Alzheimer's Disease Genetics Consortium

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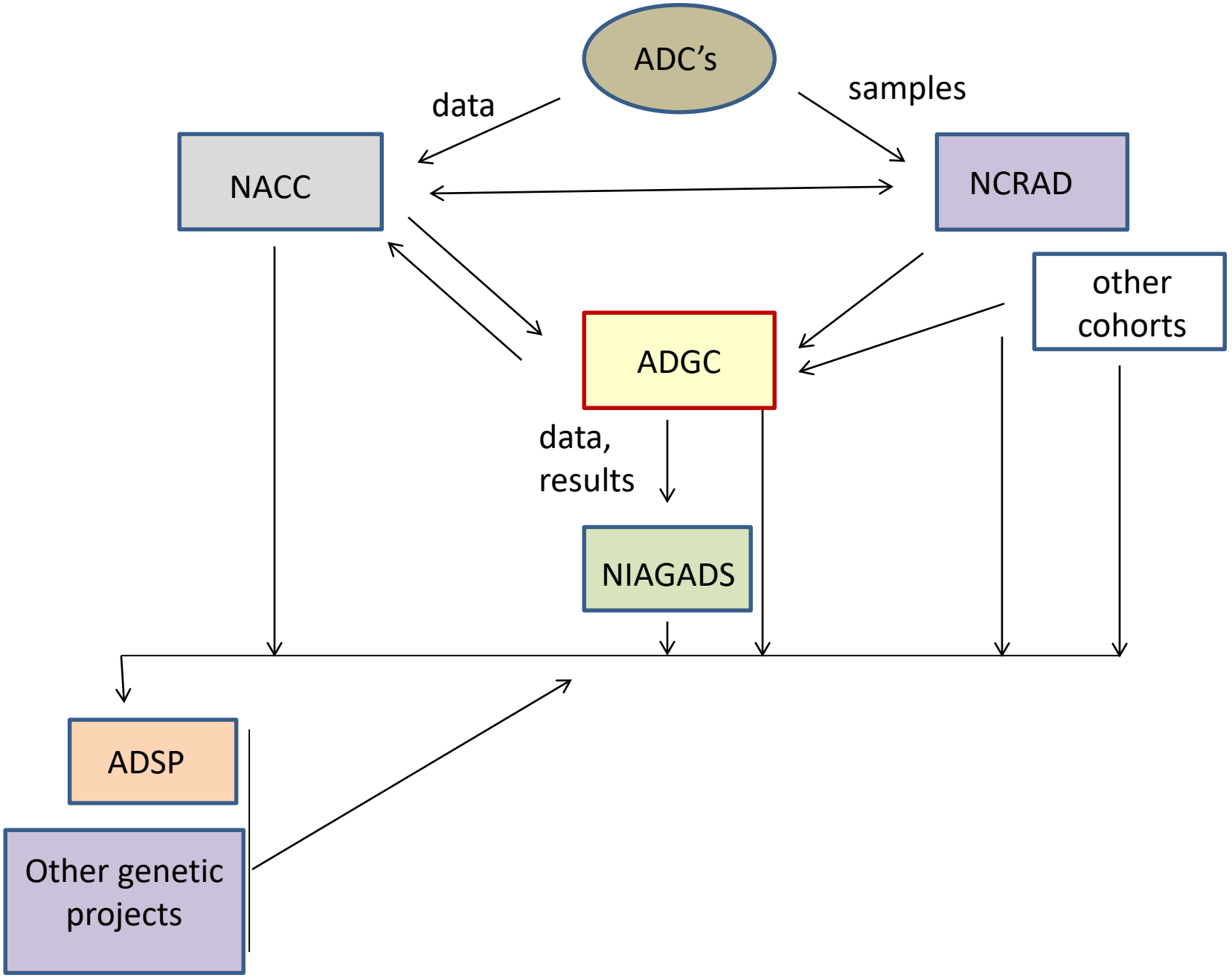
Updates:

Alzheimer's Disease Genetics Consortium - ADGC

Alzheimer's Disease Sequencing Project - ADSP

Partners:

NIA-funded Alzheimer's Disease Centers - ADCs
National Alzheimer Coordinating Center – NACC
National Cell Repository for Alzheimer's Disease - NCRAD
National Institute on Aging Genetics of Alzheimer's Disease Storage site - NIAGADS


ADC's
data
samples
NACC
NCRAD
other cohorts
ADGC
data, results
NIAGADS
ADSP
Other genetic projects

- **Team Science:** University of Pennsylvania, Boston University, Columbia, Case Western, University of Miami

- Increase sample size:
  - Caucasians
  - African Americans
  - Caribbean Hispanics
  - Other Latino populations

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	908
ACT	532	1,571
ADNI	268	173
BIOCARD	6	112
CHAP	27	144
EAS	9	141
GSK	666	712
NIA-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

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

In progress

Cohort	Cases	Controls
UKS	596	170
UMVUMSSM	1,177	1,126
UPITT	1,255	829
WASHU	339	187
WASHU2	38	94
NIA-LOAD 2	89	188
WHICAP	73	560
Totals	16,328	17,200
Grand total	33,528	

IGAP

Consortium	Cases	Controls
ADGC	16,328	17,200
CHARGE	2,137	13,474
EADI	2,240	6,631
GERAD	3,177	7,277
Totals	23,882	44,582

Cohort expansion: existing cohorts, minority cohorts

- Texas Alzheimer Research and Care Consortium (NCH: 375 cases, 224 MCI, 417 controls: Hispanics, 98 cases, 229 MCI, 492 controls, actively recruiting new subjects)
- MESA (Multi-Ethnic Study of Atherosclerosis) (n=6418)
  40% Caucasian, 26% African-American, 21% Hispanic, 13% Chinese-Americans.
  adjudication of case-control status
  whole genome sequencing
- REGARDS
  (The REasons for Geographic and Racial Differences in Stroke)
  n = 30,239
  DNA available, no genetic data
  Adjudication of case-control status needed
  ~12,000 African Americans
- Kaiser Permanente. 100,000 subjects with GWAS data linked to EMRs.
  ~2,000 dementia cases
  88% NHC, 7% AA, and 5% other.
- Numerous additional cohorts

- **Team Science:** University of Pennsylvania, Boston University, Columbia, Case Western, University of Miami

- Increase sample size: Caucasians
  African Americans
  Caribbean Hispanics
  Other Latino populations

- GWAS: common-variants

- Rare variants: exome chip
  de novo sequence (WES and WGS)

ARTICLE

doi:10.1038/nature18642

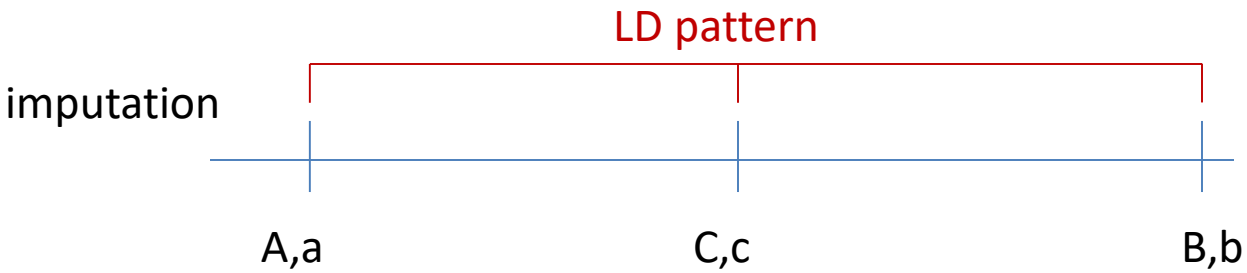
The genetic architecture of type 2 diabetes

A list of authors and affiliations appears in the online version of the paper

The genetic architecture of common traits, including the number, frequency, and effect sizes of inherited variants that contribute to individual risk, has been long debated. Genome-wide association studies have identified scores of common variants associated with type 2 diabetes, but in aggregate, these explain only a fraction of the heritability of this disease. Here, to test the hypothesis that lower-frequency variants explain much of the remainder, the GoT2D and T2D-GENES consortia performed whole-genome sequencing in 2,657 European individuals with and without diabetes, and exome sequencing in 12,940 individuals from five ancestry groups. To increase statistical power, we expanded the sample size via genotyping and imputation in a further 111,548 subjects. Variants associated with type 2 diabetes after sequencing were overwhelmingly common and most fell within regions previously identified by genome-wide association studies. Comprehensive enumeration of sequence variation is necessary to identify functional alleles that provide important clues to disease pathophysiology, but large-scale sequencing does not support the idea that lower-frequency variants have a major role in predisposition to type 2 diabetes.

Combined sequence and chip data

WGS, cases/controls:	2,657
WES, cases/controls:	12,940
Chip genotyping/imputation, cases/controls:	111,548



African American WES: by study

Study	Affected	Unaffected	Total
MIRAGE	117	138	255
Miami/Duke/North Carolina	396	582	978
Alzheimer's Disease Centers	**517**	**681**	**1,198**
GenerAAtions	246	206	452
Case/Vanderbilt	91	171	262
Rush	227	1,026	1,253
Total	1,594	2,804	4,398

Autopsy	**Affected**	**Unaffected**	**Total**
Yes	171	34	205
No	1,423	2,770	4,193

Alzheimer's Disease Sequencing Project (ADSP)

Whole exome sequencing:

5,000 unrelated cases:	4,220 from the ADGC **2,430 from ADC's**
5,000 elderly normal controls:	3,240 from the ADGC **840 from the ADC's**

1,000 cases from multiplex families – one/family

Whole-genome sequencing:	585 subjects 111 multiplex families

In progress: sequencing completed data processing started	415 subjects old and new families

WGS – 10,000 subjects

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

3,000 total sequencing completed – November 2016

7,000 – subjects TBD

- 1,600 WGS – ADNI
- >3,000 WES – Caribbean Hispanics (Mayeux/Columbia)
- others

Sequence-based data: candidate variants
Chip-based data: follow up

Exome chip:	16,097 Cases 18,077 Controls
De novo genotyping:	43 candidate variants 14,041 Cases 21,921 Controls
Imputed data:	6,652 Cases 8,345 Controls
Total:	36,790 Cases 40,483 Controls **77,273 total**

- *TREM2* R62H; *TREM2* R47H
  P = 1.7 x 10^{-16}, OR = 2.43, freq. = 0.36%
  P = 7.7 x 10^{-14}, OR = 1.64, freq. = 1.19%
- *P*----
  P = 5.5 x 10^{-9}, OR = 0.68 (1/x = 1.47), freq. = 0.8%
- *A*----
  P = 7.1 x 10^{-9}, OR = 1.44, freq. = 0.97%

- In brain; all three are exclusively expressed in microglial cells
- ~ 20% of GWAS signals may be microglial cell genes

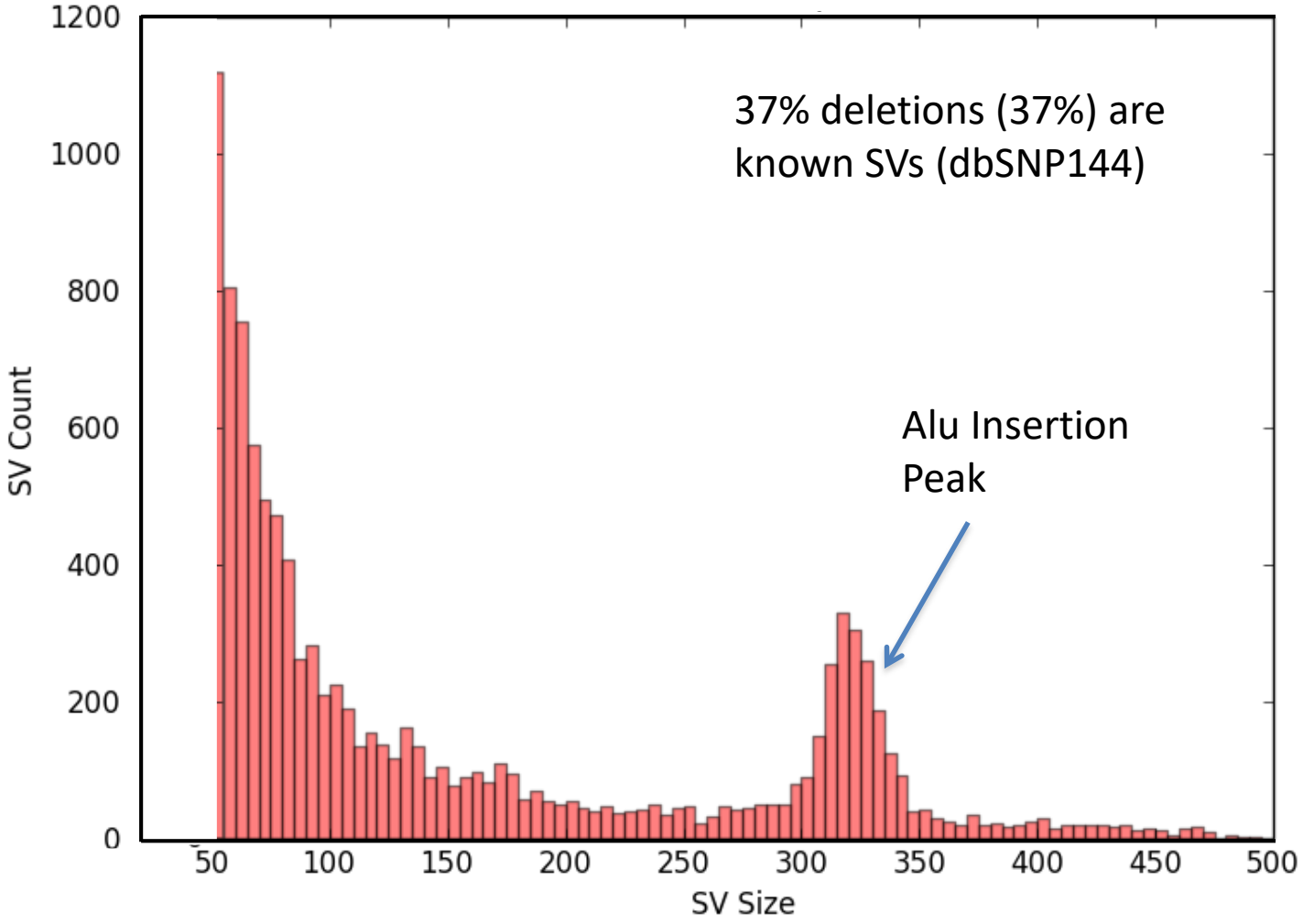
Structural Variants (SVs) Introduction

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

- Size
  - 1 bp - Mb

- Alzheimer's/other neurodegenerative/neurologic disorders
  - *APP* duplication
  - *SNCA* duplication
  - *PSEN1* indel
  - *PMP22* deletion/duplication
  - *MAPT* inversion/CNVs
  - ABCA7 LOF deletions

Deletion Size Frequency 50-500 bp



SV detection:

~2,000 bp and above:	genotyping arrays
1bp and above:	only from WGS sensitivity ~ 80-90% specificity - ?

Alzheimer's Disease Genetics Consortium

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ADGC

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Thank you!