The Genetics of Alzheimer's Disease and other Tauopathies

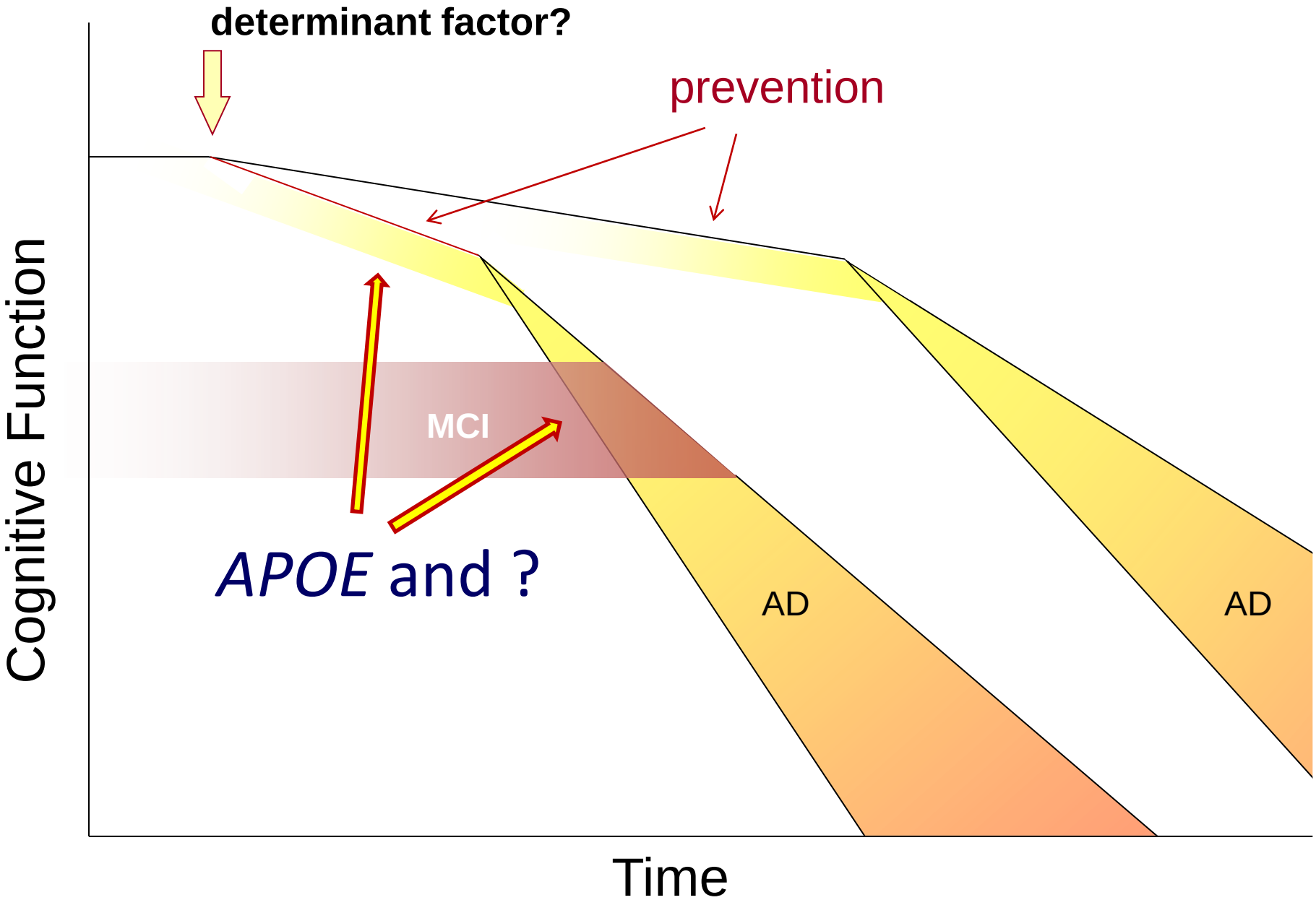
Alzheimer's Disease Genetics Consortium

Perelman School of Medicine
University of Pennsylvania

Alzheimer's Disease Genetics Consortium

ADGC goal: Completely solve the genetic architecture of Alzheimer's disease

Alzheimer's Disease Genetics Consortium



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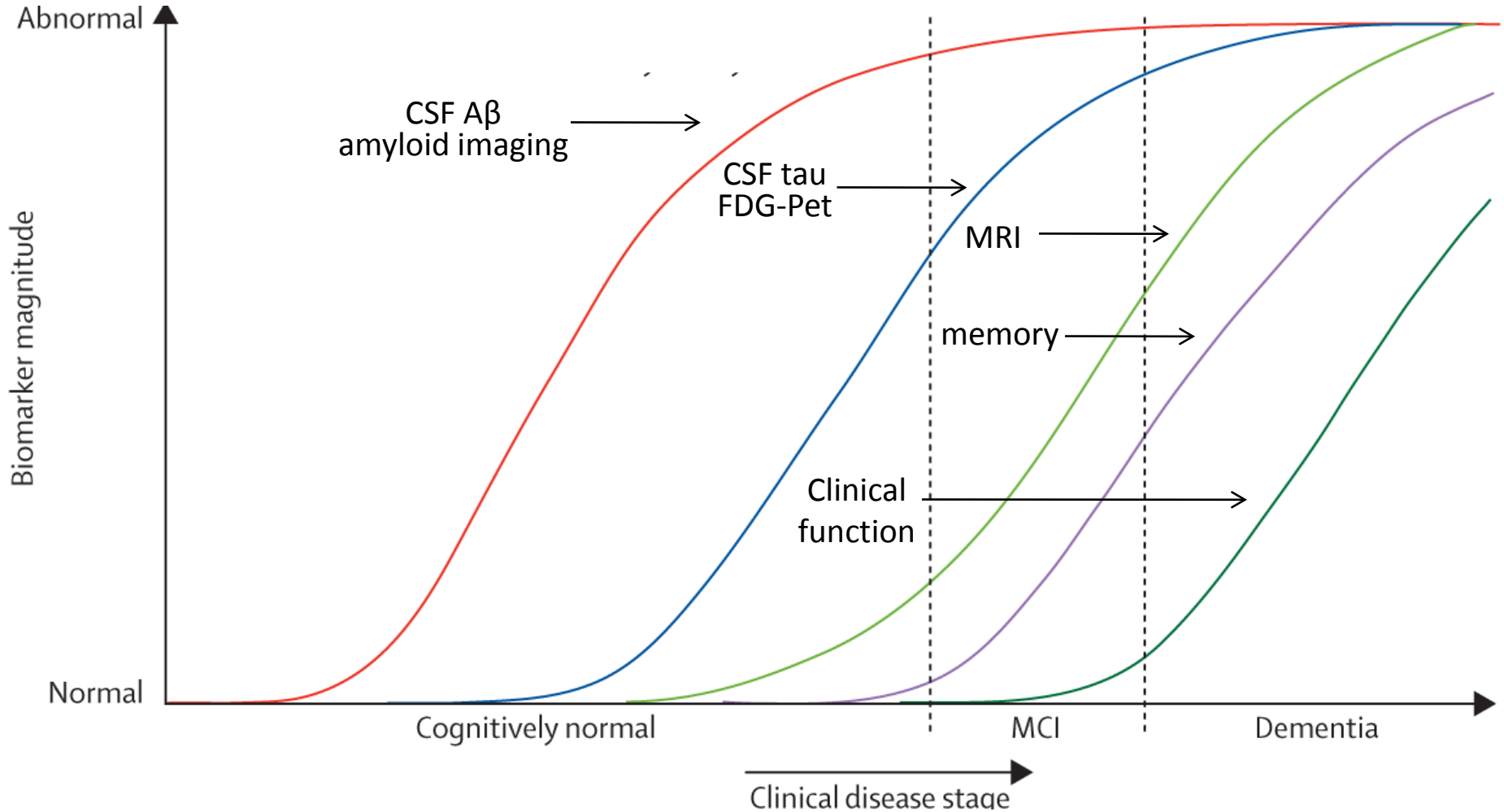

AD biomarkers:
- Aβ/amyloid comes first
- tau comes second

Jack *et al*. 2010 Lancet Neurology 9, 119-128

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ADGC goal: Completely solve the genetic architecture of Alzheimer's disease

Identify genes that alter:

- risk
- age-of-onset
- biomarkers (CSF and imaging)
- progression rate of:
  - Prodromal cognitive change
  - MCI
  - AD
- Neuropathologic features
- Other endophenotypes

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ADGC goal: Completely solve the genetic architecture of Alzheimer's disease

- Common variants (*e.g. APOE*)
- Rare large effect alleles at common variant sites
- Rare large effect variants at unique genes (*e.g. APP, PSEN1*, *PSEN2* mutations)

ADGC goal: Completely solve the genetic architecture of Alzheimer's disease

Why?

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ADGC goal: Completely solve the genetic architecture of Alzheimer's disease

Rationale for gene discovery

- Mechanism
- Drug targets
- Prediction

Systems biology

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ADGC goal: Completely solve the genetic architecture of Alzheimer's disease

Are there a disease mechanism(s) common to multiple/all neurodegenerative diseases?

ADGC Genome-wide association studies

- Test entire genome (~90-95%) for genes associated with Alzheimer's disease
- An unbiased approach to disease pathogenesis
- Use existing infrastructure
- Use existing populations

ADGC Genome-wide association studies

- Genotype samples for 750,000 – 2.5 million single nucleotide polymorphisms
- Clean data by standard methods
- Impute genotypes – 1,000 genomes
- Use meta-analysis/other methods to adjust for cohort differences
- Use age and gender as co-variates

Genome-wide association studies: urban myths

- Genes identified have small effects on disease risk and therefore are not biologically relevant, not useful for disease research
- Polymorphic sites are often not the disease modifying sites and thus are not useful
- Additional studies will have diminished yields and only produce very small effect genes

Myocardial infarction

Vol 466 | 5 August 2010 | doi:10.1038/nature09270 nature

ARTICLES

Biological, clinical and population relevance of 95 loci for blood lipids

....with plasma lipids in > 100,000 individuals...

A list of authors and their affiliations appears at the end of the paper.

Plasma concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides are among the most important risk factors for coronary artery disease (CAD) and are targets for therapeutic intervention. We screened the genome for common variants associated with plasma lipids in >100,000 individuals of European ancestry. Here we report 95 significantly associated loci ($P < 5 \times 10^{-8}$), with 59 showing genome-wide significant association with lipid traits for the first time. The newly reported associations include single nucleotide polymorphisms (SNPs) near known lipid regulators (for example, *CYP7A1*, *NPC1L1* and *SCARB1*) as well as in scores of loci not previously implicated in lipoprotein metabolism. The 95 loci contribute not only to normal variation in lipid traits but also to extreme lipid phenotypes and have an impact on lipid traits in three non-European populations (East Asians, South Asians and African Americans). Our results identify several novel loci associated with plasma lipids that are also associated with CAD. Finally, we validated three of the novel genes—*GALNT2*, *PPP1R3B* and *TTC39B*—with experiments in mouse models. Taken together, our findings provide the foundation to develop a broader biological understanding of lipoprotein metabolism and to identify new therapeutic opportunities for the prevention of CAD.

- Went from ~20,000 to 100,000 subjects – 59 new loci
- Two genes identified are drug targets

Myocardial infarction

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Gene*	P-value	Trait	Effect size (mg/dl)	
HMG co-A reductase	9×10^{-47}	TC	+2.84	← statin target
NPC1L1	3×10^{-11}	TC	+2.01	← Zetia (ezetimibe) target
Apolipoprotein E (*APOE*)	9×10^{-147}	LDL	+7.14	
Sortilin 1 (*SORT1*)	1×10^{-170}	LDL	-5.65	

Myocardial infarction

nature Vol 466|5 August 2010|doi:10.1038/nature09266

ARTICLES

From noncoding variant to phenotype via *SORT1* at the 1p13 cholesterol locus

Kiran Musunuru[1,2,3]*, Alanna Strong[4]*, Maria Frank-Kamenetsky[5], Noemi E. Lee[1], Tim Ahfeldt[1,6], Katherine V. Sachs[4], Xiaoyu Li[4], Hui Li[4], Nicolas Kuperwasser[1], Vera M. Ruda[1], James P. Pirruccello[1,2], Brian Muchmore[7], Ludmila Prokunina-Olsson[7], Jennifer L. Hall[2,8], Eric E. Schadt[9], Carlos R. Morales[10], Sissel Lund-Katz[11], Michael C. Phillips[11], Jamie Wong[5], William Cantley[5], Timothy Racie[5], Kenechi G. Ejebe[1,2], Marju Orho-Melander[12], Olle Melander[12], Victor Koteliansky[5], Kevin Fitzgerald[5], Ronald M. Krauss[13], Chad A. Cowan[1,2], Sekar Kathiresan[1,2]* & Daniel J. Rader[4]*

- **"…functional evidence for a novel regulatory pathway for lipoprotein metabolism…"**
- **"…modulation of this pathway may alter risk for MI in humans."**
- **"…common noncoding DNA variants identified by GWASs can directly contribute to clinical phenotypes."**

ADGC Genome-wide association studies

- NIA-funded Alzheimer's Disease Centers
- NACC and NCRAD
- Samples and data from on-going population-based and other studies
- Need well-characterized cases AND controls
- Need large numbers

Alzheimer's Disease Genetics Consortium

Alzheimer's Disease Center samples

Cohort	Cases	Autopsies n (percent)	Controls	Autopsies: n (percent)
ADC1	1566	1566 (100%)	515	515 (100%)
ADC2	738	195 (26%)	160	0 (0%)
ADC3	897	527 (59%)	588	4 (1%)
Totals	**3,201**	**2,288 (71%)**	**1,263**	**519 (41%)**

Alzheimer's Disease Genetics Consortium

Discovery (Stage 1)

Cohort	Cases	Autopsies	Age-onset (mean ± SD)	Age last exam (mean + SD)	Controls	Autopsies: n (percent)	Age at last exam (mean ± SD)
ACT	566	70 (12%)	83.90 (4.8)	84.72 (4.9)	1696	155 (9%)	81.08 (6.0)
ADC1	1566	1566 (100%)	72.47 (7.1)	81.61 (7.0)	515	515 (100%)	75.00 (8.0)
ADC2	738	195 (26%)	73.19 (7.1)	80.06 (7.2)	160	0 (0%)	75.68 (7.9)
ADNI	268	0 (0%)	75.30 (7.2)	77.96 (6.5)	173	0 (0%)	78.6 (5.5)
GenADA	669	9 (1%)	74.59 (6.2)	80.36 (6.2)	713	0 (0%)	74.21 (7.0)
UM/VU/MSSM	1186	409 (34%)	74.06 (7.8)	77.48 (6.9)	1135	136 (12%)	74.00 (8.3)
MIRAGE	509	0 (0%)	71.16 (6.5)	75.97 (6.6)	753	0 (0%)	72.04 (7.2)
NIA-LOAD	1811	492 (27%)	73.57 (6.7)	82.49 (7.1)	1575	50 (3%)	73.99 (8.5)
OHSU	132	132 (100%)	86.10 (5.5)	90.40 (5.2)	153	153 (100%)	83.86 (7.6)
TGEN2	864	864 (100%)	74.91 (7.2)	82.00 (7.6)	493	493 (100%)	80.19 (8.7)
TOTAL	**8309**	**3737 (45%)**	**--**	**--**	**7366**	**1502 (20%)**	**--**

Replication (Stage 2)

ADC3	897	527 (59%)	75.00 (8.5)	(8.9)	588	4 (1%)	75.30 (9.8)
MAYO	728	221 (30%)	ND	73.89 (4.9)	1173	216 (18%)	73.30 (4.4)
ROSMAP	296	291 (98%)	85.59 (6.3)	89.83 (5.7)	776	0 (0%)	82.03 (7.0)
UP	1271	? (24%)	72.91 (6.4)	77.38 (6.3)	841	0 (0%)	75.37 (6.1)
WU	339	0 (0%)	ND	74.24 (8.0)	187	0 (0%)	76.85 (8.4)
TOTAL	**3531**	**1039 (29%)**	**--**	**--**	**3565**	**220 (6%)**	**--**
Discovery + Replication	**11840**	**4776 (40%)**	**--**	**--**	**10,931**	**1,722 (16%)**	**--**

Alzheimer's Disease

Stage	Cases (% autopsied)	Controls (% autopsied)
Discovery	8,309 (45%)	7,366 (20%)
Replication – 1	3,531 (29%)	3,565 (6%)
Replication – 2	6,283	7,165
Total:	18,123	18,096

- Discovery and Replication 1: ADGC. All controls are cognitively normal elderly
- Replication – 2: CHARGE, EADI, and GERAD

Alzheimer's Disease

LETTERS

nature genetics

Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease

The Alzheimer Disease Genetics Consortium (ADGC) performed a genome-wide association study of late-onset Alzheimer disease using a three-stage design consisting of a discovery stage (stage 1) and two replication stages (stages 2 and 3). Both joint analysis and meta-analysis approaches were used. We obtained genome-wide significant results at *MS4A4A* (rs4938933; stages 1 and 2, meta-analysis P (P_M) = 1.7×10^{-9}, joint analysis P (P_J) = 1.7×10^{-9}; stages 1, 2 and 3, $P_M = 8.2 \times 10^{-12}$), *CD2AP* (rs9349407; stages 1, 2 and 3, $P_M = 8.6 \times 10^{-9}$), *EPHA1* (rs11767557; stages 1, 2 and 3, $P_M = 6.0 \times 10^{-10}$) and *CD33* (rs3865444; stages 1, 2 and 3, $P_M = 1.6 \times 10^{-9}$). We also replicated previous associations at *CR1* (rs6701713; $P_M = 4.6 \times 10^{-10}$, $P_J = 5.2 \times 10^{-11}$), *CLU* (rs1532278; $P_M = 8.3 \times 10^{-8}$, $P_J = 1.9 \times 10^{-8}$), *BIN1* (rs7561528; $P_M = 4.0 \times 10^{-14}$, $P_J = 5.2 \times 10^{-14}$) and *PICALM* (rs561655; $P_M = 7.0 \times 10^{-11}$, $P_J = 1.0 \times 10^{-10}$), but not at *EXOC3L2*, to late-onset Alzheimer's disease susceptibility[1–3].

Adam C. Naj, Gyungah Jun, Gary W. Beecham, Li-San Wang, Badri Narayan Vardarajan, Jacqueline Buros, Paul J. Gallins, Joseph D. Buxbaum, Gail P. Jarvik, Paul K. Crane, Eric B. Larson, Thomas D. Bird, Bradley F. Boeve, Neill R. Graff-Radford, Philip L. De Jager, Denis Evans, Julie A. Schneider, Minerva M. Carrasquillo, Nilufer Ertekin-Taner, Steven G. Younkin, Carlos Cruchaga, John S.K. Kauwe, Petra Nowotny, Patricia Kramer, John Hardy, Matthew J. Huentelman, Amanda J Myers, Michael M. Barmada, F Yesim Demirci, Clinton T. Baldwin, Robert C. Green, Ekaterina Rogaeva, Peter St George-Hyslop, Steven E. Arnold, Robert Barber, Thomas Beach, Eileen H. Bigio, James D. Bowen, Adam Boxer, James R. Burke, Nigel J. Cairns, Chris S. Carlson, Regina M. Carney, Steven L. Carroll, Helena C. Chui, David G. Clark, Jason Corneveaux, Carl W. Cotman, Jeffrey L. Cummings, Charles DeCarli, Steven T. DeKosky, Ramon Diaz-Arrastia, Malcolm Dick, Dennis W. Dickson, William G. Ellis, Kelley M. Faber, Kenneth B. Fallon, Martin R. Farlow, Steven Ferris, Matthew P. Frosch, Douglas R. Galasko, Mary Ganguli, Marla Gearing, Daniel H. Geschwind, Bernardino Ghetti, John R. Gilbert, Sid Gilman, Bruno Giordani, Jonathan D. Glass, John H. Growdon, Ronald L. Hamilton, Lindy E. Harrell, Elizabeth Head, Lawrence S. Honig, Christine M. Hulette, Bradley T. Hyman, Gregory A. Jicha, Lee-Way Jin, Nancy Johnson, Jason Karlawish, Anna Karydas, Jeffrey A. Kaye, Ronald Kim, Edward H. Koo, Neil W. Kowall, James J. Lah, Allan I. Levey, Andrew P. Lieberman, Oscar L. Lopez, Wendy J. Mack, Daniel C. Marson, Frank Martiniuk, Deborah C. Mash, Eliezer Masliah, Wayne C. McCormick, Susan M. McCurry, Andrew N. McDavid, Ann C. McKee, Marsel Mesulam, Bruce L. Miller, Carol A. Miller, Joshua W. Miller, Joseph E. Parisi, Daniel P. Perl, Elaine Peskind, Ronald C. Petersen, Wayne W Poon, Joseph F. Quinn, Ruchita A. Rajbhandary, Murray Raskind, Barry Reisberg, John M. Ringman, Erik D. Roberson, Roger N. Rosenberg, Mary Sano, Lon S. Schneider, William Seeley, Michael L. Shelanski, Michael A. Slifer, Charles D. Smith, Joshua A. Sonnen, Salvatore Spina, Robert A. Stern, Rudolph E. Tanzi, John Q. Trojanowski, Juan C. Troncoso, Vivianna M. Van Deerlin, Harry V. Vinters, Jean Paul Vonsattel, Sandra Weintraub, Kathleen A. Welsh-Bohmer, Jennifer Williamson, Randall L. Woltjer, Laura B. Cantwell, Beth A. Dombroski, Duane Beekly, Kathryn L. Lunetta, Eden R. Martin, M. Ilyas Kamboh, Andrew J. Saykin, Eric M. Reiman, David A. Bennett, John C. Morris, Thomas J. Montine, Alison M. Goate, Deborah Blacker, Debby W. Tsuang, Hakon Hakonarson, Walter A. Kukull, Tatiana M. Foroud, Jonathan L. Haines, Richard Mayeux, Margaret A. Pericak-Vance, Lindsay A. Farrer & Gerard D. Schellenberg

Alzheimer's Disease

Chromosome	Gene	cases	controls	p-value	OR (95% CI)	MAF
19	*TOMM40* (*APOE*)	10,011	8,949	5.7×10^{-276}	2.74 (2.59 – 2.90)	0.24
8	*CLU/APOJ*	11,840	10,931	8.5×10^{-10}	0.86 (0.82 – 0.90)	0.37
11	*PICALM*	11,840	10,931	5.7×10^{-11}	0.87 (0.83 – 0.91)	0.31
1	*CR1*	11,840	10,931	1.2×10^{-10}	1.17 (1.12 – 1.23)	0.21
2	*BIN1*	11,840	10,931	4.2×10^{-14}	1.17 (1.13 – 1.22)	0.35
6	*CD2AP*	19,490	31,000	8.6×10^{-9}	1.11 (1.07 – 1.17)	0.27
7	*EPHA1*	19,490	36,770	6.0×10^{-10}	0.90 (0.86 – 0.93)	0.19
11	*MS4A4*	11,840	10,931	2.6×10^{-11}	0.87 (0.84 – 0.91)	0.37
19	*ABCA7*	11,840	10,931	5.8×10^{-7}	1.15 (1.09 – 1.21)	0.19
19	*CD33*	19,490	31,000	1.6×10^{-9}	0.91 (0.88 – 0.93)	0.31

Data from Naj *et al.* (2011) Nature Genetics 43, 436 - 441

Alzheimer's Disease

Late-onset Alzheimer's disease susceptibility genes	
APOE:[1]	apolipoprotein E
PICALM[3]:	phosphatidylinositol-binding clathrin assembly protein
CLU/APOJ[2]*:*	clusterin
CR1[2]*:*	complement receptor 1
CD2AP[5,6]*:*	CD2-associated protein
EPHA1[5,6]*:*	ephrin receptor
MS4A4/MS4A6[5,6]*:*	membrane-spanning 4-domains, subfamily A
CD33[5,6]*:*	CD33 antigen
ABCA7[5,6]*:*	ATP-binding cassette (ABC) transporter, member A7
BIN1[4]*:*	bridging integrator 1

1. Strittmatter *et al.* P*roc. Natl. Acad. Sci. U.S.A.* **90**, 1977-1981 (1993).
2. Lambert *et al. Nat Genet* **41**, 1094-1099 (2009).
3. Harold*et al.Nat Genet* **41**, 1088-U1061 (2009).
4. Seshadri *et al. JAMA* **303**, 1832-1840, (2010).
5. Naj *et al.* Nat. Genet. (in press)
6. Hollingworth *et al.* Nat. Genet. (in press)

Alzheimer's Disease

Lipid metabolism

Inflammation

Adaptive immunity?

Alzheimer's Disease

ADGC samples

	case	control
stage2 Naj/Jun *et al.*	3,531	3,565
Post-Naj/Jun *et al,* genotyping	440	614
Phase 2 pending (UDS)	696	754

Additional cohorts

	case	control
TARC: genotypes received	500	300
DNA received	228	200
Pfizer (Xiaolan Hu)	733	792
Merck/Harvard brain bank	392	159

Totals

	case	control
Post Naj/Jun *et al.*	6,520	6,384

IGAP

International Genomics Alzheimer Project

• EADI – France and Europe	Philippe Amouyel
• ADGC – USA	Gerard Schellenberg
• CHARGE – USA + Europe population based cohorts	Sudha Seshadri
• GERAD – Great Britain	Julie Williams

Alzheimer's Association funding

IGAP

International Genomics Alzheimer Project

- Stage 1: ~20,000 cases
  ~20,000 elderly controls
  ~20,000 population controls (younger)

- Stage 2: custom chip from stage 1 data
  ~50,000 SNPs
  14,000 cases (?)
  14,000 controls (?)

ADGC primary analysis

- Case-control: expand cohort
  IGAP
  autopsy versus clinical GWAS
  African American GWAS
  Hispanic GWAS
  Japanese GWAS

- *APOE:* *TOMM40* poly-T
  APOE – additional non ε2/ε3/ε4 signal?
  GWAS stratified on *APOE* genotype

- Age-at-onset GWAS: family-based and case-control

ADGC primary analysis

- CSF biomarkers: Aβ, tau, P-tau
- Neuropathologic markers
  Braak stage
  Amyloid density
  Vascular brain injury
- Cognitive change – prospective cohorts
- Pathway analysis
- eSNP analysis
- Numerous other special analysis

African American GWAS: Total Sample

	Cases	Controls	Total
DNA received (ADGC genotyped)	1076	1909	3297
Genotypes contributed to ADGC	1243	2565	3808
Total All	2319	4474	7105

Alzheimer's Disease

ADGC Autopsy Series

Cohort	AD	Controls	Other
ADC	2860	185	105
ACT	70	155	67
GenADA	9	0	0
UM/VU/MSSM	409	136	0
NIA-LOAD	492	50	0
OHSU	132	153	421
TGEN2	864	493	0
MAYO	221	216	0
ROSMAP	291	0	0
UP	277	2	0
TOTAL	5625	1390	593

- Difference between results from autopsied cases and clinical cases
- Use Braak stage/amyloid load as semi-quantitative traits for GWAS

CSF Series with Genotype Data

	Cases	Controls	MCI	Other	Unknown	Total
Washington Univ, St Louis (A. Goate)	50	103	0	96	242	491
University of Washington (E. Peskind)	62	68	5	24	110	269
University of Pennsylvania	19	1	15	23	58	116
Sweden (A. Sjolander) - pending	367	0	0	0	0	367
Columbia Univ (D. Devenand) - pending	0	40	50	0	0	90
ADNI	96	102	176	0	0	374
Total CSF	**594**	**314**	**246**	**143**	**410**	**1707**

Alzheimer's Disease

ADGC Prospective Cohort Project

Study		PI(s)
ADC	Alzheimer's Disease Centers (UDS subjects)	Center Directors
ACT	Adult Changes in Thought	Larson/Crane/+ Kukull
ROS	Religious Orders Study	Bennett
MAP	Memory and Aging	Bennett
CHAP	CHICAGO Health and Aging	Evans
WHISCA	Women's Health Inititative Study of Cognitive Aging	Resnick
WHICAP	Washington Heights Inwood ad Columbia Aging Project	Mayeux
EAS	Einstein Aging Study	Lipton
Mayo	Mayo Clinic Study of Aging	Peterson
Cache	Cache Country	Welsh-Bohmer

Alzheimer's Disease

ADGC Prospective Cohort Project

	Estimated Total	Status
ACT	3,370	genotyped/401 in progress
WHICAP	786	In Progress - Illumina OmniExpress
WHISCA	2,275	
Cache County	5,000	
CHAP	1,225	
Einstein Aging Study (EAS)	1,600	Preparing samples for NCRAD
Mayo Clinic Study of Aging	2,000	
ROS/MAP	650	650 DNA received at NCRAD
	2,206	Previously genotyped
Total	19,112 (14,112 if Cache County not done)	

Rare variants

Rationale:

- detect genes that cannot be identified by GWAS
- detect large effect alleles at genes identified by GWAS

Approach:

- whole-exome sequencing
- whole-genome sequencing (not presently cost-effective)
- Exome chip

ADGC resources available:

- over 1,000 autopsy documented cases (n = 2,860)
- 1,000 autopsied controls (ADGC + others)
- Over 12,000 cases/12,000 controls for follow-up
- Large multiplex late-onset families (Pericak-Vance)

Progressive Supranuclear Palsy

Cohort characteristics (Caucasians only)

Cohort	genotyped (n)	gender (percent male)	onset age mean (range) ± SD	available data (n)
PSP stage 1	1,069	55 (570)	68 (41 – 93) ± 8.3	794
PSP stage 2	1,051	53 (530)	65 (40 – 91) ± 7.3	913

Stage 1

- All autopsied cases (n = 1,150 all ethnic groups)
- Genotyped for Human Illumina 660W Duo Beadchip
- Cost $400/subject
- Controls were healthy children (n = 3,658)

Stage 2

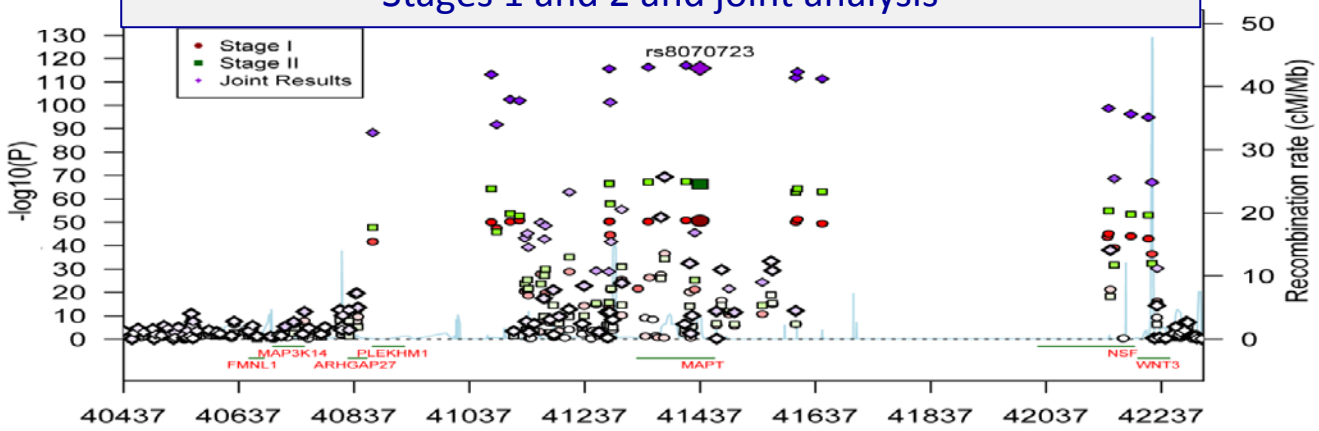
- 1,019 clinically diagnosed cases, 131 autopsied cases
- Genotyped for 5,283 SNPs
- Cost ~$100/subject
- Controls were healthy children (n = 3,203), different from Stage1

Progressive Supranuclear Palsy

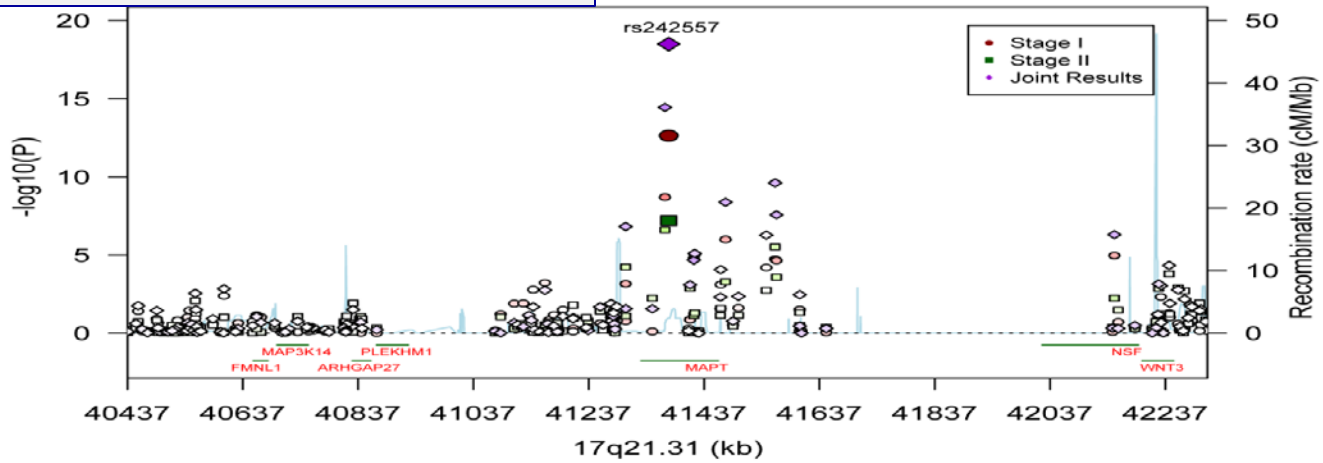
Chr band	Gene	SNP	Stage 1	Stage 2	Joint	
			P	P	OR/CI	P
1q25	*STX6*	rs1411478	1.8×10^{-9}	1.5×10^{-3}	0.79 0.74 – 0.85	2.3×10^{-10}
2p11	*EIF2AK3*	rs7571971	7.4×10^{-7}	8.7×10^{-8}	0.85 0.69 – 0.81	3.2×10^{-13}
3p22	*MOBP*	rs1768208	1.0×10^{-11}	1.3×10^{-8}	0.72 0.67 – 0.78	1.0×10^{-16}
17q21	*MAPT*	rs8070723	2.1×10^{-51}	4.8×10^{-67}	5.64 4.72 – 6.31	1.5×10^{-116}
		rs242557	2.2×10^{-37}	5.0×10^{-35}	0.51 0.47 – 0.55	4.2×10^{-70}
		rs8070723/ rs242557	1.3×10^{-11}	6.3×10^{-8}	0.70 0.65 – 0.76	9.5×10^{-18}
Loci with suggestive evidence for association						
1q41	None	rs6687758	2.3×10^{-4}	3.1×10^{-4}	0.80 0.73 – 0.87	2.8×10^{-7}
10q11	*BMS1*	rs2142991	8.6×10^{-5}	1.2×10^{-3}	1.30 1.17 – 1.44	4.9×10^{-7}
12p12	*SLCO1A2*	rs11568563	2.1×10^{-4}	2.4×10^{-4}	0.69 0.60 – 0.79	1.9×10^{-7}

Progressive Supranuclear Palsy

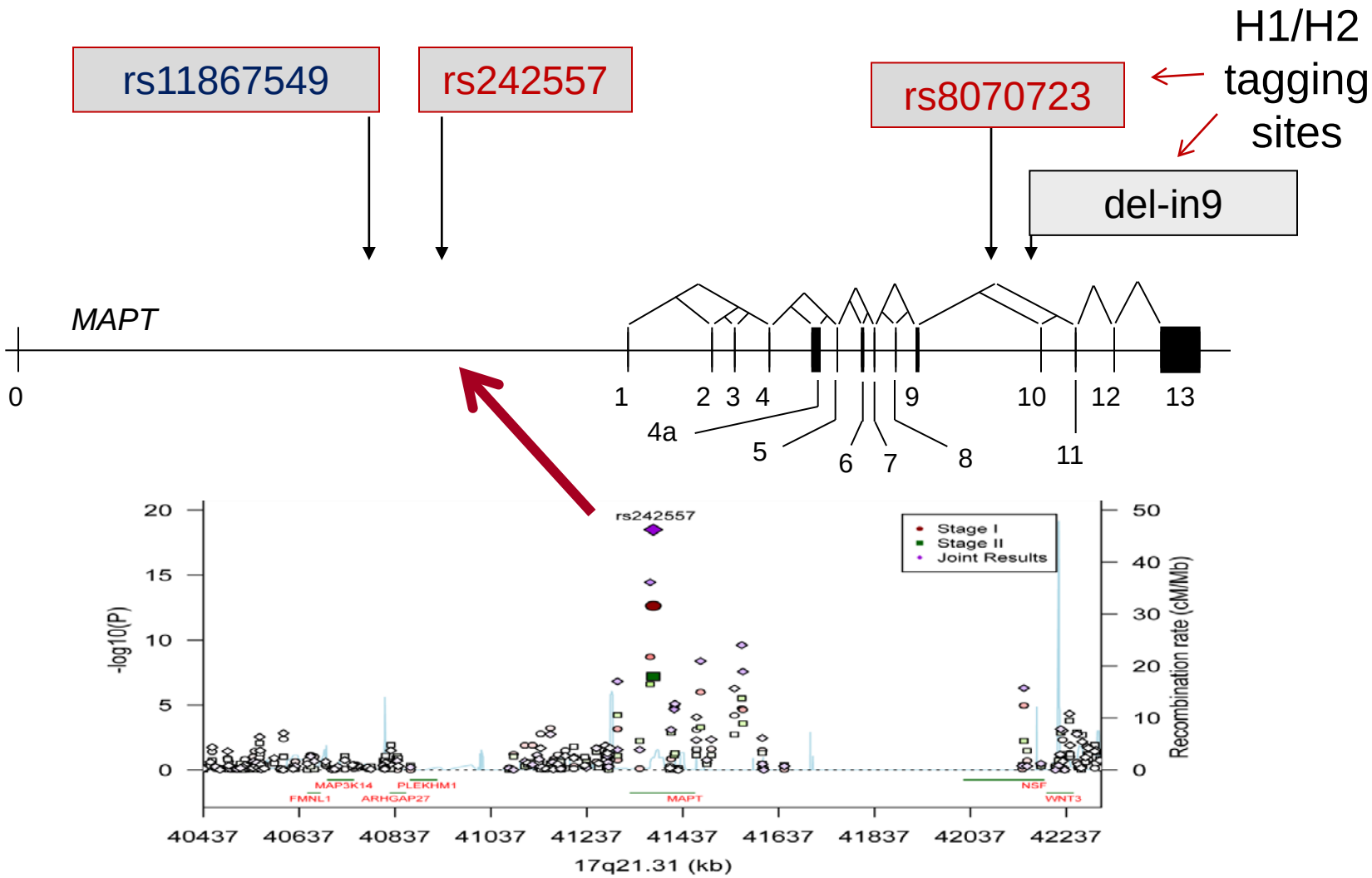
Stages 1 and 2 and joint analysis



Conditioned on rs8070723 (H1/H2)

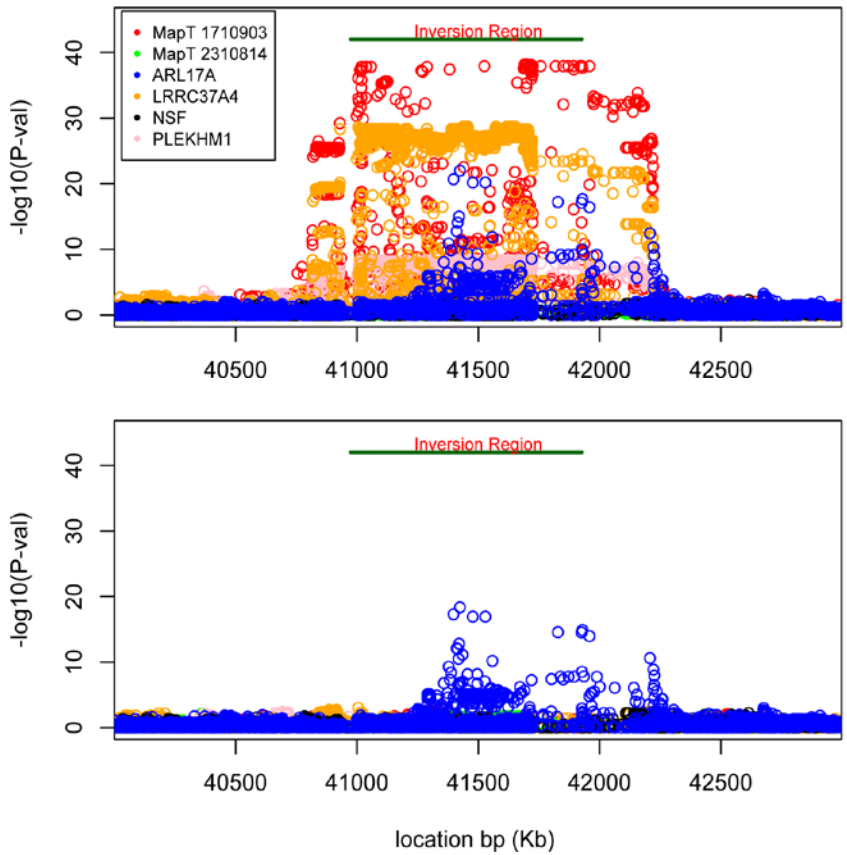


Progressive Supranuclear Palsy

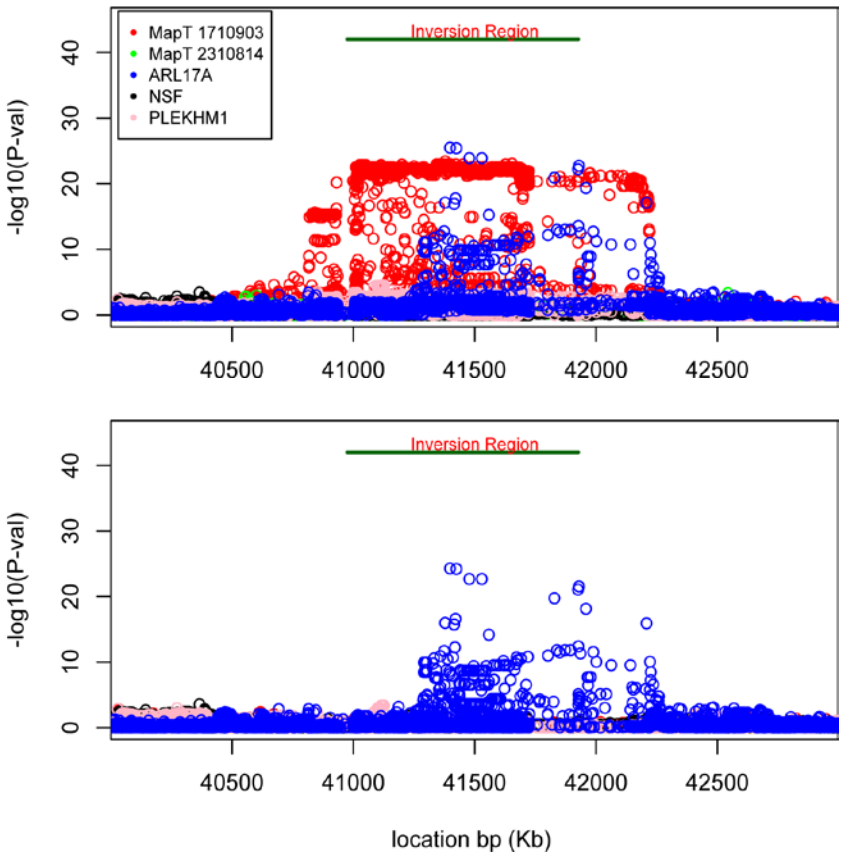


Progressive Supranuclear Palsy

Cerebellum

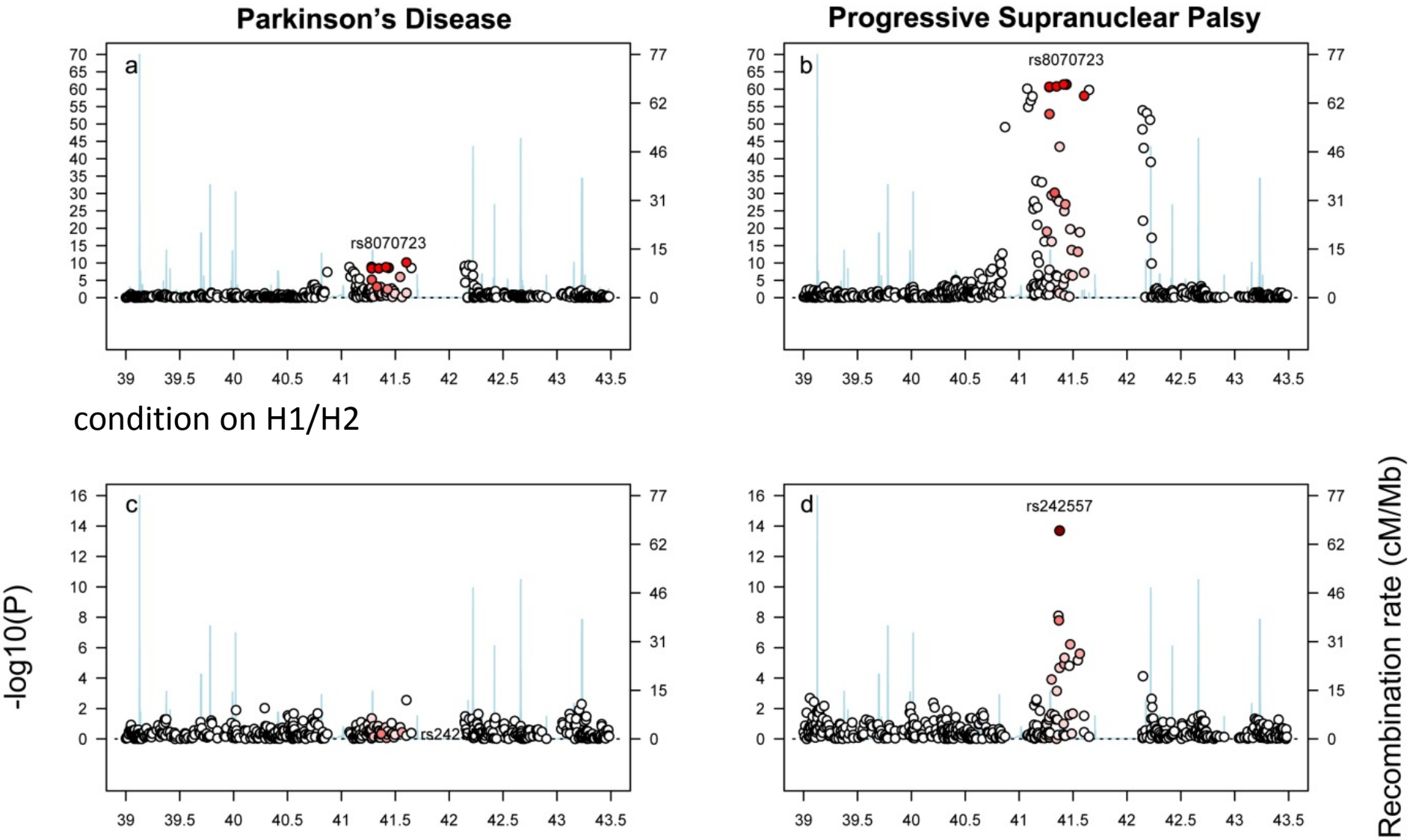


Frontal Cortex



387 normal subjects
Illumina genotypes - Illumina 550, 610, 660
Expression – Illumina HT-12 v3

Parkinson disease



condition on H1/H2

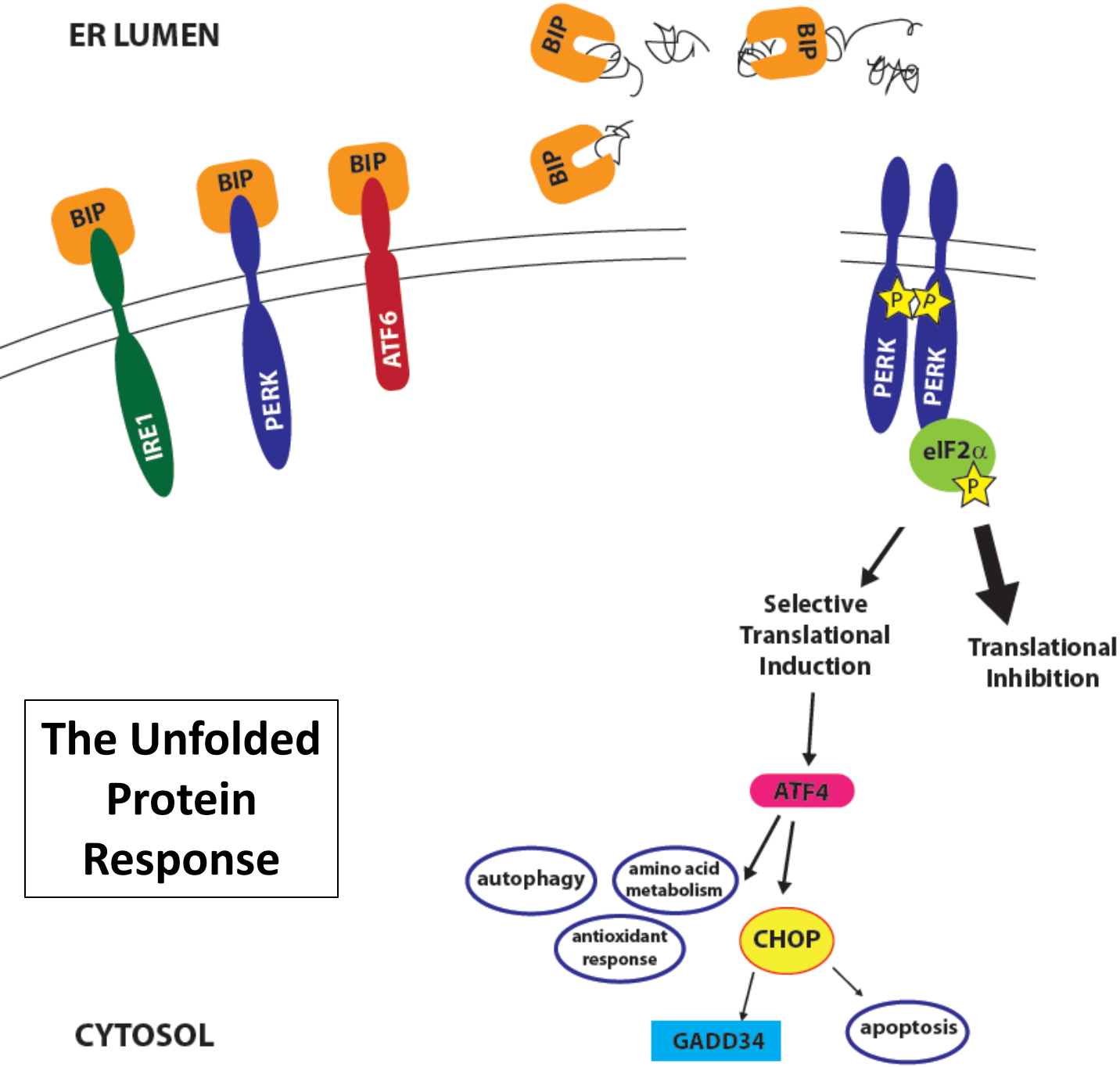
Alzheimer's Disease Genetics Consortium

- H1 haplotype is a susceptibility allele for: PSP
  CBD
  Parkinson's
- H1 allele expresses higher levels of tau
- There is no overt tau pathology in PD
- There is no MAPT association in AD

Progressive Supranuclear Palsy

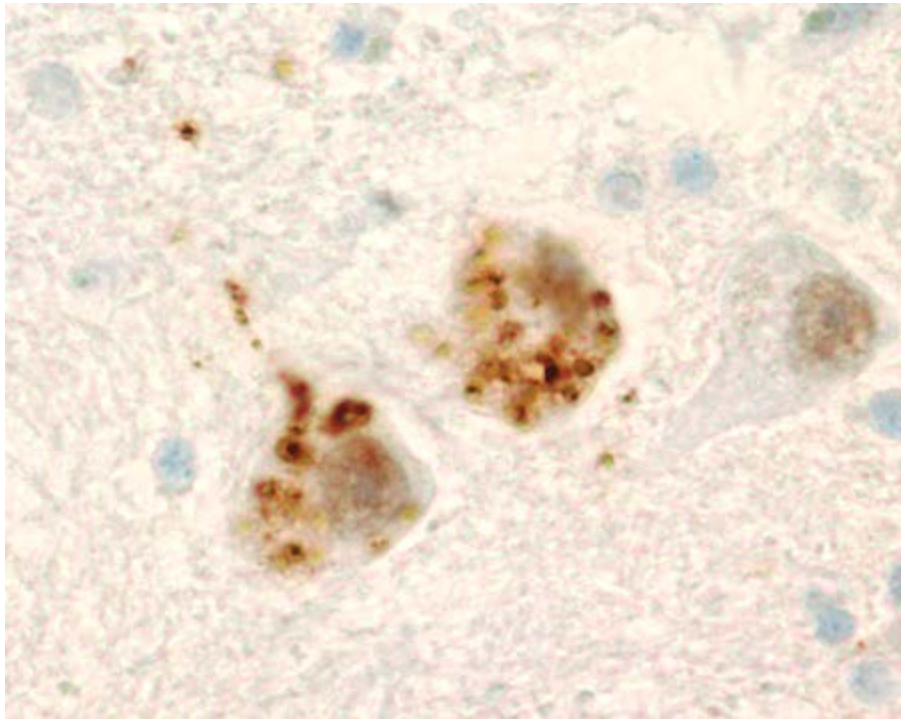
Chr band	Gene	SNP	Stage 1	Stage 2	Joint	
			P	P	OR/CI	P
1q25	*STX6*	rs1411478	1.8×10^{-9}	1.5×10^{-3}	0.79 0.74 – 0.85	2.3×10^{-10}
2p11	*EIF2AK3*	rs7571971	7.4×10^{-7}	8.7×10^{-8}	0.85 0.69 – 0.81	3.2×10^{-13}
3p22	*MOBP*	rs1768208	1.0×10^{-11}	1.3×10^{-8}	0.72 0.67 – 0.78	1.0×10^{-16}
17q21	*MAPT*	rs8070723	2.1×10^{-51}	4.8×10^{-67}	5.64 4.72 – 6.31	1.5×10^{-116}
		rs242557	2.2×10^{-37}	5.0×10^{-35}	0.51 0.47 – 0.55	4.2×10^{-70}
		rs8070723/ rs242557	1.3×10^{-11}	6.3×10^{-8}	0.70 0.65 – 0.76	9.5×10^{-18}
Loci with suggestive evidence for association						
1q41	None	rs6687758	2.3×10^{-4}	3.1×10^{-4}	0.80 0.73 – 0.87	2.8×10^{-7}
10q11	*BMS1*	rs2142991	8.6×10^{-5}	1.2×10^{-3}	1.30 1.17 – 1.44	4.9×10^{-7}
12p12	*SLCO1A2*	rs11568563	2.1×10^{-4}	2.4×10^{-4}	0.69 0.60 – 0.79	1.9×10^{-7}

The Unfolded Protein Response

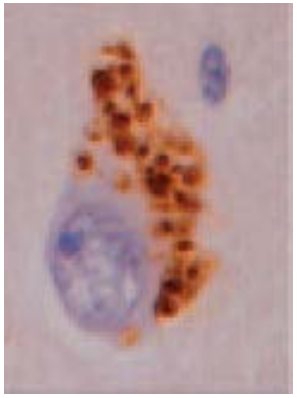


Progressive Supranuclear Palsy

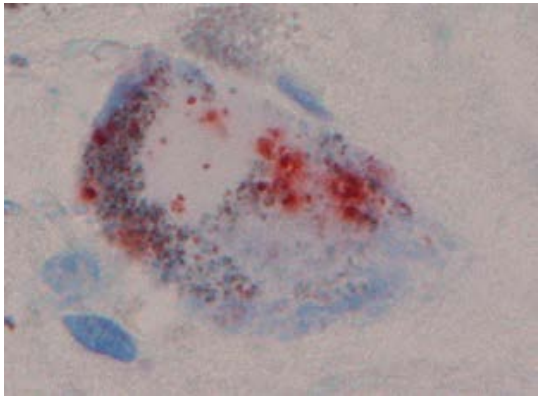
Characterize the UPR in PSP, AD, and normal post-mortem human brain tissue



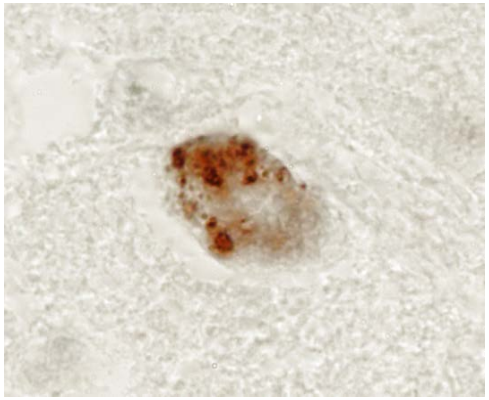
pPERK:



AD hippocampus



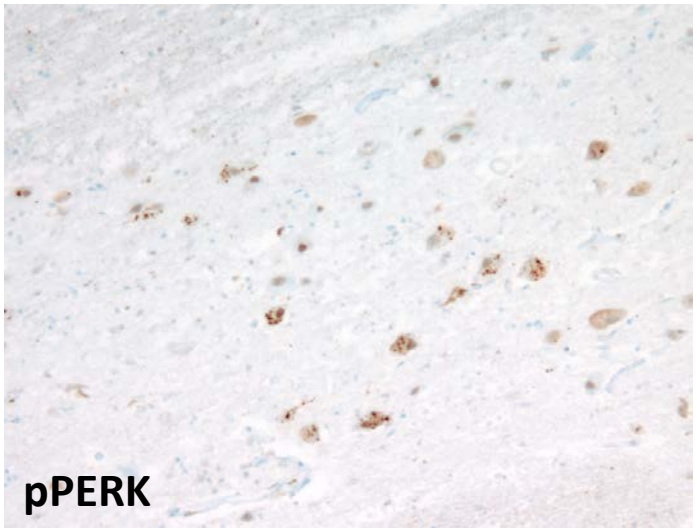
PD substantia nigra pars compacta

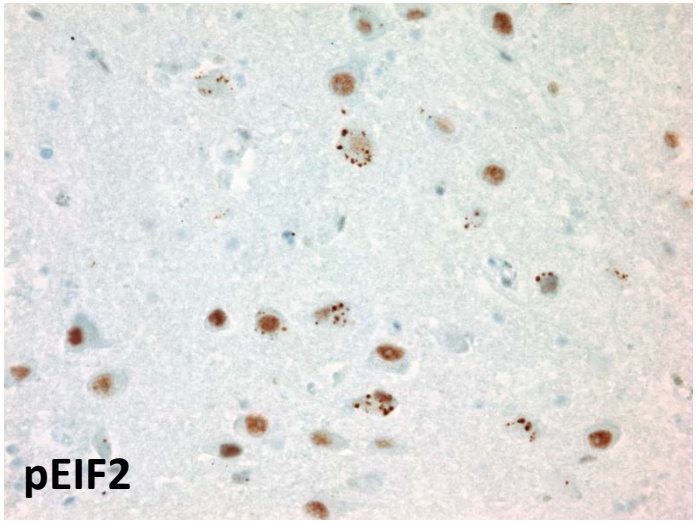


PSP Pons

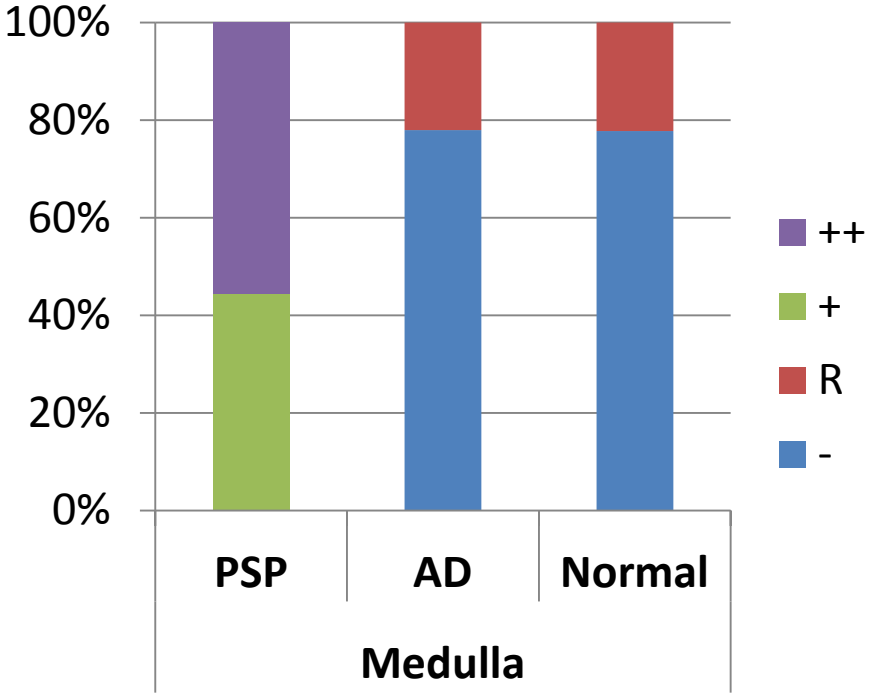
Hoozemans et al . , 2007, 2010

Progressive Supranuclear Palsy





pPERK: Results similar for pPERK: pons and pEIF2: pons and medulla



ER-stress-related diseases

Disease	Gene	Function
Wolcott-Rallison	*EIF2AK3*	ER stress loss-of-function
Inclusion body myopathy with Paget's disease	VCP AAA+ ATPase	ER stress ERAD
Parkinson disease juvenile onset, recessive	PARK2	E3 ubiquitin ligase proteasome system
Marinesco-Sjogren recessive	SIL1	BiP nucleotide exchange factor

Summary

1. Alzheimer's disease genetic studies are identifying novel genes that are clinically relevant and contribute to understanding disease mechanisms

2. AD studies in progress will identify additional genes relevant to AD

3. Large sample sizes are needed

4. Cooperation is essential

5. Genetic studies of neurodegenerative diseases may yield information on common pathways

6. Genetics, biomarker studies, neuropathology, clinical research AD neuroscience need to be thought of as an integrated approach.

Alzheimer's Disease

University of Pennsylvania
- Li-San Wang
- Laura Cantwell
- Beth Dombroski
- Sherry Beecher

Familial AD
- Richard Mayeux
- Deborah Blacker

Clinical Group
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- Debbie Tsuang

Neuropathology Group
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- Eric Reiman

Biomarker Group
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- Andy Saykin

Prospective Cohort Group
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- Bernadino Ghetti
- Brad Hyman
- Denis Evans
- Eric Larson
- Paul Crane
- John Hardy
- Ilyas Kamboh
- Eric Reiman
- Nilifur Taner
- Julie Schneider
- Steve Younkin
- Denis Dickson
- Charlie DeCarli
- Douglas Galasko
- Elaine Peskind
- Neil Graff-Radford
- Matthew Frosch
- John Trojanowski
- Vivianna Van Deelin
- John Morris

NACC
- Bud Kukull
- Duane Beekly

NCRAD
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- Kelly Michelle Faber

University of Miami
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- Adam Naj
- Gary Beecher
- Paul Gallins
- Eden Martin

Boston University
- Lindsey Farrer
- Gyungah Jun
- Jacqueline Buros

Vanderbilt
- Jonathan Haines

NIA/NIH, Alzheimer's Association

Progressive Supranuclear Palsy

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Lauren Stutzbach
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Cure PSP Society
Charles D. Peebler Foundation
NIA/NIH

The
End