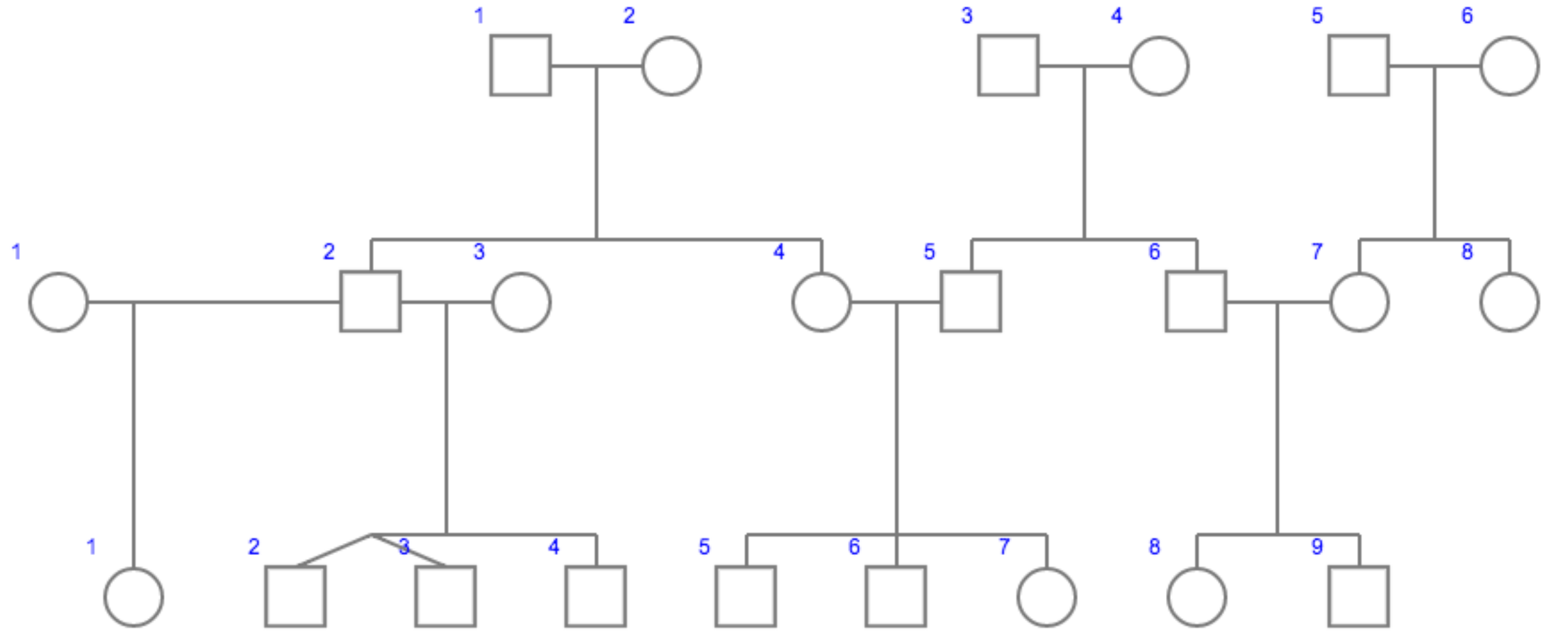
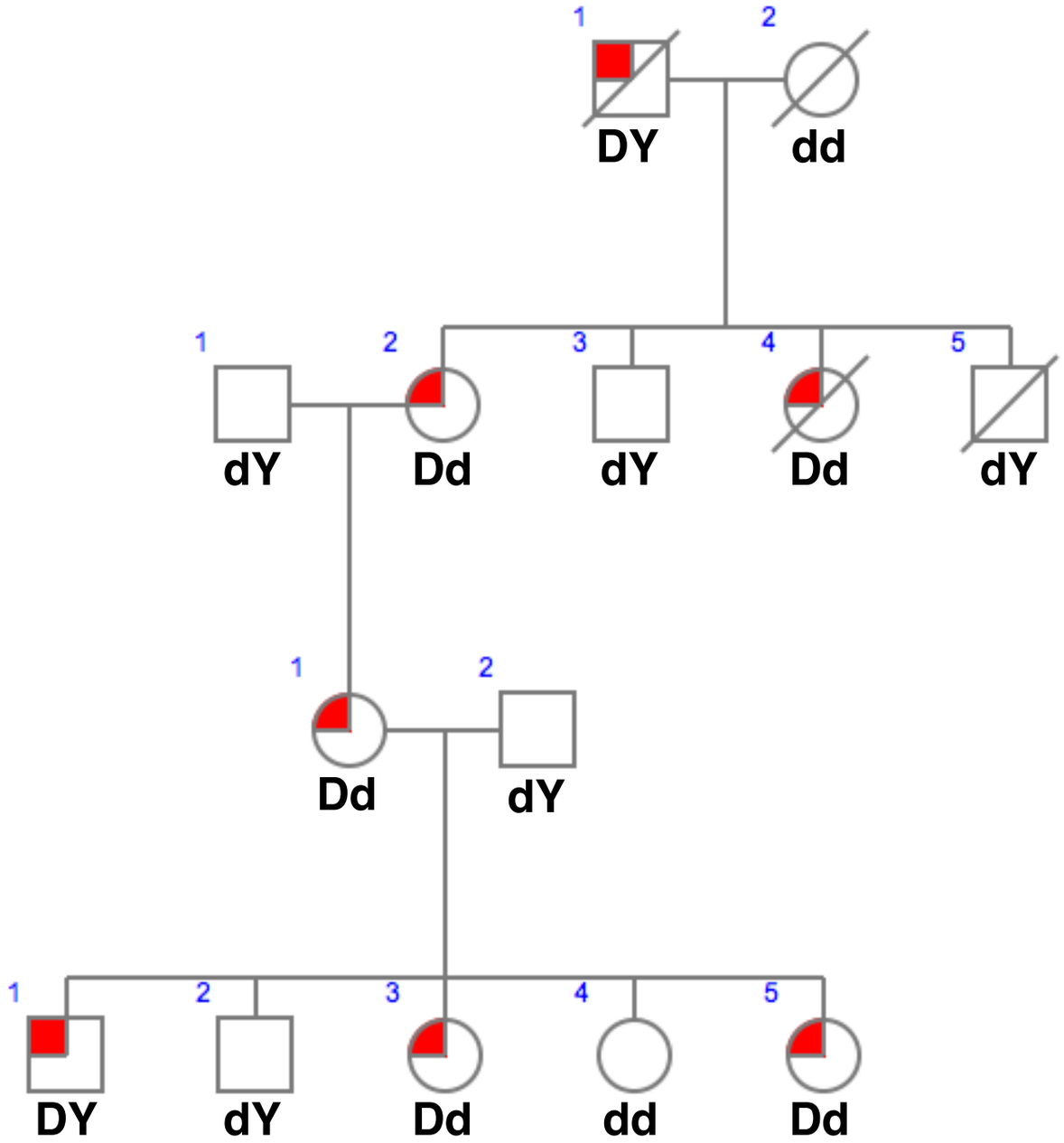
Bio393: Genetic Analysis

Family-based analysis, Modes of inheritance, Phase



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?

X-linked dominant

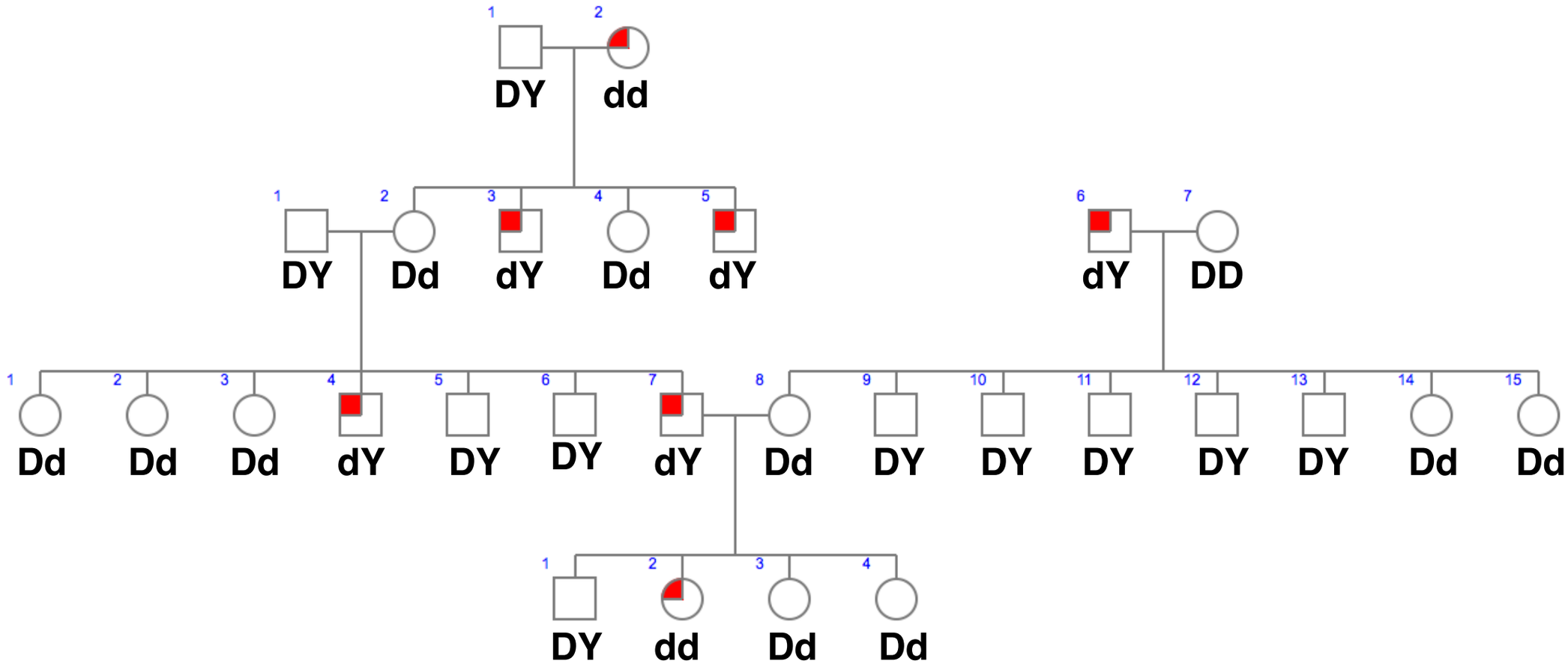
Examples of human X-linked dominant disorders

Rett syndrome

Fragile X syndrome

All daughters of affected fathers are affected

Modes of inheritance



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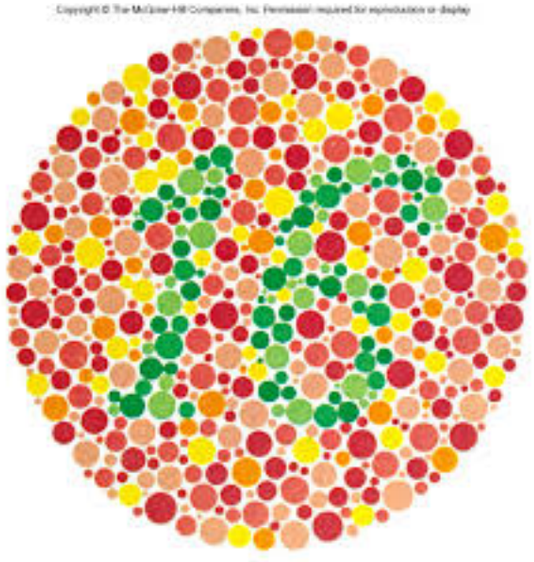
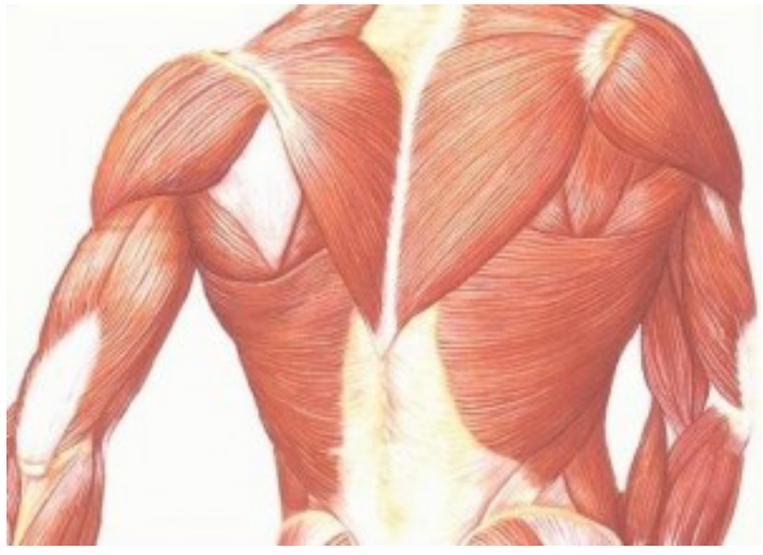
X-linked recessive

Examples of human X-linked recessive disorders



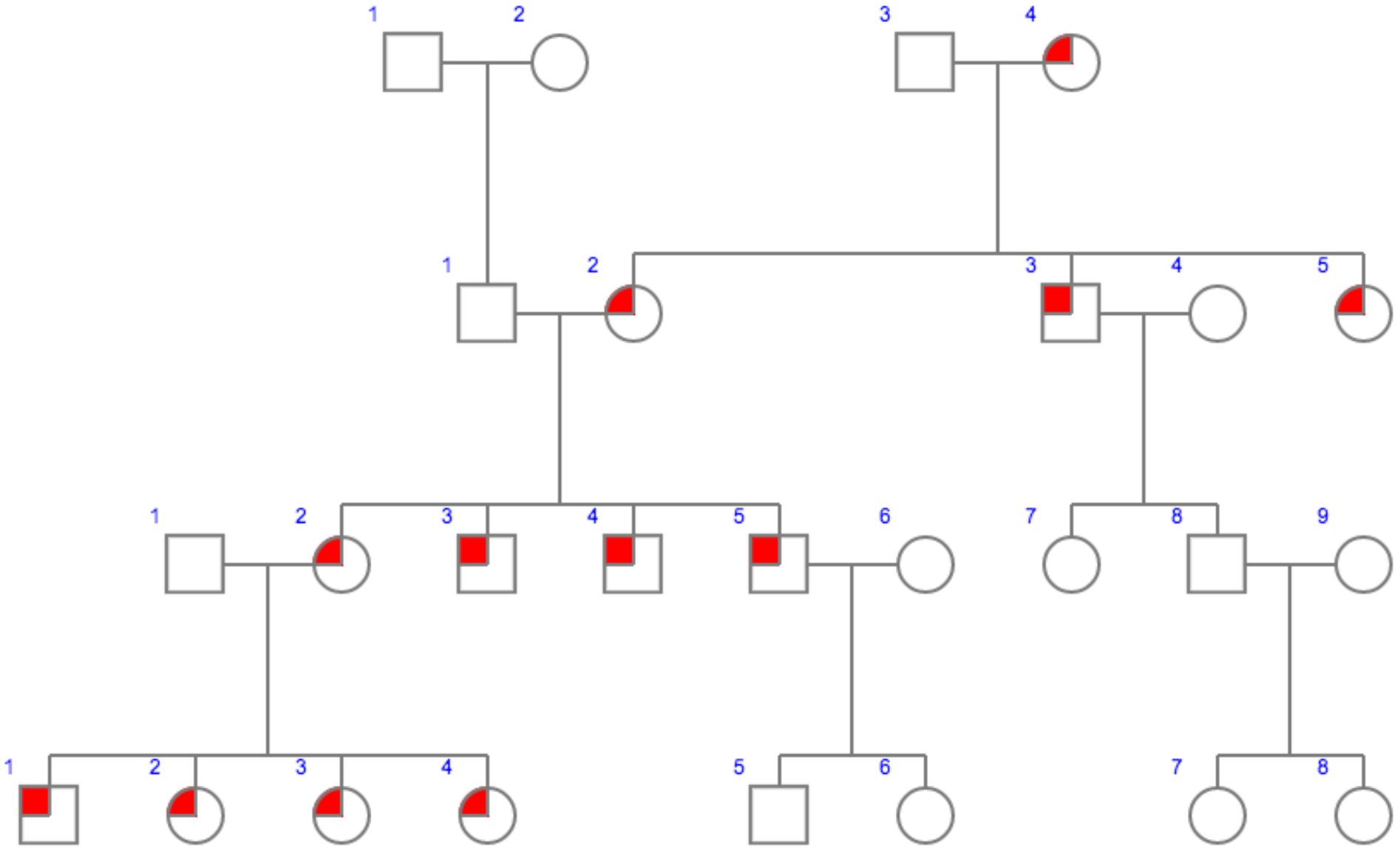
Red-green color blindness



Duchenne muscular dystrophy

All sons of affected mothers are affected

Modes of inheritance



- How many individuals are affected?
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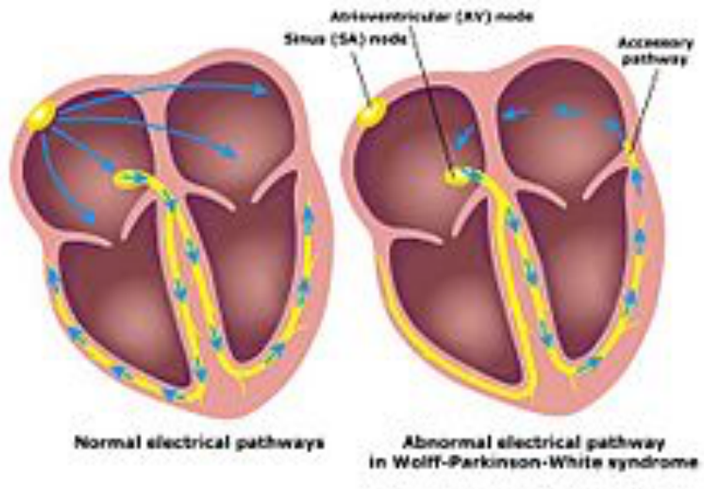
Cytoplasmic inheritance

Examples of human cytoplasmic inheritance disorders

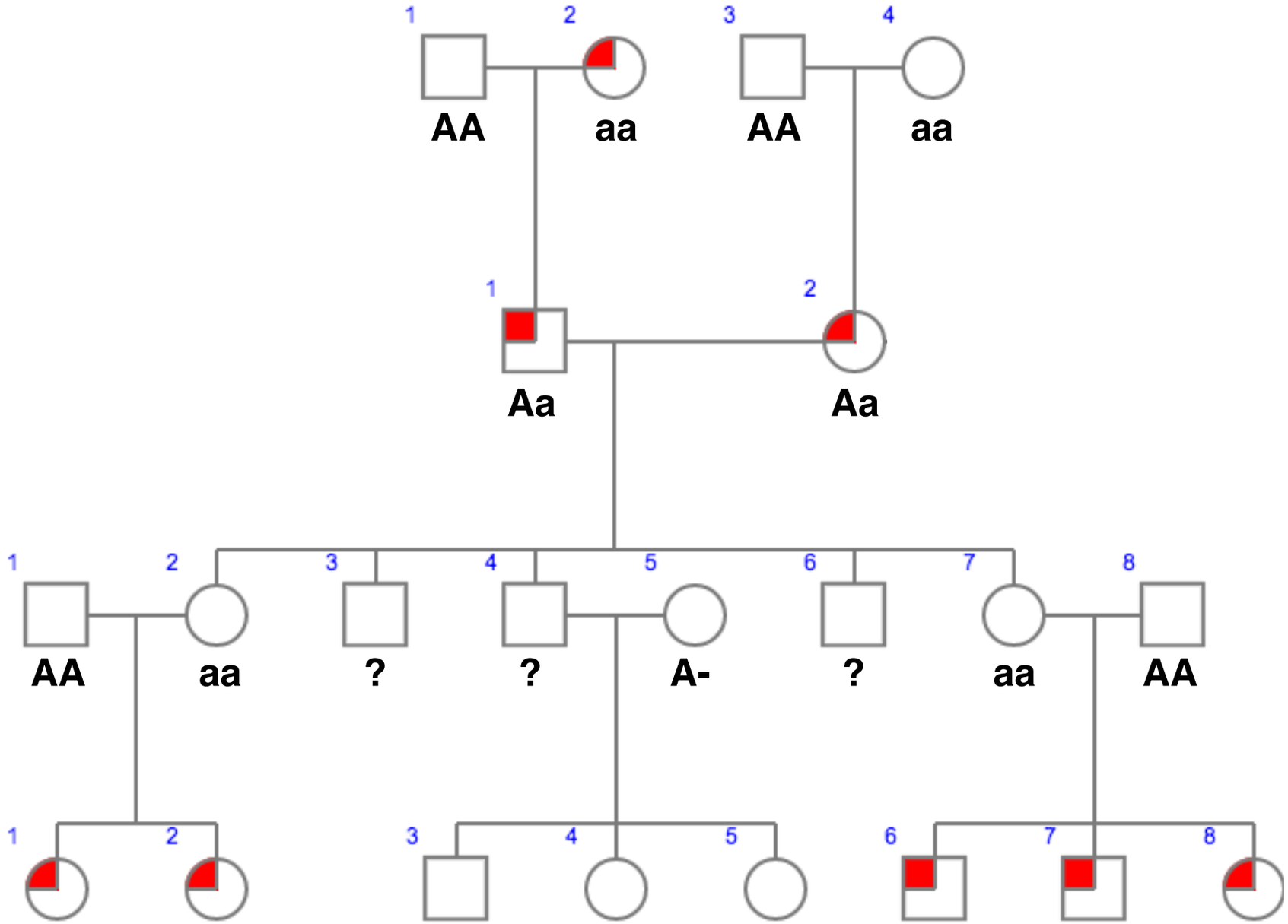
Mitochondrial myopathy



Wolff-Parkinson-White syndrome

All children of affected mothers are affected

Modes of inheritance



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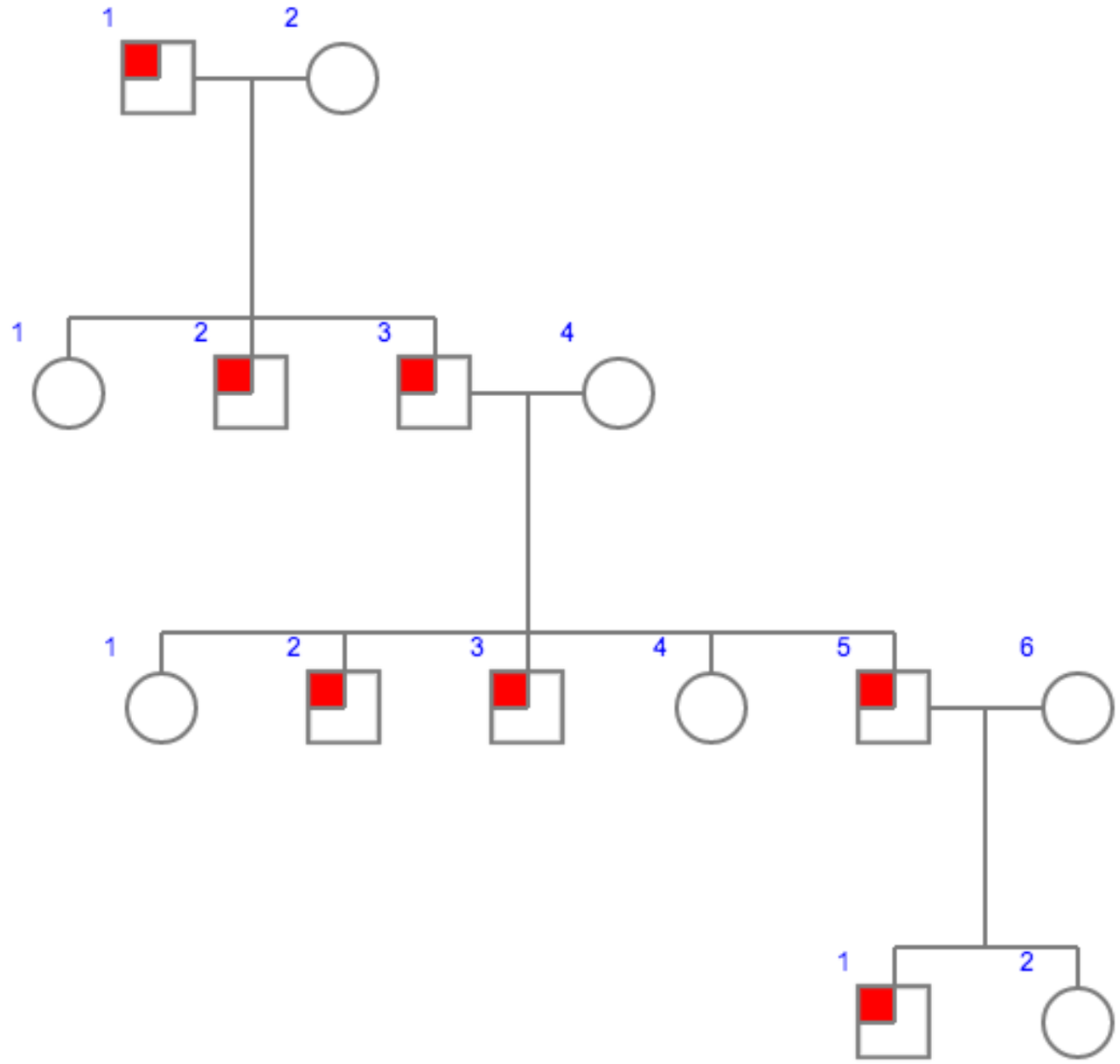
Recessive maternal-effect inheritance

Modes of inheritance



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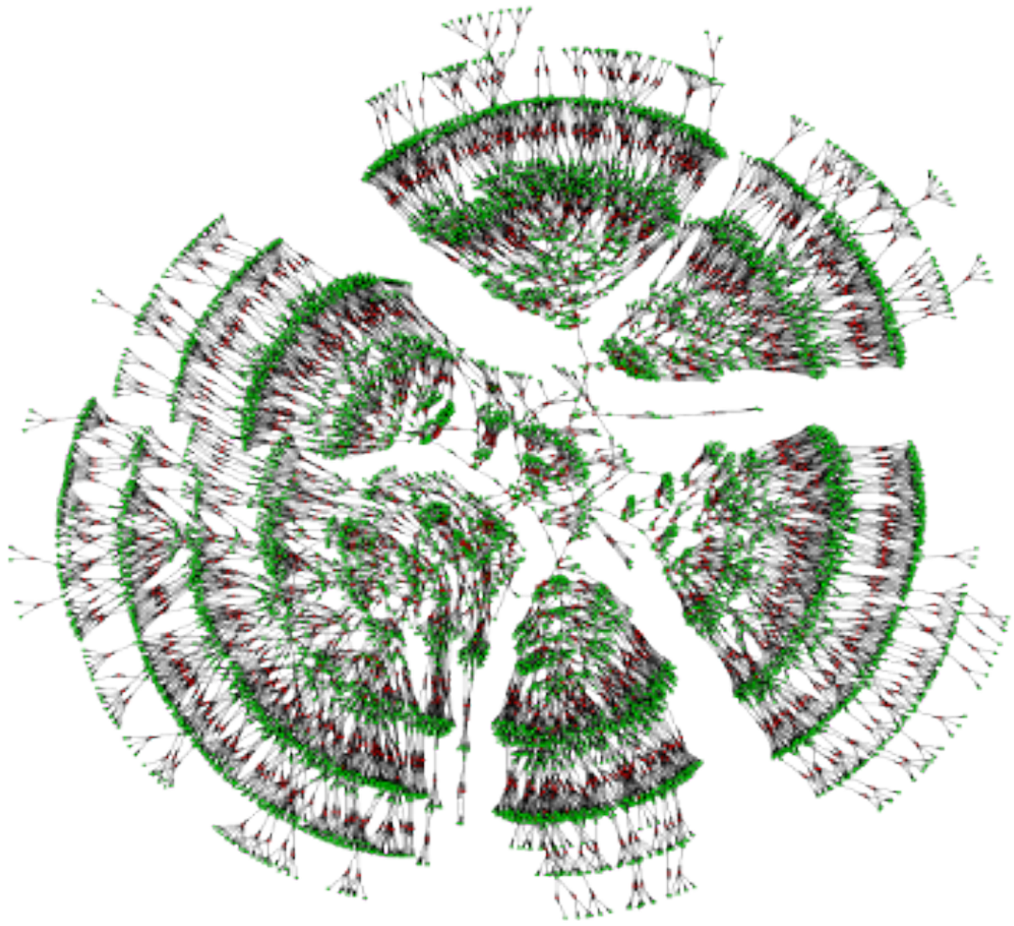
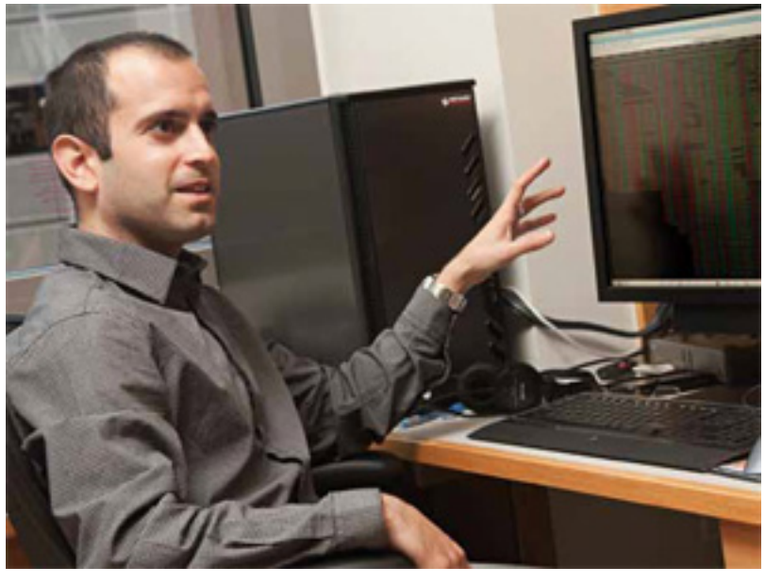
Y-linked inheritance

Some pedigrees can contain millions of individuals

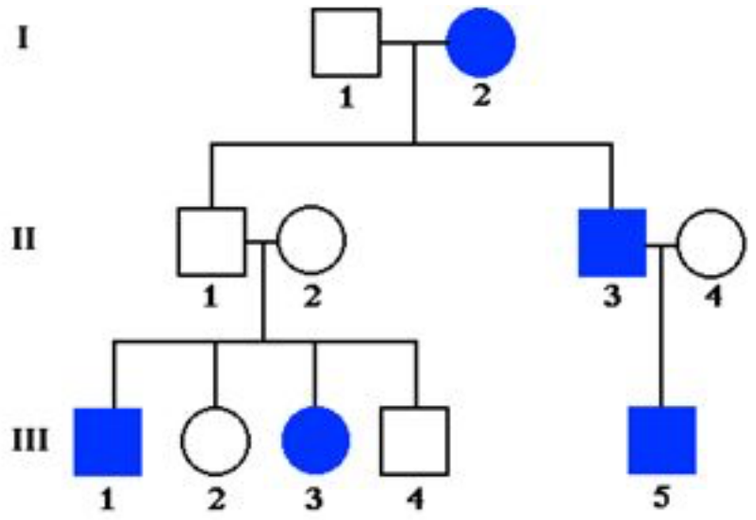




Yaniv Erlich

Ancestry websites offer rich family data

Remember all of the genetics we've learned so far



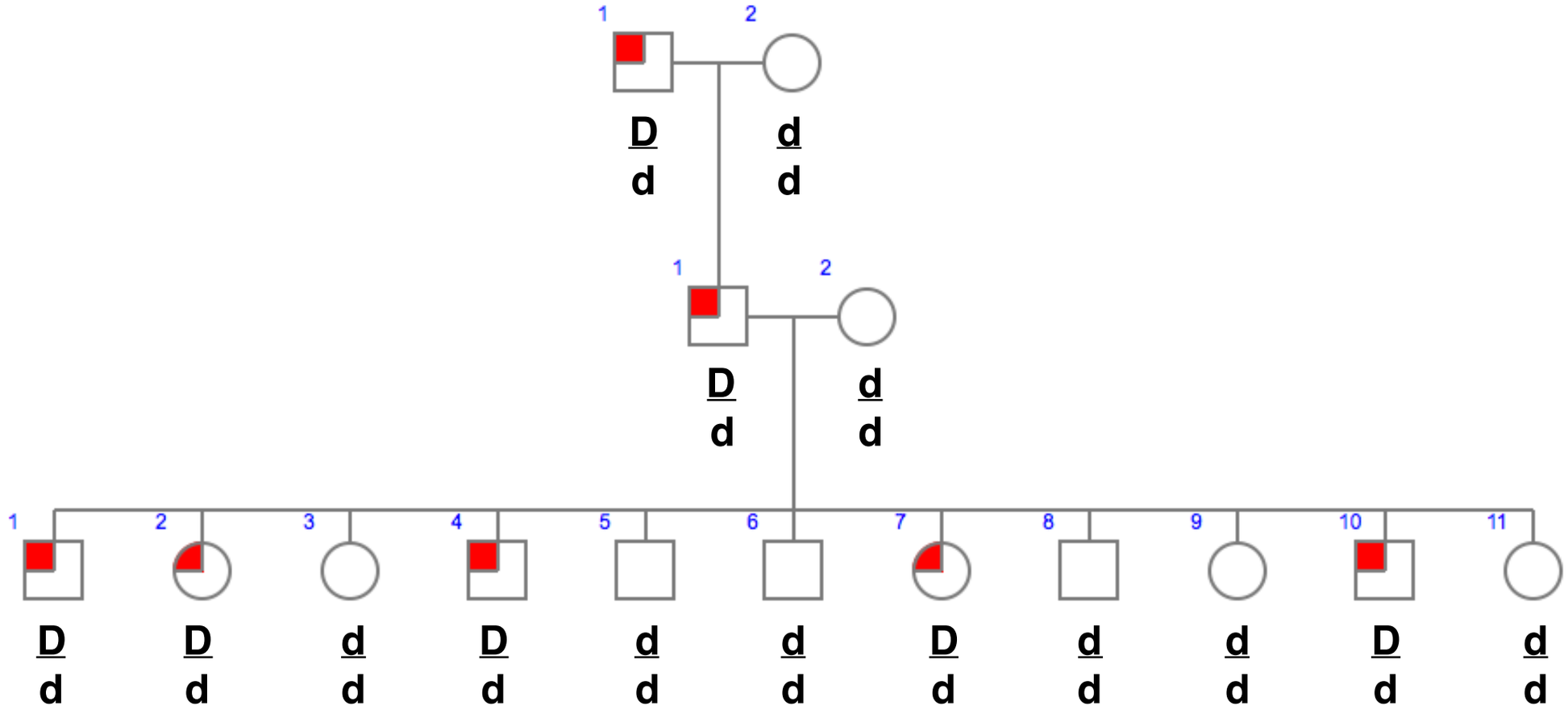
Incomplete penetrance

Non-complementation

Haploinsufficiency

Suppression and enhancement

We want to be able to find a marker linked with the disease to identify the disease gene



Autosomal dominant

Genetic variants are used as markers to track disease

Single nucleotide variants (SNVs)

Reference **ATGTGCAGACGTAGACGTA**

Alternative **ATGTGCAGACTTAGACGTA**

Insertion-deletion variants (indels)

Reference **ATGTGCAGACGTAGACGTA**

Alternative **ATGTGCAGACGTAGACGTA**

Addition of 126 bp

Copy-number variants (CNVs)

Reference Diploid (2 copies)

Alternative More (or fewer) than 2 copies

Microsatellites or short tandem repeats (STRs)

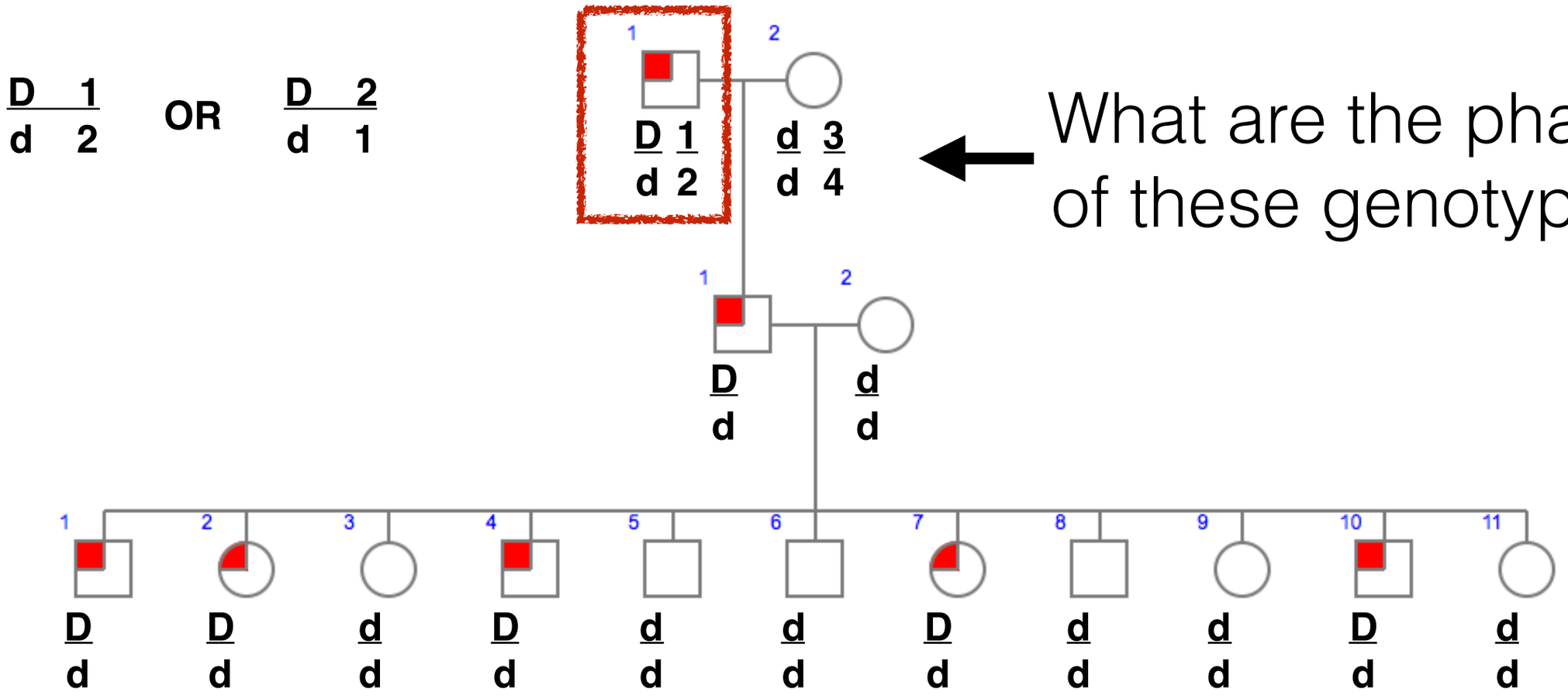
Reference **ATGTGCAGCAGCAGCAGCGTA**

Alternative **ATGTGCAGCAGCGTAGTGACT**

Recombination between the marker and the disease-causing allele will confound the mapping

We must determine phase or the allelic combination found in the parent so we can tell if the offspring is a parental or a recombinant.

Linkage to genetic markers tells us where disease genes are



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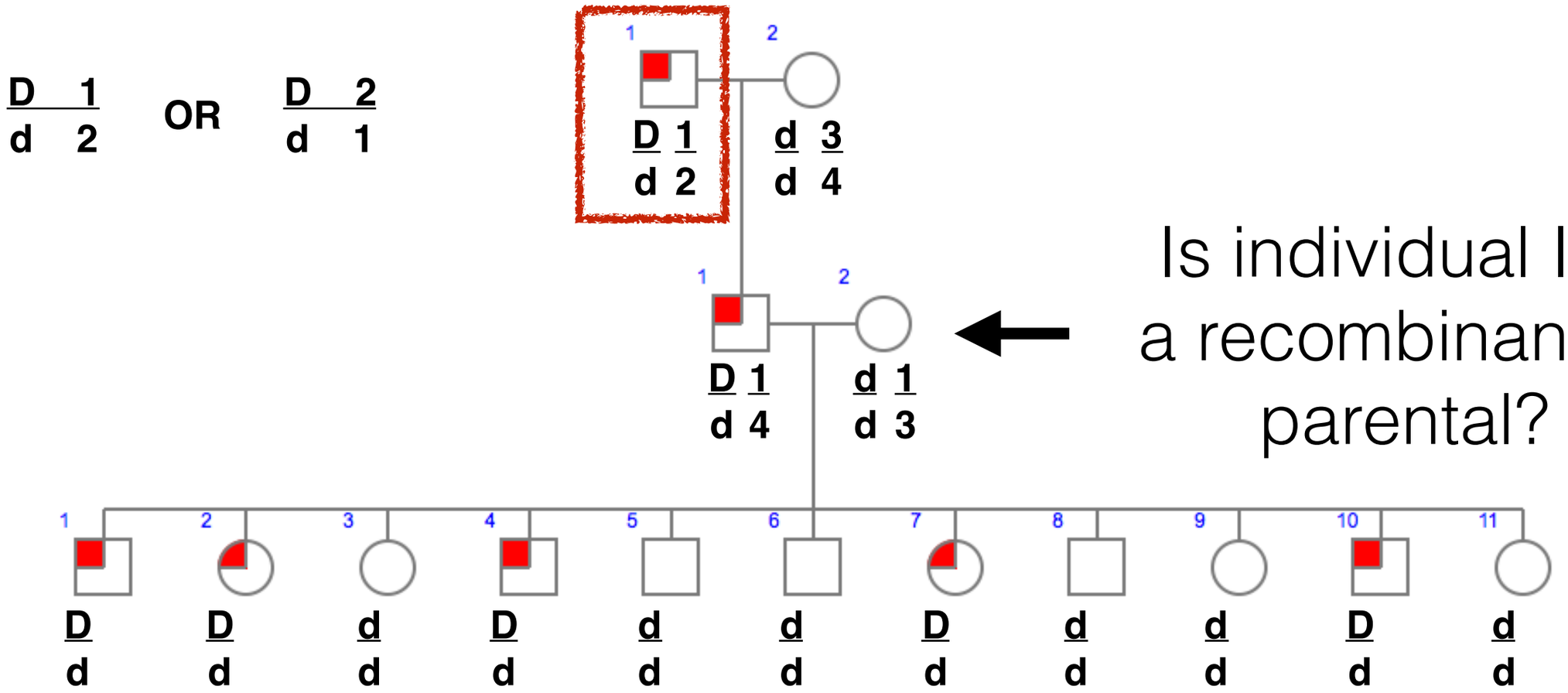
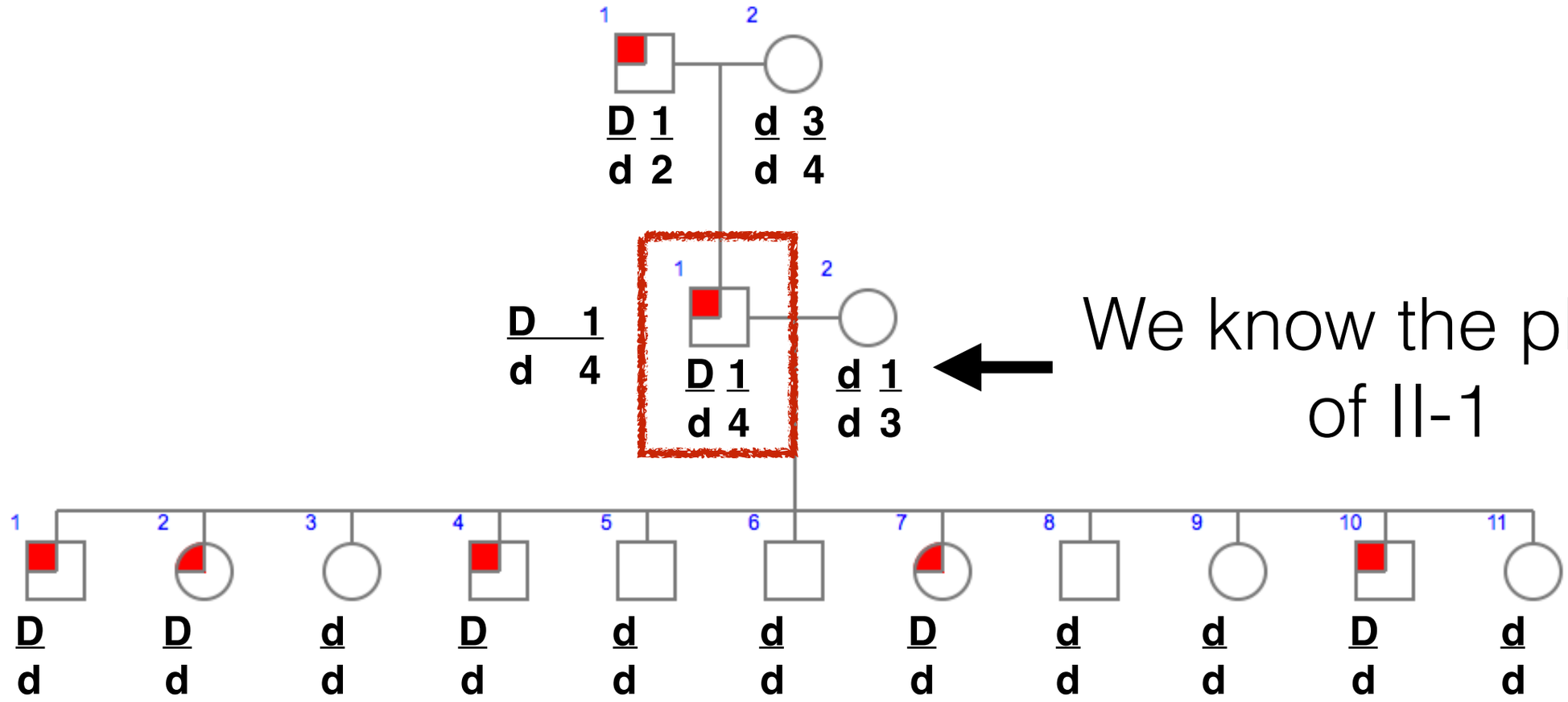
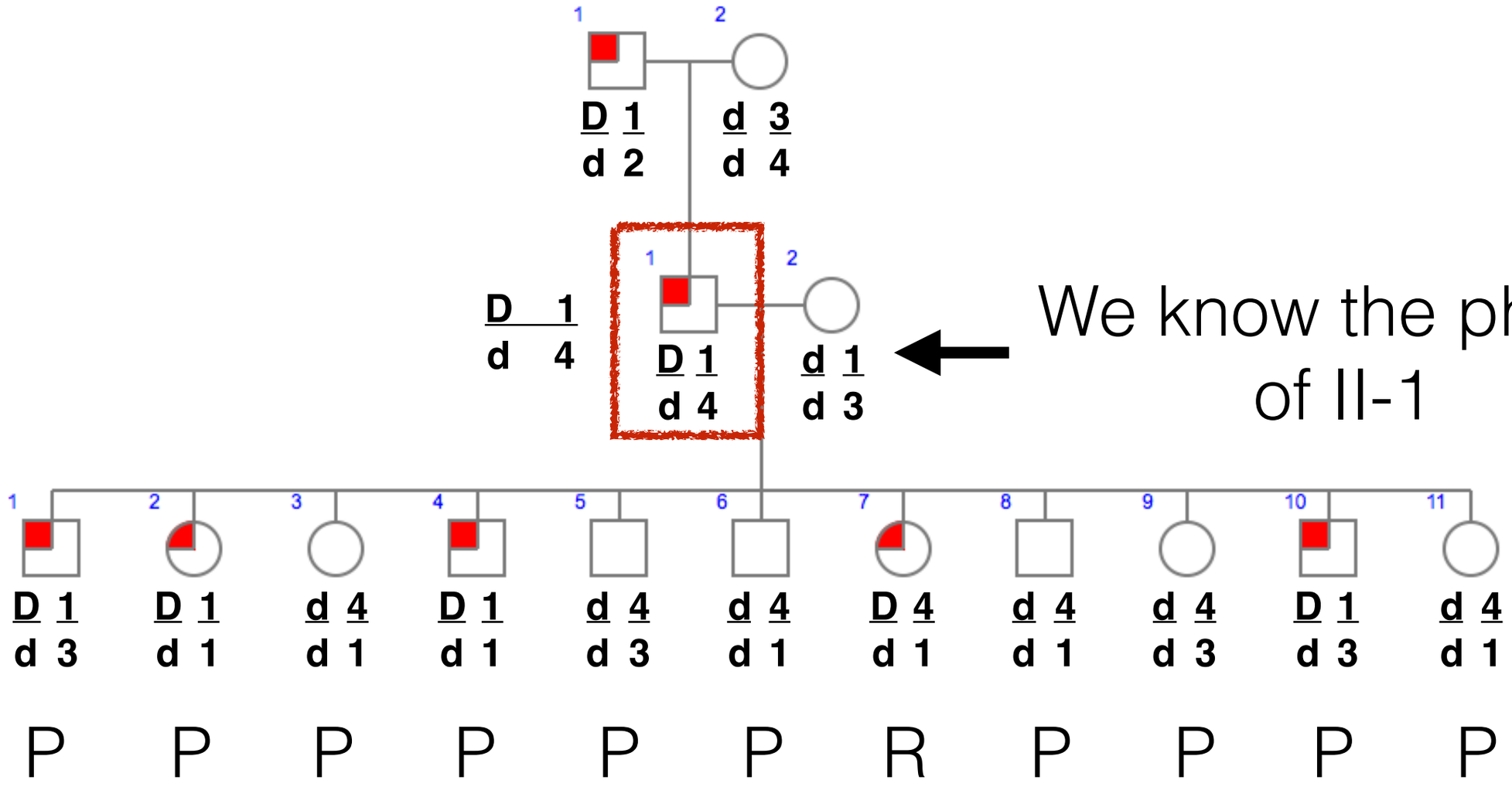


Is individual II-1 a recombinant or parental?

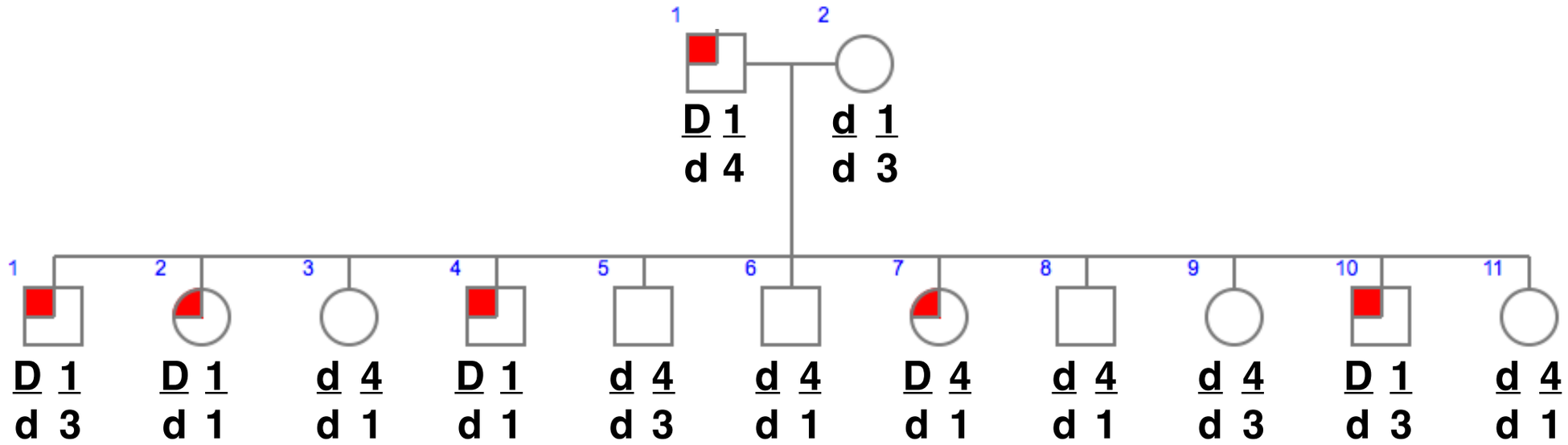
Linkage to genetic markers tells us where disease genes are



Linkage to genetic markers tells us where disease genes are



Linkage to genetic markers tells us where disease genes are



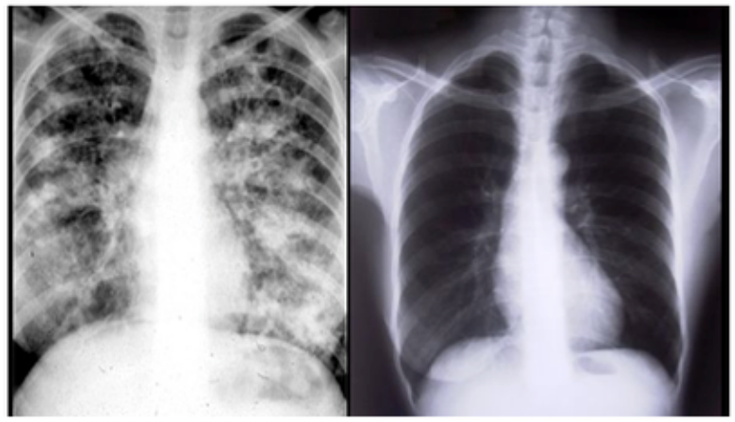
P P P P P P R P P P P

OR

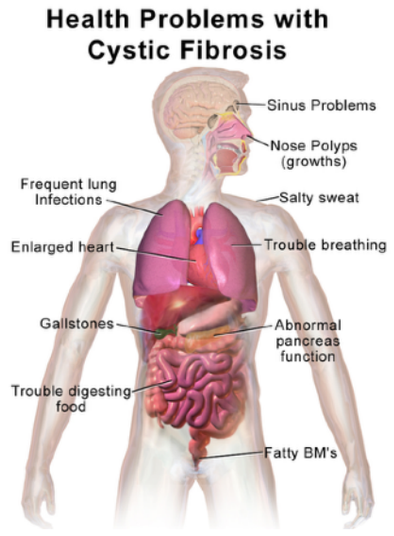
R R R R R R P R R R R

Sometimes, we don't know the phase of the parent, and both possibilities of phase are equally likely

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

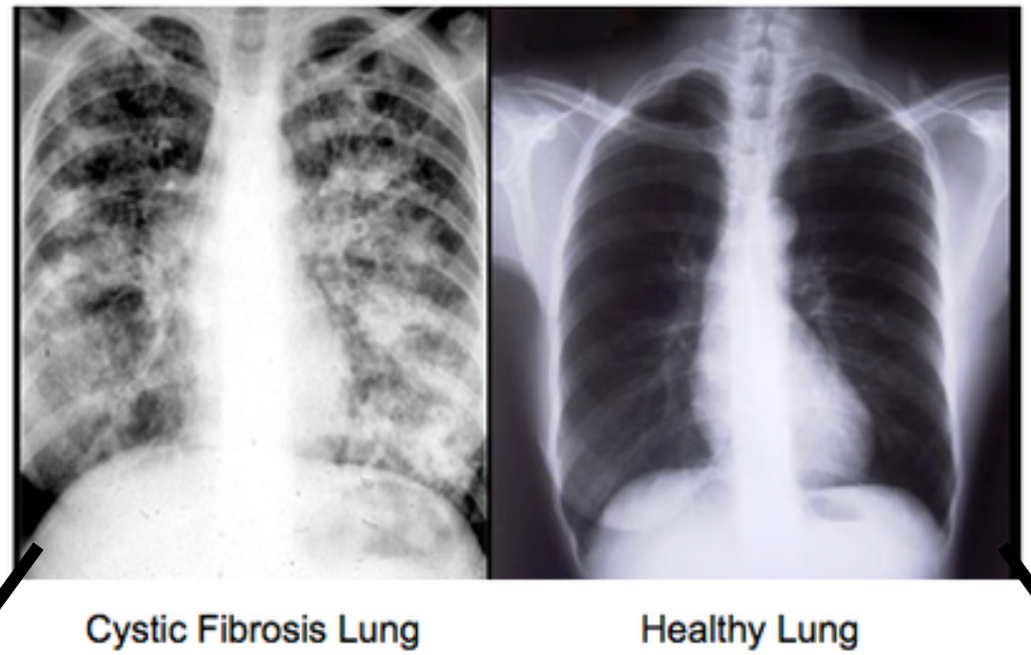
5. Compound heterozygosity (failure to complement) is common

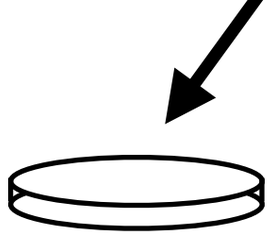
6. No known epistatic genes to CF gene

7. Genetic enhancers are known (immune modulatory genes)

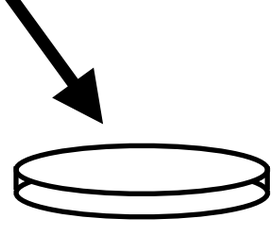
8. No genetic suppressors are known yet.

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



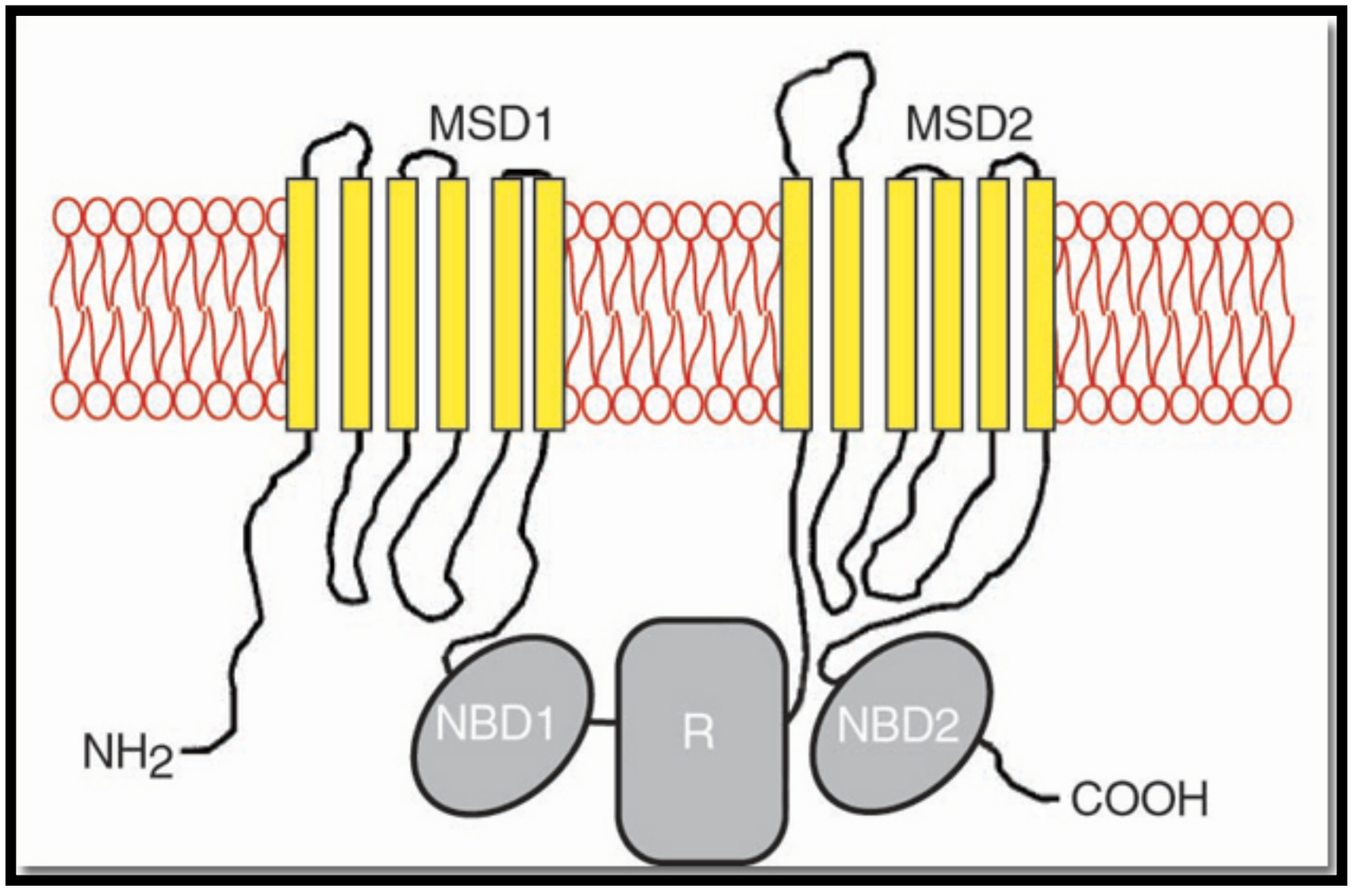


Cells failed to secrete Cl^-

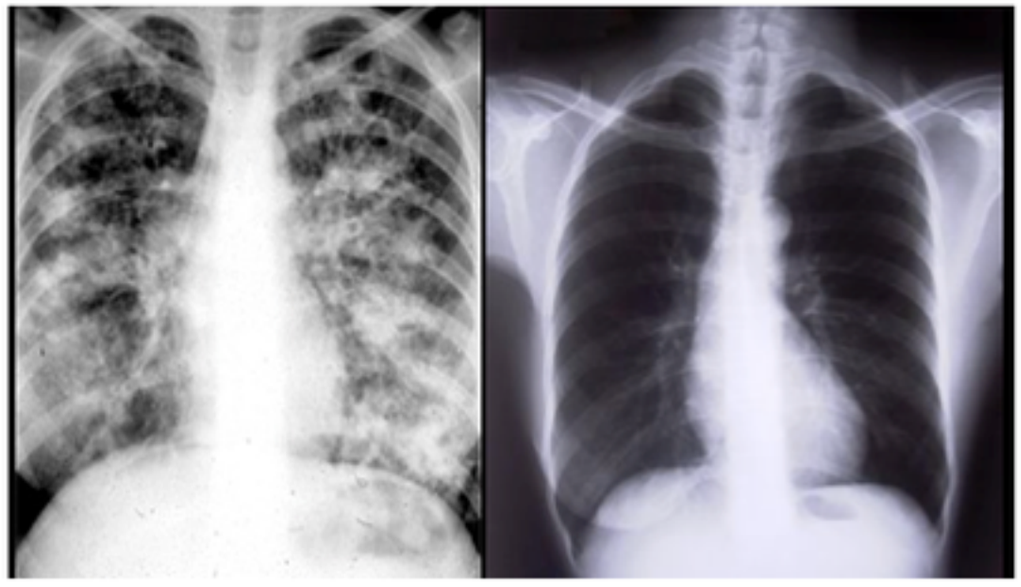


Cells secreted Cl^-

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

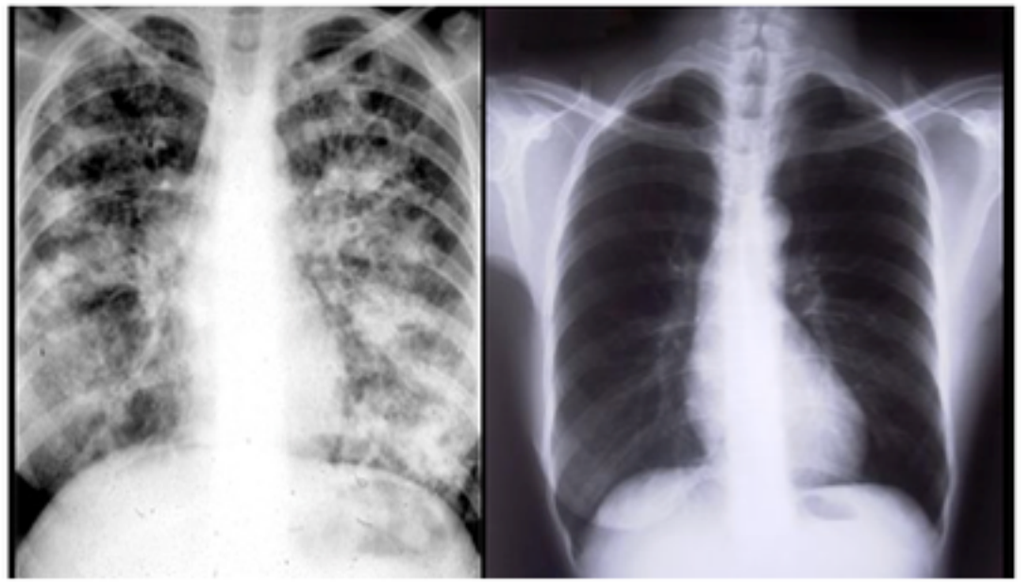
Caused by mutations in the CFTR gene

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

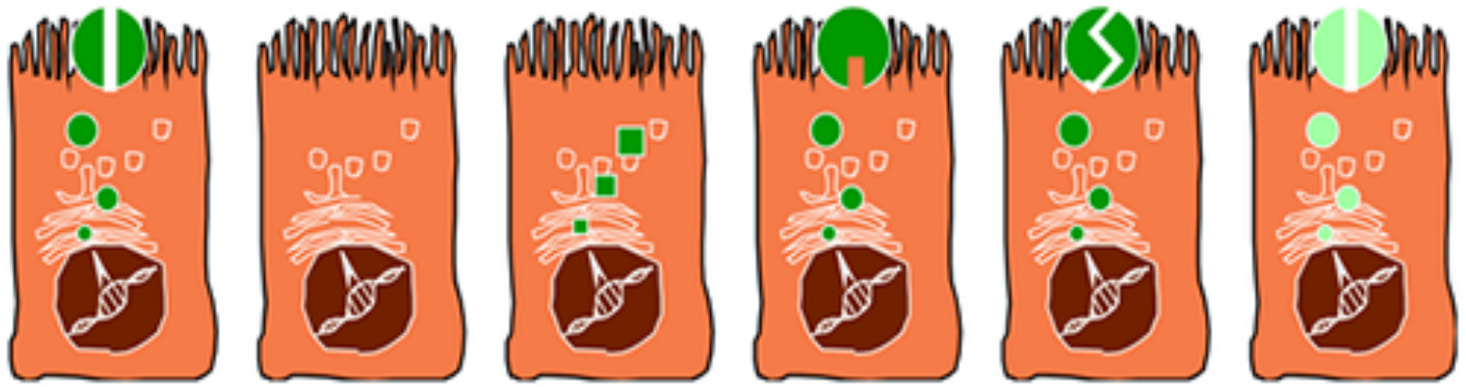
Over 1000 other mutations are known

Compound heterozygotes found often

Genetic heterogeneity

CFTR

Classes of Mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	R117H D1152H	3849+10kbC→T 5T A455E

What do you think the phenotypes of these mutations are?