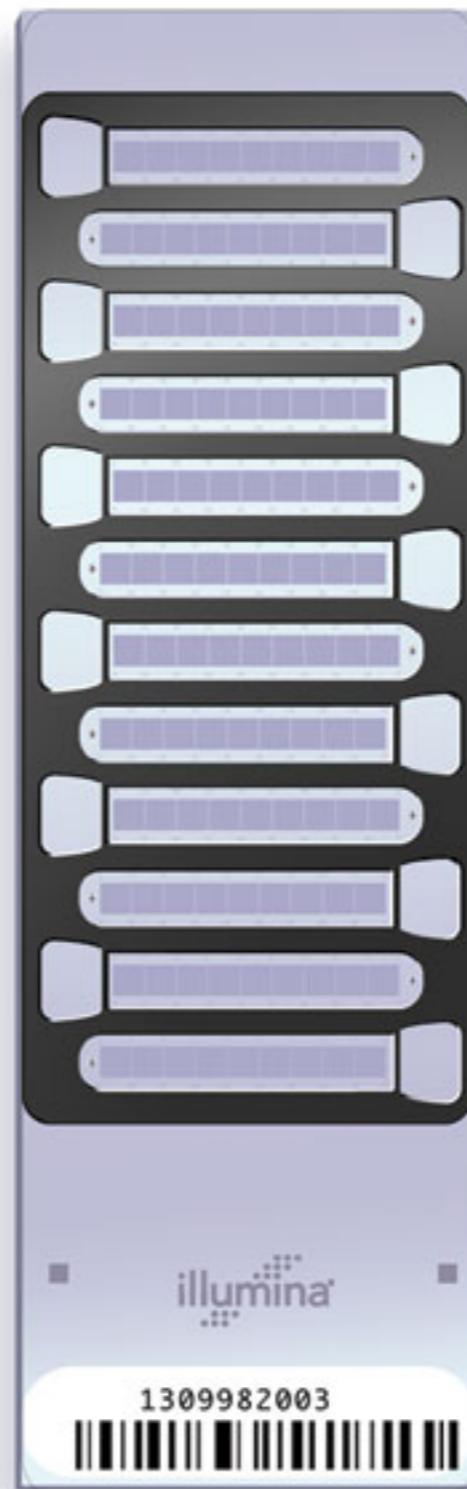


Human variation and allele frequency spectrum

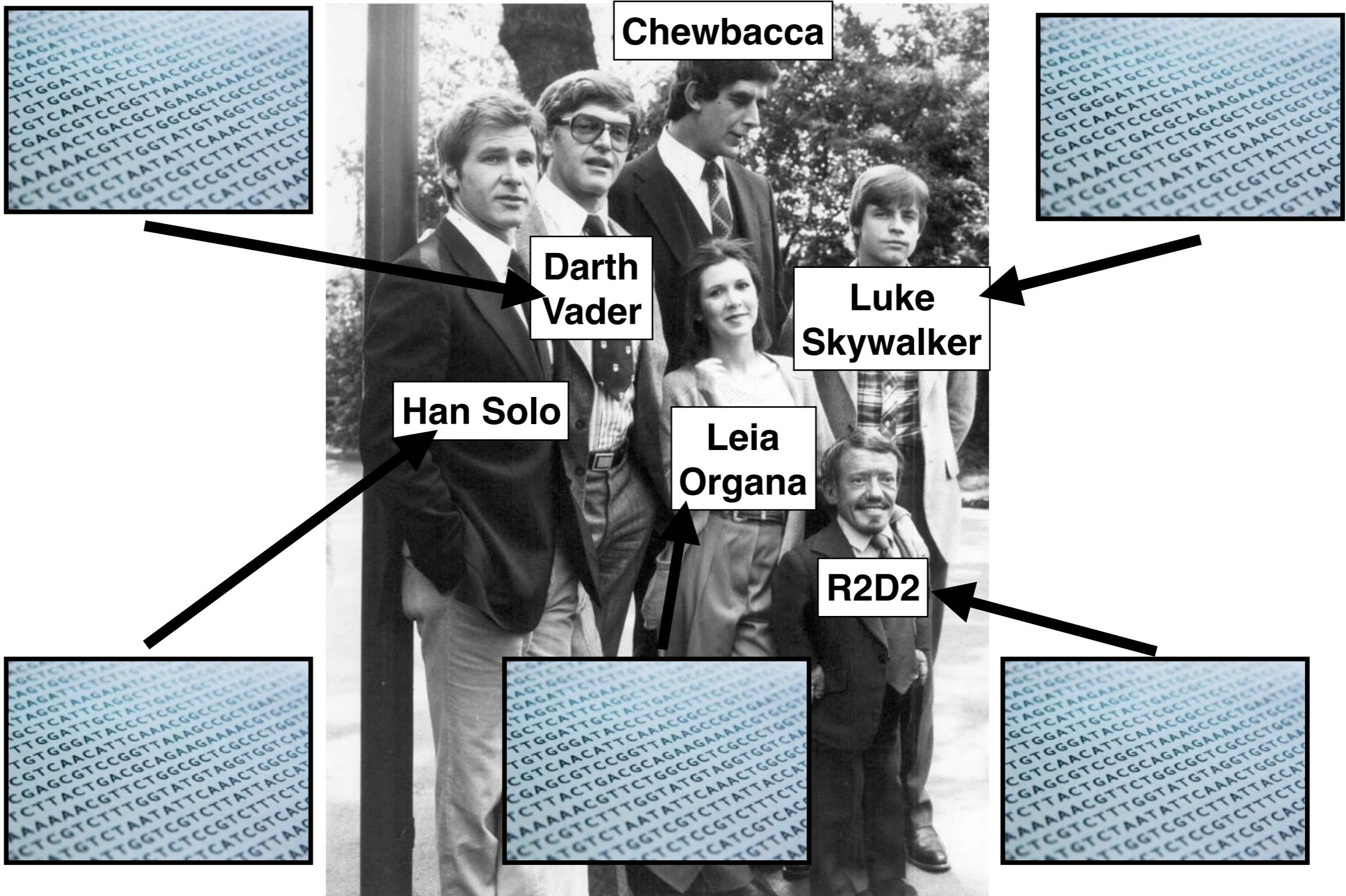


An array to genotype at >4.3 million sites

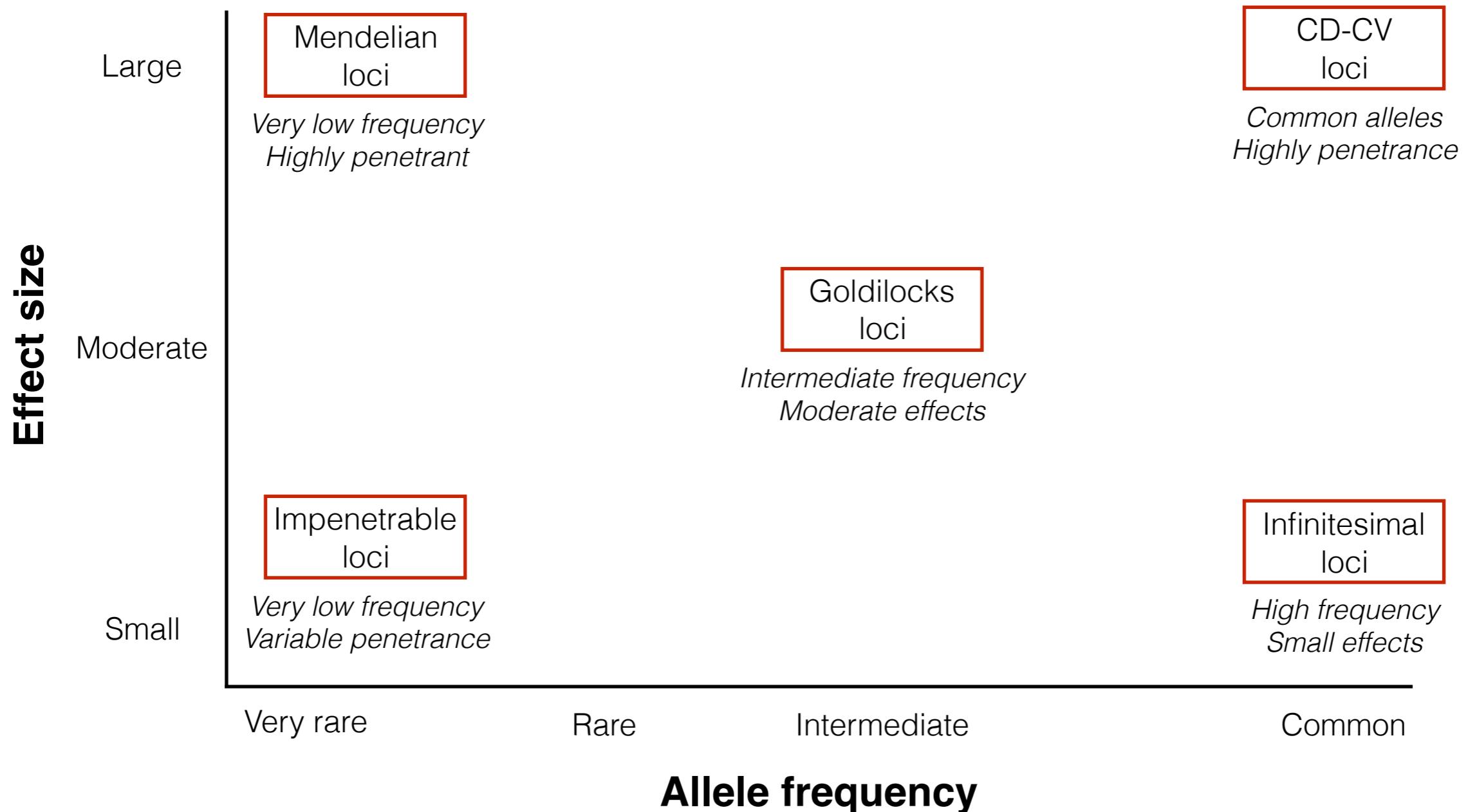


Tool to genotype intermediate and common variation

We want to be able to read genomes and make predictions



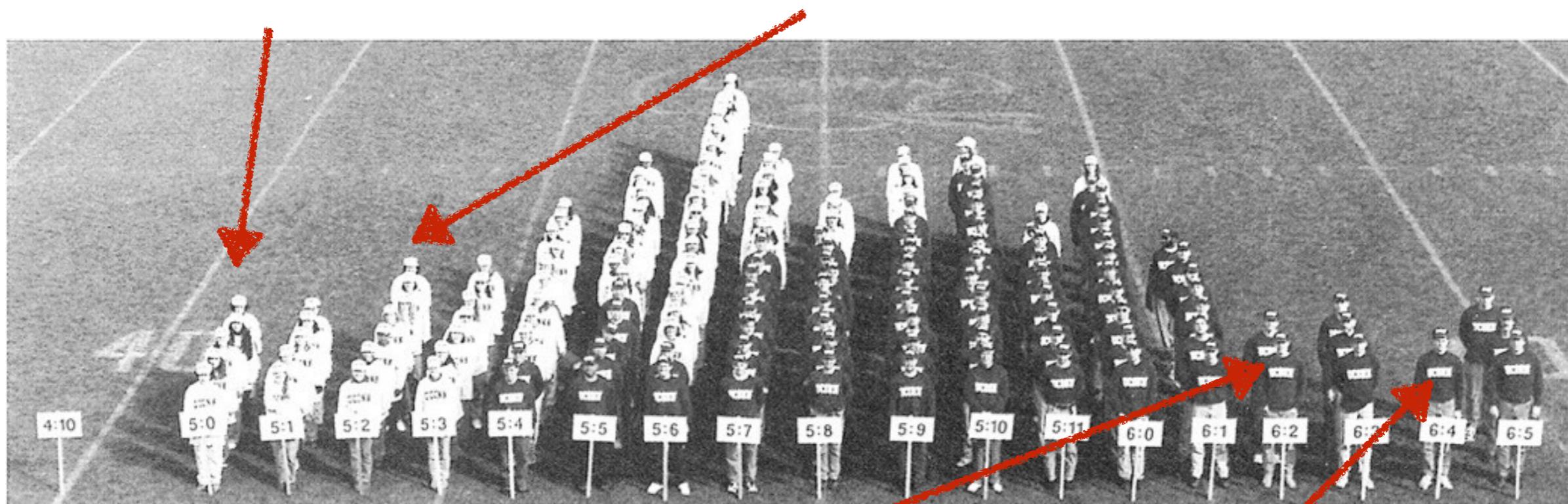
The spectrum of how variation contributes to disease



How do we find the variants that cause common disease?

To find genes in humans, we must correlate genotype with phenotype

CAGCGATAGGCTTAATGTT	CAGCGATAGGCTTAATGTT
AGCCC G T T T <u>T</u> ATGACCAACG	AGCCC G T T T <u>T</u> ATGACCAACG
GGGTTCACAGTGAGCTGTGT	GGGTTCACAGTGAGCTGTGT

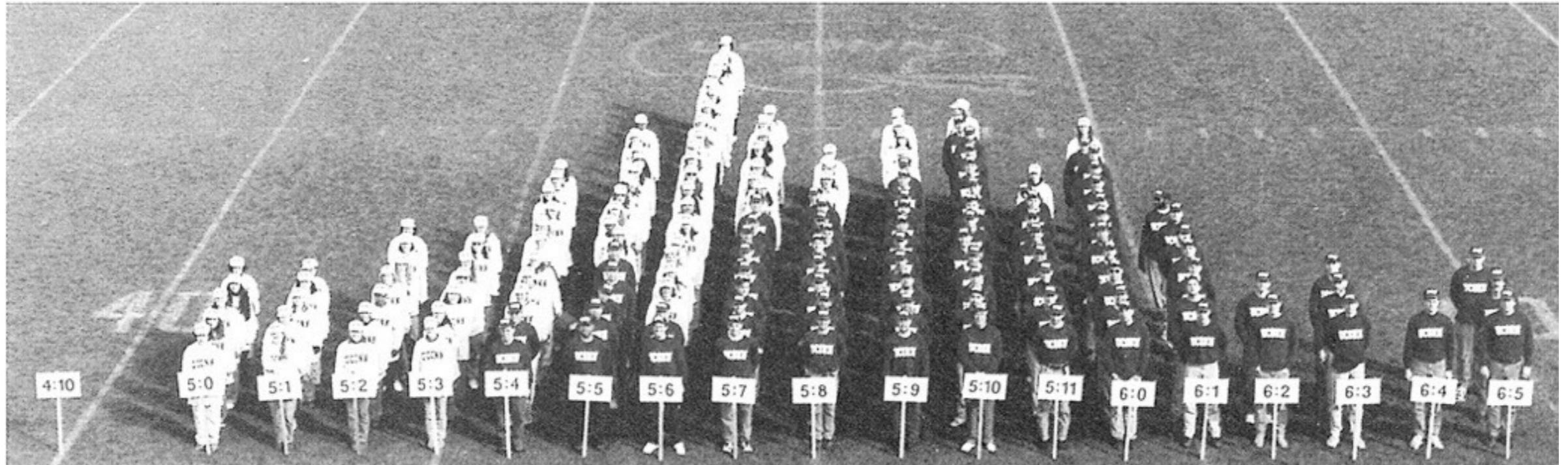


University of Connecticut, 1997

CAGCGATAGGCTTAATGTT
AGCCC G T T T <u>G</u> ATGACCAACG
GGGTTCACAGTGAGCTGTGT

CAGCGATAGGCTTAATGTT
AGCCC G T T T <u>G</u> ATGACCAACG
GGGTTCACAGTGAGCTGTGT

For traits controlled by many genes, we need many, many people

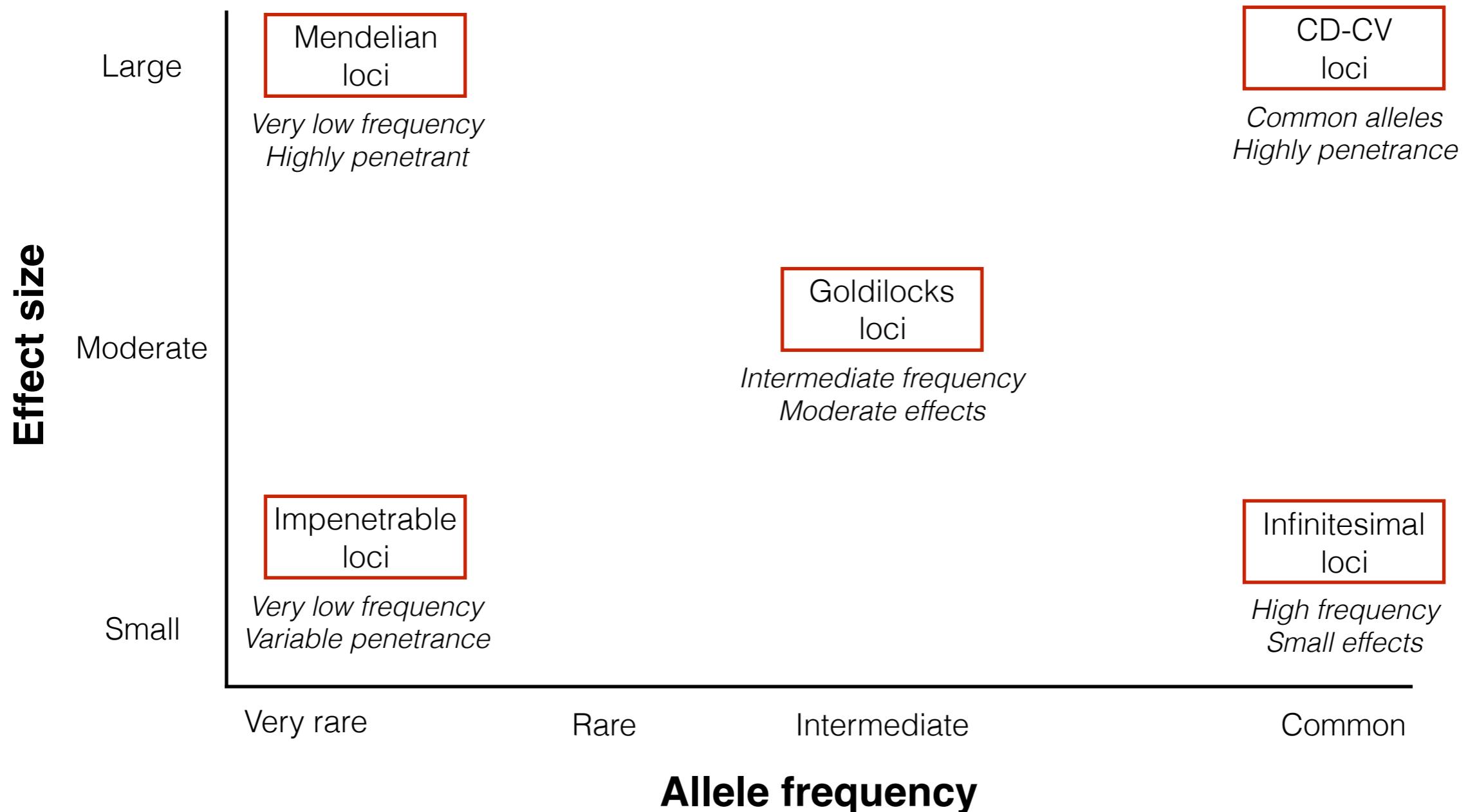


University of Connecticut, 1997

Variation shared by lots of tall people
and not shared by lots of short people

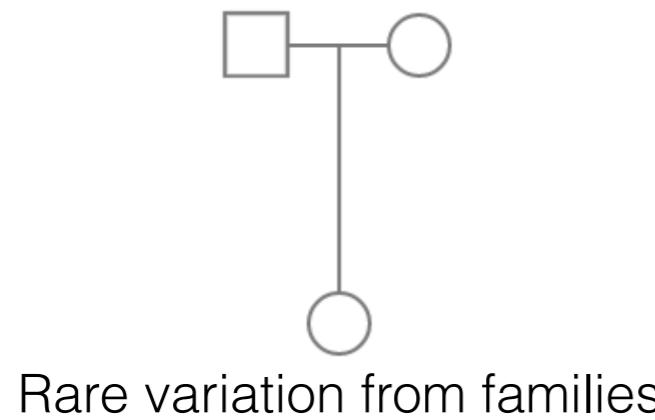
~700,000 people genotyped led to 60%
of height differences explained

The spectrum of how variation contributes to disease

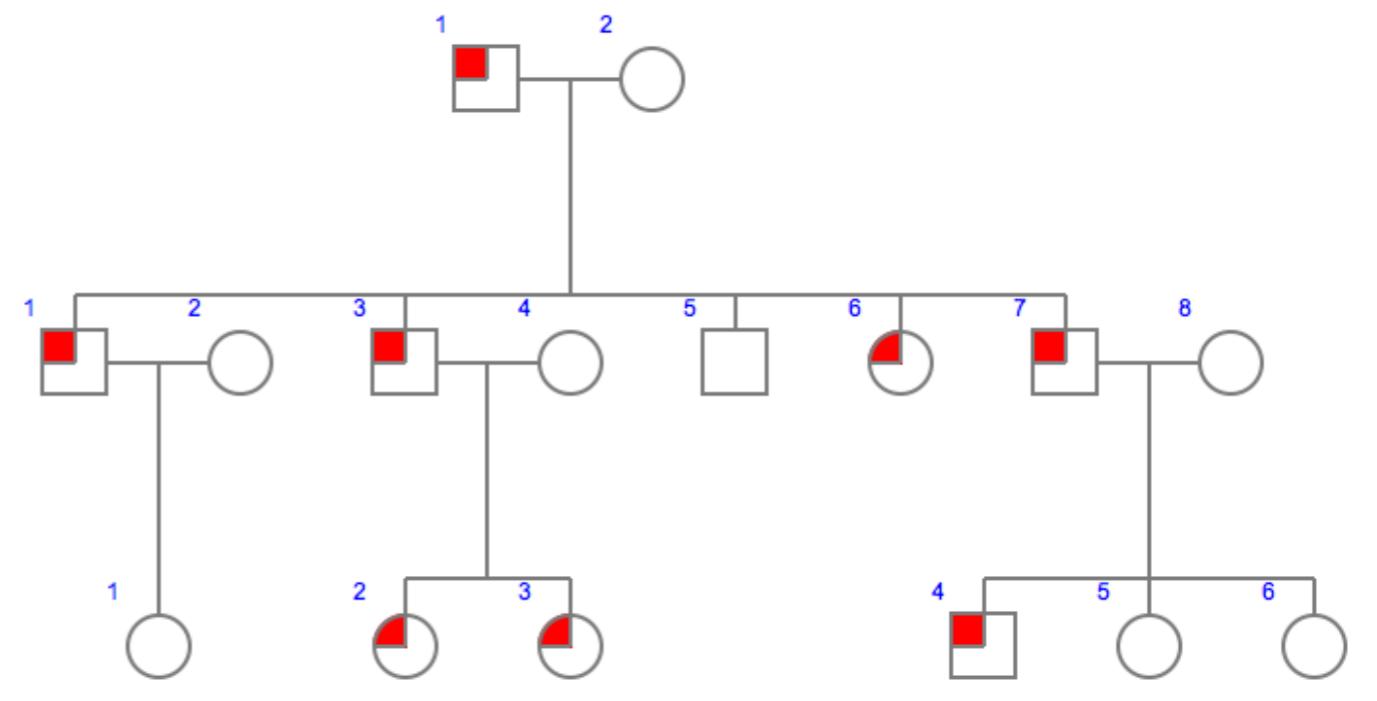


How do we find the variants that cause rare disease?

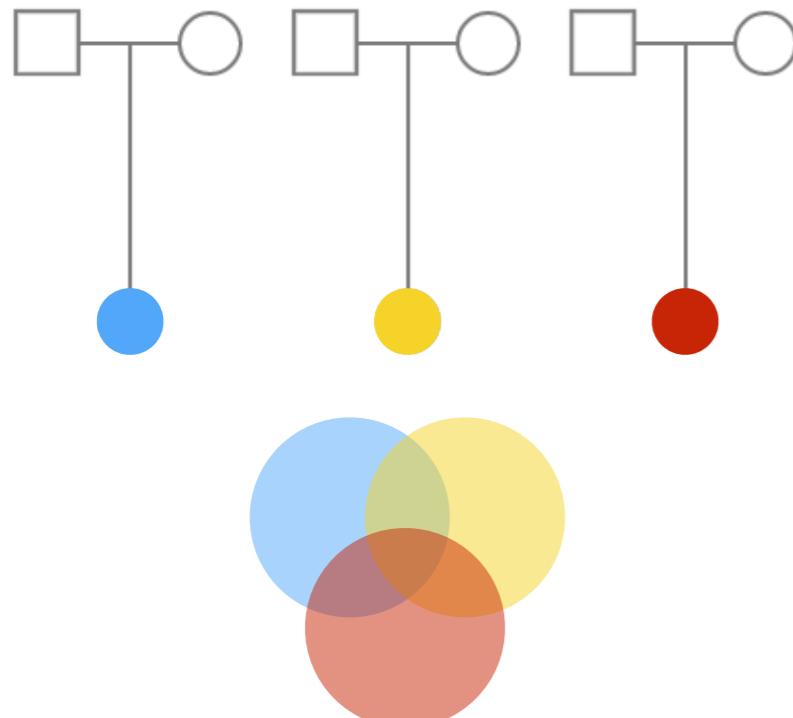
Strategies to identify disease-causing rare variants



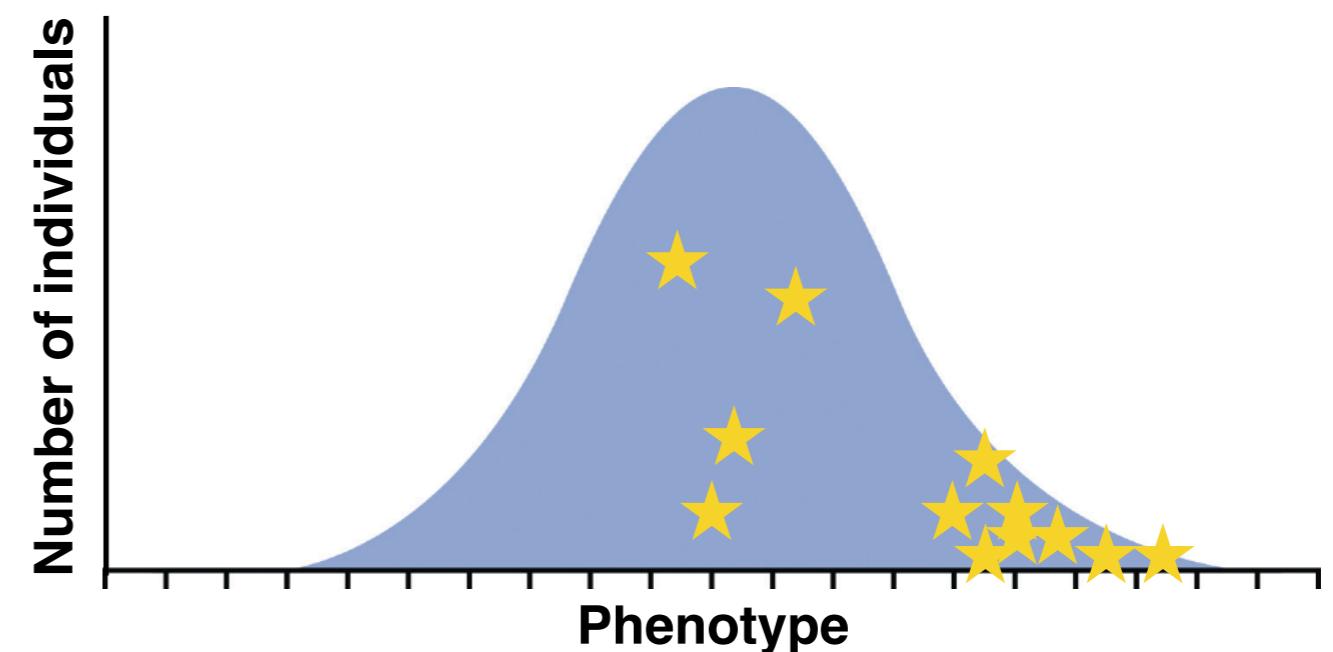
Rare variation from families



Shared variants from affected individuals in large families

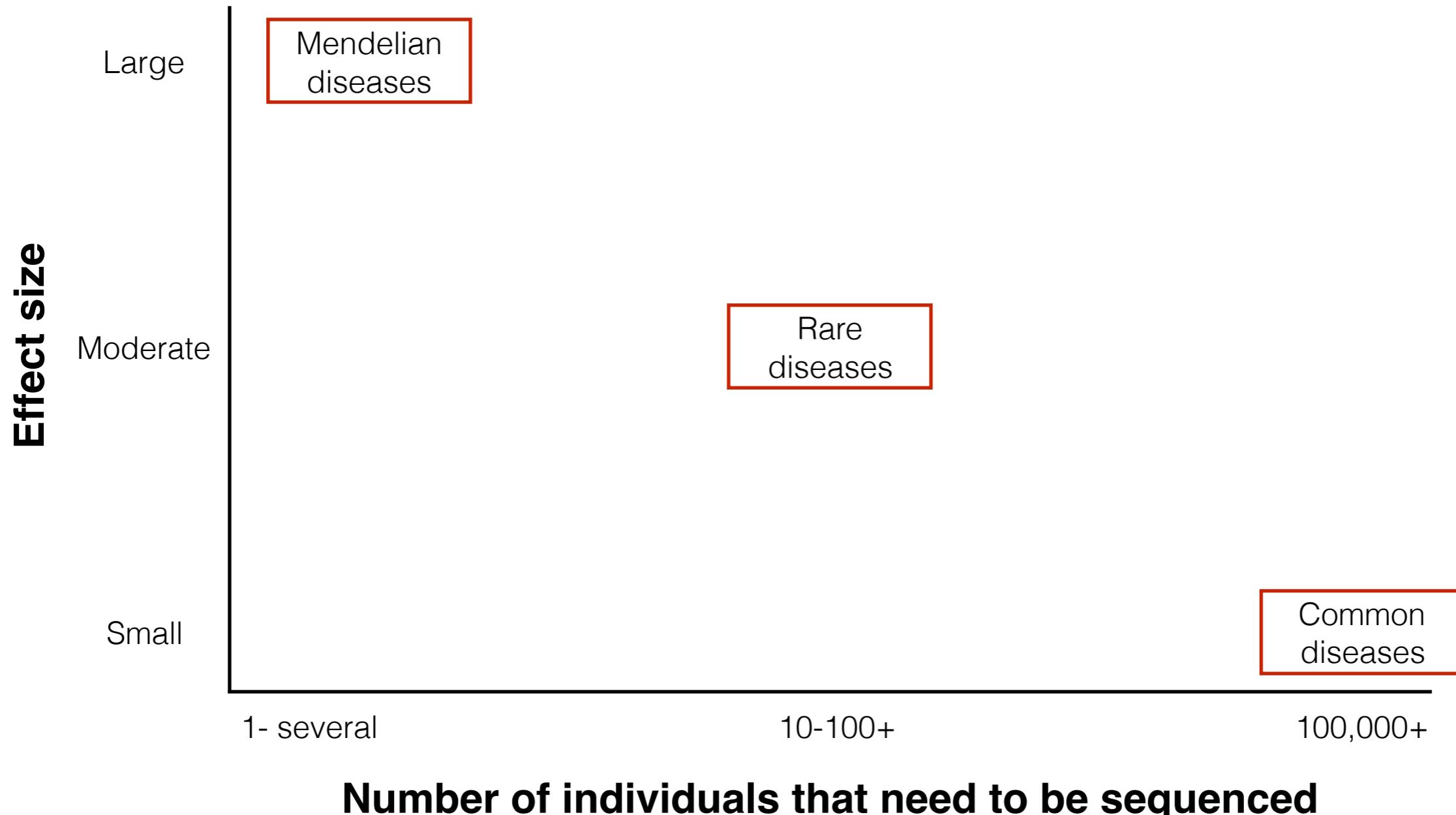


Shared variation from trios



Shared variants from many people

How can sequencing help us to identify these variants?



Why can't we read the genome?



We don't know all the variants.

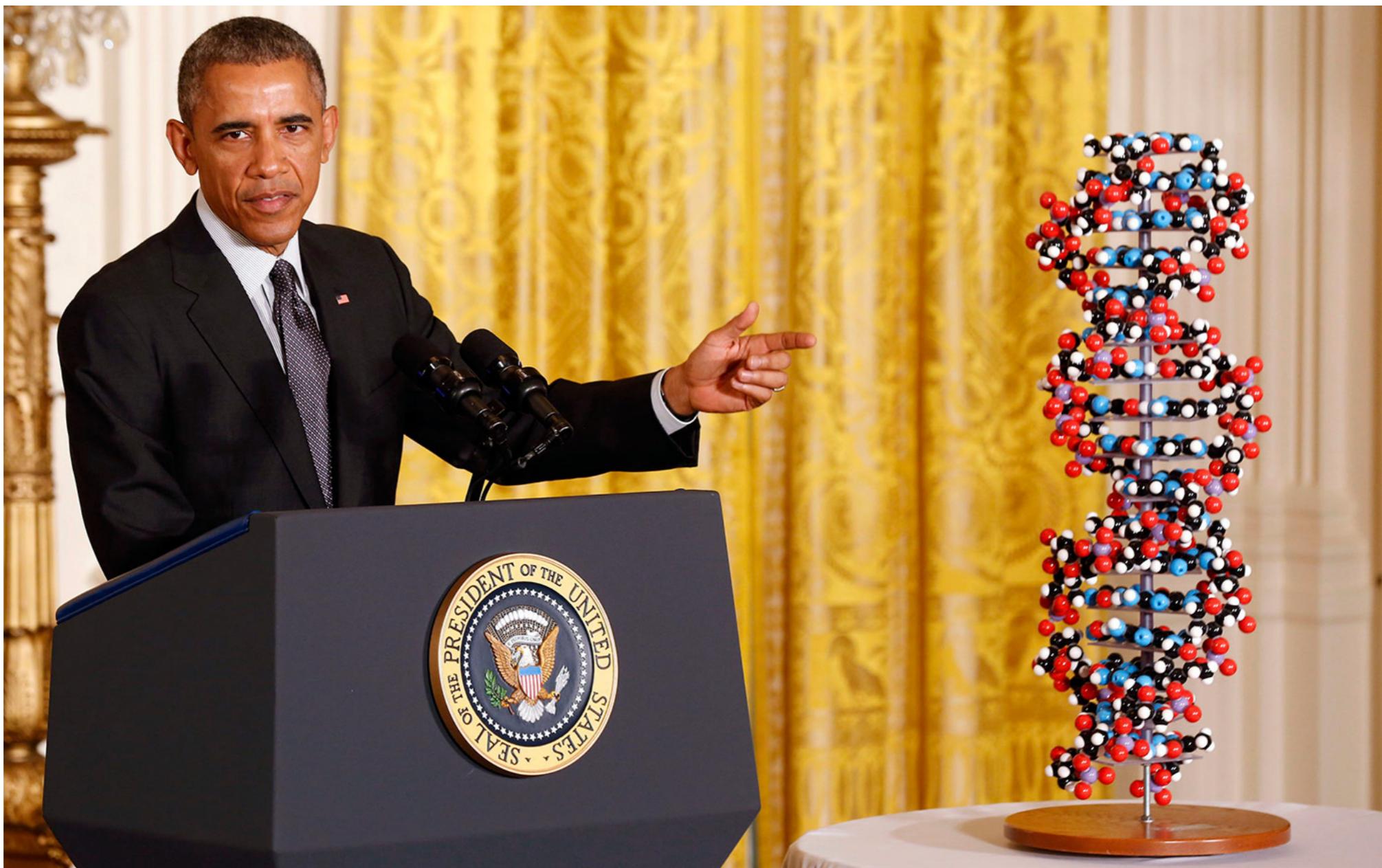
We don't know which ones affect phenotype.

Single genes don't cause most disease or control most traits

The human genome is big.

Phenotypes are highly variable.

What is precision medicine?

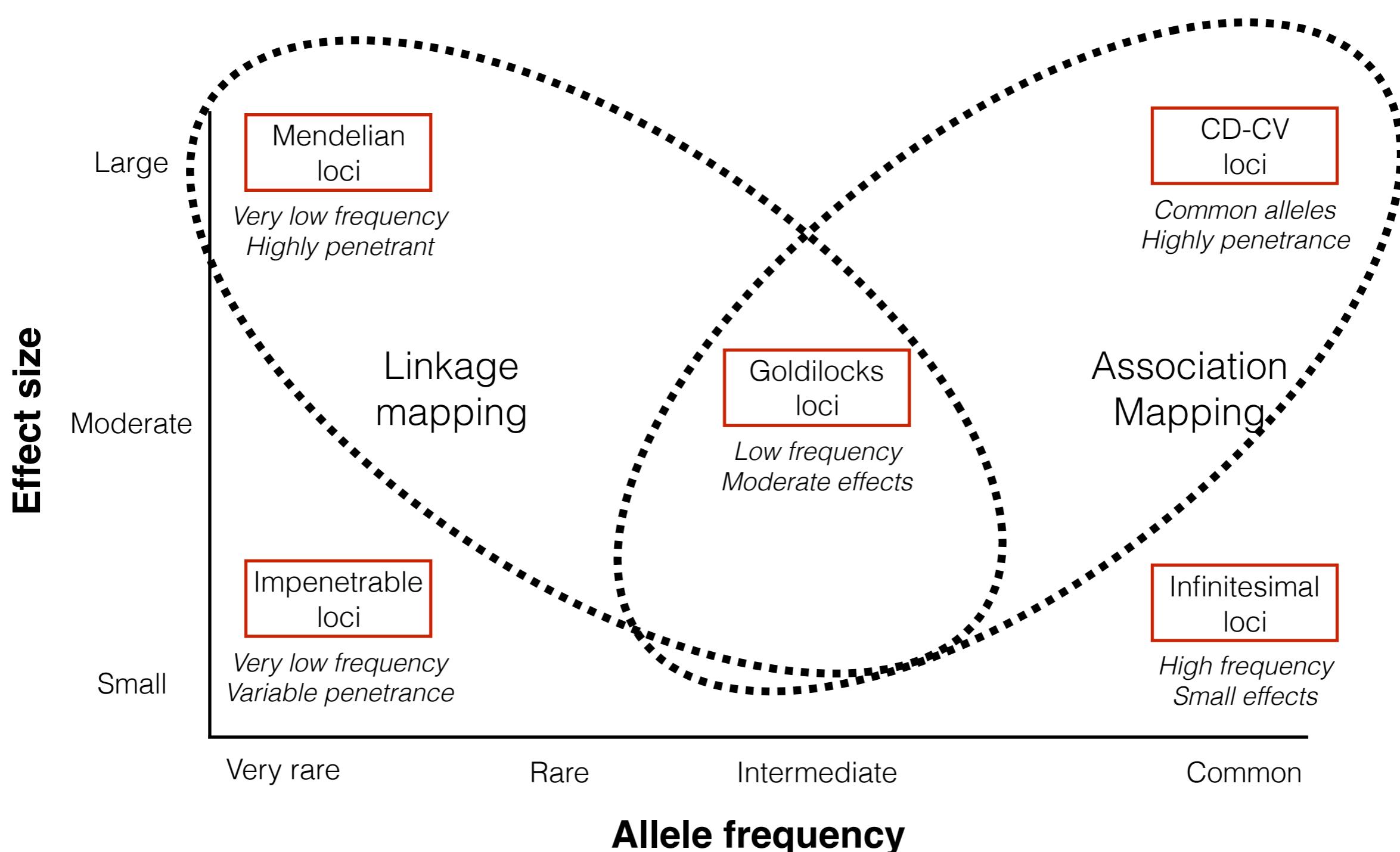


We are living in the human genetics renaissance



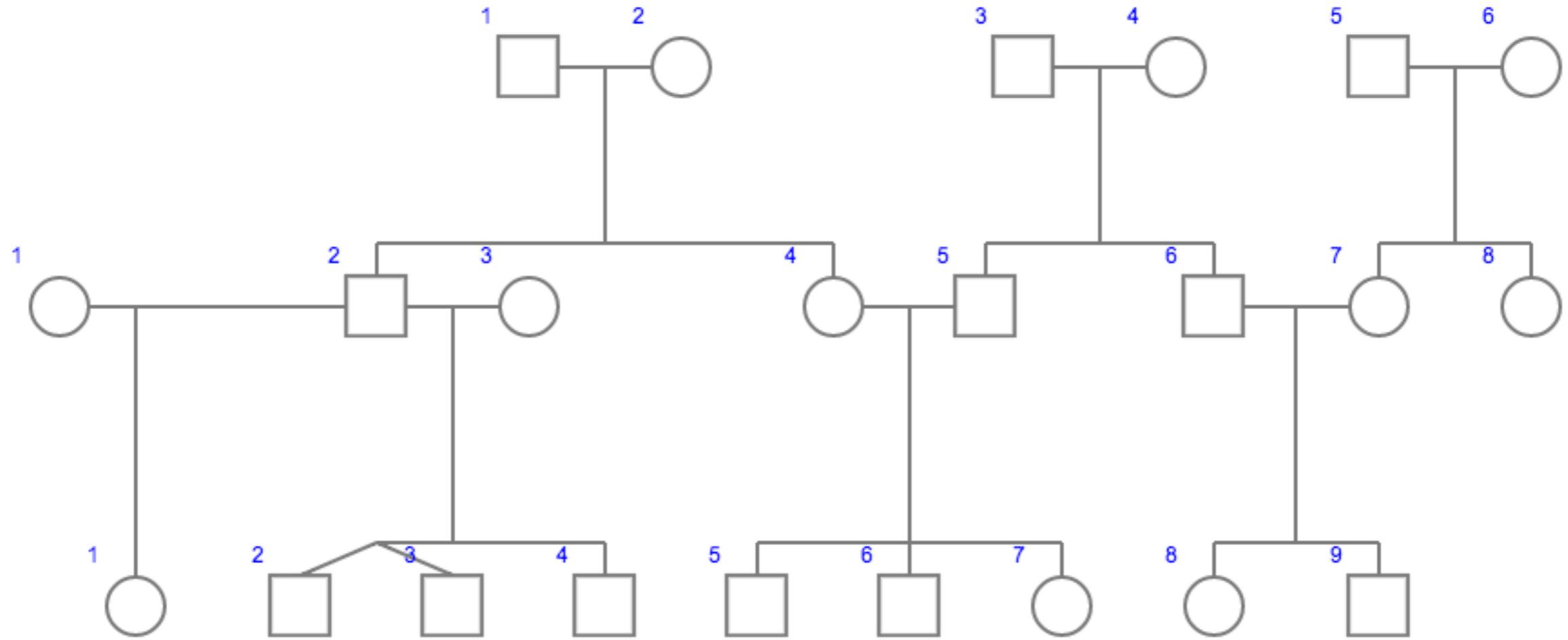
Under \$1000 genome
Rare disease sequencing for Mendelian disorders
Family genetics
Fetal testing from sequence
Disease outbreaks and diagnosis
Drug response prediction
Cancer genome sequencing

The spectrum of how variation contributes to disease



Linkage mapping studies or family-based mapping studies

Why do we study inheritance in families?

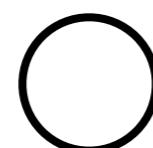


Correlating genetic variants with disease tells us the disease gene is near that variant (or is that variant)

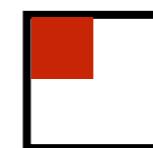
Human pedigree analysis allows us to follow traits in families



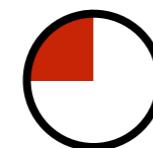
Male



Female



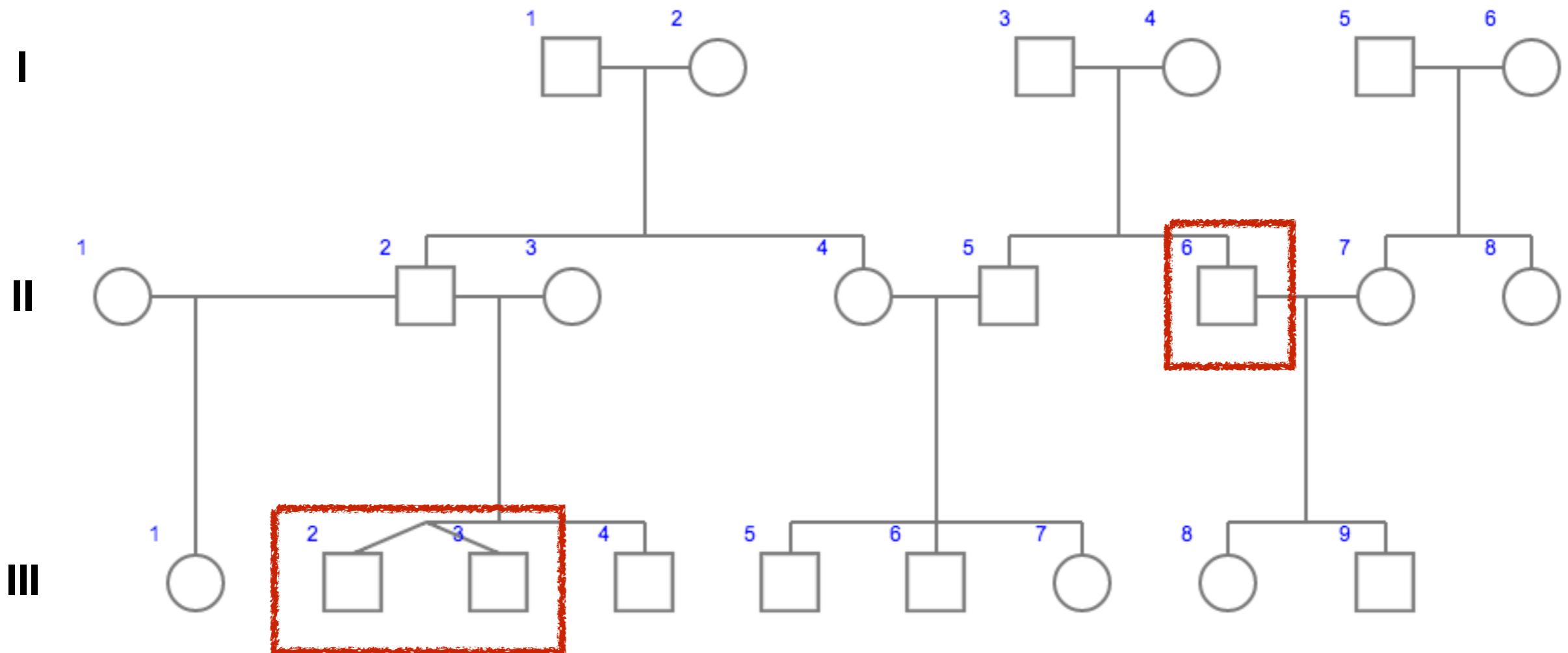
Affected male



Affected female

Remember that humans are diploid.

Human pedigree analysis allows us to follow traits in families

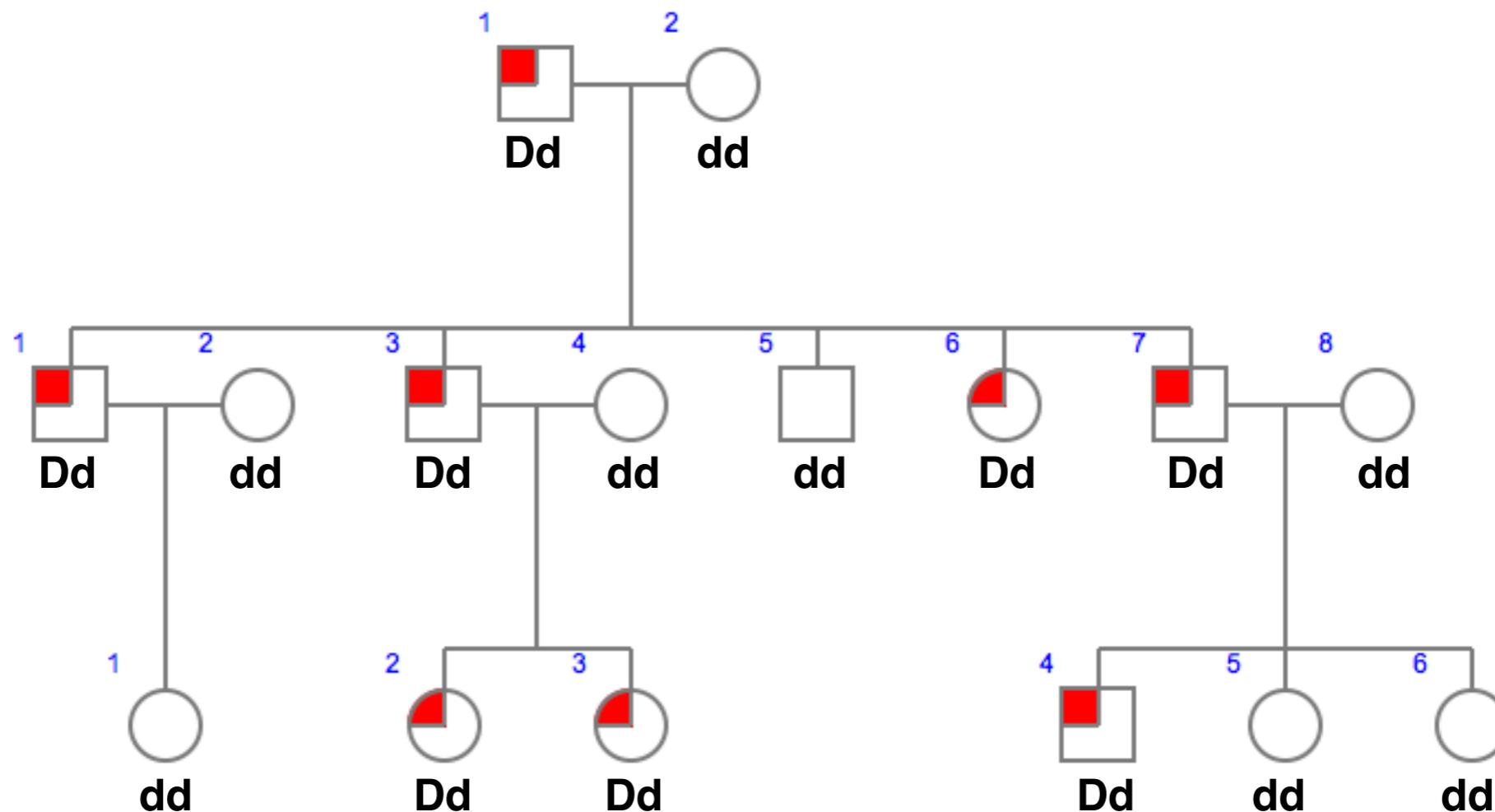


Individuals are numbered from left to right

Generations are numbered from top to bottom in Roman numerals

Most diseases are rare, individuals breeding into families are usually unaffected

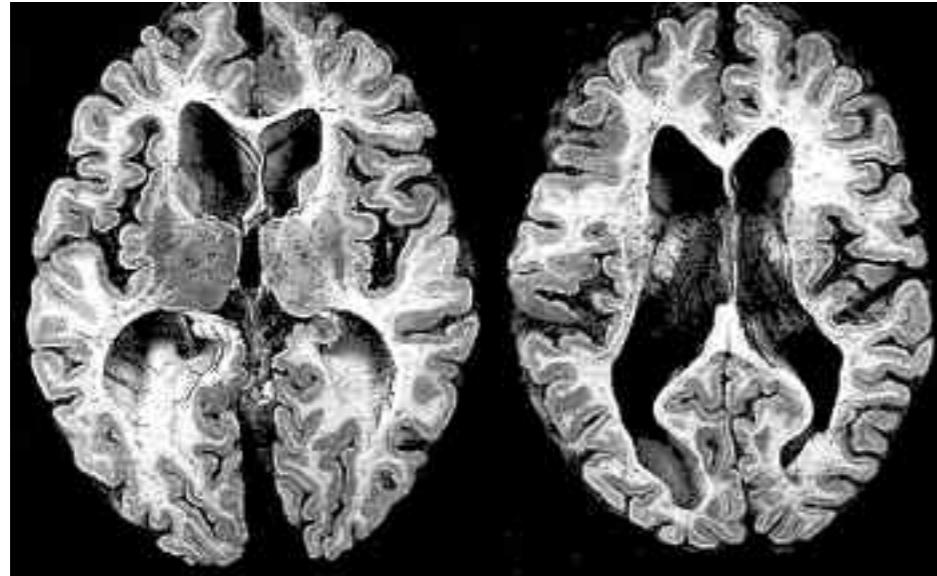
Modes of inheritance



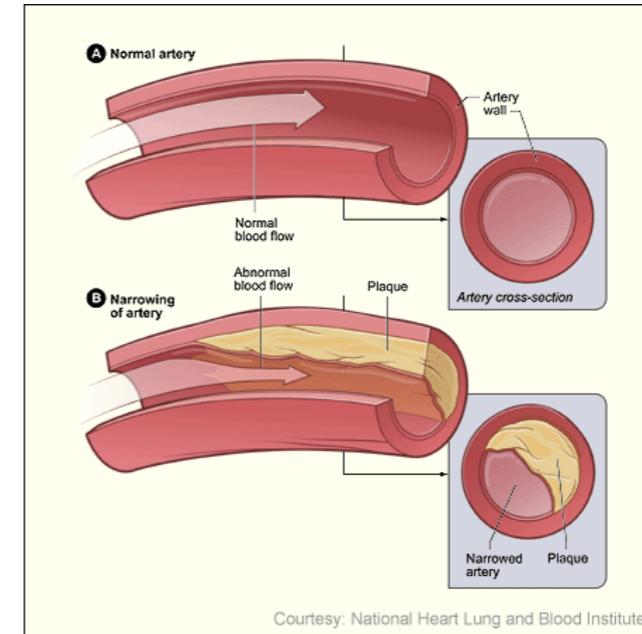
- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Autosomal dominant

Examples of human autosomal dominant disorders



Huntington's Disease
chr. 4



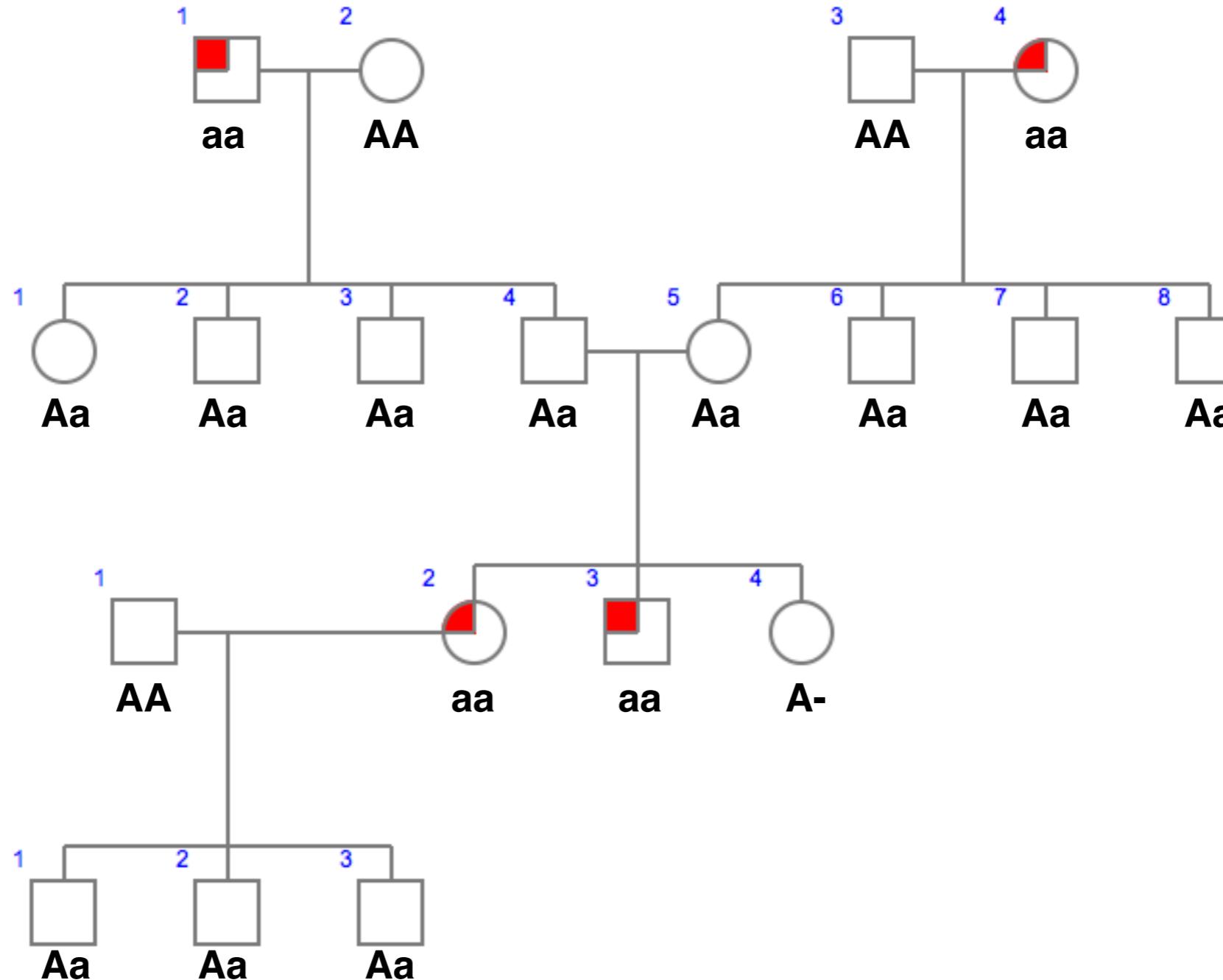
Familial Hypercholesterolemia
chr. 19

Caused by loss-of-function or gain-of-function?

Most affected individuals are heterozygotes

What is the chance that a child is affected?

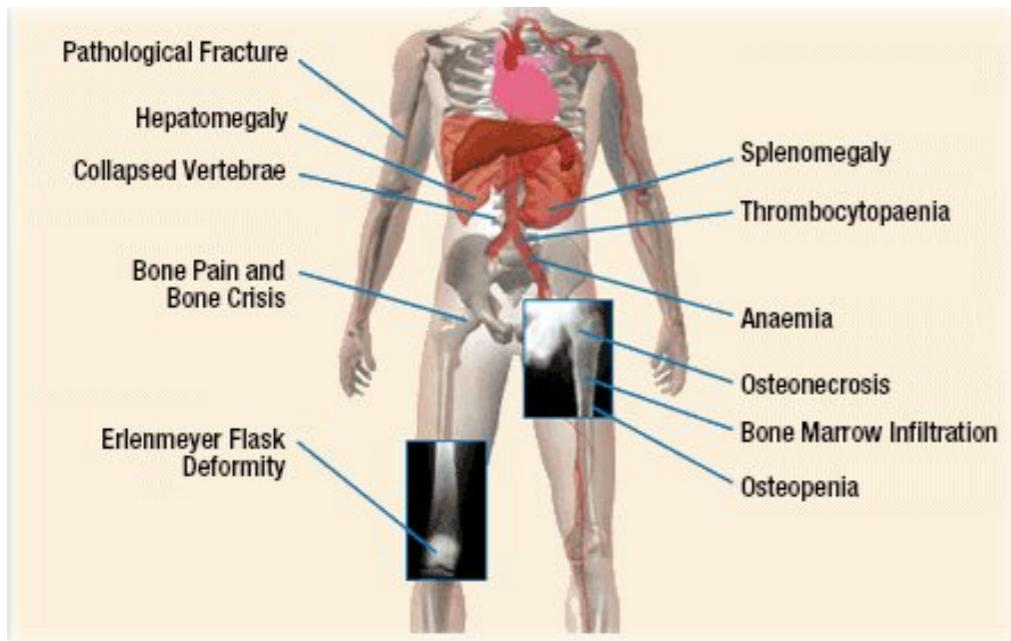
Modes of inheritance



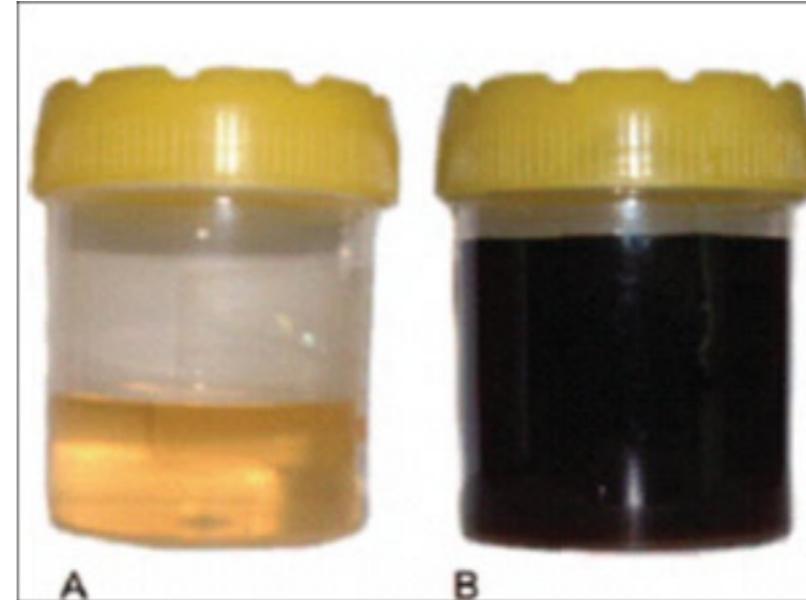
- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Autosomal recessive

Examples of human autosomal recessive disorders



Gaucher's Disease
chr. 1



Maple Syrup Urine Disease
chr. 1, 6, or 19

Caused by loss-of-function or gain-of-function?

All affected individuals are homozygotes