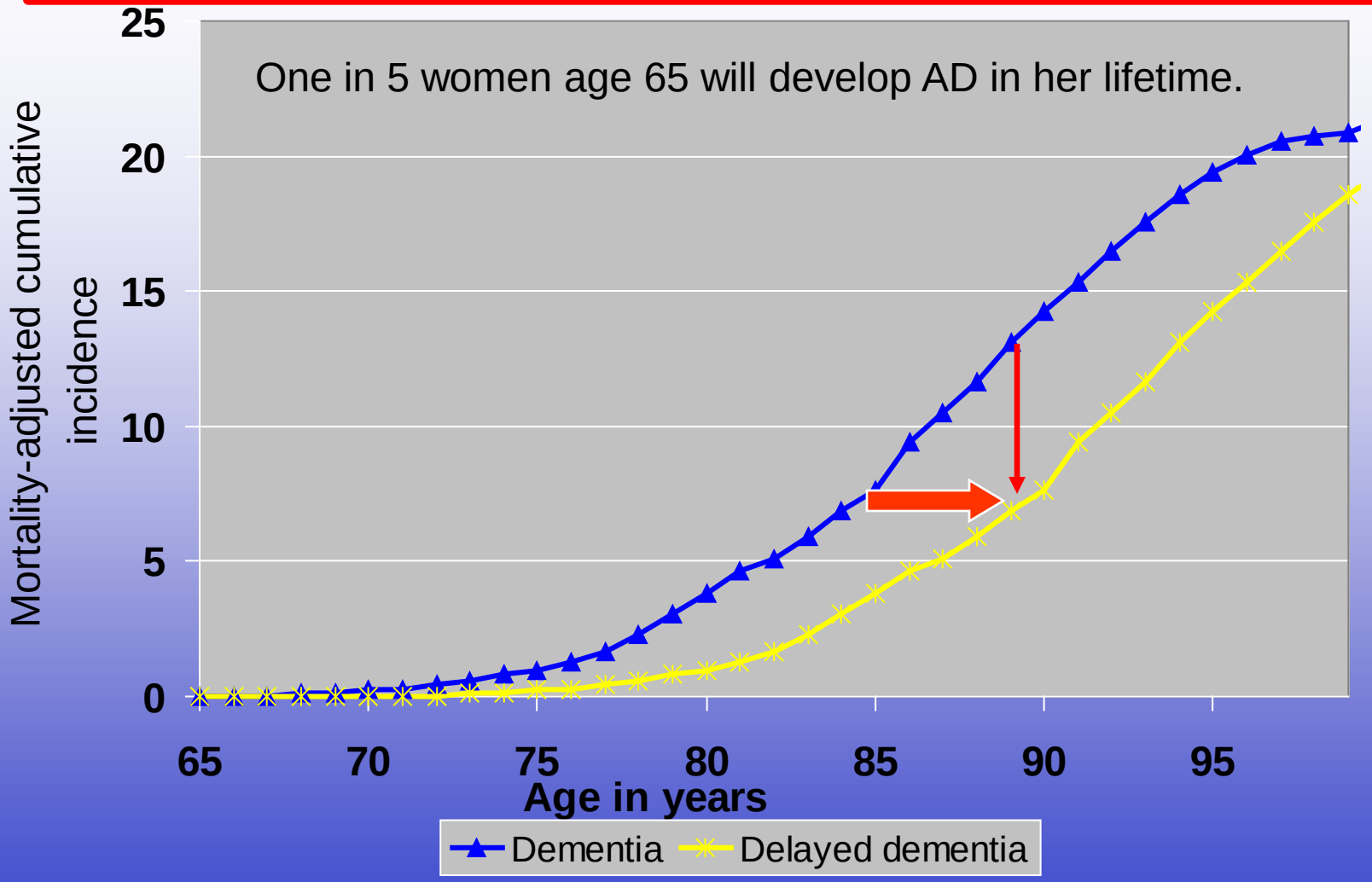
published by the Alzheimer's Association.

2008 Alzheimer's Disease Facts and Figures



10 million U.S. baby boomers will develop Alzheimer's disease

Lifetime Risk of Alzheimer's Disease: Women - 65 yrs



Seshadri et al. Lifetime Risk of Stroke: The Framingham Study. Stroke 2006; 37: 344-349.

Genetics of AD

- AD is heritable
- Identifying genes helps uncover biology

APP
PSEN1
PSEN2

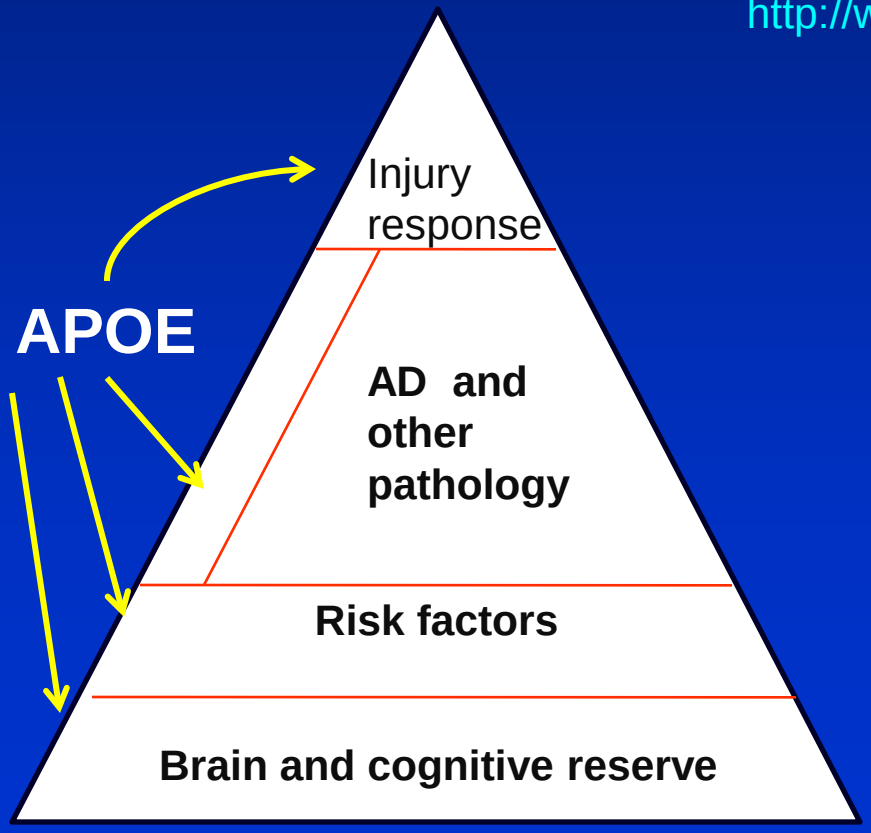
APOE

- Agnostic approaches vs. Candidate Genes
- Endophenotypes: Opportunities and Pitfalls

Candidate Gene Approach

- Con: Limited by our current understanding of biology
- Pro: Fewer comparisons, greater power

http://www.alzforum.org/res/com/gen/alzgene/default.asp



Candidate gene pathways

??

Amyloid synthesis and removal, metalloproteins tau phosphorylation, vacuolar sorting proteins

glucose and insulin metabolism, adipokines nitrous oxide synthesis, oxidative stress, inflammation and lipid pathways

renin-angiotensin, thrombosis and hemostasis endothelial function

Neurotrophic factors

CARe: The NHLBI's Candidate Gene Association Resource

http://www.broad.mit.edu/gen_analysis/care/index.php/Main_Page

CARe Genotyping Plan

Phase II (Illumina iSelect---IBC Chip)

-~49,000 SNPs covering ~2100 candidate genes

typed on ~50,000 persons from all CARe Cohorts

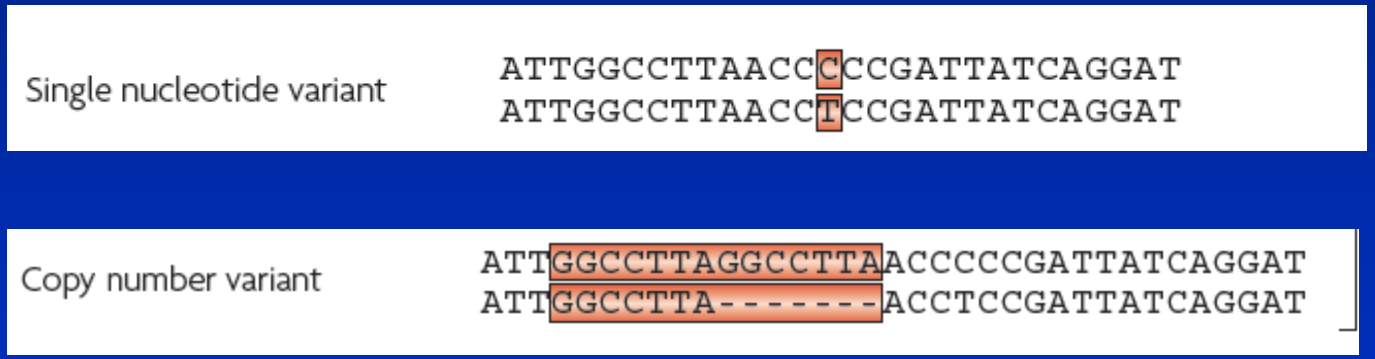
BROAD INSTITUTE

Penn Medicine | ITMAT

Human genetic variation and its contribution to complex traits

Kelly A. Frazer, Sarah S. Murray, Nicholas J. Schork and Eric J. Topol

Nature Reviews Genetics, April 2009; 241-249.



3 billion base pairs; 3 million SNPs

Arrays genotype 300,000 to 1 M

We can impute 80-90% of SNPs since we know linkage disequilibrium patterns

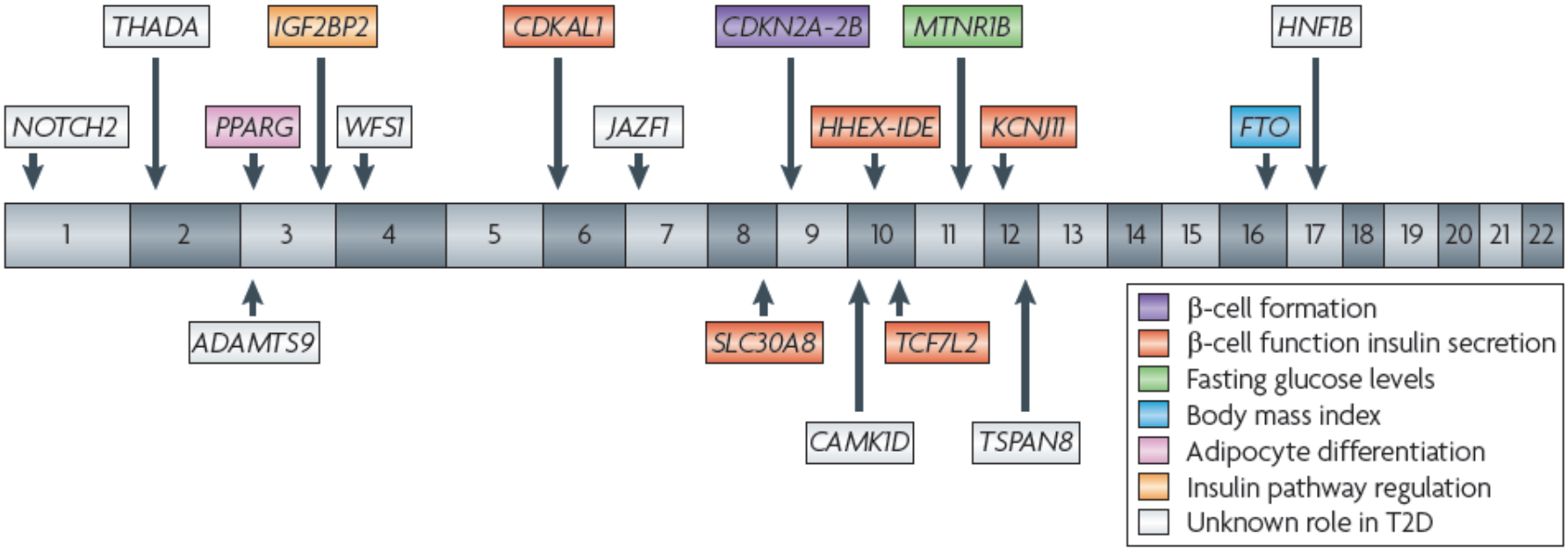


Figure 2 | **Insights into the genetic basis of type 2 diabetes (T2D).** Genome-wide association (GWA) studies have identified 18 genomic intervals that confer increased risk to T2D in Caucasians[58,59,72–75,123–127]. Four of these contain previously known candidate genes, based on the involvement of rare mutations in monogenic forms of diabetes. However, the remaining 14 intervals contain genes that were previously unsuspected in playing a part in the genetic

Genetics of AD

- AD is heritable
- Identifying genes helps uncover biology
- Agnostic approaches vs. Candidate Genes
- Endophenotypes: Opportunities and Pitfalls

What is an Endophenotype?

- Endophenotypes (or intermediate phenotypes) are heritable traits that reflect the actions of genes predisposing an individual to a disorder

- Predict risk of incident disease
- Manifest years before clinical & pathological diagnostic criteria are met

Problems

- Genetic heterogeneity
- Overwhelming effect of APOE ε4 locus but parental AD impacts cognition in APOE ε4 +ve offspring
- Gene-gene and gene-environment interactions

- Late onset of clinical disease
  - competing risk of mortality
- Selection and survival biases

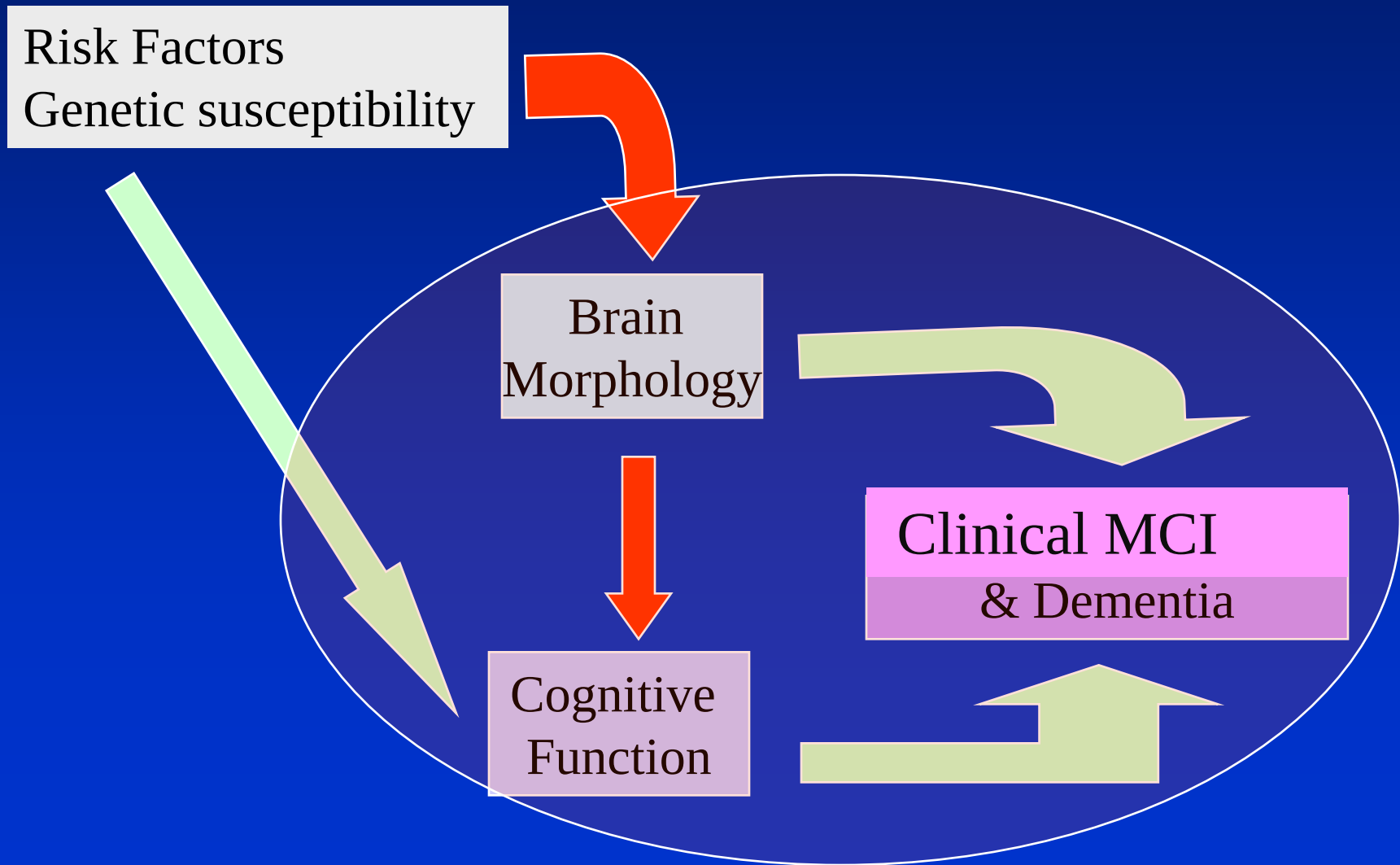
Solutions

- Genetic heterogeneity
  - Careful phenotypic definition
- Gene-APOE ε4 interactions
  - Stratified analyses
- Competing risk of mortality
- Gene-environment interactions and selection/survival biases
  - Cohort studies of incident disease
    morbid environment
- Collaborative efforts to increase numbers

So we study endophenotypes!

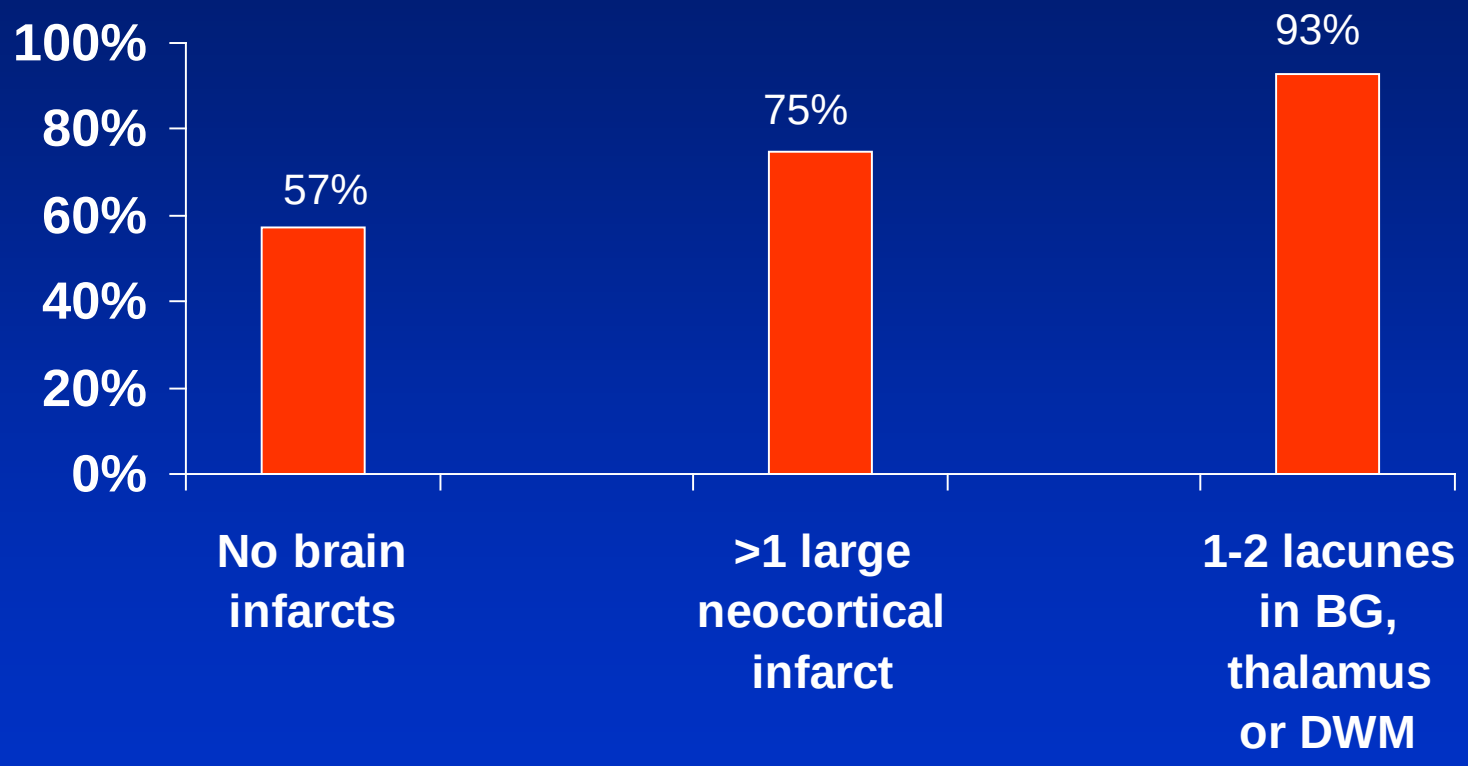
In community-based cohorts

Conceptual Model for Pathways from Genes to Dementia



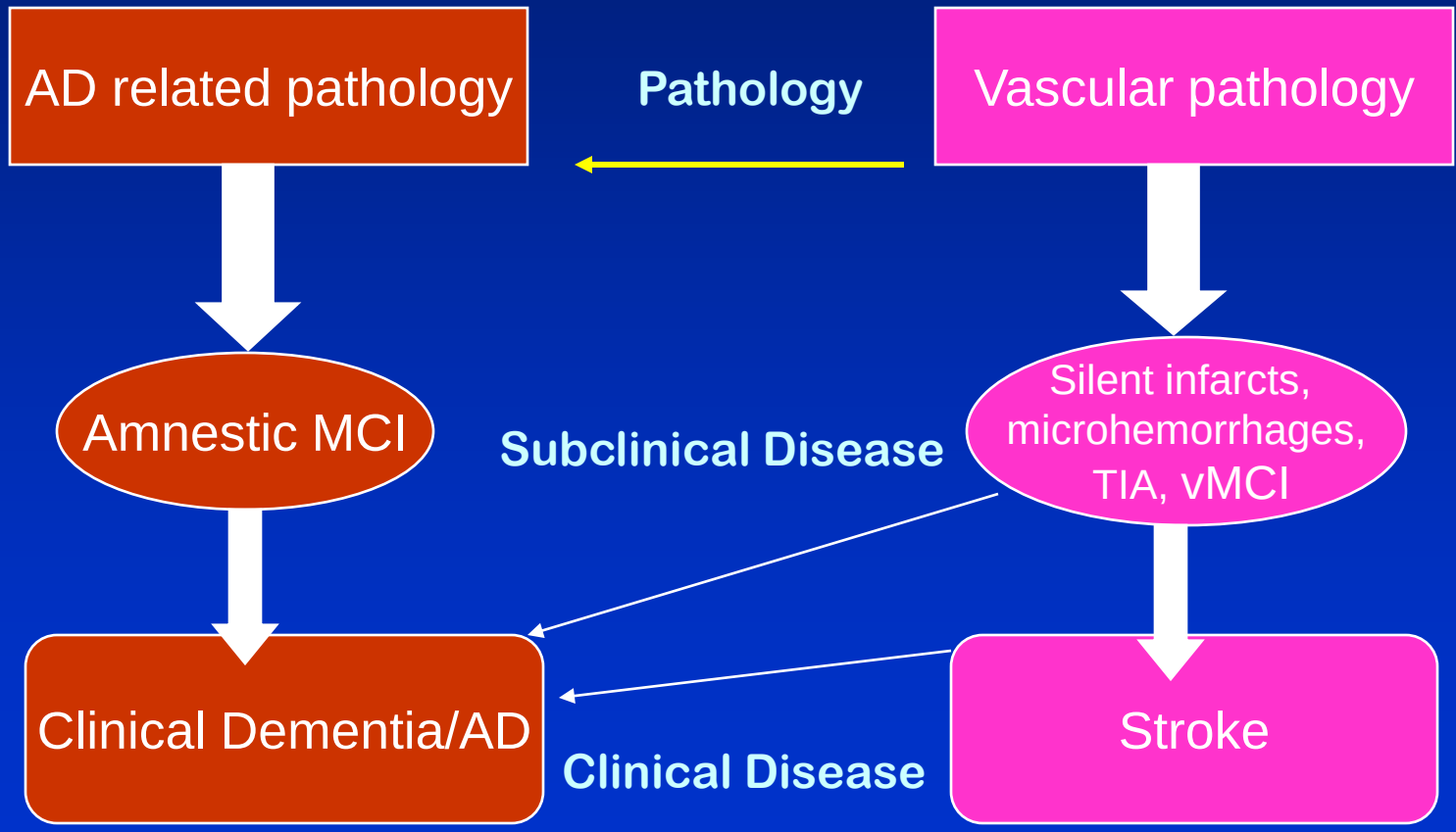
Neuropathological AD: Prevalence of Clinical Dementia

Snowdon DA et al., JAMA 1997;277:813-7



Adjusted OR for clinical dementia	1	6.7	20.7

Multiple Axes of Brain Aging Interact



Vascular disease may accelerate the pathological processes in AD

- Ischemia induces PS1 and increases APP expression in mouse models of AD

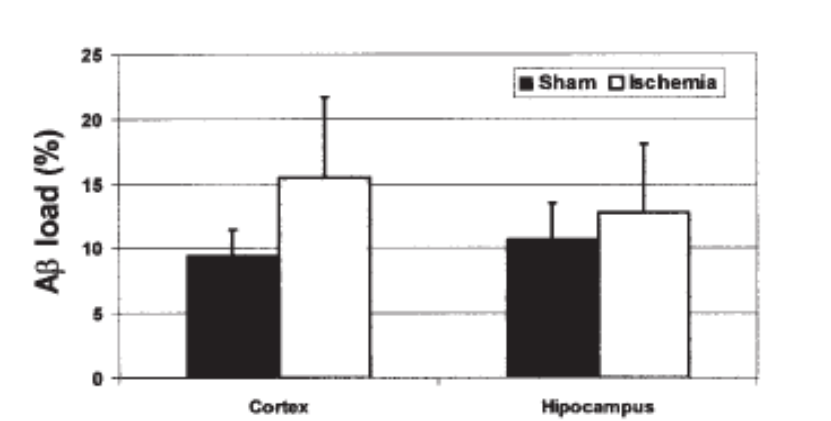


Fig. 3. Aβ load in the cortex and in the hippocampus (average ± standard deviation) 2 months following either sham surgery or bilateral carotid ischemia. There was a trend for increased Aβ deposition

Sadowski et al., Neurochem Res 2004;29:1257-66

AD Endophenotypes

- Two types:
  - Risk Marker (whether & when clinical AD develops)
  - Disease Severity Marker

- Quantitative or Qualitative traits
- With moderate to high heritability
- Reflect pathology

Risk Marker (True) Endophenotypes

- Cognitive Measures
- Volumetric MRI measures

- PET measures of amyloid burden, regional flow
- Functional MRI

- CSF biomarkers
- Circulating and cell expression markers

Quantitative Traits as Disease Severity Markers

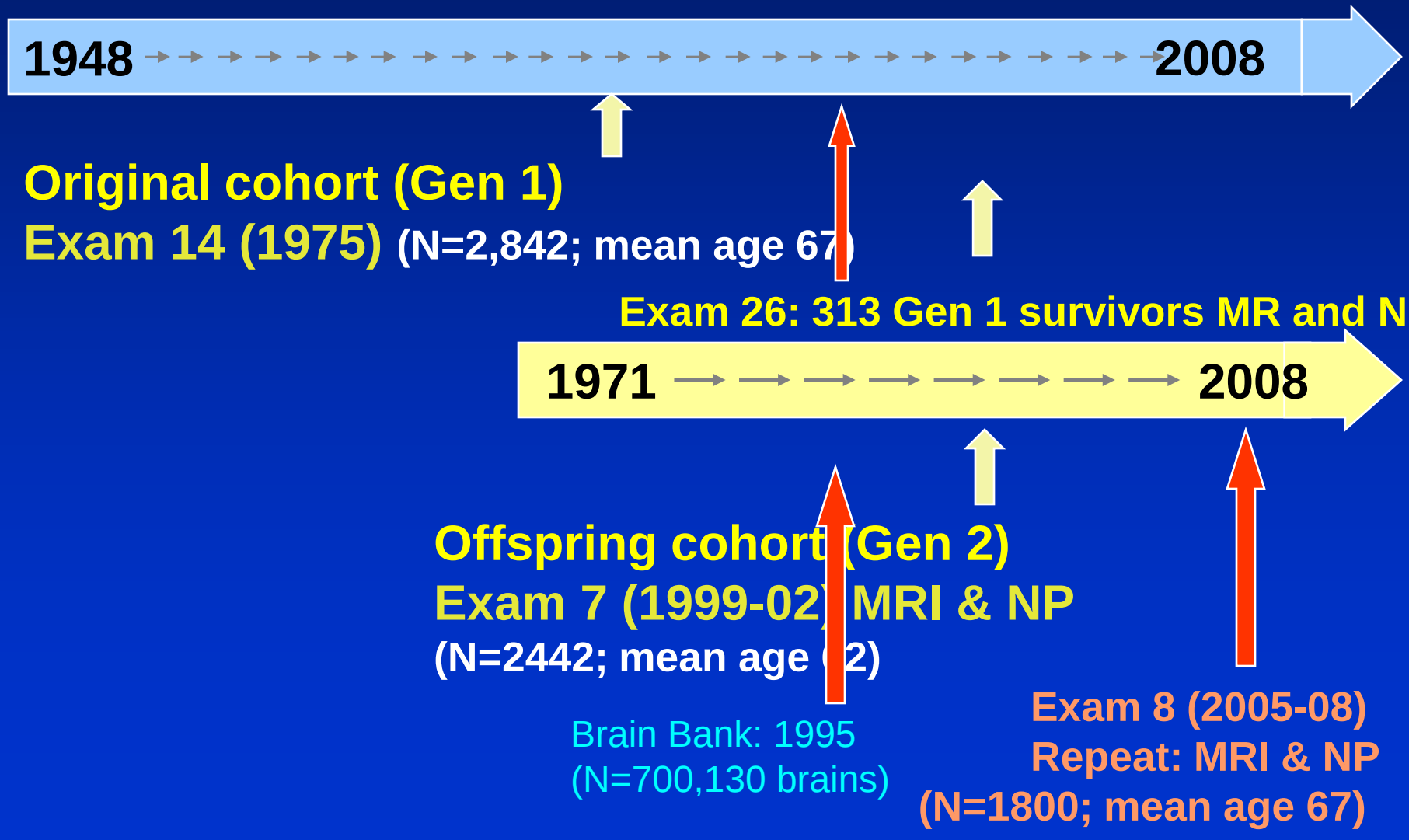
- Cognitive Performance
- Neurological Exam Findings
- MRI measures
- Pathological Scores
- Treatment Response

- Disease only sample is adequate

- Pharmacogenomics: Personalized Prevention & Therapy

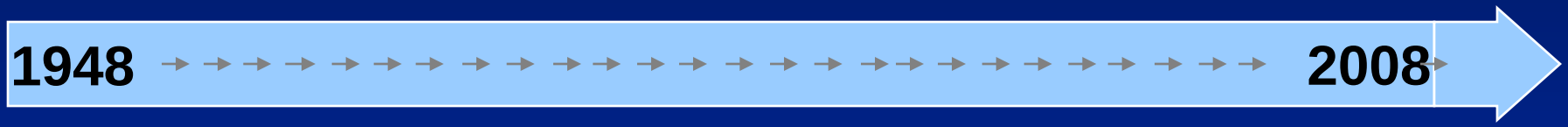
Framingham Heart Study

Stroke, Dementia and MRI/NP Studies

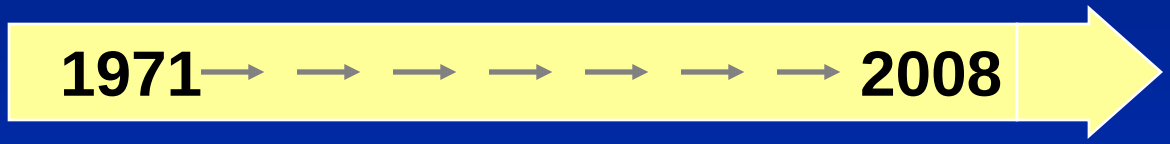


Framingham Heart Study

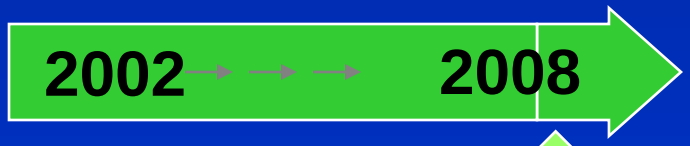
Longitudinal Community-Based Family Study



Gen 1 Original cohort



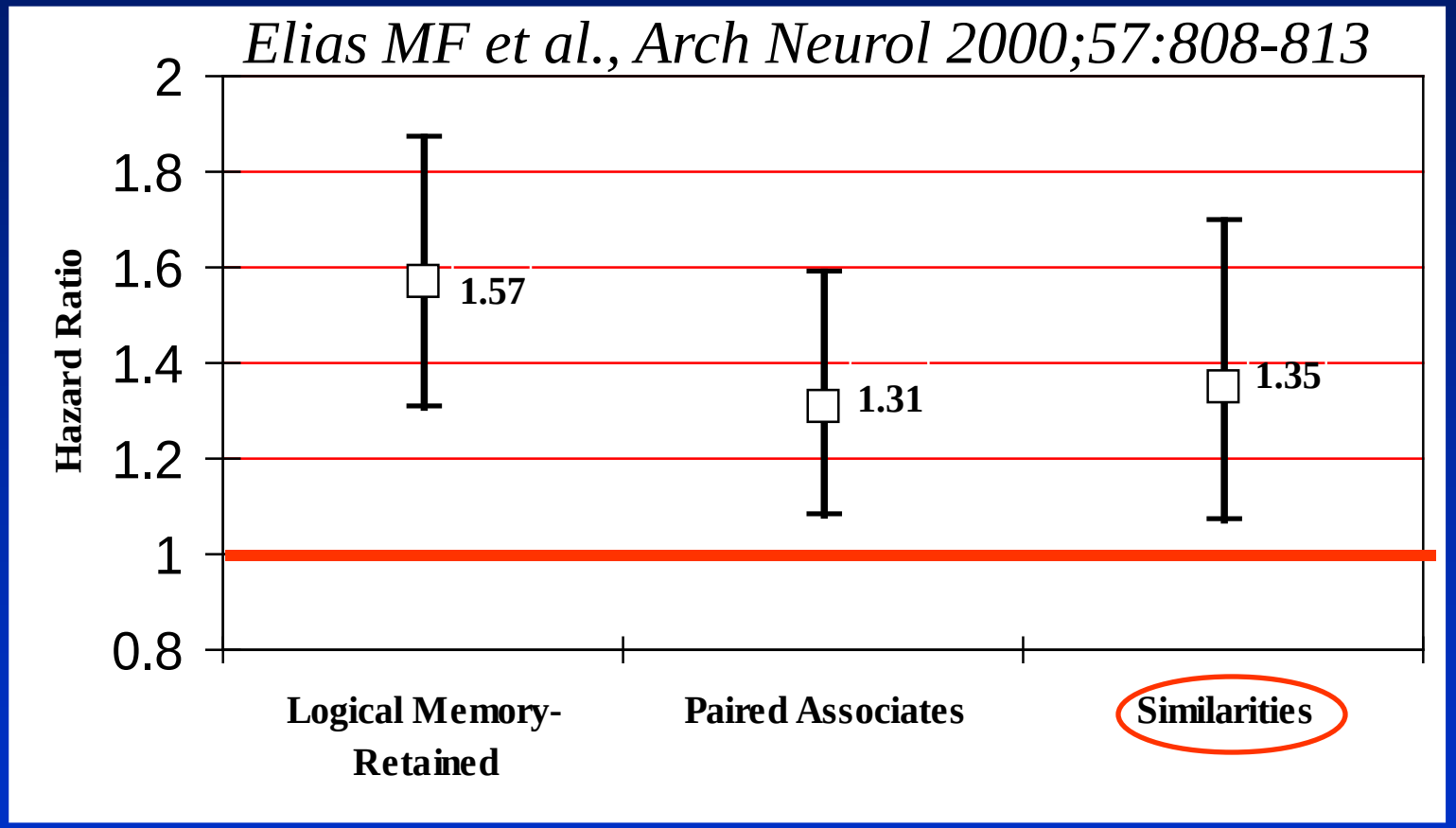
Gen 2 Offspring cohort



Gen 3 cohort

Exam 2 (2009-11) MRI
NP & Biomarkers

Endophenotypes Predict Incident Disease: Cognitive Tests



1076 stroke- and dementia-free subjects underwent neuropsychological testing in 1975. Odds-ratio of developing AD (on 22 year follow-up) increased 31-57% with each SD decrement in baseline performance, after adjusting for age, sex, education, occupation.

Brain Volumes are Endophenotypes

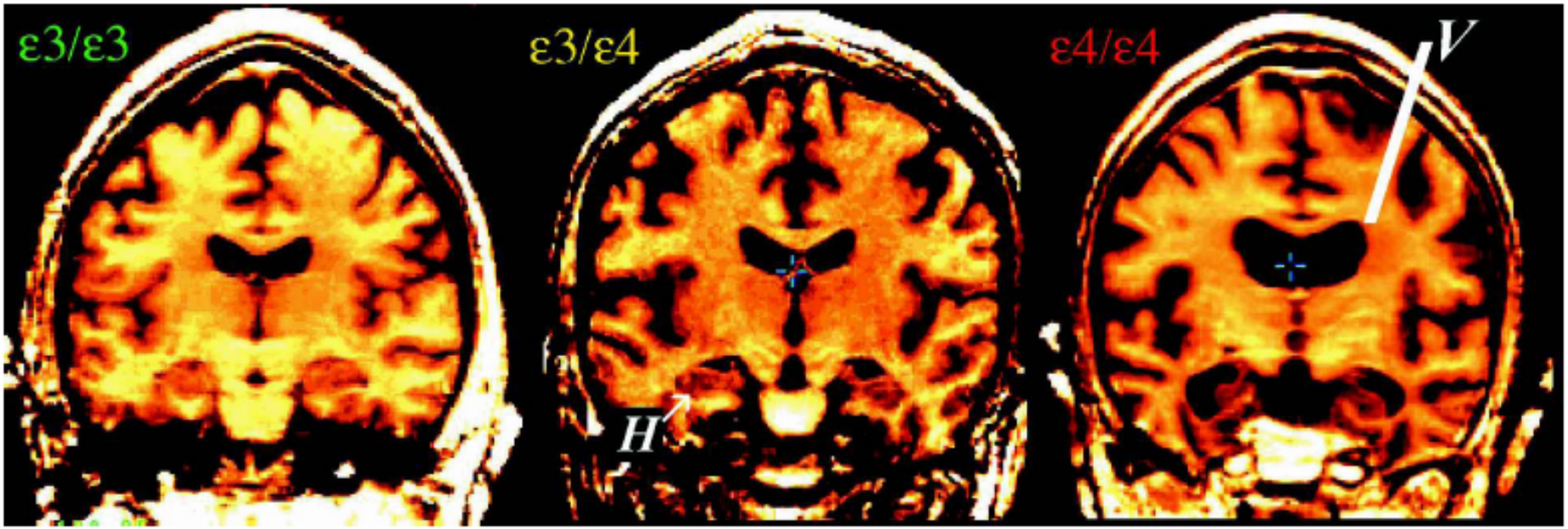


Figure 5. Risk genes and brain structure. Typical MRI scans are shown from healthy elderly subjects with zero, one, and two $\varepsilon 4$ alleles of the ApoE gene, which confers increased risk for late-onset Alzheimer's disease (data courtesy of Gary Small MD, UCLA Center on Aging). The $\varepsilon 3$ allele is more prevalent, and considered normal. Patients at genetic risk may display metabolic and structural deficits before overt symptoms appear, suggesting that genetic and imaging information may identify candidates for early treatment in dementia (100). Note the hippocampal atrophy (*H*) and ventricular enlargement (*V*) in those at risk.

TCBV, HV are associated with verbal memory performance and subsequent risk of AD

Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study

Basil H Ridha, Josephine Barnes, Jonathan W Bartlett, Alison Godbolt, Tracey Pepple, Martin N Rossor, Nick C Fox

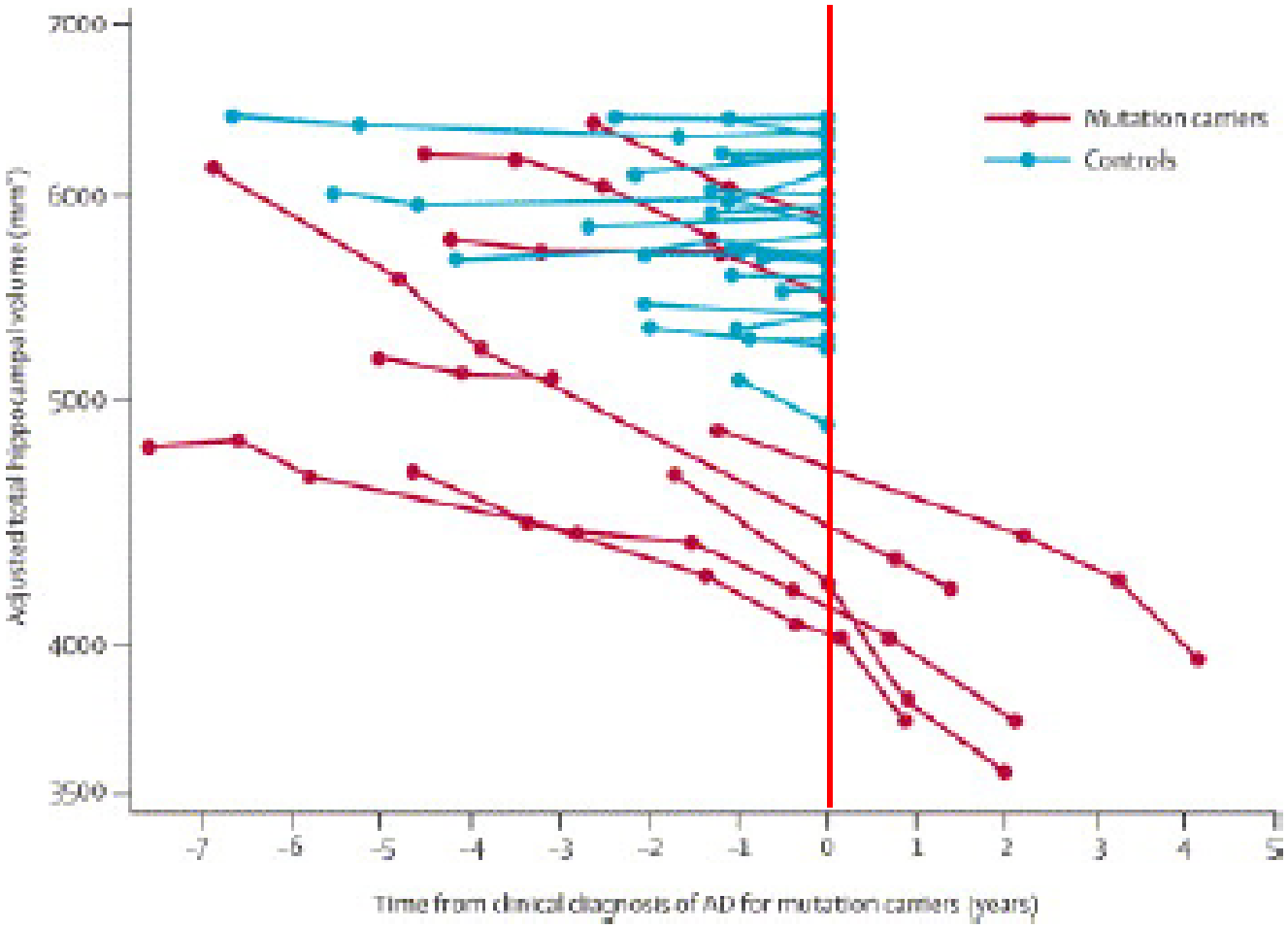
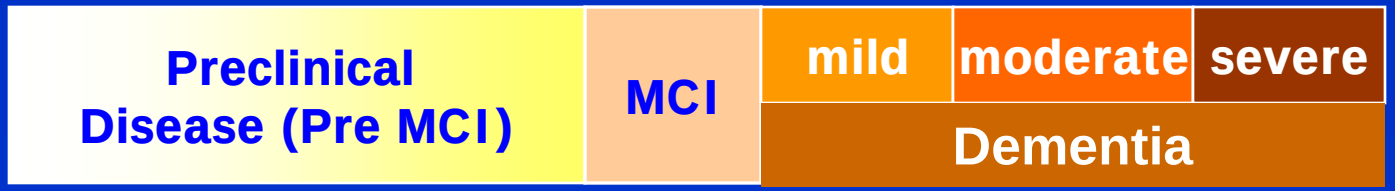


Figure 1. Adjusted total hippocampal volume measurements of mutation carriers (relative to time of clinical diagnosis of AD) and controls (relative to the date of their last scan)

The y-axis scale is logarithmic. AD=Alzheimer's disease.

Genetic Epidemiology

- **Epidemiological correlates of genetic variation: show an association of variant with**
  - **Brain MRI and Cognitive test of AD risk (intermediate or endophenotypes)**
  - **Mild Cognitive Impairment (MCI)**
  - **All dementia**
  - **Alzheimer's Disease (AD)**

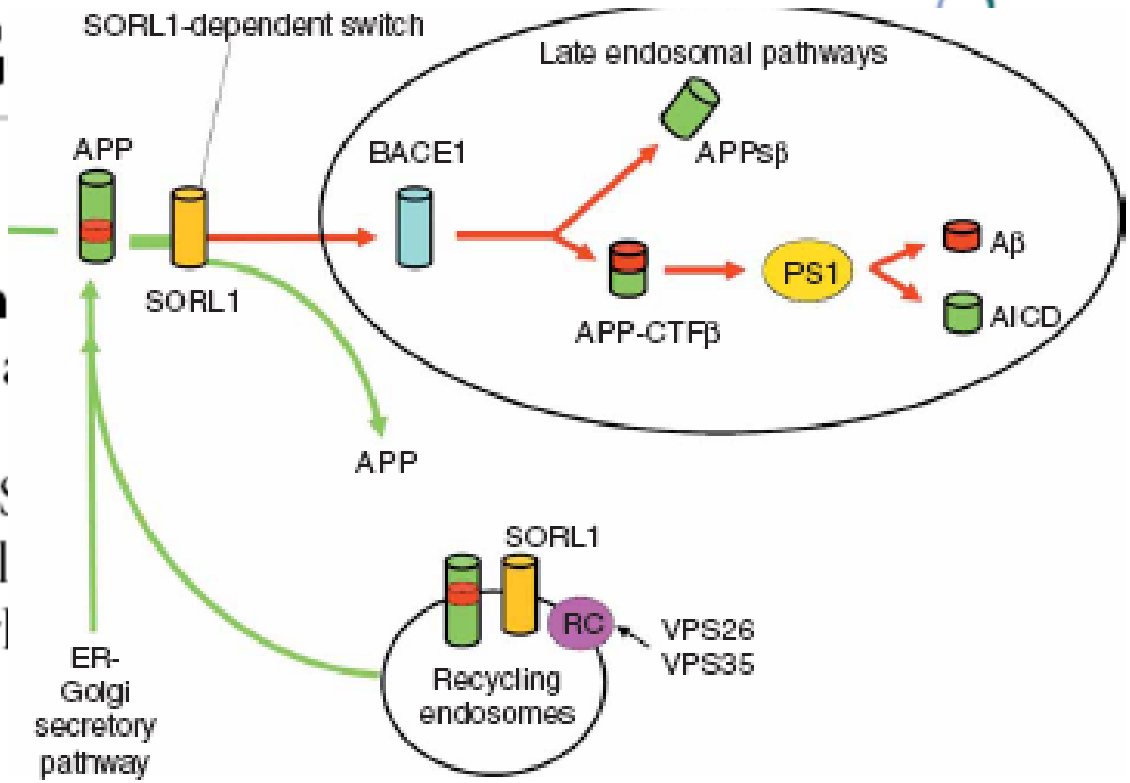


BMC Medical G

Research

Genetic correlates of brain measures: a genome-wide Framingham study

Sudha Seshadri*[1,2], Anita L DeS
Alexa S Beiser[1,2,3], Margaret Kel
Ralph B D'Agostino Sr[1,4], Charl
Philip A Wolf[1,2]



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This article is available from: http://www.biomedcentral.com/1471-2350/8/S1/S15

Study Sample

- 71,000 SNPs related to
- MRI/Cognitive endophenotypes

- in 705 stroke- and dementia-free FHS Gen 1 and 2 participants
  - Age 62±9 yrs
  - 50% men

Volumetric Brain MRI

Brain Volumes	Total Cerebral (TCBV)	Adjusted for: Age Current smoking Diabetes Systolic blood pressure Anti-hypertensive drugs Atrial fibrillation EKG-LVH Homocysteine
	Frontal (FBV)	
	Parietal (PBV)	
	Occipital (OBV)	
	Temporal (TBV)	
	Hippocampal (HPV)	
Ventricular Volumes	Lateral (LVV)	
	Temporal Horn (THV)	
White Matter Hyperintensity Volume (WMHV)		

All volumes were expressed as a ratio of total intracranial volume (TCV).

Cognitive Measures

Factor 1: Verbal Memory: LM	Adjusted for: Birth cohort by decade Education Framingham Stroke Risk Profile score ApoE genotype (ε4 +/-)
Factor 2: Visual Memory and Organization: VM, HVOT	
Factor 3: New Learning: PAS	
Factor 4: Attention and Executive Function: Trails A and B	
Boston Naming Test	
Abstract Reasoning: Similarities	
Reading and Vocabulary: Wide-Range Achievement Test (WRAT)	

Results: Unbiased Analyses

- Strongest SNP-trait association
  - On FBAT: ***SORL1*** (rs1131497; $p=3.2 \times 10^{-6}$) and abstract reasoning

SORL1 and AD related endophenotypes

- Another 100K SNP on *SORL1* (rs726601) that was in LD (D'=1, r^2 >0.8) with flanking SNPs (rs2282649, rs1010159) associated with AD in all Caucasian samples

Rogaeva et al., Nature Genetics, February 2007; pp168-177

- Was also associated with abstract reasoning, (FBAT p=8.2 X 10^{-4})

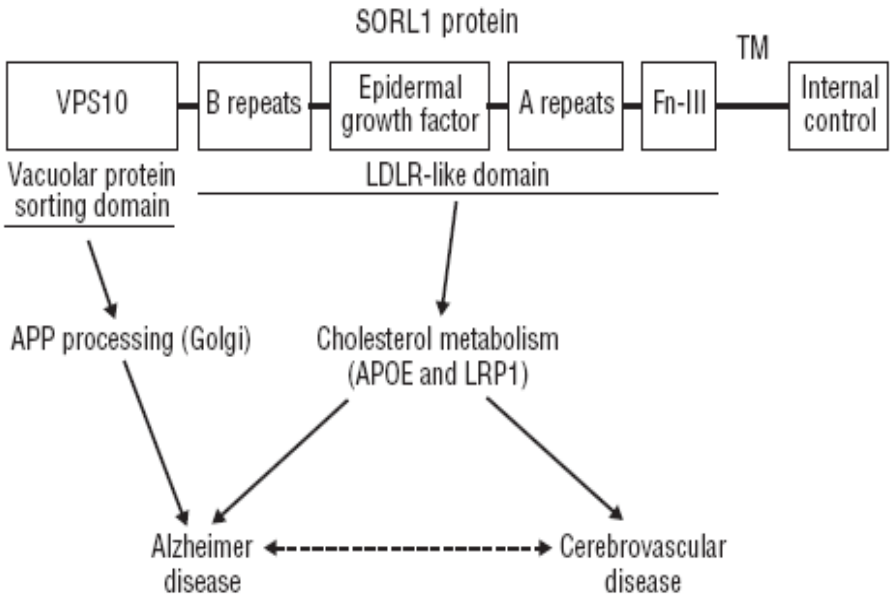
Association of Distinct Variants in *SORL1* With Cerebrovascular and Neurodegenerative Changes Related to Alzheimer Disease

Karen T. Cuenco, PhD; Kathryn L. Lunetta, PhD; Clinton T. Baldwin, PhD; Ann C. McKee, MD; Jianping Guo, MS; L. Adrienne Cupples, PhD; Robert C. Green, MD, MPH; Peter H. St. George-Hyslop, MD; Helena Chui, MD; Charles DeCarli, MD; Lindsay A. Farrer, PhD; for the MIRAGE Study Group

Arch Neurol. 2008;65(12):1640-1648

Table 3. *SORL1* SNPs Showing Association With at Least 1 MRI Trait in the MIRAGE White Families

SNP	*P* Value (No. of Informative Families)[a]			
	WMH	CVR	CA	MTA
1	.053 (73)	**.046** (73)	.43 (73)	.21 (T^b/73)
6	**.03** (66)	.16 (66)	.65 (66)	.18 (T^b/66)
8	**.001** (81)	**.006** (81)	.35 (81)	.34 (C^b/81)
9	<**.001** (76)	**.002** (76)	.44 (76)	.29 (G^b/76)
10	**.006** (78)	**.02** (78)	.94 (78)	.16 (C^b/78)
11	.08 (76)	.42 (76)	.57 (T^b/76)	**.050** (T^b/76)
15	**.04** (G^b/80)	.47 (80)	.42 (G^b/80)	.12 (80)
16	.33 (A^b/31)	.21 (A^b/31)	**.004** (31)	.36 (A^b/31)
18	.15 (29)	**.03** (29)	.45 (29)	.98 (29)
21	.38 (G^b/38)	.35 (G^b/38)	**.02** (38)	.24 (38)



SNP Health Association Resource (SHARe): A Genome-Wide Association Study in the NHLBI's Framingham Heart Study

Collaboration Between National Heart, Lung, and Blood Institute
And Boston University School of Medicine

550,000 SNPs, 9934 persons across 3 generations
Became available October 2007

National Heart Lung and Blood Institute
People Science Health

Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium

http://depts.washington.edu/chargeco/wiki/Main_Page

Overview of CHARGE

- CVD/Aging cohorts with GWAS data
  - ARIC, CHS, AGES, ASPS, FHS and Rotterdam
  - Sharing of within-study analyses for cross-study meta-analysis
  - Imputation to HapMap permitted meta-analyses despite use of different platforms in each study

Genes Underlying Stroke & VCI

Expected to belong to 1 or both of 2 classes:

- Genes that predispose individuals to cerebrovascular disease, and

- Genes that determine tissue responses to cerebrovascular disease (e.g. ischemic tolerance)

The NEW ENGLAND JOURNAL of MEDICINE

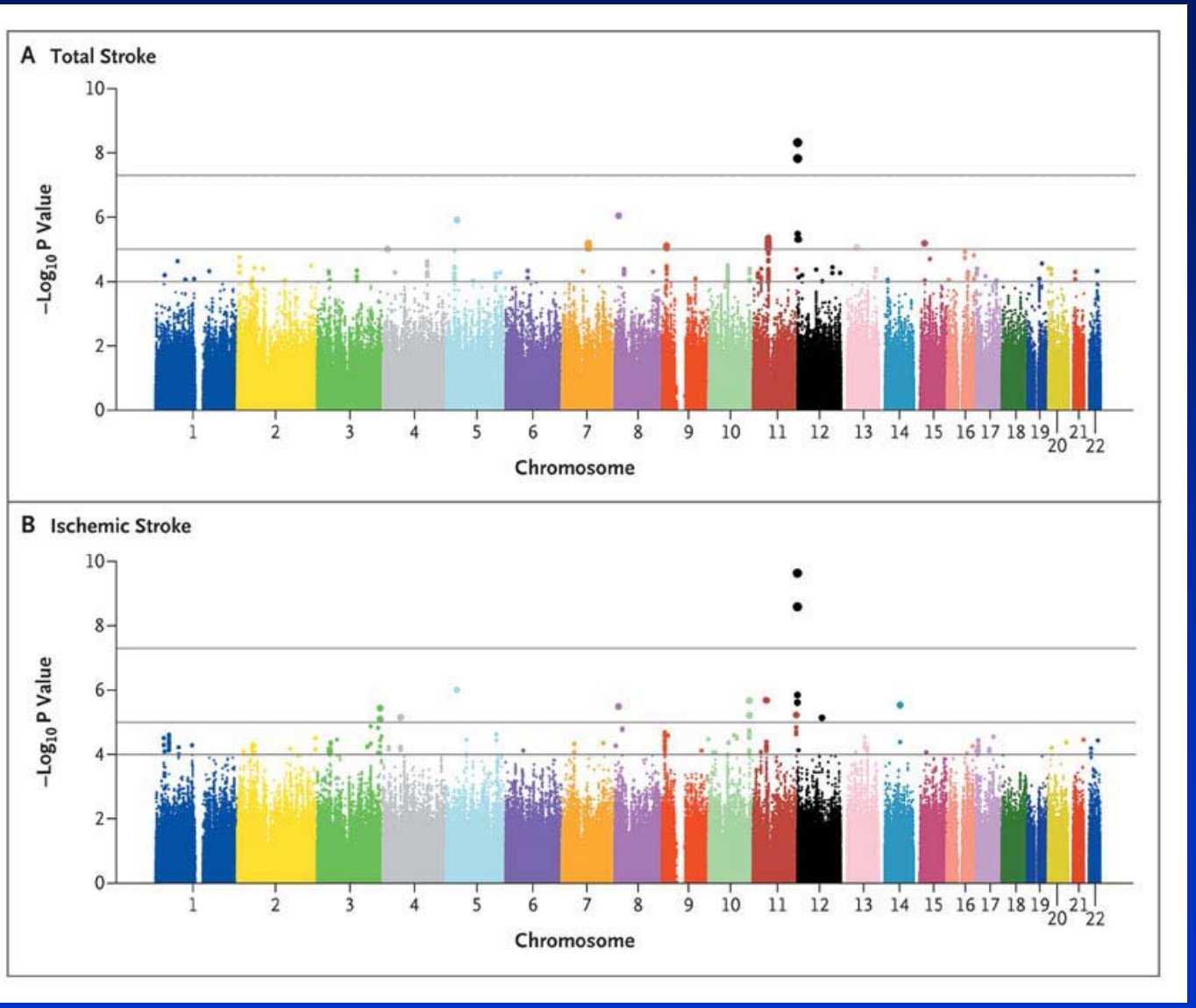
ORIGINAL ARTICLE

Genomewide Association Studies of Stroke

M. Arfan Ikram, M.D., Sudha Seshadri, M.D., Joshua C. Bis, Ph.D., Myriam Fornage, Ph.D., Anita L. DeStefano, Ph.D., Yurii S. Aulchenko, Ph.D., Stephanie Debette, M.D., Ph.D., Thomas Lumley, Ph.D., Aaron R. Folsom, M.D., M.P.H., Evita G. van den Herik, M.D., Michiel J. Bos, M.D., Ph.D., Alexa Beiser, Ph.D., Mary Cushman, M.D., M.Sc., Lenore J. Launer, Ph.D., Eyal Shahar, M.D., M.P.H., Maksim Struchalin, M.Sc., Yangchun Du, B.A., Nicole L. Glazer, Ph.D., Wayne D. Rosamond, Ph.D., Fernando Rivadeneira, M.D., Ph.D., Margaret Kelly-Hayes, R.N., D.Ed., Oscar L. Lopez, M.D., Josef Coresh, M.D., Ph.D., Albert Hofman, M.D., Ph.D., Charles DeCarli, M.D., Susan R. Heckbert, M.D., Ph.D., Peter J. Koudstaal, M.D., Ph.D., Qiong Yang, Ph.D., Nicholas L. Smith, Ph.D., Carlos S. Kase, M.D., Kenneth Rice, Ph.D., Talin Haritunians, Ph.D., Gerwin Roks, M.D., Ph.D., Paul L.M. de Kort, M.D., Ph.D., Kent D. Taylor, Ph.D., Lonneke M. de Lau, M.D., Ph.D., Ben A. Oostra, Ph.D., Andre G. Uitterlinden, Ph.D., Jerome I. Rotter, M.D., Eric Boerwinkle, Ph.D., Bruce M. Psaty, M.D., Ph.D., Thomas H. Mosley, Ph.D., Cornelia M. van Duijn, Ph.D., Monique M.B. Breteler, M.D., Ph.D., W.T. Longstreth, Jr., M.D., and Philip A. Wolf, M.D.

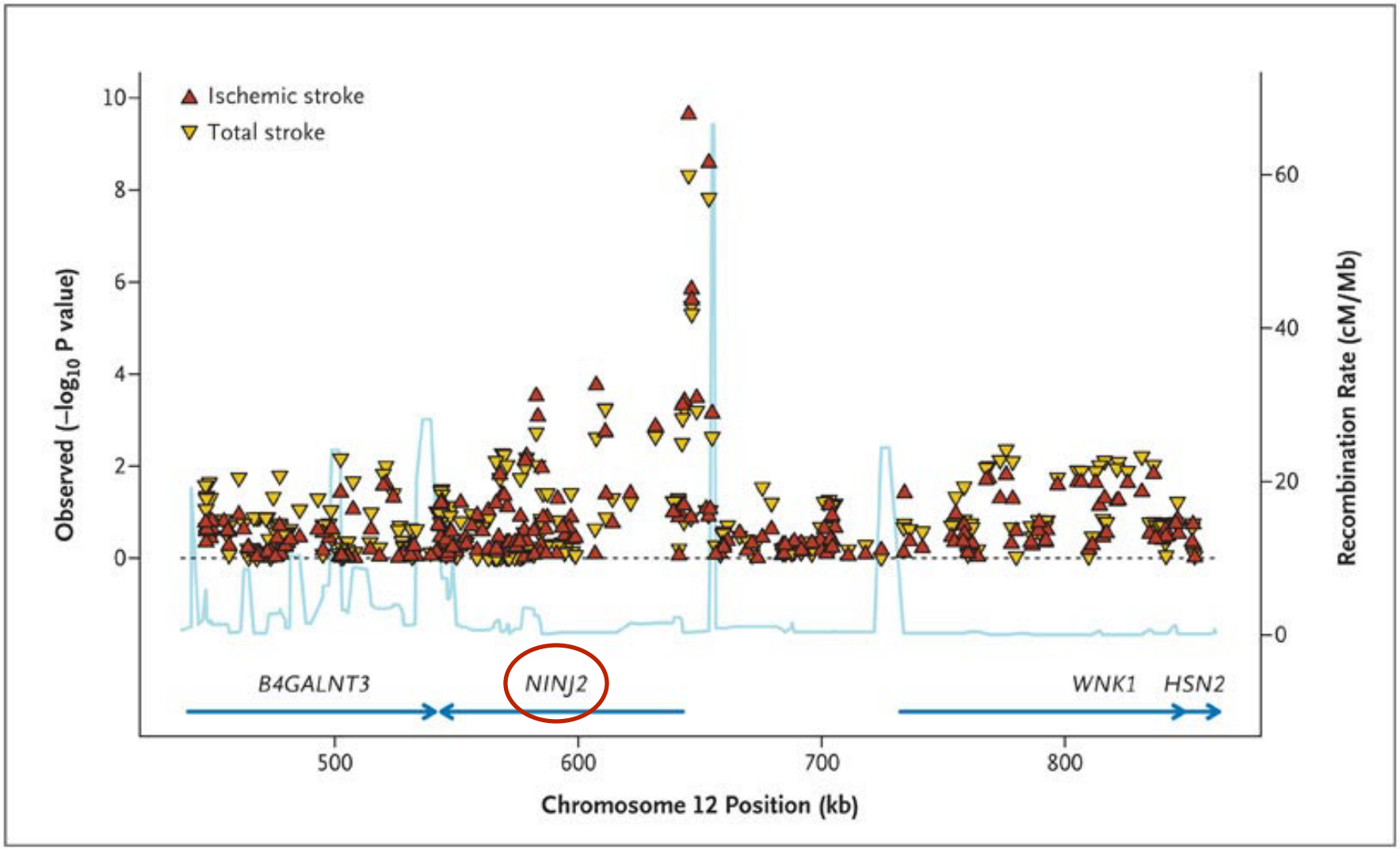
N Engl J Med 2009;360:1718-28.

Results of Tests for the Association between Stroke and Each SNP Measured in the Genomewide Association Study



Ikram M et al. N Engl J Med 2009;10.1056/NEJMoa0900094

Associations in the Region Centered on rs11833579 and Containing NINJ2



Ikram M et al. N Engl J Med 2009;10.1056/NEJMoa0900094

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genomewide Association Studies of Stroke

M. Arfan Ikram, M.D., Sudha Seshadri, M.D., Joshua C. Bis, Ph.D.

- Genome-wide significant association of stroke with 2 SNPs located in the regulatory region of *Ninjurin-2* (rs11833579 and rs12425791).

- Ninjurin-2: Transmembrane protein in the “nerve-injury-induced protein” family
  - cell-cell adhesion molecule, expressed in glia-
  - shown to promote neurite extension after nerve injury
  - may also modify brain response to ischemic injury

Brain Aging, AD & Cerebrovascular Disease Phenotypes in CHARGE

- Total and ischemic stroke
- Total dementia, AD, Pure AD, VaD, MCI
- Cerebral MRI measures
  - White matter disease - Covert brain infarcts
  - Total cranial & brain volumes, hippocampal, lobar
- Cognitive Function
  - Tests of verbal and visual memory; processing speed, executive function; other domains

Univariate vs. Cross-Phenotype Analyses

Information on multiple correlated phenotypes is not utilized

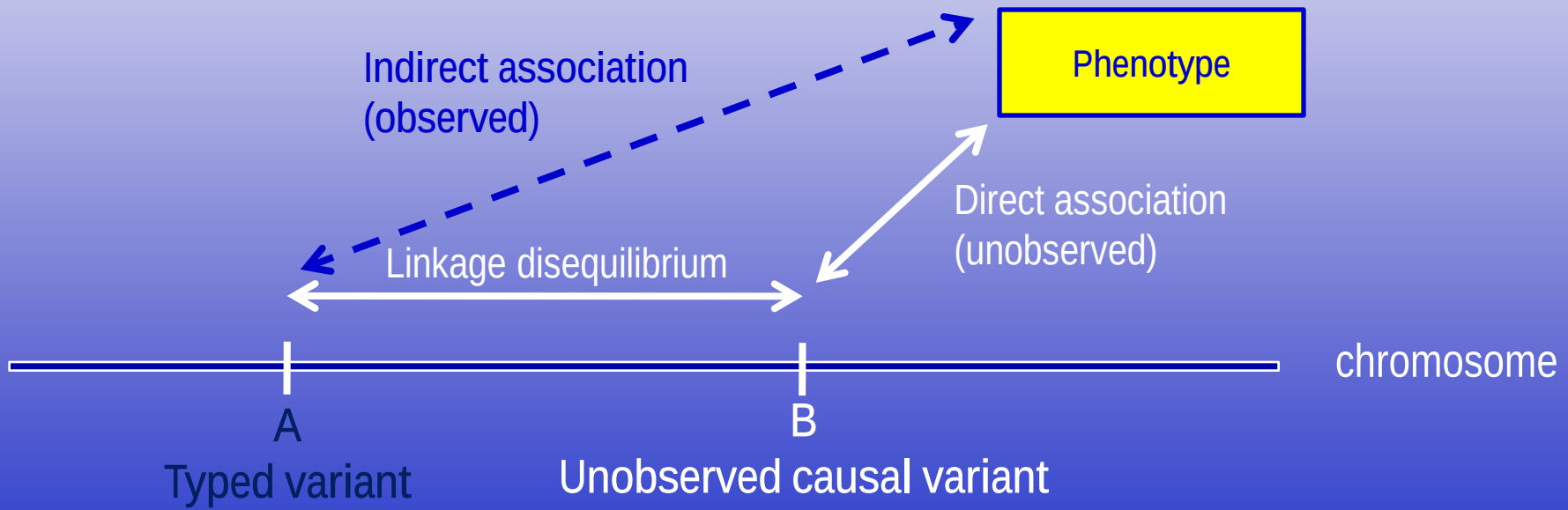
- Cross Phenotype Analyses
  - Pros:
    - increase power to detect associations of genetic variants with disease by making younger subjects informative
    - Increase statistical power to detect associations with each phenotype
    - identify genetic variants with pleiotropic effects → common biological pathways

Klei, Genet Epidemiol 2008

Need Sequencing & Functional Studies to Find Causal Variant(s).

- An allele is associated with a phenotype when its frequency differs between cases and controls more than would be predicted by chance.

  → But this does NOT necessarily imply causality



Use Genetic, Risk Factor, Biomarker & Phenotype Data

Replication and finding **causal variant**

Look at gene-environment and gene-gene interactions

Explore links genes → gene expression → endophenotype → disease

Develop Predictive Models

Mendelian Randomization

- Association of cholesterol/statin use with decreased AD risk could be causal or an effect of disease-

- Genetic variation is determined at birth; if we stratify

Neuroimage. 2008 April 15; 40(3): 1214–1221.

CHOLESTEROL-RELATED GENETIC RISK SCORES ARE ASSOCIATED WITH HYPOMETABOLISM IN ALZHEIMER'S-AFFECTED BRAIN REGIONS

Eric M. Reiman, M.D.[1,2,9,12], **Kewei Chen, Ph.D.**[1,3,4,12], **Richard J. Caselli, M.D.**[6,12], **Gene E. Alexander, Ph.D.**[5,12], **Daniel Bandy, M.S.**[1,12], **Jennifer L. Adamson, M.B.A.**[8], **Wendy Lee, M.S.**[1,12], **Ashley Cannon, B.S.**[8], **Elizabeth A. Stephan, Ph.D.**[9,12], **Dietrich A. Stephan, Ph.D.**[9,12], and **Andreas Papassotiropoulos, M.D.**[9,10,11,12]

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