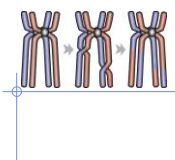
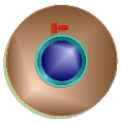
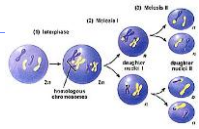


Wrapping up Genetics

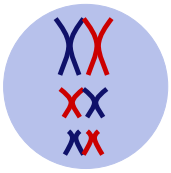
Chromosomal Abnormalities and Human Genetic Conditions





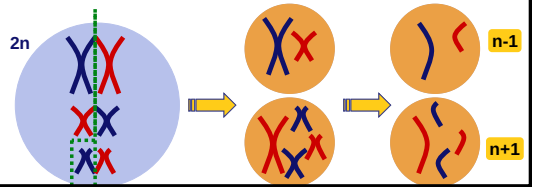
Chromosomal abnormalities

- Incorrect number of chromosomes
  - nondisjunction
    - chromosomes don't separate properly during meiosis
  - breakage of chromosomes
    - deletion
    - duplication
    - inversion
    - translocation

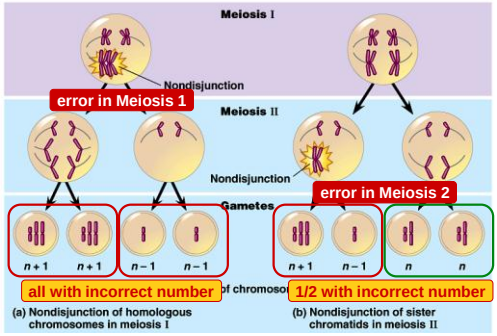


Nondisjunction

- Problems with meiotic spindle cause errors in daughter cells
  - homologous chromosomes do not separate properly during Meiosis 1
  - sister chromatids fail to separate during Meiosis 2
  - too many or too few chromosomes

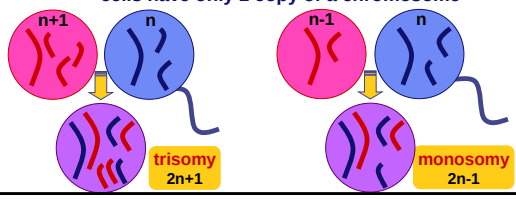


Alteration of chromosome number



Nondisjunction

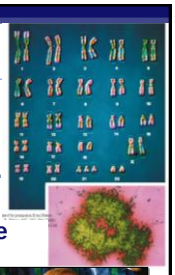
- Baby has wrong chromosome number
  - trisomy
    - cells have 3 copies of a chromosome
  - monosomy
    - cells have only 1 copy of a chromosome



Human chromosome disorders

- High frequency in humans
  - most embryos are spontaneously aborted
  - alterations are too disastrous
  - developmental problems result from biochemical imbalance
    - imbalance in regulatory molecules?
      - hormones?
      - transcription factors?
- Certain conditions are tolerated
  - upset the balance less = survivable
  - but characteristic set of symptoms = syndrome

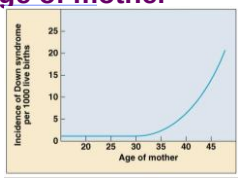
Down syndrome



- Trisomy 21
  - 3 copies of chromosome 21
  - 1 in 700 children born in U.S.
- Chromosome 21 is the smallest human chromosome
  - but still severe effects
- Frequency of Down syndrome correlates with the age of the mother

Down syndrome & age of mother

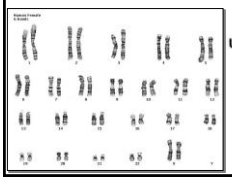
Mother's age	Incidence of Down Syndrome
Under 30	<1 in 1000
30	1 in 900
35	1 in 400
36	1 in 300
37	1 in 230
38	1 in 180
39	1 in 135
40	1 in 105
42	1 in 60
44	1 in 35
46	1 in 20
48	1 in 16
49	1 in 12

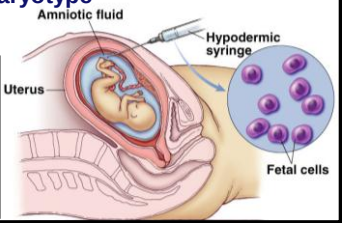


Rate of miscarriage due to amniocentesis:
- 1970s data
  0.5%, or 1 in 200 pregnancies
- 2006 data
  <0.1%, or 1 in 1600 pregnancies

Genetic testing

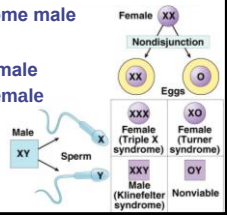
- Amniocentesis in 2nd trimester
  - sample of embryo cells
  - stain & photograph chromosomes
- Analysis of karyotype





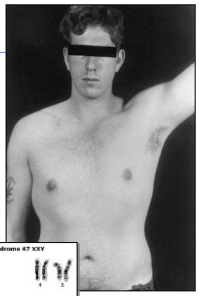
Sex chromosomes abnormalities

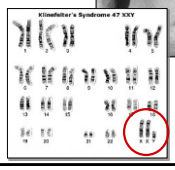
- Human development more tolerant of wrong numbers in sex chromosome
- But produces a variety of distinct syndromes in humans
  - XXY = Klinefelter's syndrome male
  - XXX = Trisomy X female
  - XYY = Jacob's syndrome male
  - XO = Turner syndrome female



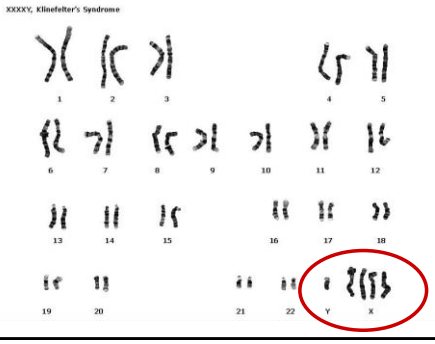
Klinefelter's syndrome

- XXY male
  - one in every 2000 live births
  - have male sex organs, but are sterile
  - feminine characteristics
    - some breast development
    - lack of facial hair
  - tall
  - normal intelligence



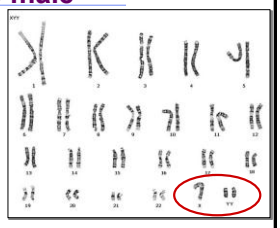


Klinefelter's syndrome



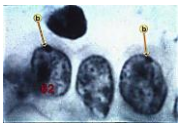
Jacob's syndrome male

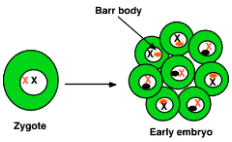
- XYY Males
  - 1 in 1000 live male births
  - extra Y chromosome
  - slightly taller than average
  - more active
  - normal intelligence, slight learning disabilities
  - delayed emotional maturity
  - normal sexual development



Trisomy X

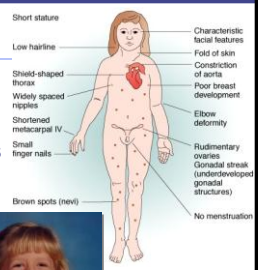
- XXX
  - 1 in every 2000 live births
  - produces healthy females
    - Why?
    - Barr bodies
      - all but one X chromosome is inactivated





Turner syndrome

- Monosomy X or X0
  - 1 in every 5000 births
  - varied degree of effects
  - webbed neck
  - short stature
  - sterile



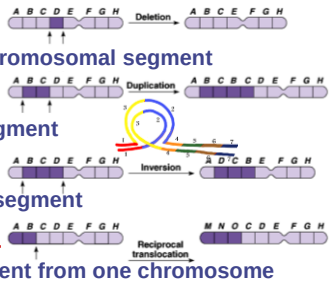
Changes in chromosome structure

error of replication

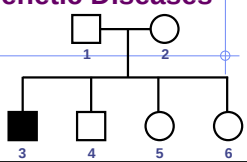
- deletion
  - loss of a chromosomal segment
- duplication
  - repeat a segment

error of crossing over

- inversion
  - reverses a segment
- translocation
  - move segment from one chromosome to another

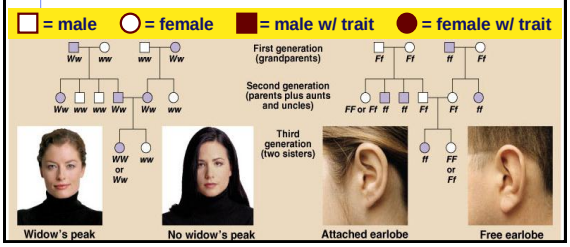


Human Genetic Diseases

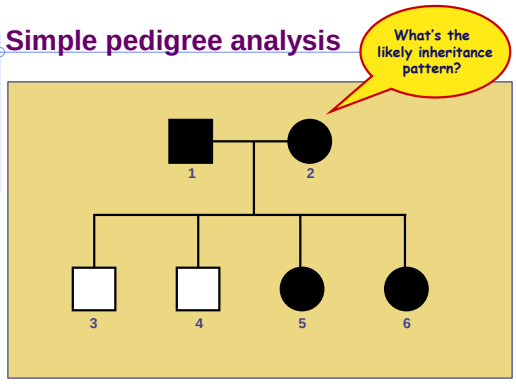


Pedigree analysis

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



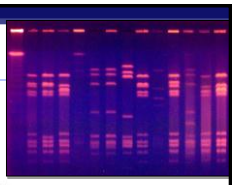
Simple pedigree analysis

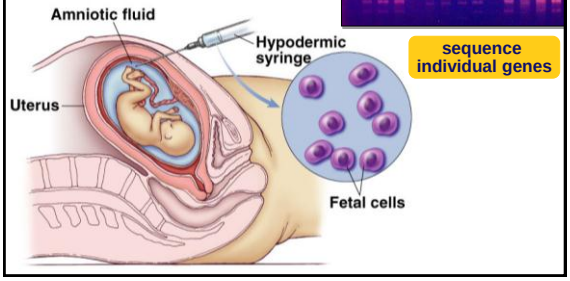


Genetic counseling

- Pedigree 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

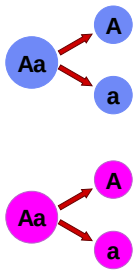
Heterozygote crosses

- Heterozygotes as carriers of recessive alleles

Aa x Aa

male / sperm

female / eggs	A	a
A	AA	Aa carrier
a	Aa carrier	aa disease



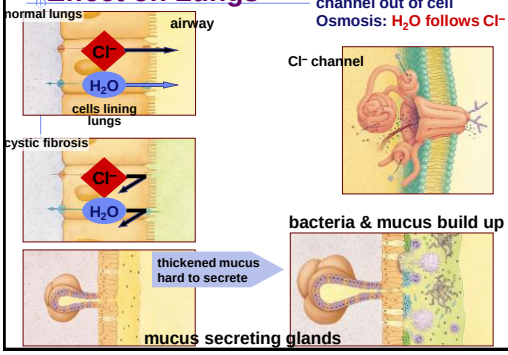
Cystic fibrosis (recessive)

normal lung tissue

- Primarily whites of European descent
  - strikes 1 in 2500 births
    - 1 in 25 whites is a carrier (Aa)
  - normal allele of the CFTR gene codes for a membrane protein that transports Cl^- across cell membrane
    - defective or absent channels limit transport of Cl^- & H_2O across cell membrane
    - normally Cl- is pumped out of cells, decreasing H_2O potential in extracellular environment = watery mucus
    - defective CFTR means higher H_2O potential outside of cells
    - thicker & stickier 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

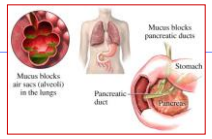
Effect on Lungs

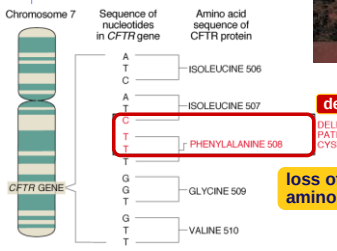
Chloride channel
transports salt through protein channel out of cell
Osmosis: H_2O follows Cl^-



Cl^- channel

bacteria & mucus build up





Tay-Sachs (recessive)

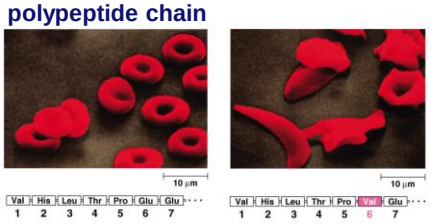
- Primarily Jews of eastern European (Ashkenazi) descent & Cajuns (Louisiana)
  - strikes 1 in 3600 births
    - 100 times greater than incidence among non-Jews
  - non-functional enzyme fails to breakdown lipids in brain cells
    - fats collect in cells destroying their function
    - symptoms begin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

Sickle cell anemia (recessive)

- Primarily Africans
  - strikes 1 out of 400 African Americans
    - high frequency
  - 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

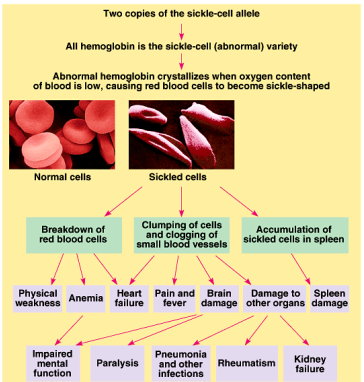
Sickle cell anemia

- Substitution of one amino acid in polypeptide chain



hydrophilic amino acid

hydrophobic amino acid



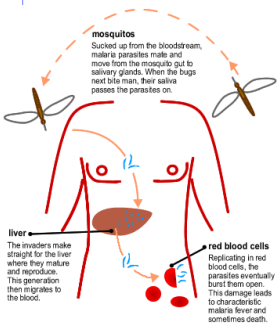
Sickle cell phenotype

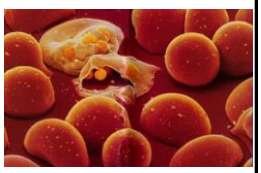
- 2 alleles are codominant
  - both normal & mutant hemoglobins are synthesized in heterozygote (Aa)
  - 50% cells sickle; 50% cells normal
  - carriers usually healthy
  - sickle-cell disease triggered under blood oxygen stress
    - exercise

Heterozygote advantage

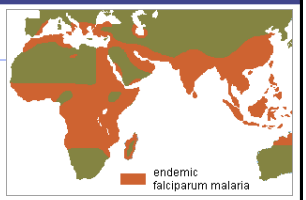
- Malaria
  - single-celled eukaryote parasite spends part of its life cycle in red blood cells
- In tropical Africa, where malaria is common:
  - homozygous dominant individuals die of malaria
  - homozygous recessive individuals die of sickle cell anemia
  - heterozygote carriers are relatively free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

Malaria

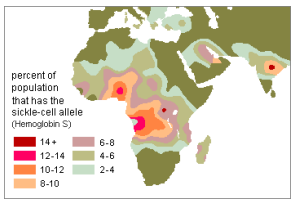




Prevalence of Malaria

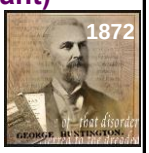


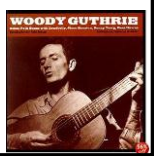
Prevalence of Sickle Cell Anemia



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



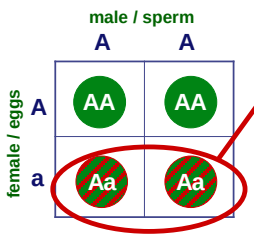


Genetics & culture

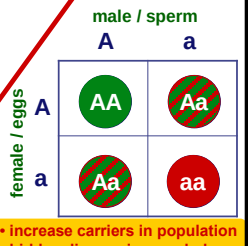
- Why do all cultures have a taboo against incest?
  - laws or cultural taboos forbidding marriages between close relatives are fairly universal
- Fairly unlikely that 2 unrelated carriers of same rare harmful recessive allele will meet & mate
  - but matings between close relatives increase risk
  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

A hidden disease reveals itself

AA x Aa



Aa x Aa



- increase carriers in population
- hidden disease is revealed

Any questions?