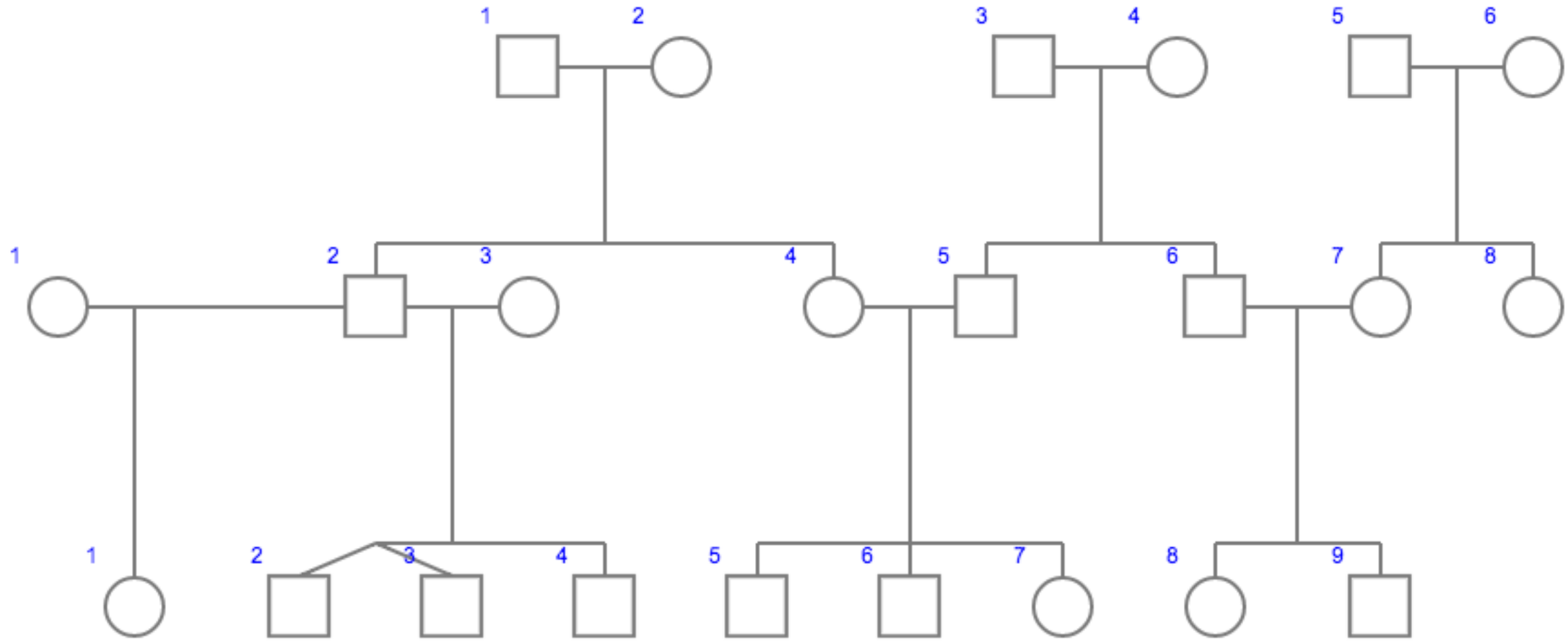
Bio393: Genetic Analysis

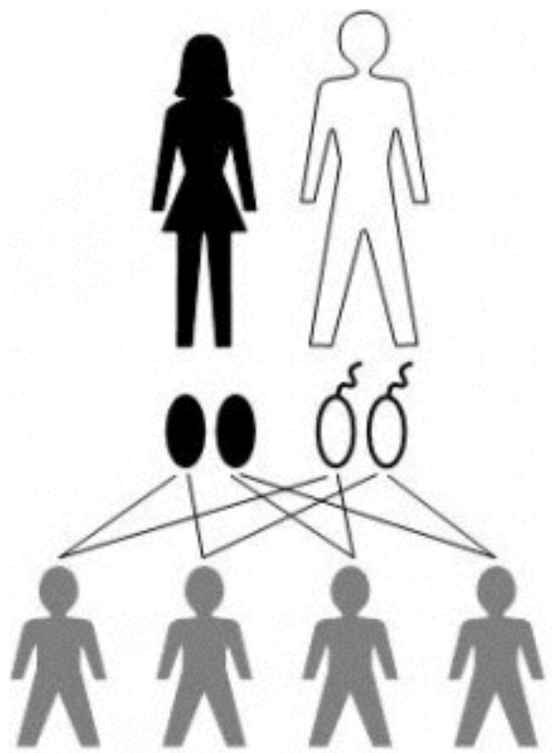
Family-based analysis, Modes of inheritance, Phase



Lecture 15

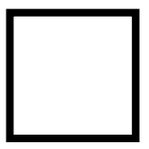
Why do we study inheritance in families?

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

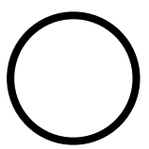


- Map Mendelian (single-gene) disorders
- Map disorders caused by rare variation

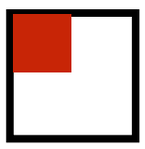
Human pedigree analysis allows us to follow traits in families



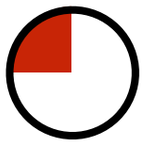
Male



Female



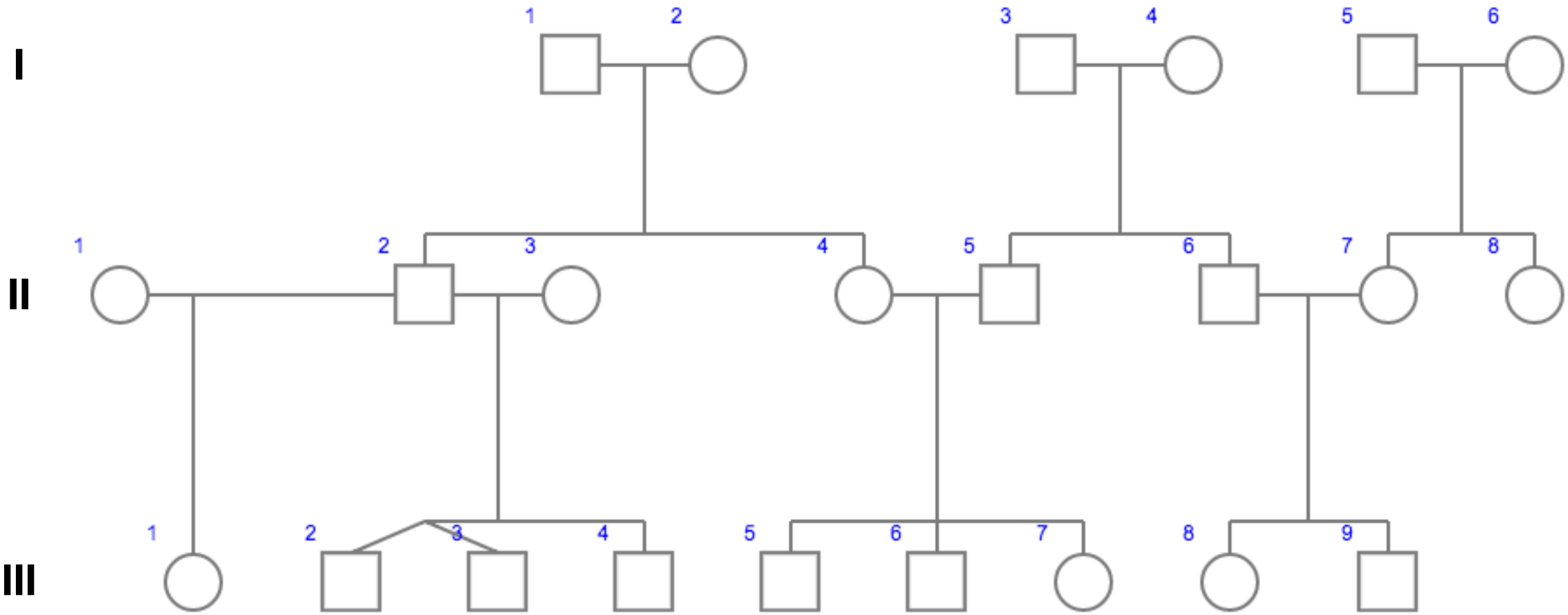
Affected male



Affected female

Remember that humans are diploid.

Human pedigree analysis allows us to follow traits in families

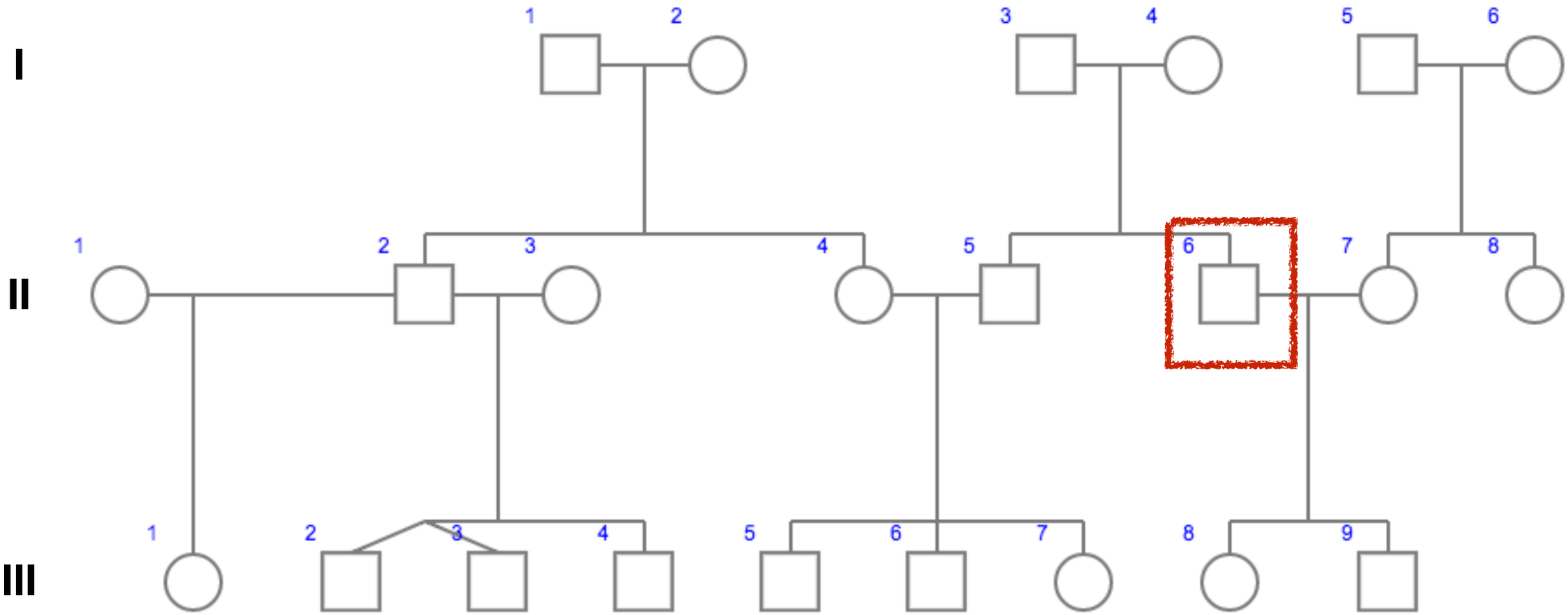


Individuals are numbered from left to right

Generations are numbered from top to bottom in Roman numerals

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

Human pedigree analysis allows us to follow traits in families



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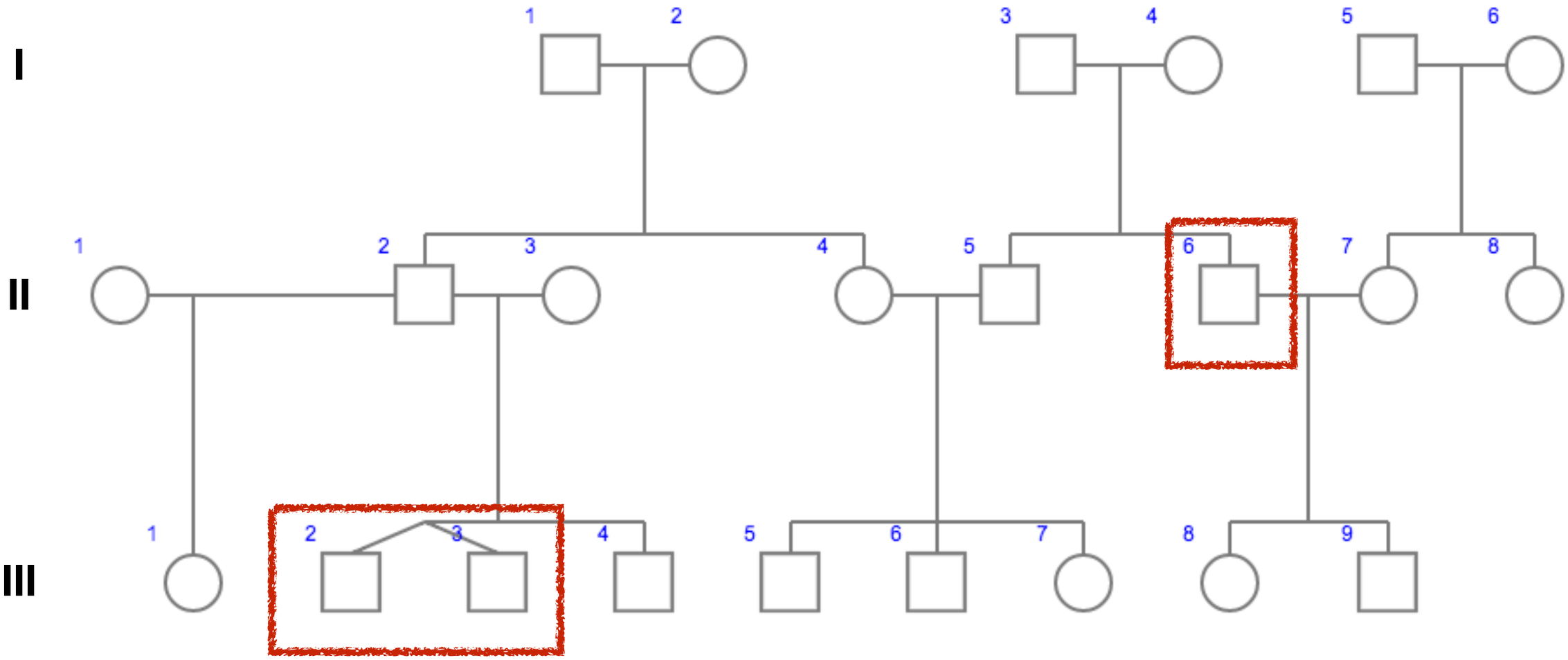

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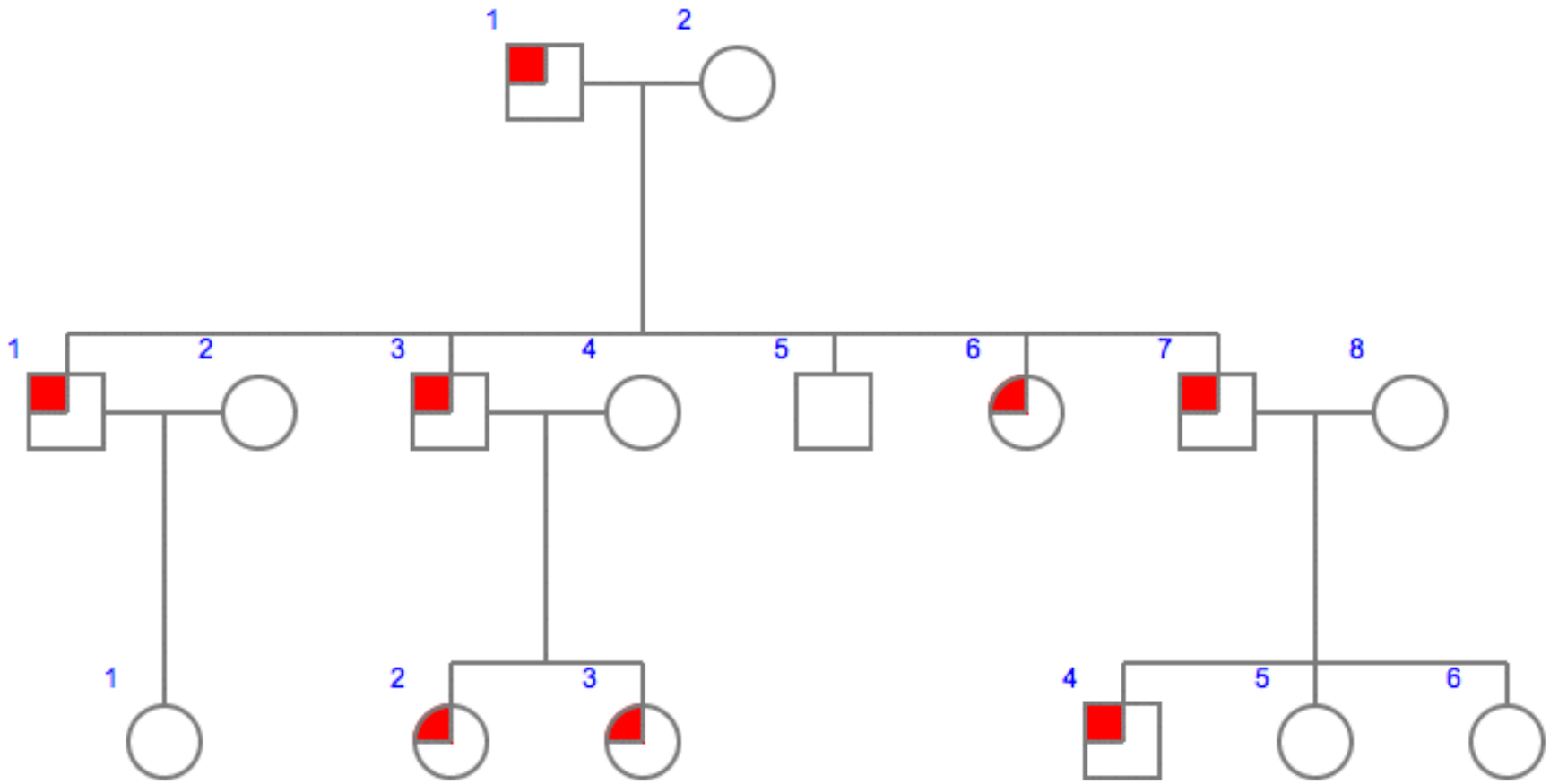
Modes of inheritance



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- In each generation?
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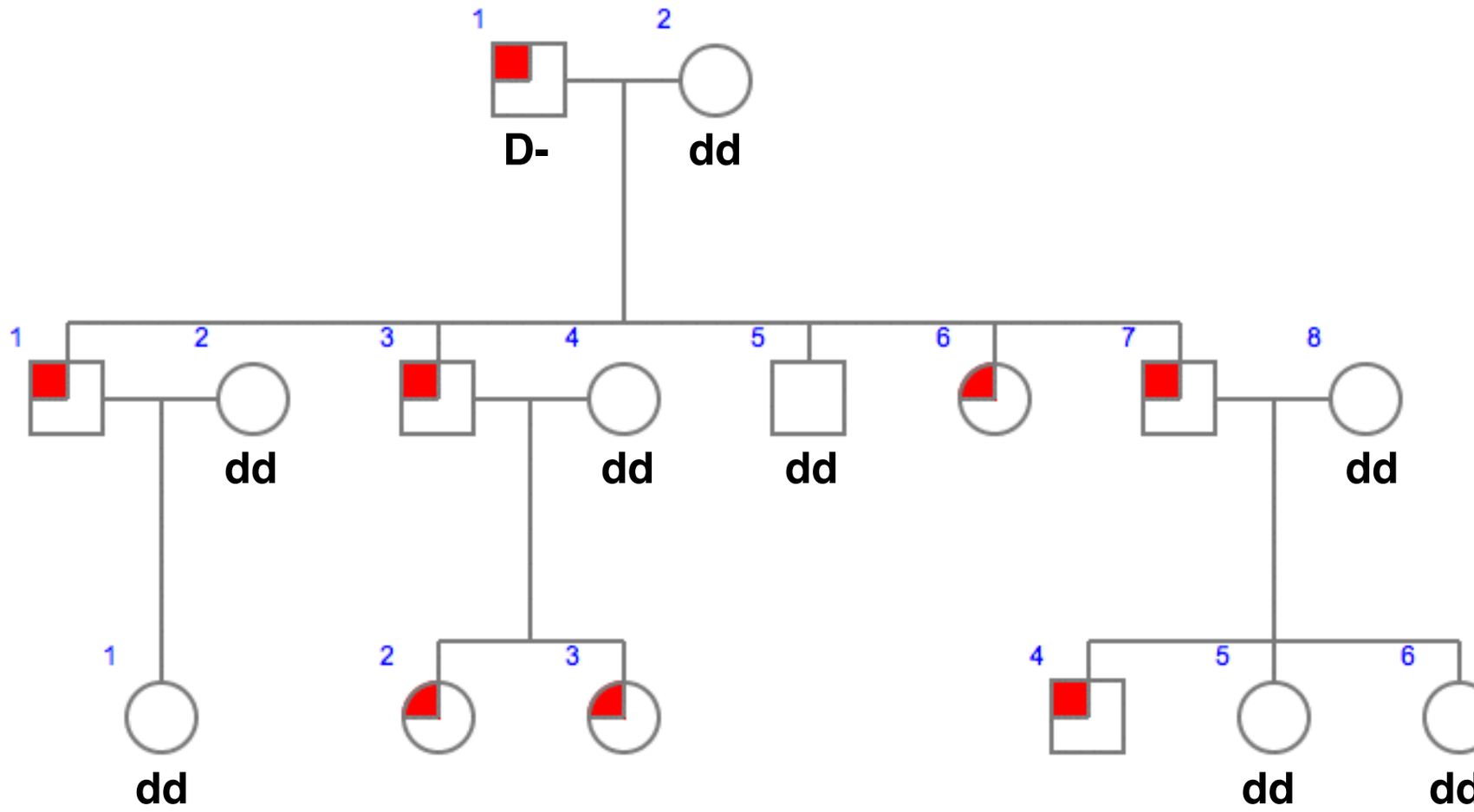

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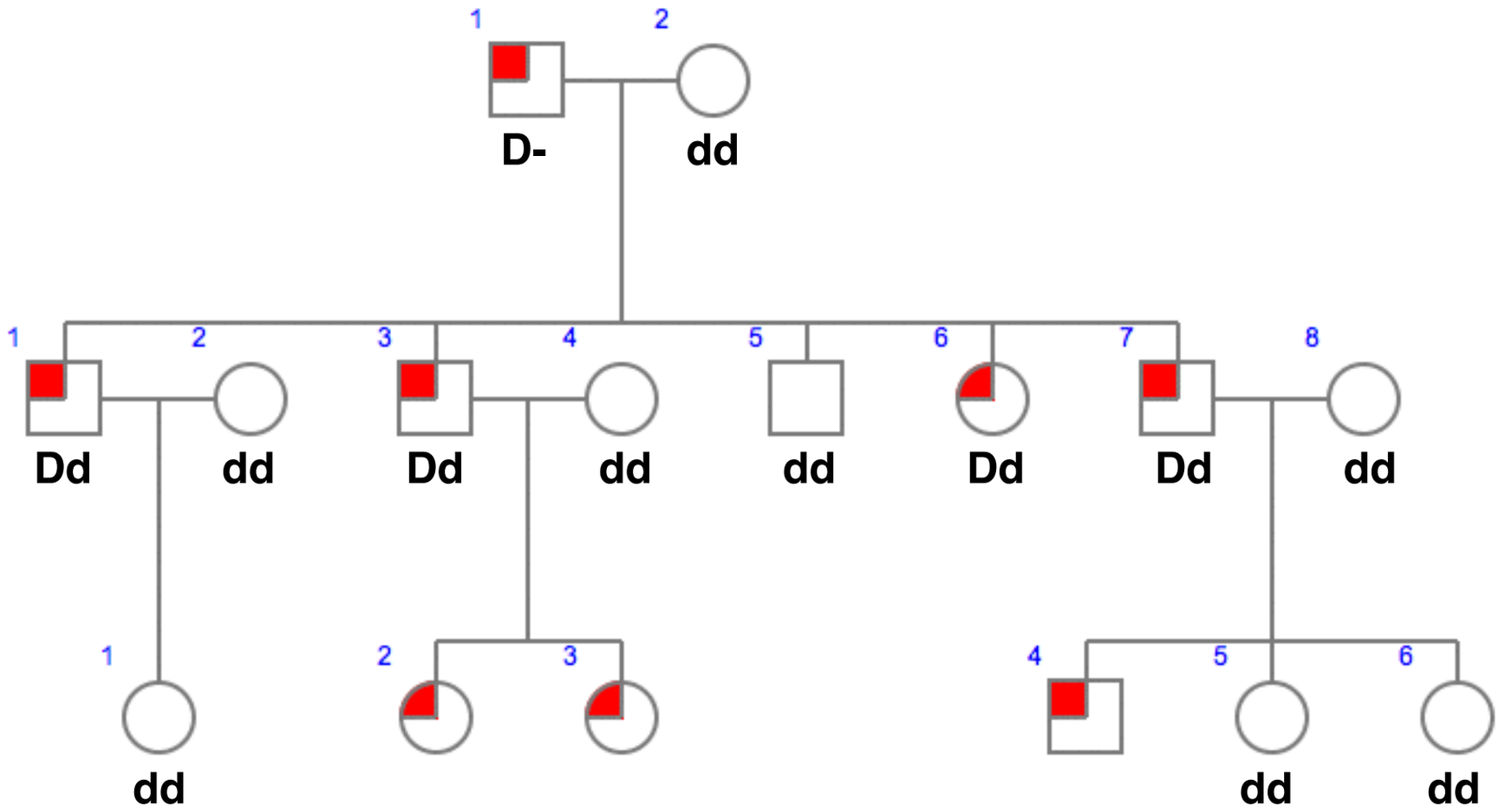

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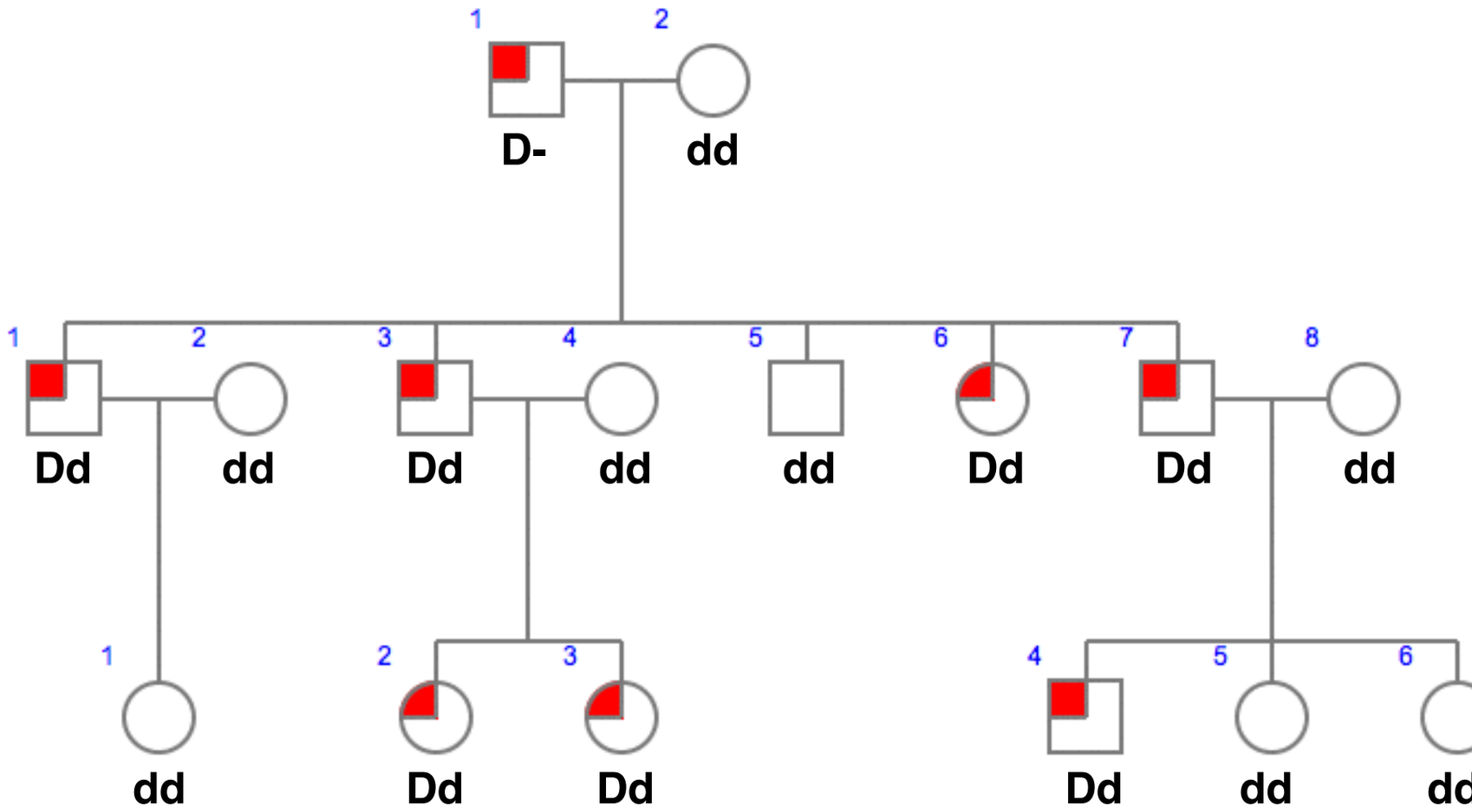

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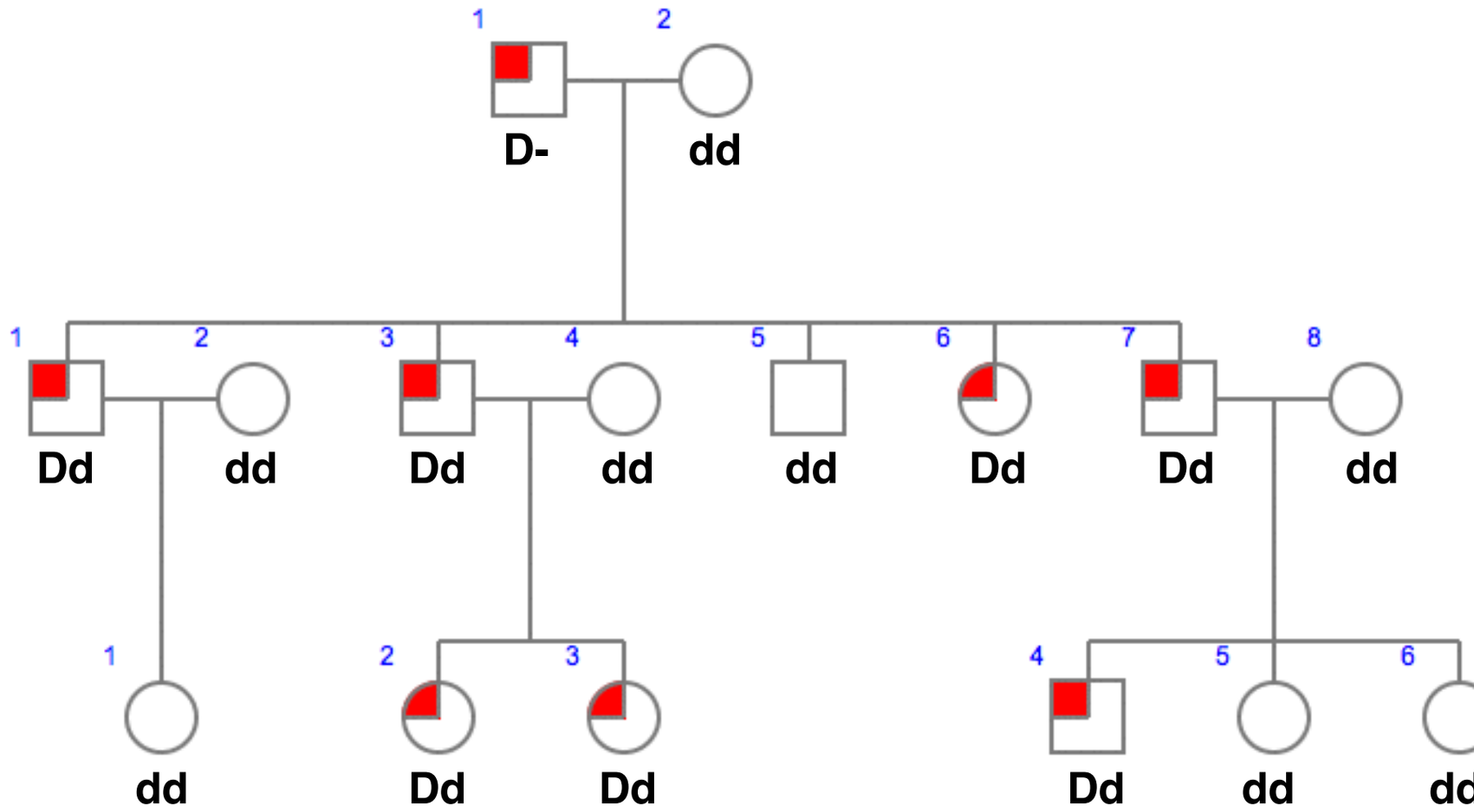

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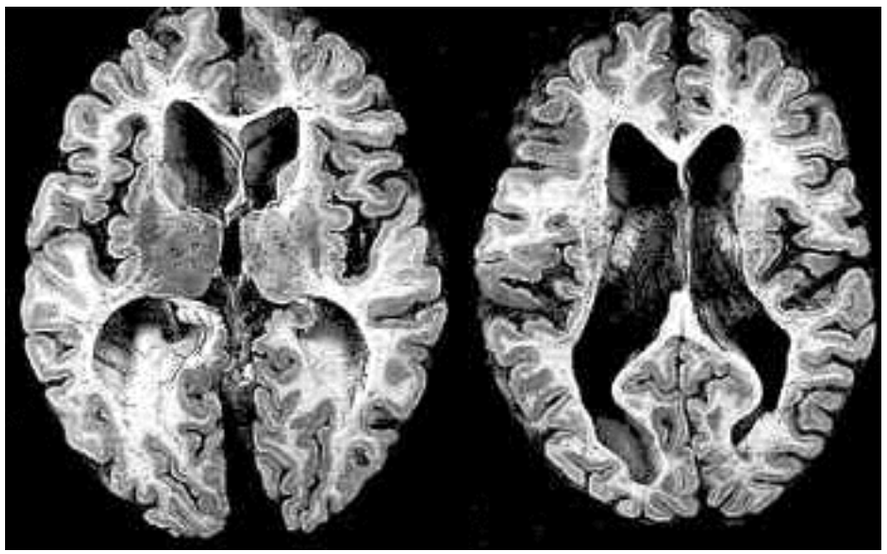
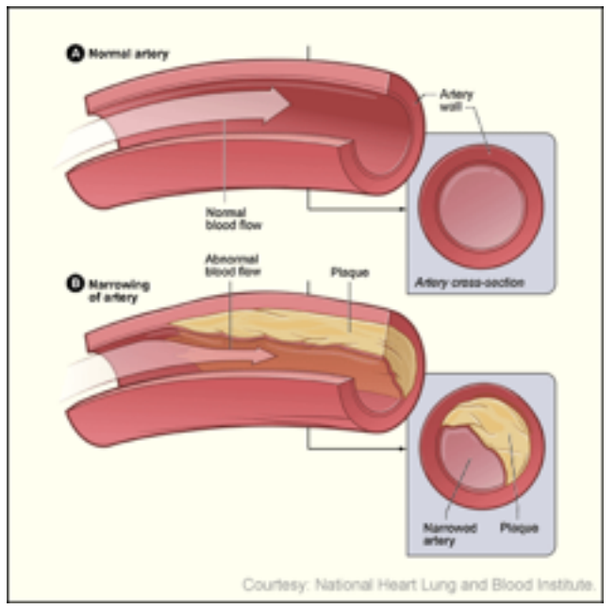
Autosomal dominant

Examples of human autosomal dominant disorders



Huntington's Disease
chr. 4



Familial Hypercholesterolemia
chr. 19

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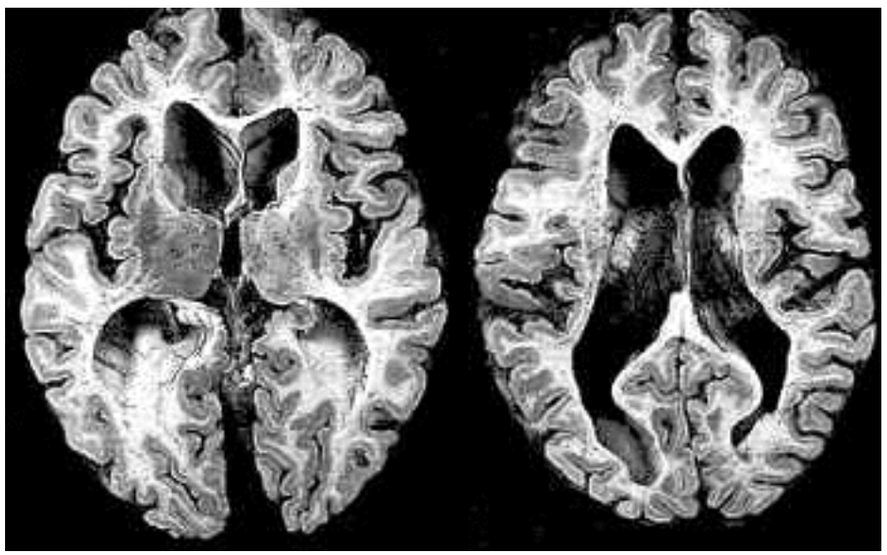

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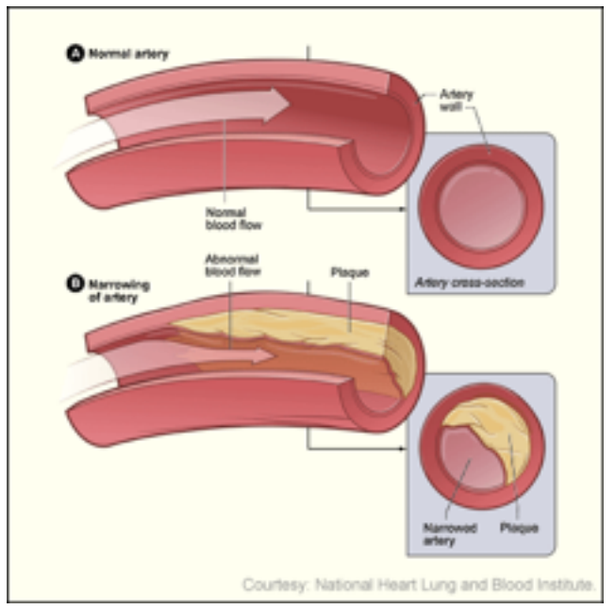

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Caused by loss-of-function or gain-of-function?

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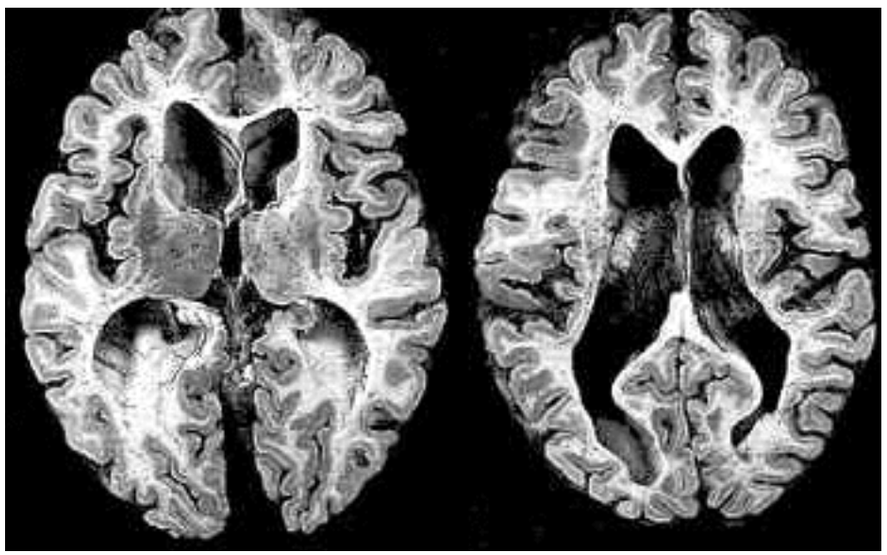

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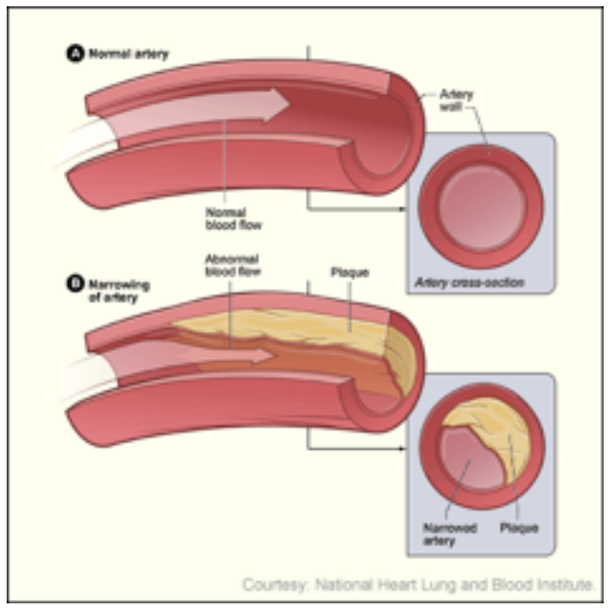

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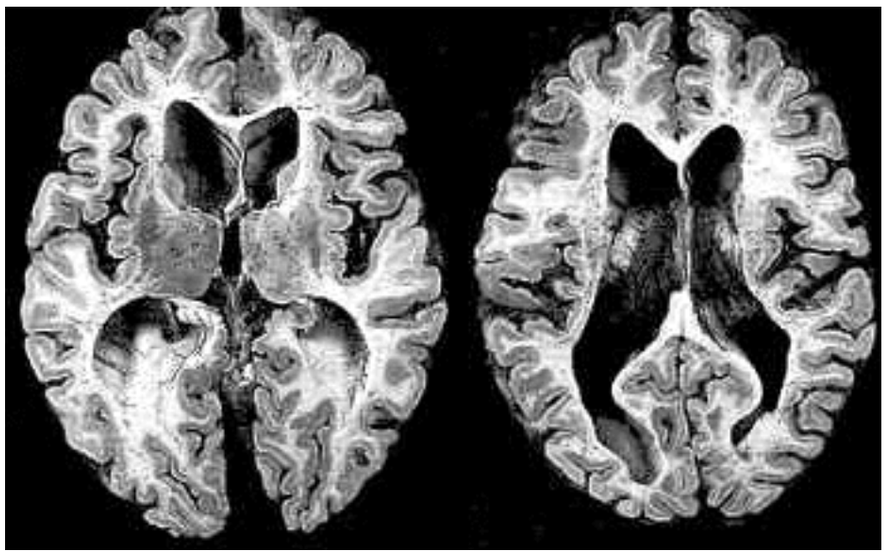

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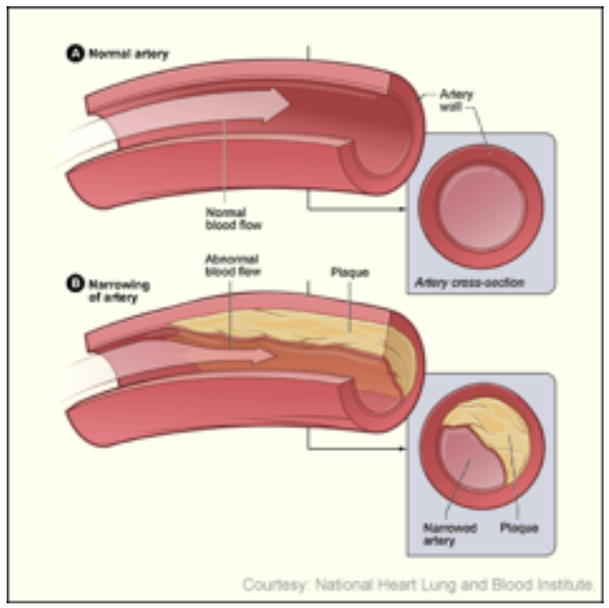

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Most affected individuals are heterozygotes

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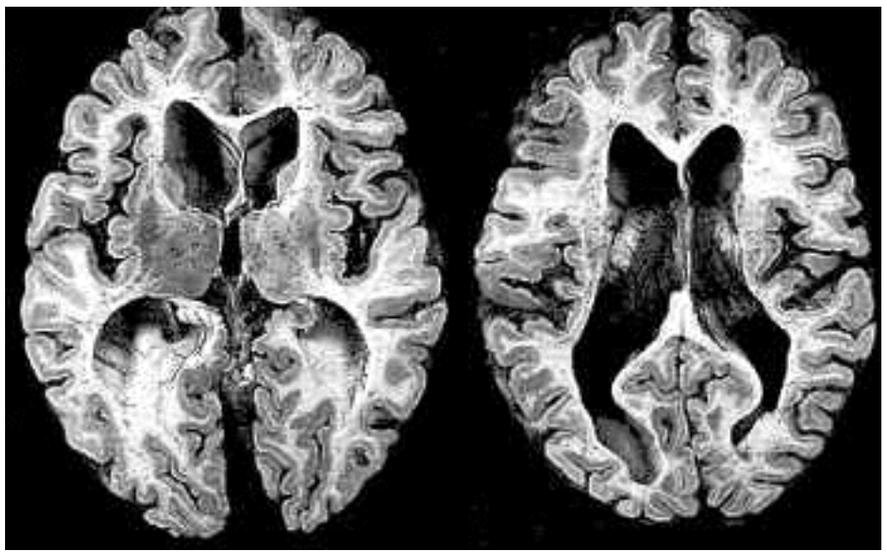

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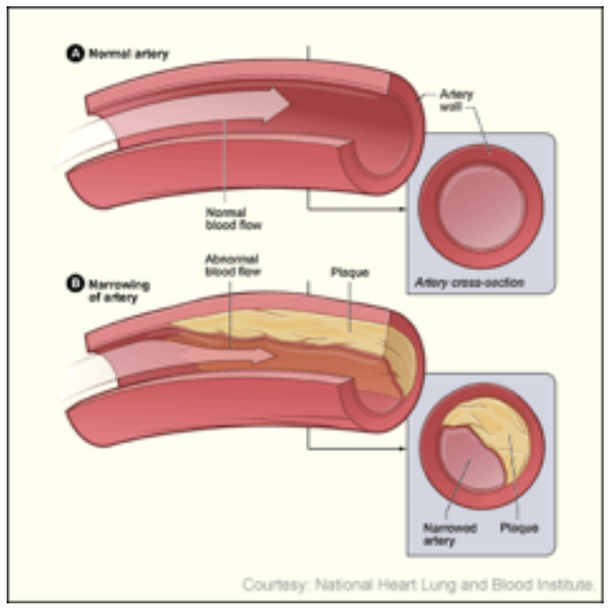

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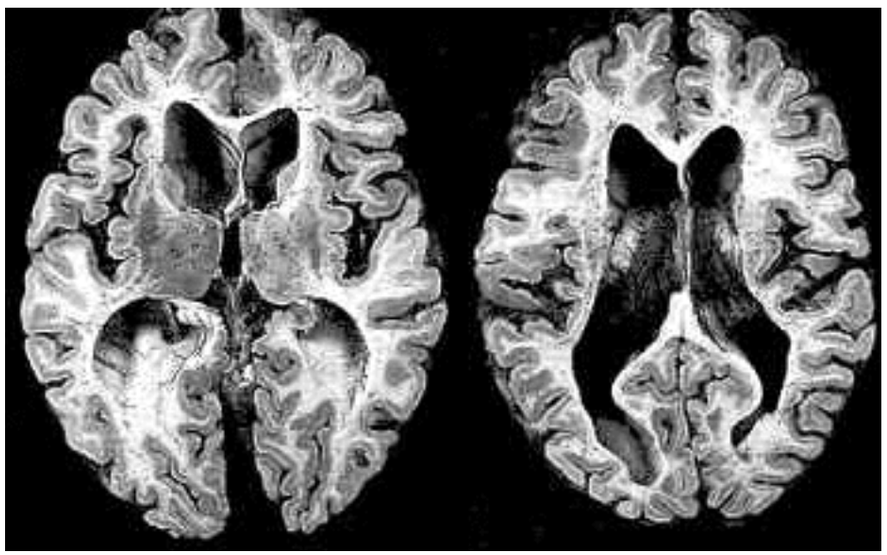

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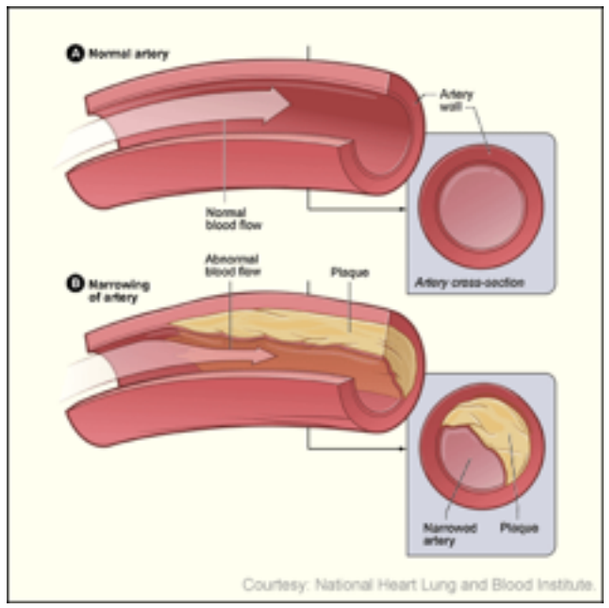

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Caused by loss-of-function or gain-of-function?

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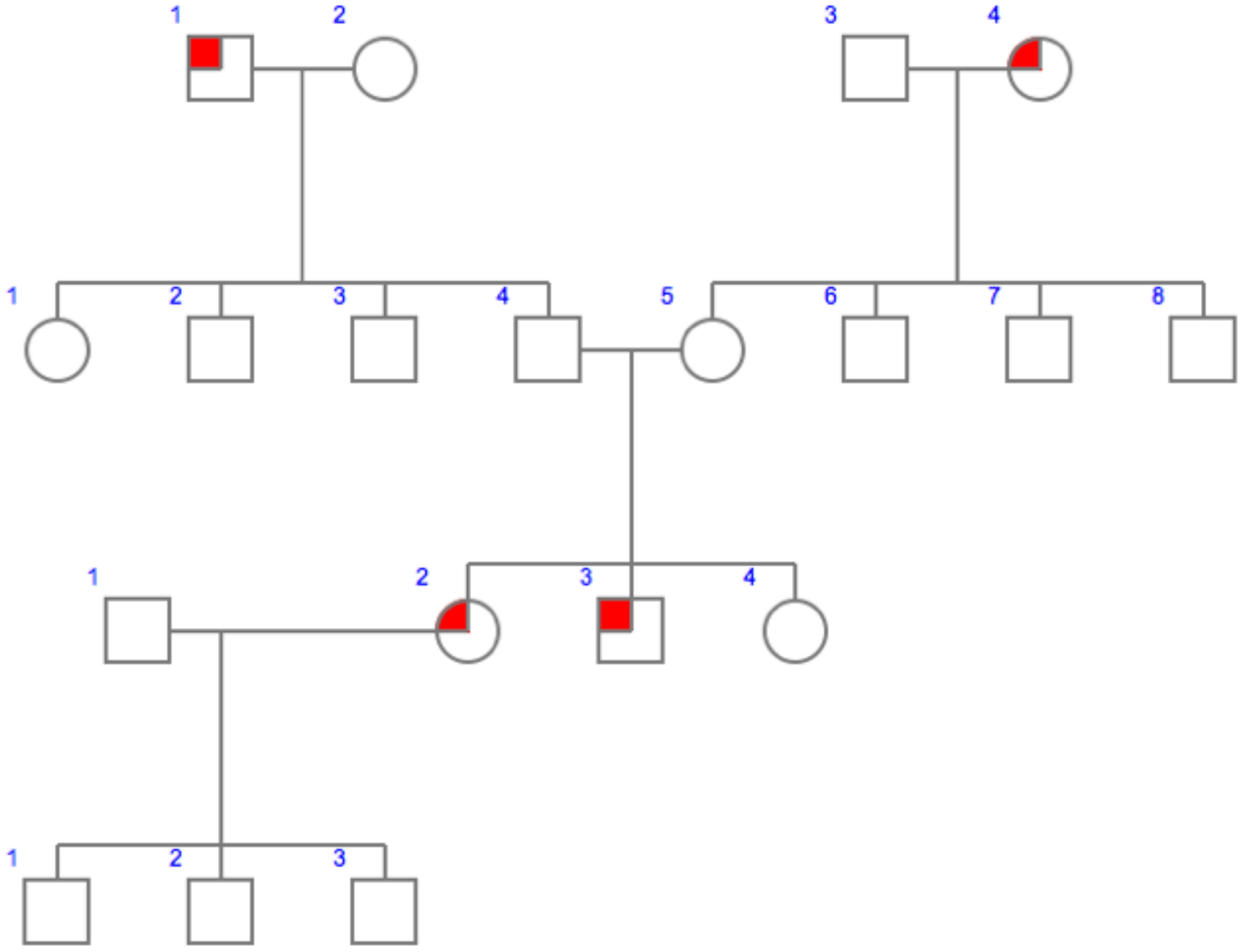
What is the chance that a child is affected?

Modes of inheritance



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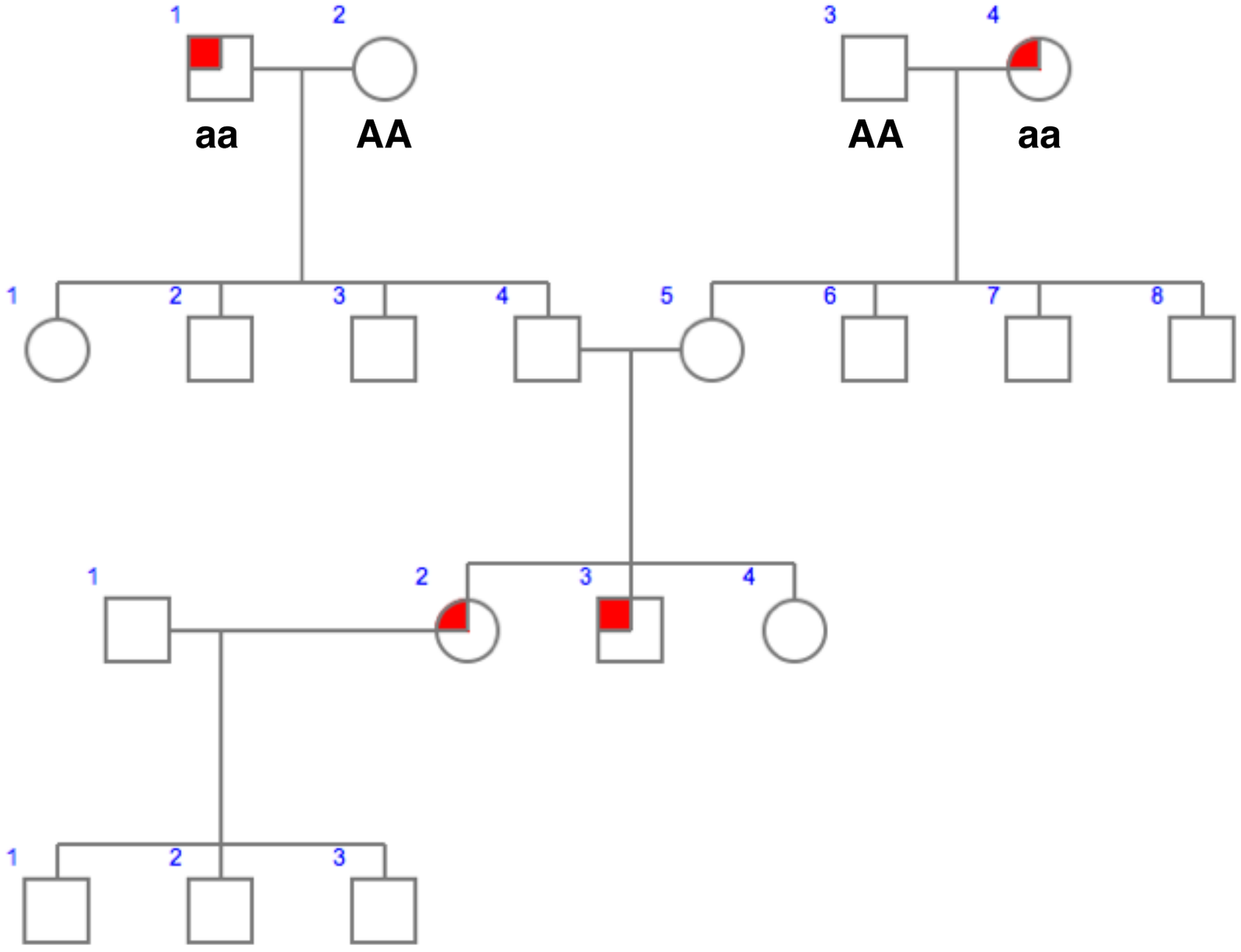

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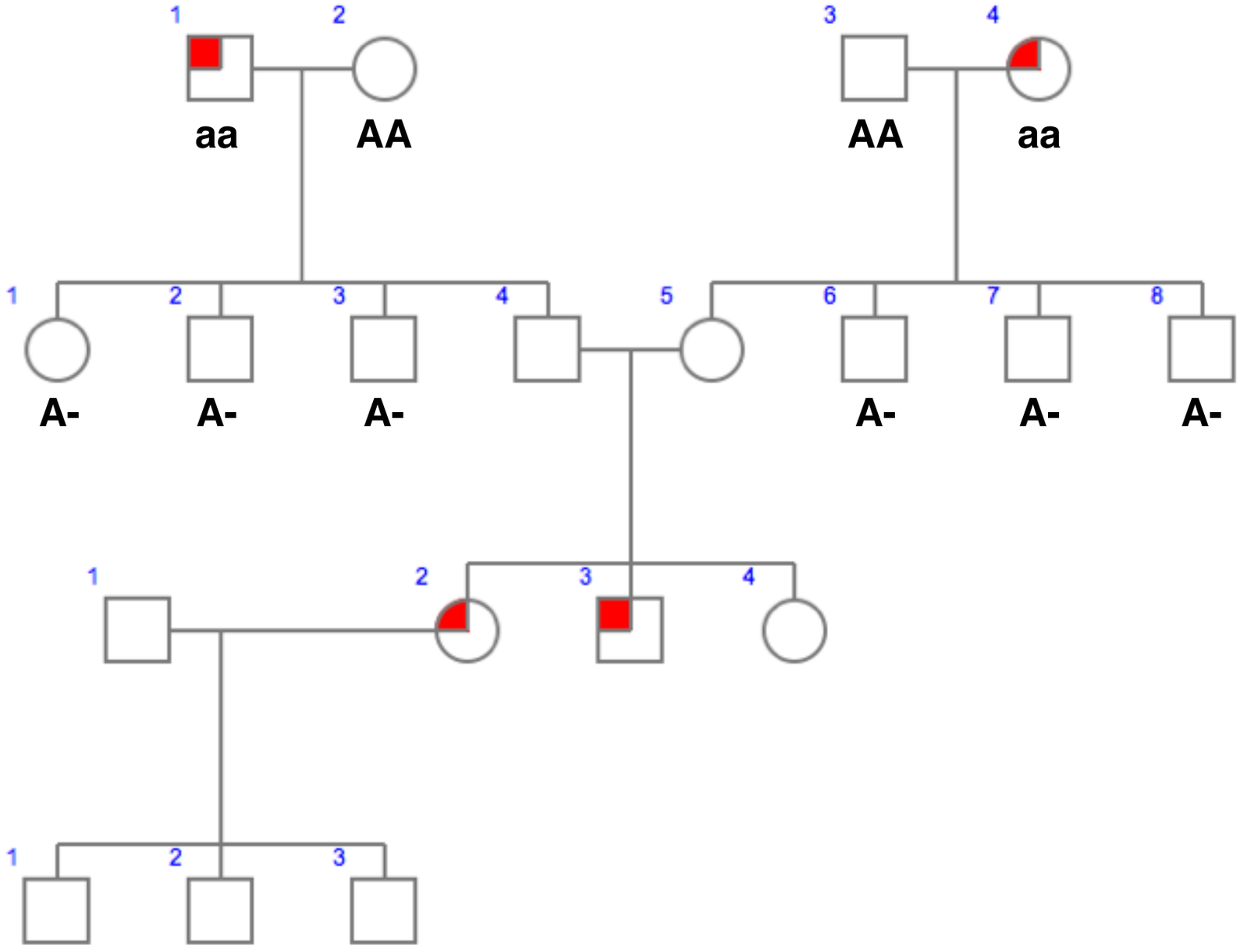

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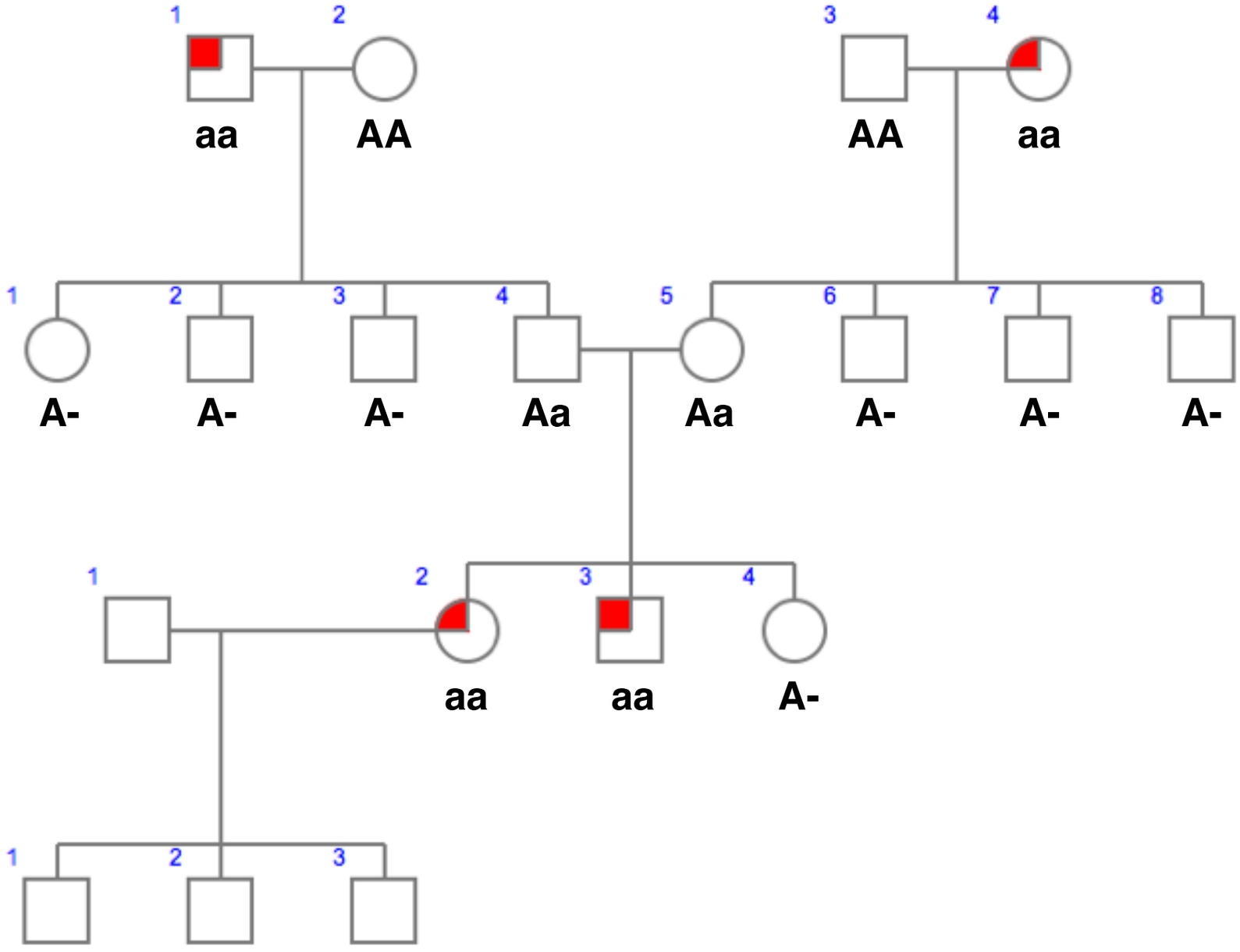

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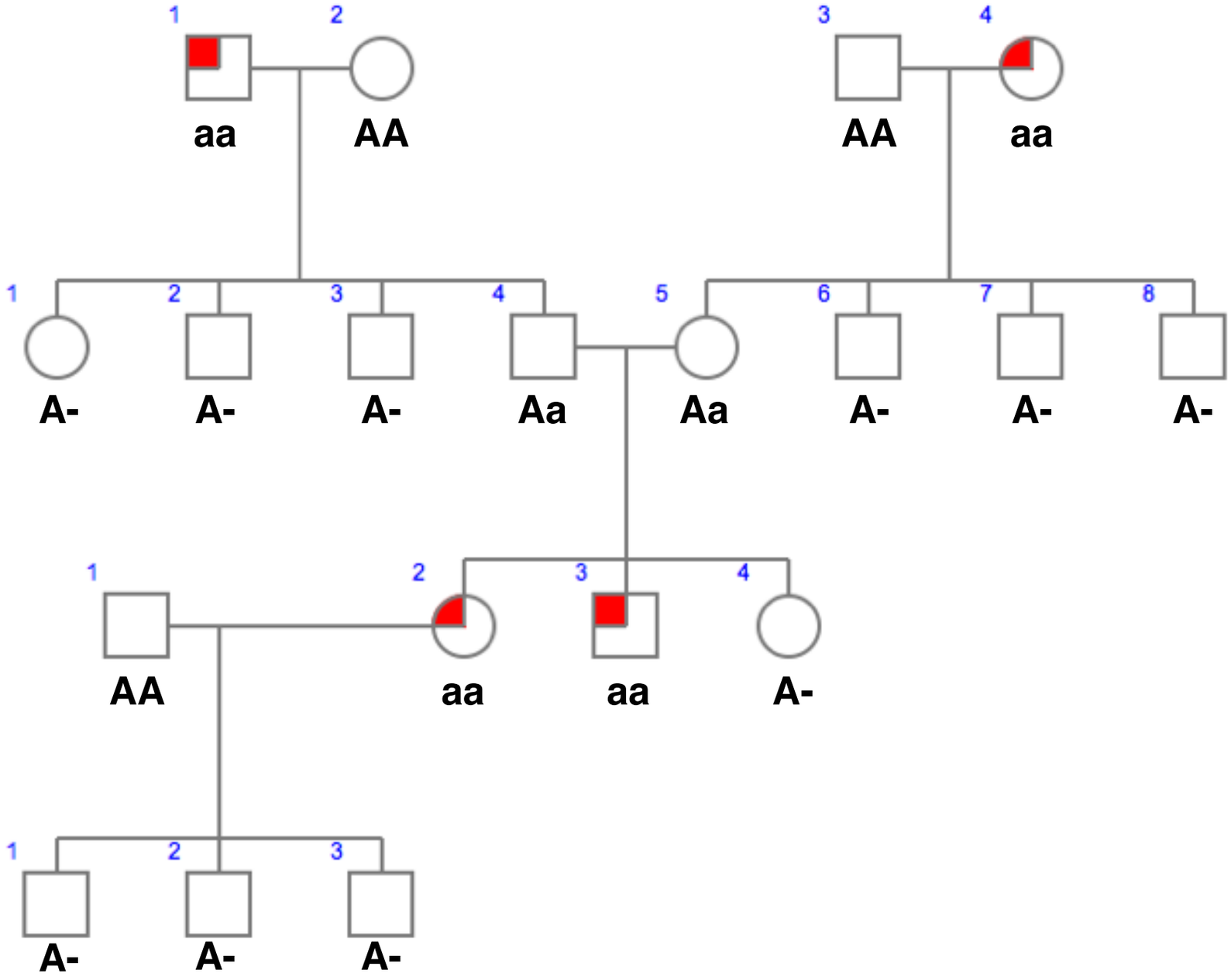

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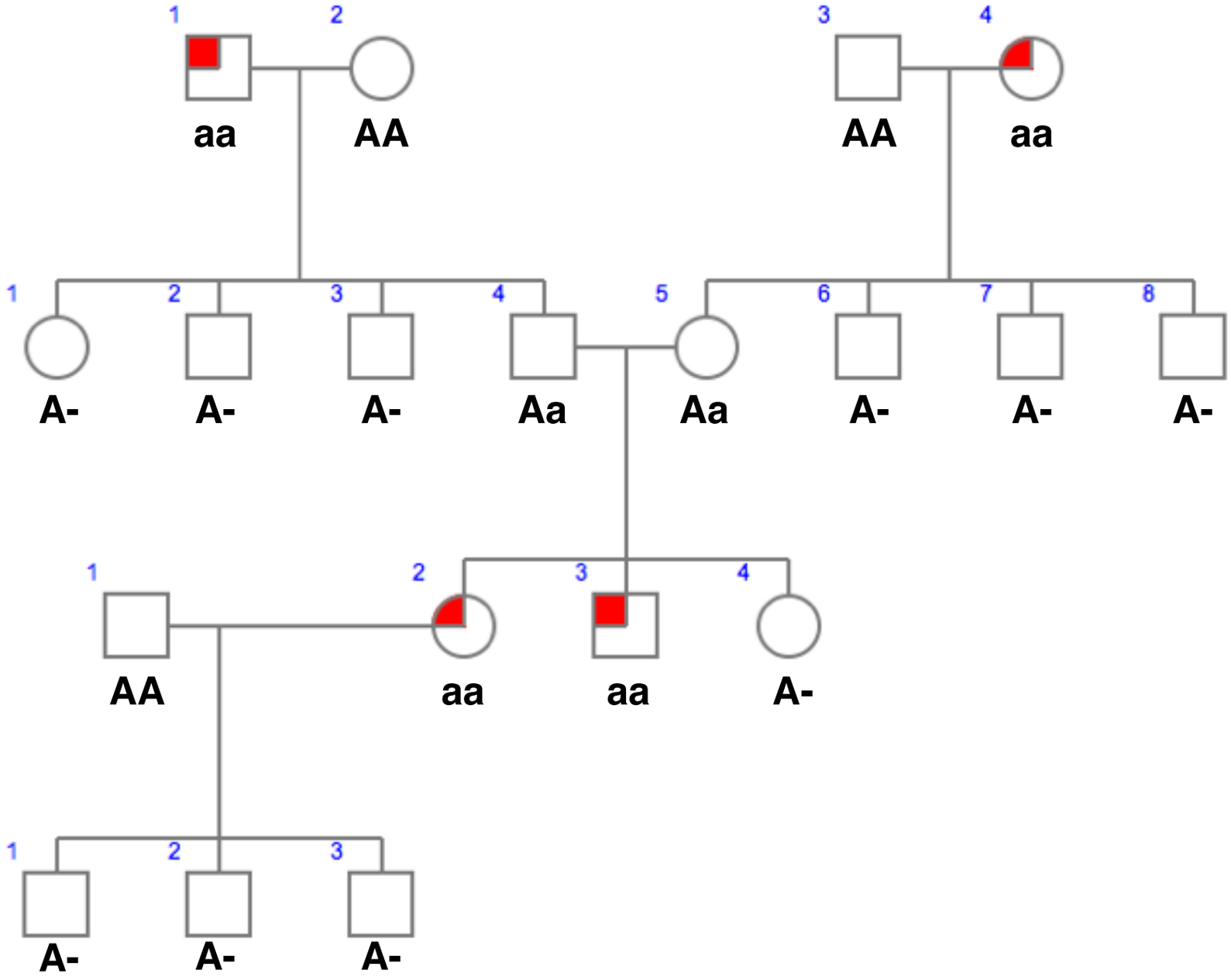

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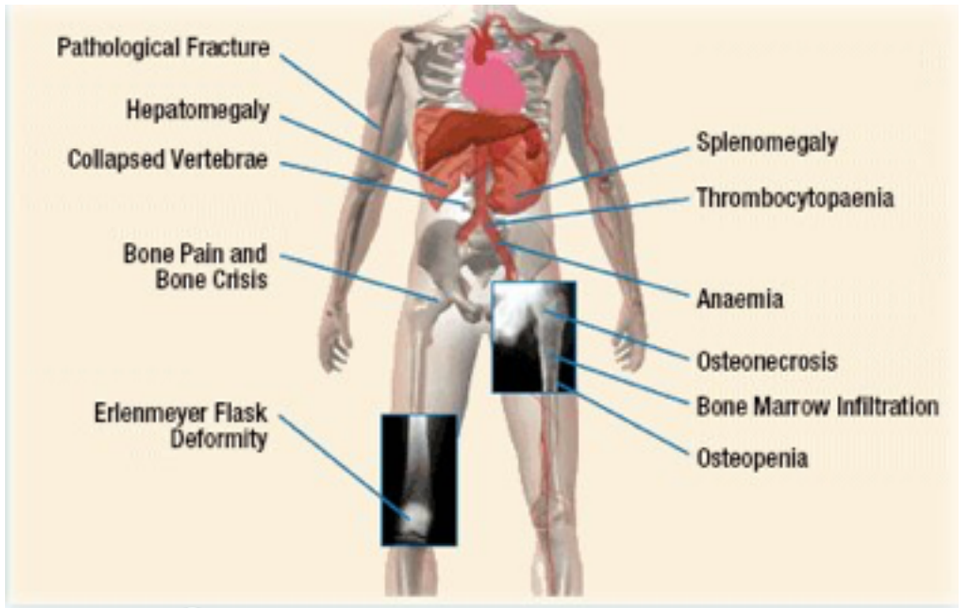
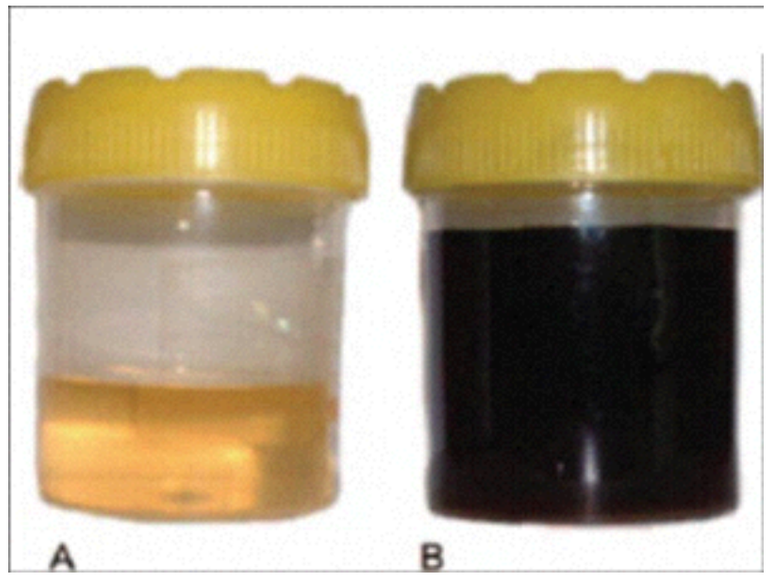
Autosomal recessive

Examples of human autosomal recessive disorders



Gaucher's Disease

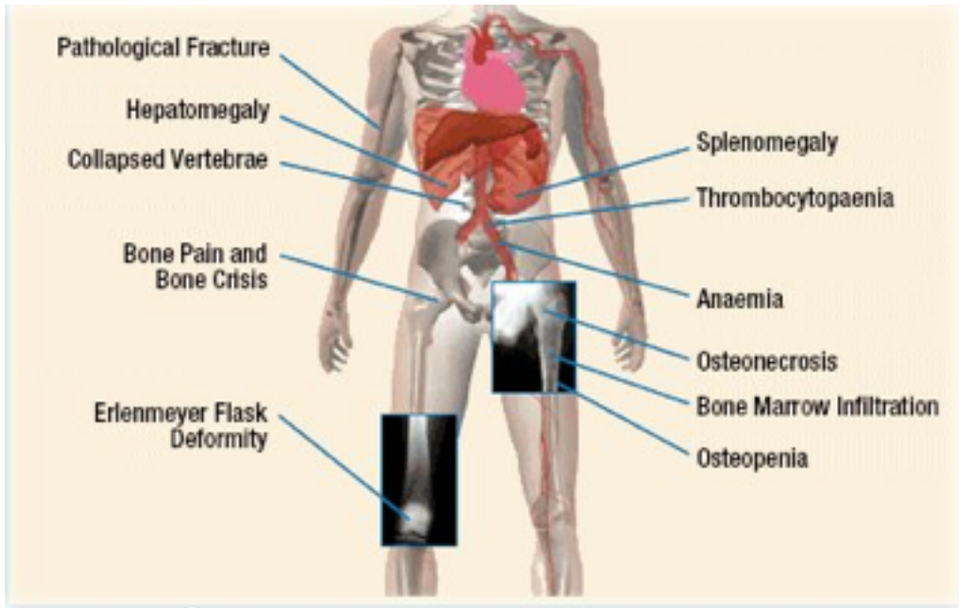
chr. 1



Maple Syrup Urine Disease

chr. 1, 6, or 19

Examples of human autosomal recessive disorders



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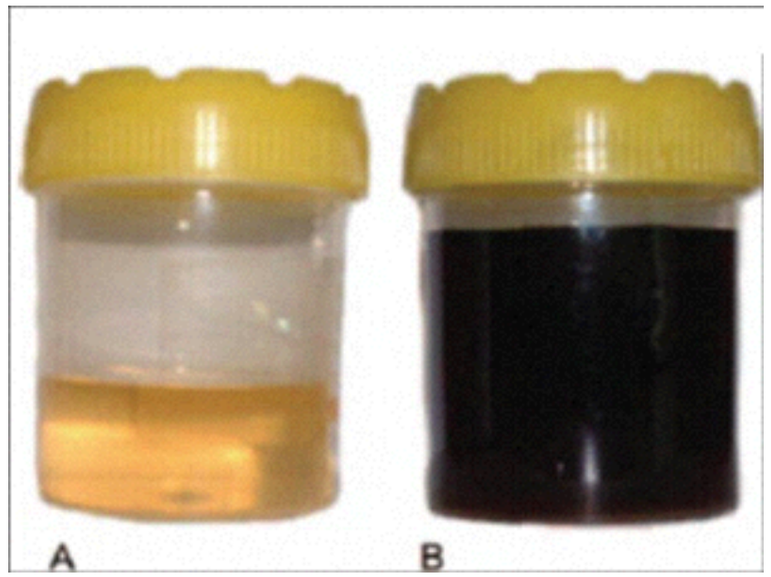

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Caused by loss-of-function or gain-of-function?

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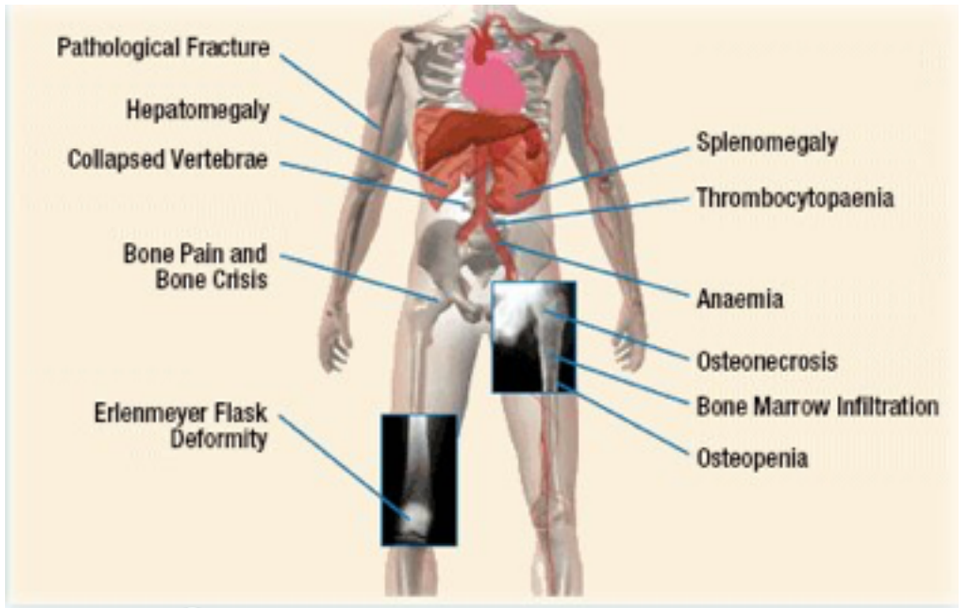

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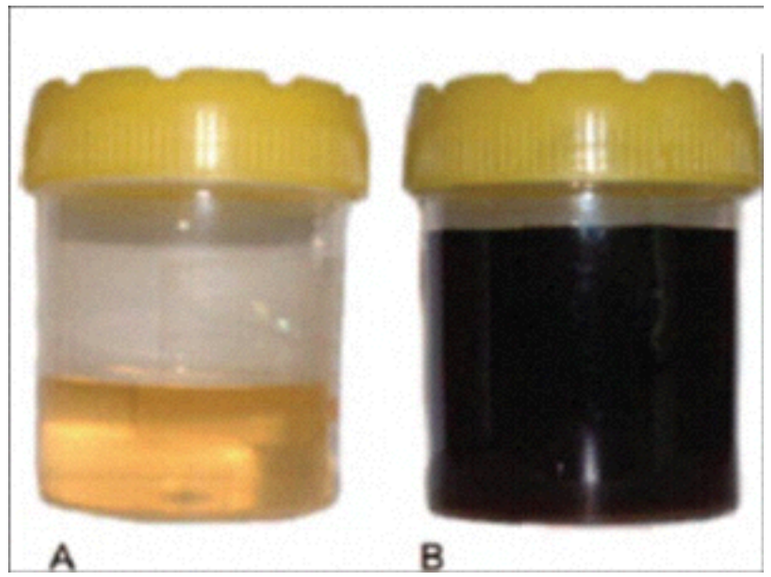

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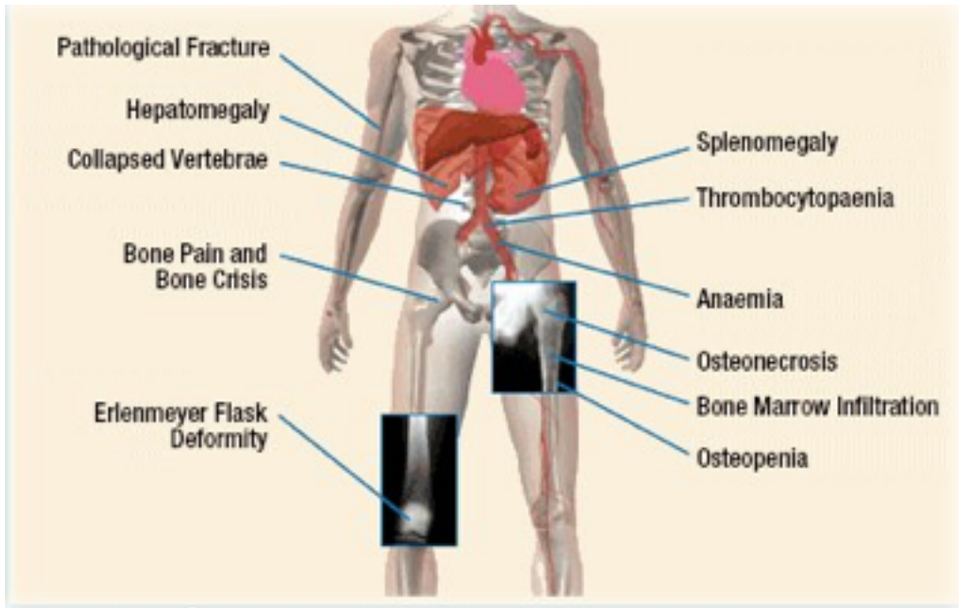

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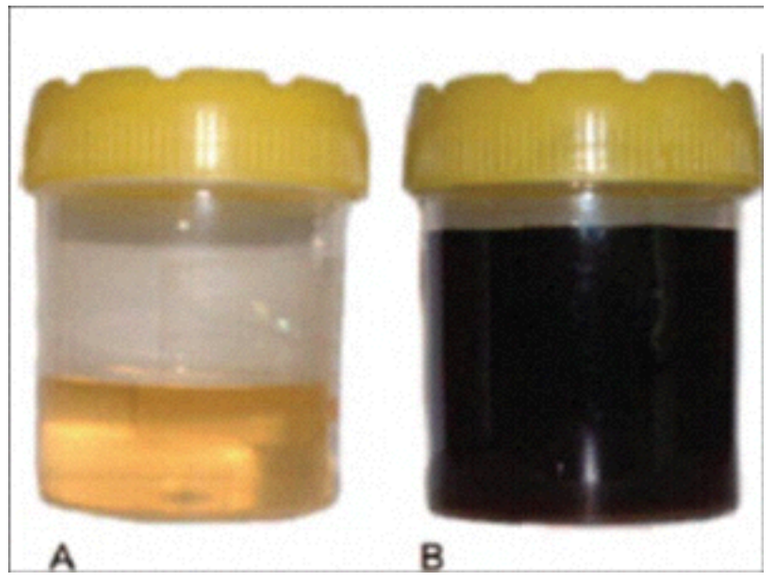

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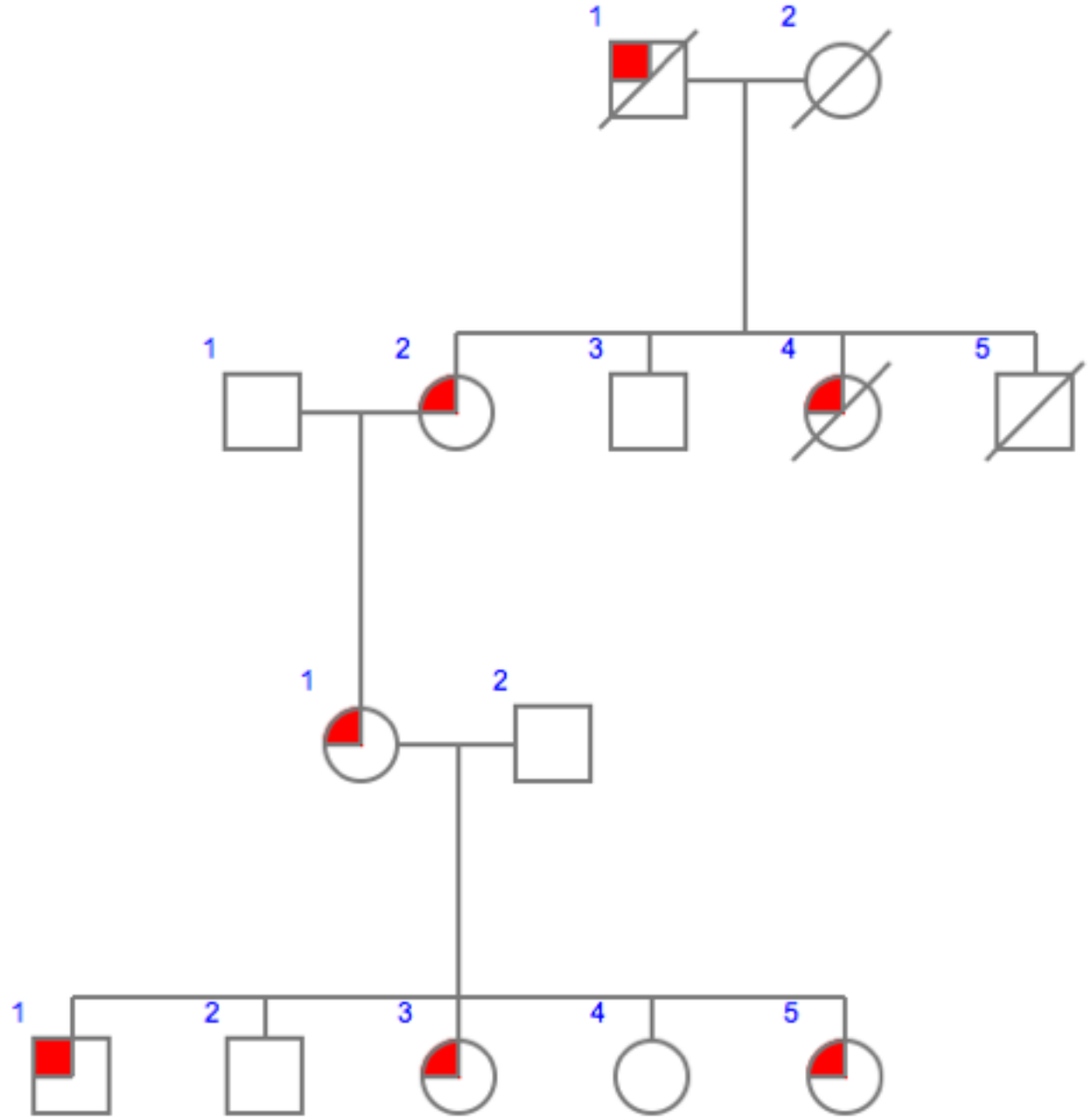
Caused by loss-of-function or gain-of-function?

All affected individuals are homozygotes

Modes of inheritance



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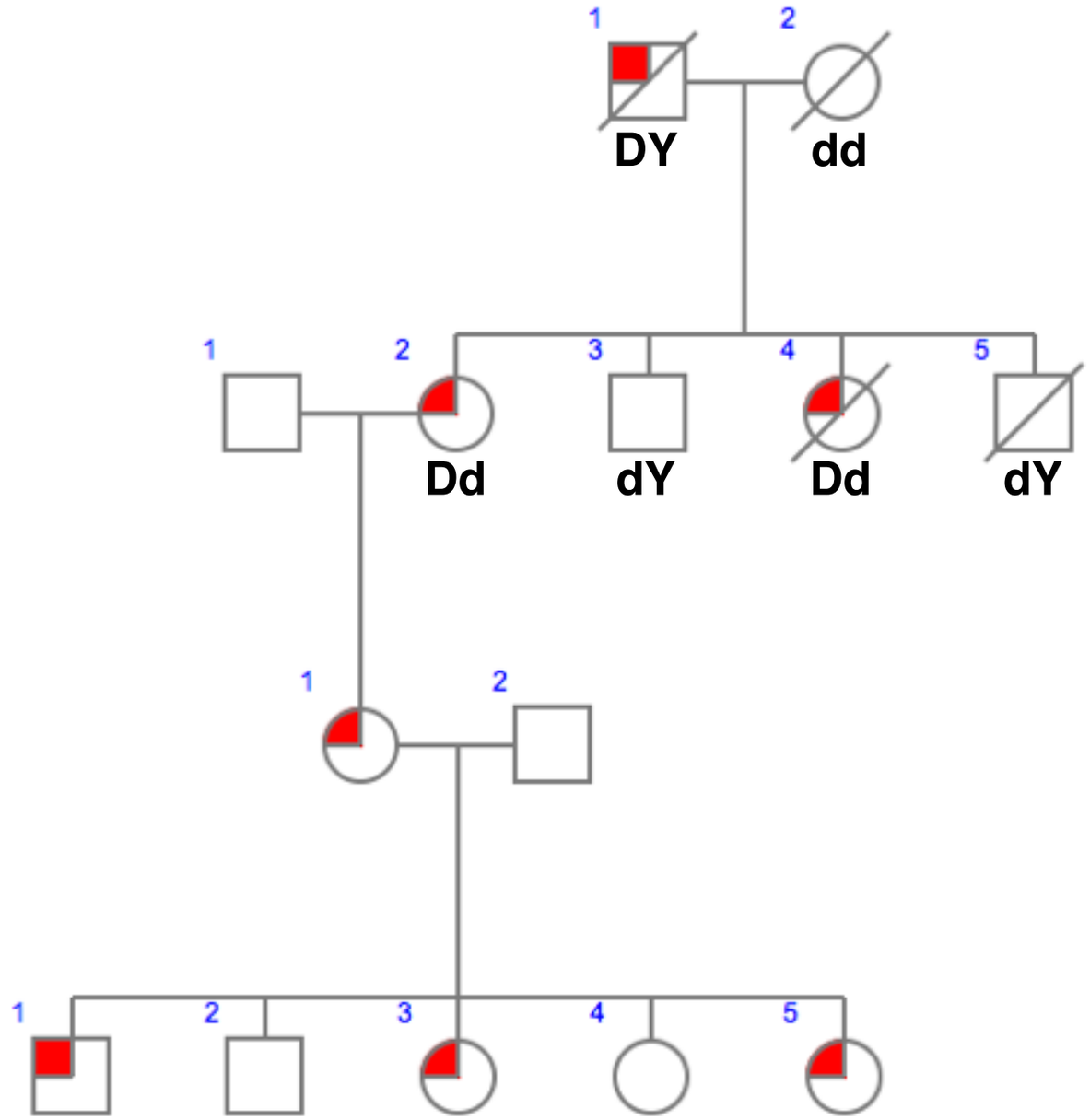

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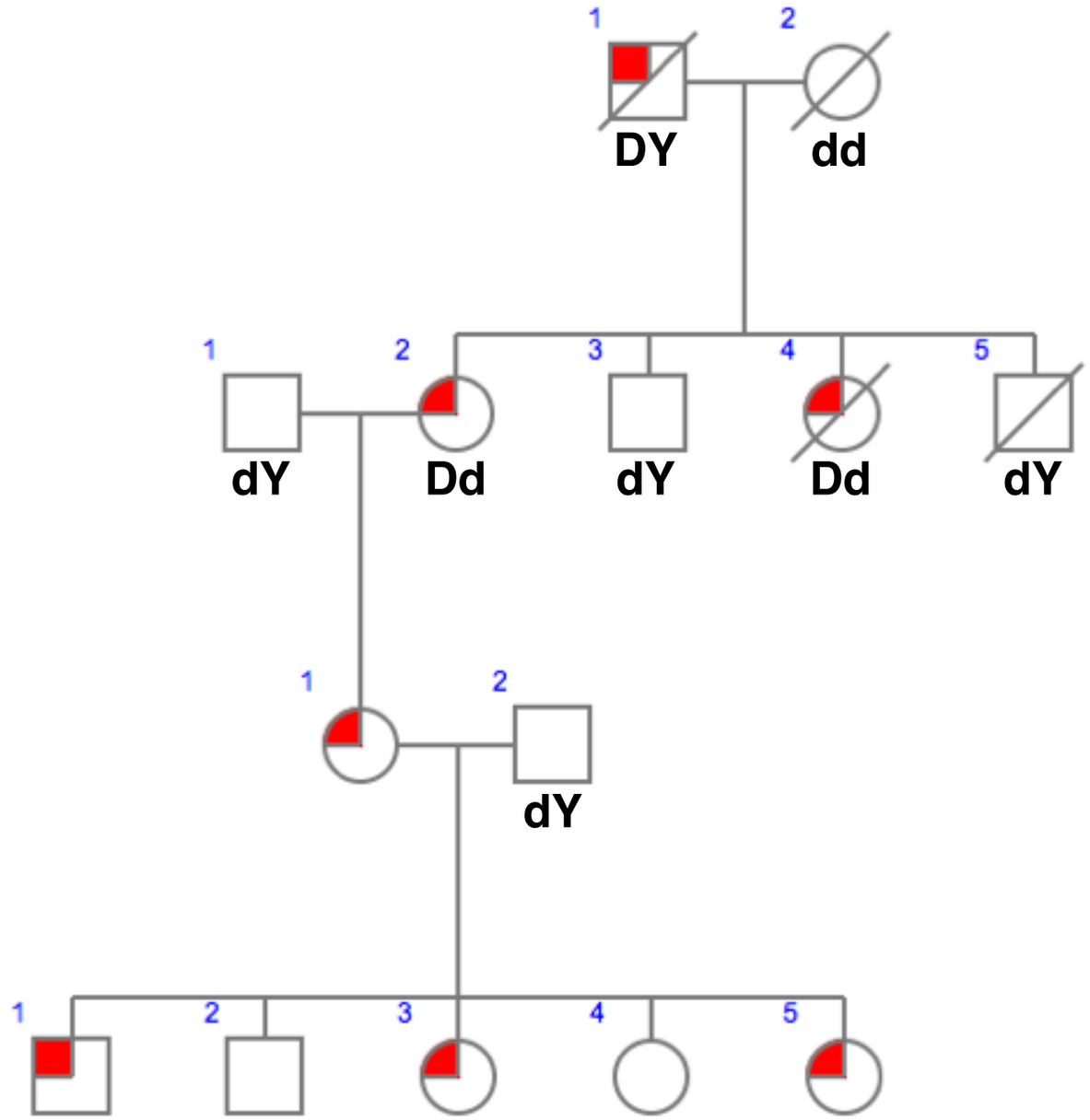

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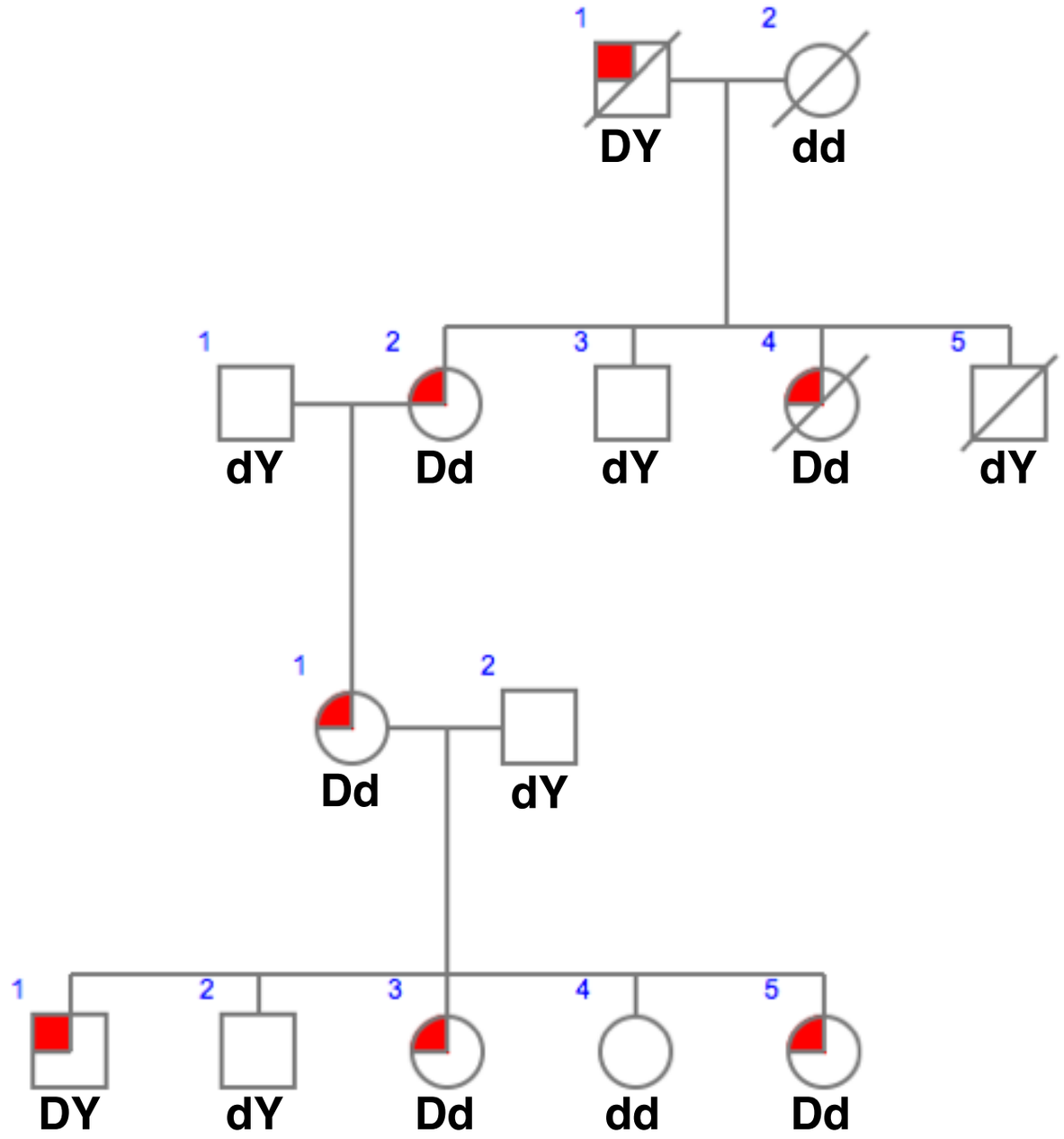

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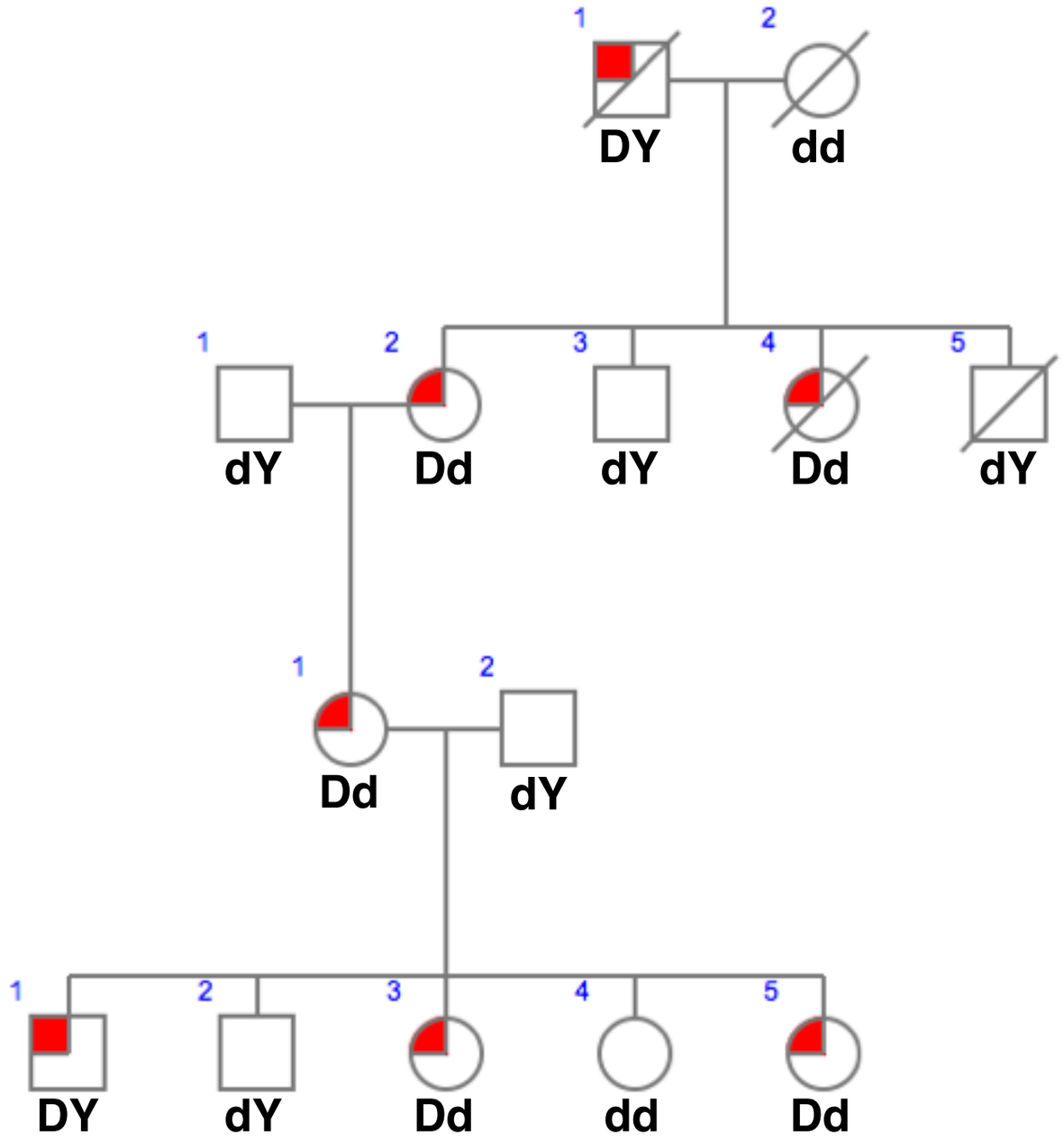

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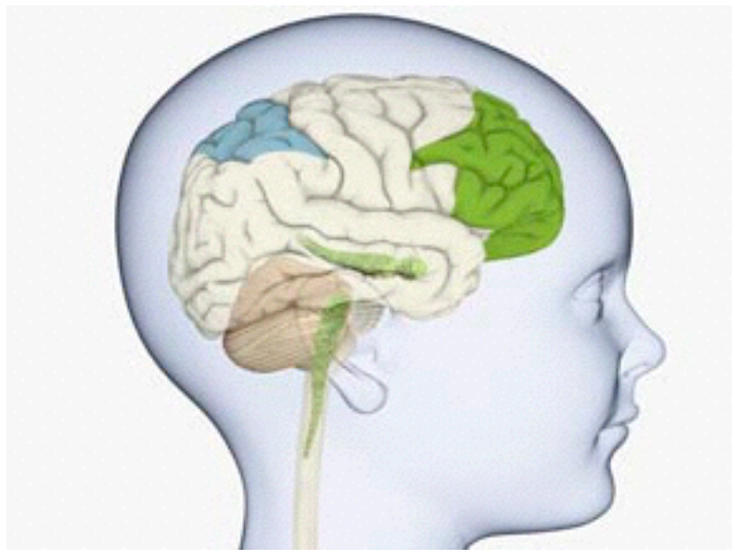
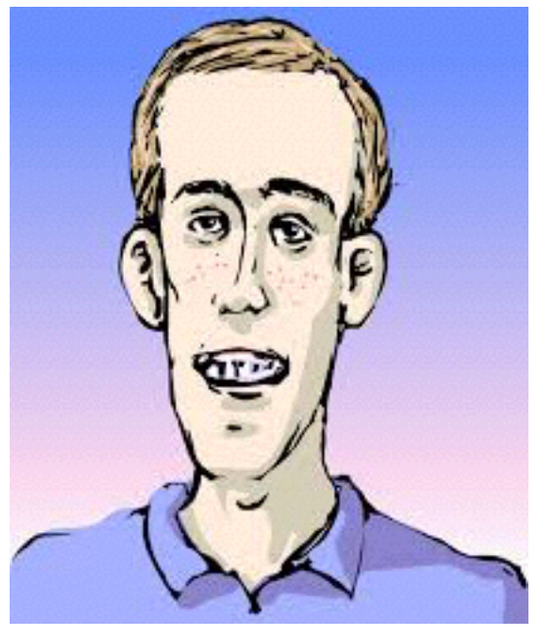
X-linked dominant

Examples of human X-linked dominant disorders

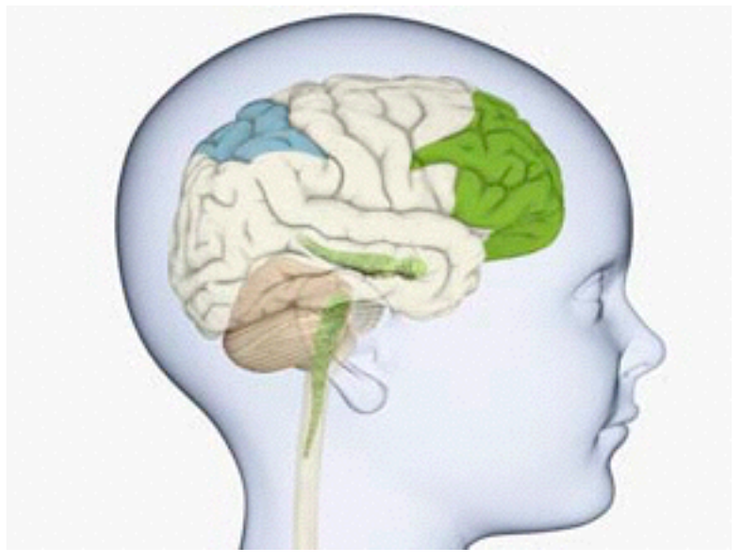


Rett syndrome

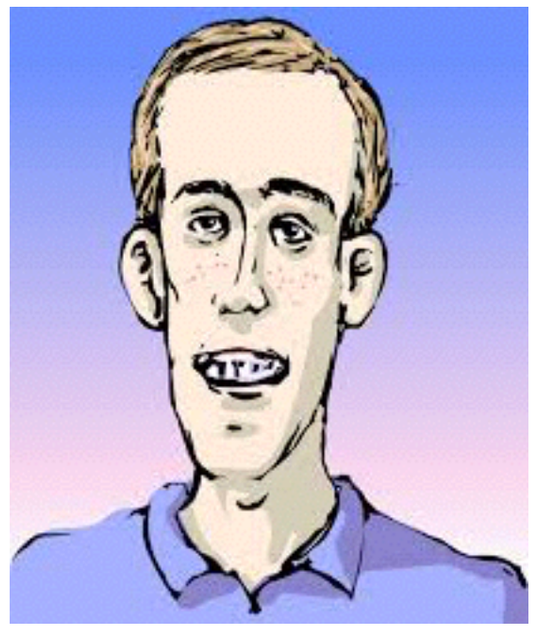


Fragile X syndrome

Examples of human X-linked dominant disorders



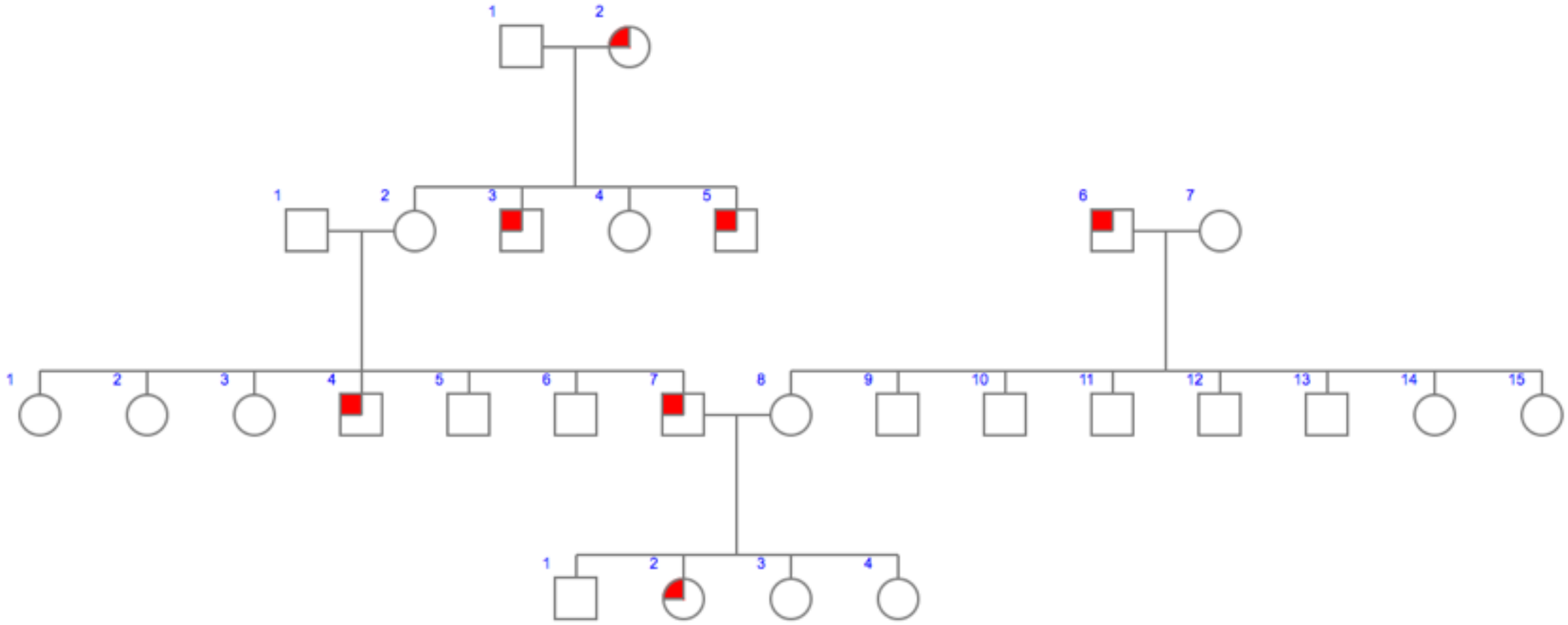
Rett syndrome



Fragile X syndrome

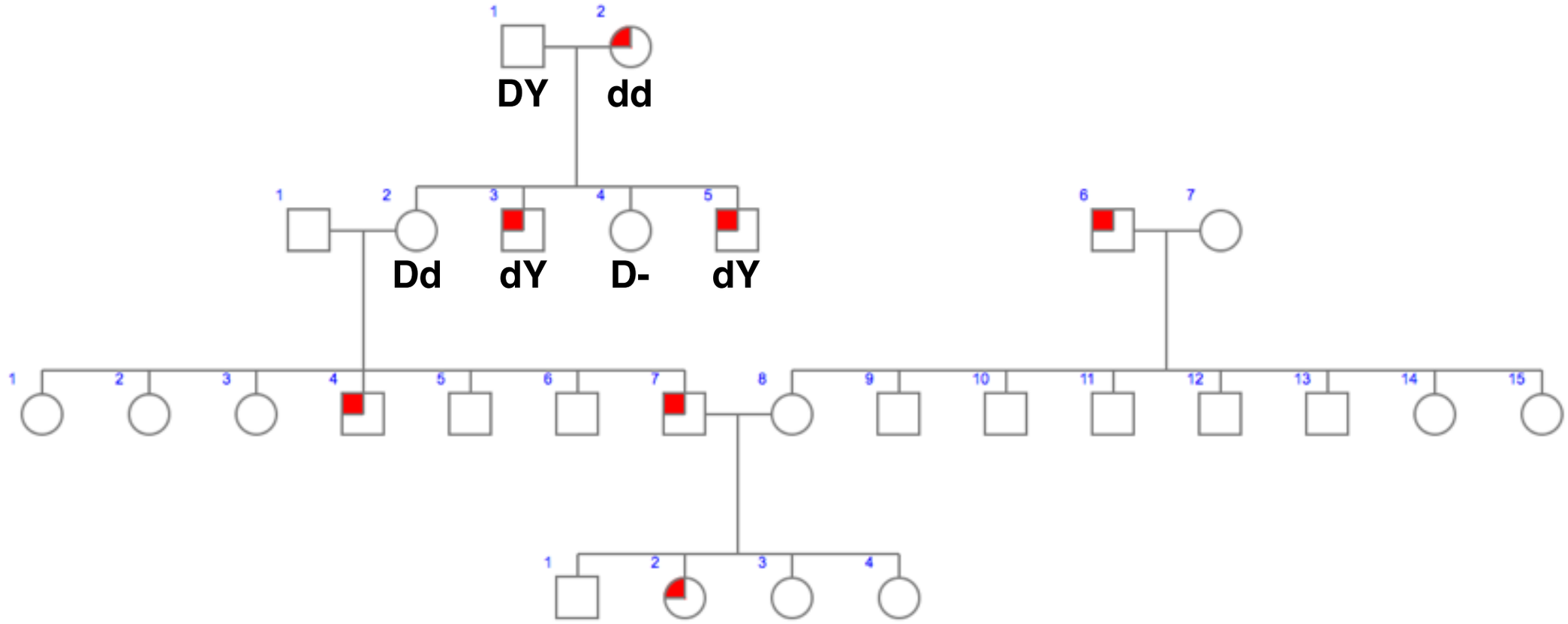
All daughters of affected fathers are affected

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?

Modes of inheritance



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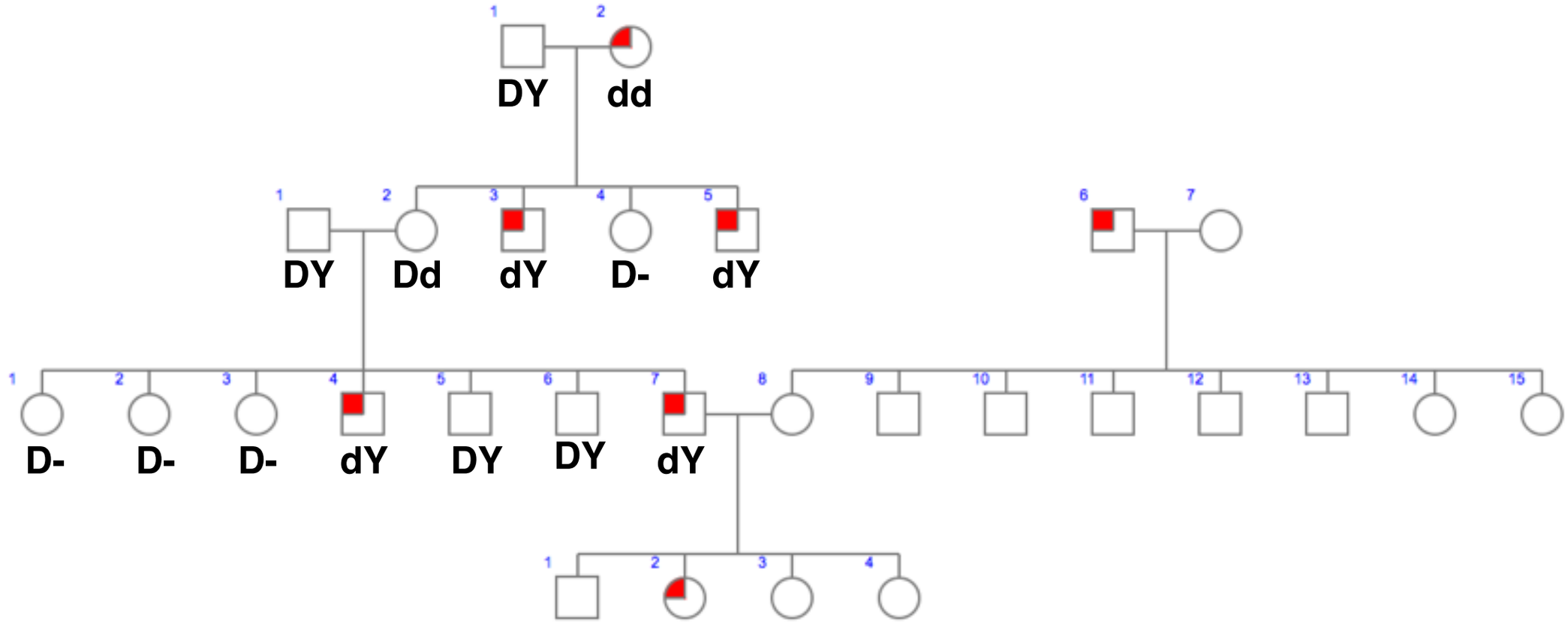
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Modes of inheritance



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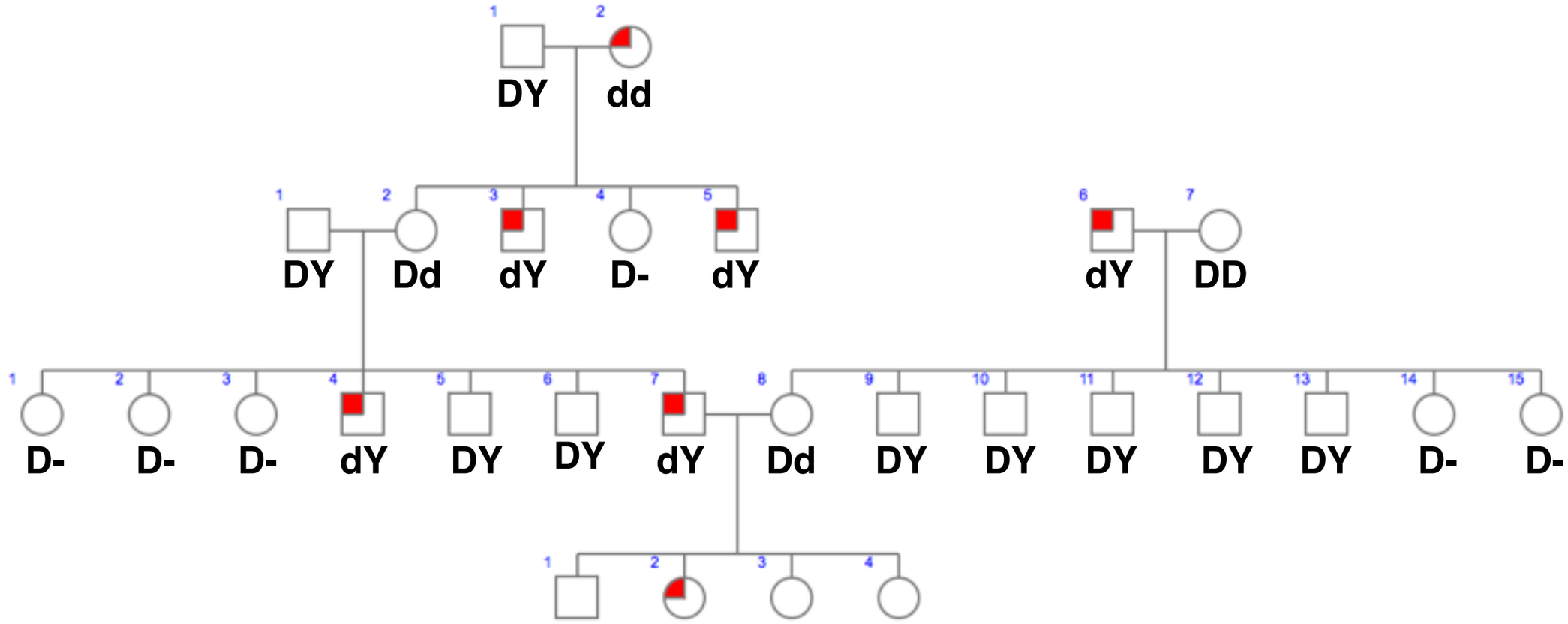
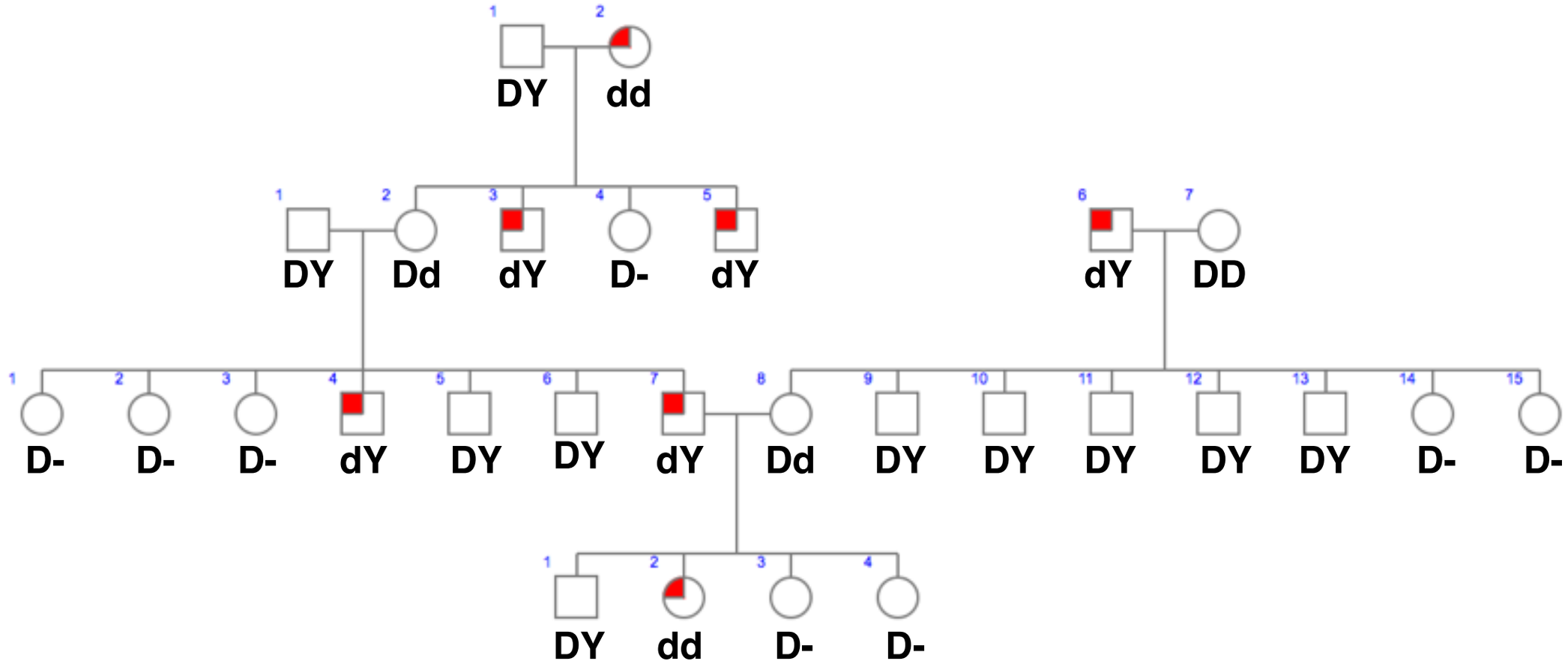
Modes of inheritance



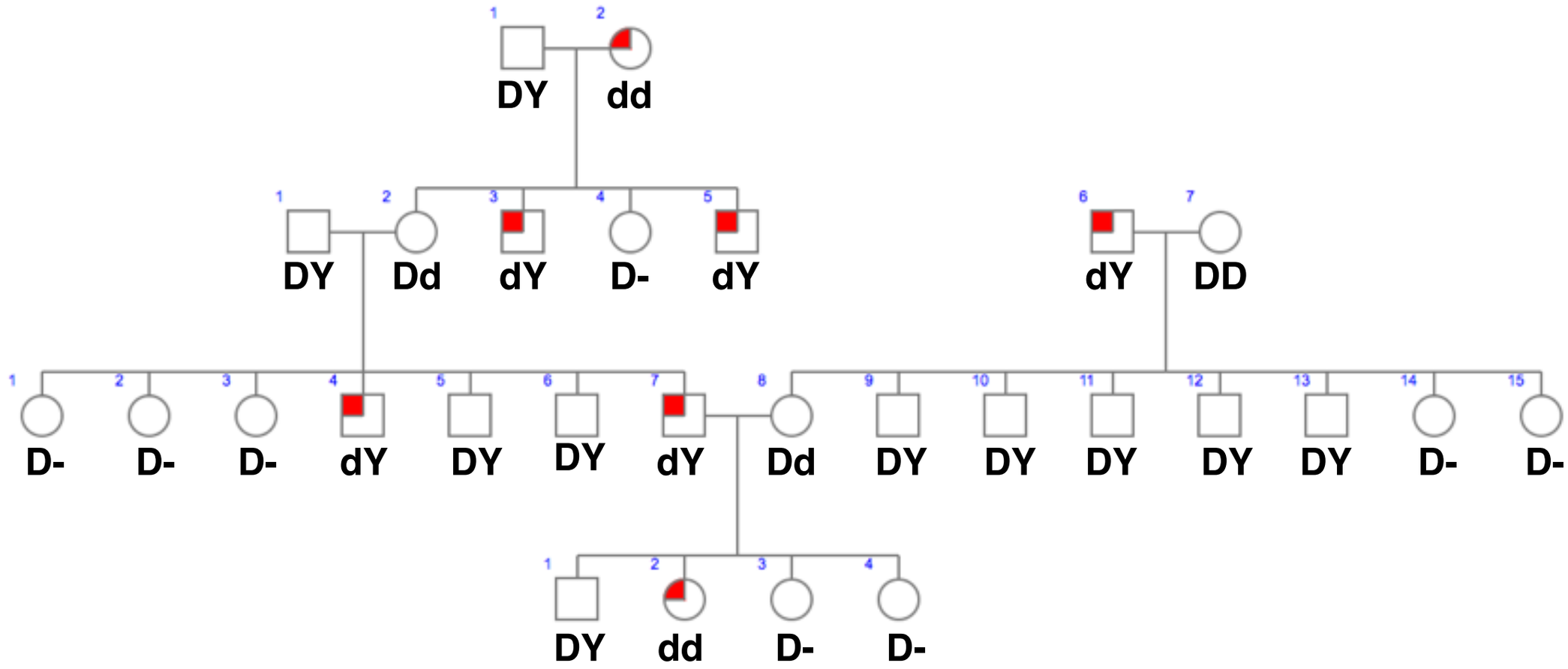
- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

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?

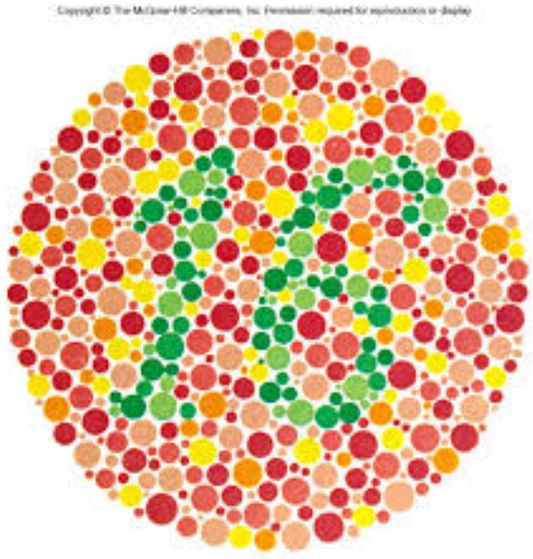
Modes of inheritance



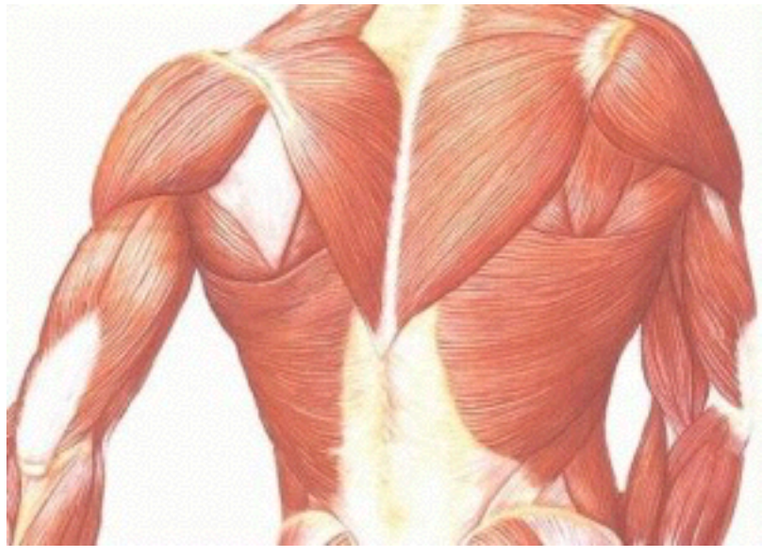
- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

X-linked recessive

Examples of human X-linked recessive disorders

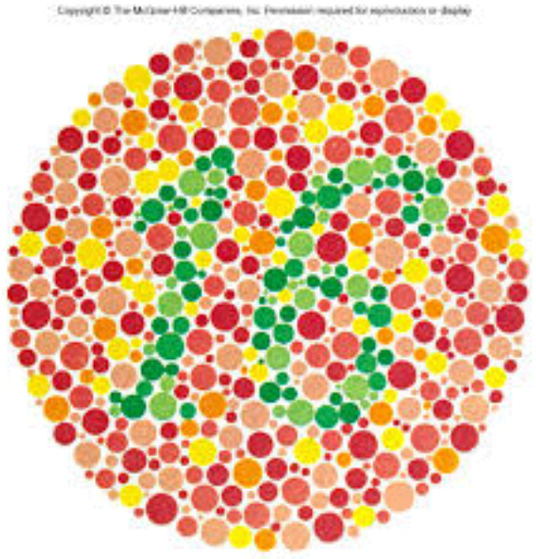


Red-green color blindness

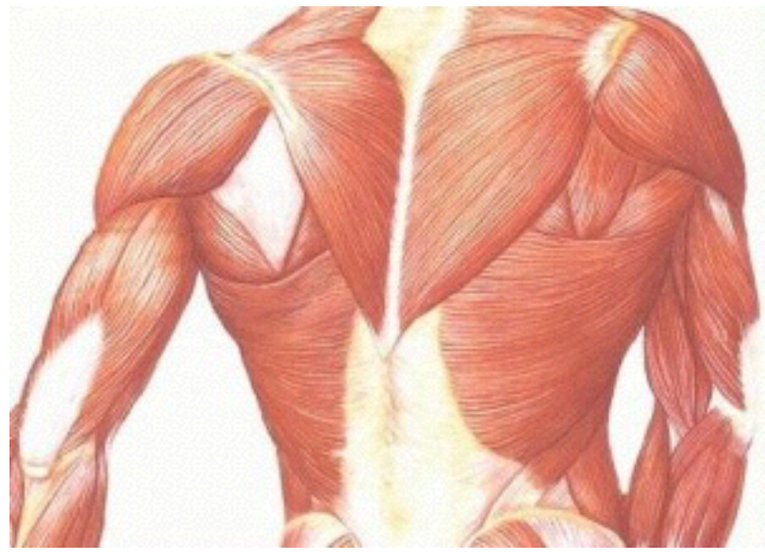


Duchenne muscular dystrophy

Examples of human X-linked recessive disorders



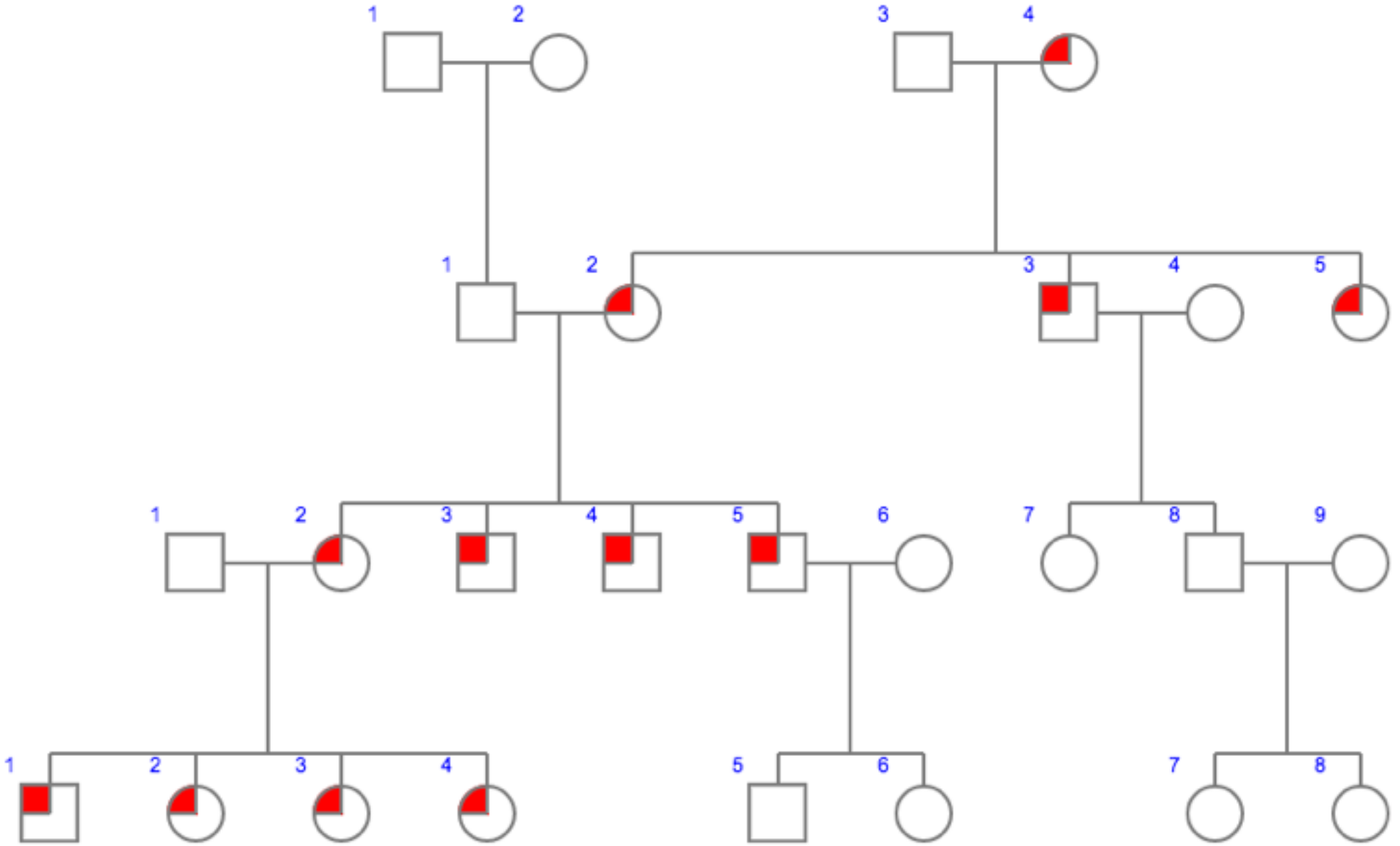
Red-green color blindness



Duchenne muscular dystrophy

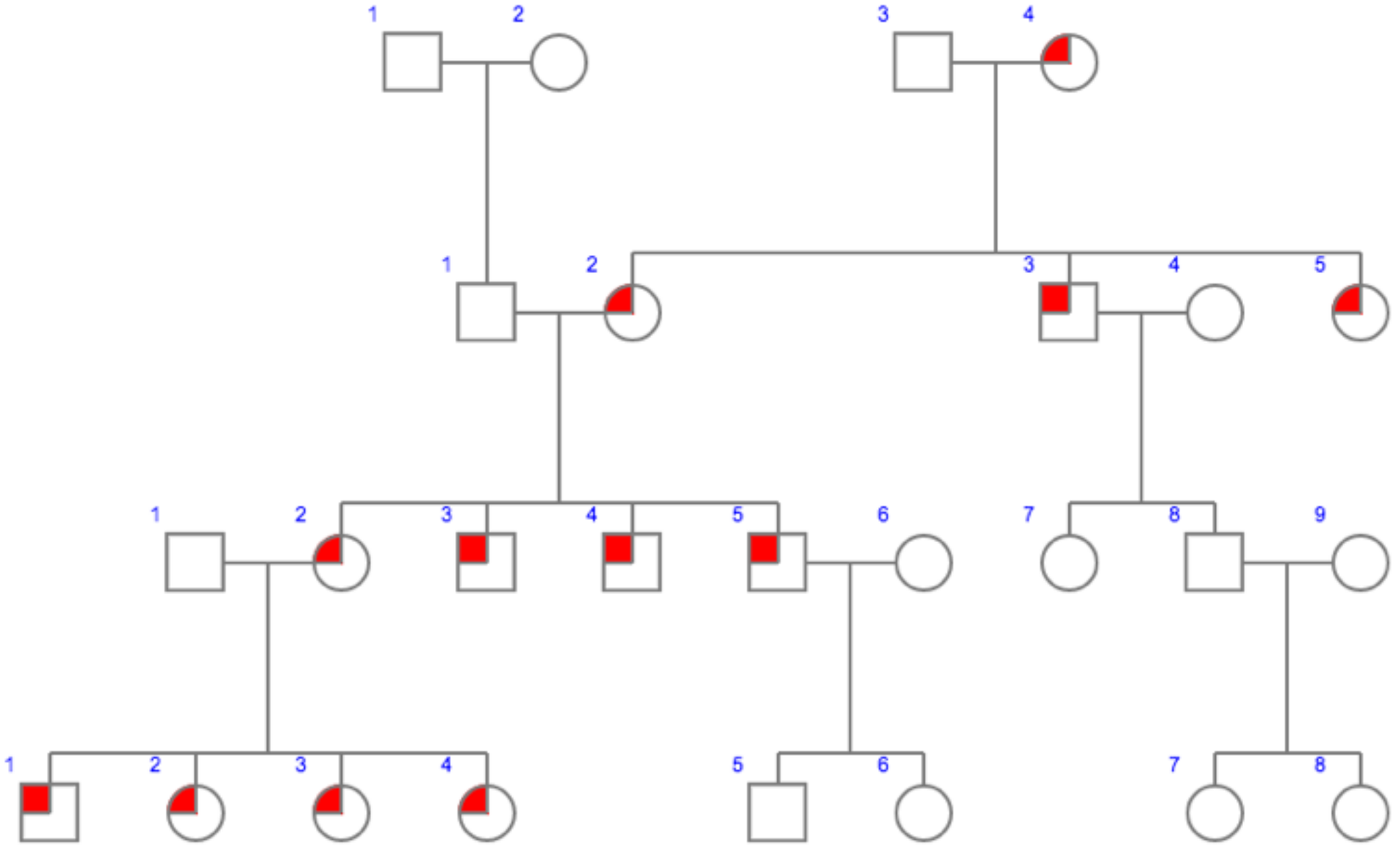
All sons of affected mothers are affected

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?

Modes of inheritance



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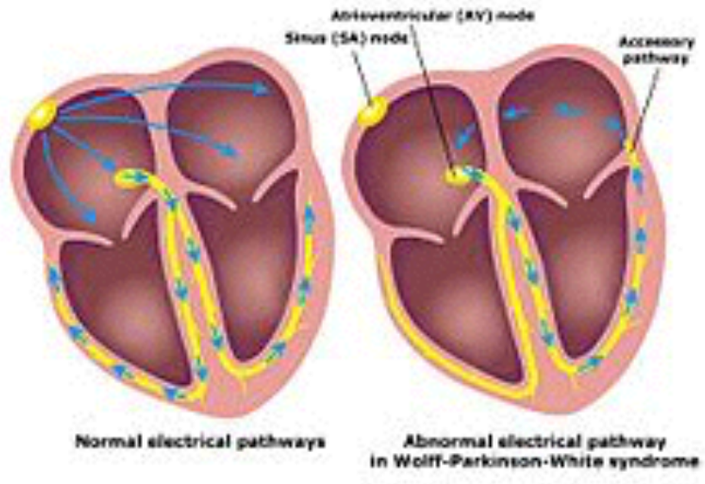
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Cytoplasmic inheritance

Examples of human cytoplasmic inheritance disorders

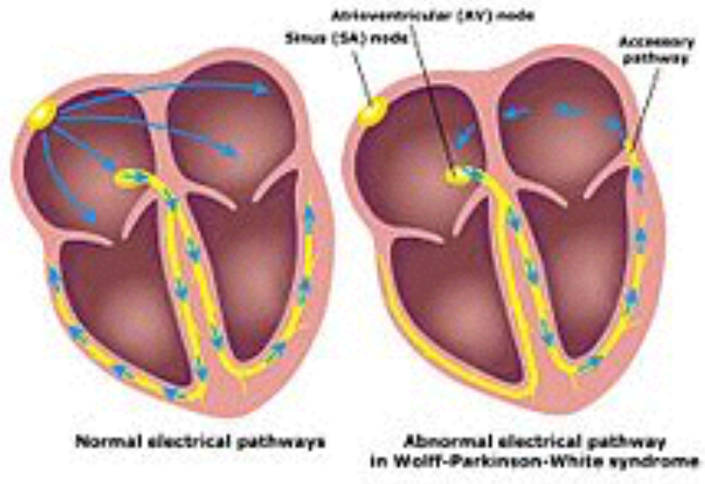
Mitochondrial myopathy



Wolff-Parkinson-White syndrome

Examples of human cytoplasmic inheritance disorders

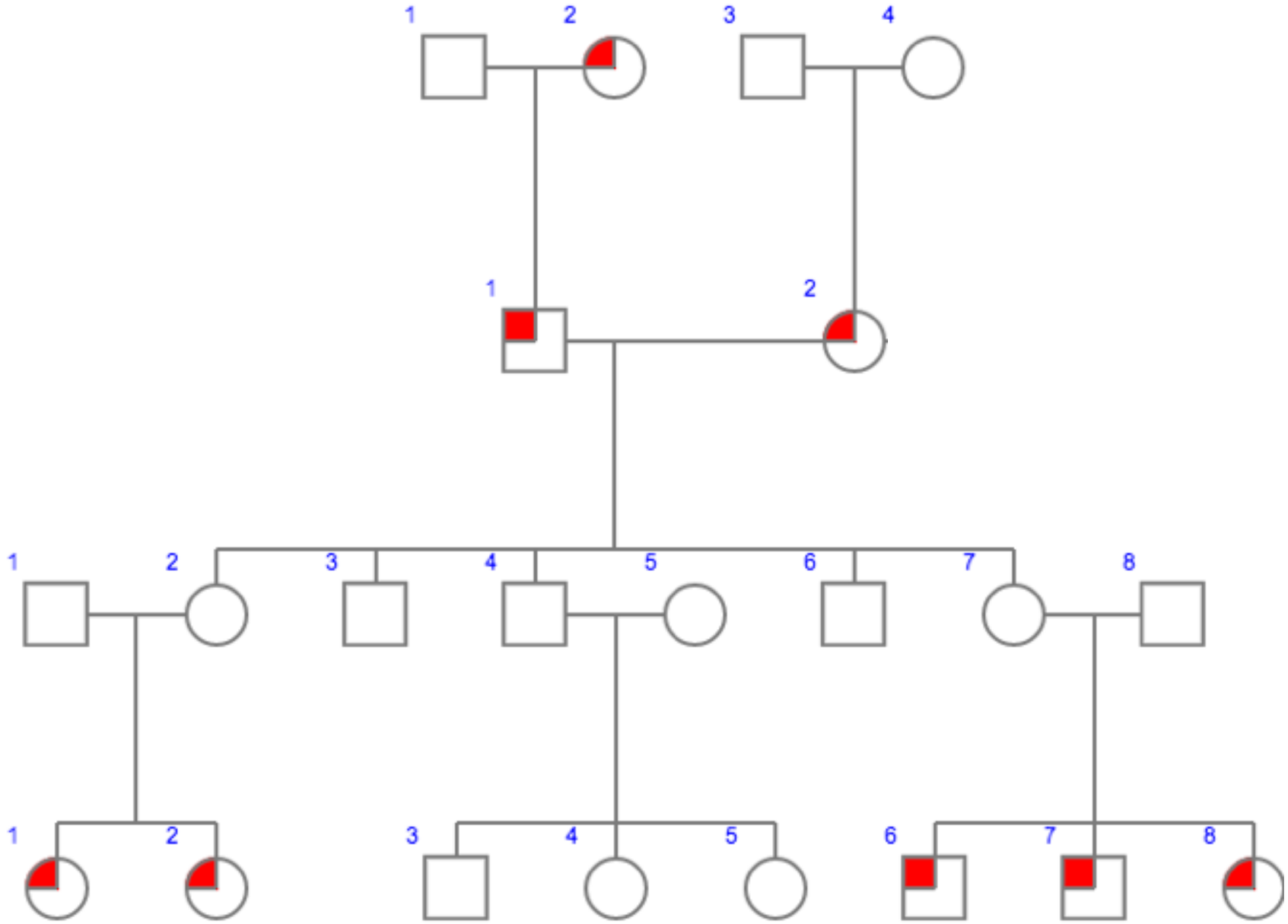
Mitochondrial myopathy



Wolff-Parkinson-White syndrome

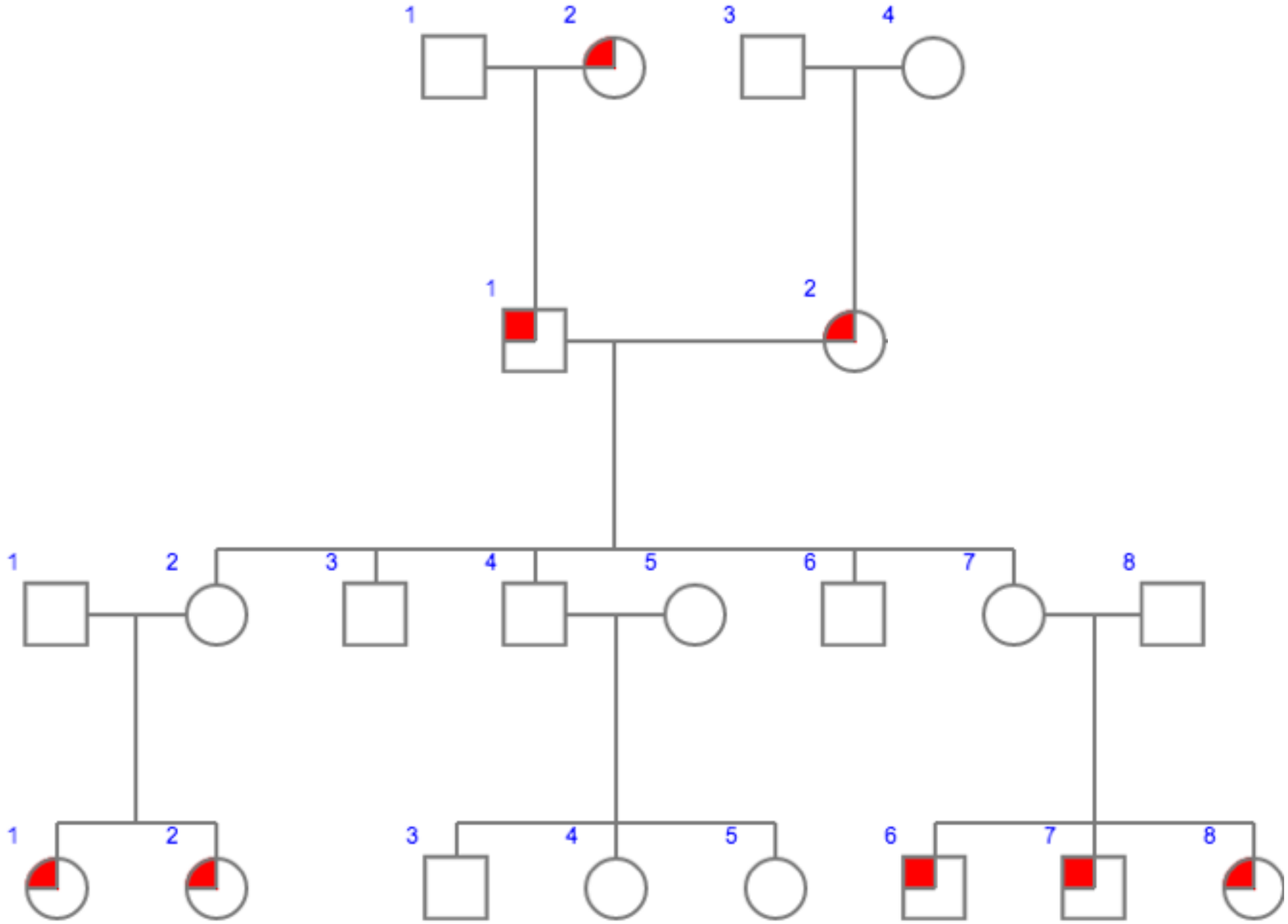
All children of affected mothers are affected

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?

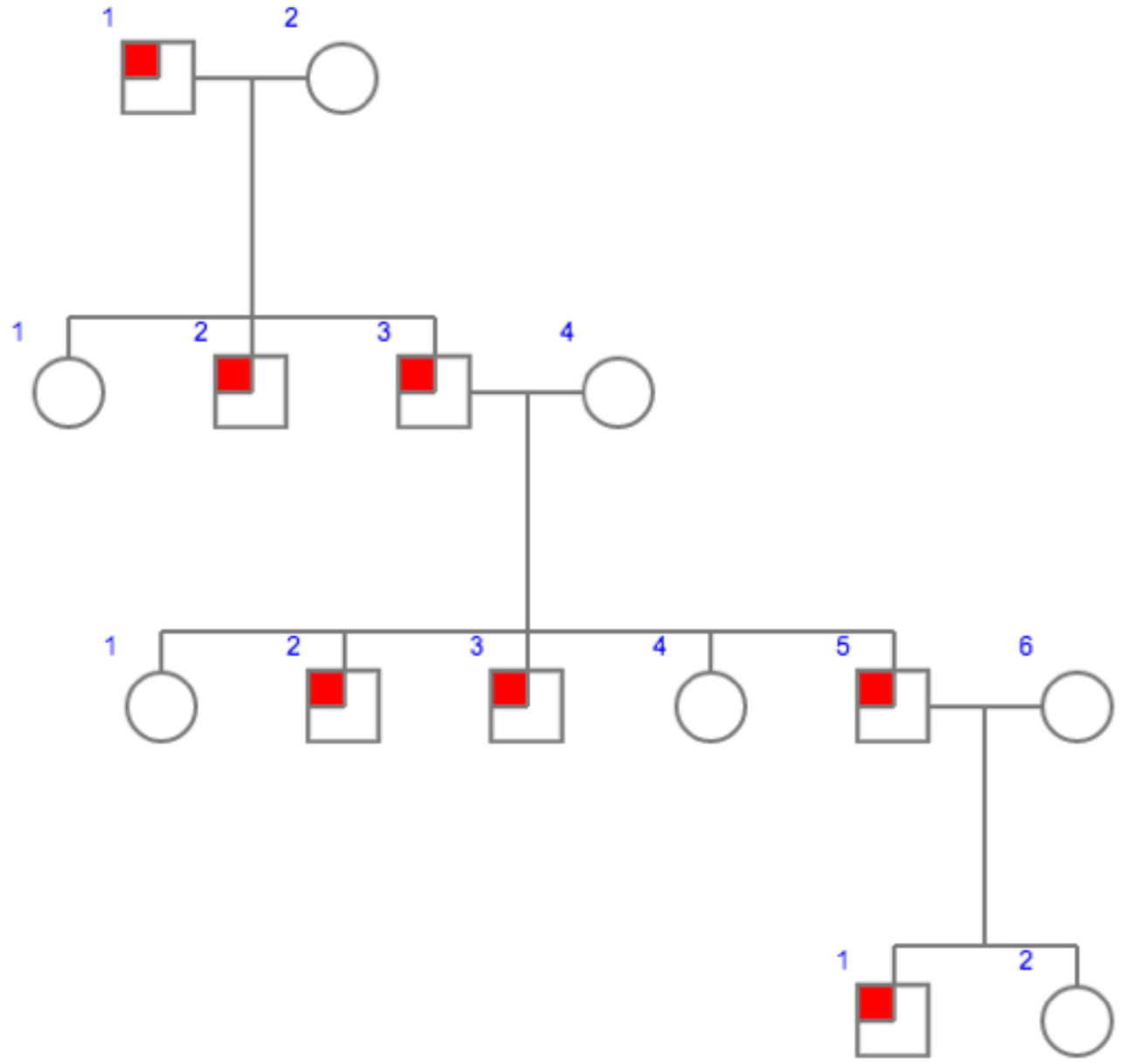
Modes of inheritance



- 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?
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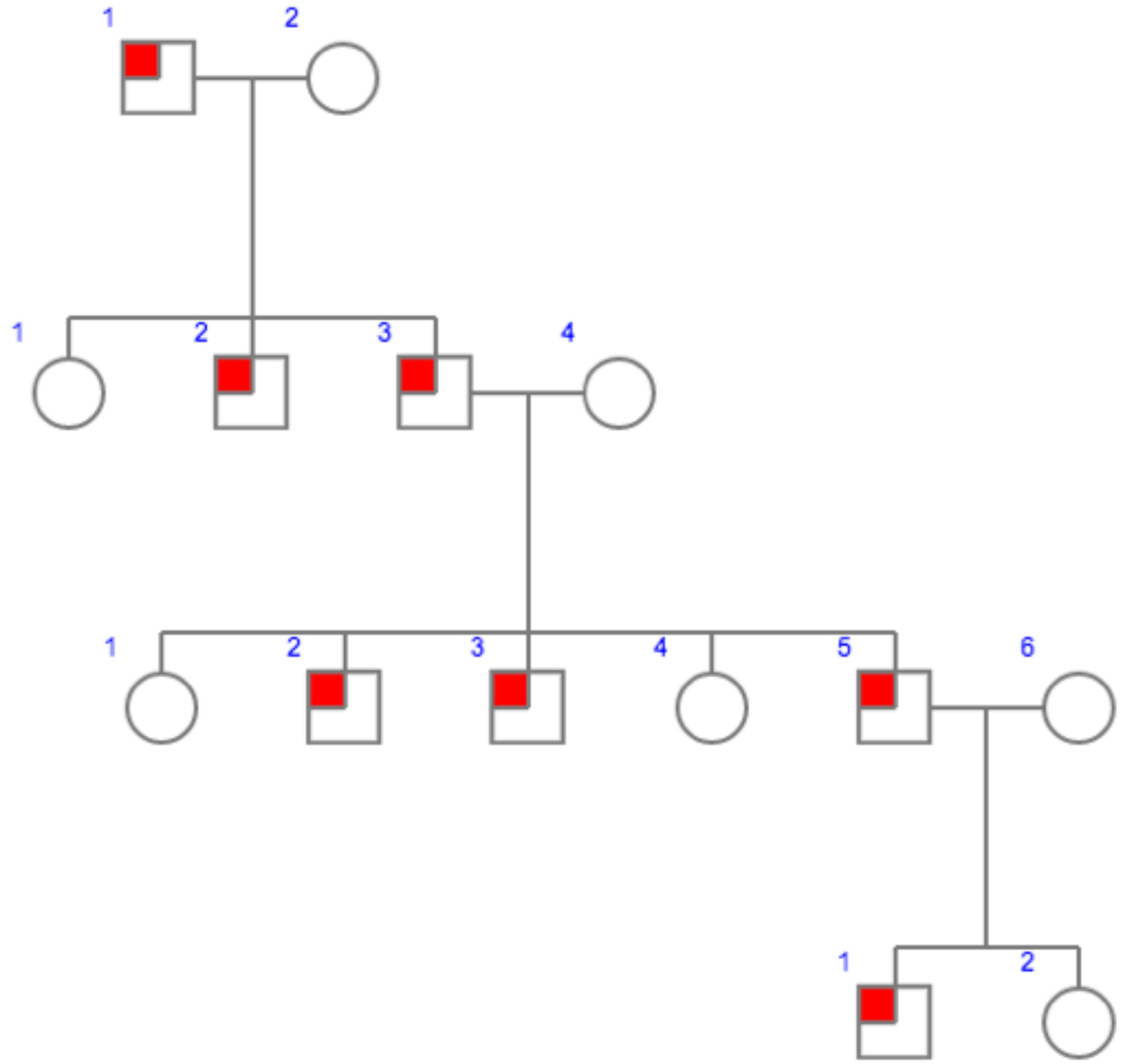
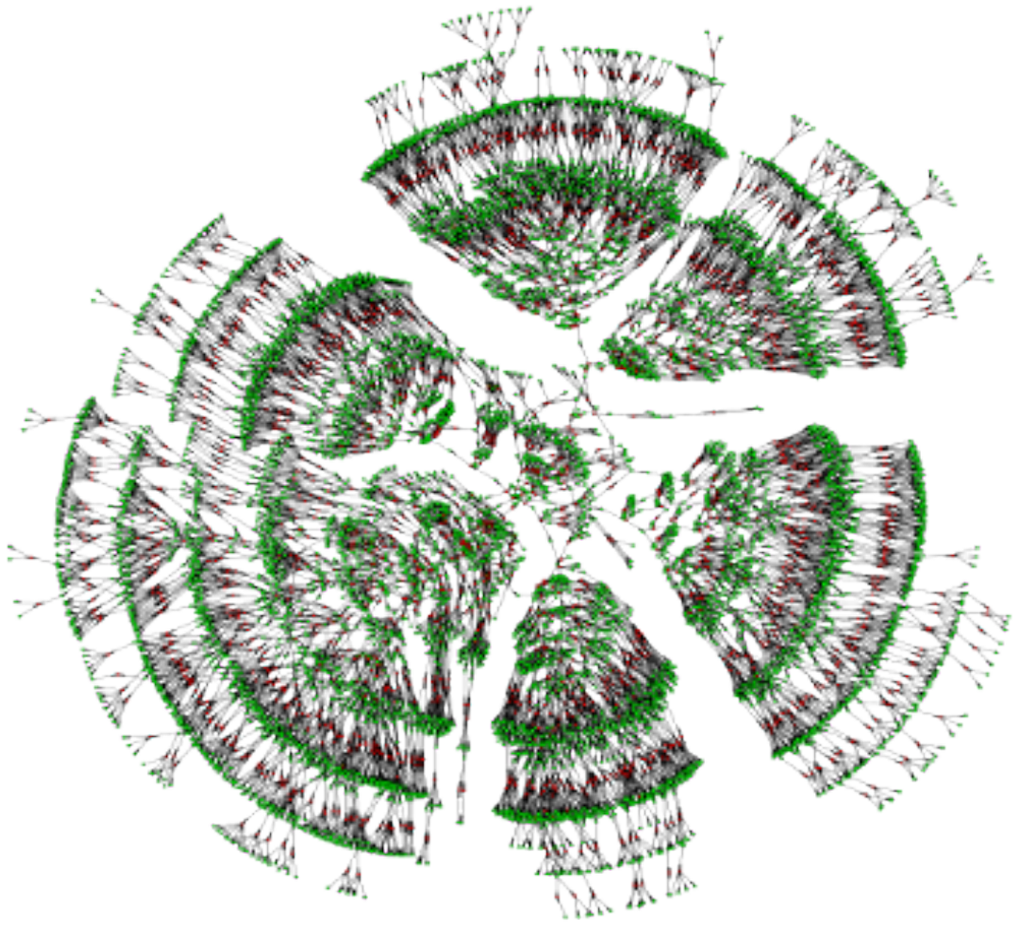
Modes of inheritance

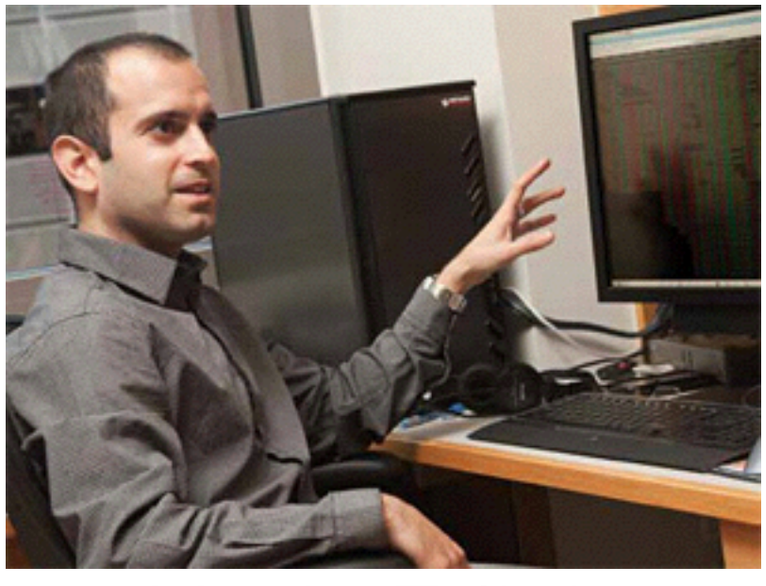


- How many individuals are affected?
- In each generation?
- Are males preferentially affected from affected mothers?
- Are females preferentially affected from affected fathers?

Y-linked inheritance

Some pedigrees can contain millions of individuals

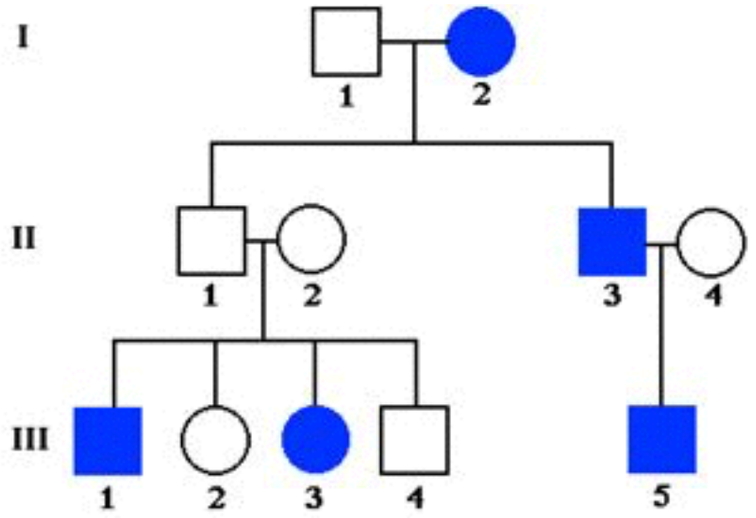




Yaniv Erlich

Ancestry websites offer rich family data

Remember all of the genetics we've learned so far



Incomplete penetrance

Non-complementation

Haploinsufficiency

Suppression and enhancement

Genetic variants are used as markers to track disease

Single nucleotide variants (SNVs)

Reference **ATGTGCAGACGTAGACGTA**

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

Genetic variants are used as markers to track disease

Single nucleotide variants (SNVs)

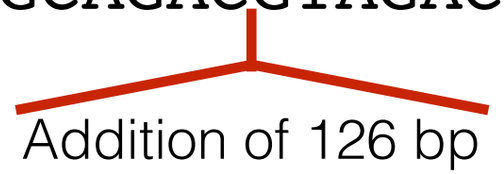
Reference **ATGTGCAGACGTAGACGTA**

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

Insertion-deletion variants (indels)

Reference **ATGTGCAGACGTAGACGTA**

Alternative **ATGTGCAGACGTAGACGTA**



Addition of 126 bp

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

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)

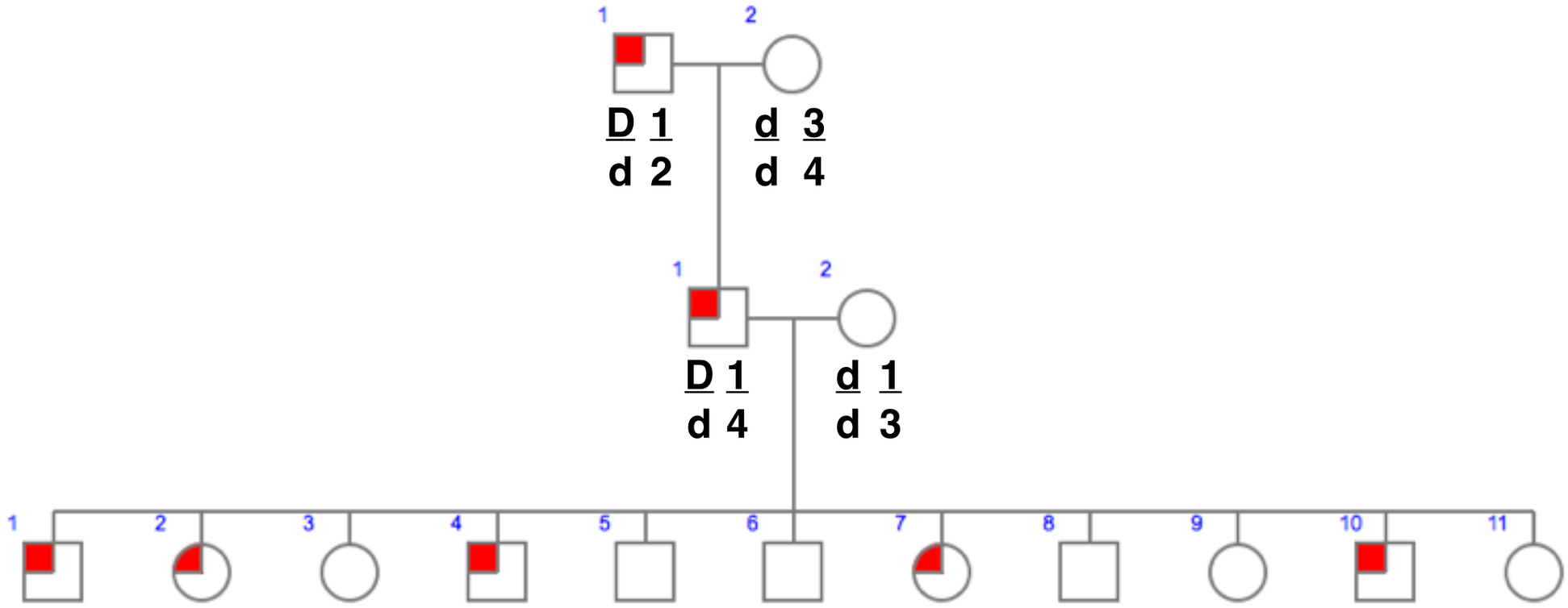
Alternative More (or fewer) than 2 copies

Microsatellites or short tandem repeats (STRs)

Reference **ATGTGCAGCAGCAGCAGCGTA**

Alternative **ATGTGCAGCAGCGTAGTGACT**

Linkage to genetic markers tells us where disease genes might be

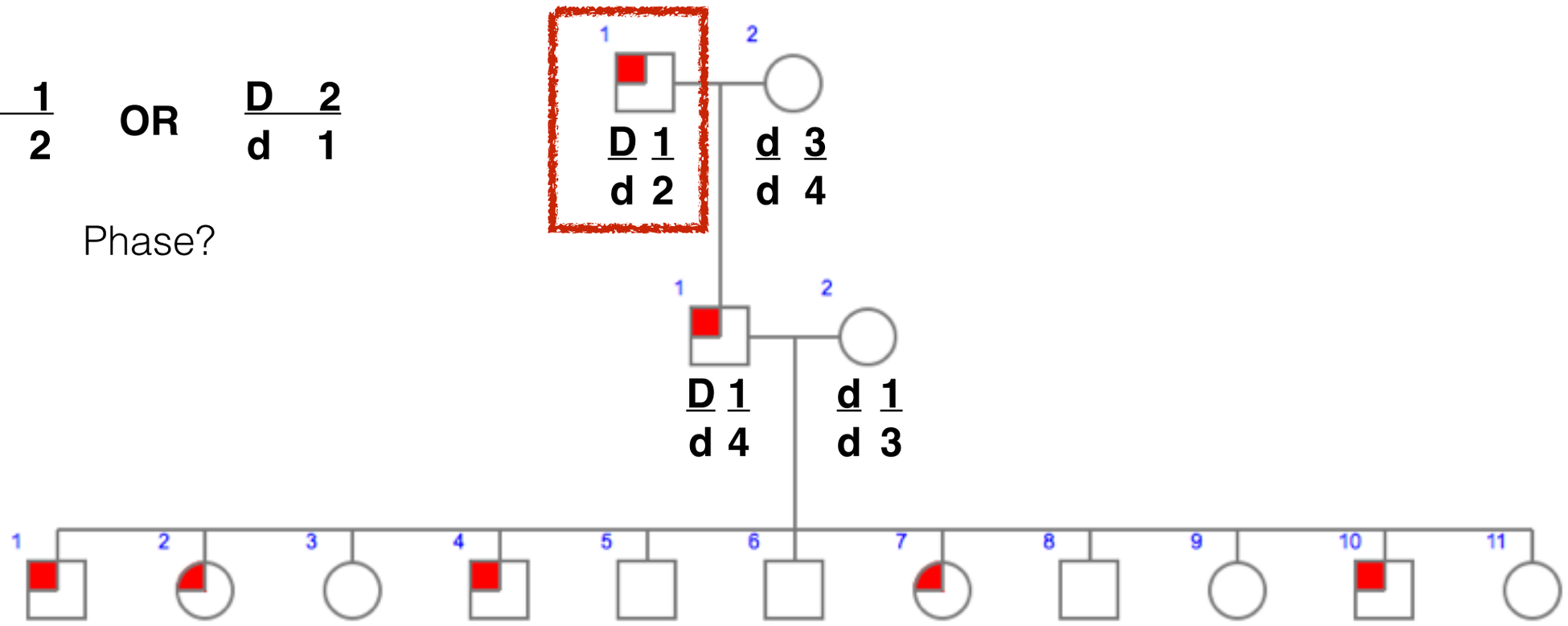


Autosomal dominant

Linkage to genetic markers tells us where disease genes might be

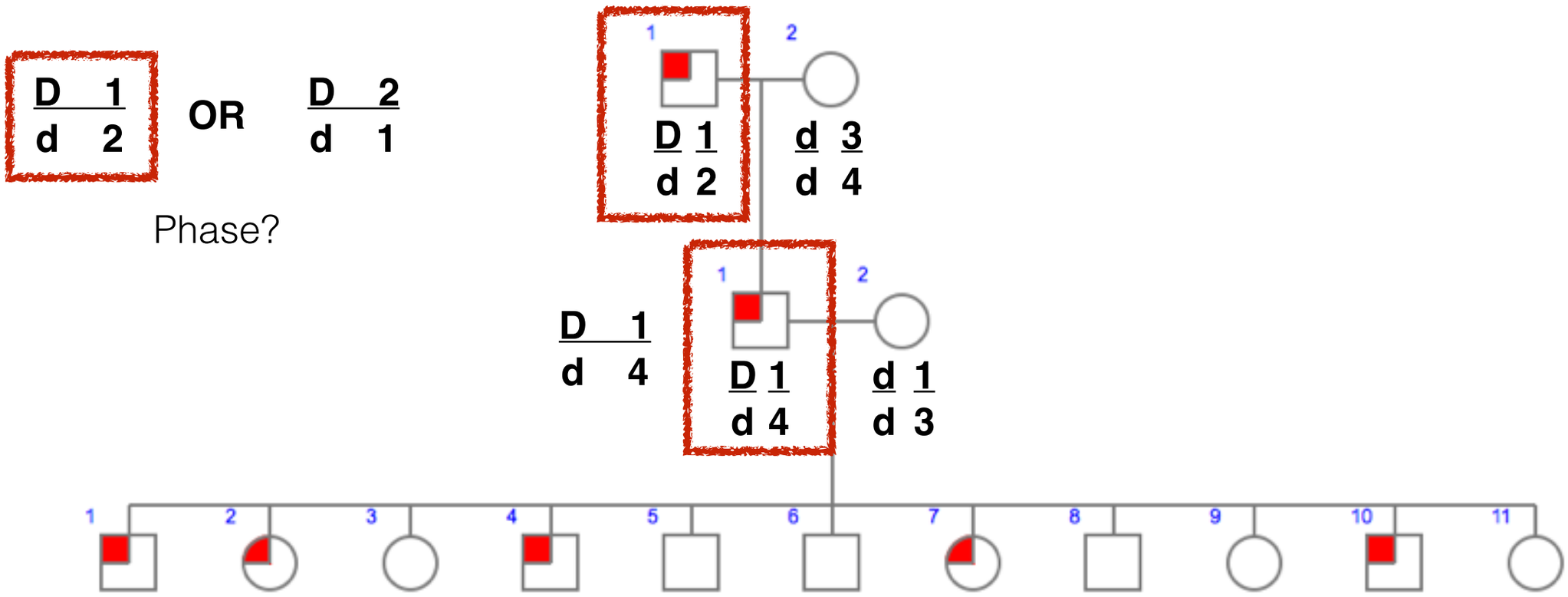
$$\frac{D\ \ 1}{d\ \ 2} \quad \text{OR} \quad \frac{D\ \ 2}{d\ \ 1}$$

Phase?



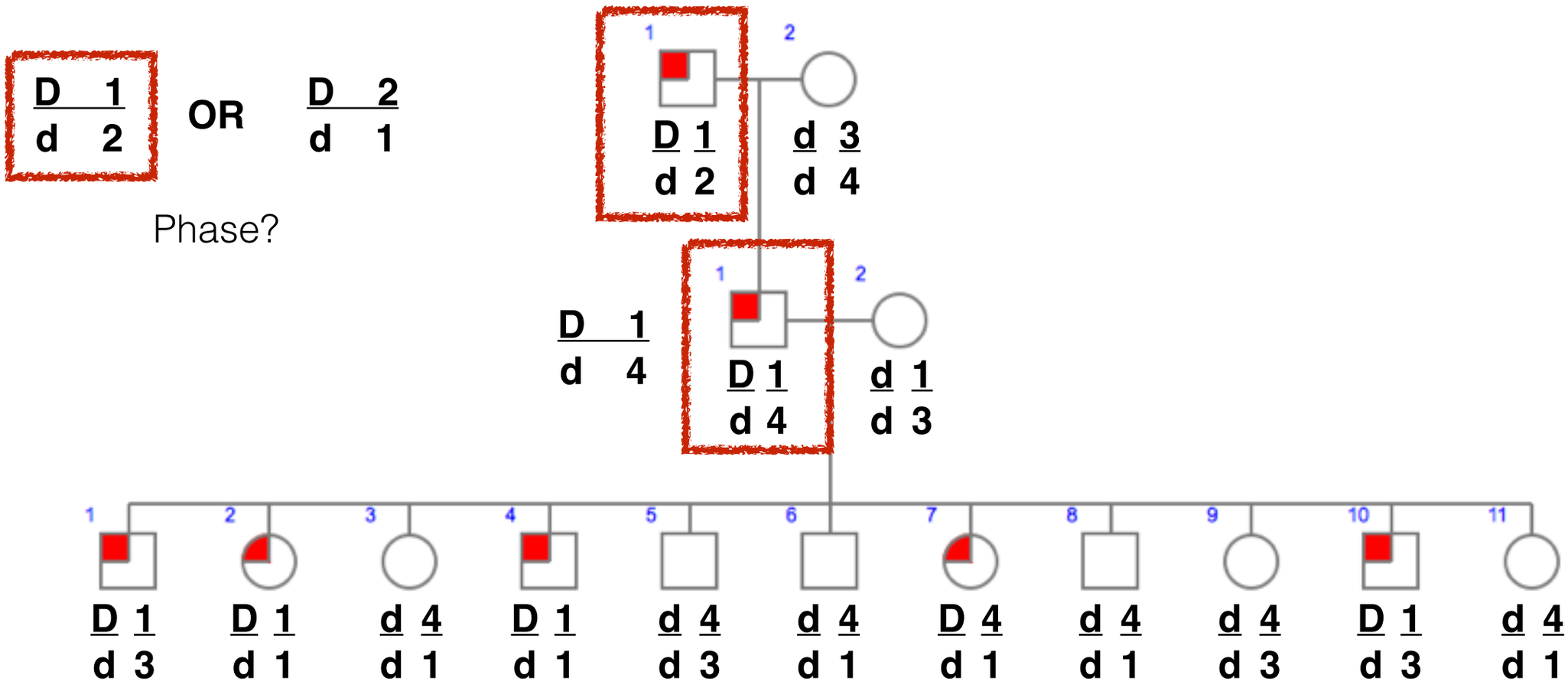
Autosomal dominant

Linkage to genetic markers tells us where disease genes might be



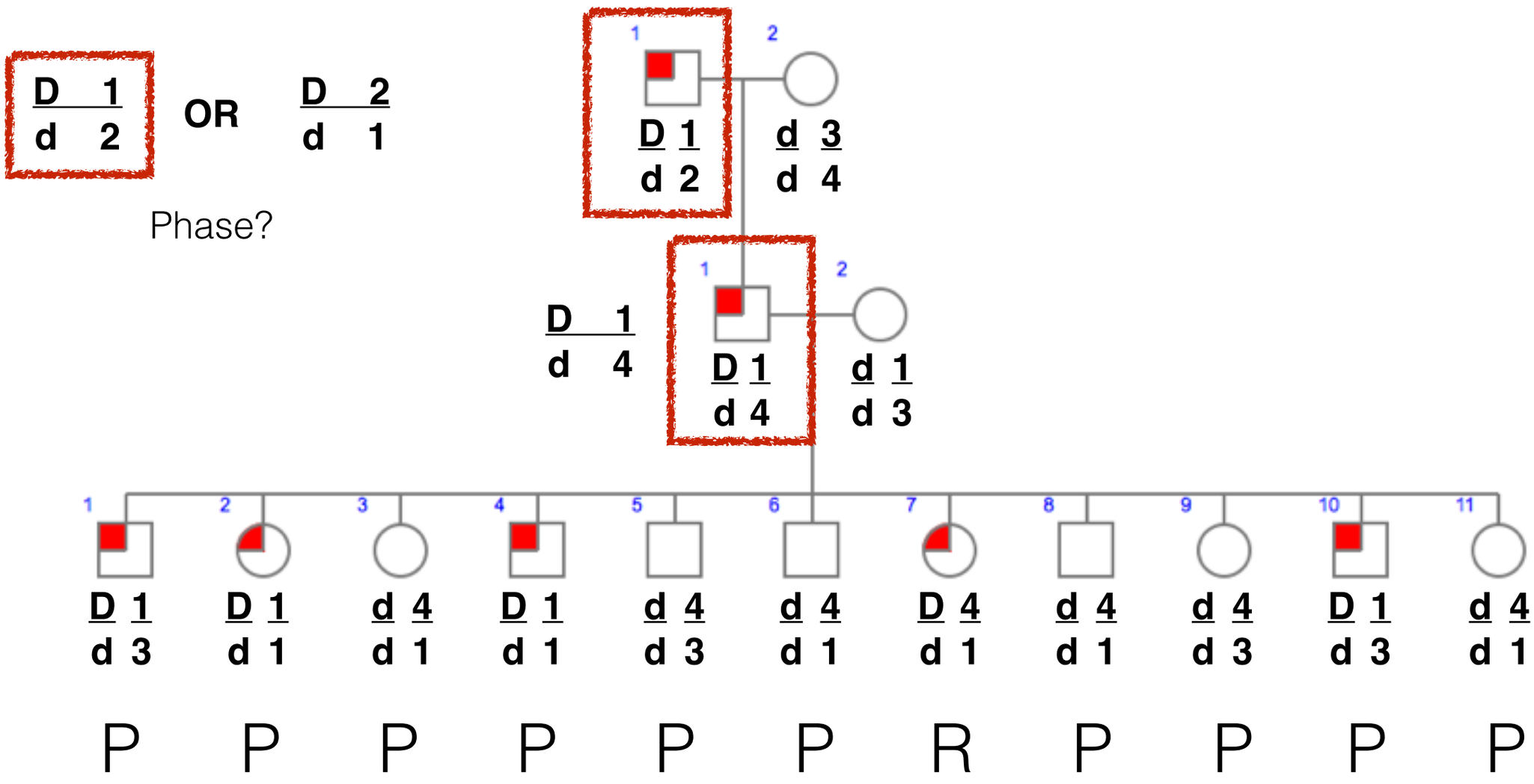
Autosomal dominant

Linkage to genetic markers tells us where disease genes might be



Autosomal dominant

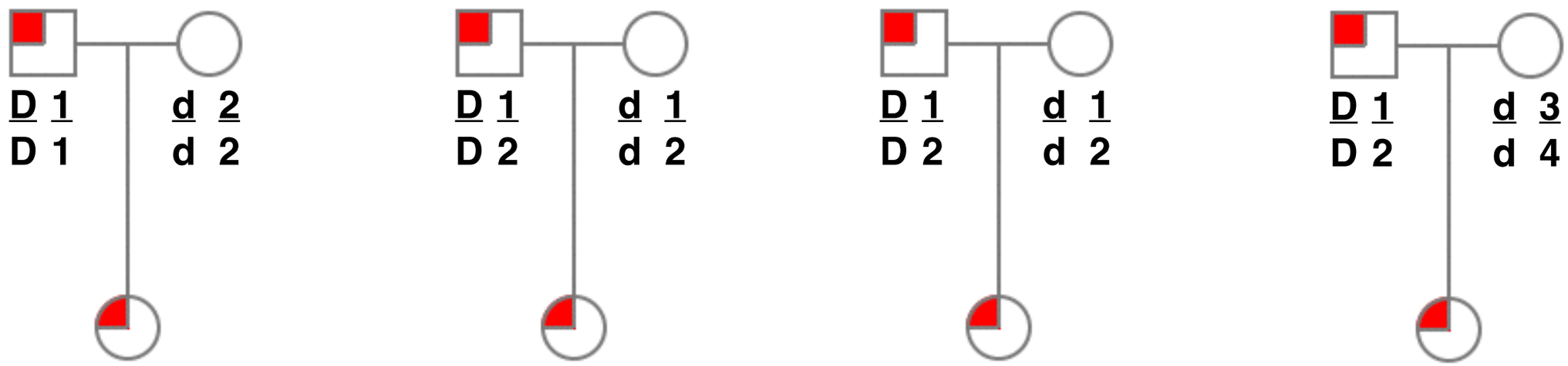
Linkage to genetic markers tells us where disease genes might be



Autosomal dominant

The phase of the parental chromosomes helps in linkage mapping

Consider a dominant trait and a variant marker:



Uninformative | Uninformative | Informative | Informative

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

Imagine you could genotype millions of markers in each individual