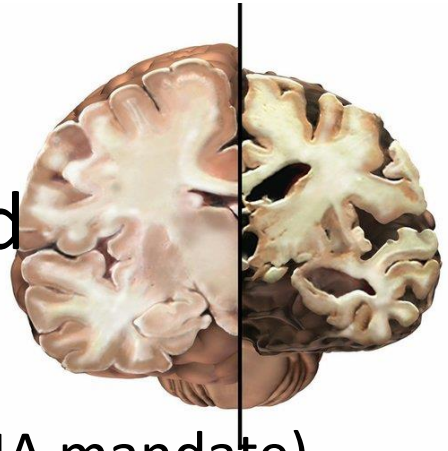
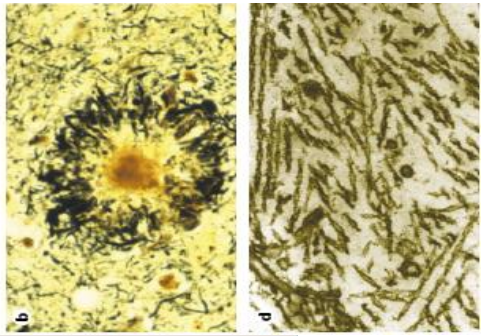
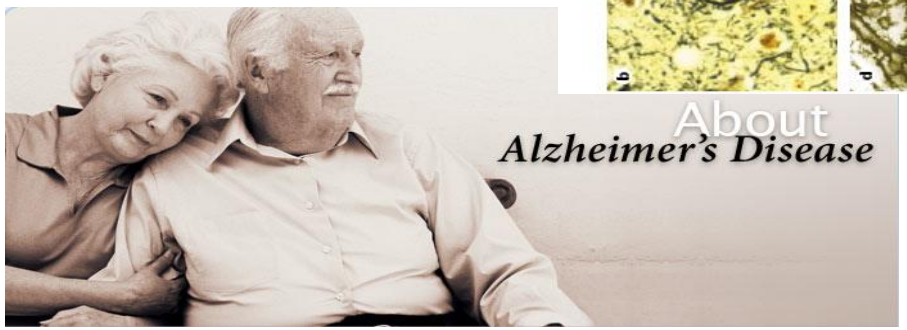
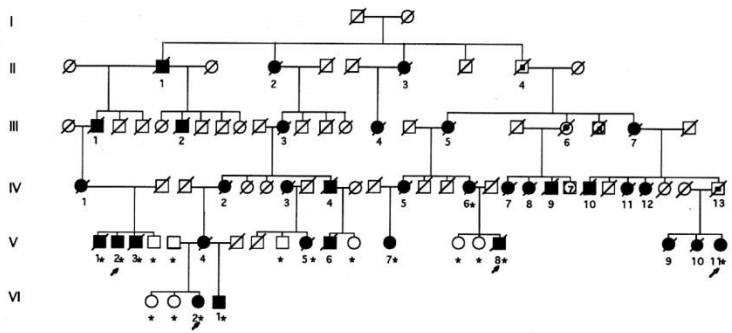
Alzheimer's Disease Introduction

- Aging population.
- AD is common dementia with a shared pathology, but likely not etiology.
- No proven treatment or prevention (NIA mandate)



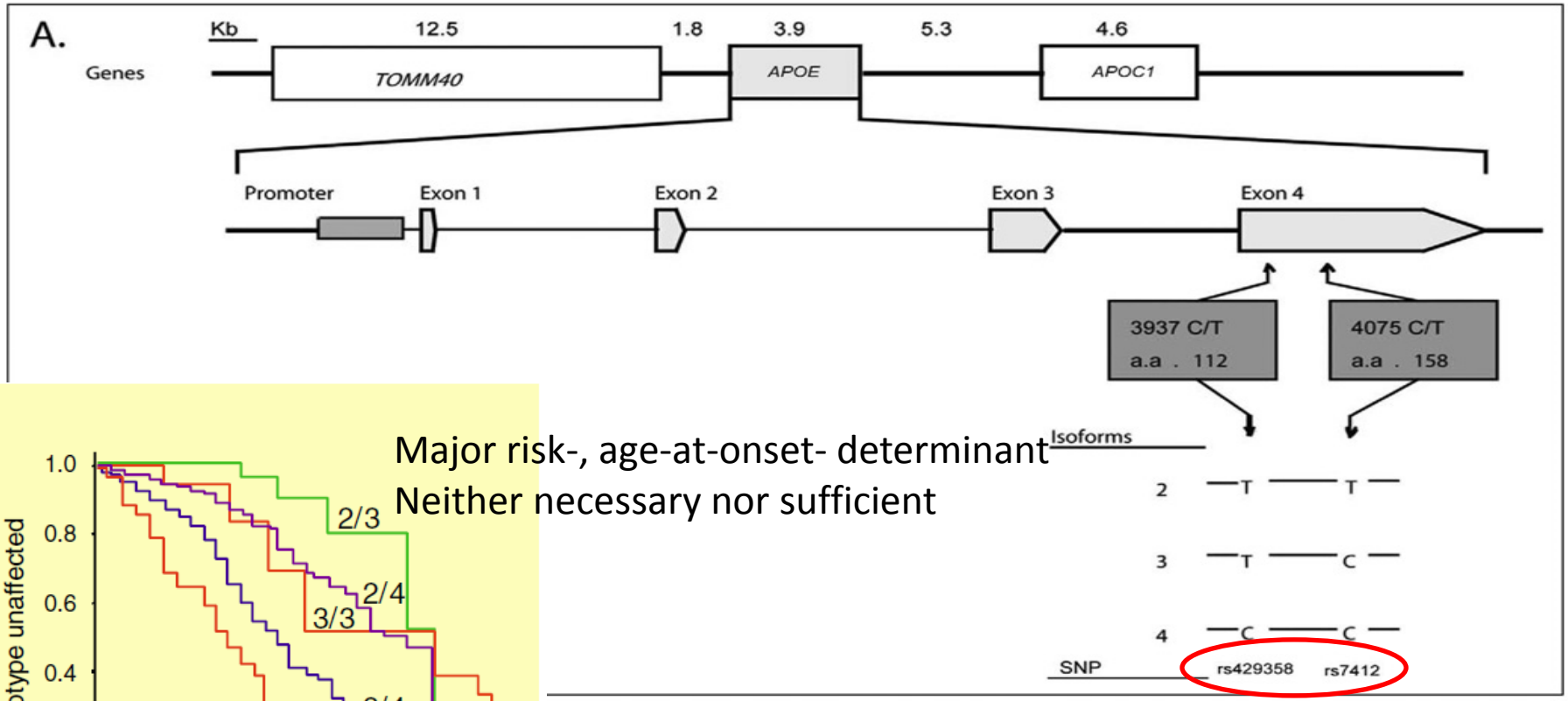






Pedigree of FAD-RO1.

Major gene: *APOE* locus



Major risk-, age-at-onset- determinant

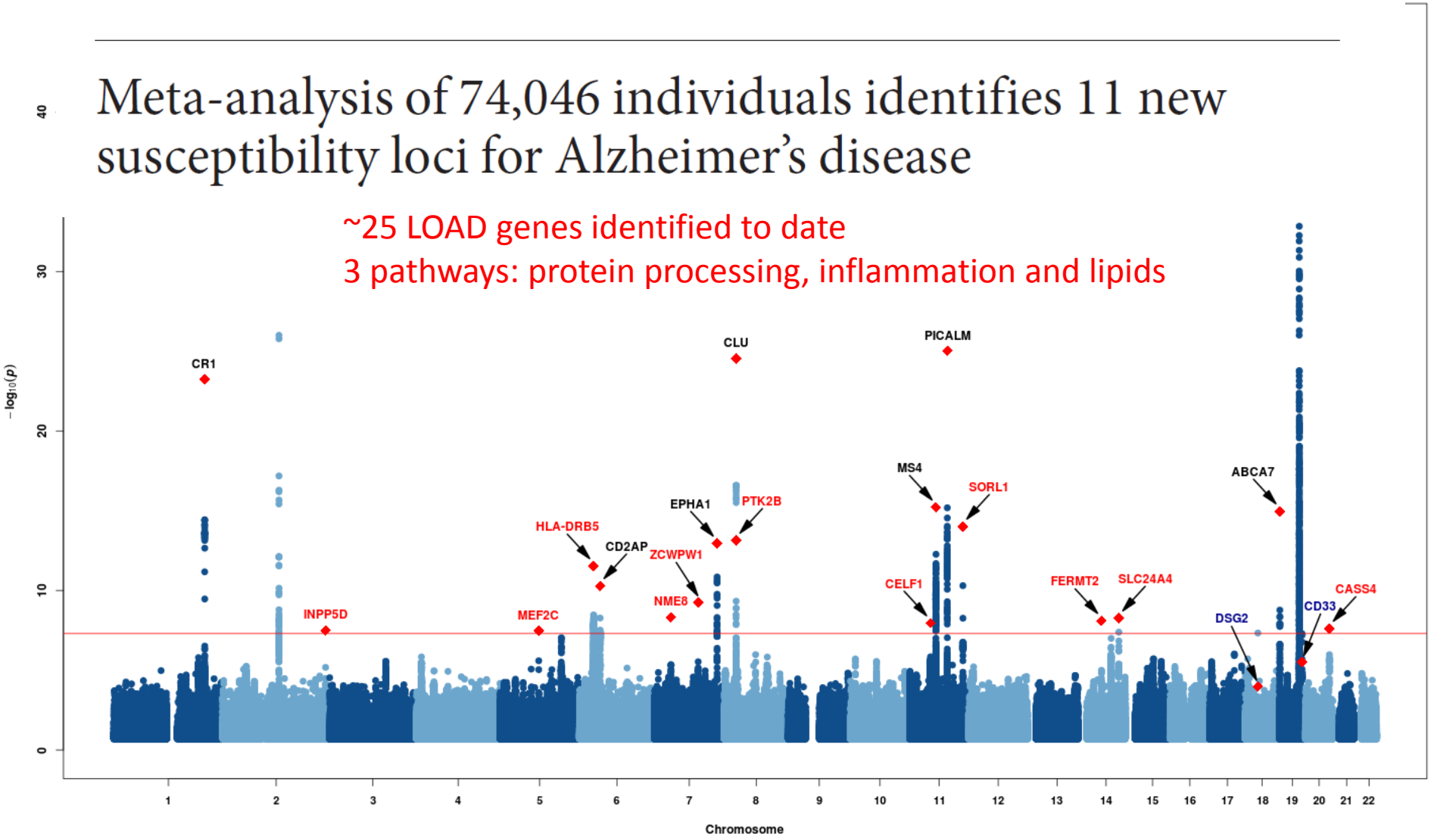
Neither necessary nor sufficient

nature genetics

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

~25 LOAD genes identified to date

3 pathways: protein processing, inflammation and lipids



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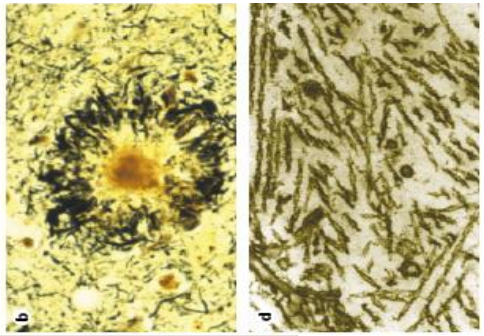
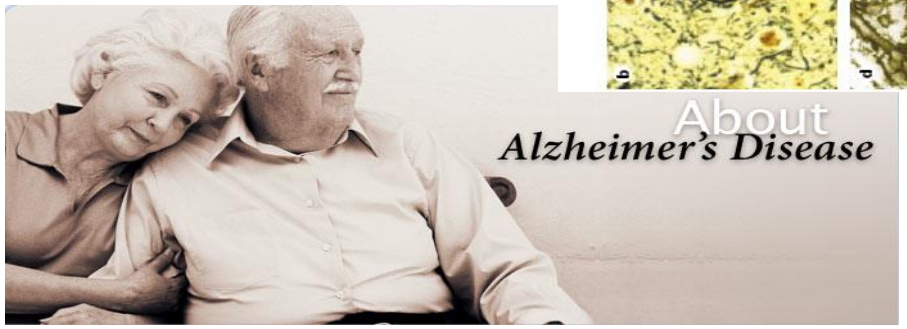
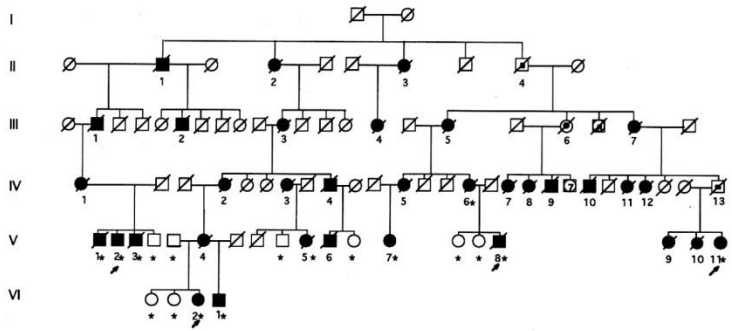
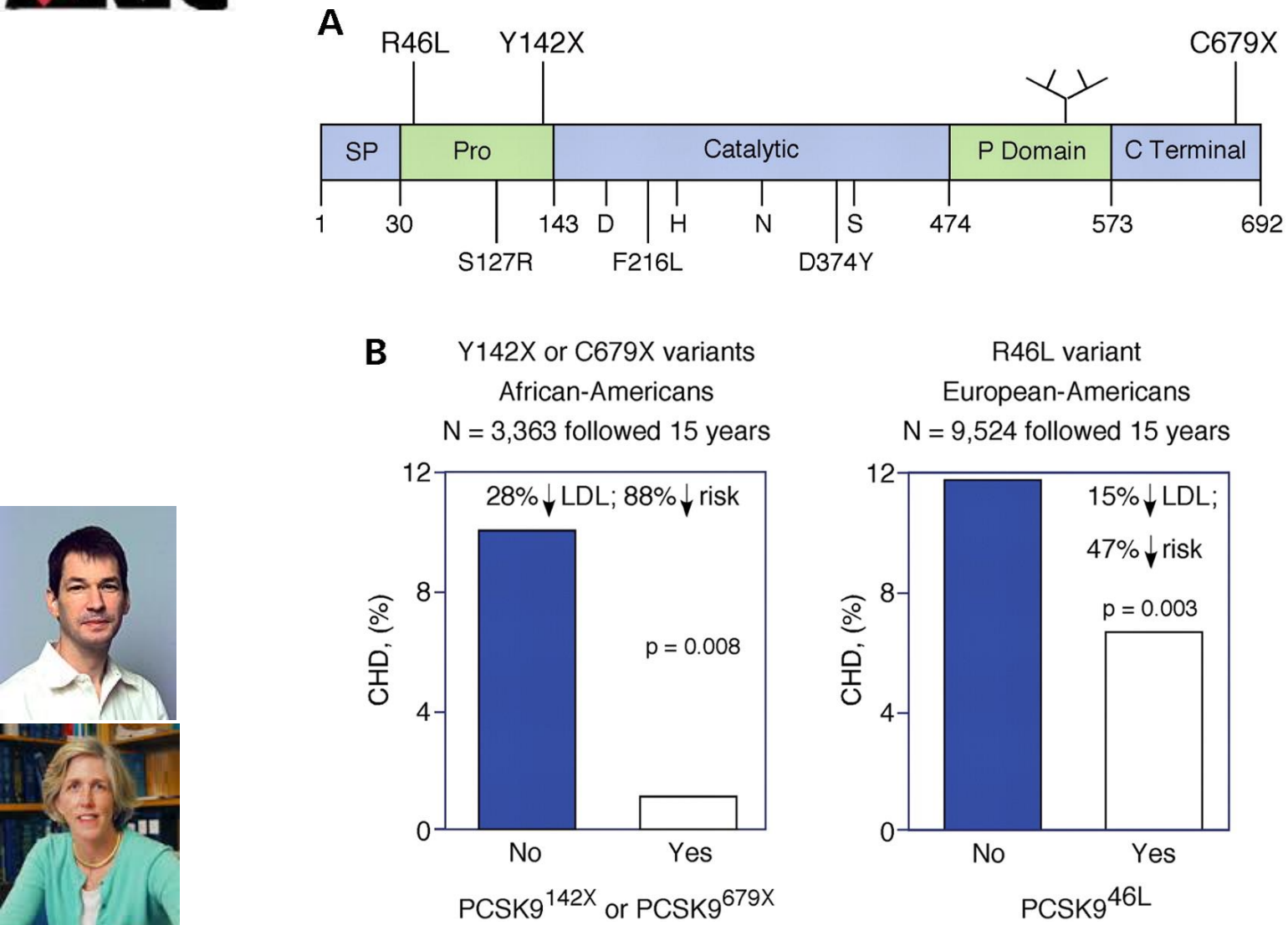




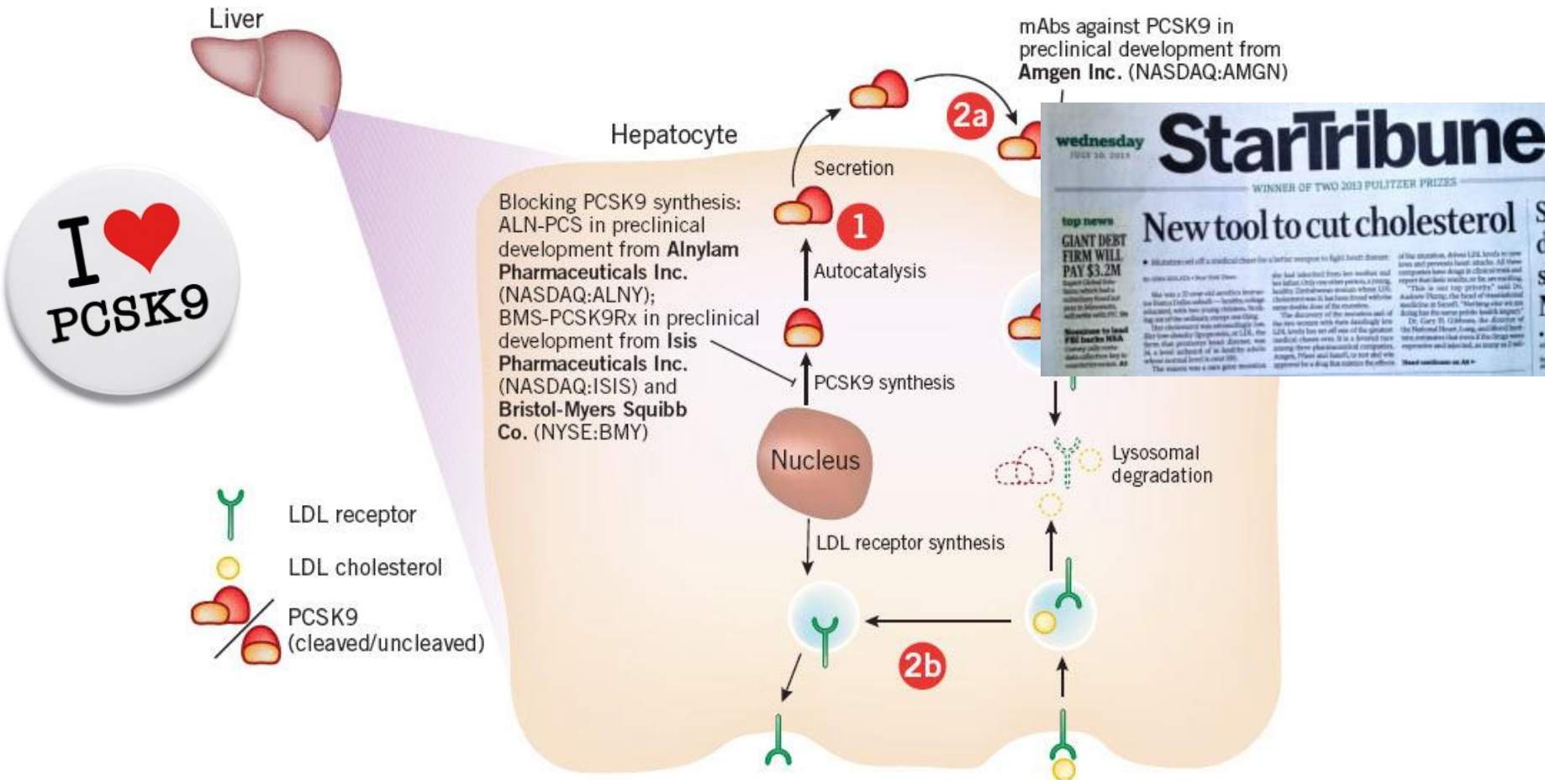


Pedigree of FAD-RO1.

PCSK9 schematic of nonsense mutations associated with low LDL cholesterol



Drivers of Discovery



The New York Times

LETTER

Low frequency and rare variants

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]

- 1,795 Icelanders had whole genome sequencing
- Coding mutation (A673T) in the APP gene that
  - protects against AD
  - ↓cognitive decline in 'normal' elderly

Alzheimer Disease Sequencing Project: ADSP

- Objective 1: Identify novel **risk** raising genes and alleles for late-onset AD
- Objective 2: Identify novel **protective** genes and alleles for late-onset AD.

- Can a single design achieve both objectives?
- Power estimations
- WGS versus WES

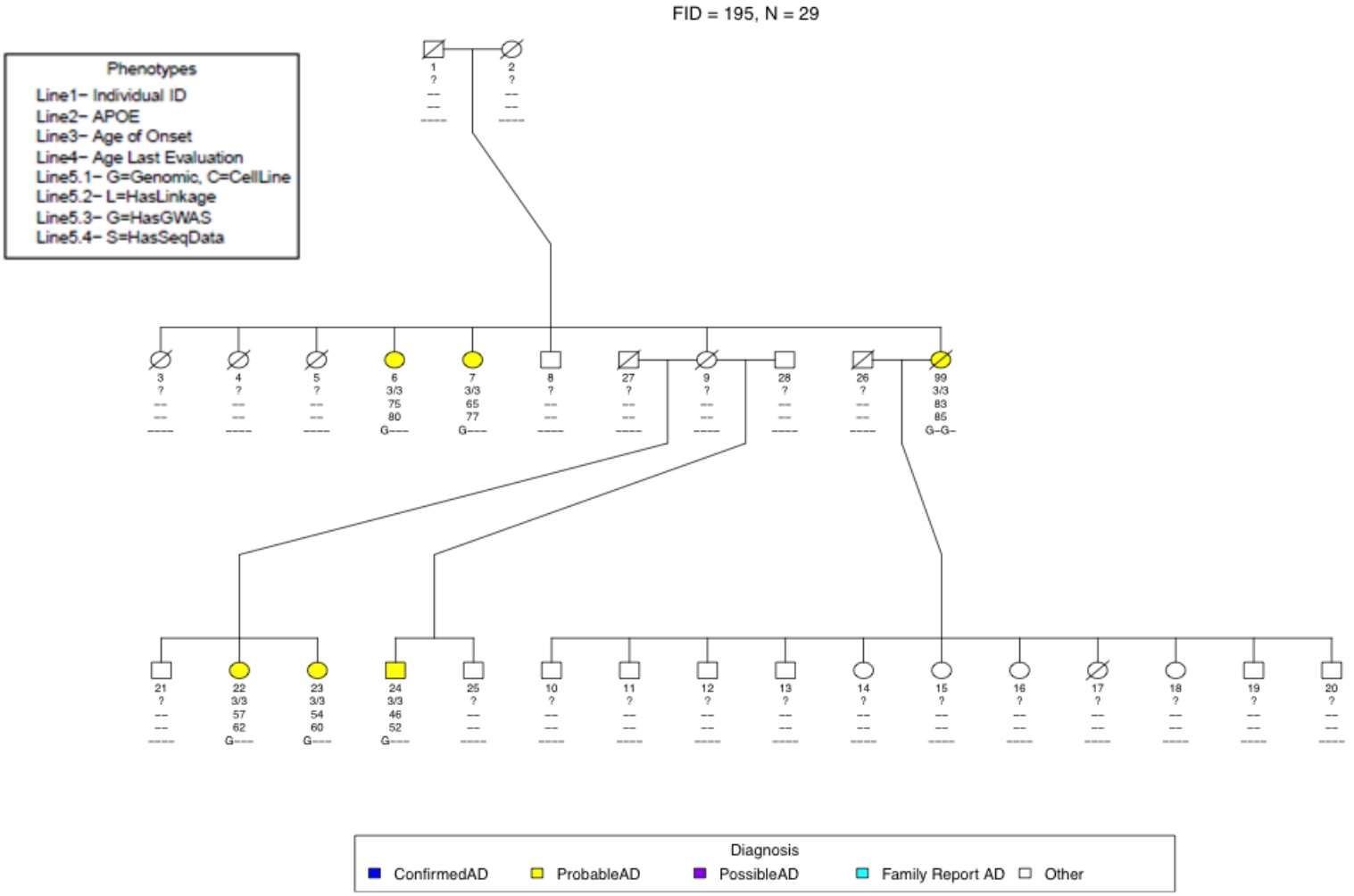
Whole Genome Sequencing (30X)

Families	Number
Caucasian families	42
Caribbean Hispanic families	67
Dutch families	2
Total:	111

502 cases, 82 unaffected, 584 total

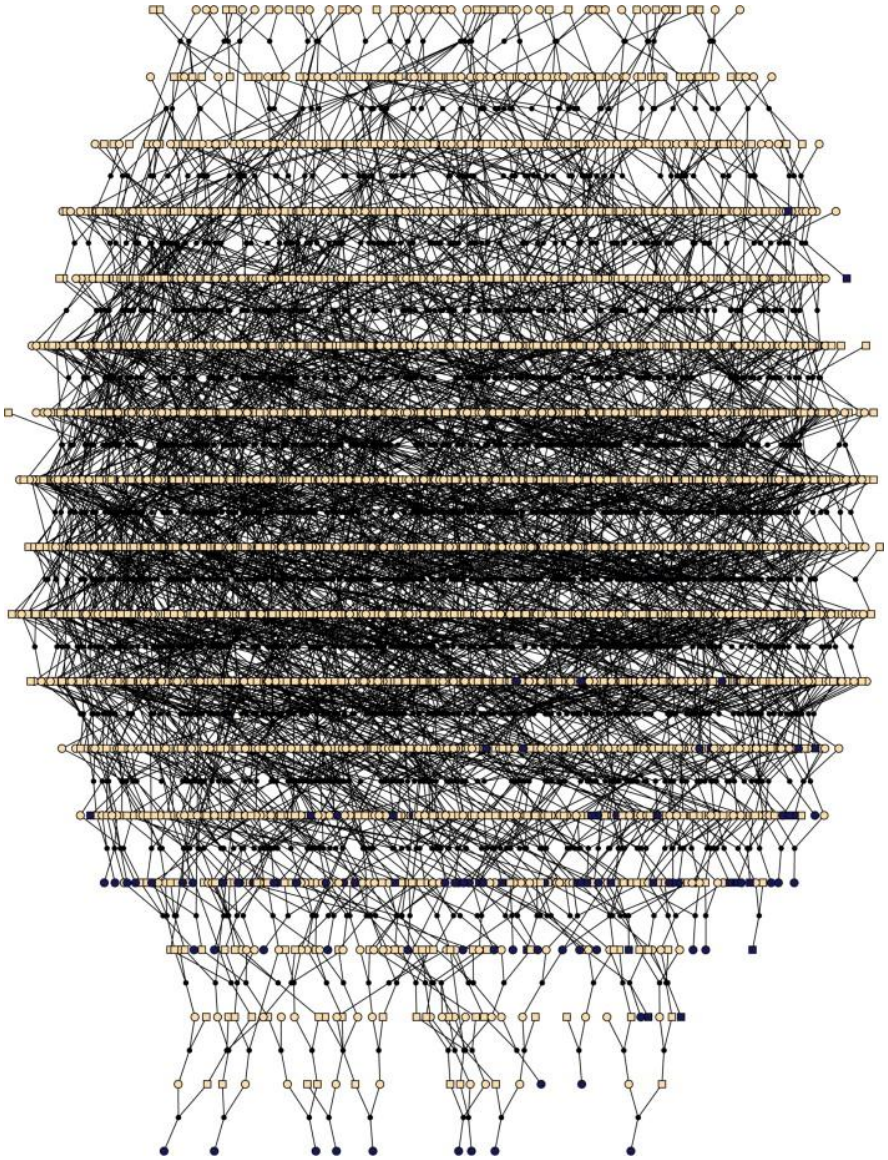
Flat; Phasing

ADSP Family Study (Tier 1a)



Pedigree connecting 103 patients with late-onset Alzheimer's Disease (LOAD) from the ERF/GRIP population.

4,465 persons across 18 generations



Whole Exome Sequencing (30X)

5,000 (actual 5,107) unrelated 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 (actual 4,976) unrelated elderly cognitively normal controls

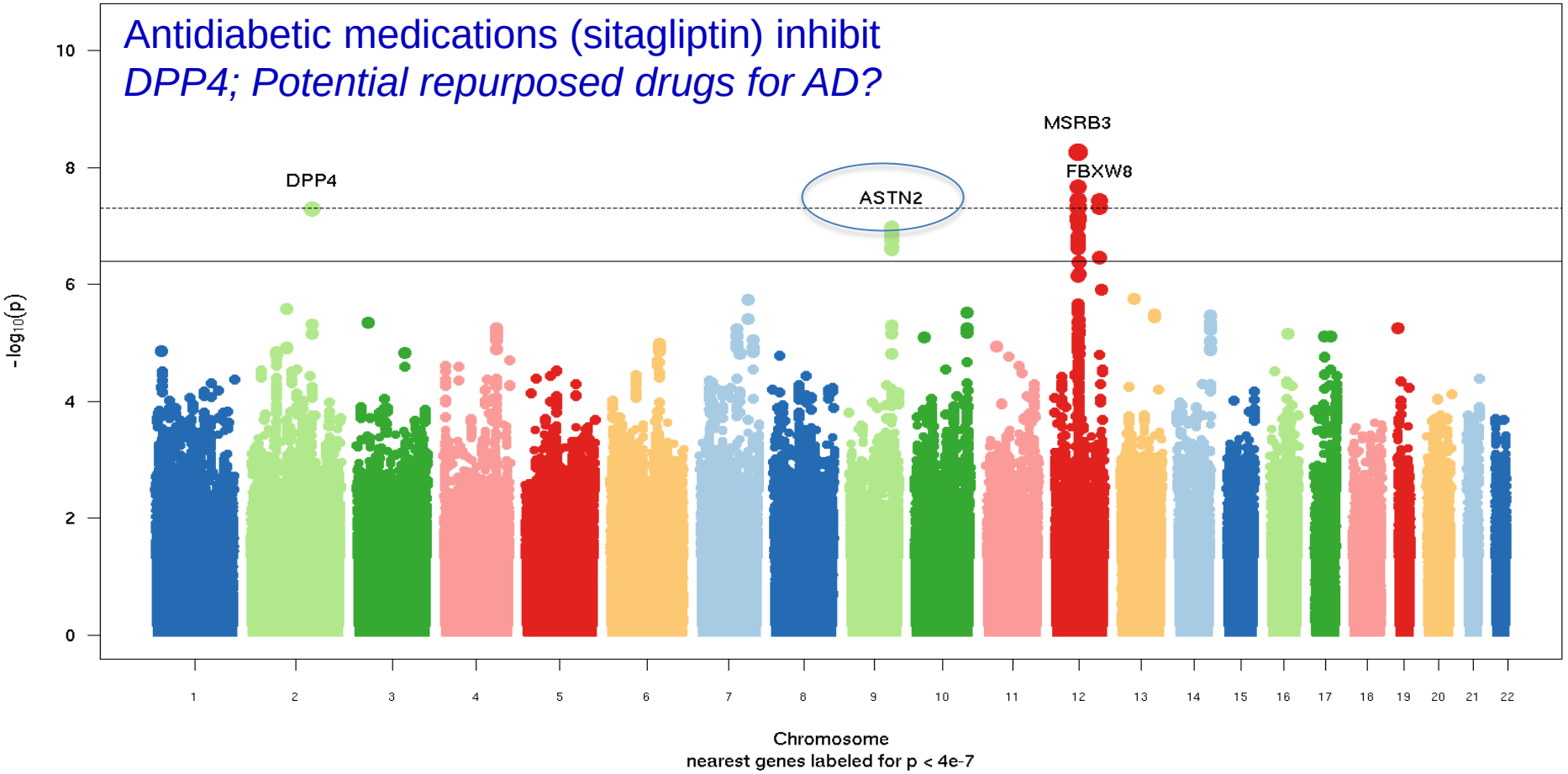
- selected as controls least likely to convert to a case, based on age, *APOE*, and autopsy data - old, *APOE* ε2/ε2, ε2/ε3, or ε3/ε3 little or no AD neuropathology

1,000 cases from multiplex families – one/family

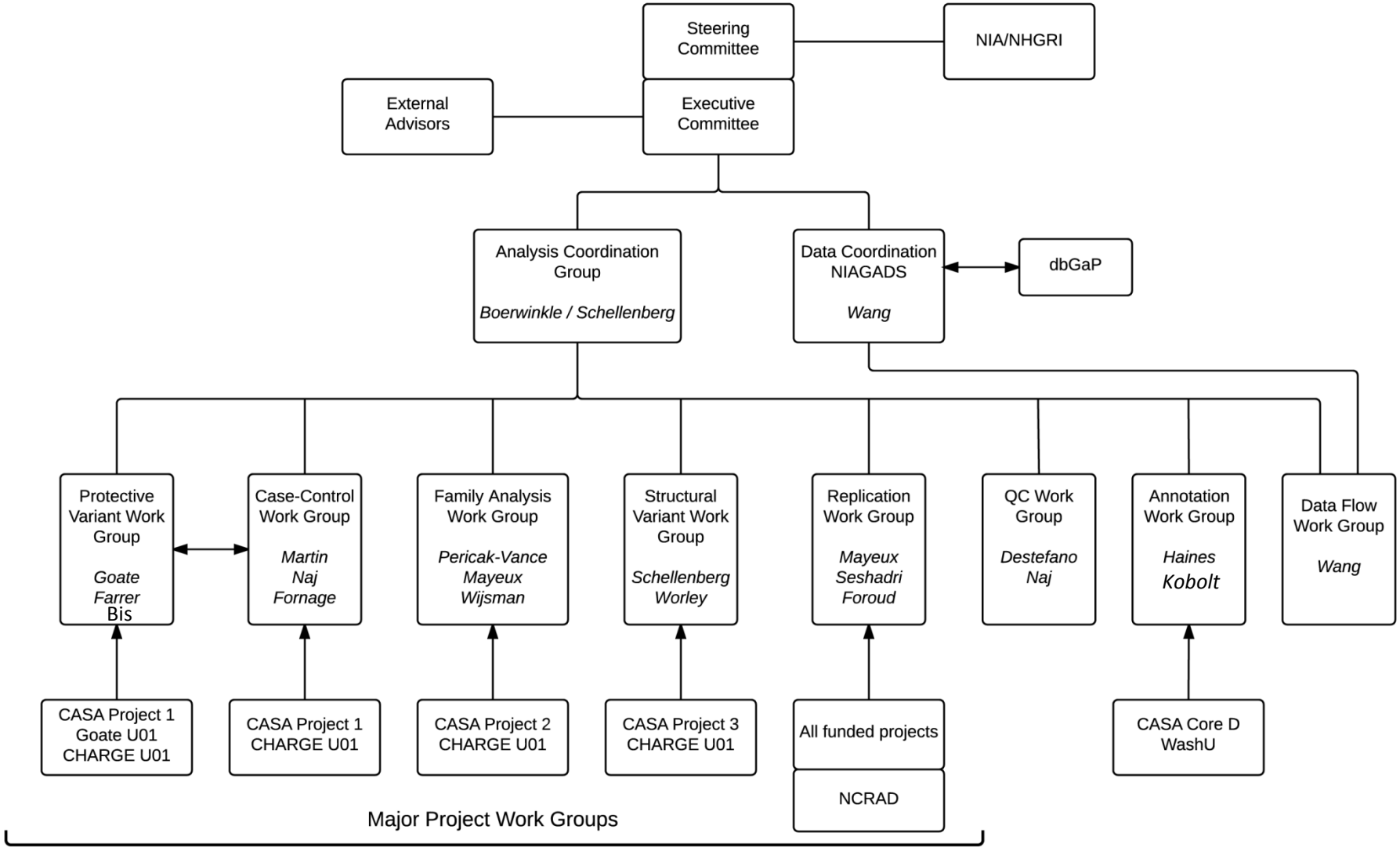
- (actual: 685 cases + 171 Caribbean Hispanic controls)

Endophenotypes: e.g. 21,150 Hippocampal volumes, 1811 with WES
e.g. 39,693 with verbal memory, 7493 EA and 2488 AA with WES

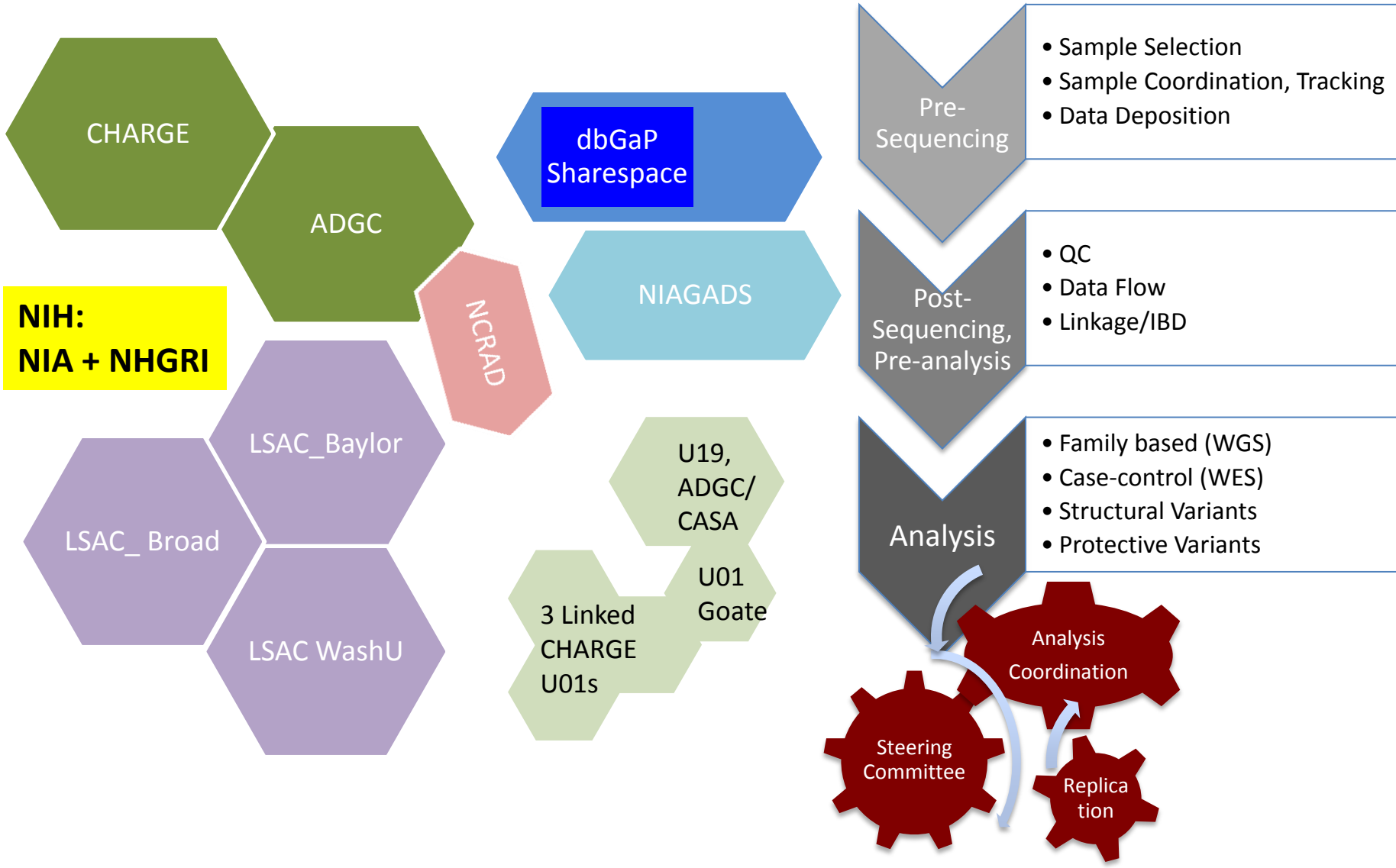
CHARGE: Hippocampal Volume GWAS



Loci in or near genes related to apoptosis (*HRK*), ubiquitinylation (*FBXW8*), embryonic development (*WIF1*), oxidative stress (*MSRB3*), neuronal migration (*ASTN2; associated with cognition, AD risk*), glucose metabolism, proline cleaving enzymes targeted by incretins like sitagliptin (*DPP4*).


Steering Committee
NIA/NHGRI
External Advisors
Executive Committee
Analysis Coordination Group
Boerwinkle / Schellenberg
Data Coordination NIAGADS
Wang
dbGaP
Protective Variant Work Group
Goate
Farrer
Bis
Case-Control Work Group
Martin
Naj
Fornage
Family Analysis Work Group
Pericak-Vance
Mayeux
Wijsman
Structural Variant Work Group
Schellenberg
Worley
Replication Work Group
Mayeux
Seshadri
Foroud
QC Work Group
Destefano
Naj
Annotation Work Group
Haines
Kobolt
Data Flow Work Group
Wang
CASA Project 1
Goate U01
CHARGE U01
CASA Project 1
CHARGE U01
CASA Project 2
CHARGE U01
CASA Project 3
CHARGE U01
All funded projects
NCRAD
CASA Core D
WashU
Major Project Work Groups

ADSP: Set-Up at a Glance



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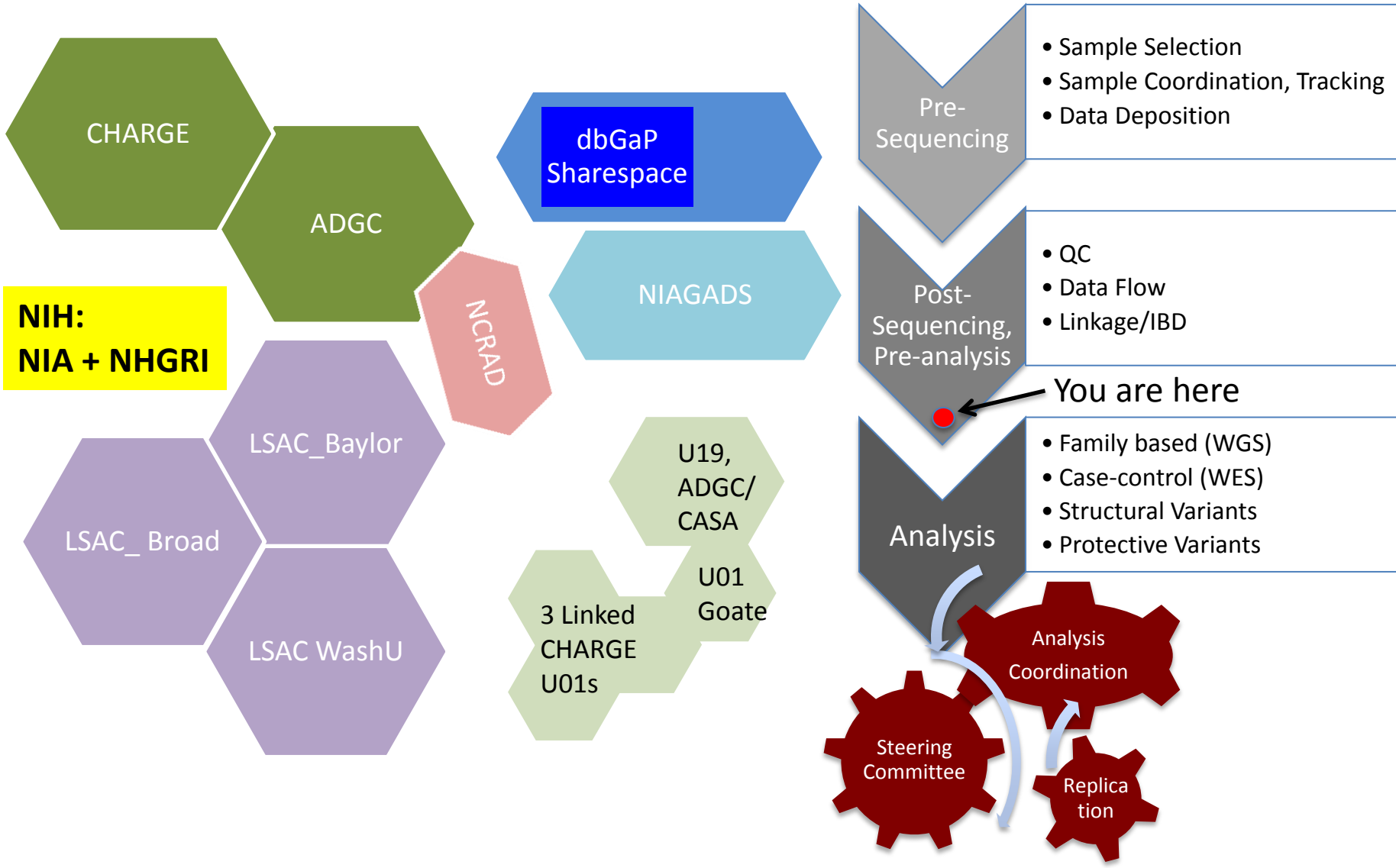
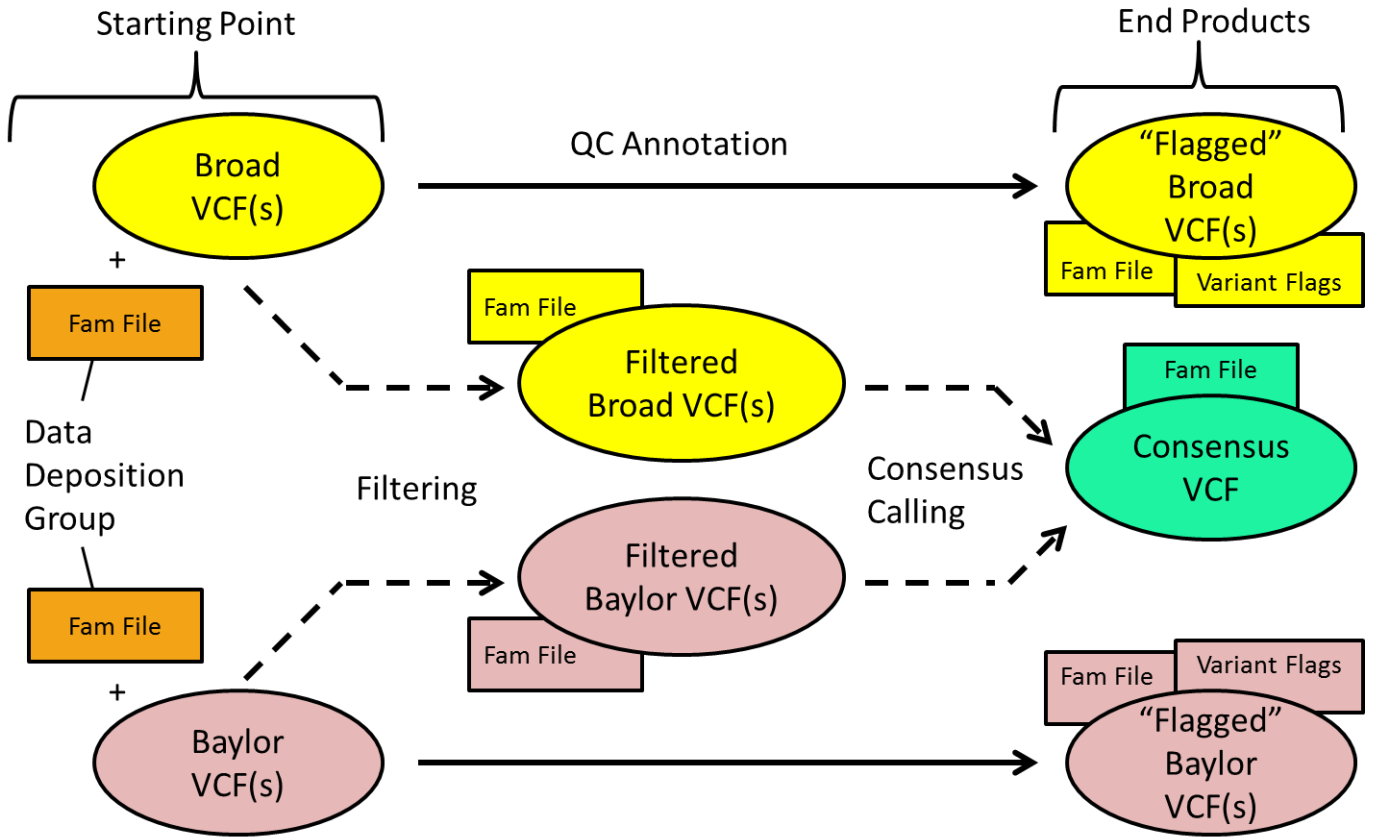


ADSP Progress Update

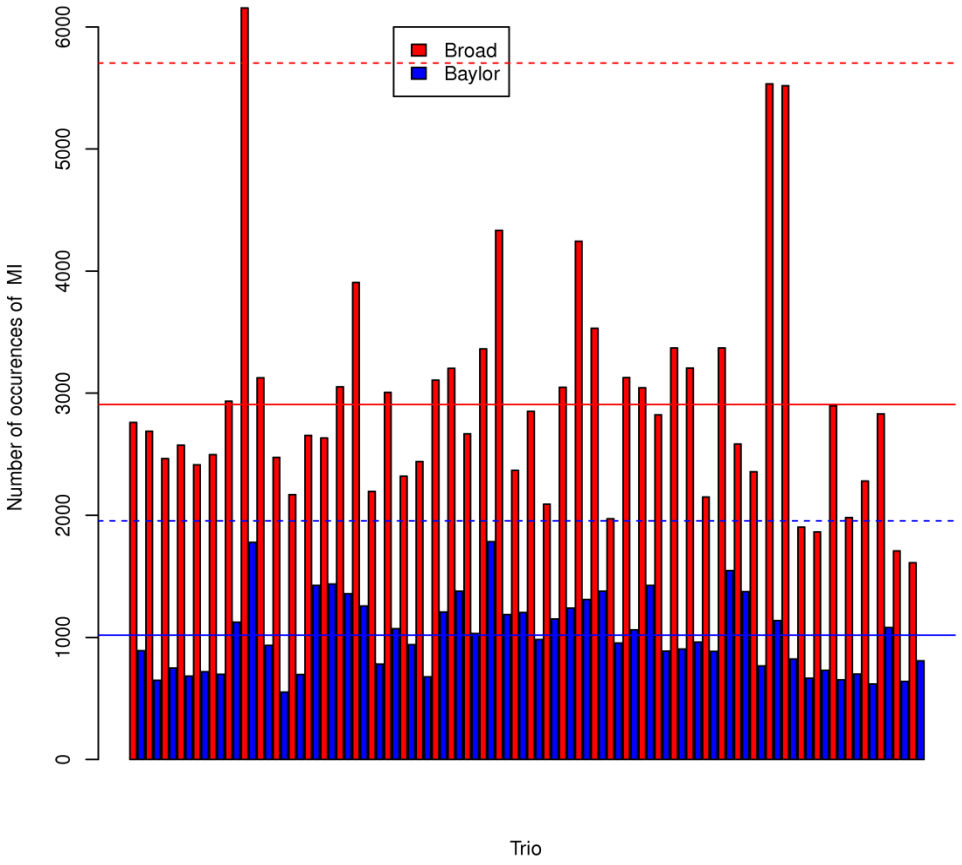
- Unique challenge: Starting with VCFs from two pipelines
  - GATK-HaplotypeCaller (from Broad Institute)
  - Atlas V2 (from Baylor HGSC)



WGS
Release
Tire kicking
V1.0: March 31i

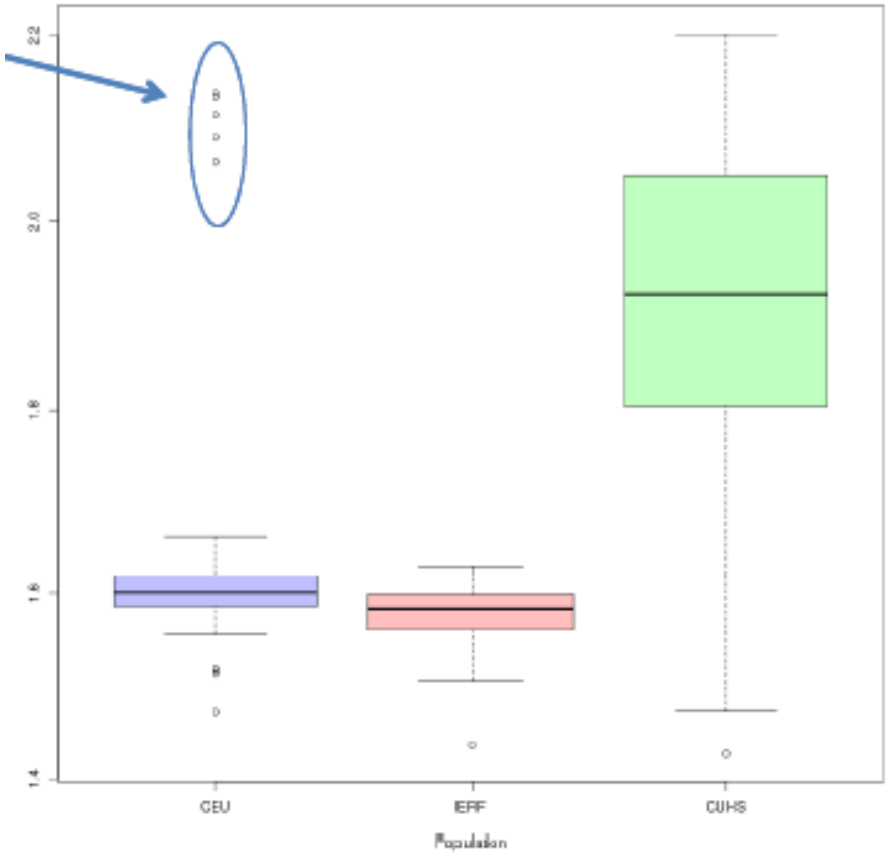
Example QC: Mendelian Inconsistencies

- Relationships appear consistent with pedigree info
- # SNVs with inconsistencies per trios



Example QC: Apparent ethnicity mismatch

- Sample-level QC identified 5 samples that were outliers for heterozygosity measures



Replication Study Goals

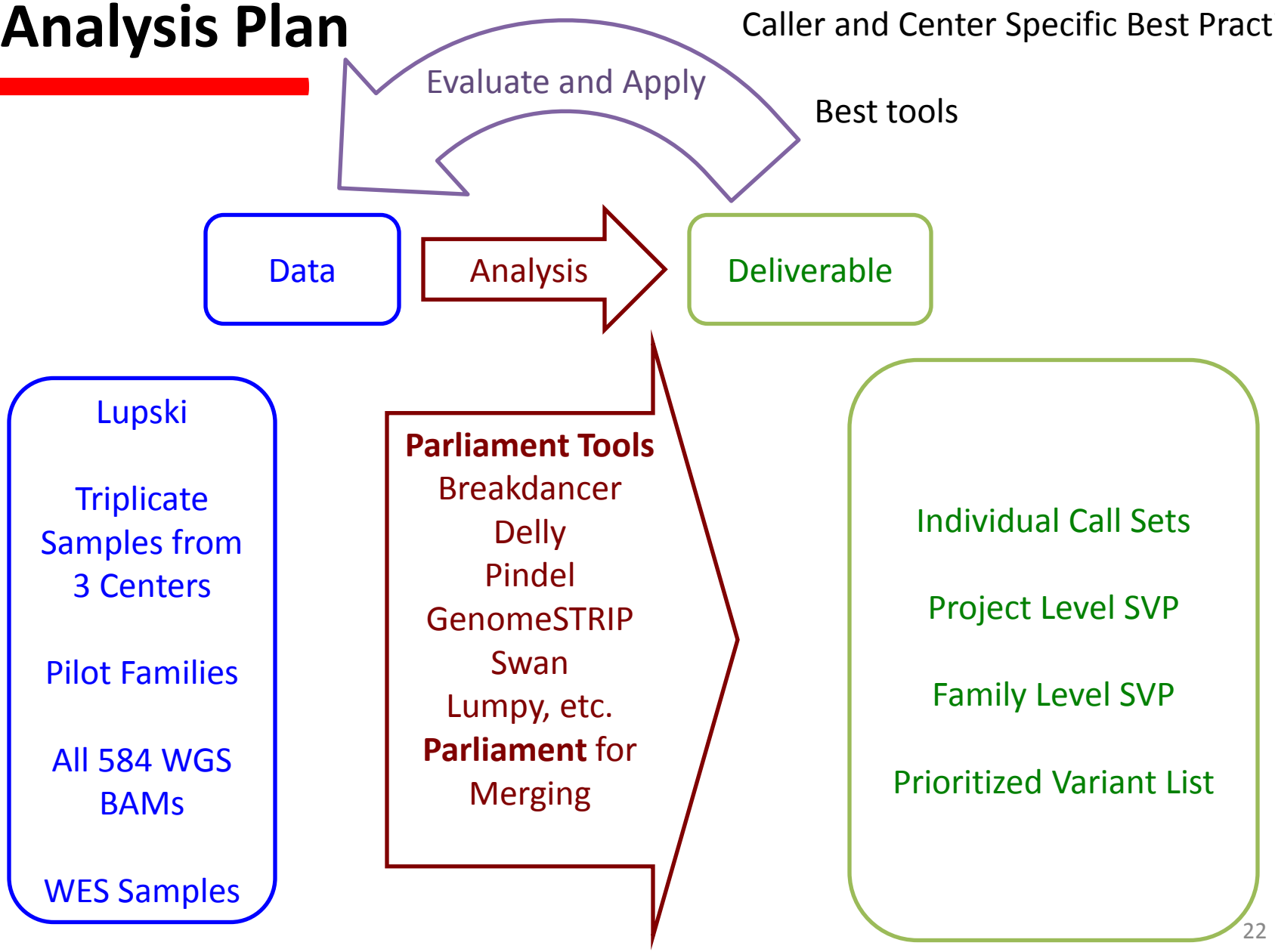
- To provide a well phenotyped dataset of at least 40,000 European-ancestry (EA) samples (~20,000 cases and ~20,000 controls) for replicating and extending findings and a sample ~10,000 individuals from one or more other ethnic groups.
- Targeted re-sequencing of loci, genes or regions containing rare variants or structural variations associated with LOAD.
- Additional WES or WGS for replication and to increase sample size

Likely Available Samples with DNA, Phenotype and Consent

Study	Total ADSP Cases	Total ADSP Controls
MAP		
ROS		
MARS	708	1837
ACT	652	2631
ADC	3494	5031
AA Genetics	27	432
Indianapolis AA	180	1346
MIRAGE	1024	1758
Miami	1326	1632
OHSU	266	223
GenADA	164	169
EAS	49	476
EFIGA*	2325	2057
NIA LOAD	1436	2465
WHICAP*	1019	3435
NOMAS	72	720
NCRAD	690	0
Genetic Differences	281	293
Total (3/28/14)	**13713**	**24505**

CHARGE + Study	Total Cases	Total Controls	Cases with WES	Controls with WES
ASPS/PROD EM	364	848	80	5
CHS EA	615	2238	494	1776
CHS AA	153	352	28	61
ERF	198	2921	?	?
FHS	394	4048	153	2899
Rotterdam	1081	7540	609	2852
ARIC* EA	139	9777	120	4000
ARIC* AA	111	2123	240	2123
90+ Study*	540	270	0	0
SALSA	101	1371	0	0
Fundacio ACE	3645	1127	0	0
GEMS*	343	1987	0	0
HRS	600	13,000	0	0
Total (3/28/14)	**8577**	**47,602**		
Also GERAD, EADI				

Innovative SV Analysis Plan



Early Manuscripts

Design paper: Gary Beecham and Sudha Seshadri

Dominican linkage: Mayeux, submitted

European-American linkage: Pericak-Vance, submitted

QC “best” practices: Anita DeStefano, Adam Naj, Adrienne Cupples, Jennifer Brody

Other?

Sample of ADSP Investigators

- Marilyn Miller, Adam Felsensfeld, Shannon Biello
- Stacey Gabriel, Namrata Gupta, Rick Wilson, Dan Kobolt, Dave Larson, Richard Gibbs, Eric Boerwinkle, Will Salerno
- Gerard Schellenberg, Richard Mayeux, Margaret Pericak-Vance, Lindsay Farrer, Jonathan Haines, Adam Naj, Gary Beecham, Amanda Patch
- Sudha Seshadri, Ellen Wijsman, Anita DeStefano, Adrienne Cupples, Cornelia van Duijn, Josh Bis, Ken Rice, Myriam Fornage
- Allison Goate, Carlos Cruchaga
- And many others