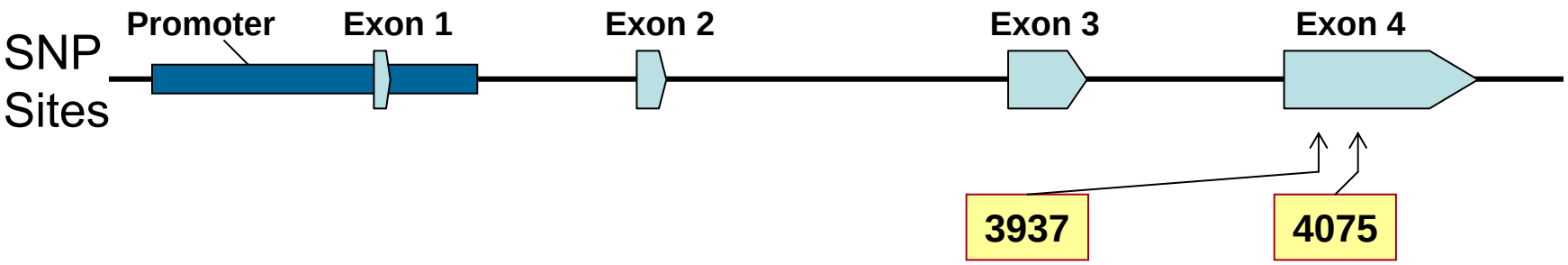
Alzheimer's Disease Genetics Consortium (ADGC)

Use genome-wide association (GWA) methods to solve the genetics of Alzheimer's disease

ApoE association with AD



Controls	AD		3937	4075
0.135	0.355	ε4	C (Arg)	C (Arg)
0.765	0.607	ε3	T (Cys)	C (Arg)
0.10	0.038	ε2	T (Cys)	T (Cys)

GWAS – test all (most) genes and regions in one experiment

Genetic Variability

SNP: single nucleotide polymorphism

-AGTAT C TCAAG-

-AGTAT T TCAAG-

---------C/T----------

C/C
C/T
T/T

~550,000 SNPs test approximately
85 – 92% of the genome
(Caucasians)

~$400/subject

Genetic Variability

SNP: single nucleotide polymorphism

-AGTAT C TCAAG-

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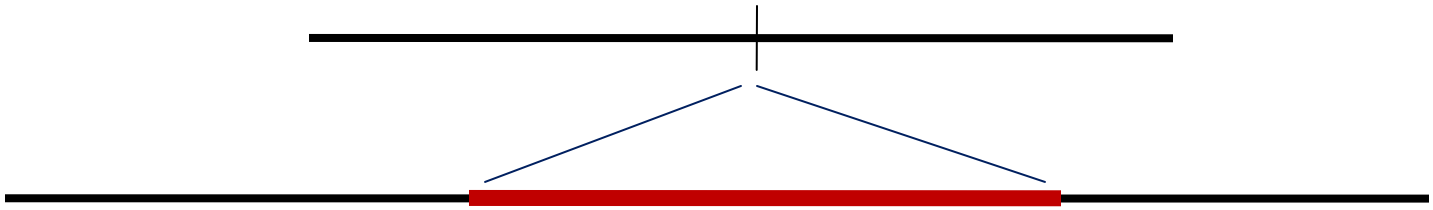
---------C/T----------

CNV: copy number variation



1 bp to > 10 Mb

20kb to > 10 Mb

Multiple testing

test 550,000 sites at $p < 0.05$
expect 27,500 false-positive results

need $p < 10^{-8}$ for genome-wide significance

avoid both false-positive AND false-negative results

~550,000 SNPs test approximately
85 – 92% of the genome
(Caucasians)

~$400/subject

Multiple testing

test 500,000 sites at $p < 0.05$
expect 25,000 false-positive results

need $p < 10^{-8}$ for genome-wide significance

avoid both false-positive AND false-negative results

Solutions

Large sample size

Discovery and replication dataset

Better analysis tools

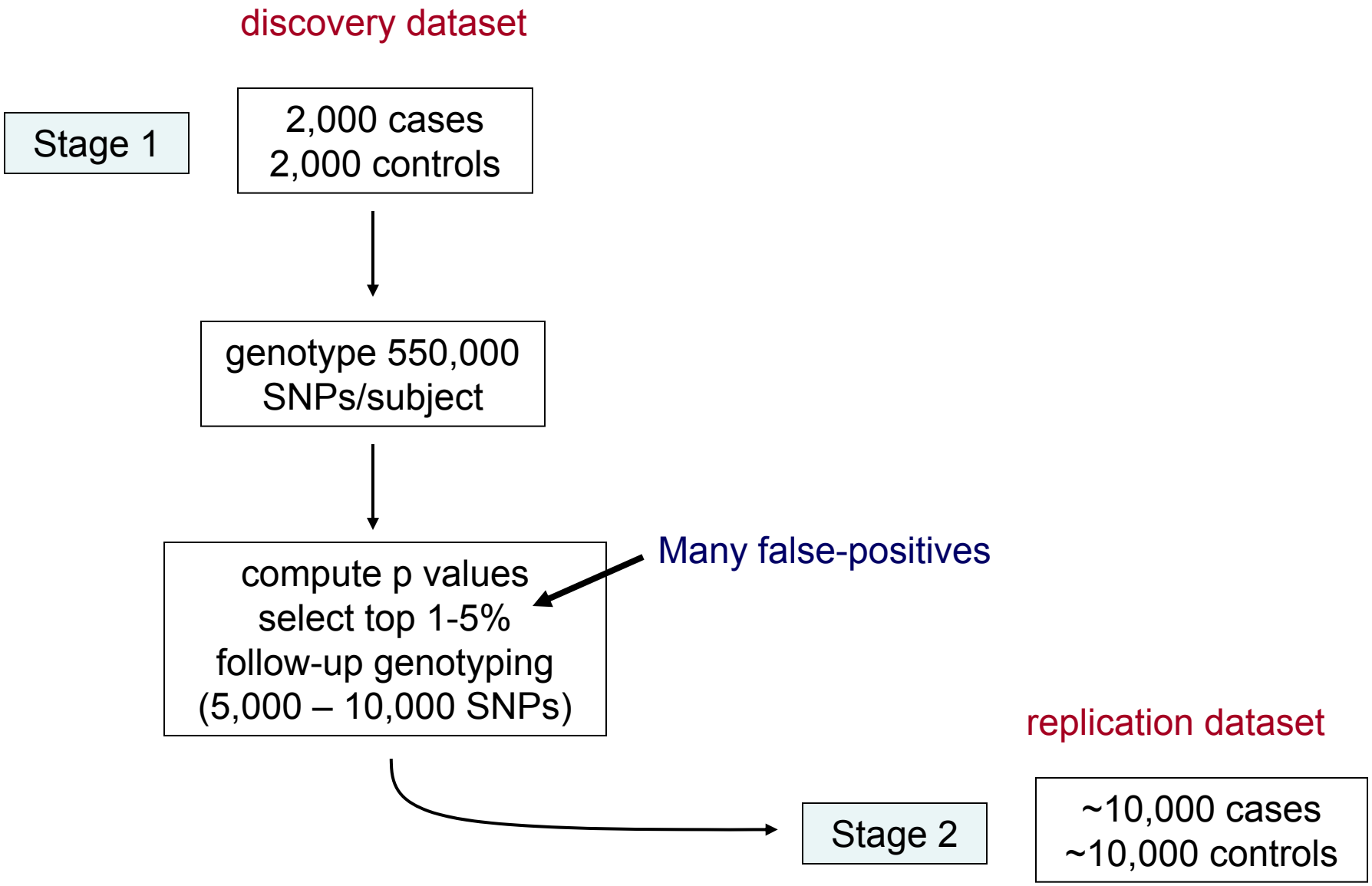
Initial Goals for AD

1. Large discovery dataset ~2,000 cases
   ~2,000 controls

2. Large replication dataset ~10,000 cases
   ~10,000 controls

or larger

- Use existing subjects/data
  (no new subjects being enrolled)
- Use NACC database for phenotype data
- For prospective cohort samples, use existing studies underway
- Use NCRAD to bank DNA for GWAS


discovery dataset
Stage 1
2,000 cases
2,000 controls
genotype 550,000
SNPs/subject
compute p values
select top 1-5%
follow-up genotyping
(5,000 – 10,000 SNPs)
Many false-positives
replication dataset
Stage 2
~10,000 cases
~10,000 controls

Alzheimer's disease and related traits

age-at-onset:	time to initiating trigger rate of progression through MCI
endophenotypes: (traits related to the disease)	plaque density tangle distribution CSF Aβ, tau, P-tau, and ApoE cognitive decline

Progress

1. developed a comprehensive research plan
2. obtain funding for initial meta-analysis
3. established criteria for autopsy case and control definition
4. call for tissue/DNA for GWA studies
5. funding obtained for a GWAS of the LOAD families (Richard Mayeux)

Merge existing data - use dbGAP tools

Framingham	Affimetrix 100K	1087 subjects, 350 cases
TGEN	Affimetric 550K	664 cases, 422 controls
University of Miami	Illumina 550K	496 cases, 500 controls
Mayo Jacksonville	Illumina 300K	1,000 cases, 1,000 controls
ADNI GWAS	Illumina 550K	200 cases, 200 controls, 400 MCI
Kramer	Illumina 370K	225 cases, 480 controls
GlaxoSmithKline		
NIMH family dataset		
Texas GWAS		

Merge existing data - use dbGAP tools

Difficulties

each study underpowered
different platforms
different coverage by platforms
different ascertainment/phenotype data

pilot funding for analysis proposals

Research Plan

1. ADC cohort; 2,000 cases, 2,000 controls

   preference given to autopsied samples (all cases)
   controls supplemented with clinical controls

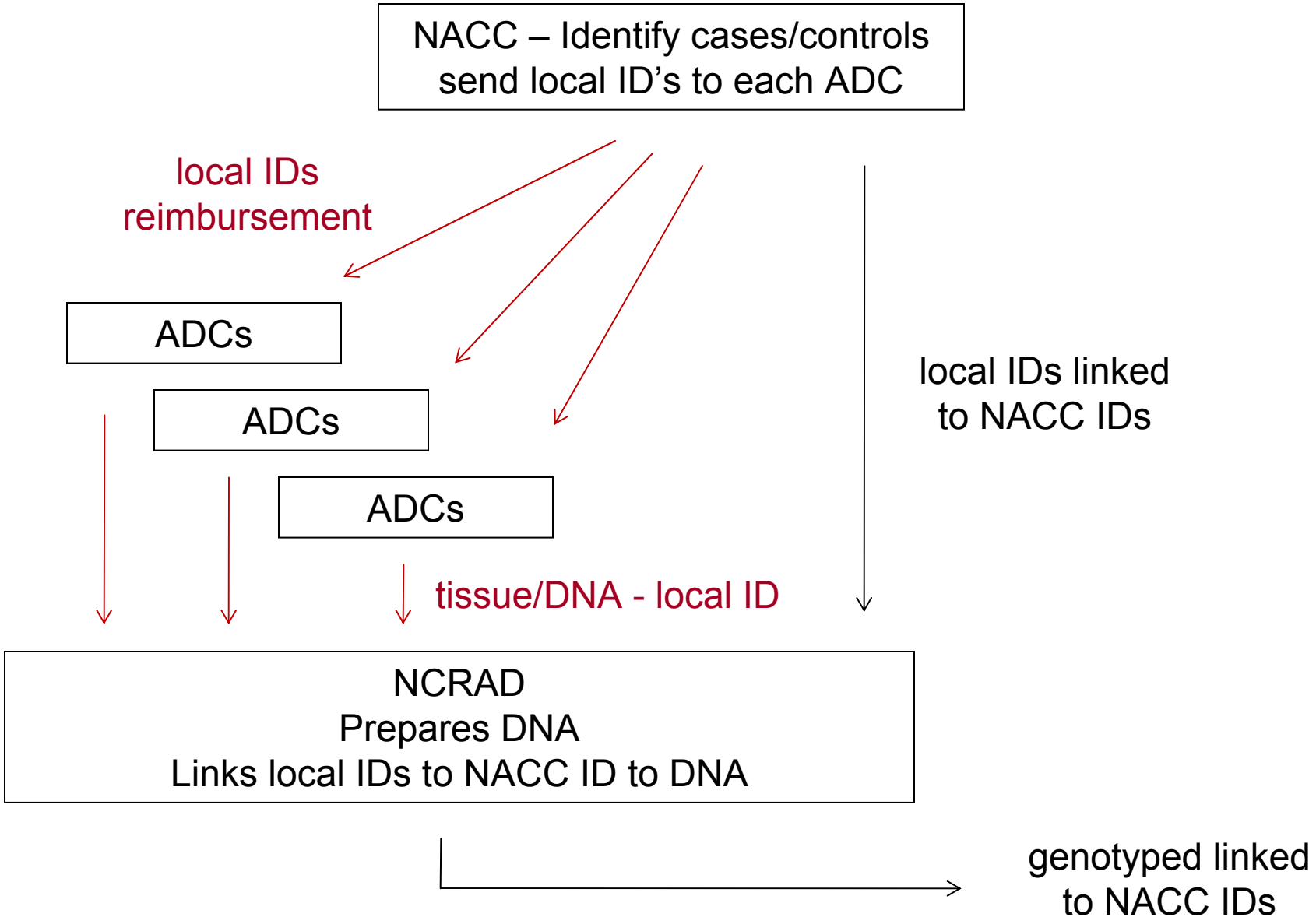
   Analysis: case versus controls
   Braak stage
   plaque density

Research Plan

Case:	clinical diagnosis of dementia		
	NIA/Reagan:	intermediate or high	3,118
Case:	clinical diagnosis of dementia		
	NIA/Reagan:	not done/missing/criteria not met/unknown	
	Braak staging:	3-6	
	neuritic plaques:	frequent to moderate	334
Controls:	clinical diagnosis	normal	
	NIA/Reagan:	low	194
Controls:	clinical diagnosis	normal	
	NIA/Reagan:	not done/missing/criteria not met/unknown	
	Braak staging	0 – 2	
	neuritic plaques	none to sparse	170
Controls:	clinical diagnosis	normal	
	Braak staging	3-4	
	neuritic plaques	none	29

Exclusion criteria

1. age ≤ 60 years
2. DNA/frozen tissue available
3. diagnosis of FTD, prion disease, other major neurologic diseases
4. known relevant mutations


NACC – Identify cases/controls
send local ID's to each ADC
local IDs
reimbursement
ADCs
ADCs
ADCs
local IDs linked
to NACC IDs
tissue/DNA - local ID
NCRAD
Prepares DNA
Links local IDs to NACC ID to DNA
genotyped linked
to NACC IDs

Research Plan

1. ADC cohort; 2,000 cases, 2,000 controls

   preference given to autopsied samples (all cases)
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   Analysis: case versus controls
   Braak stage
   plaque density

2. Combined data with other datasets

Research Plan

3. Replication dataset (consortium members)

   9,263 cases
   9,069 controls

4. CSF sample

Site	samples	Age-range	percent non-demented
Univ. of Washington	>500	47 (21-101)	64%
Washington University	431	67 (43-91)	73%
ADNI	~500		~25%
Univ. Pennsylvania	283	71 (41-94)	13%
	1,705		

Research Plan

5. Prospective cohorts

Study	PI	N	> 3 evals	incident dementia	incident MCI
CHAP	Evans	2,300	1,500	210	270
WHICAP	Mayeux	904	586	59	105
MAP	Bennett	1,050	950	150	250
WHISCA	Resnick	2,275	2,000	85	170

Quantitative trait: Cognitive decline

Work Groups

Analytic group

Peggy Pericak-Vance/Lindsey Farrer

Jonathan Haines/Bernie Devlin

Neuropathologic sample

Tom Montine/Eric Reiman

Family-based studies

Richard Mayeux/Deborah Blacker

Biomarker group

Alison Goate/Andy Saykin

Clinical sample

John Morris/Debbie Tsuang

Epidemiologic group

David Bennett