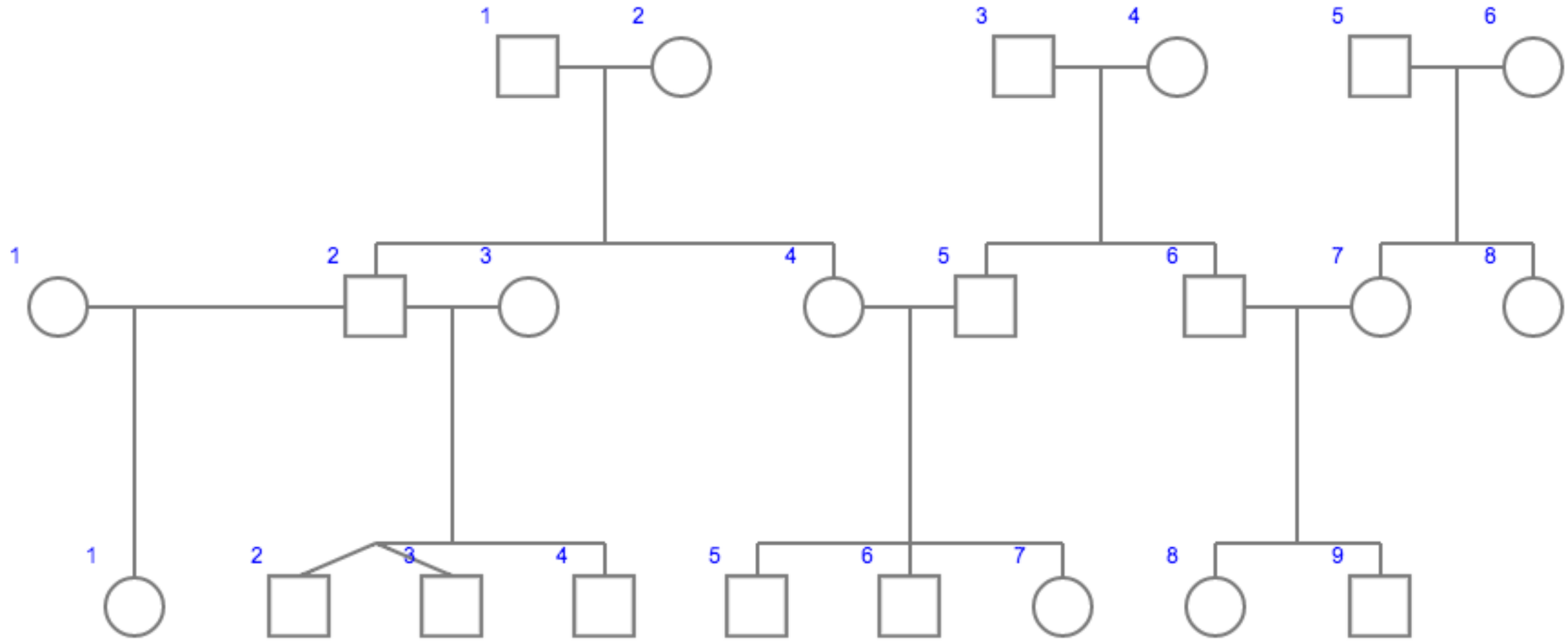
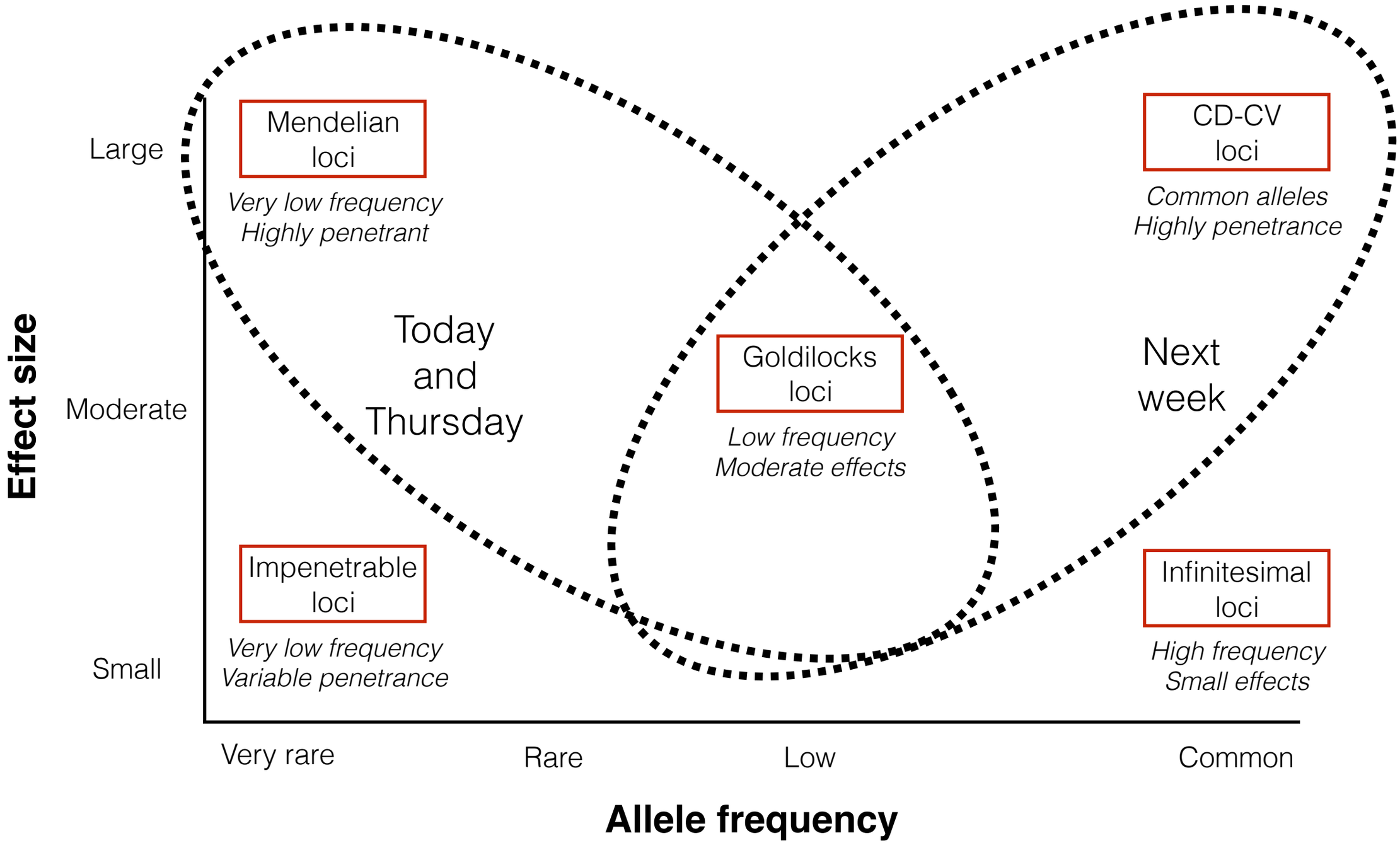
Bio393: Genetic Analysis

Family-based analysis, Modes of inheritance, Phase



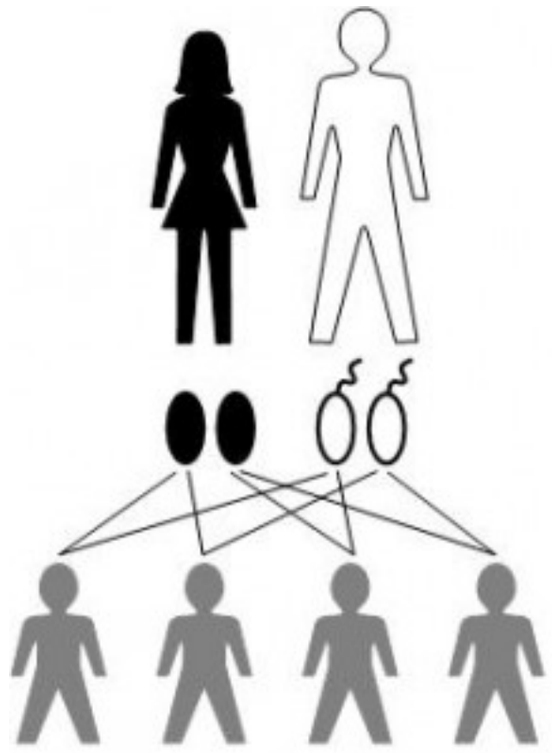
Lecture 14

The spectrum of how variation contributes to disease



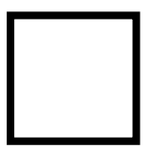
Linkage mapping studies or family-based mapping studies

Why do we study inheritance in families?

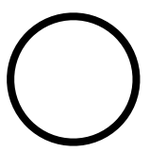


Correlating genetic variants with disease
tells us the disease gene is near that variant
(or is that variant)

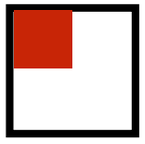
Human pedigree analysis allows us to follow traits in families



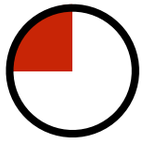
Male



Female



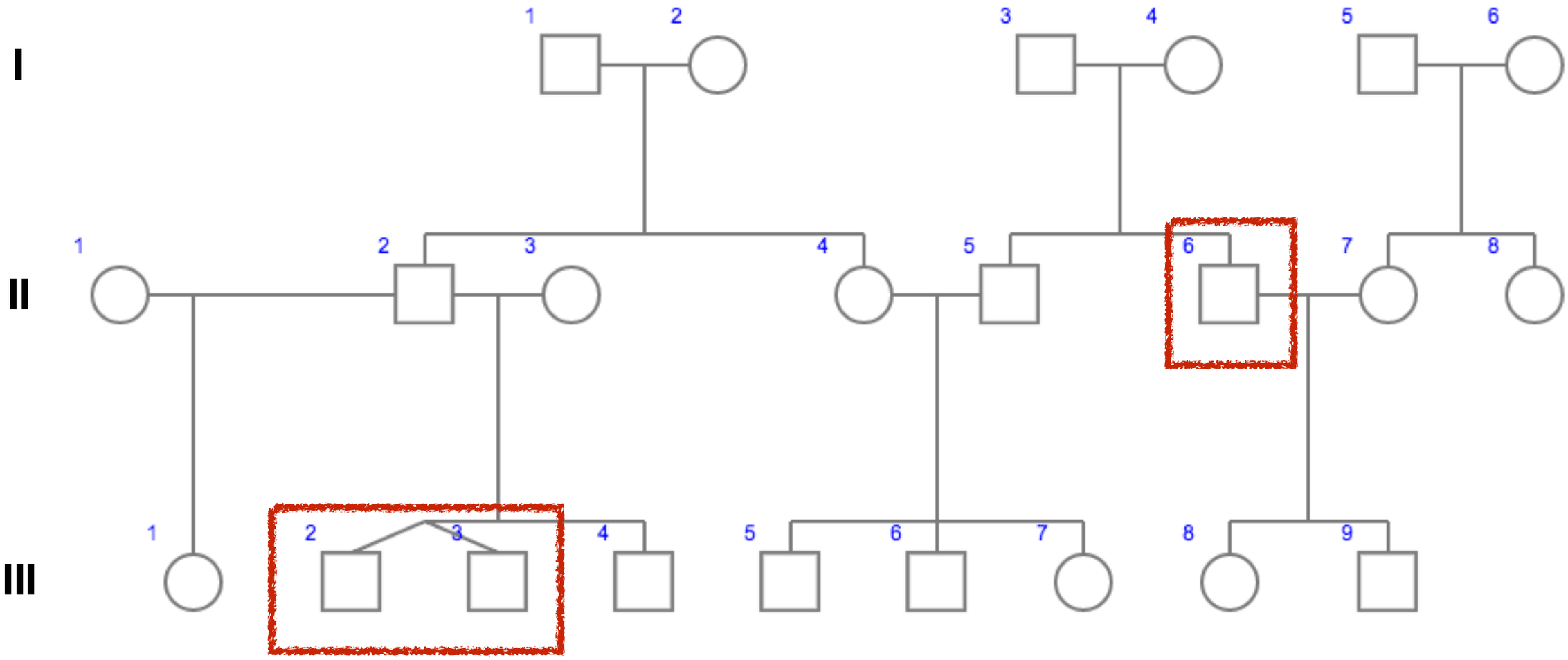
Affected male



Affected female

Remember that humans are diploid.

Human pedigree analysis allows us to follow traits in families

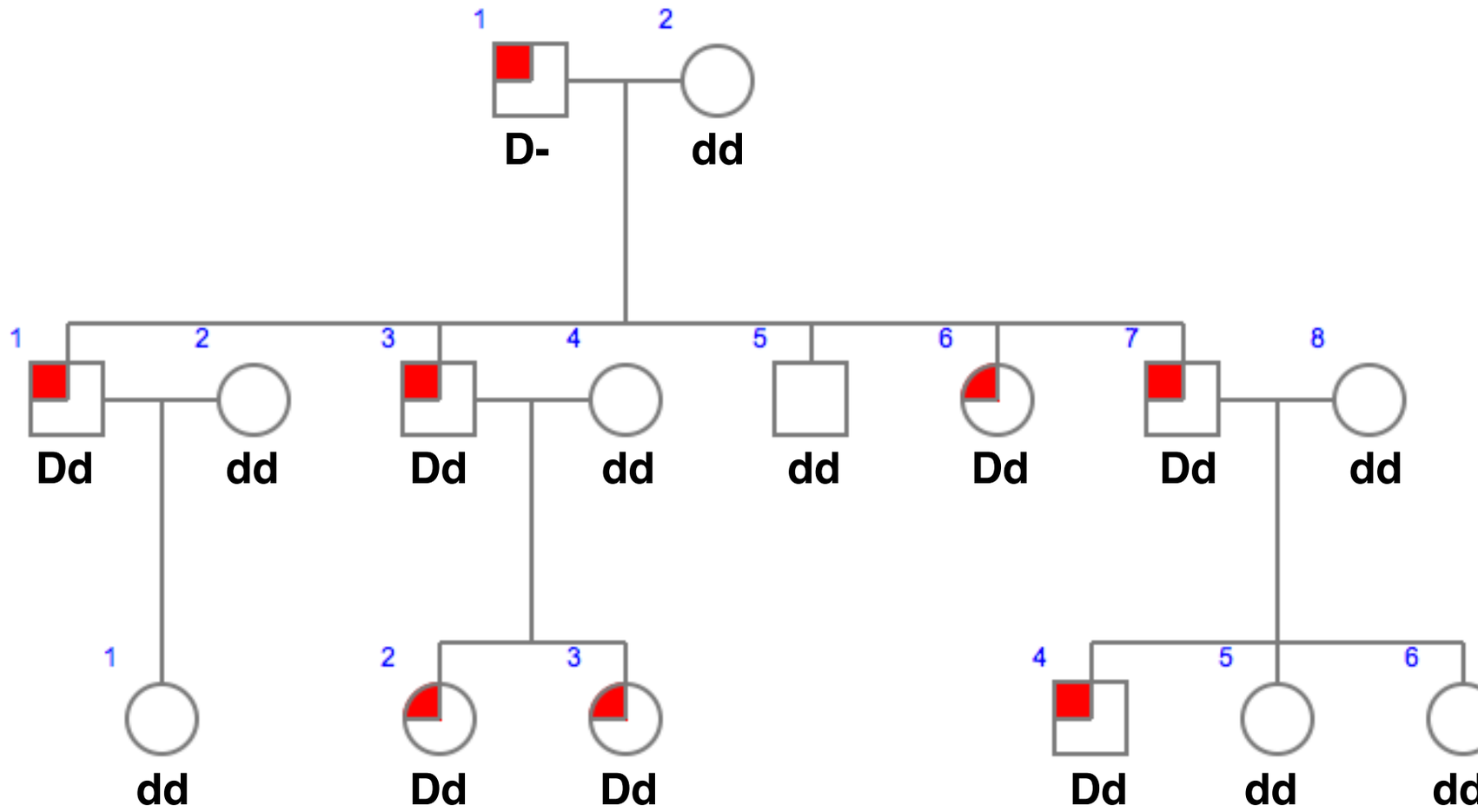


Individuals are numbered from left to right

Generations are numbered from top to bottom in Roman numerals

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

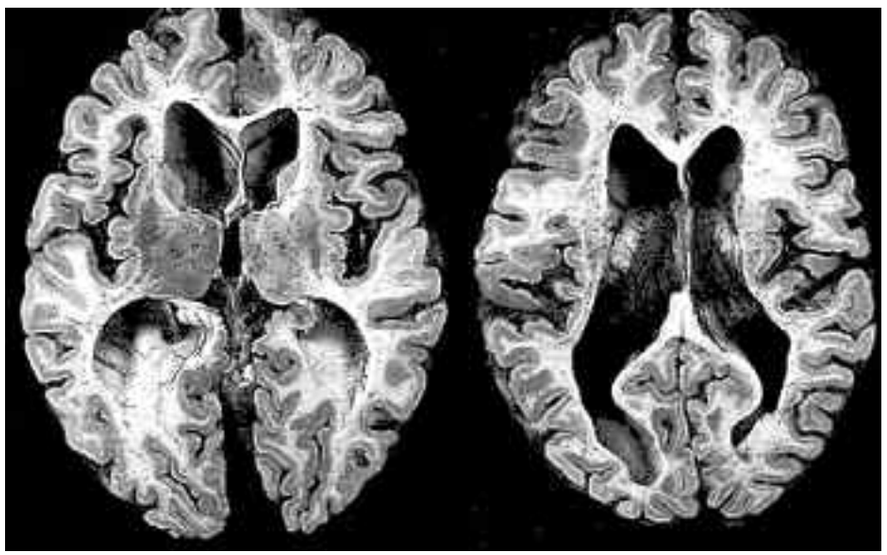
Modes of inheritance



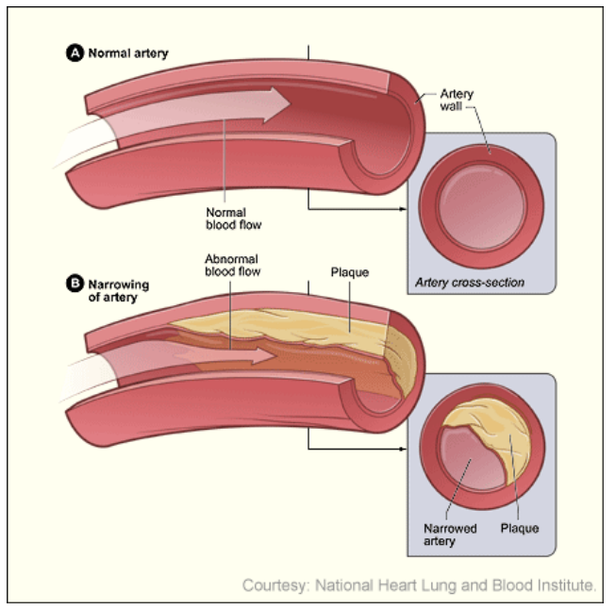
- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Autosomal dominant

Examples of human autosomal dominant disorders



Huntington's Disease
chr. 4



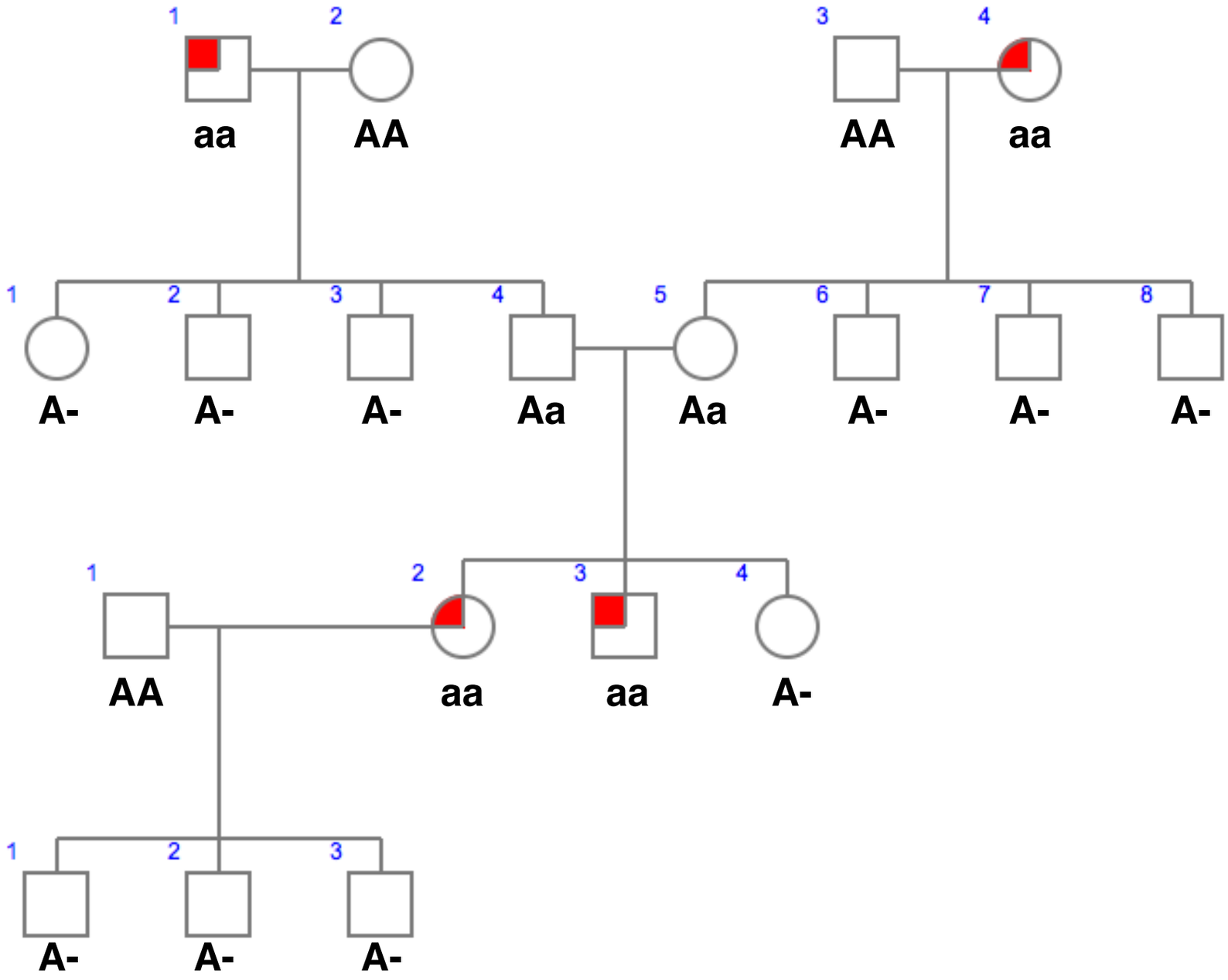
Familial Hypercholesterolemia
chr. 19

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



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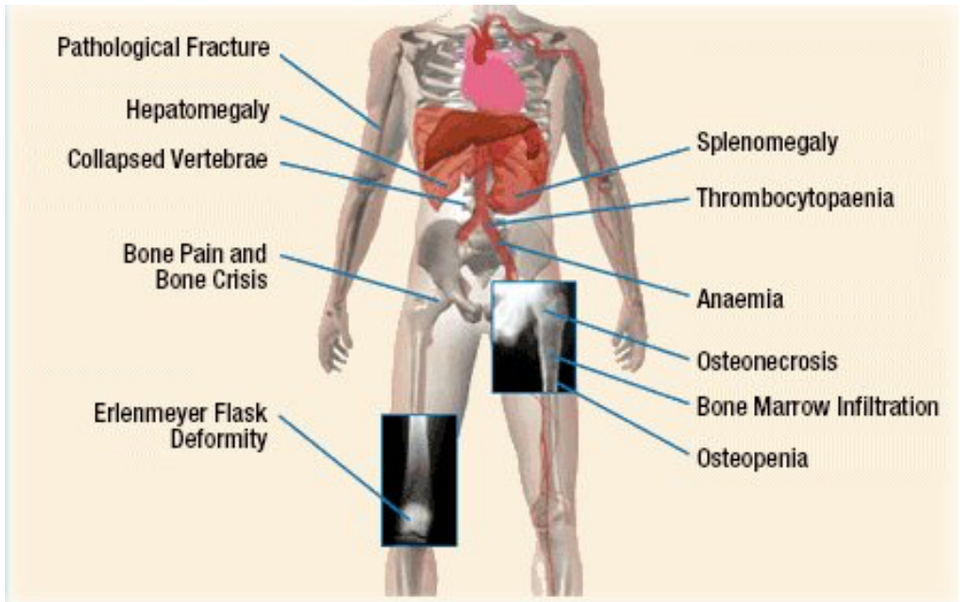
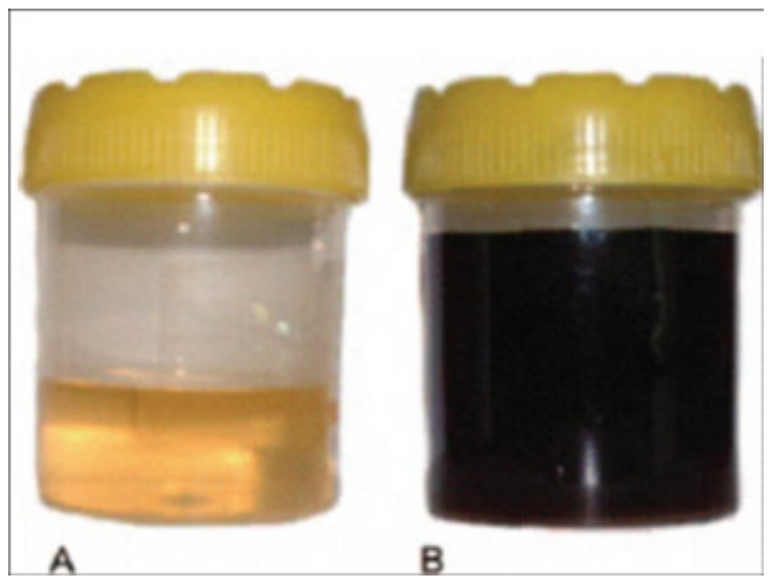
Autosomal recessive

Examples of human autosomal recessive disorders



Gaucher's Disease

chr. 1



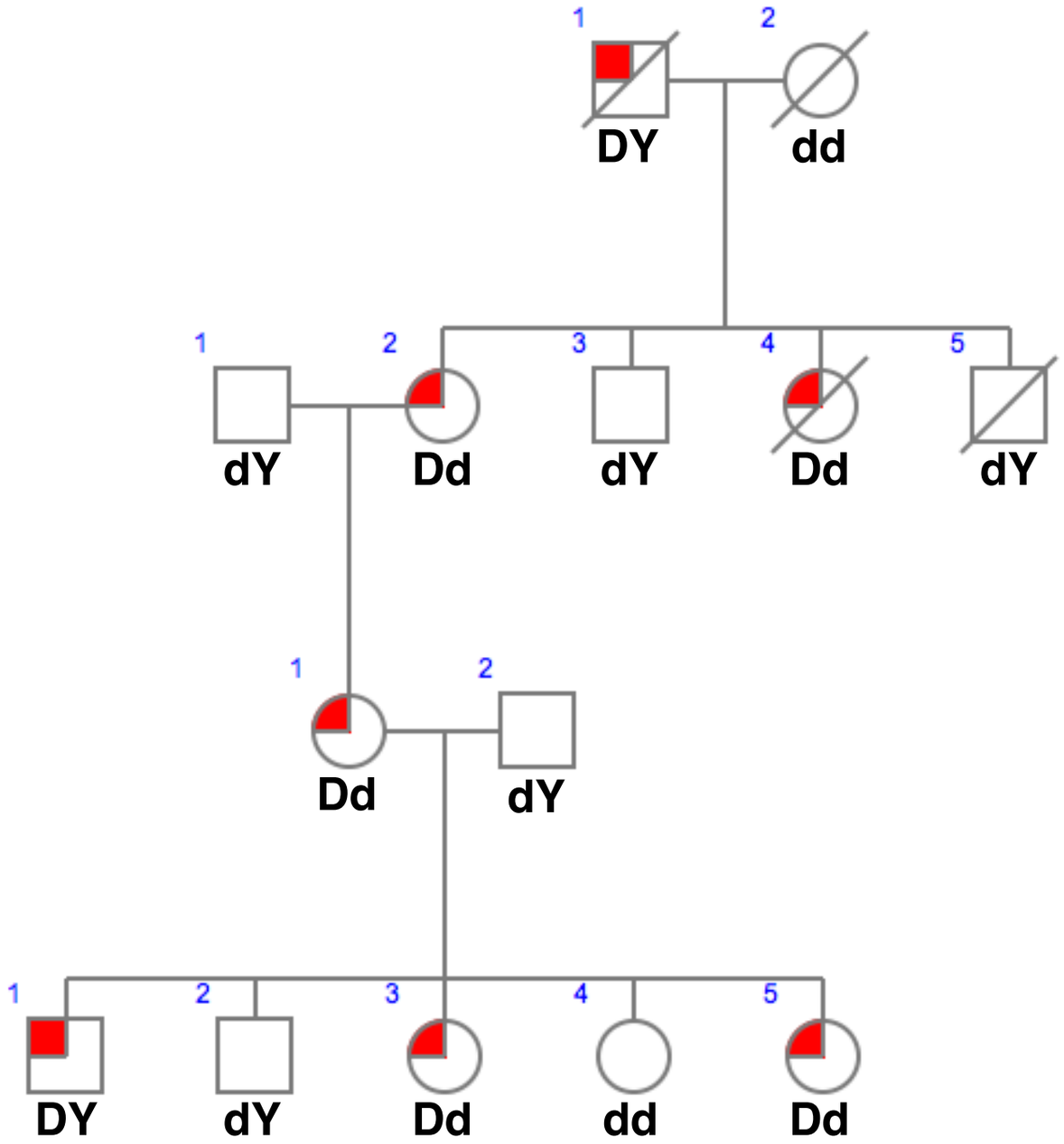
Maple Syrup Urine Disease

chr. 1, 6, or 19

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

All affected individuals are homozygotes

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

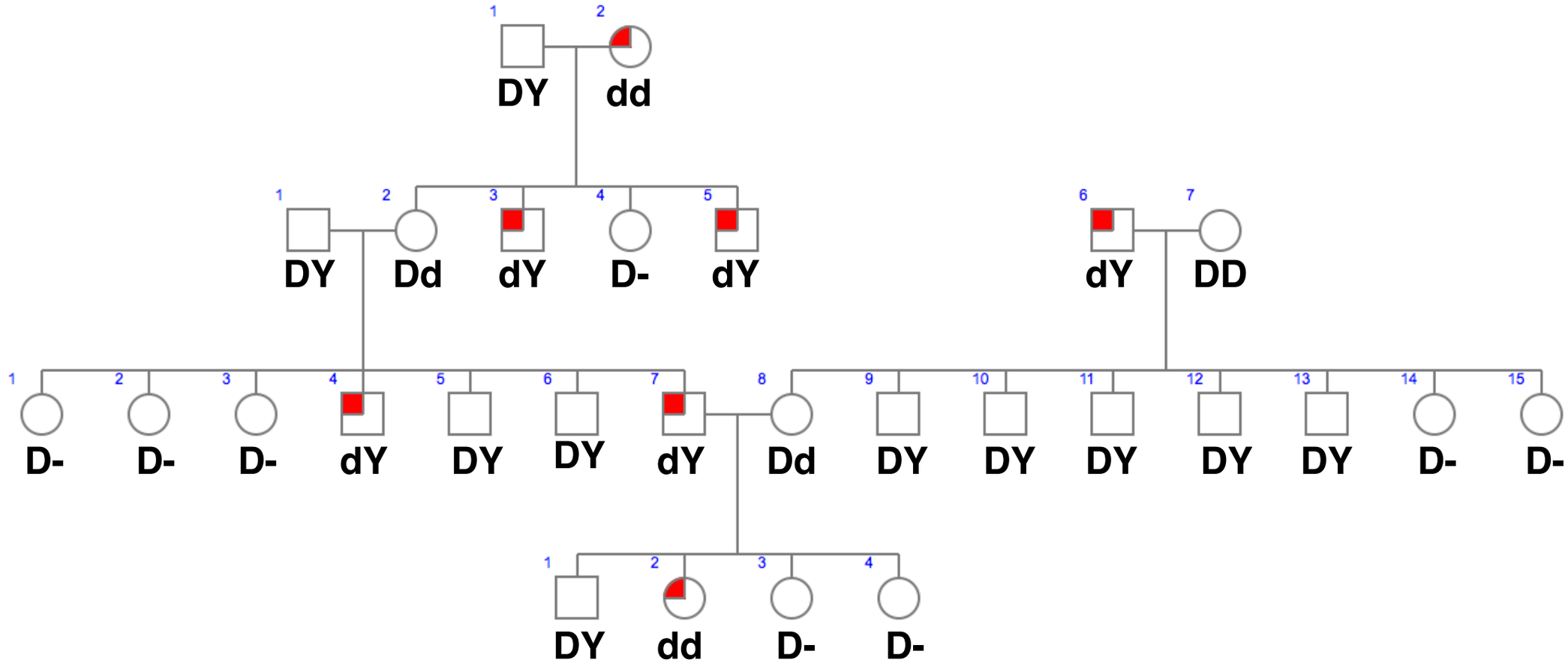
Examples of human X-linked dominant disorders

Rett syndrome

Fragile X syndrome

All daughters of affected fathers are affected

Modes of inheritance



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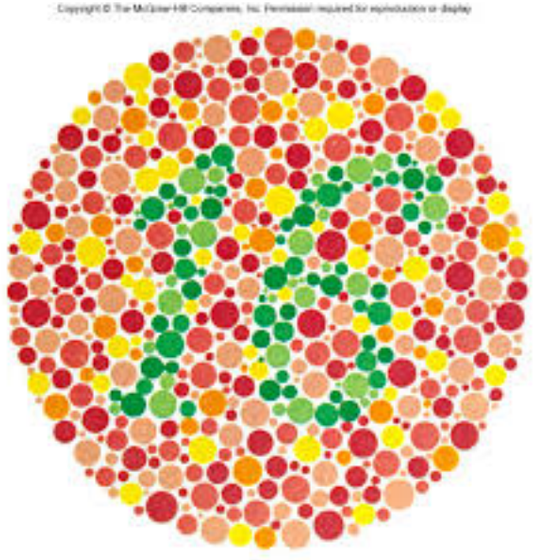
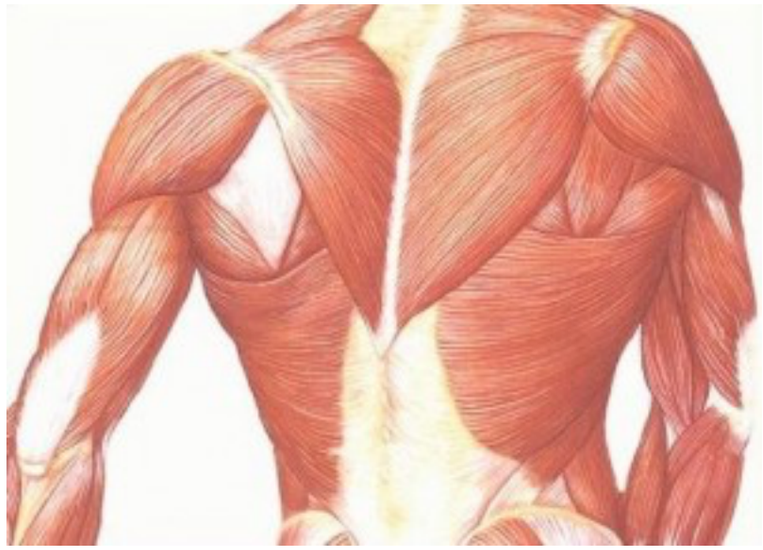
X-linked recessive

Examples of human X-linked recessive disorders



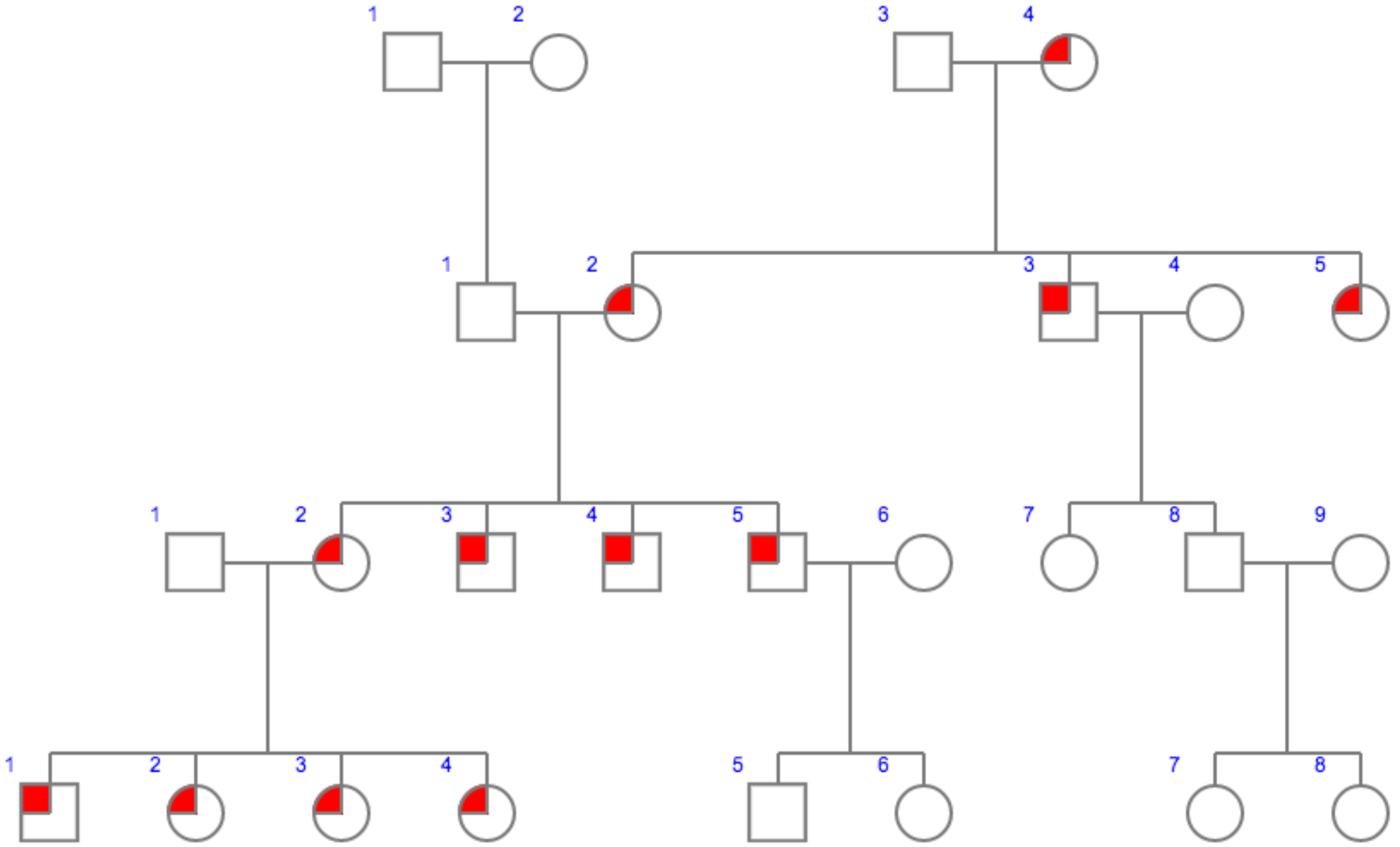
Red-green color blindness



Duchenne muscular dystrophy

All sons of affected mothers are affected

Modes of inheritance

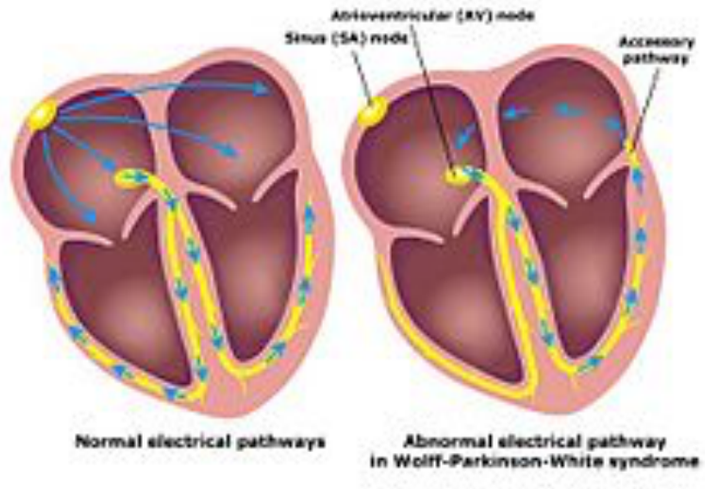


- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Cytoplasmic inheritance

Examples of human cytoplasmic inheritance disorders

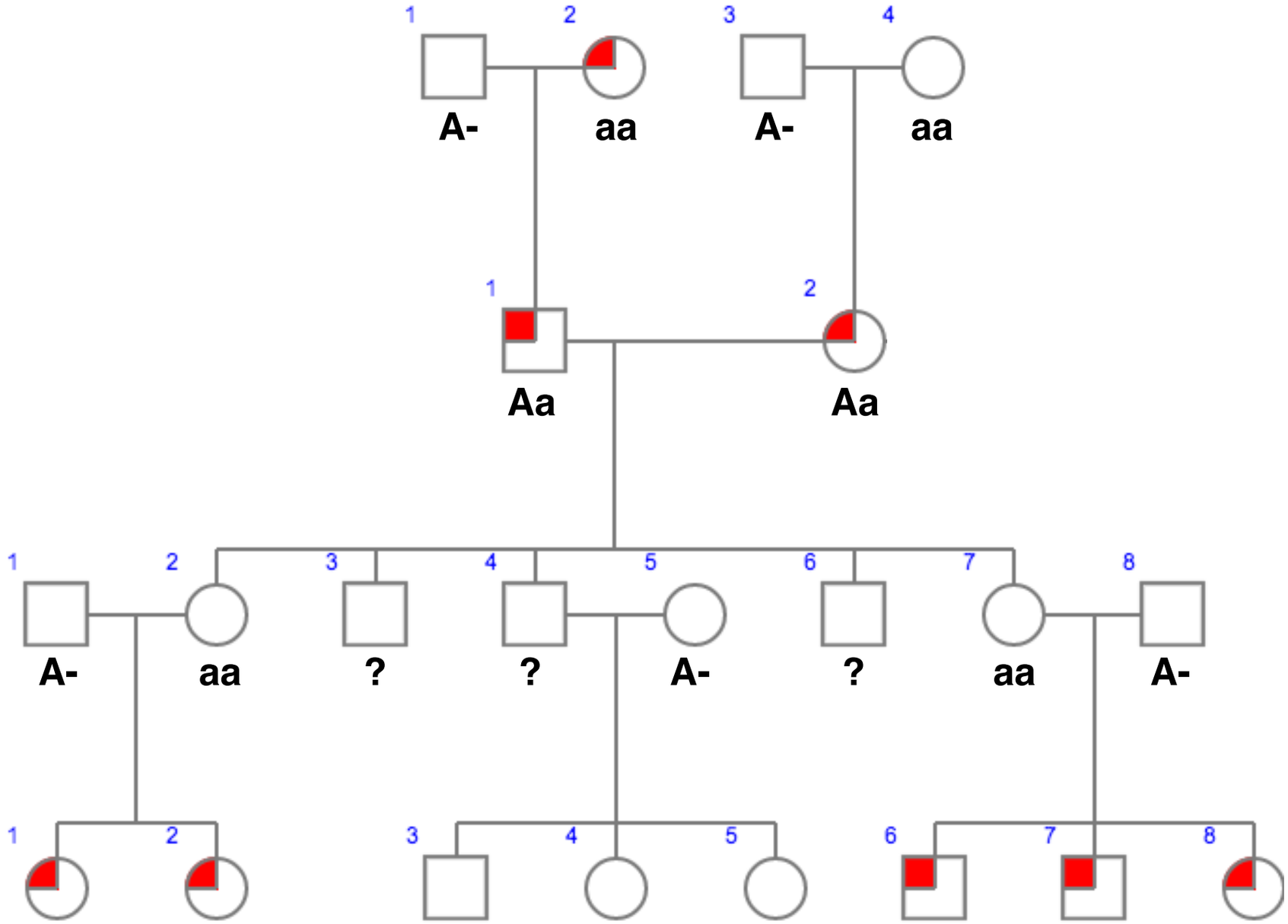
Mitochondrial myopathy



Wolff-Parkinson-White syndrome

All children of affected mothers are affected

Modes of inheritance



- How many individuals are affected?
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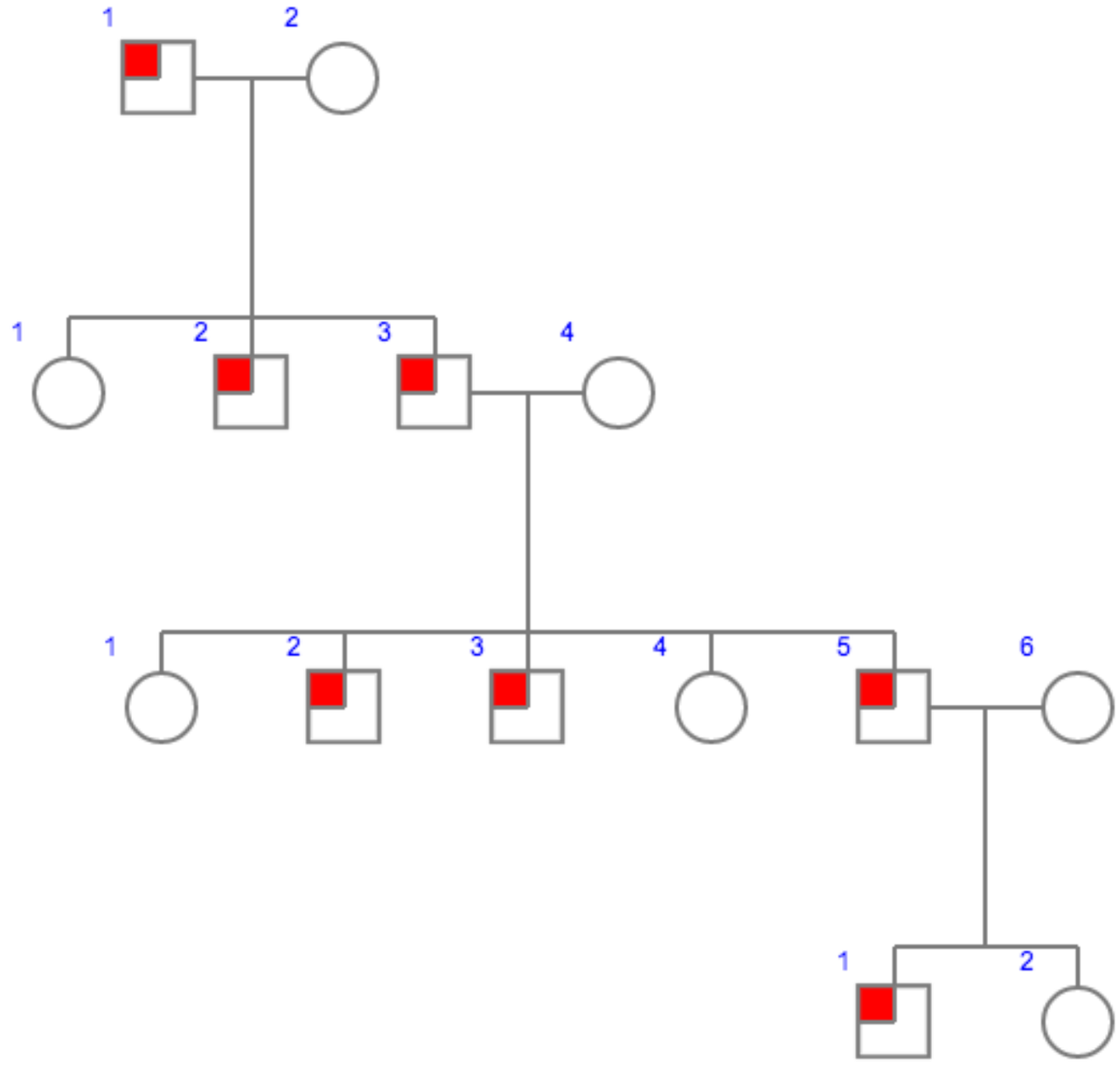
- Are females preferentially affected from affected fathers?

Recessive maternal-effect inheritance

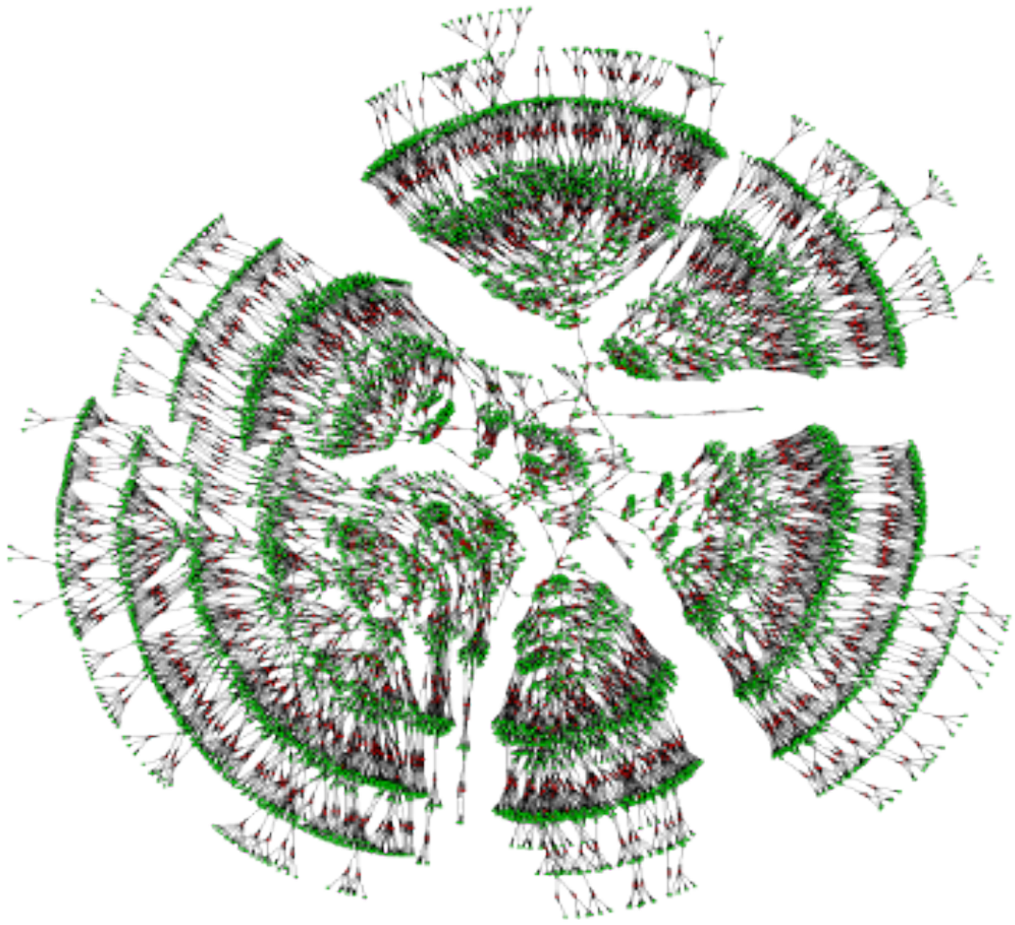
Modes of inheritance

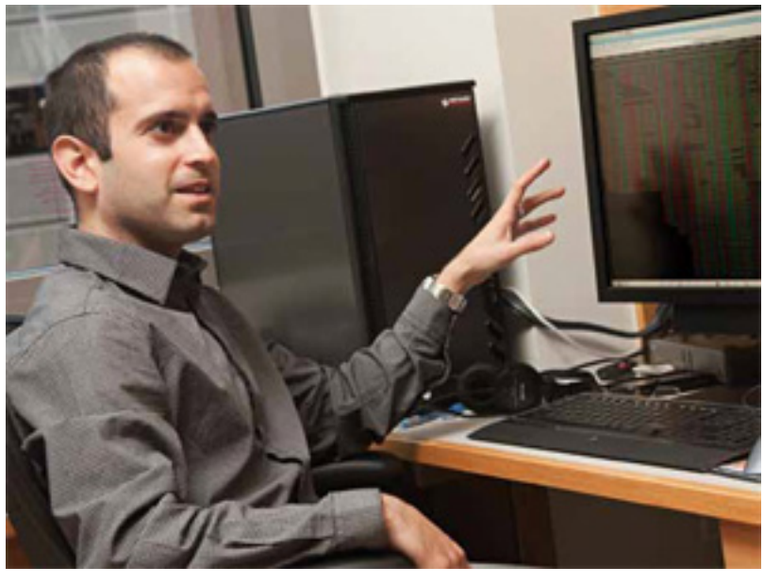


- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Y-linked inheritance

Some pedigrees can contain millions of individuals

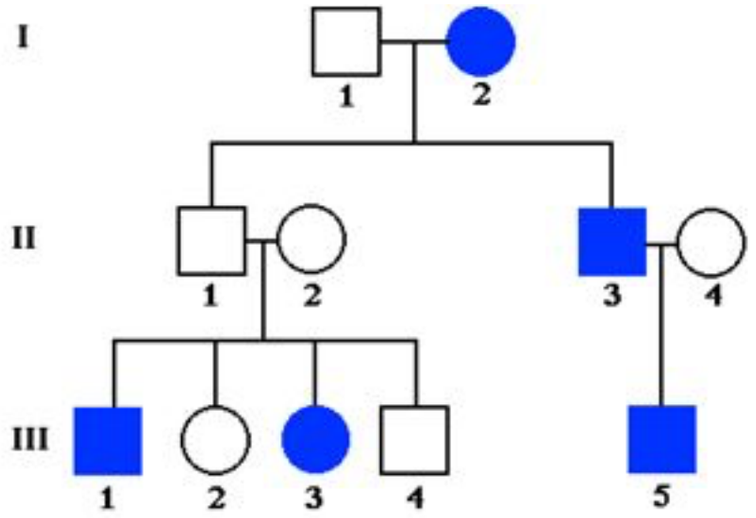




Yaniv Erlich

Ancestry websites offer rich family data

Remember all of the genetics we've learned so far



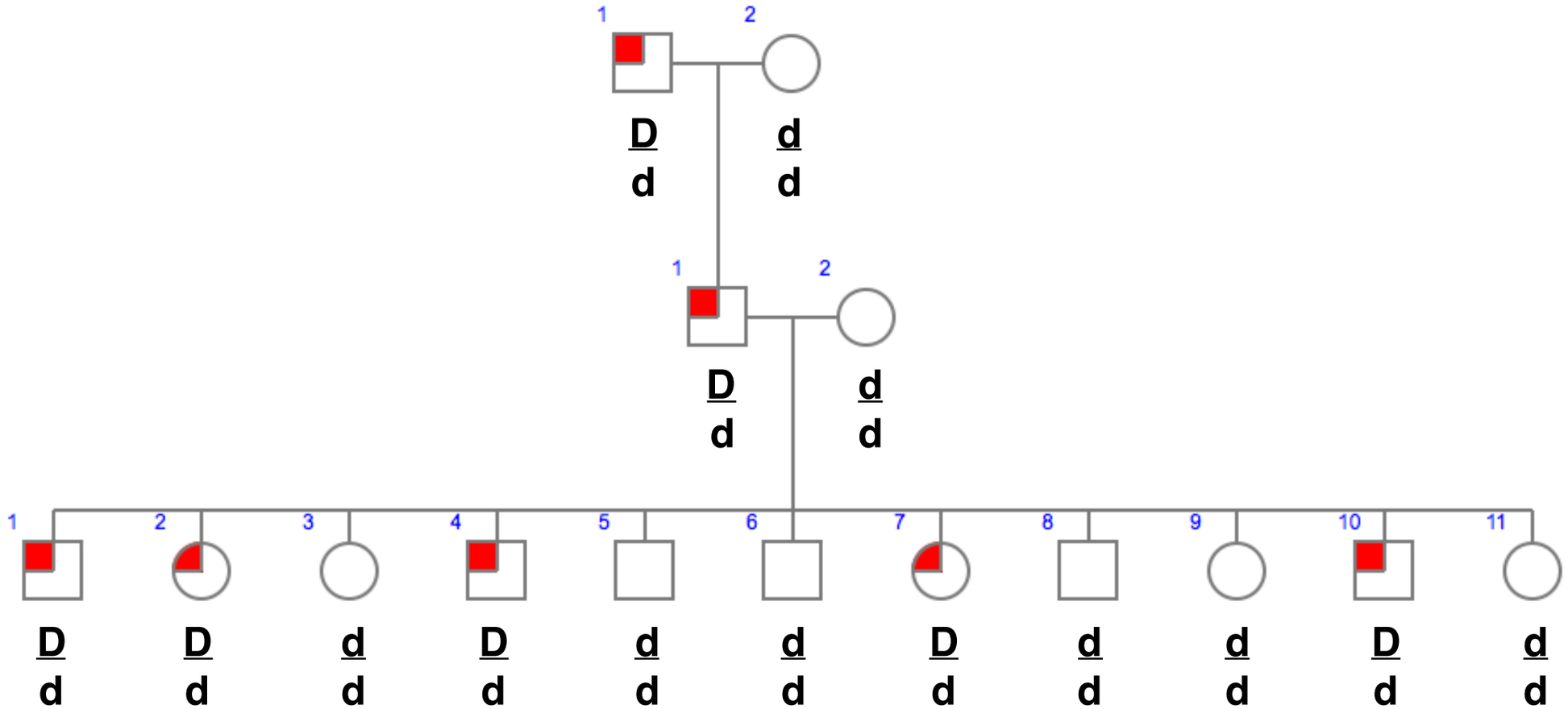
Incomplete penetrance

Non-complementation

Haploinsufficiency

Suppression and enhancement

We want to be able to find a marker linked with 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

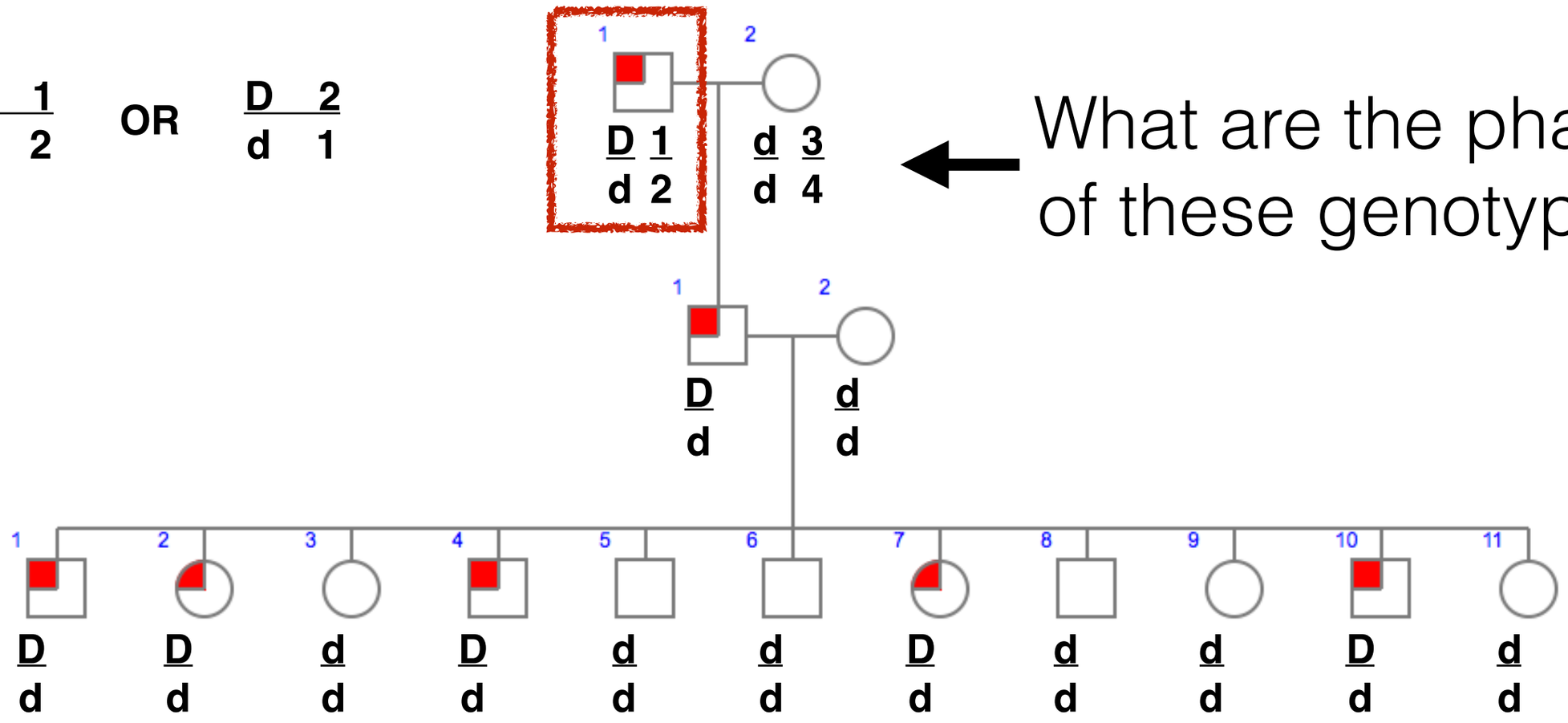
Microsatellites or short tandem repeats (STRs)

Reference **ATGTGCAGCAGCAGCAGCGTA**

Alternative **ATGTGCAGCAGCGTAGTGACT**

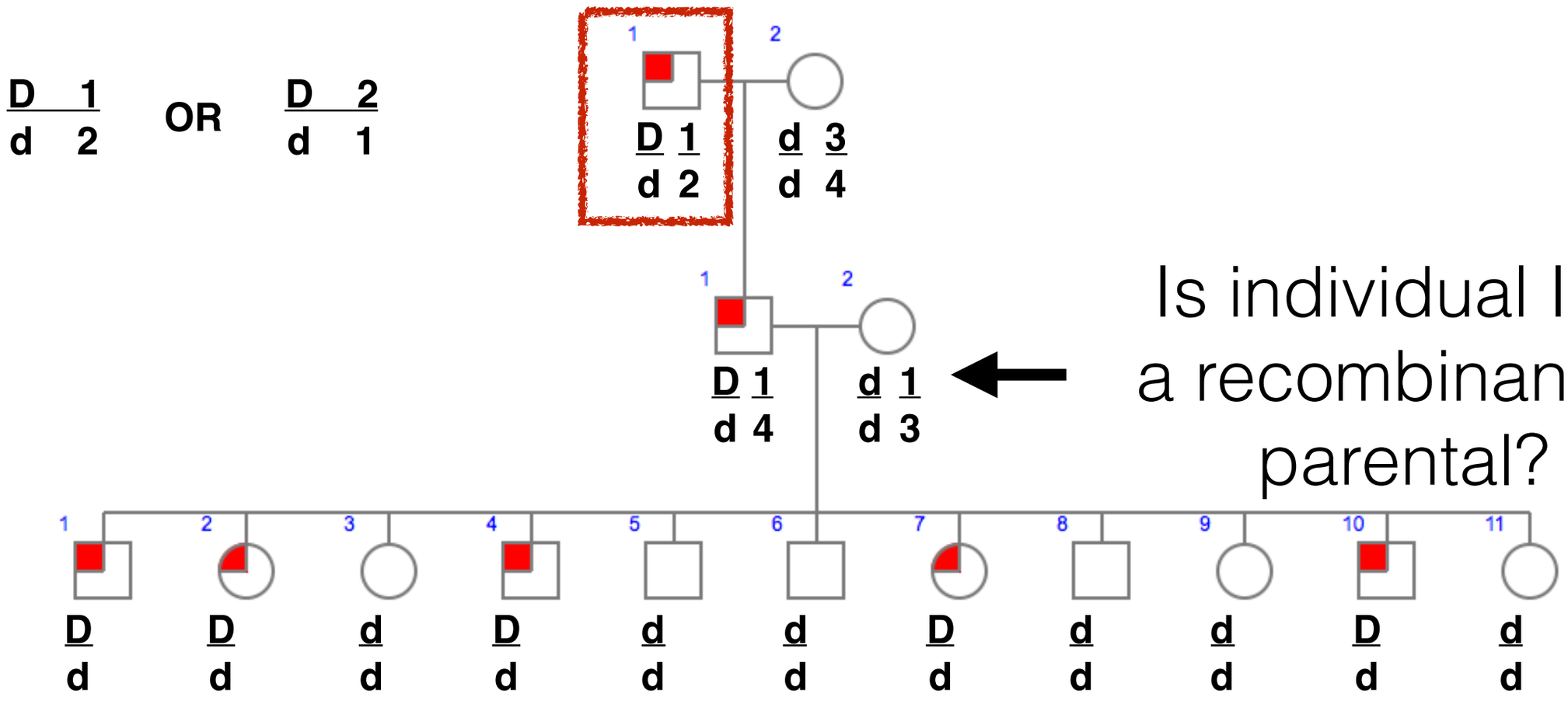
Linkage to genetic markers tells us where disease genes are

$\frac{D\ \ 1}{d\ \ 2}$ OR $\frac{D\ \ 2}{d\ \ 1}$

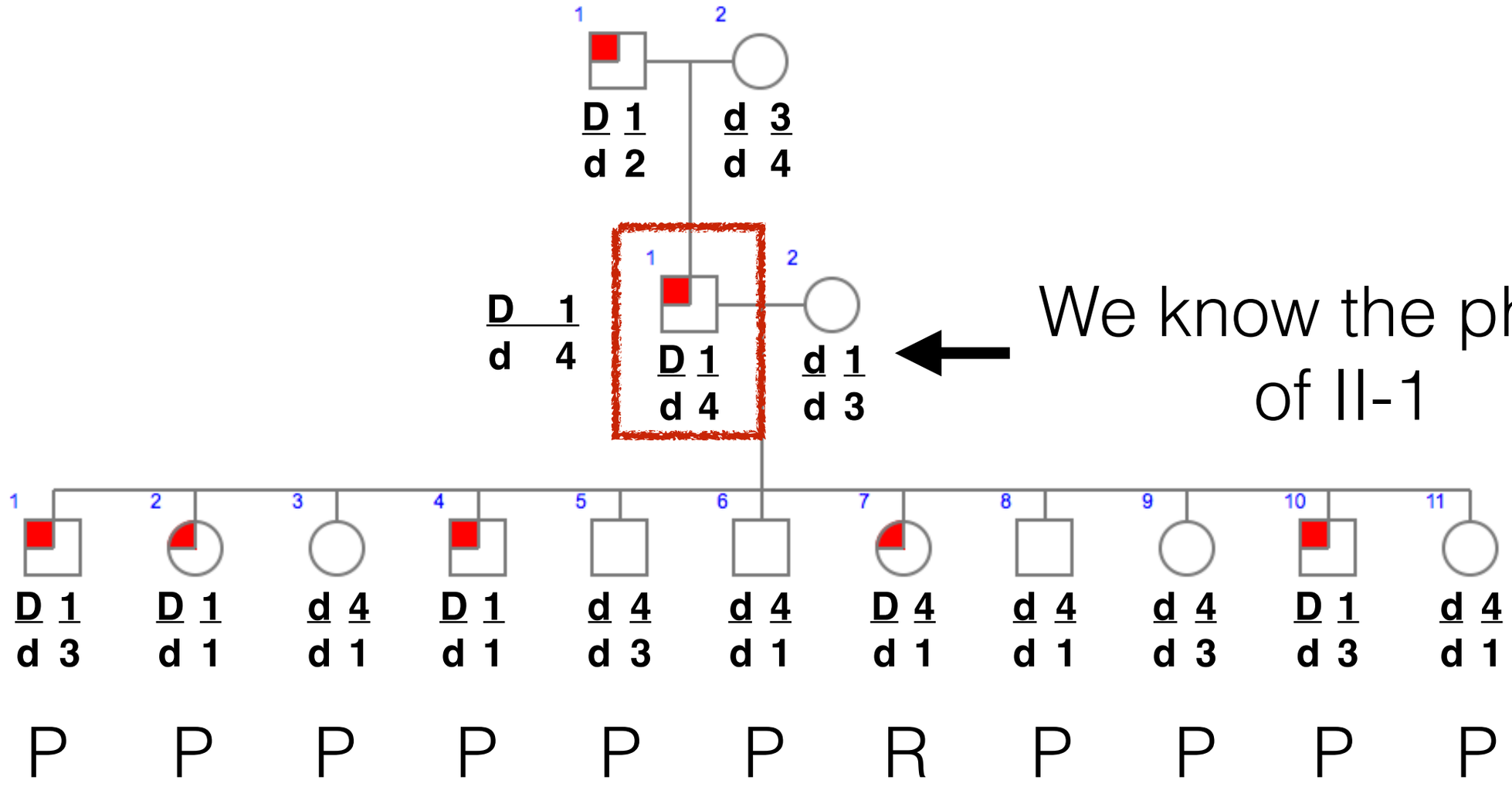


What are the phases of these genotypes?

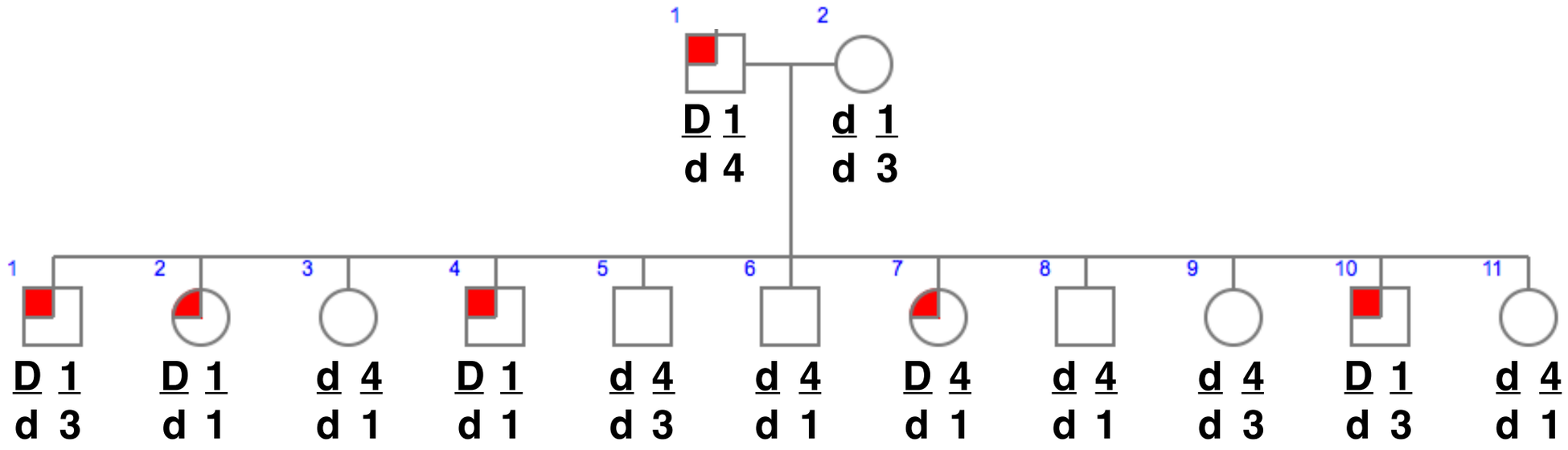
Linkage to genetic markers tells us where disease genes are



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

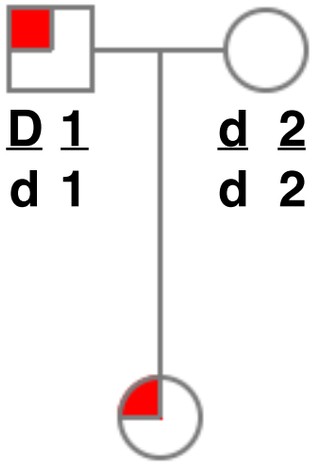
OR

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

Some allelic combinations are non-informative and can not be included in mappings

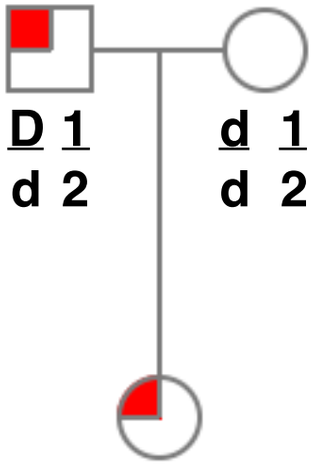
Consider a dominant trait and a variant marker:



D 1
d 2

Uninformative

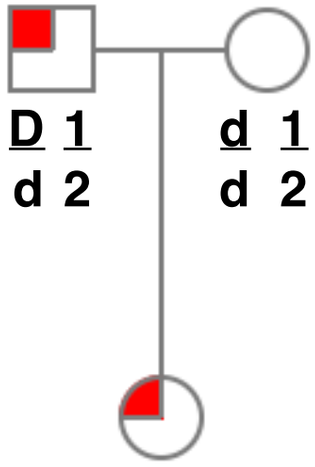
Which marker
is linked
to disease allele?



D 1
d 2

Uninformative

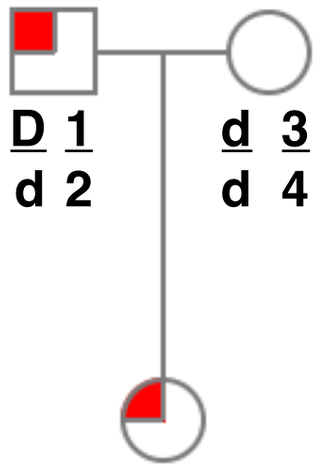
Which marker 1
is inherited
from Dad?



D 1
d 1

Informative

Each marker 1
must have come
from Mom and Dad



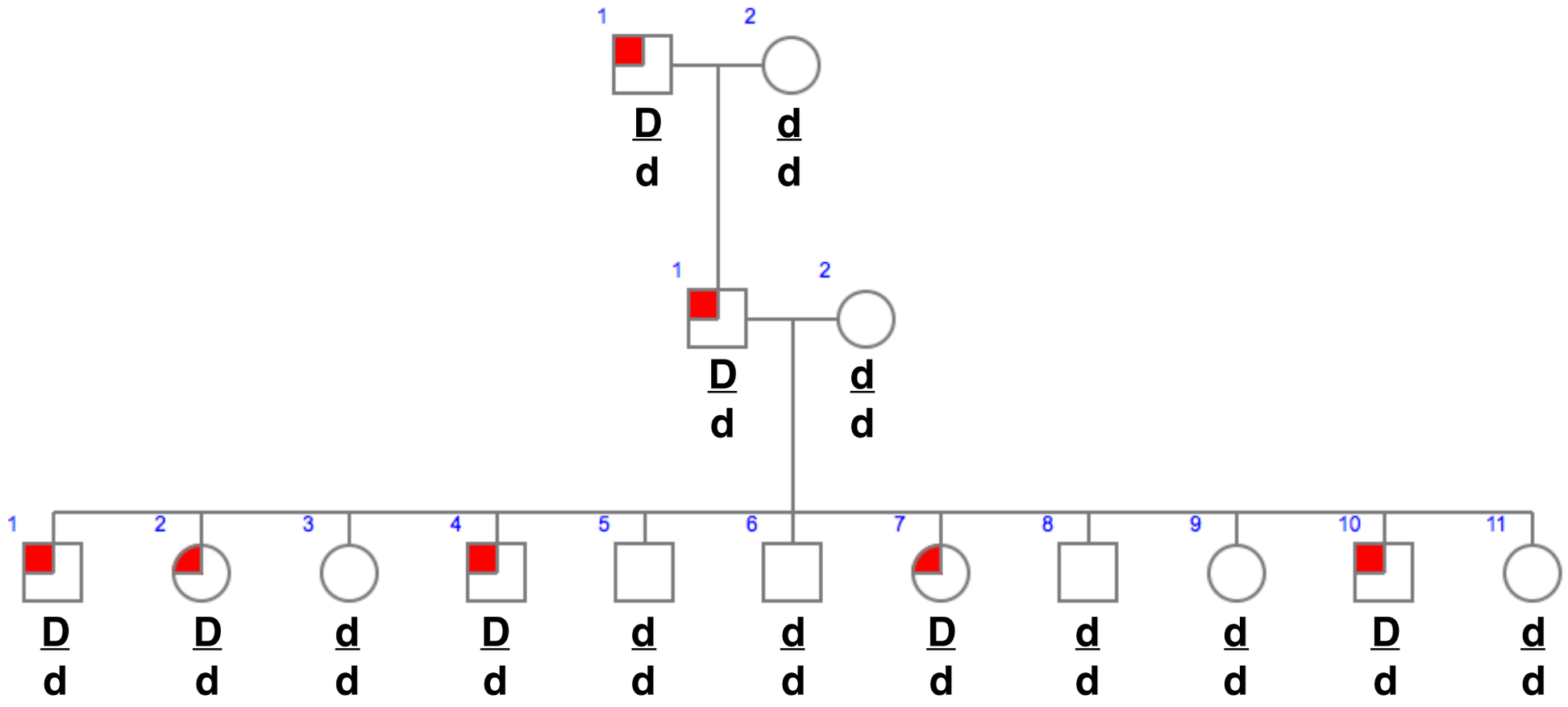
D 1
d 3

Informative

Different marker
alleles

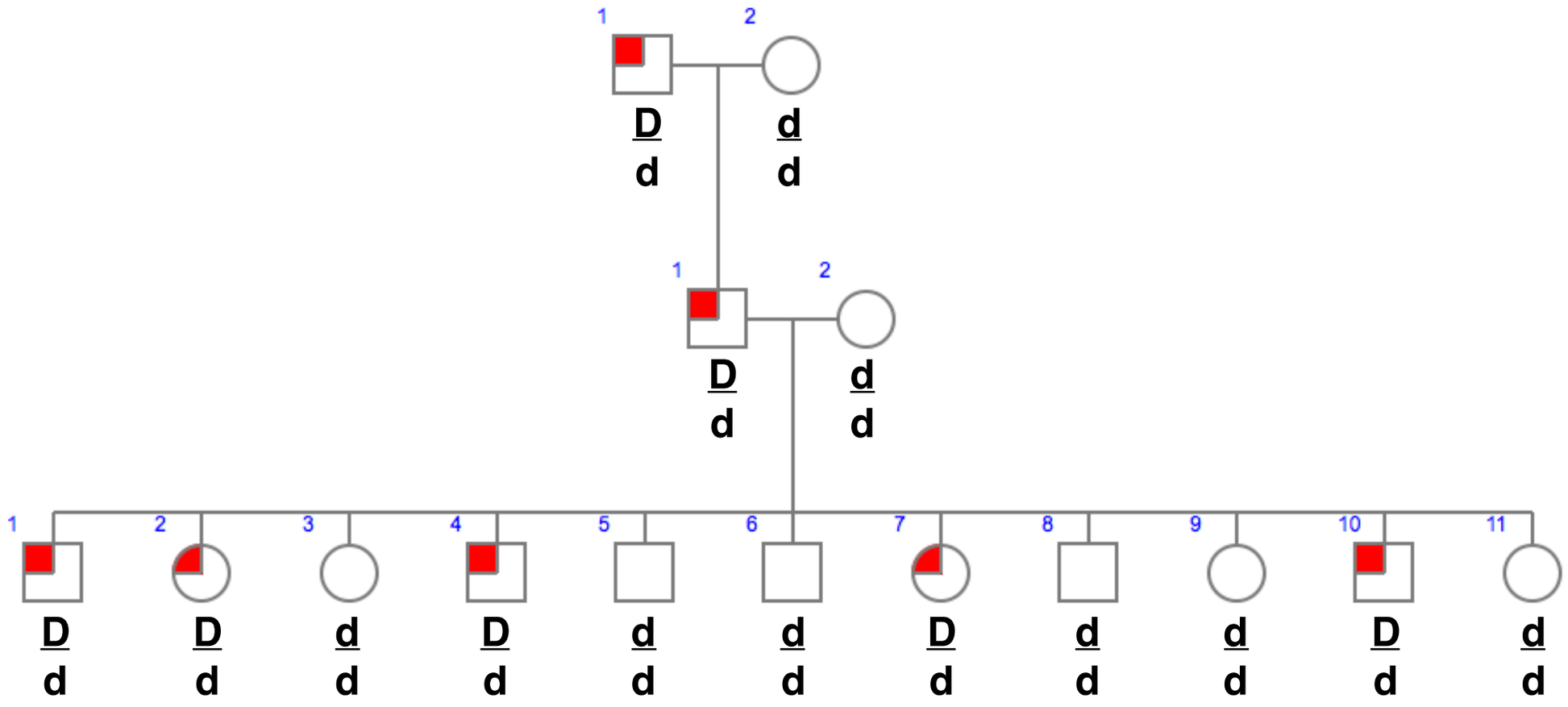
We want to determine if the daughter inherited a recombinant or parental chromosome

Imagine you could genotype millions of markers in each individual



The goal is to measure linkage of many markers to the disease-causing allele to map the gene

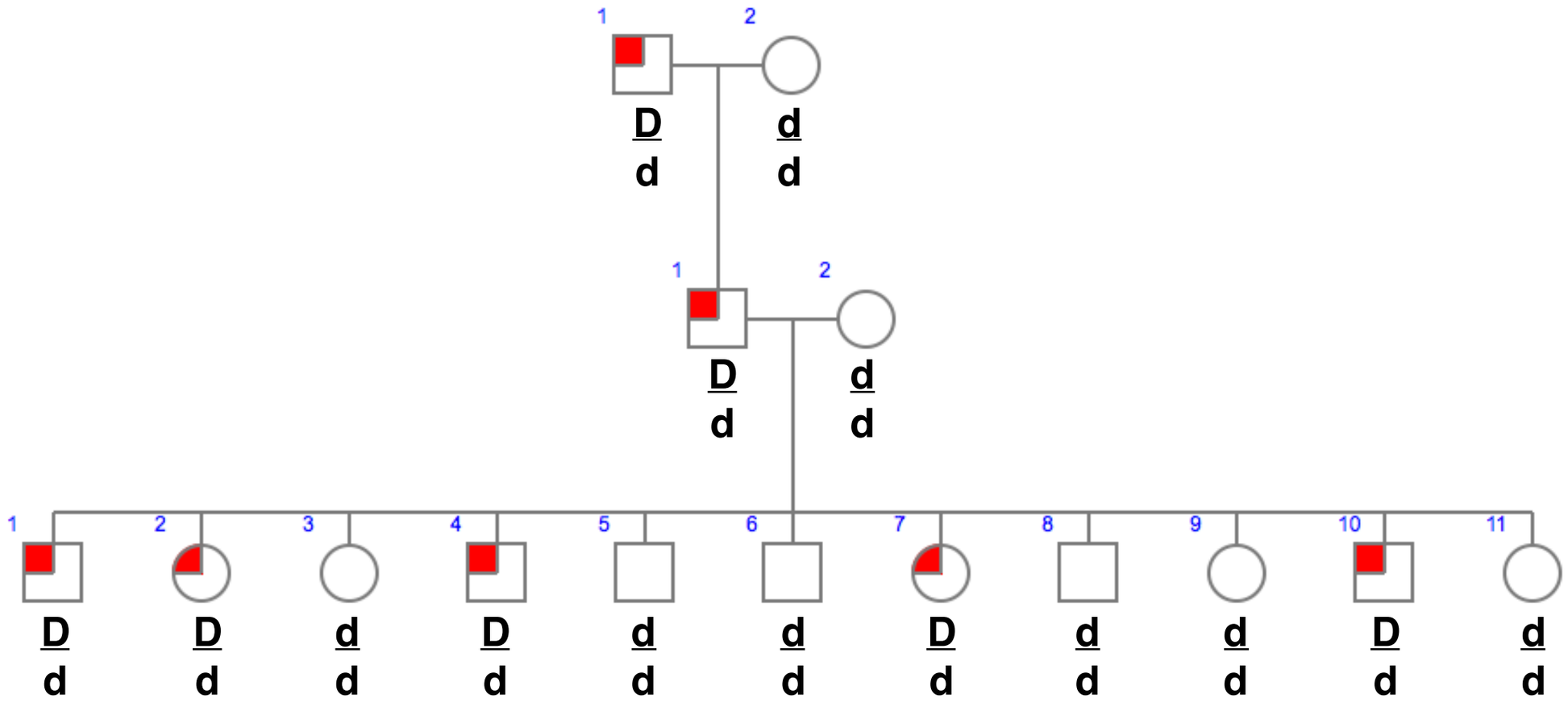
We want to measure how close each marker is to the disease-causing allele



$$\frac{\textbf{Number of recombinants}}{\textbf{Total progeny}} \times \textbf{100} = \textbf{Recombination frequency}$$

But we don't know who is a recombinant because we don't have true-breeding strains

We want to measure how close each marker is to the disease-causing allele



Likelihood of linkage between marker and disease-causing allele

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Likelihood of NO linkage between marker and disease-causing allele