

Summer Institutes of Statistical Genetics, 2023

Module 2: INTRODUCTION TO GENETICS AND GENOMICS

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Lecture 3: QUANTITATIVE GENETICS

# The ACE Model and Twin Studies

Identical / Maternal



$$r_{mz} = A + C$$



Dizygotic / Fraternal



$$r_{dz} = \frac{1}{2}A + C$$



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

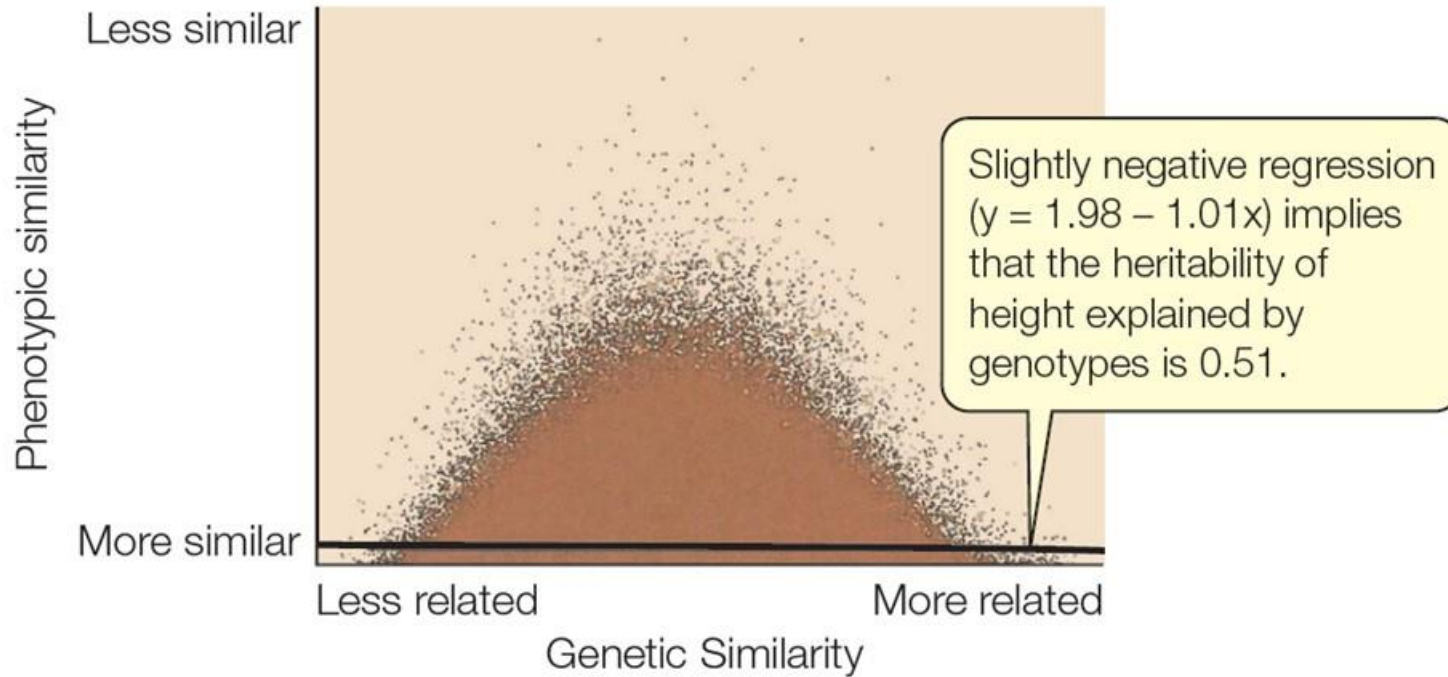
From: [The Genetics of Voting: An Australian Twin Study](#)

	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
<i>N</i> pairs <sup>a</sup>	1239	732	579	328	782

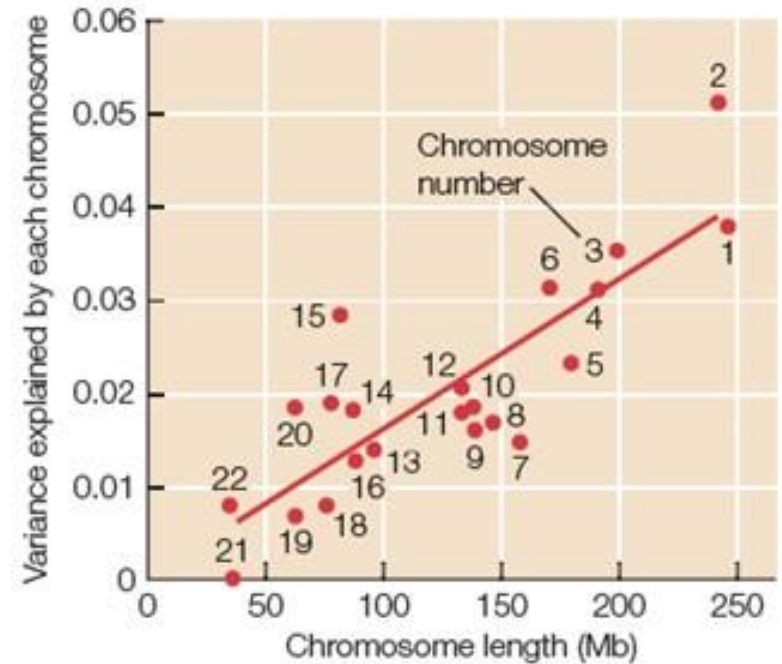
Note: (a) Correlations were estimated using full information maximum likelihood observations on incomplete pairs. Due to missingness, the number of complete pairs range from: MZF (1133–1239), DZF (689–732), MZM (528–732), DZM (308–328)

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

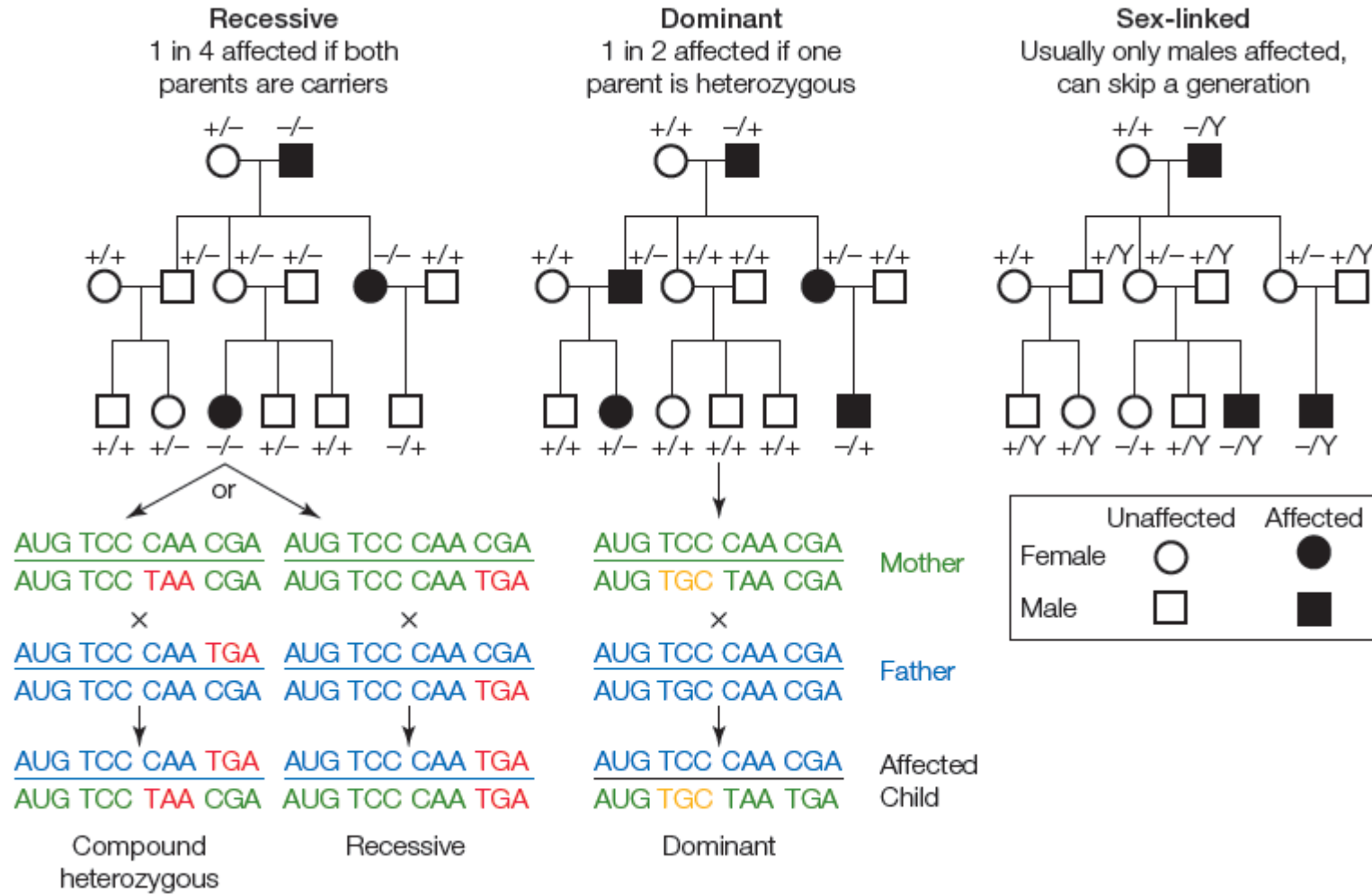
# SNP-Based Heritability



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  $p \sim 0.01$ ), 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 dysmorphism, 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



## OMIM

OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh. Its official home is [omim.org](http://omim.org).

## Using OMIM

[Getting Started](#)

[FAQ](#)

## OMIM tools

[OMIM API](#)

## Related Resources

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[Gene](#)

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fibromyalgia Search

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## #300623

### FRAGILE X TREMOR/ATAXIA SYNDROME; FXTAS

ICD+

#### External Links

- Protein
- Clinical Resources
- Animal Models

#### Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Cene/Locus MIM number
Xq27.3	Fragile X tremor/ataxia syndrome	300623	XLD	3	FMR1	309550

[Clinical Synopsis](#)

#### TEXT

A number sign (#) is used with this entry because fragile X tremor/ataxia syndrome (FXTAS) is caused by an expanded trinucleotide repeat in the FMR1 gene (309550.0004).

In FXTAS, the expanded repeats range in size from 55 to 200 repeats and are referred to as 'premutations'; full repeat expansions with greater than 200 repeats results in fragile X mental retardation syndrome (300624) (Jacquemont et al., 2003). [\[1\]](#)

#### Description

Jacquemont et al. (2007) provided a review of fragile X syndrome, which they characterized as a neurodevelopmental disorder, and FXTAS, which they characterized as a neurodegenerative disorder. Amiri et al. (2008) provided a review of FXTAS and noted that the pathogenesis of the disorder is distinct from that in fragile X syndrome. FXTAS results form a toxic gain of function of FMR1 RNA, whereas fragile X syndrome results from a loss of FMR1 function. [\[2\]](#)

The penetrance of FXTAS in male carriers aged 50 years and over, ascertained through families with a fragile X syndrome proband, is at least 33% (Hagerman and Hagerman, 2004); its penetrance in female carriers is approximately 5-10% (Greco et al., 2008). [\[3\]](#)

#### Clinical Features

Hagerman et al. (2001) reported 5 men with a fragile X premutation, ranging from 78 to 98 repeats, who presented in the sixth decade with

## 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 ( $50 \times 1/5,000 = 1$  in 100)

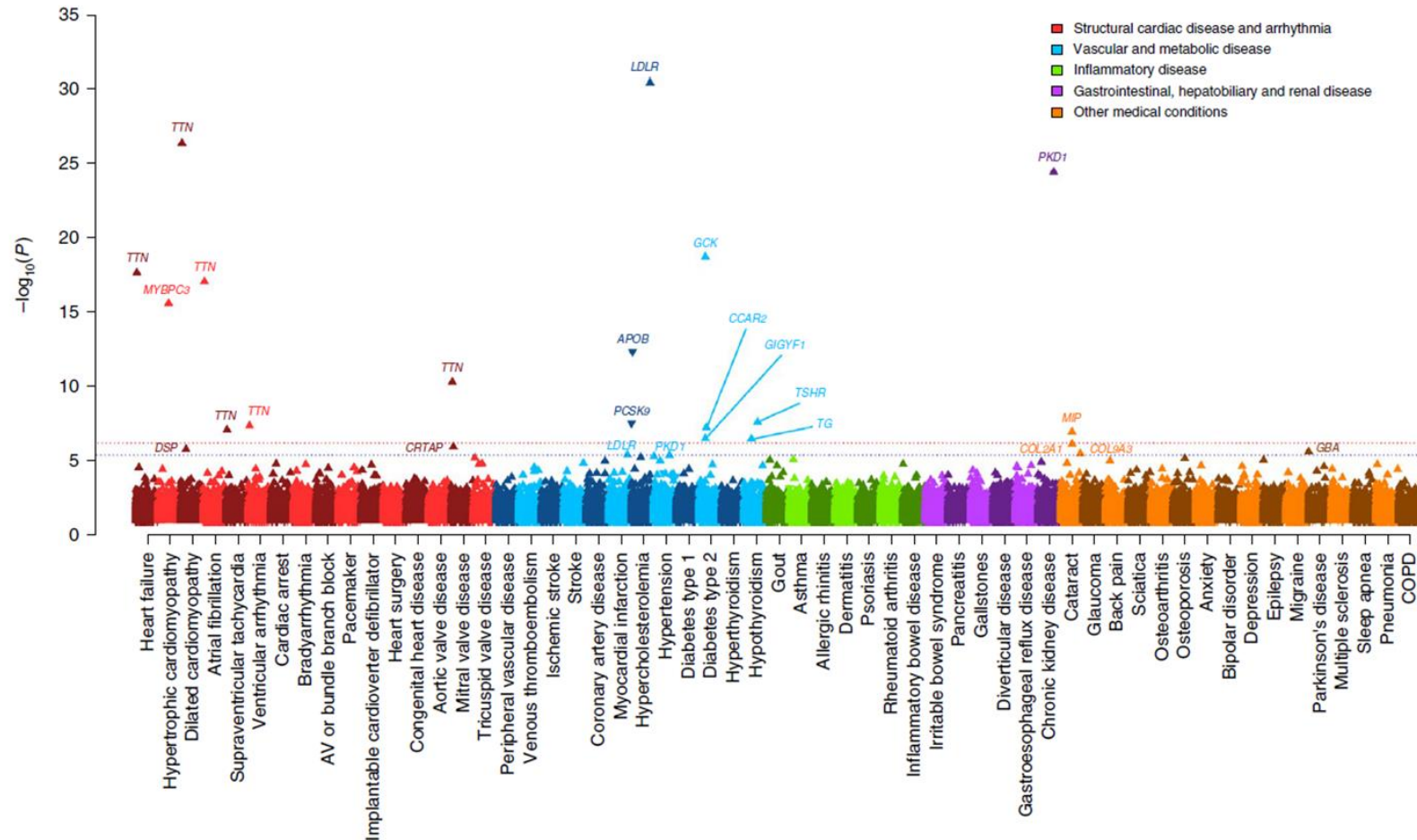
However, comprehensive scans have failed to uncover more than a handful of such alleles for any common disease.

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.

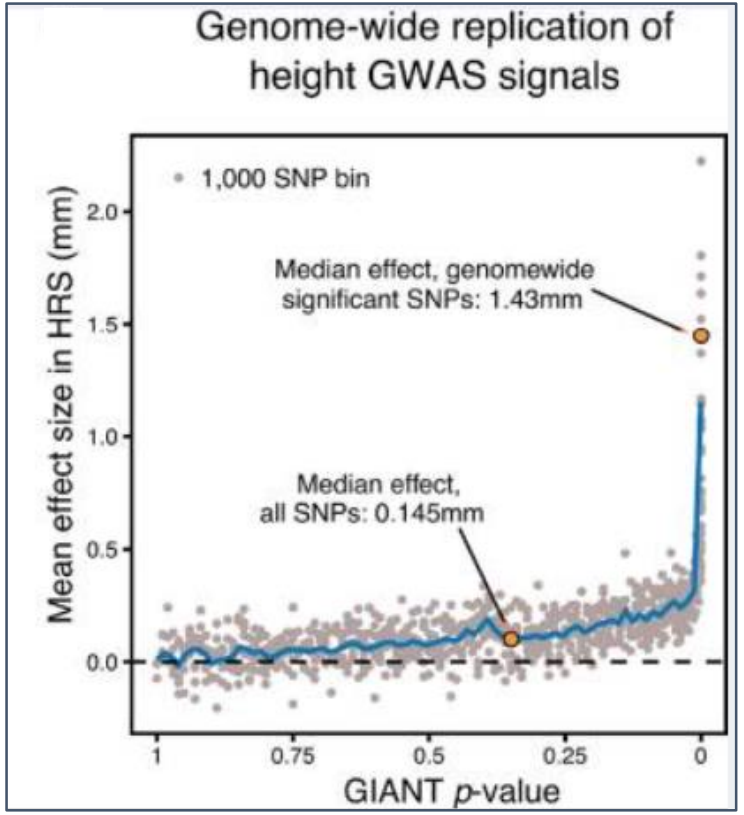
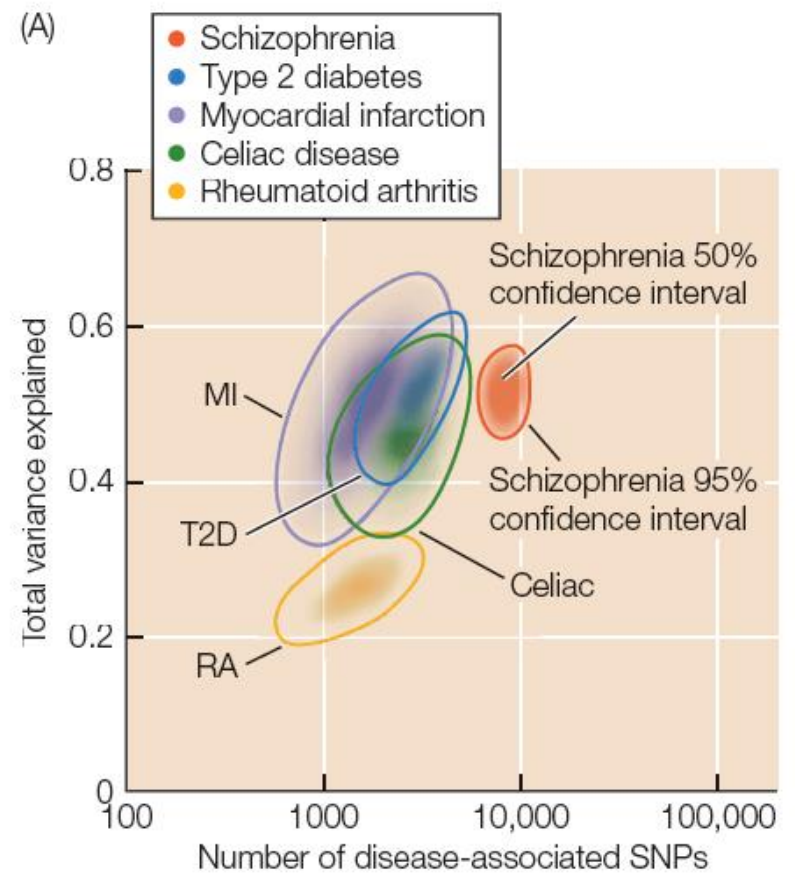


# Rare Alleles Influencing Cardiometabolic disease



Between 1% and 2.4% of European ancestry individuals carry a rare dominant pathogenic CM-D variant on one of 68 genes

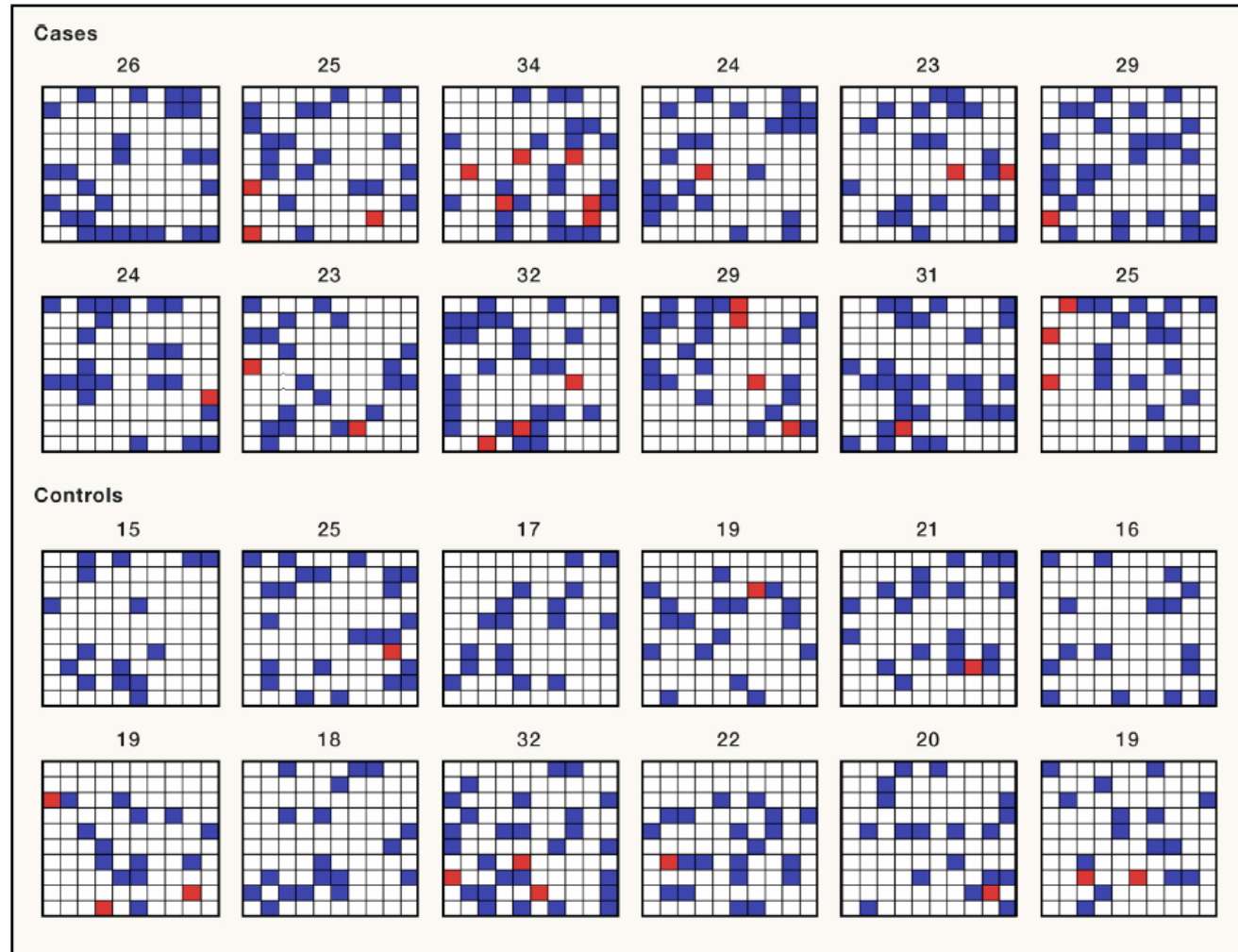
# The Infinitesimal Model



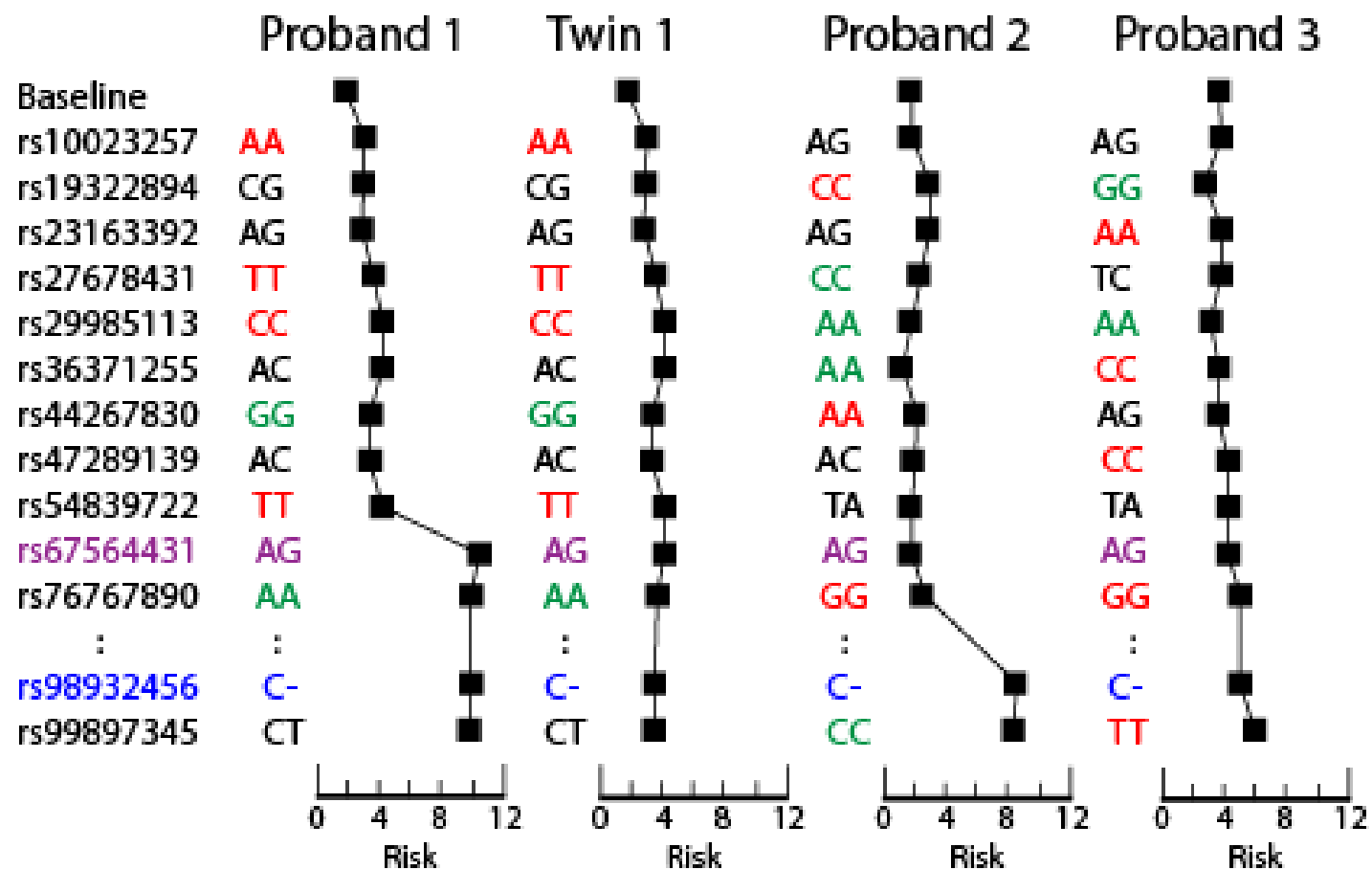
Boyle et al (20187) *Cell* **169**: 1177-1186.

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.

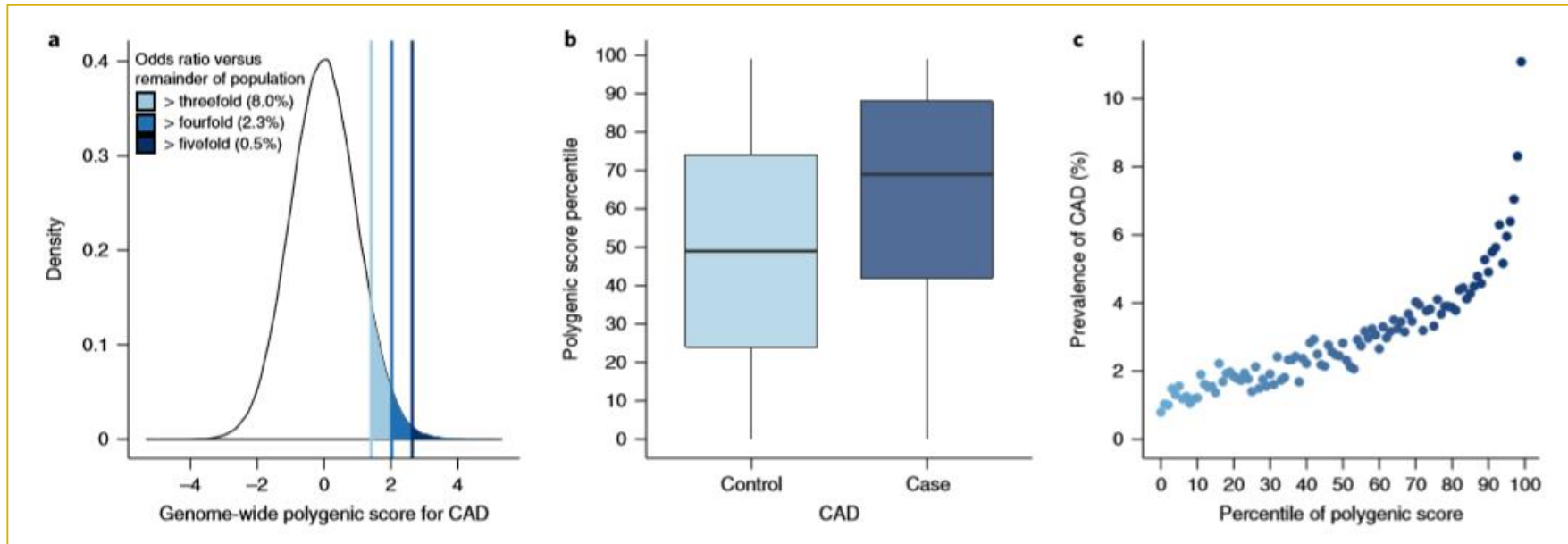
# The Prediction Problem



# The Polygenic Risk Model



# Polygenic Risk Scores

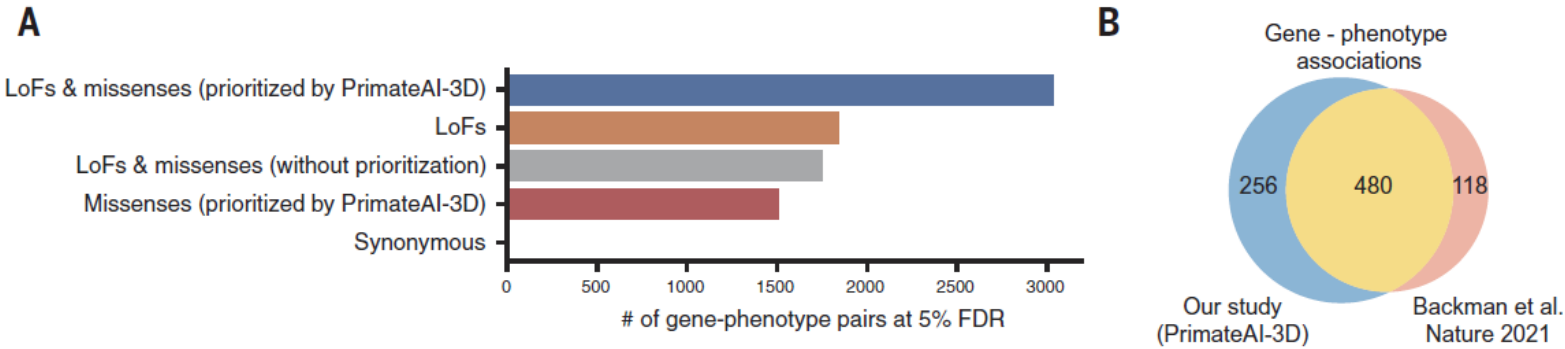


More people are at elevated risk due to common variants than rare mutations

Some people believe that PRS are the future of personalized medicine

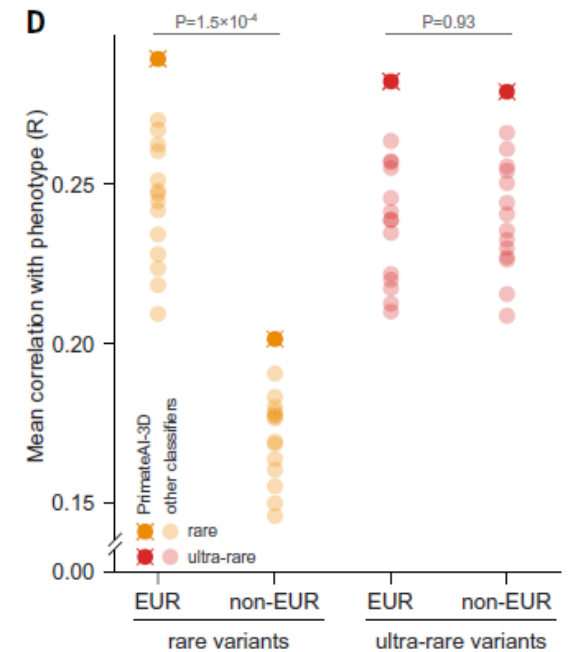
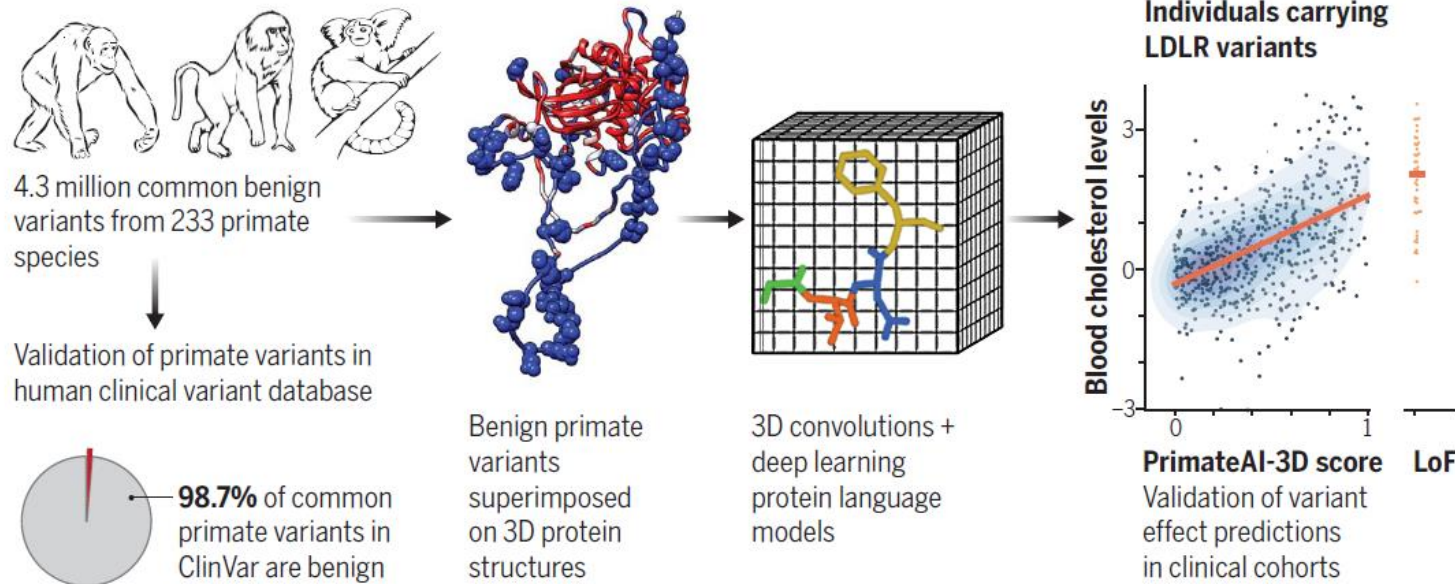
I think they are also useful for negative prediction, namely finding those at low risk

# Rare and Polygenic Risk Scores



PrimateAI-3D models pathogenicity using AI 3D convol neural network trained on 233 Primate genomes.

Ultra-rare variants are much more portable across ancestries.



# Polygenic Risk and Environment work together

