Bio393: Genetic Analysis

Human variation and allele frequency spectrum

In human genetics, experiments are all *post hoc*

No controlled crosses

No defined genetic backgrounds

Large genome (haploid three gigabase pairs)

Good phenotyping!

Lots of $$$

How do we identify genes in humans?

Draft human genome announced in June 2000


The New York Times

TUESDAY, JUNE 27, 2000

tic Code of Human Life Is Cracked by Scientist

The Book of Life

A SHARED SUCC

2 Rivals' Announcem

Marks New Medic

Era, Risks and Al

It took more than 10 years and $3 billion

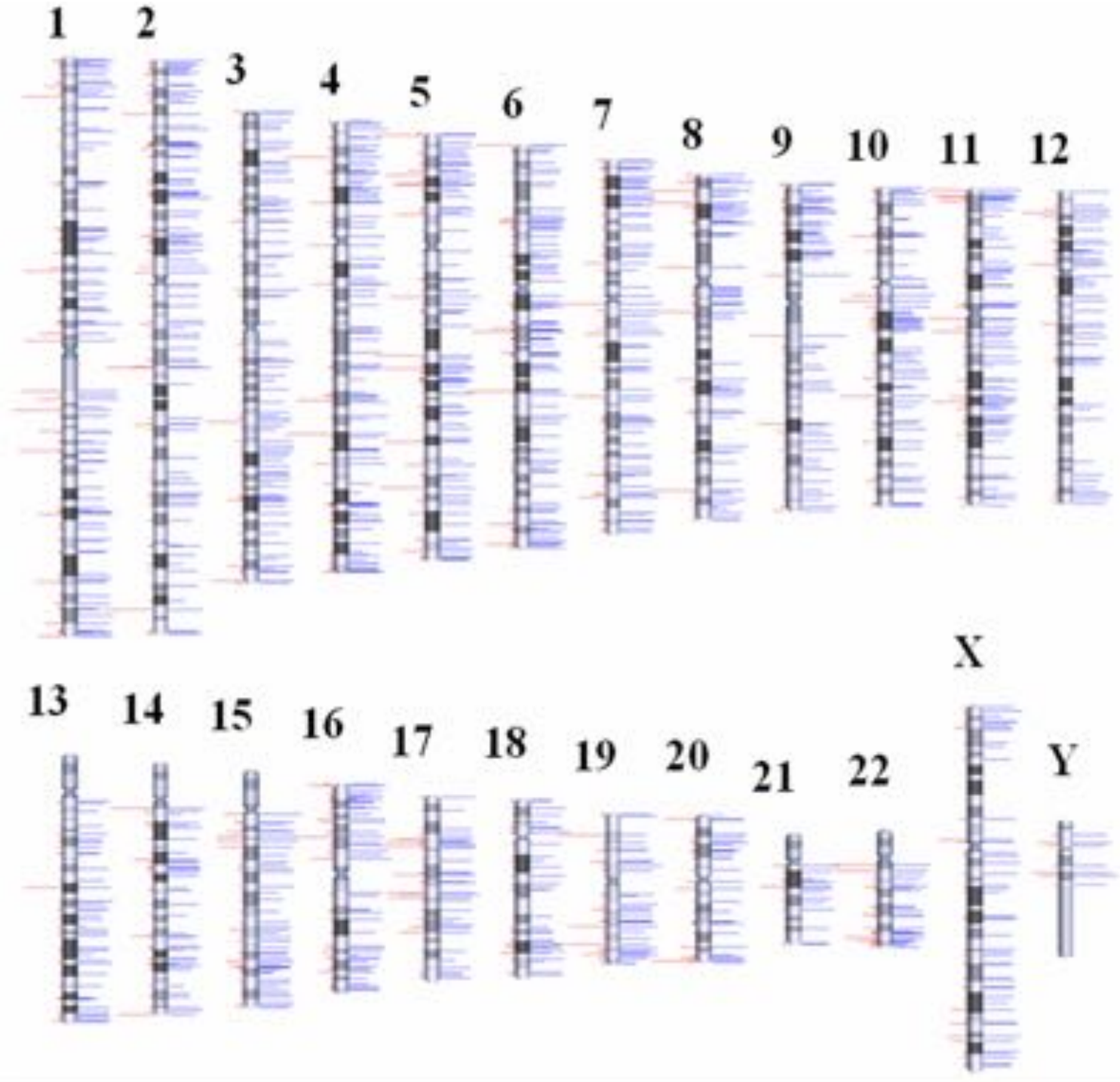
We need physical pieces of DNA to sequence

Who was sequenced?

We don’t have one human genome

Nine humans had parts of their genomes sequenced to make the first draft.

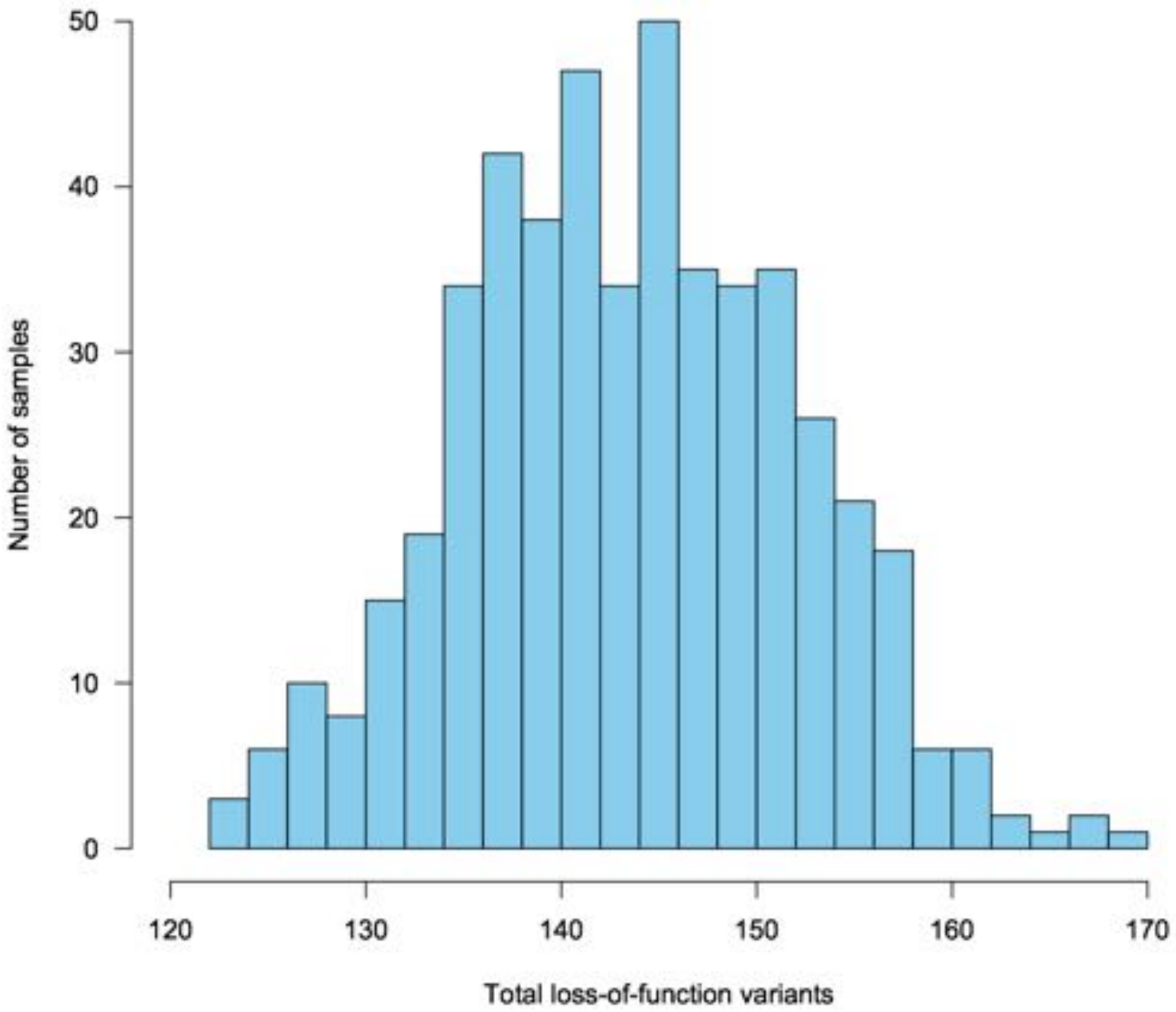
A genome sequence gives us the (incomplete) parts list



Types of variation

Rare = variants found in less than 1% in population

We each have over 100 unique loss-of-function rare variants



Francioli *et al.* 2014 Nature Genetics

Over 3,000 rare diseases have a known underlying genetic cause

One in twelve people have a rare disease

Compound heterozygosity underlies many diseases

Types of variation

Rare = variants found in less than 1% in population

Common = variants found in more than 5% of the population

Intermediate = variants found in 1-5% of the population

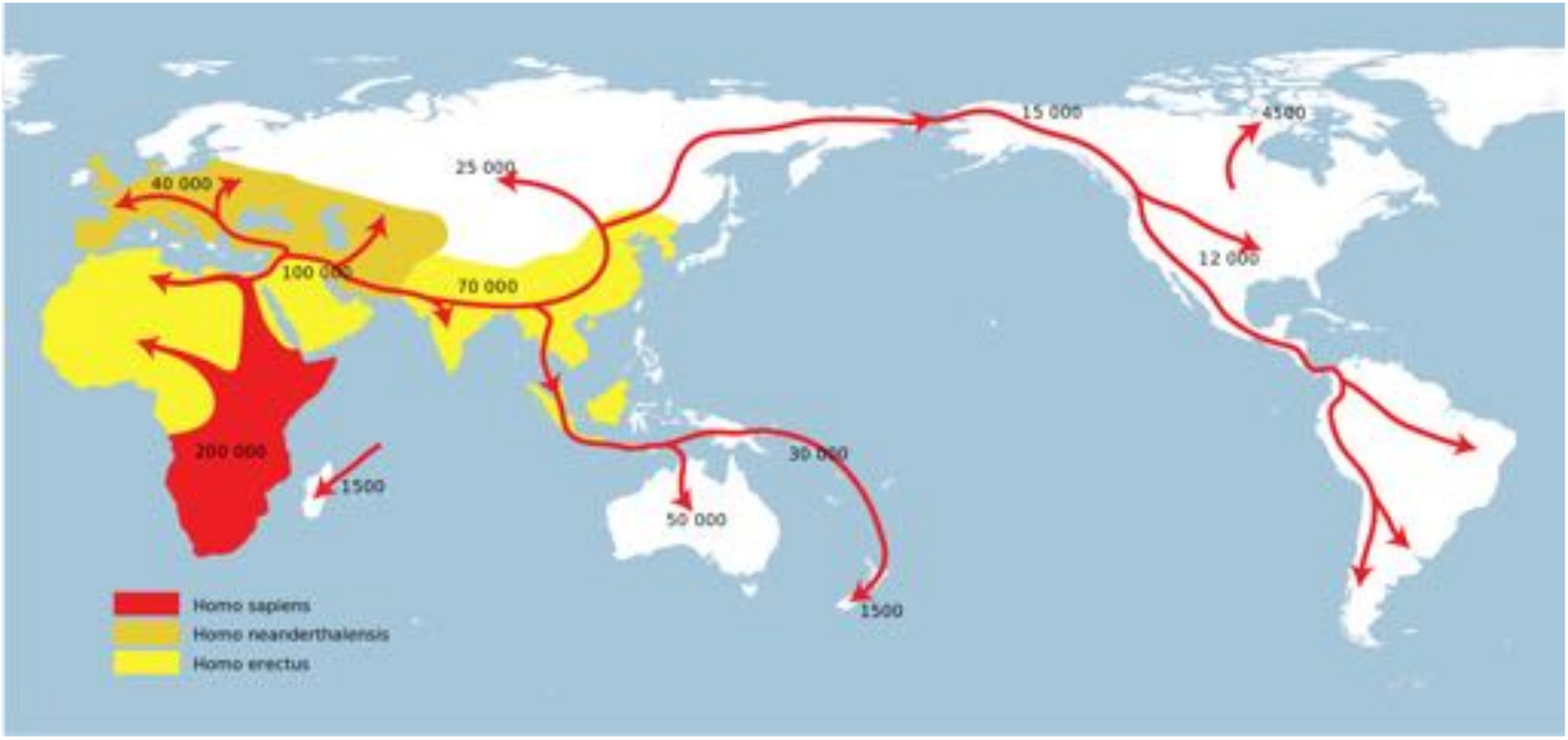
Where does variation come from?

Random errors in replication, transcription, DNA repair, etc.

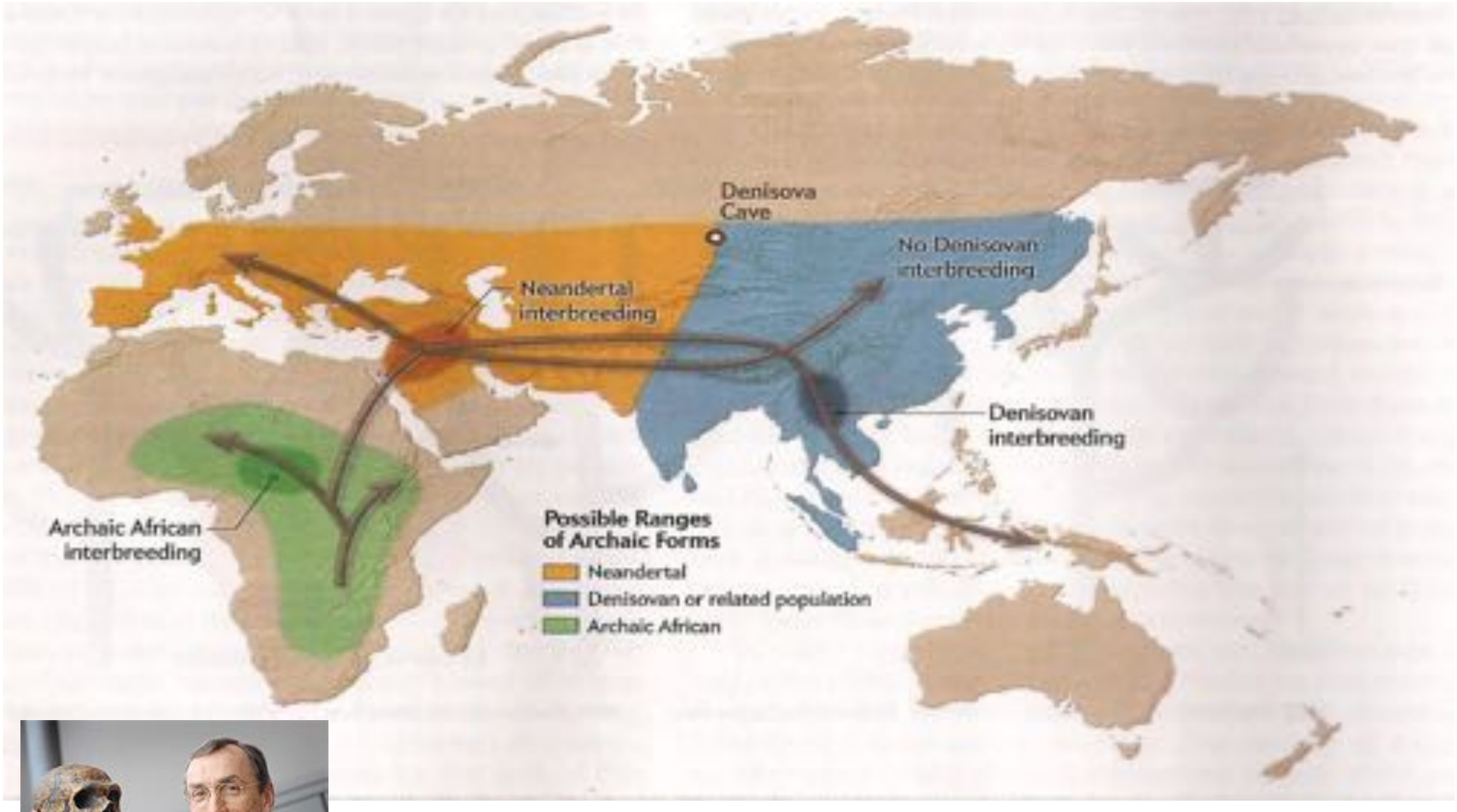
Somatic or germline errors

Once generated, germline variants are inherited

Human history drives our genetics

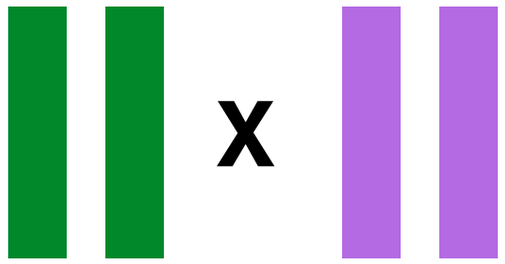


Human history drives our genetics



Svante Pääbo

H. neanderthalensis



H. sapiens

50%

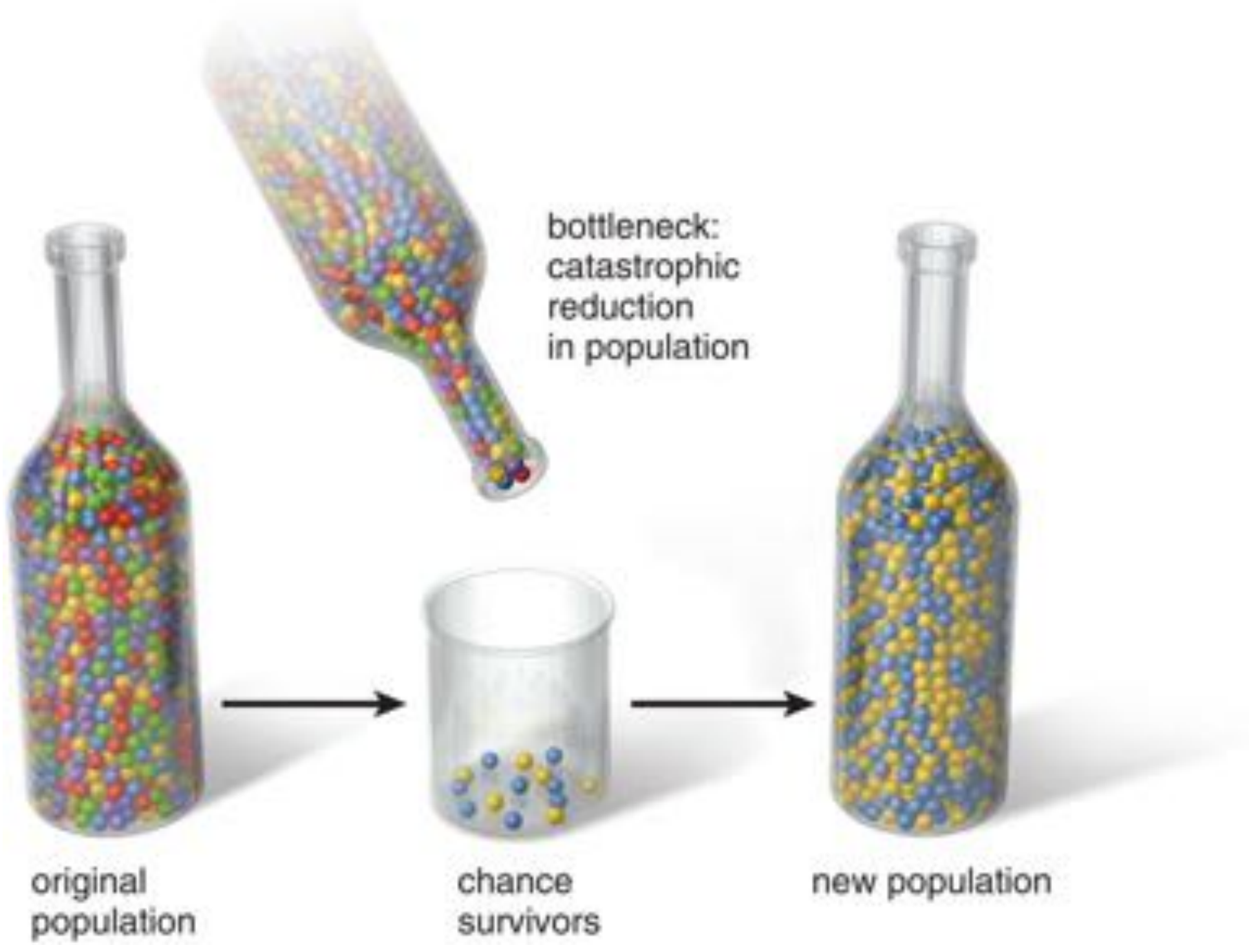
25%

12.5%

6.25%

3.125%

Human history drives our genetics



The common disease - common variant (CD-CV) hypothesis

Diseases shared by lots of people
will be caused by variants shared by those same people

How do we find all these common variants?

To find common variants, we need markers shared by lots of people

Goal is to find all the common variants

After the HGP, the HapMap project was born.

All three types of variation can cause disease

Rare = variants found in less than 1% in population

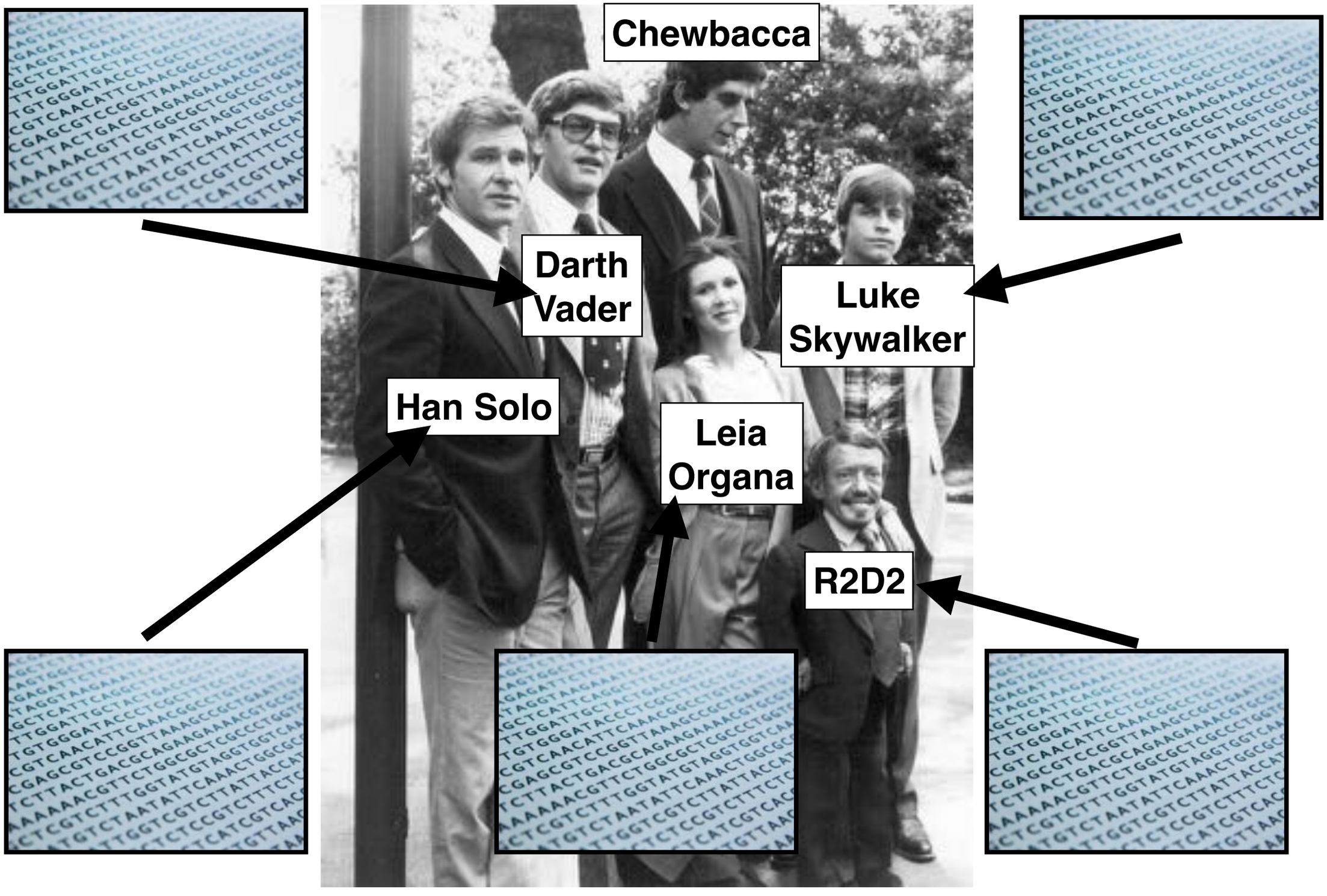
Common = variants found in more than 5% of the population

Intermediate = variants found in 1-5% of the population

An array to genotype at >4.3 million sites

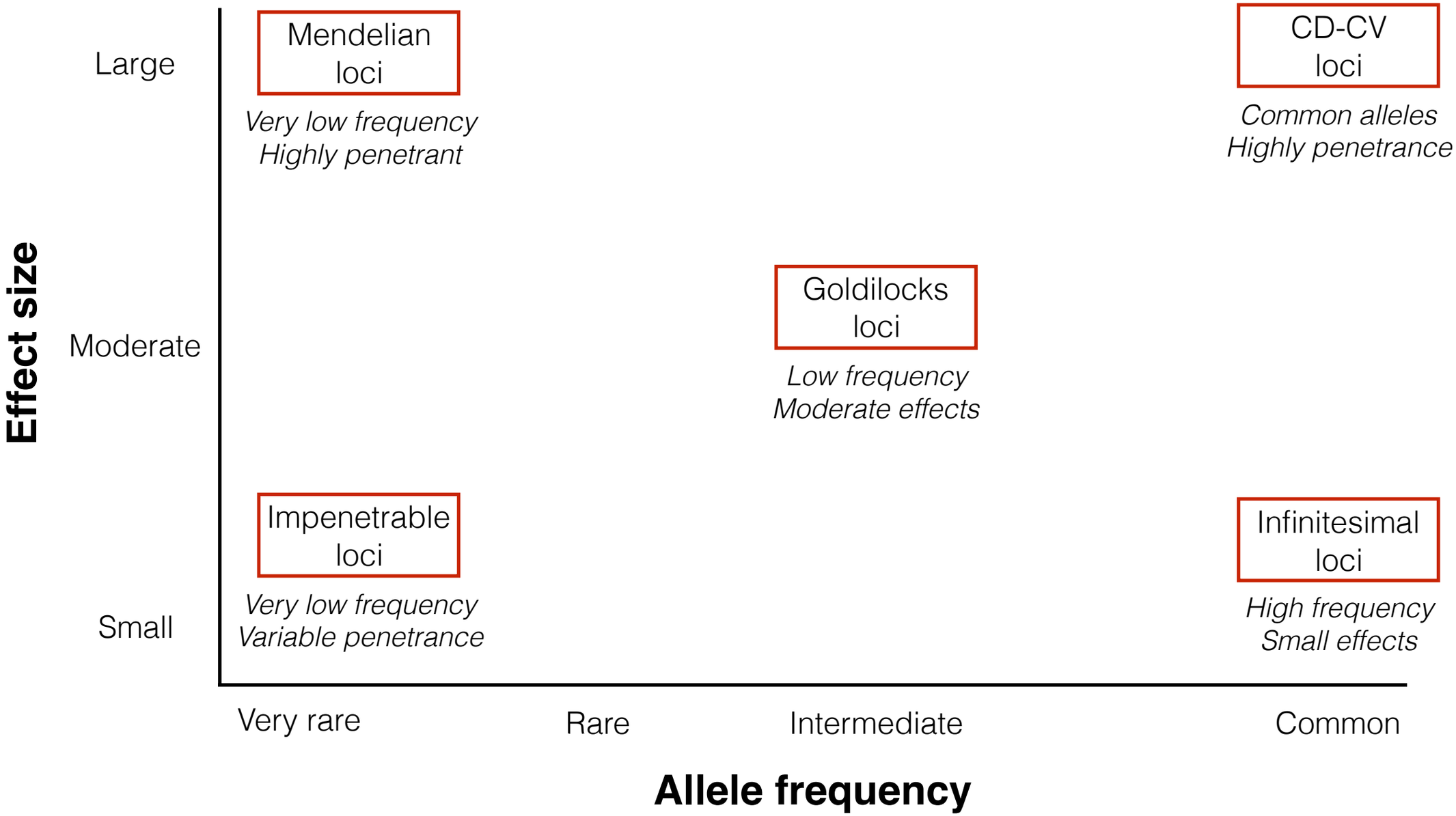
Tool to genotype intermediate and common variation

We want to be able to read genomes and make predictions



The cast of the original *Star Wars*

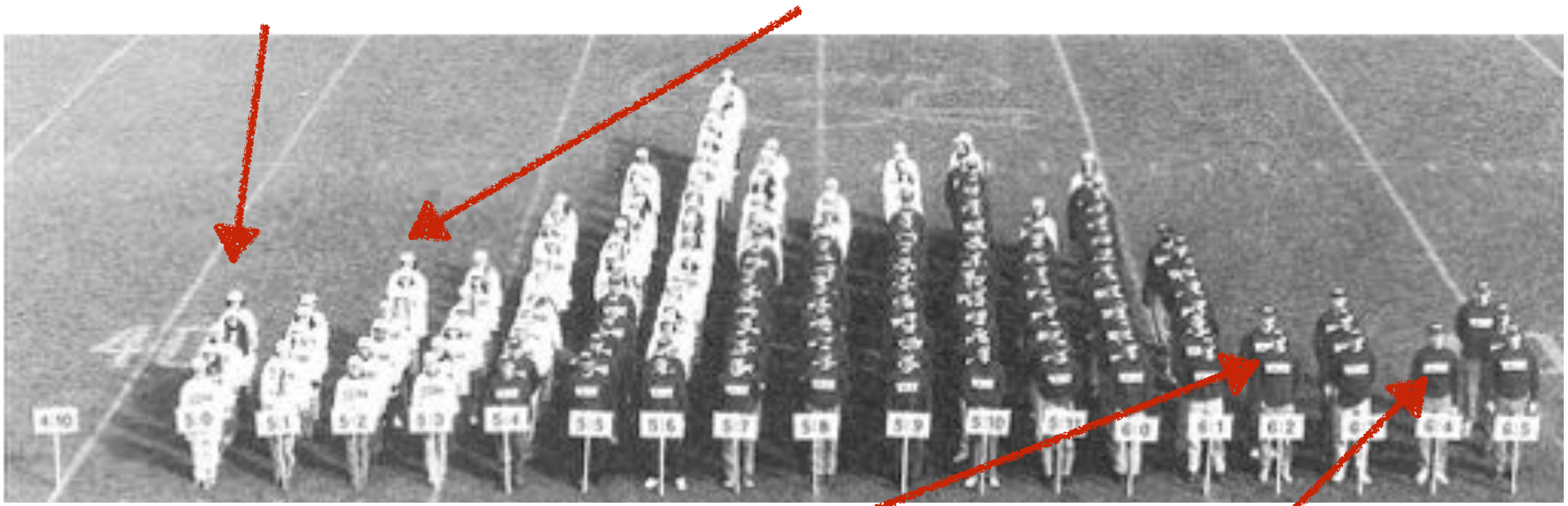
The spectrum of how variation contributes to disease



How do we find the variants that cause common disease?

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

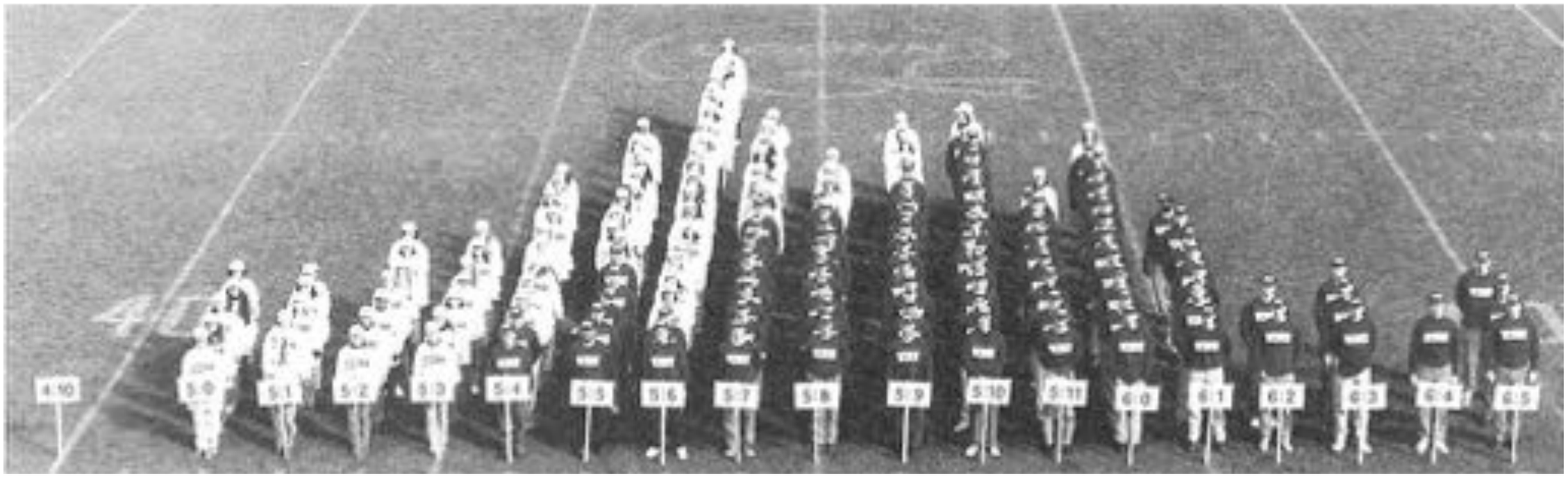
```
CAGCGATAGGCTTTAATGTT  CAGCGATAGGCTTTAATGTT
AGCCCGTTTTATGACCAACG  AGCCCGTTTTATGACCAACG
GGGTTCACAGTGAGCTGTGT  GGGTTCACAGTGAGCTGTGT
```



University of Connecticut, 1997

```
CAGCGATAGGCTTTAATGTT  CAGCGATAGGCTTTAATGTT
AGCCCGTTTGATGACCAACG  AGCCCGTTTGATGACCAACG
GGGTTCACAGTGAGCTGTGT  GGGTTCACAGTGAGCTGTGT
```

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

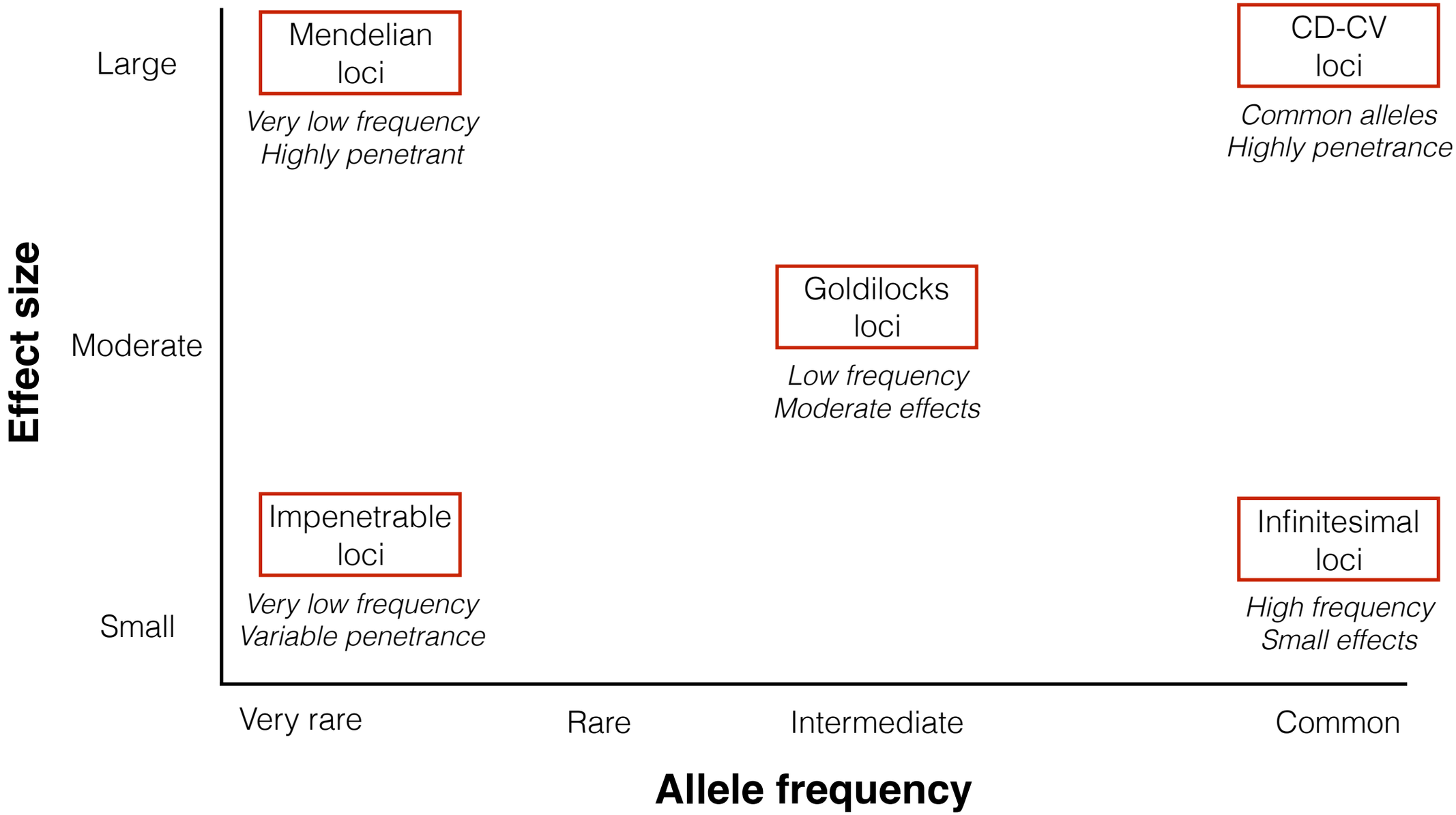


University of Connecticut, 1997

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

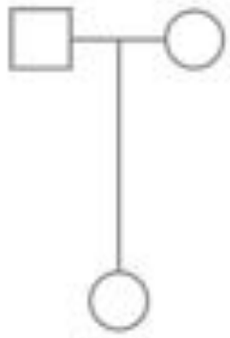
~250,000 people genotyped led to 20%
of height differences explained

The spectrum of how variation contributes to disease

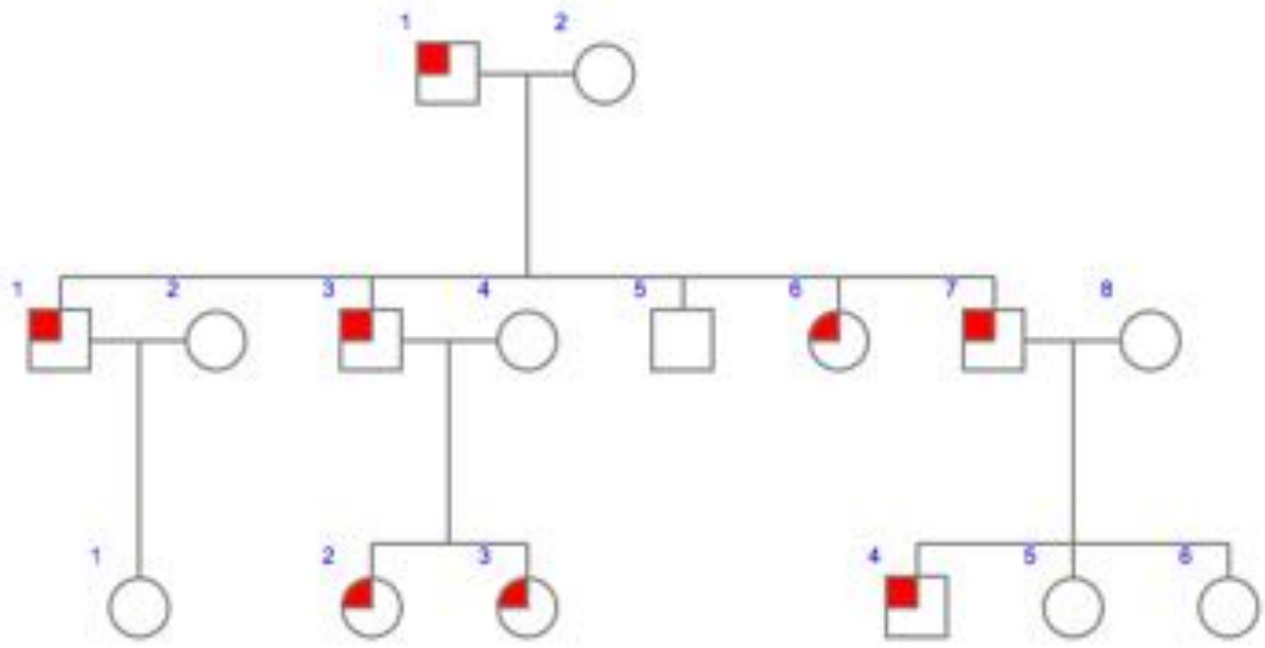


How do we find the variants that cause rare disease?

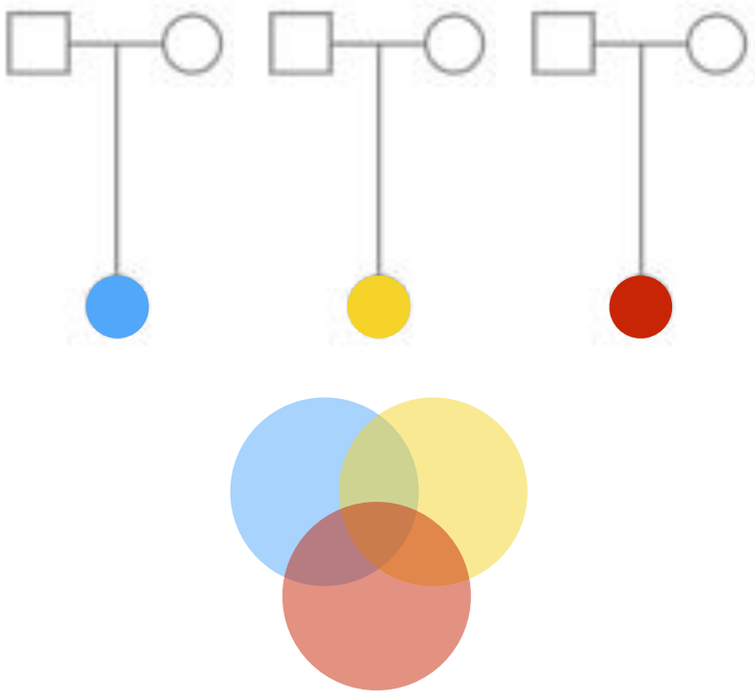
Strategies to identify disease-causing rare variants



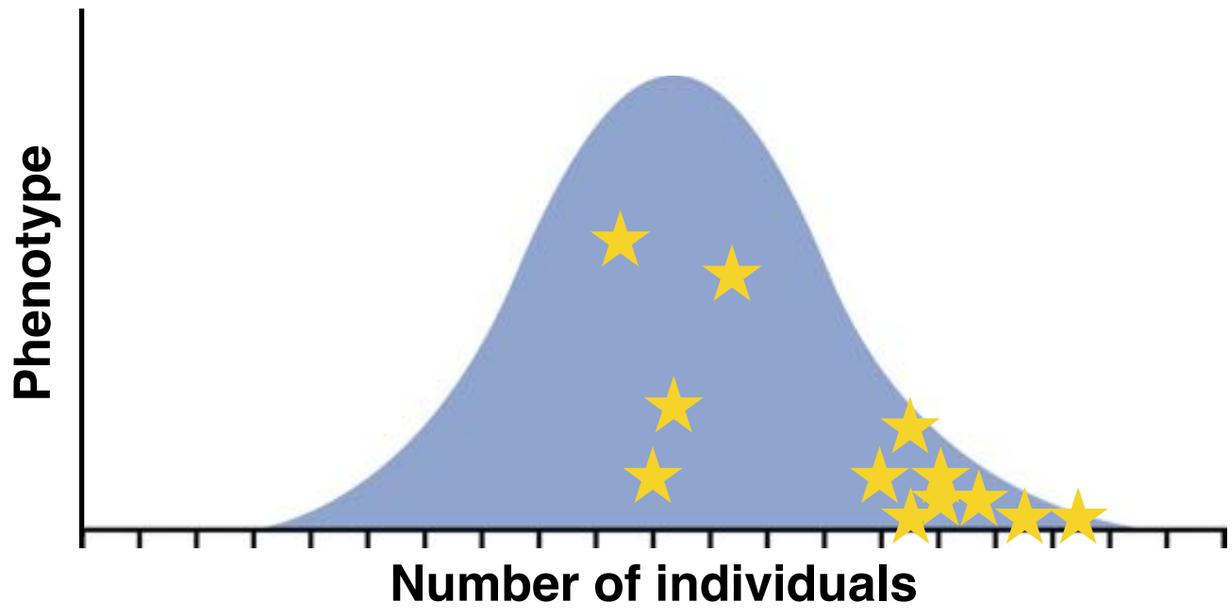
Rare variation from families



Shared variants from affected individuals in large families

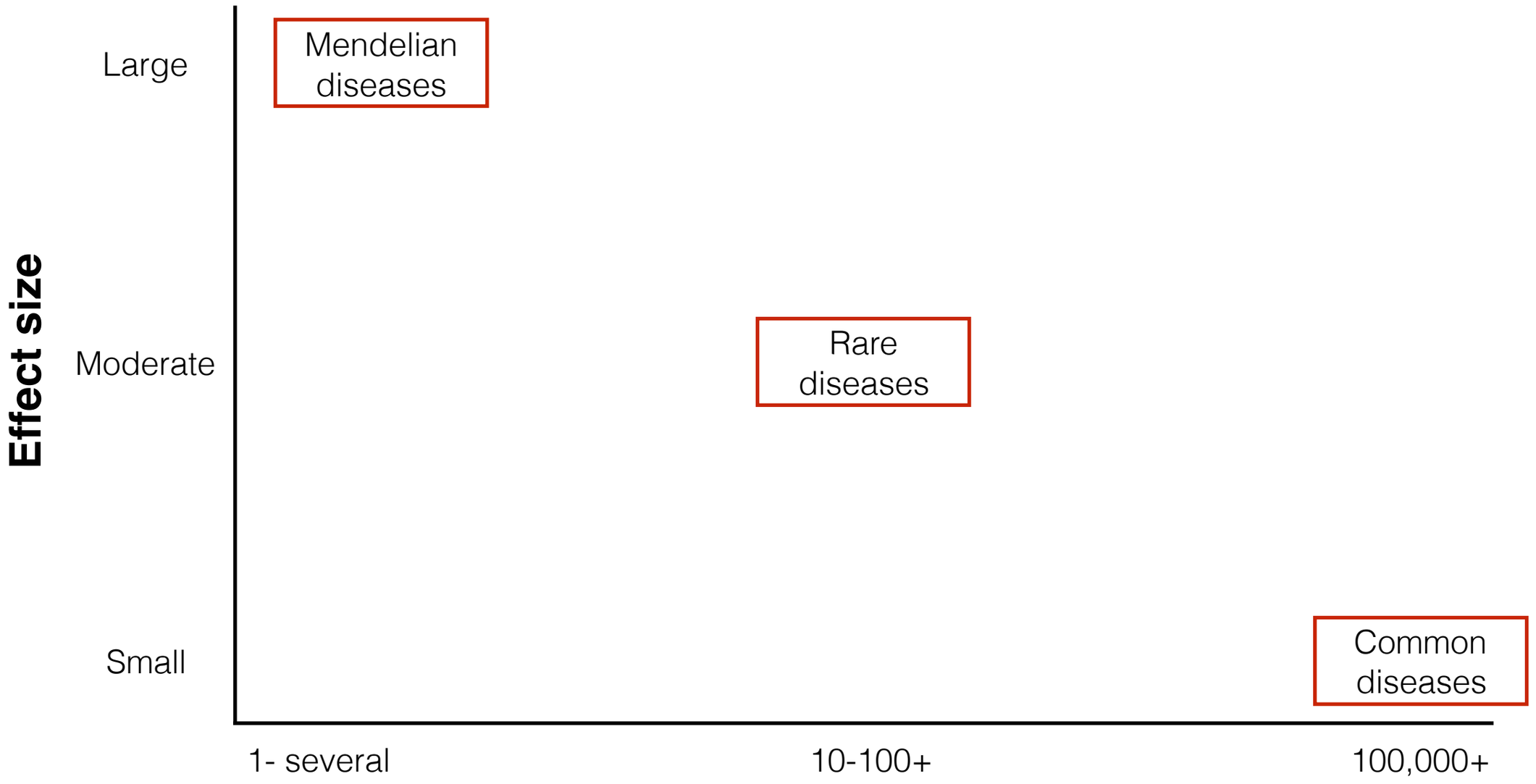


Shared variation from trios



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.

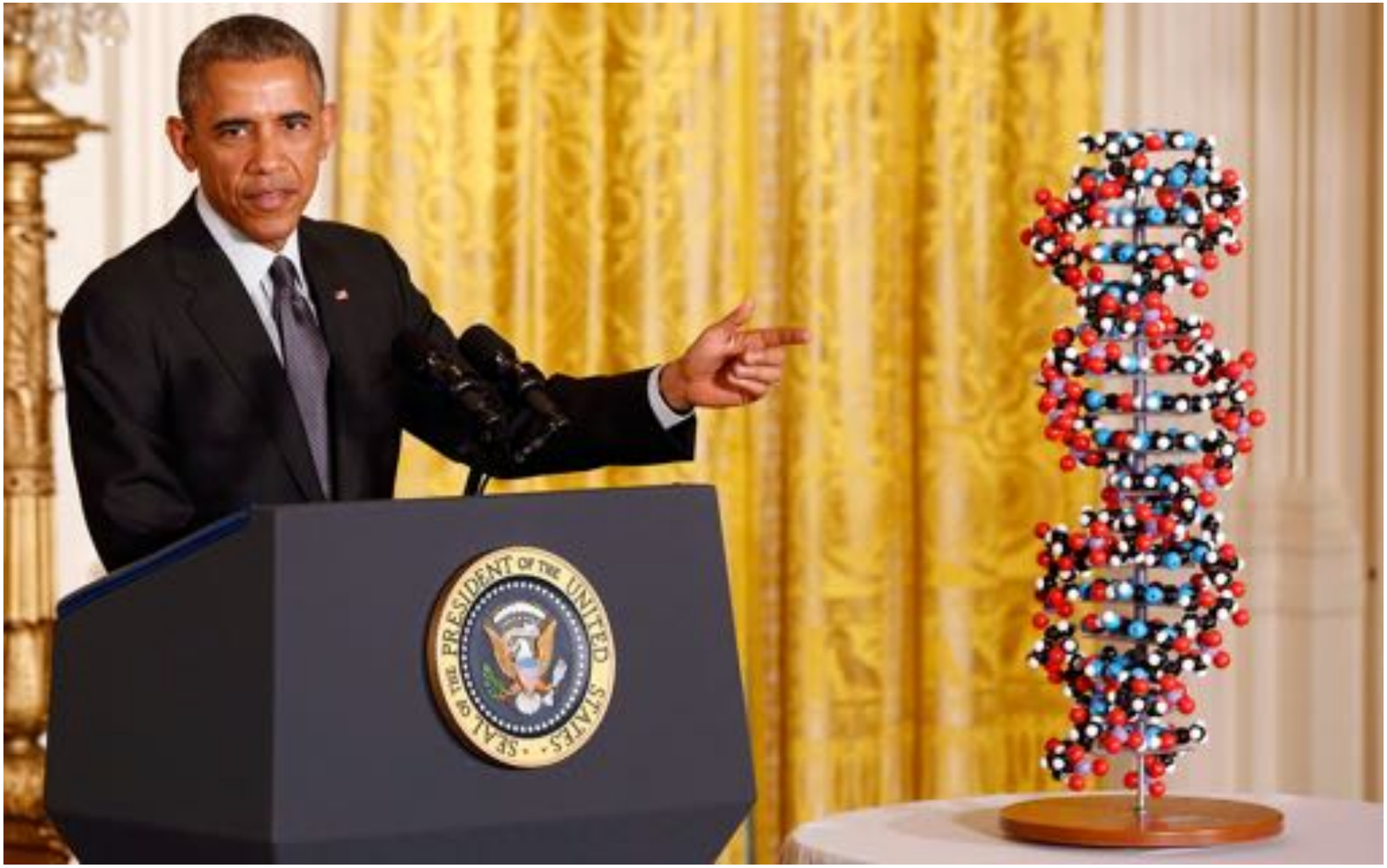
We don’t know which ones affect phenotype.

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

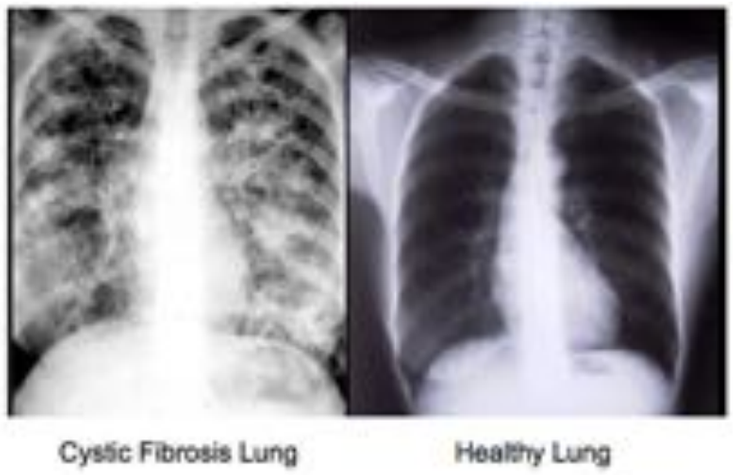
The human genome is big.

Phenotypes are highly variable.

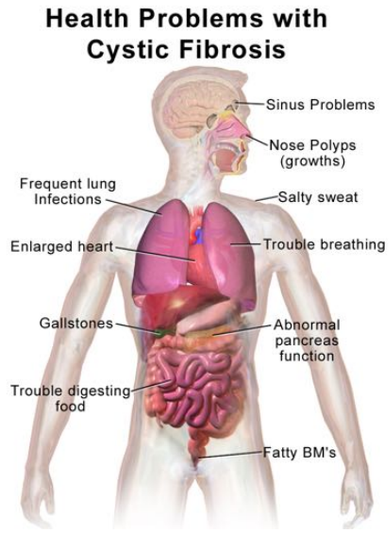
What is precision medicine?



What about cystic fibrosis?



Cystic Fibrosis Lung Healthy Lung



1. Autosomal recessive disorder

2. Not caused by chromosomal aberrations or meiotic NDJ

3. Mapped to chromosome 7

4. Mutations in CF gene are null or hypomorphs

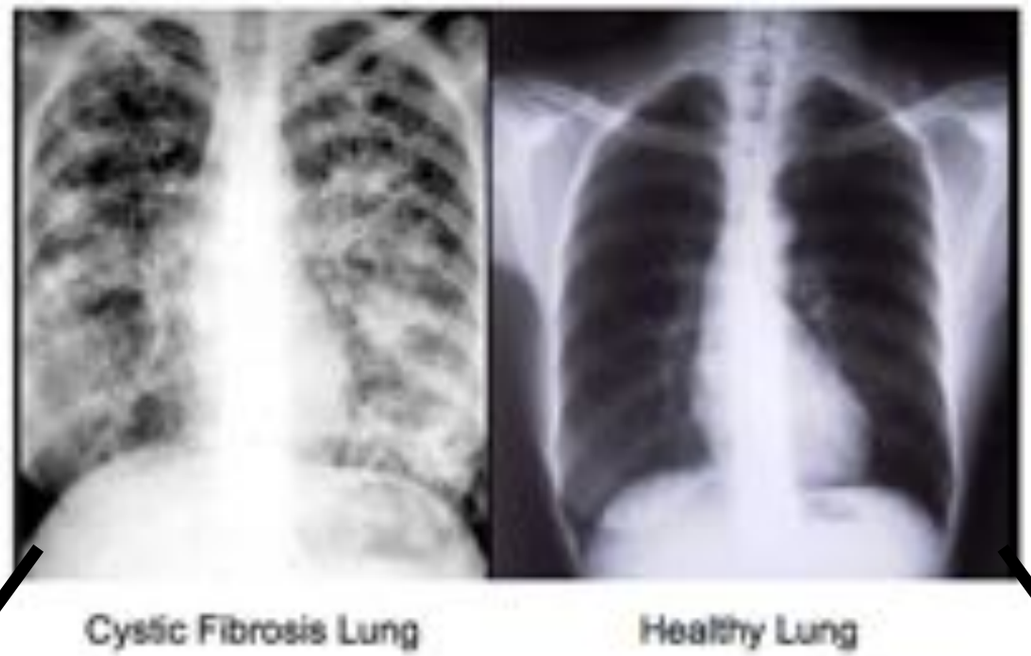
5. Compound heterozygosity (failure to complement) is common

6. No known epistatic genes to CF gene

7. Genetic enhancers are known (immune modulatory genes)

8. No genetic suppressors are known yet.

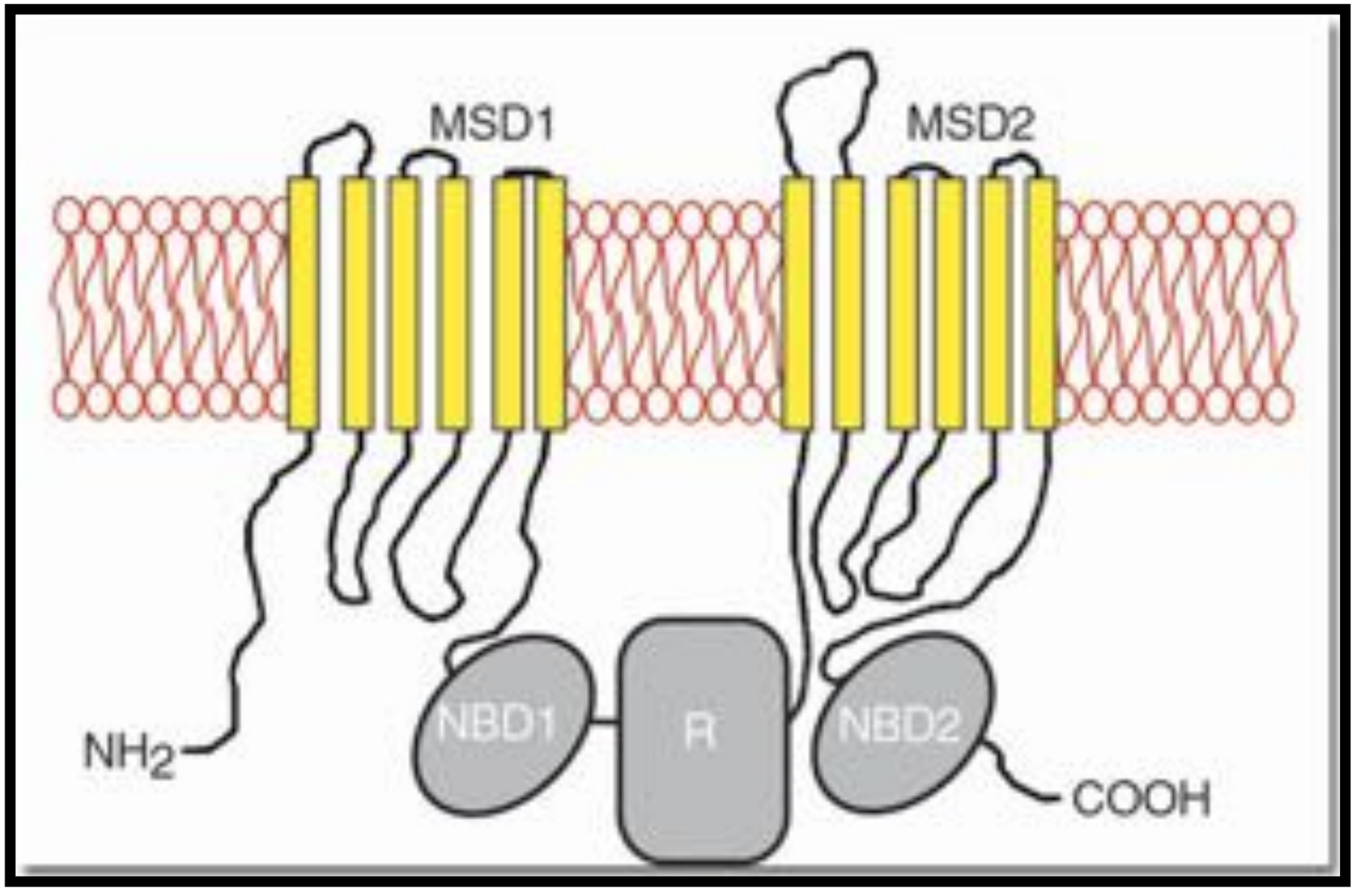
Cell autonomy of CF mutation was shown in the 1960's



Cells failed to secrete Cl^-

Cells secreted Cl^-

Cystic fibrosis was mapped to the chloride ion channel CFTR



Cystic fibrosis is caused by a mix of common and rare variants

Cystic Fibrosis Lung Healthy Lung

Rare disease affects 1/10,000 live births

Caused by mutations in the CFTR gene

Selection removes homozygotes from population

Hardy-Weinberg equilibrium tell us that 1/50 people are carriers

Why is eugenics (or genome editing) next to impossible?

Cystic fibrosis is caused by a mix of common and rare variants

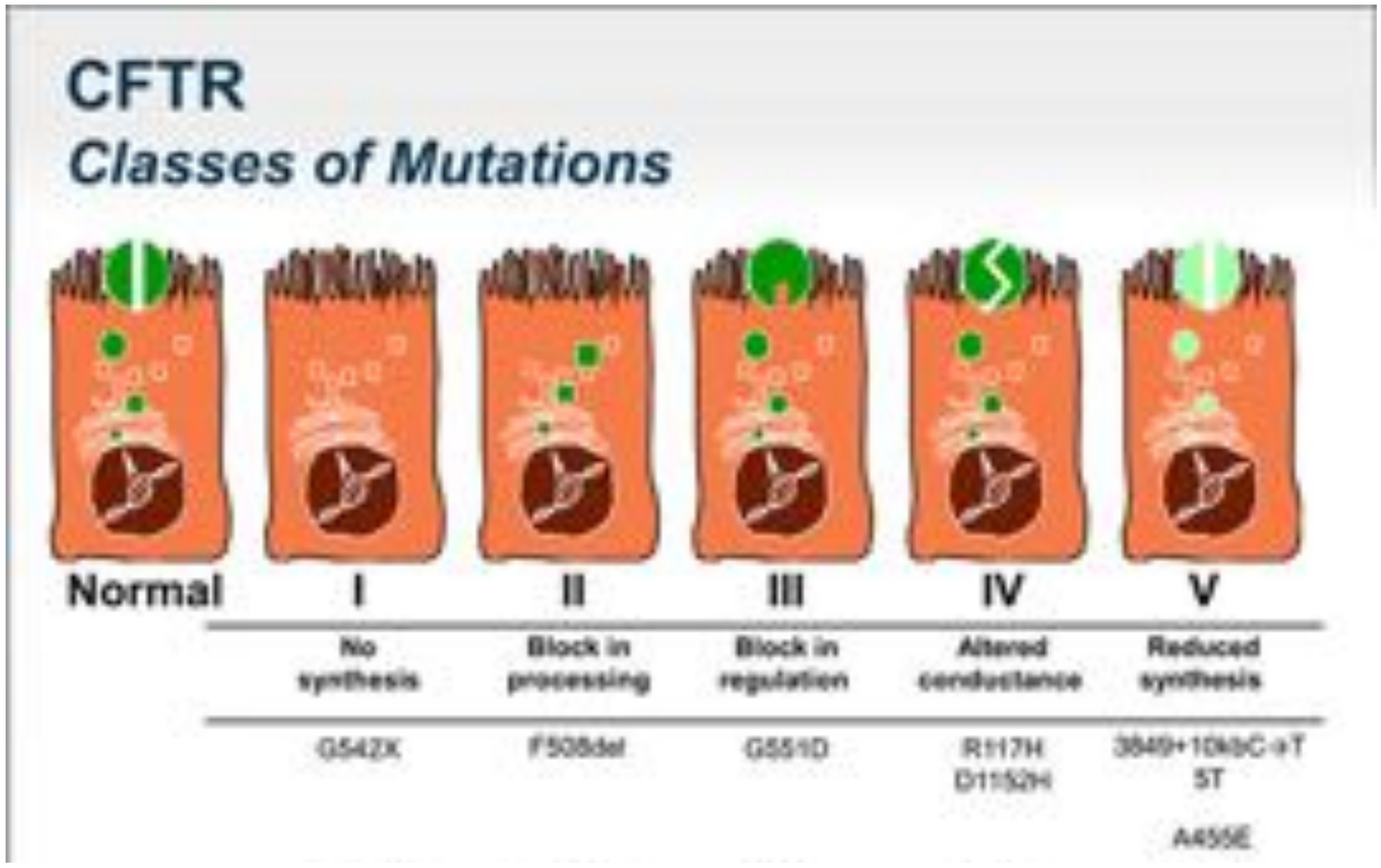
Cystic Fibrosis Lung Healthy Lung

50% of all cases have the same allele ΔF508

Over 1000 other mutations are known

Compound heterozygotes found often

Genetic heterogeneity



What do you think the phenotypes of these mutations are?

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