Alzheimer's Disease Genetics Consortium (ADGC)

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2. Identify AD sub-phenotype genes

    rate-of-progression

    plaque/tangle load/distribution

    biomarker variability

Alzheimer's Disease Genetics Consortium (ADGC)

1. Identify genes responsible for AD susceptibility
2. Identify AD sub-phenotype genes
   - rate-of-progression
   - plaque/tangle load/distribution
   - biomarker variability
3. Generate a genetic data resource for the AD research community

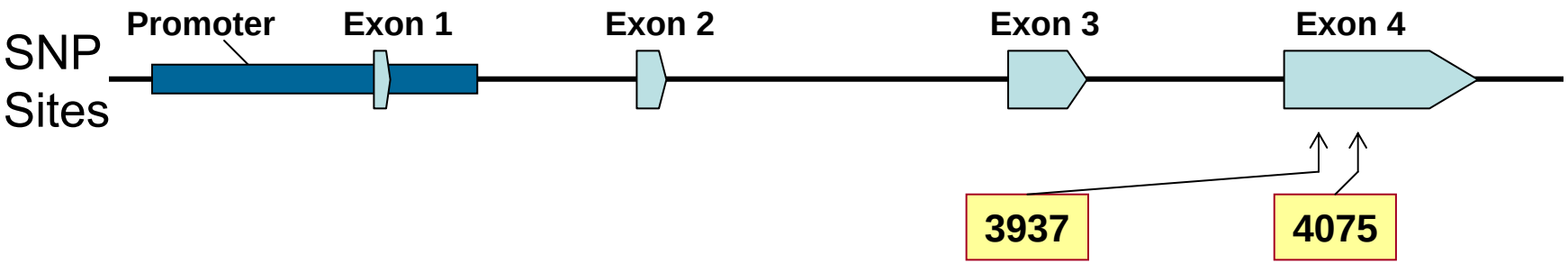
To achieve these goals –

Use the combined resources and expertise of the AD research community in a collaborative manner

Genetic variability and AD

1. Linkage analysis
2. Genome-wide Association Studies (GWAS)

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)

In GWAS, all (most) genes tested simultaneously

Genome-wide Association Studies

1. Inexpensive high-density genotyping (550,000 genotypes/subject, ~$400 - $650)

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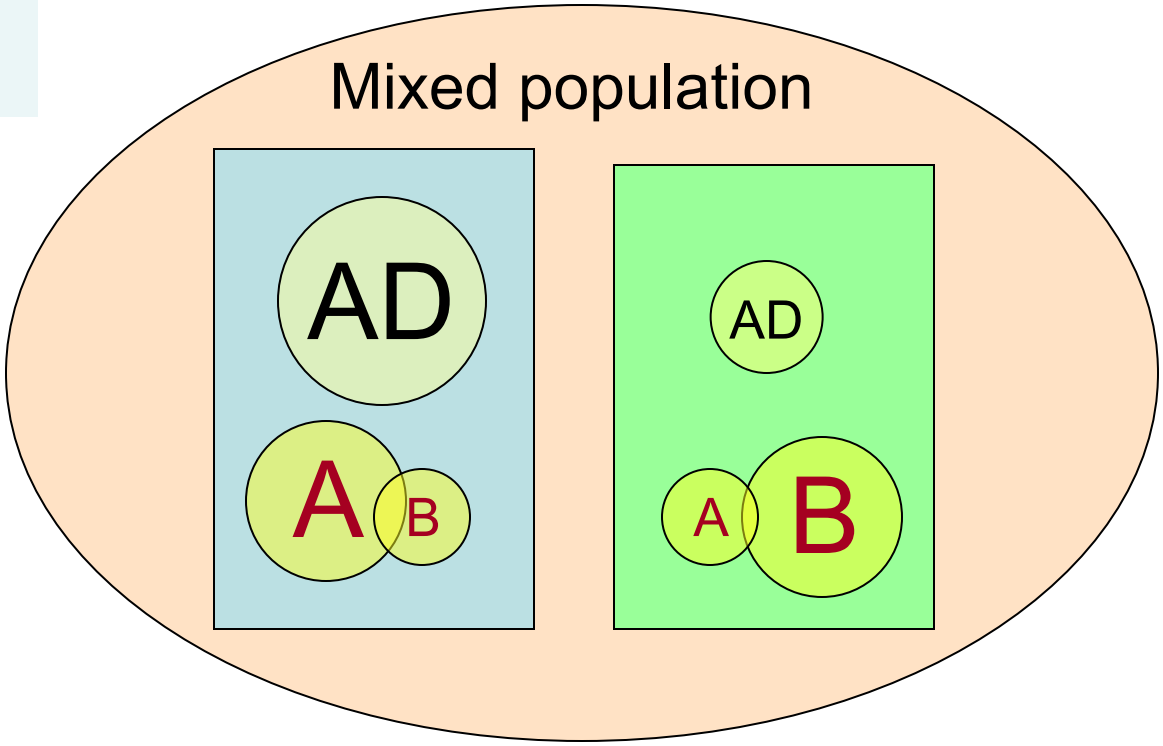
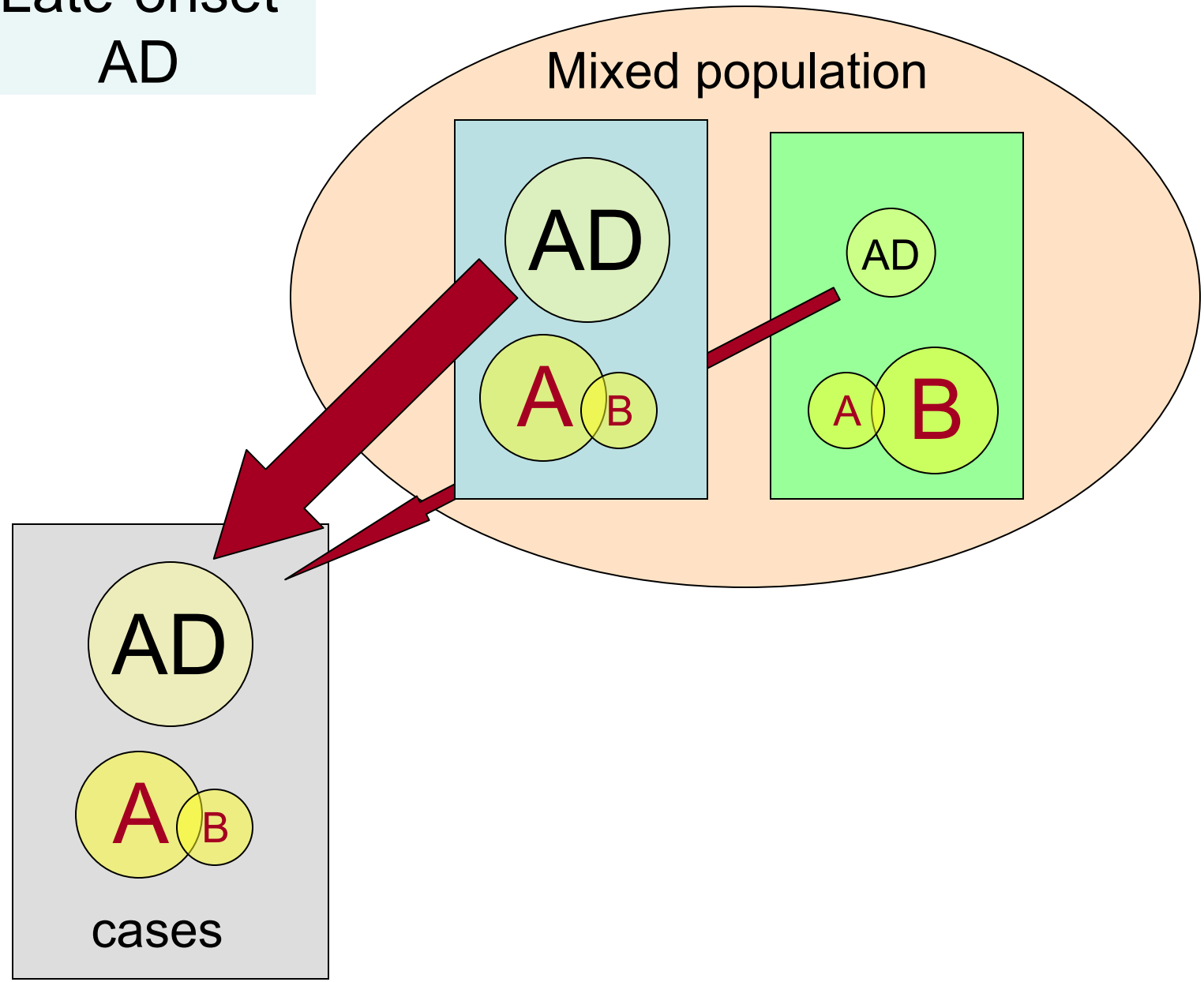
2. Statistical methods for dealing with population admixture

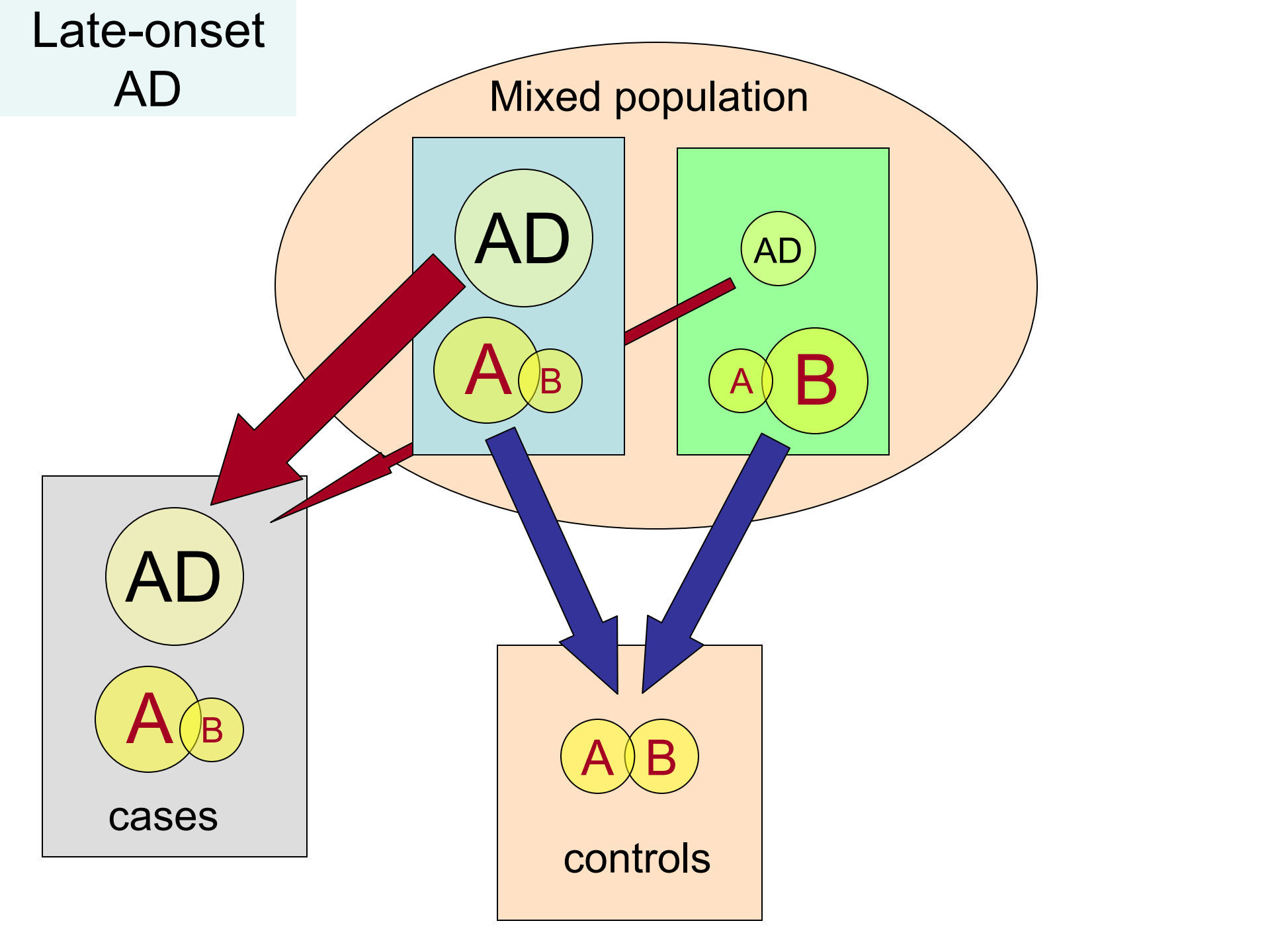
Late-onset AD



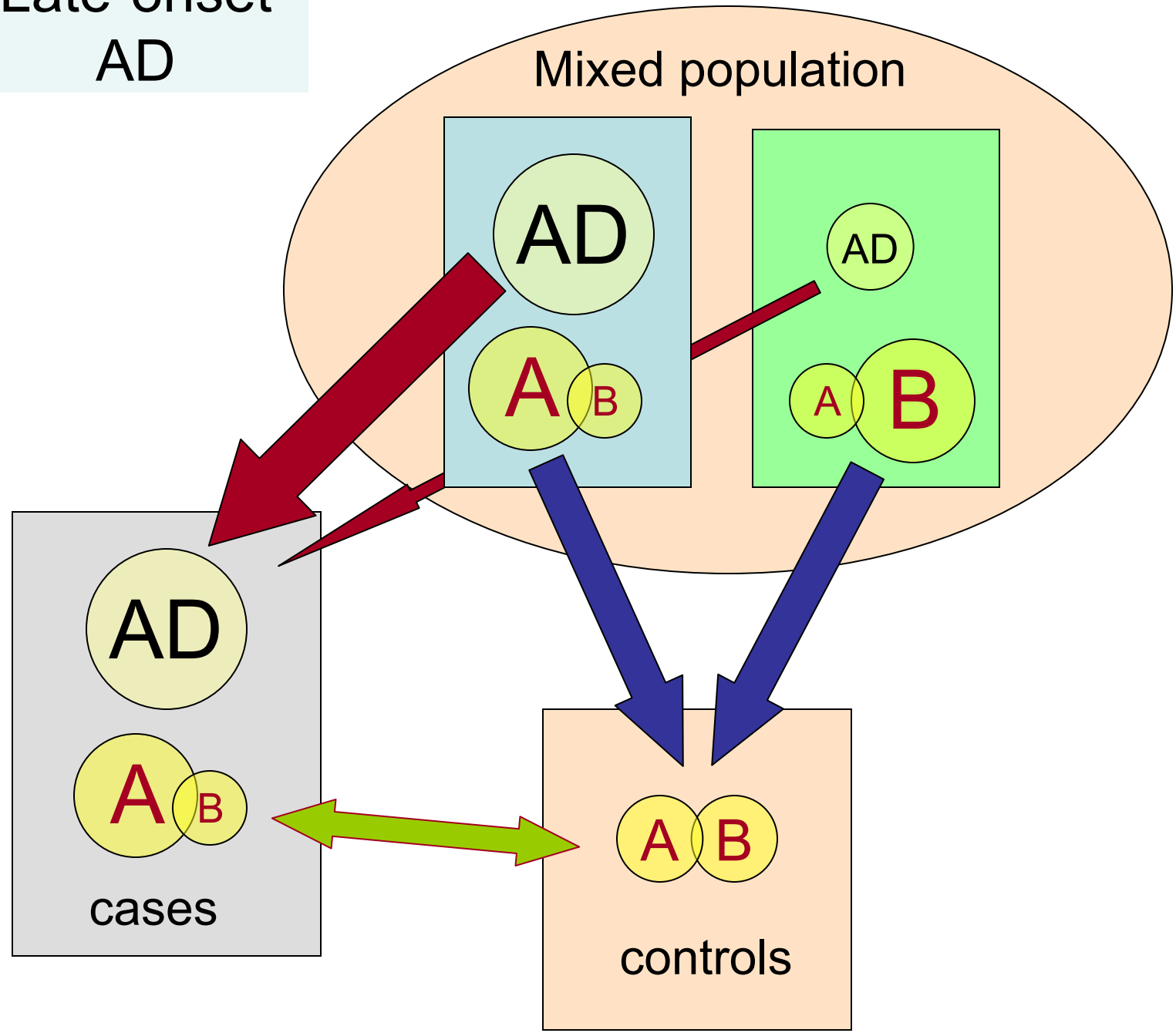
Admixture and false-positive results in case-control studies

Late-onset AD



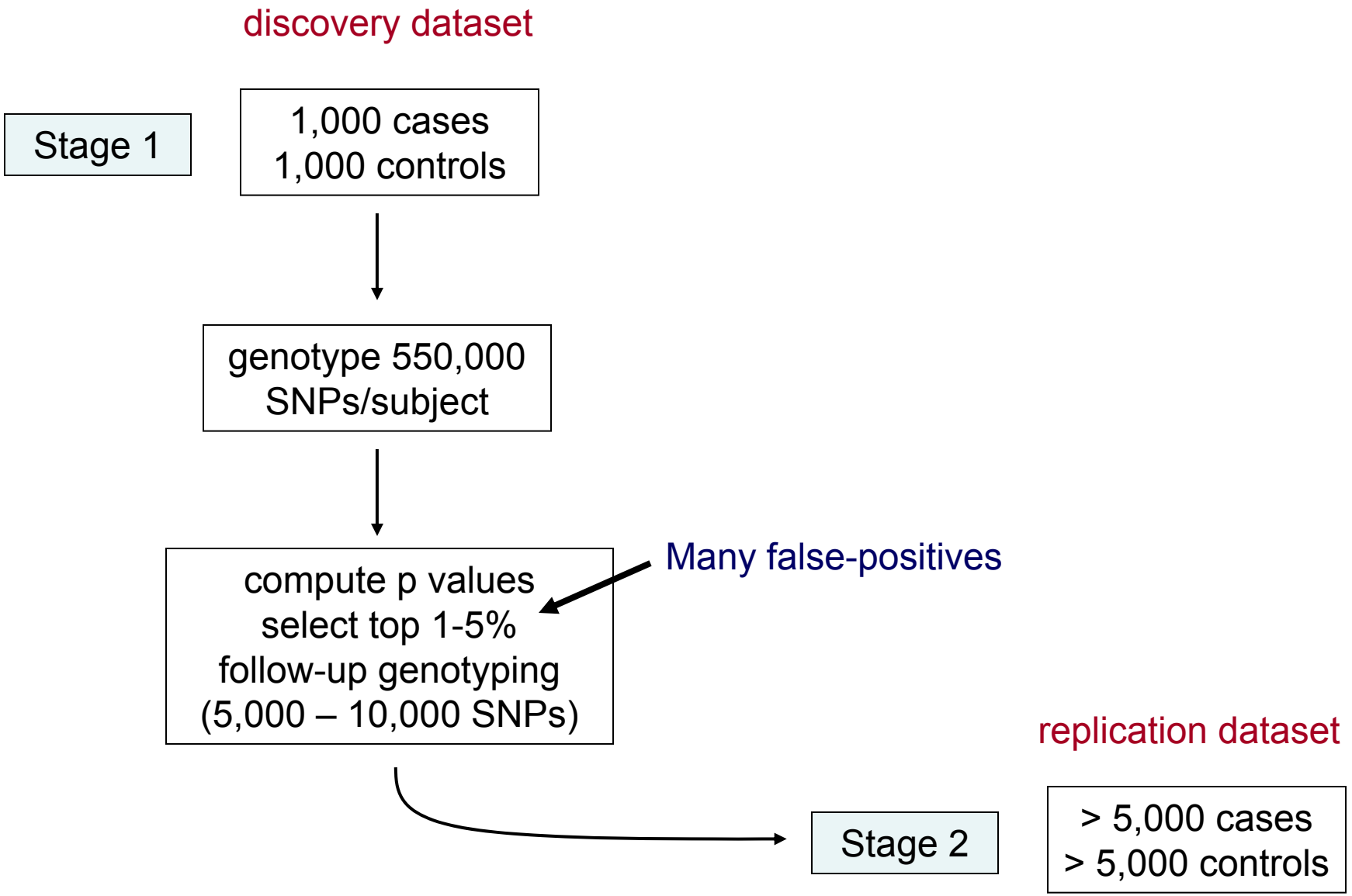

Late-onset AD
Mixed population
AD
A
B
AD
A
B
AD
A
B
cases
A
B
controls

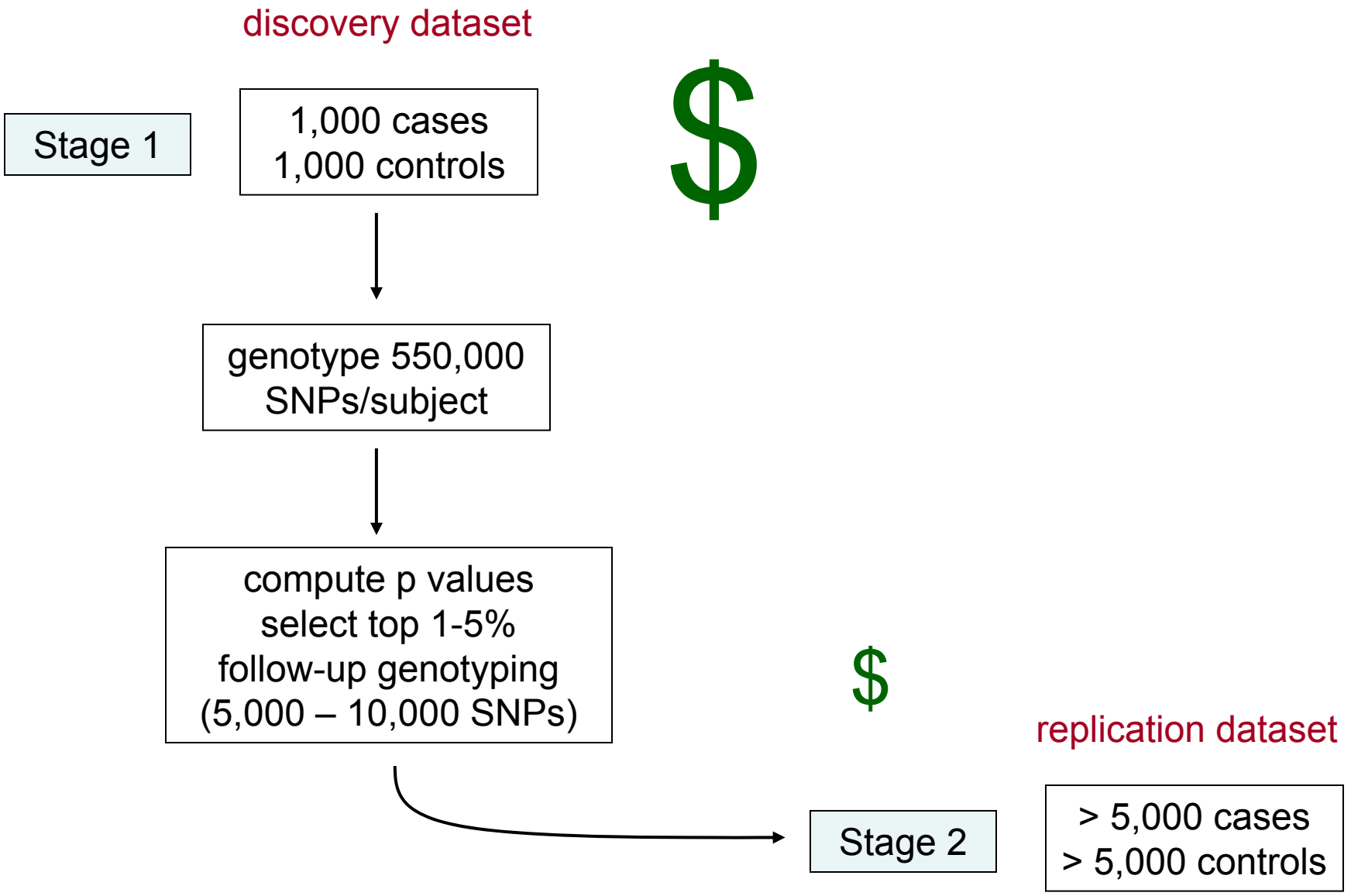
Late-onset AD



Genome-wide Association Studies

1. Inexpensive high-density genotyping (550,000 genotypes/subject, ~$400 - $650)
2. Statistical methods for dealing with population admixture
3. Large well-characterized sample


discovery dataset
Stage 1
1,000 cases
1,000 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
> 5,000 cases
> 5,000 controls


discovery dataset
Stage 1
1,000 cases
1,000 controls
$
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SNPs/subject
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(5,000 – 10,000 SNPs)
$
replication dataset
Stage 2
> 5,000 cases
> 5,000 controls

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen L. Mohlke,[2] Lori L. Bonnycastle,[3] Cristen J. Willer,[1] Yun Li,[1] William L. Duren,[1] Michael R. Erdos,[3] Heather M. Stringham,[1] Peter S. Chines,[3] Anne U. Jackson,[1] Ludmila Prokunina-Olsson,[3] Chia-Jen Ding,[1] Amy J. Swift,[3] Narisu Narisu,[3] Tianle Hu,[1] Randall Pruim,[4] Rui Xiao,[1] Xiao-Yi Li,[1] Karen N. Conneely,[1] Nancy L. Riebow,[3] Andrew G. Sprau,[3] Maurine Tong,[3] Peggy P. White,[1] Kurt N. Hetrick,[5] Michael W. Barnhart,[5] Craig W. Bark,[5] Janet L. Goldstein,[5] Lee Watkins,[5] Fang Xiang,[1] Jouko Saramies,[6] Thomas A. Buchanan,[7] Richard M. Watanabe,[8,9] Timo T. Valle,[10] Leena Kinnunen,[10,11] Gonçalo R. Abecasis,[1] Elizabeth W. Pugh,[5] Kimberly F. Doheny,[5] Richard N. Bergman,[9] Jaakko Tuomilehto,[10,11,12] Francis S. Collins,[3]* Michael Boehnke[1]*

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research*†

Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini,[1,2]* Michael N. Weedon,[3,4]* Cecilia M. Lindgren,[1,2]* Timothy M. Frayling,[3,4]* Katherine S. Elliott,[2] Hana Lango,[3,4] Nicholas J. Timpson,[2,5] John R. B. Perry,[3,4] Nigel W. Rayner,[1,2] Rachel M. Freathy,[3,4] Jeffrey C. Barrett,[2] Beverley Shields,[4] Andrew P. Morris,[2] Sian Ellard,[4,6] Christopher J. Groves,[1] Lorna W. Harries,[4] Jonathan L. Marchini,[7] Katharine R. Owen,[1] Beatrice Knight,[4] Lon R. Cardon,[2] Mark Walker,[8] Graham A. Hitman,[9] Andrew D. Morris,[10] Alex S. F. Doney,[10] The Wellcome Trust Case Control Consortium (WTCCC),† Mark I. McCarthy,[1,2]‡§ Andrew T. Hattersley[3,4]‡

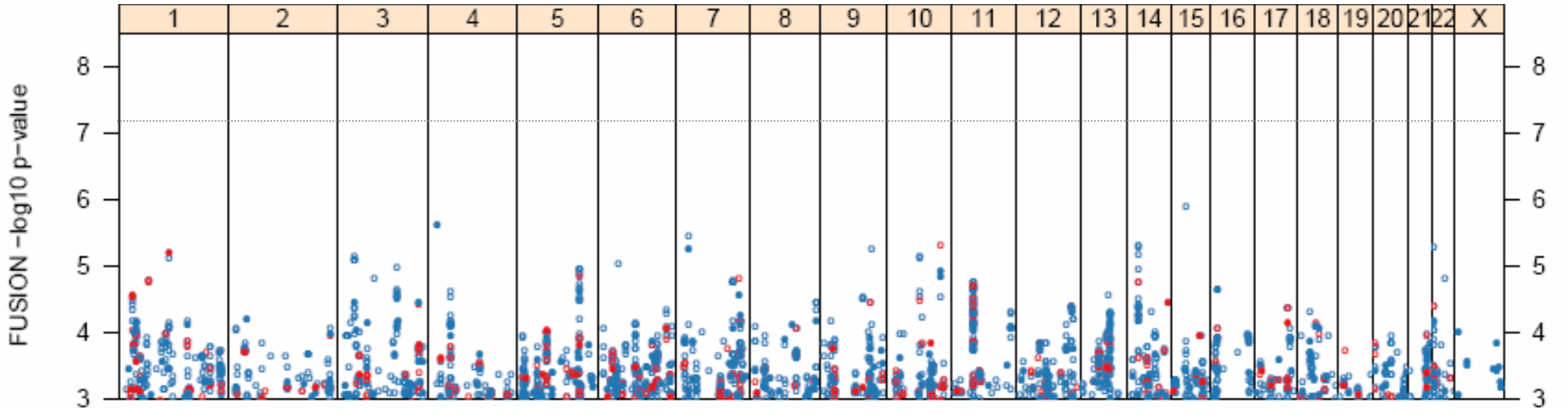
Type 2 Diabetes

discovery datasets

Stage 1

1,161 cases
1,174 controls

FUSION



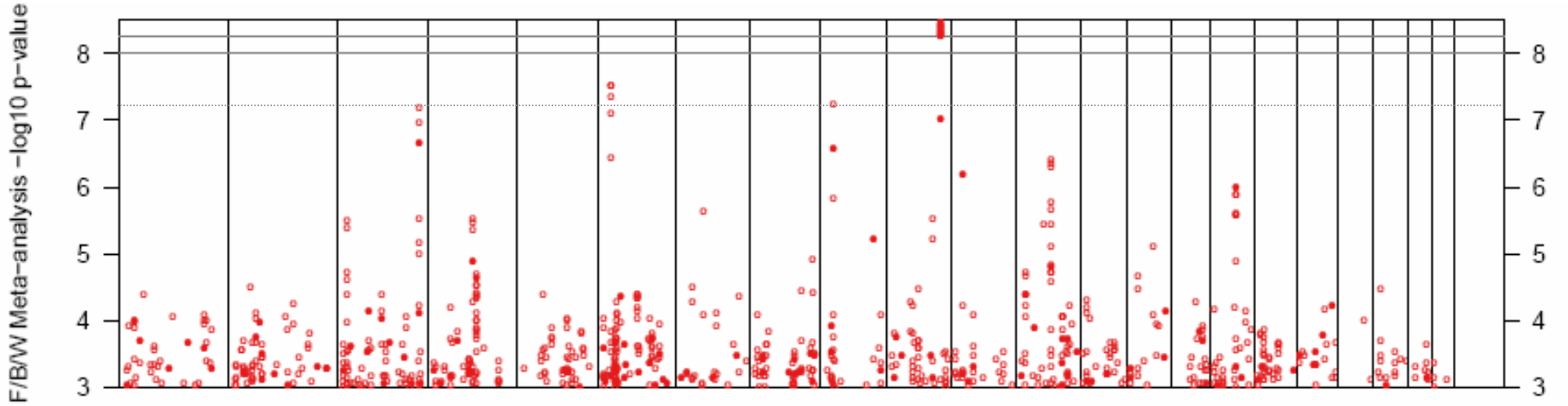
Type 2 Diabetes

discovery datasets

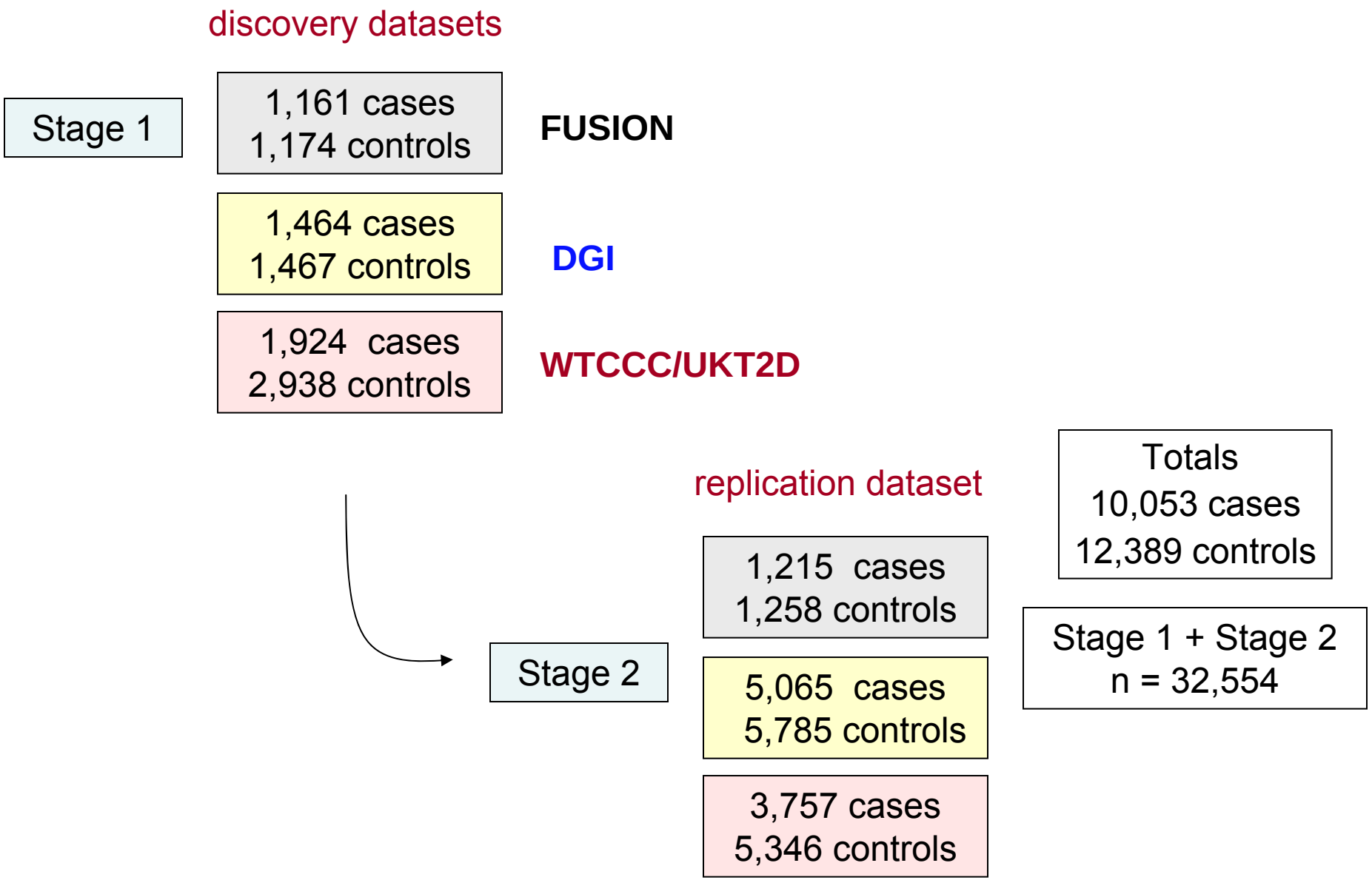
Stage 1

1,161 cases 1,174 controls	**FUSION**
1,464 cases 1,467 controls	**DGI**
1,924 cases 2,938 controls	**WTCCC/UKT2D**

Totals
4,549 cases
5,579 controls



Type 2 Diabetes



Gene	odds ratio	p value
TCF7L2	1.37	1.0×10^{-48}
IGF2BP2	***1.14***	**8.9×10^{-16}**
CDKN2A/B	***1.20***	**7.8×10^{-15}**
FTO	***1.17***	**1.3×10^{-12}**
CDKAL1	***1.12***	**4.1×10^{-11}**
KCNJ11	***1.14***	**6.7×10^{-11}**
HHEX	***1.13***	**5.7×10^{-10}**
SLC30A8	***1.12***	**5.3×10^{-8}**
Chr 11	**1.23**	**4.3×10^{-7}**
PPARG	***1.14***	**1.7×10^{-6}**

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Risk Alleles for Multiple Sclerosis Identified by a Genomewide Study

The International Multiple Sclerosis Genetics Consortium*

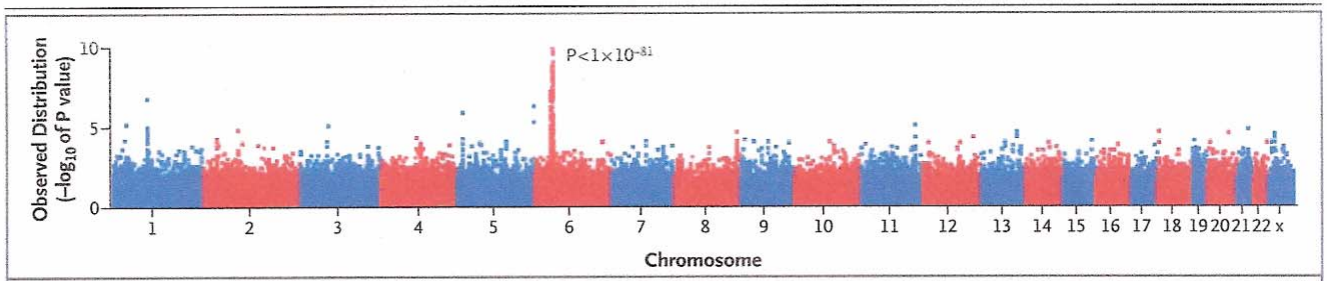

Figure 2. Overview of the Primary Genomewide Association Scan Involving 931 Family Trios.

P values (shown as $-\log_{10}$ values) for results of transmission disequilibrium testing are plotted across the genome. The classic HLA-DR risk locus on chromosome 6p21 stands out with strong statistical significance ($P<1\times10^{-81}$).

Initial Goals for AD

1. Large discovery dataset ~5,000 cases
   ~5,000 controls

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

- Susceptibility genes
- Sub-phenotypes (endophenotypes)

  biomarkers (CSF, others)
  MRI features
  clinical phenotypes
    rate of-progression
    co-morbid conditions
    psychosis
  neuropathologic features
  environmental factors

Discovery dataset

Replication dataset

Work Groups

Analytic group

Peggy Pericak-Vance/Lindsey Farrer

Neuropathologic sample

Eric Reiman/Julie Schneider

Family-based studies

Richard Mayeux

Biomarker group

Alison Goate/Andy Saykin

Clinical sample

Gerard Schellenberg

Epidemiologic group

David Bennett

Work Groups

Analytic group

1. Merge GWAS datasets

2. Work with dbGAP – imput GWAS to generate common marker set across genome for different platforms.

3. Select SNPs for follow-up analysis

4. Coordinate final analysis (Phase 1 and 2)

Work Groups

Neuropathologic sample

1. Assemble a cohort of autopsy-documented AD cases

2. Assemble a cohort of autopsy-documented controls

Rationale: diagnostic certainty
human subjects issues
potential source of neuropath-based endophenotypes

Purpose: discovery dataset
replication dataset

Work Groups

Clinical samples

Cases/controls: ADC UDS samples

Rationale: extensive phenotype data
careful diagnosis

Purpose: discovery dataset for phenotypic variables
replication (stage 2) sample

Sample: 3,136 probable AD (primary diagnosis)
1,921 with DNA
1,083 without DNA – follow-up scheduled

Work Groups

Family-based studies

LOAD sample ← CIDR genotyping
NCRAD families ←
NIMH families

Miami families (Pericak-Vance)
St Louis families (Alison Goate)
Seattle families (Tom Bird)

Different genetic architecture
Different methods

Work Groups

Epidemiologic group

Cohort studies with prospective risk factor data

Purpose: gene/environment interactions

Over multiple studies: 2,000 incident cases by 2010

Advantages: representative of AD
prospective data
some linked to medical/pharmacy records

Seattle Group Health cohort is now funded to explore linking data from electronic medical records with high-density genotype data

Work Groups

Biomarker group

CSF samples
- ADNI
- St Louis
- Seattle
- others

MRI features

Controls

- database controls: cognitive function unknown
  young/middle aged
- cognitively normal/autopsy controls
- elderly controls – cognitively normal

Goals for AD

1. Large discovery dataset ~5,000 cases
   ~5,000 controls

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

Authorship

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