

Alzheimer's Disease Genetics Consortium ADGC

Goal: Identify all genes/inherited factors that increase risk or protect against Alzheimer's disease.



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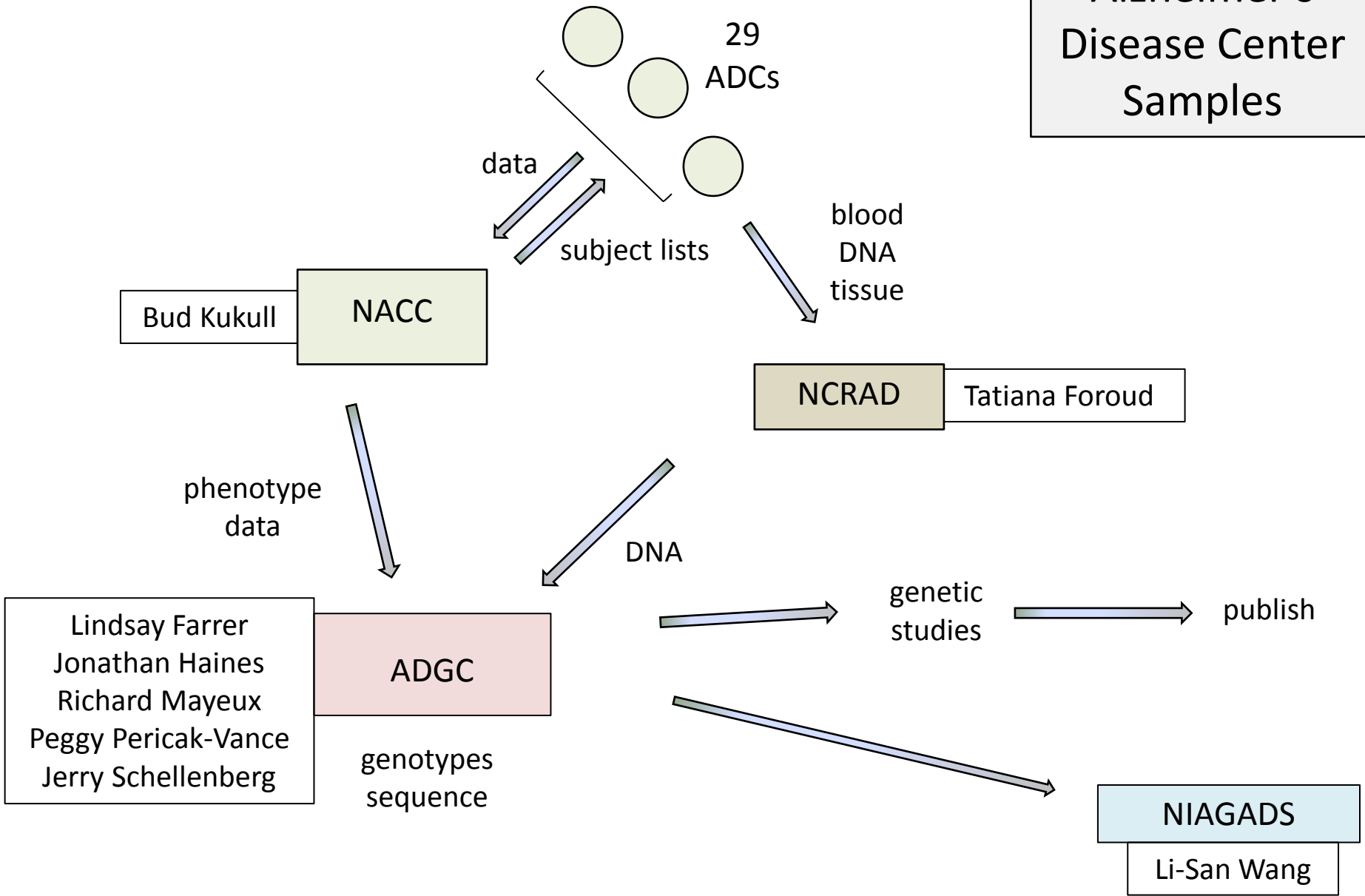


Why is Alzheimer's disease genetics important?

- Study human disease mechanisms directly in humans
- Prediction
- Mechanism
- Drug targets



Alzheimer's Disease Center Samples



Bud Kukull
NACC

NCRAD
Tatiana Foroud

Lindsay Farrer
Jonathan Haines
Richard Mayeux
Peggy Pericak-Vance
Jerry Schellenberg

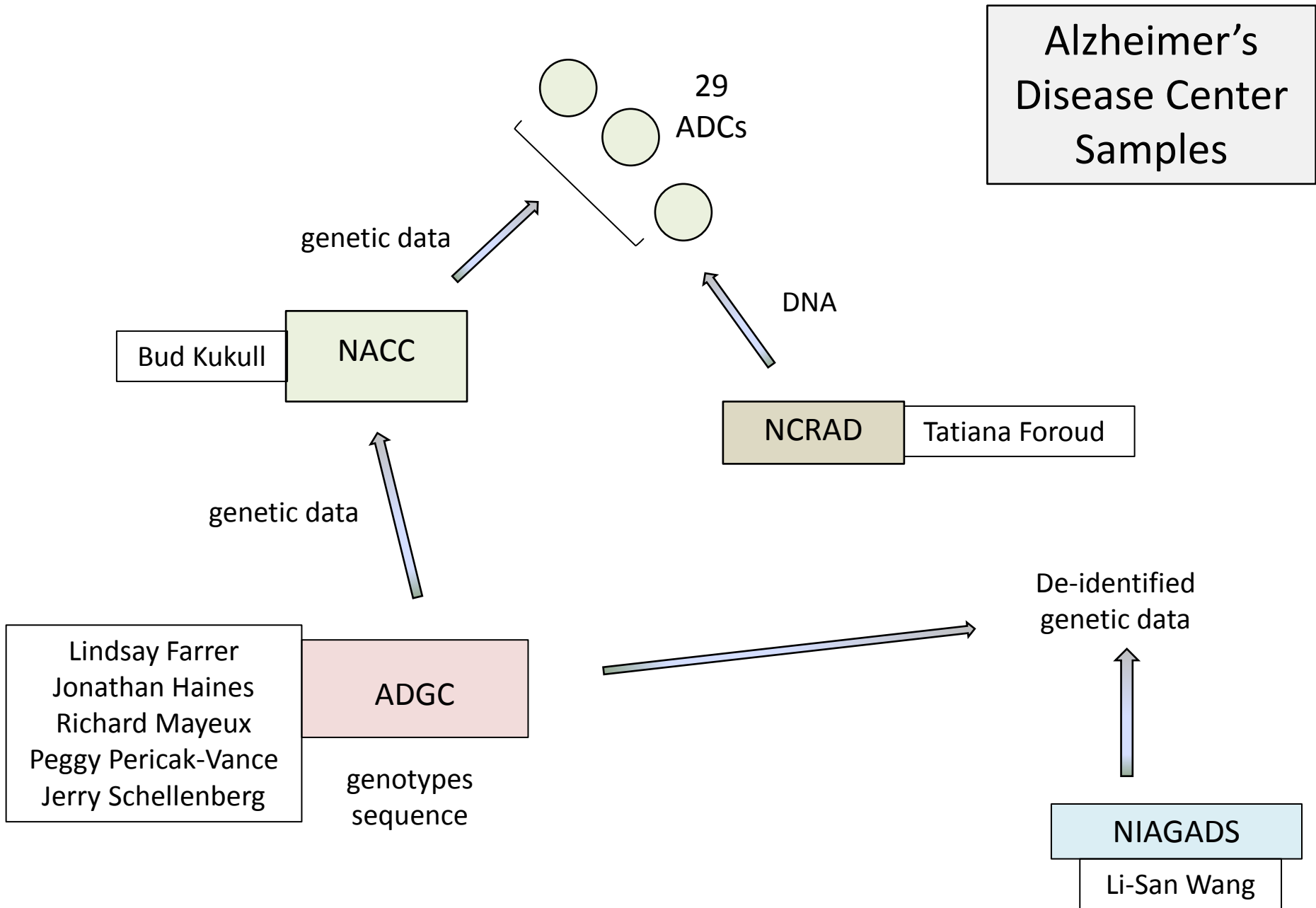
ADGC

genotypes
sequence

NIAGADS

Li-San Wang

Alzheimer's Disease Center Samples



Return to ADCs

- DNA
- *APOE* genotypes
- Genome-wide SNP array data
- **Key SNP genotypes for risk-loci**
- Exome chip data
- Sequence data – exome/whole genome

- recognition

Phase 1 – autopsy series

| Autopsied AD | Autopsied Controls | other | Total |
|--------------|--------------------|-------|-------|
| 3,386 | 388 | 211 | 3,985 |

Phase 2 - UDS

| Clinical AD | Clinical Controls | MCI | Other non-AD ¹ | total |
|-------------|-------------------|-------|---------------------------|--------|
| 3,801 | 5,034 | 1,348 | 3,544 | 13,727 |

| | AD cases | Control | Combined |
|--------|----------|---------|----------|
| Totals | 7,187 | 5,433 | 12,620 |

¹Non-AD is a catch-all for PSP, FTD, CBD, Huntingtons, Prion, etc.

| | Active Subjects on GWAS List | Active Subjects with Sample | Active Subjects with no sample |
|--------|---------------------------------|--------------------------------|-----------------------------------|
| Totals | 14,784 | 7,910 | 6,874 |



All new subjects

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 *MS4A4* (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 = 8.2×10^{-12}), *CD2AP* (rs9349407; stages 1, 2 and 3, P_M = 8.6×10^{-9}), *EPHA1* (rs11767557; stages 1, 2 and 3, P_M = 6.0×10^{-10}) and *CD33* (rs3865444; stages 1, 2 and 3, P_M = 1.6×10^{-9}). We also replicated previous associations at *CR1* (rs6701713; P_M = 4.6×10^{-10} , P_J = 5.2×10^{-11}), *CLU* (rs1532278; P_M = 8.3×10^{-8} , P_J = 1.9×10^{-8}), *BIN1* (rs7561528; P_M = 4.0×10^{-14} , P_J = 5.2×10^{-14}) and *PICALM* (rs561655; P_M = 7.0×10^{-11} , P_J = 1.0×10^{-10}), but not at *EXOC3L2*, to late-onset Alzheimer's disease susceptibility¹⁻³.

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 Rogava, 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

Alzheimer's Disease Center samples

| Cohort | Cases | Autopsies n (percent) | Controls | Autopsies: n (percent) |
|---------------|--------------|----------------------------------|-----------------|-----------------------------------|
| ADC1 | 1566 | 1566 (100%) | 515 | 515 (100%) |
| ADC2 | 738 | 195 (26%) | 160 | 0 (0%) |
| ADC3 | 897 | 527 (59%) | 588 | 4 (1%) |
| Totals | 3,201 | 2,288 (71%) | 1,263 | 519 (41%) |

ADGC GWAS is the first project to use data and samples from all NIA-funded Alzheimer's Disease Centers

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 | | | Controls | | |
|-----------------------|---------------|---------|----------------|---------------|---------|-----------------------|
| | N | % women | Mean Onset Age | N | % women | 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

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

Jean-Charles Lambert^{*1,2,3}, Carla A Ibrahim-Verbaas^{*4}, Denise Harold^{*5}, Adam C Naj^{*6}, Rebecca Sims⁵, Céline Bellenguez^{1,2,3}, Gyungah Jun^{7,8,9}, Anita L DeStefano⁹, Joshua C Bis¹⁰, Gary W Beecham^{11,12}, Benjamin Grenier-Boley^{1,2,3}, Giancarlo Russo¹³, Tricia A Thornton-Wells¹⁴, Nicola Jones⁵, Albert V Smith^{15,16}, Vincent Chouraki^{1,2,3}, Charlene Thomas⁵, M Arfan Ikram^{17,18}, Diana Zelenika¹⁹, Badri N Vardarajan⁷, Yoichiro Kamatani²⁰, Chiao-Feng Lin²¹, Amy Gerrish⁵, Helena Schmidt²², Brian Kunkle¹¹, Melanie L Dunstan⁵, Agustín Ruiz²³, Marie-Thérèse Bihoreau¹⁹, Seung-Hoan Choi⁹, Christiane Reitz^{24,25}, Florence Pasquier^{2,26}, Paul Hollingworth⁵, Alfredo Ramirez²⁷, Olivier Hanon²⁸, Annette L Fitzpatrick^{10,29}, Joseph D Buxbaum^{30,31,32}, Dominique Campion³³, Paul K Crane³⁴, Clinton Baldwin⁷, Tim Becker³⁵, Vilmundur Gudnason^{15,16}, Carlos Cruchaga³⁶, David Craig³⁷, Najaf Amin³⁸, Claudine Berr³⁹, Oscar L Lopez⁴⁰, Philip L De Jager^{41,42}, Vincent Deramecourt^{2,26}, Janet A Johnston³⁷, Denis Evans⁴³, Simon Lovestone⁴⁴, Luc Letteneur⁴⁵, Francisco J Morón⁴⁶, David C Rubinsztein⁴⁷, Gudny Eiriksdottir¹⁶, Kristel Slegers^{48,49}, Alison M Goate³⁶, Nathalie Fiévet^{1,3}, Matthew J Huentelman⁵⁰, Michael Gill⁵¹, Kristelle Brown⁵², M Ilyas Kamboh^{53,54}, Lina Keller⁵⁵, Pascale Barberger-Gateau⁴⁵, Bernadette McGuinness³⁷, Eric B Larson^{34,56}, Robert Green⁵⁷, Amanda J Myers⁵⁸, Carole Dufouil⁴⁵, Stephen Todd³⁷, David Wallon³³, Seth Love⁵⁹, Ekaterina Rogaeva⁶⁰, John Gallacher⁶¹, Peter St George-Hyslop^{60,62}, Jordi Clarimon^{63,64}, Alberti Lleo^{63,64}, Anthony Bayer⁶¹, Debby W Tsuang⁶⁵, Lei Yu⁶⁶, Magda Tsolaki⁶⁷, Paola Bossù⁶⁸, Gianfranco Spalletta⁶⁹, Petra Proitsi⁴⁴, John Collinge⁶⁹, Sandro Sorbi^{70,71}, Florentino Sanchez Garcia⁷², Nick C Fox⁷³, John Hardy⁷⁴, Maria Candida Deniz Naranjo⁷², Paolo Bosco⁷⁵, Robert Clarke⁷⁶, Carol Brayne⁷⁷, Daniela Galimberti⁷⁸, Michelangelo Mancuso⁷⁹, MRC CFAS⁷⁷, Susanne Moebus⁸⁰, Patrizia Mecocci⁸¹, Maria Del Zompo⁸², Wolfgang Maier⁸³, Harald Hampel^{84,85}, Alberto Pilotto⁸⁶, Maria Bullido^{87,88,89}, Francesco Panza⁹⁰, Paolo Caffarra^{91,92}, Benedetta Nacmias^{70,71}, John R Gilbert^{11,12}, Manuel Mayhaus⁹³, Lars Lannfelt⁹⁴, Hakon Hakonarson⁹⁵, Sabrina Pichler⁹³, Minerva M Carrasquillo⁹⁶, Martin Ingelsson⁹⁴, Duane Beekly⁹⁷, Victoria Alvarez⁹⁸, Fanggeng Zou⁹⁶, Otto Valladares²¹, Steven G Younkin⁹⁶, Eliecer Coto⁹⁸, Kara L Hamilton-Nelson¹¹, Wei Gu⁹⁹, Cristina Razquin¹⁰⁰, Pau Pastor^{100,101}, Ignacio Mateo¹⁰², Michael J Owen⁵, Kelley M Faber¹⁰³, Palmi V Jonsson^{15,103}, Onofre Combarros¹⁰², Michael C O'Donovan⁵, Laura B Cantwell²¹, Hilka Soininen^{105,106}, Deborah Blacker^{107,108}, Simon Mead⁶⁹, Thomas H Mosley Jr¹⁰⁹, David A Bennett^{66,110}, Tamara B Harris¹⁰, Laura Fratiglioni^{112,113}, Clive Holmes¹¹⁴, Renee FAG de Bruijn¹¹⁵, Peter Passmore³⁸, Thomas J Montine¹¹⁶, Karolien Bettens⁴, Kukull¹²⁰, Didier Hannequin³³, Kauwe¹²³, Eric Boerwinkle¹², Martin^{11,12}, Reinhold Schmidt¹²⁹, Christophe Tzourio¹²⁹, Albert Hofman^{17,18}, Markus M Nöthen¹³⁰, Caroline Graff^{113,131}, Bruce M Psaty^{10,132}, Lesley Jones⁵, Jonathan L Haines^{14,133}, Peter A Holmans⁵, Mark Lathrop^{19,20,134}, Margaret A Pericak-Vance^{11,12}, Lenore J Launer¹¹¹, Lindsay A Farrer^{7,8,9,107,135}, Cornelia M van Duijn^{18,38,136}, Christine Van Broeckhoven^{48,49}, Valentina Moskvina⁵, Sudha Seshadri^{*137}, Julie Williams^{*5}, Gerard D Schellenberg^{*21}, Philippe Amouyel^{*1,2,3,26,138}.

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Late-Onset: common variants

$P < 5 \times 10^{-8}$

| 1991 - 2007 | 2013 |
|------------------|------------------------------|
| 1. <i>APOE</i> | 11. <i>HLA-DRB5/HLA-DRB1</i> |
| 2. <i>SORL1</i> | 12. <i>PTK2B</i> |
| | 13. <i>SLC24A4/RIN3</i> |
| 2008 - 2011 | 14. <i>CASS4</i> |
| 3. <i>CR1</i> | 15. <i>INPP5D</i> |
| 4. <i>CLU</i> | 16. <i>MEF2C</i> |
| 5. <i>PICALM</i> | 17. <i>NME8</i> |
| 6. <i>BIN1</i> | 18. <i>ZCWPW1</i> |
| 7. <i>CD2AP</i> | 19. <i>CELF1</i> |
| 8. <i>EPHA1</i> | 20. <i>FERMT2</i> |
| 9. <i>MS4A4A</i> | 21. <i>TREM2/TREML2/NCR2</i> |
| 10. <i>ABCA7</i> | 22. <i>GLIS3</i> |
| | 23. <i>SNAR1</i> |

CSF Tau/Ptau

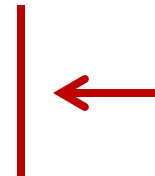
$5 \times 10^{-8} < P < 1 \times 10^{-7}$

| 2013 | |
|-------------------------------|--|
| 24. <i>ACE</i> | 3.1×10^{-7} |
| 25. <i>ADAMST20</i> | 3.0×10^{-7} |
| 26. <i>AP2A2</i> | 6.3×10^{-7} |
| 27. <i>ECHDC3</i> | 2.9×10^{-7} |
| 28. <i>HS3ST1</i> | 6.6×10^{-8} |
| 29. <i>IGH@</i> | 2.7×10^{-7} |
| 30. <i>NDUFAF6</i> | 8.0×10^{-8} |
| 31. None | 3.4×10^{-7} |
| 32. <i>rs145848414</i> | 6.9×10^{-8} |
| 33. <i>SCIMP</i> | 3.7×10^{-7} |
| 34. <i>SPPL2A</i> | 3.2×10^{-7} |
| 35. <i>SQSTM1</i> | 7.4×10^{-7} |
| 36. <i>TRIP4</i> | 4.3×10^{-7} |

African American

New ADGC Datasets

| Cohort Label | Cohort | Case | Control | Total |
|--------------|-------------------------|--------------|--------------|--------------|
| ACT2 | ACT | 21 | 8 | 29 |
| ADC4 | ADC | 322 | 371 | 693 |
| ADC5 | ADC | 293 | 514 | 807 |
| ADC6 | ADC | 213 | 337 | 550 |
| BIOCARD | BIOCARD | 6 | 110 | 116 |
| CHAP | CHAP | 27 | 142 | 169 |
| EAS | Einstein Aging Study | 9 | 141 | 150 |
| MTV | Miami | 68 | 46 | 114 |
| MTV | Vanderbilt | 16 | 69 | 85 |
| MTV | TARC | 171 | 74 | 245 |
| NBB | Reimenschneider/Germany | 80 | 48 | 128 |
| PFIZER | Pfizer | 694 | 761 | 1455 |
| RMAYO | Rochester Mayo | 12 | 233 | 245 |
| ROSMAP2 | ROS, MAP | 57 | 215 | 272 |
| TARC1 | TARC | 323 | 181 | 504 |
| UKS | Reimenschneider/Germany | 596 | 170 | 766 |
| WASHU2 | Washington Univ | 38 | 94 | 132 |
| WHICAP | WHICAP | 73 | 560 | 633 |
| Total | | 3,019 | 4,074 | 7,093 |



Alzheimer's Disease Sequencing Project (ADSP)

| | |
|--------------------------|---|
| Whole exome sequencing: | 5,000 unrelated cases 5,000 unrelated elderly controls 1,000 cases – multiplex families 11,000 total |
| Whole-genome sequencing: | 585 subjects from 111 multiplex families (multiple case/family) |

Alzheimer's Disease Sequencing Project (ADSP)

Whole exome sequencing

5,000 unrelated cases

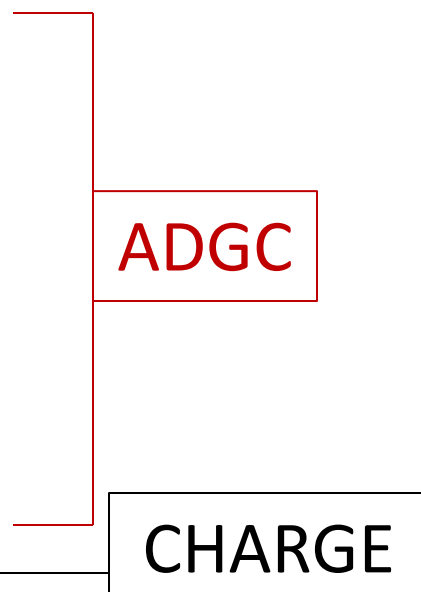
- selected as cases with the lowest risk explained by *APOE* and age - young onset, *APOE* $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 3/\epsilon 3$
- 4,220 from the ADGC
- **2,430 from ADC's**

5,000 unrelated elderly cognitively normal controls

- selected as controls least likely to convert to a case, based on age, *APOE*, and autopsy data - old, *APOE* $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, or $\epsilon 3/\epsilon 3$ little or no AD neuropathology
- 3,240 from the ADGC
- **840 from the ADC's**

1,000 cases from multiplex families – one/family

Alzheimer's Disease Sequencing Project (ADSP)

| Families | investigator(s) | number of families | |
|------------------------|----------------------|--------------------|---|
| NIA-LOAD: | Richard Mayeux | 18 |  |
| Caribbean Hispanics | Richard Mayeux | 67 | |
| NCRAD: | Tatiana Foroud | 4 | |
| Miami: | Peggy Pericak-Vance | 12 | |
| Seattle: | Raskind/Schellenberg | 7 | |
| Vanderbilt: | Jonathan Haines | 1 | |
| Erasmus: | Cornelia Van Duijn | 2 | |
| Total: | | 111 | |

501 cases, 84 unaffected, 583 total

553 from the ADGC investigators

Alzheimer's Disease Sequencing Project (ADSP)

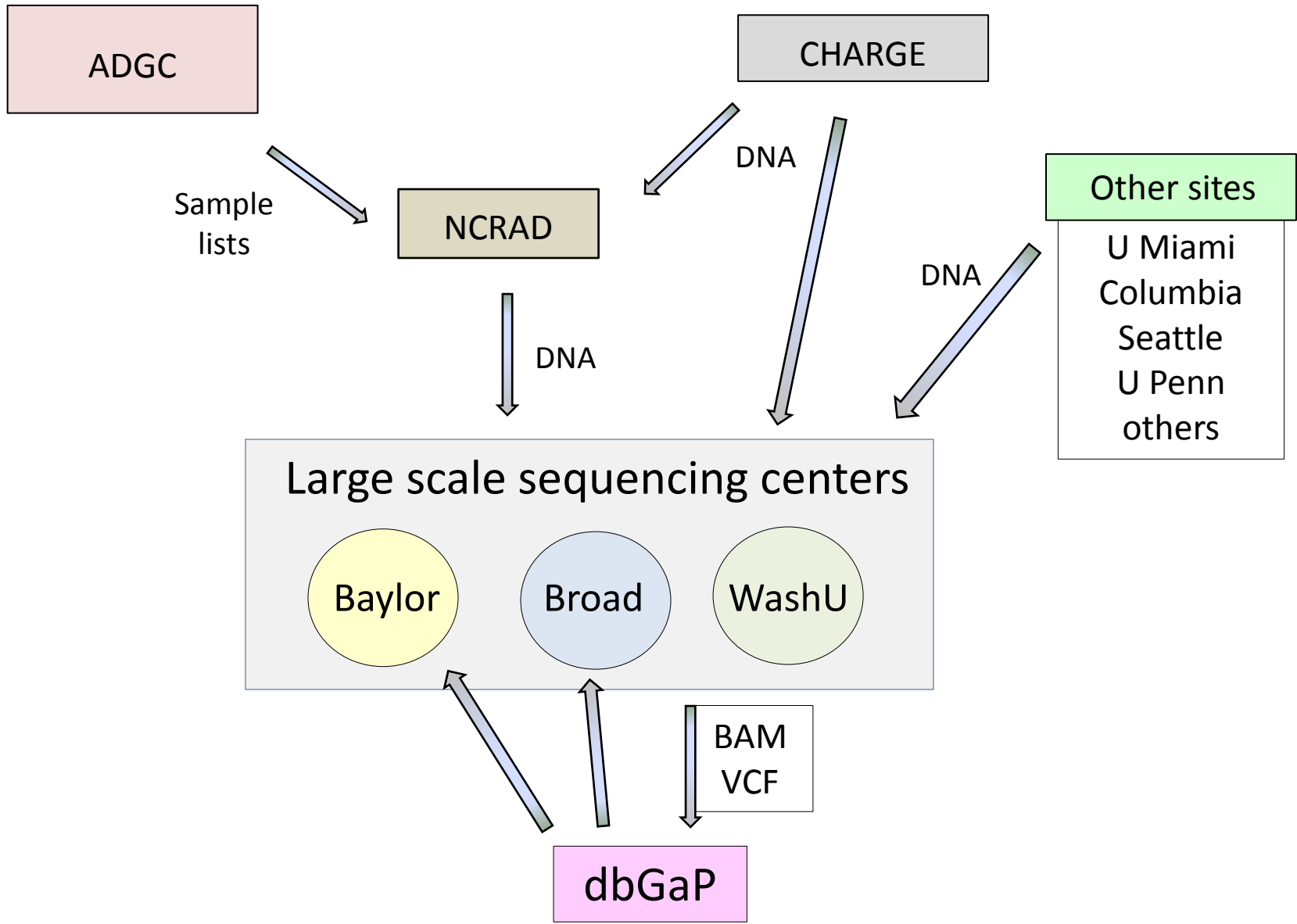
Replication

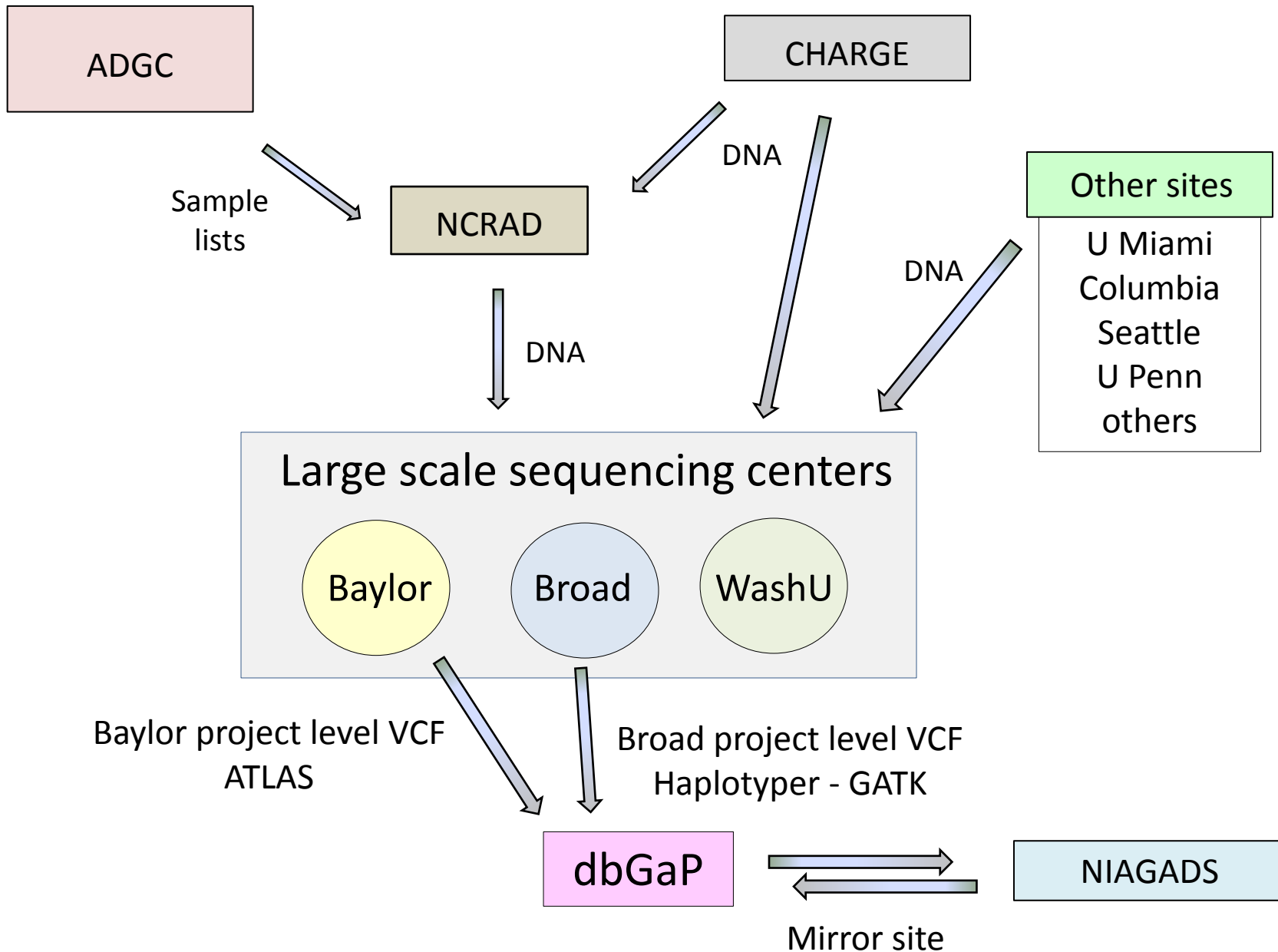
- 25,000 additional cases
- 25,000 additional controls

ADGC + CHARGE +
IGAP Collaborators

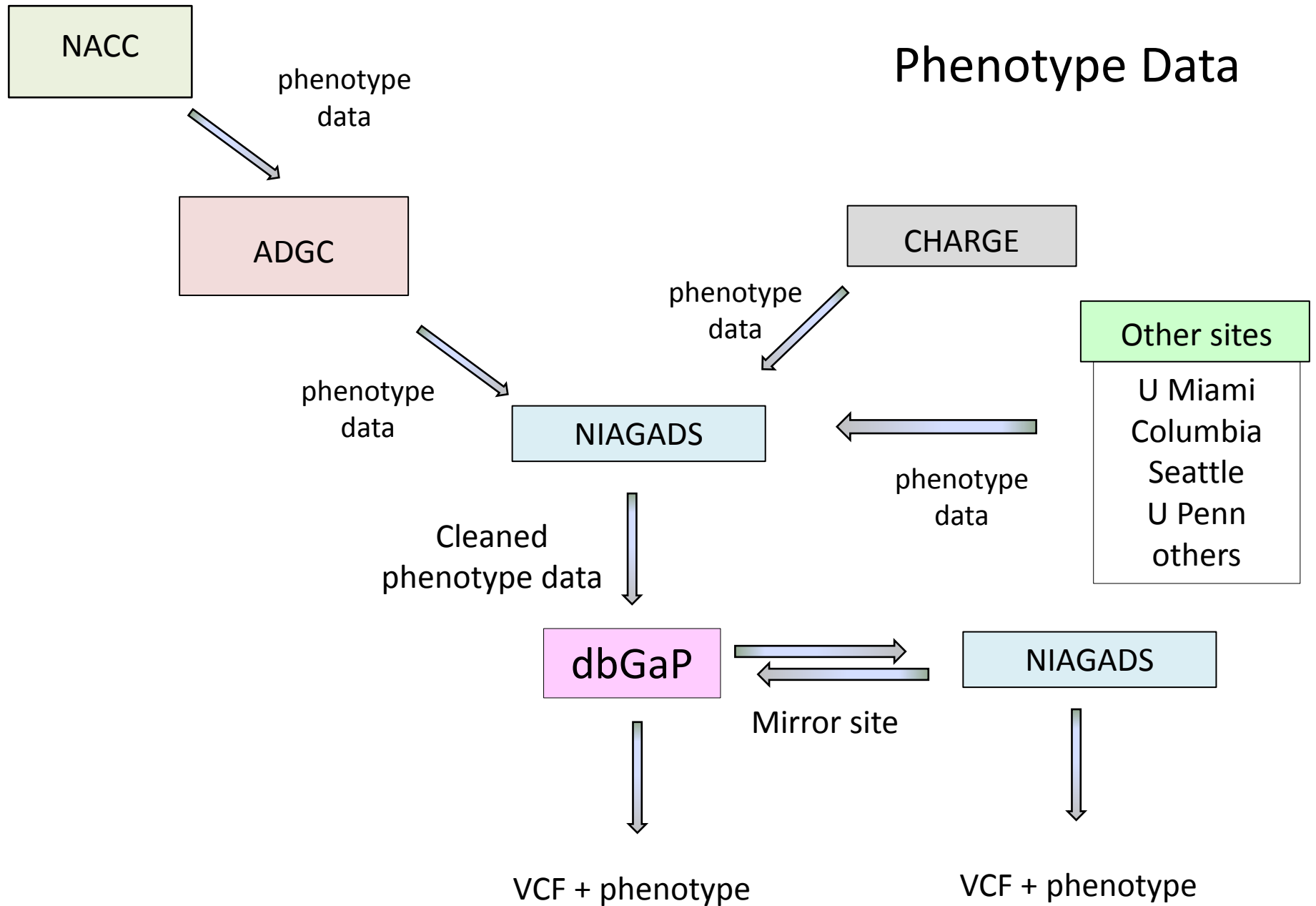
- Targeted sequencing
 - exons
 - introns
 - intergenic regions

Selected based on
results from WES/WGA





Phenotype Data



Alzheimer's Disease Sequencing Project (ADSP)

Progress

Activities

- Collaborative agreements
- Study design
- Family selection
- Data flow
- Sequence analysis pipeline
- Sample shipping
- Sequence variant quality control protocol
- Segregation analysis – families
- Analysis plan – families
- Analysis plan – structural variants

Alzheimer's Disease Sequencing Project (ADSP)

Progress

Whole genome sequencing

- All samples at the sequence centers
- ~400 completed - data freeze – September
- All 583 to be completed January, 2013

Whole exome sequencing

- ~90% of all samples are at the sequencing centers
- QC completed
- Limited sequencing is in progress
- Completion expected – late 2014

Thank you!