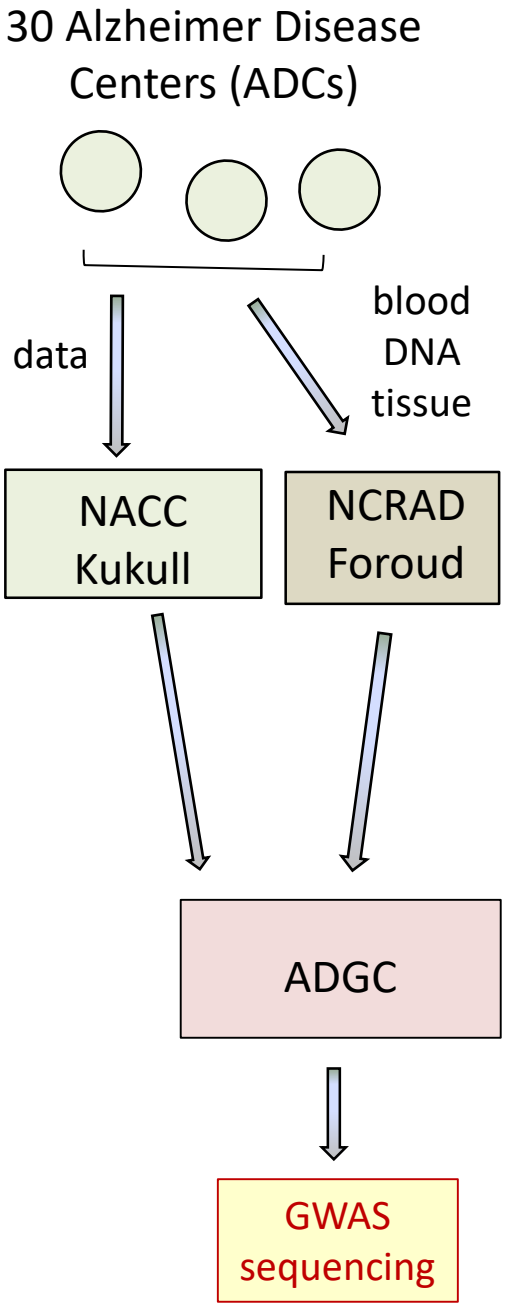
Alzheimer's Disease Center Directors Meeting

San Diego
October 14, 2017

Perelman School of Medicine
University of Pennsylvania

Penn
University of Pennsylvania



Alzheimer's Disease Centers

- AD cases and controls
- Standardized phenotype data and autopsy data

ADCs

National Alzheimer Coordinating Center

- Collect/distribute all ADC data
- Manage phenotype definitions

NACC

National Cell Repository for Alzheimer disease

- Collect tissue/DNA
- Distribute samples

NCRAD

Alzheimer's Disease Genetics Consortium

- Genetic association studies
- Sequencing
- Common/rare variant discovery

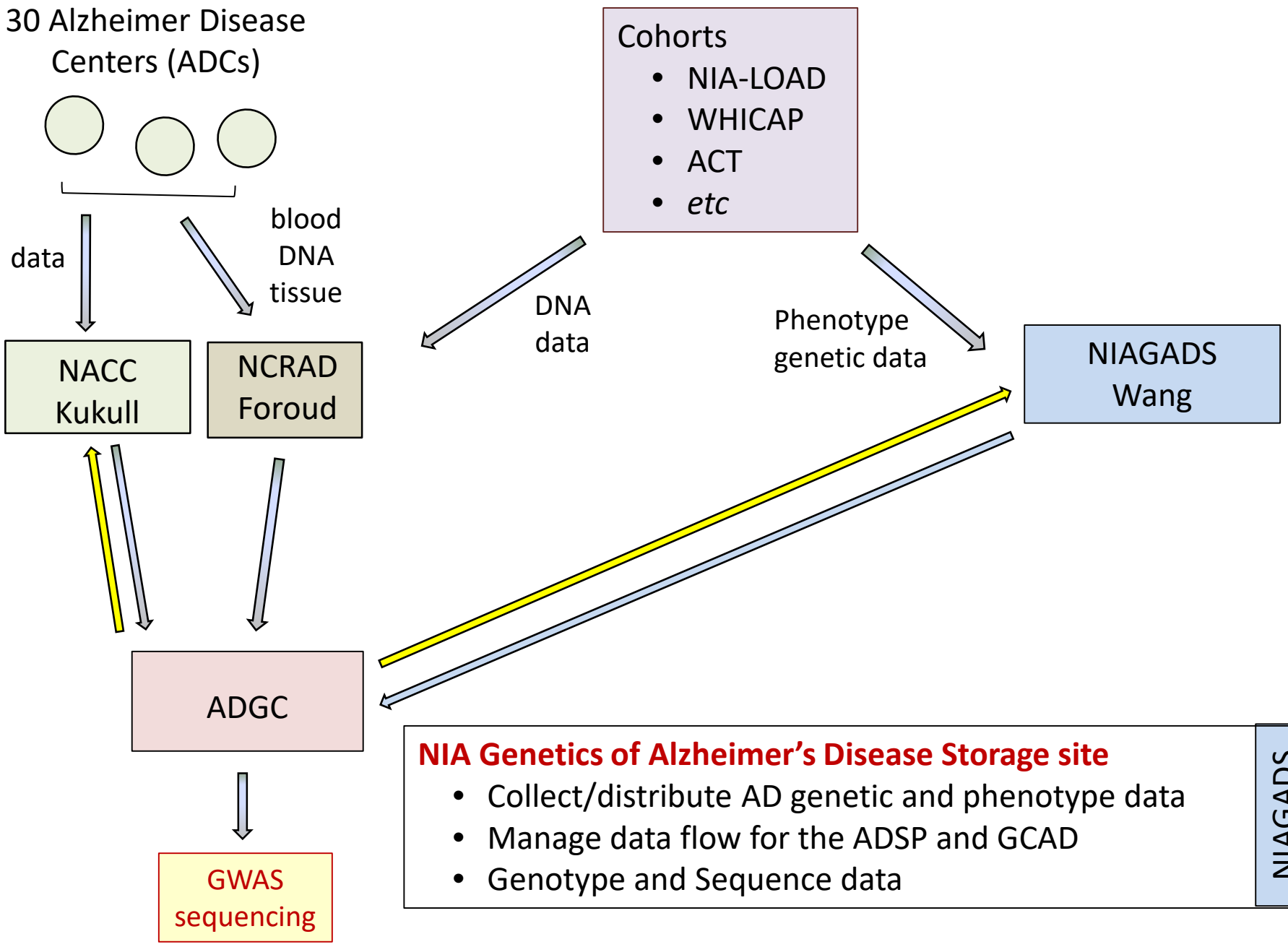
ADGC

ADGC Cohorts

Cohort	Cases	Controls
ADC1	1,549	512
ADC2	727	156
ADC3	894	586
ADC4	304	377
ADC5	286	505
ADC6	213	338
ADC7	566	878
ADC8	517	664
ADC9	728	896

5,771 cases
4,912 controls
10,683 total

Fully QC'ed
Ready for use


30 Alzheimer Disease Centers (ADCs)
data
blood
DNA
tissue
Cohorts
• NIA-LOAD
• WHICAP
• ACT
• etc
DNA data
Phenotype genetic data
NACC Kukull
NCRAD Foroud
NIAGADS Wang
ADGC
GWAS sequencing
NIA Genetics of Alzheimer's Disease Storage site
• Collect/distribute AD genetic and phenotype data
• Manage data flow for the ADSP and GCAD
• Genotype and Sequence data
NIAGADS

ADGC Cohorts

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
ADC7	566	878
ADC8	517	664
ADC9	728	896
ADNI	268	173
BIOCARD	6	122
CHAP	27	144
EAS	9	141
GSK	666	712
NIA-LOAD	1,788	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	354	986
TARCC	323	181
TGEN	668	365

5,771 cases
4,912 controls
10,683 total

Cohort	Cases	Controls
UKS	596	170
UMVUMSSM	1,177	1,126
UPITT	1,255	829
WASHU	339	187
WASHU2	38	94
WHICAP	76	560
Totals	**16,229**	**17,010**

Grand total **33,129**

IGAP

Consortium	Cases	Controls
ADGC	14,428	14,562
CHARGE	2,137	13,474
EADI	2,240	6,631
GERAD	3,177	7,277
Totals	**21,972**	**41,935**

ADGC African American WES

	Cases	Controls
Reitz et al (2013)	1,968	3,928
New GWAS samples	763	1,073
Percent increase	39%	27%
Total	2,731	5,001

Sequencing completed
Data being transferred to GCAD

- gVCFs – November 1
- Project level VCF – January?

ADGC African American WES

Study	Affected	Unaffected	Total
MIRAGE	105	125	230
Miami/Duke	180	309	489
North Carolina A&T	186	256	442
Case Western	44	60	104
Alzheimer's Disease Centers	**572**	**740**	**1,312**
GenerAAtions	211	187	471
Rush	78	84	162
Total	1,376	1,761	3,210

Case-control WGS (ADSP extension)

Caucasians:	500 cases/500 normal controls
African Americans:	500 cases/500 normal controls
Caribbean Hispanics:	500 cases/500 normal controls

- Sequencing completed – March 2017
- Processing – summer 2017 - 2018

Controls are elderly cognitively normal subjects

Asian Cohorts

Cohort	cases	controls
Taiwan	900	1,500
China	6,000	6,000
Korea	1,200	2,300
Singapore	600	1500
Japan	4,000	4,000

Country	University	PI
Taiwan	Yang-Ming University	Jong-Ling Fu
China	Chinese Capitol Medicine University	Jianping Jia
Korea	National research center for dementia	Kun Ho Lee, PhD,
Singapore	SHHQ	Adeline Ng Su Lyn
Japan	Niigata University	Takeshi Ikeuchi
	National Center- Geriatrics/Gerontology	Kouichi Ozaki
		Ryuozo Kuwano (retired)

ADGC Special Analysis Proposals – all: 105
ADGC Special Analysis Proposals – 2017: 23

SAGs: defined as a collaboration
Reviewed by Analysis committee

Change: Assign ADGC PI/senior investigator to be responsible for each SAG to insure quality of work and compliance.

Collaborators: ADCs
PIs who submit cohorts
PI analysts

ADGC Publications

2010 – 2017: 84 publications
2016 – 2017: 21 published/in press
Present: 5 submitted

1. Mez et al. , (2017) Two novel loci, COBL and SLC10A2, for Alzheimer's disease in African Americans. Alzheimer's & Dementia **13**, 119-129.
2. Chapuis et al,. (2017) Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism. Acta Neuropathologica **133**, 955-966.
3. Jun et al. (2017) Transethnic Genome-Wide Scan Identifies Novel Alzheimer Disease Loci. Alzheimer's & Dementia **3**:727-738
4. Desikan et al. (2017) Genetic assessment of age-associated Alzheimer's disease risk: development and validation of a polygenic hazard score. PLOS Medicine **14**(3): e1002258. PMID:28323831
5. Deming et al. (2017) Genome-wide association study identifies four novel loci associated with Alzheimer's endophenotypes and disease modifiers. Acta Neuropathol. **133**, 839–856.
6. Huang et al. (2017) A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease. Nat. Neurosci. (in press)
7. Kunkle et al. (2017) Early-onset Alzheimer disease and candidate risk genes involved in endo-lysosomal transport. JAMA Neurology (in press)
8. Gusareva et al. (2017) Male-specific epistasis between WWC1 and TLN2 genes is associated with Alzheimer's disease. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring (in press)
9. **Sims et al. (2017) Novel rare coding variants in *PLCG2*, *ABI3* and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease. (2017) Nat. Genet. (in press)**
10. Haddick et al. P (2017) A Common Variant of IL-6R is Associated with Elevated IL-6 Pathway Activity in Alzheimer's Disease Brains. J Alzheimer's Dis. **56**:1037-1054.

nature genetics

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease

We identified rare coding variants associated with Alzheimer's disease in a three-stage case–control study of 85,133 subjects. In stage 1, we genotyped 34,174 samples using a whole-exome microarray. In stage 2, we tested associated variants ($P < 1 \times 10^{-4}$) in 35,962 independent samples using *de novo* genotyping and imputed genotypes. In stage 3, we used an additional 14,997 samples to test the most significant stage 2 associations ($P < 5 \times 10^{-8}$) using imputed genotypes. We observed three new genome-wide significant nonsynonymous variants associated with Alzheimer's disease: a protective variant in *PLCG2* (rs72824905: p.Pro522Arg, $P = 5.38 \times 10^{-10}$, odds ratio (OR) = 0.68, minor allele frequency $(MAF)_{cases} = 0.0059$, $MAF_{controls} = 0.0093$), a risk variant in *ABI3* (rs616338: p.Ser209Phe, $P = 4.56 \times 10^{-10}$, OR = 1.43, $MAF_{cases} = 0.011$, $MAF_{controls} = 0.008$), and a new genome-wide significant variant in *TREM2* (rs143332484: p.Arg62His, $P = 1.55 \times 10^{-14}$, OR = 1.67, $MAF_{cases} = 0.0143$, $MAF_{controls} = 0.0089$), a known susceptibility gene for Alzheimer's disease. These protein-altering changes are in genes highly expressed in microglia and highlight an immune-related protein–protein interaction network enriched for previously identified risk genes in Alzheimer's disease. These genetic findings provide additional evidence that the microglia-mediated innate immune response contributes directly to the development of Alzheimer's disease.

nature genetics

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease

Stage 1: exome chip genotyping:
18,077 controls; 16,097 cases

WES sequence-based array

Stage 2: *de novo* genotyping, $P < 10^{-4}$, n = 43 SNVs
21,921 controls; 14,041 cases

Stage 3: ADGC **HRC imputation** – top 4 variants
8,345 controls; 6,652 cases

Total: 85,133 subjects

Exome Chip Meta-Analyses

Gene	location	P-value	OR	MAF cases	MAF controls	n
TREM2	chr6:41,129,252	5.4×10^{-24}	2.46	0.004	0.002	80,733
TREM2	chr6:41,129,207	1.6×10^{-14}	1.67	0.014	0.008	53,042
PLCG2	chr16:81,942,028	5.4×10^{-10}	0.68	0.006	0.009	84,905
ABI3	chr17:47,297,297	4.6×10^{-10}	1.43	0.011	0.008	84,493

1/OR = 1.47

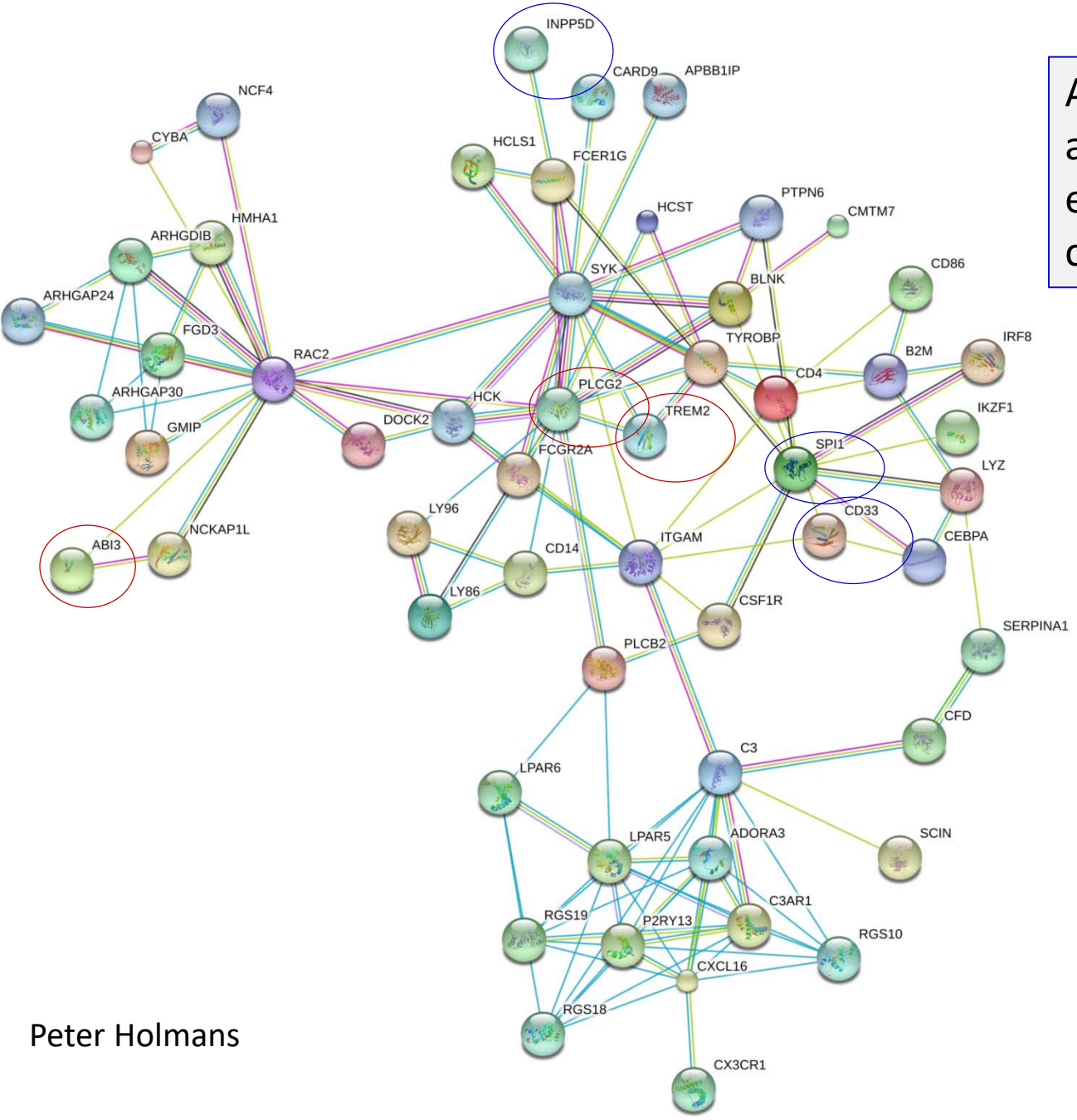
TREM2: triggering receptor expressed on myeloid cells 2 - R47H, R62H

PLCG2: Phospholipase C-γ2 – P522R

ABI3: ABI family member 3, part of Abi/WAVE complex which regulates actin polymerization – S209F

Other AD genes highly expressed in microglial cells:

- *HLA-DRB5*
- *MS4A cluster*
- *SORL1*



All genes in this network are predominantly expressed in microglial cells

STRING database.

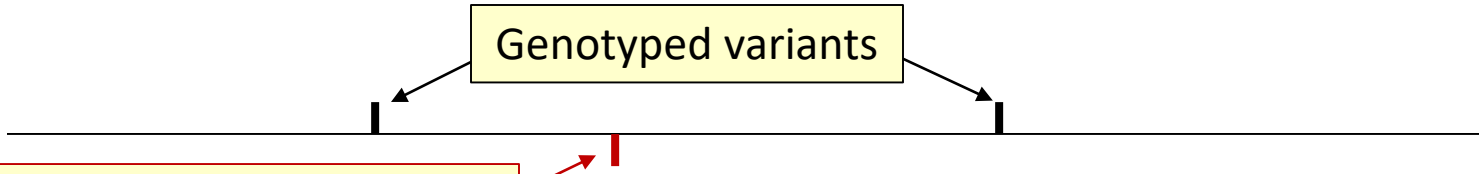
- red=gene fusion
- dark blue = co-occurrence
- black = co-expression
- magenta = experiments
- cyan=databases
- light green = text mining
- mauve = homology

Peter Holmans

Conclusions

1. The innate immune response is part of the AD disease process – not just downstream injury response
2. We can detect rare variants – **WITH VERY LARGE SAMPLE SIZES**
3. The rare variants detected have larger effect sizes than most GWAS loci
4. Imputation is a powerful new genetics tool

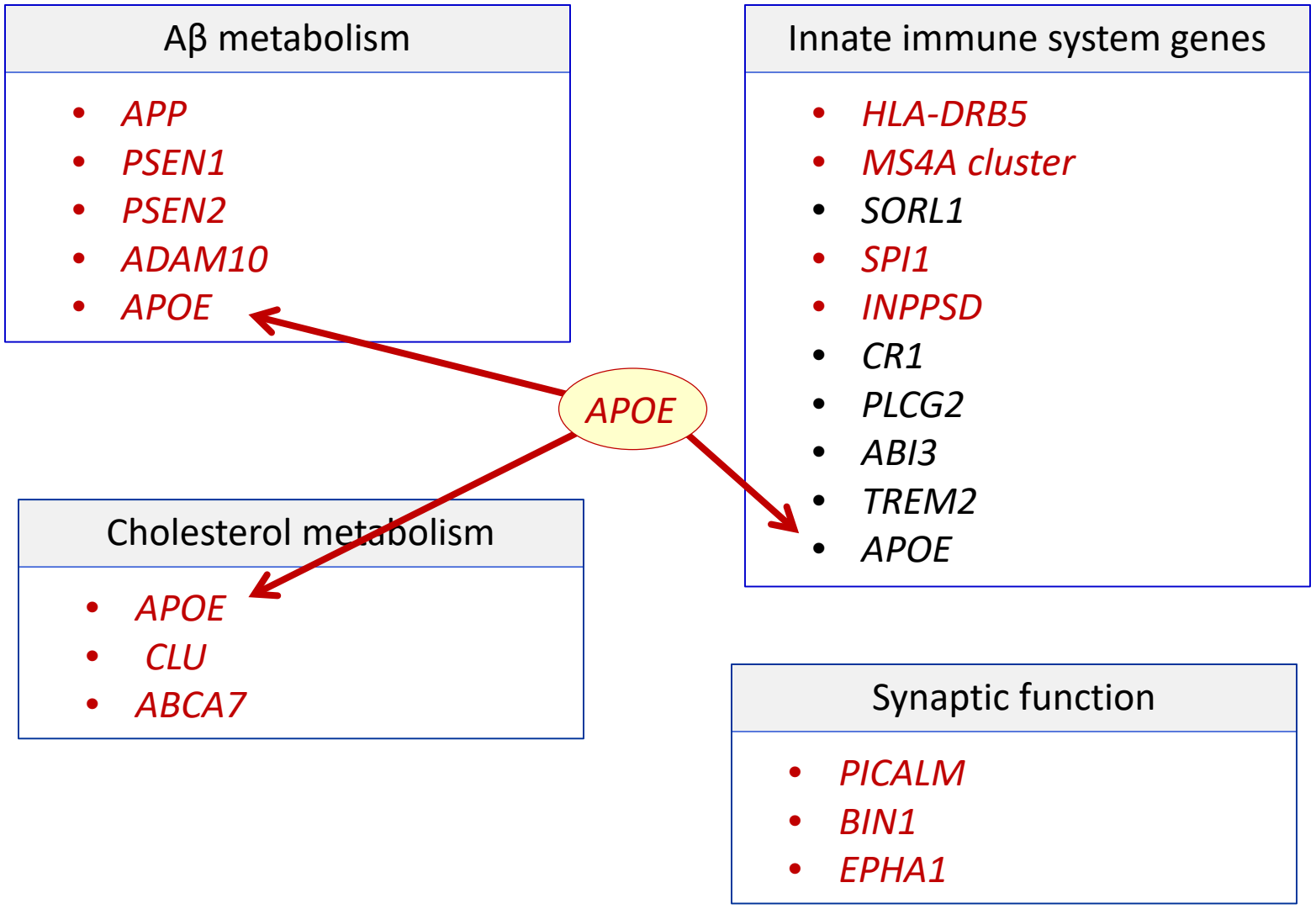
MAF: minor allele frequency
Common: MAF $\geq$ 2%
Rare: MAF < 2%



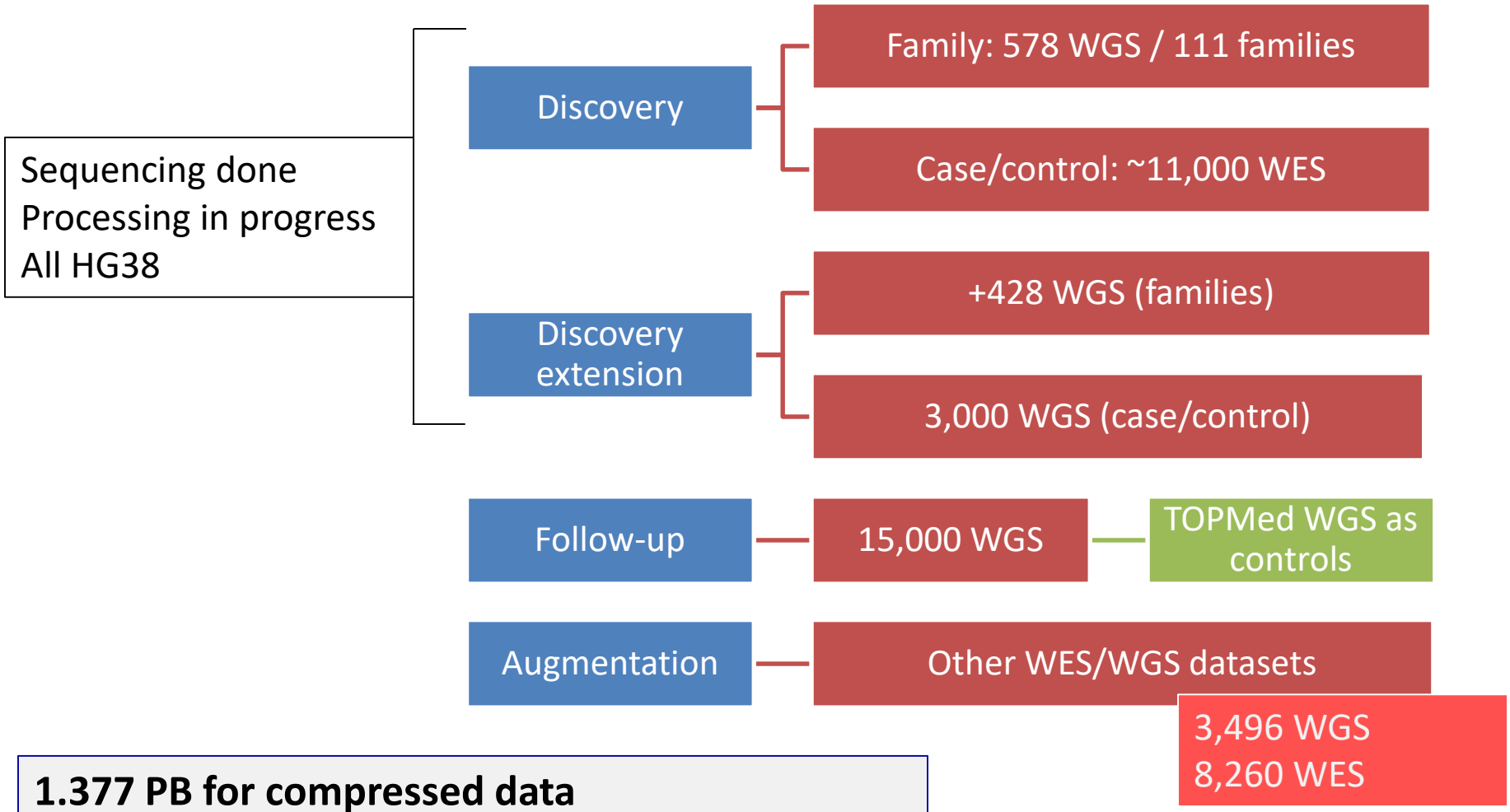
Imput genotype from external haplotype reference panel

Imputation panels: 1,000 - lower quality genomes (2010)
~30,000 mostly high quality genomes (HRC 2015)
~65,000 mostly high quality genomes (2017)

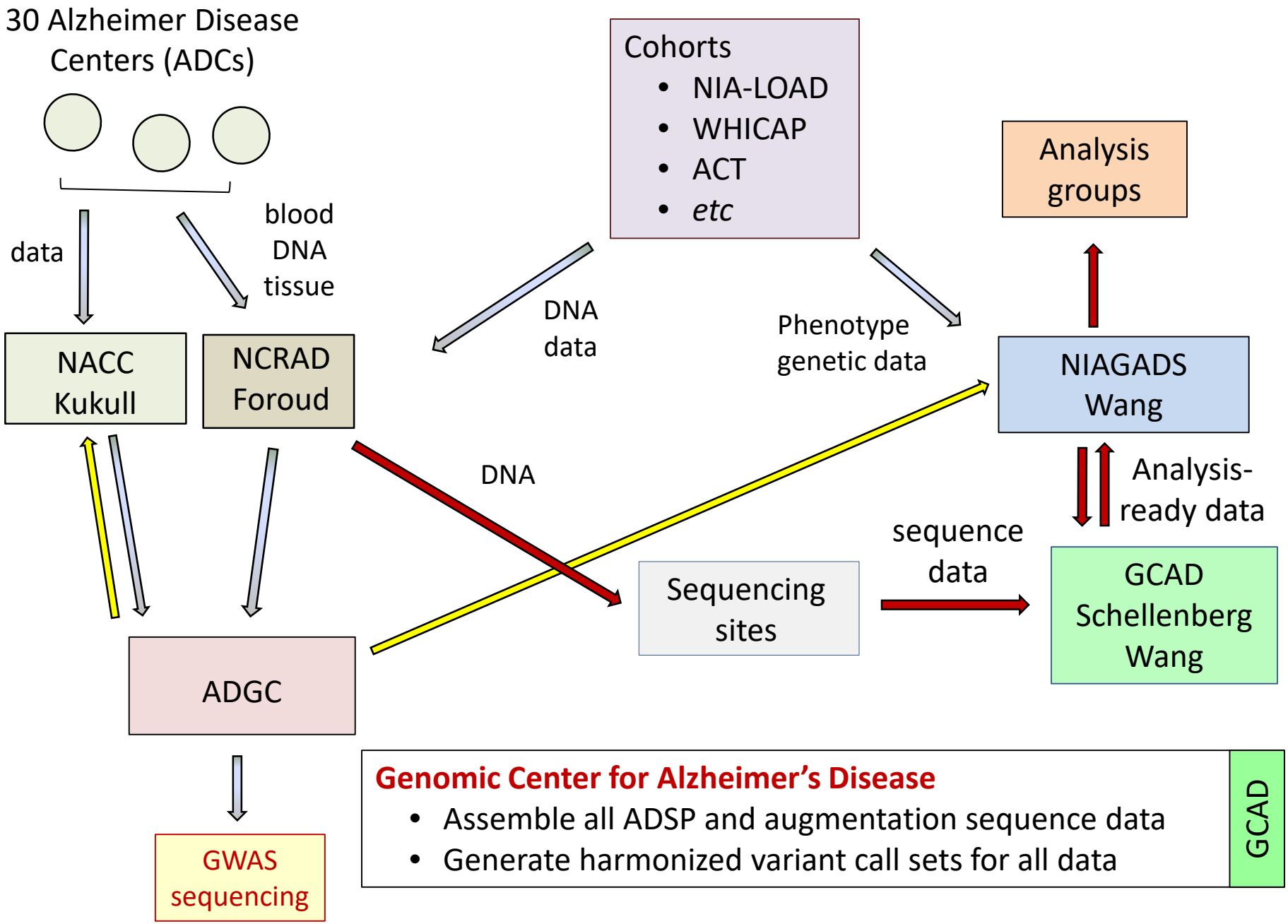
Imputation R^2: 0.7 for MAF = 0.01%
0.8 for MAF = 0.1%


Aβ metabolism
APP
PSEN1
PSEN2
ADAM10
APOE
Innate immune system genes
HLA-DRB5
MS4A cluster
SORL1
SPI1
INPPSD
CR1
PLCG2
ABI3
TREM2
APOE
APOE
Cholesterol metabolism
APOE
CLU
ABCA7
Synaptic function
PICALM
BIN1
EPHA1

Alzheimer's Disease Sequence analysis



1.377 PB for compressed data
- 350 4TB hard drives
- 305 days on a 10Gbit/s direct link to Amazon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Analysis groups
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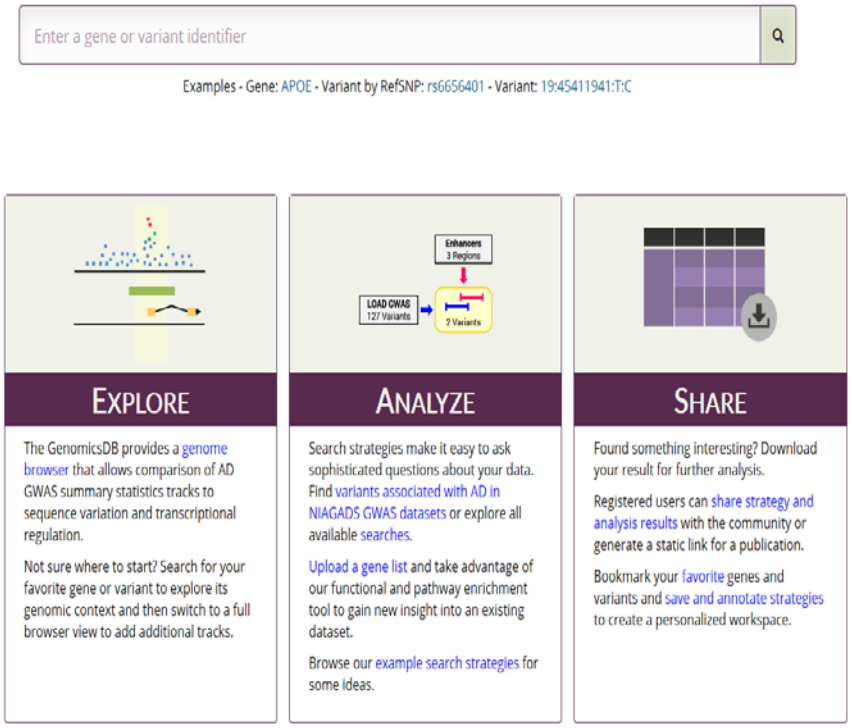
Phenotype
genetic data
NACC
Kukull
NCRAD
Foroud
NIAGADS
Wang
DNA
Analysis-
ready data
sequence
data
Sequencing
sites
GCAD
Schellenberg
Wang
ADGC
GWAS
sequencing
Genomic Center for Alzheimer's Disease
• Assemble all ADSP and augmentation sequence data
• Generate harmonized variant call sets for all data
GCAD

Explore Alzheimer's Disease genetics and genomic annotations using the NIAGADS Genomics Database.



Ask sophisticated questions

about your data,
mine NIAGADS GWAS summary statistics,

and share your results.

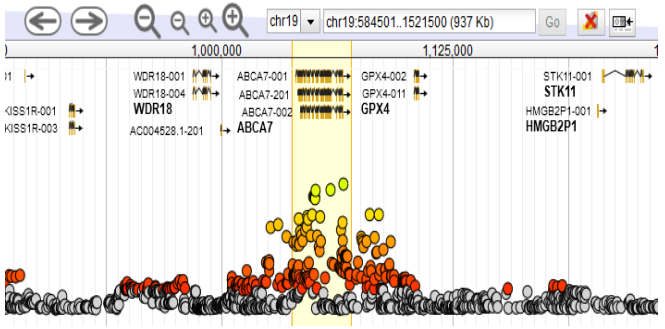
https://www.niagads.org/genomics

Search 35 NIAGADS GWAS Datasets

interactively browse and mine summary statistics datasets to learn more about AD genes and variants, or discover new regions of interest

Integrated with variant annotations

mapped to chromosomal position and allele, allowing annotation of novel variants identified in NIAGADS studies



Browse AD GWAS summary statistics

on our genome browser and compare to sequence features and functional genomics tracks from ENCODE and FANTOM5

Follow links to view detailed annotations

for variants, genes, and genomic region, including genetic variation (NIAGADS, NHGRI GWAS Catalog, 1000 Genomes), gene function and pathways (GO, KEGG), and functional genomics (ENCODE, FANTOM5)

Collaborative Network PIs

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Case Western

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The End