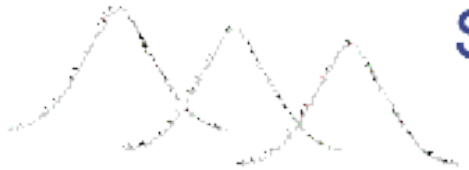

Summer Institute
in Statistical Genetics

2016

Introduction to Genetics and Genomics

1. Genes and Inheritance

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Course Outline

1. Genes and Inheritance (GG)
2. Molecular Biology of the Genome (JL)
3. Association Studies (GG)
4. Population and Evolutionary Genetics (JL)
5. Evolution and Disease Risk (JL) / Precision Medicine (GG)

Genotype and Phenotype

The genotype of an organism is the sequence of it's genes.

The phenotype of an organism the way it appears.

In general, genes are not deterministic. Genotypic variation among organisms specifies the information that, in combination with the environment, influences the phenotype.

Pleiotropy refers to the ability of single genes to influence multiple phenotypes.

Penetrance is the proportion of individuals with a genotype who have the phenotype / disease.

Expressivity is the degree / severity of the phenotype in affected individuals.

Mendelian Genetics

$$\frac{A}{A} \times \frac{a}{a}$$

F0: Pure breeding parents

$$\frac{A}{a} \times \frac{A}{a}$$

F1: Heterozygous offspring

$$\frac{A}{A} ; \frac{A}{a} ; \frac{a}{A} ; \frac{a}{a}$$

F2: Mendelain proportions of Homozygotes + Heterozygotes

3 Models of Complex Disease

CDCV: Common Disease / Common Variant

The proposition that most disease susceptibility can be attributed to 10 to 20 loci, each of which explain around 5% of disease risk.

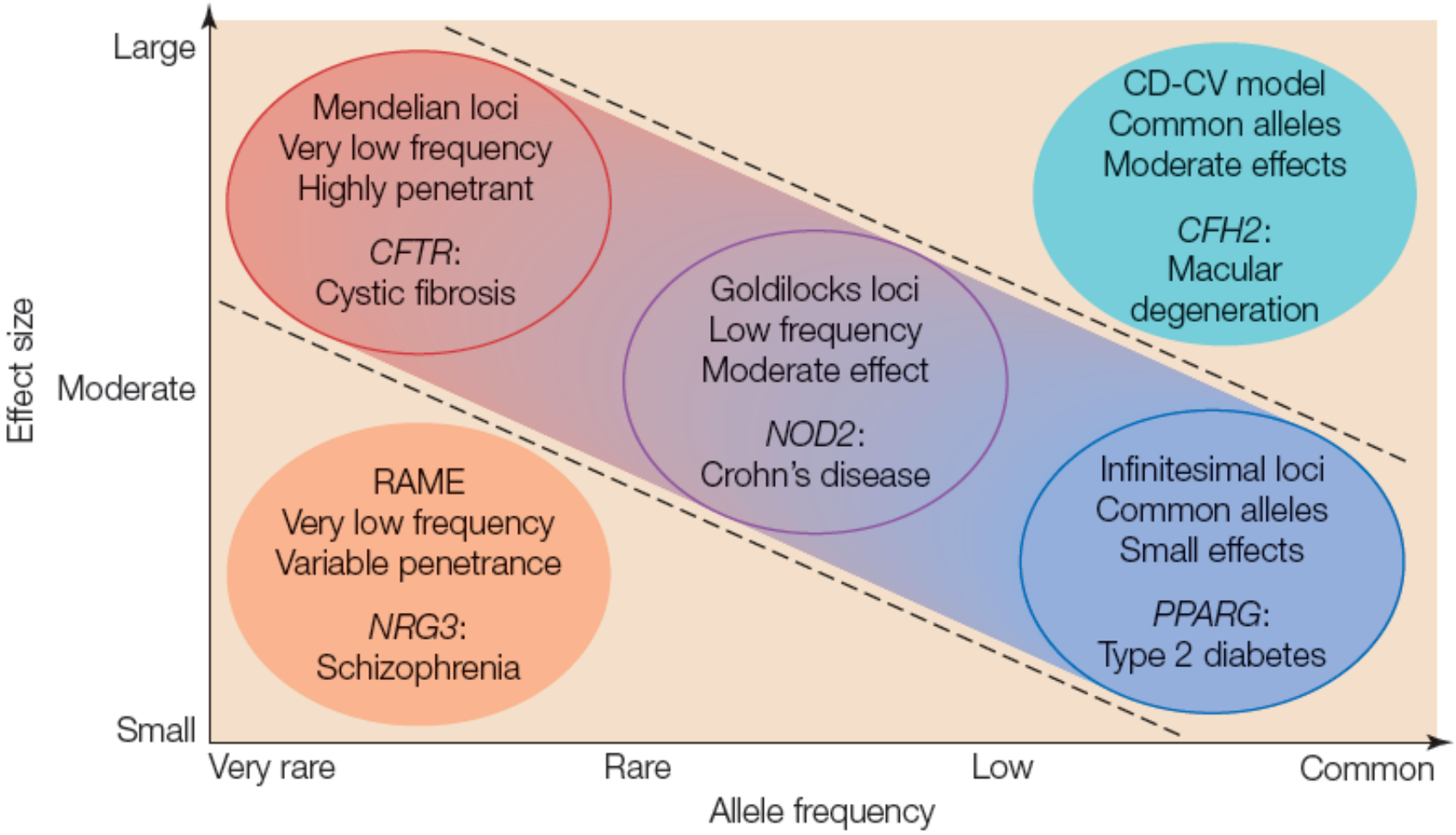
RAME: Rare alleles of Major Effect

The proposition that diseases are highly heterogeneous, with hundreds or thousands of rare mutations causing individual cases of disease.

Infinitesimal:

The proposition that we all carry thousands of very weak susceptibility alleles, and those unlucky enough to have too many are at highest risk, where rare variants or environmental triggers push us over the edge.

Models of the Genetics of Complex Traits



Manolio et al (2009) *Nature* **461**: 747-753

Heritability

Heritability is the proportion of variance in a population that can be attributed to genotypic differences

$$h^2 = V_G/V_P \text{ where } V_P = V_G + V_E$$

The phenotypes may be discrete, such as disease status; categorical, such as number of digits; or continuous, such as height or a biochemical measure.

1. Heritability is not a statement about individuals.

A heritability of 50% for diabetes does not imply that half the reason why someone is diabetic is genetic, the other half environmental. Rather, it suggests that there would be half as much diabetes in the population if everyone was genetically identical.

2. Heritability is only a statement about a single population.

A heritability of 80% for height does not imply that most of the average difference in height between populations is due to genetic differences. Heritability estimates alone should not be used to draw inferences about genetic divergence between groups.

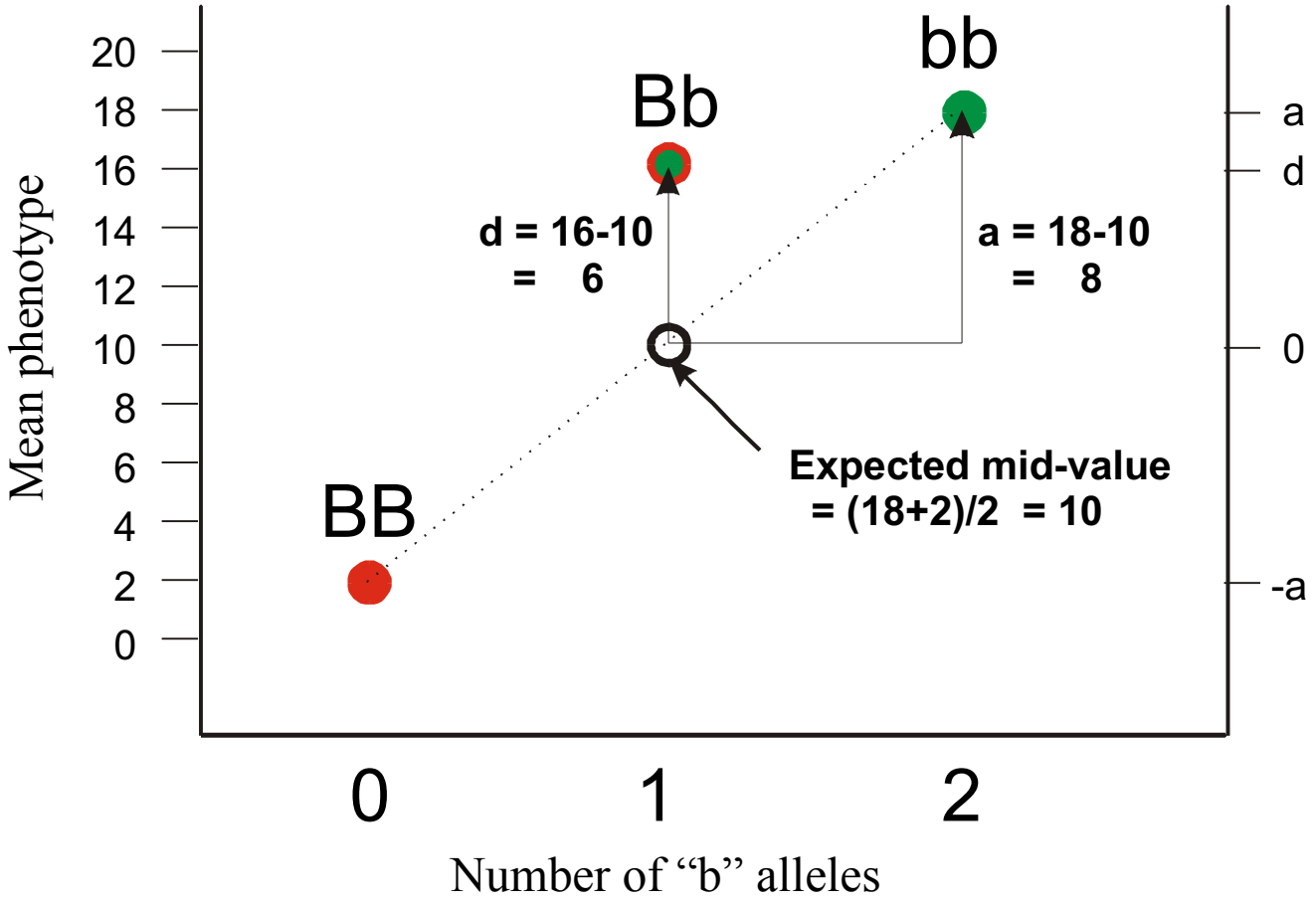
3. Heritability is not the same as inheritance.

Inheritance is the correspondence between children and their biological parents. It can be due to environmental, including cultural, factors that are shared by family members, or to effects. The only way to confidently interpret heritability is to actually measure the genotypic contribution.

4. Very low heritability does not imply very little genetic contribution.

It may either be due to relatively high environmental variance (hence, a large demominator V_P), or to an absence of variance in the genes that contribute. Many important genes, including drug targets, are not polymorphic and will only be discovered through other types of approach including model organism research.

Dominance ratio



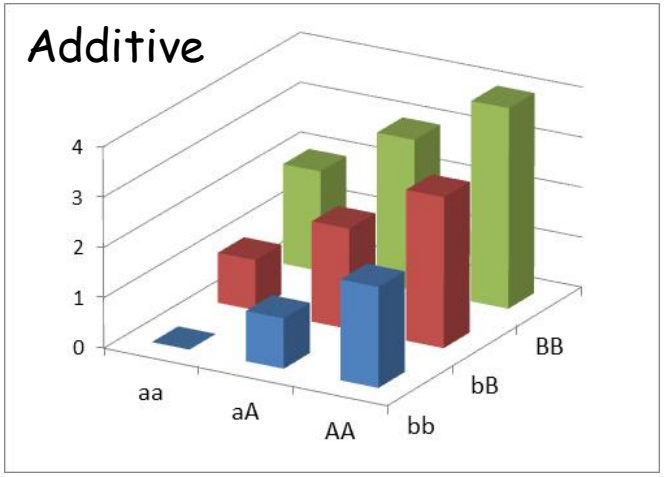
$$V_P = V_A + V_D + V_I + V_{GxE} + V_E$$

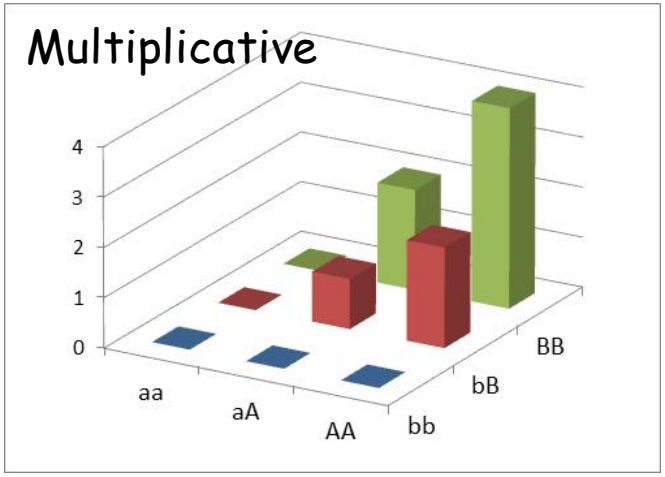
- Loci are said to have *Additive* effects if the contributions of each individual allele can simply be added algebraically to arrive at a prediction of a phenotype given a genotype.
- *Dominance* refers to the observation that heterozygotes resemble one class of homozygotes more than the other.
- *Epistasis* refers to a locus-by-locus Interaction, such as when alleles at two loci antagonize or synergize with one another.
- V_E is the *environmental* variance

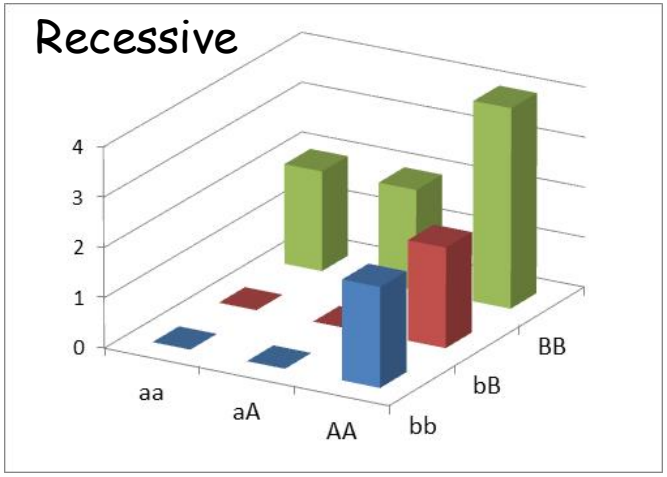
Broad Sense Heritability

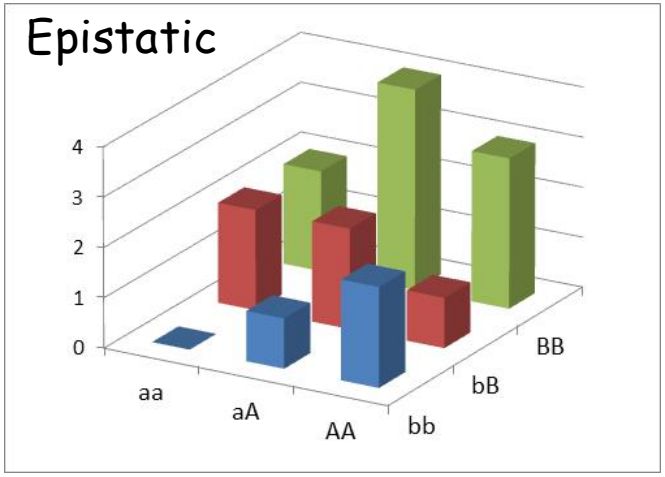
$$V_G = V_A + V_D + V_I + V_{G\times E}$$

Narrow sense heritability is only the additive component whereas Broad sense heritability includes dominance, interaction and genotype-by-environment effects.

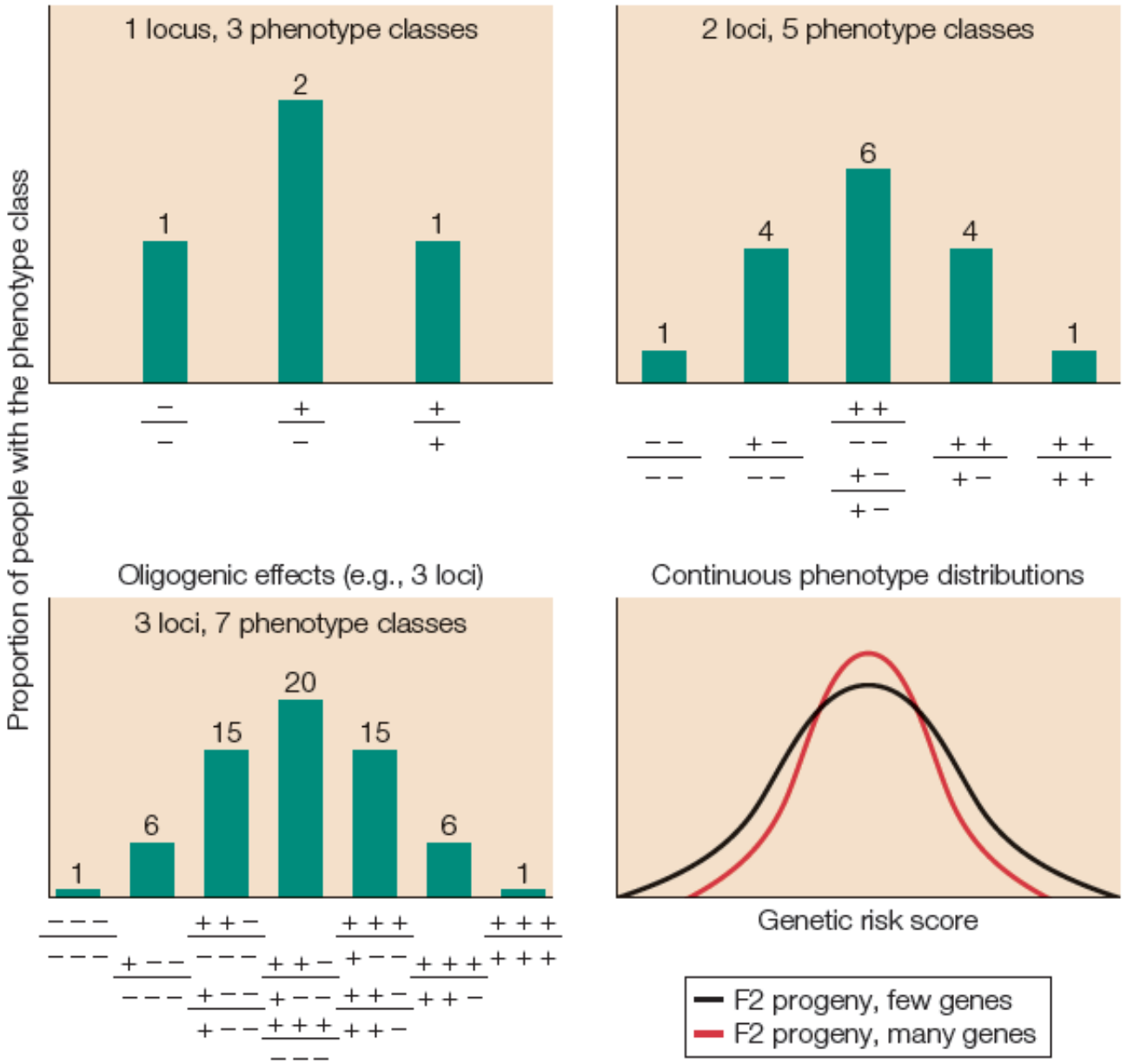






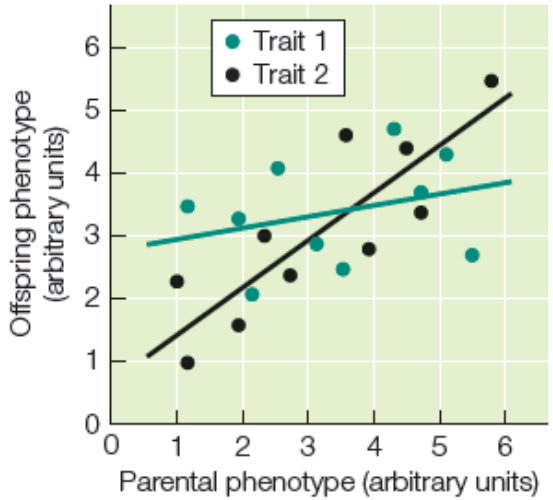


From Mendelian to Quantitative genetics

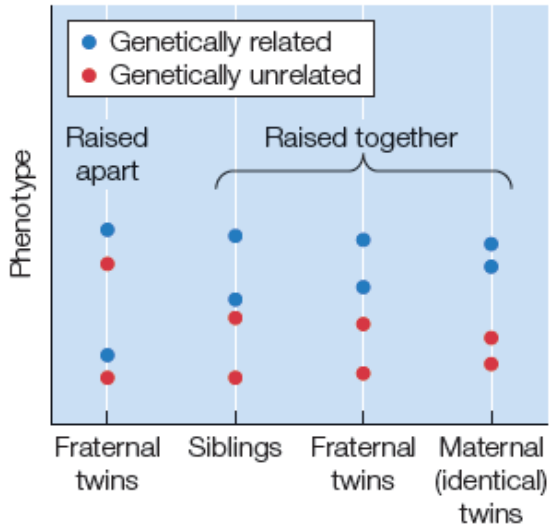


Estimating Heritability

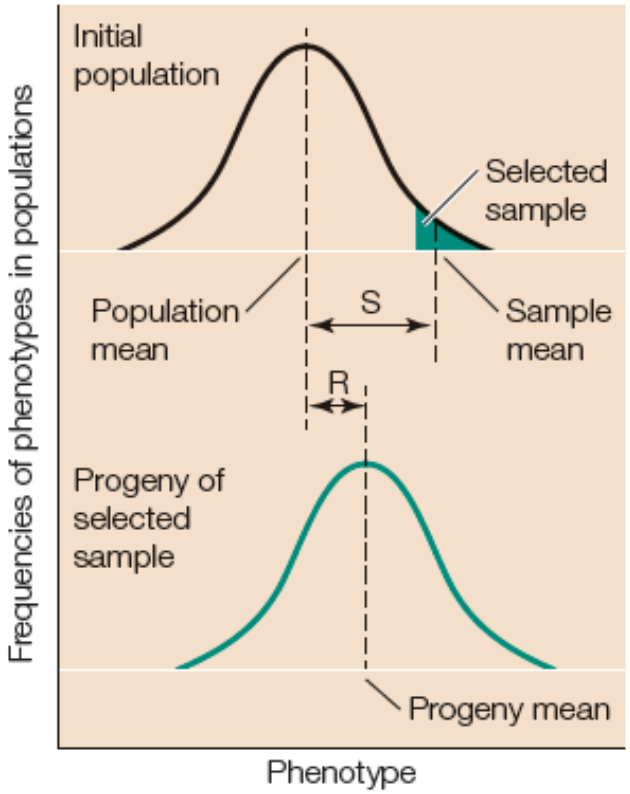
(A) Parental-offspring regression



(B) Twin studies



(C) Realized heritability



Twin Studies

Identical / Maternal

$r_{mz} = A + C$

Dizygotic / Fraternal

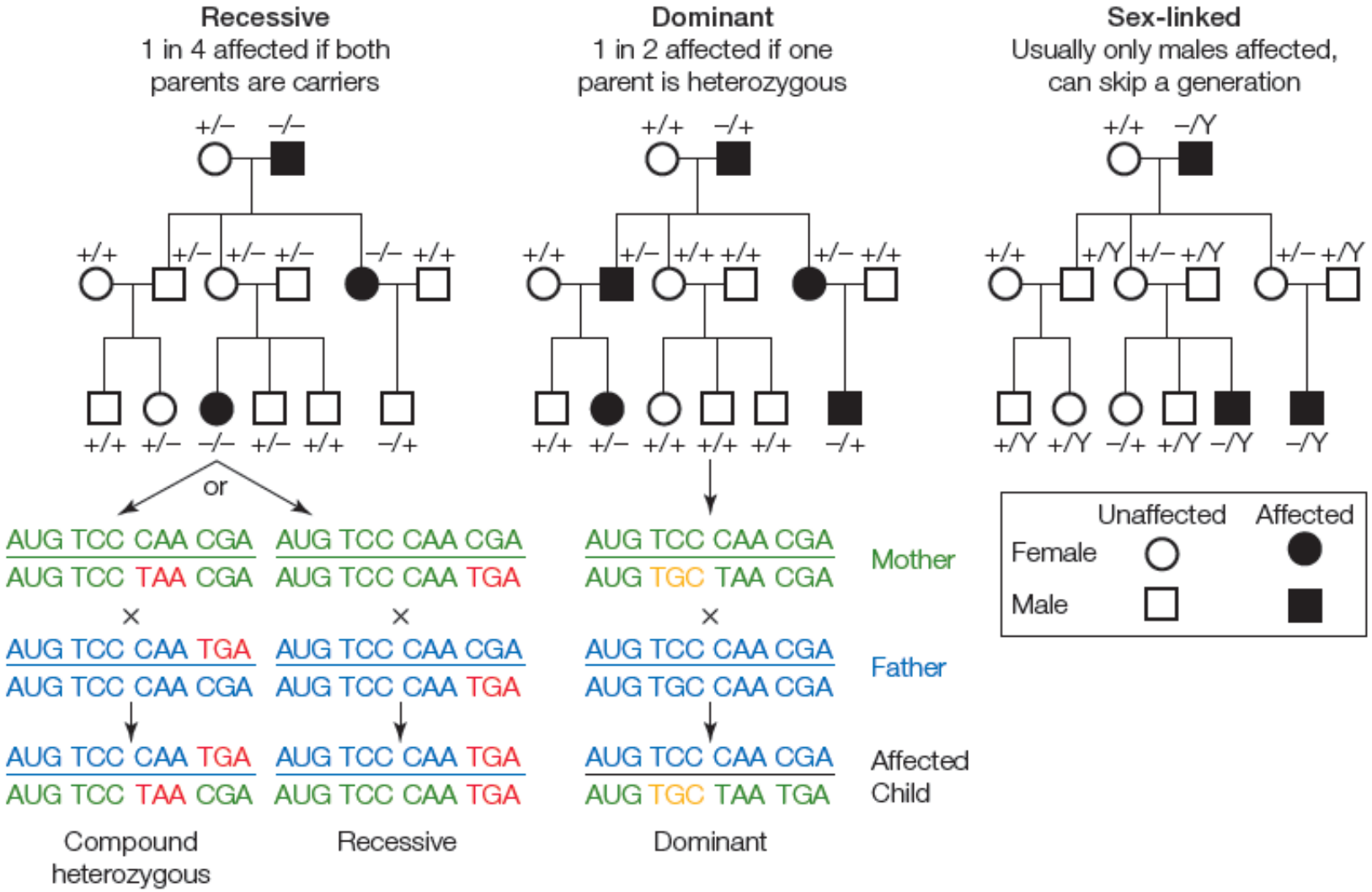
$r_{dz} = ½A + C$

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

Mendelian Pedigree Studies



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

Online Mendelian Inheritance in Man (OMIM)

OMIM® **Online Mendelian Inheritance in Man®**
An Online Catalog of Human Genes and Genetic Disorders
Updated 24 June 2016

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Advanced Search : OMIM, Clinical Synopses, Gene Map

Need help? : Example Searches, OMIM Search Help, OMIM Tutorial

Mirror site : mirror.omim.org

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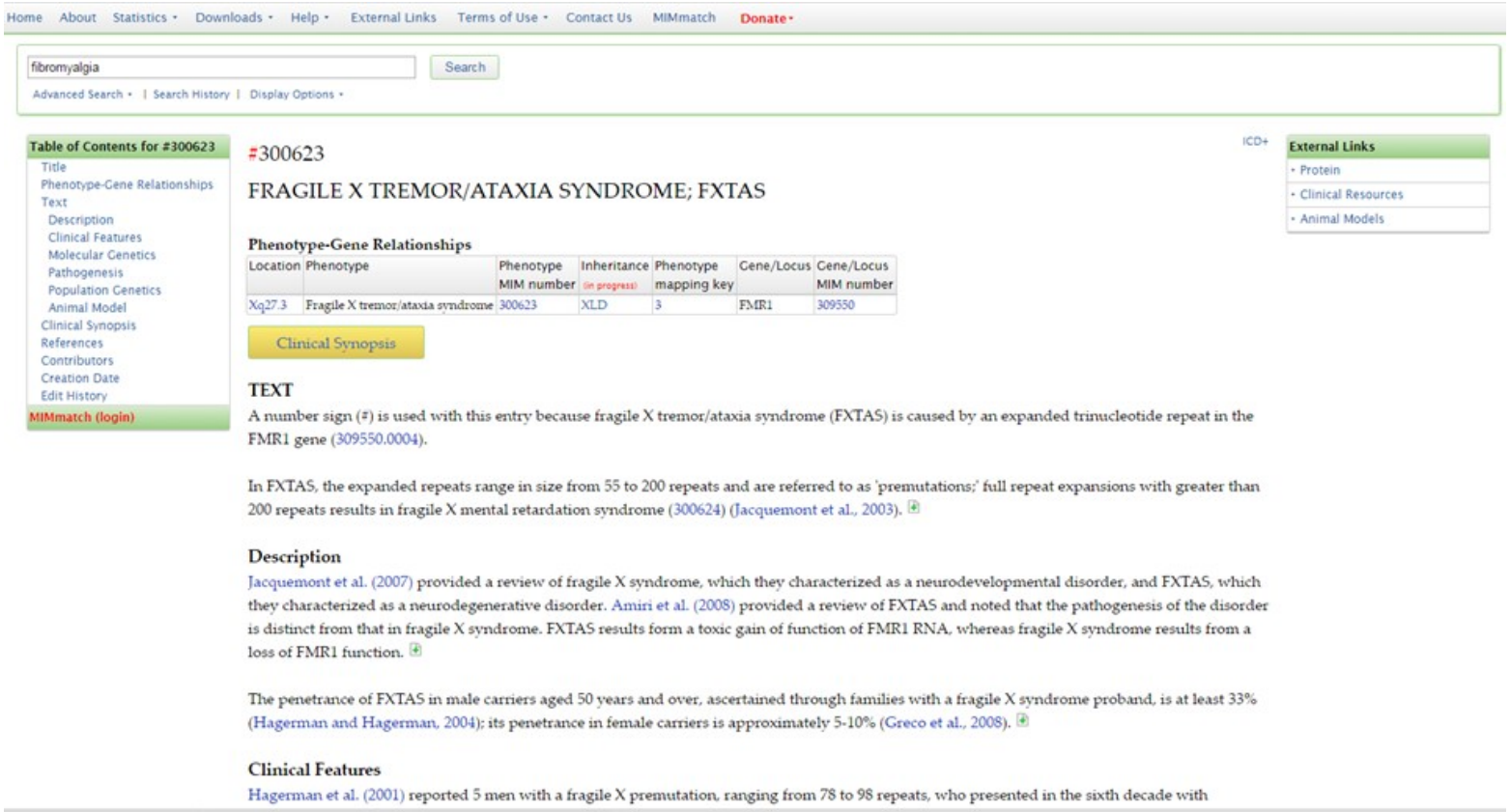
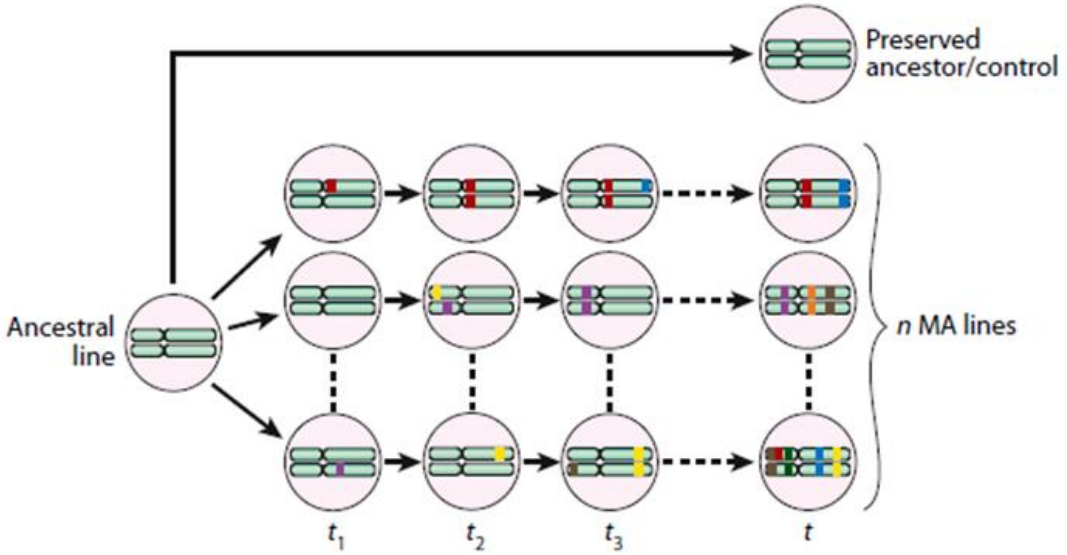
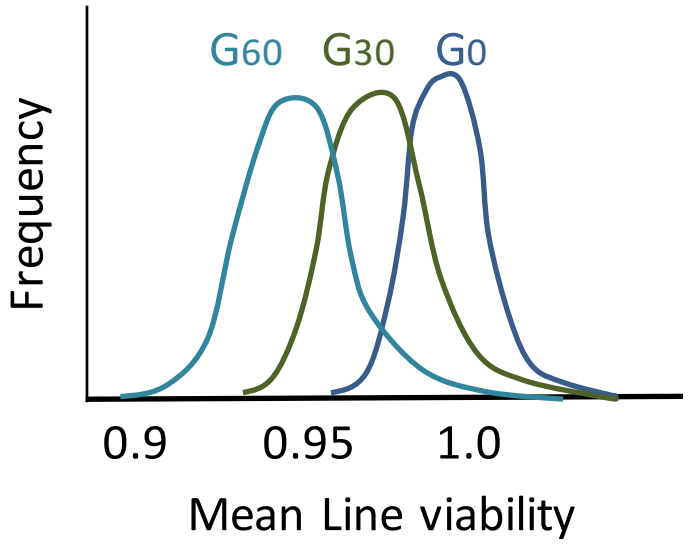


Mutation Accumulation

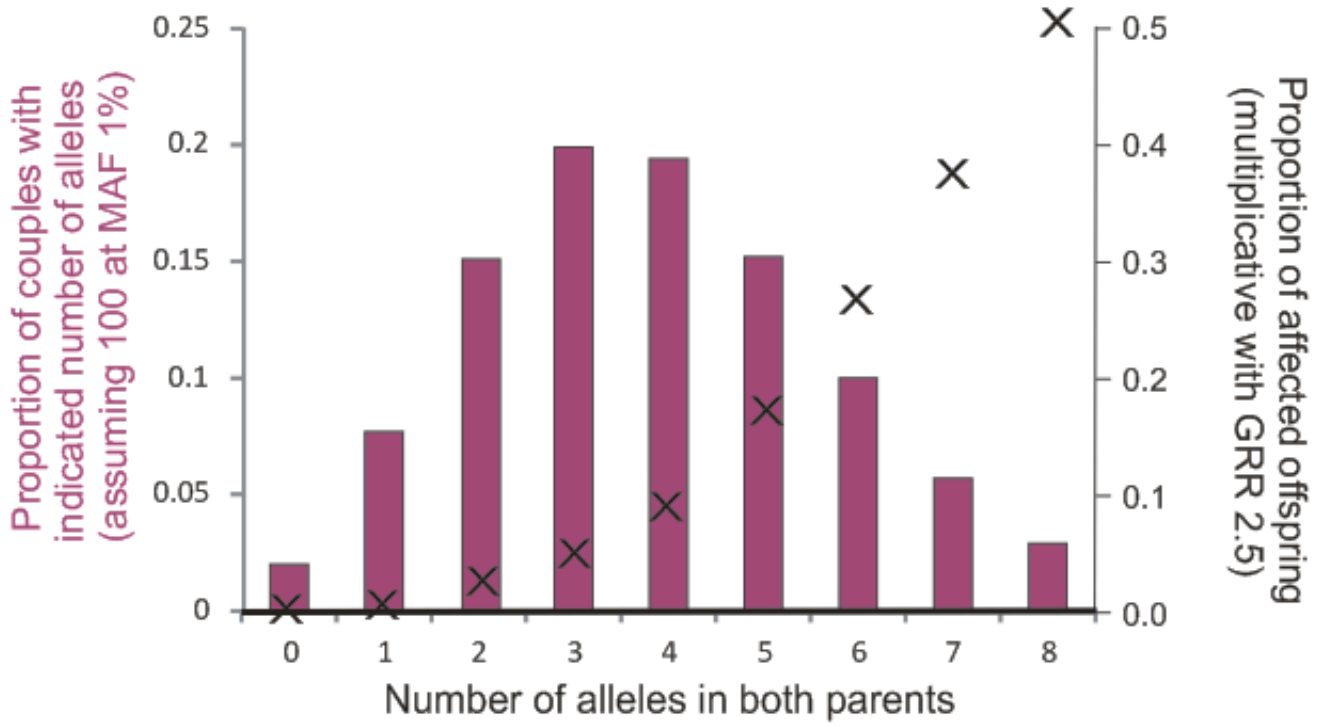




In each generation, slightly deleterious mutations add ~ 0.1% of the standing environmental variance to the heritability of traits, also reducing viability.

Halligan and Keightley (2009) *Annu Rev Ecol Evol Syst.* **40**: 151-172

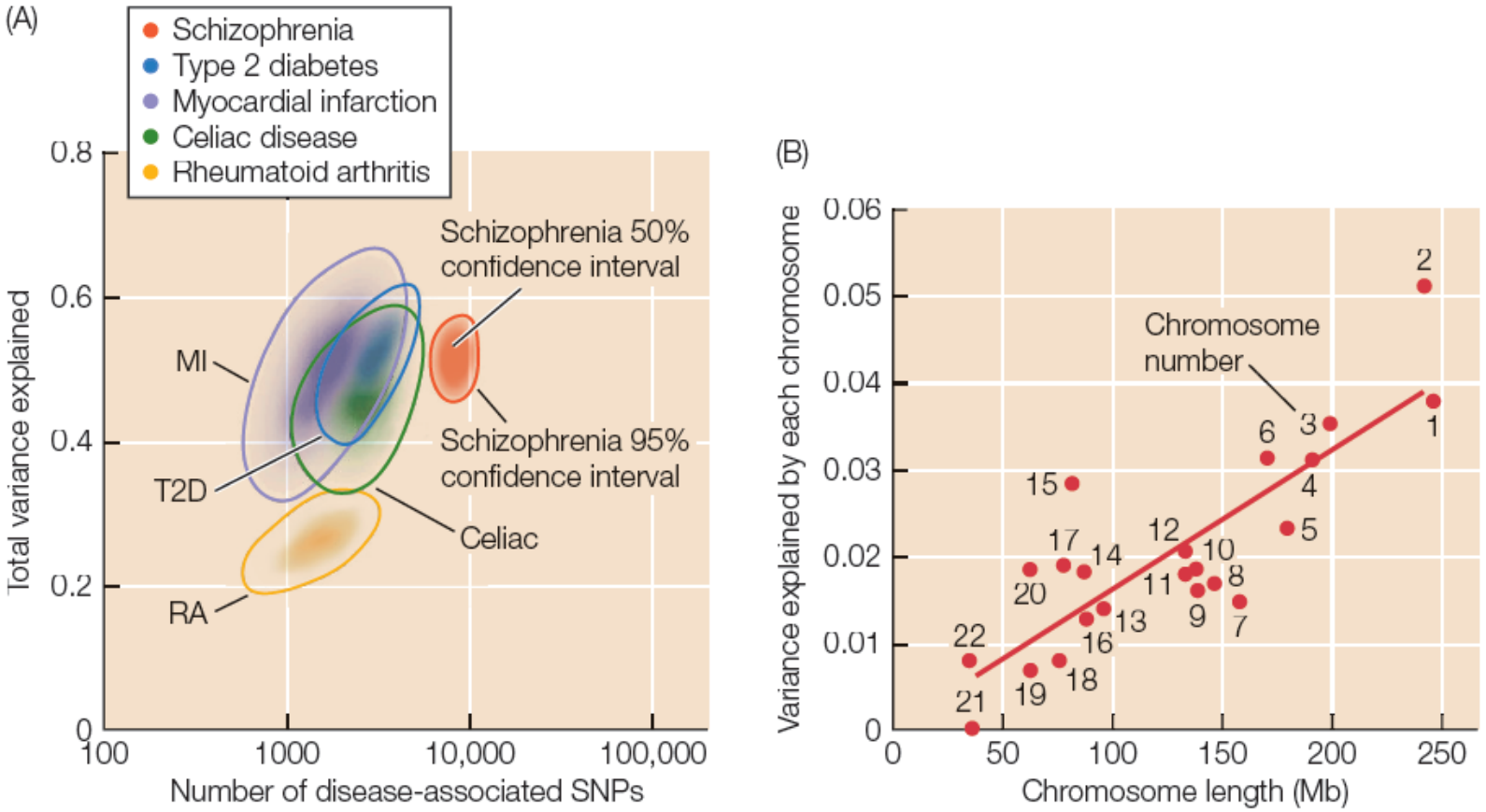
Multiplicative Rare Alleles of Major Effect



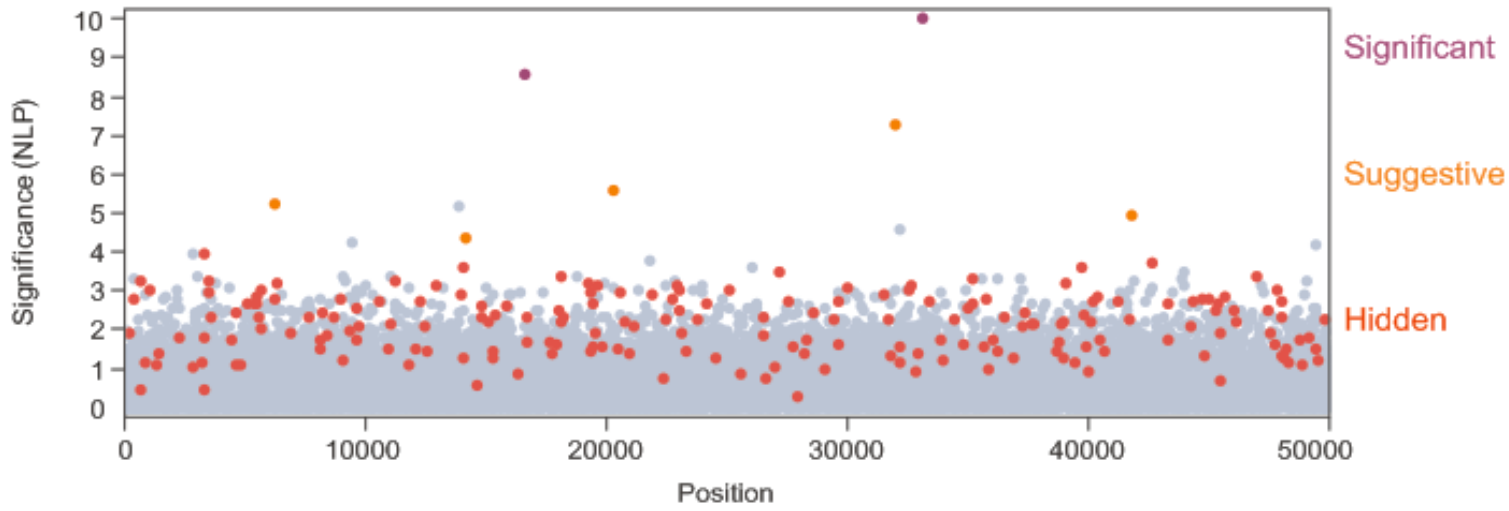
Assume there are 100 mutations at 1% frequency, each of which increases the risk of disease 2.5-fold over a baseline environmental risk of 1%.

Whence 0 alleles have a risk of 1%, 1 of 2.5%, 2 of 6%, 3 of 15%, 4 of 39%, 5 or more is highly penetrant.

The Infinitesimal Model Triumphs – for now



The Complexity of Disease Risk



The missing heritability problem is that variants discovered by GWAS only explain a minor fraction of the expected heritability. This may be because:

- The effect sizes are much smaller than previously thought (GRR 1.1 rather than 2)
- Narrow sense heritability has been over-estimated in pedigree studies
- It is rare, not common, variants, that contribute most of the variation
- Epigenetic inheritance accounts for much of the resemblance among relatives
- Broad sense heritability is prevalent, but hard to detect
- Genotyping chips do not tag causal variants effectively enough