Genetic Pathways linking Neuroinflammation, Vascular Disease and Neurodegeneration

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NIA: R01 AG33193, U0149505
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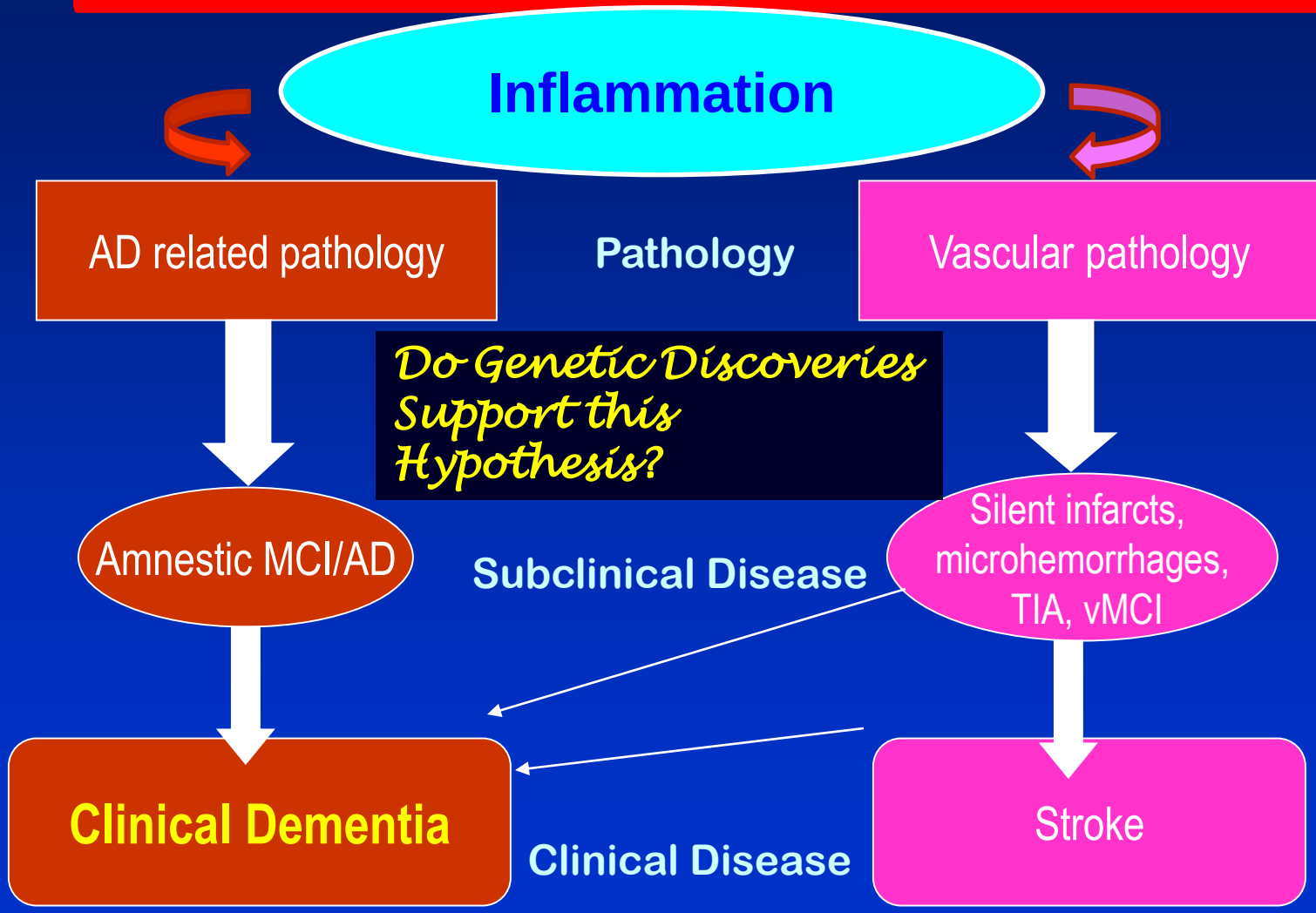
R01 AG049607
NINDS: R01 NS17950

Disclosure

- No conflicts of interest
- I will not be discussing off-label uses of medical procedures or pharmaceuticals

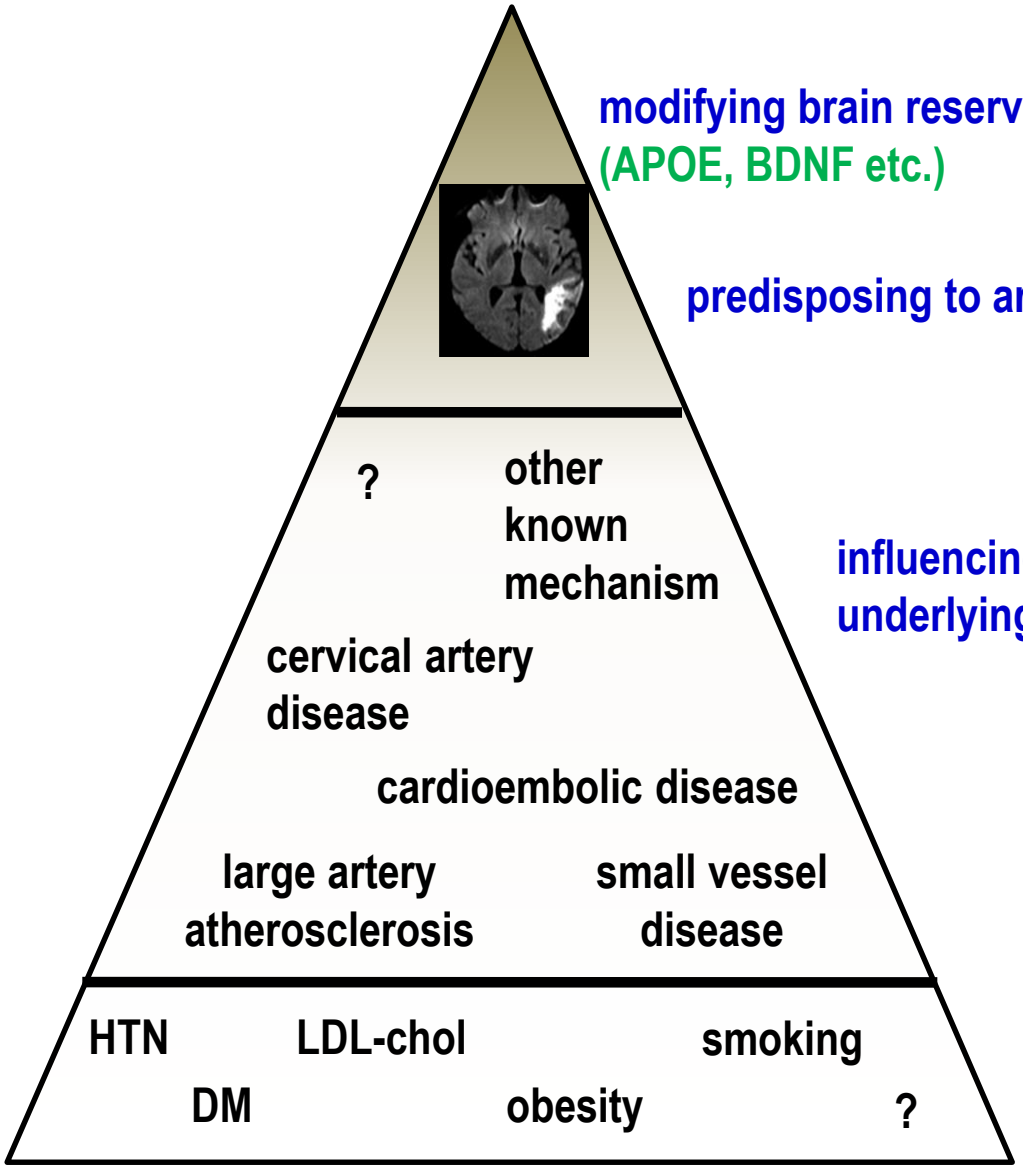
Neurodegeneration and Vascular Injury may be parallel processes



Outline

- **Genetics of Vascular Brain Injury**
- Inflammation Genes Impact Brain Aging
- AD Genes Act Through Vascular/Inflam Paths

‘Vascular Injury genes’ can act at various levels



Genetics of Vascular Brain Injury

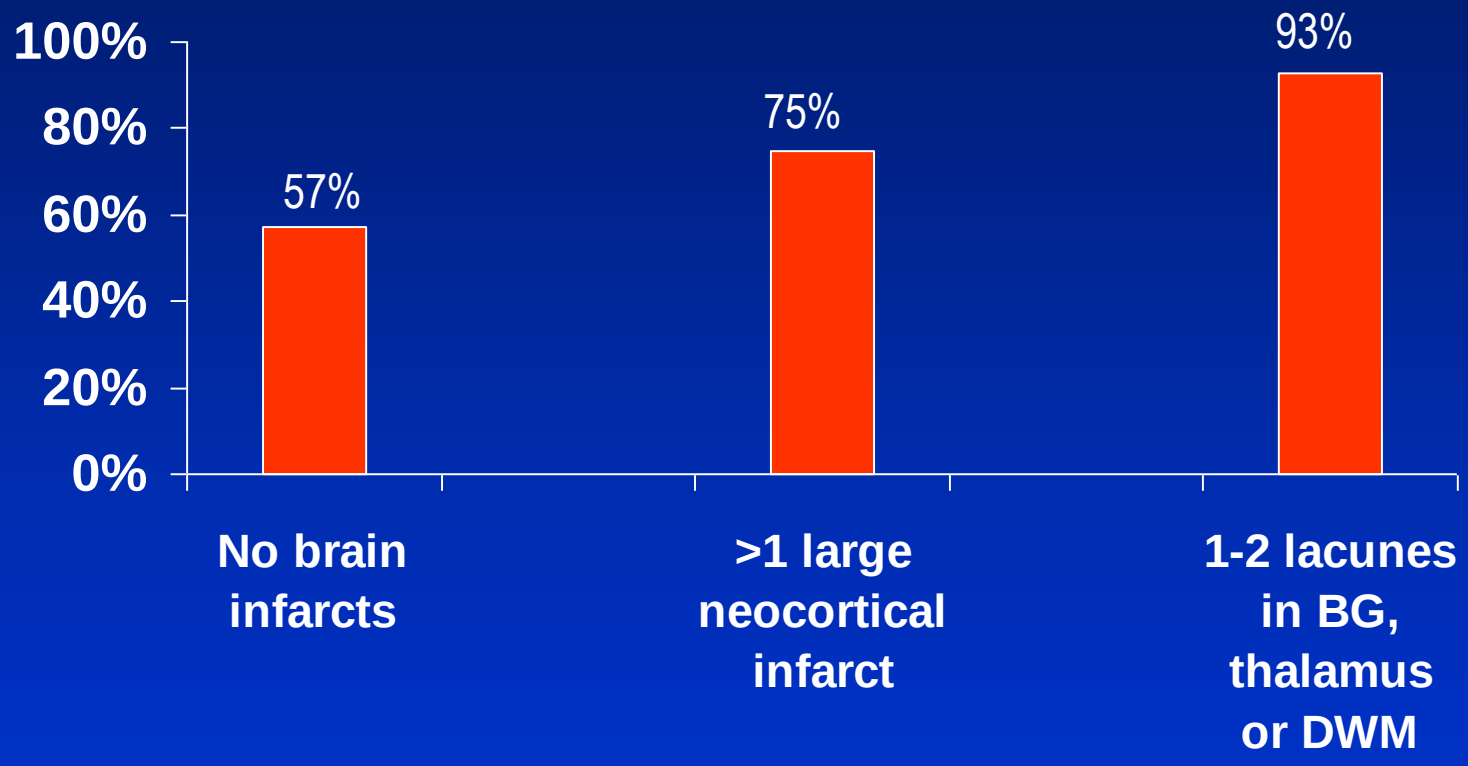
- Clinical Stroke is a syndrome with subtypes:
  - Ischemic (large artery, small artery, cardio-embolic)
  - Hemorrhagic (lobar, deep)
  - Mendelian syndromes with dementia (e.g. CADASIL)

Various Presentations of 'Small Vessel Disease'

- Subclinical Vascular Brain Injury also has types:
  - 'Covert' infarcts (most are small, subcortical 'lacunes')
  - White Matter hyperintensities
  - Others
    - Microbleeds, perivascular spaces, DTI, regional volumes

In 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**

GWAS of Stroke

Risk Variants for Atrial Fibrillation on Chromosome 4q25 Associate with Ischemic Stroke

Closest gene is 50,000kb away, PITX2

Solveig Gretarsdottir, PhD,[1] Gudmar Thorleifsson, PhD,[1] Andrei Manolescu, PhD,[1] Unnur Styrkarsdottir, PhD,[1] Anna Helgadottir, MD,[1] Andreas Gschwendtner, MD,[2] Konstantinos Kostulas, MD, PhD,[3] Gregor Kuhlenbäumer, MD,[4,5] Steve Bevan, PhD,[6] Thorbjorg Jonsdottir, BSc,[1] Hjordis Bjarnason, BSc,[1] Jona Saemundsdottir, BSc,[1] Stefan Palsson, MSc,[1] David O. Arnar, MD, PhD,[7] Hilma Holm, MD,[1] Gudmundur Thorgeirsson, MD, PhD,[7] Einar Mar Valdimarsson, MD,[7] Sigurlaug Sveinbjörnsdottir, MD,[7] Christian Gieger, PhD,[8,9] Klaus Berger, MD,[10] H-Erich Wichmann, MD,[8,9] Jan Hillert, MD,[3] Hugh Markus, MD,[6] Jeffrey Robert Gulcher, MD, PhD,[1] E. Bernd Ringelstein, MD,[4] Augustine Kong, PhD,[1] Martin Dichgans, MD,[2] Daniel Fannar Gudbjartsson, PhD,[1] Unnur Thorsteinsdottir, PhD,[1,11] and Kari Stefansson, MD, PhD[1,11]

Ann Neurol 2008;64:402-409.

Objective: To find sequence variants that associate with the risk for ischemic stroke (IS), we performed a genome-wide association study.

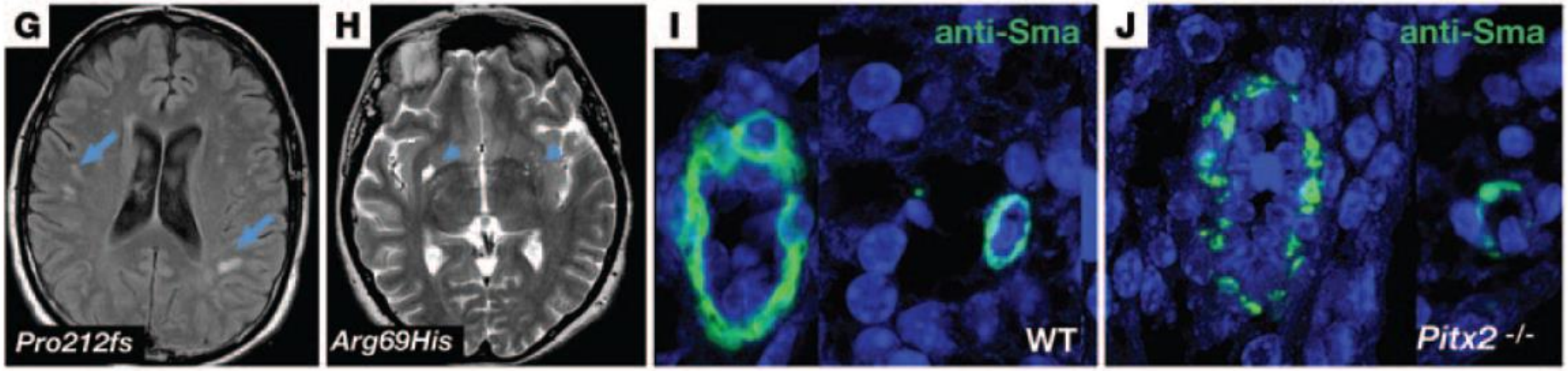
Methods: We genotyped 1,661 Icelandic IS patients and 10,815 control subjects using the Infinium HumanHap300 chip (Illumina, San Diego, CA). A total of 310,881 single nucleotide polymorphisms (SNPs) were tested for association with IS, and the most significant signals were replicated in two large European IS sample sets (2,224 cases/2,583 control subjects). Two SNPs, rs2200733 and rs10033464, were tested further in additional European IS samples (2,327 patients and 16,760 control subjects).

Results: In the Icelandic samples and the two replication sets combined, rs2200733 associated significantly with cardioembolic stroke (CES) (odds ratio [OR], 1.54; $p = 8.05 \times 10^{-9}$). No other variants associated with IS or any of its subtypes. rs2200733

The Journal of Clinical Investigation BRIEF REPORT

Mutation of *FOXC1* and *PITX2* induces cerebral small-vessel disease

Curtis R. French,[1] Sudha Seshadri,[2] Anita L. Destefano,[3] Myriam Fornage,[4] Corey R. Arnold,[5] Philip J. Gage,[6] Jonathan M. Skarie,[7] William B. Dobyns,[8] Kathleen J. Millen,[8] Ting Liu,[9] William Dietz,[9] Tsutomu Kume,[9] Marten Hofker,[10] Derek J. Emery,[11] Sarah J. Childs,[5] Andrew J. Waskiewicz,[12] and Ordan J. Lehmann[1,13]



A pediatric eye-brain syndrome, WMH changes in adult humans and altered actin deposition, hemorrhagic stroke in zebrafish

JCI 2014;124:4877-1881.

PITX2 also associated with non-cardioembolic stroke in 2nd wave 1000K CHARGE GWAS

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genomewide Association Studies of Stroke

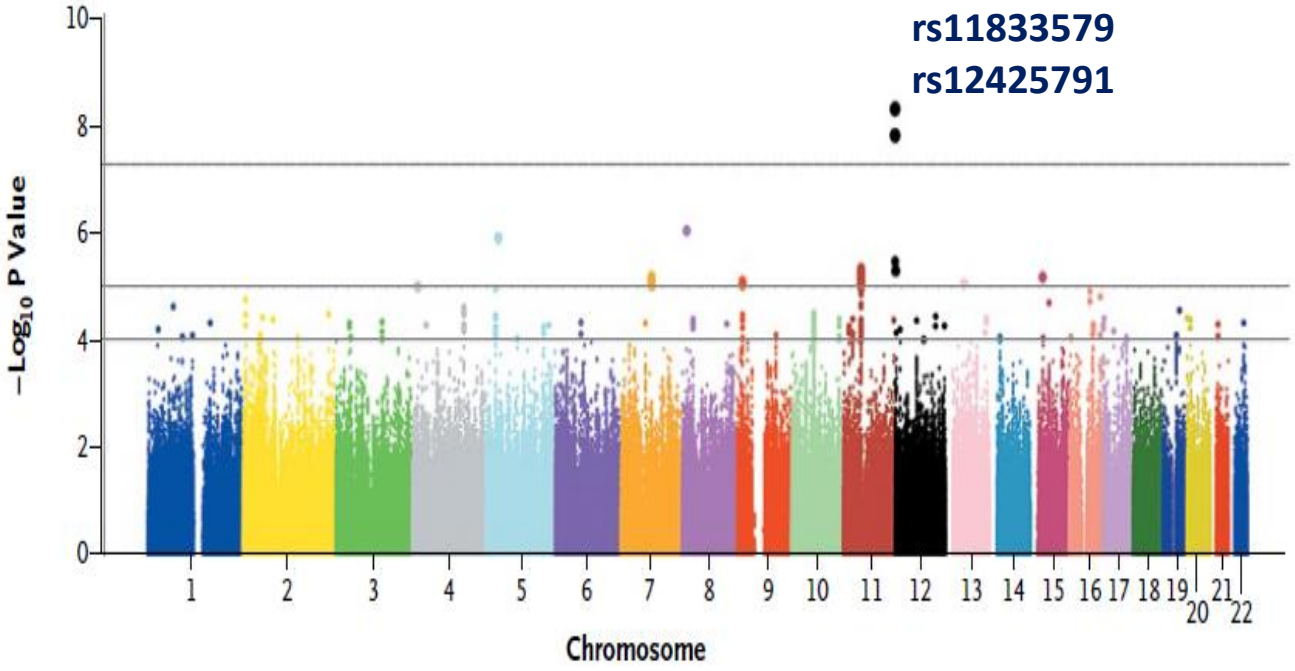
M. Arfan Ikram, M.D., Sudha Seshadri, M.D., Joshua C. Bis, Ph.D., Myriam Fornage, Ph.D., Anita L. DeStefano, Ph.D., Yurii S. Aulchenko, Ph.D., Stephanie Debette, M.D., Ph.D., Thomas Lumley, Ph.D., Aaron R. Folsom, M.D., M.P.H., Evita G. van den Herik, M.D., Michiel J. Bos, M.D., Ph.D., Alexa Beiser, 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.

2nd GWAS discovery

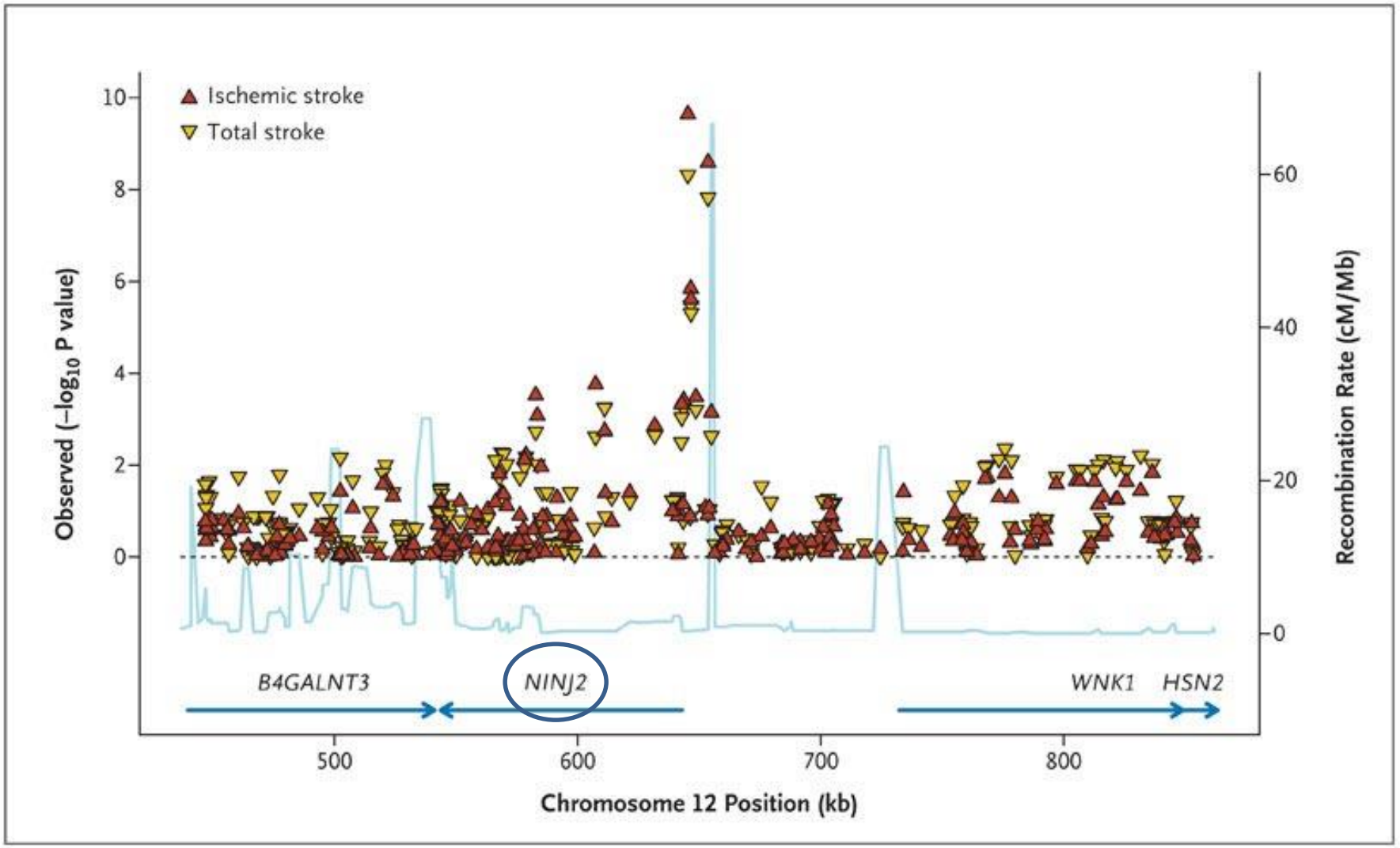
GWAS of Incident Stroke

- Association of incident stroke, especially ischemic non-cardioembolic stroke, with locus on chr12p13



CHARGE

N= 19,602 with
1,544 incident strokes



Ninjurin-2: Transmembrane protein in the “nerve-injury-induced protein” family

The NEW ENGLAND JOURNAL of MEDICINE

OPEN ACCESS Freely available online

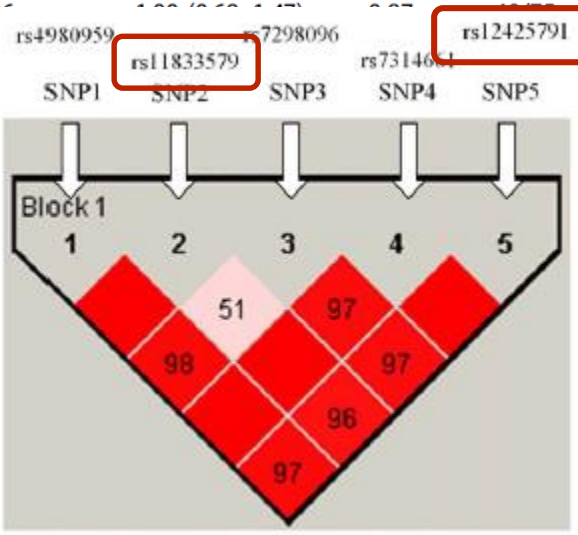
PLoS one

Genetic Polymorphisms of a Novel Vascular Susceptibility Gene, Ninjurin2 *(NINJ2)*, Are Associated with a Decreased Risk of Alzheimer's Disease

Kun-Pei Lin[1,2], Shih-Yuan Chen[1], Liang-Chuan Lai[3], Yi-Ling Huang[1], Jen-Hau Chen[1,2], Ta-Fu Chen[4], Yu Sun[5], Li-Li Wen[6], Ping-Keung Yip[7], Yi-Min Chu[8], Wei J. Chen[1,9,10], Yen-Ching Chen[1,9,10]*

Table 3. *NINJ2* SNP analysis by genotype for dementia patients and controls.

	Co-dominant model								Additive model
SNP	0 copies		1 copy			2 copies			
	Case/control	OR	Case/control	OR (95%CI)	*p*	Case/control	OR (95%CI)	*p*	OR (95%CI)
AD	(Global test $P<0.0001$)								
SNP1	98/156	1.00	123/198	1.18 (0.81–1.72)	0.35	52/63	1.25 (0.76–2.07)	0.35	1.13 (0.89–1.43)
SNP2	127/172	1.00	121/196	0.97 (0.67–1.39)	0.81	21/49	**0.43 (0.23–0.80)**	**0.01***	**0.76 (0.58–0.98)**
SNP3	95/134	1.00	133/2				0.77 (0.46–1.29)	0.25	0.90 (0.70–1.15)
SNP4	224/346	1.00	46/72				2.99 (0.48–18.15)	0.23	1.20 (0.80–1.80)
SNP5	162/235	1.00	104/1				**0.33 (0.12–0.96)**	**0.04**	0.84 (0.63–1.14)
VaD	(Global test $P=0.43$)								
SNP1	47/156	1.00	55/19				0.83 (0.40–1.69)	0.65	0.97 (0.70–1.34)
SNP2	50/172	1.00	50/19				0.98 (0.49–1.96)	0.95	0.93 (0.67–1.29)
SNP3	39/134	1.00	59/20				0.92 (0.46–1.83)	0.64	0.98 (0.71–1.37)
SNP4	89/346	1.00	29/72				NA	NA	1.27 (0.76–2.15)
SNP5	66/235	1.00	47/16				1.19 (0.43–3.30)	0.72	1.06 (0.72–1.54)



All models were adjusted for age and gende
Abbreviation: NA, not applicable.
*Result remains significant after controlling f

doi:10.1371/journal.pone.0020573.t003

).

Inverse Association with Memory

- *NINJ2* (rs*11833579*)
  - Associated with memory decline (p=9x10^{-5}) &
  - With AD susceptibility
  - In Religious Orders Study/ Memory and Aging Project (p=0.001)
  - In CHARGE (p=0.02).

Sequence Variants on Chromosome 9p21.3 Confer Risk for Atherosclerotic Stroke

Andreas Gschwendtner, MD,[1] Steve Bevan, PhD,[2] John W. Cole, MD, MS,[3] Anna Plourde, BA,[4] Mar Matarin, PhD,[5] Helen Ross-Adams, PhD,[6] Thomas Meitinger, MD,[7] Erich Wichmann, MD, PhD,[8,9] Braxton D. Mitchell, PhD,[3] Karen Furie, MD, MPH,[4] Agnieszka Slowik, MD, PhD,[10] Stephen S. Rich, PhD,[11] Paul D. Syme, MD,[12] Mary J. MacLeod, PhD,[6] James F. Meschia, MD,[13] Jonathan Rosand, MD, MSc,[4] Steve J. Kittner, MD, MPH,[3] Hugh S. Markus, FRCP,[2] Bertram Müller-Myhsok, MD,[14] Martin Dichgans, MD,[1] on behalf of the International Stroke Genetics Consortium

Objective: Recent studies have identified a major locus for risk for coronary artery disease and myocardial infarction on chromosome 9p21.3. Stroke, in particular, ischemic stroke caused by atherosclerotic disease, shares common mechanisms with myocardial infarction. We investigated whether the 9p21 region contributes to ischemic stroke risk.

Methods: In an initial screen, 15 single nucleotide polymorphisms (SNPs) covering the critical genetic interval on 9p21 were genotyped in samples from Southern Germany (1,090 cases, 1,244 control subjects) and the United Kingdom (758 cases, 872 control subjects, 3 SNPs). SNPs significantly associated with ischemic stroke or individual stroke subtypes in either of the screening samples were subsequently genotyped in 2,528 additional cases and 2,189 additional control subjects from Europe and North America.

Results: Genotyping of the screening samples demonstrated associations between seven SNPs and atherosclerotic stroke (all $p < 0.05$). Analysis of the full sample confirmed associations between six SNPs and atherosclerotic stroke in multivariate analyses controlling for demographic variables, coronary artery disease, myocardial infarction, and vascular risk factors (all $p < 0.05$). The odds ratios for the lead SNP (rs1537378-C) were similar in the various subsamples with a pooled odds ratio of 1.21 (95% confidence interval, 1.07–1.37) under both fixed- and random-effects models ($p = 0.002$). The point estimate for the population attributable risk is 20.1% for atherosclerotic stroke.

Interpretation: The chromosome 9p21.3 region represents a major risk locus for atherosclerotic stroke. The effect of this locus on stroke appears to be independent of its relation to coronary artery disease and other stroke risk factors. Our findings support a broad role of the 9p21 region in arterial disease.

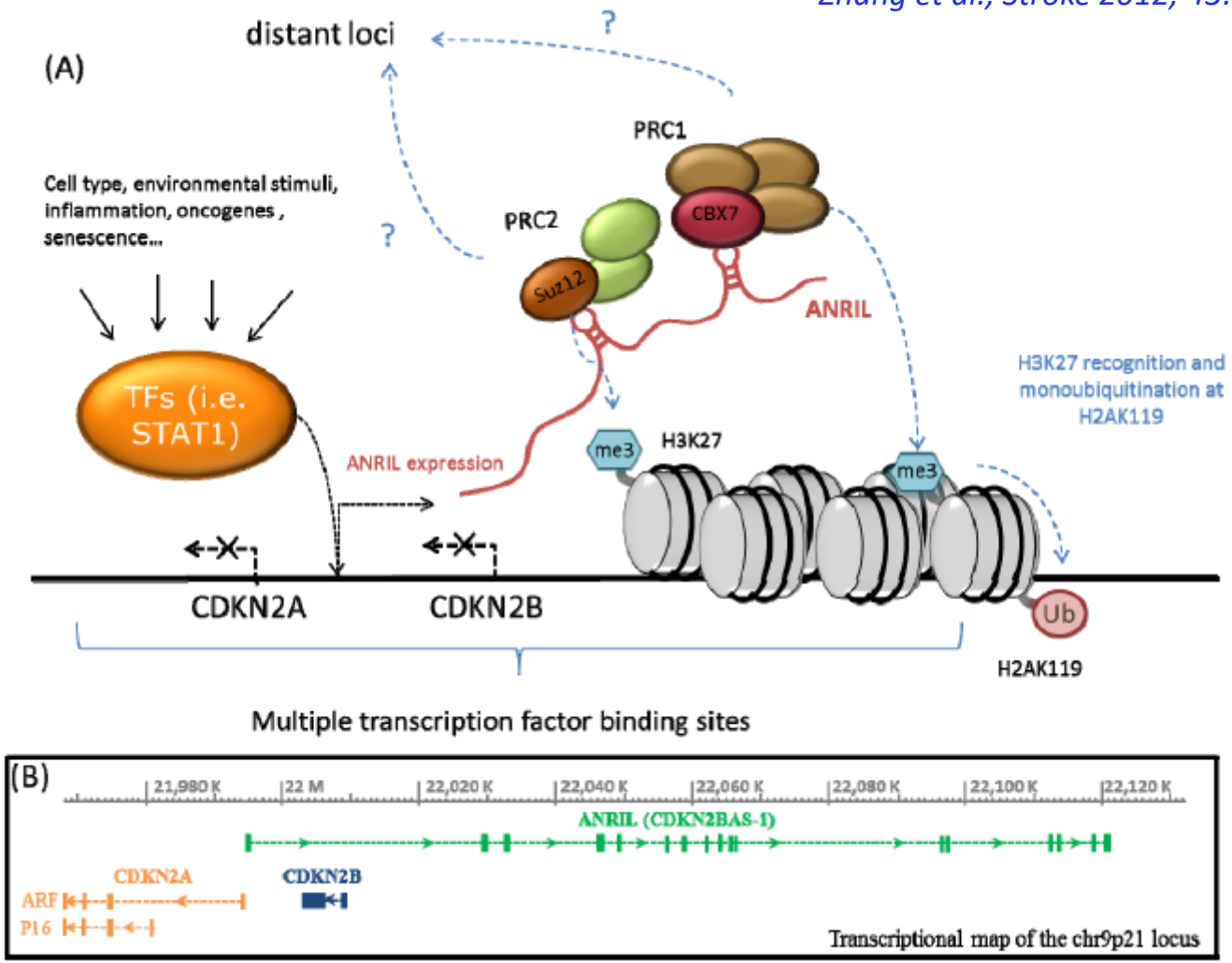
Independent of relation to CHD

Ann Neurol 2009;65:531–539

Gene for long non-coding RNA, ANRIL

Top SNP rs10757274 at 9p21.3 is associated with ANRIL expression in atheromatous plaque

Zhang et al., Stroke 2012; 43:14-21.



Congrains A et al., Int. J. Mol. Sci. 2013; 14:1278-1292

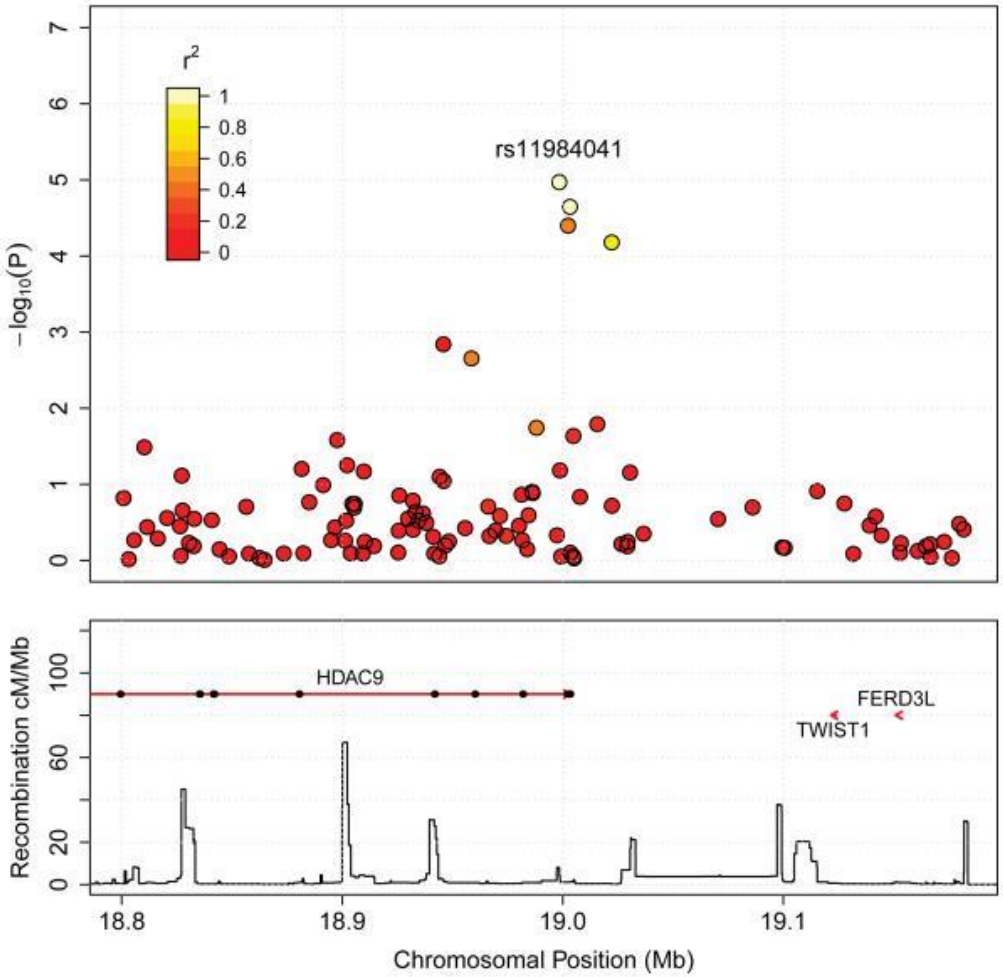
Also associated with generalized aggressive periodontitis *Ernst FD et al., BMC Med Gen 2010*

Genome-wide association study identifies a variant in *HDAC9* associated with large vessel ischemic stroke

Bellenguez C et al., Nat Genet 2012

The International Stroke Genetics Consortium (ISGC)[1] & the Wellcome Trust Case Control Consortium 2 (WTCCC2)[1]

3,548 affected, 5,972 controls; replication in 5,859 affected, 6,281 controls.



4th GWAS discovery

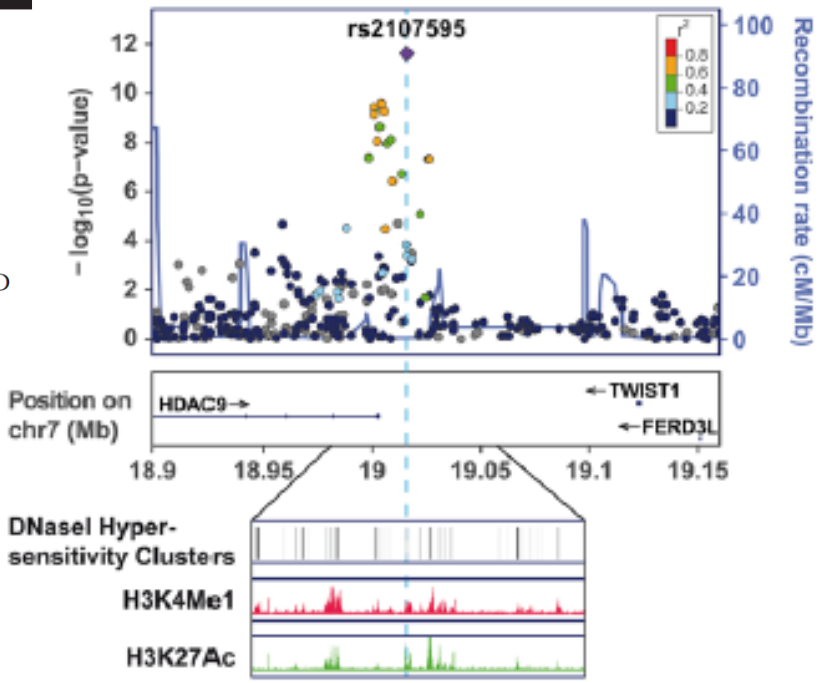
Original Contribution

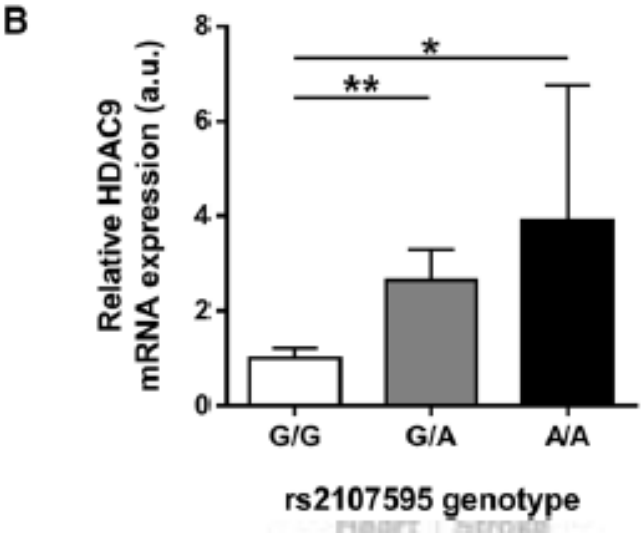
Deficiency of the Stroke Relevant *HDAC9* Gene Attenuates Atherosclerosis in Accord With Allele-Specific Effects at 7p21.1

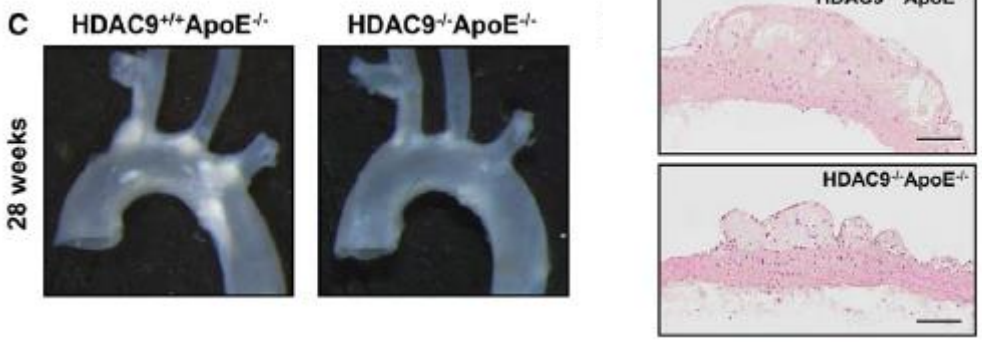
Sepiede Azghandi, BSc*; Caroline Prell, Dipl. Biol.*; Sander W. van der Laan, MSc; Manuela Schneider, DVM; Rainer Malik, PhD; Kerstin Berer, PhD; Norbert Gerdes, PhD; Gerard Pasterkamp, MD, PhD; Christian Weber, MD; Christof Haffner, PhD; Martin Dichgans, MD

Genotyping and phenotyping in 1838 carotid plaque samples from Athero-Express Study and mRNA expression in PBMC showed allele specific differences in HDAC expression.

In mouse models, HDAC KO mice had less atheromatous plaque and different plaque composition

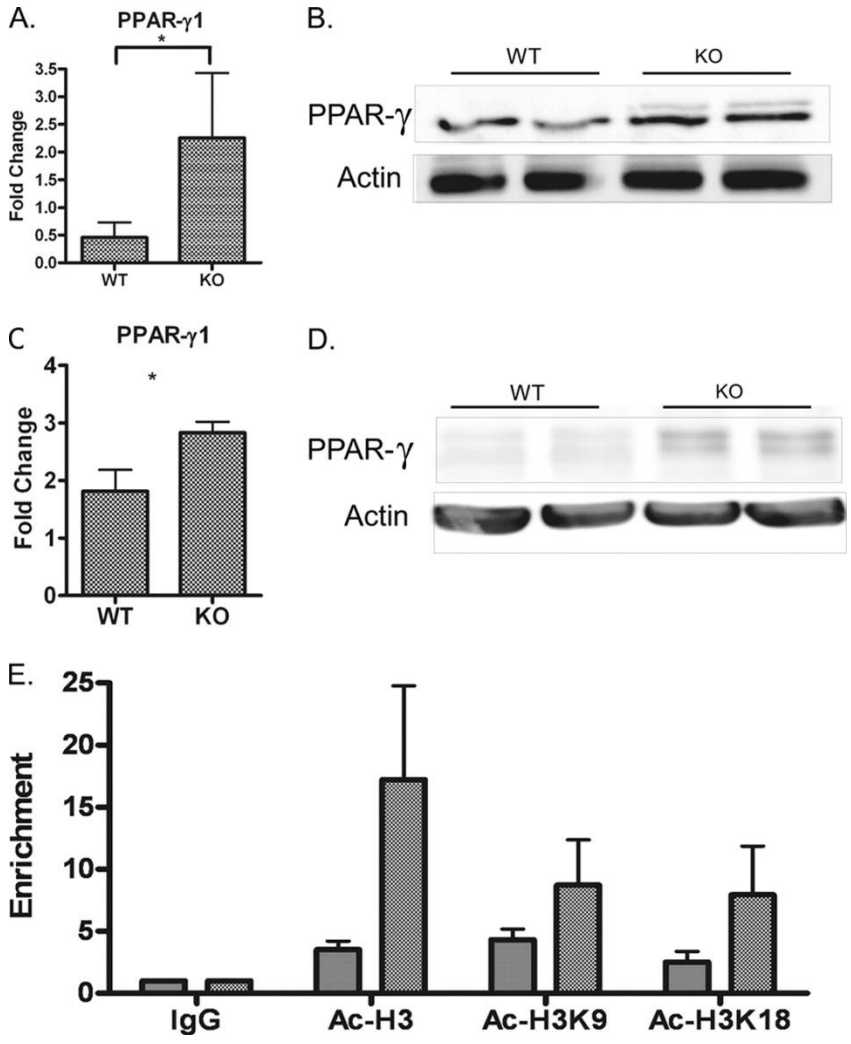






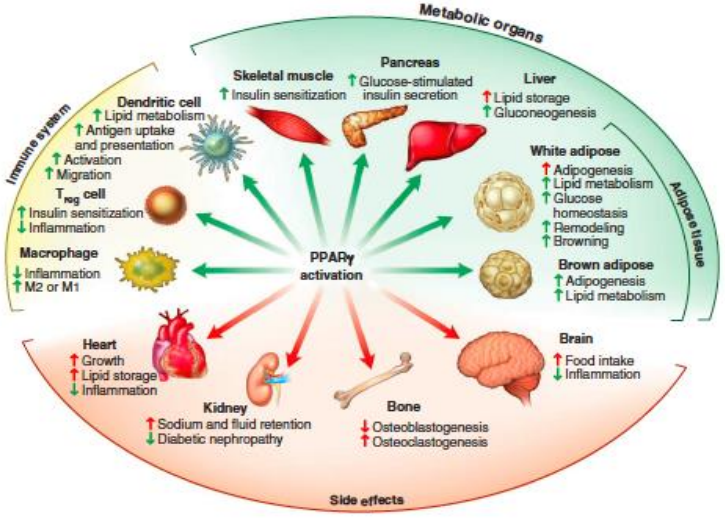
Stroke 2015

Decreased inflammatory cytokines and chemokine production in HDAC9-deficient MRL/lpr mice through increased PPAR-γ expression.



Kailin Yan et al. J. Biol. Chem. 2011;286:28833-28843

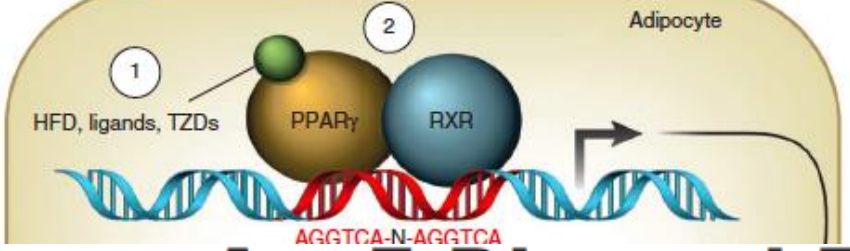
PPAR-gamma modifies brain inflammation



Interacts with RXR

Target of AD treatment trials with TZD- pioglitazone, rosiglitazone

jbc



ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models

Science, 2012

Paige E. Cramer,[1] John R. Cirrito,[2] Daniel W. Wesson,[1,3] C. Y. Daniel Lee,[1] J. Colleen Karlo,[1] Adriana E. Zinn,[1] Brad T. Casali,[1] Jessica L. Restivo,[2] Whitney D. Goebel,[2] Michael J. James,[4] Kurt R. Brunden,[4] Donald A. Wilson,[3] Gary E. Landreth[1]*

Alzheimer's disease (AD) is associated with impaired clearance of β-amyloid (Aβ) from the brain, a process normally facilitated by apolipoprotein E (apoE). ApoE expression is transcriptionally induced through the action of the nuclear receptors peroxisome proliferator–activated receptor gamma and liver X receptors in coordination with retinoid X receptors (RXRs). Oral administration of the RXR agonist bexarotene to a mouse model of AD resulted in enhanced clearance of soluble Aβ within hours in an apoE-dependent manner. Aβ plaque area was reduced more than 50% within just 72 hours. Furthermore, bexarotene stimulated the rapid reversal of cognitive, social, and olfactory deficits and improved neural circuit function. Thus, RXR activation stimulates physiological Aβ clearance mechanisms, resulting in the rapid reversal of a broad range of Aβ-induced deficits.

Bexarotene

- Works best in younger mice
- May improve cognition by increasing APOE expression, independent of plaque burden
- Genotype dependent effect?
- Hyperlipidemia, hypothyroidism

- Trials: BEAT-AD (Cummings), ReXceptor (Landreth)

Common variants at 6p21.1 are associated with large artery atherosclerotic stroke

Nat Genet 2012;44:1147-1151.

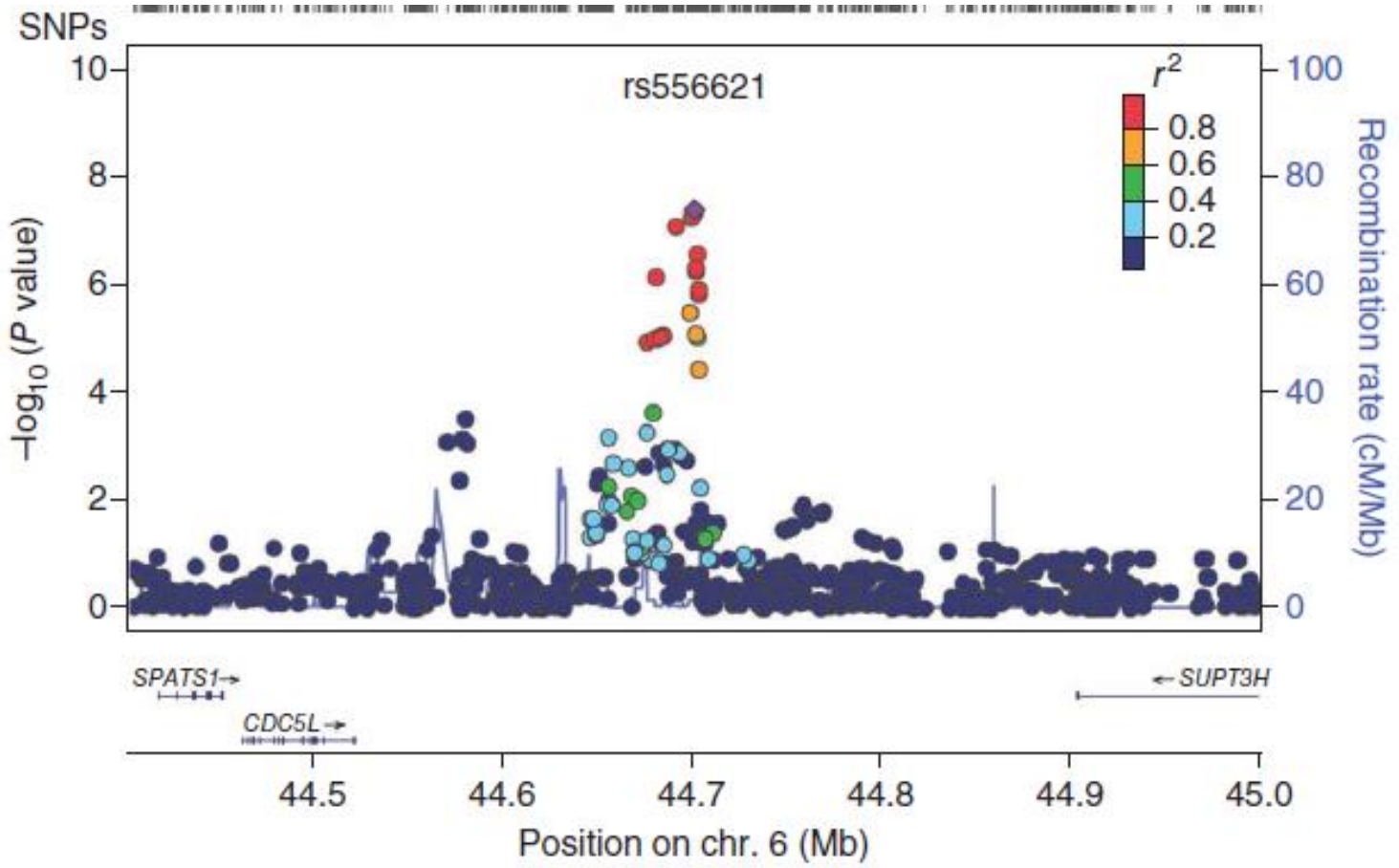


Figure 2 Regional association results for the chromosome 6p21.1 locus showing association at genome-wide significance with LAA. The index

CDC5L associated with tumor progression in gliomas;
6p21.1 region also has *VEGFA, TREM2* genes

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PLOS | GENETICS

A Novel *MMP12* Locus Is Associated with Large Artery Atherosclerotic Stroke Using a Genome-Wide Age-at-Onset Informed Approach

Matthew Traylor[1*], Kari-Matti Mäkelä[2,3], Laura L. Kilarski[1], Elizabeth G. Holliday[4,5], William J. Devan[6,7], Mike A. Nalls[8], Kerri L. Wiggins[9], Wei Zhao[10], Yu-Ching Cheng[11,12], Sefanja Achterberg[13], Rainer Malik[14], Cathie Sudlow[15], Steve Bevan[16], Emma Raitoharju[2,3], METASTROKE, International Stroke Genetics Consortium, Wellcome Trust Case Consortium 2 (WTCCC2)[¶], Niku Oksala[2,3,17], Vincent Thijs[18,19,20], Robin Lemmens[18,19,20], Arne Lindgren[21,22], Agnieszka Slowik[23], Jane M. Maguire[4,5,24,25], Matthew Walters[26], Ale Algra[13,27], Pankaj Sharma[28], John R. Attia[4,5,25], Giorgio B. Boncoraglio[29], Peter M. Rothwell[30], Paul I. W. de Bakker[7,27,31,32], Joshua C. Bis[9], Danish Saleheen[33,34], Steven J. Kittner[12], Braxton D. Mitchell[11], Jonathan Rosand[6,7], James F. Meschia[35], Christopher Levi[5,25], Martin Dichgans[14,36], Terho Lehtimäki[2,3], Cathryn M. Lewis[37,38☯], Hugh S. Markus[16☯]

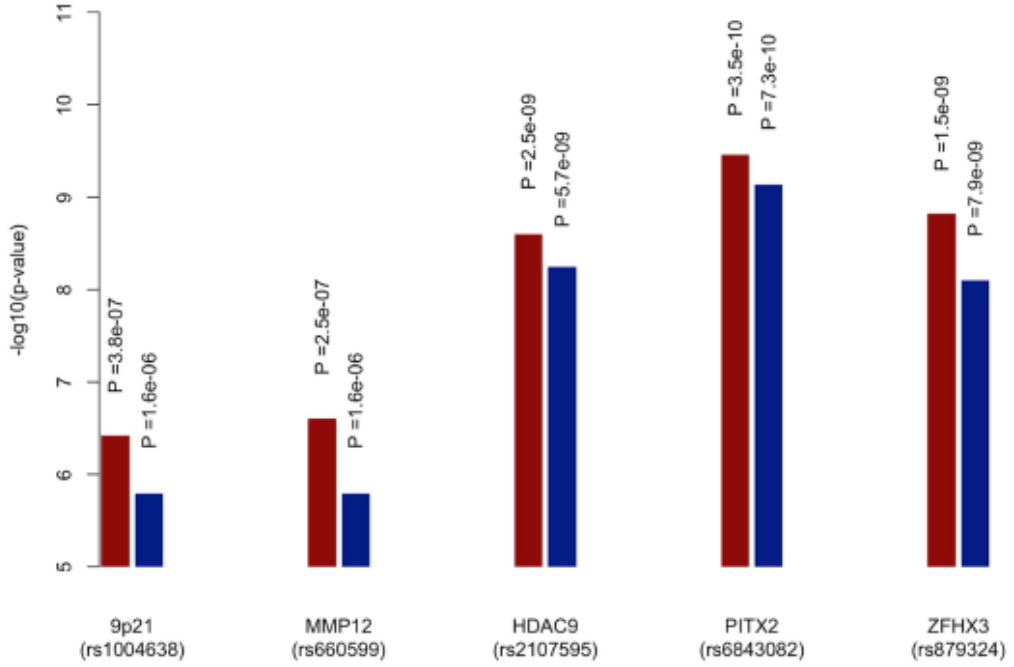


Figure 3. Meta-analysis p-values of known loci for ischaemic stroke subtypes using age-at-onset informed approach compared to uninformed approach. -log10 of p-values derived from meta-analysis of all discovery cohorts using age-at-onset informed approach (red) and

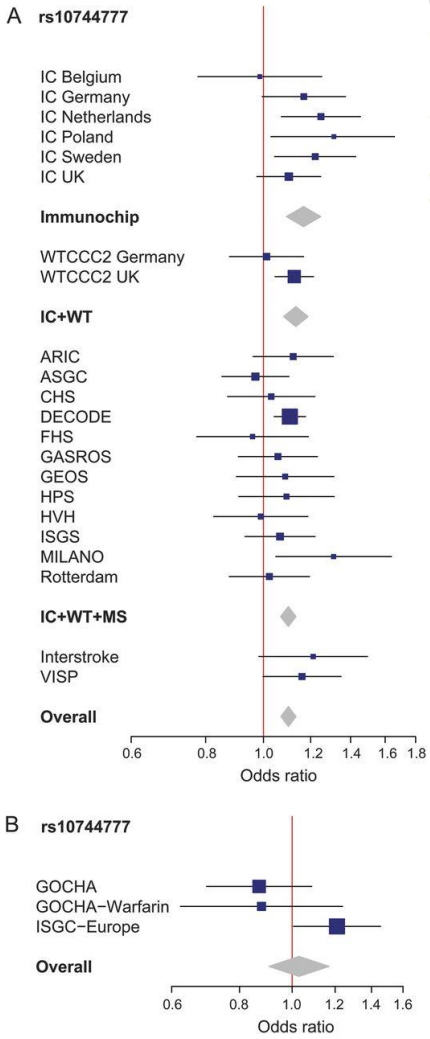
Combining Immunochip based discovery with GWAS based replication

Meta-analysis in more than 17,900 cases of ischemic stroke reveals a novel association at 12q24.12

by Laura L. Kilarski, Sefanja Achterberg, William J. Devan, Matthew Traylor, Rainer Malik, Arne Lindgren, Guillame Pare, Pankaj Sharma, Agniesczka Slowik, Vincent Thijs, Matthew Walters, Bradford B. Worrall, Michele M. Sale, Ale Algra, L. Jaap Kappelle, Cisca Wijmenga, Bo Norrving, Johanna K. Sandling, Lars Rönnblom, An Goris, Andre Franke, Cathie Sudlow, Peter M. Rothwell, Christopher Levi, Elizabeth G. Holliday, Myriam Fornage, Bruce Psaty, Solveig Gretarsdottir, Unnar Thorsteinsdottir, Sudha Seshadri, Braxton D. Mitchell, Steven Kittner, Robert Clarke, Jemma C. Hopewell, Joshua C. Bis, Giorgio B. Boncoraglio, James Meschia, M. Arfan Ikram, Bjorn M. Hansen, Joan Montaner, Gudmar Thorleifsson, Kari Stefanson, Jonathan Rosand, Paul I.W. de Bakker, Martin Farrall, Martin Dichgans, Hugh S. Markus, and Steve Bevan

Neurology
Volume 83(8):678-685
August 19, 2014

rs10744777, an eQTL for *ALDH2*



Open
ORIGINAL ARTICLE

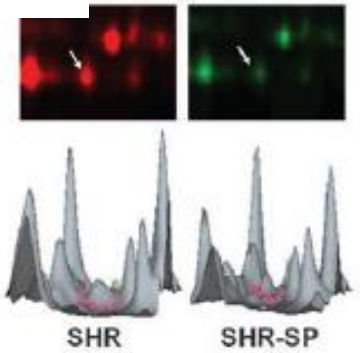
Cell Research (2013) 23:915-930.

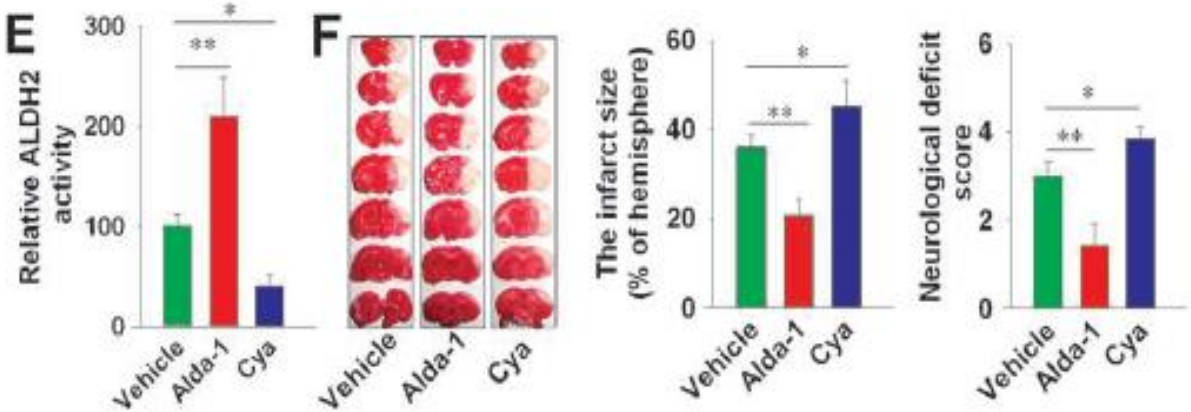
www.nature.com/cr

ALDH2 protects against stroke by clearing 4-HNE

Jin-Min Guo[1, 2, *], Ai-Jun Liu[1, *], Pu Zang[1], Wen-Zhe Dong[1], Li Ying[3], Wei Wang[1], Pu Xu[1], Xu-Rui Song[1], Jun Cai[4], She-Qing Zhang[5], Jun-Li Duan[6], Jawahar L Mehta[7], Ding-Feng Su[1]

Implicated in hepatic inflammation, AD & PD (small studies), cognition (neuroCHARGE)





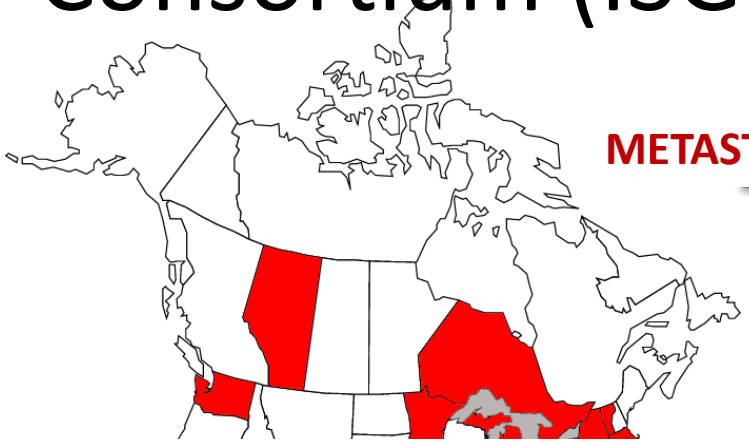
Kilarski L L et al. Neurology 2014;83:678-685

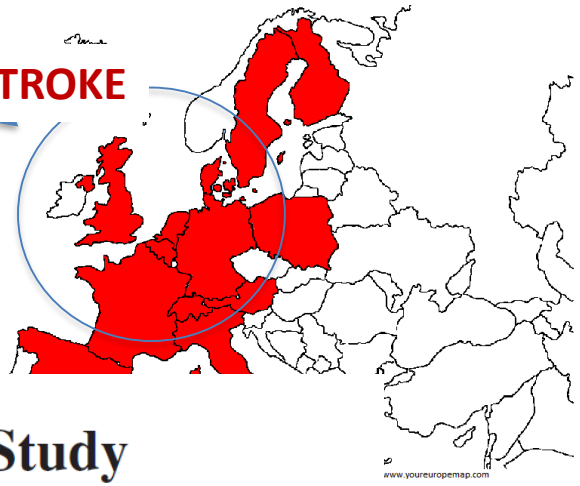
AMERICAN ACADEMY OF NEUROLOGY

Summary of Ischemic Stroke Genes

SNP in chromosome	Gene region	Relation to
4q25	*PITX2*	CE, All IS
7p21	*HDAC9*	LVD, All IS
6p21.1	*SUPT3H/CDC5L*	LVD
9p21	*CDKN2A/CDKN2B/ANRIL*	LVD, All IS
9q34	*ABO* blood locus	LVD and CE
11q22	*MMP12*	LVD
12p13.33	*NINJ*	All IS
12q24.12	*ALDH2*	All IS
16q22	*ZFHX3*	CE

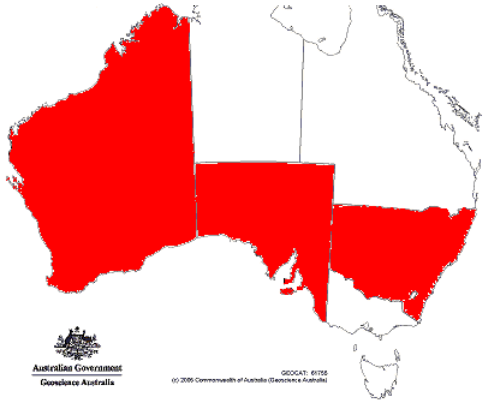
International Stroke Genetics Consortium (ISGC) Sites

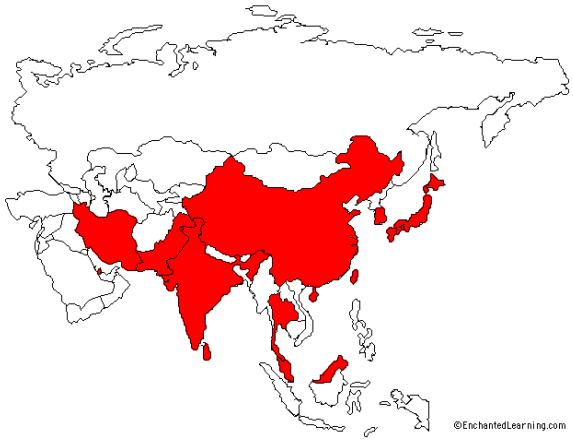


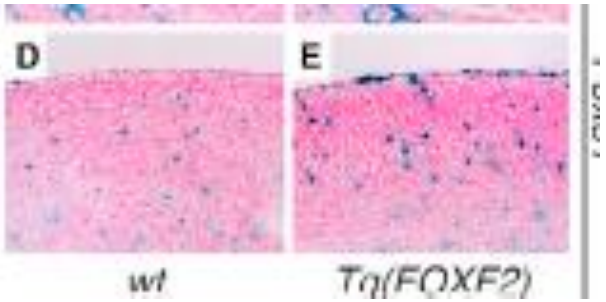


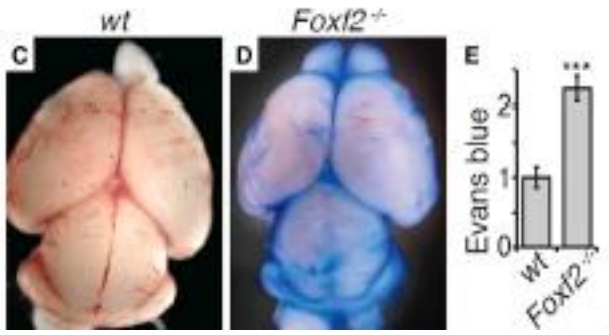
Stroke Genetics Network (SiGN) Study

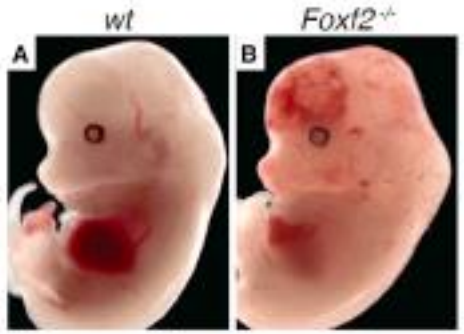
Design and Rationale for a Genome-Wide Association Study of Ischemic Stroke Subtypes

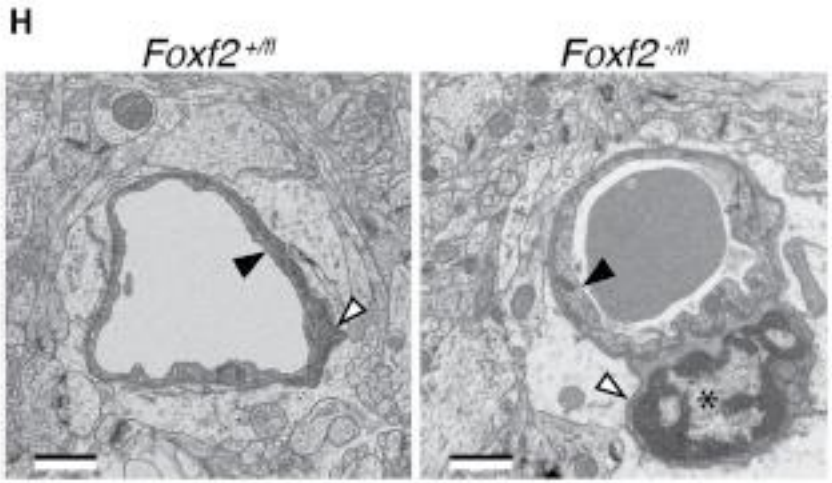


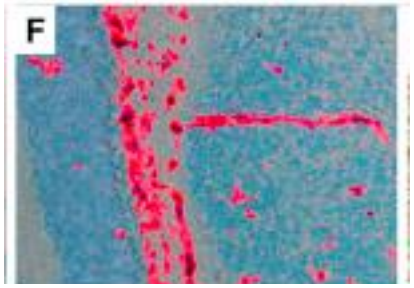












Article

Developmental Cell

Foxf2 Is Required for Brain Pericyte Differentiation and Development and Maintenance of the Blood-Brain Barrier

Foxf2-expressing neural crest cells are progenitors of cerebrovascular mural cells

Inactivation of *Foxf2* leads to hyperplasia and defective differentiation of brain pericytes, a leaky BBB, and attenuation of Pdgfrβ and Tgfβ-Smad2/3 signaling

Brain hemorrhages in zebrafish, mice; FOXF2 was top gene associated with ‘all stroke’ and ‘ischemic stroke’ in CHARGE 2nd wave (1000K) GWAS

NATURE COMMUNICATIONS | DOI: 10.1038/ncomms3932

ARTICLE

Received 12 Sep 2013 | Accepted 13 Nov 2013 | Published 13 Dec 2013

DOI: 10.1038/ncomms3932

Pericyte loss influences Alzheimer-like neurodegeneration in mice

Abhay P. Sagare[1,*], Robert D. Bell[2,*], Zhen Zhao[1,*], Qingyi Ma[1], Ethan A. Winkler[2], Anita Ramanathan[1] & Berislav V. Zlokovic[1]

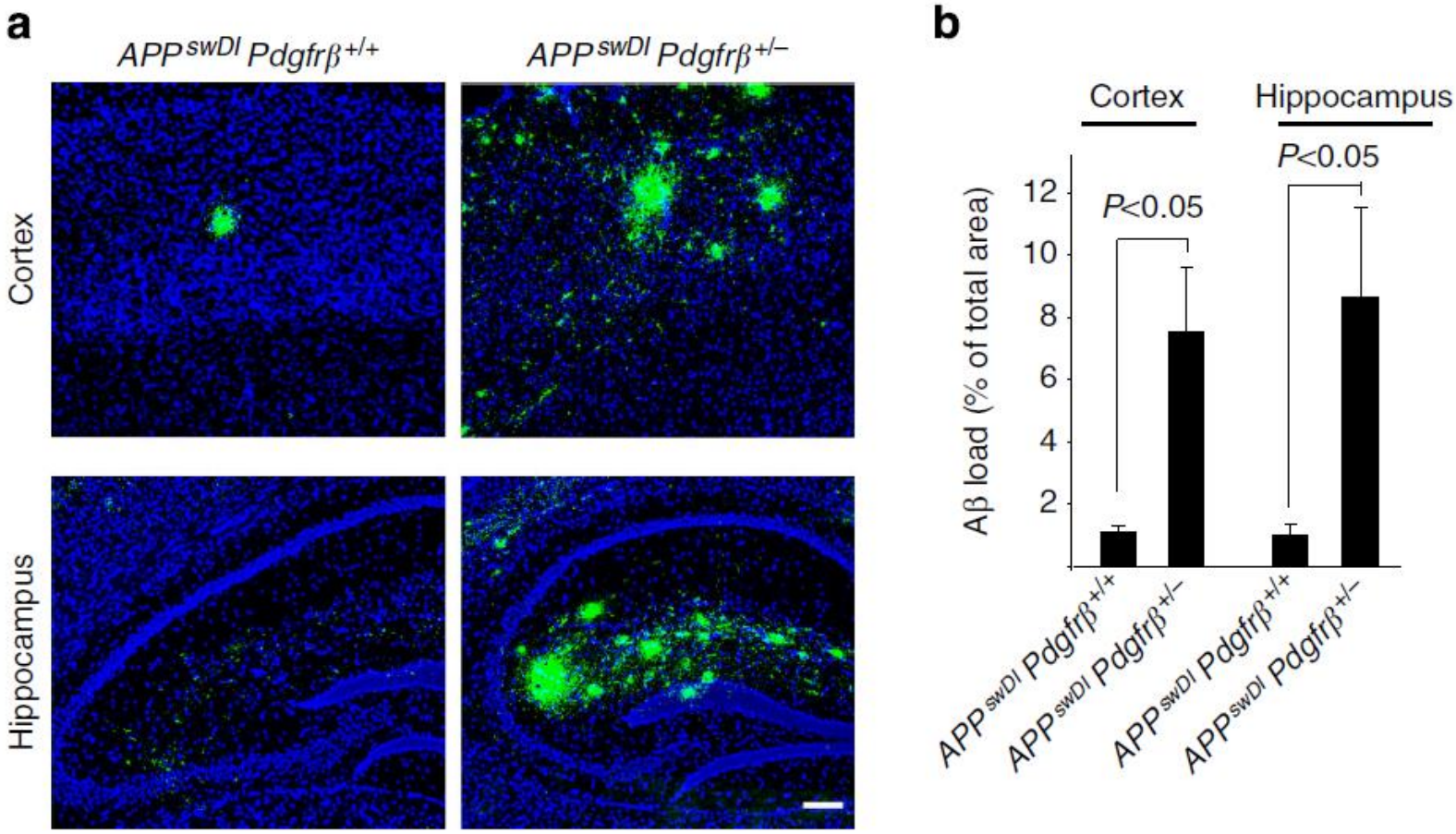


Figure 6 | Accelerated Aβ pathology in *APP*^{swDI} *Pdgfr*$\beta^{+/-}$ mice. (**a**) Representative cortex and hippocampus sections stained against Aβ (6E10; green) and nuclei (blue) in 5-month-old *APP*^{swDI}; *Pdgfr*$\beta^{+/+}$ and *APP*^{swDI}; *Pdgfr*$\beta^{+/-}$ mouse. Scale bar, 100 μm.

patient-oriented and epidemiological research

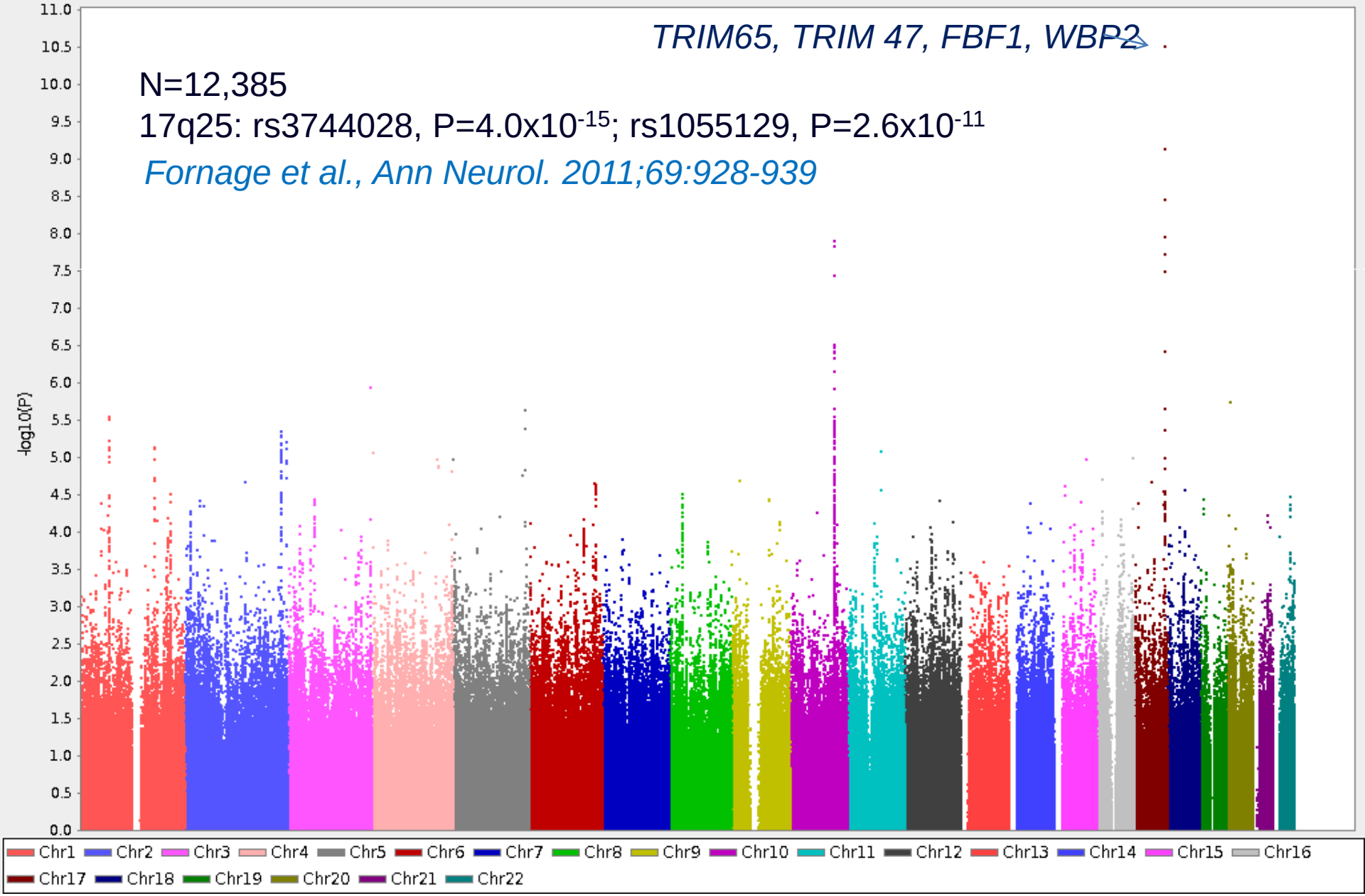
Rare coding variation in paraoxonase-1 is associated with ischemic stroke in the NHLBI Exome Sequencing Project[S]

Daniel Seung Kim,[*,†] David R. Crosslin,[*,†] Paul L. Auer,[§,**] Stephanie M. Suzuki,[*] Judit Marsillach,[*,†] Amber A. Burt,[*] Adam S. Gordon,[†] James F. Meschia,[††] Mike A. Nalls,[§§] Bradford B. Worrall,[***,†††,§§§] W. T. Longstreth, Jr.,[****,††††] Rebecca F. Gottesman,[§§§§] Clement E. Furlong,[*,†] Ulrike Peters,[§,††††] Stephen S. Rich,[***] Deborah A. Nickerson,[†] and Gail P. Jarvik[1,*,†] on behalf of the NHLBI Exome Sequencing Project

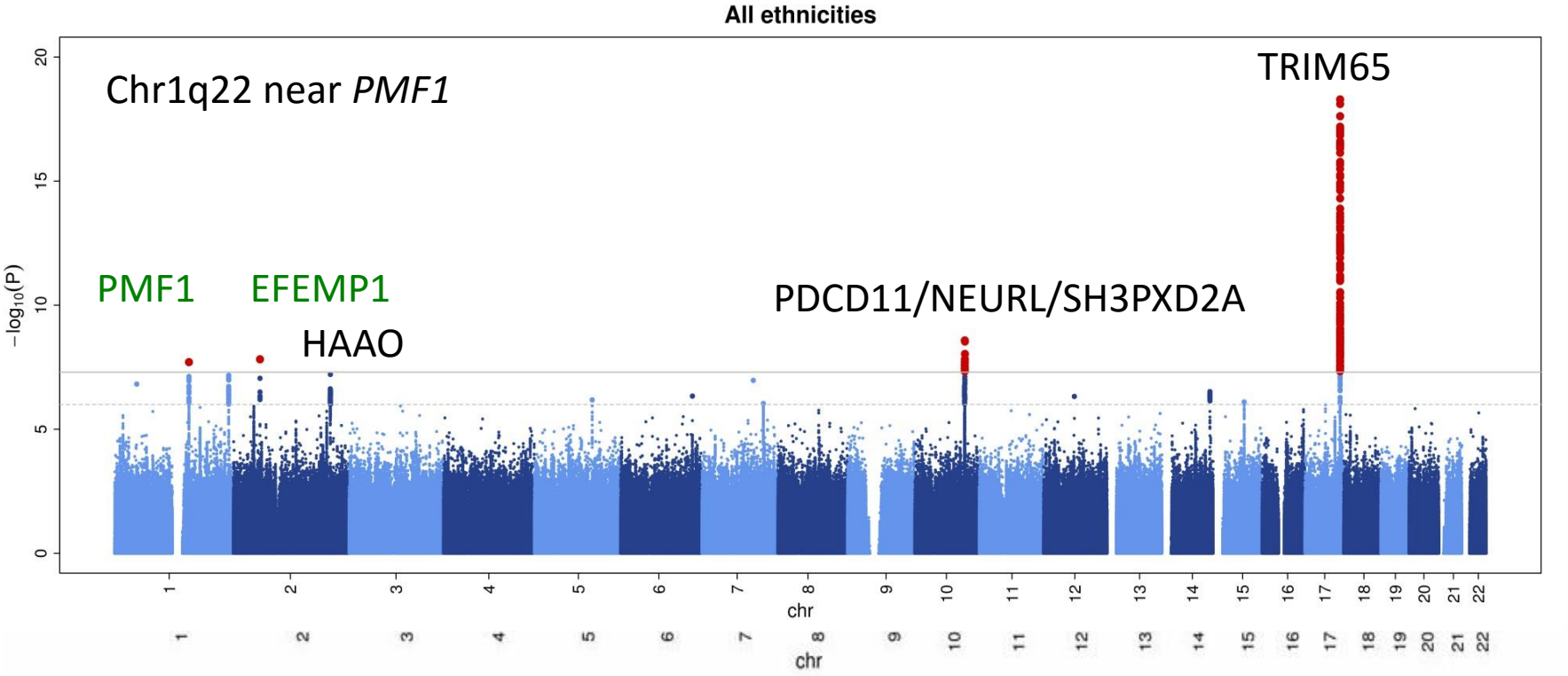
J. Lipid Res. 2014. 55: 1173–1178.

Putative Associations on PON1 with WMH and with AD, PD, ALS

GWAS of White Matter Hyperintensities in CHARGE



CHARGE: GWAS of WMH, 1000G



29 population based cohorts;
17,936 EA, 1,943 AA, 795 Hispanic 204 Chinese, and 201 Malays

Verhaaren et al; Circulation CVG, 2015

Meta-analysis of Genome-wide Association Studies Identifies 1q22 as a Susceptibility Locus for Intracerebral Hemorrhage

Examples of SNPs related to ICH risk

SNP in chromosome	Gene region	Relation to
19q13	*APOE*	Lobar ICH
1q22	*PMF1/SLC25A44*	Non-lobar ICH
13q34	*COL4A1*	ICH
6p21	*KCNK17*	ICH

SNP, single nucleotide polymorphism; ICH, intracerebral hemorr

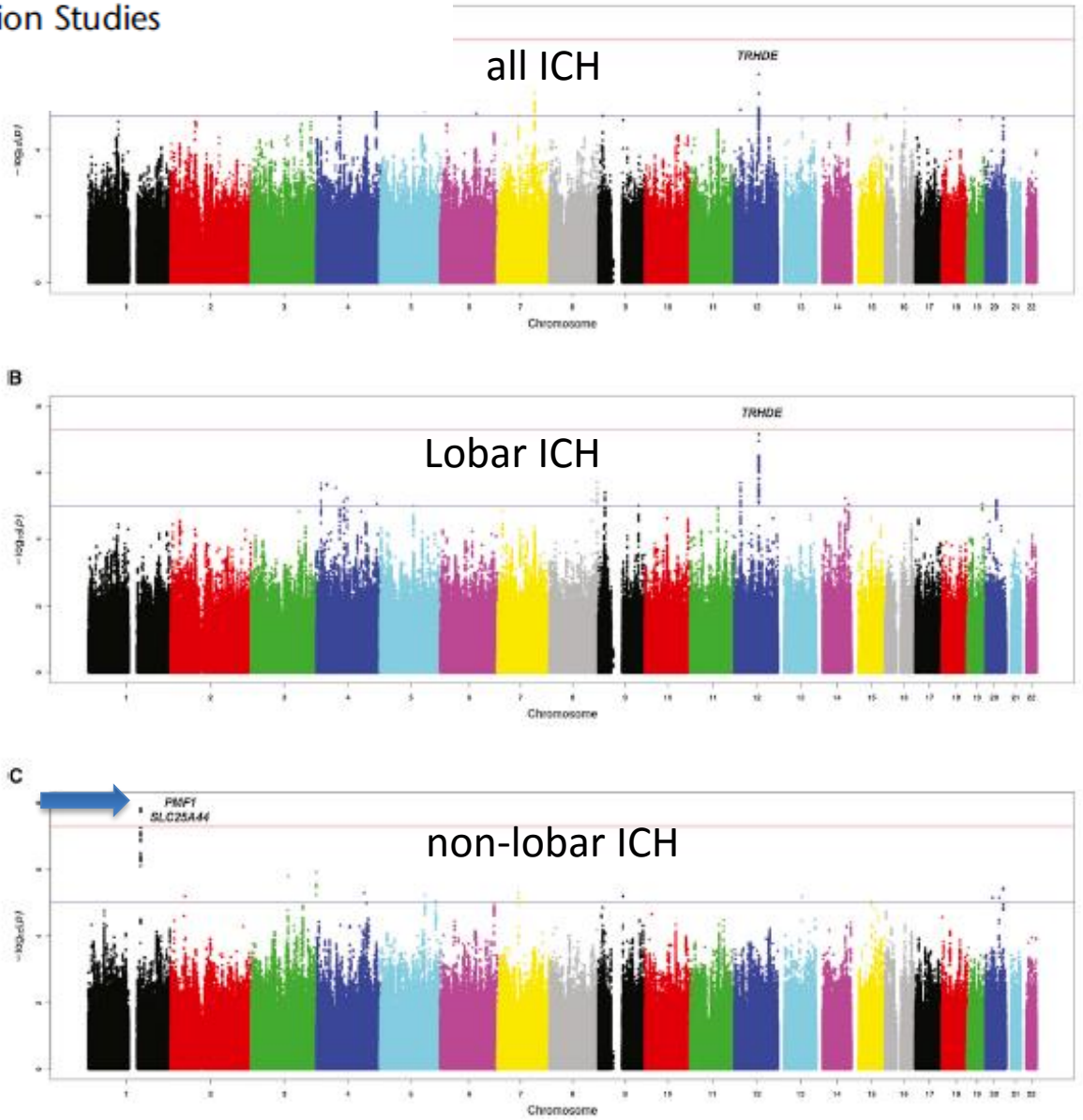


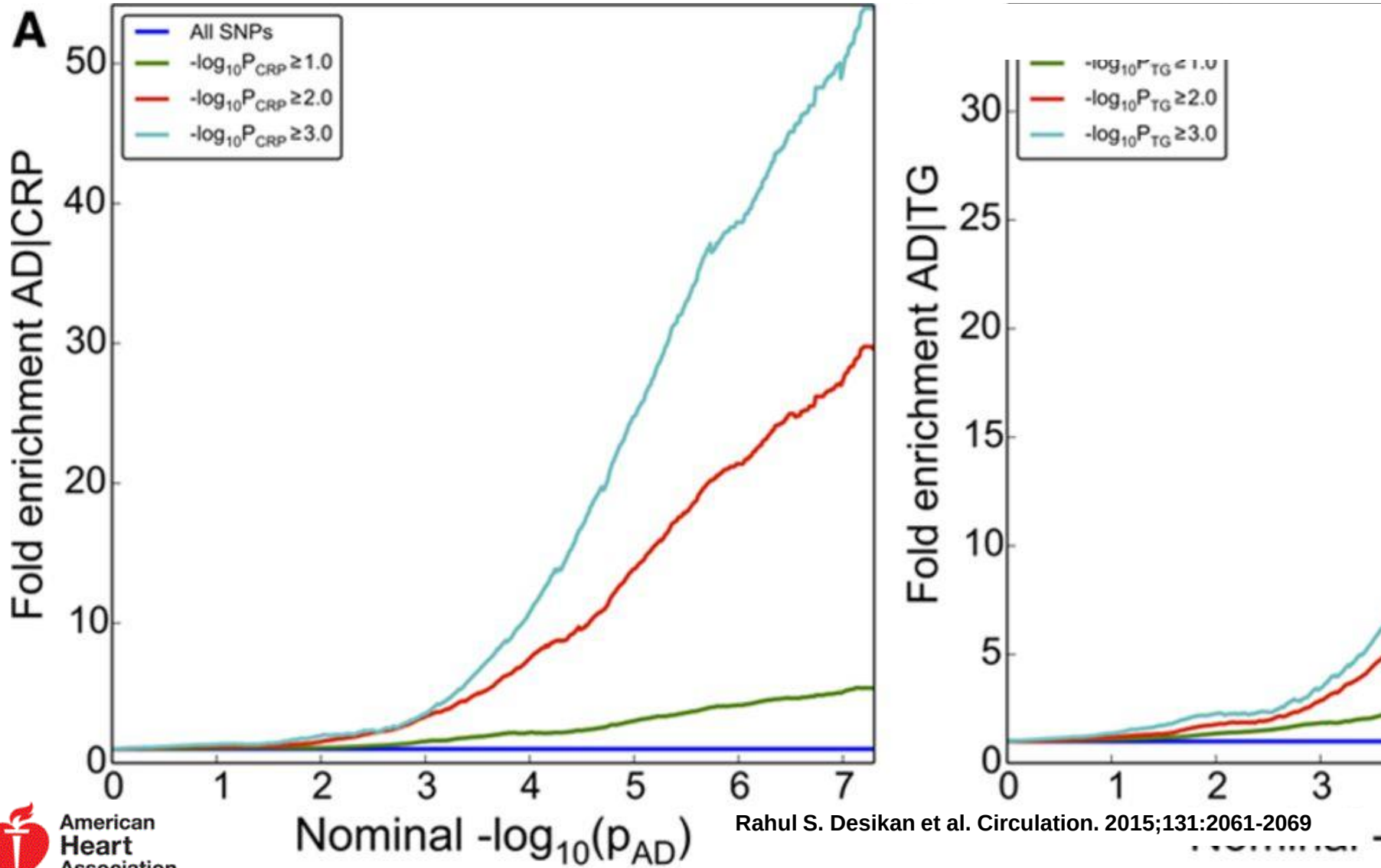
Figure 1. Genome-wide Association Study Results

's: (A) all (lobar ICH and nonlobar ICH combined), (B) lobar ICH, and (C) es for genotyped and imputed SNPs with respect to their physical positions. e ($p = 5 \times 10^{-8}$) is shown by the upper dashed line, and the lower dashed licated for loci that reached the threshold to pursue replication.

Outline

- Genetics of Vascular Brain Injury
- **Inflammation Genes Impact Brain Aging**
- AD Genes Act Through Vascular/Inflam Paths

Fold-enrichment plots of enrichment vs nominal −log10 P values (corrected for inflation) in Alzheimer disease (AD) below the standard GWAS threshold of P<5×10−8 as a function of significance of association with CRP



Rahul S. Desikan et al. Circulation. 2015;131:2061-2069

ELSEVIER

CrossMark

Alzheimer's & Dementia 11 (2015) 658-671

Alzheimer's & Dementia

Convergent genetic and expression data implicate immunity in Alzheimer's disease

International Genomics of Alzheimer's Disease Consortium (IGAP)[†]

Abstract

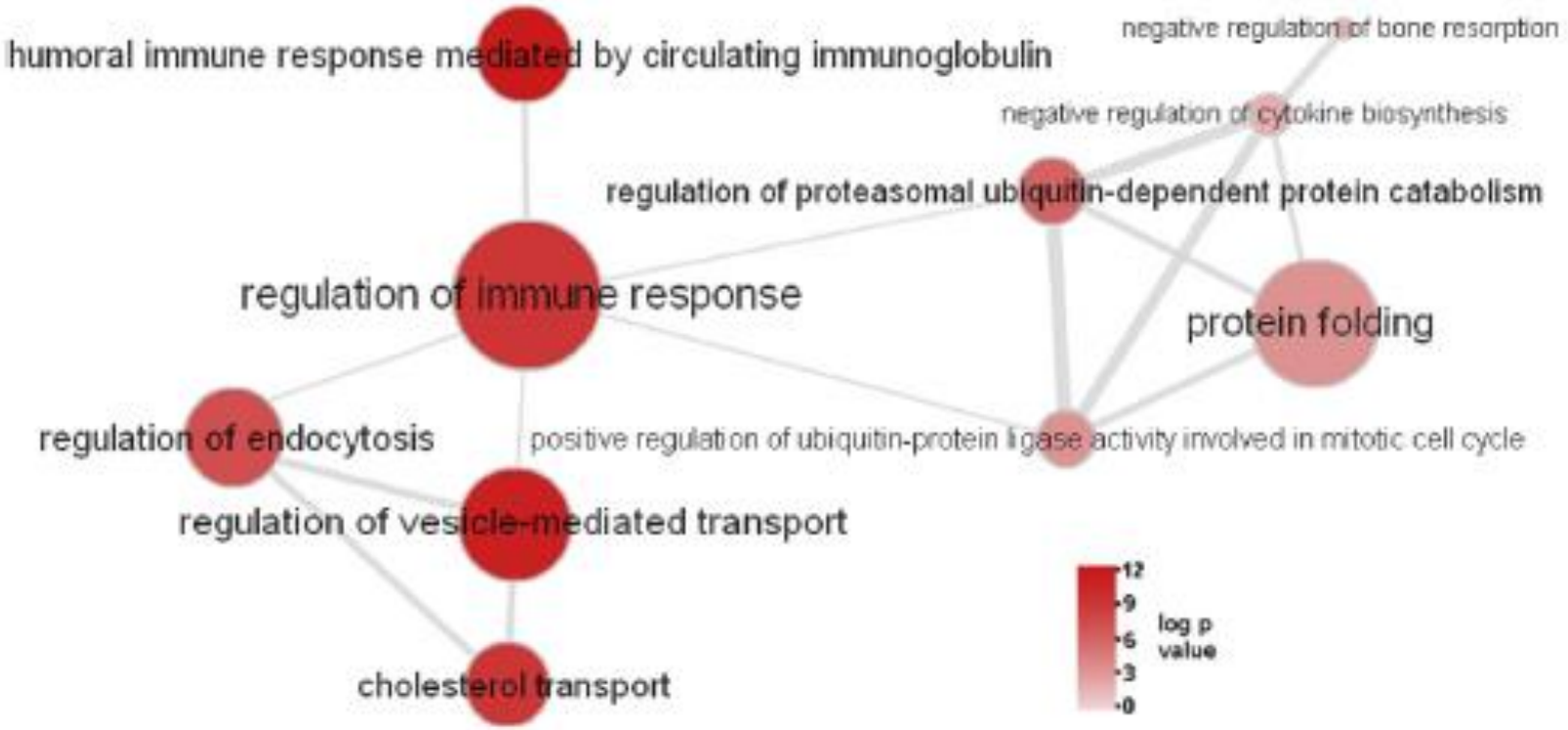
Background: Late-onset Alzheimer's disease (AD) is heritable with 20 genes showing genome-wide association in the International Genomics of Alzheimer's Project (IGAP). To identify the biology underlying the disease, we extended these genetic data in a pathway analysis.

Methods: The ALIGATOR and GSEA algorithms were used in the IGAP data to identify associated functional pathways and correlated gene expression networks in human brain.

Results: ALIGATOR identified an excess of curated biological pathways showing enrichment of association. Enriched areas of biology included the immune response ($P = 3.27 \times 10^{-12}$ after multiple testing correction for pathways), regulation of endocytosis ($P = 1.31 \times 10^{-11}$), cholesterol transport ($P = 2.96 \times 10^{-9}$), and proteasome-ubiquitin activity ($P = 1.34 \times 10^{-6}$). Correlated gene expression analysis identified four significant network modules, all related to the immune response (corrected $P = .002–.05$).

Conclusions: The immune response, regulation of endocytosis, cholesterol transport, and protein ubiquitination represent prime targets for AD therapeutics.

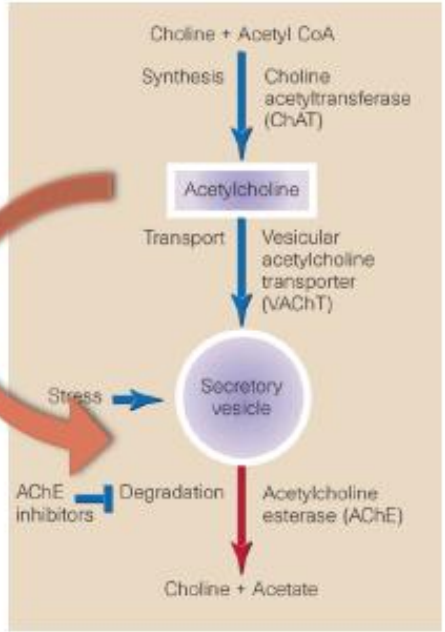
Keywords: Alzheimer's disease; Dementia; Neurodegeneration; Immune response; Endocytosis; Cholesterol metabolism;


humoral immune response mediated by circulating immunoglobulin
negative regulation of bone resorption
negative regulation of cytokine biosynthesis
regulation of proteasomal ubiquitin-dependent protein catabolism
regulation of immune response
protein folding
regulation of endocytosis
positive regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
regulation of vesicle-mediated transport
cholesterol transport
12
9
6
3
0
log p value

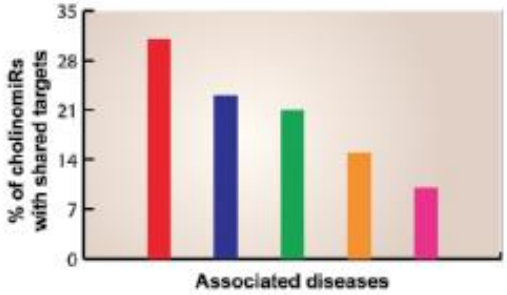
frontiers in
MOLECULAR NEUROSCIENCE
ORIGINAL RESEARCH ARTICLE
published: 10 February 2014
doi: 10.3389/fnmol.2014.00009

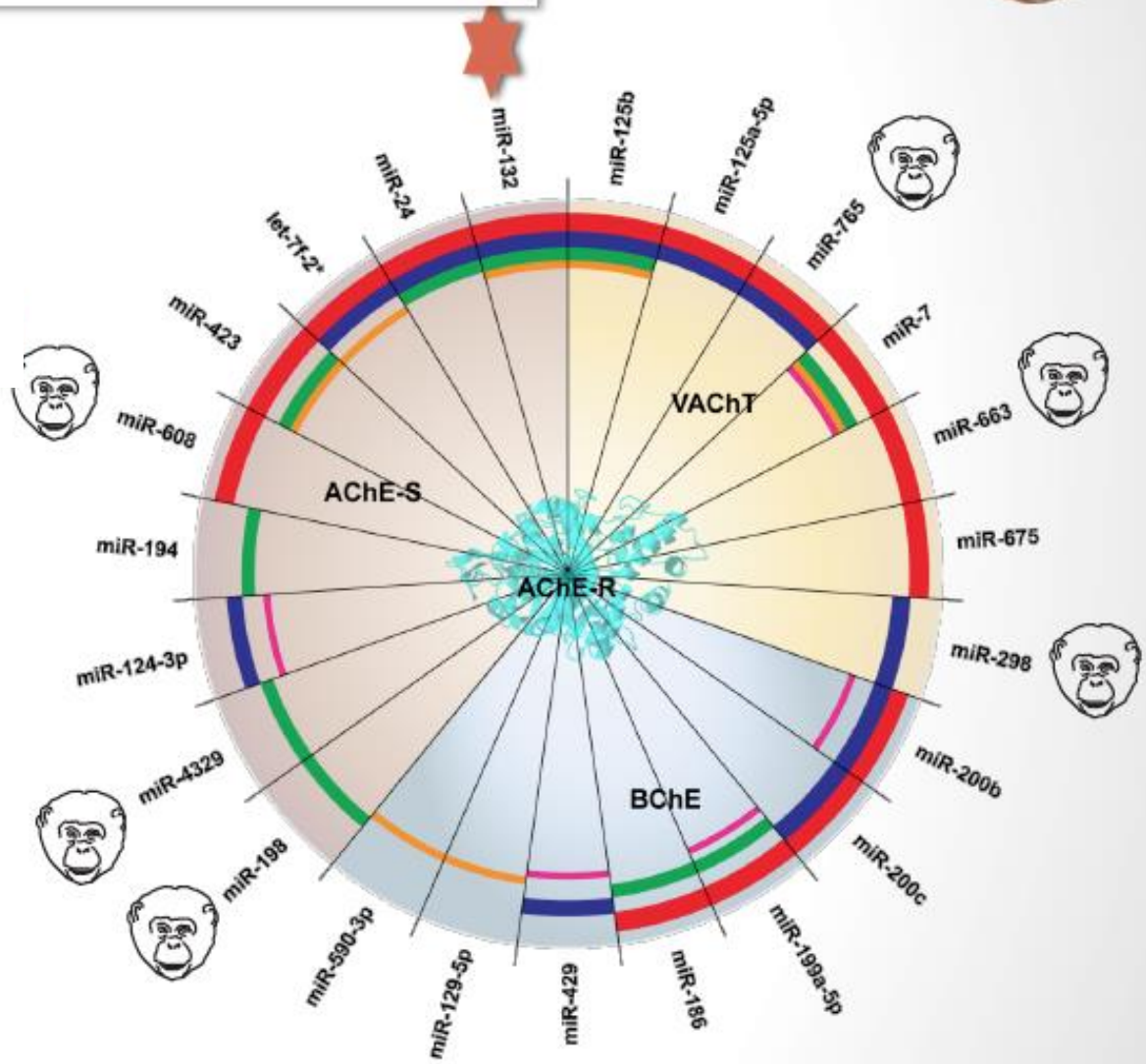
Predicted overlapping microRNA regulators of acetylcholine packaging and degradation in neuroinflammation-related disorders

*Bettina Nadorp and Hermona Soreq**



- Inflammation and anxiety
- Brain damage (stroke)
- Cardiac diseases
- Neurodegenerative diseases
- Pain



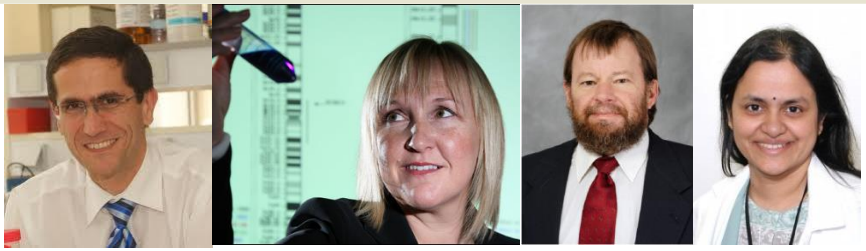


Courtesy H Soreq

Outline

- Genetics of Vascular Brain Injury
- Inflammation Genes Impact Brain Aging
- **AD Genes Act Through Vascular/Inflam Paths**

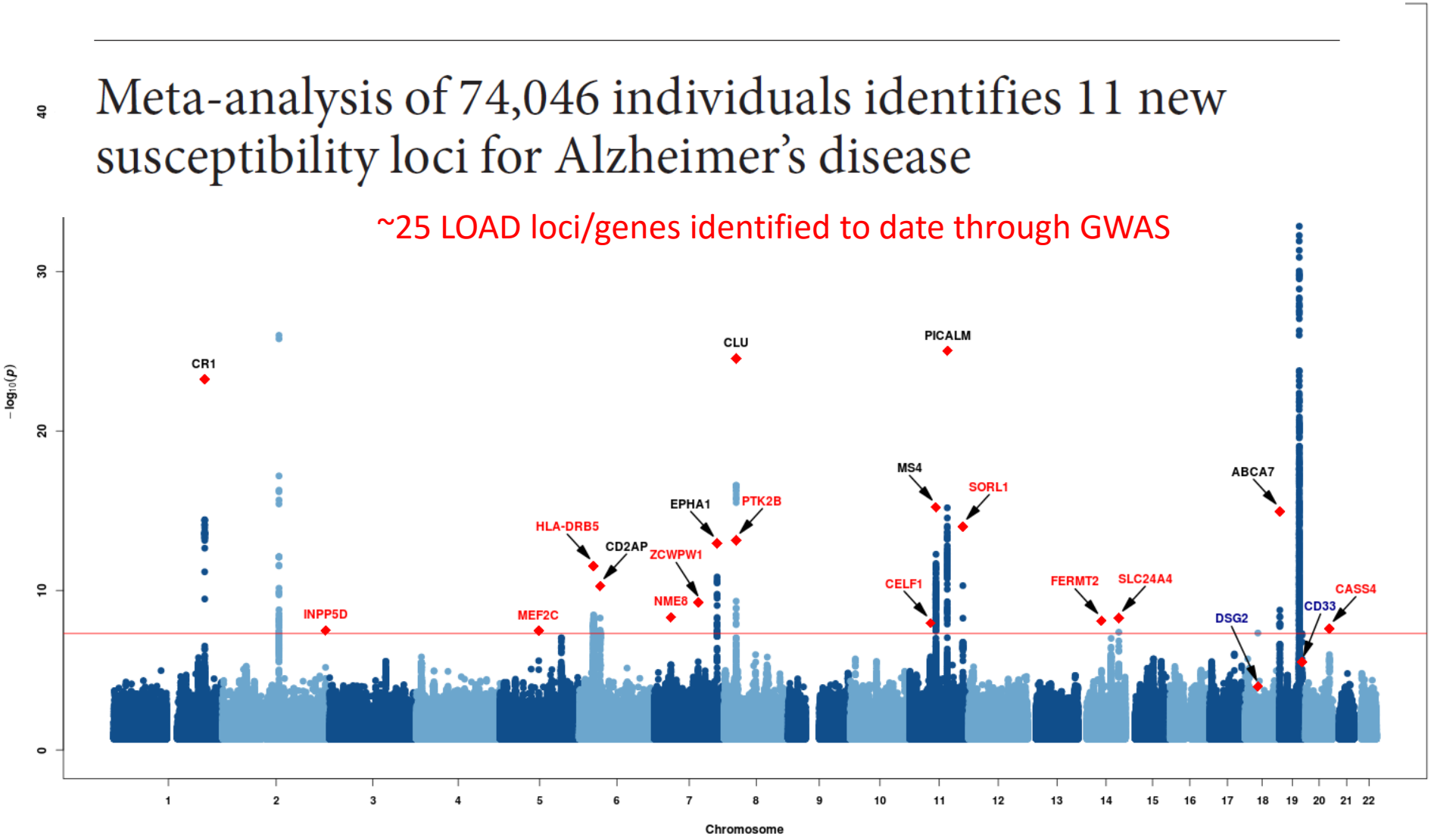
nature genetics



IGAP INTERNATIONAL GENOMICS OF ALZHEIMER'S PROJECT

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

~25 LOAD loci/genes identified to date through GWAS



Newer Late-Onset AD Genes

- APP/Tau: *SORL1, CASS4, FERMT2, BIN1*
- Clathrin-mediated endocytosis: *PICALM, BIN1*
- Lipid Metabolism: *APOE, CLU (APOJ), ABCA7, SORL1, CELF1*
- Immune/Inflammation: *APOE, CR1, CLU, ABCA7, EPHA1, CD2AP, HLA-DRB5/DRB1, CD33, INPP5D, MEF2C*
- Synaptic Function and Plasticity: *PICALM, BIN1, MEF2C, PTK2B*
- Cytoskeletal function, axonal transport: *CELF1, NME8, EPHA1 (axonal guidance)*

From: **Cerebrovascular Effects of Apolipoprotein E: Implications for Alzheimer Disease**
JAMA Neurol. 2013;70(4):440-444. doi:10.1001/jamaneurol.2013.2152

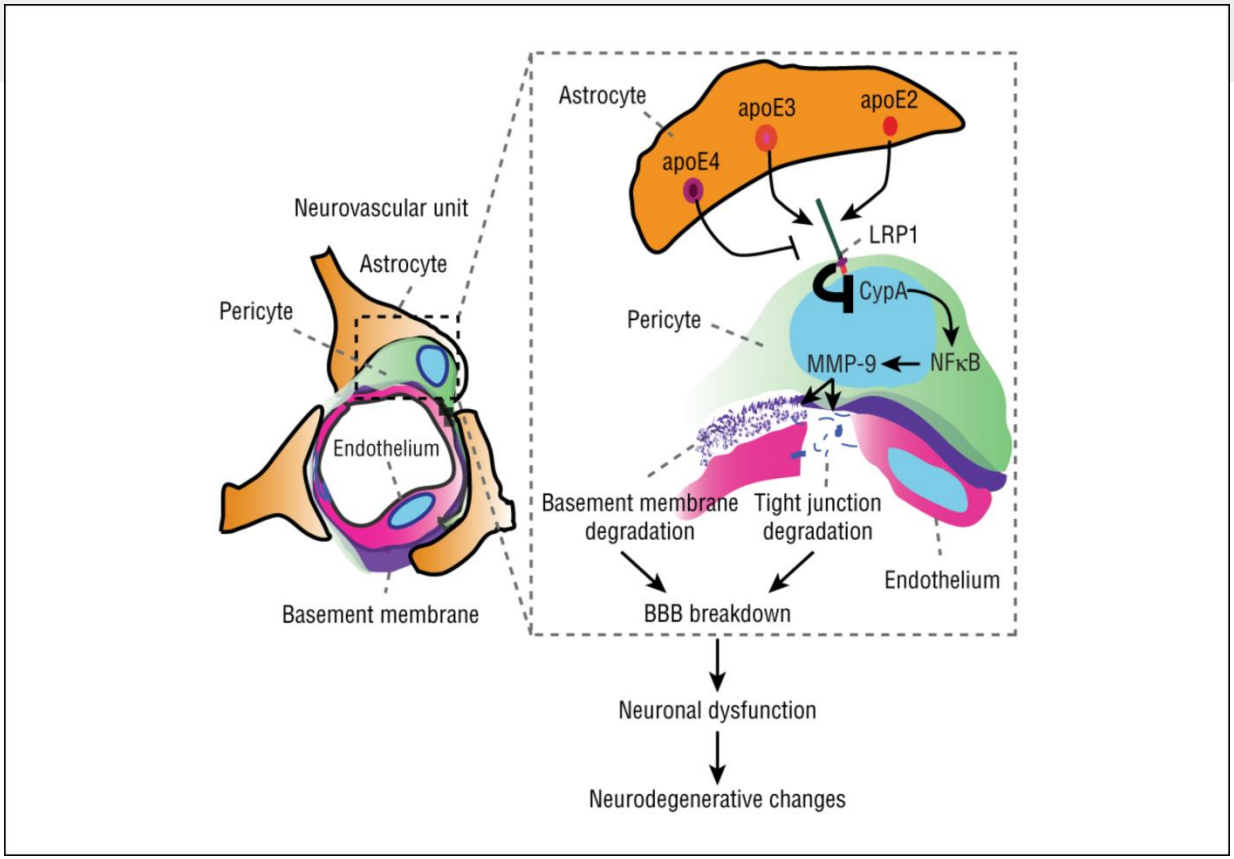
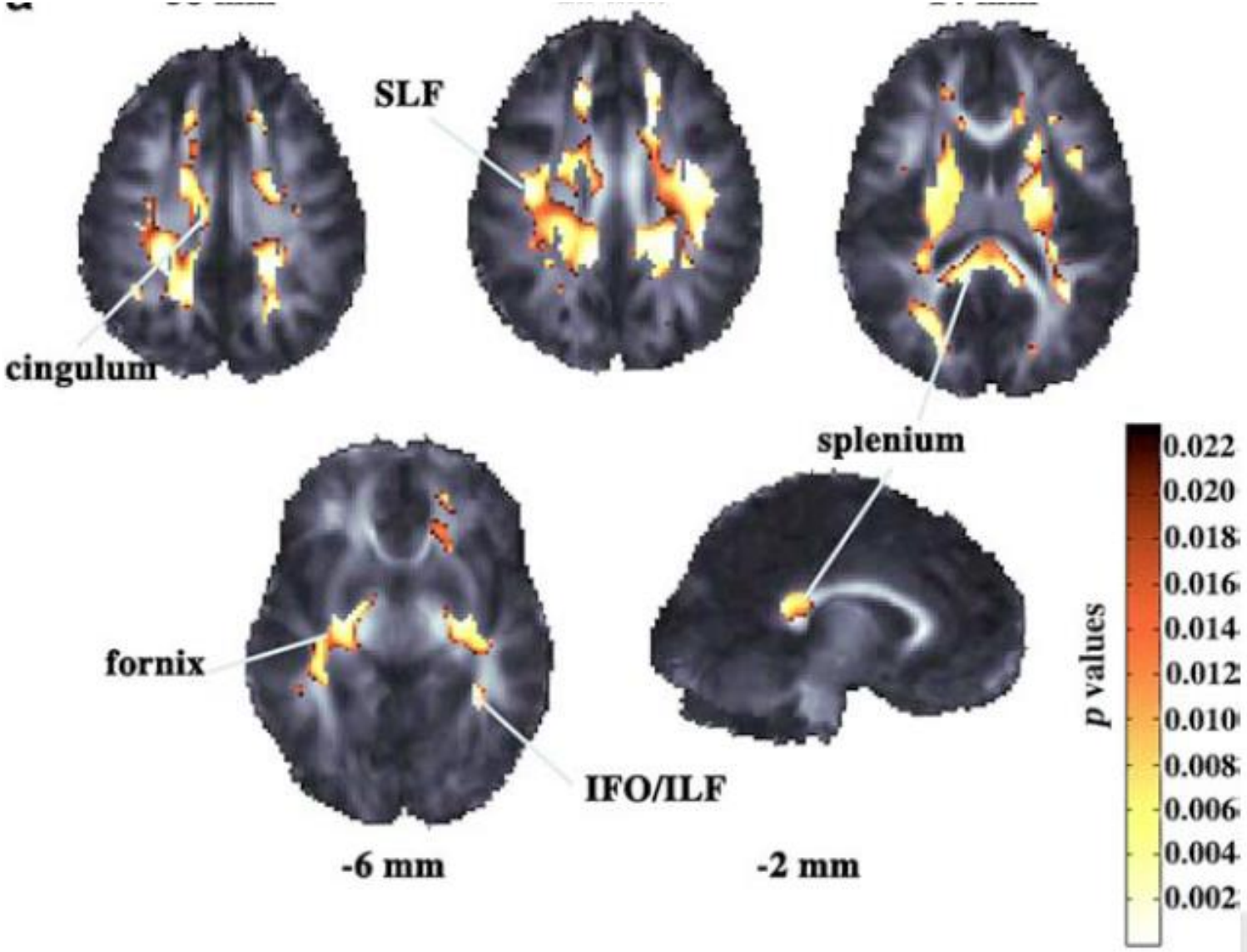


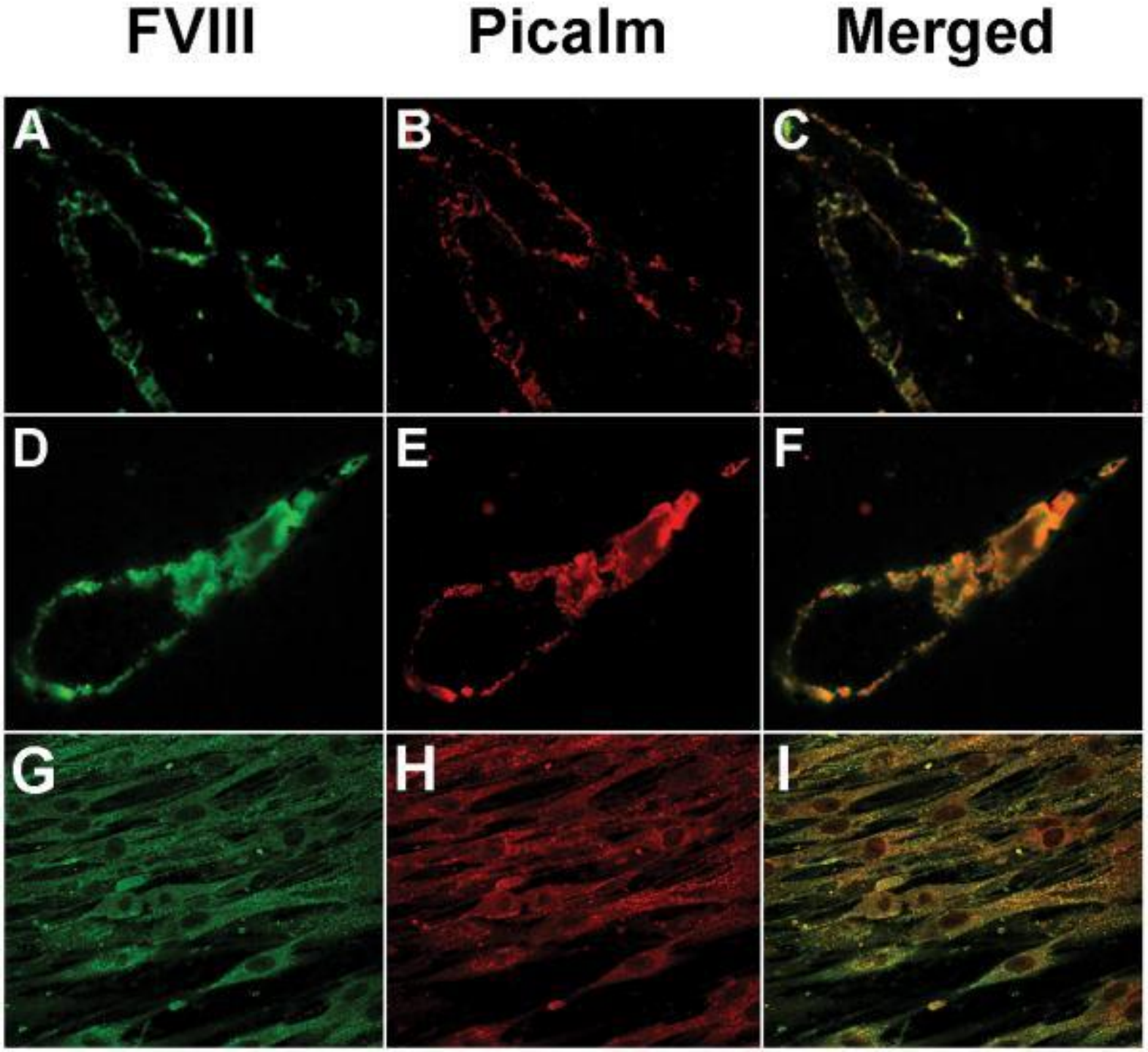
Figure Legend:

Figure 1. A schematic showing that astrocyte-secreted apolipoprotein E2 (apoE2) and apoE3, but not apoE4, signal to pericytes via low-density lipoprotein receptor-related protein 1 (LRP1), suppressing the cyclophilin A (CypA)–nuclear factor κB (NFκB)–matrix metalloproteinase 9 (MMP-9) proinflammatory pathway that causes blood-brain barrier (BBB) breakdown by MMP-9–mediated degradation of tight junction and basement membrane proteins. Dysfunction of the BBB is associated with accumulation of several neurotoxins in the brain, affecting neuronal function and contributing to the development of neurodegenerative changes. Modified from Bell et al.

Braskie et al., 2011

Common Alzheimer's Disease Risk Variant Within the *CLU* Gene Affects White Matter Microstructure in Young Adults

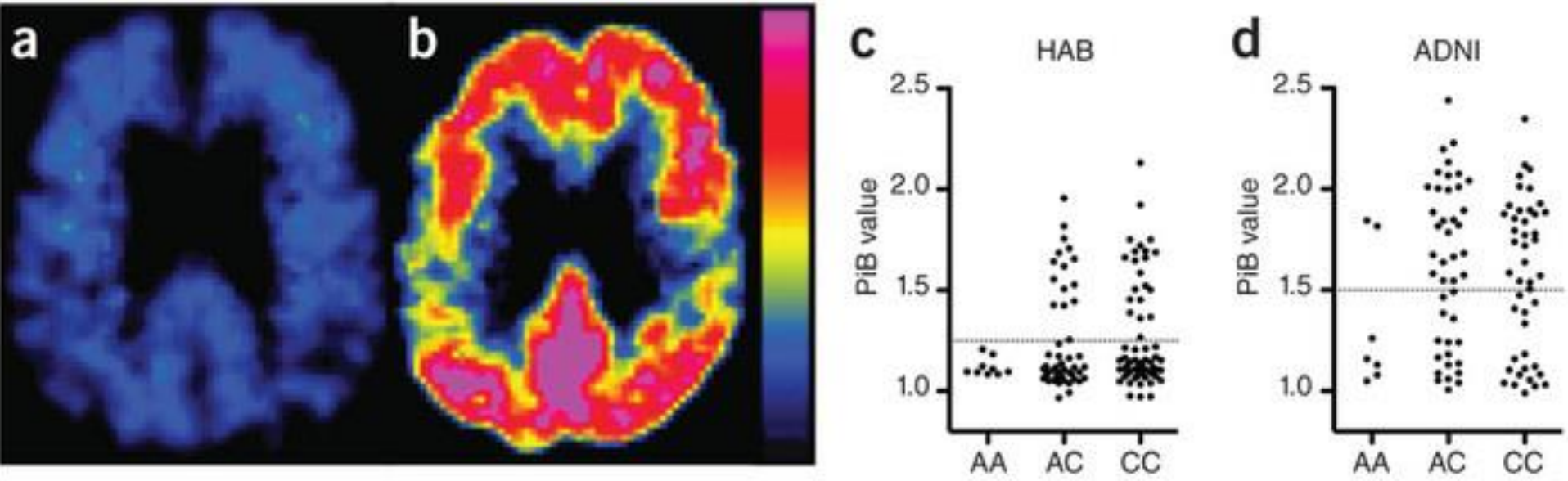



FVIII
Picalm
Merged
A
B
C
D
E
F
G
H
I

CD33

- rs3865444C risk allele associated with ↑ expression in monocytes, ↑ activated microglia, ↑amyloid on PET

Bradshaw et al., Nature Neuroscience, 2013



Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

Thorlakur Jonsson, Ph.D., Hreinn Stefansson, Ph.D., Stacy Steinberg Ph.D., Ingileif Jonsdottir, Ph.D., Palmi V. Jonsson, M.D., Jon Snaedal, M.D., Sigurbjorn Bjornsson, M.D., Johanna Huttenlocher B.S., Allan I. Levey, M.D., Ph.D., James J. Lah, M.D., Ph.D., Dan Rujescu, M.D., Harald Hampel, M.D., Ina Giegling, Ph.D., Ole A. Andreassen, M.D., Ph.D., Knut Engedal, M.D., Ph.D., Ingun Ulstein, M.D., Ph.D., Srdjan Djurovic, Ph.D., Carla Ibrahim-Verbaas, M.D., Albert Hofman, M.D., Ph.D., M.Arfan Ikram, M.D., Ph.D., Cornelia M van Duijn, Ph.D., Unnur Thorsteinsdottir, Ph.D., Augustine Kong, Ph.D., and Kari Stefansson, M.D., Ph.D.

Identified Novel Pathway, Possible Drug Target

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TREM2 Variants in Alzheimer's Disease

Rita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D., Minerva Carrasquillo, Ph.D., Ekaterina Rogaeva, Ph.D., Elisa Majounie, Ph.D., Carlos Cruchaga, Ph.D., Celeste Sassi, M.D., John S.K. Kauwe, Ph.D., Steven Younkin, M.D., Ph.D., Lilinaz Hazrati, M.D., Ph.D., John Collinge, M.D., Jennifer Pocock, Ph.D., Tammaryn Lashley, Ph.D., Julie Williams, Ph.D., Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D., Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D., Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D., for the Alzheimer Genetic Analysis Group*

'Trigger Receptor Expressed on Myeloid Cells 2' protein

On chromosome 6

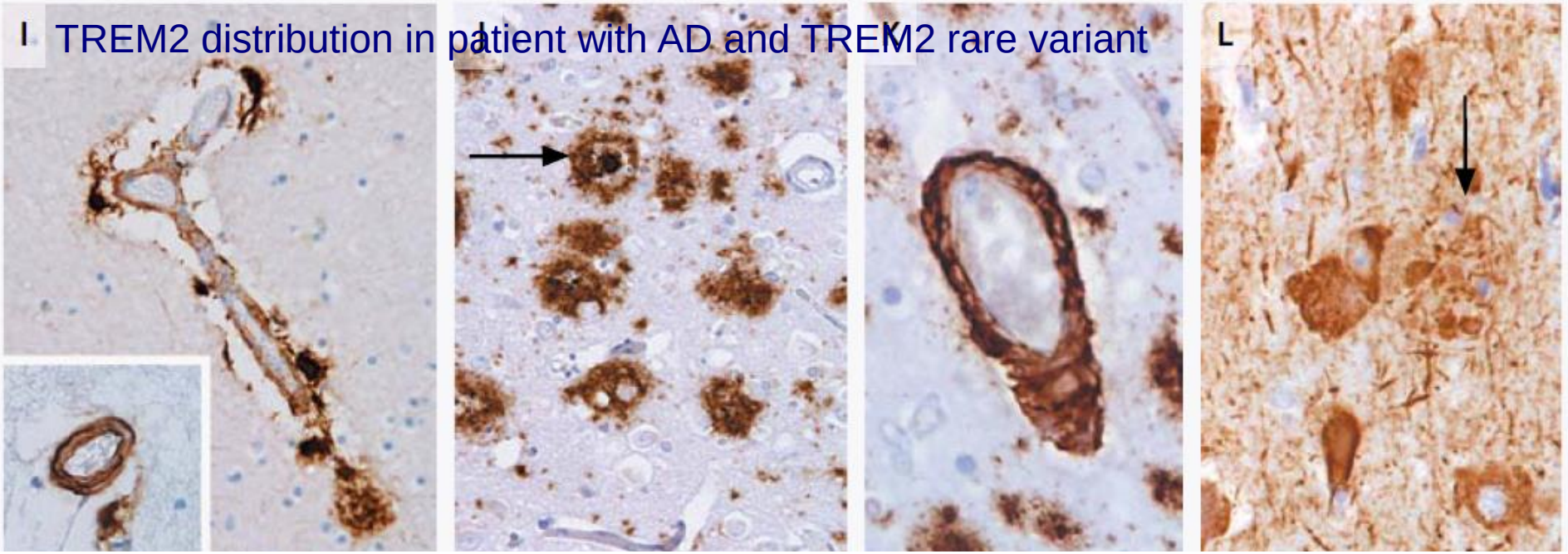
R47H (rs75932628)
27 rare variants;
1 more risk variant

May activate **microglia** to permit beta-amyloid oligomer removal

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, (Nasu-Hakola)

N Engl J Med 2013; 368:107-116 &117-127

TREM2 distribution in patient with AD and TREM2 rare variant



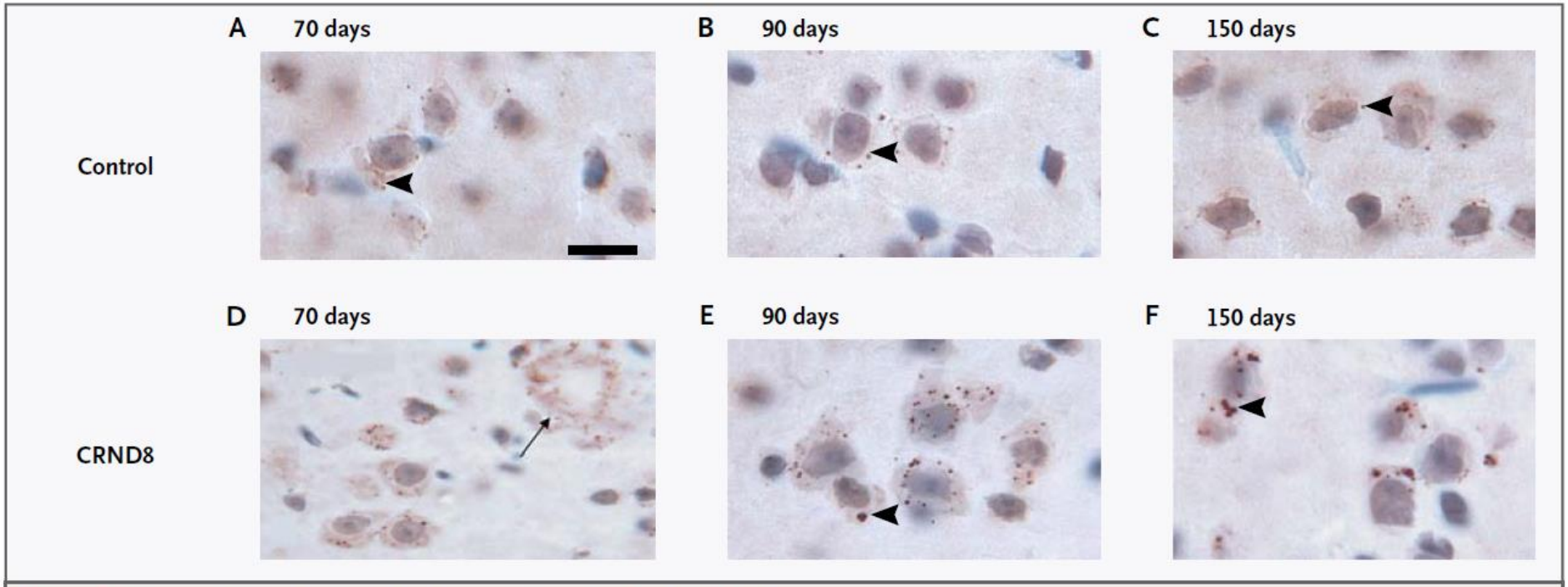
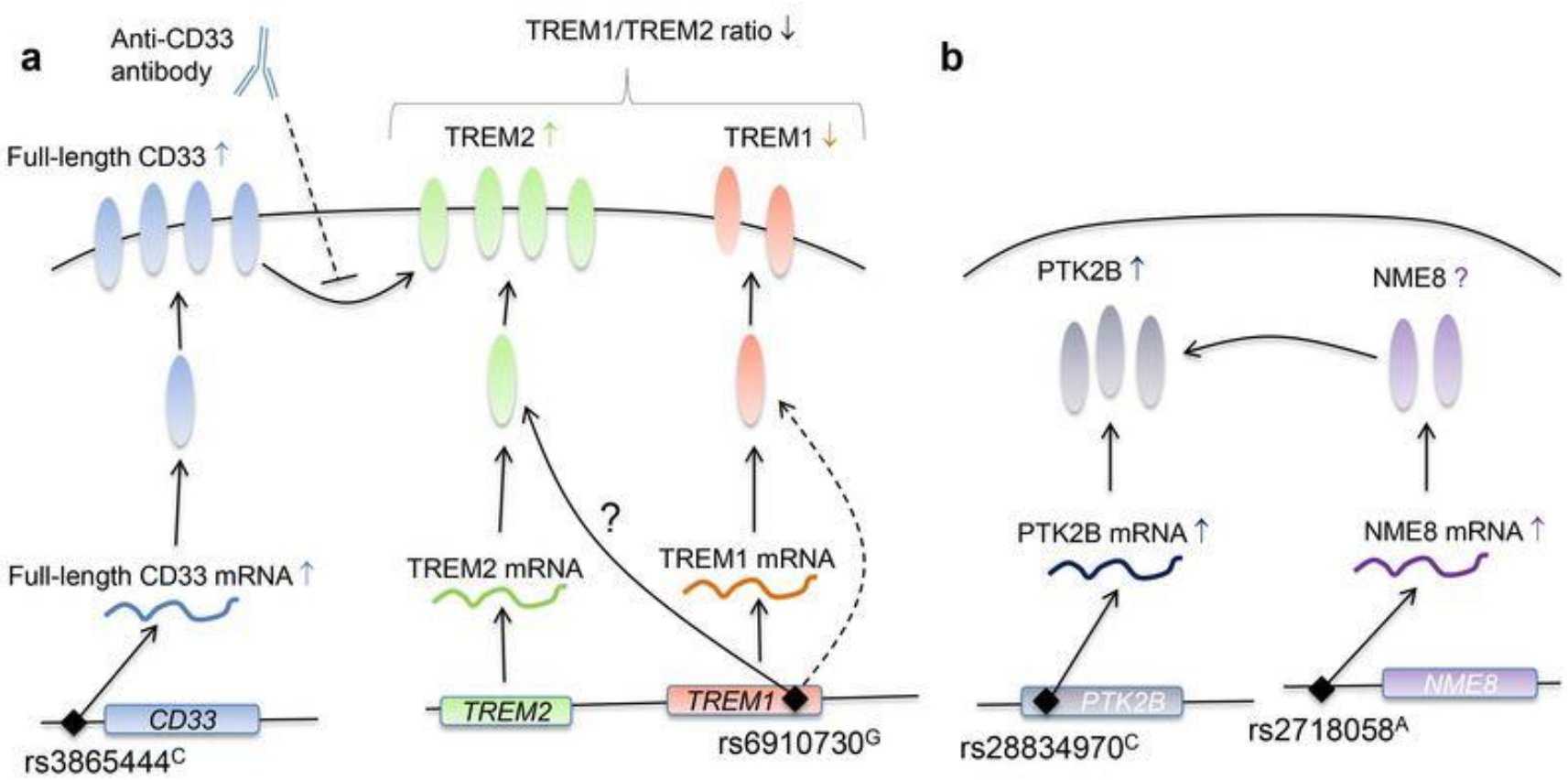


Figure 2. Immunohistochemical Analyses of *Trem2* in TgCRND8 Mice

CD33 modulates TREM2: convergence of Alzheimer loci

Gail Chan[1–5], Charles C White[1–4], Phoebe A Winn[1–4], Maria Cimpean[1–4], Joseph M Replogle[1–5], Laura R Glick[1–4], Nicole E Cuerdon[1–4], Katie J Ryan[1–5], Keith A Johnson[5–7], Julie A Schneider[8], David A Bennett[8], Lori B Chibnik[1–5], Reisa A Sperling[5–7], Elizabeth M Bradshaw[1–5,9] & Philip L De Jager[1–5,9]

We used a protein quantitative trait analysis in monocytes from 226 individuals to evaluate cross-talk between Alzheimer loci. The *NME8* locus influenced PTK2B and the *CD33* risk allele led to greater TREM2 expression. There was also a decreased TREM1/TREM2 ratio with a *TREM1* risk allele, decreased TREM2 expression with CD33 suppression and elevated cortical *TREM2* mRNA expression with amyloid pathology.



Summary

- Phenotypic studies support role for inflammation, vascular injury in neurodegeneration
- As yet, genetics provides only a series of intriguing clues-
- May be premature to craft an overarching hypothesis
- Certainly needs further studies
  - with human and animal model data
- Interventions will likely need to be carefully targeted

Thanks to

BOSTON UNIVERSITY

FRAMINGHAM HEART STUDY
Three Generations of Dedication
1948 1971 2002