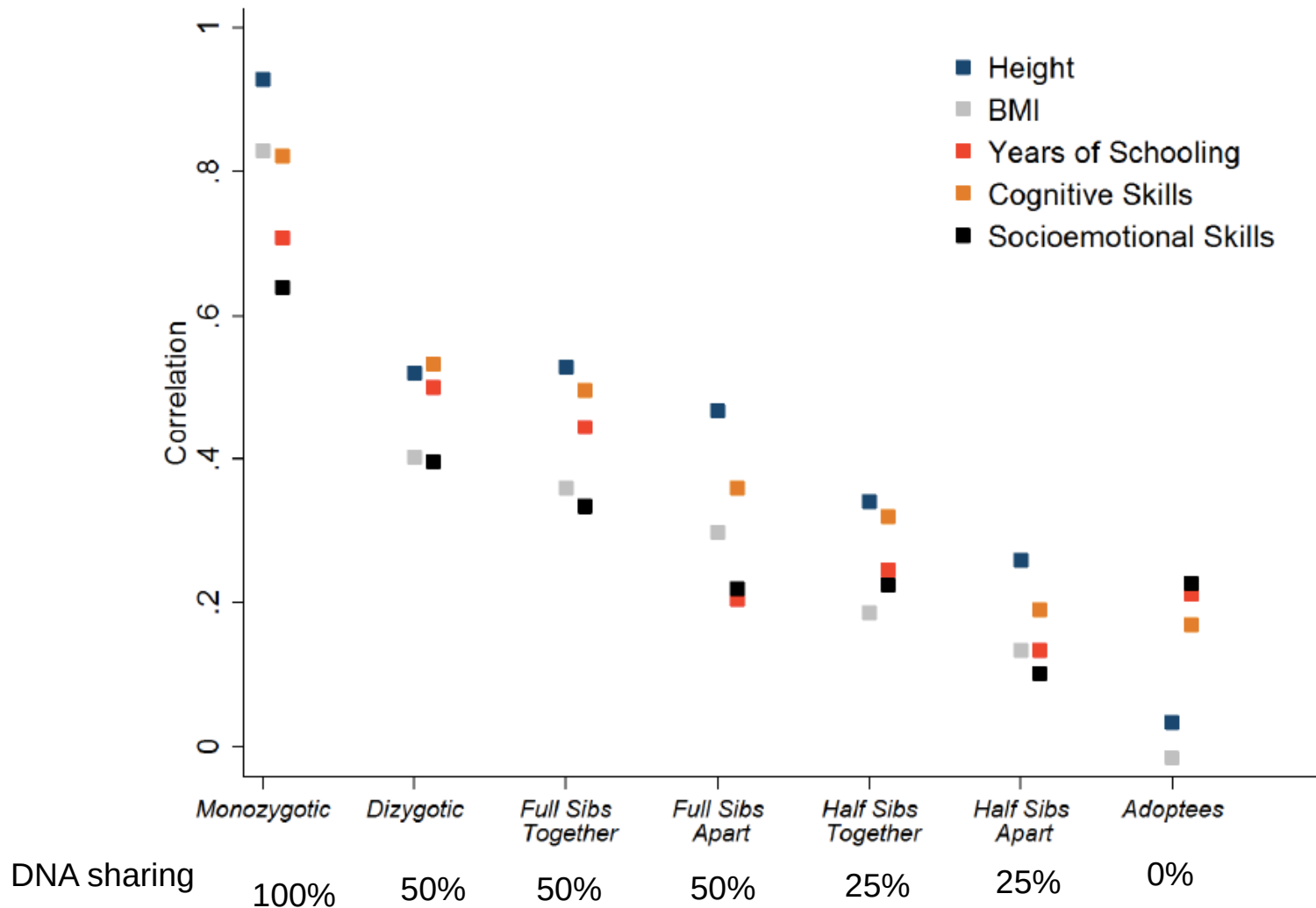


Emerging Science for the Courts

Human Genetics of Behavior

Steven E. Hyman
Harvard University
Broad Institute of MIT and Harvard

I. Introduction: Correlation of Traits by Relatedness; evidence for heritability



Source: David Cesarini

Heritability

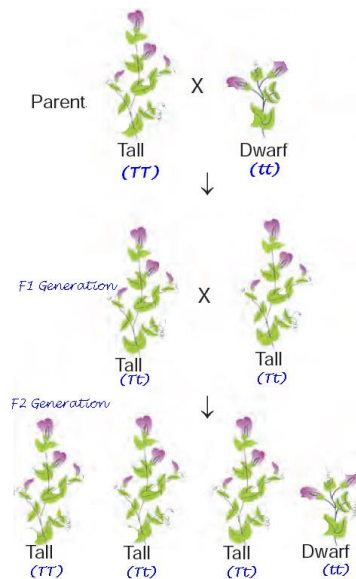
- The heritability of a trait represents the proportion of variation explained by inherited DNA sequences *in a specified population*
- The heritability of a trait *is a property of populations not individuals.*
 - Heritability depends on how a trait is measured
 - It also depends on the environment to which the population is subjected (e.g., poor population nutrition affects adult height)
- High heritability *does not* signify immutability
 - Better nutrition produced greater mature height (to a point)
 - Phenylketonuria is 100% heritable and 100% preventable

Our brains are not like Mendel's peas

The heritable risk architecture of cognition and behavior is highly polygenic resulting in quantitative traits like human—but not pea plant—mature height



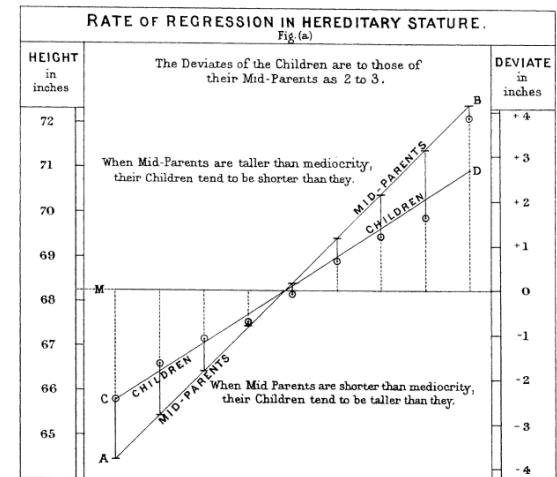
Gregor Mendel
1822-1884



Pea Plant Height: Few highly penetrant alleles



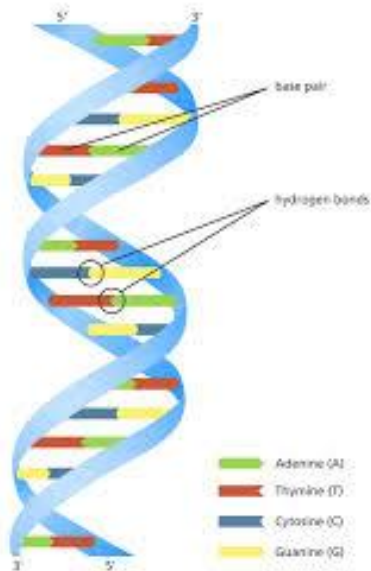
Francis Galton
1822-1911



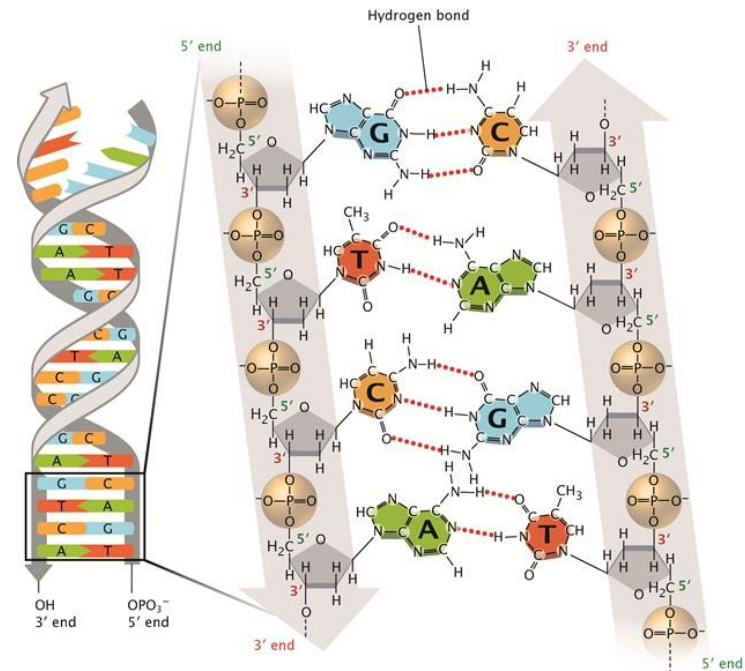
Human Height: >3000 low penetrance significant loci found to date (Yengo, GIANT Consortium, et al 2018)

Genes are composed of deoxyribonucleic acid (DNA)

- DNA specifies the building blocks of cells (RNA and protein) by the precise ordering of four “letters”, the nucleotide bases: Adenine (A), Thymine (T), Cytosine (C), and Guanine (G)
- Differences in human traits reflect differences in the ordering of bases



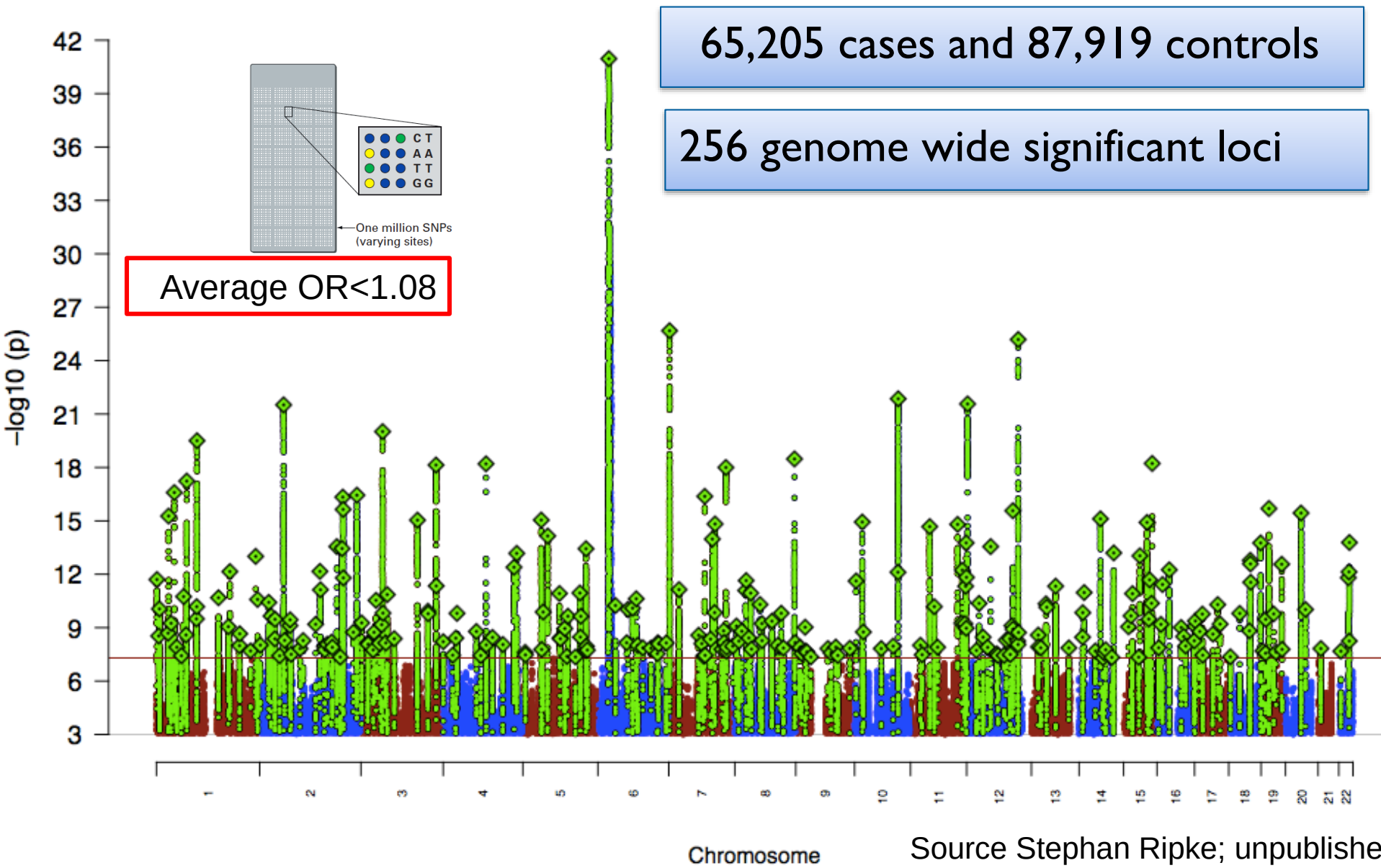
DNA double helix



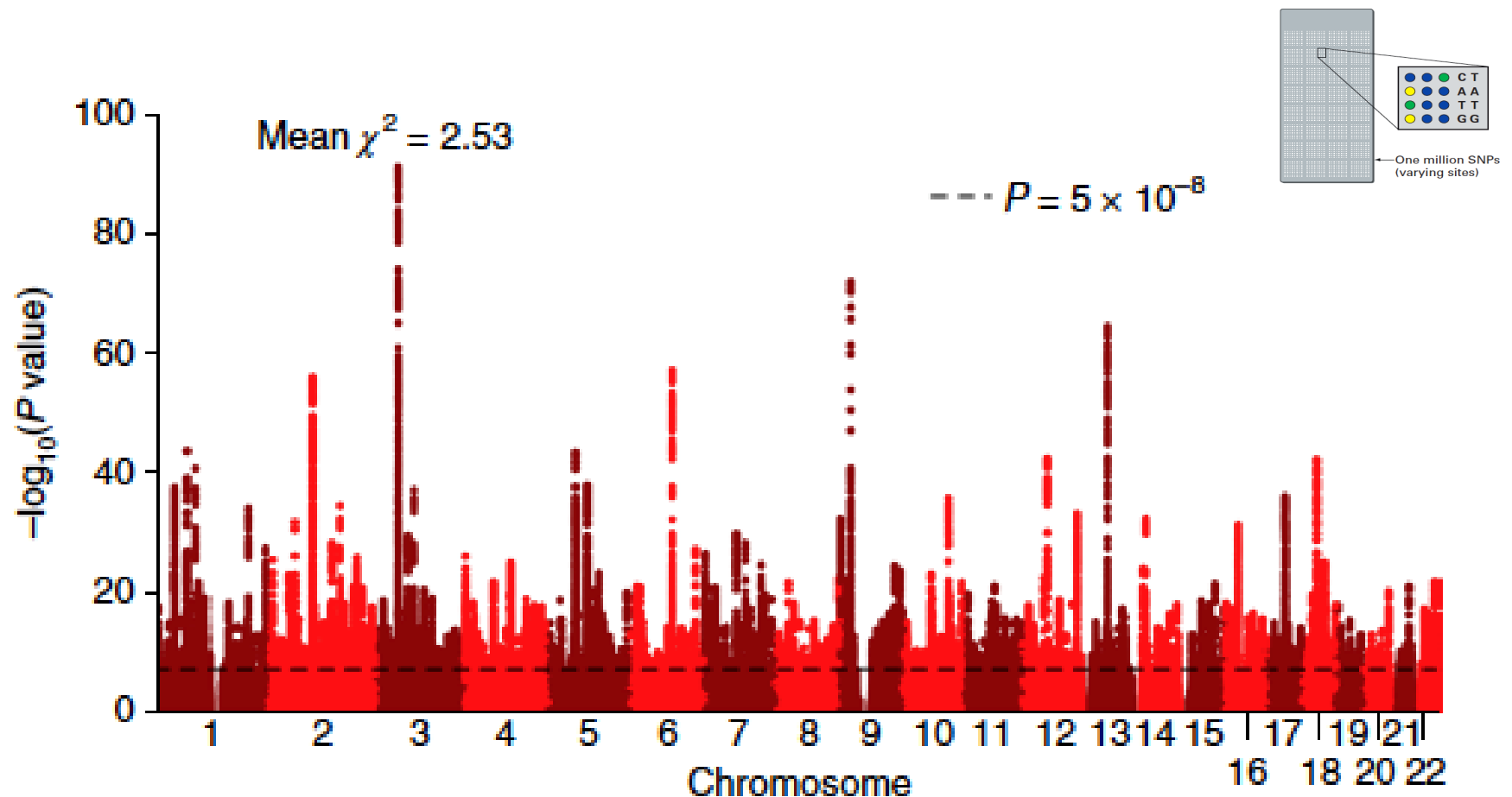
The double helix unwound to show bases

Schizophrenia is a polygenic trait

PGC wave 3 schizophrenia GWAS

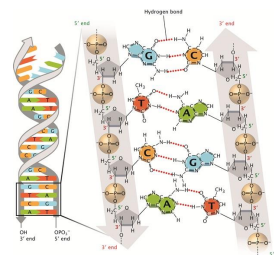
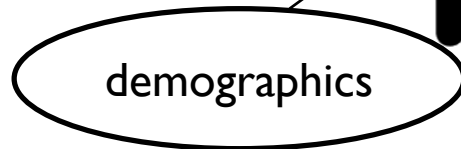
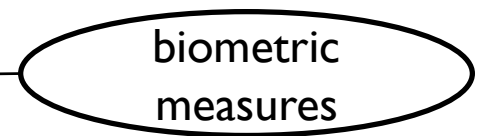
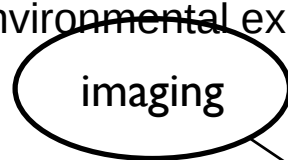


GWAS results for Educational Attainment based on 1.1 million subjects



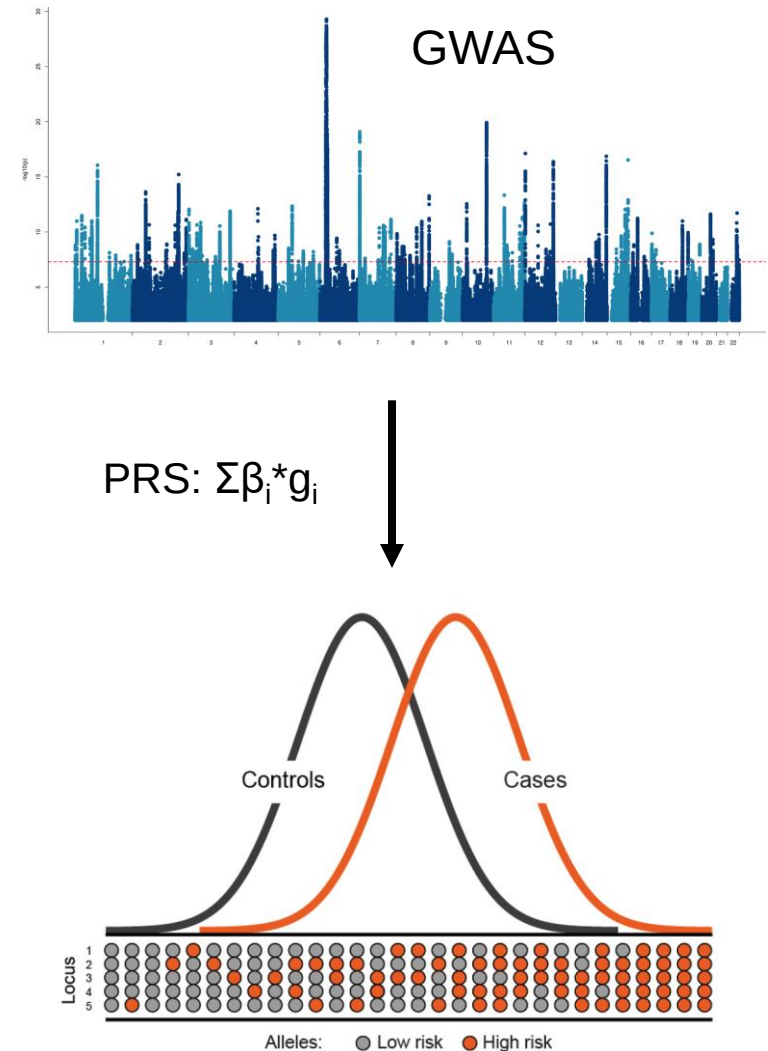
Large and growing genomic datasets are increasingly sharing:

- Genotypes and increasingly, sequence data
- Rich phenotypic data including blood & urine biomarkers; imaging of brain, heart, other organs
- Sociodemographic data including educational data, employment data, family income
- Linked to electronic health records; cancer registries, death registries
- Cognitive and sensory measures, responses to survey questions
- Lifestyle factors; environmental exposures



Aggregate signals for risk prediction: Polygenic Risk Scores (PRS)

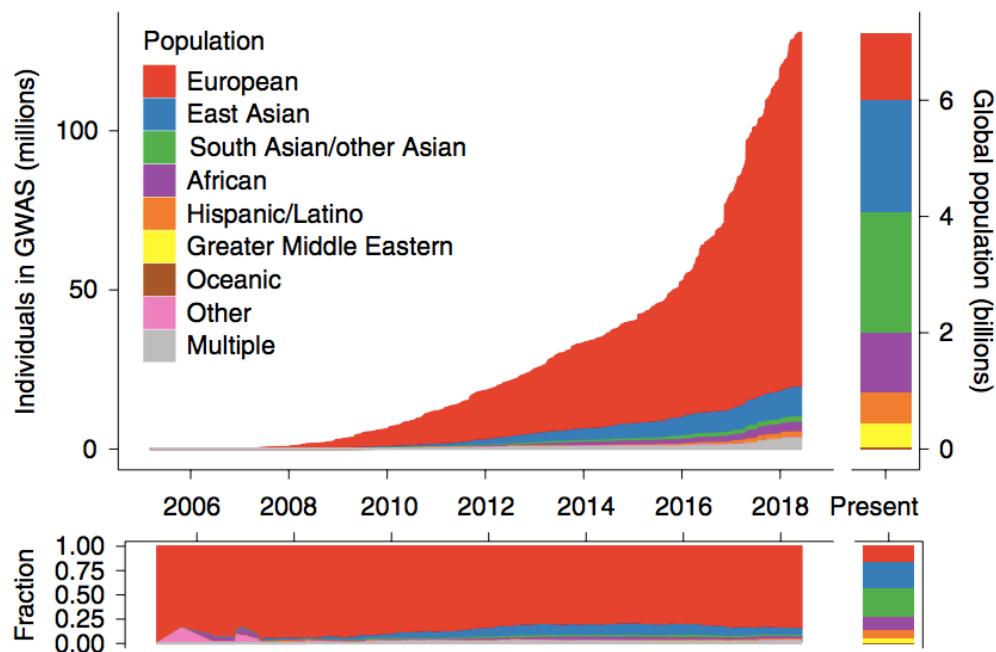
- Take largest GWAS meta-analysis *appropriate for person's genetic background*
- For each individual calculate weighted sum (based on effect size) of risk alleles across the whole genome.
- PRS **can** stratify subjects
- PRS **cannot** make good individual predictions or diagnoses



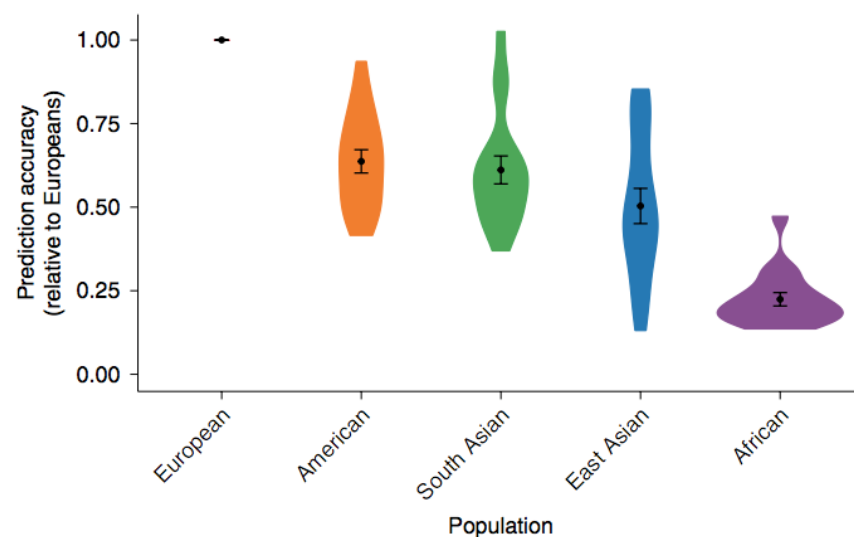
Genetics has a diversity problem

Must be addressed for fine mapping and global health equity

Martin, A. R. *et al. Nat Genet* 2019

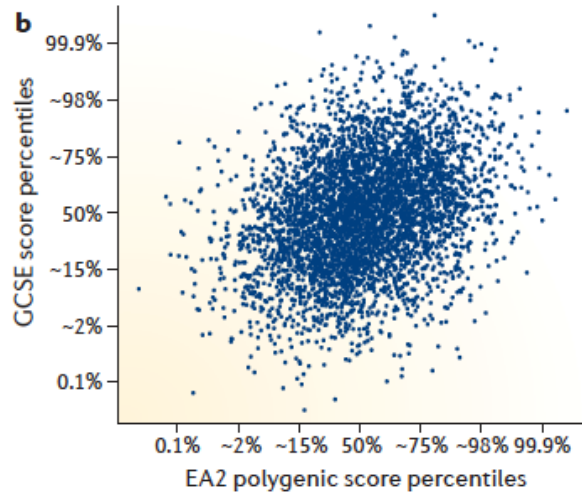


Loss of PRS prediction accuracy is due to differences in allele frequencies and LD blocks, not disease mechanisms

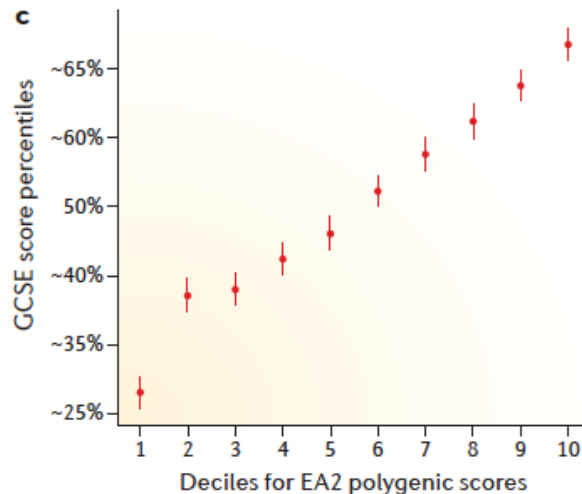


Alicia Martin

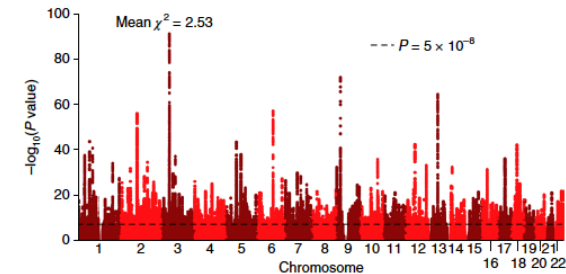
Educational attainment (EA2) polygenic scores predict UK-wide General Certificate of Secondary Education (Age 16)



Individual prediction is poor



Correlation of group averages
when polygenic scores divided into
deciles



The New York Times

Why Progressives Should Embrace the Genetics of Education

By Kathryn Paige Harden

Dr. Harden is a psychologist who studies how genetic factors shape adolescent development.

July 24, 2018

- Genetic tests can reveal that our society fails to be meritocratic:
- Genetic advantage is not earned
- Genetic stratification can help us optimize educational environments

Why We Shouldn't Embrace the Genetics of Education

It's a trap!

By [John Warner](#) // July 26, 2018

Inside Higher Ed

- Polygenic scores will readily be misused
- Optimization of educational interventions for disadvantaged children has rarely occurred or been sustained.
- Importing a 'precision medicine' model to education could excuse damaging educational tracking of students at the lower end of the PRS distribution

Exclusive: A new test can predict IVF embryos' risk of having a low IQ

A new genetic test that can predict if embryos will have a low IQ could soon become available in the US

A company, Genomic Prediction is looking for partner IVF clinics to offer this service

High disease risk could soon

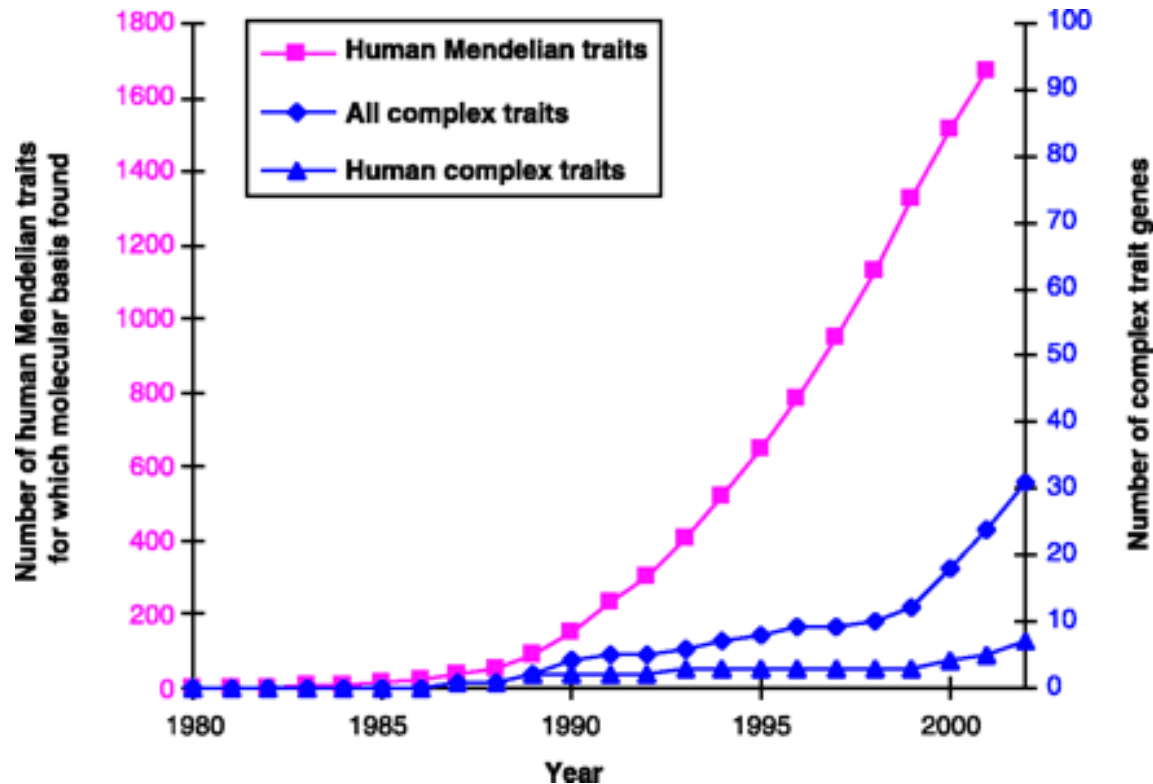
HEALTH 15 November 2018



How will screening for intelligence affect parents' decisions?
ERproductions Ltd/Getty

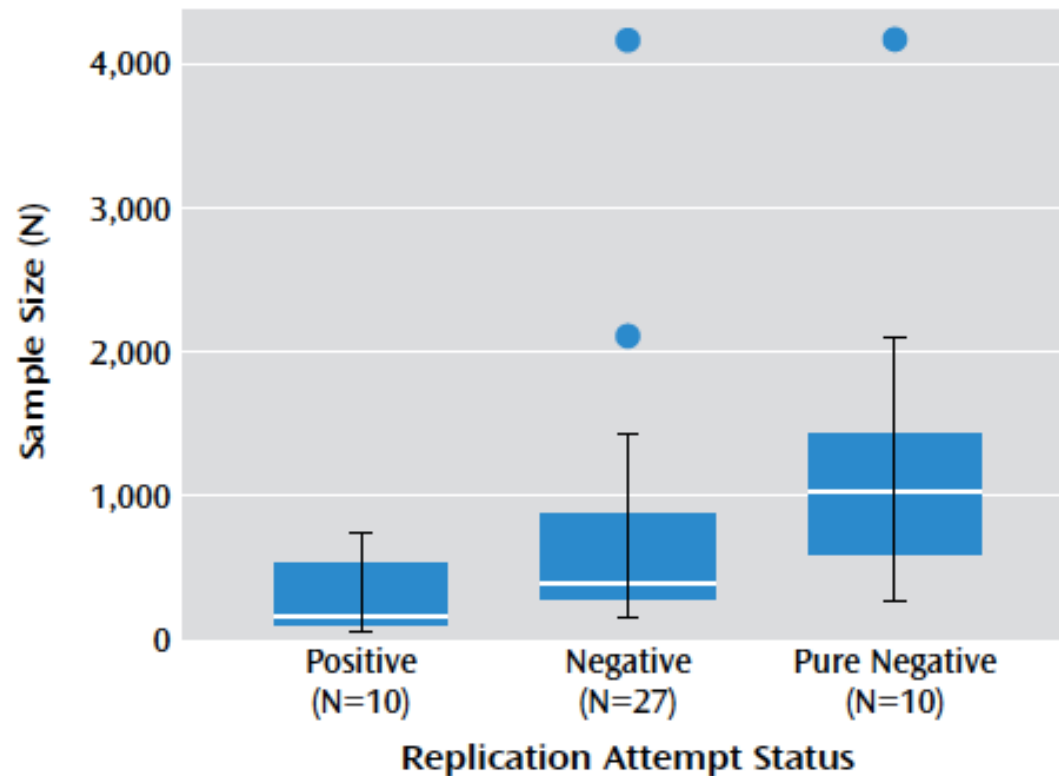
Dark ages of complex trait genetics

- Linkage and candidate gene association assumed alleles of large effect
- Candidate gene and candidate GXE association vastly overestimated our understanding of biology and underestimated their multiple comparisons
- Examples from nonsense studies: MAOA ‘Warrior Gene’ and cGXE



Source; Glazier, Nadeau, Aitman, *Science* 2002

Candidate G X E studies: Publication bias in replication studies



Source: Laramie Duncan