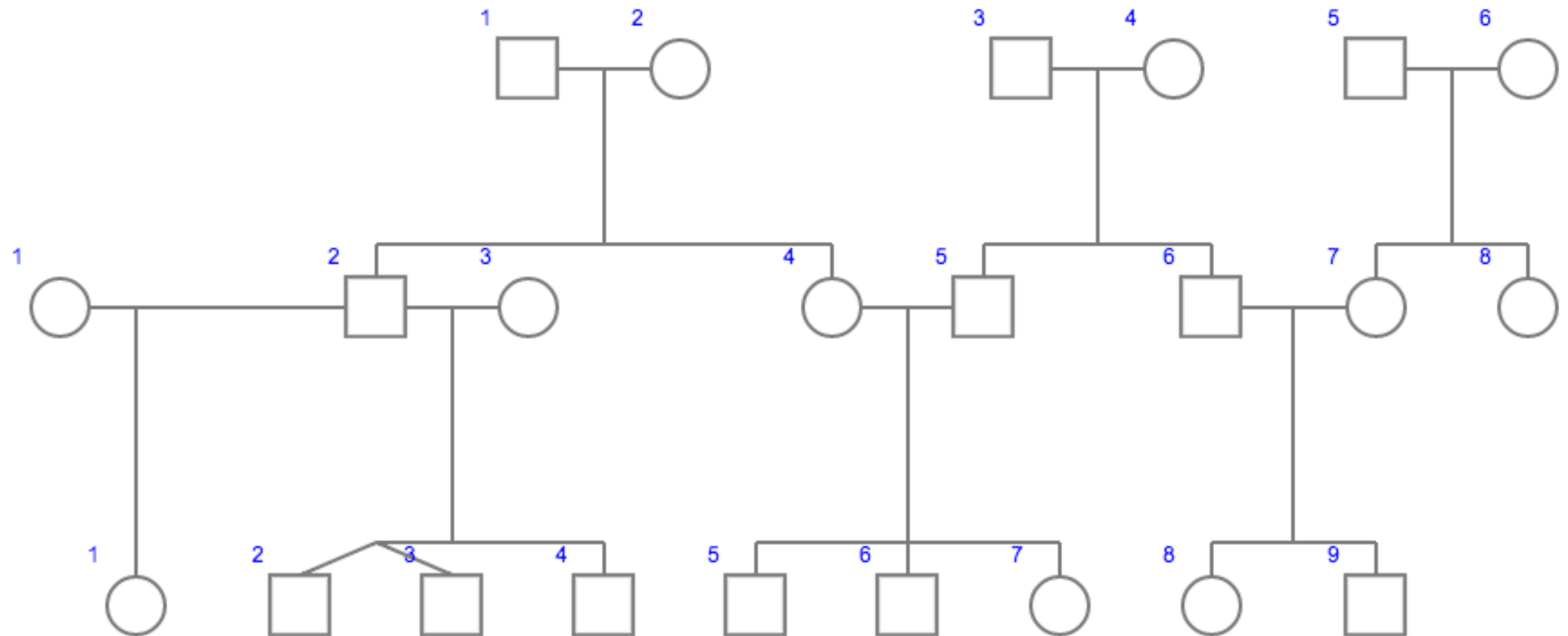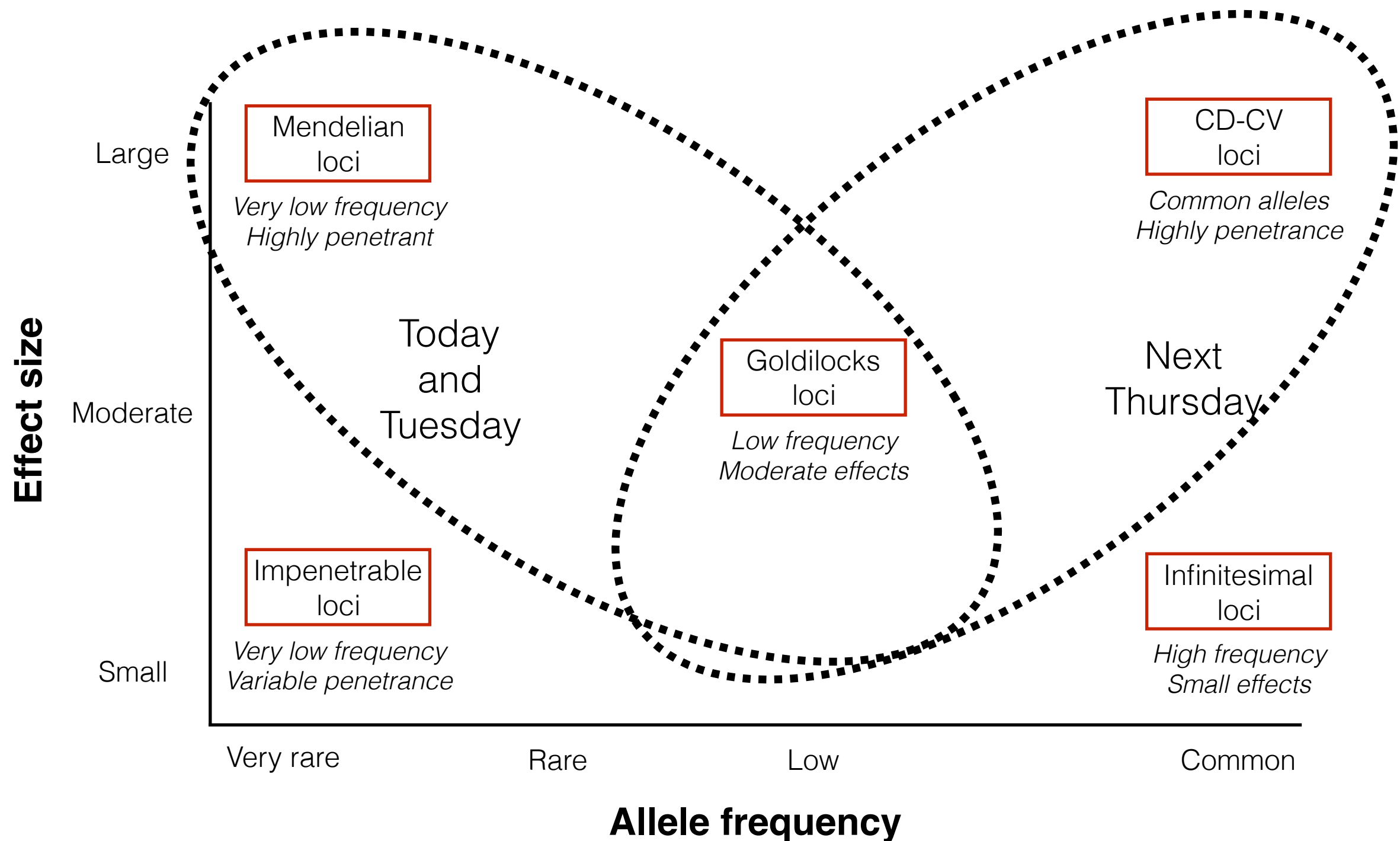# Bio393: Genetic Analysis

Family-based analysis, Modes of inheritance, Phase
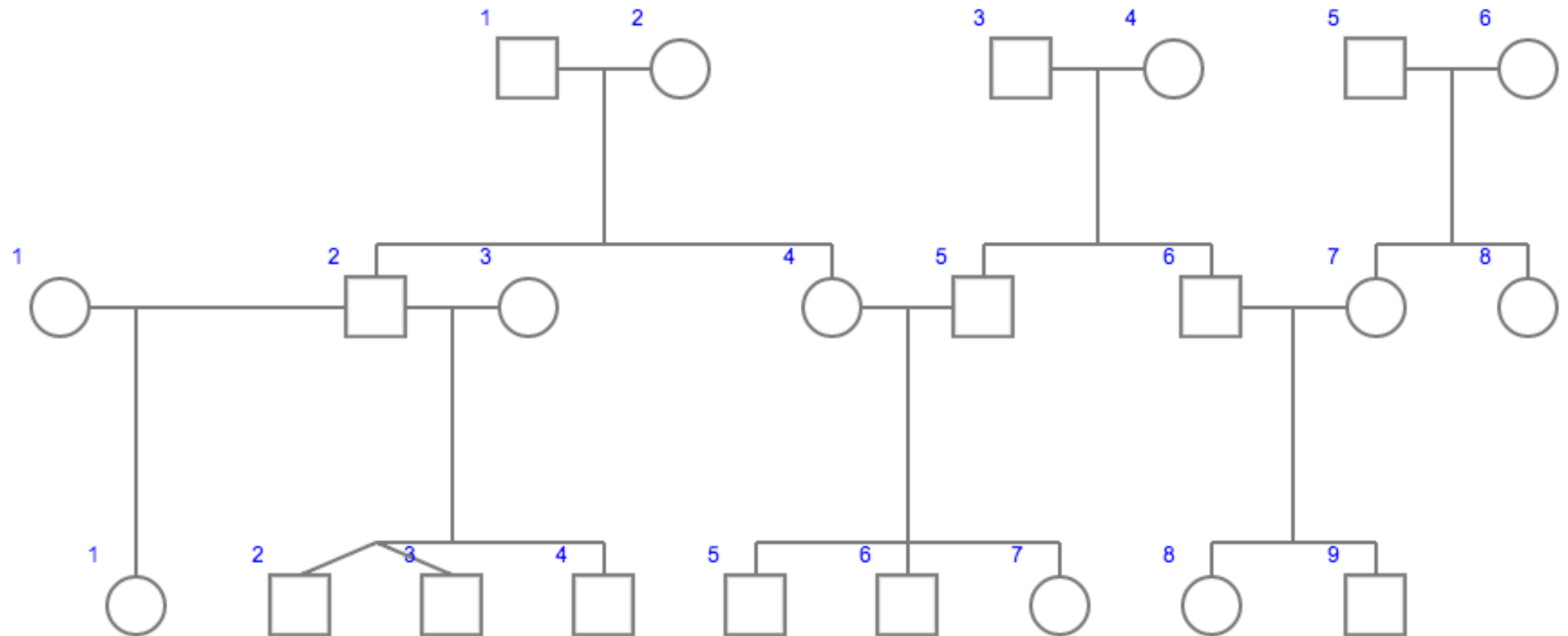
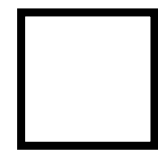# The spectrum of how variation contributes to disease

Linkage mapping studies or family-based mapping studies

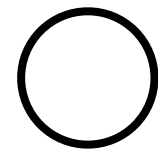# Why do we study inheritance in families?

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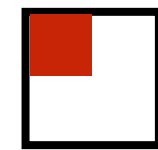(or is that variant)

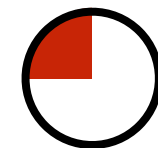# Human pedigree analysis allows us to follow traits in families
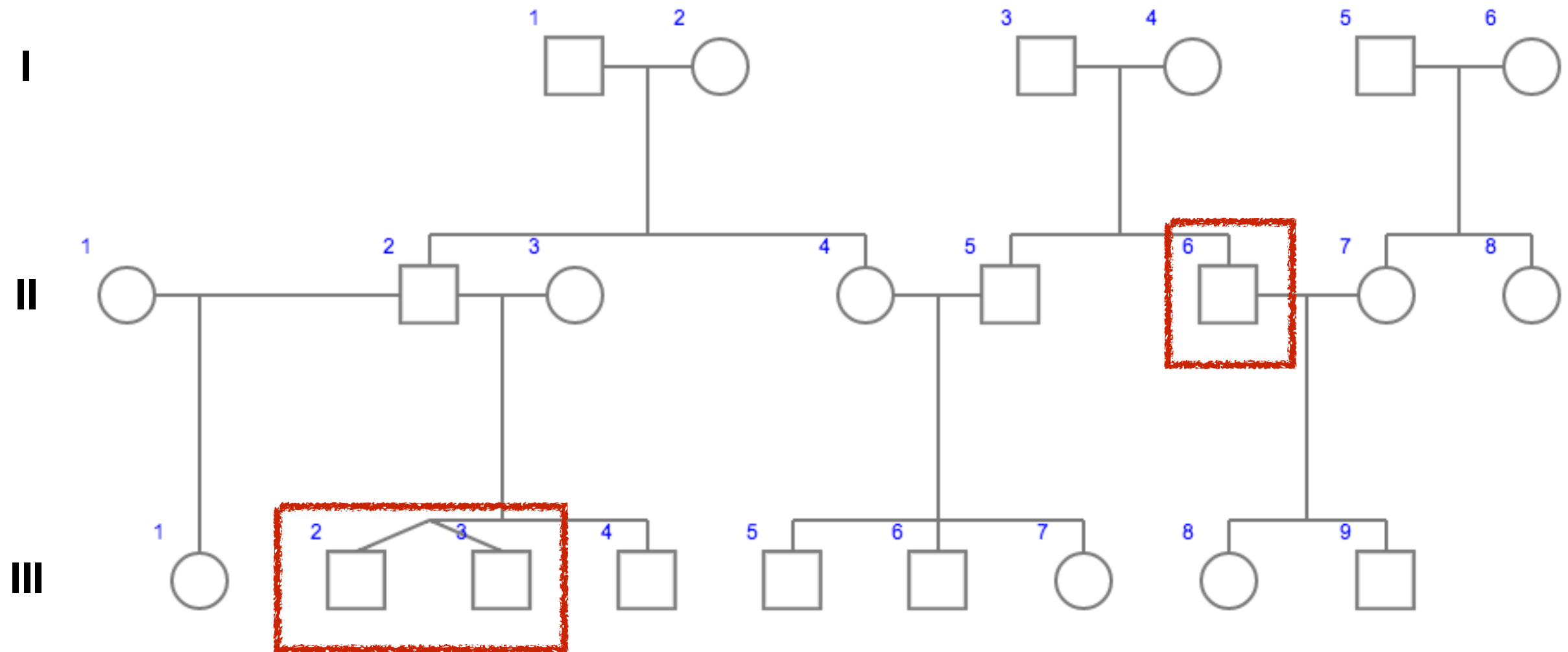
☐ Male

◯ Female

◧ Affected male

◖ Affected female

Remember that humans are diploid.

Human pedigree analysis allows us to follow traits in families

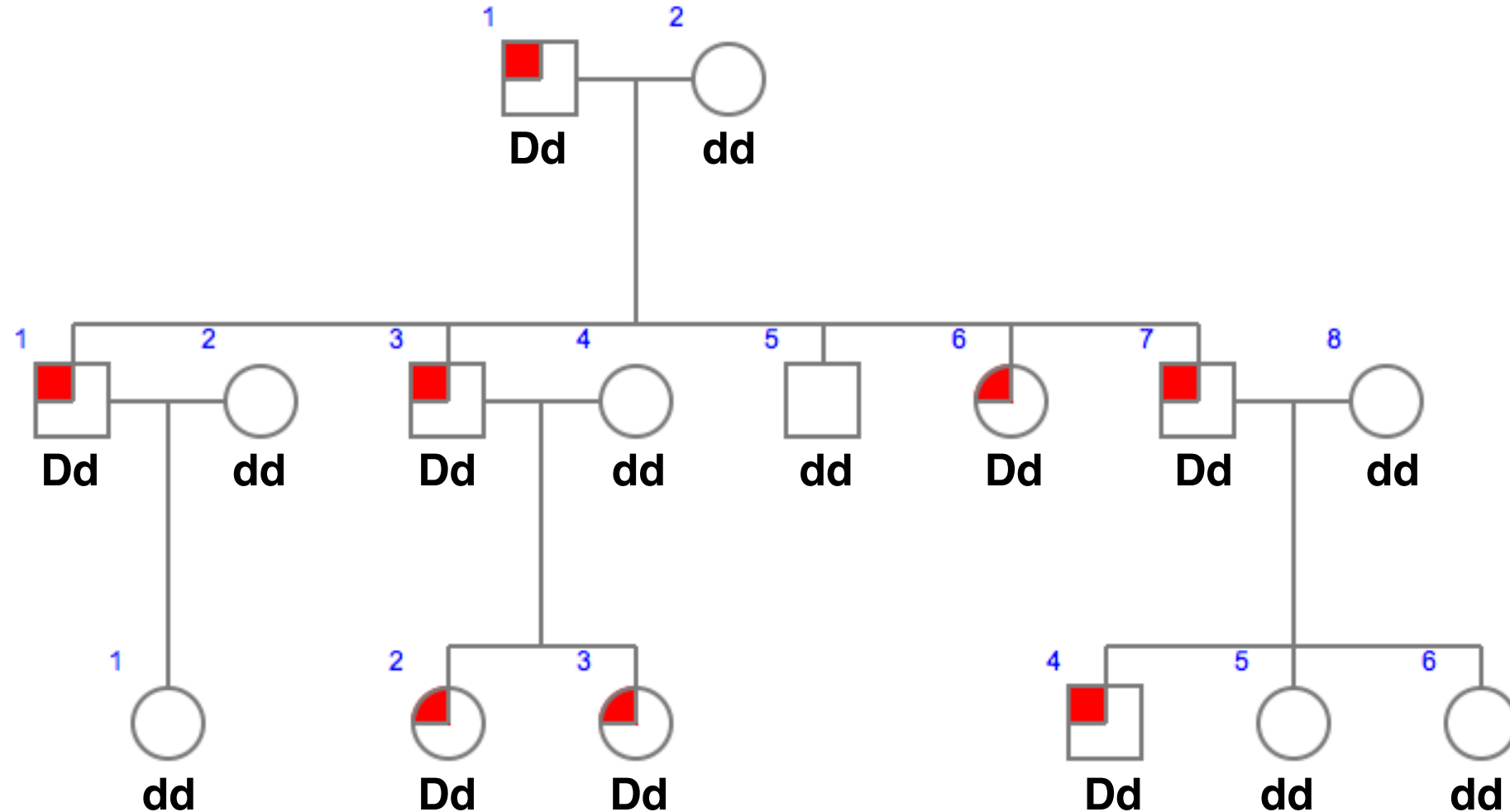Individuals are numbered from left to right

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

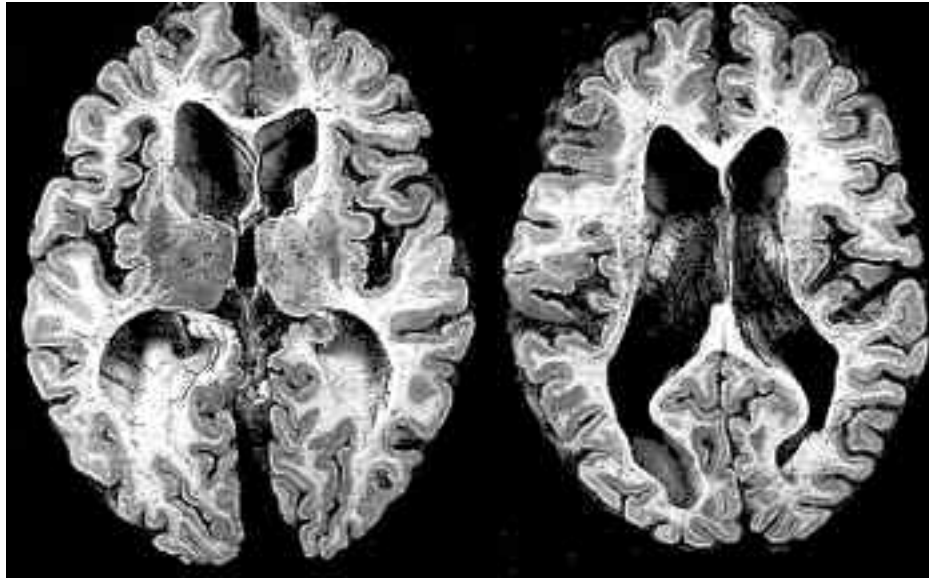What is the chance that a child is affected?
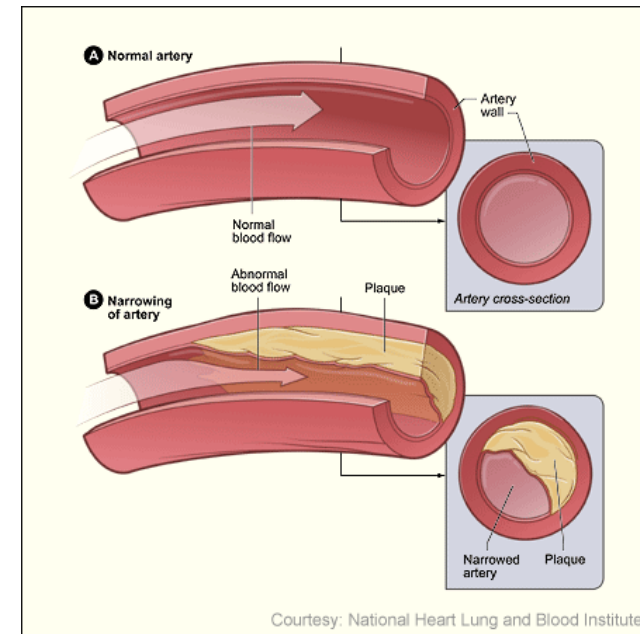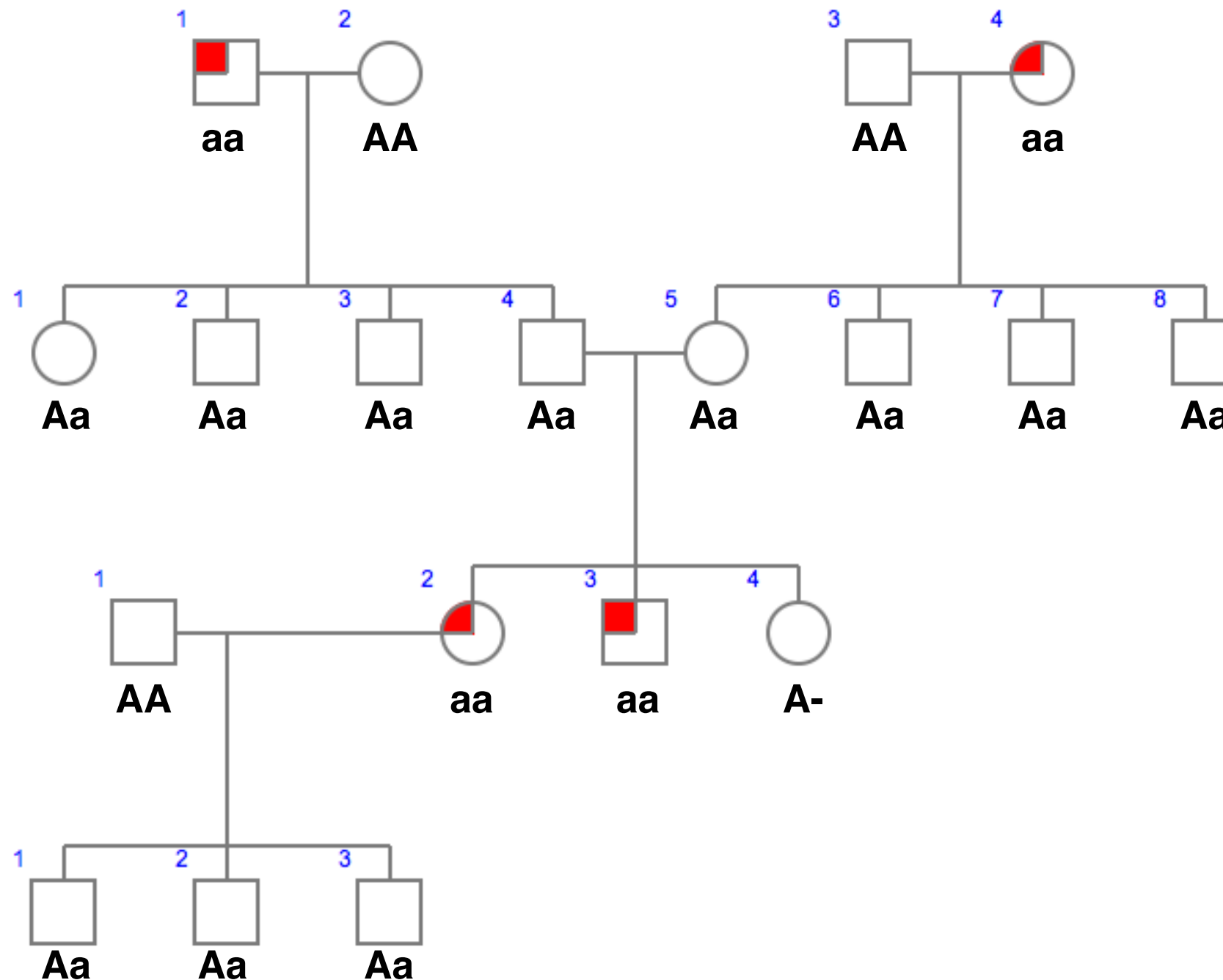
Modes of inheritance

- 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?

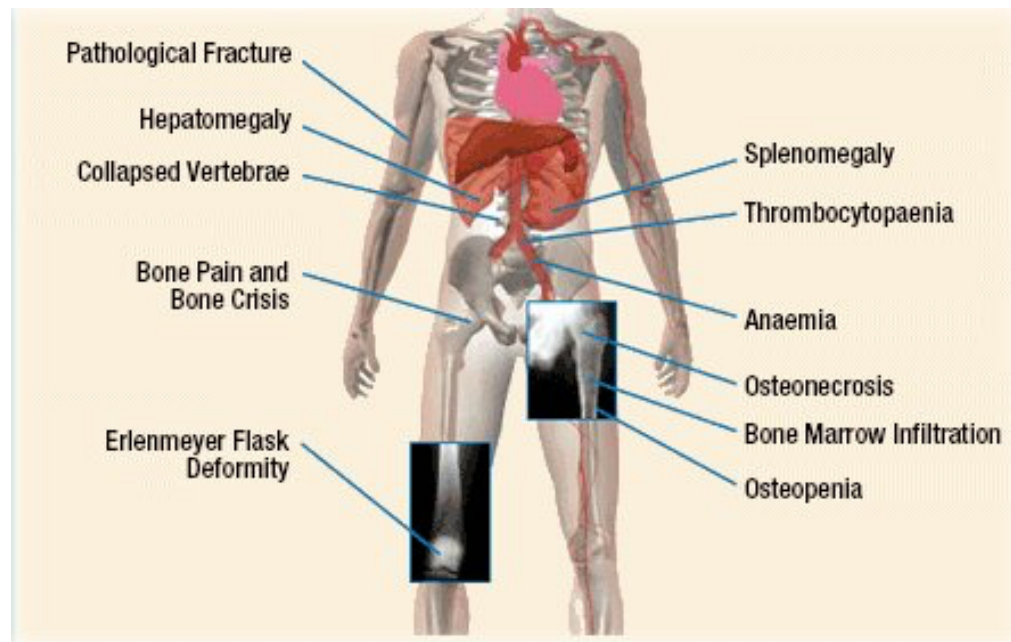All affected individuals are homozygotes
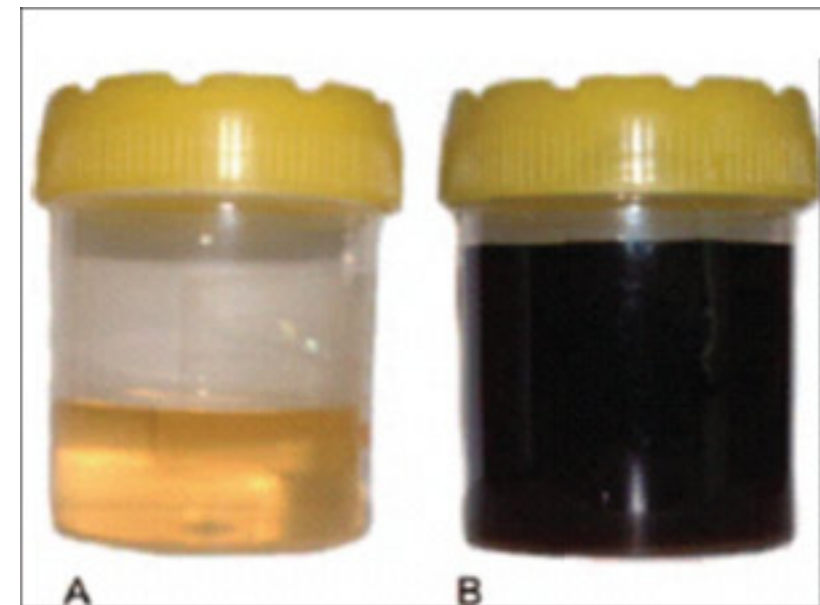
Modes of inheritance
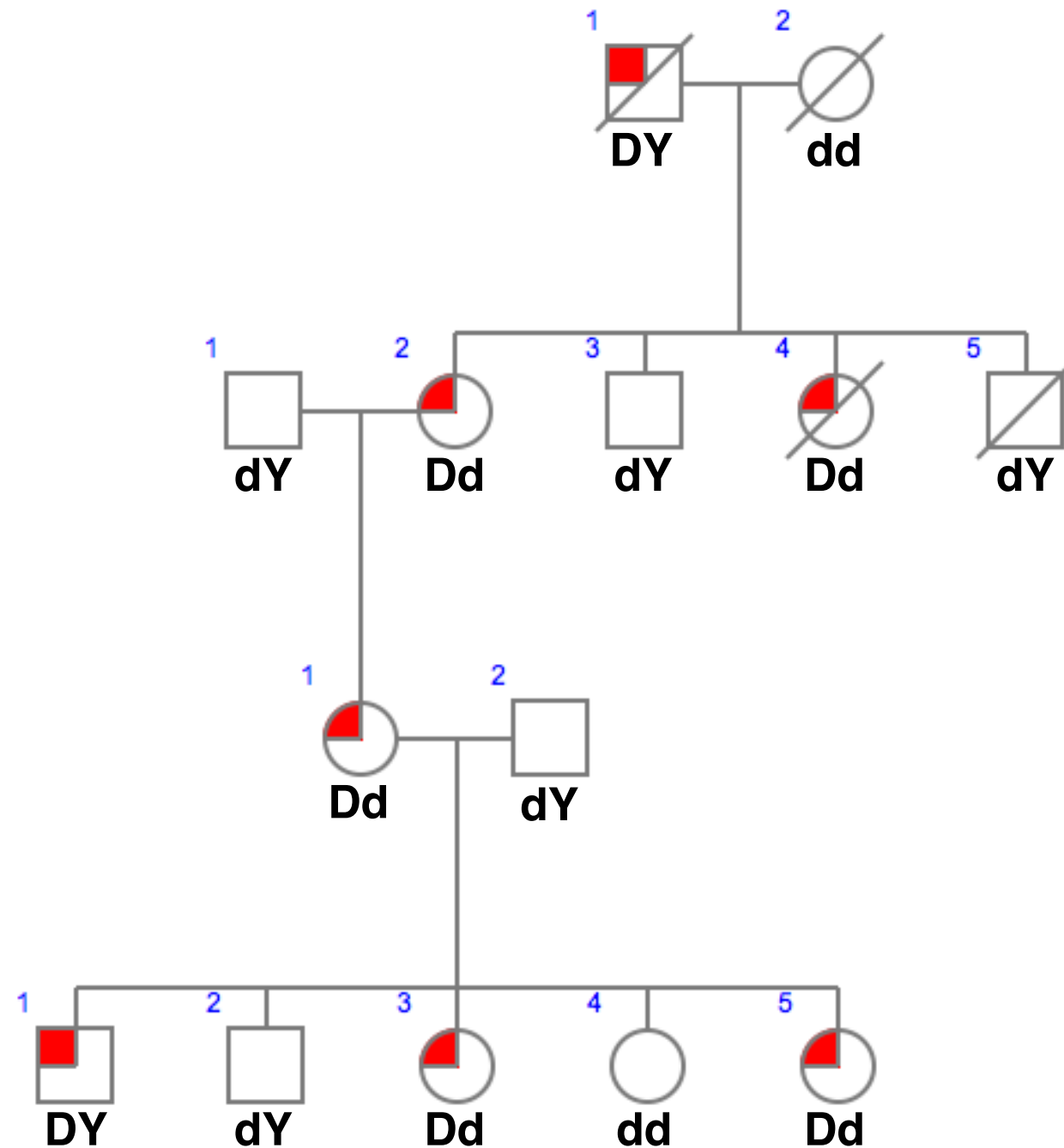
- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

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

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

X-linked recessive

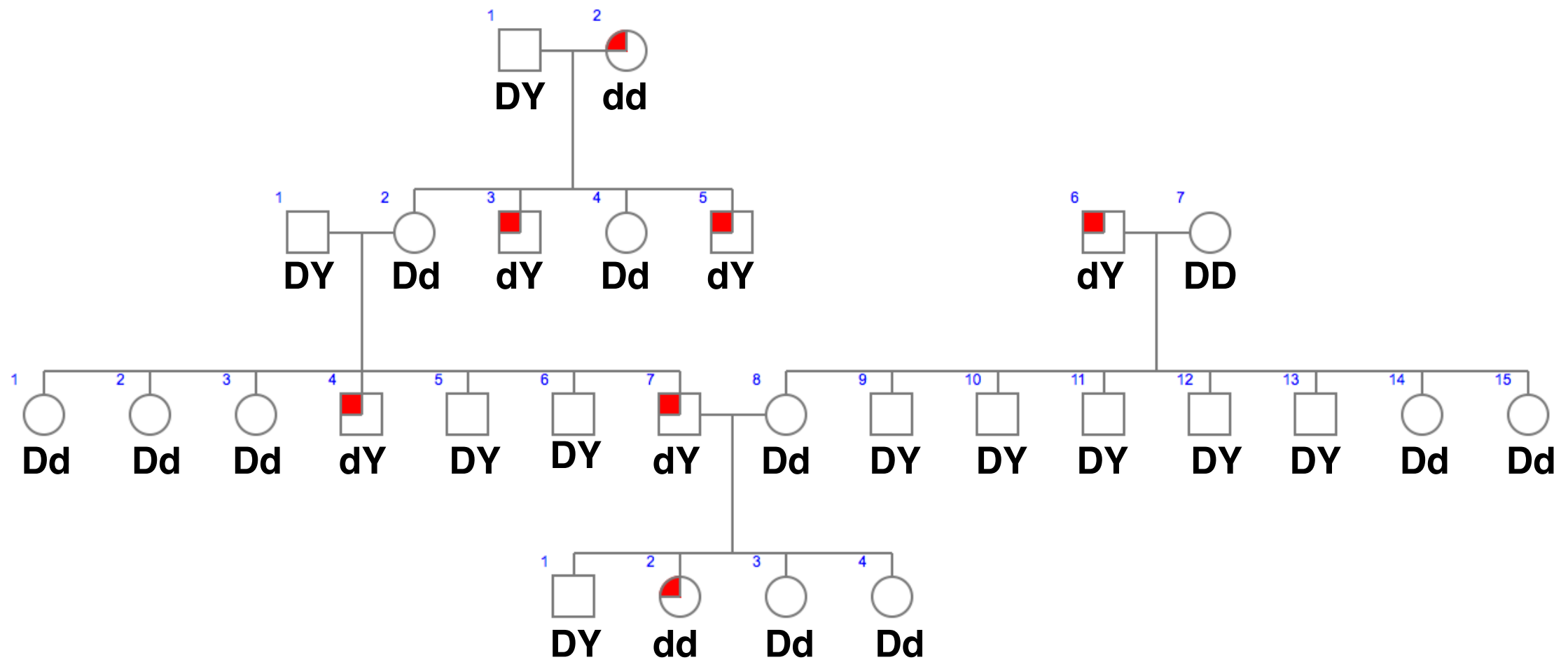# Examples of human X-linked recessive disorders

Red-green color blindness

Duchenne muscular dystrophy

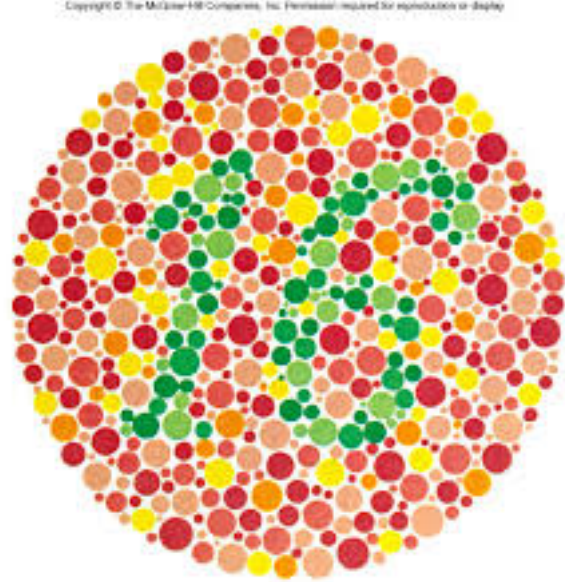All sons of affected mothers are affected
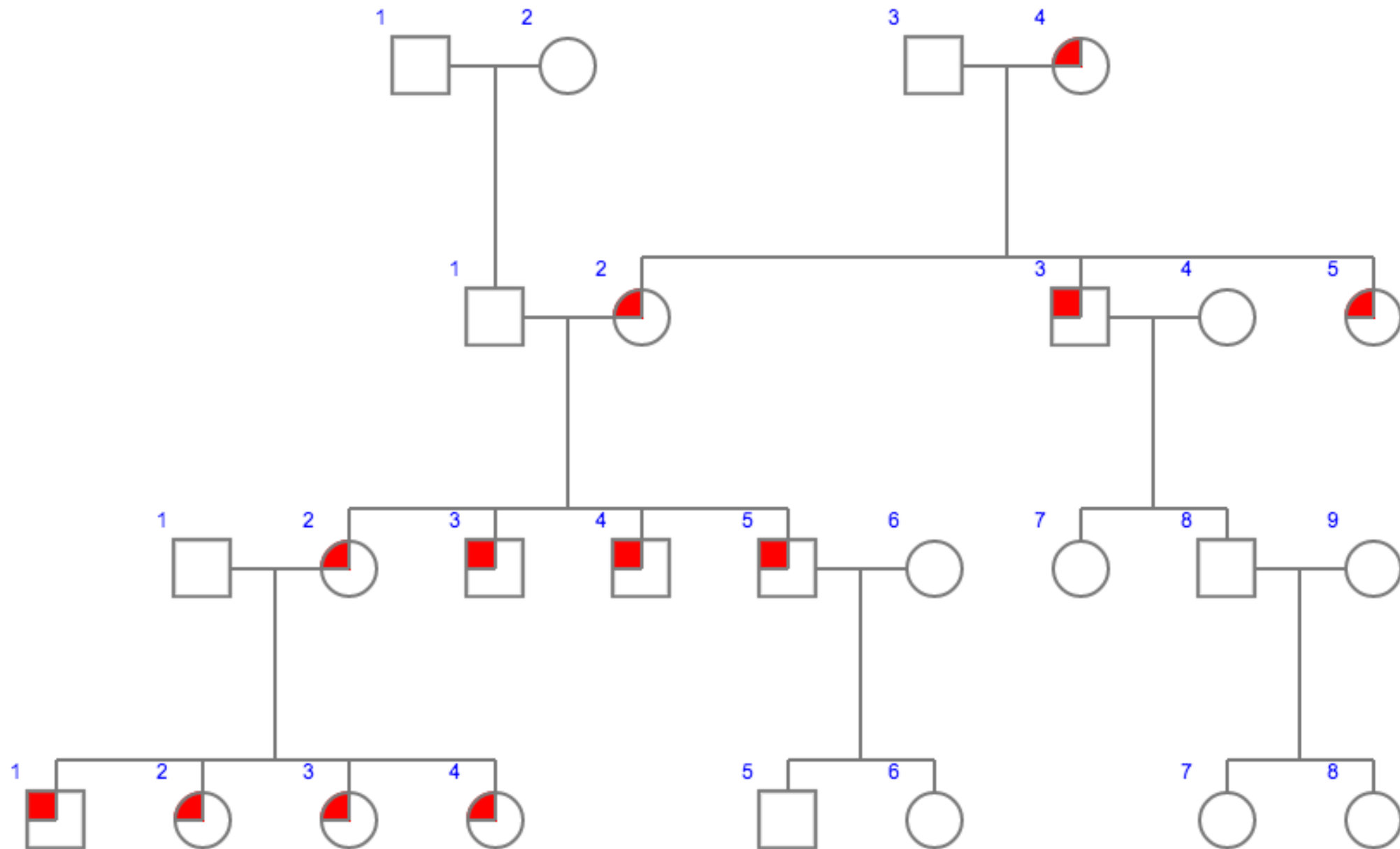
Modes of inheritance

- 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
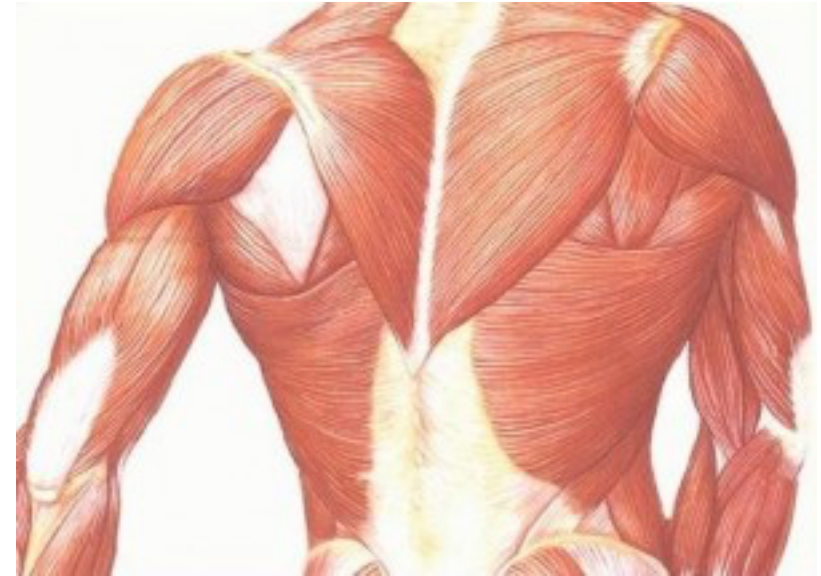
Modes of inheritance

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

Recessive maternal-effect inheritance
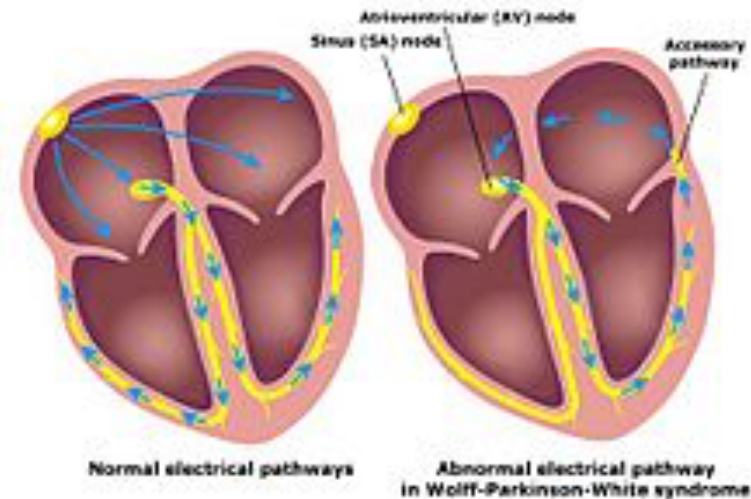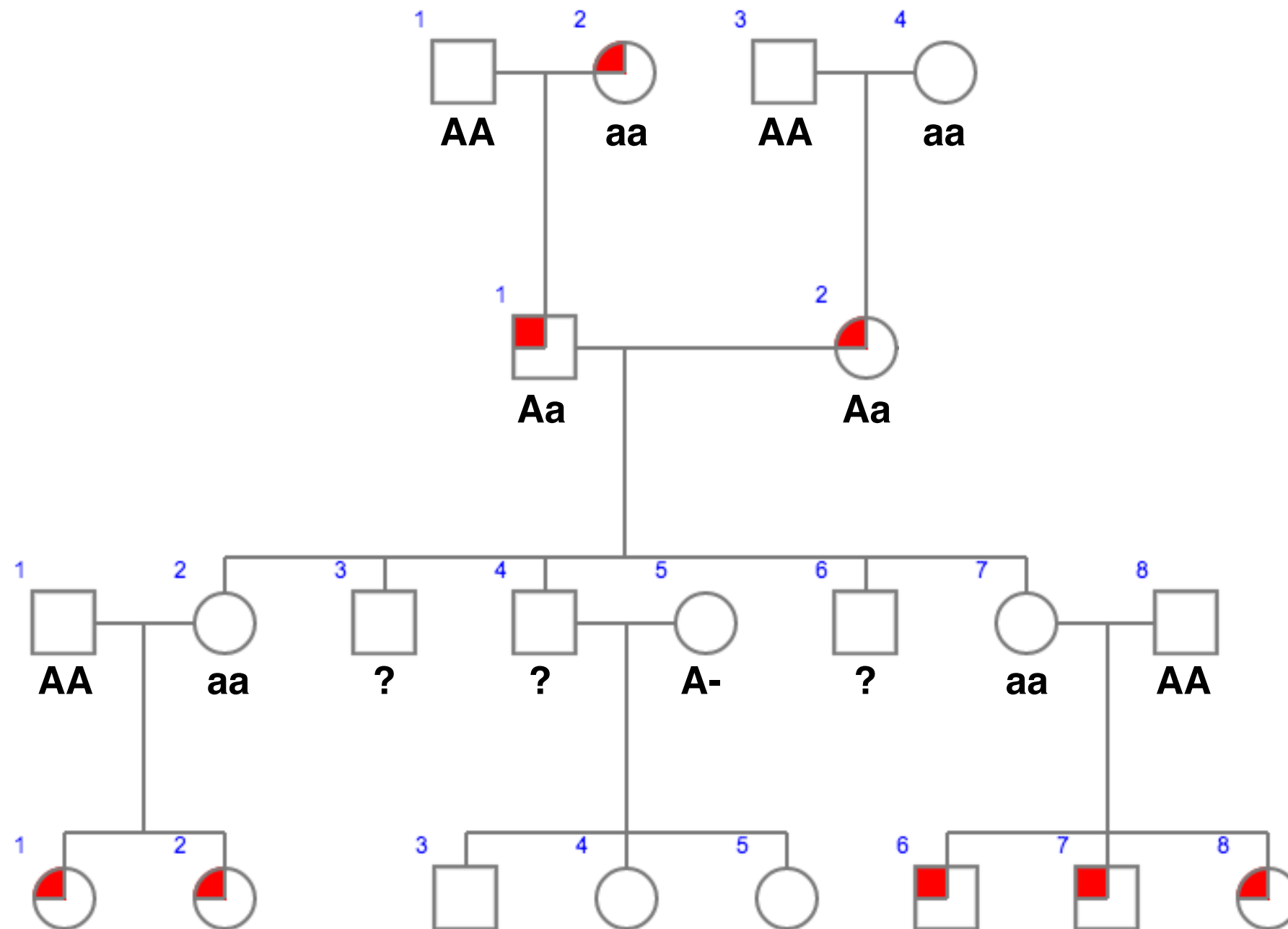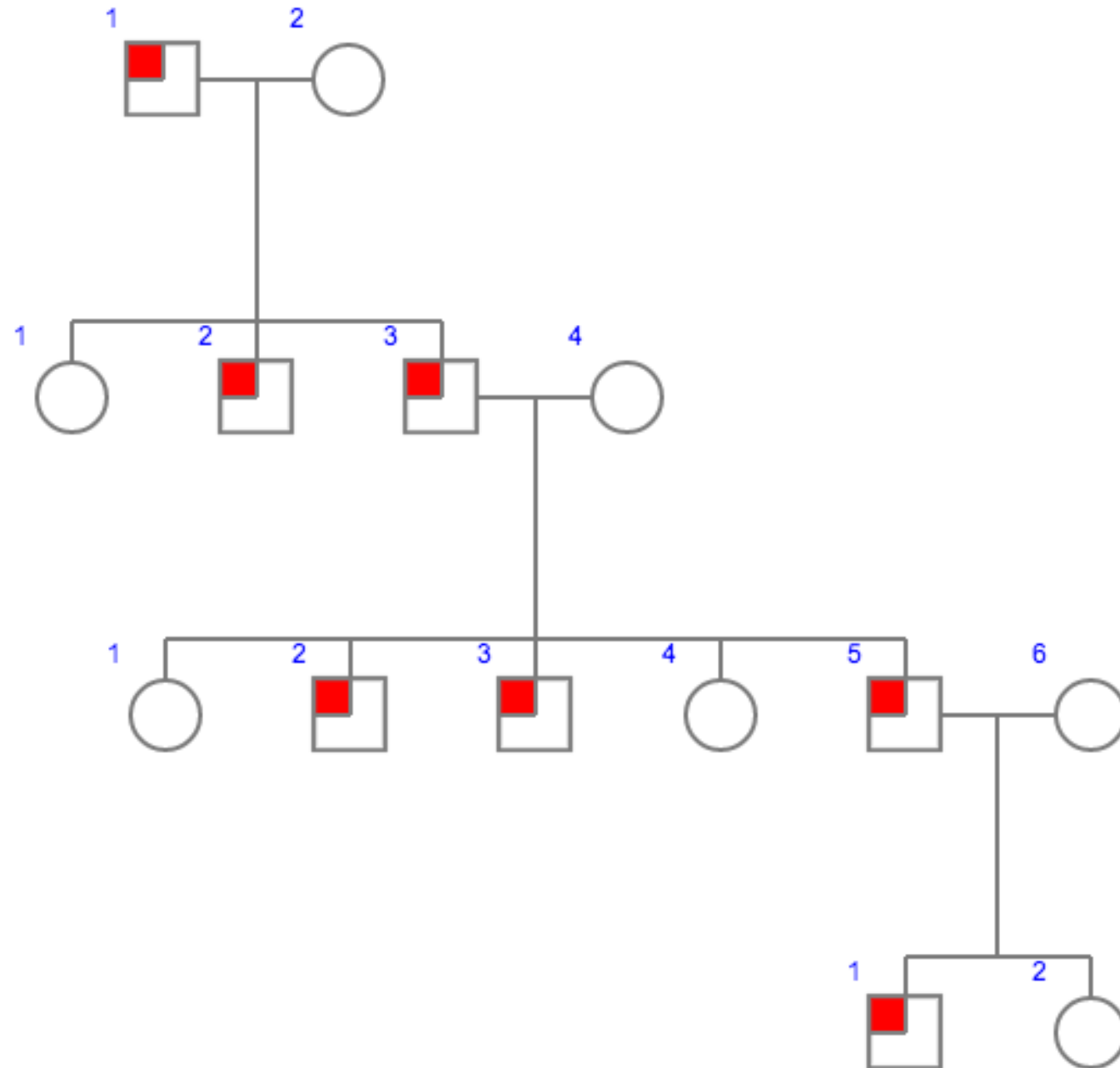
Modes of inheritance

- 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

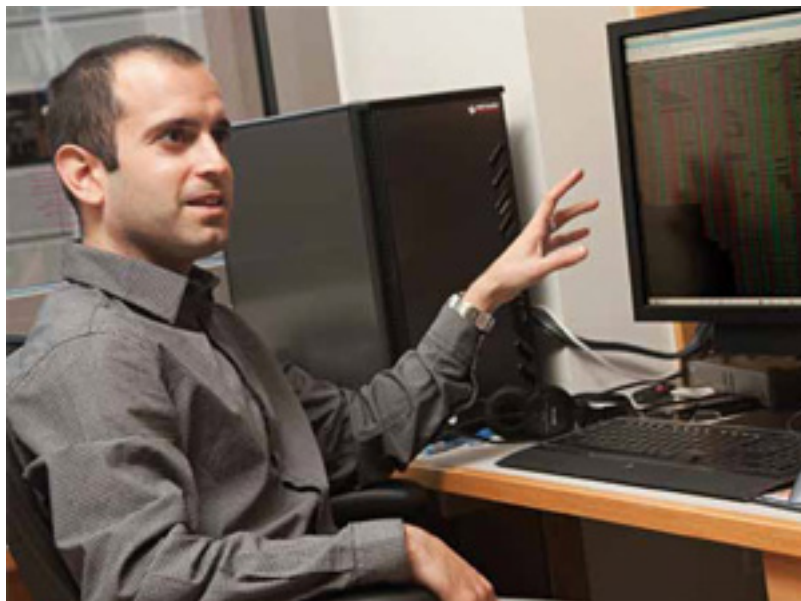# Some pedigrees can contain millions of individuals
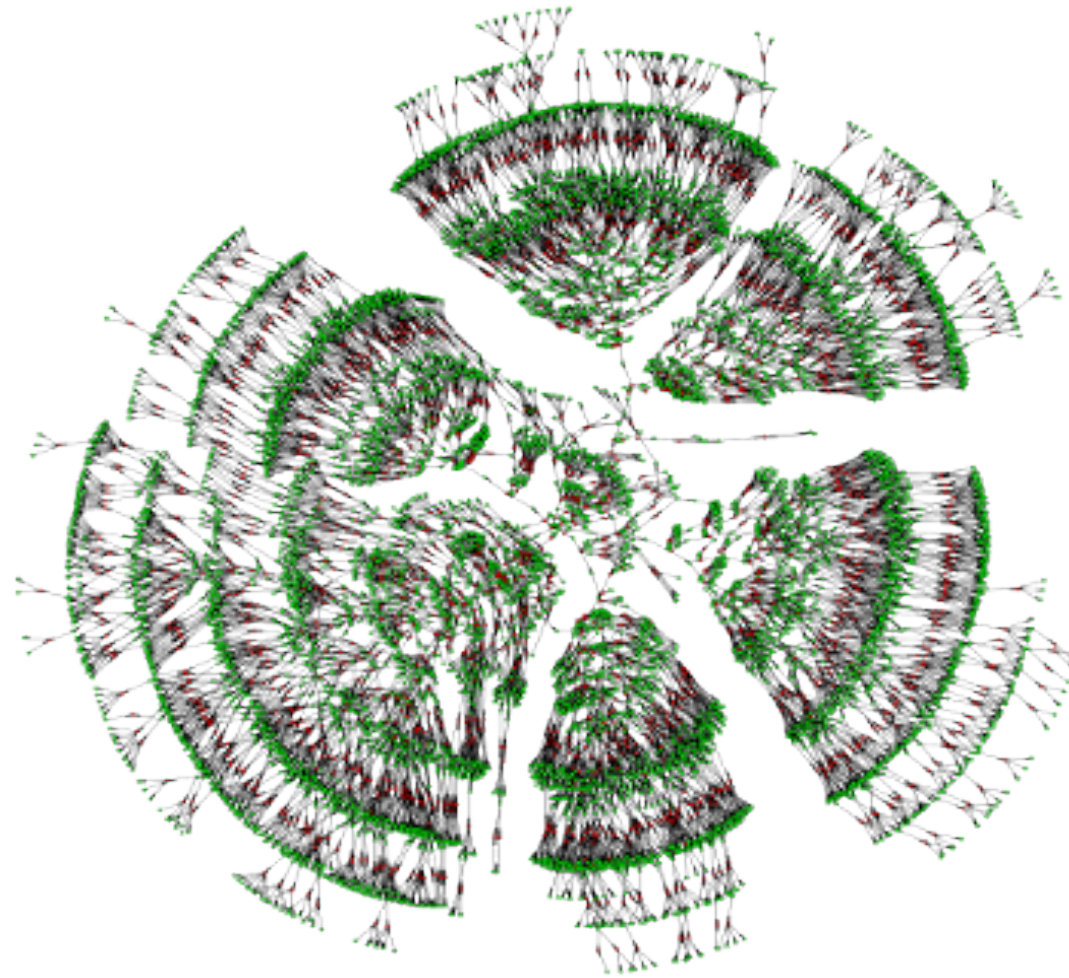
Yaniv Erlich

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
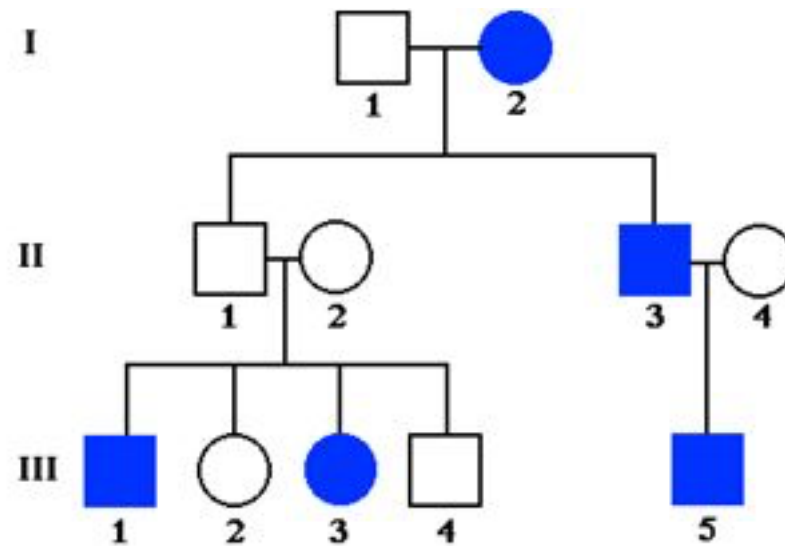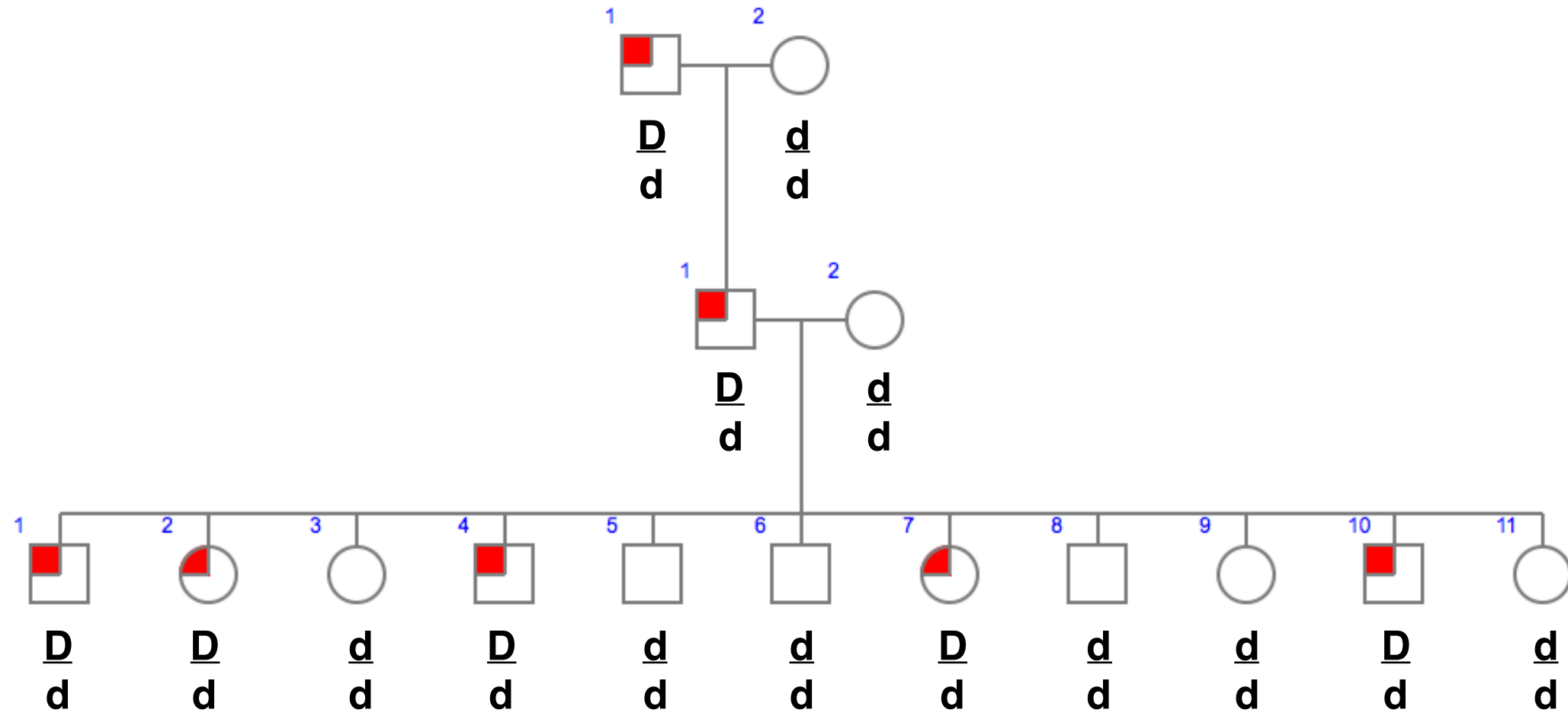
Single nucleotide
variants (SNVs)

Reference   **ATGTGCAGACGTAGACGTA**

Alternative   **ATGTGCAGAC** <u>T</u> **TAGACGTA**

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   **ATGTG** <u>CAG</u><u>CAG</u><u>CAG</u><u>CAG</u>**CGTA**

Alternative   **ATGTG** <u>CAG</u><u>CAG</u>**CGTAGTGACT**

Linkage to genetic markers tells us where disease genes are
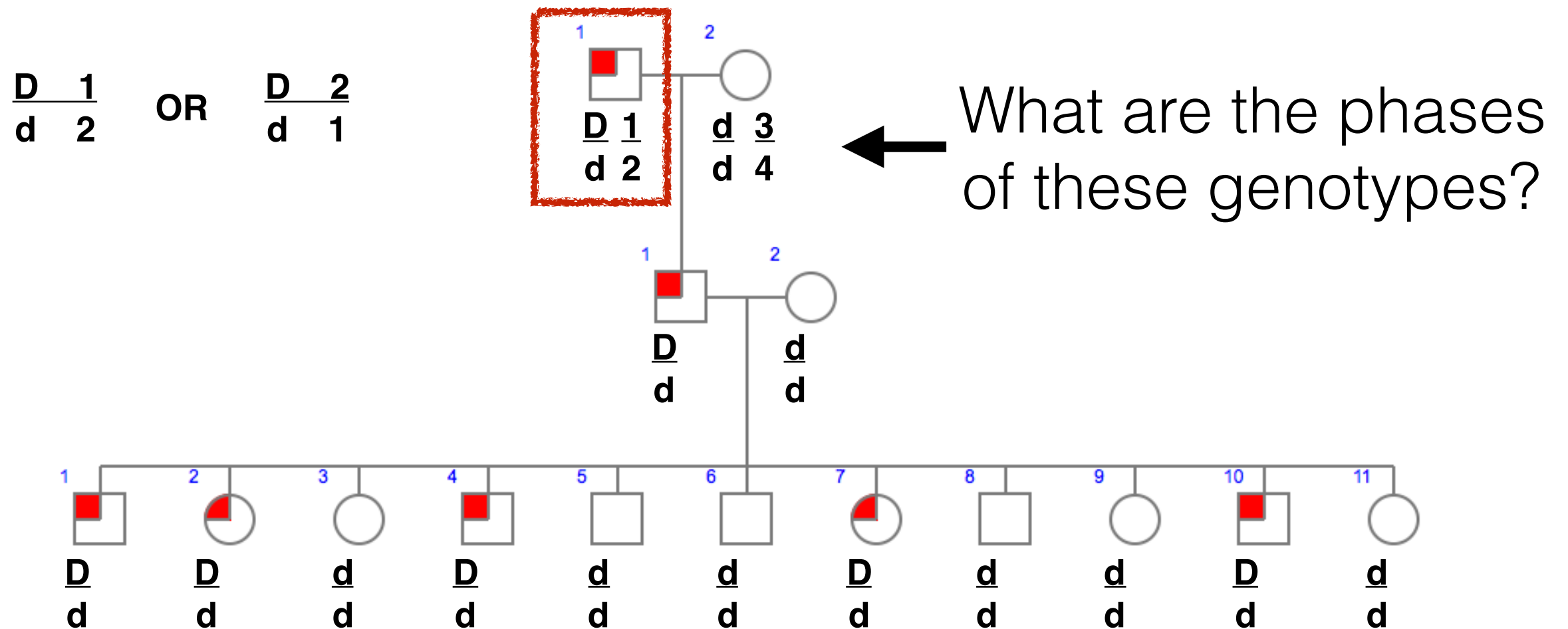
$$\frac{D}{d}\frac{1}{2}$$ **OR** $$\frac{D}{d}\frac{2}{1}$$

$$\frac{D}{d}\frac{1}{2}$$ $$\frac{d}{d}\frac{3}{4}$$

← What are the phases of these genotypes?

$$\frac{D}{d}$$ $$\frac{d}{d}$$

$$\frac{D}{d}$$ $$\frac{D}{d}$$ $$\frac{d}{d}$$ $$\frac{D}{d}$$ $$\frac{d}{d}$$ $$\frac{d}{d}$$ $$\frac{D}{d}$$ $$\frac{d}{d}$$ $$\frac{d}{d}$$ $$\frac{D}{d}$$ $$\frac{d}{d}$$

Linkage to genetic markers tells us where disease genes are

$$\frac{D\quad 1}{d\quad 2} \quad \text{OR} \quad \frac{D\quad 2}{d\quad 1}$$
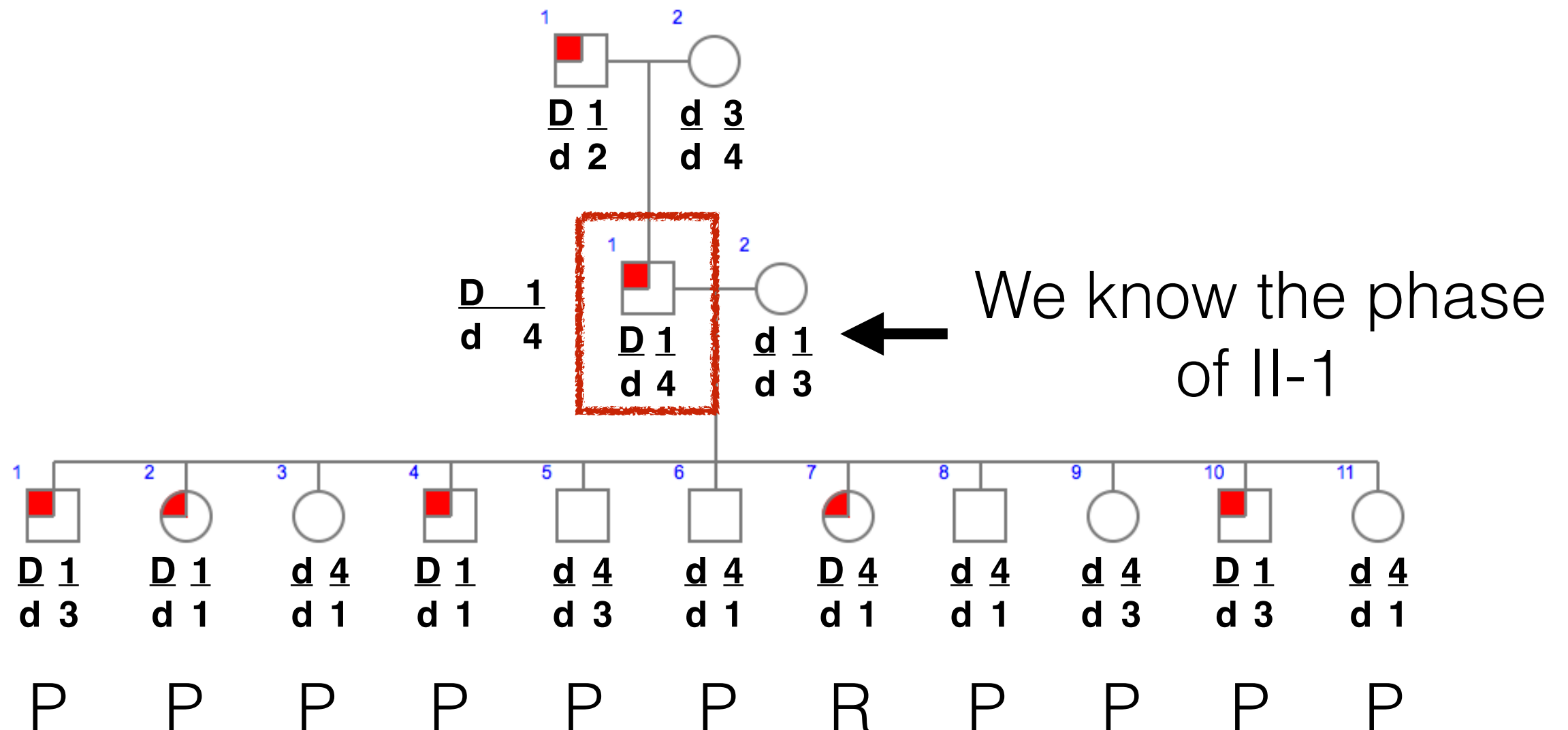
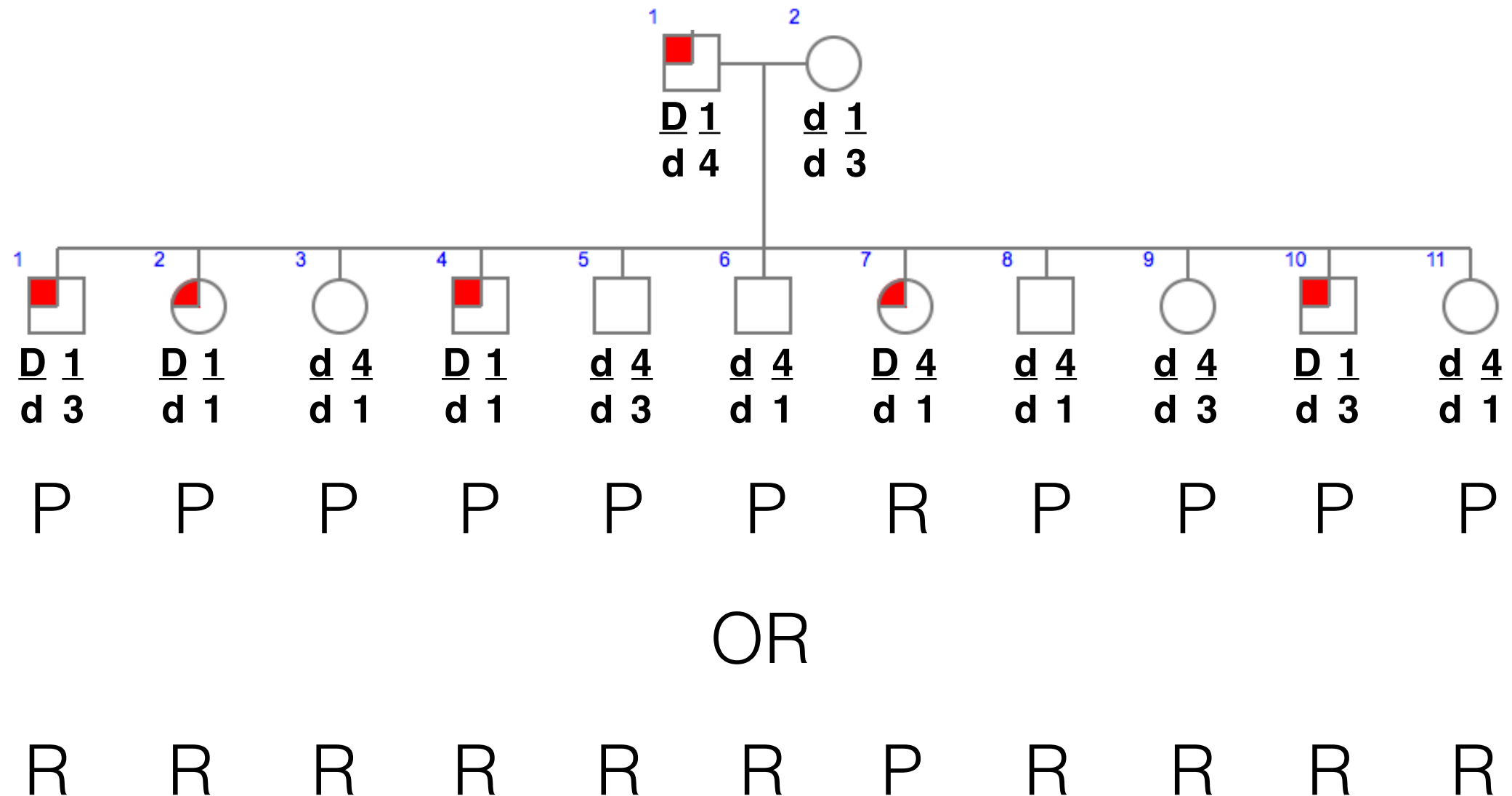Is individual II-1 a recombinant or parental?

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

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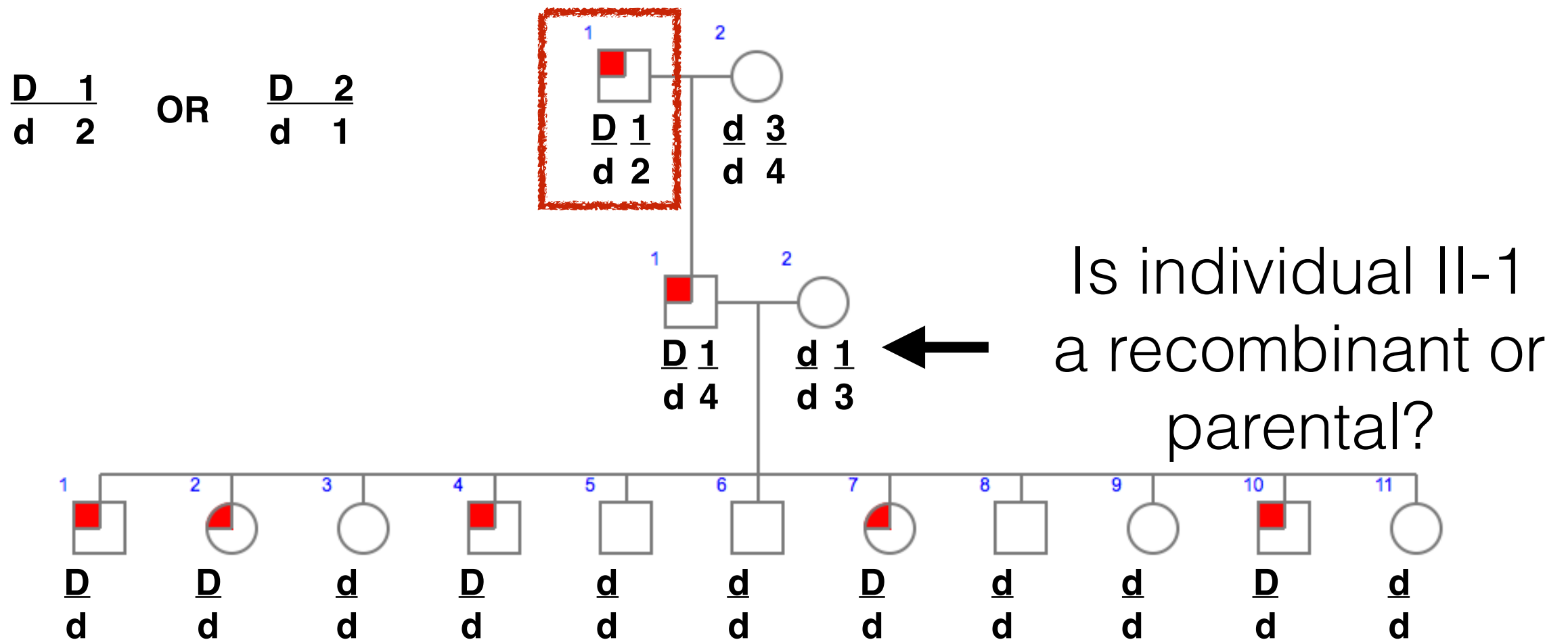
Sometimes, we don't know the phase of the parent, and both possibilities of phase are equally likely