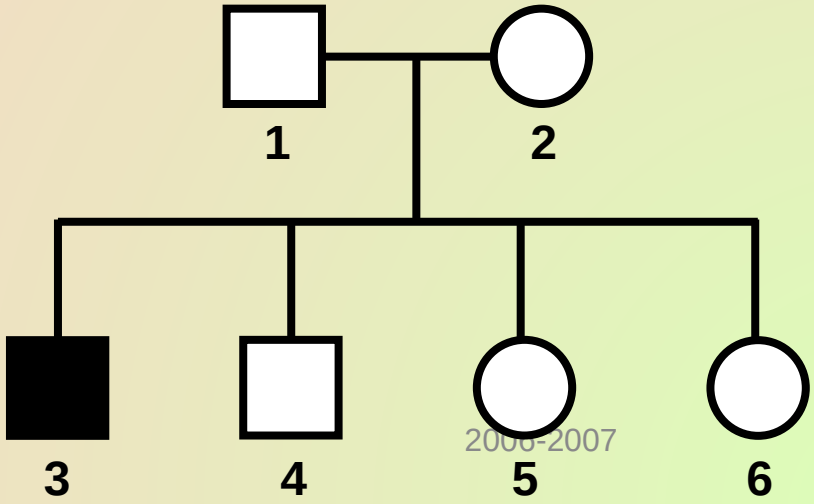
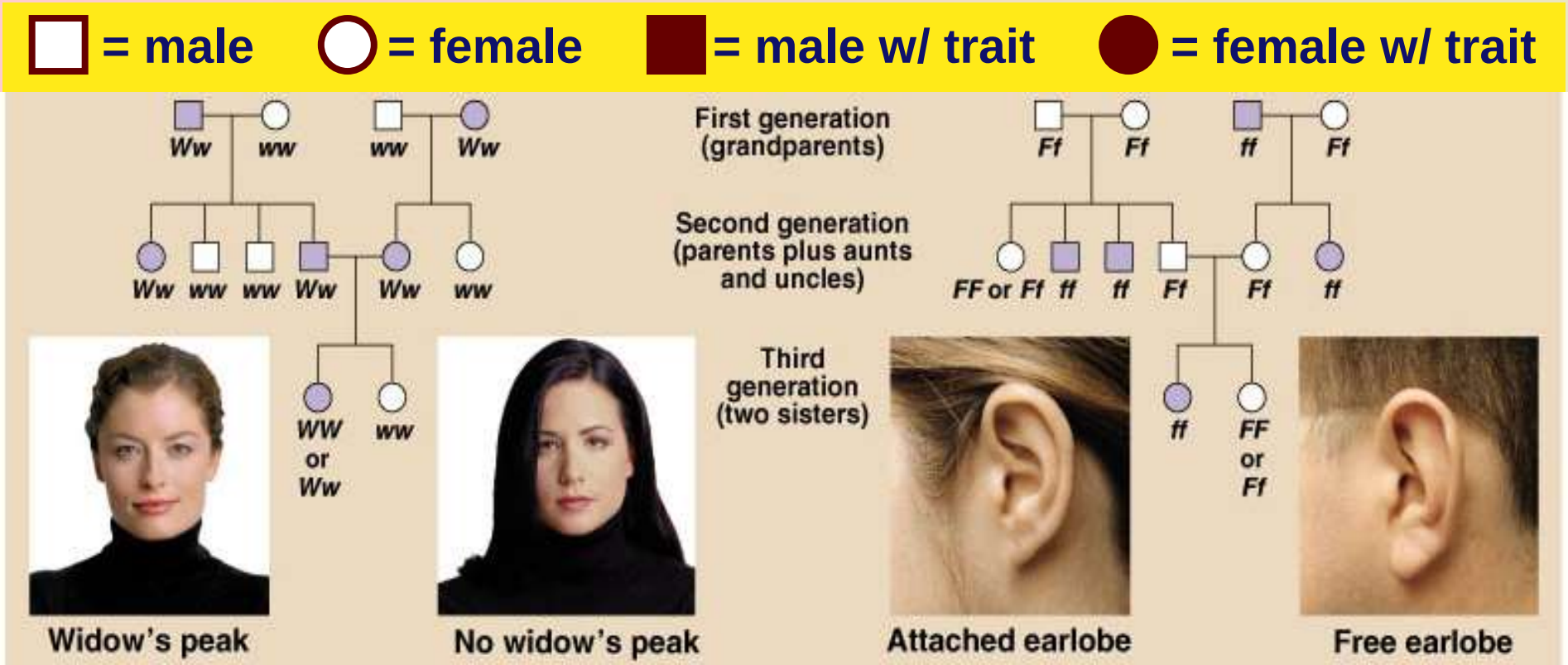
Human Genetic Diseases

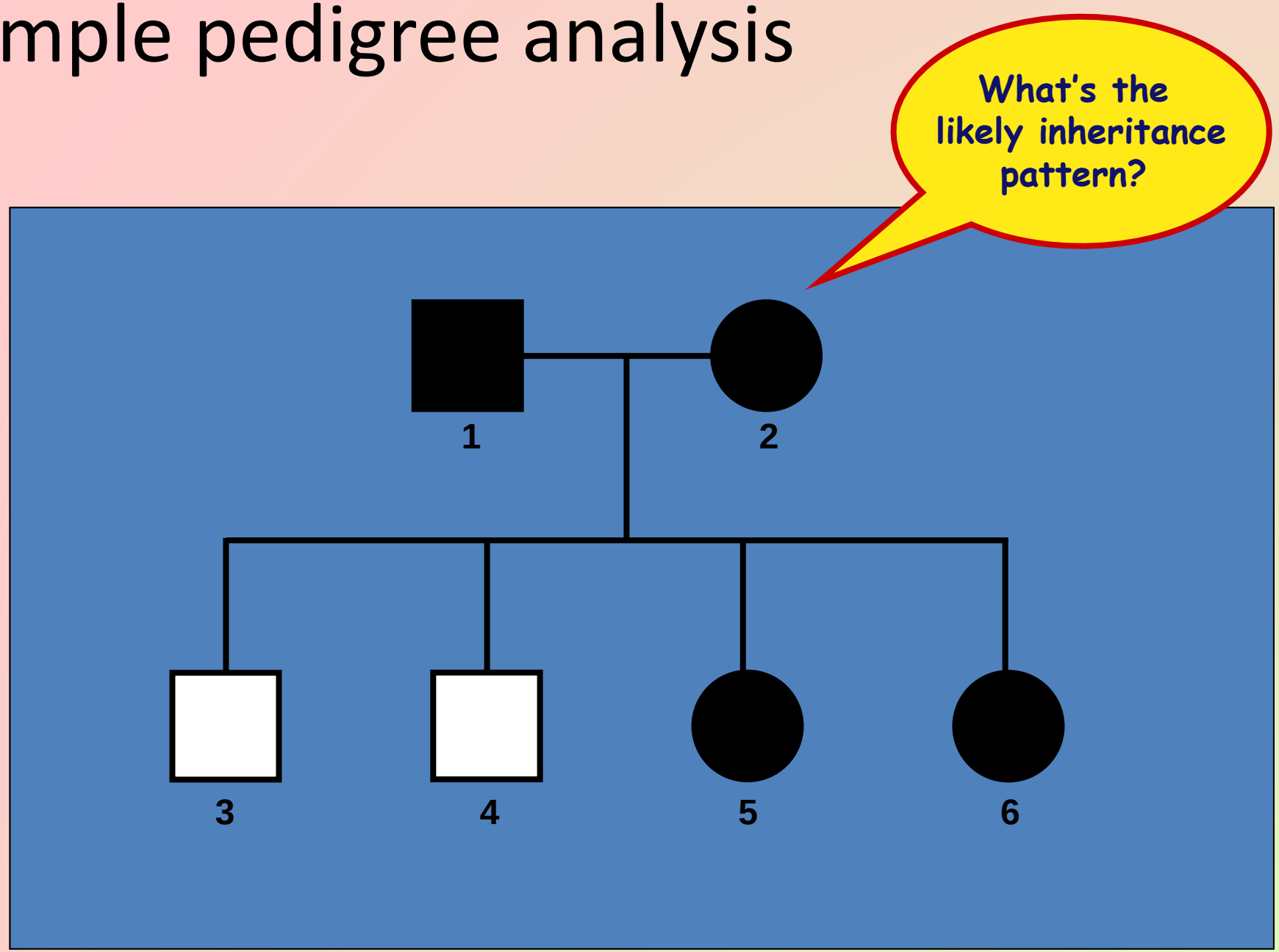


Pedigree analysis

- Pedigree analysis reveals Mendelian patterns in human inheritance
  - data mapped on a family tree



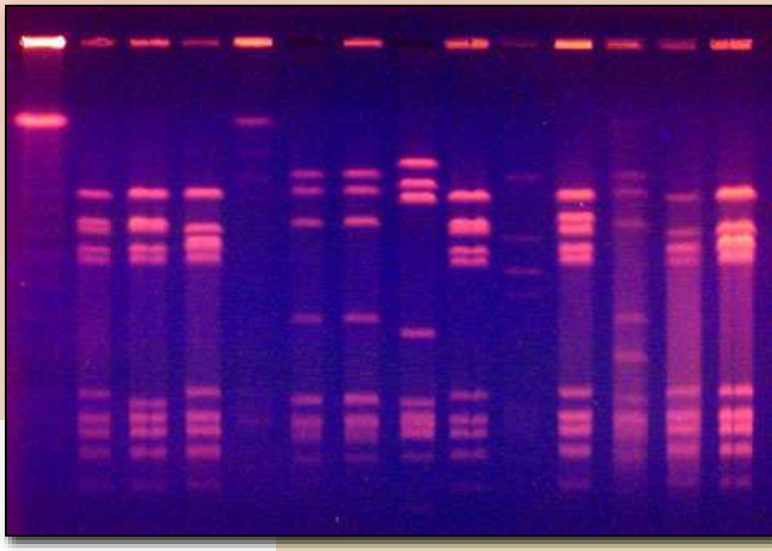
Simple pedigree analysis

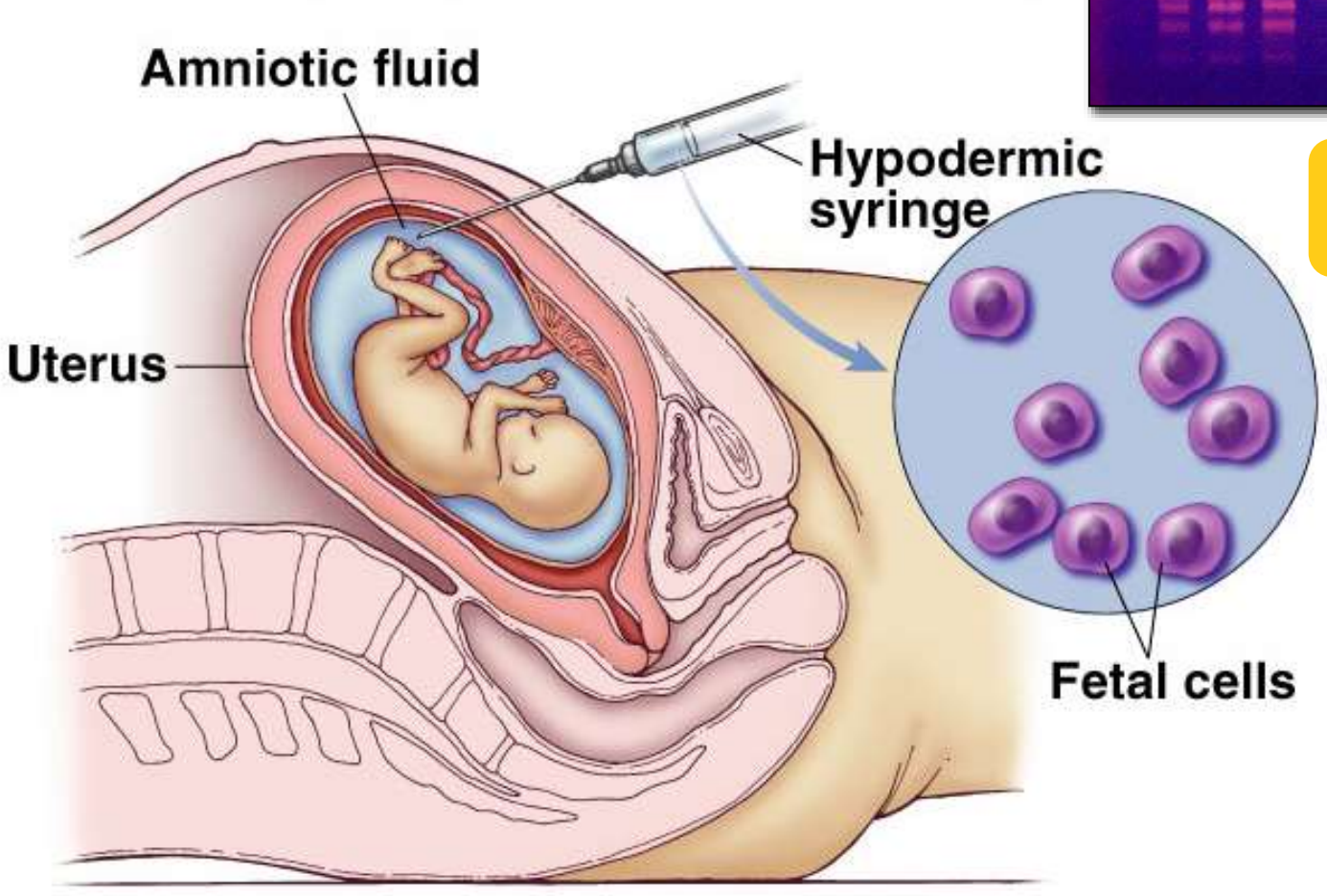


Genetic counseling

- Pedigrees can help us understand the past & predict the future
- Thousands of genetic disorders are inherited as simple recessive traits
  - from benign conditions to deadly diseases
    - albinism
    - cystic fibrosis
    - Tay sachs
    - sickle cell anemia
    - PKU

Genetic testing





sequence individual genes

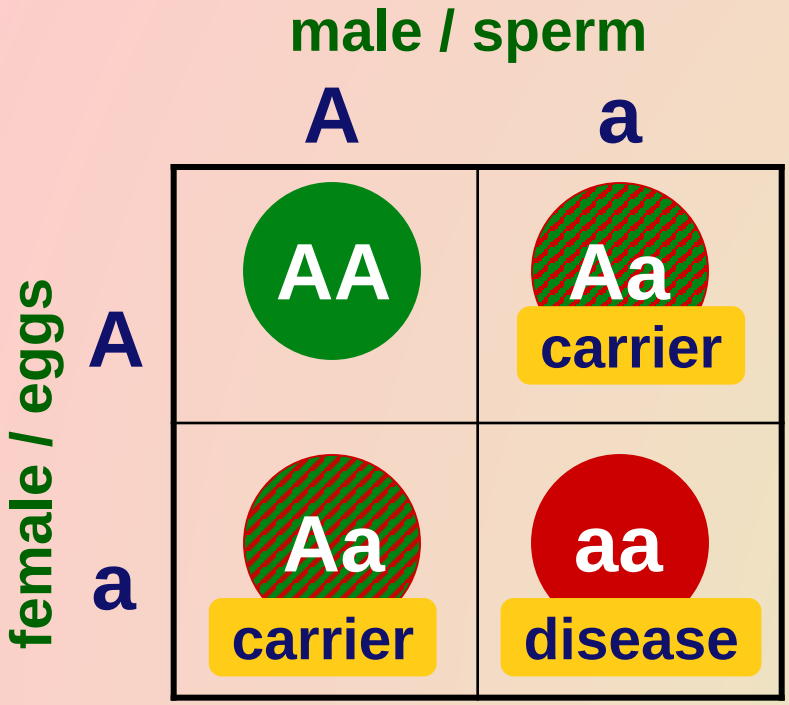
Recessive diseases

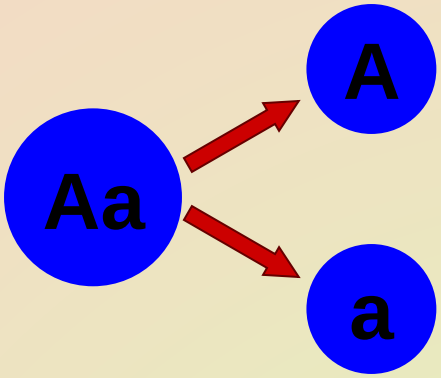
- The diseases are recessive because the allele codes for either a malfunctioning protein or no protein at all
  - Heterozygotes (Aa)
    - carriers
    - have a normal phenotype because one “normal” allele produces enough of the required protein

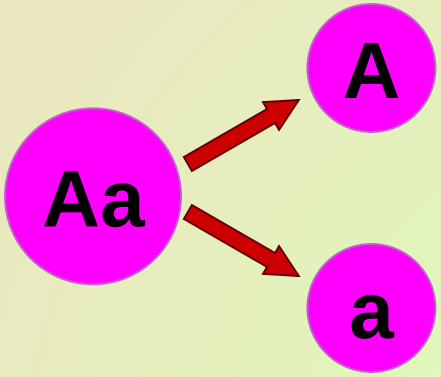
Heterozygote crosses

- Heterozygotes as carriers of recessive alleles

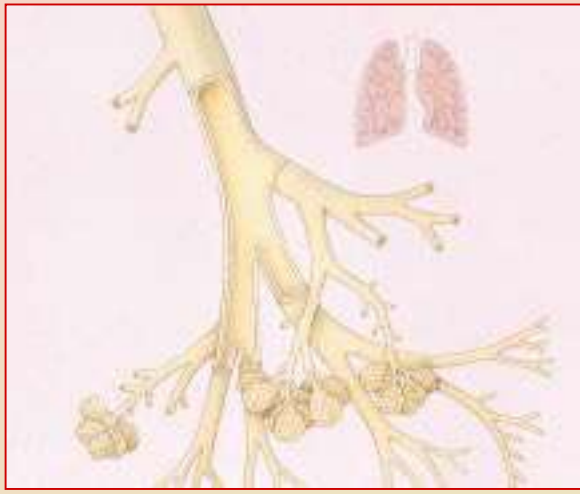
Aa x Aa







Cystic fibrosis (recessive)



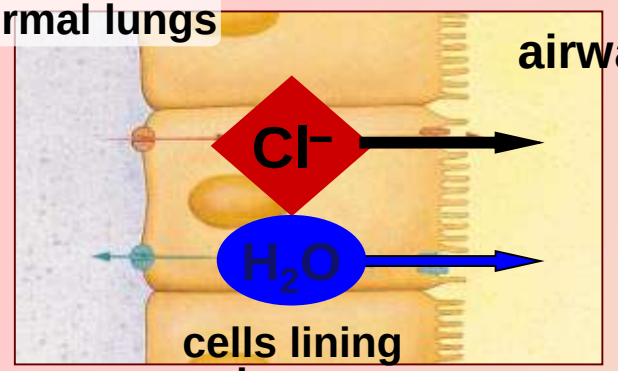
normal lung tissue

- 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
    - Thick, sticky, mucus coats around cells
    - mucus build-up in the pancreas, lungs, digestive tract & causes bacterial infections
  - without treatment children die before 5; with treatment can live past their late 20s

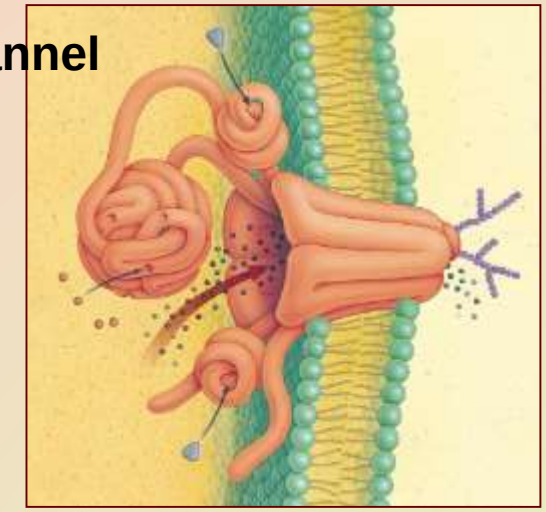
Effect on Lungs

Chloride channel
transports salt through protein channel out of cell
Osmosis: H_2O follows Cl^-

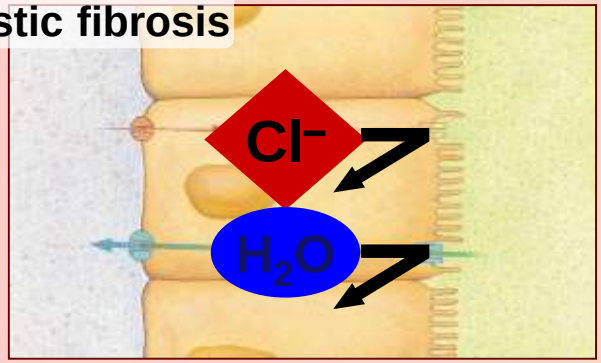
normal lungs



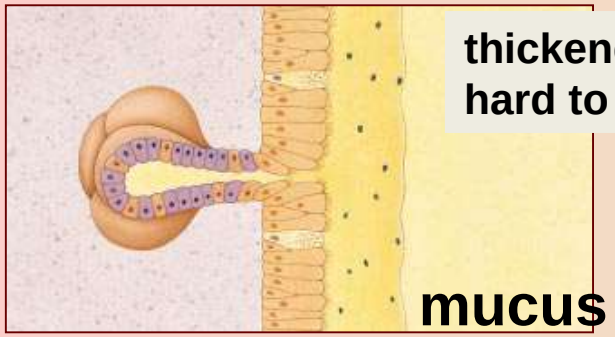
Cl^- channel



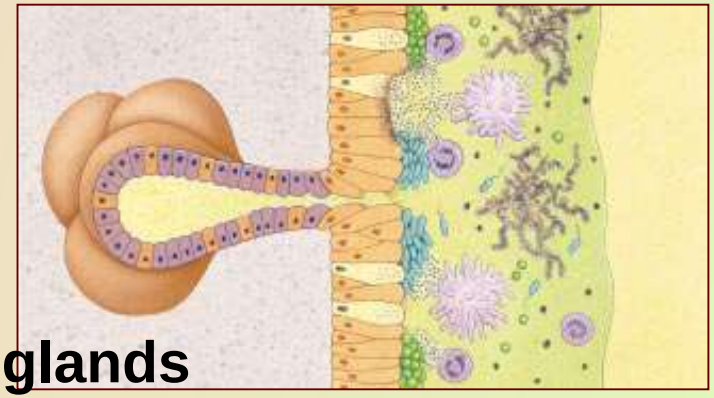
cystic fibrosis



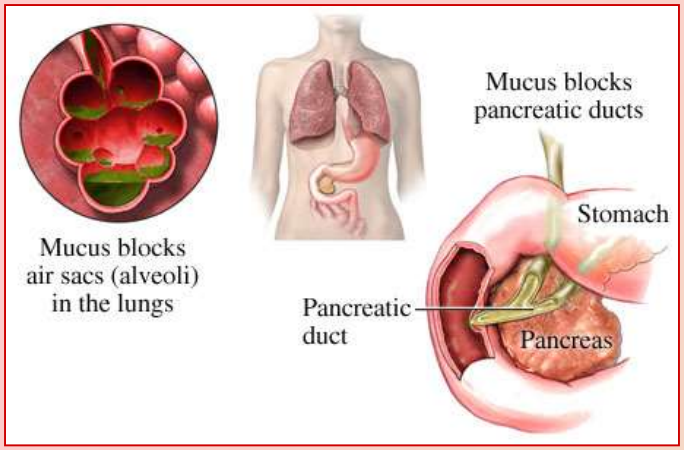
bacteria & mucus build up

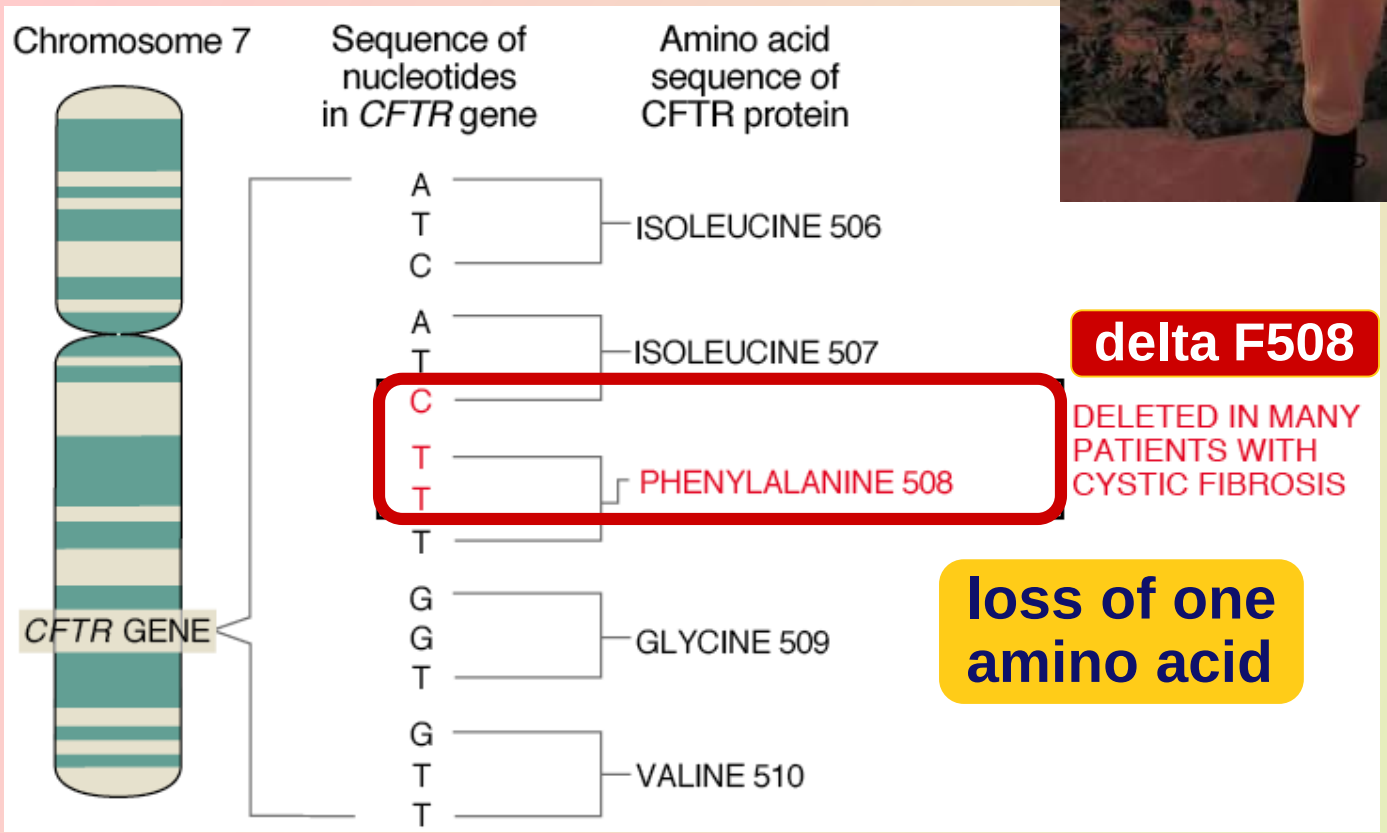


thickened mucus
hard to secrete



mucus secreting glands





delta F508

DELETED IN MANY PATIENTS WITH CYSTIC FIBROSIS

loss of one amino acid

Tay-Sachs (recessive)

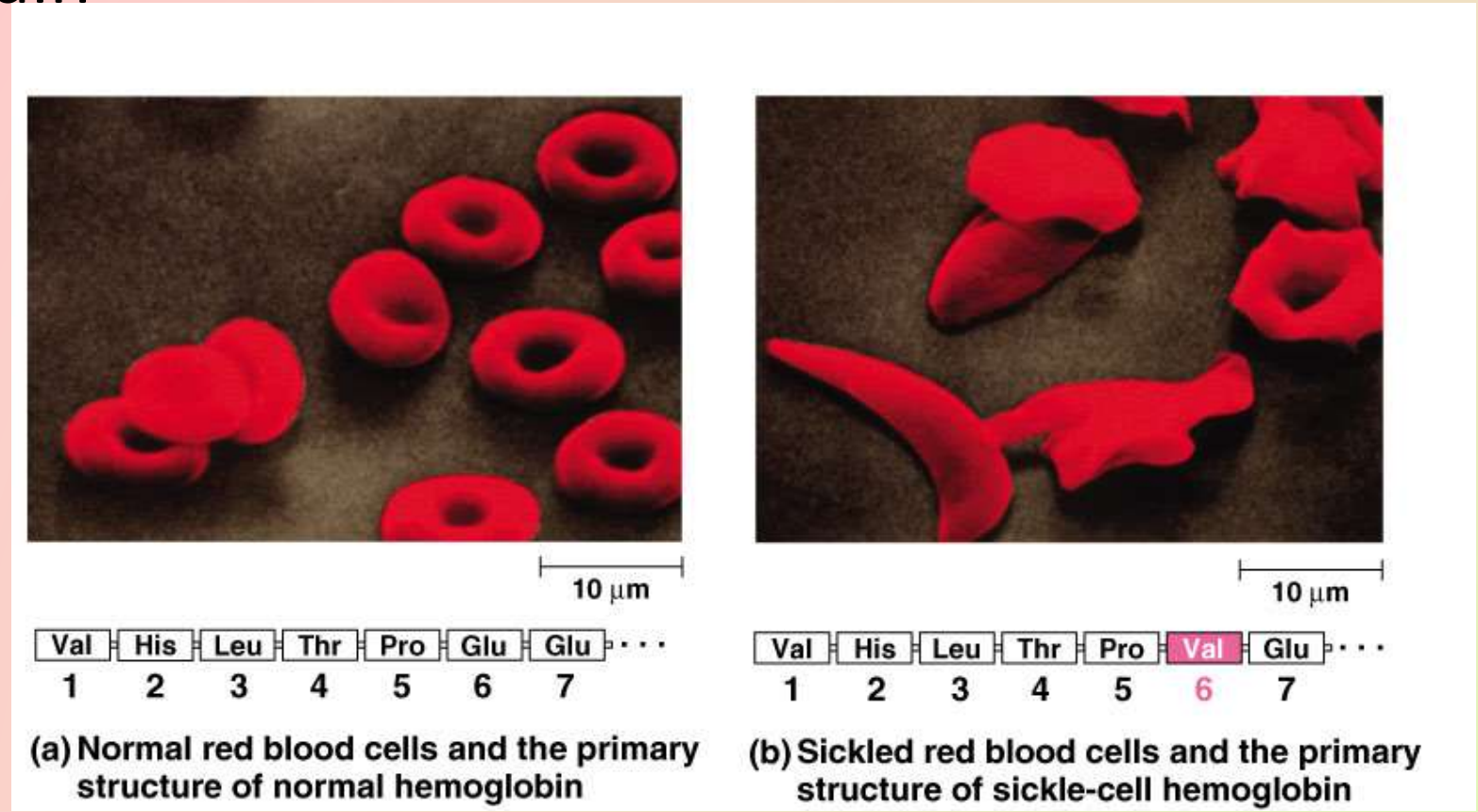
- Primarily Jews of eastern European (Ashkenazi) descent & Cajuns (Louisiana)
  - 1 in 3600 births
  - non-functional enzyme fails to breakdown lipids in brain cells
    - fats collect in cells destroying their function
    - symptoms begin few months after birth
    - seizures, blindness, muscular & mental degeneration
    - child usually dies before 5

Sickle cell anemia (recessive)

- Primarily Africans
  - 1 out of 400 African Americans
  - 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

Sickle cell anemia

- Substitution of one amino acid in polypeptide chain



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
    - Impaired mental function
    - Paralysis
    - Pneumonia and other infections
    - Rheumatism
    - Kidney failure
- Accumulation of sickled cells in spleen
  - Spleen damage

Sickle cell phenotype

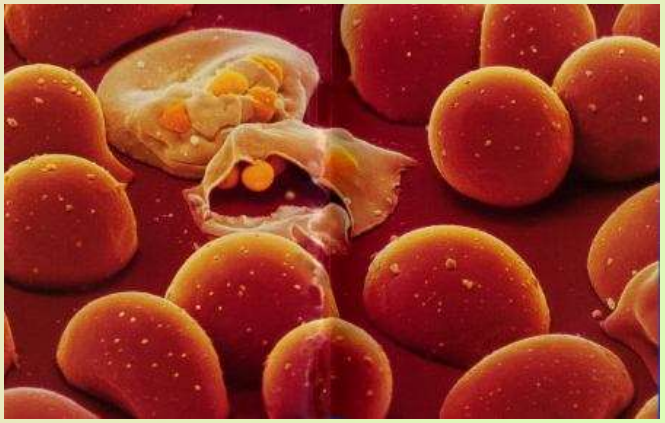
- 2 alleles are codominant
  - both normal & mutant hemoglobins are synthesized in heterozygote (Aa)
  - 50% cells sickle; 50% cells normal
  - carriers usually healthy
  - sickle-cell disease triggered under blood oxygen stress
    - exercise

Sickle Cell

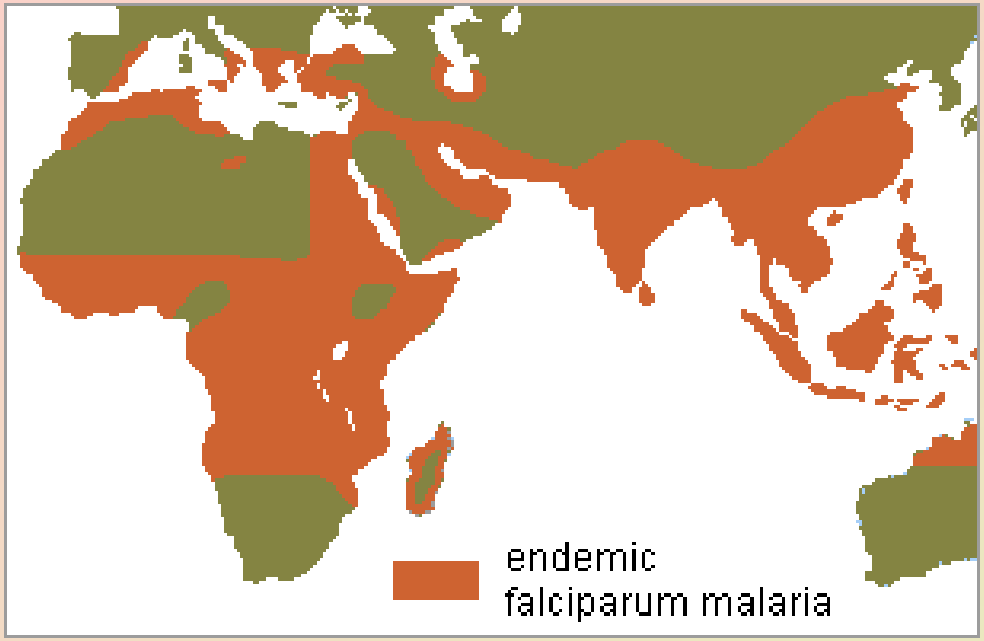
Heterozygote advantage

- Malaria
  - single-celled eukaryote parasite spends part of its life cycle in red blood cells
- In tropical Africa, where malaria is common:
  - homozygous dominant individuals die of malaria
  - homozygous recessive individuals die of sickle cell anemia
  - heterozygote carriers are relatively free of both
    - reproductive advantage

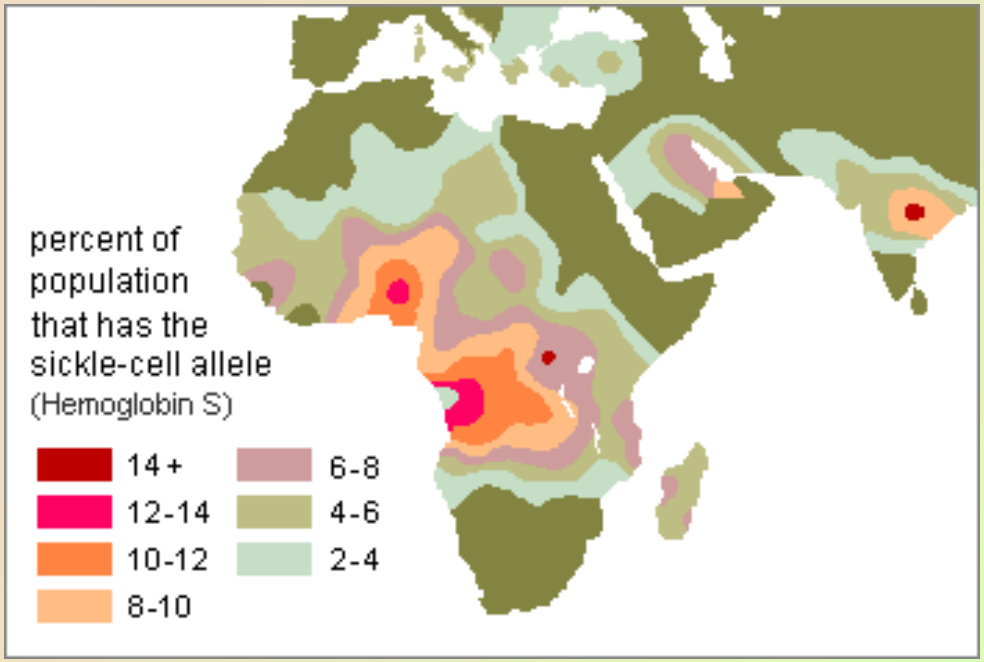
?????



Prevalence of Malaria

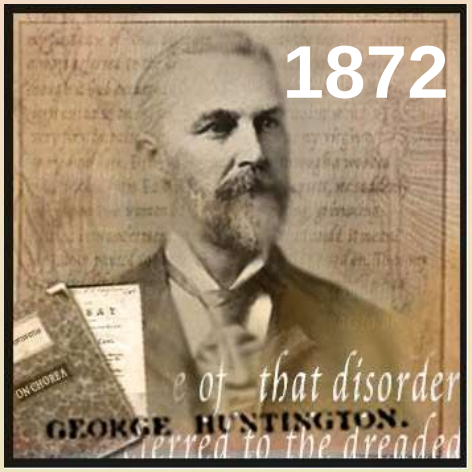


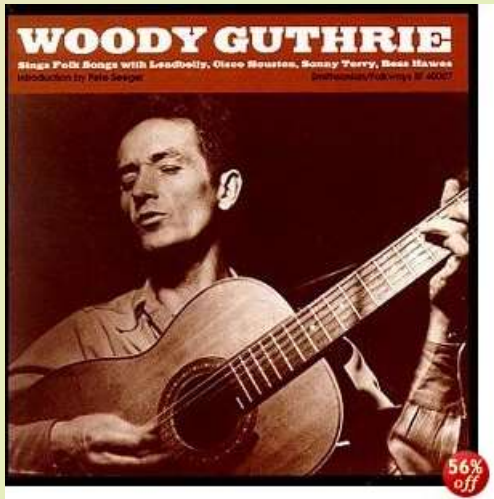
Prevalence of Sickle Cell Anemia



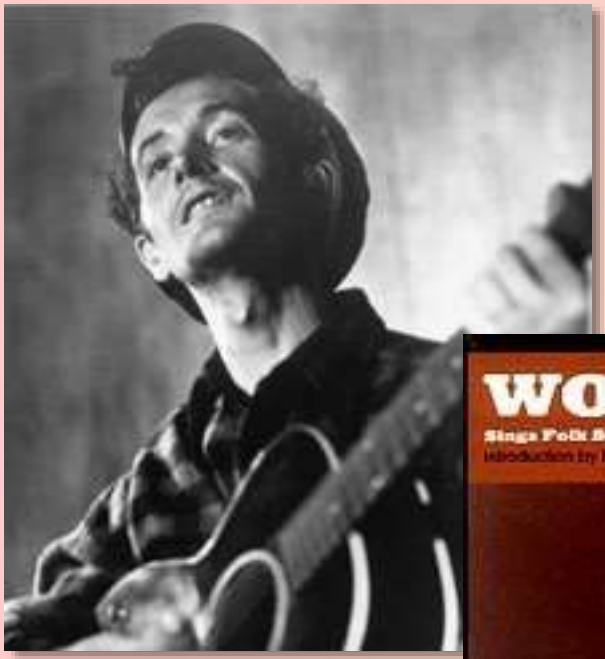
Huntington's chorea (dominant)

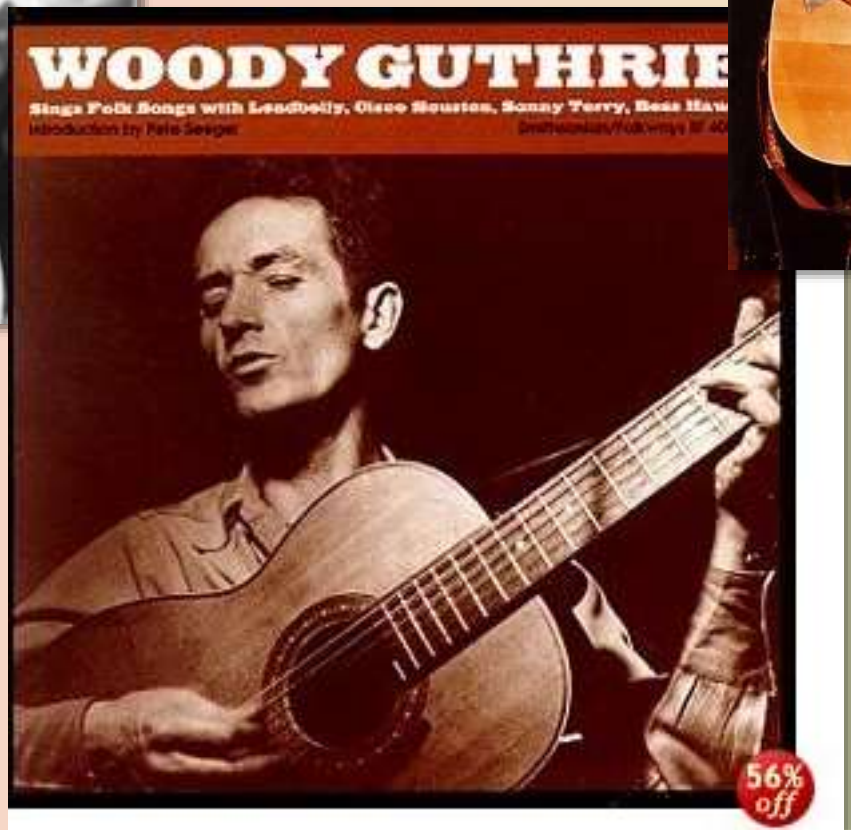
- Dominant inheritance
  - repeated mutation on end of chromosome 4
    - mutation = CAG repeats
    - glutamine amino acid repeats in protein
    - one of 1st genes to be identified
  - build up of "huntingtin" protein in brain causing cell death
    - memory loss
    - muscle tremors, jerky movements
      - "chorea"
    - starts at age 30-50
    - early death: 10-20 years after start





Woody Guthrie & Arlo Guthrie

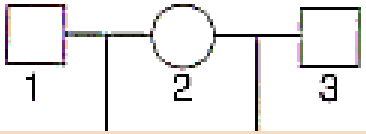


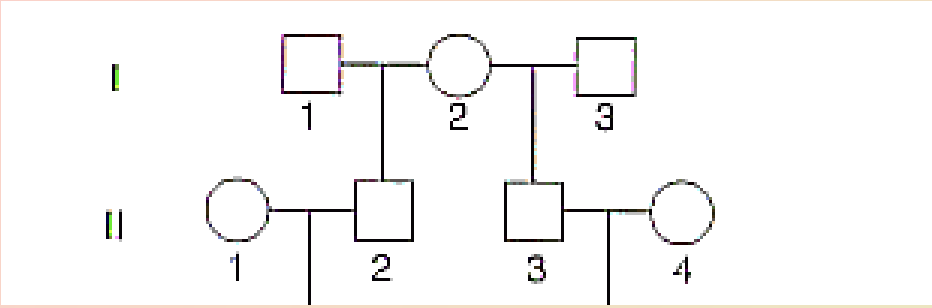


Another Sample Pedigree

Not Like Yours -- hopefully

I

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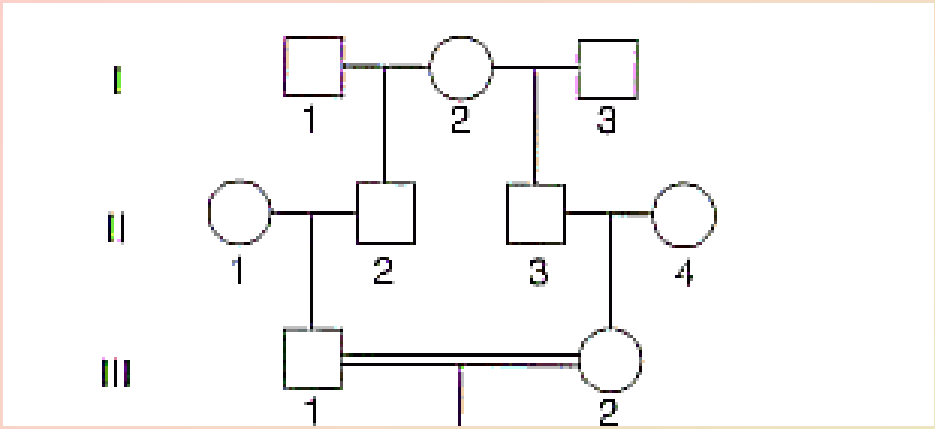
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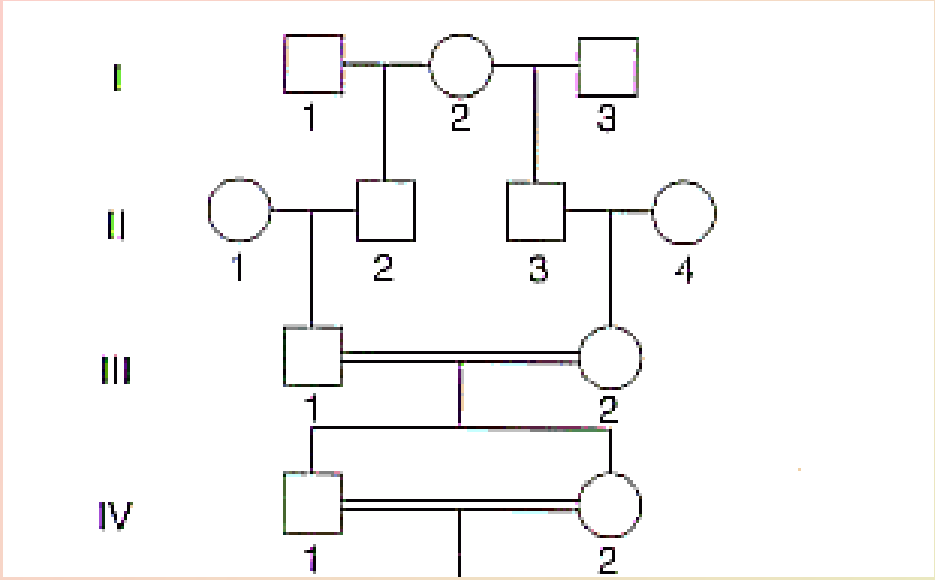
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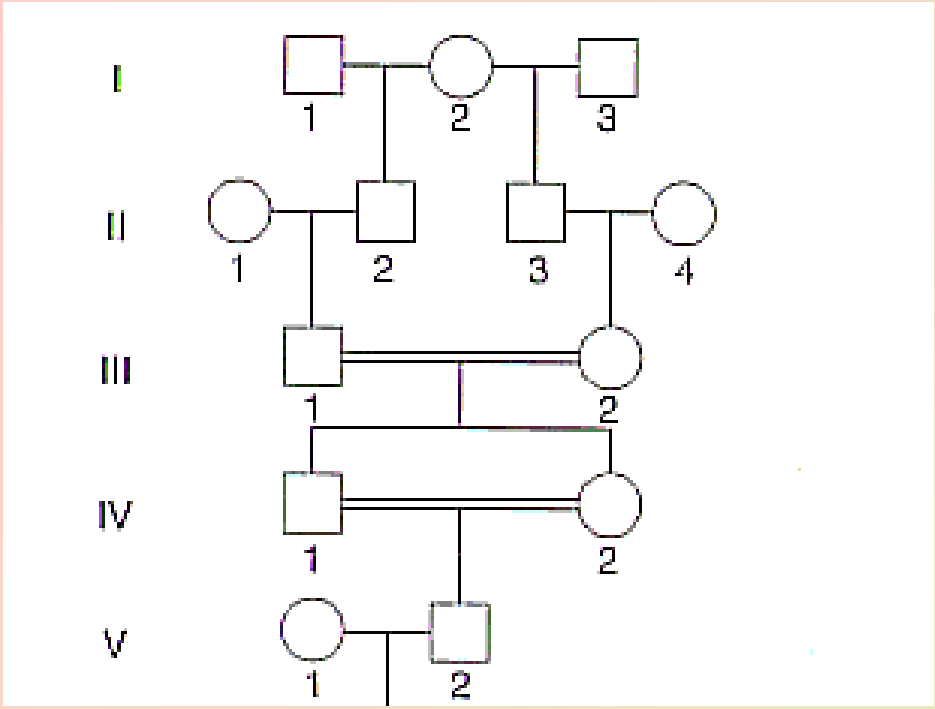
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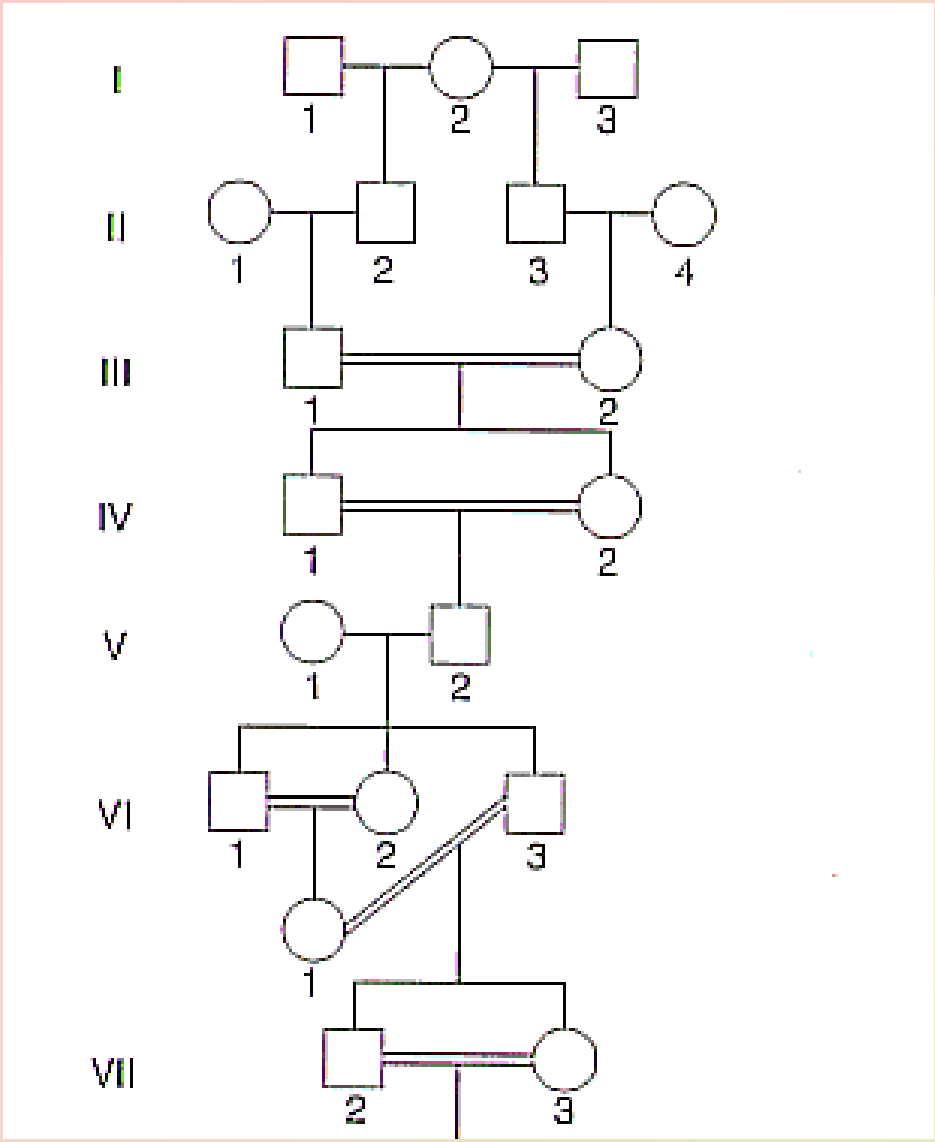
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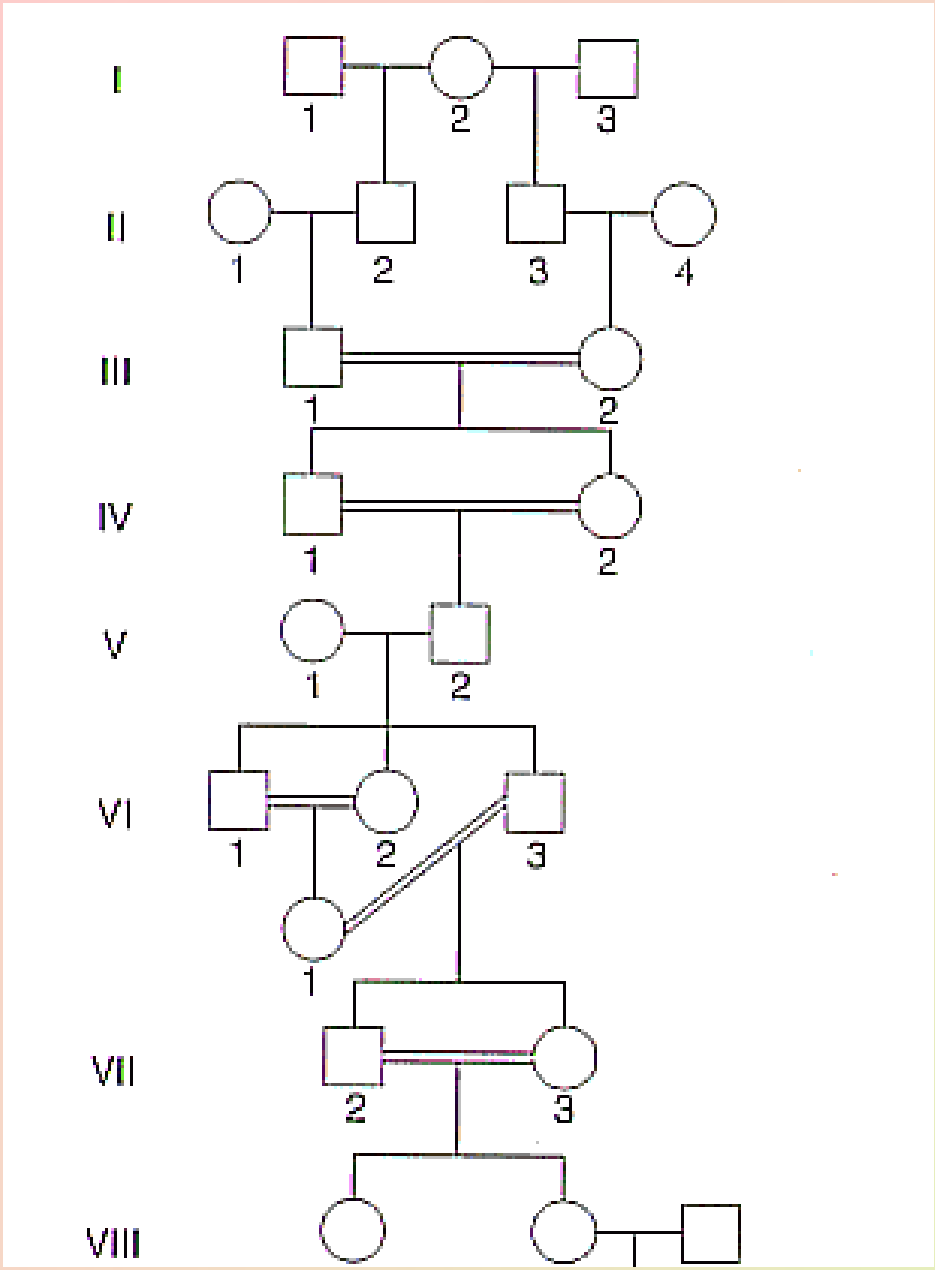
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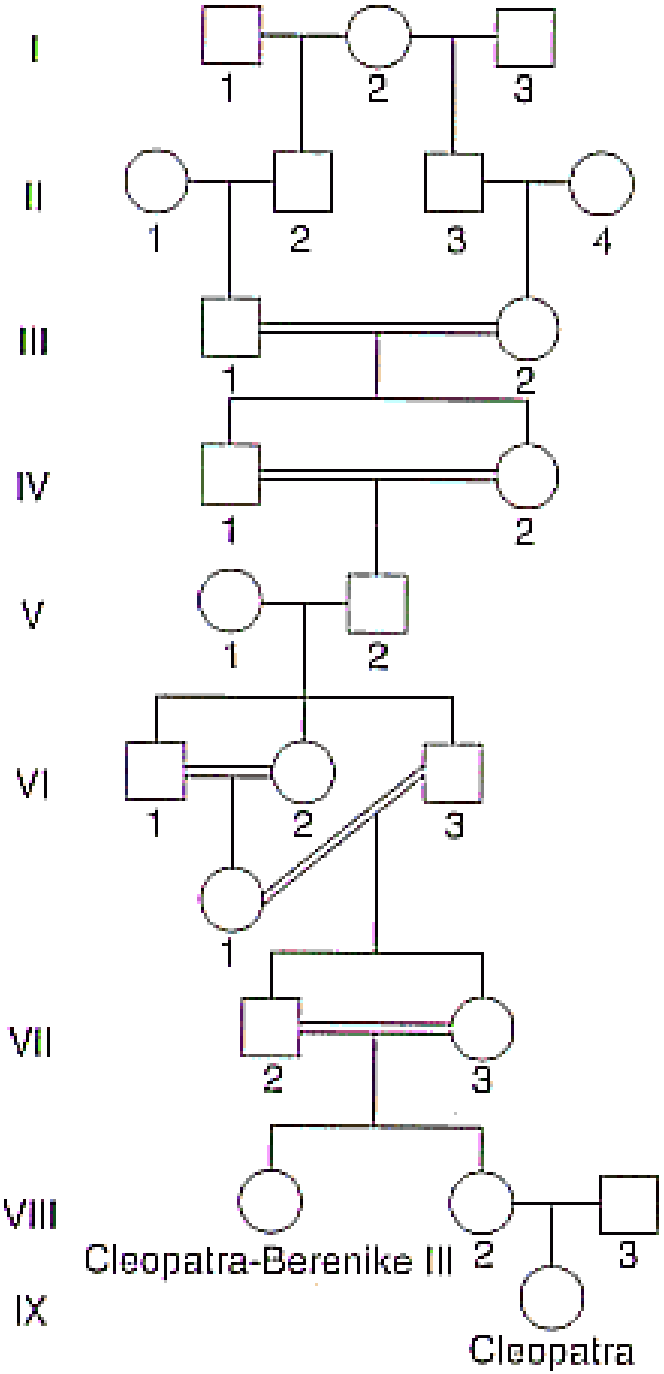
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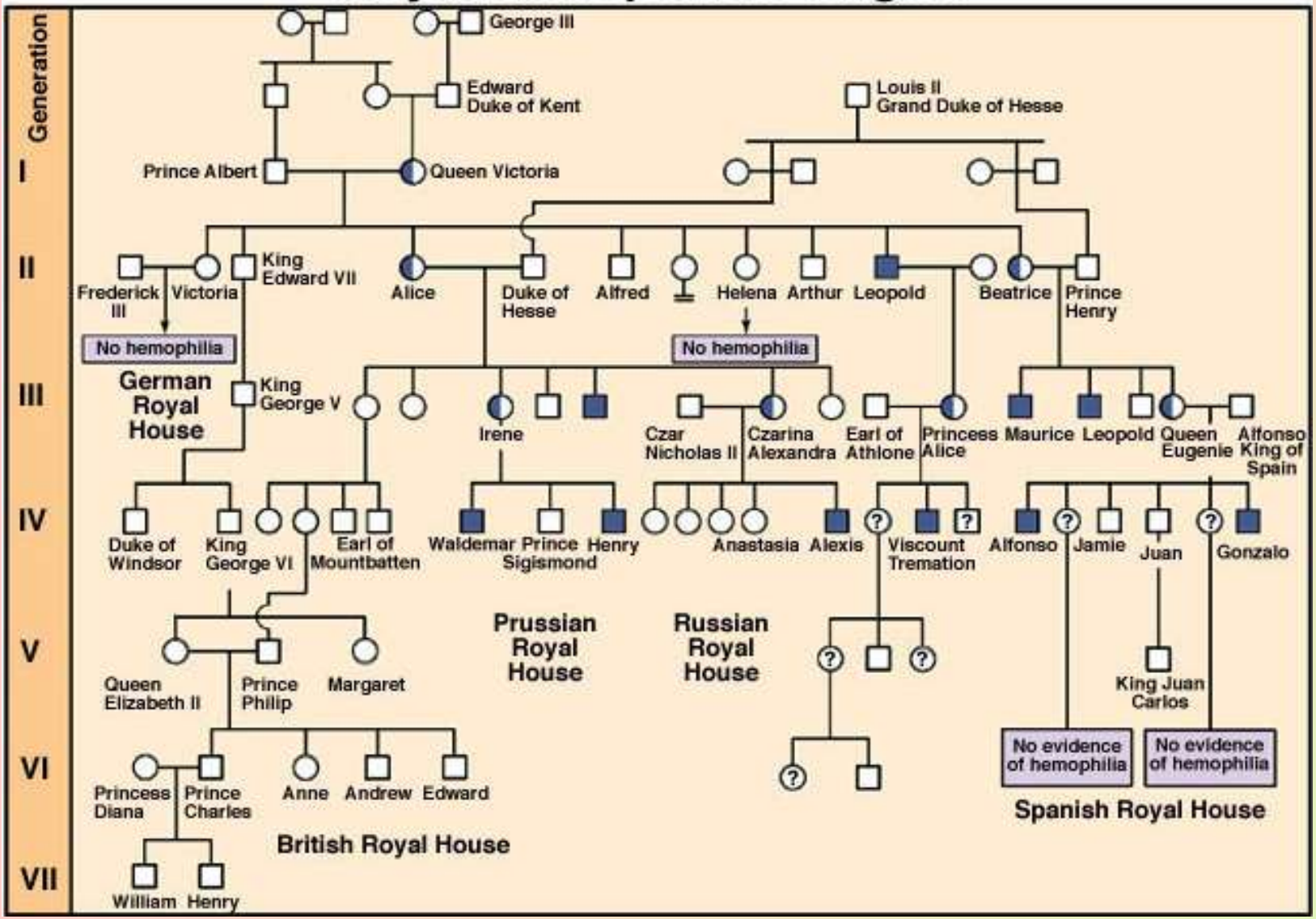
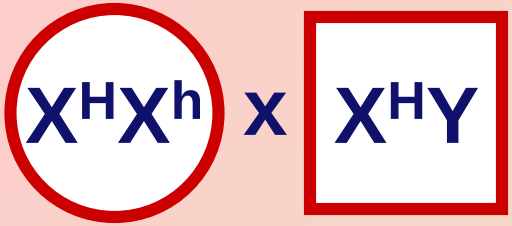
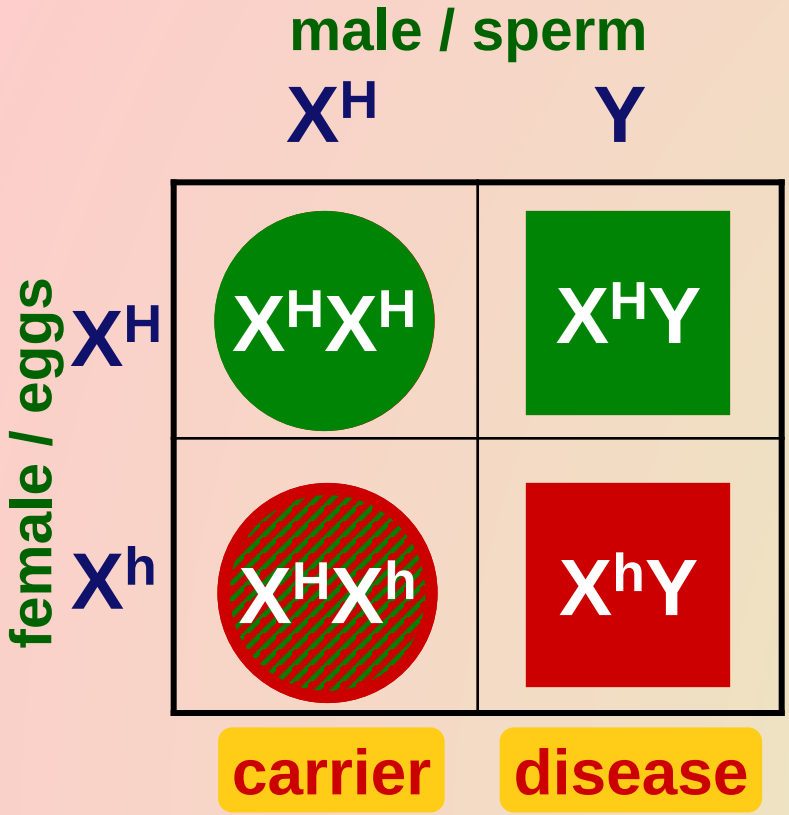
Royal Hemophilia Pedigree

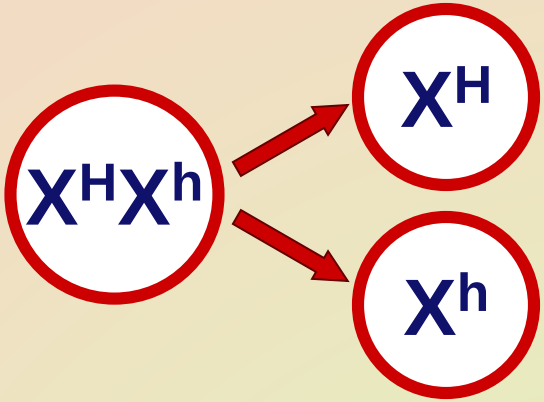


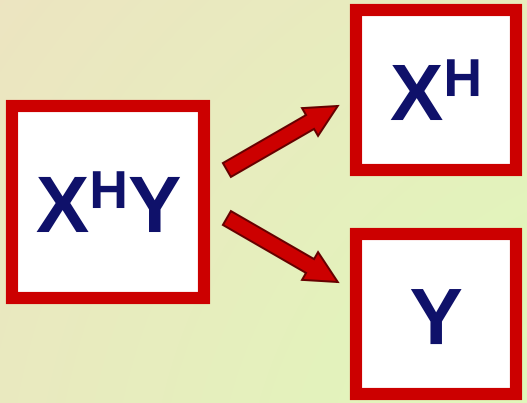
Hemophilia

sex-linked recessive







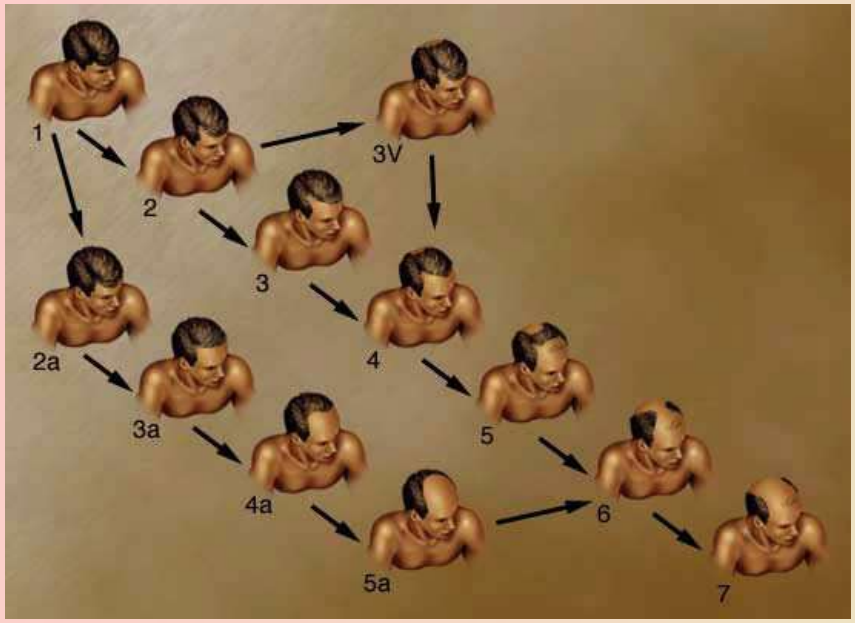


Genetics & culture

- All cultures have a taboo against incest.
  - laws or cultural taboos forbidding marriages between close relatives are fairly universal
- Fairly unlikely that 2 unrelated carriers of same rare harmful recessive allele will meet & mate
  - matings between close relatives increase risk
    - "consanguineous" (same blood) matings
  - individuals who share a recent common ancestor are more likely to carry same recessive alleles

Male pattern baldness

- Sex influenced trait
  - autosomal trait influenced by sex hormones
    - age effect as well = onset after 30 years old
  - dominant in males & recessive in females
    - B_ = bald in males; bb = bald in females



Any questions?

1. A couple who are both carriers of the gene for cystic fibrosis have two children who have cystic fibrosis. What is the probability that their next child will have cystic fibrosis?
   A. 0%
   B. 25%
   C. 50%
   D. 75%
   E. 100%

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A. 0%
B. 25%
C. 50%
D. 75%
E. 100%

3. A woman and her spouse both show the normal phenotype for pigmentation, but both had one parent who was an albino. Albinism is an autosomal recessive trait. If their first two children have normal pigmentation, what is the probability that their third child will be an albino?

   A. 0
   B. 1/4
   C. 1/2
   D. 3/4
   E. 1

3. A woman and her spouse both show the normal phenotype for pigmentation, but both had one parent who was an albino. Albinism is an autosomal recessive trait. If their first two children have normal pigmentation, what is the probability that their third child will be an albino?

A. 0

B. 1/4

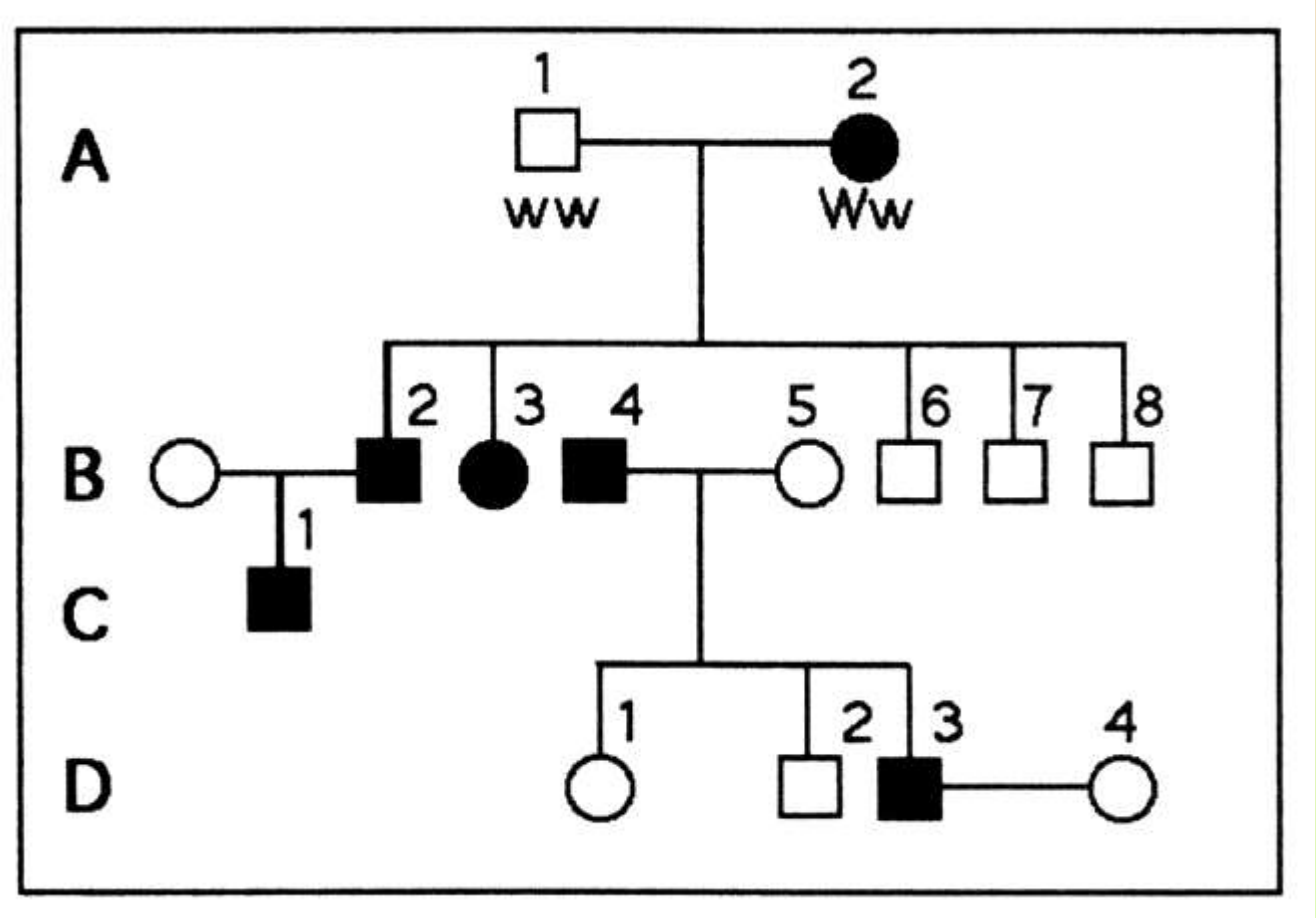
C. 1/2

D. 3/4

E. 1

4. What is the probability that individual C-1 is *Ww*?

A. 3/4
B. 1/4
C. 2/4
D. 2/3
E. 1



4. What is the probability that individual C-1 is *Ww*?

A. 3/4
B. 1/4
C. 2/4
D. 2/3
E. 1