Genes, AD Pathology, Cerebrovascular Disease, and AD Dementia

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Risk Factors for Cognitive Decline
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Study Participants
Religious Orders Study
Rush Memory and Aging Project

I have no relevant disclosures

Objectives

- Two Studies of Aging and Dementia with Organ Donation
- Neurobiology of AD dementia
- Genes, Pathology, and AD dementia

The Religious Orders Study

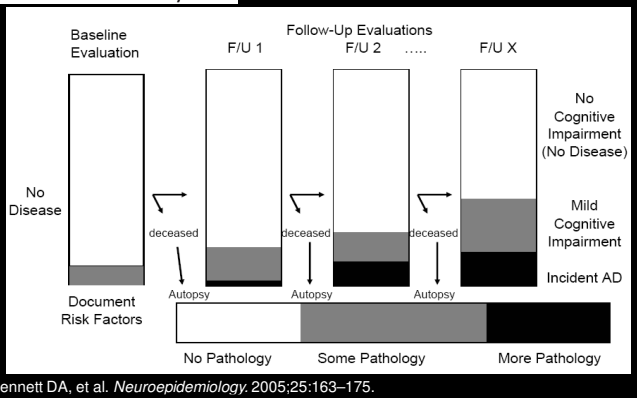
- Began in 1993
- ~ 1,350 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual clinical evaluation, blood donation at baseline, and repeated on a subset
- All agreed to brain donation
- ~ 500 have developed MCI
- ~ 400 have developed dementia
- ~ 675 brain autopsies

The Memory and Aging Project

… because memories should last a lifetime

- Began in 1997
- >1,850 older persons without dementia from across northeastern Illinois
- All agreed to annual clinical evaluation and annual blood donation
- All agreed to donate brain, spinal cord, muscle, nerve
- ~ 450 have developed MCI
- ~ 325 have developed dementia
- > 650 autopsies

The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort

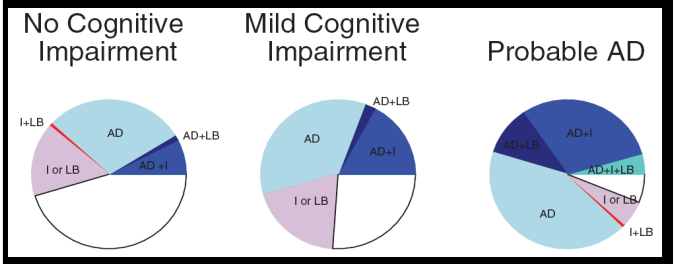


Bennett DA, et al. *Neuroepidemiology.* 2005;25:163–175.

Objectives

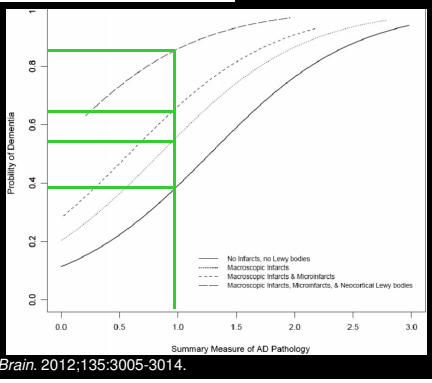
- Two Studies of Aging and Dementia with Organ Donation
- Neurobiology of AD dementia
- Genes, Pathology, and AD dementia

The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment



Schneider JA, et al. *Annals Neurology.* 2009;66:200-208.

Cognitive impairment, decline and fluctuations in older community-dwelling subjects with Lewy bodies

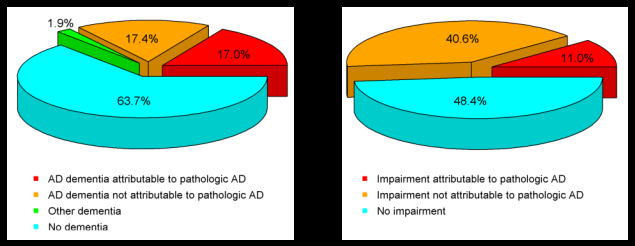


Schneider JA, et al. *Brain.* 2012;135:3005-3014.

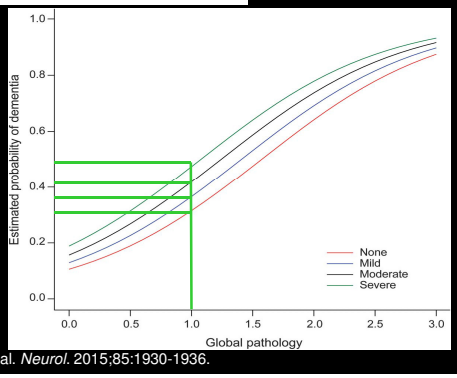
Completely eliminating AD pathology would only prevent less than half of AD dementia and MCI

~50% of AD dementia attributable to pathologic AD

~20% of MCI attributable to pathologic AD

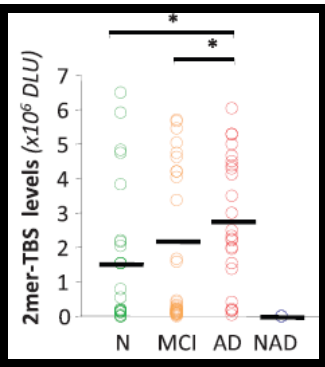


Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons



Boyle PA, et al. *Neurol.* 2015;85:1930-1936.

Brain amyloid-β oligomers in ageing and Alzheimer's disease

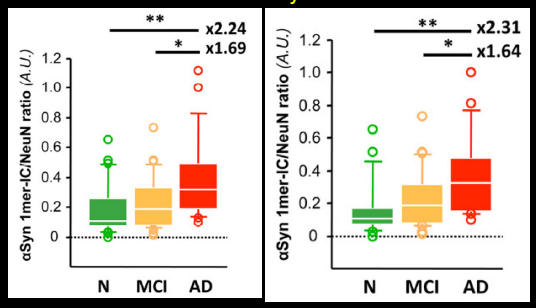


Elevated amyloid-β dimer levels in AD

Lesné S, et al. *Brain*. 2013;136:1383-1398.

Soluble α-Synuclein Is a Novel Modulator of Alzheimer's Disease Pathophysiology

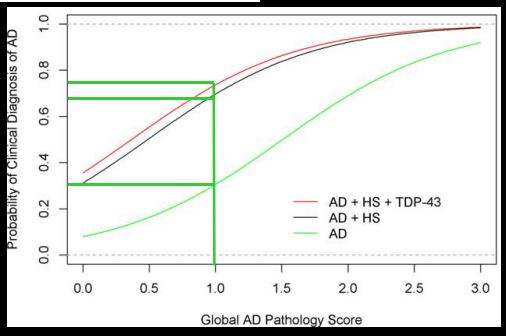
Elevated monomeric α-synuclein levels in AD



Brains without Lewy bodies or neurites

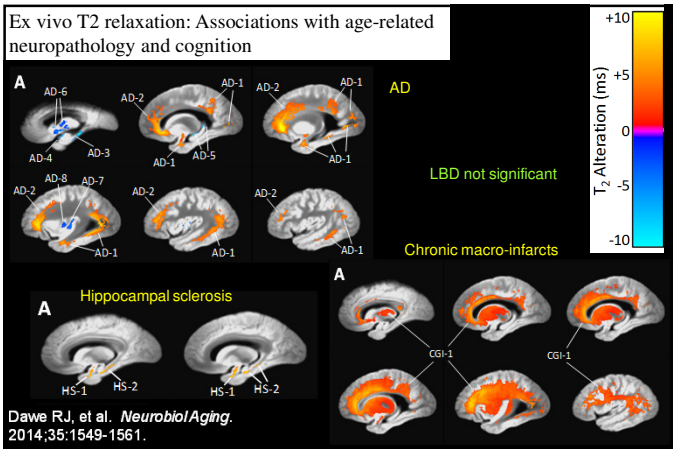
Larson ME, et al. *J Neurosci*. 2012;32:10253-66.

Hippocampal Sclerosis and TDP-43 Pathology in Aging and Alzheimer Disease



Nag S, et al. Annals Neurology. 2015;77:942-52.

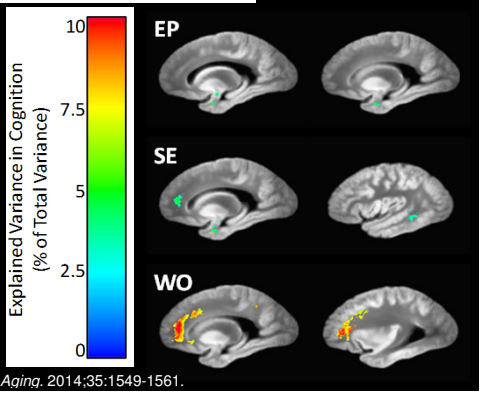
Ex vivo T2 relaxation: Associations with age-related neuropathology and cognition



Dawe RJ, et al. *Neurobiol Aging*. 2014;35:1549-1561.

Ex vivo T2 relaxation: Associations with age-related neuropathology and cognition

Association of T_2 changes with cognition controlling for demographics, AD, CVD, LBD and HS



Dawe RJ, et al. *Neurobiol Aging*. 2014;35:1549-1561.

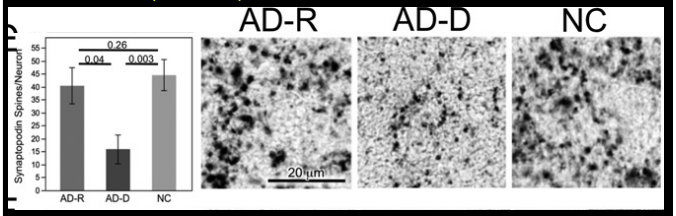
Summary

- Mixed pathology is the most common cause of AD dementia
- Many pathologies contribute to AD dementia
- Much of AD dementia is not explained by pathology

- Are there neurobiologic factors that protect us from AD dementia despite the accumulation of pathology?

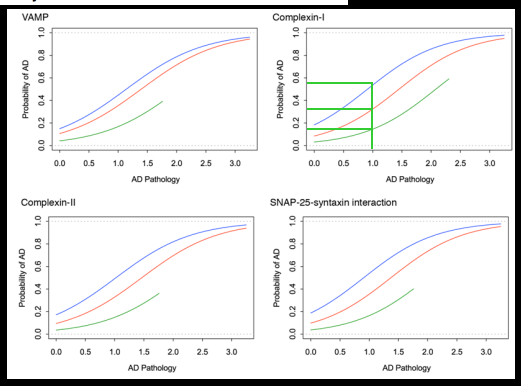
Cellular, synaptic, and biochemical features of resilient cognition in Alzheimer's disease

synaptopodin spines higher in pathologic AD without dementia (resilient)



Arnold SE, et al. *Neurobiology of Aging.* 2013;34:157-168.

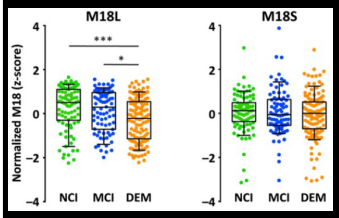
Cognitive reserve, presynaptic proteins and dementia in the elderly

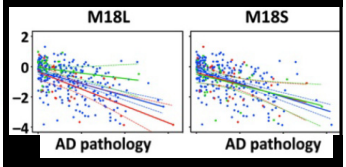


Honer WG, et al. *Translational Psychiatry.* 2012;2:e114.

Loss of Munc18-1 long splice variant in GABAergic terminals is associated with cognitive decline and increased risk of dementia in a community sample

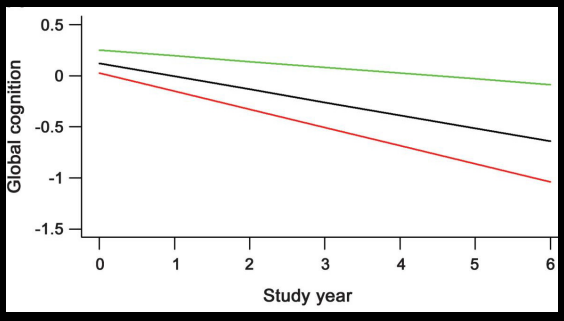
Presynaptic protein Munc18-1, alternatively spliced into long (M18L) or short (M18S)





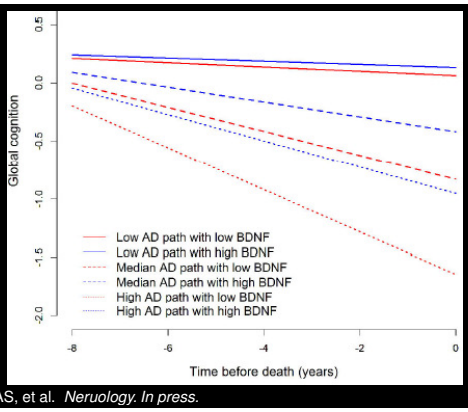
Ramos-Miguel A, et al. *Molecular Neurodegeneration.* 2015;10:65.

Neural reserve, neuronal density in the locus coeruleus, and cognitive decline



Wilson RS, et al. *Neurology.* 2013;80:1202-1208.

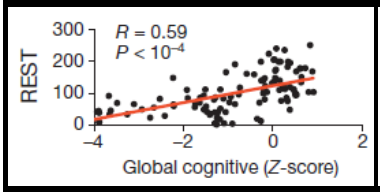
Higher brain *BDNF* gene expression is associated with slower cognitive decline in older adults

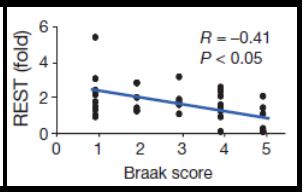


Buchman AS, et al. *Neruology. In press.*

REST and stress resistance in ageing and Alzheimer's disease

Nuclear REST (repressor element 1-silencing transcription Factor)





Lu T, et al. *Nature.* 2014;507:448-54.

Summary

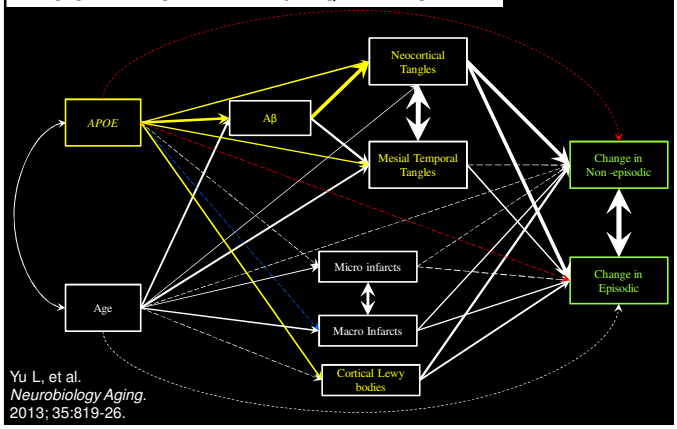
•A number of neurobiologic factors appear to protect us from AD dementia despite the accumulation of pathology?

•Given the complexity of the AD dementia phenotype, it is likely that some or many genomic variants for AD dementia are not related to AD pathology

Objectives

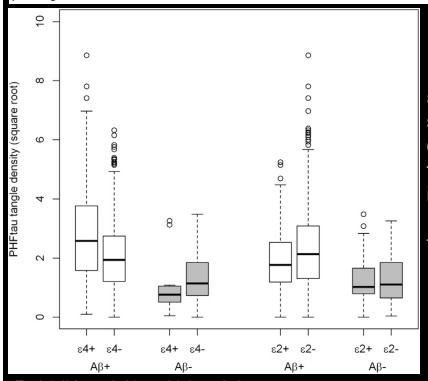
- Two Studies of Aging and Dementia with Organ Donation
- Neurobiology of AD dementia
- Genes, Pathology, and AD dementia

Disentangling the effects of age and *APOE* on neuropathology and late life cognitive decline



Yu L, et al. *Neurobiology Aging.* 2013; 35:819-26.

Association of *APOE* with tau-tangle pathology with and without β-amyloid

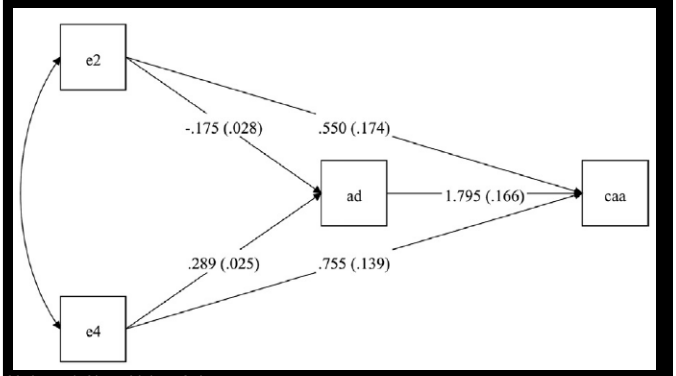


Interaction between *APOE* ε4 carriers and β-amyloid such that the association of *APOE* ε4 with PHFtau tangles is much stronger in brains with β-amyloid;

the converse for *APOE* ε2.

Farfel JM, et al. *Neurobiology Aging.* 2016;37:19-25.

APOE and cerebral amyloid angiopathy in community-dwelling older persons



Yu L, et al. *Neurobiology Aging.* 2015; 36:2946-53.

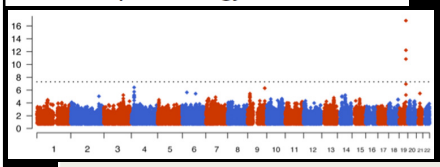
Genetic Susceptibility for Alzheimer Disease Neuritic Plaque Pathology

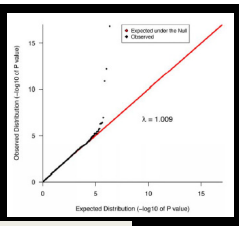
Table 1. Association of Alzheimer Disease Susceptibility Loci With Neuritic Plaque Pathologic Burden

Gene	SNP[a]	A1	A2	MAF	Beta (SE)[b]	*P* Value
CR1 ★	rs6701713	A	G	0.20	0.077 (0.03508)	.03
CLU	rs1532278	T	C	0.39	0.000 (0.03058)	.99
PICALM	rs561655	G	A	0.35	−0.045 (0.02883)	.12
BIN1	rs7561528	A	G	0.34	−0.009 (0.02801)	.76
ABCA7 ★	rs3764650	G	T	0.09	0.180 (0.08262)	.03
MS4A	rs4938933	C	T	0.43	−0.004 (0.02772)	.89
CD33	rs3865444	A	C	0.30	−0.040 (0.02954)	.17
CD2AP ★	rs9349407	C	G	0.25	0.071 (0.03223)	.03
EPHA1	rs11767557	C	T	0.18	0.024 (0.04087)	.56

Shulman JM, et al. *JAMA Neurology.* 2013;70:1150-57.

Genetic Susceptibility for Alzheimer Disease Neuritic Plaque Pathology

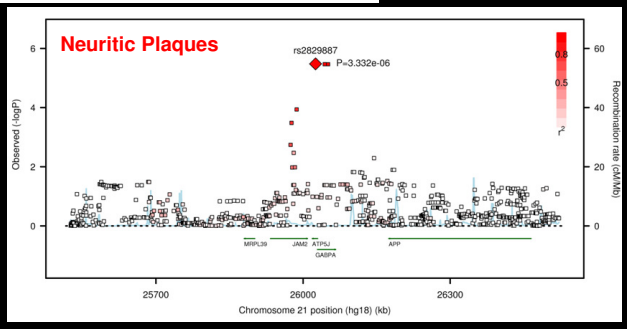




Chromosome	SNP	A1	A2	MAF	Beta (SE)[c]	*P* Value	Genes
19	rs4420638	G	A	0.18	0.3463 (0.0395)	1.49×10^{-17}	*APOE*
4	rs6817475	G	T	0.33	0.1672 (0.0326)	3.80×10^{-7}	*KCNIP4*
9	rs12551233	G	A	0.06	−0.3216 (0.0632)	4.79×10^{-7}	*PTGS1*
6	rs3892710	T	C	0.15	−0.2007 (0.0421)	2.32×10^{-6}	*HLA-DQA2*
21	rs2829887	T	C	0.43	−0.1384 (0.0295)	3.33×10^{-6}	*ATP5J-APP*
9	rs9407730	G	A	0.13	−0.2118 (0.0453)	3.61×10^{-6}	
6	rs4642480	G	A	0.48	0.1432 (0.0307)	3.65×10^{-6}	
3	rs4564921	C	G	0.37	0.1388 (0.0304)	6.12×10^{-6}	*NMNAT3*
14	rs187911	G	A	0.41	−0.1434 (0.0315)	6.23×10^{-6}	*SLC35F4*
14	rs10149826	T	C	0.12	0.2210 (0.0494)	9.15×10^{-6}	*NPAS3*
2	rs12613305	A	G	0.47	0.1311 (0.0293)	9.36×10^{-6}	*PARD3B*

Shulman JM, et al. *JAMA Neurology.* 2013;70:1150-57.

Genetic Susceptibility for Alzheimer Disease Neuritic Plaque Pathology



rs2829887 a/w amyloid-β load: β=-0.216, $p=9.52 \times 10^{-5}$

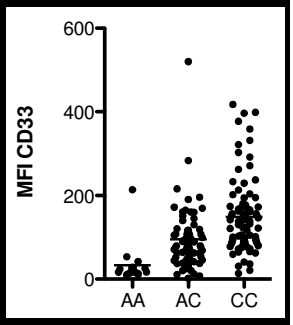
Shulman JM, et al. *JAMA Neurology.* 2013;70:1150-57.

CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology

CD33 (Siglec-3) is expressed on the surface of mature monocytes and macrohages

association of rs3865444[c] with monocyte CD33 expression

rs3865444[c] a/w neuritic plaques; this association mediated in part by level of CD33 expression

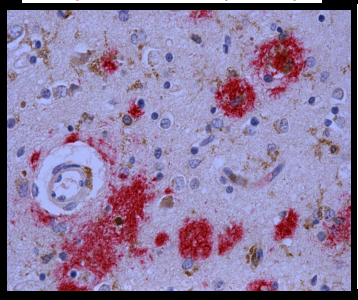


Bradshaw EM, et al. *Nature Neuroscience.* 2013;16:848-50.

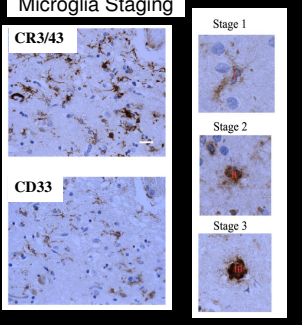
CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology

CD33 is expressed on microglia/macrophages in the brain

Amyloid and **CD33** positivity



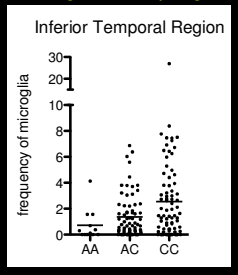
Microglia Staging

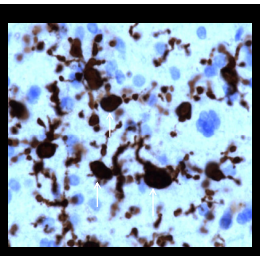


Bradshaw EM, et al. *Nature Neuroscience.* 2013;16:848-50

CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology

rs3865444 a/w frequency of stage III microglia/macrophages





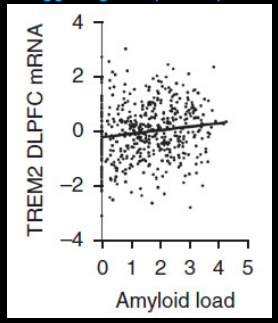
Association between rs3865444[c] and Microglia/Macrophage Traits

Region†	β (95% CI)	p-value
Inferior Temporal Lobe	0.336 (0.110,0.551)	0.0025
Posterior Putamen	0.252 (0.047,0.458)	0.0172
Mid-Frontal	0.157 (-0.091,0.405)	0.2160
Ventral Medial Caudate	0.057 (-0.142,0.255)	0.5772

Bradshaw EM, et al. *Nature Neuroscience.* 2013;16:848-50

CD33 modulates TREM2: convergence of Alzheimer loci

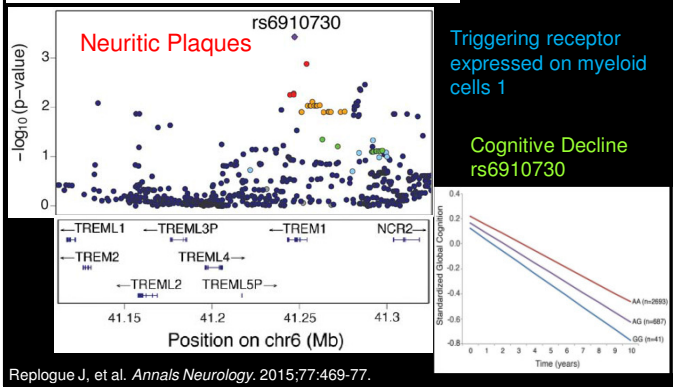
Triggering receptor expressed on myeloid cells 2



TREM2 mRNA expression in dorsolateral prefrontal cortex tissue in relation to amyloid load.

Chan G, et al. *Nature Neuroscience.* 2015;18:1556-1558.

A *TREM1* Variant Alters the Accumulation of Alzheimer-Related Amyloid Pathology



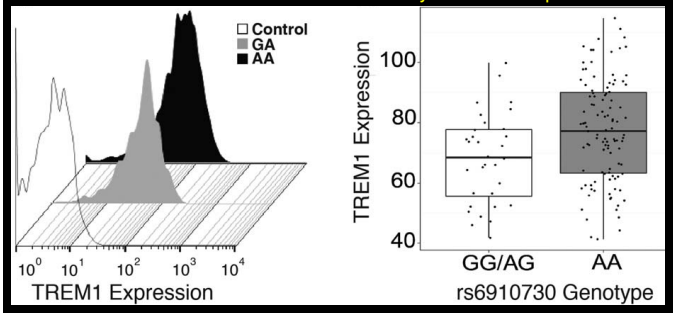
Triggering receptor expressed on myeloid cells 1

Cognitive Decline rs6910730

Replogue J, et al. *Annals Neurology.* 2015;77:469-77.

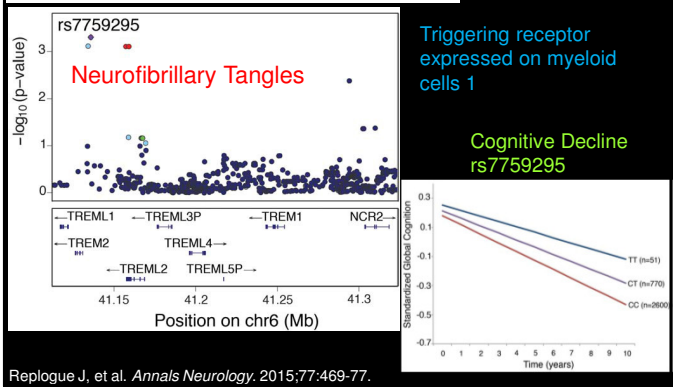
A *TREM1* Variant Alters the Accumulation of Alzheimer-Related Amyloid Pathology

Association of rs6910730 with *TREM1* monocyte surface expression



Replogue J, et al. *Annals Neurology.* 2015;77:469-77.

A *TREM1* Variant Alters the Accumulation of Alzheimer-Related Amyloid Pathology



Triggering receptor expressed on myeloid cells 1

Cognitive Decline rs7759295

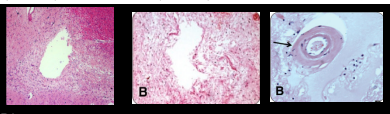
Replogue J, et al. *Annals Neurology.* 2015;77:469-77.

Genetic Susceptibility for Ischemic Infarction and Arteriolosclerosis Based on Neuropathologic Evaluations

48 SNPs associated stroke or proven stroke risk factors

CHR	SNP	Allele	GWAS	Macroscopic infarcts		Microscopic infarcts		Arteriolosclerosis	
				OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
2	rs7578326	A	DMII	**0.73 (0.58, 0.93)**	**0.0110**	**0.71 (0.55, 0.92)**	**0.0088**	0.90 (0.73, 1.11)	0.3375
5	rs3846663	T	LDL	**1.30 (1.04, 1.63)**	**0.0212**	1.11 (0.87, 1.41)	0.4083	1.08 (0.89, 1.31)	0.4230
3	rs1470579	C	DMII	**1.32 (1.04, 1.68)**	**0.0222**	1.21 (0.94, 1.57)	0.1365	1.04 (0.85, 1.28)	0.6794
19	rs2075650	G	LDL	**1.64 (1.07, 2.52)**	**0.0241**	1.46 (0.93, 2.30)	0.0976	1.14 (0.79, 1.66)	0.4843
10	rs12779790	G	DMII	**1.40 (1.03, 1.89)**	**0.0292**	**1.43 (1.04, 1.96)**	**0.0285**	1.03 (0.79, 1.34)	0.8450
12	rs2681472	A	HYP	**1.38 (1.03, 1.86)**	**0.0304**	0.98 (0.72, 1.32)	0.8787	0.96 (0.75, 1.23)	0.7579
1	rs12740374	G	LDL	**1.33 (1.01, 1.75)**	**0.0422**	1.15 (0.86, 1.54)	0.3400	1.11 (0.88, 1.39)	0.3781
5	rs4457053	G	DMII	0.85 (0.63, 1.15)	0.2876	**0.71 (0.51, 0.99)**	**0.0441**	0.86 (0.67, 1.11)	0.2520
7	rs864745	T	DMII	0.91 (0.73, 1.12)	0.3620	1.00 (0.80, 1.26)	0.9939	**0.80 (0.66, 0.96)**	**0.0142**
12	rs7961581	C	DMII	1.03 (0.81, 1.32)	0.7941	1.10 (0.85, 1.43)	0.4732	**1.26 (1.01, 1.56)**	**0.0382**
16	rs7193343	T	AF	1.10 (0.80, 1.51)	0.5526	1.08 (0.77, 1.52)	0.6524	**0.75 (0.57, 0.99)**	**0.0392**
11	rs5215	C	DMII	0.98 (0.79, 1.22)	0.8758	1.03 (0.82, 1.30)	0.7896	**0.82 (0.68, 0.99)**	**0.0428**
1	rs11206510	T	LDL	0.91 (0.69, 1.21)	0.5217	1.10 (0.81, 1.49)	0.5465	**1.28 (1.01, 1.63)**	**0.0451**

DMII – T2 diabetes, LDL, HYP-hypertension, AF-atrial fibrillation

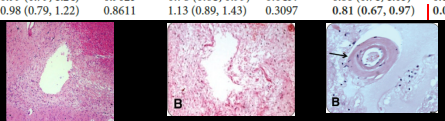


Chou SH, et al. *Cerebrovascular Disease.* 2013;36:181-188.

Genetic Susceptibility for Ischemic Infarction and Arteriolosclerosis Based on Neuropathologic Evaluations

51 SNPs putative stroke risk factors

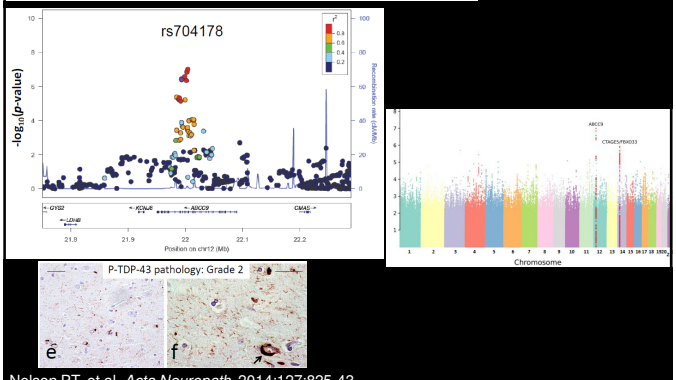
CHR	SNP	Allele	GWAS	Macroscopic infarcts		Microscopic infarcts		Arteriolosclerosis	
				OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
9	rs1883025	T	HDL	**1.38 (1.08, 1.75)**	**0.0094**	0.86 (0.66, 1.12)	0.2591	1.04 (0.84, 1.28)	0.7468
18	rs4939883	T	HDL	**0.68 (0.51, 0.92)**	**0.0116**	0.89 (0.65, 1.21)	0.4569	0.93 (0.73, 1.19)	0.5873
16	rs1864163	A	HDL	**1.59 (1.08, 2.34)**	**0.0179**	1.25 (0.83, 1.88)	0.2818	1.16 (0.83, 1.63)	0.3710
17	rs12936587	G	CAD	**1.29 (1.03, 1.61)**	**0.0262**	1.16 (0.91, 1.47)	0.2295	1.04 (0.86, 1.26)	0.6824
9	rs2383207	G	MI	**1.26 (1.02, 1.55)**	**0.0314**	1.10 (0.88, 1.38)	0.3932	1.11 (0.93, 1.33)	0.2660
17	rs46522	T	CAD	**0.80 (0.64, 1.00)**	**0.0491**	1.03 (0.81, 1.30)	0.8099	0.96 (0.79, 1.15)	0.6362
8	rs2954029	A	TG	0.98 (0.79, 1.21)	0.8196	**0.74 (0.58, 0.92)**	**0.0084**	0.97 (0.81, 1.17)	0.7546
15	rs3825807	A	CAD	0.99 (0.79, 1.24)	0.9025	**0.78 (0.61, 0.99)**	**0.0437**	0.86 (0.71, 1.05)	0.1330
11	rs7395662	G	HDL	0.98 (0.79, 1.22)	0.8611	1.13 (0.89, 1.43)	0.3097	**0.81 (0.67, 0.97)**	**0.0244**



HDL – High Density Lipoprotein, CAD – coronary artery disease, TG - Triglycerides

Chou SH, et al. *Cerebrovascular Disease.* 2013;36:181-188.

ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology



Nelson PT, et al. *Acta Neuropath.* 2014;127:825-43.

Summary

- Genomic risk factors for AD dementia operate through a number pathways including some in the cerebrovascular disease pathway and others involved in immune and inflammatory function
- Neuropathologic traits can be exploited for gene discovery and for mechanistic studies

Objectives

- Two Studies of Aging and Dementia with Organ Donation
- Neurobiology of AD dementia
- Genes, Pathology, and AD dementia
  - Epigenome and transcriptome

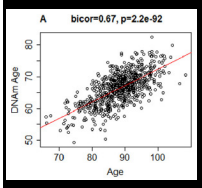
Association of Brain DNA Methylation in *SORL1*, *ABCA7*, *HLA-DRB5*, *SLC24A4*, and *BIN1* With Pathological Diagnosis of Alzheimer Disease

Table 1. Omnibus Test for DNA Methylation in Associated Alzheimer Disease Loci With Pathological Alzheimer Disease

Locus	Chromosome	Covered Region	No. of CpGs	Observed Test Statistic	*P* Value	
					Permuted	Adjusted[b]
SORL1	11	121222911:121604471	69	289.6763	$<1.0 \times 10^{-6}$	<.0000280
ABCA7	19	940101:1165570	255	666.5471	6.0×10^{-6}	.0000840
HLA-DRB5	6	32385153:32598006	48	157.3848	5.0×10^{-5}	.0004667
SLC24A4	14	92688924:93067825	62	188.9191	.00013	.0009100
BIN1	2	127705598:127964903	95	247.3020	.0032	.0179200
INPP5D	2	233825035:234216549	87	214.4398	.0188	.0877333
FERMT2	14	53223988:53517815	54	138.7177	.0239	.0917000
TREM2	6	41026245:41230922	74	182.7488	.0262	.0917000
CLU	8	27354433:27572328	70	173.0821	.0316	.0983111

Yu L, et al. *JAMA Neurology*. 2015;72:15-24.

Epigenetic age of the pre-frontal cortex is associated with neuritic plaques, amyloid load, and Alzheimer's disease related cognitive functioning



	β (SE)	P-value
GCF	-0.340 (0.163)	0.019

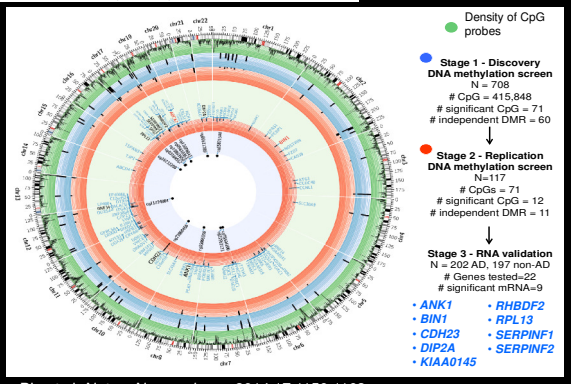
	Beta Coefficient (One-Tailed P-Value)
Amyloid Load	0.100 (0.006)
NP	0.451 (0.004)
DP	0.468 (0.004)
NFT	0.377 (0.021)
Tangle Score	0.030 (0.041)

Results are from independent multivariate models that adjust for age at death, study, and sex

GCF	-0.336 (0.020)	-0.229 (0.087)	-0.114 (0.256)
Amyloid		0.094 (0.015)	
Neuritic Plaques			0.553 (0.004)

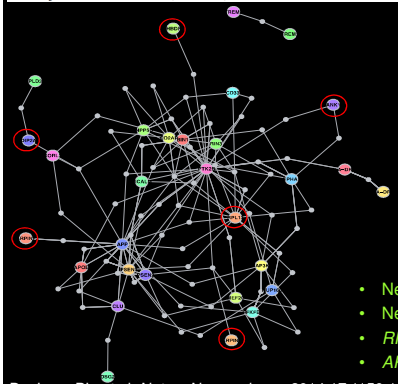
Levine ME, et al. *Aging*. 2015;12:1198-1211.

Alzheimer's disease: early alterations in brain DNA methylation at *ANK1*, *BIN1*, *RHBDF2* and other loci



De Jager PL, et al. *Nature Neuroscience*. 2014;17:1156-1163.

Alzheimer's disease: early alterations in brain DNA methylation at *ANK1*, *BIN1*, *RHBDF2* and other loci



Input:
- 20 AD susceptibility loci
- Mendelian AD genes
- 9 genes from DMR with altered RNA expression

Result:
- 6/9 methylation defined genes connect to the genetically defined network

- Network direct connectivity: p=0.007
- Network indirect connectivity: p=0.04
- *RHBDF2* connection: p= 0.0015
- *APP* connection: p= 0.00021

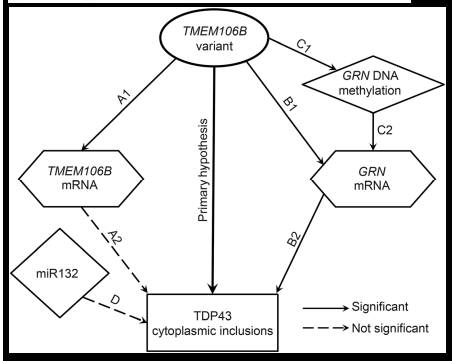
De Jager PL, et al. *Nature Neuroscience*. 2014;17:1156-1163.

Alzheimer's disease: early alterations in brain DNA methylation at *ANK1*, *BIN1*, *RHBDF2* and other loci

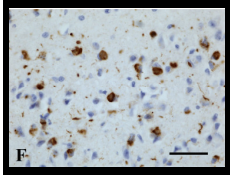
ANK1 and RHBDF2 connect to PTK2B, an AD gene that is a key element of the signaling cascade involved in modulating the activation of microglia and infiltrating macrophages. Several other AD genes, such as CD33 and EPHA1, connect to this molecule as well.

De Jager PL, et al. *Nature Neuroscience*. 2014;17:1156-1163.

The *TMEM106B* locus and TDP-43 pathology in older persons without FTLD



Variants in *TMEM106B* serve as a distinct risk factor for TDP43



Yu L, et al. *Neurology*. 2015;84:927-934.

Summary

- Multiple pathologies and resilience factors are associated wit AD dementia
- Genomic risk factors for AD dementia operate through a number pathways including some in the cerebrovascular disease pathway and others involved in immune and inflammatory function
- Neuropathologic traits can be exploited for gene discovery and mechanistic studies, alone or combined with other layers of molecular genomics