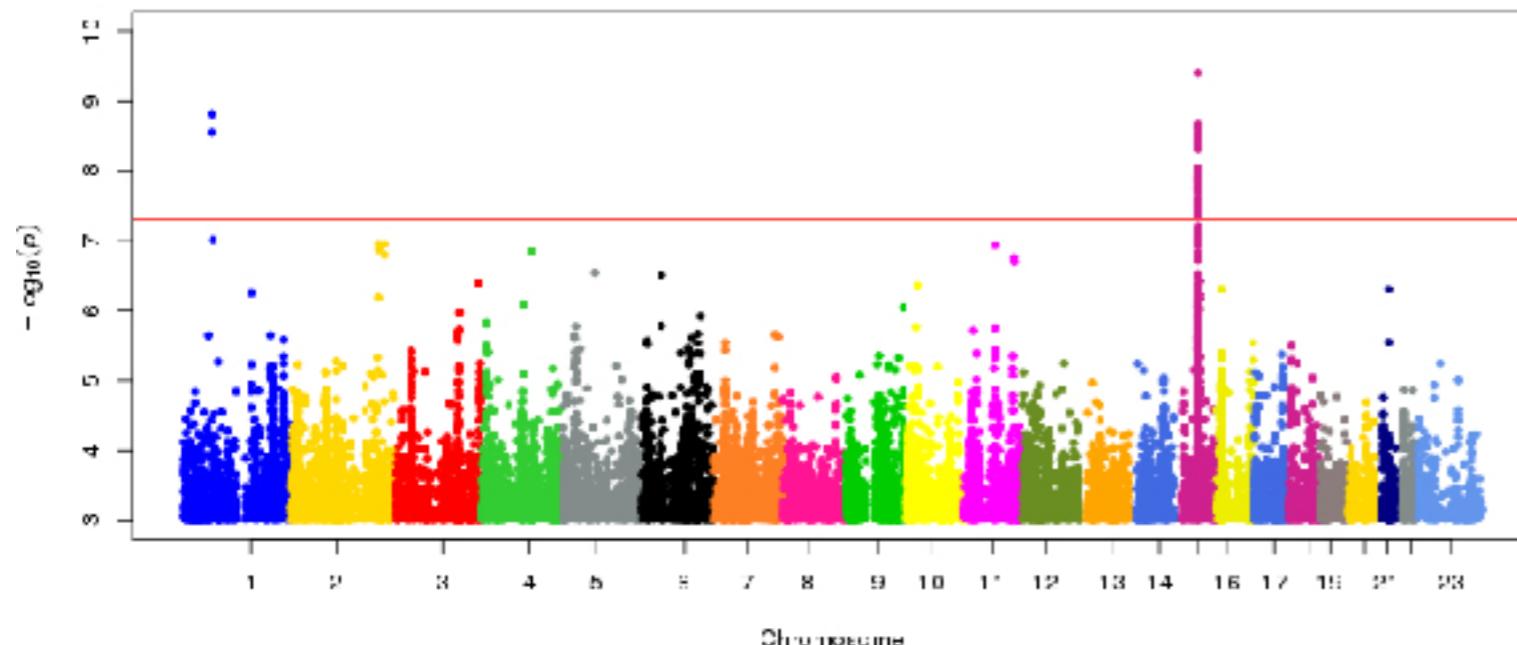


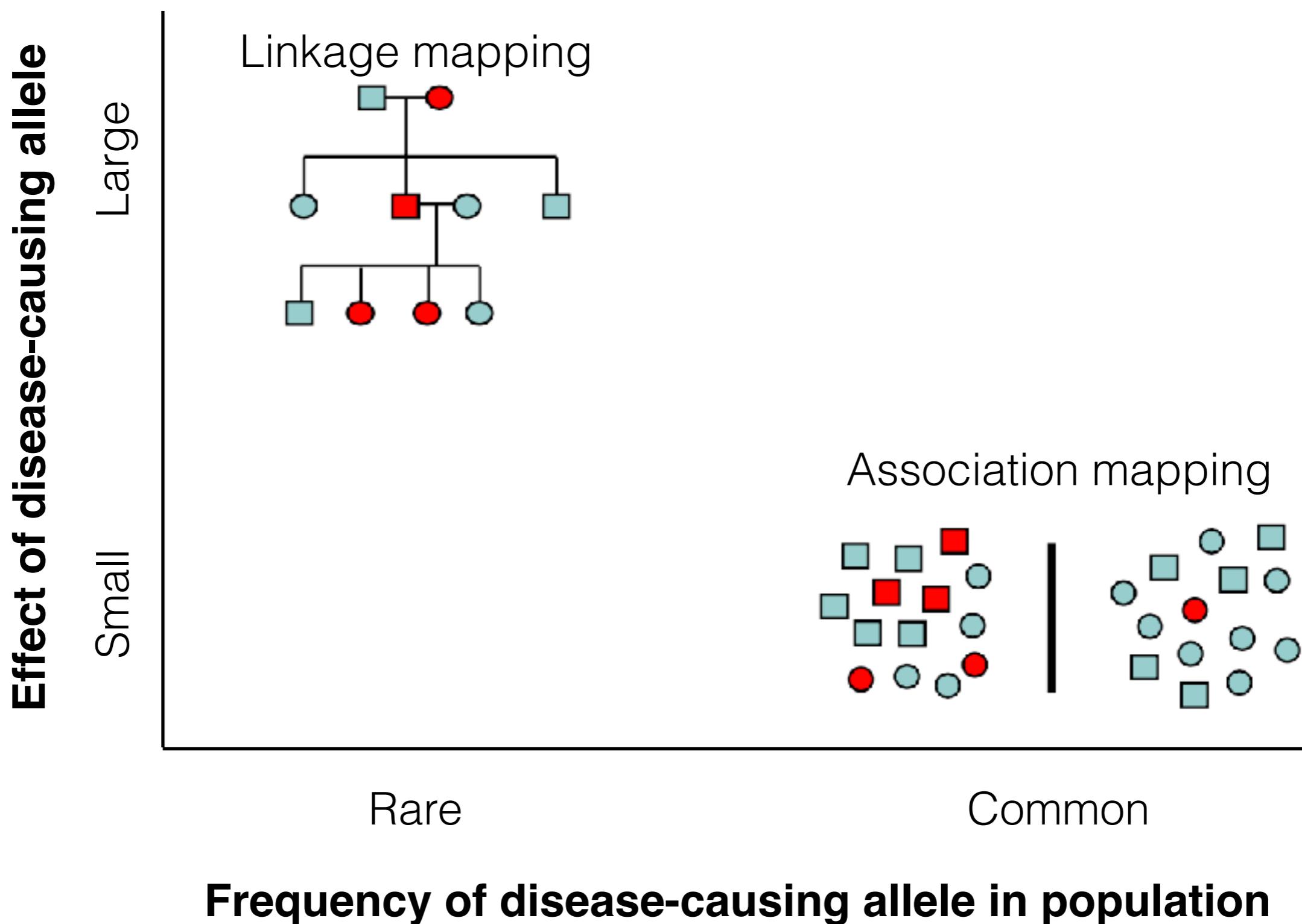
Bio393: Genetic Analysis

GWAS, relative risk, complex traits, and the future of genetic medicine



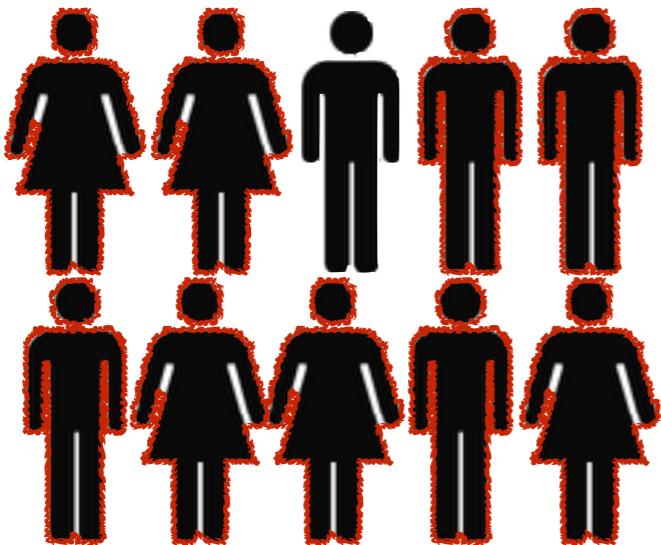
Styrkarsdottir *et al.* Nature 2014

Human gene mapping has two general flavors

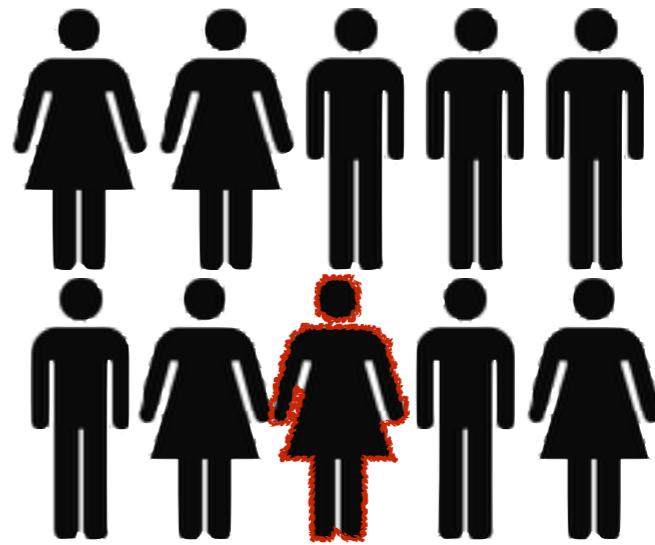


The set up of a genome-wide association (GWA) mapping

Case-control study design



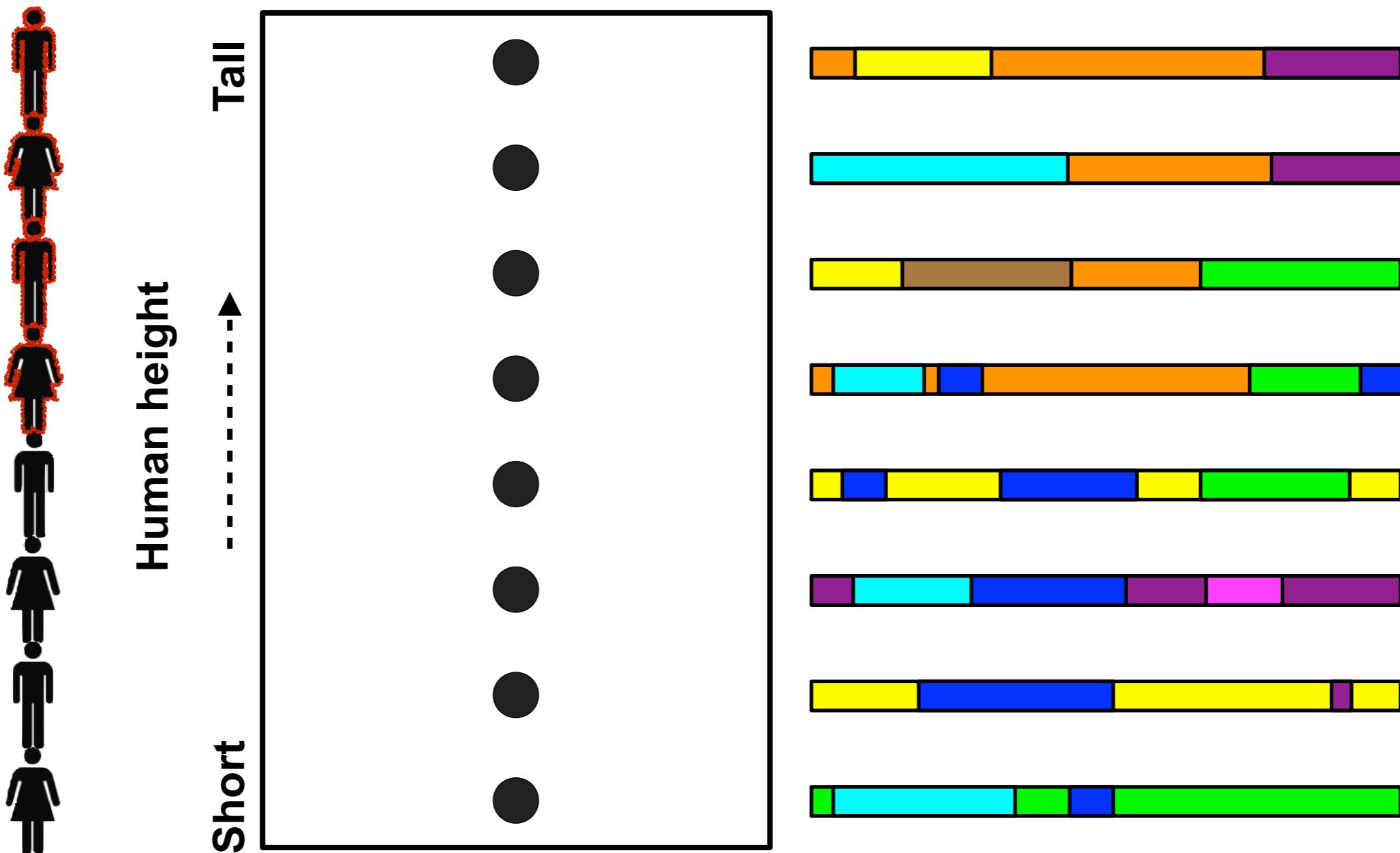
Cases
(People with trait)



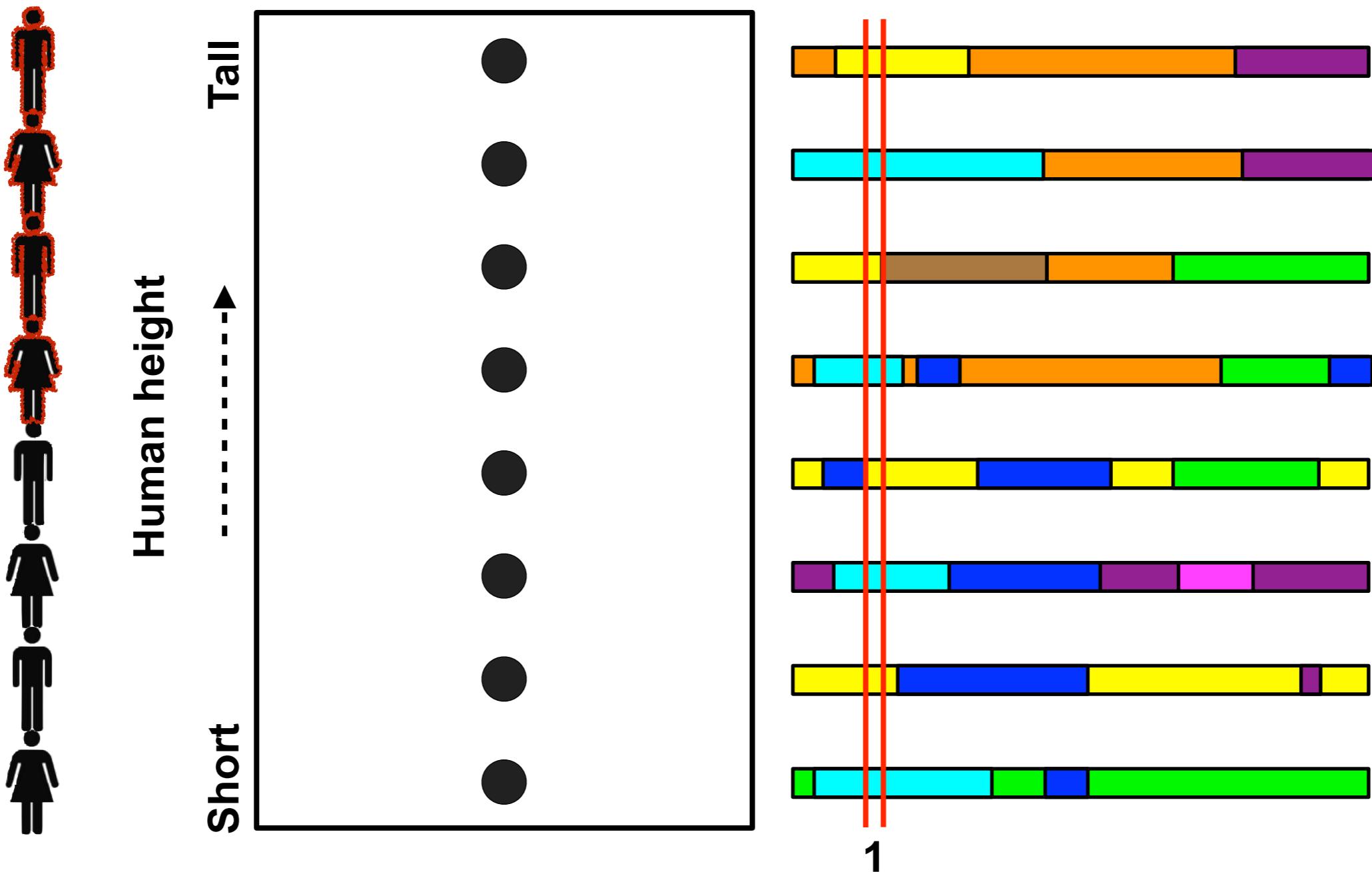
Controls
(People without trait)

What alleles do the cases share that the controls lack?

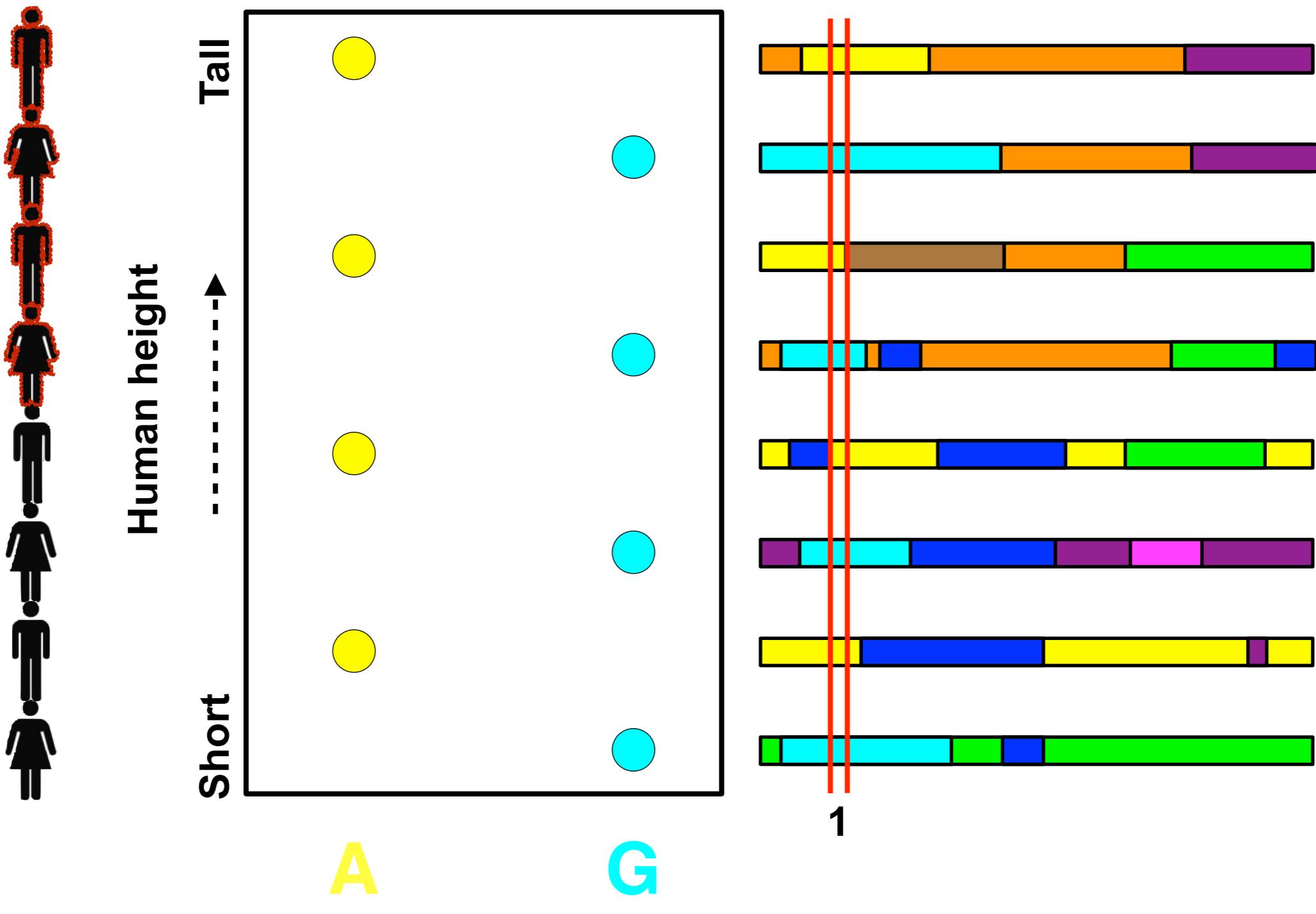
Association mapping: Correlating genotype with phenotype



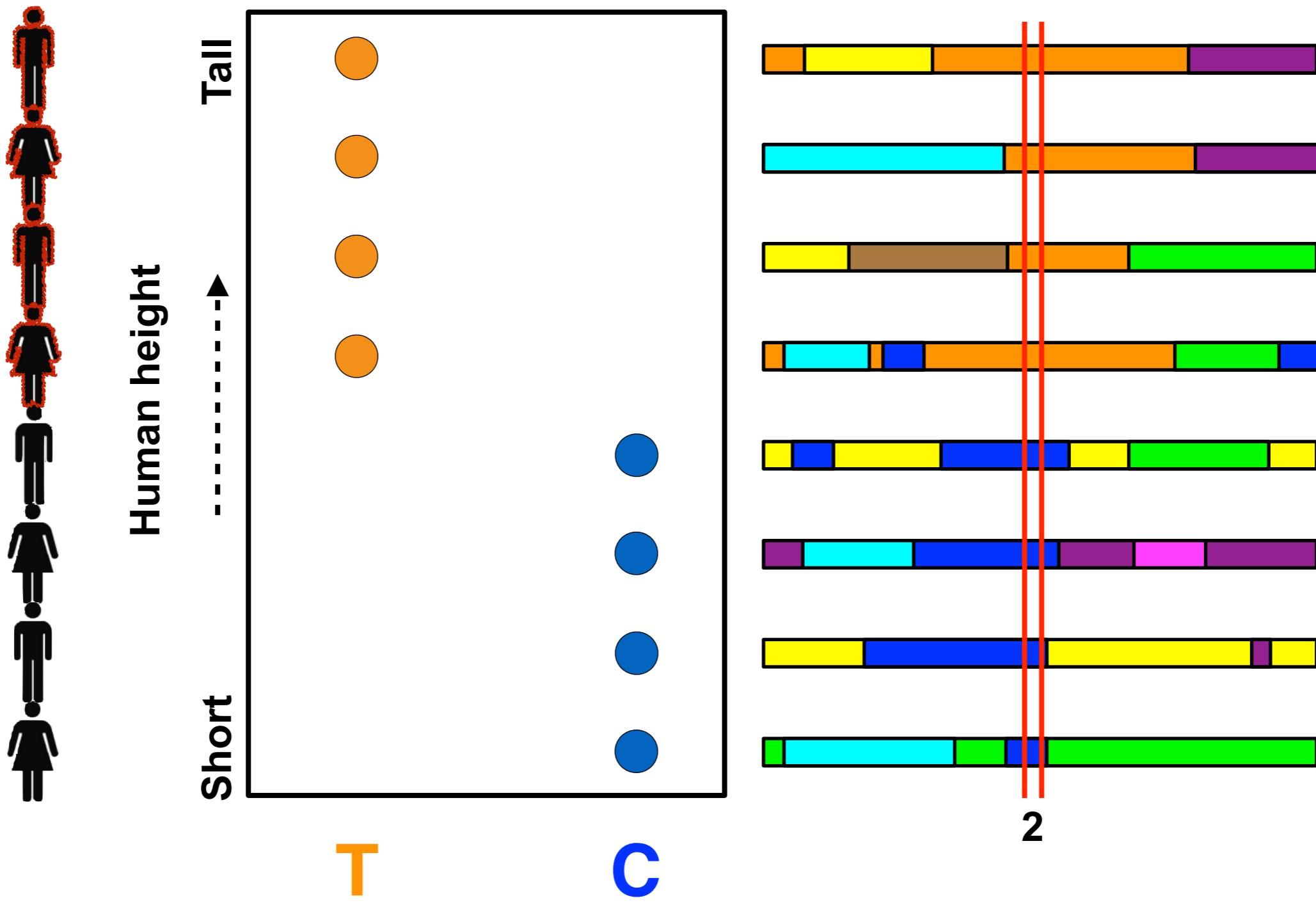
Association mapping: Correlating genotype with phenotype



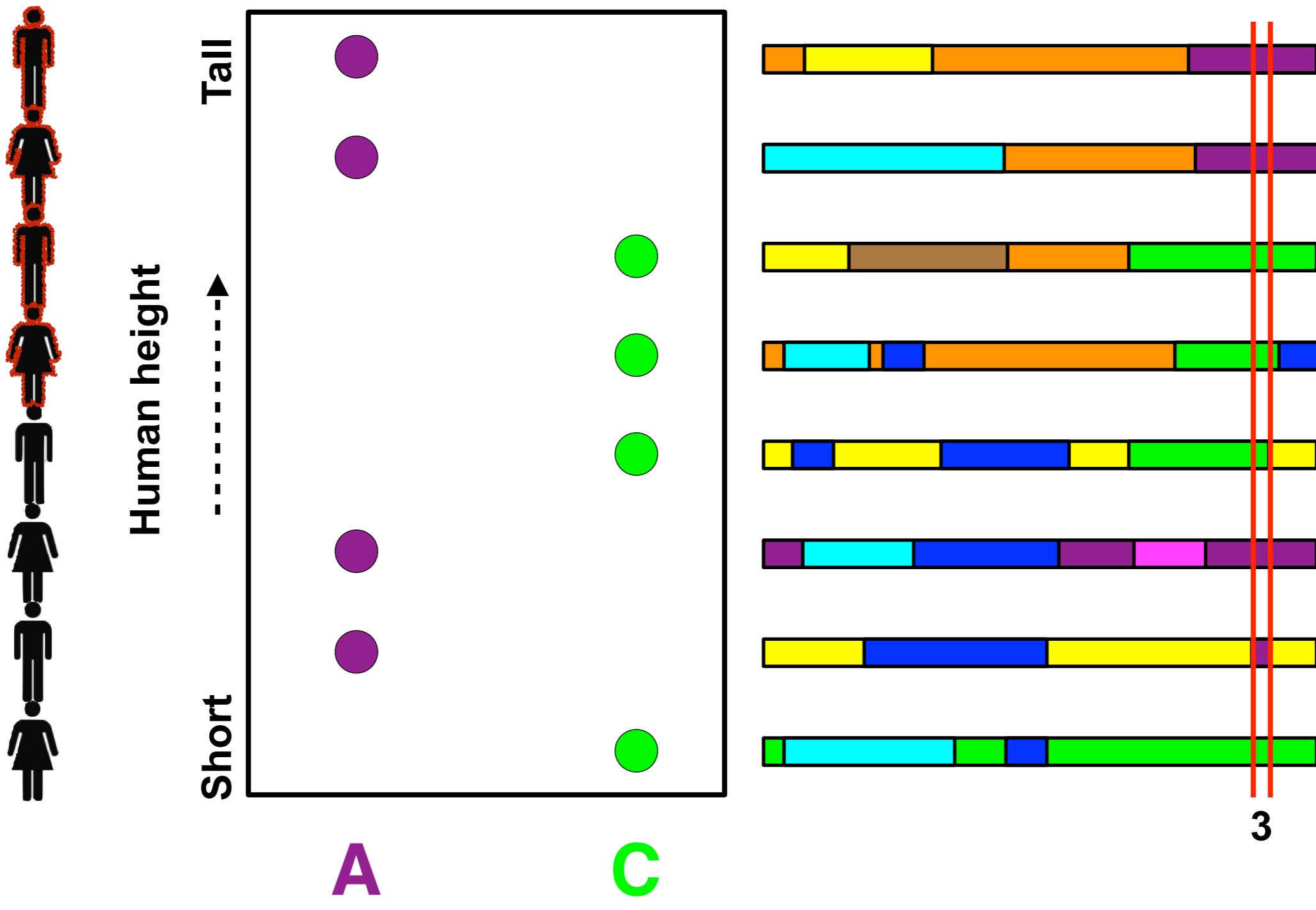
Association mapping: Correlating genotype with phenotype



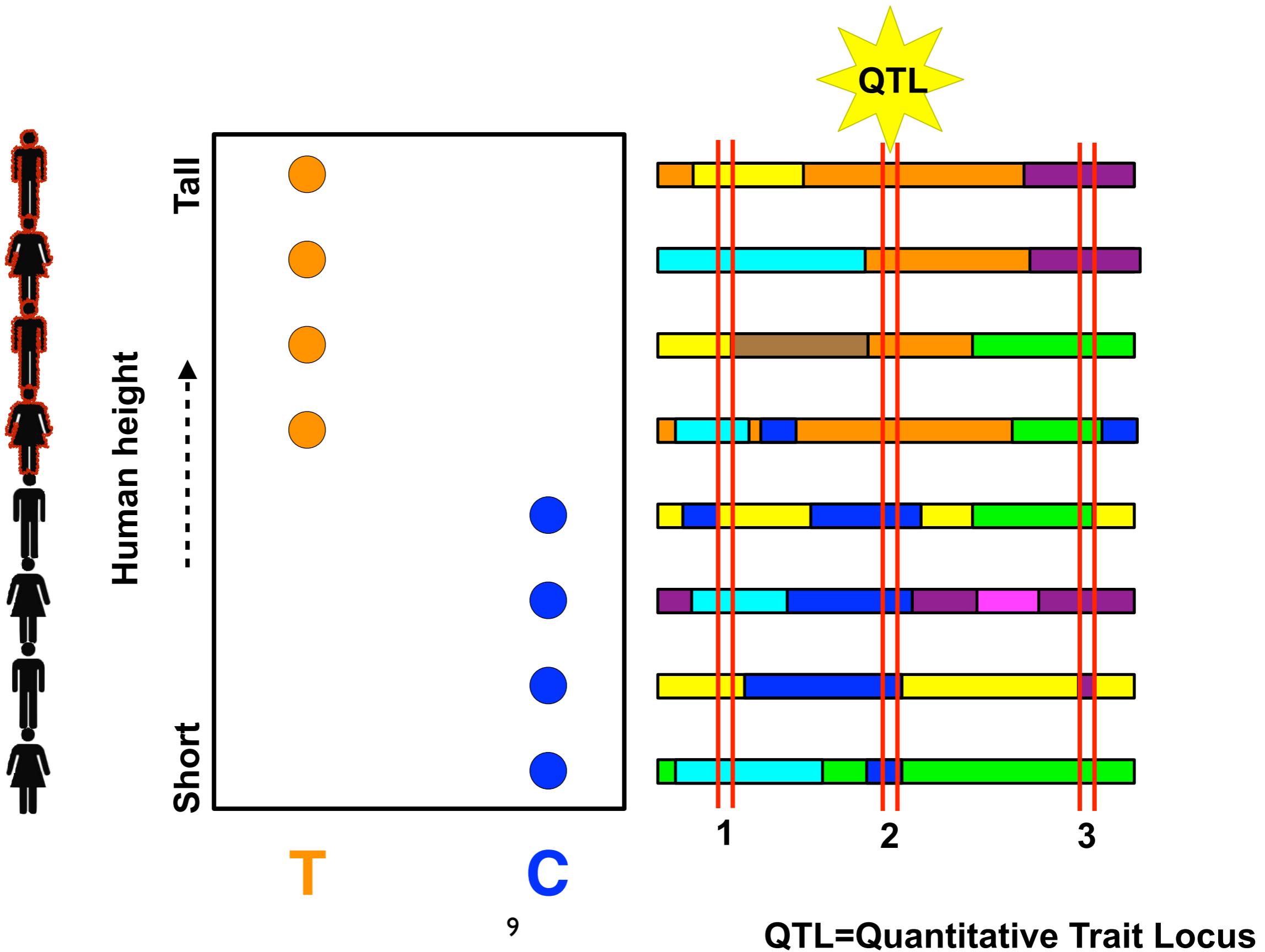
Association mapping: Correlating genotype with phenotype



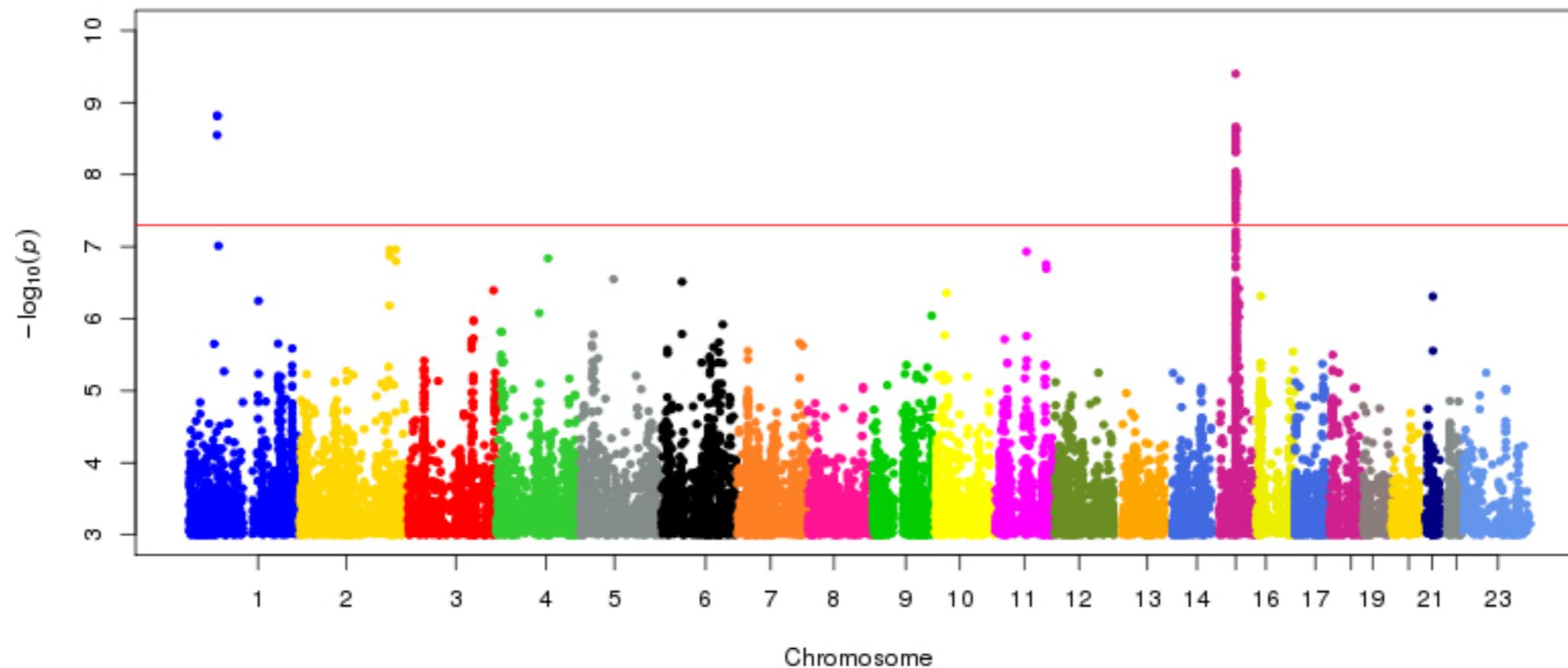
Association mapping: Correlating genotype with phenotype



Association mapping: Correlating genotype with phenotype

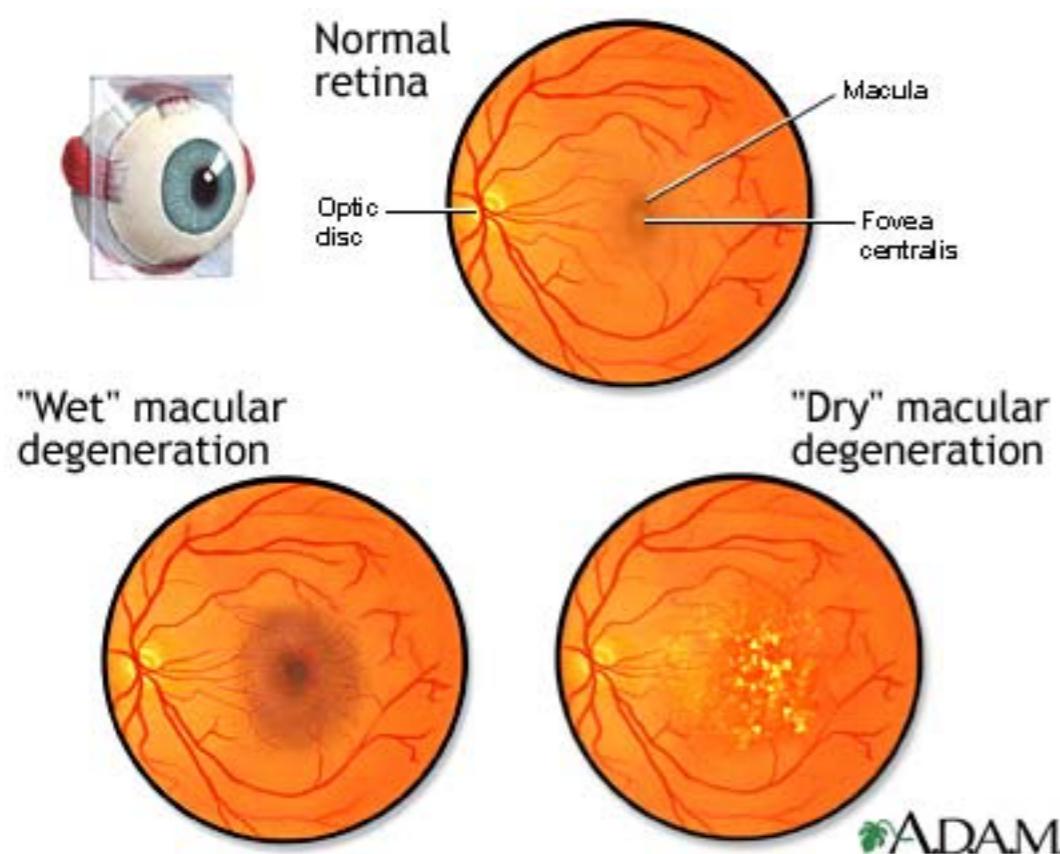


An example Manhattan plot of GWA mapping results



Styrkarsdottir *et al.* Nature 2014

Age-related macular degeneration: first (and best) GWAS



- 30-50 million people globally
- Age-related loss of vision
- Accumulation of extracellular material on the retina



Age-related macular degeneration: first (and best) GWAS



96 Cases



50 Controls

Klein *et al.* Science 2005

103,611 SNPs genotyped (Bonferroni p-value $0.05/103,611 = 4.8\text{E-}7$)

Age-related macular degeneration: first (and best) GWAS



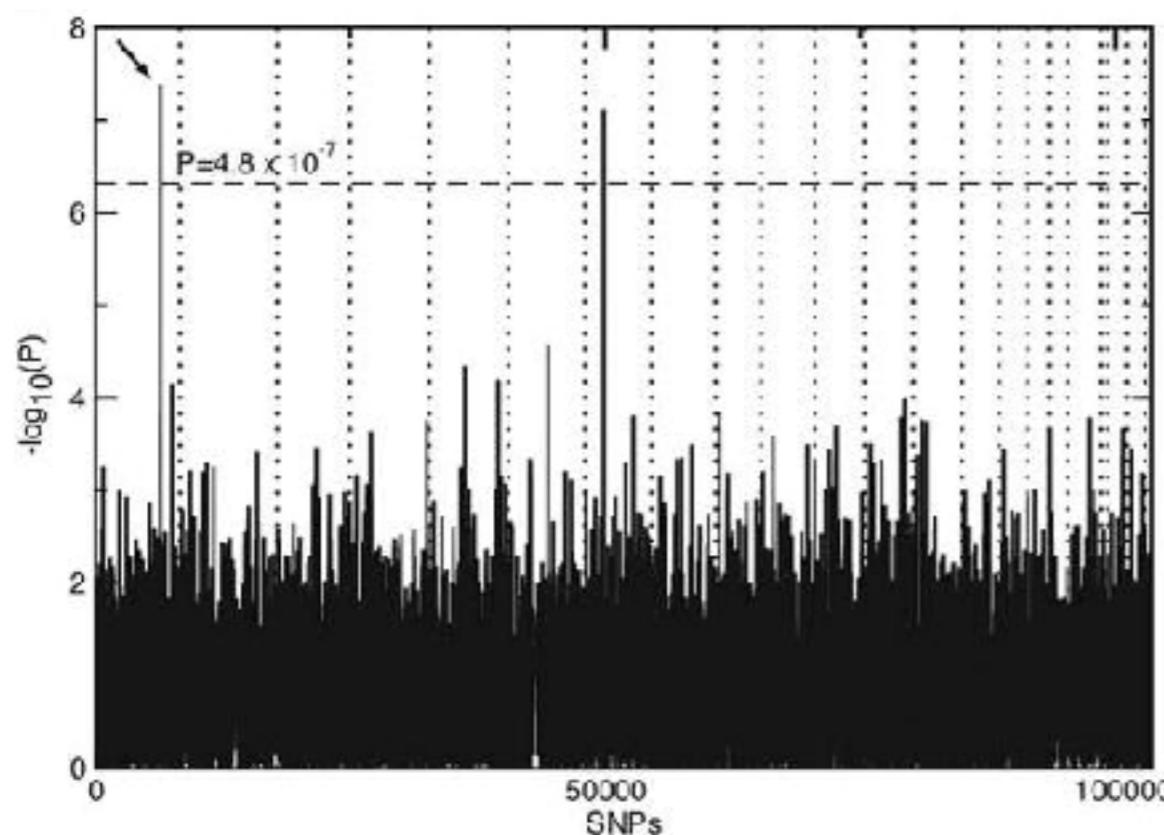
96 Cases



50 Controls

Klein *et al.* Science 2005

103,611 SNPs genotyped (Bonferroni p-value $0.05/103,611 = 4.8E-7$)



- Complement Factor H
- Haploinsufficient gene
- Inhibitor of inflammatory cascade
- Six family-based linkage studies found same region of genome

Age-related macular degeneration: first (and best) GWAS



96 Cases



50 Controls

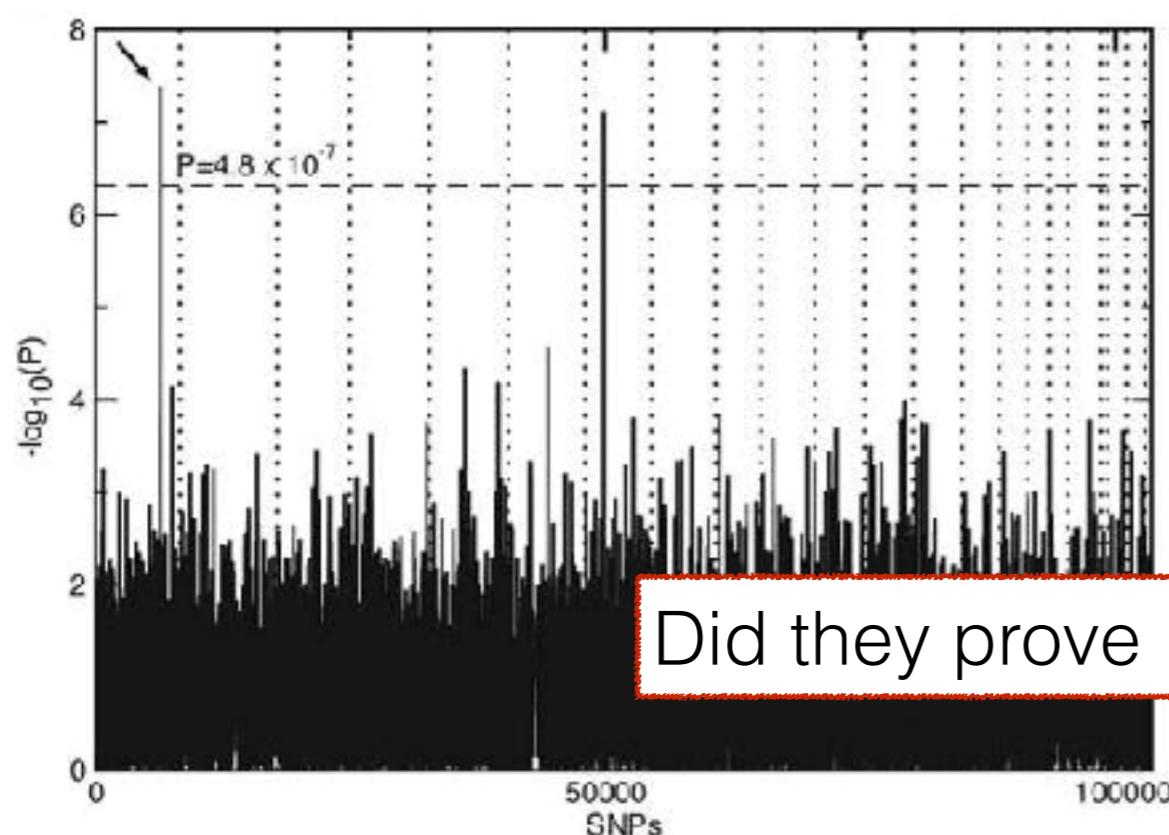
Klein *et al.* Science 2005

103,611 S

What does this success tell us

= 4.8E-7)

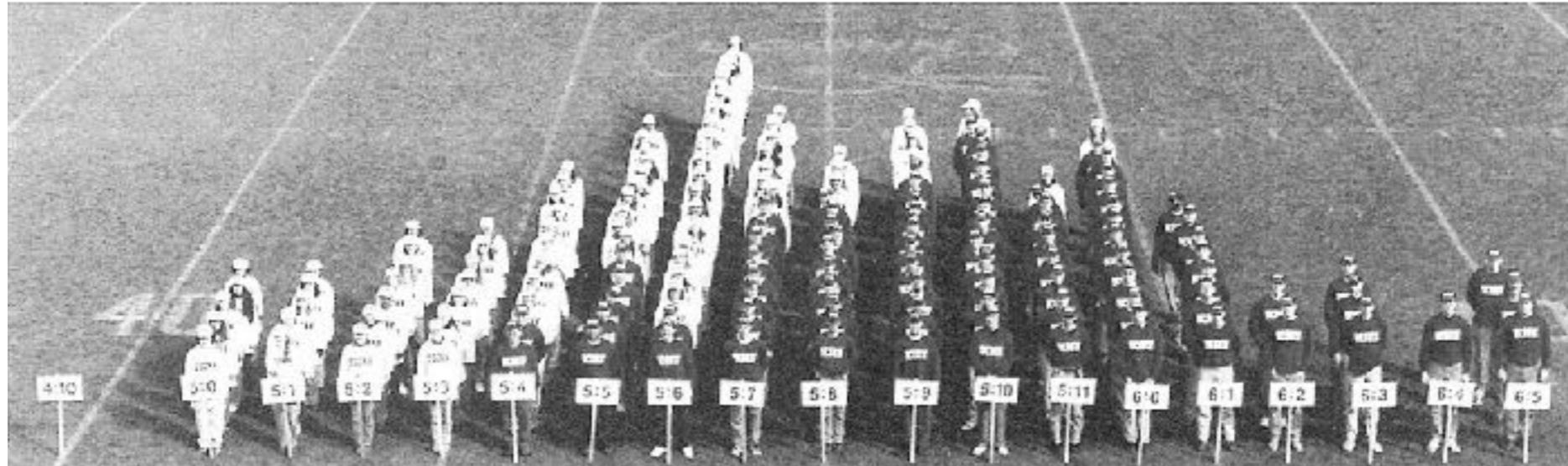
about the genetic underpinnings of AMD?



Did they prove *CFH* is the gene?

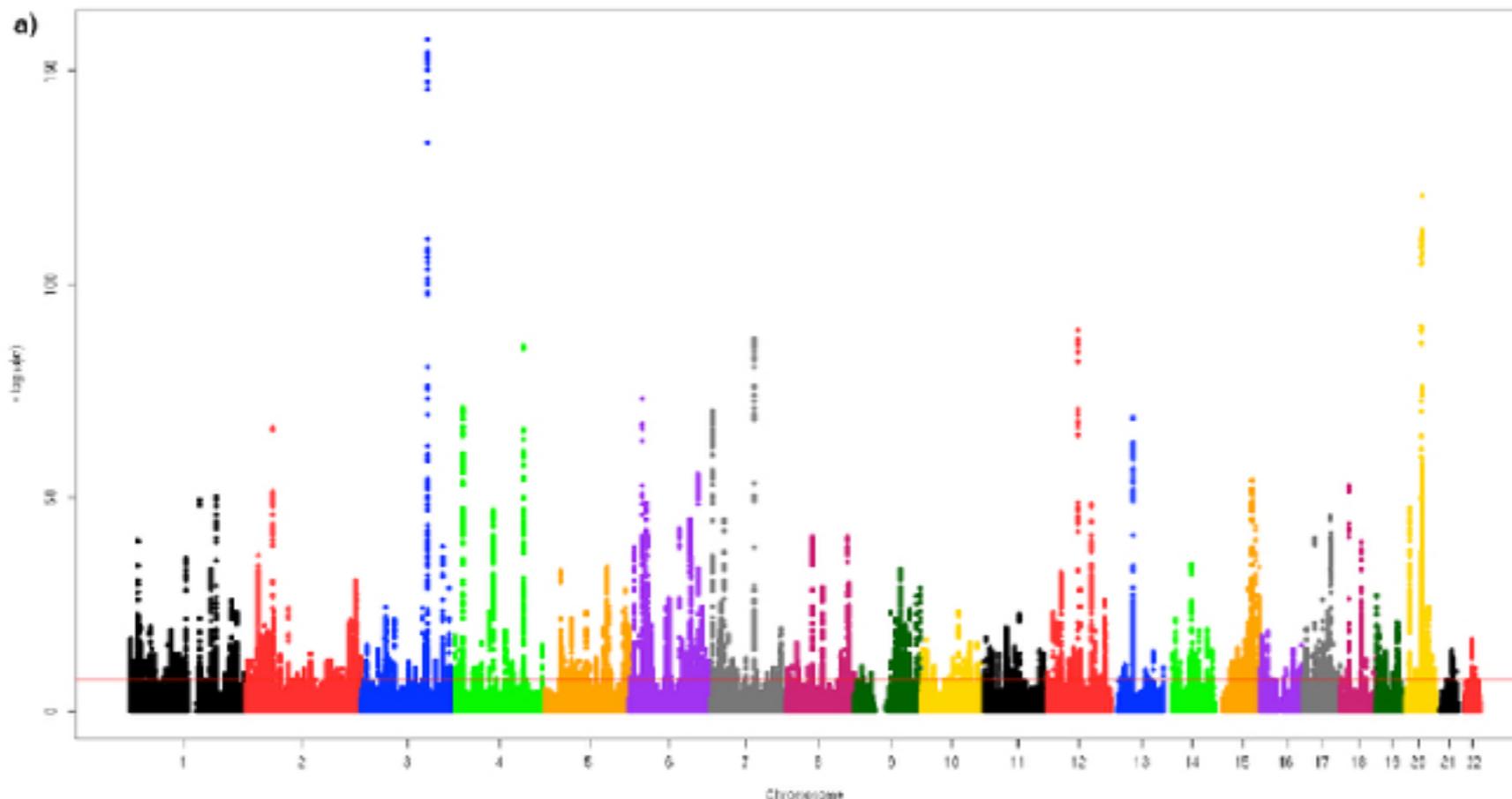
- Complement Factor H
- Haploinsufficient gene
- Inhibitor of inflammatory cascade
- Six family-based linkage studies found same region of genome

Human height: the most powerful GWAS



University of Connecticut, 1997

253,288 individuals genotyped and phenotyped



- 697 loci reach significance
- Enriched for “growth” genes
- Each individually explains very little variation

Lessons from the GWAS era

- Many traits are polygenic
- Effect sizes of common variants are very small
- Many associated SNPs are near genes
- Most functional variants *might* affect gene expression as opposed to protein function

Do we have predictive ability?

What is your “risk” of having the trait given your genotype?

Genotype relative risk (GRR)

For a diallelic locus (A or a), we have three genotypes: AA, Aa, aa

Choose one genotype as the reference (aa), and express GRR for the other two genotypes

$$GRR_{AA} = \frac{\text{Risk for AA genotype}}{\text{Risk for aa genotype}}$$

$$GRR_{Aa} = \frac{\text{Risk for Aa genotype}}{\text{Risk for aa genotype}}$$

Risks are estimated as odds ratios

Genotype	Cases	Controls	Case:Control Ratio
AA	D _{AA}	H _{AA}	D _{AA} / H _{AA}
Aa	D _{Aa}	H _{Aa}	D _{Aa} / H _{Aa}
aa	D _{aa}	H _{aa}	D _{aa} / H _{aa}

Case:control ratios are equivalent to the odds of disease given genotype in the population

Ratios of case:control ratios estimate relative risks in a population

What is your “risk” of having the trait given your genotype?

Genotype relative risk (GRR)

Risks are estimated as odds ratios

Genotype	Cases	Controls	Case:Control Ratio
AA	D_{AA}	H_{AA}	D_{AA} / H_{AA}
Aa	D_{Aa}	H_{Aa}	D_{Aa} / H_{Aa}
aa	D_{aa}	H_{aa}	D_{aa} / H_{aa}

Case:control ratios are equivalent to the odds of disease given genotype in the population

Ratios of case:control ratios estimate relative risks in a population

$$GRR_{AA} = \frac{\text{Risk for AA genotype}}{\text{Risk for aa genotype}}$$

$$GRR_{AA} = \frac{D_{AA} / H_{AA}}{D_{aa} / H_{aa}}$$

$$GRR_{Aa} = \frac{\text{Risk for Aa genotype}}{\text{Risk for aa genotype}}$$

$$GRR_{Aa} = \frac{D_{Aa} / H_{Aa}}{D_{aa} / H_{aa}}$$

Genotype relative risk (GRR) - example

Risks are estimated as odds ratios

Genotype	Cases	Controls	Case:Control Ratio
AA	400	250	400 / 250
Aa	350	250	350 / 250
aa	400	300	400 / 300

$$GRR_{AA} = \frac{\text{Risk for AA genotype}}{\text{Risk for aa genotype}}$$

$$GRR_{AA} = \frac{400 / 250}{400 / 300} = 1.2$$

$$GRR_{Aa} = \frac{\text{Risk for Aa genotype}}{\text{Risk for aa genotype}}$$

$$GRR_{Aa} = \frac{350 / 250}{400 / 300} = 1.05$$

The AA genotype is 1.2x more likely than the aa genotype to have the disease

The Aa genotype is 1.05x more likely than the aa genotype to have the disease

My genotype relative risks (GRR) for some traits

SHOW RESULTS FOR Erik Andersen

[SEE NEW AND RECENTLY UPDATED REPORTS »](#)

These reports provide information about your possible risk for developing certain health conditions based on genetics. Environmental and lifestyle factors also often play a large role in your risk for developing these conditions.

Elevated Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Atrial Fibrillation	★★★★	33.9%	27.2%	1.25x 
Prostate Cancer ♂	★★★★	23.8%	17.8%	1.33x 
Gallstones	★★★★	11.1%	7.0%	1.58x 
Exfoliation Glaucoma	★★★★	2.2%	0.7%	2.90x 
Ulcerative Colitis	★★★★	1.00%	0.77%	1.30x 
Esophageal Squamous Cell Carcinoma (ESCC)	★★★★	0.43%	0.36%	1.21x 
Stomach Cancer (Gastric Cardia Adenocarcinoma)	★★★★	0.28%	0.23%	1.22x 
Abdominal Aortic Aneurysm	★★★			
Alopecia Areata	★★★			

My genotype relative risks (GRR) for some traits

Decreased Risk ?

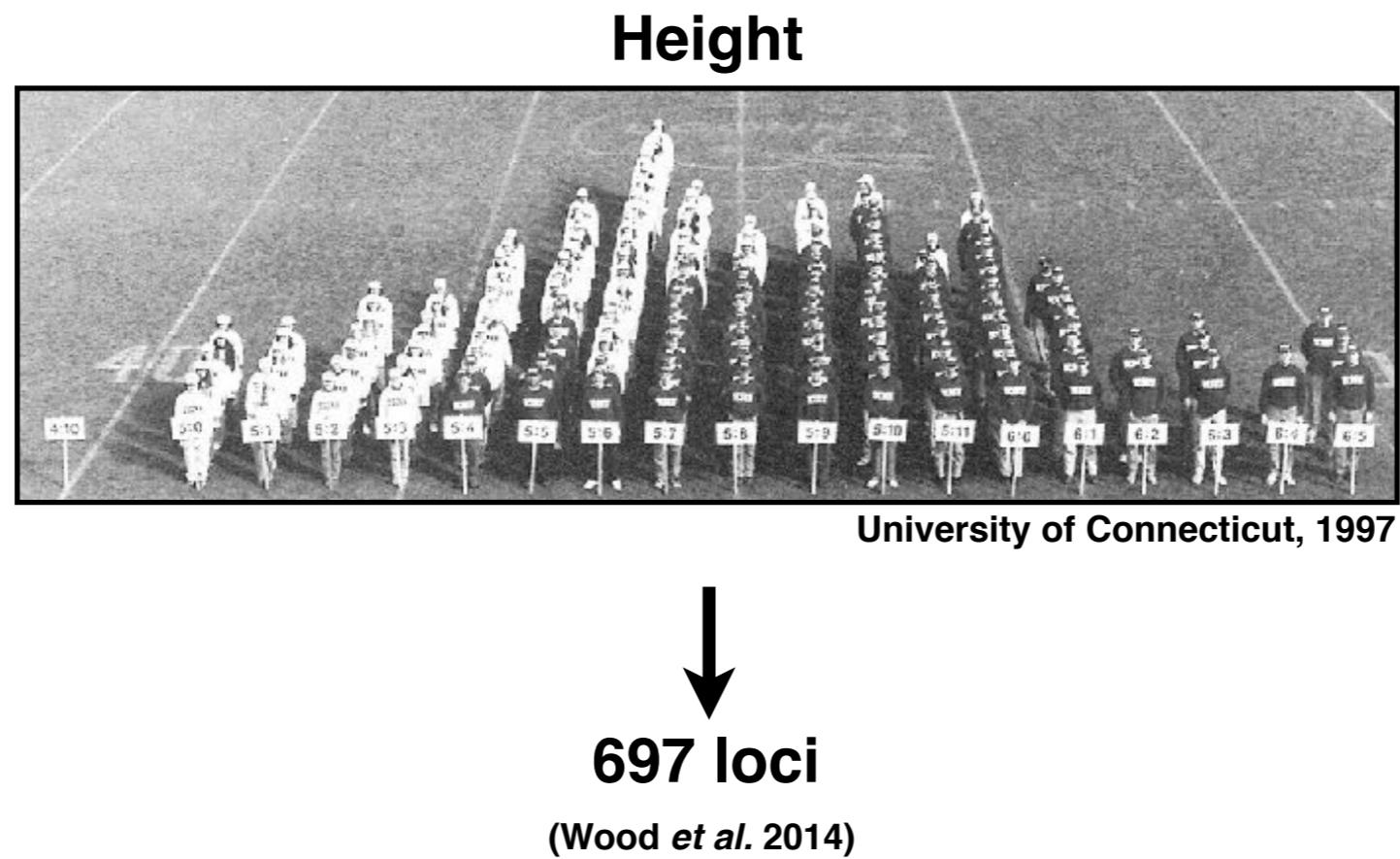
NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Gout	★★★★	17.1%	22.8%	0.75x 
Venous Thromboembolism	★★★★	9.0%	12.3%	0.73x 
Alzheimer's Disease	★★★★	4.3%	7.2%	0.60x 
Age-related Macular Degeneration	★★★★	3.1%	6.5%	0.48x 
Melanoma	★★★★	2.2%	2.9%	0.75x 
Rheumatoid Arthritis	★★★★	1.5%	2.4%	0.63x 
Restless Legs Syndrome	★★★★	1.5%	2.0%	0.74x 
Parkinson's Disease	★★★★	0.94%	1.61%	0.58x 
Multiple Sclerosis	★★★★	0.24%	0.34%	0.69x 
Crohn's Disease	★★★★	0.16%	0.53%	0.30x 
Type 1 Diabetes	★★★★	0.11%	1.02%	0.10x 
Celiac Disease	★★★★	0.06%	0.12%	0.54x 
Primary Biliary Cirrhosis	★★★★	0.04%	0.08%	0.48x 
Atopic Dermatitis	★★★			
Basal Cell Carcinoma	★★★			

Most well understood traits are determined by single genes with large phenotypic effects

Round vs. Wrinkled



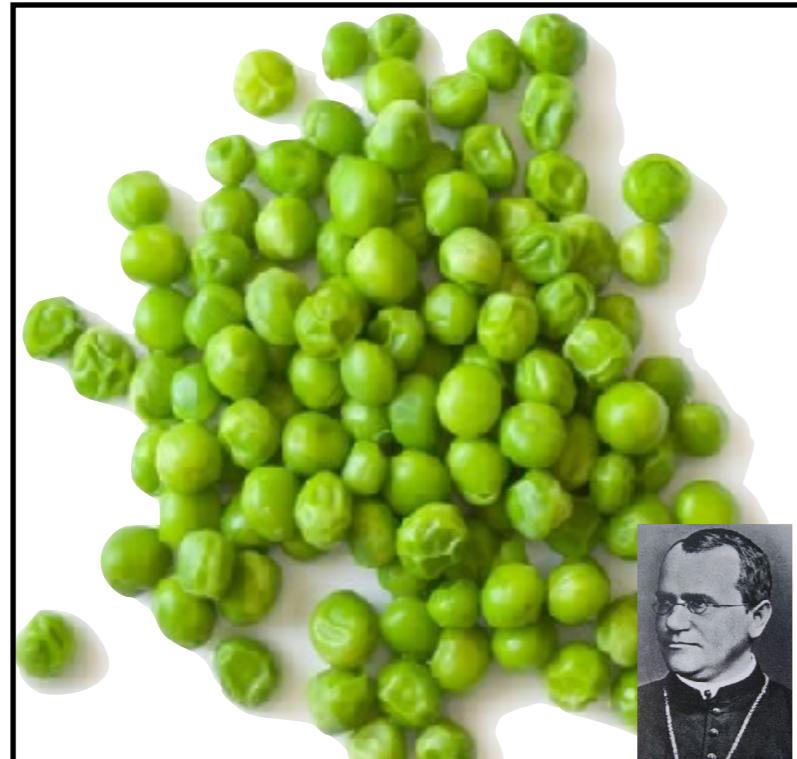
Complex traits are controlled by many genes and interactions with the environment



20% phenotypic variance explained

Complex traits are controlled by many genes and interactions with the environment

Round vs. Wrinkled

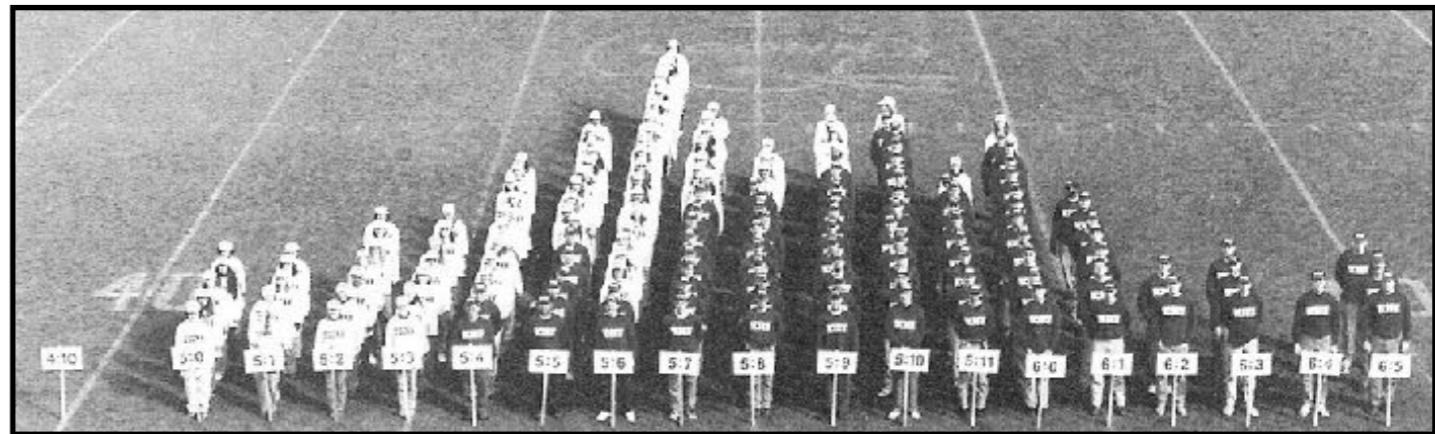


Starch branching enzyme 1
(Bhattacharyya *et al.* 1990)

100% phenotypic variance explained

binary traits

Height



University of Connecticut, 1997



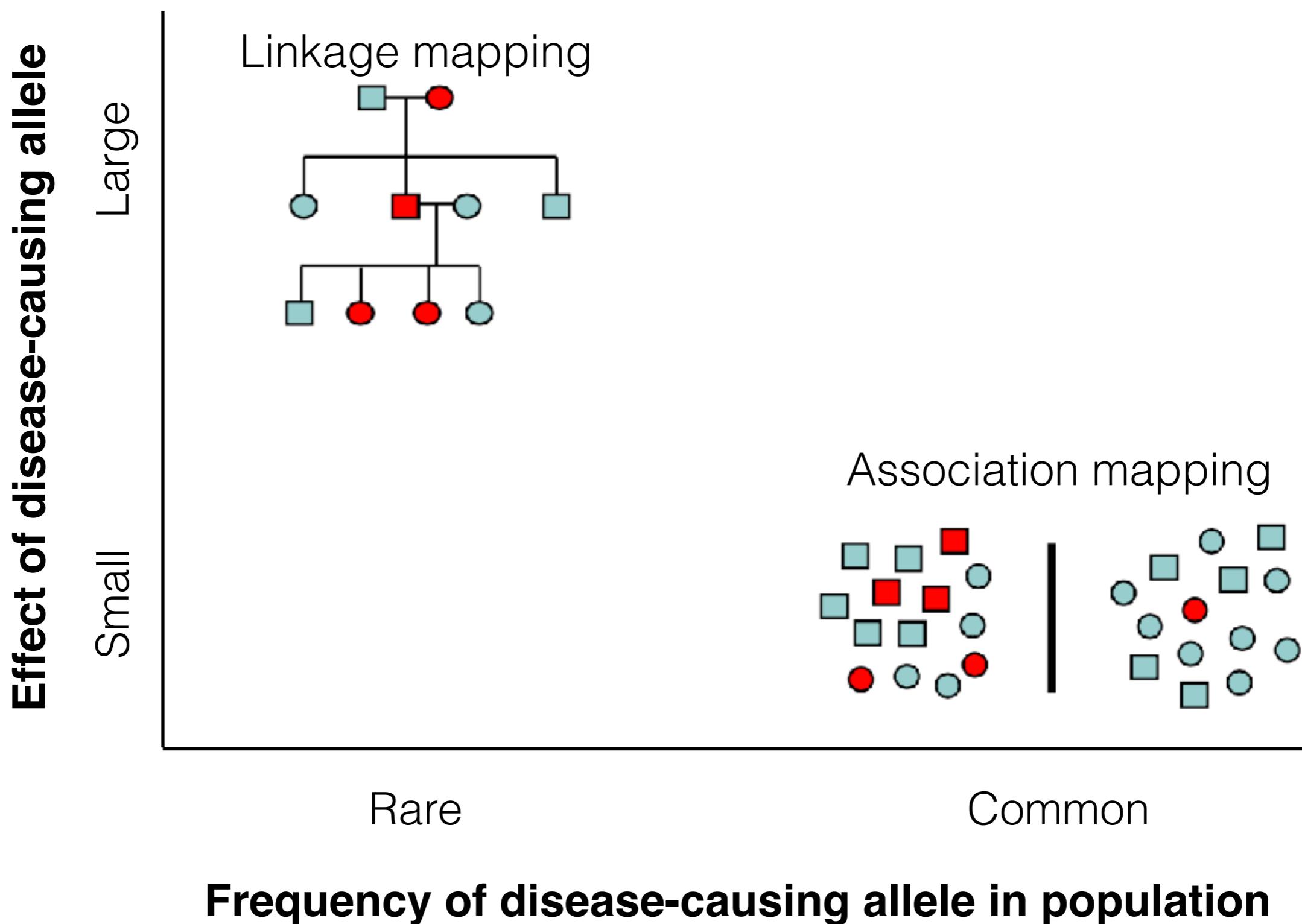
697 loci

(Wood *et al.* 2014)

20% phenotypic variance explained

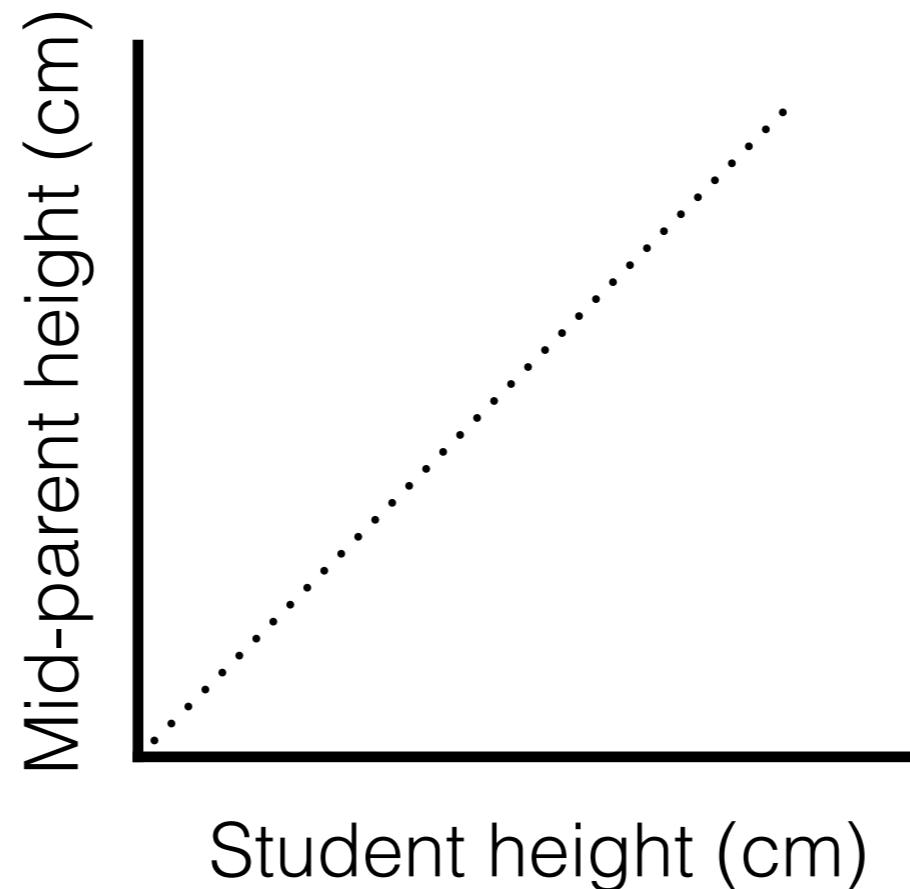
continuous traits

Complex traits can be mapped using both techniques



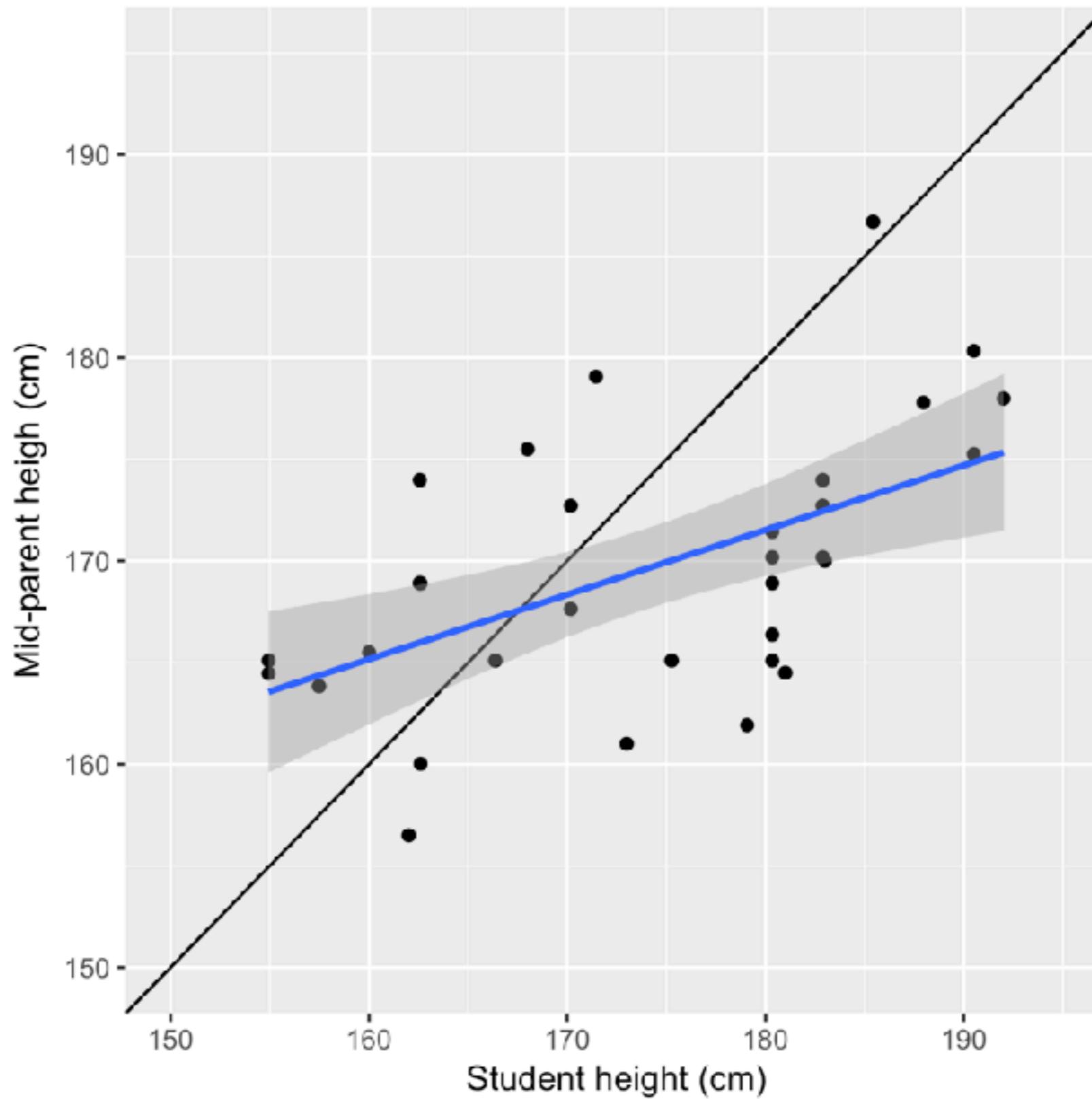
Heritability

The amount of trait variance that is from differences in genetics across a population

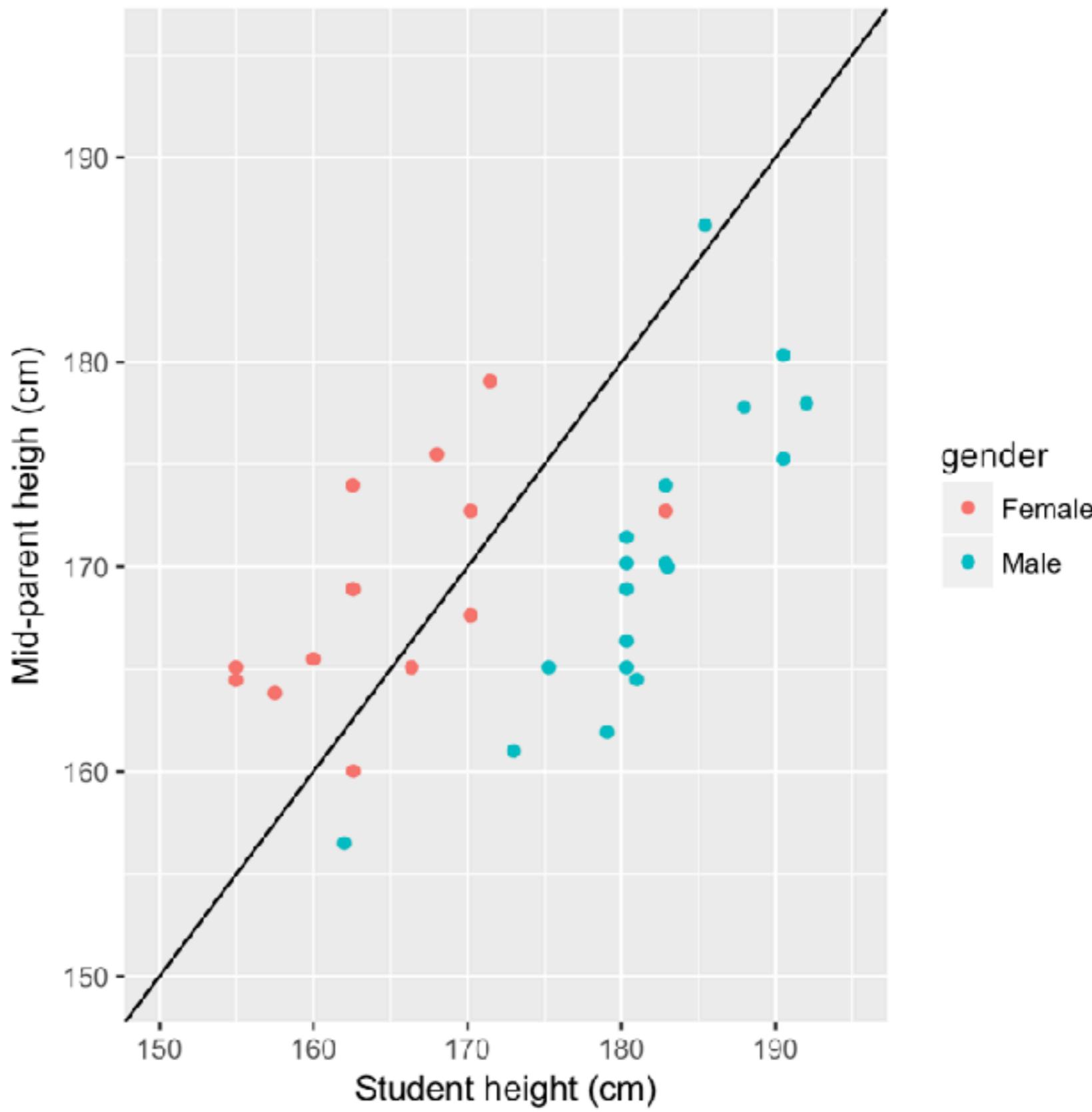


Perfect correlation suggests strong role for genetics
(and shared environment)

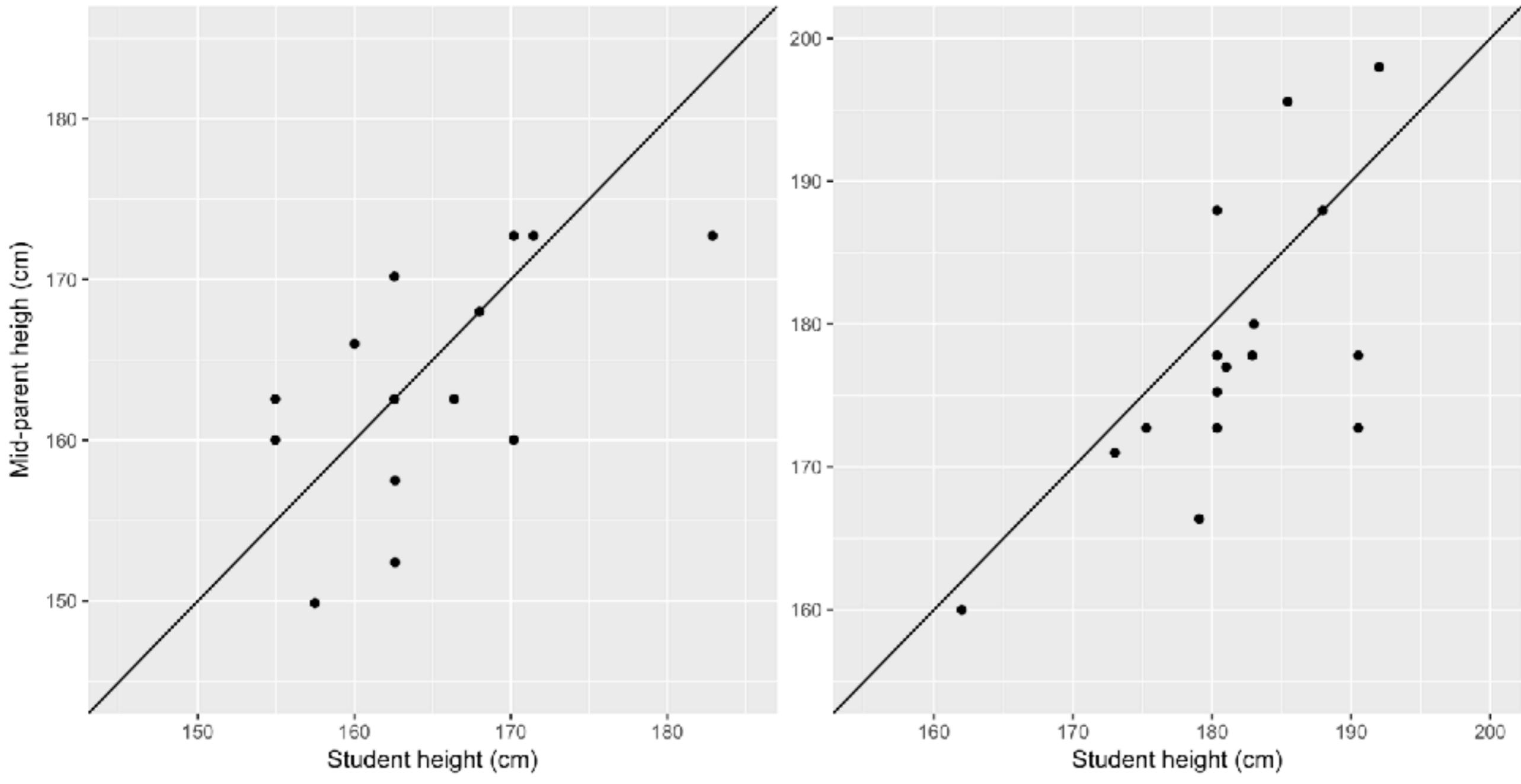
Most students are taller than their respective mid-parent heights



Most male students are taller than their respective mid-parent heights



Most male students are taller than their respective mid-parent heights

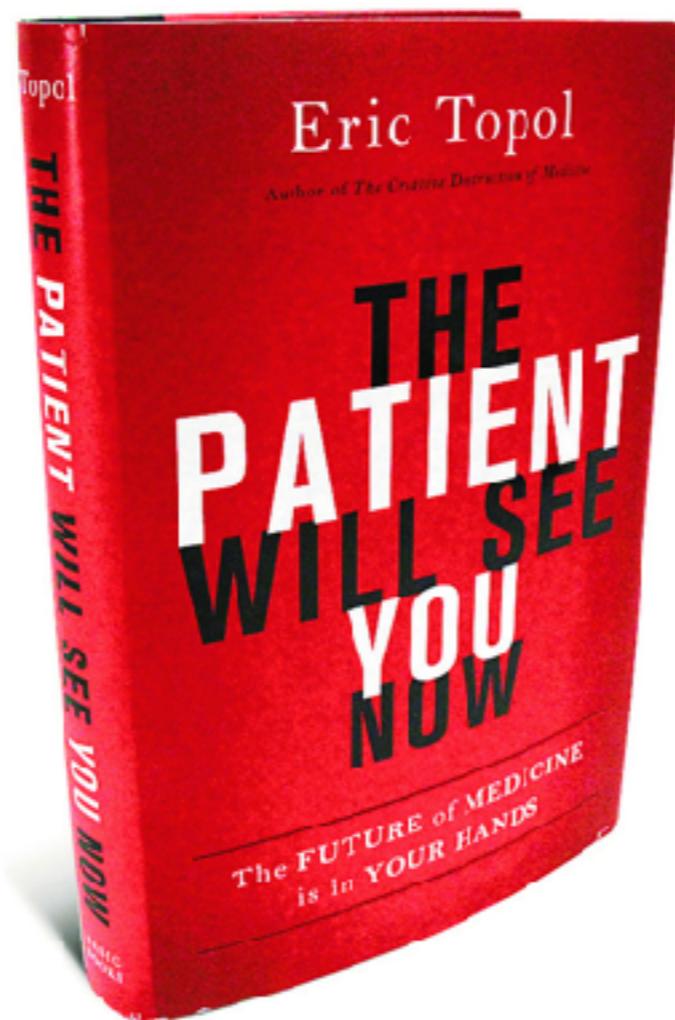


Females

Males

Present and future of genetic medicine (positives)

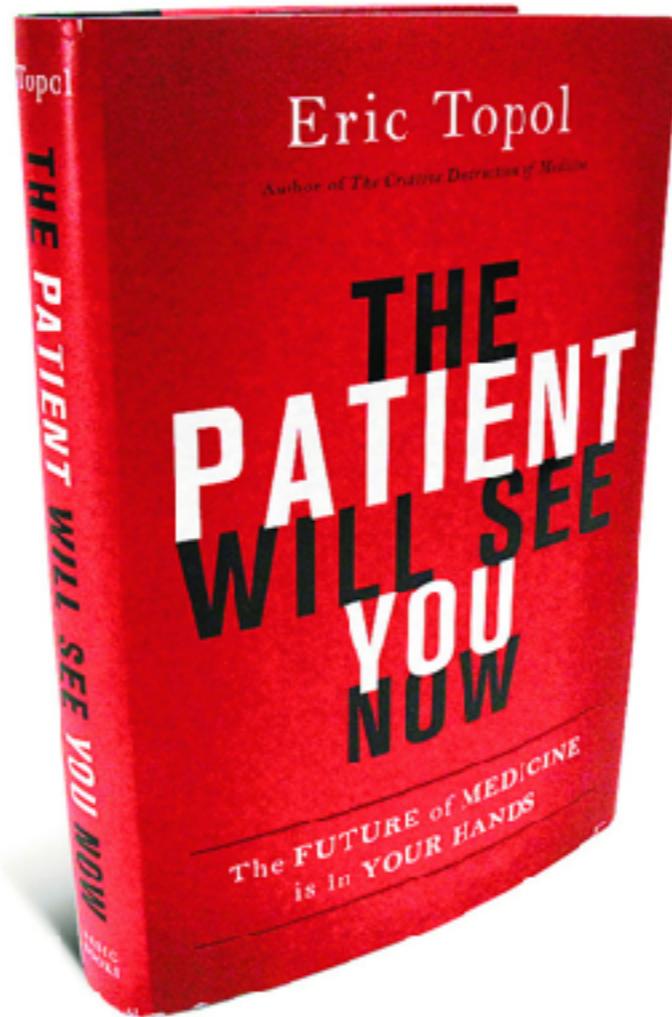
Sequencing
will be
cheap,
accessible,
and
standard practice.



With sequencing,
do we still need
genetics?

- Rare disease causal genes found
- 12 drugs approved by FDA with genetic test since 2012
- More than 120 drugs have genotype on label - check before use
- Fetal sequencing is safer than amniocentesis
- Infectious disease ID, sepsis

Present and future of genetic medicine (negatives)



- Lots of taxpayers' money spent on little valuable data
- Genotype data are being sold
- Genotype data are being evaluated by insurance companies
- Most common diseases are influenced more by behavior, diet, and environment than genes

Be skeptical!

