Alzheimer's Disease Genetics Consortium

Perelman School of Medicine

University of Pennsylvania

Alzheimer's Disease Genetics Consortium

- Genome-wide association studies – progress
- NIA/NHGRI Alzheimer's Disease Sequencing Project - ADSP

Extended meta-analysis of 74,538 individuals identifies 11 new susceptibility loci for Alzheimer's disease

Submitted, Nature Genetics

Author groups: ADGC, CHARGE, EADI, GERAD

ADGC (2011): 10,273 cases, 10,575 controls

ADCs: 2,512 cases, 1,245 controls

2013 – ADC samples

MDS: 3,774

UDS: 11,614

Total: 15,388

Use of CSF tau and phospho-tau level as endophenotypes for Alzheimer's disease identifies novel candidate variants for disease risk, tangle pathology and global cognitive decline.
Cruchaga et al. Neuron (in press, 2013)

SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians.
Miyashita et al. PloS One (in press, 2013).

Common variants in *ABCA7,* and other genes in the chromosome 19q region around *APOE,* are associated with late-onset Alzheimer's disease in African Americans
Reitz et al. JAMA in press

$25 million dollars of "in kind" sequencing

Alzheimer's Disease Sequencing Project ADSP

Whole exome sequencing

- 6,000 cases
- 5,000 controls

Whole-genome sequencing

- ~ 580 subjects from ~111 multiplex families

Alzheimer's Disease Sequencing Project
ADSP

Multiplex family study: ~ 580 subjects from ~111 multiplex families

Rationale:
1. Families are more likely to have AD variants

2. Can use co-segregation of sequence variants with AD to identify disease-related sequence variants

30X Whole Genome Sequencing

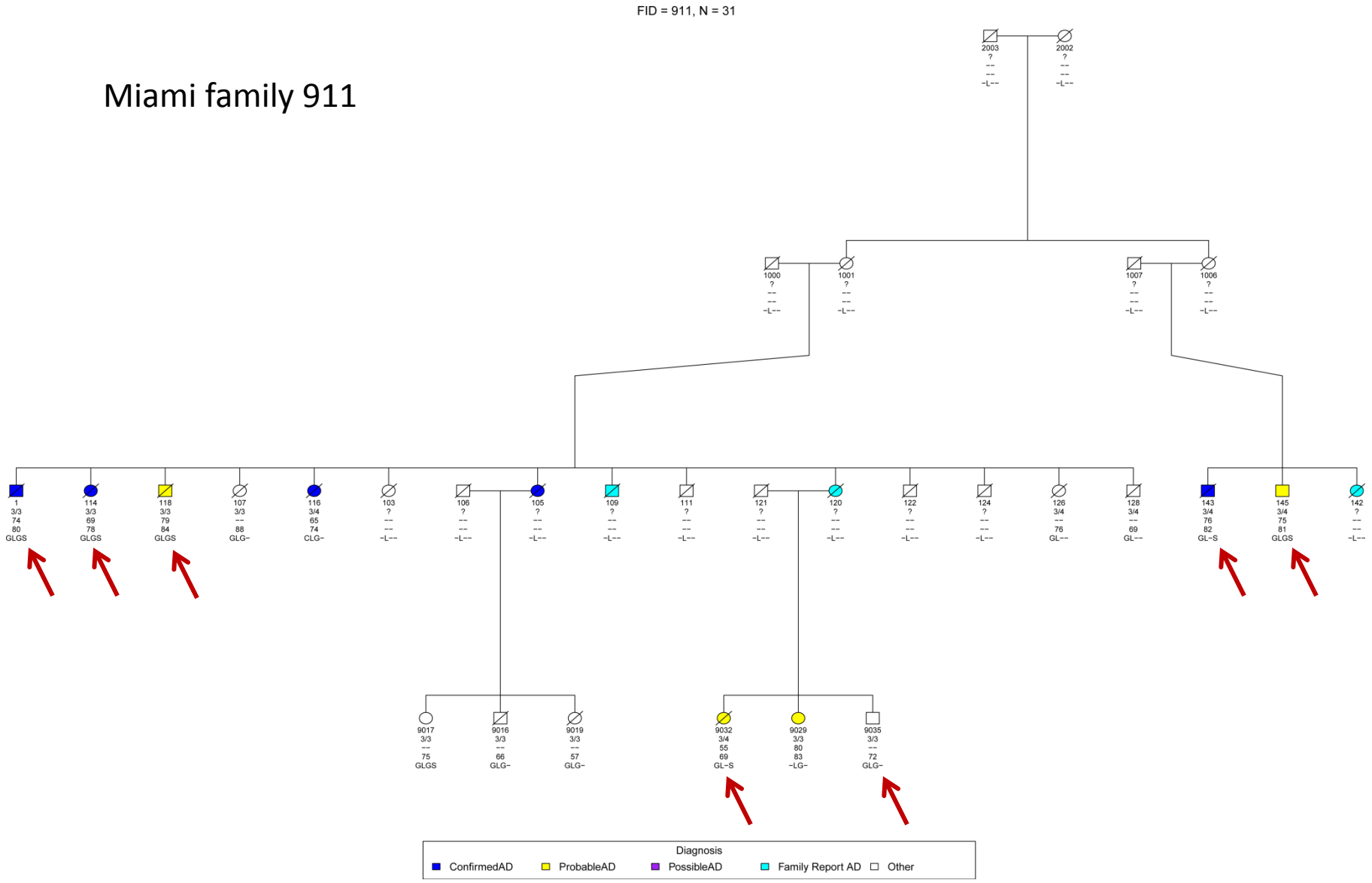
Alzheimer's Disease Sequencing Project
ADSP

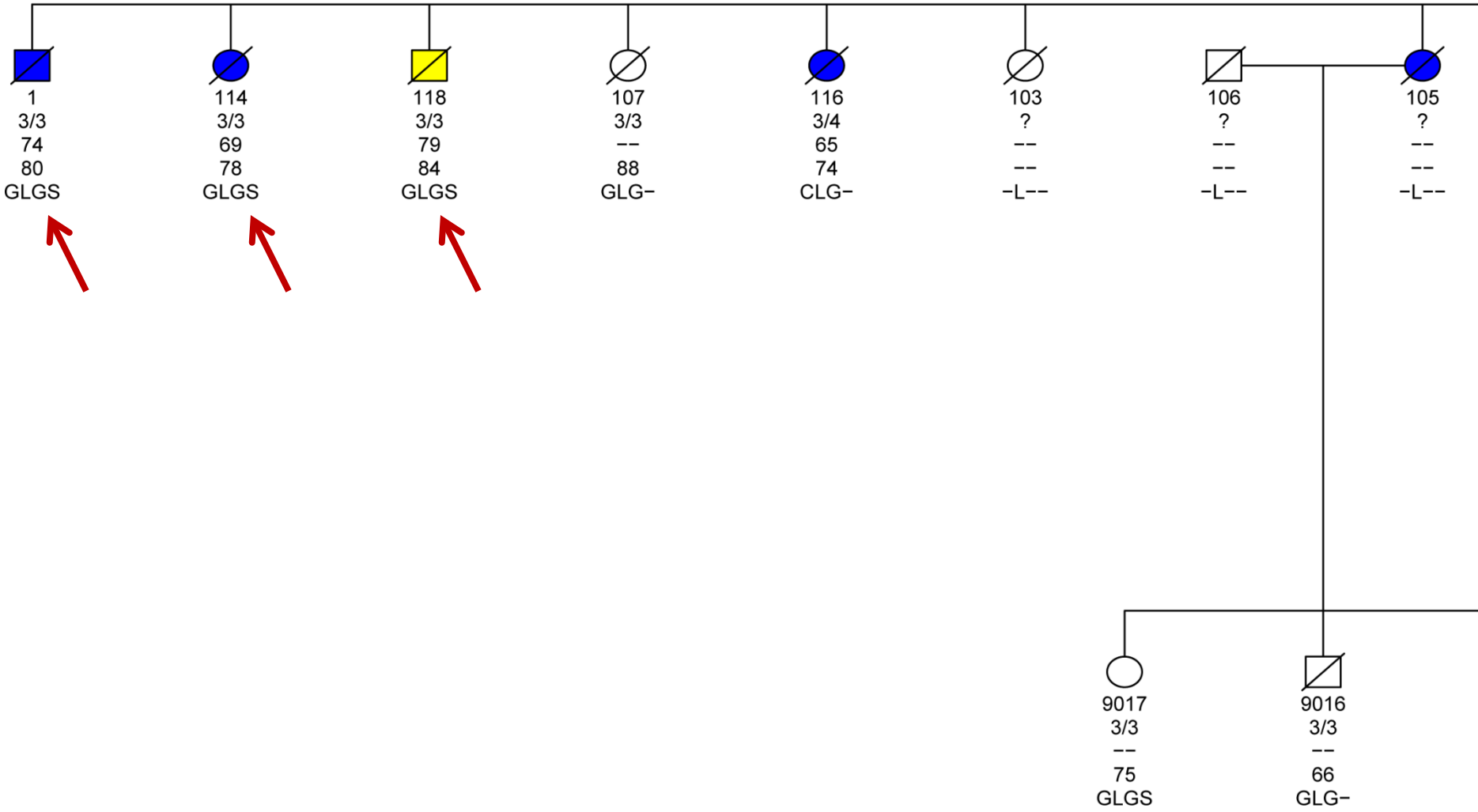
Families

NIA-LOAD:	Richard Mayeux	18
Caribbean Hispanics:	Richard Mayeux	67
NCRAD:	Tatiana Foroud	4
Miami:	Peggy Pericak-Vance	12
Seattle:	Tom Bird	7
Vanderbilt:	Jonathan Haines	1
Erasmus:	Cornelia Van Duijn	2
Total:		111

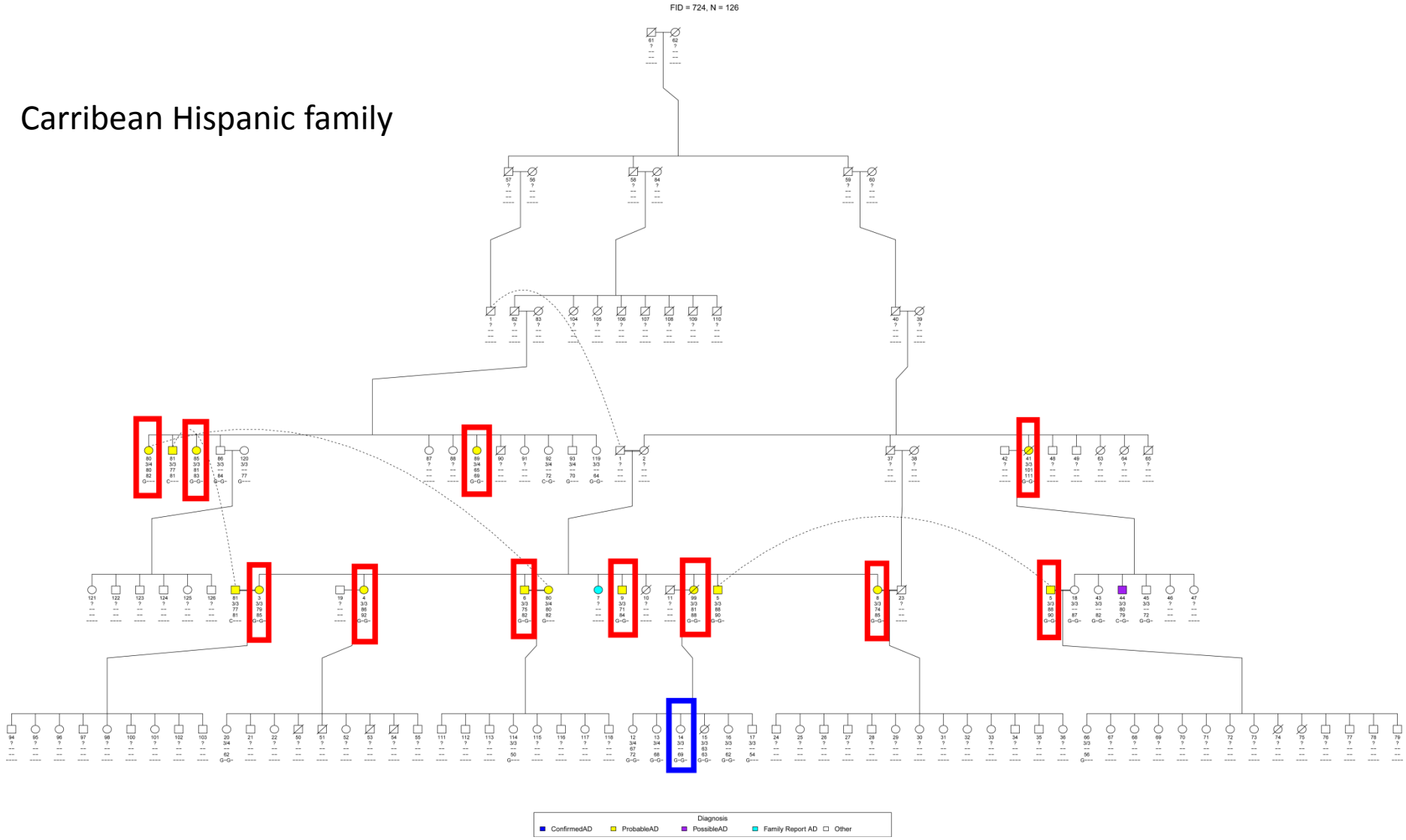
2

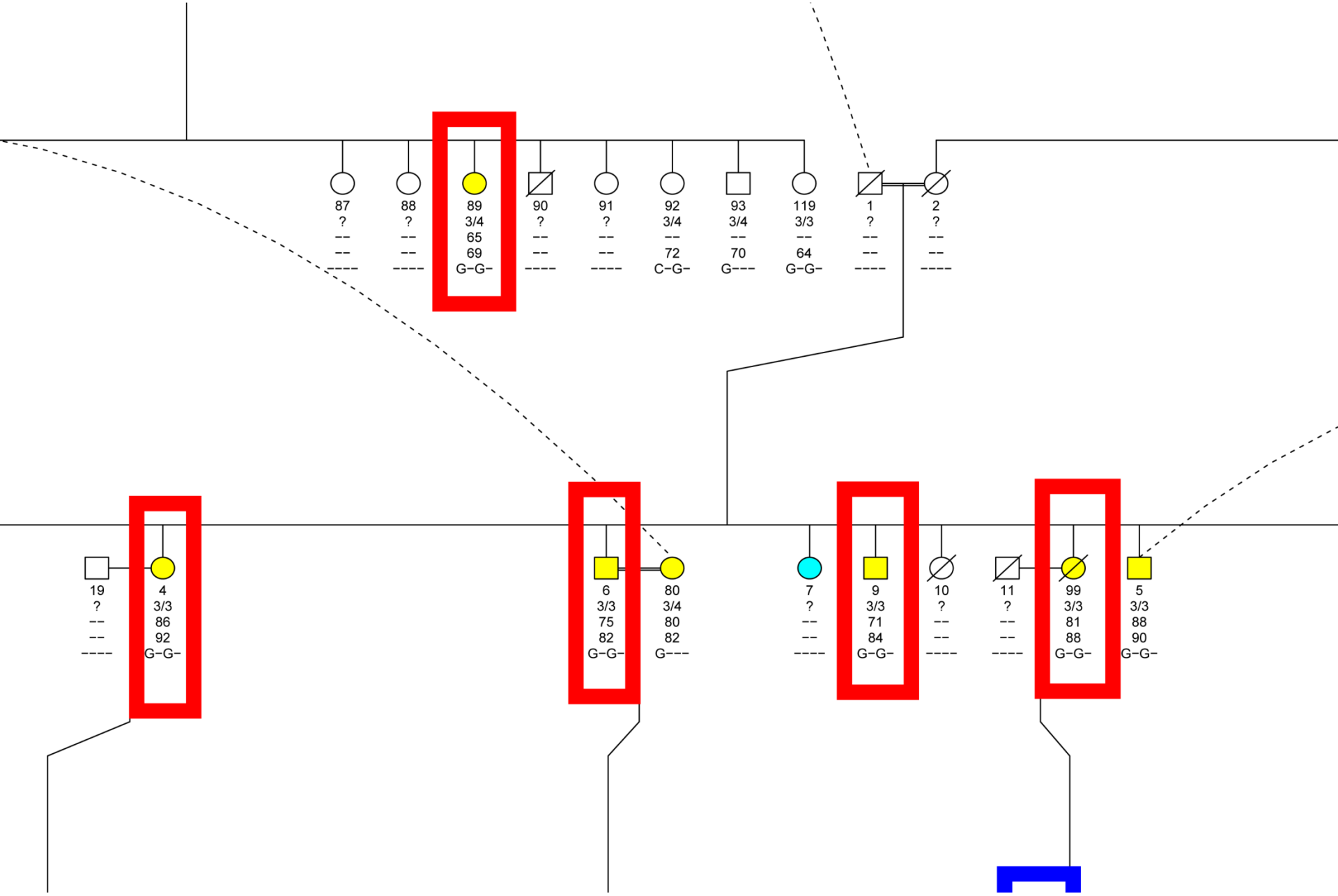
Miami family 911




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-
103
?
--
--
-L--
106
?
--
--
-L--
105
?
--
--
-L--
9017
3/3
--
75
GLGS
9016
3/3
--
66
GLG-

Carribean Hispanic family




87
?
--
--

88
?
--
--

89
3/4
65
69
G-G-
90
?
--
--

91
?
--
--

92
3/4
--
72
C-G-
93
3/4
--
70
G---
119
3/3
--
64
G-G-
1
?
--
--

2
?
--
--

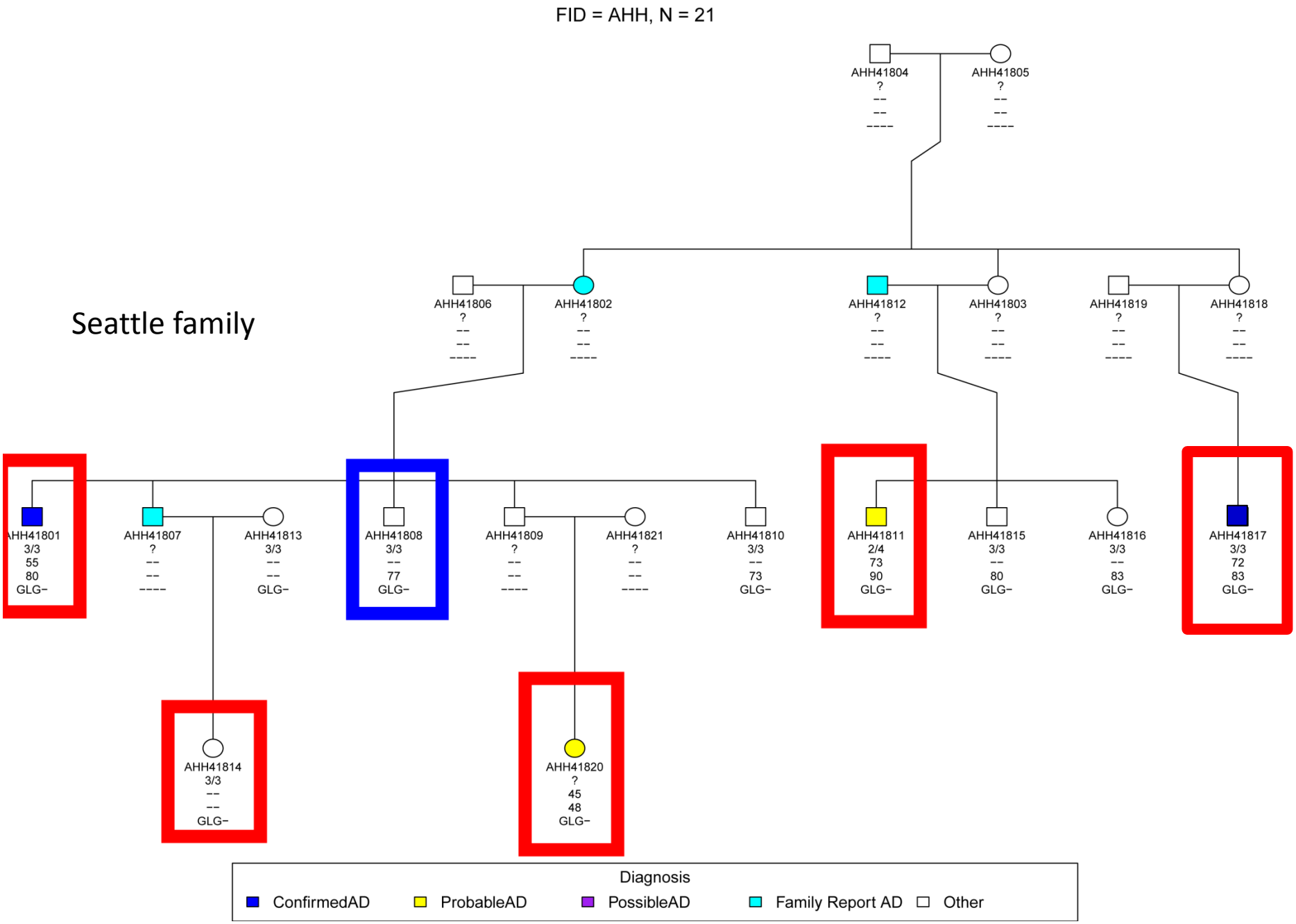
19
?
--
--

4
3/3
86
92
G-G-
6
3/3
75
82
G-G-
80
3/4
80
82
G---
7
?
--
--

9
3/3
71
84
G-G-
10
?
--
--

11
?
--
--

99
3/3
81
88
G-G-
5
3/3
88
90
G-G-


FID = AHH, N = 21
Seattle family
AHH41804
?
--
--

AHH41805
?
--
--

AHH41806
?
--
--

AHH41802
?
--
--

AHH41812
?
--
--

AHH41803
?
--
--

AHH41819
?
--
--

AHH41818
?
--
--

AHH41801
3/3
55
80
GLG-
AHH41807
?
--
--

AHH41813
3/3
--
--
GLG-
AHH41808
3/3
--
77
GLG-
AHH41809
?
--
--

AHH41821
?
--
--

AHH41810
3/3
--
73
GLG-
AHH41811
2/4
73
90
GLG-
AHH41815
3/3
--
80
GLG-
AHH41816
3/3
--
83
GLG-
AHH41817
3/3
72
83
GLG-
AHH41814
3/3
--
--
GLG-
AHH41820
?
45
48
GLG-
Diagnosis
ConfirmedAD
ProbableAD
PossibleAD
Family Report AD
Other

Alzheimer's Disease Sequencing Project - ADSP

Case-control study: Whole exome sequencing

5,000 AD cases: selected as cases with the lowest risk explained by *APOE* and age

young onset, *APOE* ε2/ε2, ε2/ε3, or ε3/ε3

5,000 controls: selected as 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 additional multiplex families (one case/family)

	Cases	Controls
ADGC		
ADC	**2,354**	**843** ←
ACT	269	983
CHAP	28	186
LOAD	0	164
MAP	136	299
Mayo	288	134
Miami	307	92
MIRAGE	322	12
NCRAD	101	0
ROS	78	210
TARCC	112	9
Vanderbilt	182	23
WHICAP	25	152
CHARGE	830	1919

Planning

case/control selection
family selection
data flow planning
database planning
existing genetic data – submit to ADSP
phenotype data

conference calls: 3-4/week, past 6 months

Timeline

- Next week: Send family samples to sequencing centers
- Whole Genome Sequencing – 6 months to 1 year
- June 2013: Send case-control samples to sequencing centers
- Whole exome sequencing – end of 2013 into 2014 – 6 months to 1 year to complete

The End

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

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

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

ADGC projects

Expand GWAS dataset
International Genomics Alzheimer Project (IGAP)

Age at Onset GWAS	Adam Naj/Peggy Pericak-Vance
APOE GWAS	Gyungah Jun/Lindsay Farrrer
Neuropath GWAS	Gary Beecham/Tom Montine
CSF biomarker GWAS	Carlos Cruchaga/Alison Goate
Cognitive decline GWAS	Lori Chibnik/David Bennet
African American GWAS	Christiane Reitz
Japanese GWAS	Gyungah Jun/Lindsay Farrrer
Hispanic GWAS	Richard Mayeux
Exome Chip	Li-San Wang/Adam Naj

ADC Contribution

	Phase 1/MDS	Phase 2/UDS	Total
NACC Subjects	4,727	24,190	28,917
Received at NCRAD			
Tissue	3,519	0	3,519
DNA	255	9,488	9,743
Blood	0	931	931
Buffy Coat	0	609	609
Total Submitted	3,774	11,028	14,802
Illumina 660/Omni Express	2,990	7,046	10,036
Exome Chip	2,673	4,418	7,091

ADGC Genotyping

Cohort	Cases	Controls	Other	Total
ACT	20	7	372	399
ADC*	**5341**	**3617**	**1078**	**10,036**
Miami	92	71	3	166
ROS/MAP	81	68	501	650
TARCC	203	97	0	300
Vanderbilt	17	81	4	102
WHICAP	82	605	0	687
CHAP	16	54	778	848
Total	**5,874**	**5,835**	**2,770**	**14,479**

Other Genotype Data Contributed

Cohort	Cases	Controls	Total
ACT	566	1696	2262
ADNI	268	173	441
GenADA	669	713	1382
London	61	137	198
Mayo	728	1173	1901
Merck/NYU	392	159	551
MIRAGE	509	753	1262
NIA-LOAD	1811	1575	3386
OHSU	132	153	285
Pfizer	733	792	1525
ROS/MAP	296	776	1072
TGen	864	493	1357
Univ Pittsburgh	1271	841	2112
Wash U	339	187	526
Total	**8639**	**9621**	**18260**

ADGC Genotyping – CSF cohorts

Cohort	Cases	Controls	Other	Total
BIOCARD*	0	244	105	349
Blennow/Sweden*	300	0	0	300
Peskind/UW	0	0	269	269
Vanderbilt	17	81	4	102
Wash U	113	233	197	543
Total	**430**	**558**	**575**	**1563**

*Genotyping in progress

Cohort	Total
Mayo Rochester	636

Samples received 7/11/2012

	cases	controls	other	total
Current analysis	130	314	470	914
Final analysis	430	558	1,106	2,094

African American GWAS

1,970 cases
3,932 controls

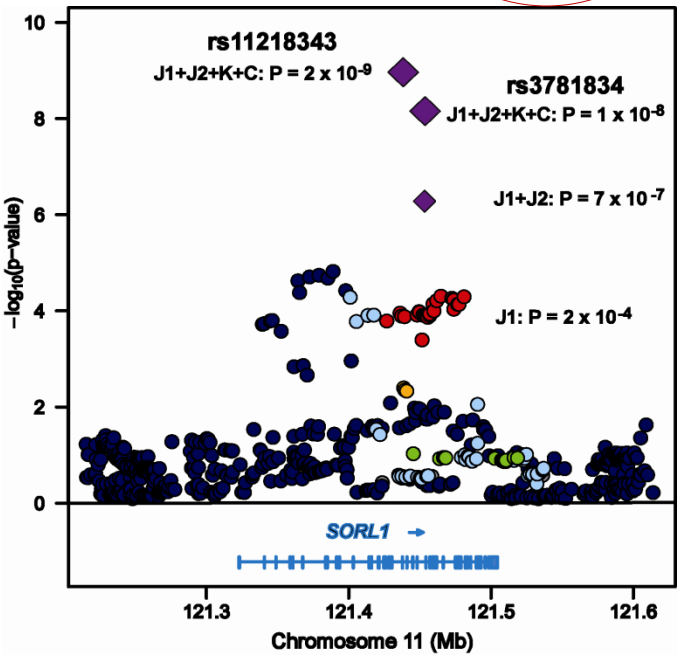
NIA-ADC
CHAP
CU
Mayo Clinic
U Miami
Vanderbilt
NIA-LOAD families
NCRAD families
ROS/MAP
MARS/CORE
U Pittsburgh
Washington U
WHICAP
OHSU
Duke University
Indianapolis
New York U
U California San Francisco
U Texas Southwestern

Cohort	Cases			Controls			Total
	N	percent female	Onset age mean (SD)	N	percent female	Age at exam mean (SD)	
Japanese-1	1,008	72%	73.0 (4.3)	1,016	57%	77.0 (5.9)	2,024
Japanese-2	885	63%	74.3 (7.0)	985	63%	73.7 (5.8)	1,870
Korean	339	72%	NA	1,129	49%	71.0 (4.9)	1,469
Caucasian	11,840	71%	76.4 (5.2)	10,931	59%	76.8 (3.6)	22,771
Totals	15,963			16,062			32,027

	Cases			Controls		
Cohort	ε2	ε3	ε4	ε2	ε3	ε4
Japanese-1	0.02	0.63	0.33	0.04	0.87	0.09
Japanese-2	0.02	0.69	0.29	0.05	0.86	0.09
Korean	0.02	0.69	0.27	0.06	0.83	0.09
Caucasian	0.04	0.61	0.27	0.08	0.78	0.14

	Japanese (Stage 1 + 2)		Korean (Stage 3)		Caucasian (Stage 4)		Meta-Analysis
SNP	MAF	OR (95% CI) P value	MAF	OR (95% CI) P value	MAF	OR (95% CI) P value	OR (95% CI) P value
rs11218343	0.34	0.83 (0.75-0.92) 3.8×10^{-4}	0.31	0.96 (0.79-1.17) 0.68	0.04	0.75 (0.67-0.83) 1.0×10^{-7}	0.81 (0.75-0.87) 2.2×10^{-9}
rs3781834	0.23	0.74 (0.66-0.84) 7.3×10^{-7}	0.23	0.94 (0.75-1.16) 0.55	0.02	0.78 (0.68-0.90) 7.9×10^{-4}	0.78 (0.72-0.85) 9.9×10^{-9}

Meta-analysis of top-ranked association results with *SORL1* in Japanese, Korean, and Caucasian datasets.



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

Stage 1 Subjects

Consortium	AD cases N	AD cases % women	AD cases Mean Onset Age	Controls N	Controls % women	Controls Mean Age at last exam
ADGC (13 cohorts)	10,273	42-70	71–86	10,892	37–72	72–84
CHARGE (4 cohorts)	1,315	50–75	80–86	21,776	45–62	69–76
EADI	2,243	64.9	68.5 (8.9)	6,017	60.7	74.0 (5.4)
GERAD	3,177	64.0	73.0 (8.5)	7,277	51.8	51.0 (11.8)
Totals	**17,008**			**45,962**		

ADGC cohorts: Alzheimer's disease centers
case-control studies
family-based cohorts

CHARGE: Rotterdam Study
Framingham
Age, Gene, Environment Study
Cardiovascular Health Study

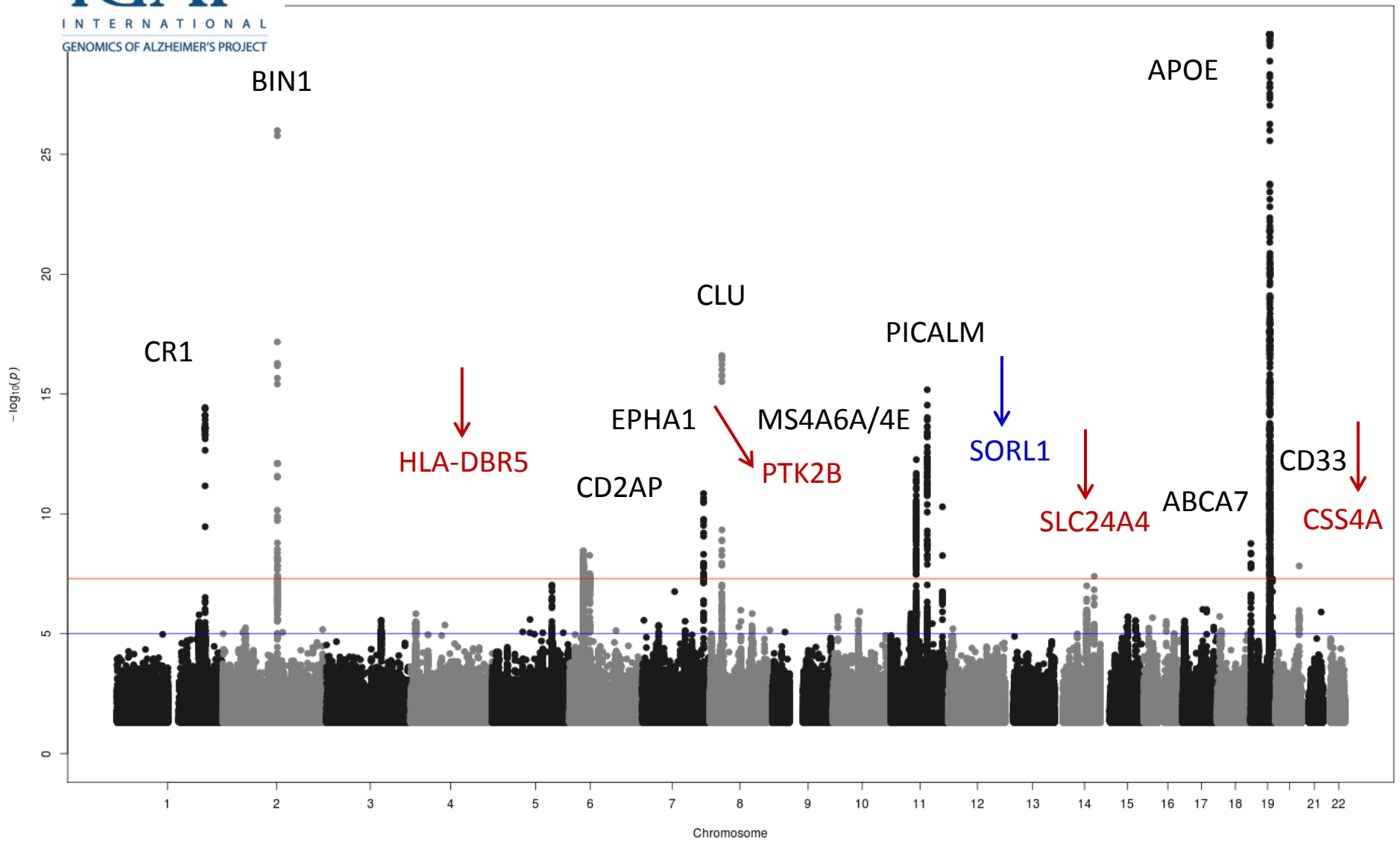
IGAP
INTERNATIONAL
GENOMICS OF ALZHEIMER'S PROJECT

Stage 1: discovery data set
genome-wide SNP arrays

Stage 2: custom chip from stage 1 data
~50,000 SNPs
$p < 0.001$

Genotype: 14,000 new cases
14,000 new controls

IGAP
INTERNATIONAL
GENOMICS OF ALZHEIMER'S PROJECT



Exome Chip Content

Non-synonymous Variants	**243,094**
Splice site variants	12,662
Stop Altering Variants	7,137
Previously Described GWAS Hits	5,325
Ancestry Informative Markers	
European descent versus African Americans	3,241
European descent versus Native Americans	998
Scaffold for Identity by Descent	5,710
Grid of common variants	5,286
Random set of synonymous variants	4,651
Fingerprint SNPs	259
Mitochondrial SNPs	246
Chromosome Y SNPs	128
HLA tag SNPs	2,459
Indels	181

Exome Chip

Cohort	Cases	Controls	Total
ADC	177	138	315
NIMH	396	0	396
NIA-LOAD	797	481	1,278
NCRAD	417	0	417
MIRAGE	633	0	633
Miami	219	0	219
Vanderbilt/Miami	970	917	1,887
ACT	423	1,615	2,038
Genetic Differences	356	356	712
WHICAP	78	337	415
Univ of Toronto	87	0	87
GSK	101	0	101
Hapmap	0	48	48
Subtotal	4,652	3,892	8,544
Genentech ADC	2,673	4,418	7,091
Total	**7,325**	**8,310**	**15,635**

ScienceInsider
Breaking news and analysis from the world of science policy

NIH Scrambling to Shift $50 Million Into Alzheimer's Research
by Jocelyn Kaiser on 8 February 2012

setting aside $50 million for Alzheimer's studies from this year's budget.

As for the $50 million from this year's budget, half will go to genomics studies, NIH Director Francis Collins said yesterday.

using DNA from the same groups of Alzheimer's patients and healthy people that were part of the GWAS studies. Those cohorts give the initiative "a great head start and is why something like that could actually be done this year," Hodes says.

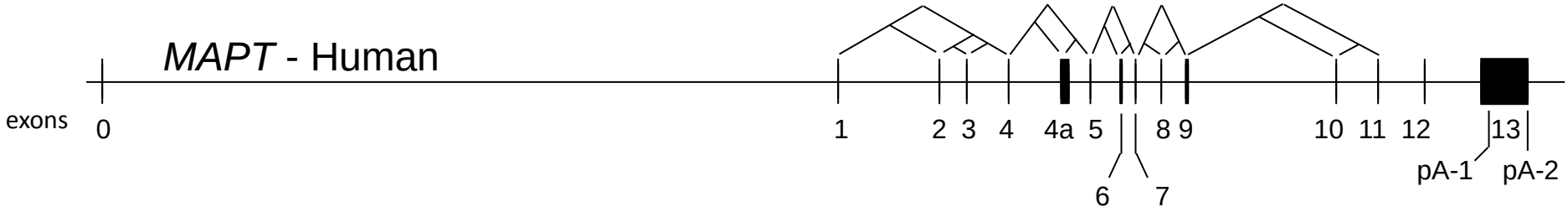
Hypothesis:

- Rare-variants contribute to late-onset Alzheimer's disease
- These rare variants have a larger effect size than most GWAS loci
- These rare variants can be detected by new DNA sequencing methodology

Need a large sample size

Whole exome sequencing – only sequence exons

- less expensive than whole-genome sequencing (~$1,000/subject)
- can do more samples
- miss all variants not in exons
- limited ability to detect structural variants
- exome chip may detect most rare exonic variants



Complete gene:	130 kb
Coding:	~1.4 kb
3”UTR:	3 kb

LETTER

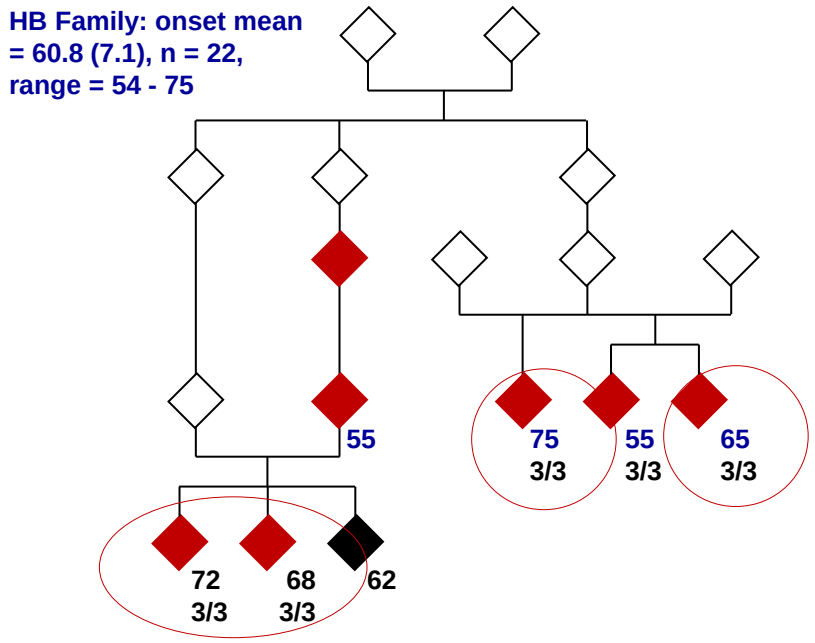
doi:10.1038/nature11283

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],

190 | NATURE | VOL 487 | 12 JULY 2012

Presenilin 2 mutations



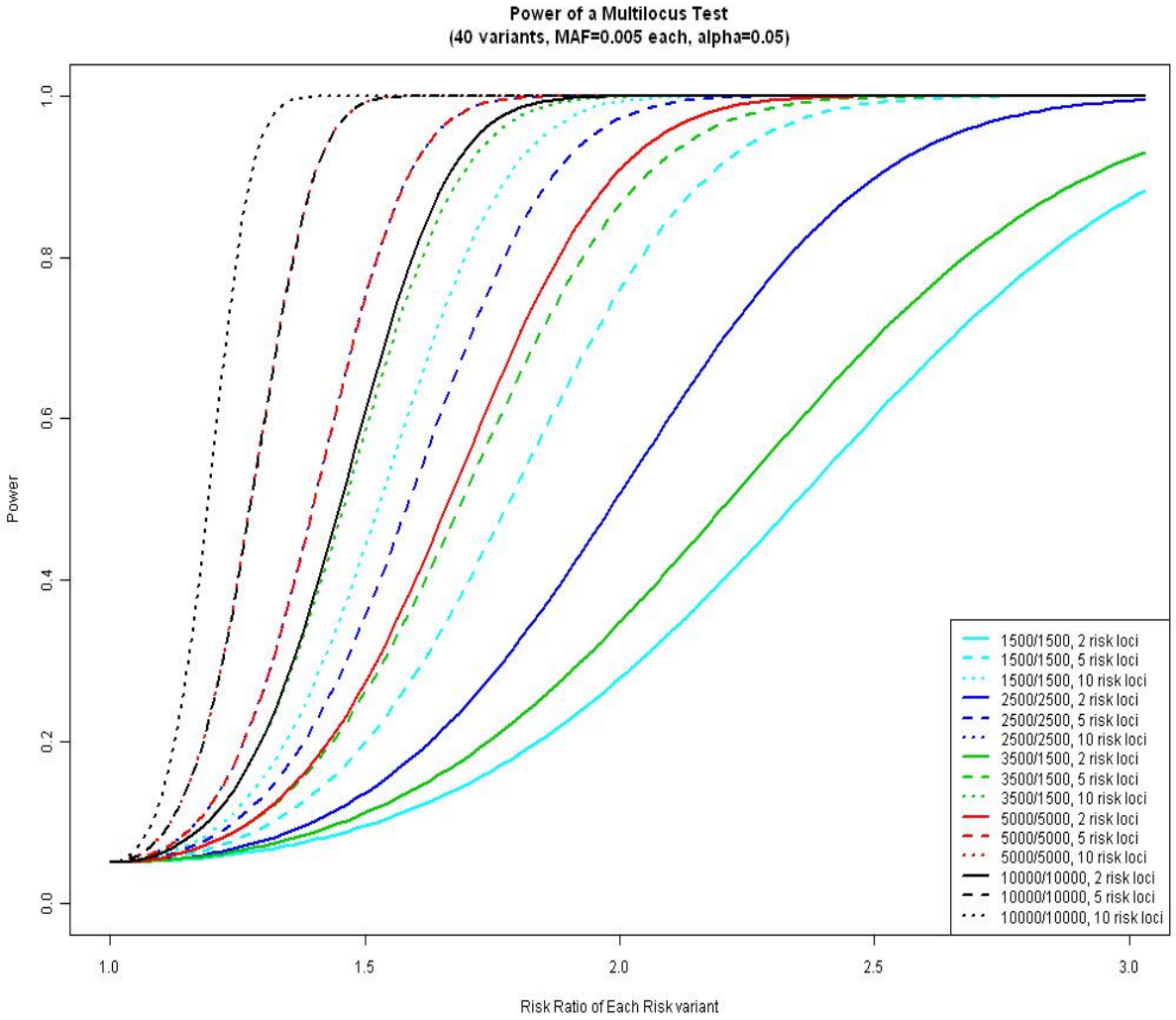
Case-control study

Cases: Subjects who develops Alzheimer's disease despite having a "low risk" profile based on gender, age, *APOE* genotypes

e.g. - male, *APOE* ε2/ε3 or ε2/ε3 who develops Alzheimer's disease at 60 yrs.

Case-control study

whole-exome sequencing
5,000 cases
5,000 controls



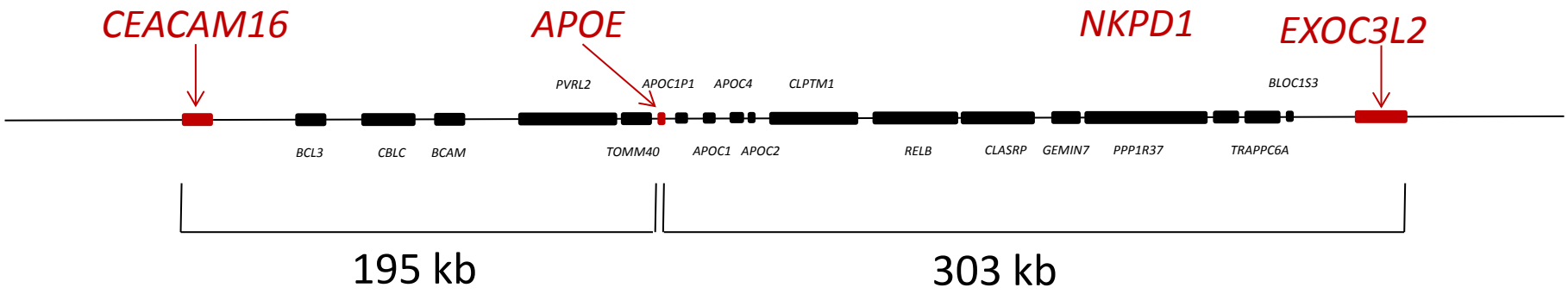
Family-based study

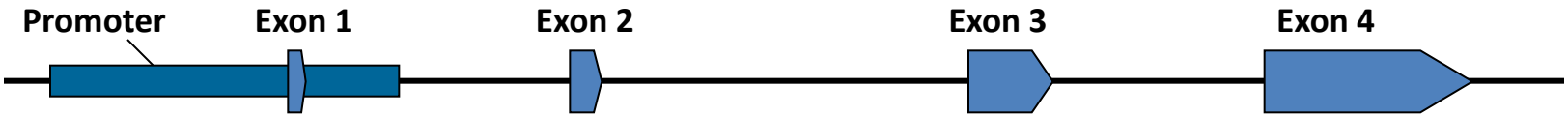
- Select families with multiple affected subjects
- At least 4 affected sampled
- Perform whole-genome sequencing on 3 subjects/family
- Use genome-wide SNP data in other subjects to track variants

- Families are likely to be highly loaded with genetic variants
- Can use co-segregation to examine candidate variants
- Unlikely that these are “Mendelian” families
  (highly penetrant dominant or recessive variants)
- Co-segregation will not be perfect

Top 100 families
Whole-genome sequencing on 3/family

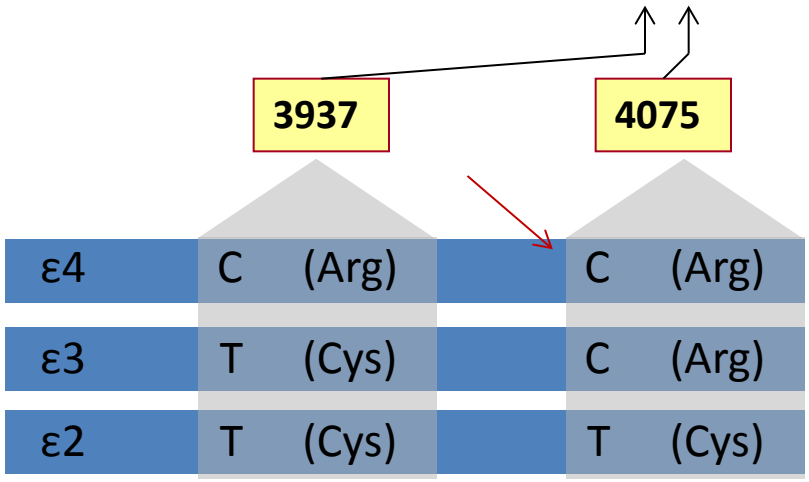
ADGC	Laura Cantwell
NACC	Bud Kukull/Duane Beekly
NCRAD	Tatiana Foroud/Kelly Faber
NIAGADS	Li-San Wang





Do *TOMM40* genotypes influence Alzheimer's disease risk?

Is the *APOE* association fully explained by ε2/ε3/ε4?



Answer: The ε2/ε3/ε4 polymorphism completely explains the effect of *APOE* on Alzheimer's disease risk

not *TOMM40* genotypes (poly-T)
not *APOE* promoter SNPs
not another gene in the *APOE* region

Do *TOMM40* genotypes influence Alzheimer's disease risk?

Is the *APOE* association fully explained by ε2/ε3/ε4?

IGAP: Previously Identified Late-onset Alzheimer's Disease Genes

		Stage 1 mega-meta analysis		Stage 2- Custom array		Stage 1 + Stage 2	
SNP	Chr	Closest gene	Meta P-value	OR (95% CI)	Meta P-value	OR (95% CI)	Meta P-value
rs6656401	1	*CR1*	7.7×10^{-15}	1.20 (1.13-1.27)	3.0×10^{-10}	1.18 (1.14-1.22)	2.2×10^{-23}
rs6733839	2	*BIN1*	1.7×10^{-26}	1.23 (1.18-1.29)	1.0×10^{-18}	1.22 (1.18-1.25)	1.3×10^{-43}
rs10948363	6	*CD2AP*	3.3×10^{-8}	1.10 (1.04-1.15)	2.6×10^{-4}	1.10 (1.07-1.13)	3.4×10^{-11}
rs75045569	7	*EPHA1*	2.8×10^{-11}	0.89 (0.84-0.95)	2.6×10^{-4}	0.87 (0.84-0.90)	3.8×10^{-14}
rs9331896	8	*CLU*	9.6×10^{-17}	0.86 (0.82-0.90)	1.4×10^{-9}	0.86 (0.84-0.89)	8.2×10^{-26}
rs11824773	11	*MS4A4A*	3.7×10^{-12}	0.93 (0.89-0.97)	1.6×10^{-3}	0.91 (0.88-0.93)	4.8×10^{-14}
rs10792832	11	*PICALM*	6.5×10^{-16}	0.86 (0.82-0.90)	4.2×10^{-10}	0.87 (0.85-0.90)	2.6×10^{-24}
rs4147929	19	*ABCA7*	1.7×10^{-9}	1.14 (1.08-1.21)	4.2×10^{-6}	1.14 (1.11-1.19)	3.6×10^{-14}
rs3865444	19	*CD33*	5.1×10^{-8}	0.99 (0.93-1.04)	6.4×10^{-1}	0.94 (0.91-0.96)	2.6×10^{-6}

IGAP: Meta-analysis Late-onset Alzheimer's Disease Genes Confirmed in Second Stage

		Stage 1 mega-meta analysis		Stage 2- Custom array		Stage 1 + Stage 2	
SNP	Chr	Closest Gene	Meta P-value	OR (95% CI)	Meta P-value	OR (95% CI)	Meta P-value
6:32,578,476	6	*HLA-DRB5/HLA-DRB1*	1.7×10^{-8}	1.14 (1.08-1.20)	6.3×10^{-7}	1.12 (1.09-1.16)	6.5×10^{-14}
rs28834970	8	*PTK2B*	3.3×10^{-9}	1.11 (1.06-1.16)	1.5×10^{-5}	1.10 (1.07-1.13)	2.2×10^{-13}
rs11218343	11	*SORL1*	5.0×10^{-11}	0.82 (0.73-0.92)	6.6×10^{-4}	0.78 (0.73-0.83)	1.9×10^{-13}
rs10498633	14	*SLC24A4/RIN3*	1.5×10^{-7}	0.92 (0.87-0.98)	4.5×10^{-3}	0.91 (0.88-0.94)	3.1×10^{-9}
rs8093731	18	*DSG2*	4.6×10^{-8}	1.03 (0.80-1.32)	8.2×10^{-1}	0.72 (0.61-0.84)	7.5×10^{-5}
rs927174	20	*CASS4*	1.5×10^{-8}	0.93 (0.87-1.02)	1.2×10^{-1}	0.89 (0.85-0.92)	1.7×10^{-8}

HLA-DRB1/5 *major histocompatibility complex class II DR beta 1/5*
PTK2B *protein tyrosine kinase 2 beta*
SORL1 *Sortilin-related protein 1*
SLC24A4 *solute carrier family 24 (sodium/potassium/calcium exchanger) member 4*
RIN3 *Ras and Rab interactor 3*
CASS4 *Cas scaffolding protein family member 4*

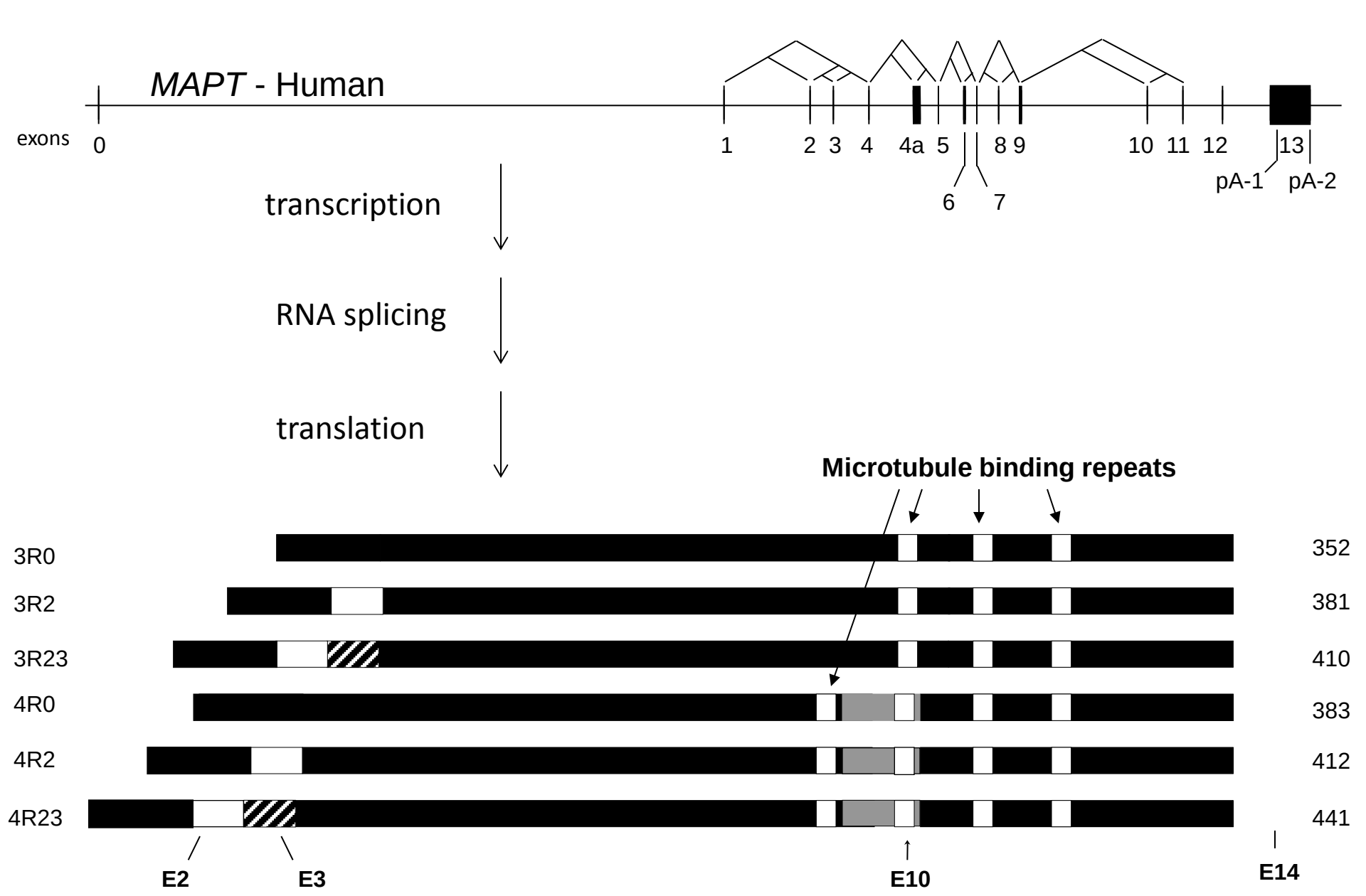
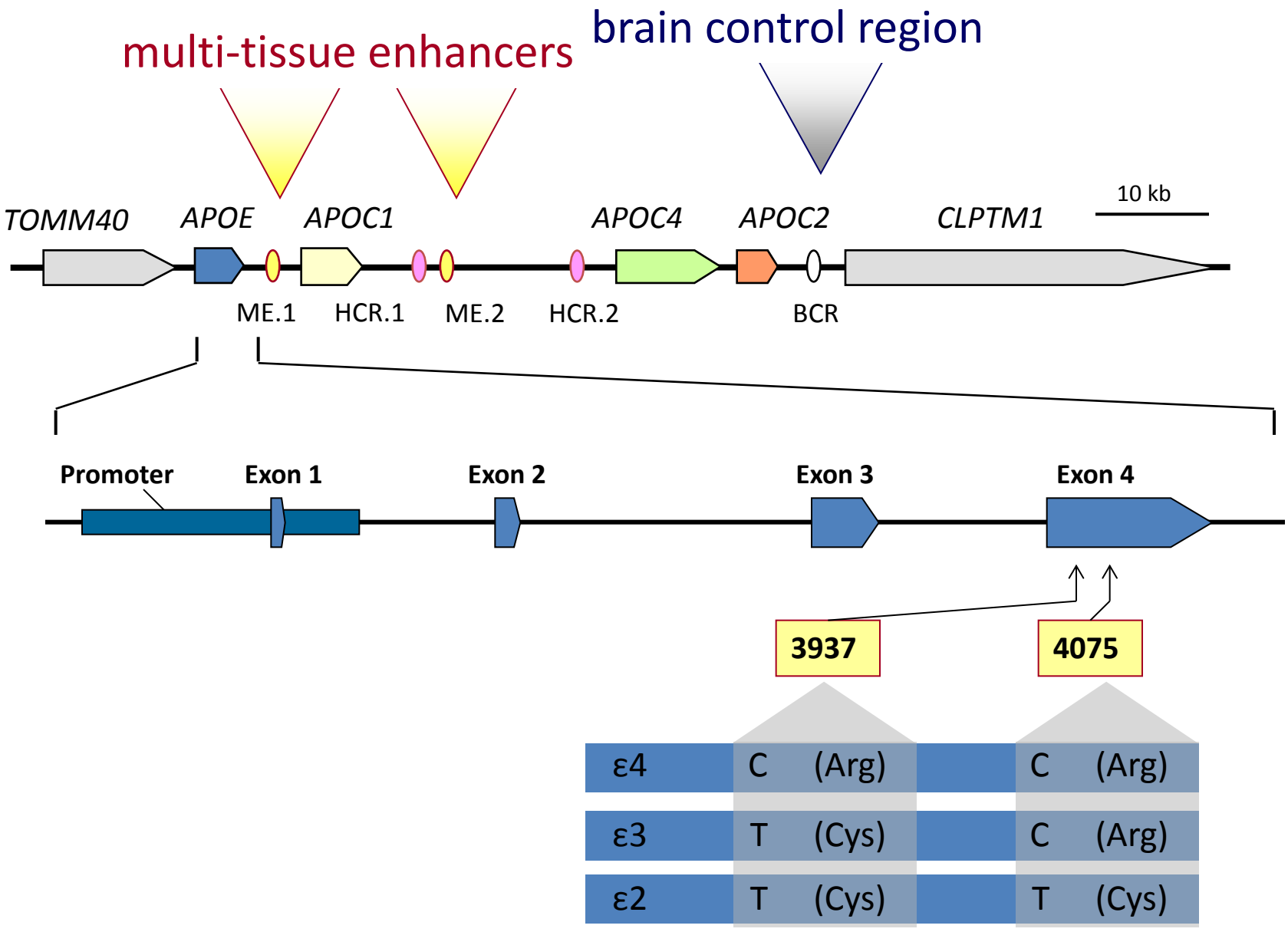
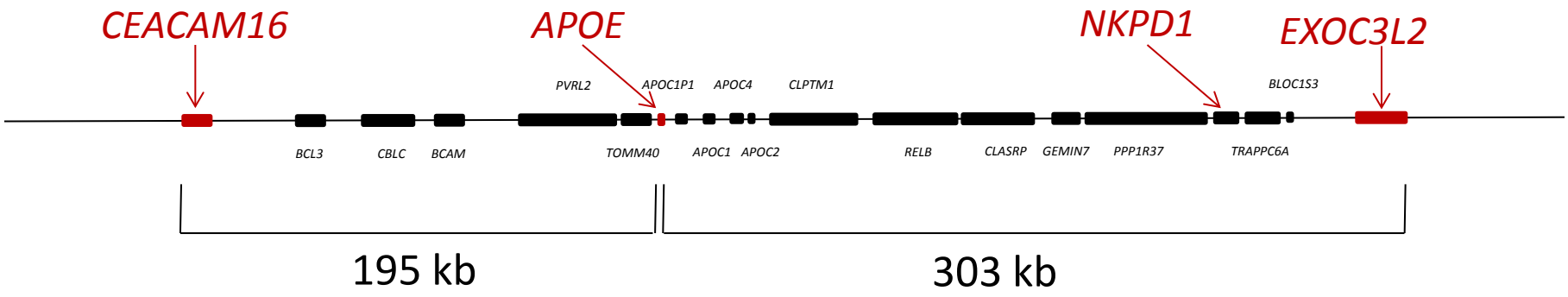

MAPT - Human
exons
0
1
2
3
4
4a
5
6
7
8
9
10
11
12
13
pA-1
pA-2
transcription
RNA splicing
translation
Microtubule binding repeats
3R0
3R2
3R23
4R0
4R2
4R23
352
381
410
383
412
441
E2
E3
E10
E14

Table 1		
Misclassification/Heterogeneity at Risk Loci		
Design	Cases	Controls
1. WGS, balanced (1500/1500)	0	0
2. WGS, unbalanced (3500/1500)	0	0
3. WGS, balanced (2500/2500)	0	0
4. WGS, protective (2500/2500)	1.00	0.082
5. WES, reduced (5000/5000)	0	0.002
6. WES, full (10000/10000)	0.099	0.021
Misclassification/Heterogeneity at Protective Loci		
Design	Cases	Controls
1. WGS, balanced (1500/1500)	0	0
2. WGS, unbalanced (3500/1500)	0	0
3. WGS, balanced (2500/2500)	0	0
4. WGS, protective (2500/2500)	0	0.082
5. WES, reduced (5000/5000)	0	0.008
6. WES, full (10000/10000)	0	0.179


multi-tissue enhancers
brain control region
TOMM40
APOE
APOC1
APOC4
APOC2
CLPTM1
10 kb
ME.1
HCR.1
ME.2
HCR.2
BCR
Promoter
Exon 1
Exon 2
Exon 3
Exon 4
3937
4075
ε4 C (Arg) C (Arg)
ε3 T (Cys) C (Arg)
ε2 T (Cys) T (Cys)

SNP	Gene	OR (95% CI)	P value
rs2965109	*CEACAM16*	0.81 (0.78-0.85)	4.43×10^{-21}
rs2075650	*TOMM40*	2.81 (2.66-2.97)	1.28×10^{-299}
rs4420638	*APOCI*	3.64 (3.42-3.87)	1.00×10^{-300}
rs10415983	*EXOC3L2*	1.19 (1.13-1.26)	5.11×10^{-10}

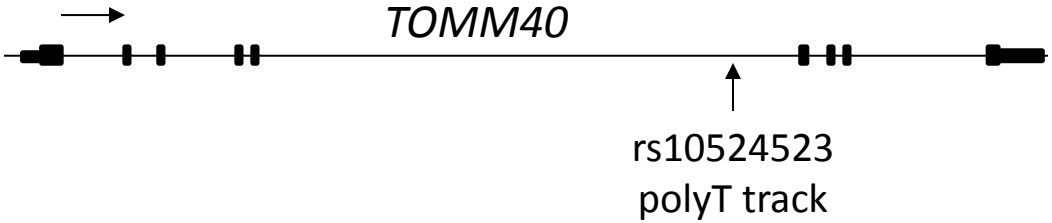
		Basic Model	
SNP	Gene	OR (95%CI)	P value
rs17643262	*NKPD1*	1.33 (1.25–1.42)	5.1×10^{-14}
rs7249082	*EXOC3L*	1.19 (1.12–1.25)	1.1×10^{-9}

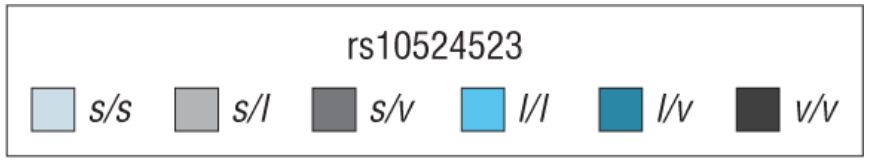


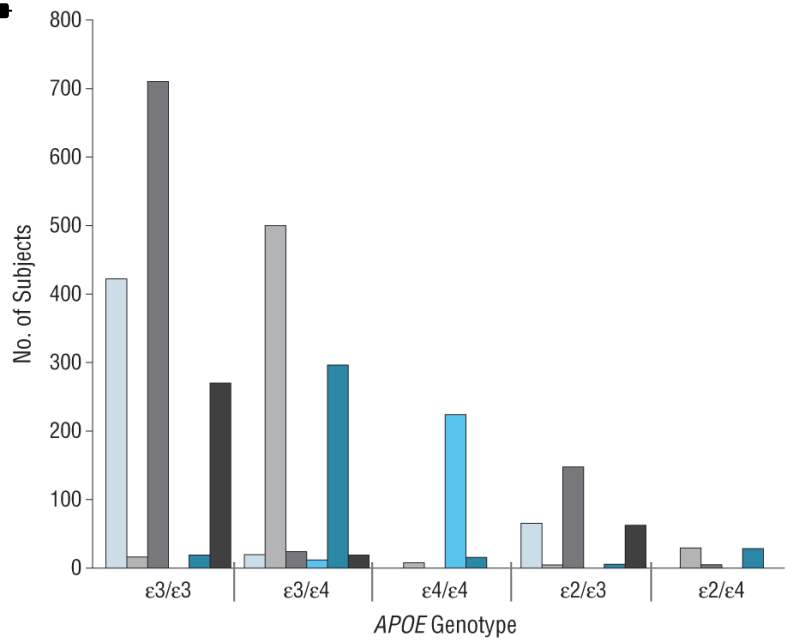
	Basic model	
	OR (95% CI)	P value
AD	2.83 (1.62-2.68)	3.9×10^{-33}

kb

	Basic model		Condition on ε4 dosage		ε3/ε3 Subgroup	
Age-at-onset	β(SE)	P-value	β(SE)	P-value	β(SE)	P-value
	-1.79 (0.31)	1.0×10^{-8}	1.48 (0.97)	0.12	0.78 (2.90)	0.79







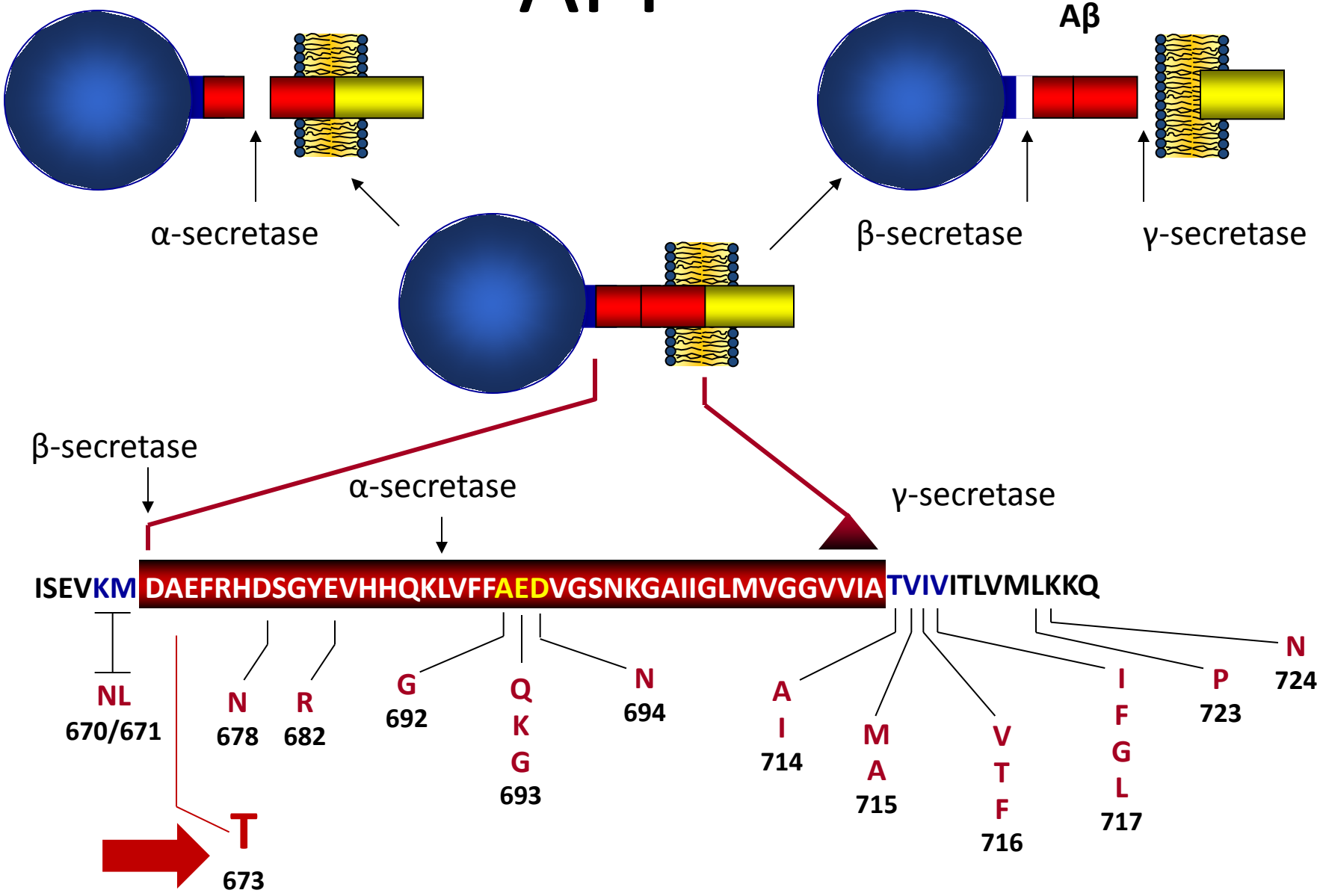
LETTER

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],

APP


Aβ
α-secretase
β-secretase
γ-secretase
β-secretase
α-secretase
γ-secretase
ISEVKM DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA TVIVITLVMLKKQ
NL
670/671
N
678
R
682
G
692
Q
K
G
693
N
694
A
I
714
M
A
715
V
T
F
716
I
F
G
L
717
P
723
N
724
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],

Table 1 | APP A673T protects against Alzheimer's disease

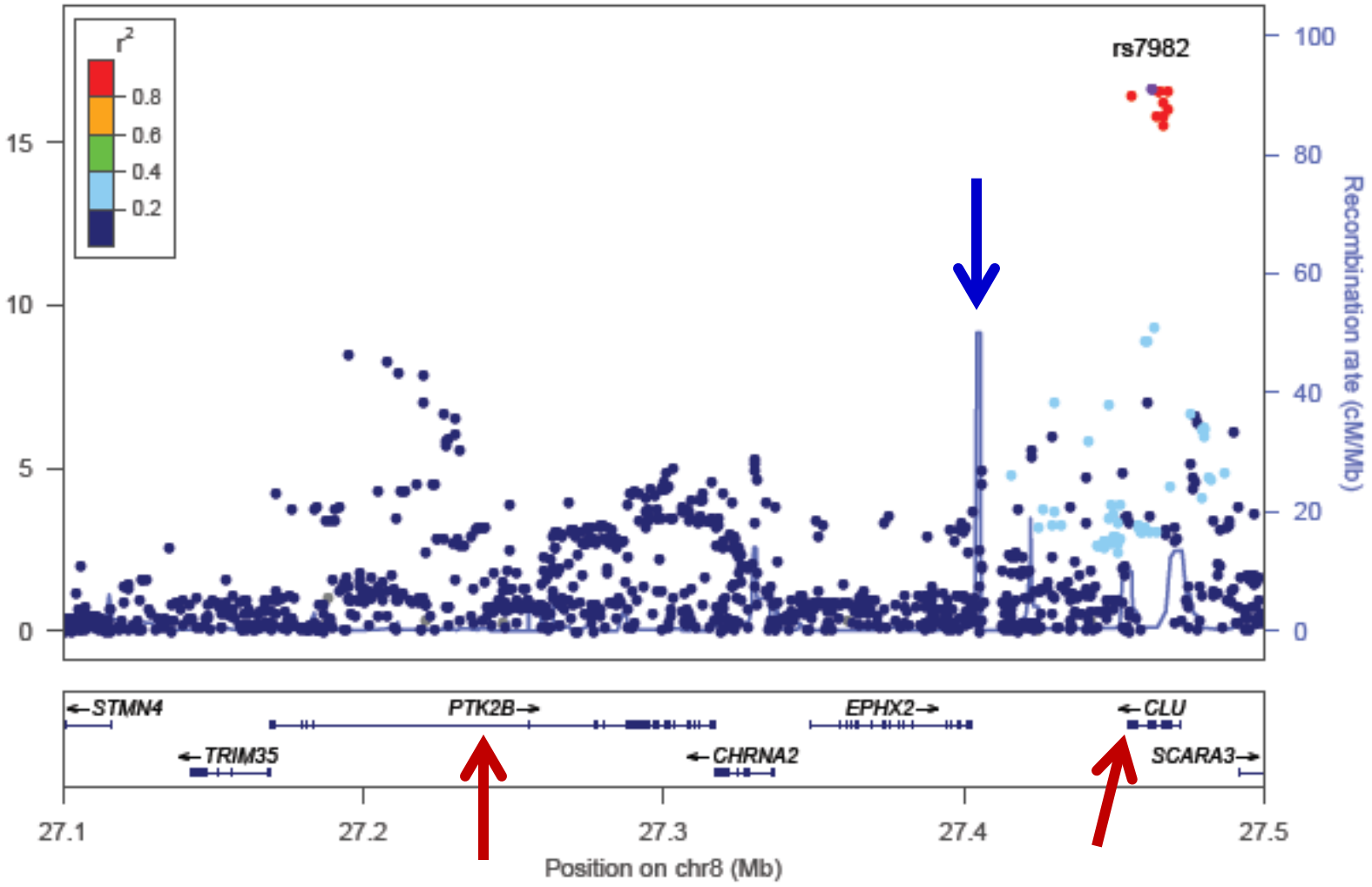
Analysis	1/OR	OR	*P* value	Controls		
				Frequency (%)	N_{chip}	$N_{in\ silico}$
AD	-	-	-	0.13	2,199	849
AD versus population controls	4.24	0.236	4.19×10^{-5}	0.45	57,174	22,074
AD versus population controls aged 85 or greater	5.29	0.189	4.78×10^{-7}	0.62	7,653	1,350
AD versus cognitively intact controls at age 85	7.52	0.133	6.92×10^{-6}	0.79	827	407

The table shows association results, comparing patients with Alzheimer's disease (AD) to three different control groups (top line gives numbers for patients with Alzheimer's disease only). N_{chip}, number of individuals with chip-based genotype information; $N_{in\ silico}$, number of individuals with genealogy-based genotype information.

		frequency	n
Alzheimer's disease	7,325	0.00007	1
Elderly controls	8,310	0.00006	1

Icelandic

Chr 8 CLU/PTK2B



- Cholesterol metabolism
- Inflammation
- Adaptive immunity
- Synaptic vesicle trafficking
- Intracellular vesicle trafficking (exocytosis)

IGAP: International Genomics Alzheimer Project

Once we get your DNA, I won't need your _____ to tell if_____ _____ _____

In a few months when I'm a lame-duck buddy, you are _____ _____.

Francis! What happened to the $1,000 genome you have been telling me about?

$25 million dollars of "in kind" sequencing

Whole exome sequencing

- 5,000 cases
- 5,000 controls

Whole-genome sequencing

- 300 subjects from 100 multiplex families