Alzheimer's Disease Genetics Consortium

ADGC

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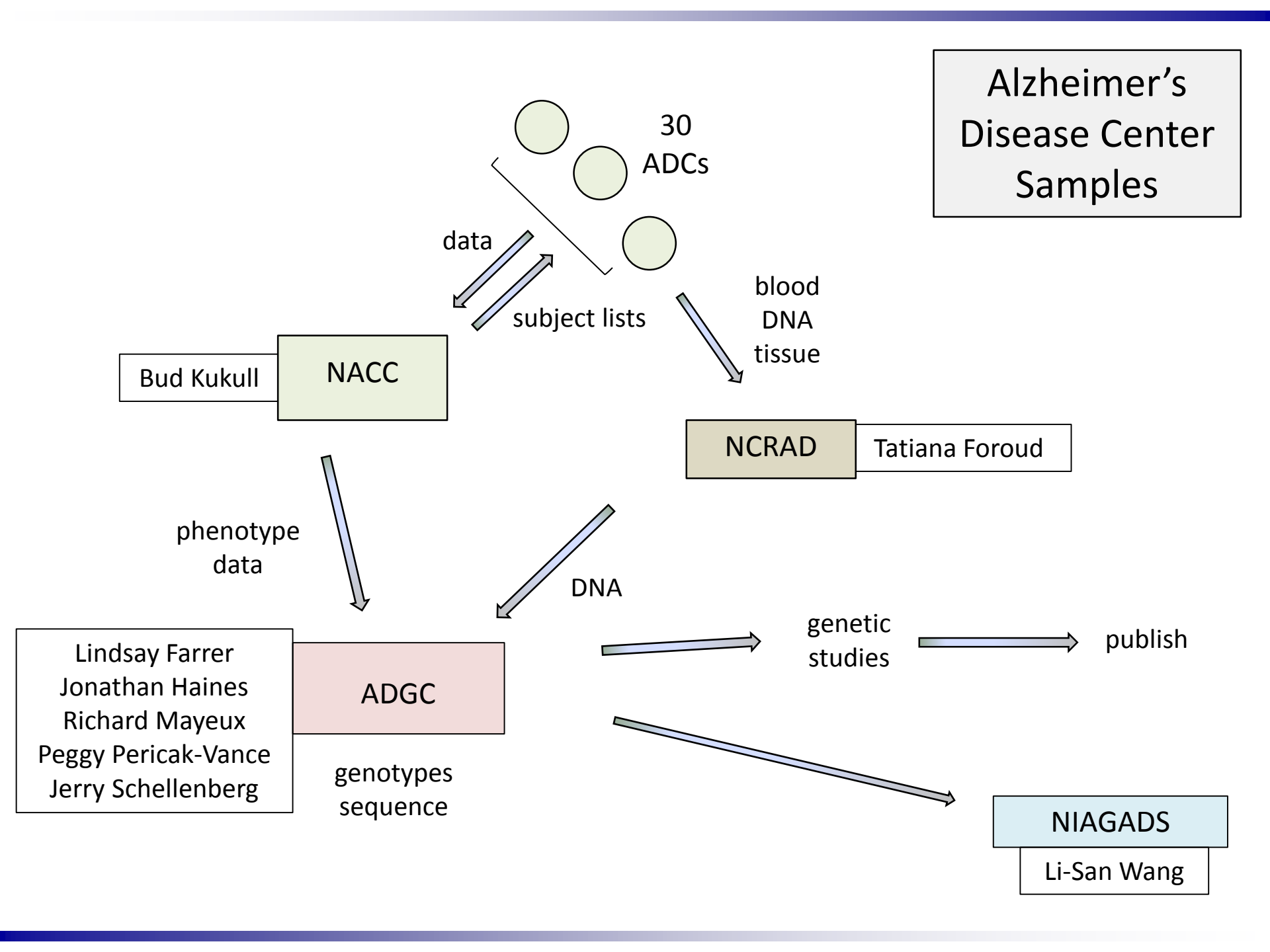
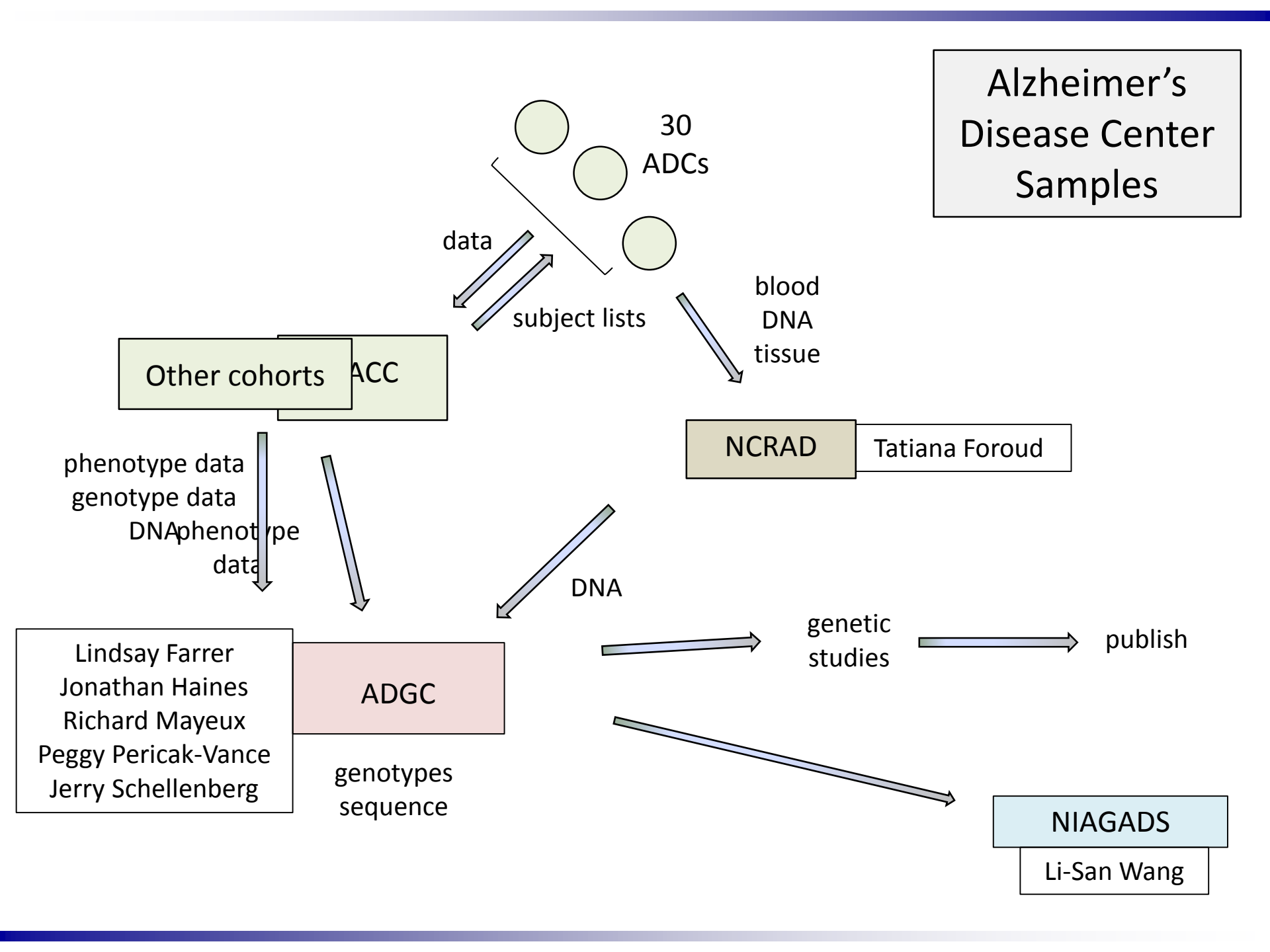
ADGC

Formed to do large-scale genetic studies on Alzheimer's disease

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


Alzheimer's Disease Center Samples
30 ADCs
data
subject lists
blood DNA tissue
Bud Kukull
NACC
NCRAD
Tatiana Foroud
phenotype data
DNA
Lindsay Farrer
Jonathan Haines
Richard Mayeux
Peggy Pericak-Vance
Jerry Schellenberg
ADGC
genotypes sequence
genetic studies
publish
NIAGADS
Li-San Wang


Alzheimer's Disease Center Samples
30 ADCs
data
subject lists
blood
DNA
tissue
Other cohorts
ACC
NCRAD
Tatiana Foroud
phenotype data
genotype data
DNA phenotype data
DNA
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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

ADC Contribution

	Phase 1/MDS	Phase 2/UDS	Total
Total Submitted	3774	10550	14324
Illumina 660/Omni Express	2990	8405	11395
Exome Chip	2673	4418	7091

ADC Genotyping

Cohort	Cases	Controls	MCI	Other	Total
Received	**8066**	**6450**	**1628**	**4466**	**20610**
Genotyped	**5873**	**4499**	**560**	**463**	**11395**

Late-onset AD

LETTERS

nature genetics

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

Jean-Charles Lambert[1–3,145], Carla A Ibrahim-Verbaas[4,5,145], Denise Harold[6,145], Adam C Naj[7,8,145], Rebecca Sims[6], Céline Bellenguez[1–3], Gyungah Jun[9–11], Anita L DeStefano[11], Joshua C Bis[12], Gary W Beecham[13,14], Benjamin Grenier-Boley[1–3], Giancarlo Russo[15], Tricia A Thornton-Wells[16], Nicola Jones[6], Albert V Smith[17,18], Vincent Chouraki[1–3], Charlene Thomas[6], M Arfan Ikram[4,5,19,20], Diana Zelenika[21], Badri N Vardarajan[9], Yoichiro Kamatani[22], Chiao-Feng Lin[23], Amy Gerrish[6], Helena Schmidt[24], Brian Kunkle[13], Melanie L Dunstan[6], Agustin Ruiz[25], Marie-Thérèse Bihoreau[21], Seung-Hoan Choi[11], Christiane Reitz[26,27], Florence Pasquier[2,28], Paul Hollingworth[6], Alfredo Ramirez[29,30], Olivier Hanon[31], Annette L Fitzpatrick[12,32,33], Joseph D Buxbaum[34–36], Dominique Campion[37], Paul K Crane[38], Clinton Baldwin[9], Tim Becker[39,40], Vilmundur Gudnason[17,18], Carlos Cruchaga[41,42], David Craig[43], Najaf Amin[5], Claudine Berr[44], Oscar L Lopez[45], Philip L De Jager[46,47], Vincent Deramecourt[2,28], Janet A Johnston[43], Denis Evans[48], Simon Lovestone[49], Luc Letenneur[50], Francisco J Morón[51], David C Rubinsztein[52], Gudny Eiriksdottir[18], Kristel Sleegers[53,54], Alison M Goate[41,42], Nathalie Fiévet[1,3], Matthew J Huentelman[55], Michael Gill[56], Kristelle Brown[57], M Ilyas Kamboh[58,59], Lina Keller[60], Pascale Barberger-Gateau[50], Bernadette McGuinness[43], Eric B Larson[38,61], Robert Green[62], Amanda J Myers[63], Carole Dufouil[50], Stephen Todd[43], David Wallon[37], Seth Love[64], Ekaterina Rogaeva[65], John Gallacher[66], Peter St George-Hyslop[52,65,67], Jordi Clarimon[68,69], Alberto Lleo[68,69], Anthony Bayer[66], Debby W Tsuang[70], Lei Yu[71], Magda Tsolaki[72], Paola Bossù[73], Gianfranco Spalletta[73], Petroula Proitsi[49], John Collinge[74], Sandro Sorbi[75,76], Florentino Sanchez-Garcia[77], Nick C Fox[78], John Hardy[79,80], Maria Candida Deniz Naranjo[77], Paolo Bosco[81], Robert Clarke[82], Carol Brayne[83], Daniela Galimberti[84], Michelangelo Mancuso[85], Fiona Matthews[86], European Alzheimer's Disease Initiative (EADI)[87], Genetic and Environmental Risk in Alzheimer's Disease (GERAD)[87], Alzheimer's Disease Genetic Consortium (ADGC)[87], Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)[87], Susanne Moebus[88], Patrizia Mecocci[89], Maria Del Zompo[90], Wolfgang Maier[29,39], Harald Hampel[91,92], Alberto Pilotto[93], Maria Bullido[94–96], Francesco Panza[97], Paolo Caffarra[98,99], Benedetta Nacmias[75,76], John R Gilbert[13,14], Manuel Mayhaus[100], Lars Lannfelt[101], Hakon Hakonarson[102], Sabrina Pichler[100], Minerva M Carrasquillo[103], Martin Ingelsson[101], Duane Beekly[104], Victoria Alvarez[105], Fanggeng Zou[103], Otto Valladares[23], Steven G Younkin[103], Eliecer Coto[105], Kara L Hamilton-Nelson[13], Wei Gu[100], Cristina Razquin[106], Pau Pastor[106,107], Ignacio Mateo[108,109], Michael J Owen[6], Kelley M Faber[110], Palmi V Jonsson[17,111], Onofre Combarros[108,109], Michael C O'Donovan[6], Laura B Cantwell[23], Hilkka Soininen[112,113], Deborah Blacker[114,115], Simon Mead[74], Thomas H Mosley Jr[116], David A Bennett[71,117], Tamara B Harris[12], Laura Fratiglioni[60,118], Clive Holmes[119], Renee F A G de Bruijn[4,5,20], Peter Passmore[43], Thomas J Montine[120], Karolien Bettens[53,54], Jerome I Rotter[121], Alexis Brice[122,123], Kevin Morgan[57], Tatiana M Foroud[110], Walter A Kukull[32], Didier Hannequin[37], John F Powell[49], Michael A Nalls[124], Karen Ritchie[44,125], Kathryn L Lunetta[11], John S K Kauwe[126], Eric Boerwinkle[127–129], Matthias Riemenschneider[100], Mercè Boada[25,130], Mikko Hiltunen[112,113], Eden R Martin[13,14], Reinhold Schmidt[131], Dan Rujescu[132], Li-San Wang[23], Jean-François Dartigues[50,133], Richard Mayeux[26,27], Christophe Tzourio[134], Albert Hofman[5,20], Markus M Nöthen[135], Caroline Graff[117,136], Bruce M Psaty[12,32,61,137], Lesley Jones[6], Jonathan L Haines[16,138], Peter A Holmans[6], Mark Lathrop[21,22,139], Margaret A Pericak-Vance[13,14], Lenore J Launer[140], Lindsay A Farrer[9–11,141,142], Cornelia M van Duijn[5,20,143], Christine Van Broeckhoven[53,54], Valentina Moskvina[6], Sudha Seshadri[142,145,146], Julie Williams[6,145,146], Gerard D Schellenberg[23,145,146] & Philippe Amouyel[1–3,28,144–146]

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.

Published
2013/2014

Christiane Reitz *et al.*
ABCA7 and AD in African Americans.
JAMA **309**, 1483-1492. (2013)

Patrick Holton *et al.*
Pathogenic mechanisms of AD risk Loci.
Ann. Hum. Genet. **77**: 85-105.

Perry G. Ridge *et al.*
AD and missing heritability
PLoS One, Nov **7**;8(11):e79771.

Bruno A. Benitez *et al.*
TREML2 variants protects against AD.
Neurobiol. Aging 35 1510.e19e

Agustín Ruiz *et al.*
TRIP4 - a novel AD gene.
Translational Psychiatry **4**, e358.

Published 2013/2014 (cont).

Christiane Reitz *et al.*
VPS10-d receptor and AD loci
Transl. Psychiatry 14;3:e256. doi: 10.1038/tp.13

Christiane Reitz *et al.*
TREM2 Variants in AD – African Americans
New Engl. J. Med. **369**:1564

Akinori Miyashita *et al.,*
SORL1 in AD - Japanese, Koreans and Caucasians.
PLOS One **8**: 1-11, e58618.

Carlos Cruchaga *et al.*
GWAS of CSF tau/Aβ
Neuron **78**, 256-268

In press 2014

Valentina Escott-Price *et al.*

Gene-wide analysis - two new susceptibility genes for AD.

Plos One

Adam Naj *et al.*

Age-at-Onset Modified by Multiple Genetic Loci.

JAMA Neurol.

Peter Nelson *et al.*

ABCC9 and hippocampal sclerosis.

Acta Neuropathol.

Submitted 2014

Tom Montine, Gary Beecham:
Neuropathology trait GWAS

Li-San Wang
APP A673T, an AD protective variant in the US

4 other manuscripts

Ongoing Analyses

- Cognitive decline GWAS
- Exome chip - rare variants

Cohort	Cases	Controls	Total
GWAS 1	10,491	11,449	21,940
New samples	3,000	4,079	7,079
Totals	13,491	15,528	29,019

- Expanded common variant GWAS
- Rare variant GWAS

Alzheimer's Disease Sequencing Project (ADSP)

Whole-genome sequencing: families (multiple case/family)

585 subjects from 111 multiplex

Sequencing complete
Data quality being evaluated

Whole exome sequencing:

5,000 unrelated cases
5,000 unrelated elderly controls
1,000 cases – multiplex families
11,000 total

Sequencing 50% complete

Replication phase:

25,000 case
25,000 controls

https://www.niagads.org/node/116

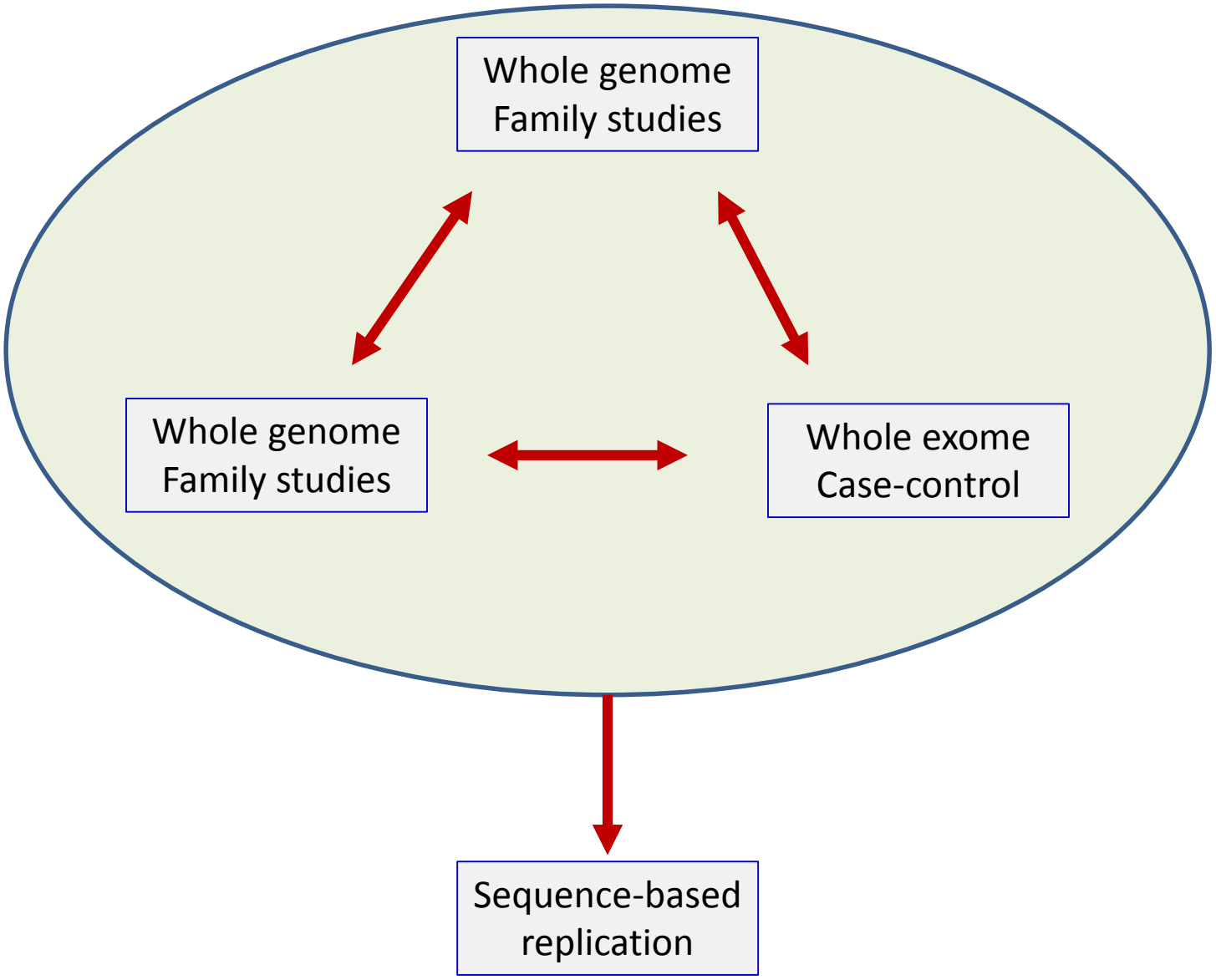
ADSP Analyses

WGS:

- Family-based analyses – rare variants
- Structural variants

  Insertion/deletions
  Copy number variation
  Inversions
  Translocation

ADSP Analyses



Thank you!