Alzheimer's Disease Genetics

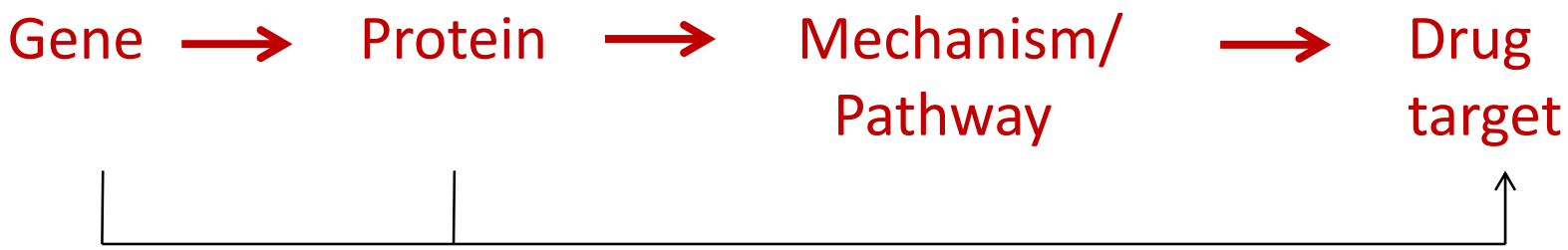
Perelman School of Medicine

University of Pennsylvania

No conflicts to disclose

Human disease genetics goals

- Study human disease mechanisms directly in humans
- Prediction
- Mechanism
- Drug targets

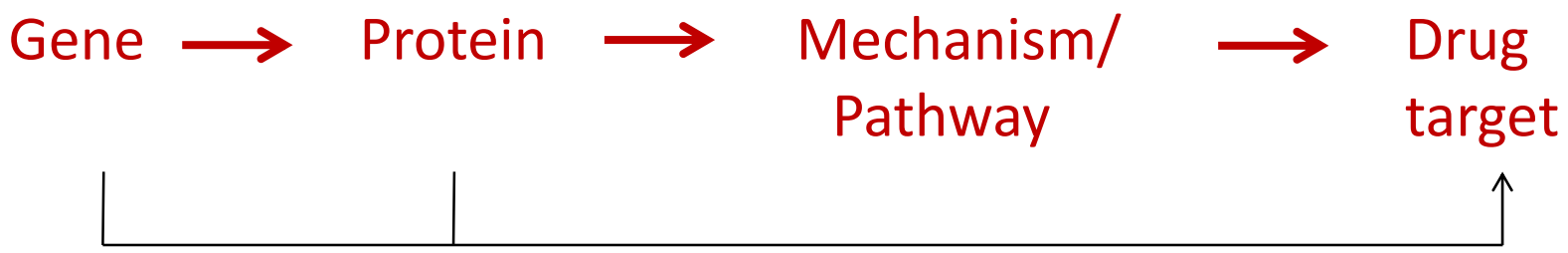


AD Genetic discoveries

APP mutations:	1991
APOE:	1993
PSEN1/2 mutations:	1995
BACE1 cloned:	1999

Genetics-based therapies

Aβ immunotherapy	2000 – present
PSEN1 inhibitor	2006 – stopped
BACE1 inhibitor	2011 – present
APOE agonist:	2013 - present

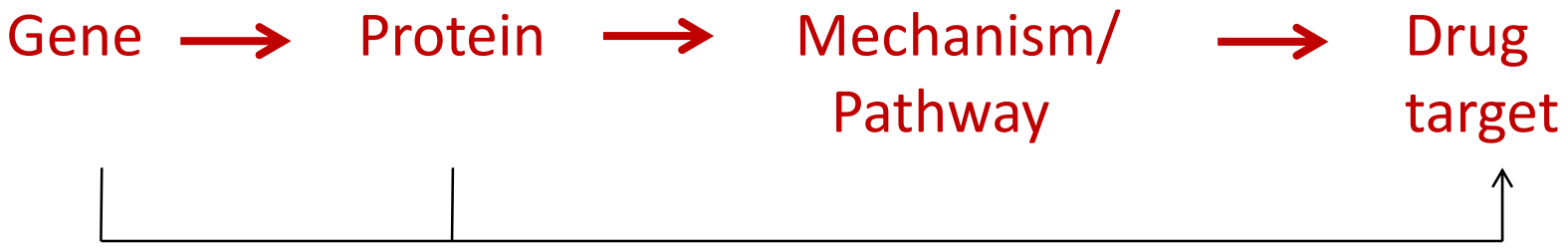


Alzheimer's disease

Gene —(9 years)→ Trial —(15 years +)→ Drug?

Coronary artery disease

ΔPCSK9 (2006) —(5 years)→ Trial (2011) —(4 years)→ Drug? (2015?)



Tools for gene-discovery

- Genome-wide association
  - common variants (MAF > 2-3%)
  - rare variants (MAF > 0.5%)
  - very rare variants (MAF > 0.1%)

- DNA Sequencing approaches

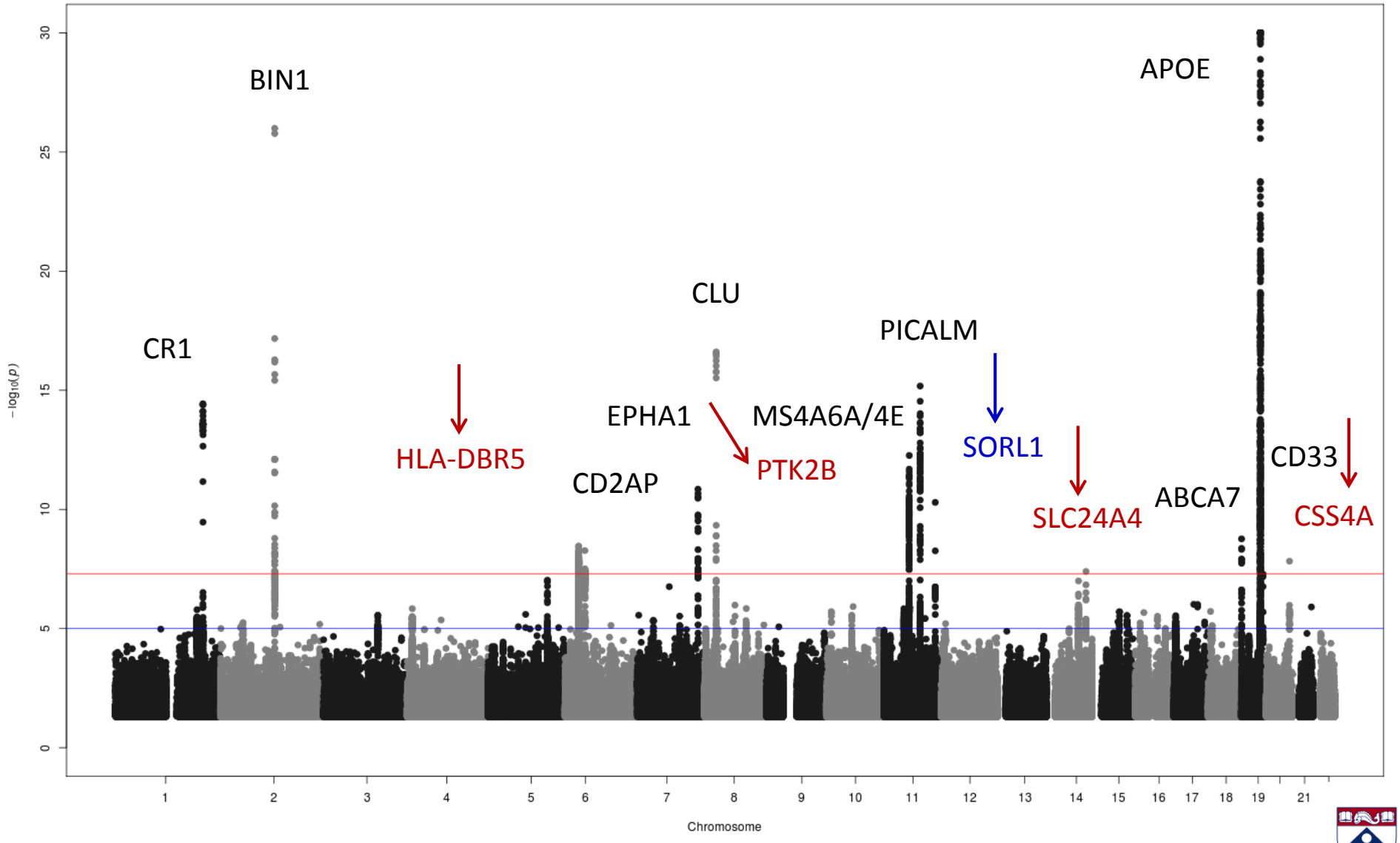
Genome-wide association studies

- Large sample
- Genotype variants covering the entire genome (~$100/subject)
- Impute additional genotypes
- Association analysis
- Correct for: population substructure
  age, sex, *etc.*
  different studies
  different genotyping platforms
- P value < 5×10^{-8}

Alzheimer's Disease Genetics Consortium

Cohort	Cases	Controls
ACT	532	1,571
ADC1	1,549	512
ADC2	727	156
ADC3	894	586
ADC4	304	377
ADC5	286	505
ADC6	213	338
ADNI	268	173
BIOCARD	6	112
CHAP	27	144
EAS	9	141
GSK	666	712
LOAD	1,798	1,568
MAYO	658	1,046
MIRAGE	491	738
MTV	256	189
NBB	80	48
OHSU	132	153
PFIZER	696	762
RMAYO	13	233
ROSMAP	295	769
ROSMAP2	59	217
TARC1	323	181
TGEN2	668	365
UKS	596	170
UMVUMSSM	1,177	1,126
UPITT	1,255	829
WASHU	339	187
WASHU2	38	94
WHICAP	73	560
Totals	14,428	14,562

ADCs
3,973 cases
2,474 controls


BIN1
APOE
CR1
CLU
PICALM
HLA-DBR5
EPHA1
MS4A6A/4E
SORL1
CD33
PTK2B
CD2AP
SLC24A4
ABCA7
CSS4A
−log10(p)
Chromosome

Gene	phenotype	P-value
APOE	multiple features	
GalNAc transferase 7 (GalNAc)	neuritic plaques	6.0×10^{-9}
ATP-Binding Cassette, Sub-Family G (ABCG1)	neuritic plaques	8.0×10^{-9}
Intergenic - chromosome 9	neuritic plaques	4.3×10^{-8}

Neuritic plagues

Braak stage (neurofibrillay tangles)

Lewy body disease

cerebral amyloid angiopathy (CAA)

hippocampal sclerosis of the elderly

vascular brain injury

Closest gene	IGAP	Primary	Complete
CR1	1.18	1.16	1.00
Bin1	1.22	**1.39**	**1.36**
CD2AP	1.22	1.10	1.08
EPH1HA1	1.11	**1.14**	**1.12**
CLU	1.16	**1.18**	**1.19**
MS4A	1.11	**1.25**	**1.18**
PICALM	1.15	**1.25**	**1.27**
ABCA7	1.15	**1.24**	**1.32**
HLA	1.11	1.04	1.08
PTK2B	1.10	1.13	1.09
SORL1	1.30	**1.47**	**1.35**
SLC4A4	1.10	1.08	0.97
INPP59	1.08	1.01	0.98
MEF2C	1.08	**1.23**	**1.23**
NME8	1.08	1.04	1.05
ZCWPW1	1.10	**1.16**	**1.16**
CELF1	1.08	1.03	1.01
FERMT2	1.14	**1.20**	**1.27**
CASS4	1.14	1.37	1.39

Conclusions: neuropathology GWAS

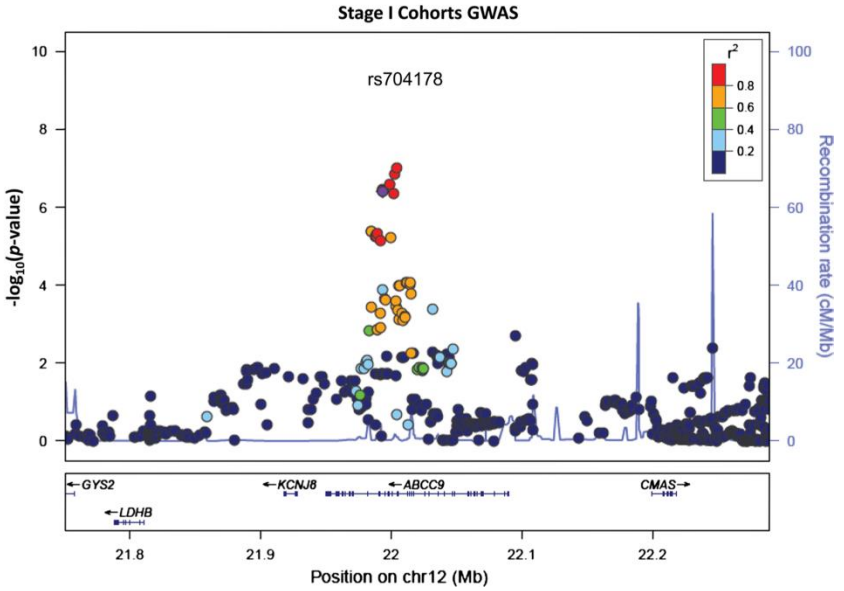
- Neuropathology phenotypes can reveal loci not found in AD-trait studies
- Larger autopsy series are needed
- Quantitative measures of neuropathology traits are needed

Acta Neuropathol (2014) 127:825–843
DOI 10.1007/s00401-014-1282-2

ORIGINAL PAPER

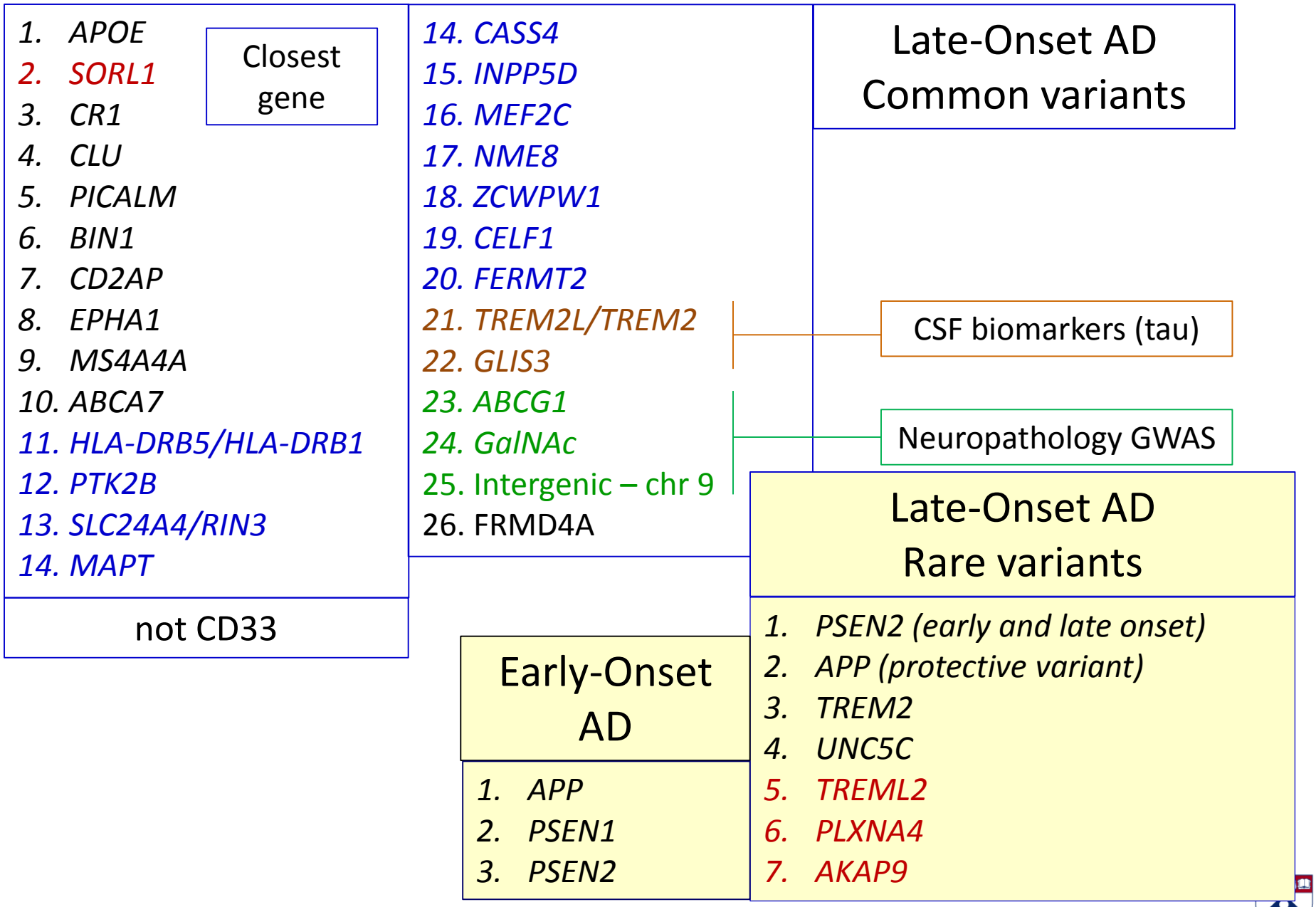
ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology

Peter T. Nelson · Steven Estus · Erin L. Abner · Ishita Parikh · Manasi Malik · Janna H. Neltner · Eseosa Ighodaro · Wang-Xia Wang · Bernard R. Wilfred · Li-San Wang · Walter A. Kukull · Kannabiran Nandakumar · Mark L. Farman · Wayne W. Poon · Maria M. Corrada · Claudia H. Kawas · David H. Cribbs · David A. Bennett · Julie A. Schneider · Eric B. Larson · Paul K. Crane · Otto Valladares · Frederick A. Schmitt · Richard J. Kryscio · Gregory A. Jicha · Charles D. Smith · Stephen W. Scheff · Joshua A. Sonnen · Jonathan L. Haines · Margaret A. Pericak-Vance · Richard Mayeux · Lindsay A. Farrer · Linda J. Van Eldik · Craig Horbinski · Robert C. Green · Marla Gearing · Leonard W. Poon · Patricia L. Kramer · Randall L. Woltjer · Thomas J. Montine · Amanda B. Partch · Alexander J. Rajic · KatieRose Richmire · Sarah E. Monsell · Alzheimer' Disease Genetic Consortium · Gerard D. Schellenberg · David W. Fardo

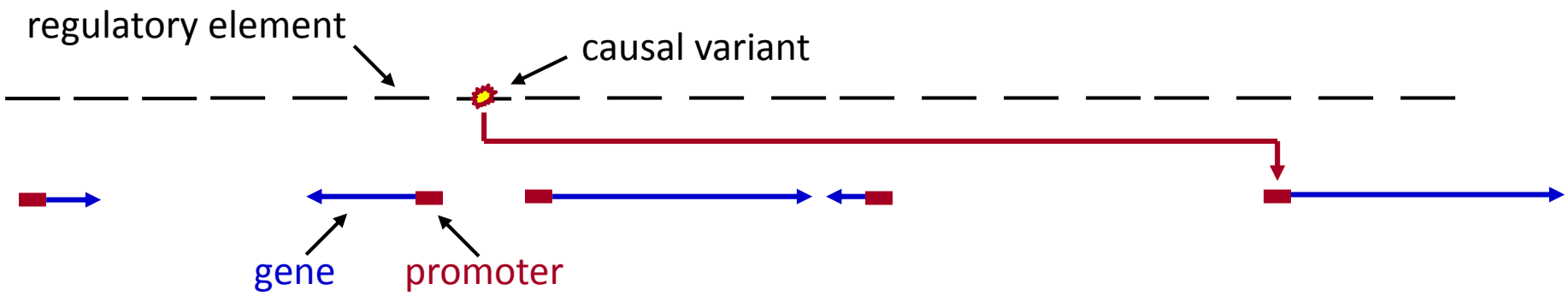


Model	OR (95%CI)	p-value
Additive	1.62 (1.37-1.92)	2.3×10^{-8}
Recessive	2.13 (1.67-2.73)	1.4×10^{-9}

No signal at: *APOE*
GRN
TMEM106B


1. APOE
2. SORL1
3. CR1
4. CLU
5. PICALM
6. BIN1
7. CD2AP
8. EPHA1
9. MS4A4A
10. ABCA7
11. HLA-DRB5/HLA-DRB1
12. PTK2B
13. SLC24A4/RIN3
14. MAPT
Closest gene
not CD33
14. CASS4
15. INPP5D
16. MEF2C
17. NME8
18. ZCWPW1
19. CELF1
20. FERMT2
21. TREM2L/TREM2
22. GLIS3
23. ABCG1
24. GalNAc
25. Intergenic – chr 9
26. FRMD4A
Late-Onset AD
Common variants
CSF biomarkers (tau)
Neuropathology GWAS
Late-Onset AD
Rare variants
1. PSEN2 (early and late onset)
2. APP (protective variant)
3. TREM2
4. UNC5C
5. TREML2
6. PLXNA4
7. AKAP9
Early-Onset
AD
1. APP
2. PSEN1
3. PSEN2

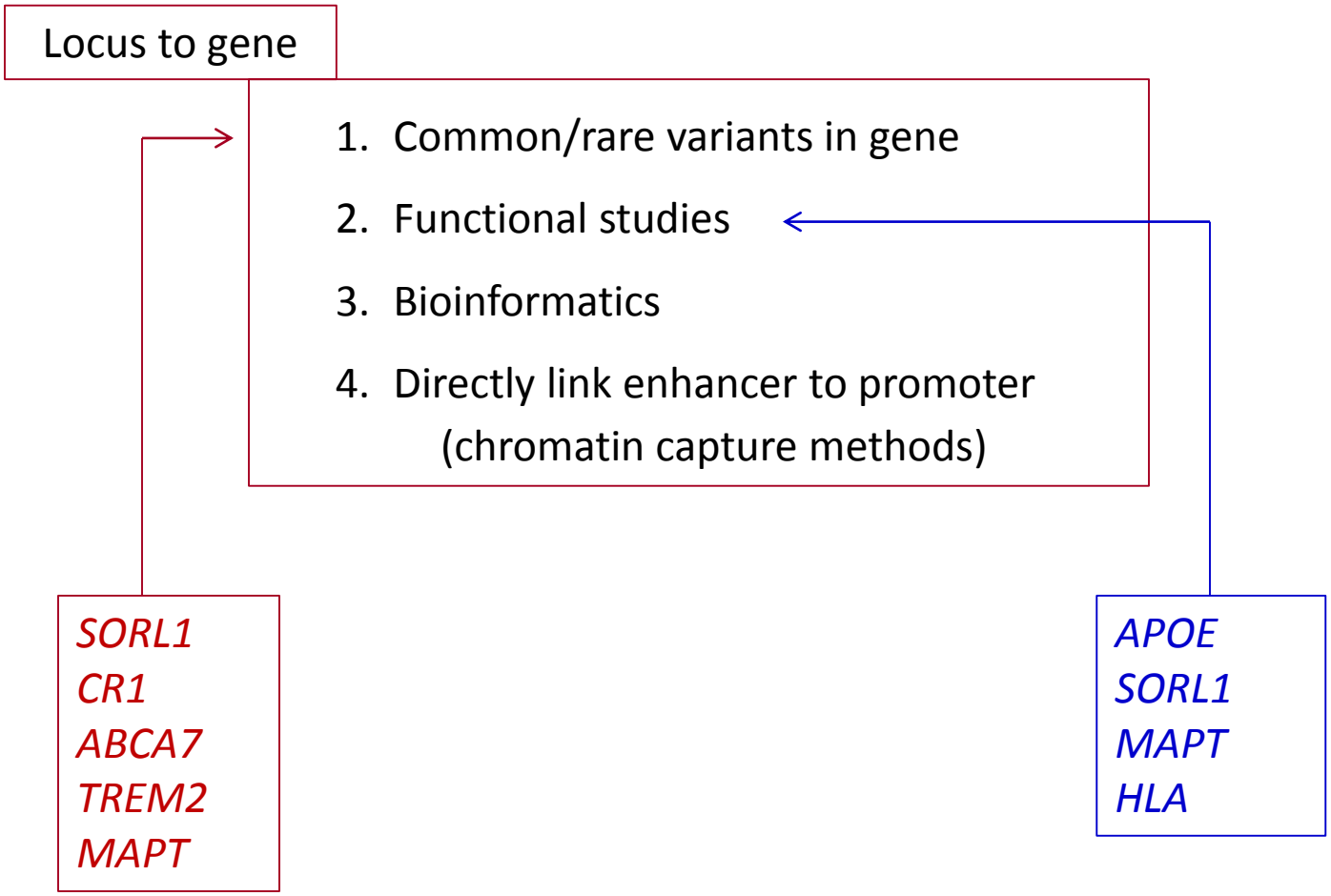
GWAS signals: 90-95% of causative variants are in non-promoter regulatory elements



1. Only 20% of regulatory elements affect the closest gene

2. Mean distance between regulatory elements and gene target is 120 kb

GWAS signal → AD gene?



APP/Aβ metabolism

APP, PSEN1, PSEN2

Cholesterol metabolism

APOE, CLU, ABCA7

Innate immune response

MS4A, CR1, HLA, TREM2, ABCA7

Synaptic dysfunction/membrane function

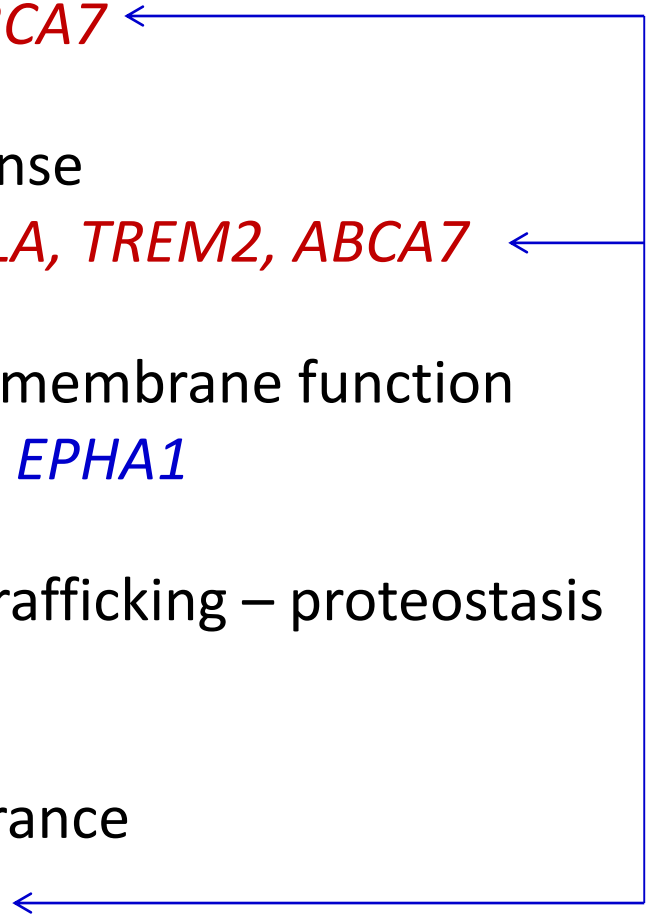
PICALM, BIN1, EPHA1

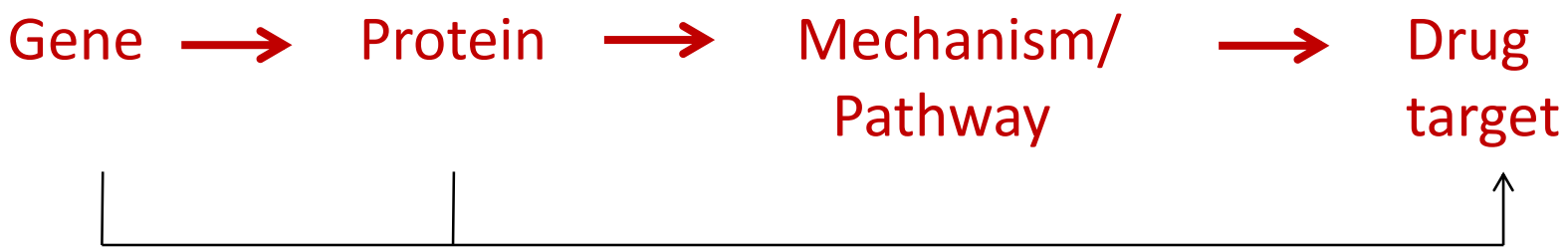
Intracellular protein trafficking – proteostasis

SORL1

Phagocytosis/Aβ clearance

ABCA7, APOE





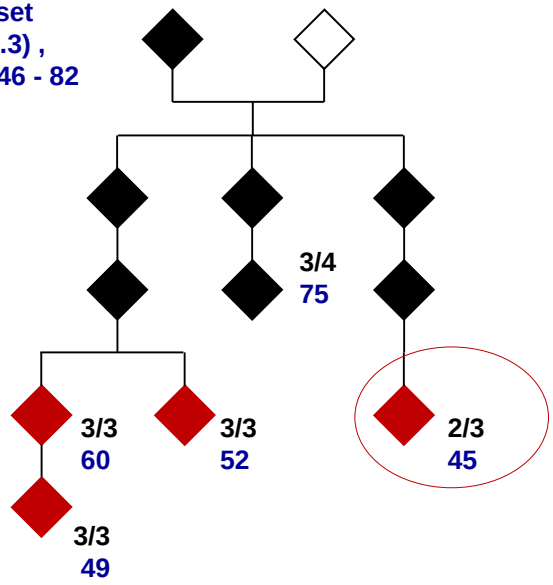
GWAS loci that are drug targets

Target	Disorder	Drug
HMG co-A reductase	**Heart disease**	**statins**
NPC1L1	Heart disease	Zetia (ezetimibe)
PCSK9	Heart disease	monoclonal antibody
VCAM1	MS	natalizumab
IL2RA	MS	daclizumab
TNF-α	RA	infliximab

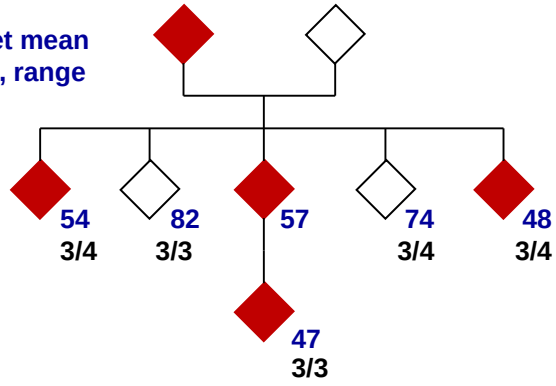
Rare Variants and late-onset AD

$^{N}141^{I}$ Presenilin 2 mutation
Volga Germans

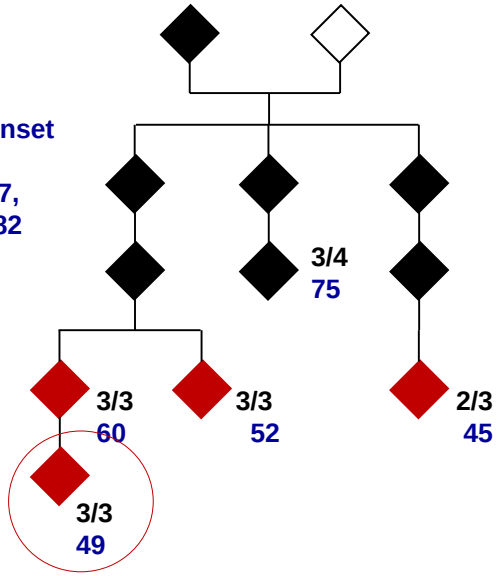
HD Family, onset mean = 59.6 (10.3) , n = 17, range = 46 - 82



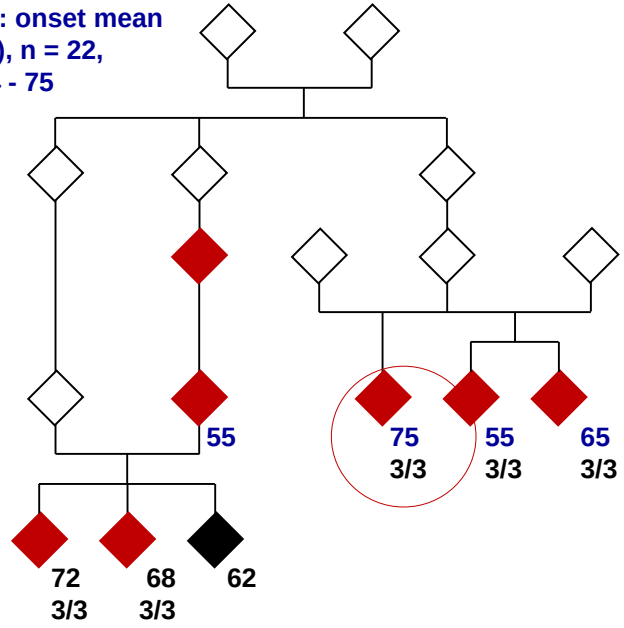
W Family: onset mean = 52.8 (4.5) n = 5, range = 47 - 58



HD Family: onset mean = 59.6 (10.3), n = 17, range = 46 - 82



HB Family: onset mean = 60.8 (7.1), n = 22, range = 54 - 75



TREM2: triggering receptor expressed on myeloid cells 2

- Whole-genome sequencing
- Whole-exom sequencing

	frequency					
allele	cases (n)		controls (n)		Odds ratio (95% CI)	
R47H	2.0%	(1,091)	0.5%	(1,105)	4.5	(1.7 – 11.9)
R47H			0.63%	(110,050)	2.26	(1.71 – 2.98)
R47H			0.12% - 0.19	(9,727)	2.83	(1.45 – 5.40)

Guerreiro et al. (2013) NEJM 368, 11
Jonsson et al. (2013) NEJM 368, 107

Neuron
Article

GWAS of Cerebrospinal Fluid Tau Levels Identifies Risk Variants for Alzheimer's Disease

Carlos Cruchaga,[1,7,25] John S.K. Kauwe,[8,25] Oscar Harari,[1] Sheng Chih Jin,[1] Yefei Cai,[1] Celeste M. Karch,[1] Bruno A. Benitez,[1] Amanda T. Jeng,[1] Tara Skorupa,[1] David Carrell,[1] Sarah Bertelsen,[1] Matthew Bailey,[8] David McKean,[8] Joshua M. Shulman,[9] Philip L. De Jager,[10,11,12] Lori Chibnik,[10,11,12] David A. Bennett,[13] Steve E. Arnold,[14] Denise Harold,[15] Rebecca Sims,[15] Amy Gerrish,[15] Julie Williams,[15] Vivianna M. Van Deerlin,[16] Virginia M.-Y. Lee,[16] Leslie M. Shaw,[16] John Q. Trojanowski,[16] Jonathan L. Haines,[17] Richard Mayeux,[18] Margaret A. Pericak-Vance,[19] Lindsay A. Farrer,[20] Gerard D. Schellenberg,[21] Elaine R. Peskind,[22,23] Douglas Galasko,[24] Anne M. Fagan,[2,6,7] David M. Holtzman,[2,5,6,7] John C. Morris,[2,3,6] GERAD Consortium, Alzheimer's Disease Neuroimaging Initiative (ADNI),[26] Alzheimer Disease Genetic Consortium (ADGC), and Alison M. Goate[1,2,4,6,7,*]
[1]Department of Psychiatry

SUMMARY

Cerebrospinal fluid (CSF) tau, tau phosphorylated at threonine 181 (ptau), and $A\beta_{42}$ are established biomarkers for Alzheimer's disease (AD) and have been used as quantitative traits for genetic analyses. We performed the largest genome-wide association study for cerebrospinal fluid (CSF) tau/ptau levels published to date (n = 1,269), identifying three genome-wide significant loci for CSF tau and ptau: rs9877502 ($p = 4.89 \times 10^{-9}$ for tau) located at 3q28 between *GEMC1* and *OSTN*, rs514716 ($p = 1.07 \times 10^{-8}$ and $p = 3.22 \times 10^{-9}$ for tau and ptau, respectively), located at 9p24.2 within *GLIS3* and rs6922617 ($p = 3.58 \times 10^{-8}$ for CSF ptau) at 6p21.1 within the *TREM* gene cluster, a region recently reported to harbor rare variants that increase AD risk. In independent data sets, rs9877502 showed a strong association with risk for AD, tangle pathology, and global cognitive decline ($p = 2.67 \times 10^{-4}$, 0.039, 4.86×10^{-5}, respectively) illustrating how this endophenotype-based approach can be used to identify new AD risk loci.

Source	# subjects
Washington University	501
ADNI	394
University of Washington	323
University of Pennsylvania	51

687 cognitively normal controls
591 AD cases
1,278 total

CSF markers
Tau
Ptau
$A\beta_{42}$

CSF tau/P-tau

Chr	Closest Gene	tau	ptau
19	*TOMM40*	**4.28×10^{-16}**	5.81×10^{-16}
3	*SNAR-I*	**4.98×10^{-9}**	1.68×10^{-7}
9	*GLIS3*	**1.07×10^{-8}**	**3.22×10^{-9}**
6	*NCR2*/TREML2	2.55×10^{-5}	**3.58×10^{-8}**

IGAP GWAS

$5 \times 10^{-8} < P < 1 \times 10^{-6}$

Closest gene	MAF	OR (95% CI)	P value
None	0.169	1.09 (1.05-1.13)	3.4×10^{-7}
HS3ST1	0.300	1.08 (1.05-1.11)	6.6×10^{-8}
SQSTM1	0.016	1.35 (1.20-1.52)	7.4×10^{-7}
→ ***TREML2***	**0.297**	**0.93 (0.91-0.96)**	**6.3×10^{-7}**
NDUFAF6	0.469	1.07 (1.04-1.10)	8.0×10^{-8}

TREM2

African Americans:	1,970 AD cases
	3,932 controls

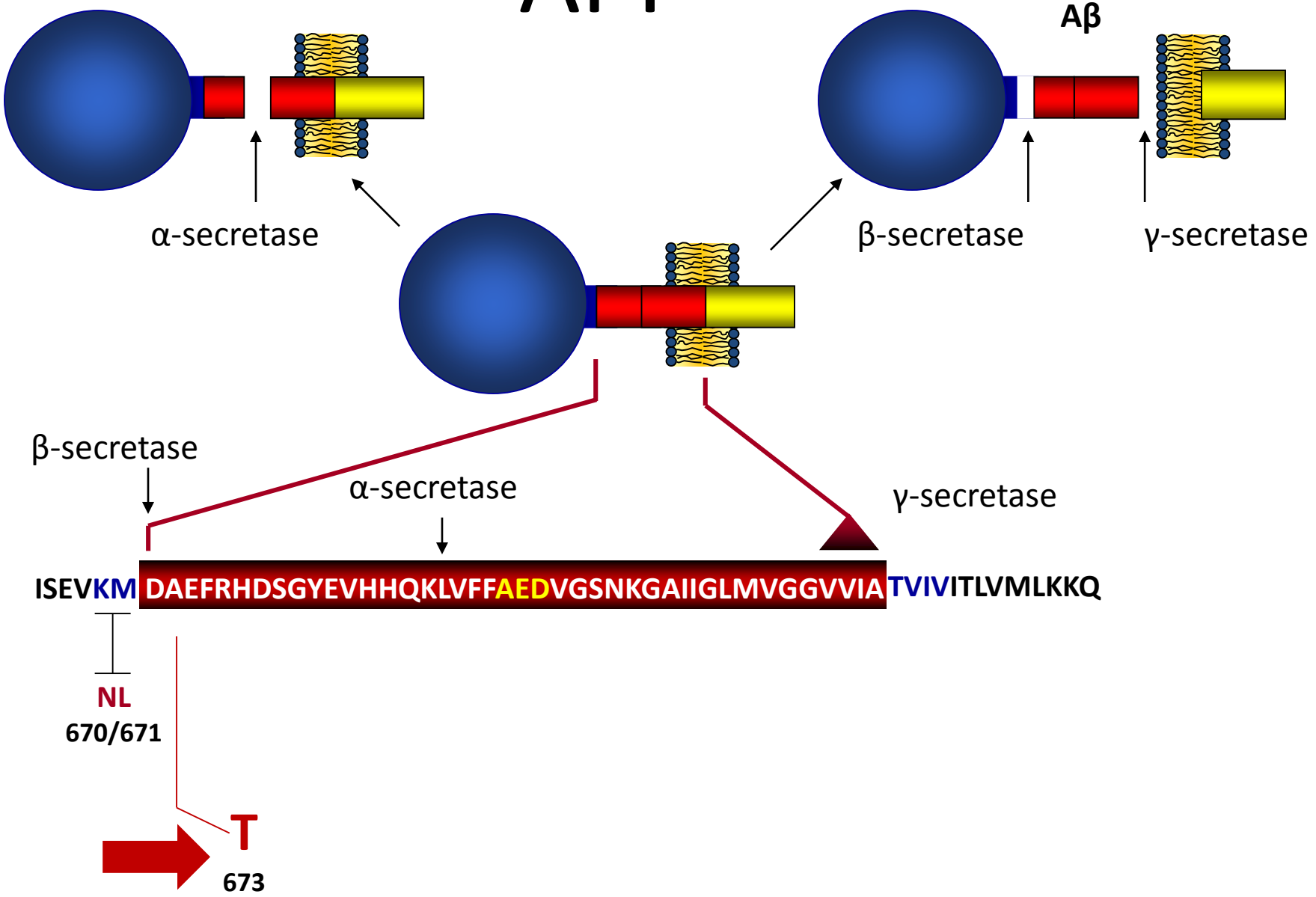
Top SNP: rs7748513

- A allele: p = 0.001, OR = 0.86±0.05 (1.16)
- In strong LD (D' = 0.99) with rs75932628 - $^{R}47^{H}$

Group	MAF frequency
African Americans	0.43
European Caucasians	< 0.05

Christiane Reitz, MD PhD, Richard Mayeux, MD MSc for the ADGC
New Eng. J. Med. 369:1564-1570

APP


Aβ
α-secretase
β-secretase
γ-secretase
β-secretase
α-secretase
γ-secretase
ISEVKM DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA TVIVITLVMLKKQ
NL
670/671
T
673

LETTER

doi:10.1038/nature11283

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

Thorlakur Jonsson[1], Jasvinder K. Atwal[2], Stacy Steinberg[1], Jon Snaedal[3], Palmi V. Jonsson[3,8], Sigurbjorn Bjornsson[3], Hreinn Stefansson[1], Patrick Sulem[1], Daniel Gudbjartsson[1], Janice Maloney[2], Kwame Hoyte[2], Amy Gustafson[2], Yichin Liu[2], Yanmei Lu[2], Tushar Bhangale[2], Robert R. Graham[2], Johanna Huttenlocher[1,4], Gyda Bjornsdottir[1], Ole A. Andreassen[5], Erik G. Jönsson[6], Aarno Palotie[7], Timothy W. Behrens[2], Olafur T. Magnusson[1], Augustine Kong[1], Unnur Thorsteinsdottir[1,8], Ryan J. Watts[2] & Kari Stefansson[1,8]

Group	Frequency	N Chip	N *in silico*
AD	0.13%	2,199	849
controls	0.45%	57,174	22,074

1/OR = 4.24

P = 4.2 X 10^{-5}

	n	frequency	n	*APOE*
Alzheimer's disease	9,091	0.011%	1	3/3
Elderly controls	11,361	0.009%	1	3/3
			1	3/4
Total	20,452			

Onset 89 years

Born in Iceland, 83 years old

77 years old

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AD	0.13%	2,199	849
controls	0.45%	57,174	22,074

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Total	20,452			

Onset 89 years

Born in Iceland, 83 years old

77 years old

	cohort 1	cohort 2	carriers
Alzheimer's disease	298 (0)	564 (0)	0
Elderly controls	220 (0)	487 (3)	3
Totals	518	1,051	3

Rare-variants can be very population-specific

Swedish Cohorts 1 + 2:	0.19%
Swedish cohorts, Jonsson *et al*:	0.42%

AD Genetics in other populations

African Americans – GWAS
1,968 case
3,982 controls

Japanese/Korean – GWAS
2,232 cases
1,542 controls

Ancestry influences effect size, importance

African Americans	*ABCA7*	OR = **1.79 (CI, 1.47 – 2.12)**, P = 2.21 x 10^{-9}
Caucasians	*ABCA7*	OR = **1.11 (CI, 1.11 – 1.19)**, P = 1.06 x 10^{-15}
Asians	*SORL1*	Minor allele frequency = **0.23 – 0.34**
Caucasians	*SORL1*	Minor allele frequency = **0.02 – 0.04**
Combined	*SORL1*	

Reitz *et al.* JAMA 309, 1483 (2013)
Miyashita et al., PLOS One 8, (4) e58618 (

Ancestry influences effect size

Effect size - modest (OR 2.3 – 4.5)

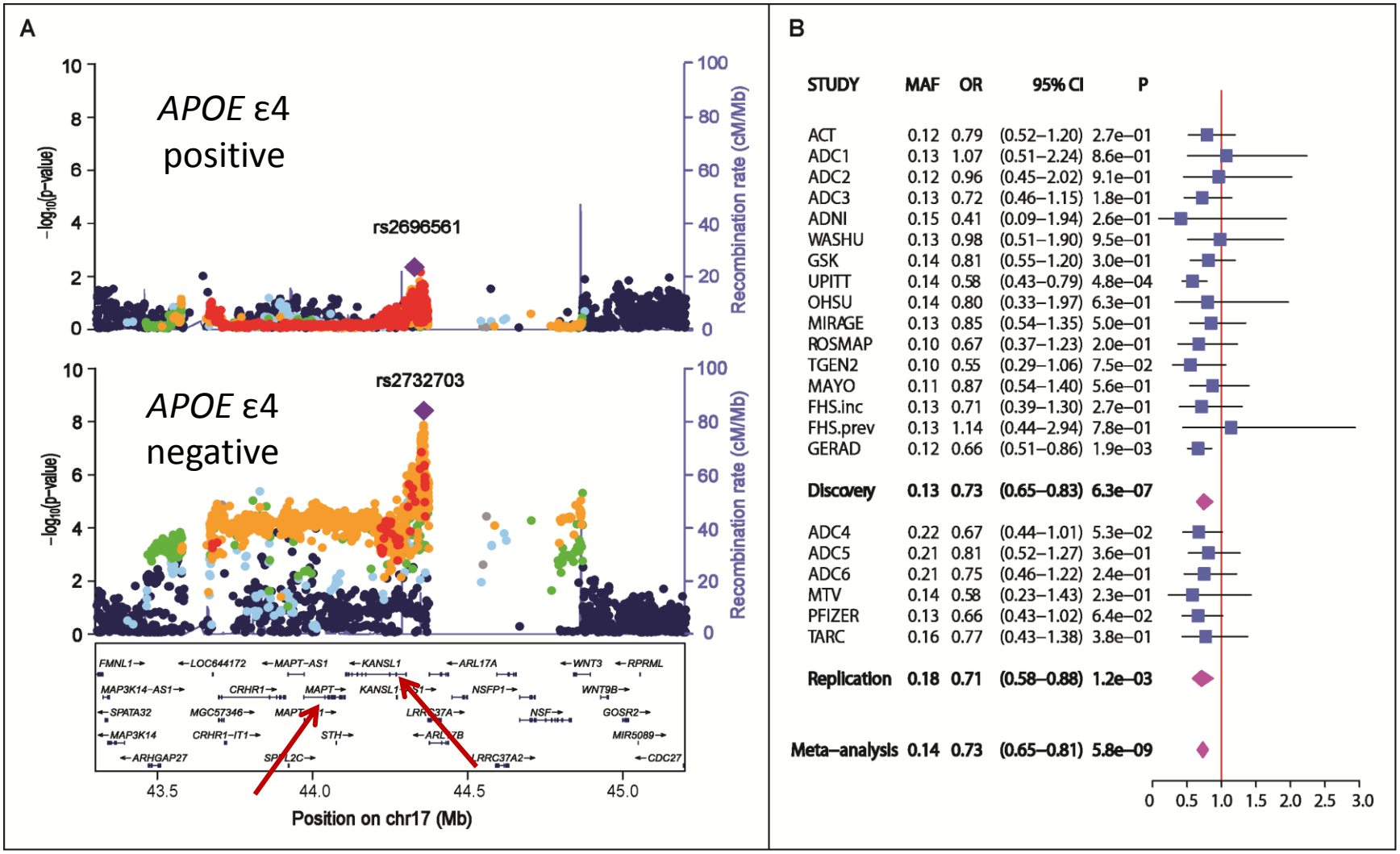
Percent of population at risk – small (~2%)

Can be specific to small populations

Missing heritability?

Gene-Gene interaction: late-onset Alzheimer's disease

- Stratified GWAS: *APOE* ε4+
  APOE ε4-

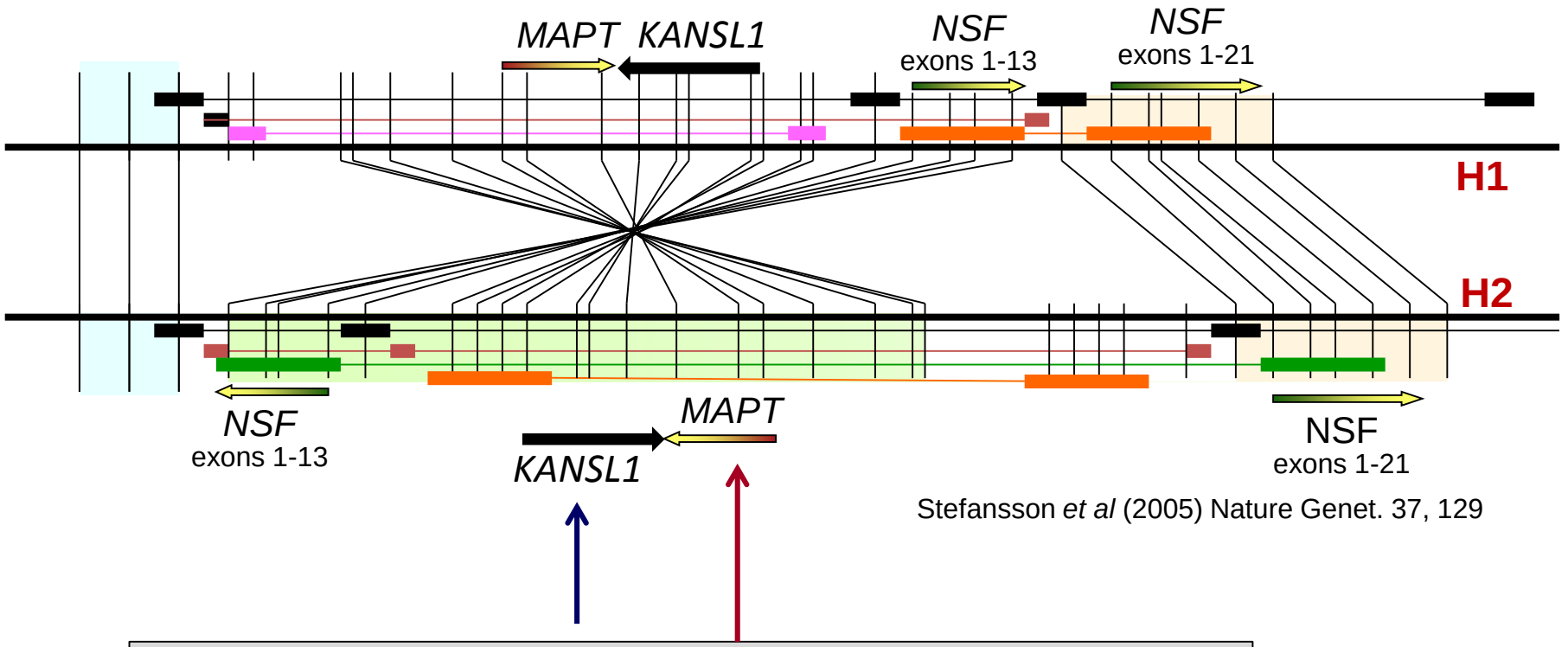


SNP	CH	Closest Gene/Region	Meta-Analysis	
			OR (95% CI)	P
rs2732703	17	KANSL1/LRRC37A	0.73 (0.65-0.81)	5.8×10^{-9}

SNP	CH	Region or Closest Gene	APOE ε4(+)		APOE ε4(-)	
			OR (95% CI)	P	OR (95% CI)	P
rs679515	1	CR1	1.22 (1.14 - 1.30)	3.6×10^{-9}	1.13 (1.07 - 1.19)	1.6×10^{-5}
rs4663105	2	BIN1	1.19 (1.12 - 1.25)	2.5×10^{-9}	1.19 (1.13 - 1.24)	1.8×10^{-12}
rs9331896	8	CLU	0.84 (0.80 - 0.89)	2.8×10^{-9}	0.90 (0.86 - 0.94)	9.6×10^{-6}
rs1582763	11	MS4 region	0.92 (0.87 - 0.97)	0.003	0.87 (0.83 - 0.91)	2.2×10^{-9}

APOE independent pathway for Alzheimer's disease?

SNP	CH	Closest Gene/Region	Replication	Meta-Analysis	
			OR (95% CI)	OR (95% CI)	P
rs2732703	17	KANSL1/LRRC37A	0.71 (0.58-0.88)	0.73 (0.65-0.81)	5.8×10^{-9}



Stefansson *et al* (2005) Nature Genet. 37, 129

MAPT encodes tau – protein in neurofibrillary tangles

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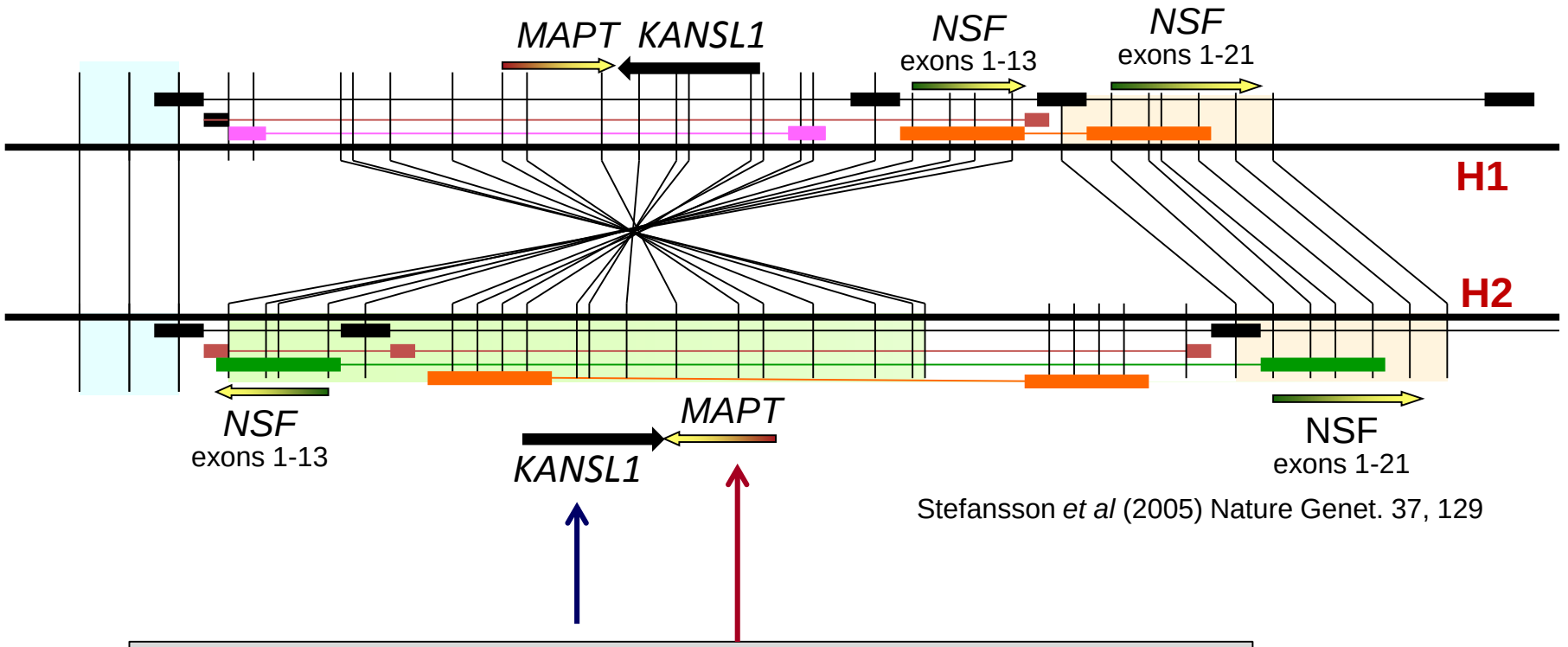
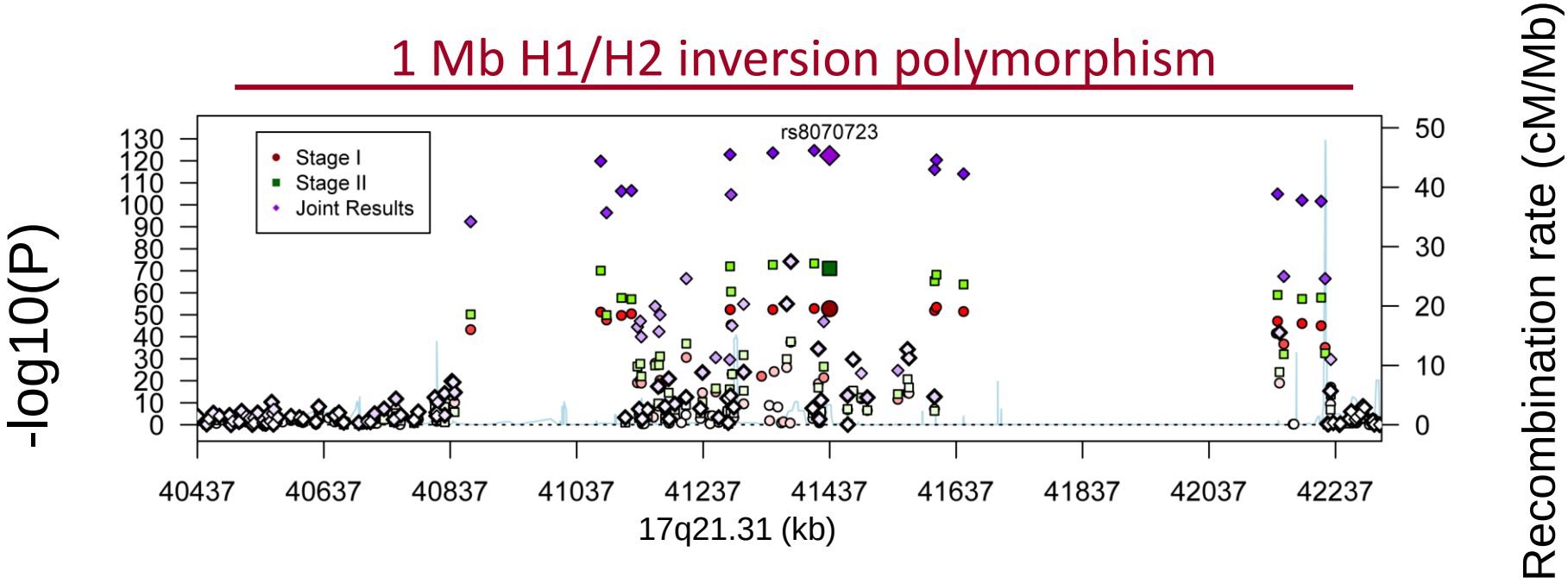


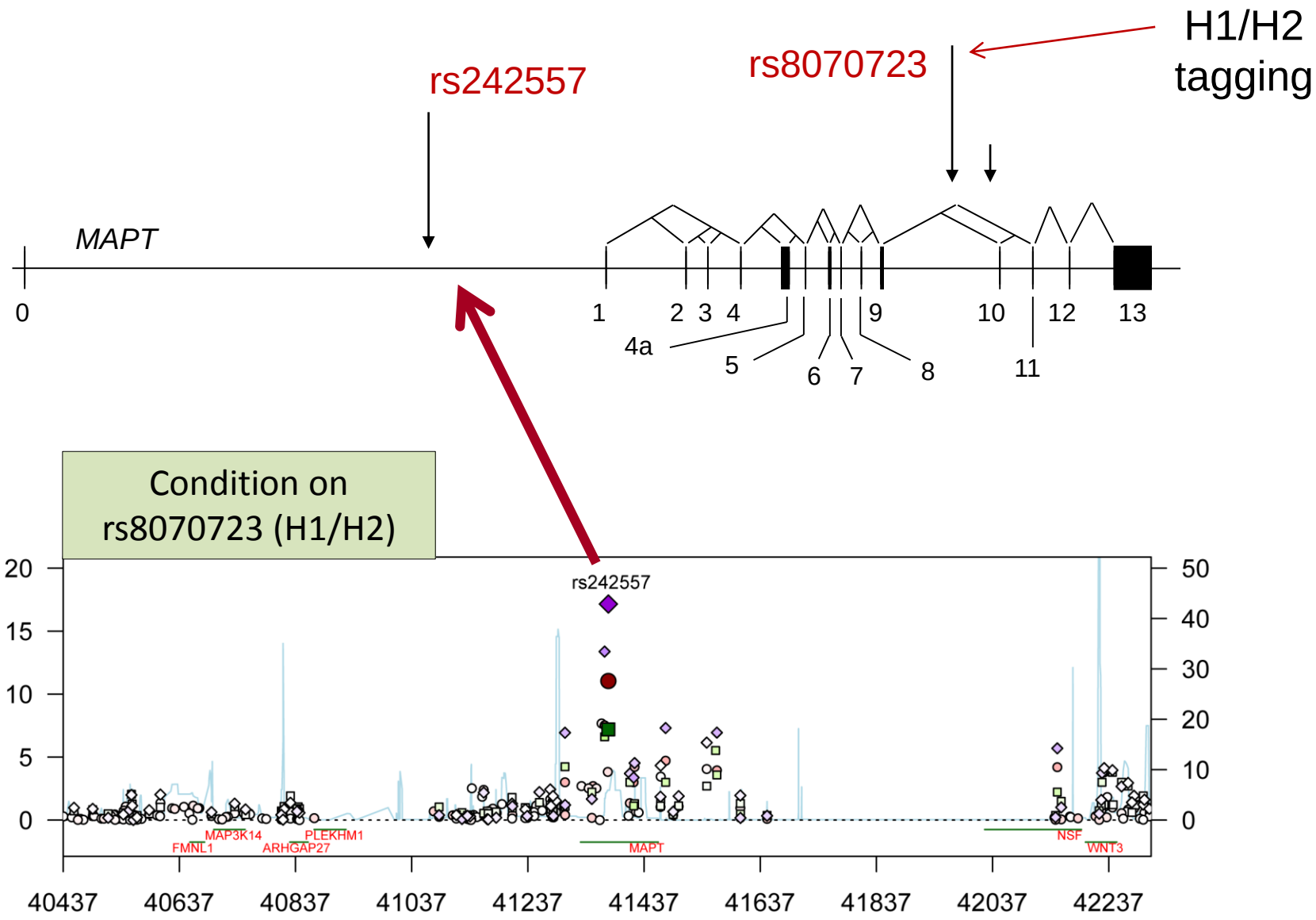
Stefansson *et al* (2005) Nature Genet. 37, 129

MAPT encodes tau – protein in neurofibrillary tangles

PSP GWAS Results

1 Mb H1/H2 inversion polymorphism




rs242557
rs8070723
H1/H2
tagging
MAPT
0
1
2
3
4
4a
5
6
7
8
9
10
11
12
13
Condition on
rs8070723 (H1/H2)
rs242557
20
15
10
5
0
50
40
30
20
10
0
FMNL1
MAP3K14
ARHGAP27
PLEKHM1
MAPT
NSF
WNT3
40437
40637
40837
41037
41237
41437
41637
41837
42037
42237

APOE and *MAPT* Conclusions

- *APOE* risk is entirely due to the ε2/ε3/ε4 variants
- *MAPT* region is an *APOE* e4 independent AD risk locus
- *MS4* region is also an *APOE* independent risk locus
- *APOE* independent pathway → AD?
- Three different signals in the *MAPT* region influence risk for neurodegeneration
- *APOE* modifies the Aβ-presenilin AD pathway

Rare-variant identification and Late-onset Alzheimer's disease:

Large-scale DNA sequencing

Whole exome sequencing

5,000 unrelated cases

- cases with the lowest risk explained by *APOE* and age
- young onset, *APOE* ε2/ε2, ε2/ε3, or ε3/ε3

5,000 unrelated elderly cognitively normal controls

- controls least likely to convert to a case, based on age, *APOE*, and autopsy data
- old, *APOE* ε2/ε2, ε2/ε3, or ε3/ε3 little or no AD neuropathology

1,000 cases from multiplex families – one/family

Whole-genome sequencing

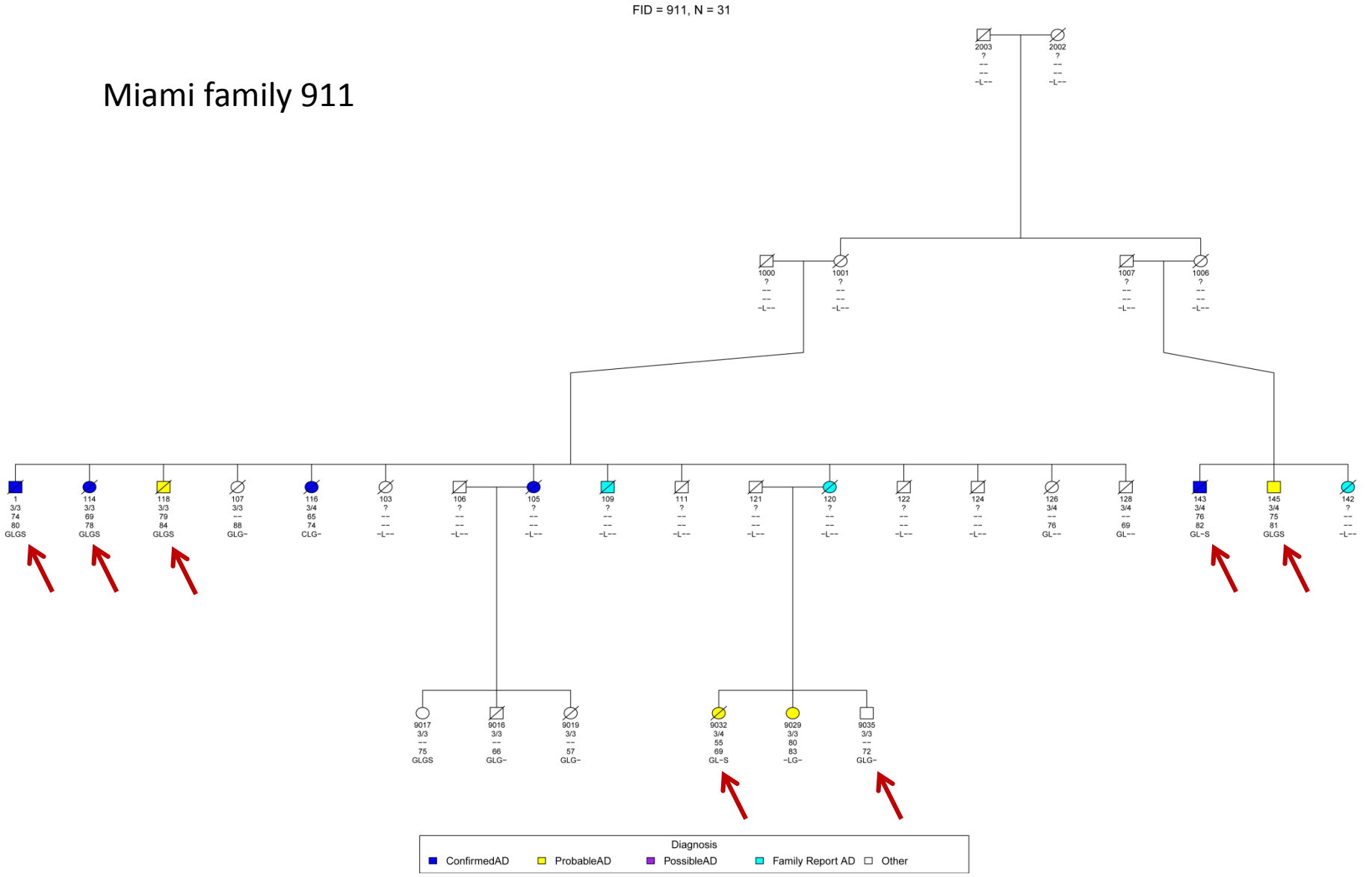
- 585 subjects from 111 multiplex families

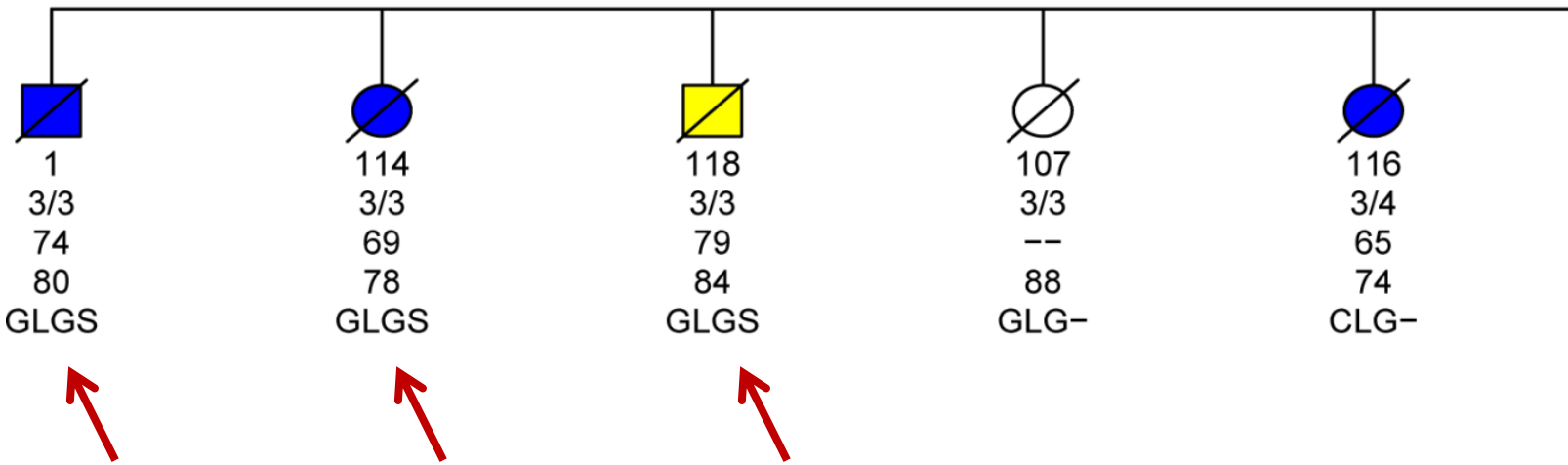
Alzheimer's Disease Sequencing Project (ADSP)

Families	investigator(s)	number of families
NIA-LOAD	Richard Mayeux	18
Caribbean Hispanics	Richard Mayeux	67
NCRAD:	Tatiana Foroud	4
Miami:	Peggy Pericak-Vance	12
Seattle:	Raskind/Schellenberg	7
Vanderbilt:	Jonathan Haines	1
Erasmus:	Cornelia Van Duijn	2
Total:		111

501 cases, 84 unaffected, 583 total

Miami family 911




1
3/3
74
80
GLGS
114
3/3
69
78
GLGS
118
3/3
79
84
GLGS
107
3/3
--
88
GLG-
116
3/4
65
74
CLG-

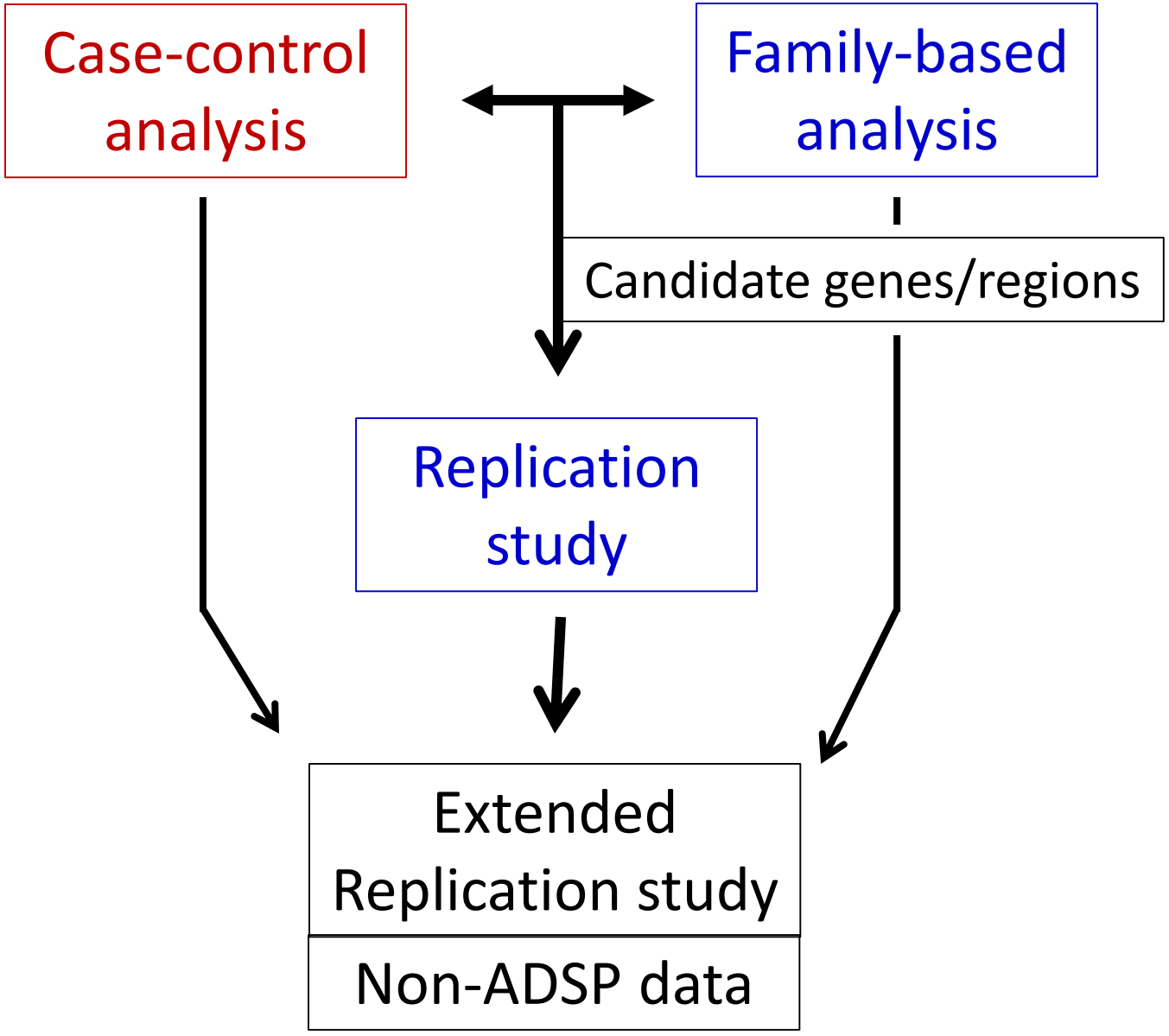
Alzheimer's Disease Sequencing Project (ADSP)

Replication

- 17,000 additional cases
- 17,000 additional controls

- Targeted sequencing
  - exons
  - introns
  - intergenic regions

Selected based on results from WES/WGA


Case-control analysis
Family-based analysis
Candidate genes/regions
Replication study
Extended Replication study
Non-ADSP data

Structural Variants (SVs) Introduction

- Type
  - Insertions
  - Deletions
  - Inversions
  - Translocations
  - Copy number variation (CNV)

- Size
  - Inversely related to frequency
  - 1bp to very large

- SVs - Alzheimer's disease/other neurologic disorders
  - *APP* duplication
  - *SNCA* duplication
  - *PSEN1* indel
  - *PMP22* deletion/duplication
  - *MAPT* inversion/CNVs

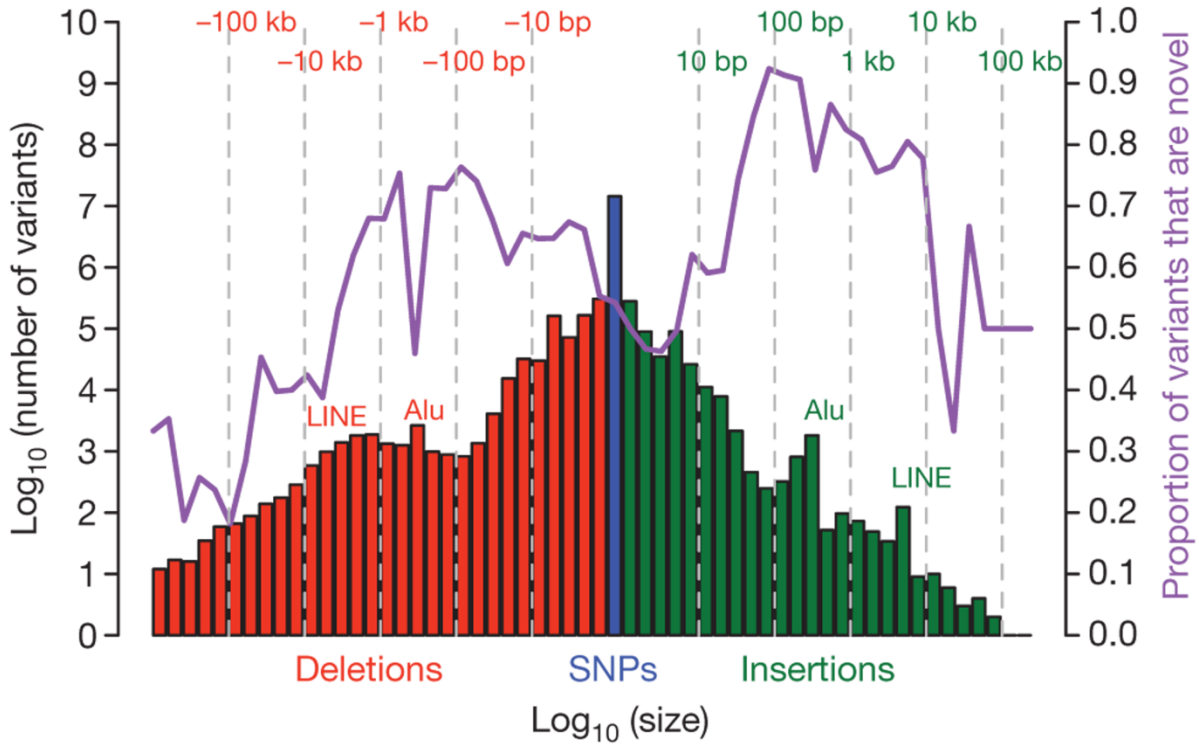
ARTICLE

doi:10.1038/nature09534

A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium*

*Lists of participants and their affiliations appear at the end of the paper.



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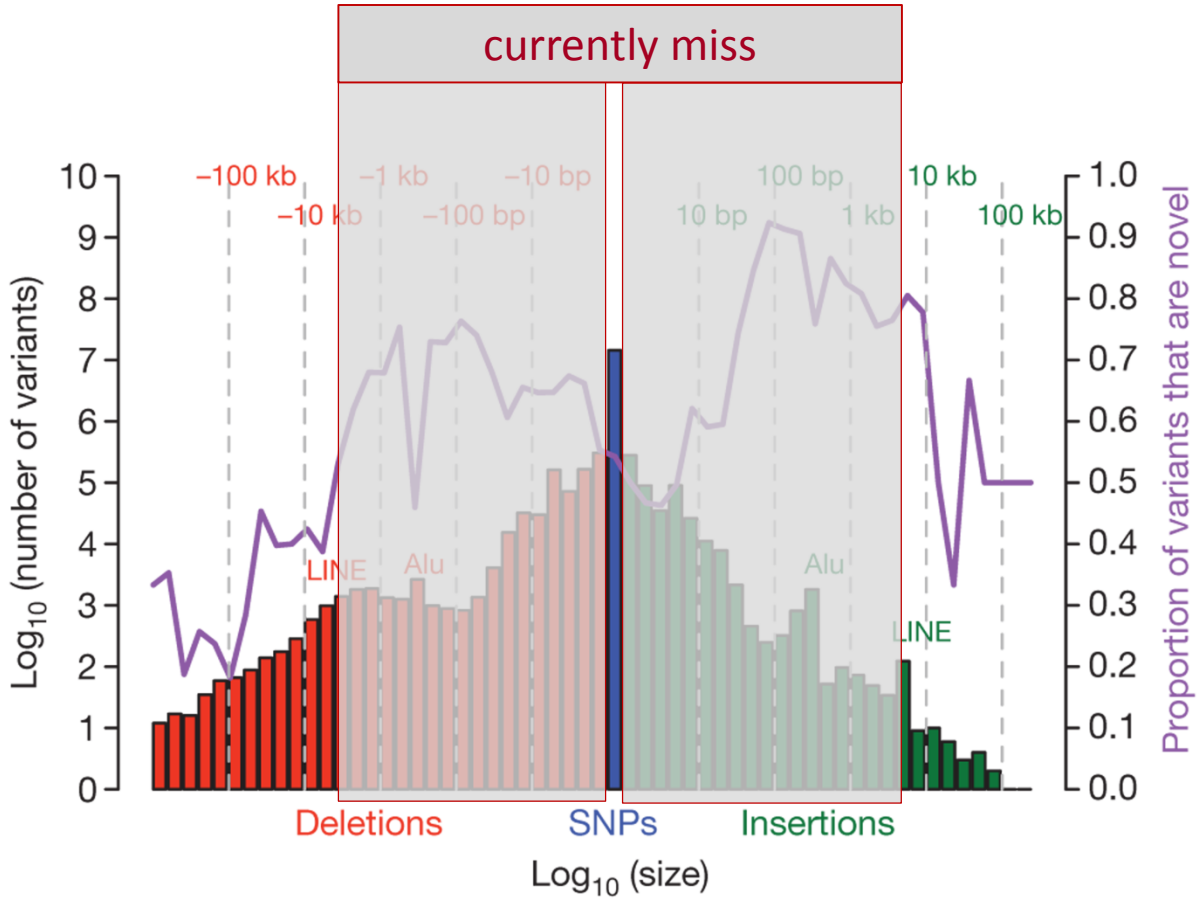
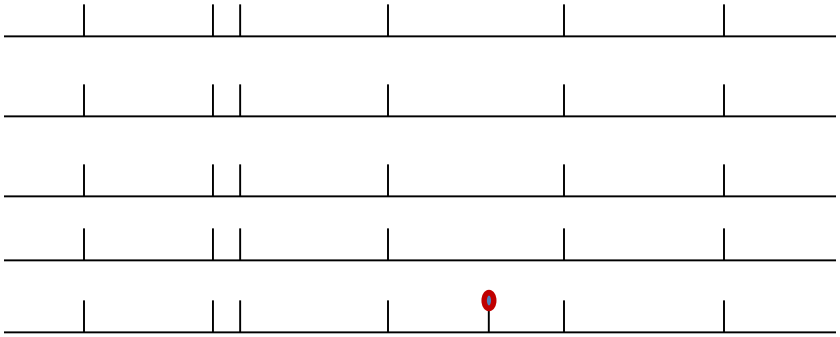
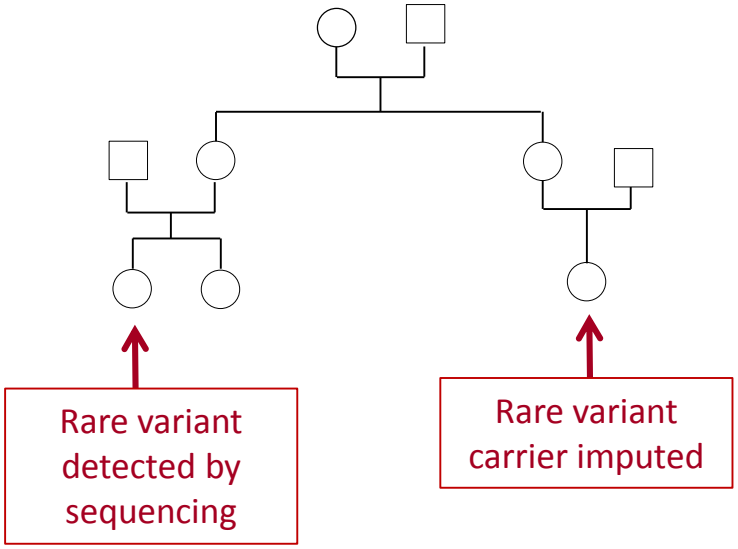
28 OCTOBER 2010 | VOL 467 | NATURE | 1061



Imputation

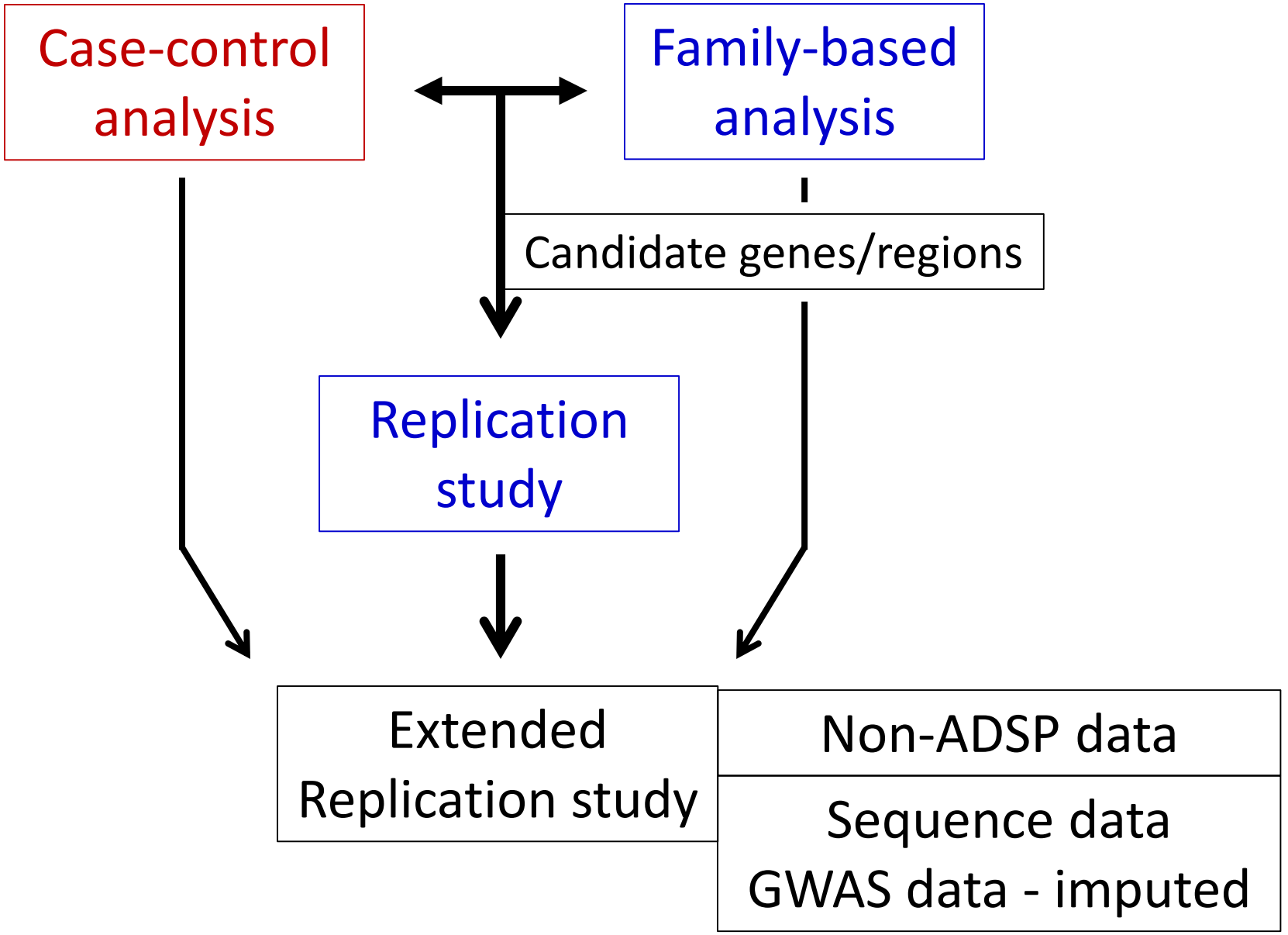


1. Combined data from different genotyping platforms
2. Test variants not directly genotypes: rare-variant GWAS
3. Infer rare variants in family members not sequenced



Reference panels

- HapMap
- 1000 Genomes
- 30,000 Genomes


Case-control analysis
Family-based analysis
Candidate genes/regions
Replication study
Extended Replication study
Non-ADSP data
Sequence data
GWAS data - imputed

Extended Replication Phase

ADGC samples - AD and normal elderly controls with genome-wide SNP array data.

Ethnic group	Cases	Controls	Total
Caucasians	16,522	17,570	34,092
African Americans	2,269	4,495	6,764
Asians	2,246	3,138	5,384
Hispanics	382	317	699
Subtotal from ADCs	6,766	4,415	10,246
Totals - all sources	**21,419**	**25,520**	**46,939**

Extended Replication Phase

Type	Number of families	Number of individuals	Number of affected	Number of unaffected
5+ affected	101	1,216	614	602
4 affected	61	434	205	229
3 affected	103	545	263	282
2 affected	202	709	320	389
Total familial	467	2,904	1,402	1,502
Total sporadic		8,247	2,071	6,176
Familial + sporadic		11,151	3,473	7,678

Summary

- 8 rare- variant genes
- 26 common variant loci
- Ancestry is important
- Additional small-effect size common variants
- Additional modest effect size rare variants
- Structural variation needs to be evaluated

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Gyungah Jun

Case Western

Jonathan Haines
Will Bush

NIA/NIH, Alzheimer's Association

ADSP

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NIA/NHGRI/dbGaP

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Mike Feolo
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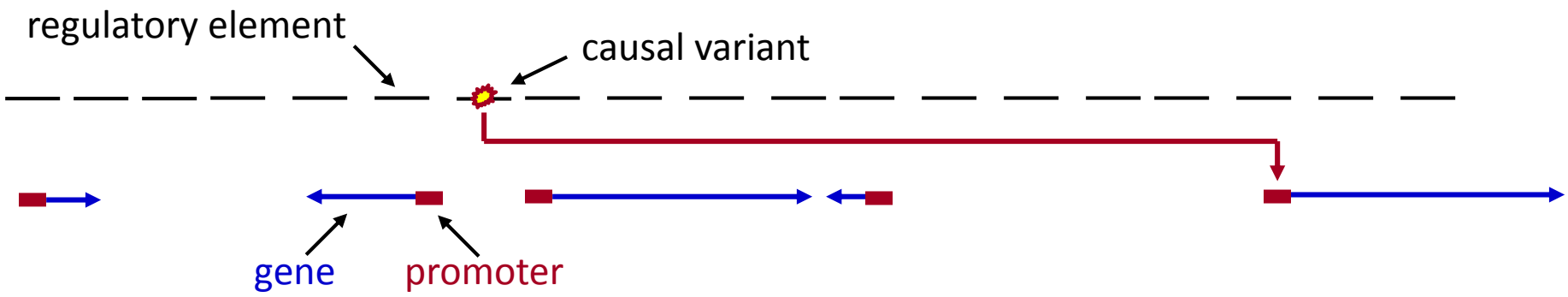
The End

GWAS signals: 90-95% of causative variants are in non-promoter regulatory elements



1. Only 20% of regulatory elements affect the closest gene
2. Mean distance between regulatory elements and gene target is 120 kb
3. Enhancer-promoter pairs can be separated by 1.4Mb (or more?)
4. Multiple enhancers can affect the same gene
5. Enhancers can affect more than one gene
6. Enhancers can be in introns but not regulate the host gene

Cholesterol metabolism

APOE, CLU, ABCA7

Innate immune response

MS4A, CR1, HLA, TREM2, ABCA7

Synaptic dysfunction/membrane function

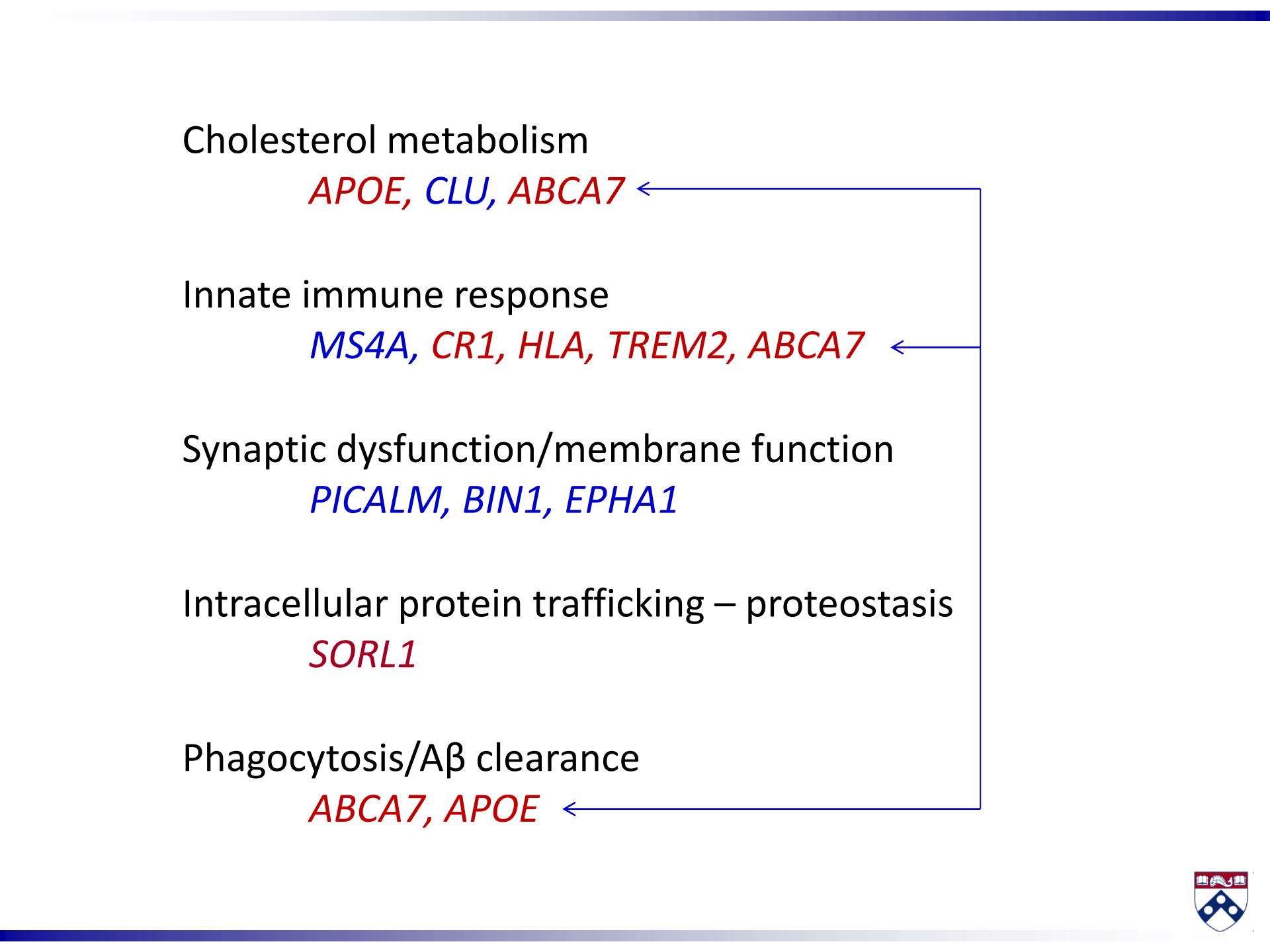
PICALM, BIN1, EPHA1

Intracellular protein trafficking – proteostasis

SORL1

Phagocytosis/Aβ clearance

ABCA7, APOE



Rare Variants

Early-Onset AD Rare variants
1. *APP* 2. *PSEN1* 3. *PSEN2*

Late-Onset AD Rare variants
1. *PSEN2 (early and late onset)* 2. *APP (protective variant)* 3. *TREM2* 4. *UNC5C* 5. *TREML2* 6. *PLXNA4* 7. *AKAP9*

1. *APOE*
2. *SORL1*
3. *CR1*
4. *CLU*
5. *PICALM*
6. *BIN1*
7. *CD2AP*
8. *EPHA1*
9. *MS4A4A*
10. *ABCA7*
11. *HLA-DRB5/HLA-DRB1*
12. *PTK2B*
13. *SLC24A4/RIN3*
14. *MAPT*

Closest gene

not CD33

14. *CASS4*
15. *INPP5D*
16. *MEF2C*
17. *NME8*
18. *ZCWPW1*
19. *CELF1*
20. *FERMT2*
21. *TREM2L/TREM2*
22. *GLIS3*
23. *ABCG1*
24. *GalNAc*
25. Intergenic – chr 9
26. FRMD4A

Late-Onset AD Common variants

APOE

- $P < 5 \times 10^{-8}$
- OR = 1.08 – 1.37, 5.22
- MAF = 3.9% - 49%

Early-Onset AD

1. *APP*
2. *PSEN1*
3. *PSEN2*

Late-Onset AD Rare variants

1. *PSEN2 (early and late onset)*
2. *APP (protective variant)*
3. *TREM2*
4. *UNC5C*
5. *TREML2*
6. *PLXNA4*
7. *AKAP9*

2010 – United States

People with Alzheimer's disease: 5.4 million

Unpaid caregivers: 14.9

Costs to economy: $200 billion/year

($140 billion to Medicare/Medicaid)

2050 – United States

People with Alzheimer's disease: 14.9 million

Costs to economy: $1.1 trillion