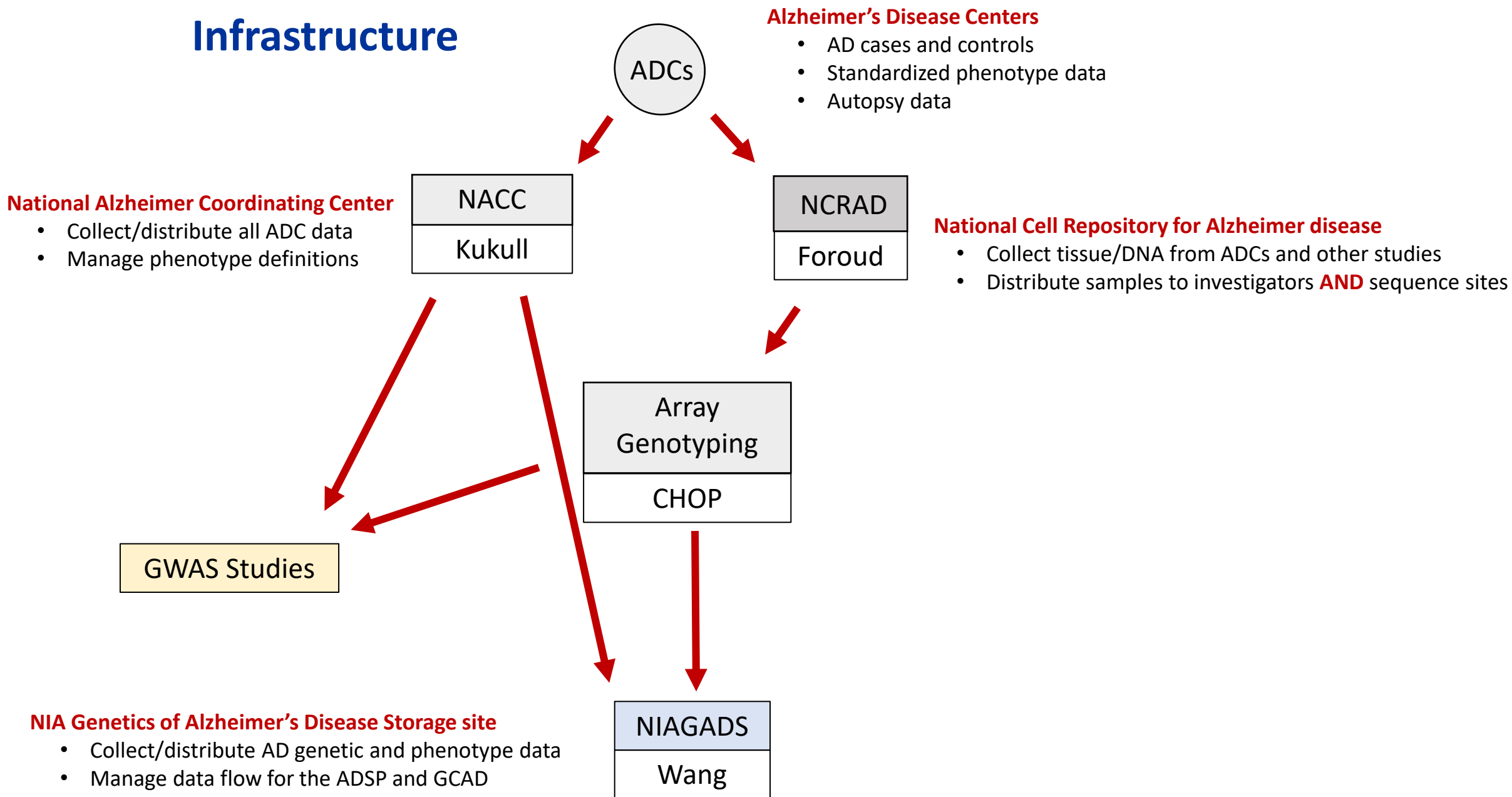


Alzheimer's Disease Genetic Studies ADC Samples/Phenotypes

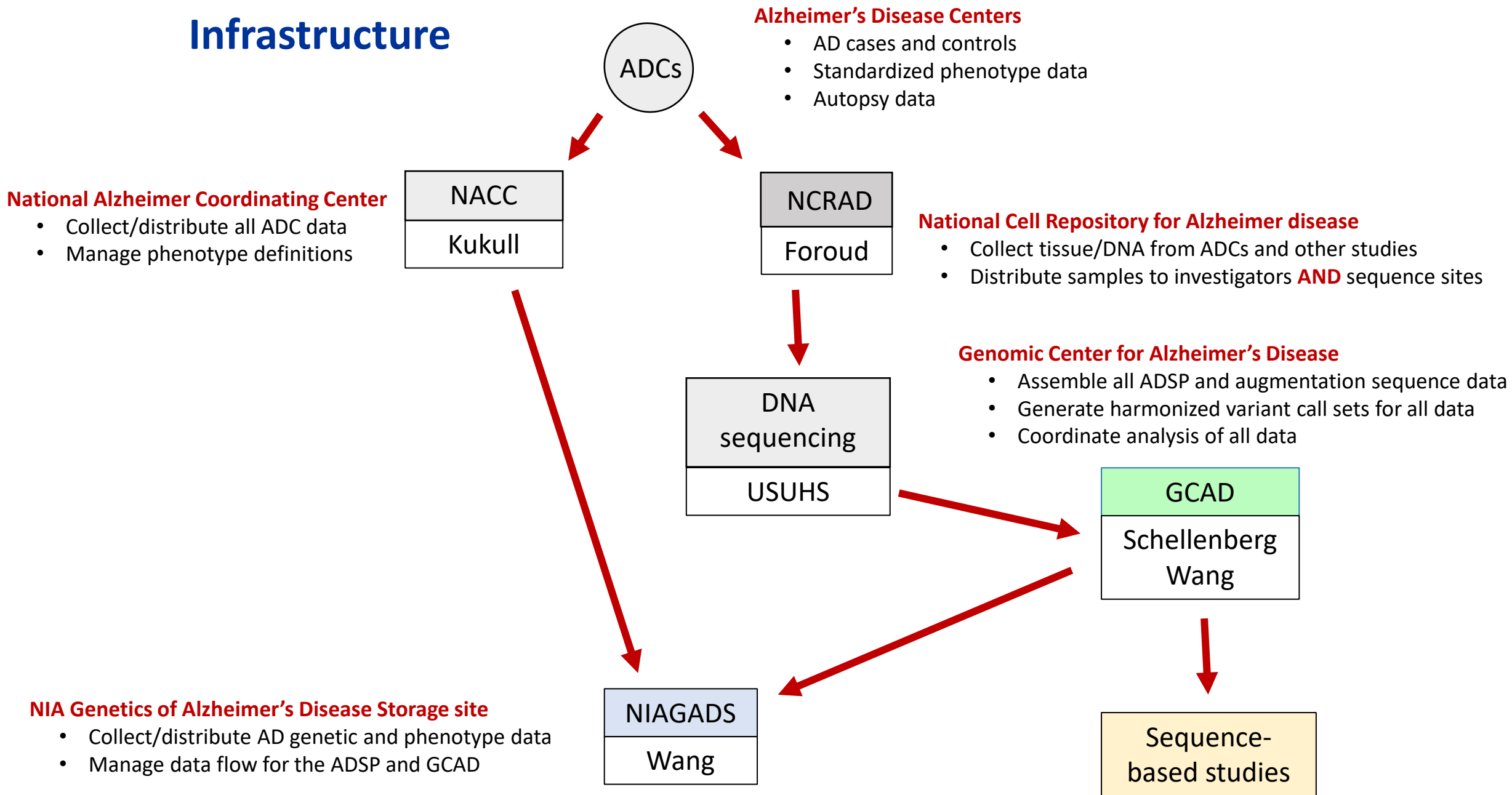
Alzheimer's Disease Genetics Consortium
Alzheimer's Disease Sequencing Project

No conflicts

Infrastructure



Infrastructure



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

Eleven susceptibility loci for late-onset Alzheimer's disease (LOAD) were identified by previous studies; however, a large portion of the genetic risk for this disease remains unexplained. We conducted a large, two-stage meta-analysis of genome-wide association studies (GWAS) in individuals of European ancestry. In stage 1, we used genotyped and imputed data (7,055,881 SNPs) to perform meta-analysis on 4 previously published GWAS data sets consisting of 17,008 Alzheimer's disease cases and 37,154 controls. In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. In addition to the *APOE* locus (encoding apolipoprotein E), 19 loci reached genome-wide significance ($P < 5 \times 10^{-8}$) in the combined stage 1 and stage 2 analysis, of which 11 are newly associated with Alzheimer's disease.

non-Hispanic Whites

Cohort	Cases	Controls	
ADC1	1,549	512	<div style="border: 1px solid blue; padding: 5px; text-align: center;"> <p>ADCs 5,784 cases 4,924 controls 10,708 total</p> </div>
ADC2	727	156	
ADC3	894	586	
ADC4	304	377	
ADC5	286	505	
ADC6	213	338	
ADC7	566	878	
ADC8	517	664	
ADC9	728	908	

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non-Hispanic Whites

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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

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	908
ADNI	268	173
BIOCARD	6	112
CHAP	27	144
EAS	9	141
GSK	666	712
NIA-LOAD	1,788	1,559
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
UKS	596	170
UMVUMSSM	1,177	1,126
UPITT	1,255	829
WASHU	339	187
WASHU2	38	94
WHICAP	73	560
Totals	15,707	15,441

ADCs
5,784 cases
4,924 controls
10,708 total

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

Eleven susceptibility loci for late-onset Alzheimer's disease (LOAD) were identified by previous studies; however, a large portion of the genetic risk for this disease remains unexplained. We conducted a large, two-stage meta-analysis of genome-wide association studies (GWAS) in individuals of European ancestry. In stage 1, we used genotyped and imputed data (7,055,881 SNPs) to perform meta-analysis on 4 previously published GWAS data sets consisting of 17,008 Alzheimer's disease cases and 37,154 controls. In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. In addition to the *APOE* locus (encoding apolipoprotein E), 19 loci reached genome-wide significance ($P < 5 \times 10^{-8}$) in the combined stage 1 and stage 2 analysis, of which 11 are newly associated with Alzheimer's disease.

non-Hispanic Whites

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11 Novel Loci

Summary statistics used in 47 non-ADGC and non-IGAP publications

- protein-lipid complex assembly
- regulation of beta-amyloid formation
- protein-lipid complex
- regulation of amyloid precursor protein catabolic process
- reverse cholesterol transport
- protein-lipid complex subunit organization
- plasma lipoprotein particle assembly
- tau protein binding
- **activation of immune response**

Multi-ethnic studies

other projects

Other studies

- Neuropath phenotypes
- Early-onset (onset < 70 yrs.)

Cohort	Cases	Controls	
ADC1	1,549	512	
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ADC7	566	878	
ADC8	517	664	
ADC9	728	908	
ADC10	457	724	
ADC11	883	1,265	
ADC12	265	445	
Totals	7,389	7,358	All: 14,747

AD, normal controls, MCI
Caucasians
Hispanics
African American
Asian

Multi-ethnic studies

other projects

Cohort	Cases	Controls
ADC1	1,549	512
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AD, normal controls, MCI
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Other studies

- Neuropath phenotypes
- Early-onset (onset < 70 yrs.)

Multi-ethnic studies

- African American GWAS
- Hispanic GWAS (international)
- **Trans-ethnic study**

Totals

7,389

7,358

All: 14,747

Brian W. Kunkle et al., (2020) Meta-analysis employing the African Genome Resources panel identifies novel Alzheimer disease risk loci and pathways in African Americans. JAMA Neurology (in press)

Trans-ethnic study

1. Array (GWAS) data from all cohorts
2. Sequence data from a subset (array data also available)
3. Impute data using TOPMed R2 panel
4. Generate an ADRD-derived imputation panel

Populations from:

- US
- Mexico
- Peru
- Puerto Rico
- Dominican Republic
- Taiwan
- Japan
- Taiwan
- China
- India
- Spain
- Portugal
- Britain
- France
- Germany
- Iceland
- Belgium
- Other European countries

Ethnicities

- Non-Hispanic Caucasians
- Caribbean Hispanics
- Non-Caribbean Hispanics
- African Americans
- Amerindian
- Asians
- Multi-ethnic populations from India

Sequence data releases

- No embargo
- CRAMs/gVCFs released first
- All released through NIAGADS

	subjects	type of data	CRAMs/gVCFs release	pVCF release
Release 1:	4,789	WGS	July, 2018	October, 2018
Release 2:	20,650	WES	February, 2020	June, 2020
Release 3:	~17,000	WGS	December, 2020?	

Release 1
WGS data
4,789 subjects

ADC subjects

Caucasians:
340 Cases, 366 Controls
African Americans:
248 Cases, 202 Controls

Multiplex Families:

Discovery:

583 subjects, 111 multiples families

501 cases, 82 controls

Discovery extension:

285 subjects in 93 families (46 from Stage 1)

145 unrelated controls

Case-control extension:

Caucasians: 500 cases/500 normal controls

African Americans: 500 cases/500 normal controls

Caribbean Hispanics: 500 cases/500 normal controls

ADNI:

818 subjects, non-Hispanic Caucasians

128 cases, 423 MCI, 267 controls

ADC Samples: Releases 2 and 3

Release 2 - WES data 20,650 subjects	ADC subjects	Cases	Controls	Other
	Non-Hispanic Caucasians	2,386	709	161
	African American	499	672	158

ADC Samples: Releases 2 and 3

Release 2 - WES data 20,650 subjects	ADC subjects	Cases	Controls	Other
	Non-Hispanic Caucasians	2,386	709	161
	African American	499	672	158

Release 3 - WGS data ~17,000 subjects	ADC subjects	Cases	Controls
	Non-Hispanic Caucasians (autopsied)	1,500	1,372
	African American	430	942
	Amerindian	45	44
	Early onset (<70 years)	1,469	

New NIA initiatives

Alzheimer's Disease Sequencing Project Harmonization Consortium (ADSP-HC). U24 grant (FOA: PAR-20-099)

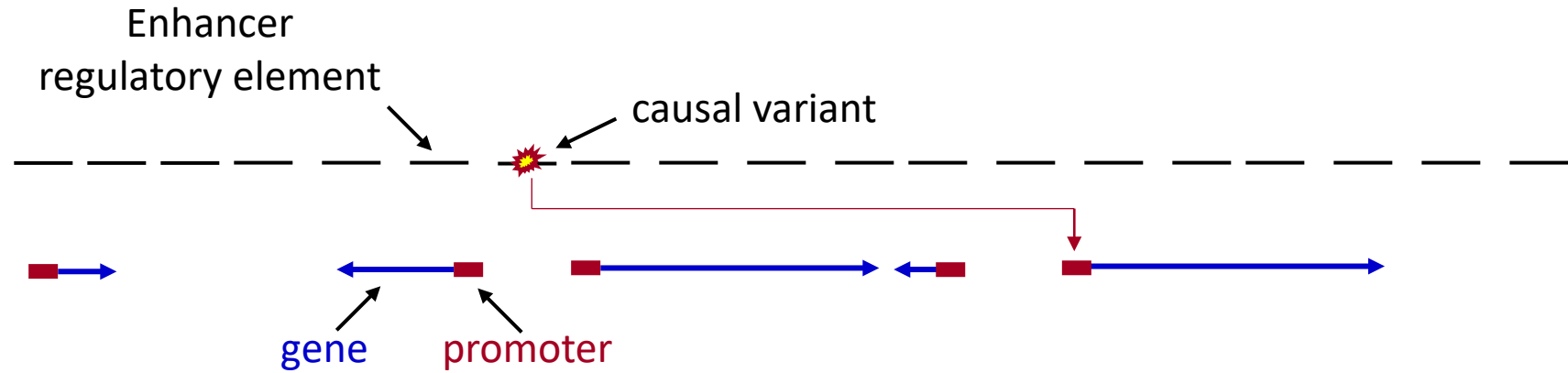
Harmonize phenotypes from multiple cohorts

- Cognitive
- Structural imaging - brain MRI
- Amyloid and Tau PET.
- Longitudinal clinical data
- Neuropathology
- Cardiovascular risk factor Biomarker data

New NIA initiatives

Alzheimer's Disease Sequencing Project Harmonization Consortium (ADSP-HC). U24 grant (FOA: PAR-20-099)

Harmonize phenotypes from multiple cohorts



Functional AD Genetics Consortium
Funding Opportunity Announcement (RFA-AG-21-006)

Identify genes corresponding to association studies

University of Pennsylvania

Li-San Wang
Adam Naj
Fanny Leong
Amanda Kuzma
Laura Cantwell

NIA

Marilyn Miller
Dallas Anderson

NIA/NIH
Alzheimer's Association

University of Miami

Peggy Pericak-Vance
Gary Beecher
Eden Martin
Brian Kunkle

Columbia University

Richard Mayeux
Bardri Vardarajan
Sandra Barral
Christiane Rietz

Boston University

Lindsay Farrer
Gyungah Jun
Jaeyoon Chung

Case Western

Jonathan Haines
Will Bush

NACC

Walter "Bud" Kukull

NCRAD

Tatiana Foroud
Kelly Michelle Faber

The End