Summer Institutes of Statistical Genetics, 2022

Module 2: INTRODUCTION TO GENETICS AND GENOMICS

Greg Gibson and Joe Lachance

Georgia Institute of Technology

Lecture 3: QUANTITATIVE GENETICS

greg.gibson@biology.gatech.edu

http://www.cig.gatech.edu

The ACE Model and Twin Studies

$r_{mz} = A + C$

Identical / Maternal

Dizygotic / Fraternal

$r_{dz} = ½A + C$

A = Additive Genetic component; C = Common Environment (smaller if reared apart)

E = unique environment = $1 - r_{mz}$

r_{dz} should be greater than r_{sib} since C is larger where the womb/upbringing is shared

A Typical Twin Study: Political Attitudes in Australia

Table 3 Twin correlations for voting, sociodemographic traits and key political attitudes

From: The Genetics of Voting: An Australian Twin Study

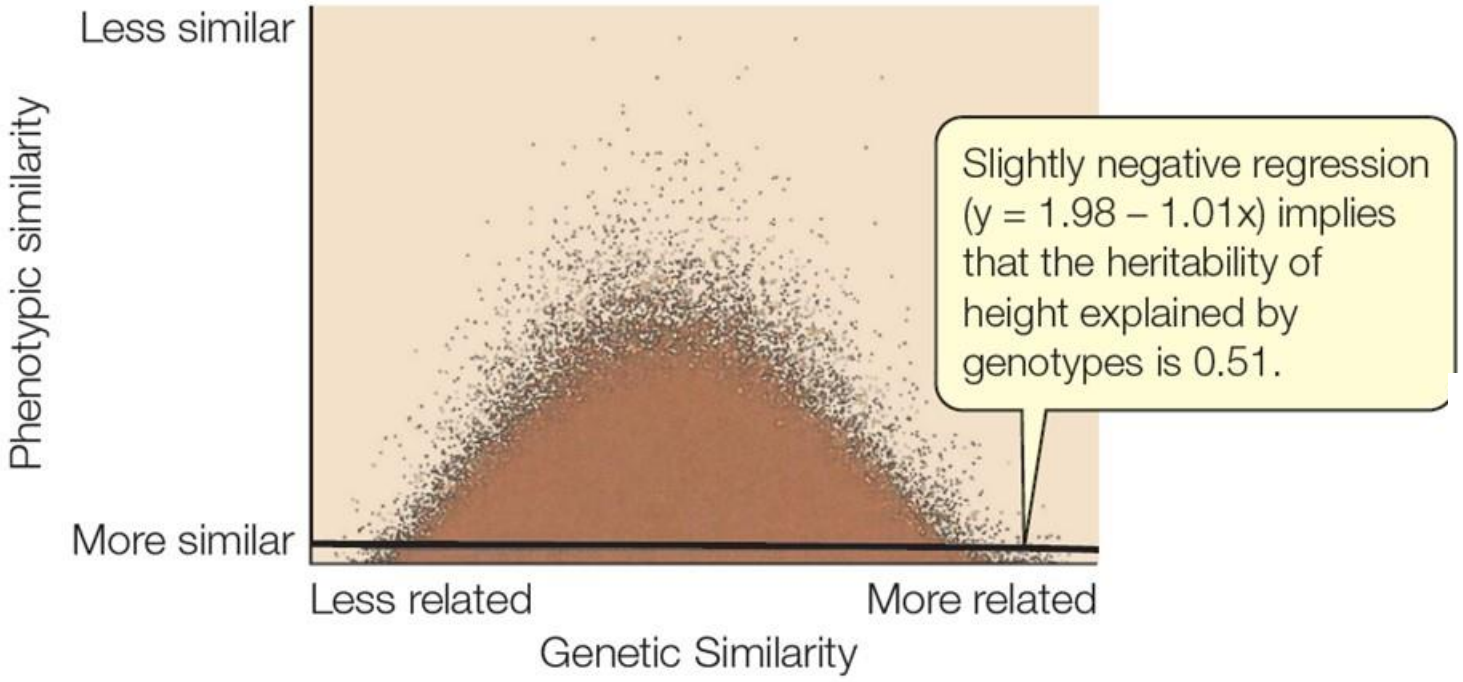
	MZF	DZF	MZM	DZM	DZOS
Conservative versus Labor	0.79	0.68	0.84	0.83	0.64
Social class	0.62	0.45	0.67	0.51	0.48
Church monthly	0.63	0.44	0.69	0.54	0.44
Socialism	0.38	0.23	0.42	0.26	0.13
Medicare	0.46	0.29	0.48	0.30	0.14
Trade unions	0.43	0.23	0.45	0.38	0.28
Private schools	0.41	0.34	0.56	0.47	0.33
N pairs[a]	1239	732	579	328	782

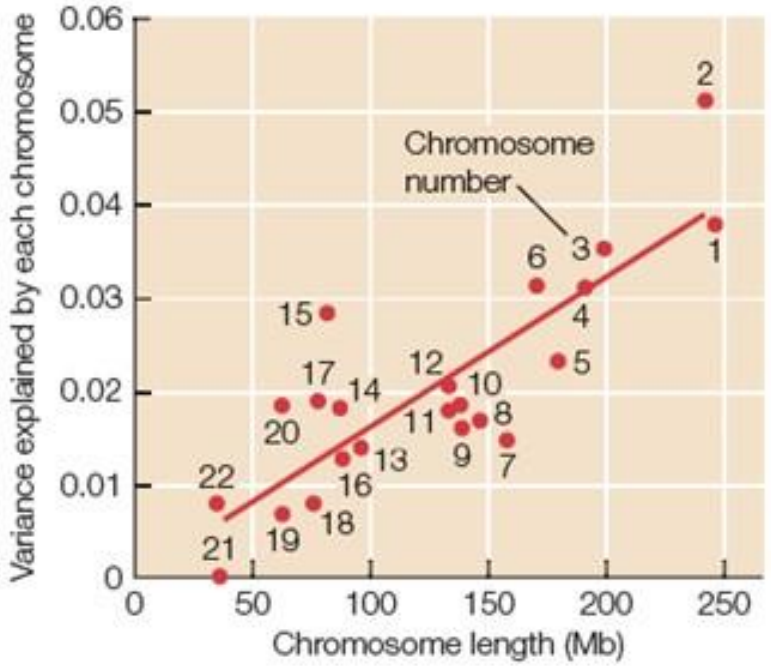
Note: (a) Correlations were estimated using full information maximum likelihood observations on incomplete pairs. Due to missingness, the number of complete pairs range from: MZF (1133–1239), DZF (689–732), MZM (528–732), DZM (308–328)

Implies that additive genetic effects account for ~25% of voting preference, and upbringing ~60%

Hatemi et al (2007) *Behavior Genetics* **37**: 435.

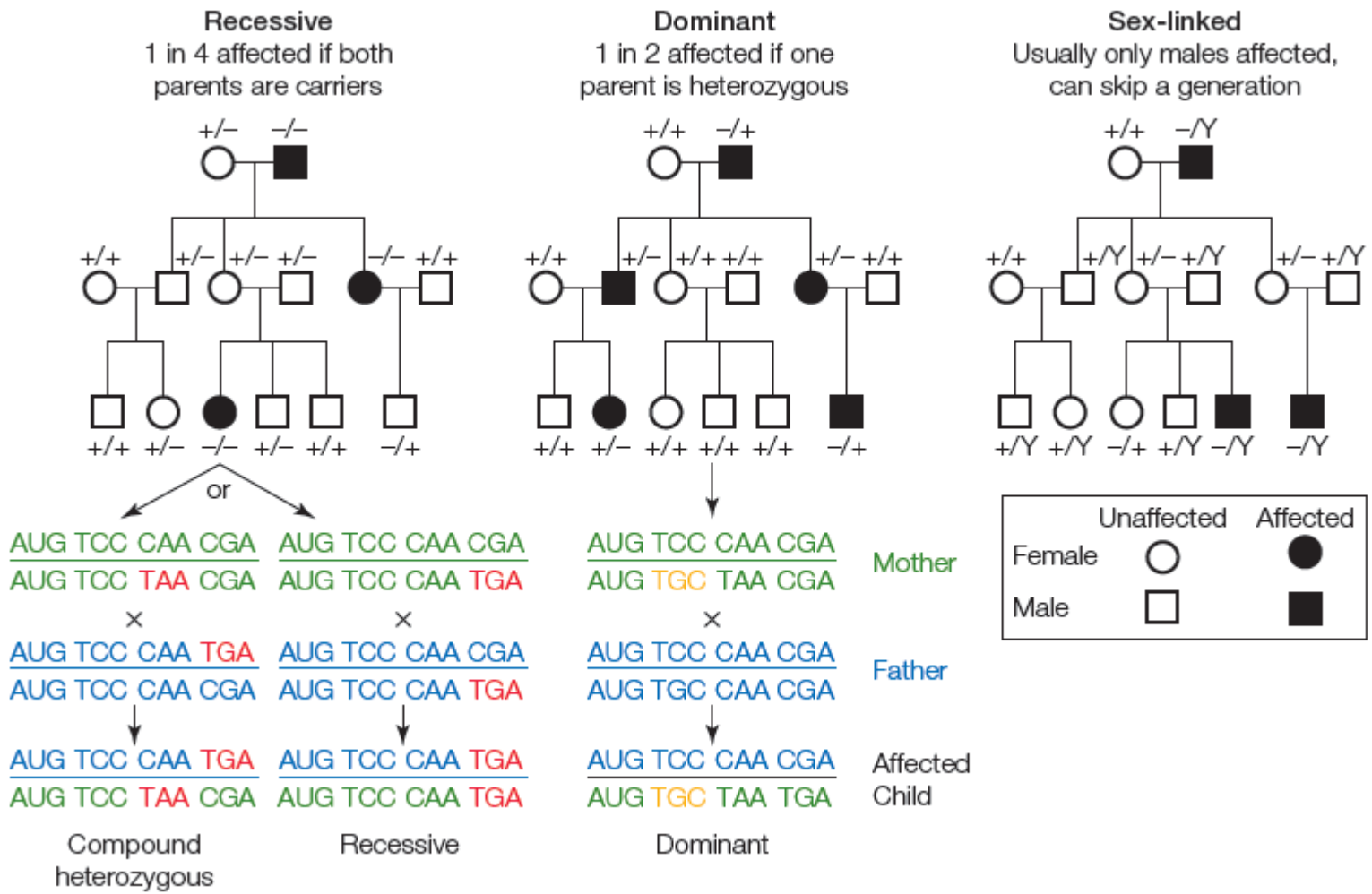
SNP-Based Heritability





Conceptually, regression of phenotypic similarity on genetic similarity genome-wide in a sample of unrelated individuals provides an unbiased estimate of heritability. By chromosome, it affirms the “omni-genicity” of traits.

Mendelian Inheritance Patterns



Incidence of Monogenic Disorders

Approximately 1 in 3,700 Americans have Cystic Fibrosis

Assuming $p^2 = 0.00027$, then $p = 0.016$, the mutant allele frequency

That is, 1 in 30 people are carriers (which is 120 times as many people as have CF),

that is, 3% of Caucasians are carriers, and less than 0.03% sufferers.

It is very likely that someone in this class is a carrier of a CF mutation

A CF carrier has a 1 in 30 chance of marrying another carrier by chance, and

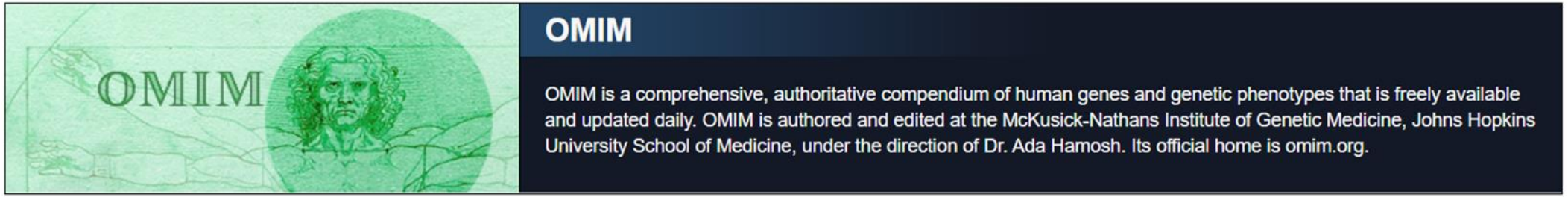
1 in 4 of their children will be expected to have CF, and only half of all 2-child families will have an affected child

There are hundreds of similar conditions (rare recessives with p ~ 0.01), so we are all carriers for multiple Mendelian disease genes. Collectively, as many as 1 in 25 couples should expect to be dual carriers for a recessive Mendelian disorder, corresponding to an approximate 1% affected rate in all children

Around 1 in 400 children have an inherited Inborn Error of Metabolism, namely an enzyme deficiency affecting amino acid, lipid or other organic molecule biosynthesis. For example:

- Phenylketonuria	1/15,000	mental retardation syndrome
- Galactosemia	1/40,000	liver dysfunction and cataracts
- Gaucher's Disease	1/60,000	facial dysmorphology, liver disease
- Zellweger Syndrome	1/50,000	seizures, low muscle tone
- Lesch-Nyhan Syndrome	1/380,000	self-inflicted injury, gout / kidney disease

OMIM: Online Mendelian Inheritance in Man



Using OMIM

Getting Started

FAQ

OMIM tools

OMIM API

Related Resources

ClinVar

Gene

GTR

MedGen

Can Rare Alleles explain Common Disease ?

Suppose an allele at a frequency of 1 in 1000 increases your risk of a rare disease like T1D 10-fold

If the background risk is 1 in 100, then 1 in 500 people have a risk of 1 in 10. That is 1 in 5,000.

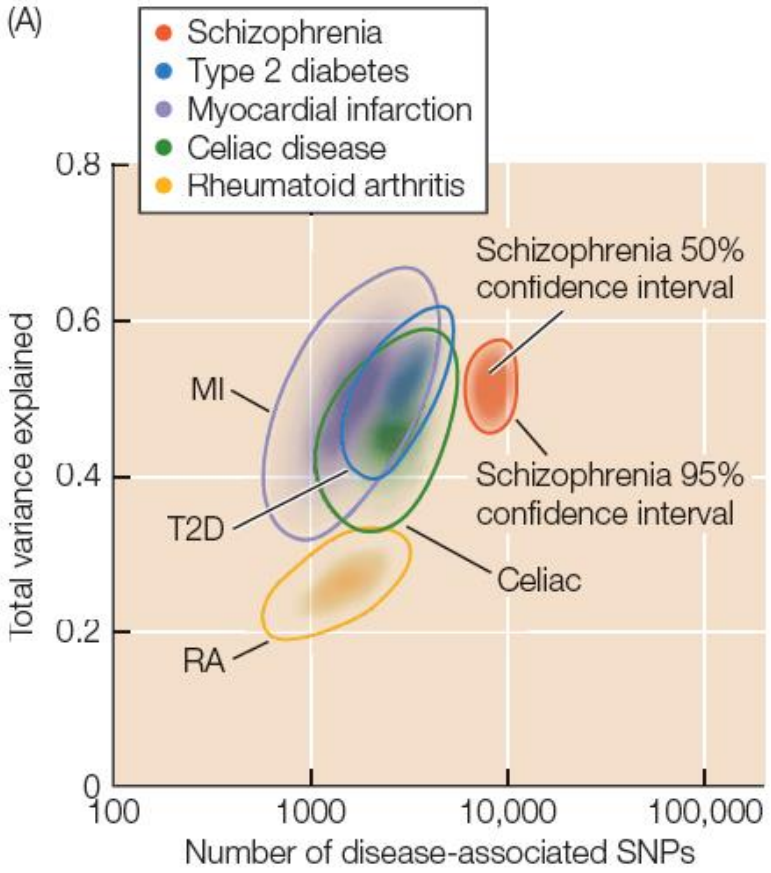
Fifty such variants would potentially explain the disease (50 x 1/5,000 = 1 in 100)

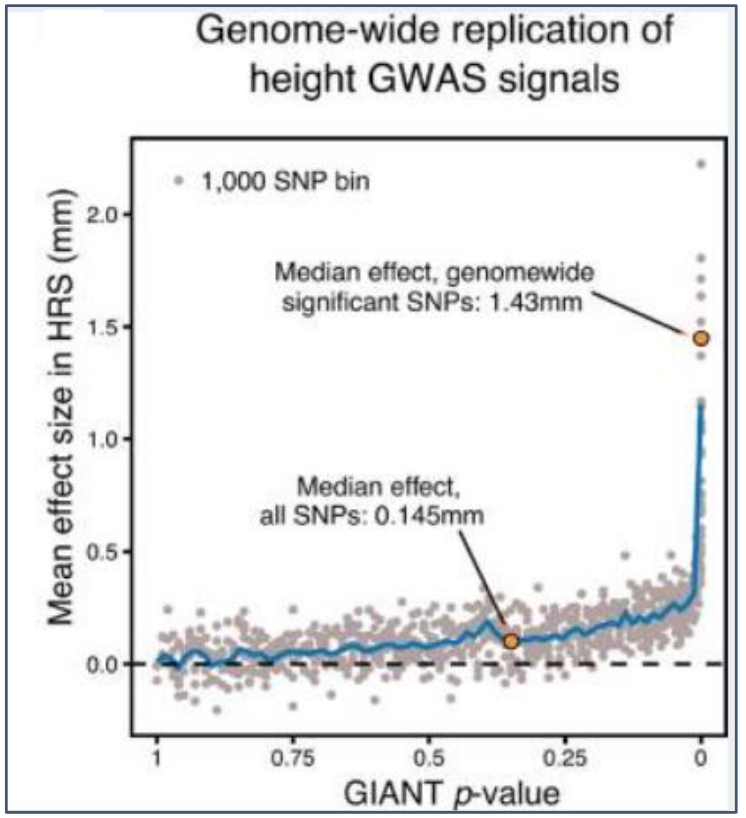
However, comprehensive scans have failed to uncover more than a handful of such alleles for any common disease.

MODY has a prevalence of 1 in 10,000, and is mostly due to mutations in 4 genes. So if rare alleles are contributing, they must have very low frequencies. This is actually consistent with natural selection against them. Humans do have an excess of very rare potentially pathogenic alleles, which clearly contribute to congenital abnormalities and certain types of disease (notably, neuro-psychiatric). But probably not common complex disease.

If allelic effects are multiplicative (1 allele 2.5%, 2 alleles 6%, 3 alleles 15%, 4 alleles 40%) then enrichment in families could explain elevated heritability.

The Infinitesimal Model

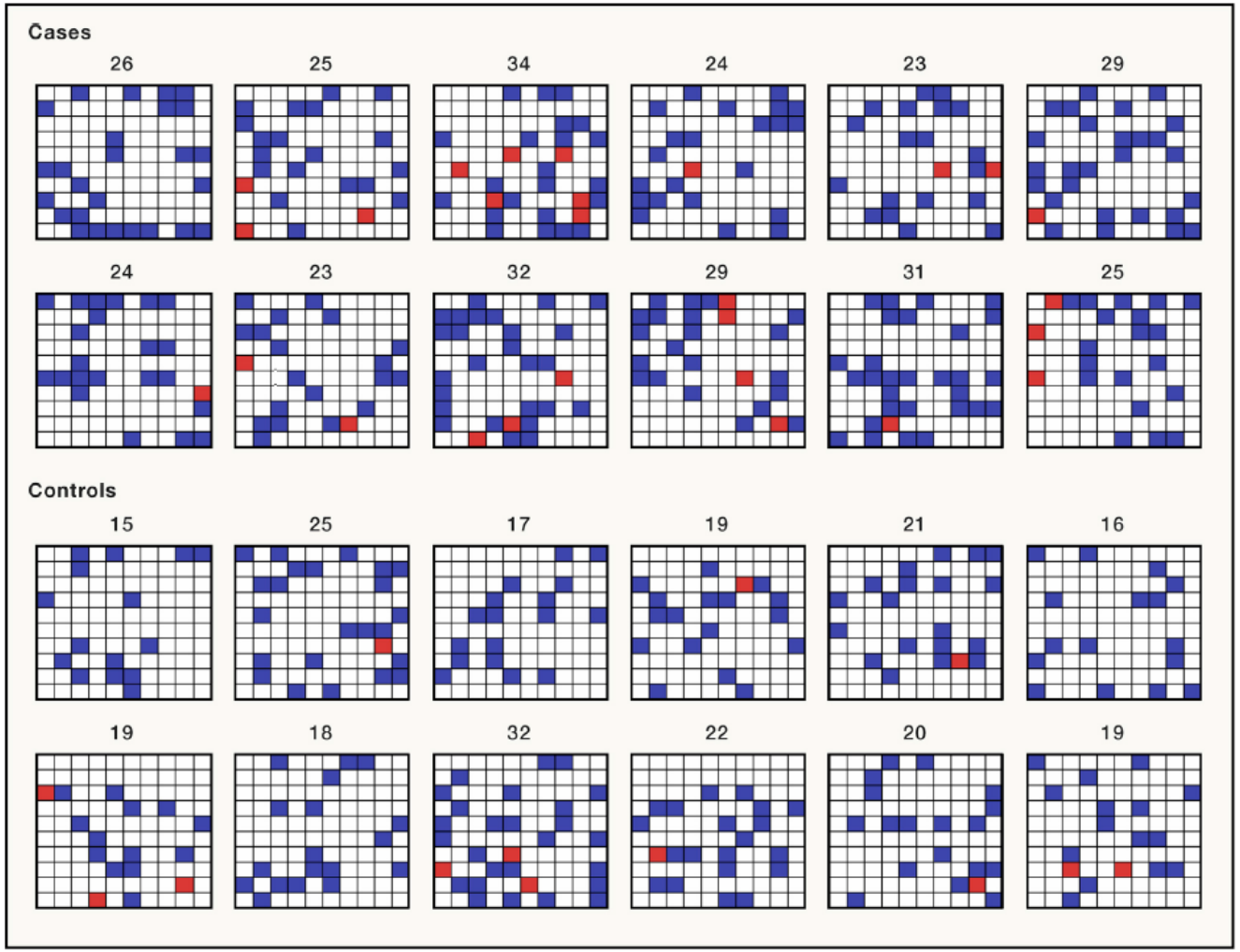




Boyle et al (20187) *Cell* **169**: 1177-1186.

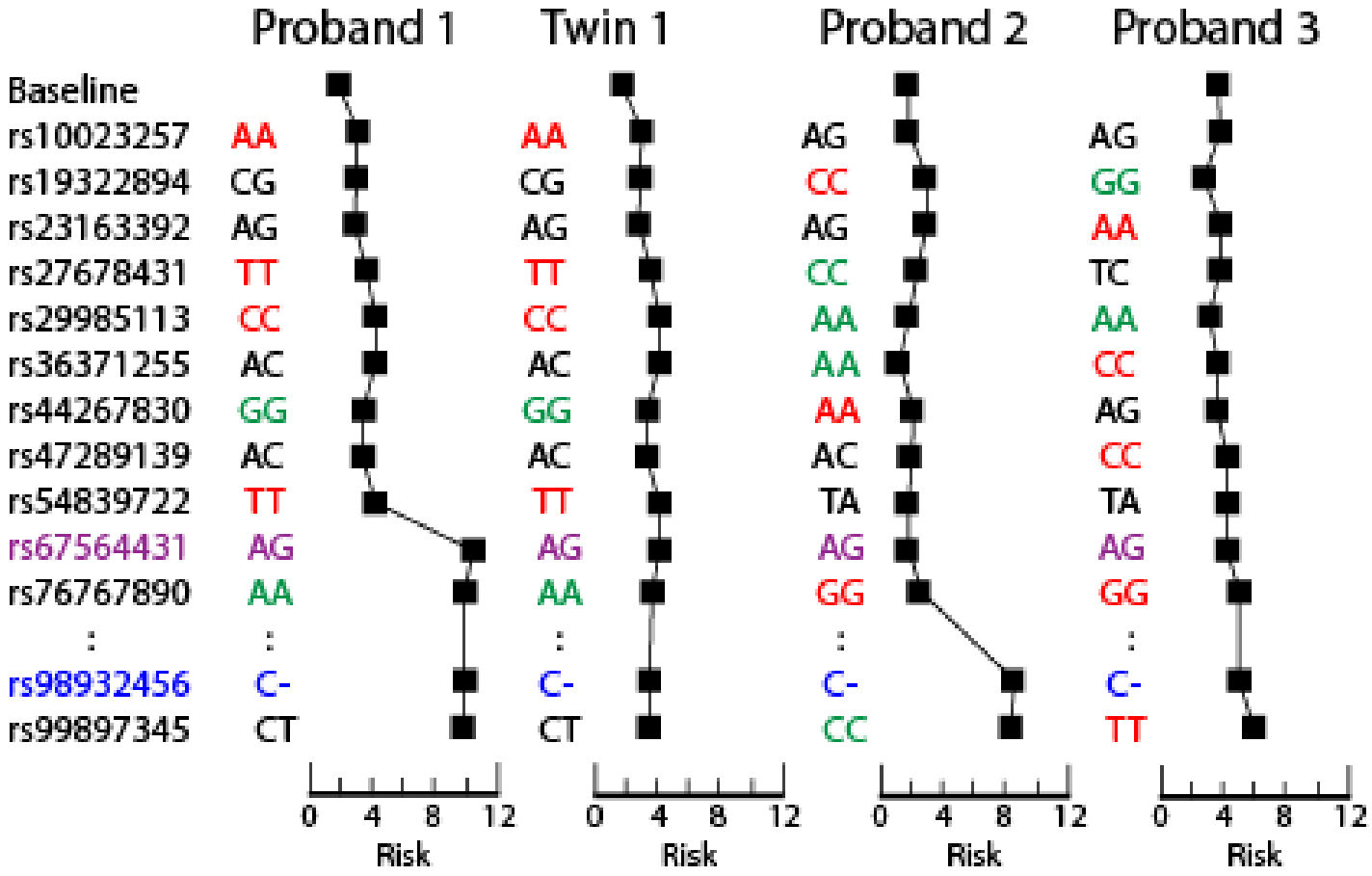
Common disease is due to thousands of alleles, each of which increase risk just 1.05 to 1.2 fold.
Most of us have an intermediate number of alleles and our risk is the population average, but individuals who by chance are in the upper percentiles have correspondingly high risk.

The Prediction Problem

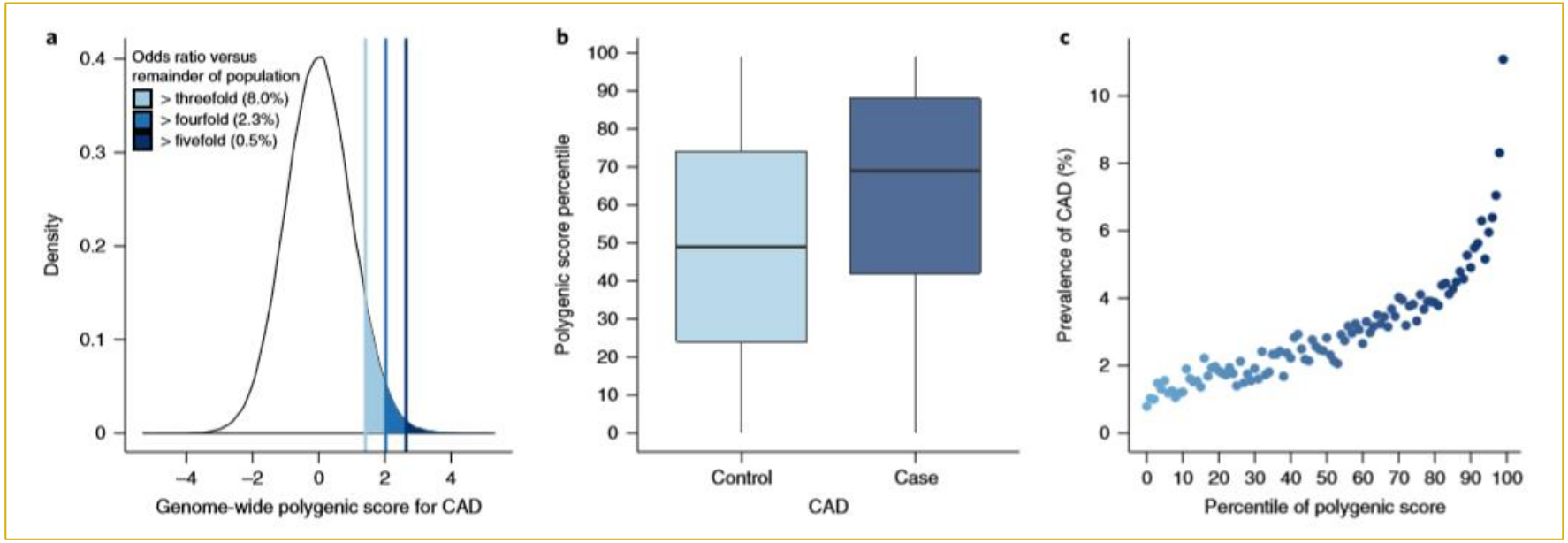


Wray et al (2018) *Cell* **173**: 1573-1580

The Polygenic Risk Model



Polygenic Risk Scores



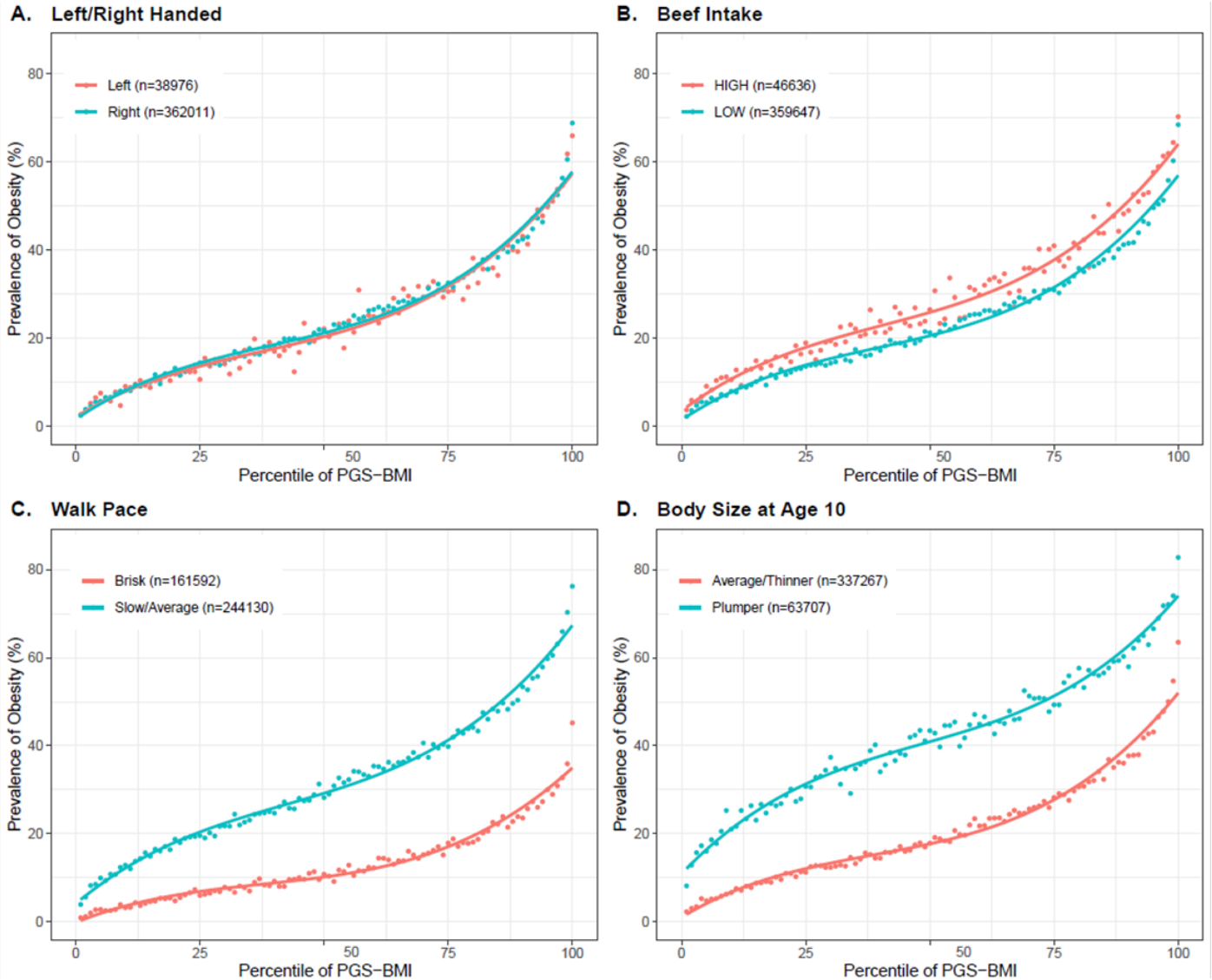
More people are at elevated risk due to common variants than rare mutations

Some people believe that PRS are the future of personalized medicine

I think they are also useful for negative prediction, namely finding those at low risk

Khera et al (2018) *Nature Genetics* **50**: 1219–1224

Polygenic Risk and Environment work together



Nagpal, Tandon and Gibson (2022) *Molecular Biology and Evolution* **39**: msac053