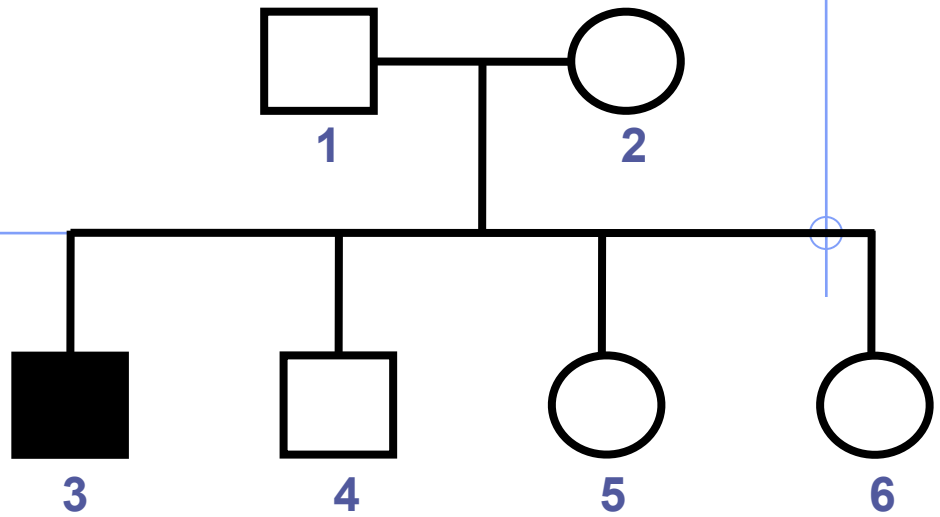
# Human Genetic Diseases



# Genetic counseling

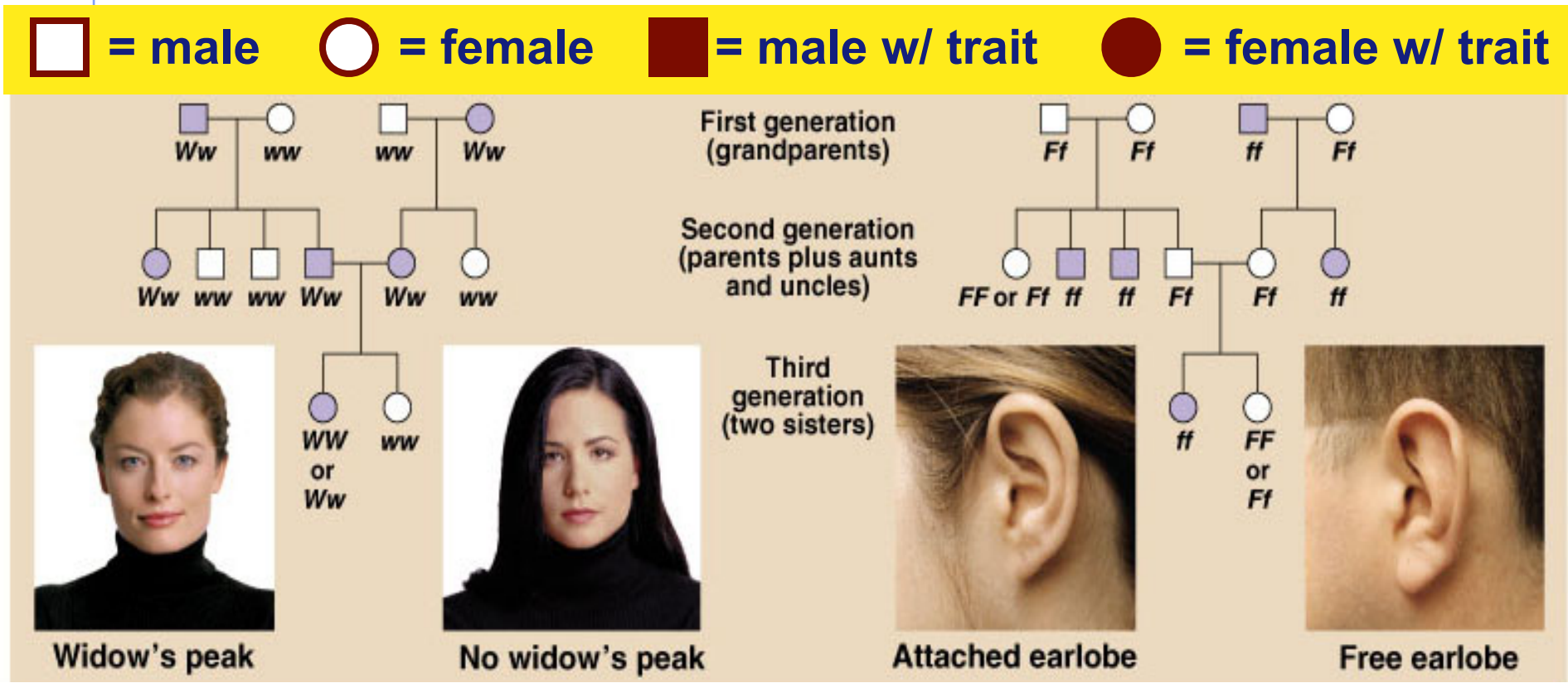
- Pedigrees can help us understand past & predict future
- Thousands of genetic disorders are inherited as simple recessive traits
  - from benign conditions to deadly diseases
    - PKU
      - Autosomal recessive genetic condition that results in an error of metabolism of the amino acid phenylalanine. A mutations in the PAH gene results in low levels of the enzyme phenylalanine hydroxylase, which results in the buildup of dietary phenylalanine to potentially toxic levels. Untreated, PKU can lead to intellectual disability, seizures, behavioral problems, and mental disorders.
    - Albinism
    - Cystic Fibrosis
    - Tay Sachs
    - Sickle Cell Anemia

# Pedigrees

- In order to look at the matings that have already
  - Collect information about traits and family history
  - Build a tree that describes the traits of parents and children over many generations
- Pedigree analysis reveals Mendelian patterns in human inheritance

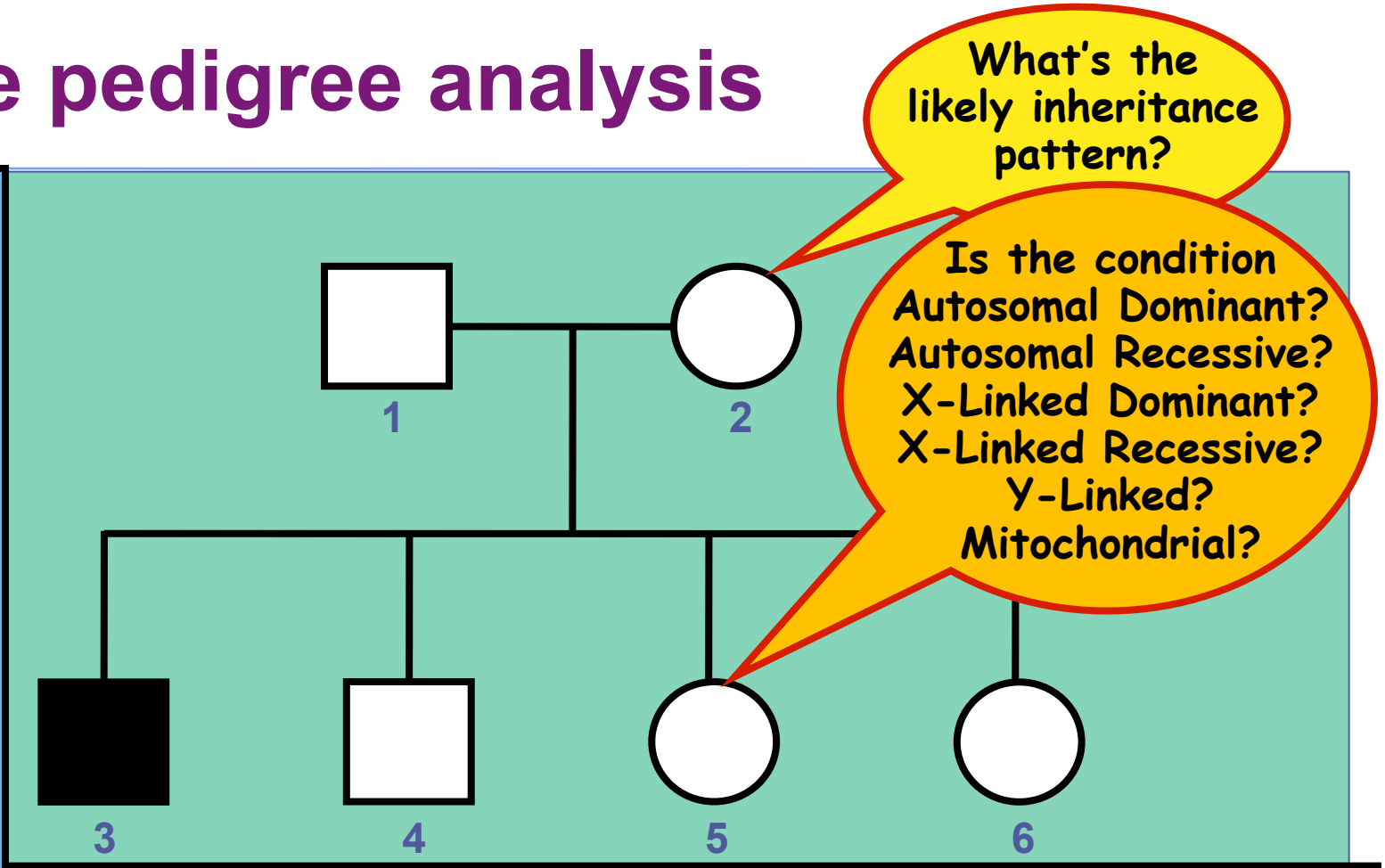
| | |
|---|---|
|  | A square represents a male individual |
|  | A circle represents a female individual |
|  | A filled-in square represents a male who has been diagnosed with a certain condition |
|  | A filled-in circle represents a female who has been diagnosed with a certain condition |
|  | A triangle (or diamond) represents an individual whose gender is unknown |
|   | A diamond with a P inside represents a pregnancy |
|  | This symbol represents twins (a horizontal line connecting the two diagonal lines would mean identical twins) |
|  | A diagonal line through a square or circle represents an individual who is deceased (cause of death and age at death should be noted underneath) |
|  | A square with a small circle inside represents a male who is a *carrier** for a genetic condition |
|  | A circle with a smaller circle inside represents a female who is a *carrier** for a genetic condition |
|  | A small triangle or diamond with a diagonal line through it represents a miscarriage or stillbirth (cause and week of pregnancy should be noted underneath) |
|  | An arrow indicates the individual who first brought attention to the family (e.g. a child with a condition, a mother requesting prenatal testing, a young man receiving cancer counseling, etc.) |

# Pedigree analysis



# Simple pedigree analysis

Assign genotypes to the parents based on each possible inheritance pattern scenario and then check if indeed they could have made the children they made and what you see is expected.

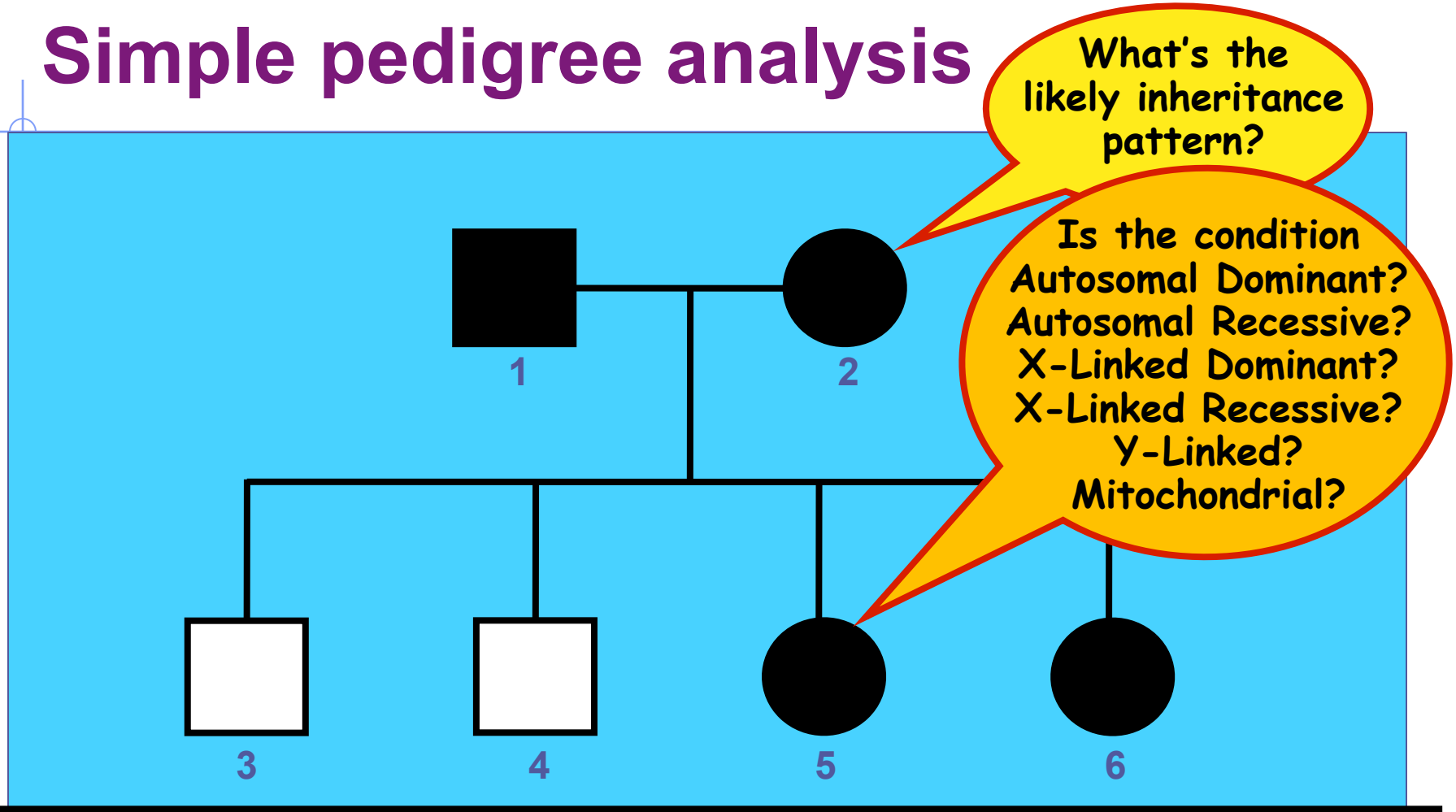



If the condition is <u>Autosomal Dominant</u>, what would the parents genotypes be? dd *(if they were Dd, they would have the condition).*

Could dd parents (dd x dd) make a Dd or DD child like individual #3? Could they make dd offspring like individuals #4, #5, & #6?

What would be the parents' genotype if the condition was <u>Autosomal Recessive</u>? *Would the pedigree make sense?*

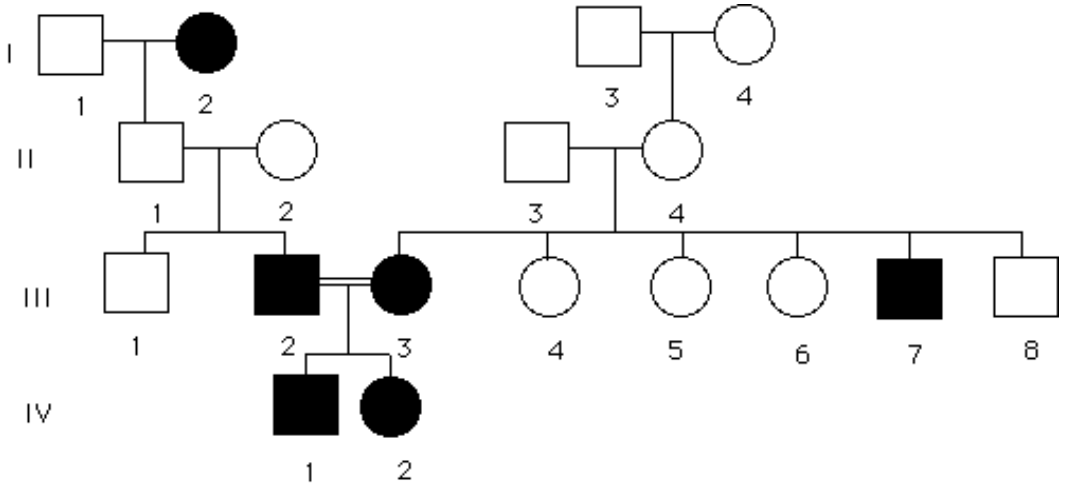
# Simple pedigree analysis




This could be Autosomal Dominant if parents are both Dd (and not DD).
This could not be Autosomal Recessive (parents being dd)
This could not be Y-Linked (all sons inherit the father's Y)
This could be X-Linked Dominant only if Dad was XDY and Mom XDXd
This could not be X-Linked Recessive
This could not be due to Mitochondrial inheritance.

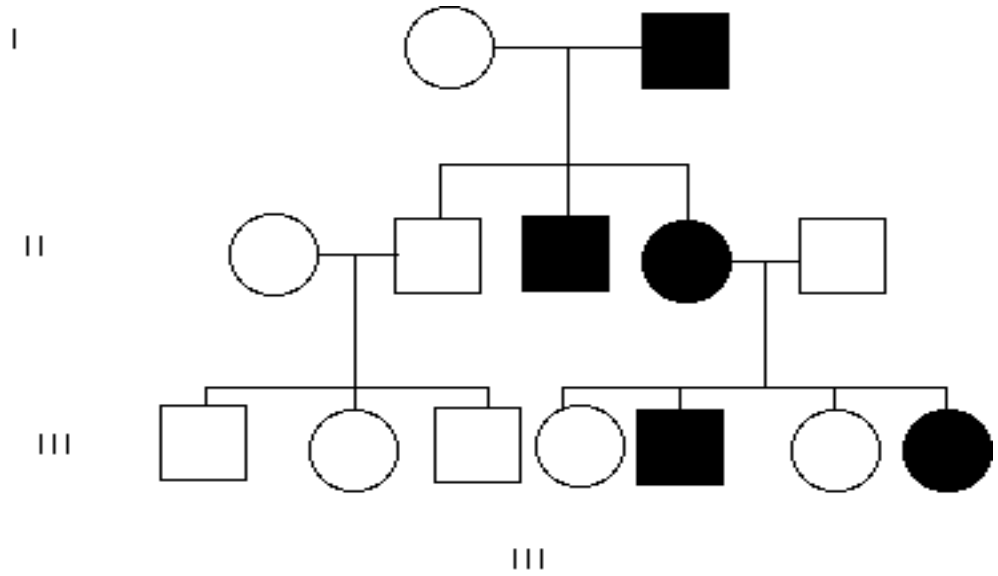
# Autosomal Recessive Pedigree

- There are several features in a pedigree that suggest a recessive pattern of inheritance:
  - 1. For rare traits, the pedigree usually involves mating between two unaffected heterozygotes and the production of one or more homozygous offspring.
  - 2. The probability of an affected child from a mating of two heterozygotes is 25%
  - 3. Two affected individuals usually produce offspring all of whom are affected
  - 4. Males and females are at equal risk, since the trait is autosomal
  - 5. In pedigrees involving rare traits, consanguinity is often involved



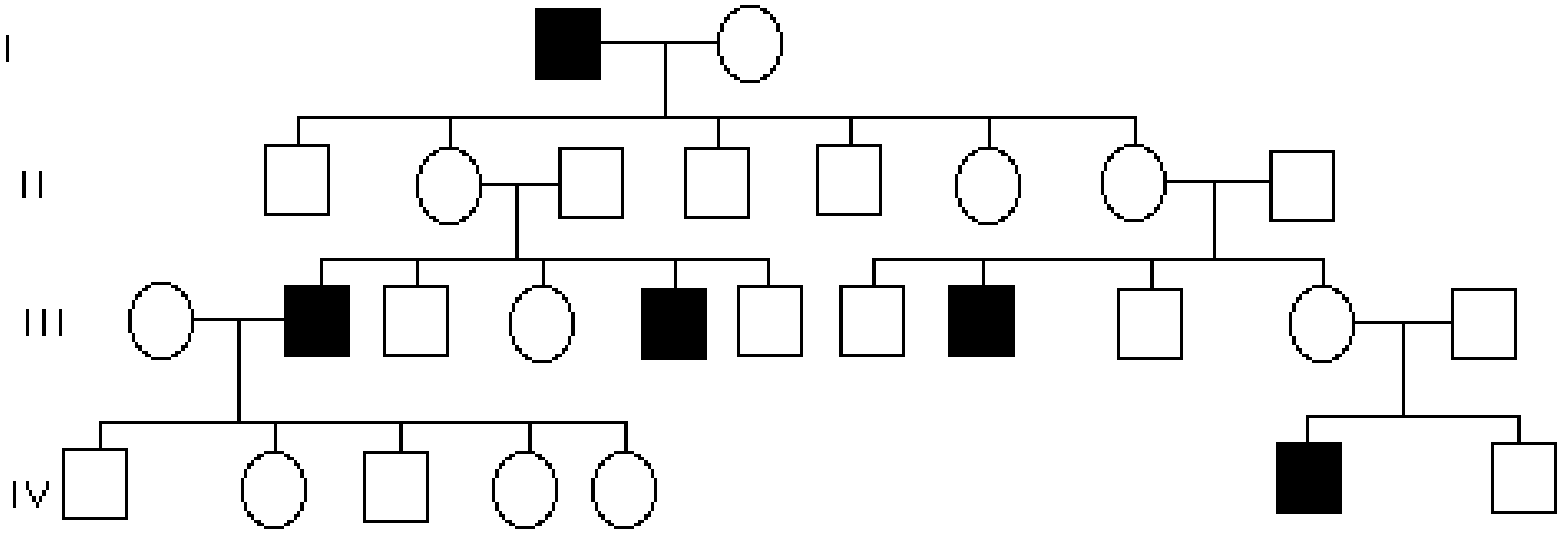
# Autosomal Dominant Pedigree

- **Characteristics of an autosomal dominant trait:**
  - **1. Every affected individual should have at least one affected parent.**
  - **2. An affected individual has a 50% chance of transmitting the trait**
  - **3. Males and females should be affected with equal frequency**
  - **4. Two affected individuals may have unaffected children if the parent is a heterozygote**



# Practice:

- The following pedigree outlines the typical inheritance pattern found in red-green color-blindness.
  - Does this fit an autosomal recessive or autosomal dominant pattern of inheritance?

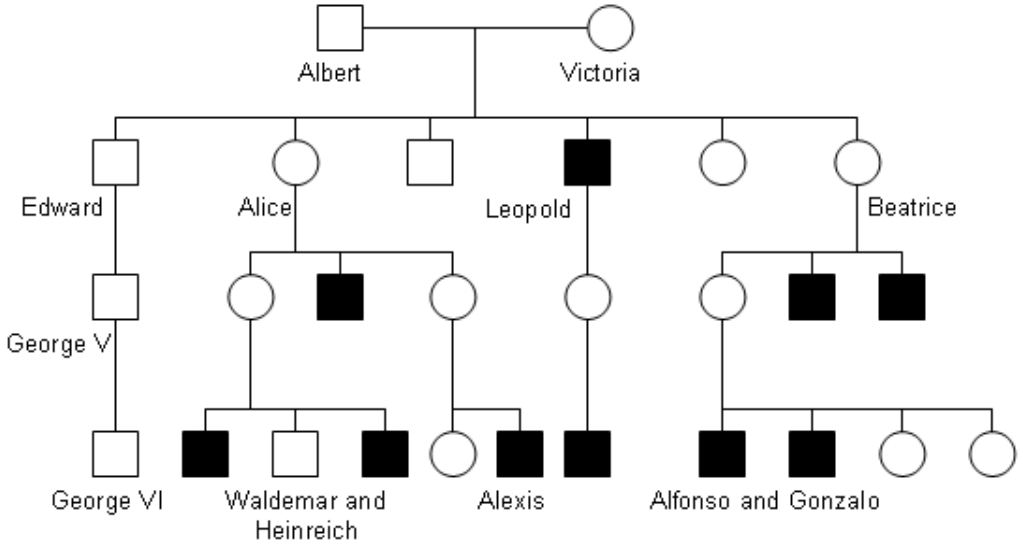



**X-Linked RECESSIVE!!!**

# Sex-linked Pedigree (x chromosome)

- **Characteristics of a Sex-linked trait**

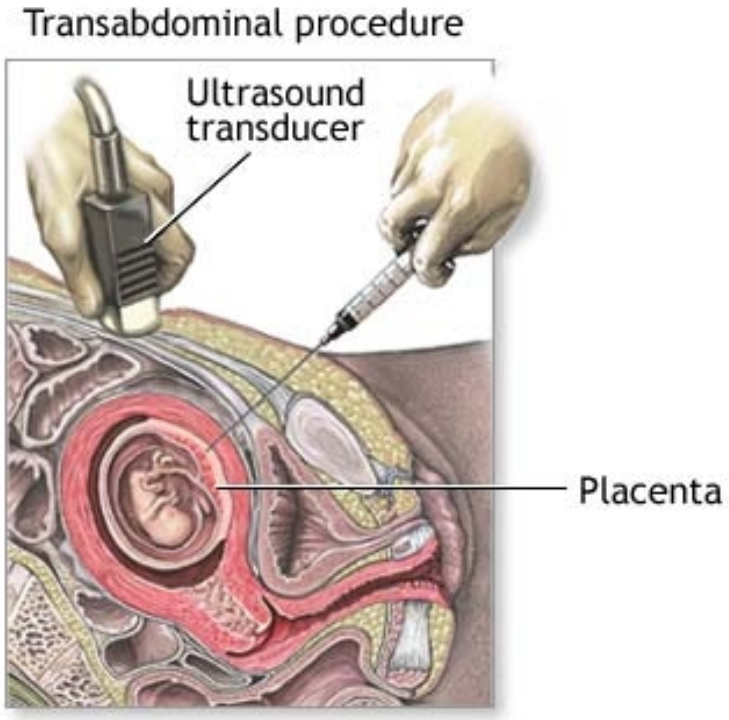
1. **Hemizygous males and homozygous females are affected**
2. **Phenotypic expression is much more common in males than in females, and in the case of rare alleles, males are almost exclusively affected**
3. **Affected males transmit the gene to all daughters but not to any sons**
4. **Daughters of affected males will usually be heterozygous and therefore unaffected. Sons of heterozygous females have a 50% chance of receiving the recessive gene.**

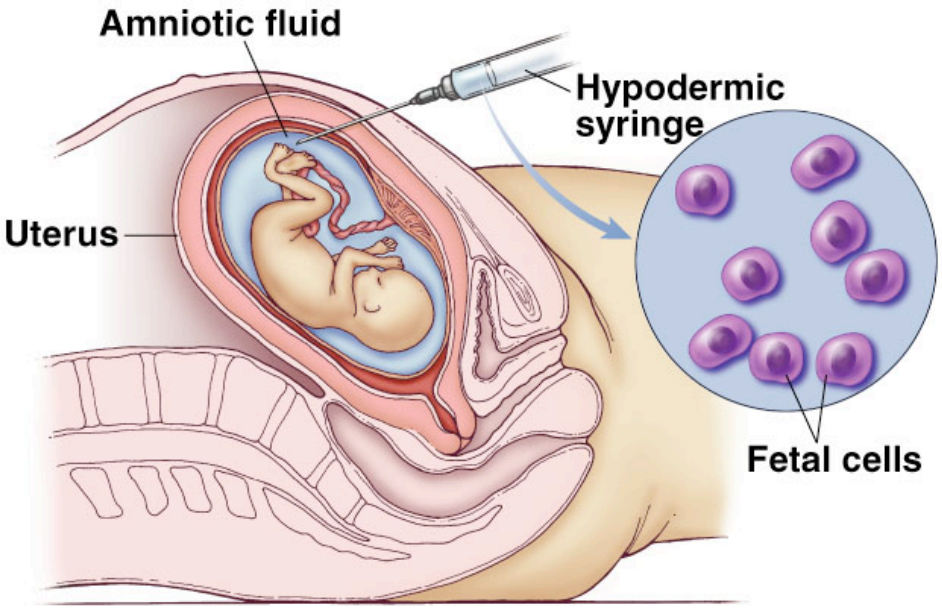


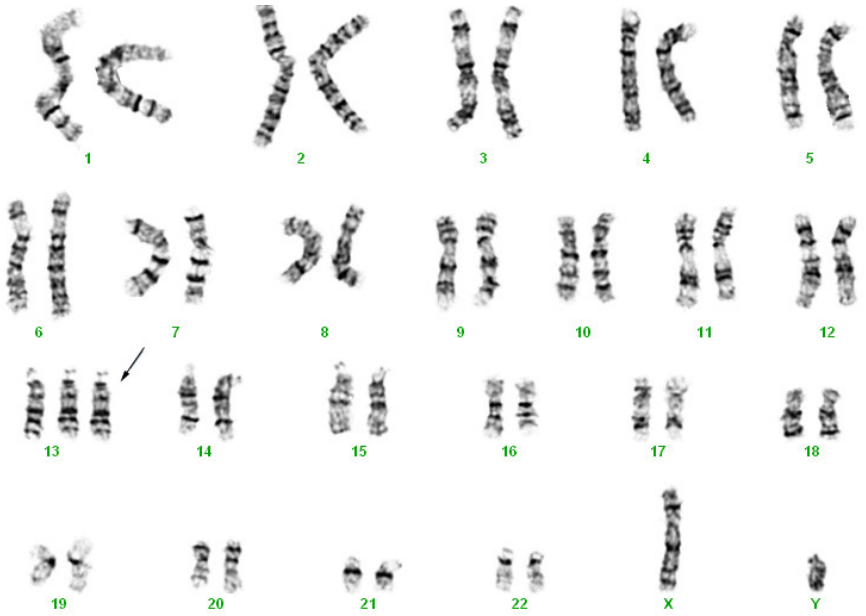
# Genetic testing

**Amniocentesis & chorionic villus sampling:**

1. Biochemical tests can detect substances associated with particular disorders.
2. Karyotyping the DNA shows whether the chromosomes of the fetus are normal in number and appearance



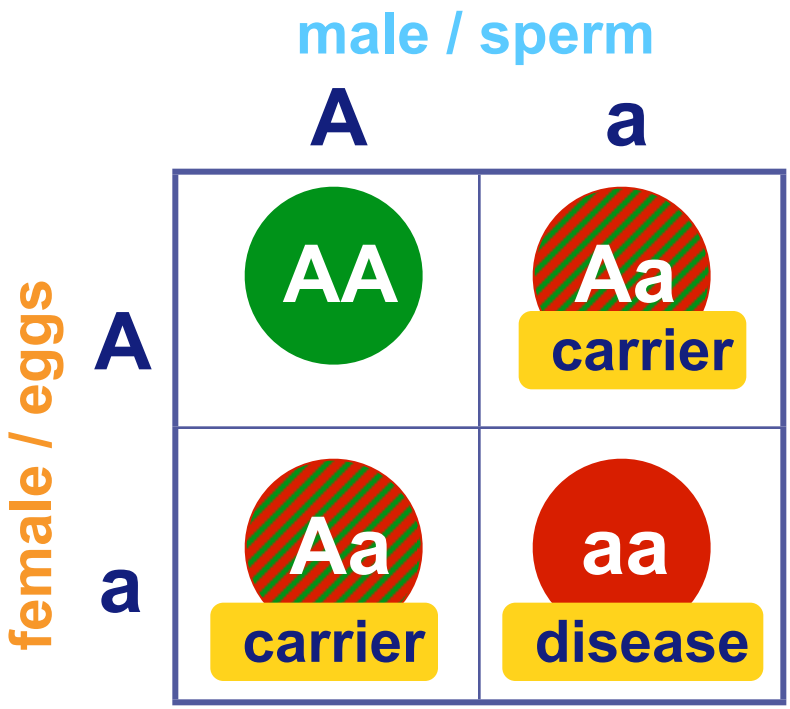
# Recessive diseases

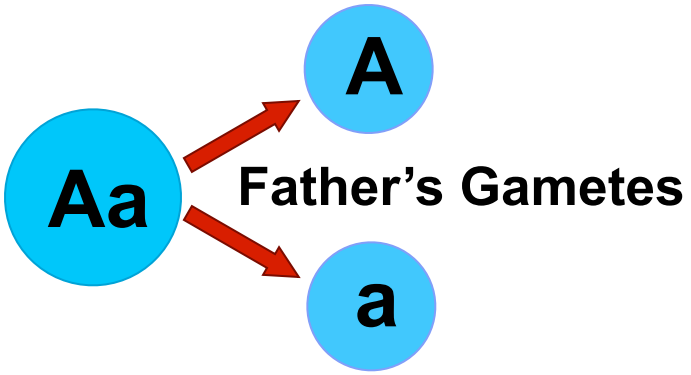
- The diseases are recessive because the allele codes for either a malfunctioning protein or no protein at all
  - Heterozygotes (Aa) do not show the phenotype "disease"
    - (their phenotype is normal)
  - Called carriers
    - have a normal phenotype because one "normal" allele produces enough of the required protein that there is no 'noticeable' difference

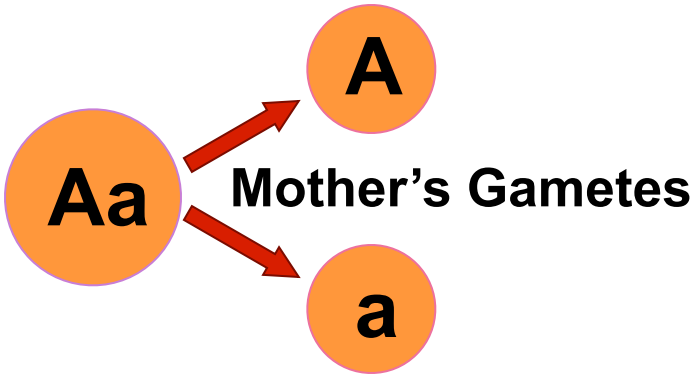
# Heterozygote crosses

- Heterozygotes act as carriers of recessive alleles

**Aa x Aa**

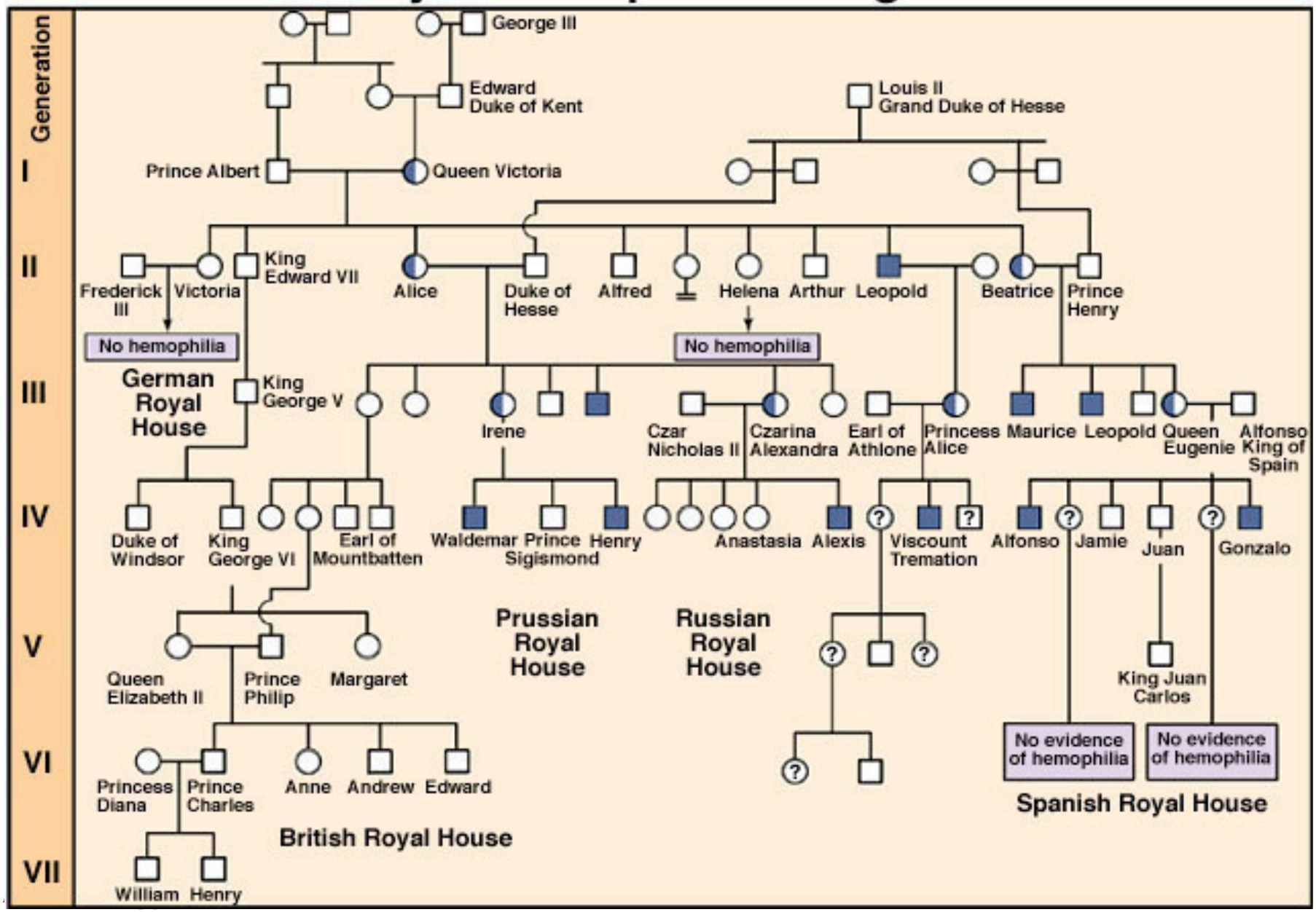


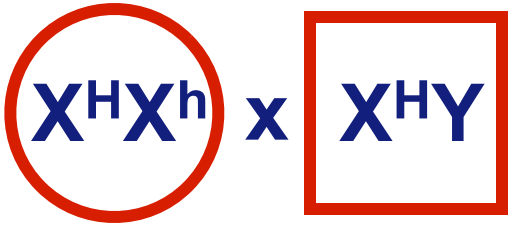
# Queen Victoria and Descendants

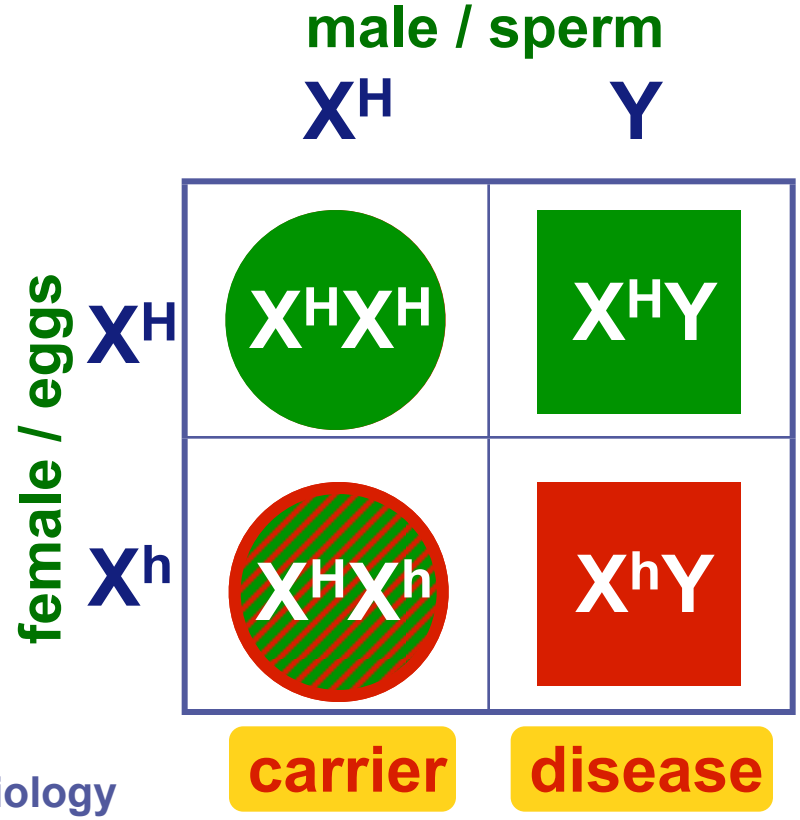
# Royal Hemophilia Pedigree

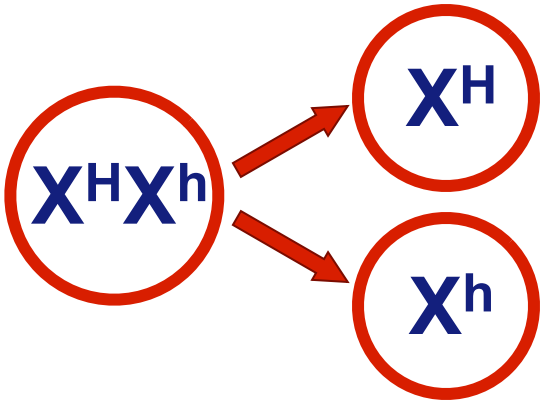


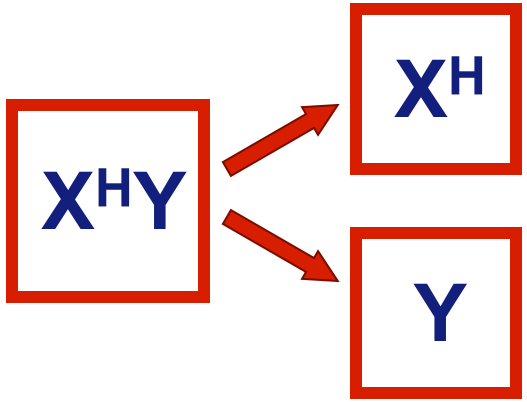
# Hemophilia

**sex-linked recessive**

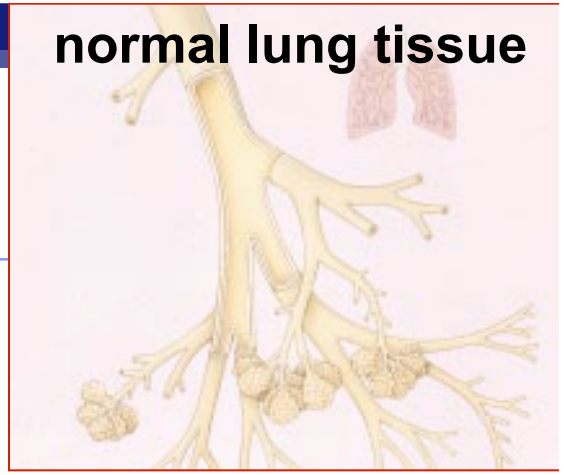


# Cystic fibrosis (recessive)



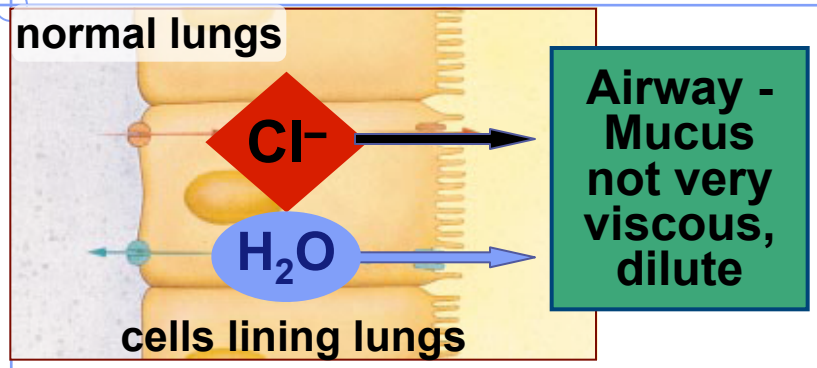

- Primarily whites of European descent
  - strikes 1 in 2500 births
    - 1 in 25 whites is a carrier (Aa)
  - normal allele codes for a membrane protein that transports $Cl^-$ across cell membrane
    - defective or absent channels limit transport of $Cl^-$ & $H_2O$ across cell membrane
      - People without cystic fibrosis have a small layer of salt water in the large airways of their lungs.
      - High $Cl^-$ concentration in cells
    - thicker & stickier mucus coats around cells
      - The mucus layer in the airways normally helps to clear dust and other inhaled particles from the lungs.
    - mucus build-up in the pancreas, lungs, digestive tract & causes bacterial infections
      - Affects pancreas, sweat glands and often causes lots of lung problems.
  - without treatment children die before 5; with treatment can live past their late 20s

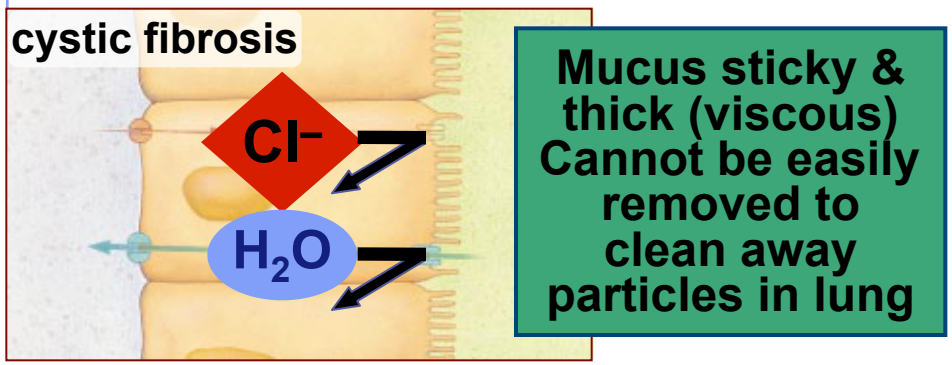
# Effect on Lungs

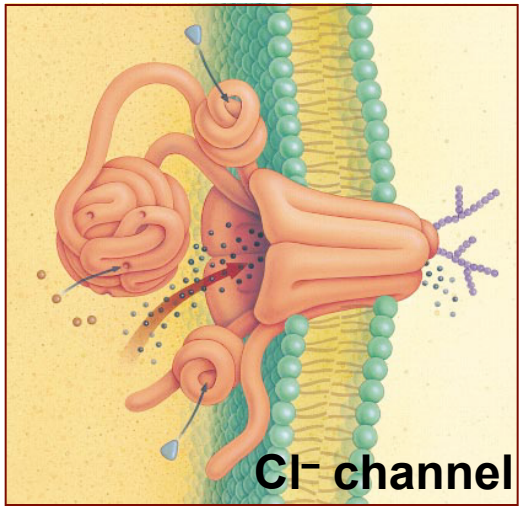
**Chloride channel**

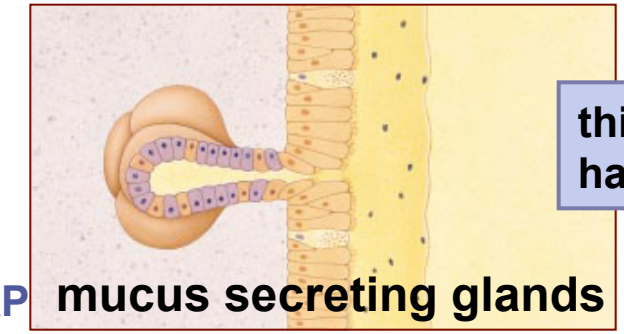
transports salt through protein channel out of cell into air space

Osmosis: $H_2O$ follows $Cl^-$

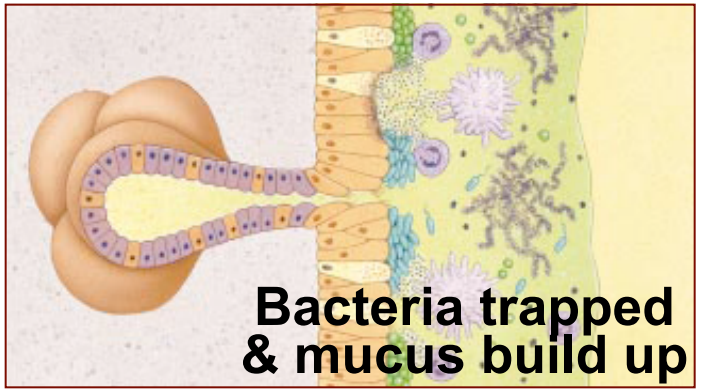



thickened mucus hard to secrete

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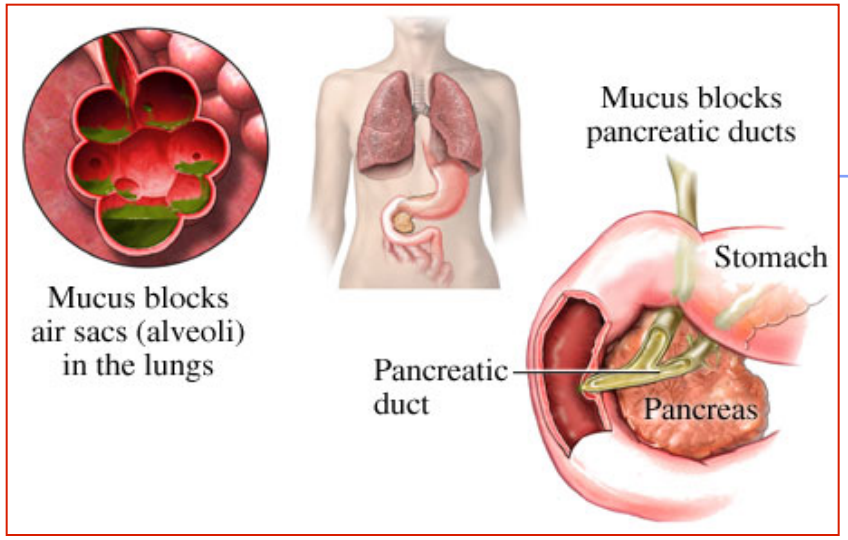
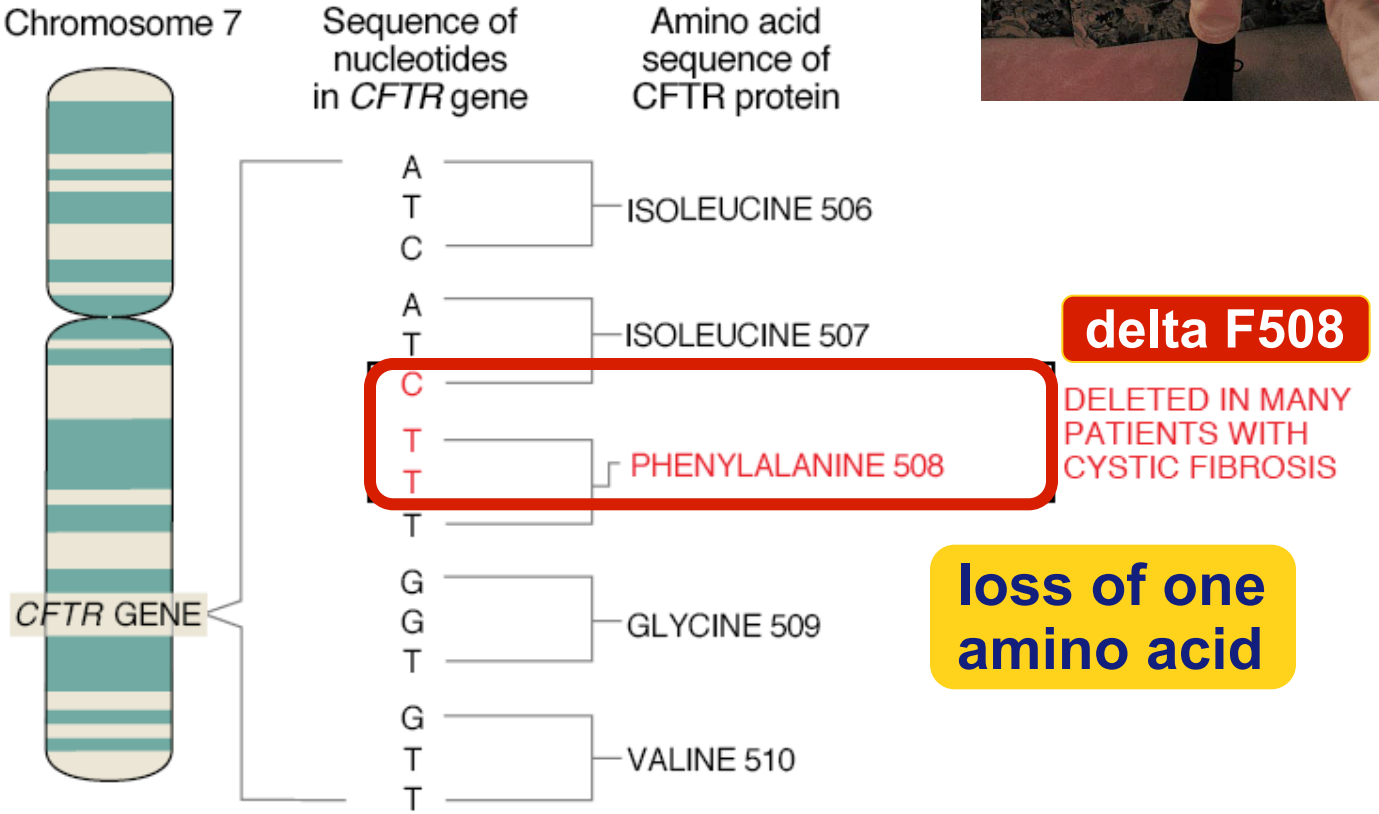


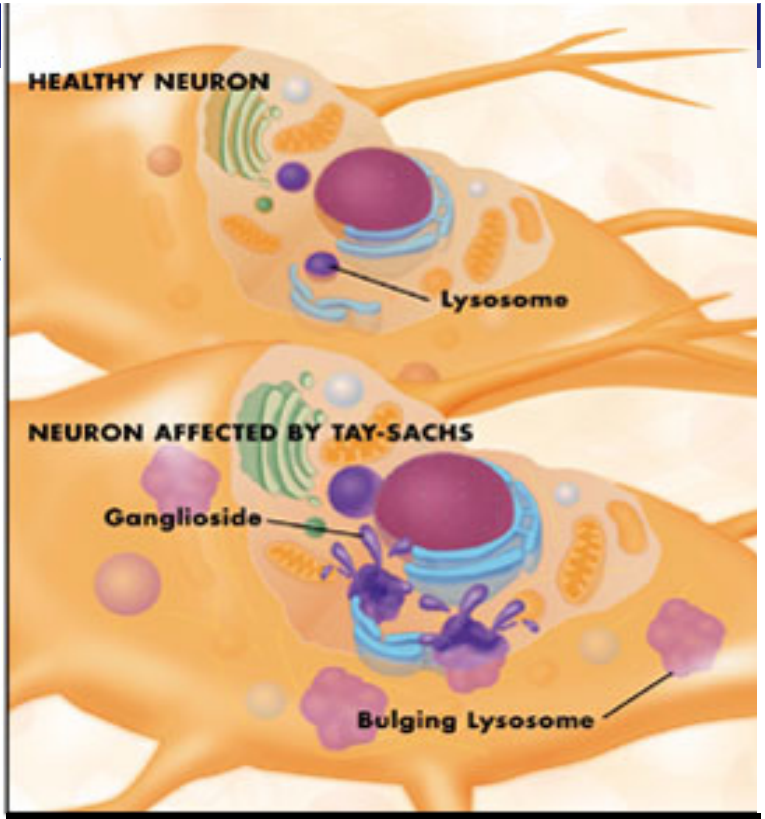

**delta F508**

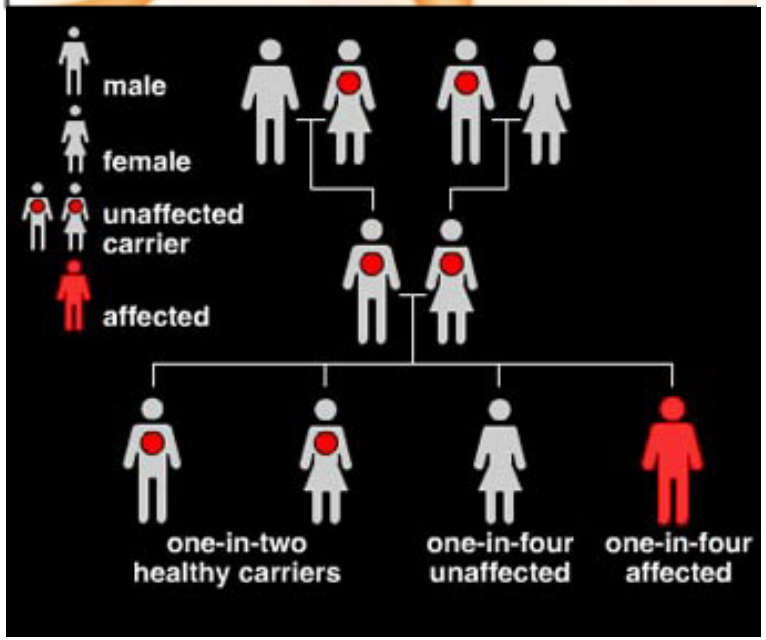
DELETED IN MANY PATIENTS WITH CYSTIC FIBROSIS

**loss of one amino acid**

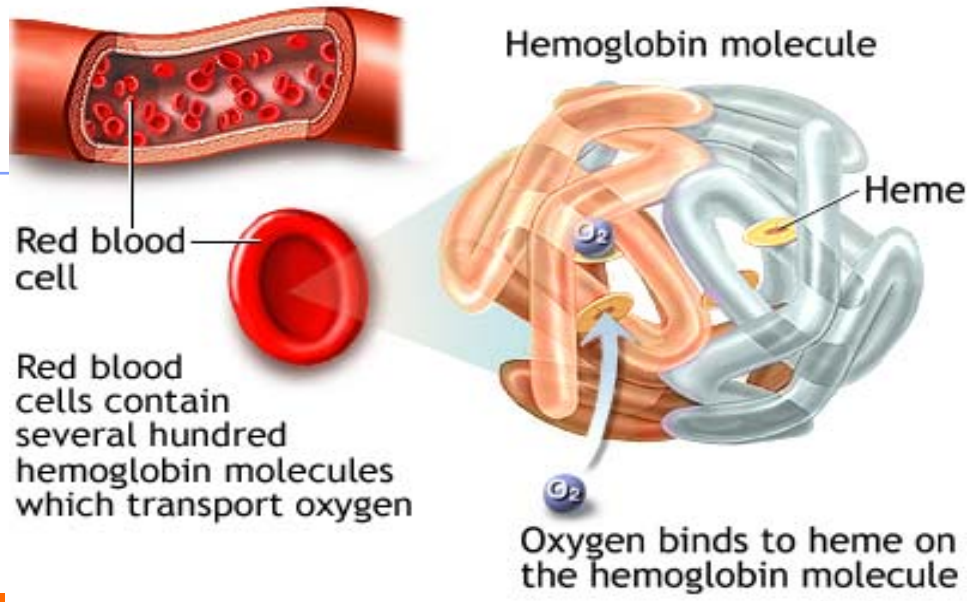
# Tay-Sachs (recessive)

- Primarily Jews of eastern European (Ashkenazi) descent & Cajuns (Louisiana)
  - strikes 1 in 3600 births
    - 100 times greater than incidence among non-Jews
  - non-functional enzyme fails to breakdown lipids in brain cells
    - fats collect in neuronal cells destroying their function
      - symptoms begin few months after birth
      - seizures, blindness & degeneration of muscle & mental performance
      - child usually dies before 5 years of age



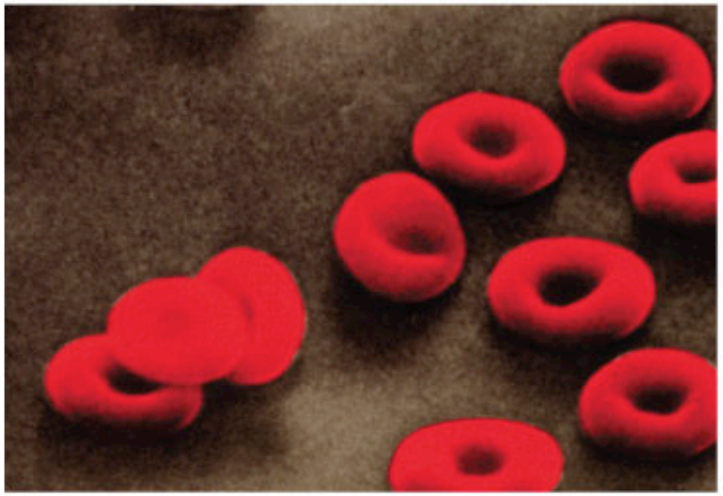
# Sickle cell anemia (recessive)




- **Primarily Africans**
  - **strikes 1 out of 400 African Americans**
    - **high frequency of heterozygotes is unusual for allele with severe detrimental effects in homozygotes**
  - **caused by substitution of a single amino acid in hemoglobin**
    - **when oxygen levels are low, sickle-cell hemoglobin crystallizes into long rods**
      - **deforms red blood cells into sickle shape**
      - **sickling creates pleiotropic effects = cascade of other symptoms all caused by one harmful allele of a gene**

# Sickle cell anemia

- Substitution of one amino acid in polypeptide chain changes the primary structure of the β Globin polypeptide and, therefore, the quaternary structure of hemoglobin.




(a) Normal red blood cells and the primary structure of normal hemoglobin


(b) Sickled red blood cells and the primary structure of sickle-cell hemoglobin

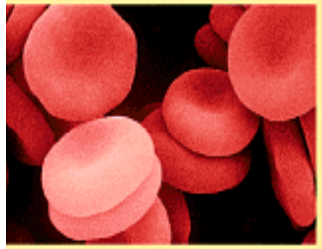
hydrophilic amino acid

hydrophobic amino acid

Two copies of the sickle-cell allele

All hemoglobin is the sickle-cell (abnormal) variety

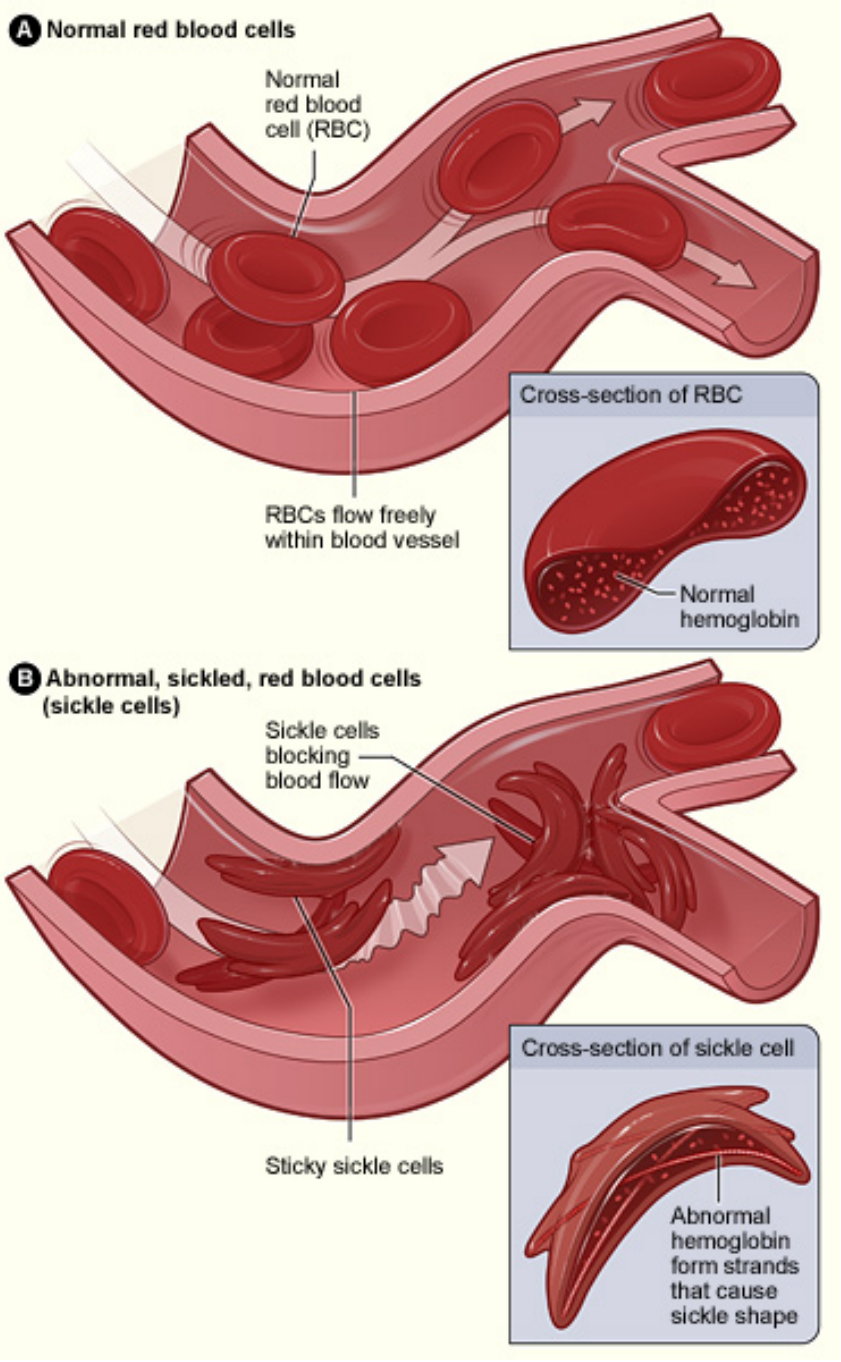
Abnormal hemoglobin crystallizes when oxygen content of blood is low, causing red blood cells to become sickle-shaped



Normal cells

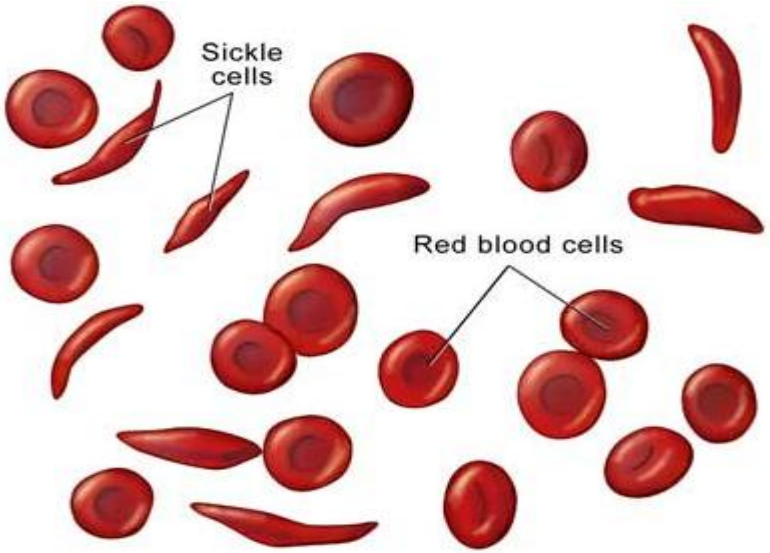
Sickled cells

- Breakdown of red blood cells
  - Physical weakness
  - Anemia
  - Heart failure
- Clumping of cells and clogging of small blood vessels
  - Heart failure
  - Pain and fever
  - Brain damage
  - Damage to other organs
- Accumulation of sickled cells in spleen
  - Spleen damage
- Physical weakness
  - Impaired mental function
- Anemia
  - Paralysis
- Heart failure
  - Pneumonia and other infections
- Damage to other organs
  - Rheumatism
  - Kidney failure

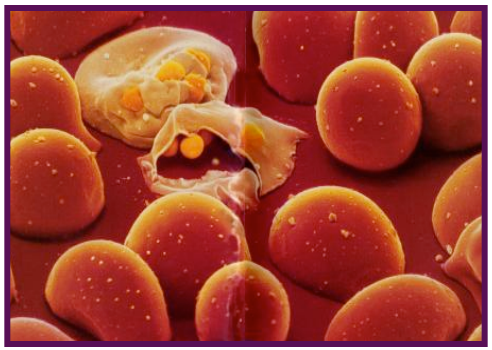


# Sickle cell phenotype

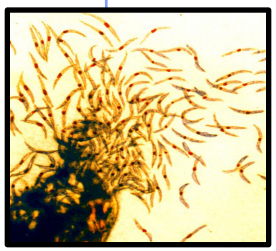
- At organismal level normal allele shows Complete Dominance
  - Phenotype normal of both heterozygote and Homozygous Dominant
- At the molecular level however 2 alleles are Codominant
  - both normal & mutant hemoglobins are synthesized in heterozygote (Aa)
    - 50% cells sickle;
      50% cells normal
  - carriers usually healthy
    - but some sickle-cell symptoms are triggered under blood oxygen stress
      *(low $O_2$ environments)*
      - Like during exercise



# "Heterozygote advantage"



- **Malaria**
  - caused by single-celled eukaryote parasite (*Plasmodium falciparum*) which spends part of its life cycle in red blood cells
  - in the process of reproducing, this parasite causes lysis of read blood cells, which can lead to death of the infected host



- In tropical Africa, where malaria is common a higher than expected frequency of the recessive "sickle cell disease" allele is seen.... but why?
  - Homozygous dominant individuals die at the highest rates of malaria
    - Parasite is very successful at parasitizing normal RBC, destroys them, and spreading to new RBCs
  - Homozygous recessive individuals die of sickle cell anemia at young pre-reproductive ages
    - They do not pass down to their offspring the "sickle cell" allele for the beta globin gene

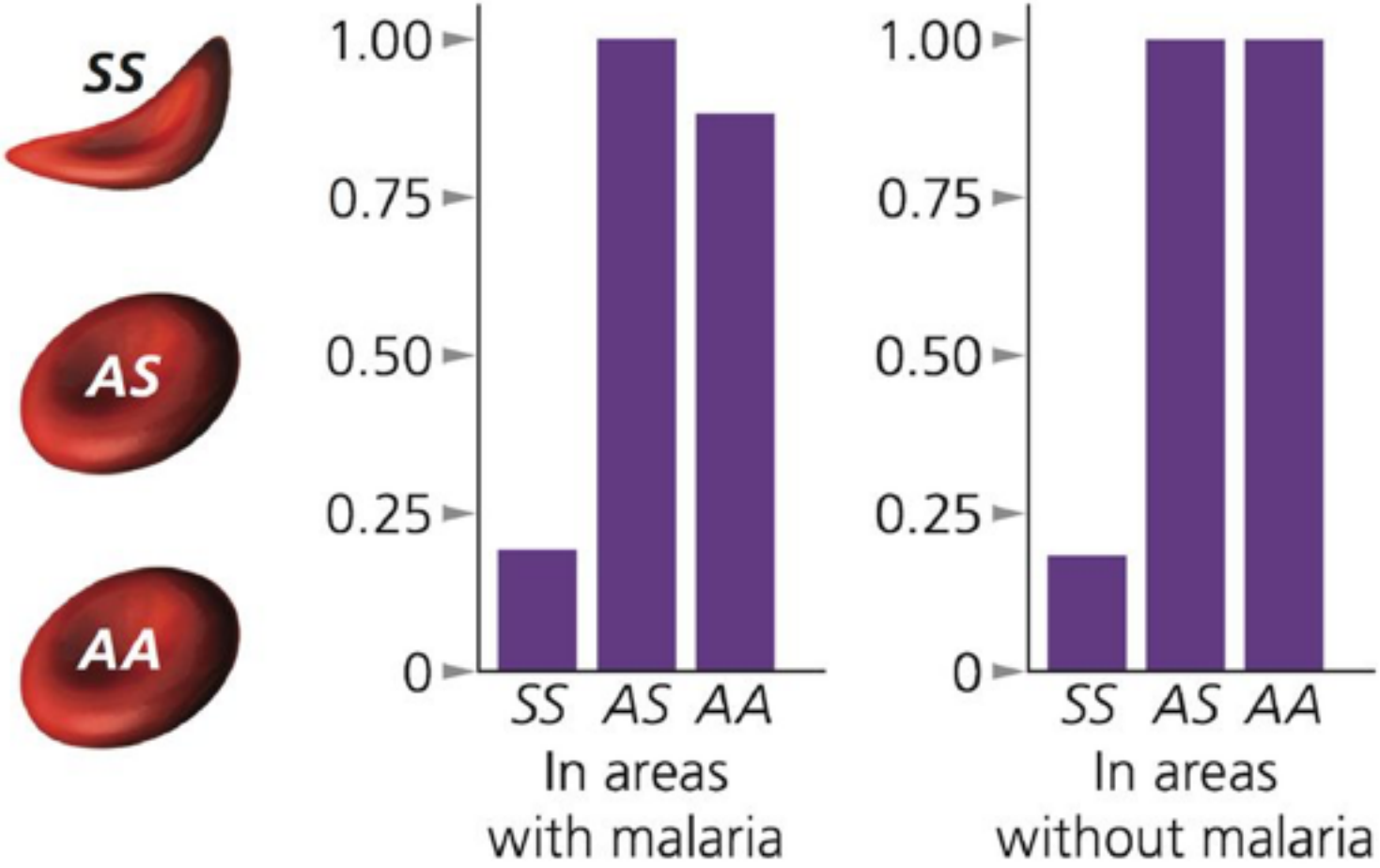
# "Heterozygote advantage"

- **Heterozygote carriers** are relatively free of any deadly sickle cell disease symptoms (they appear phenotypically "normal" at the organismal level), but they survive malaria at higher rates than homozygotes
  - the protist has a harder time successfully reproducing and spreading from red blood cell to red blood cell in the blood of a heterozygote

- Carriers survive malaria at higher rates than homozygote dominant individuals
  - Among individuals who get infected with P. falciparum, carriers are more likely to survive and therefore reach sexual maturity
- Carriers, therefore, reproduce at higher rates than they would in areas where malaria isn't present
  - Carriers have a reproductive advantage in areas where malaria is prevalent!!!!
    - Carriers can pass their hidden recessive sickle cell to offspring increasing the frequency of the sickle cell allele in the gene pool (the collection of all alleles in the population)
      - With a higher number of carriers in these populations than in populations without malaria, we also, therefore, see more incidence of sickle cell disease in offspring.

# Heterozygote advantage and sickle-cell anemia

**Relative fitness of *SS*, *AS*, and *AA* genotypes**

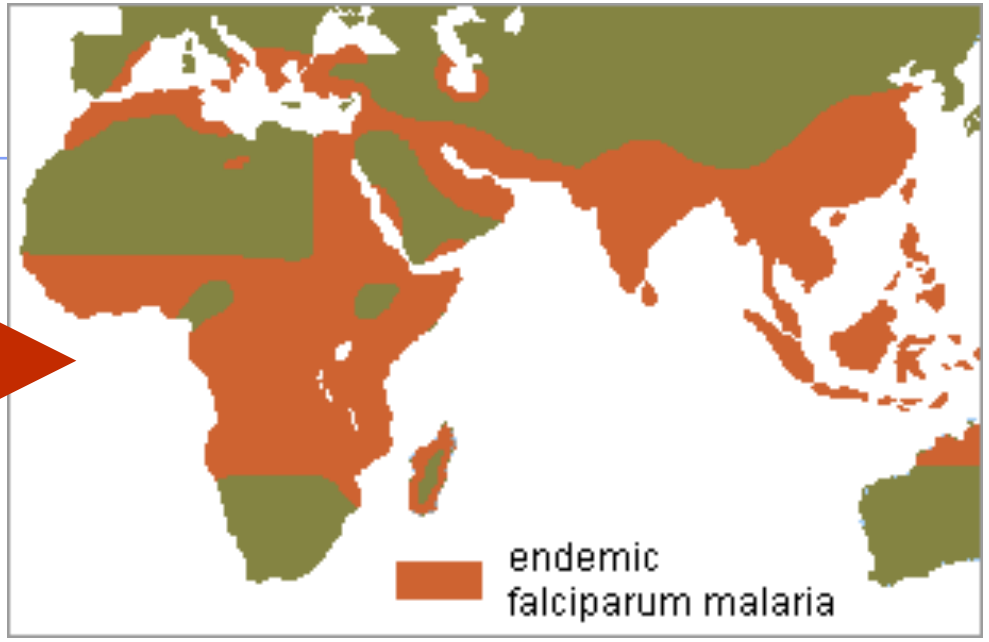


# "Heterozygote advantage"

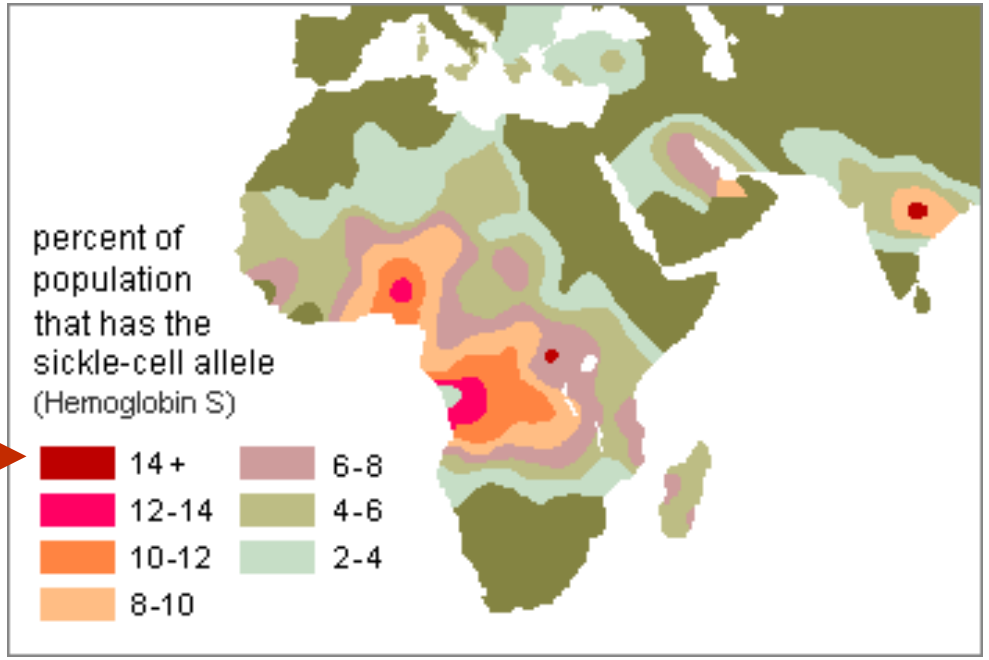
- Normally, we would expect a harmful recessive allele (one that causes death prior to reproductive age) to be prevalent in quite low frequencies in populations since homozygotes for this allele don't survive to reproduce and so the allele is not passed down by as many individuals in a population to the next generation.
  - Heterozyote Advantage is a situation where there is greater reproductive success among heterozygous individuals compared with homozygotes

  - High Frequency of reproductive success suggests some selective advantage in terms of natural selection of having the phenotype related to being a heterozygous
    - sickle cell carriers have increased resistance to malaria
    - cystic fibrosis carriers have an increased resistance to cholera
      - As a consequence, the harmful allele is indirectly selected for *(by natural selection)* even though a homozygous recessive state might still be lethal.

## Prevalence of Malaria

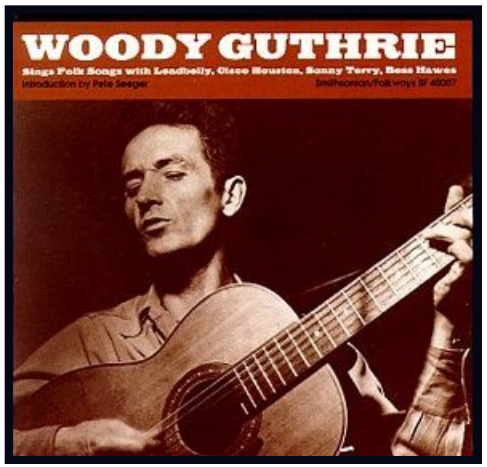


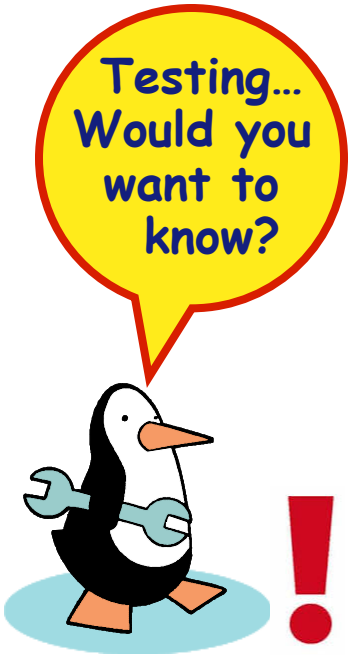

## Prevalence of Sickle Cell Anemia allele



# Huntington's chorea (dominant)

- Dominant inheritance
  - repeated mutation on end of chromosome 4
    - mutation = CAG repeats
      - glutamine amino acid repeats in protein
    - one of 1st genes to be identified
  - build up of "Huntington" protein in brain causing cell death
    - memory loss
    - muscle tremors, jerky movements
      - "chorea"
    - No obvious phenotypic effect till age 35-45
    - Irreversible degeneration and leads to inevitable early death
      - 10-20 years after symptoms start
    - Today, we can test you for the presence of the allele



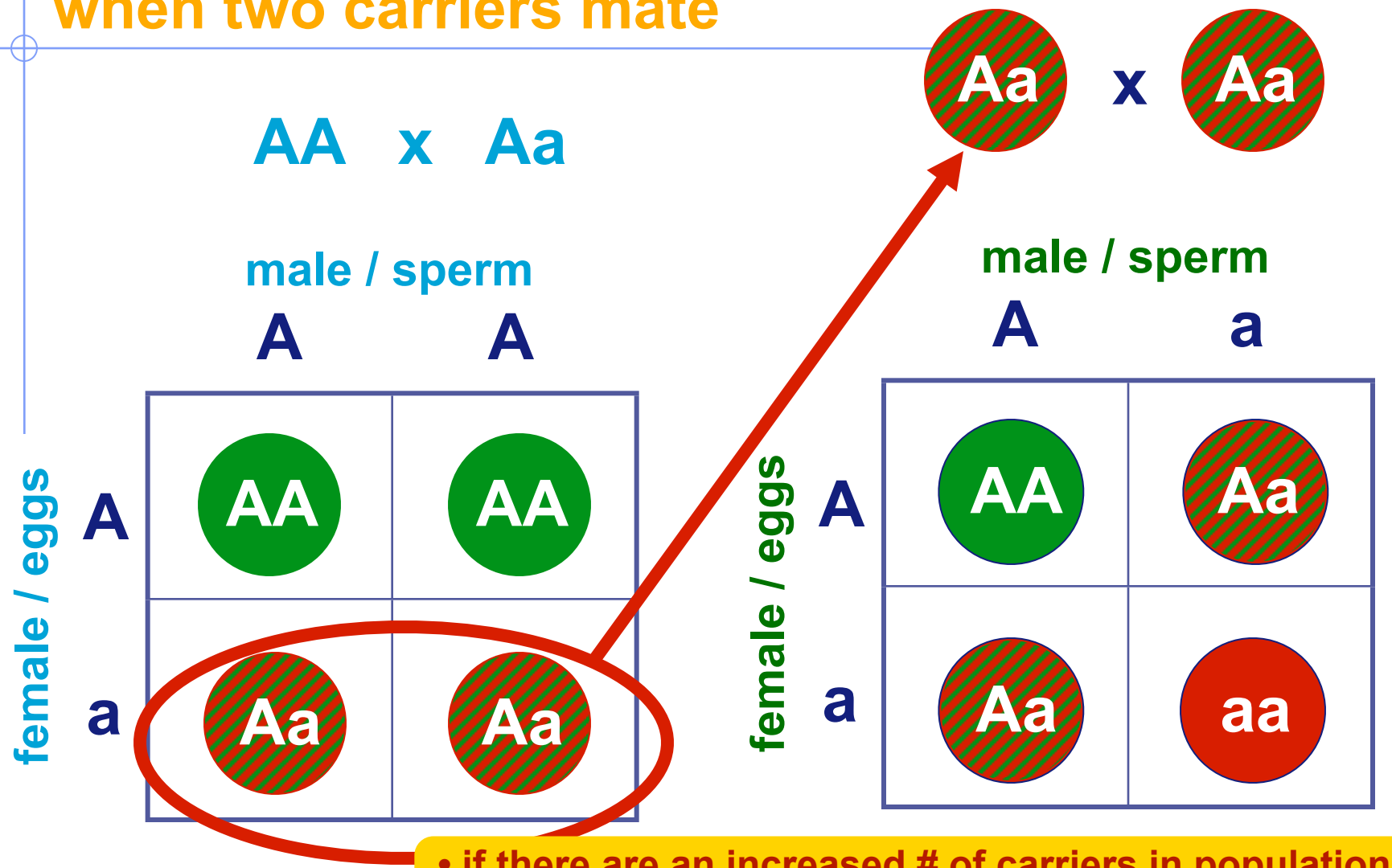




**What ethical implications arise around genetic testing? What if health insurance companies charge you higher rates because they know you will or may get sick in the future? What if you aren't hired because of what is found in your genes?**

# Genetics & culture

- Why do all cultures have a taboo against incest?
  - laws or cultural taboos forbidding marriages between close relatives are fairly universal
- If a recessive allele is less common in a population's gene pool, it is fairly unlikely that 2 unrelated carriers of (non-relatives with) the same *rare* harmful recessive allele will meet & mate
  - but close relatives (who inherited part of their DNA from the same close relative) have an increased risk of both being carriers for the same version of a gene (same allele)
    - "consanguineous" (same blood) matings
  - Offspring of these mating could potentially inherit two harmful copies of an allele, resulting in a harmful homozygous recessive phenotype

# A hidden recessive disease can reveal itself when two carriers mate




- if there are an increased # of carriers in population
- hidden disease is revealed more often in offspring phenotypes

Any questions?