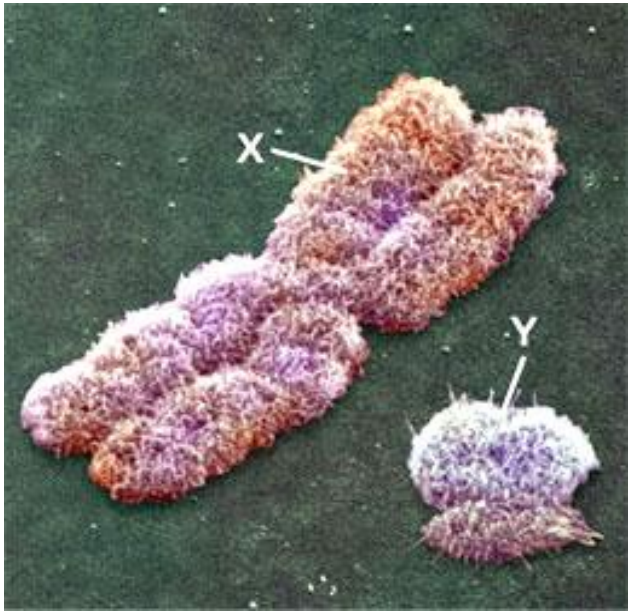


Medical Genetics

Inheritance
Pedigree Analysis
Genetic Testing

Dr. Menaka Hapugoda

Molecular Medicine Unit

Faculty of Medicine

University of Kelaniya

Contents

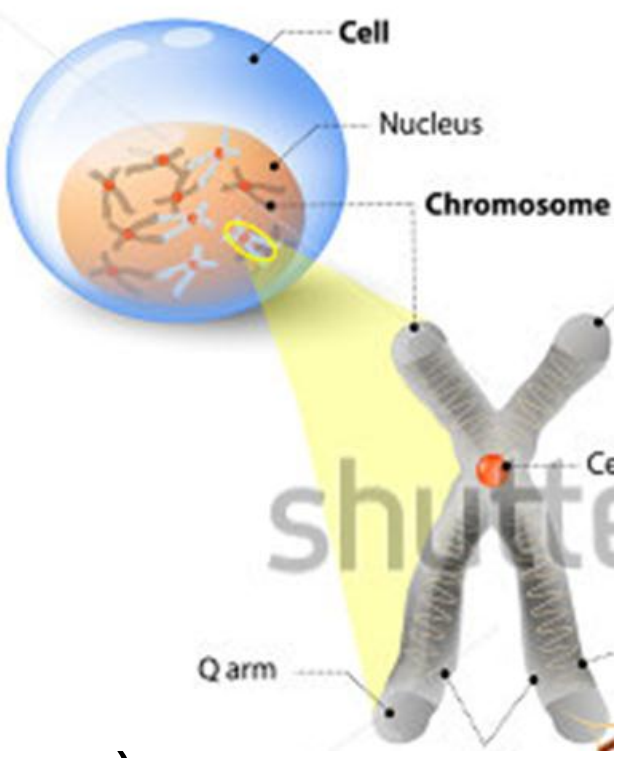
- Cellular distribution of chromosomes, genes, alleles
- Inheritance: Basics
- Definitions
  - Dominance and recessive conditions
  - Homozygosity
    Heterozygosity
    Hemizygosity
  - Genotype and phenotype
- Family Pedigrees
  - Pedigree charts
  - Recurrence risk
- Different patterns of inheritance
  - Autosomal recessive
  - Autosomal dominant
  - Sex-linked inheritance
    - X-linked recessive
    - X-linked dominant
- Deviations from simple Mendelian inheritance
- Non-Mendelian Inheritance:
  - Polygenic Inheritance
  - Mitochondrial Inheritance
- Genetic Testing
  - Newborn
  - Carrier
  - Predictive
- Basics of Genetic Counseling

Cellular distribution of chromosomes

genes and alleles

Cells

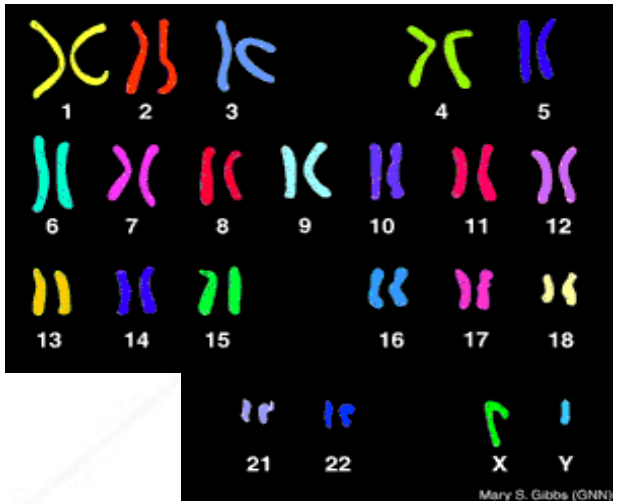
- Body contains trillions of cells
- Two types of basic cells
  - -Somatic cells
  - -Germ line cells/gametes

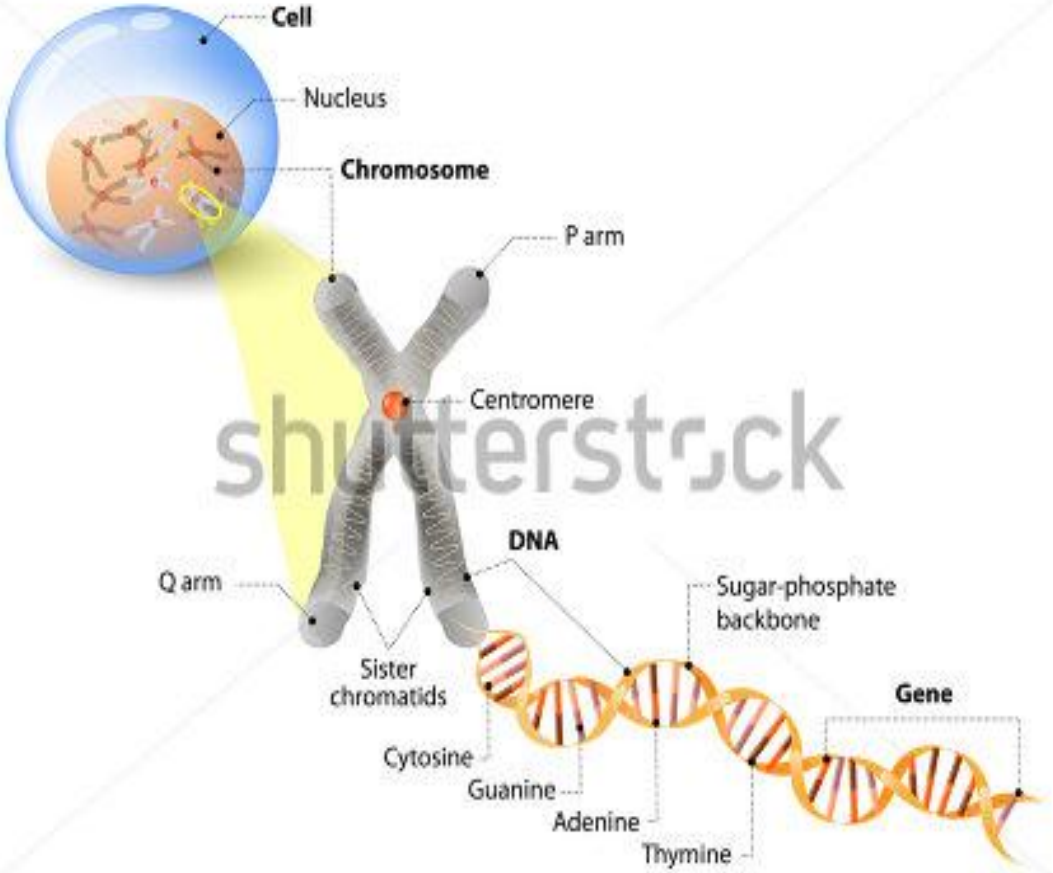


Chromosomes

- Inside the nucleus
- Somatic cells contain 46 chromosomes
  - 22 pairs of chromosomes (**autosomes**)
  - 2 **sex chromosomes** (X,Y)
  - Sex chromosomes determine the genetic basis of sex (XX = female, XY = male)
  - Normally only one x chromosome is active in females (random inactivation of second x chromosome)
- Germ line cells/gamete contains 23 chromosomes

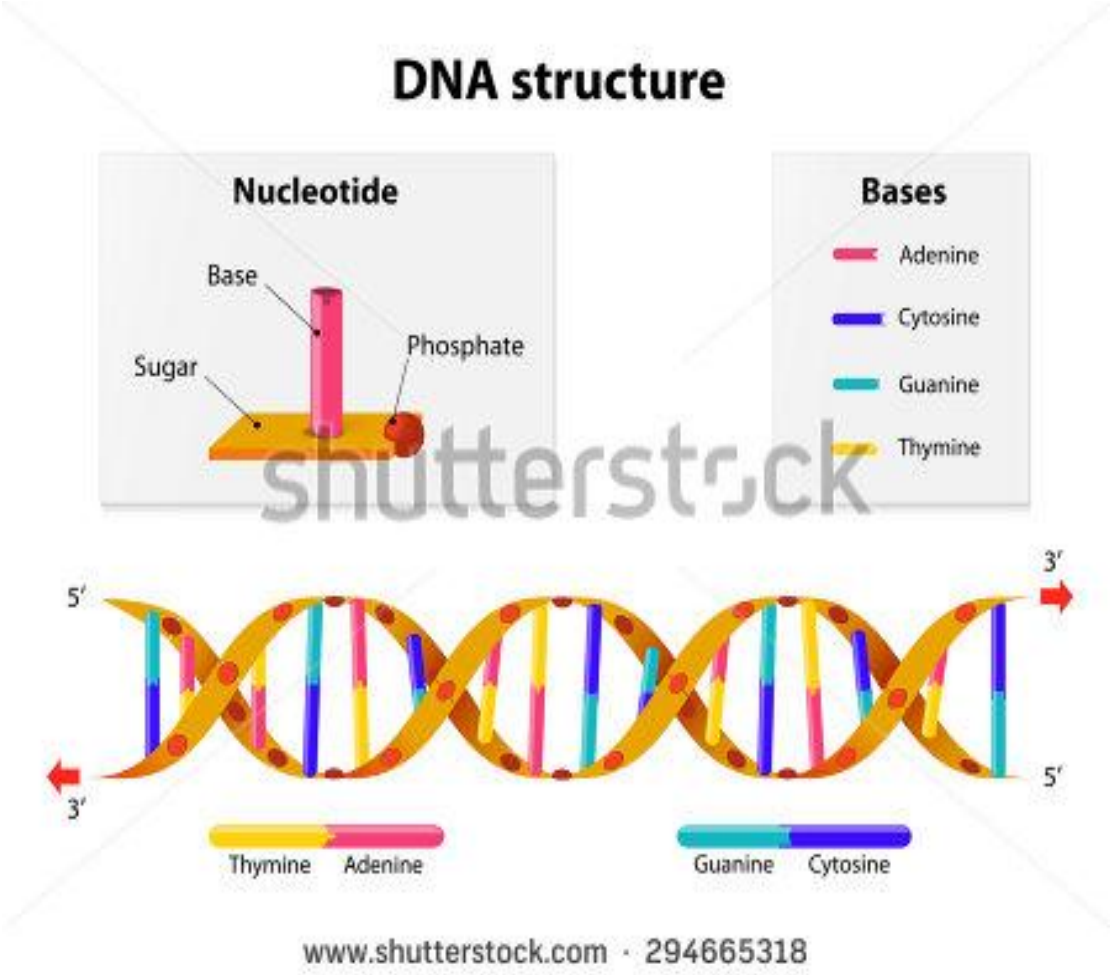
Cell


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
21
22
X
Y
Mary S. Gibbs (GNN)


Cell
Nucleus
Chromosome
P arm
Centromere
DNA
Q arm
Sugar-phosphate backbone
Sister chromatids
Gene
Cytosine
Guanine
Adenine
Thymine
shutterstock
www.shutterstock.com · 368406905

DNA

DNA

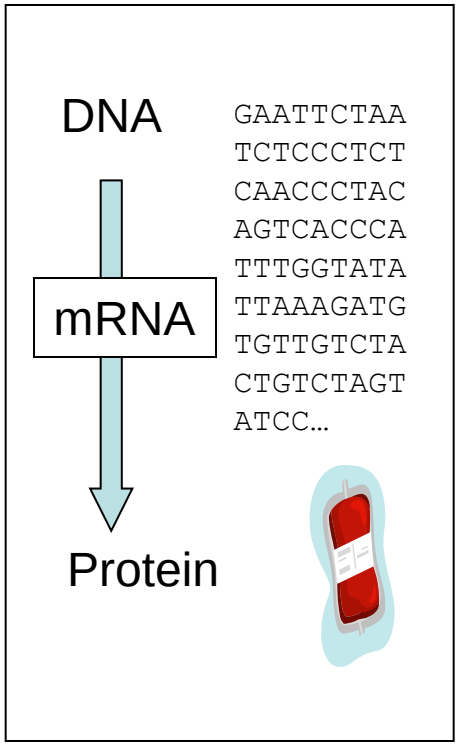


- Inside the chromosomes bound with proteins
- Polymers of nucleotides
- Nucleotides make two polynucleotide chains, run anti-parallel to each other and form DNA.

Genes

- Genes are arranged along 23 pairs of chromosomes in the cell nucleus

- A gene is a stretch of DNA



Activity 1

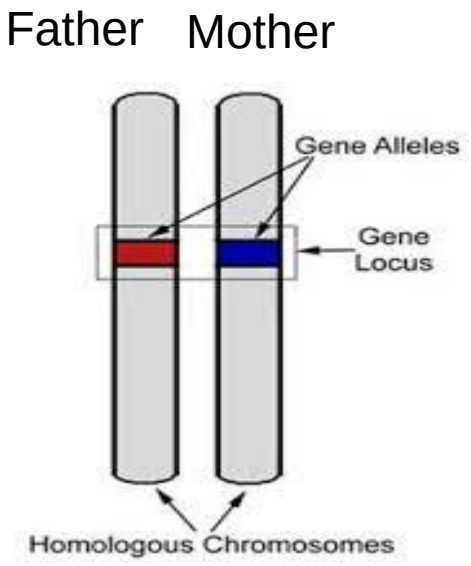
- Genetic information is contained in the genes
- Genetic information is inherited to the next generation through DNA

Activity 2

- Gene sequence determines the structure and function of a specific functional molecule (usually a protein)

- Genes work by specifying the amino acid sequence of a protein

Locus and alleles



Locus (plural loci)

Specific location/position of a chromosome

Allele

Gene/DNA sequence at a given locus

Alleles are alternate forms of a gene

One locus

Two alleles

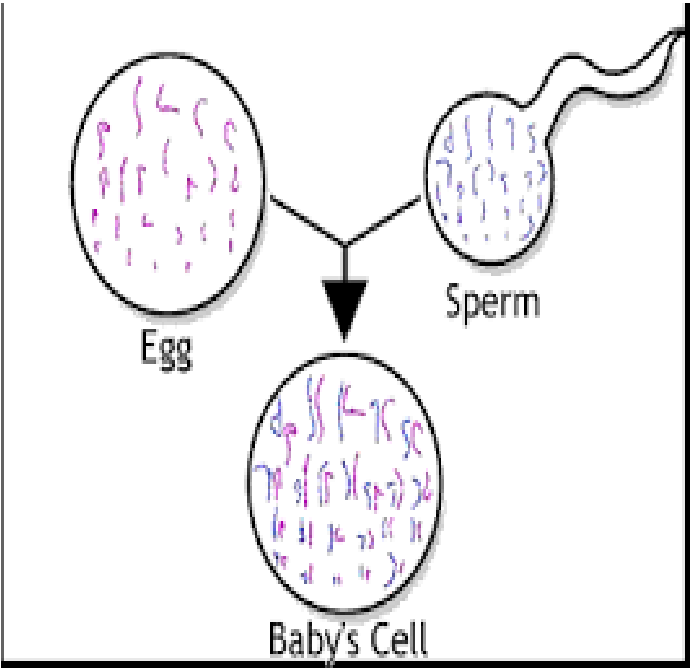
Inheritance: the basics

- Inheritance is the manner in which genes are transmitted through generations

- Inherited characteristics are determined by genetic information received from parents

- Genes are discrete units of inheritance that maintain the genetic characteristics when they are passed down.

Mother (23) **Father (23)**



Zygote (46)

One number of each chromosomal pair comes from mother and other is contributed by father.

Zygote multiplies and forms an individual.

In an individual,
50% genetic materials- Father
50% genetic materials- Mother

In an individual all cells have the same genetic materials.

Mendelian Inheritance

- Mendelian disorders/traits are defined as those that are the result of **a single mutant gene that has a large effect on phenotype**, and that are inherited in simple patterns resembling those described by Gregor Mendel.

- Mendelian traits are controlled by alleles of one locus (monogenic).

- Autosomal disorders

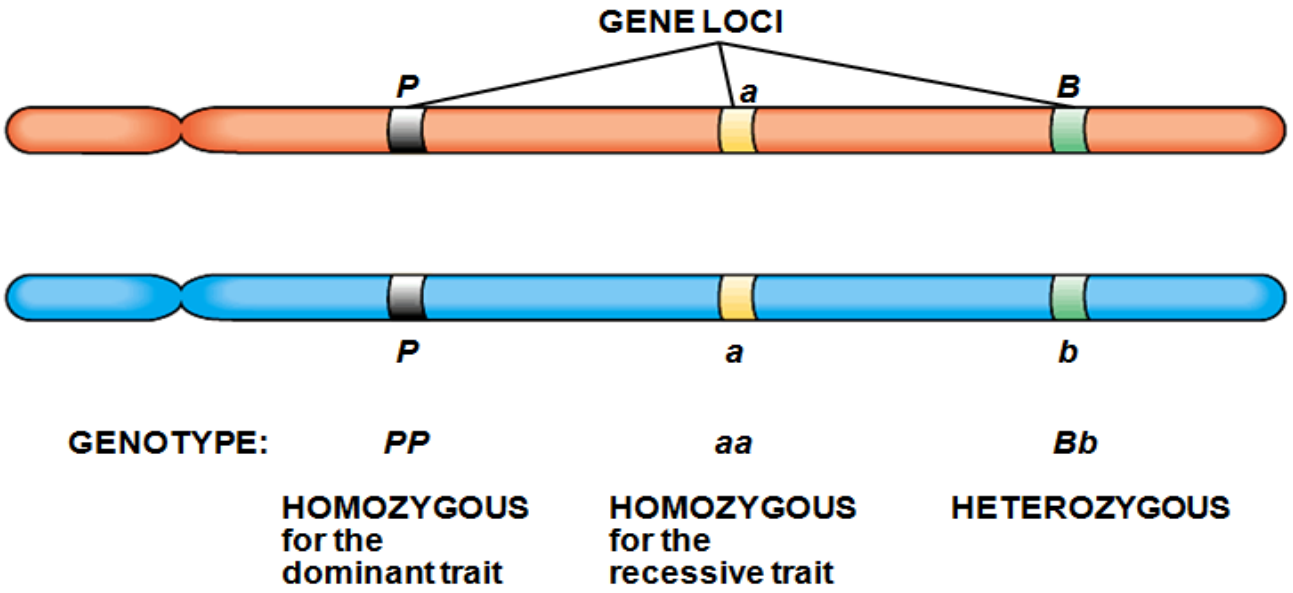
  If they are encoded by genes on one of the 22 pairs of autosomes

- X-linked disorders

  If encoded by a gene on the X chromosome

- More than 6000 human traits are known to be inherited by these principles: (OMIM databse www.ncbi.nlm.nih.gov/Omim/).

- Sometimes, different alleles can result in different observable phenotypic traits/disorders.
- Polymorphisms means the existence of multiple allelic forms at a specific locus.



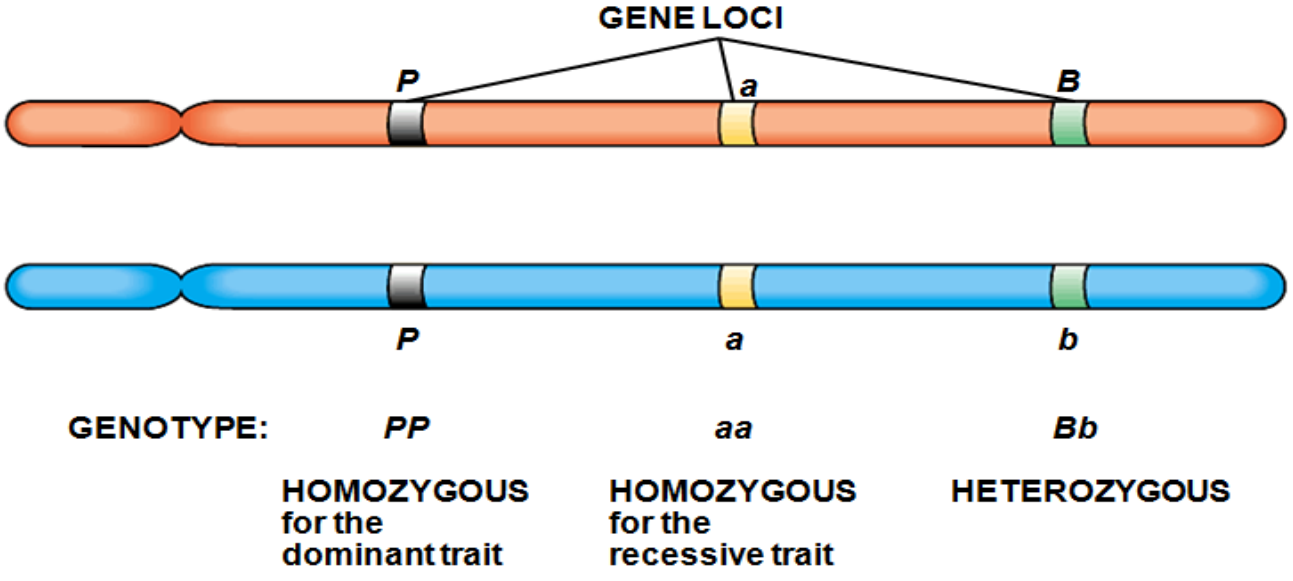
Definitions

- There are two alleles per each locus responsible for a single character.

- Dominant allele/gene- P (capital letters)
- Recessive allele/gene- p (simple letters)

- If both alleles at a locus are identical/similar, the individual is homozygous at that locus (AA or aa)

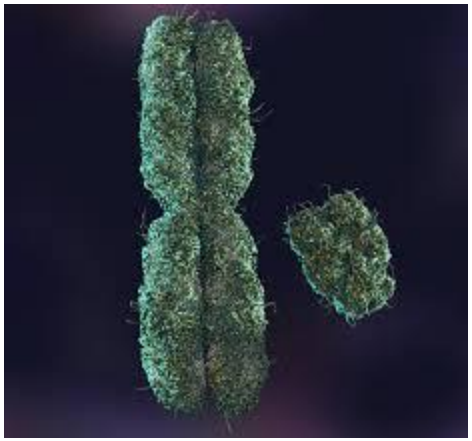
- If the alleles at a locus are different, the individual is heterozygous at that locus (Aa), first dominant, second-recessive



- If there is no second allele at a locus in a normal individual, that person is hemizygous.

- Males are hemizygous (one copy) for X linked genes (X linked genes are fully expressed who have only a single X chromosome)

X Y



- Genotype

  Genetic composition of an individual, often referring to the alleles at a specific genetic locus

- Phenotype

  Observable expression of the particular gene or the genes; is also influenced by environmental factors and interaction with other genes. May be biochemical, morphological, physiological, clinical or molecular trait

- Variable expression

  Different degrees of clinical expression given by the same genotype

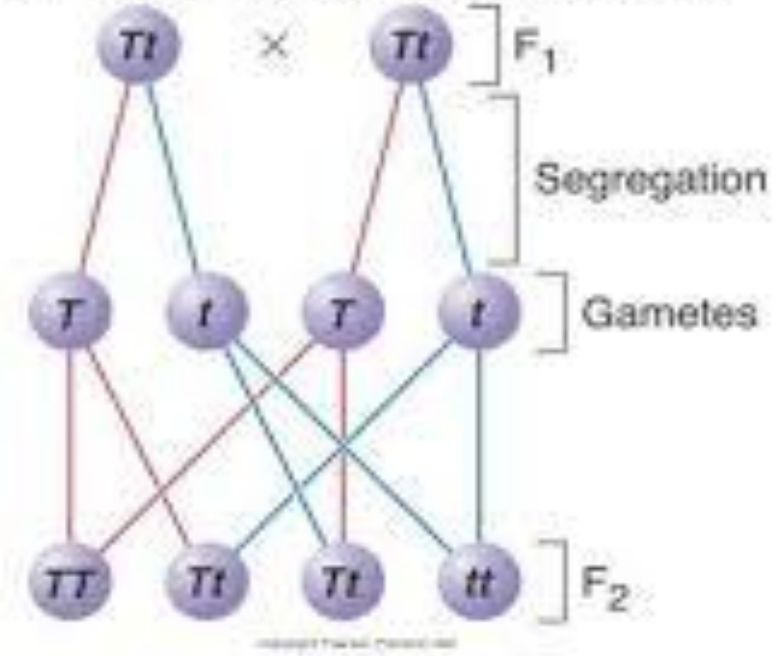
- Dominant conditions are those expressed in the homozygote (dominant) or heterozygote (individuals with one copy of a mutant allele and one copy of a normal allele.) – Aa or AA

- Recessive conditions are clinically manifest only in individuals homozygous for the mutant allele (carrying a “double dose” of an abnormal allele) – aa

- Sex – limited phenotype : the expression of a trait in only one of the sexes, due to anatomical differences (uterine or testicular defects)

- Sex-influenced phenotype: A phenotype which occurs in both males and females, but with different frequencies (male pattern baldness)

Alleles separate during gamete formation.



Understanding genotype and phenotype

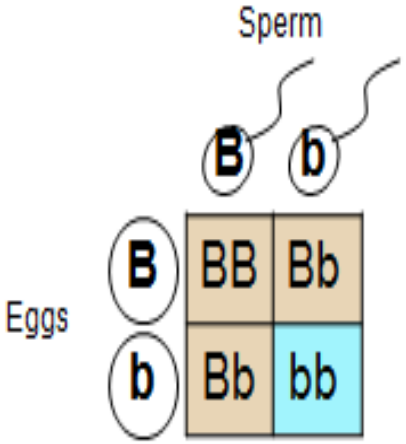
- Genotypes do not uniquely correspond to phenotypes
- Two different genotypes, a dominant homozygote and a heterozygote may have the same phenotype

  Example: Human eye color; consider union between a man and a woman with brown eyes and both are heterozygous for the trait

– Brown dominant: BB, Bb

– Blue recessive: bb

Punnett squares are the use of a grid that show reproductive events between individuals by using the possible parental gametes



- Genotypic ratio: the number of offspring with the same genotype

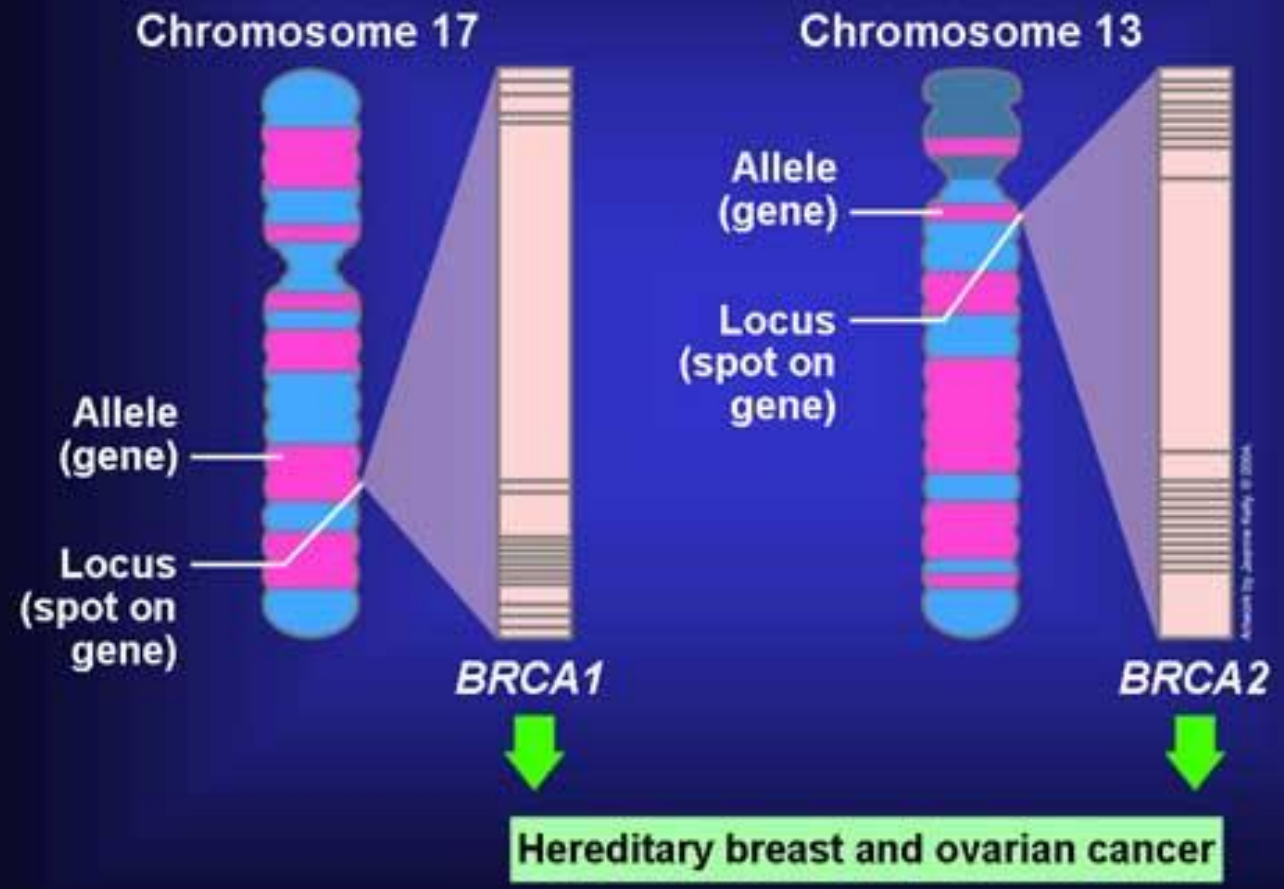
  BB: Bb: bb
  1 : 2 : 1

- Phenotypic ratio: the number of offspring with the same outward appearance

  3 Brown eyes: 1 blue eyes

- Same genotype may produce different phenotypes in different environments
- Autosomal recessive disease phenylketonuria (PKU) seen in about 1 in 10,000 white births
- Mutations for gene encoding enzyme phenylalanine hydroxylase – makes it unable to metabolize the aa phenylalanine
- PKU babies on average lose 1-2 IQ points per week during first year of life if not treated
- Low Phenylalanine diet within 1 month of birth leads to normal IQ and development!!

Different Locus, Different Allele, Same Phenotype



Family pedigrees

- Refers to a chart of family's history showing relationships and reproductive events.

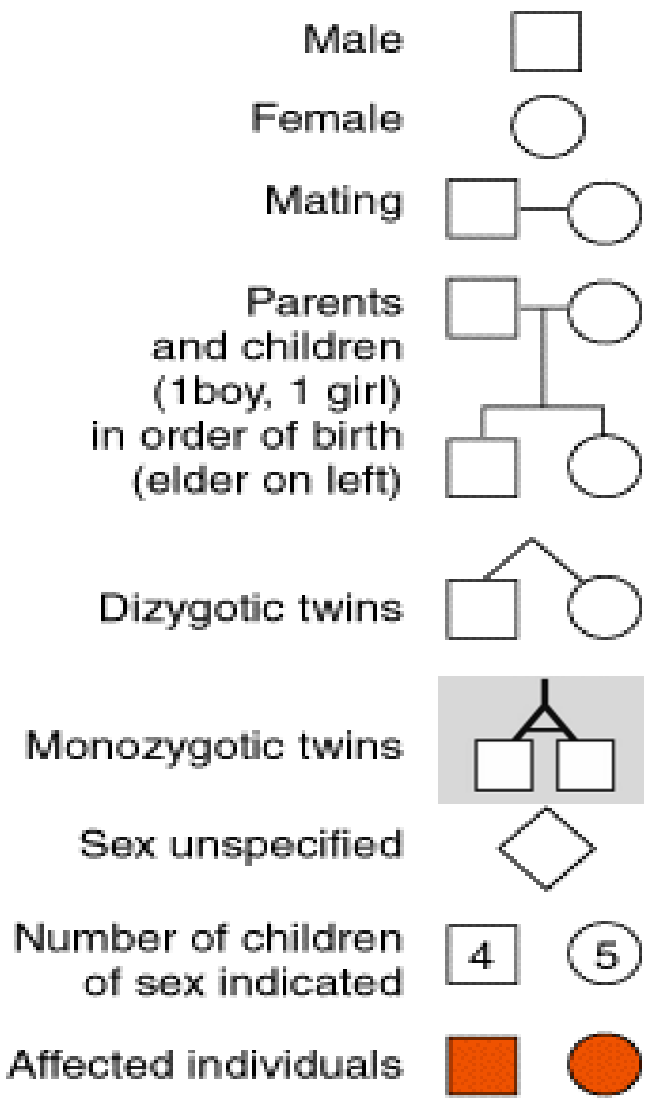
- In humans, pedigree analysis is an important tool for studying inherited diseases shows which family members are affected with a genetic disease and which are unaffected.

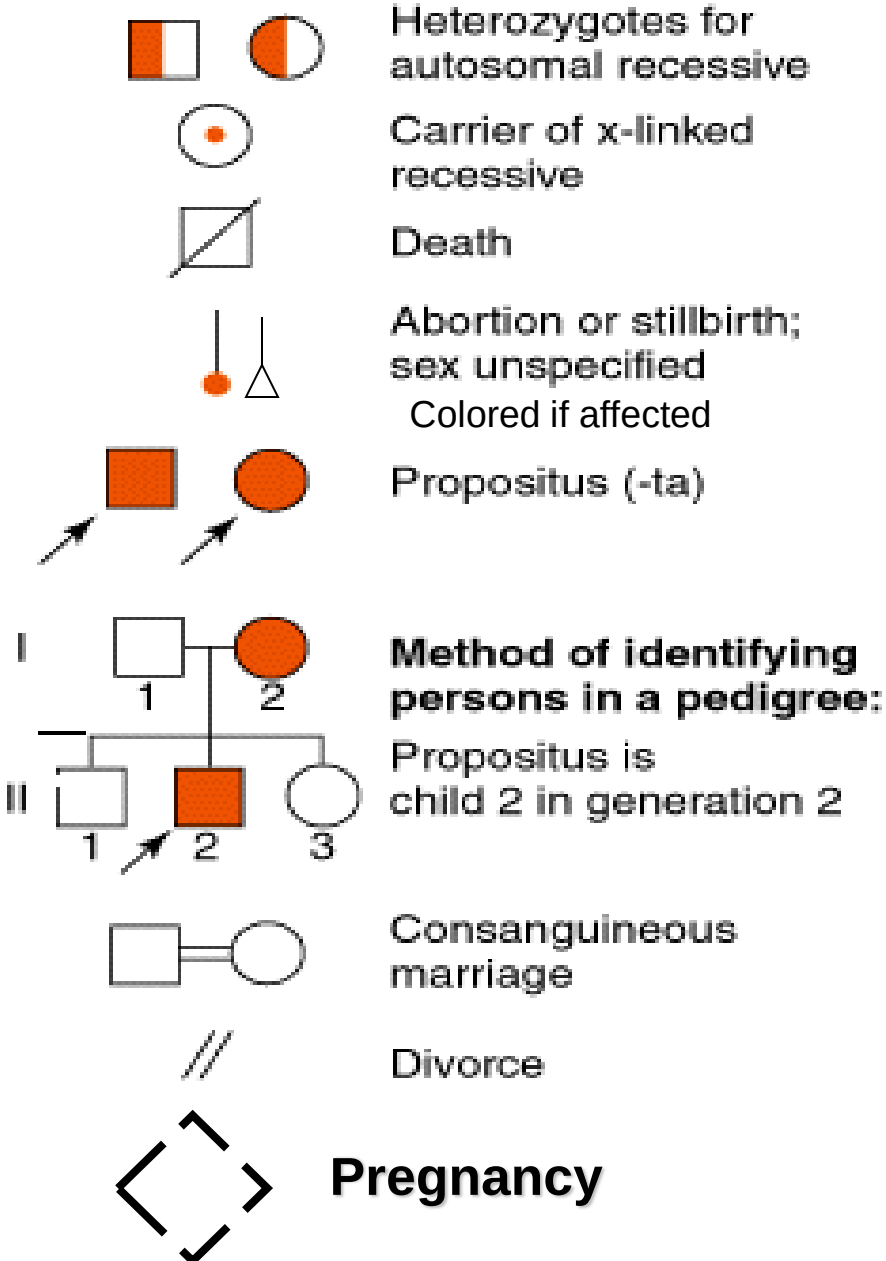
- Pedigree analysis using family trees can be used to:

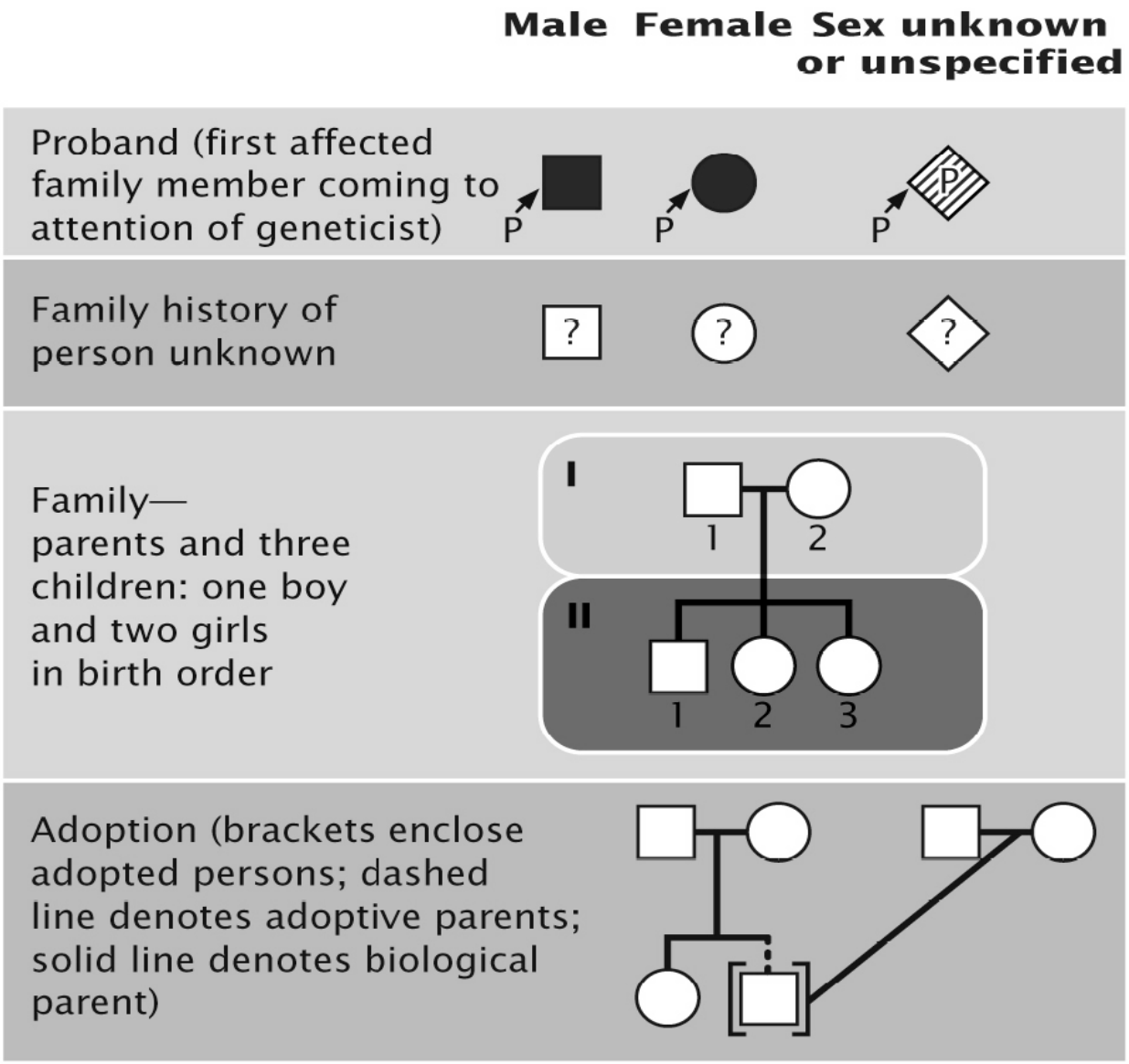
  – Figure out the genetic basis of a disease from its inheritance pattern

  – Predict the risk of a disease in future children in a family (genetic counseling)

Symbols


Male
Female
Mating
Parents and children (1boy, 1 girl) in order of birth (elder on left)
Dizygotic twins
Monozygotic twins
Sex unspecified
Number of children of sex indicated
4
5
Affected individuals


Heterozygotes for autosomal recessive
Carrier of x-linked recessive
Death
Abortion or stillbirth; sex unspecified
Colored if affected
Propositus (-ta)
I
1
2
II
1
2
3
Method of identifying persons in a pedigree:
Propositus is child 2 in generation 2
Consanguineous marriage
Divorce
Pregnancy



The proband may also be called the index case, propositus (if male), or proposita (if female).

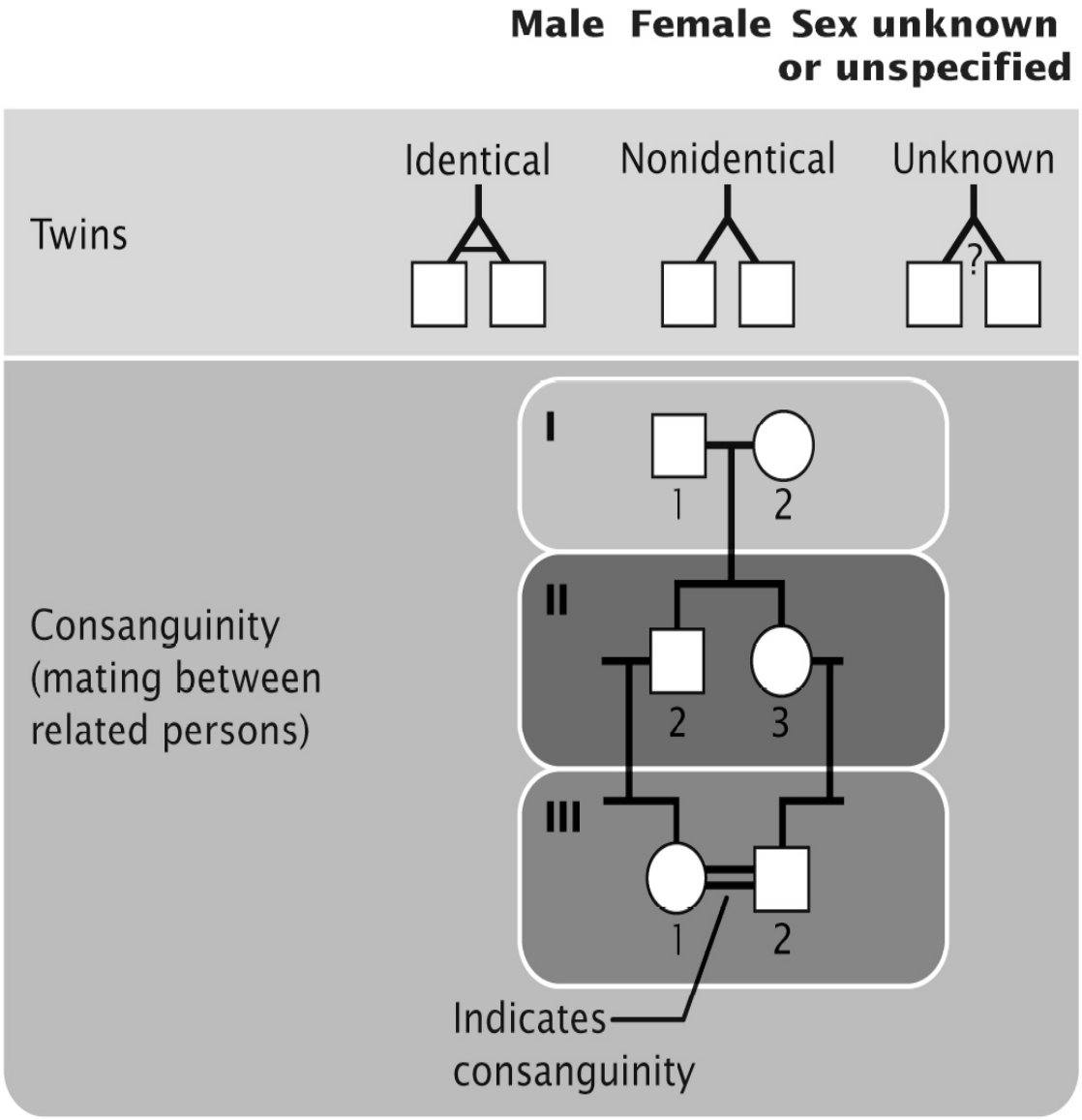
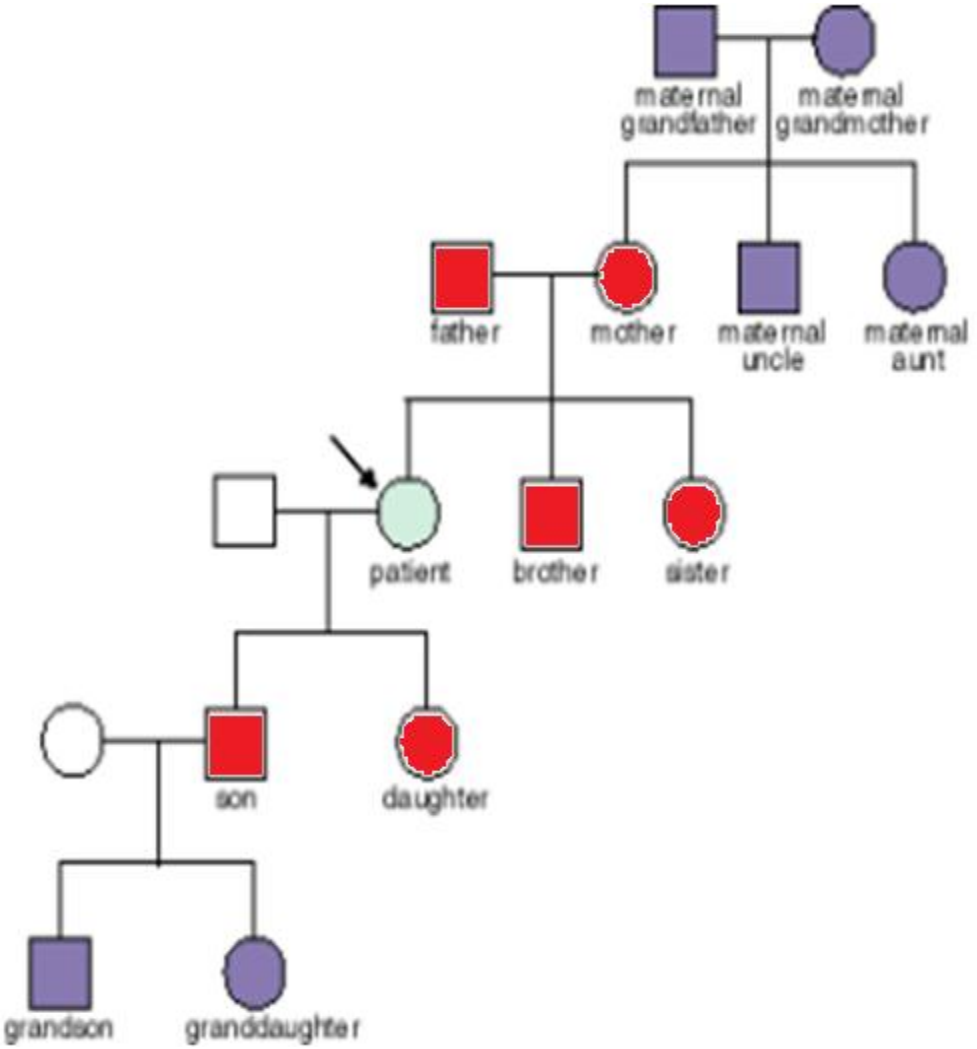


Fig_06-02-3 *Genetics, Second Edition* © 2005 W.H. Freeman and Company

New mutations may complicate pedigree analysis.

Pedigree relationships

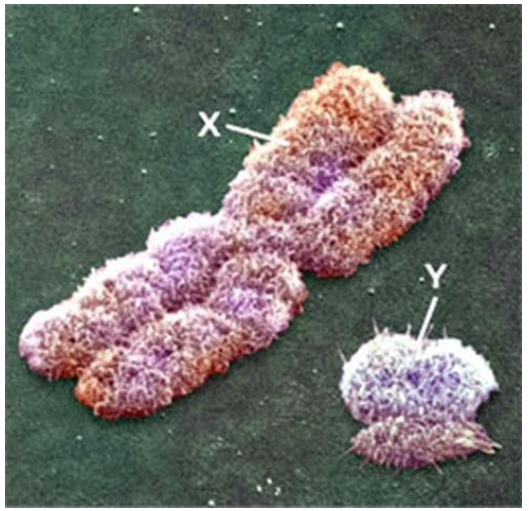
- **A basic pedigree usually include 3 generations of the consultand's (patient)**
- **First-degree relative**: A mother, brother, sister, father, son or daughter. (parents, children, siblings) –in Red
- **Second-degree relative**: An aunt, uncle, grandmother, grandfather or grandchild. – in Purple
- **Third-degree relative**: cousins
- **Proband:** First person brought to medical attention



Different patterns of inheritance

- Monogenic disorders/traits (only in one locus with two alleles)
  - Autosomal Inheritance
    - Recessive
    - Dominant
  - Sex-linked inheritance
    - X-linked
    - Y-linked

    (Since the Y chromosome is relatively small and contains very few genes, there are relatively few Y-linked disorders: eg. Male infertility)

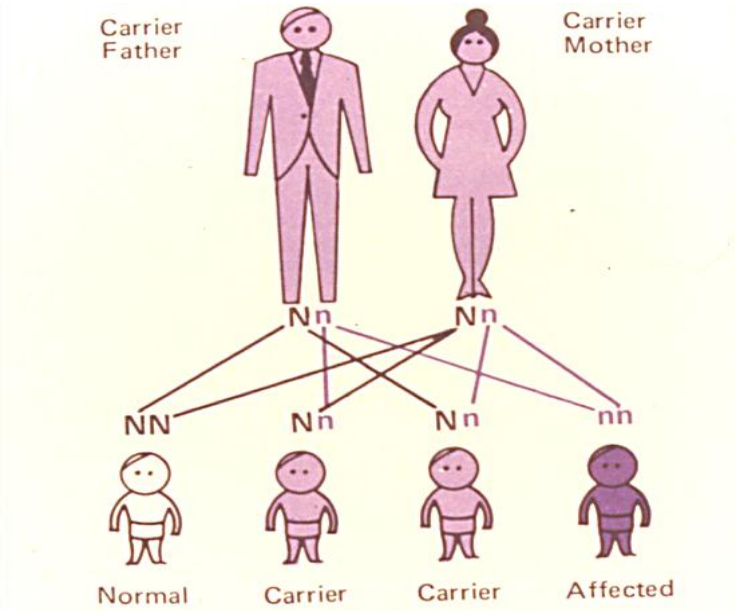


- Complex patterns
  - Multi-factorial inheritance
  - Polygenic Inheritance
- Mitochondrial inheritance

Autosomal Recessive Inheritance

- Fairly rare in populations- affected gene can be on any autosome
- Two copies of a disease allele (from each parent) are required for an individual to be affected or susceptible to expressing the phenotype.
- Typically, the parents of an affected individual are not affected, but are gene carriers or heterozygotes.
- Therefore, usual mating that results in the disease: Nn x Nn
  (Carrier parents-normal phenotype)
- Affected individuals- homozygous for the disease allele (nn)
- Individuals who inherit a single mutant allele (heterozygous) are not affected by the disease are carriers and may pass their mutant allele to their children
- Heterozygous carriers (Nn) for recessive genes are much more common than affected homozygotes (nn)

Autosomal recessive inheritance eg



N= normal allele, n = disease allele

Homozygous dominant = normal (NN)

Heterozygous dominant = normal phenotype, carrier (Nn)

Homozygous recessive = affected (nn)

Rec. risk: Probability that subsequent children will be born with the same disease - regardless of how many affected or unaffected children are born

- With each pregnancy of carrier parents

❖ There is 25% chance the offspring will inherit two copies of the disease allele, and will therefore have the phenotype.

❖ There is a 50% chance that the offspring will inherit one copy of the disease allele and will be a carrier.

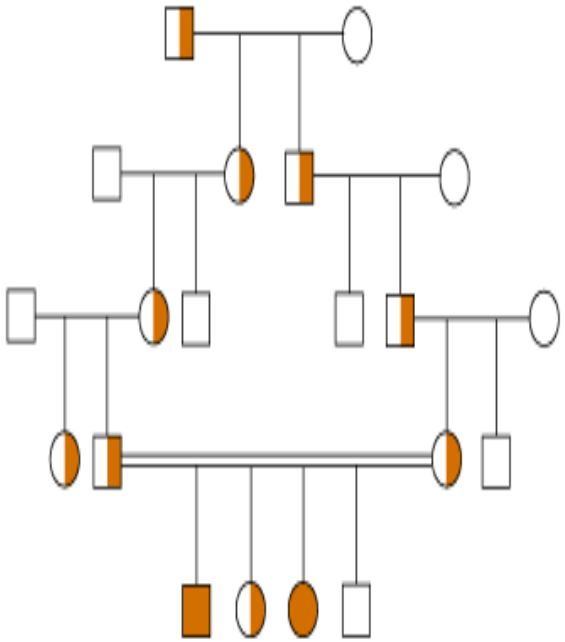
❖ There is a 25 % chance that the offspring will inherit no copies of the disease allele and will not express the phenotype or be a carrier. This individual would not be at risk for passing the disorder on to his/her offspring.

❖ For two carrier parents, the recurrence risk to have an affected child is 25%.

❖ 75% chance for normal phenotype offspring (50% carriers)

❖ The phenotypically normal siblings of an affected child have 2/3 chance of carrying the recessive allele.

Autosomal recessive pedigree chart –Features



- The proportion of affected males should be equal to the proportion of affected females in a given population (No sex bias).
- Disease is usually seen in one or more siblings but not in earlier generations
- Trait “skip” generations – trait is hidden in heterozygous carriers (Because most reproductive events are with homozygous normal individuals, no offspring are affected)
- Consanguinity is present more often in pedigrees involving AR inheritance than with other types of inheritance, because the individuals are descendants of the same ancestors and are, therefore, more likely to carry the same gene mutations.

Family history

- Because the risk is only 1 in 4 that a child will be born to two carrier parents, and because most families are small, most affected individuals will appear to be sporadic.

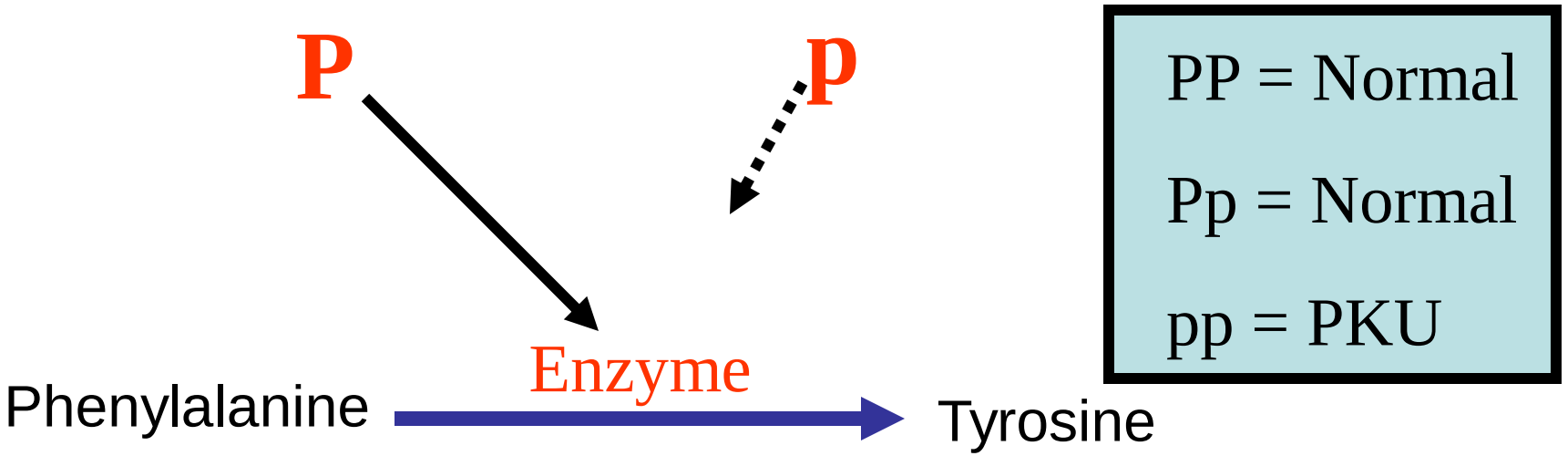
- Autosomal traits may be recognized by the occurrence in affected siblings, parental consanguinity or by the demonstration of a partial defect in heterozygotes (enzyme levels).

- Genetic Isolation
  - Small populations of individuals with a common genetic background may have increased risk of recessive disease
  - Ashkenazi :Tay-Sachs, Gaucher Disease
  - Finnish: Congenital Chloride-Losing Diarrhea

SOME AUTOSOMAL DISORDERS IN HUMANS

Disorder	Major Symptoms	Incidence
Recessive disorders		
Albinism	Lack of pigment in skin, hair, and eyes	$\frac{1}{22,000}$
Cystic fibrosis	Excess mucus in lungs, digestive tract, liver; increased susceptibility to infections; death in infancy unless treated	$\frac{1}{1,800}$ Caucasians
Galactosemia	Accumulation of galactose in tissues; mental retardation; eye and liver damage	$\frac{1}{100,000}$
Phenylketonuria (PKU)	Accumulation of phenylalanine in blood; lack of normal skin pigment; mental retardation	$\frac{1}{10,000}$ in U.S.and Europe
Sickle-cell disease (homozygous)	Sickled red blood cells; damage to many tissues	$\frac{1}{500}$ African Americans
Tay-Sachs disease	Lipid accumulation in brain cells; mental deficiency; blindness; death in childhood	$\frac{1}{3,500}$ Jews from central Europe

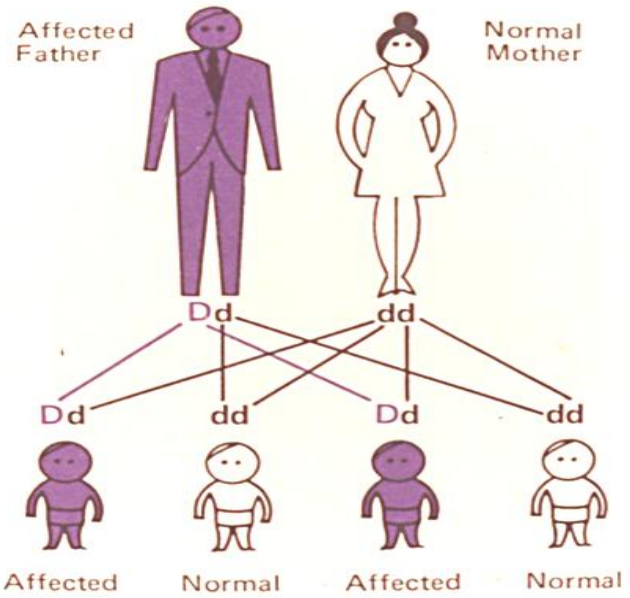
- *Phenylketonuria* (PKU)
  - affected individuals lack an enzyme needed for the normal metabolism of *phenylalanine*, coded by an allele on chromosome 12.
  - Newborns are regularly tested for elevated phenylalanine in the urine.
  - If the infant is not put on a phenylalanine-restrictive diet in infancy until age seven when the brain is fully developed, brain damage and severe mental retardation result.



Autosomal Dominant Inheritance

- More than 3700 Autosomal Dominant traits (mostly diseases) are known
- Each rather rare in population - common ones with gene frequencies of about 0.001 gene can be on any autosome.
- Only one copy of a disease allele is necessary for an individual to be susceptible to expressing the phenotype, and therefore the trait is dominant.
- Unless a new mutation has occurred, all affected individuals will have at least one parent who carries the disease allele.
- Affected individuals- heterozygous for the mutant allele (Dd)

Autosomal Dominant inheritance



- For matings of an affected heterozygote with a normal homozygote:
- With each pregnancy, there is a 50% chance that the offspring will inherit the disease allele.
- Thus, on average, half of the children will be heterozygous (Dd) and express the disease and half will not express the disease (dd)

D = disease allele

d = normal allele

Heterozygous dominant = Affected (Dd)

Homozygous recessive = normal (dd)

Homozygous dominant is often lethal (DD) eg: Achondroplasia

- ❖ 50% chance for normal phenotype offspring
- ❖ 50 % chance for affected offspring **(recurrence risk)**
- ❖ Examples: Myotonic muscular dystrophy and Huntington disease

Autosomal Dominant Pedigree – Features

Polydactaly, the presence of an extra digit next to the fifth digit can be inherited as an AD trait (If 'D" symbolizes the gene for polydactaly, and "d" the normal gene, the pedigree below will demonstrate important characteristics of AD inheritance

• Across a population, the proportion of affected males should be equal to the proportion of affected females.

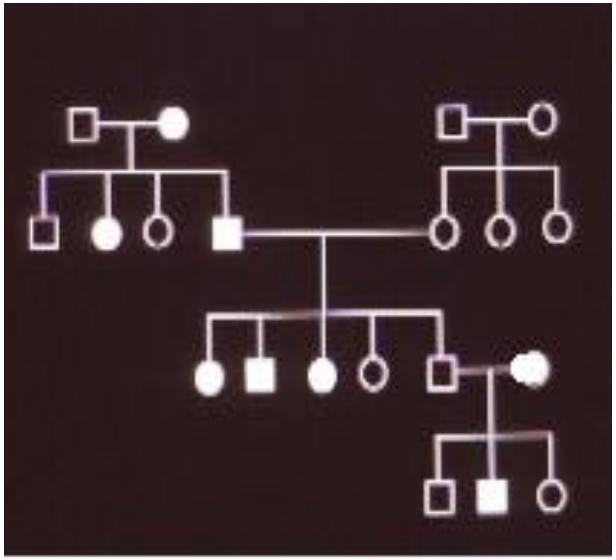
• Males and females are equally likely to transmit trait to their offspring

• No skipping of generations: if an individual has polydactaly, one parent must also have it

• Vertical transmission pattern – transmission of the disease allele from parent to offspring and therefore, disease phenotype is usually seen in one generation after another

• If neither parent has the trait, none of the children has it

• Father to son transmission may be observed



• Offspring of one affected (Dd) and one normal (dd) parents:
– 50% affected (Dd) – recurrence risk
– 50% normal offspring (dd)

Exceptions to Classical Dominant Inheritance

- True/Complete dominance – the presence of one allele (dominant) completely masks the expression of another (recessive); the recessive allele is expressed only when two copies are present in the genotype (Aa & AA same phenotype) – Huntington disease

1. Reduce/non penetrance (failure of the dominant condition to manifest – caused by other Genes /chance/ environment)

2. Variable expression: Expression of different intensities in clinical symptoms (due to environmental factors or interactions of other modifier genes)

3. Delayed-onset conditions: with manifestations occurring late in life (age-related penetrance) which might be due to slow progression of manifestations

- not possible until later in life to determine whether an individual carries a mutation
- Some examples include:
  - Huntington Disease - Polycystic kidney disease
  - Hemochromatosis - Familial Alzheimer disease
  - AD form of breast cancer

Penetrance and Expressivity

Penetrance

Refers to all or none expression of a genotype

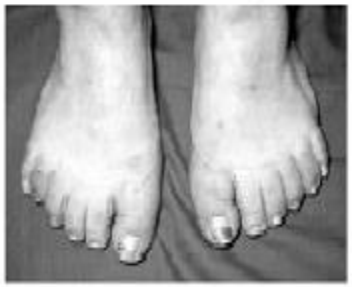
Expressivity

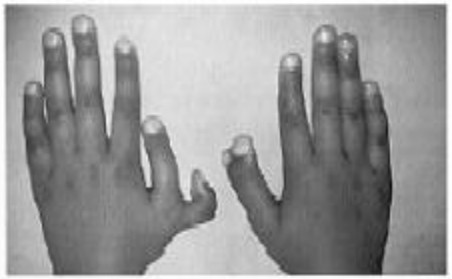
The DEGREE to which a phenotypic characteristic is expressed

Due to the effects of other genes, or to environmental factors, that can alter the effect of a particular gene

Expressivity vs Penetrance:

Example: Human Polydactyly





Complete penetrance

- everyone who inherits the disease causing alleles has the phenotype

Incomplete penetrance

- some individuals do not express the phenotype even though they inherit the alleles

- If 80 of 100 people who have the dominant allele express the phenotype, the allele is 80% penetrant (eg: polydactyly)

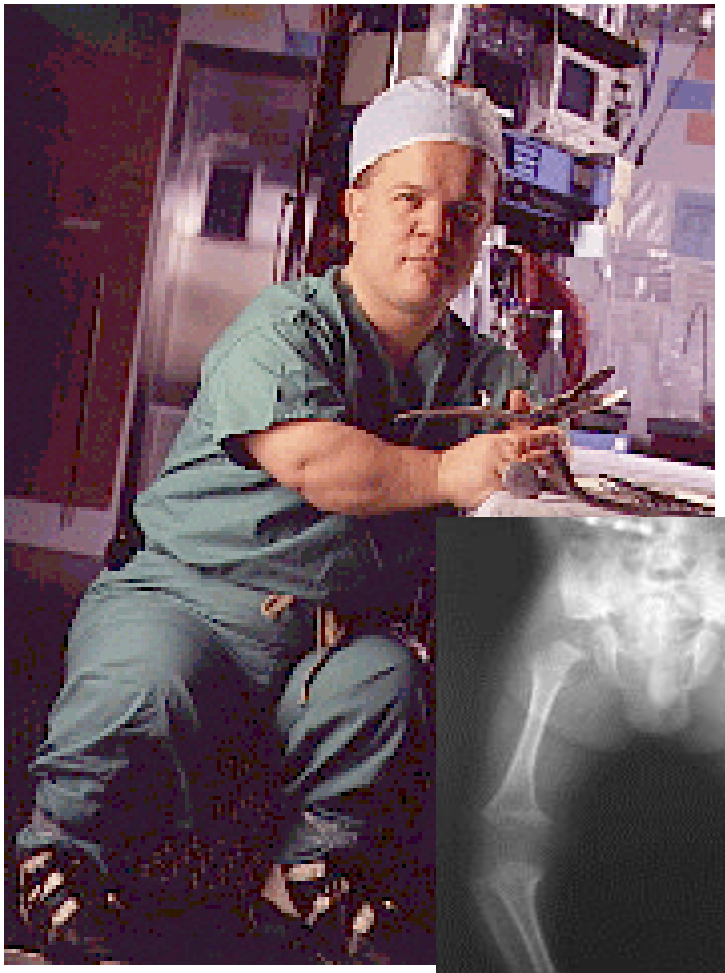
Variable expression

- A phenotype is variably expressive if the symptoms (or characteristics) vary in intensity between individuals.

- two extra digits versus three extra digits in polydactyly

Autosomal Dominant Disorders

- Marfan's Syndrome
- Huntington's
- Osteogenesis imperfecta
- Neurofibromatosis
- Retinoblastoma
- Multiple polyposis of colon
- Achondroplasia (skeletal disorder causing dwarfism)



Some A Dominant disorders are usually more severe in affected homozygotes (DD) than in heterozygotes (Dd) (homozygous achondroplasia and marfan syndrome)

Achondroplastic dwarfs - heterozygotes have almost normal life span
Homozygotes are severely affected and usually die in infancy of respiratory failure

Have short arms and legs relative to other body parts

Huntington disease

- Adult-onset, autosomal dominant inherited disorder associated with cell loss within a specific subset of neurons in the basal ganglia and cortex.

- Affected individuals experience progressive degeneration of the nervous system.

- Most patients appear normal until middle age.

- The genetic basis of HD is the expansion of a cysteine-adenosine-guanine (CAG) repeat encoding a polyglutamine tract in the *N* -terminus of the protein product called huntingtin.

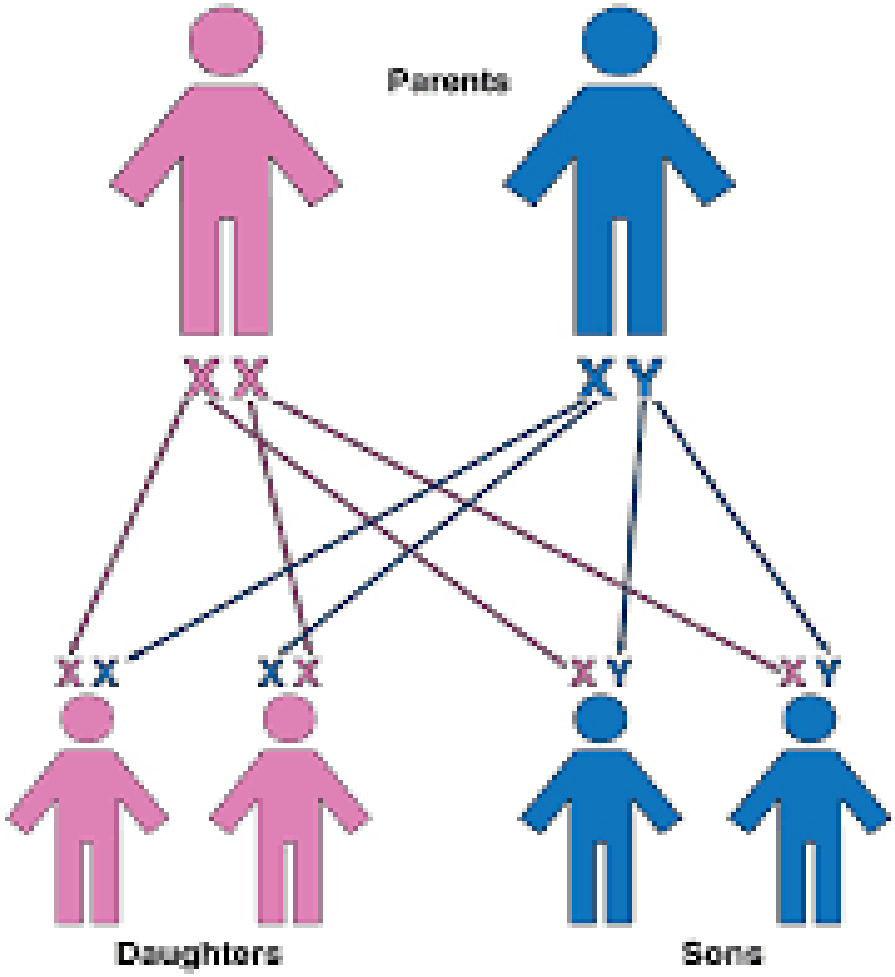
- In affected individuals, the gene coding for the protein huntington contains many more repeats of glutamines than normal.

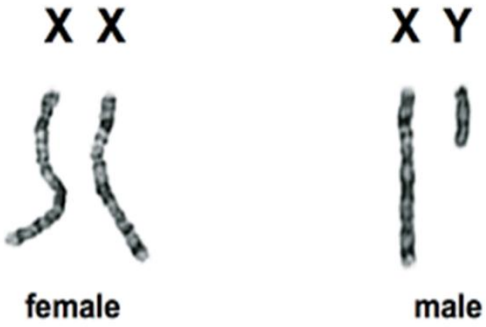
SOME AUTOSOMAL DISORDERS IN HUMANS

Disorder	Major Symptoms	Incidence
Dominant disorders		
Achondroplasia	Dwarfism	$\frac{1}{25,000}$
Alzheimer's disease (one type)	Mental deterioration; usually strikes late in life	Not known
Huntington's disease	Mental deterioration and uncontrollable movements; strikes in middle age	$\frac{1}{25,000}$
Hypercholesterolemia	Excess cholesterol in blood; heart disease	$\frac{1}{500}$ are heterozygous

X-linked inheritance: General characteristics

- Traits are controlled by the genes on the X chromosomes
- X-linked mutant genes are fully expressed in males, who have only a single X-chromosome (hemizygous for X-linked genes)
- Fathers transmit their Y chromosome to their sons, thus there is no male to male transmission of x-linked genes.
- Only one of the two X-chromosomes in human female somatic cells is genetically active. One of the two X chromosomes is randomly and permanently inactivated early in embryogenesis by a process called “lyonization”.
- Because of this random X-inactivation, X-linked traits are variably expressed in female heterozygotes.


Parents
X X
X Y
X X
X X
X Y
X Y
Daughters
Sons


X X
X Y
female
male

X-Inactivation (LYONIZATION)

Females have two X chromosomes, while males have one X and one Y chromosome.

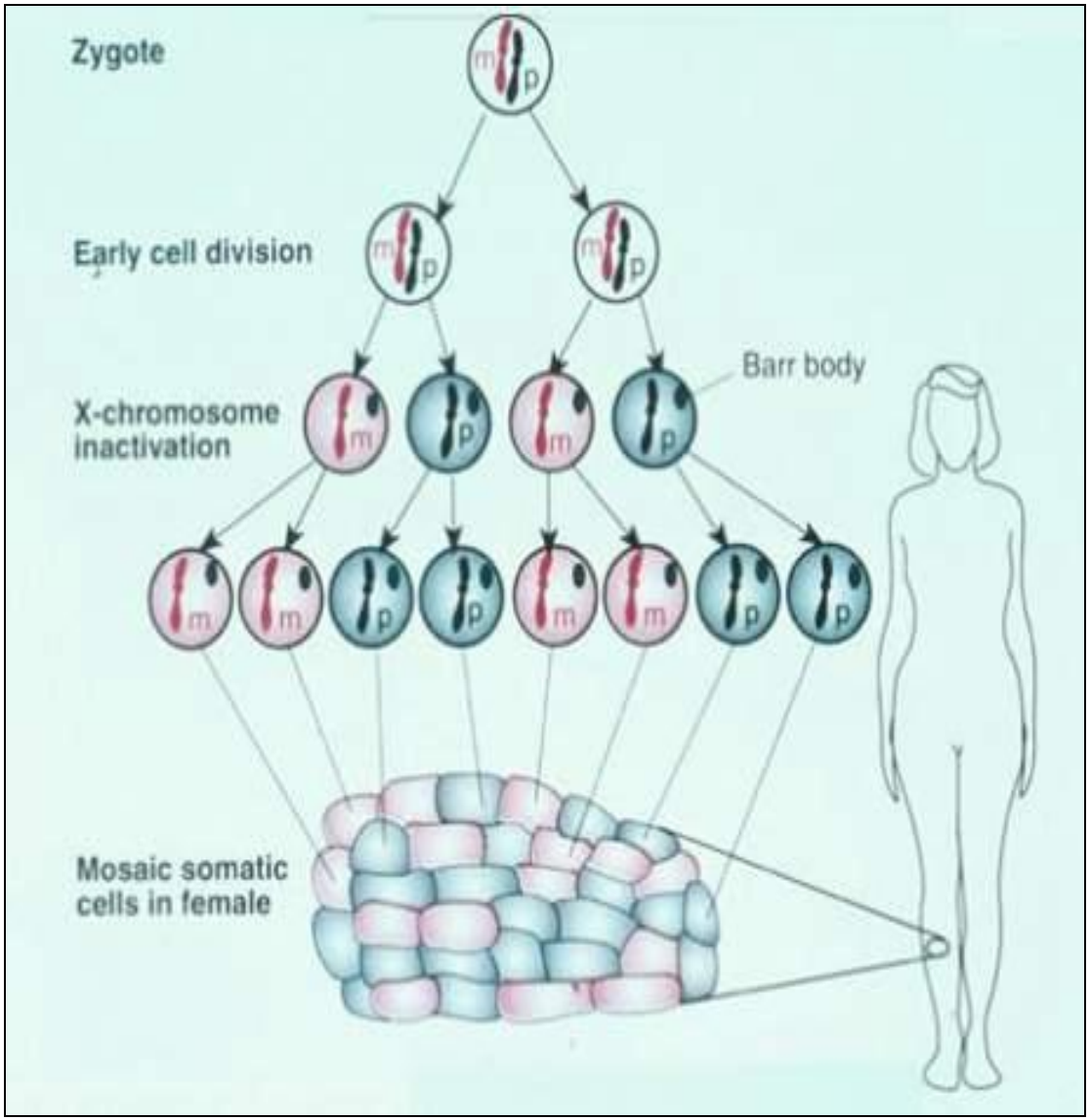
Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in cells other than egg cells.

This phenomenon is called X-inactivation or Lyonization (named after Mary Lyon, who discovered X inactivation)

Inactivated chromosome becomes a “Bar Body”

Why?
To provide gene-dosage compensation in females.

Inactivation ensures that females, like males, have one functional copy of the X chromosome in each cell and will produce X-linked gene products in quantities roughly similar to those in males



• Because X-inactivation is random, in normal females the X chromosome inherited from the mother is active in some cells, and the X chromosome inherited from the father is active in other cells.

• Clonal process

• Results in variable expression of heterozygote (X^A X^a)

• Mosaicism: The presence of two or more genotypically distinct cell lines in an individual.

X-linked recessive (XR)

One trait, 2 alleles

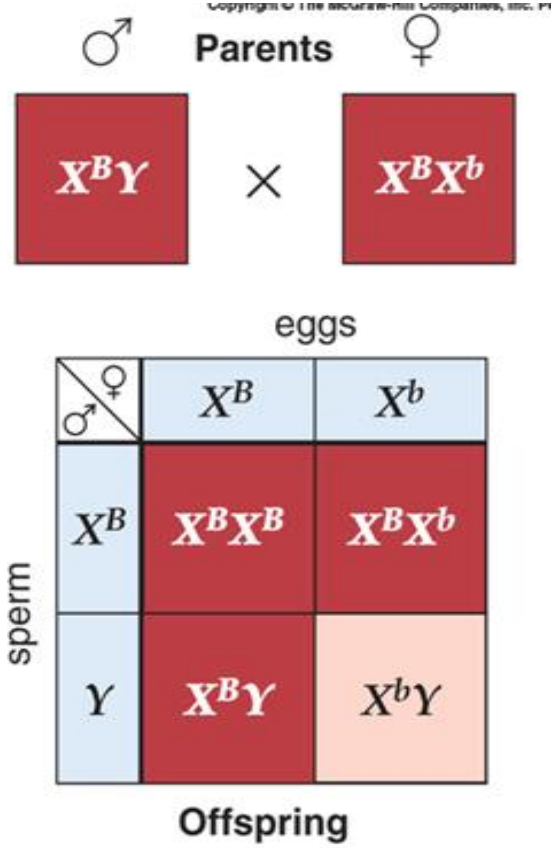
A = dominant normal allele

a = recessive abnormal allele

- Homozygous dominant = normal female (X^AX^A)
- Heterozygous dominant = normal female carrier (X^AX^a)
- Homozygous recessive = affected female (X^aX^a)
  Females express it only if they get a copy from both parents (trait is Recessive in females)
- Hemizygous dominant = normal male (X^AY)
- Hemizygous recessive = affected male (X^aY)
  Expressed in males if present (trait is Dominant in males)

- Must consider which parent has the abnormal gene when assessing risk

X-linked recessive Inheritance

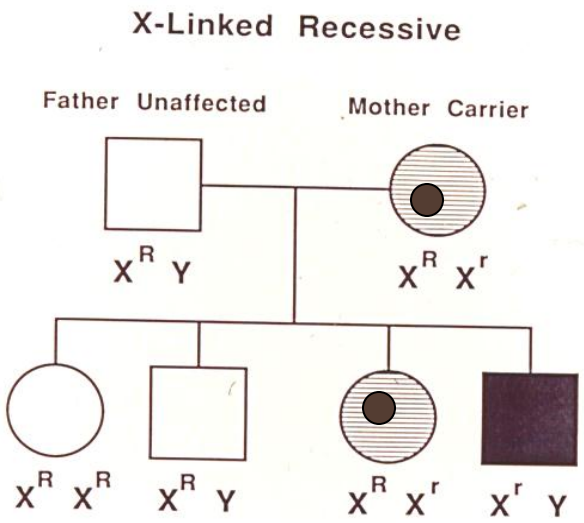


- The disorder is transmitted by healthy heterozygous female carriers.
- Mating between a heterozygous normal mother (carrier) and a normal father
- Only males are affected
  25 % risk for an affected male
  25 % risk for a normal male
  25 % risk for a carrier female
  25 % homozygous normal female

Total risk for an affected child is 25% (Recurrence risk)

- Males and females NOT equally affected

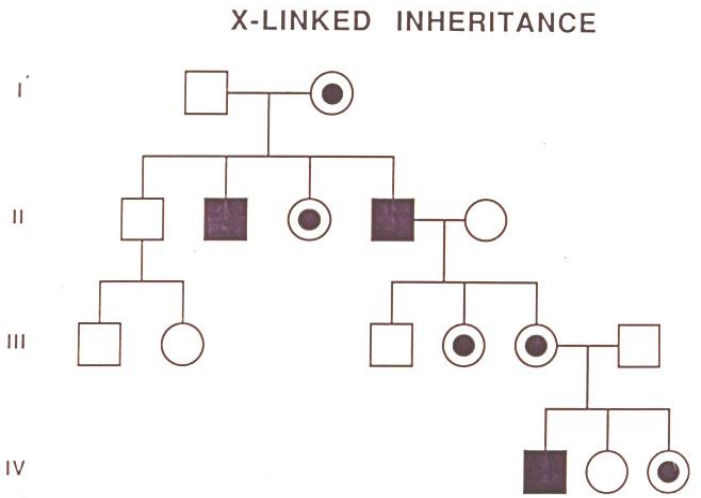
X-linked Recessive Pedigree



- "Criss-cross" inheritance pattern –trait skips generations
- Female carriers pass the character to affected sons
  - The sons of a carrier female have 50% risk of being affected or unaffected
- Female carriers produce carrier daughters
- Transmission through normal females producing affected males
- This type of pedigree is said to show "diagonal"or "knight's move" pattern of transmission.

X-linked Recessive Pedigree

- Another typical mating is affected male with homozygous normal female.
- X^aY and X^AX^A
- Offspring
  - $X^A\ X^a$ $X^A\ X^a$ (all females obligate carriers)
  - X^AY, X^AY (all males normal)



- ❖ No male to male transmission
- ❖ Affected fathers do not pass the trait to their sons-b'se X linked
- ❖ All daughters of affected males are carriers

XR Disorders

(about 70 human pathological conditions)

- Duchenne's Muscular Dystrophy
- Hemophilia
- Hunter's Syndrome
- Lesch-Nyhan Syndrome
- Pyruvate dehydrogenase deficiency
- Glucose-6-Phosphate Dehydrogenase deficiency

Skewed X inactivation - Effect on X-linked recessive inheritance

- Following X inactivation in embryogenesis, in roughly half the cells, one X chromosome is active, and in the other half, it is the other X that is active.
- Sometimes, this process results in such that the active X chromosome in most of the cells of a heterozygous female carrier is the one bearing the mutant allele.
- This phenomenon is therefore termed a "skewed" or "unfavorable" pattern of X chromosome inactivation.
- Female carrier is at least partly affected for an X-linked recessive disorder (X^A Xa).
- If this happens, a carrier female would exhibit some of the symptoms and signs of the disease and be a so called manifesting heterozygote/carrier
- Sometimes, the abnormal allele may be common enough that female heterozygotes are seen

X-linked dominant Inheritance (XD)

One trait, 2 alleles

A = dominant abnormal allele

a = recessive normal allele

Must consider which parent has the abnormal gene when assessing risk

- Males and females may be affected

- Homozygous dominant = affected female (X^AX^A)
- Heterozygous dominant = affected female (X^AX^a)
- Homozygous recessive = normal female (X^aX^a)

- Hemizygous dominant = affected male (X^AY)
- Hemizygous recessive = normal male (X^aY)

X-Linked Dominant

$X^A X^a$ Affected mother

$X^a Y$ Normal father

F / M	X^A	X^a
X^a	X^AX^a affected	X^aX^a normal
Y	X^AY affected	X^aY normal

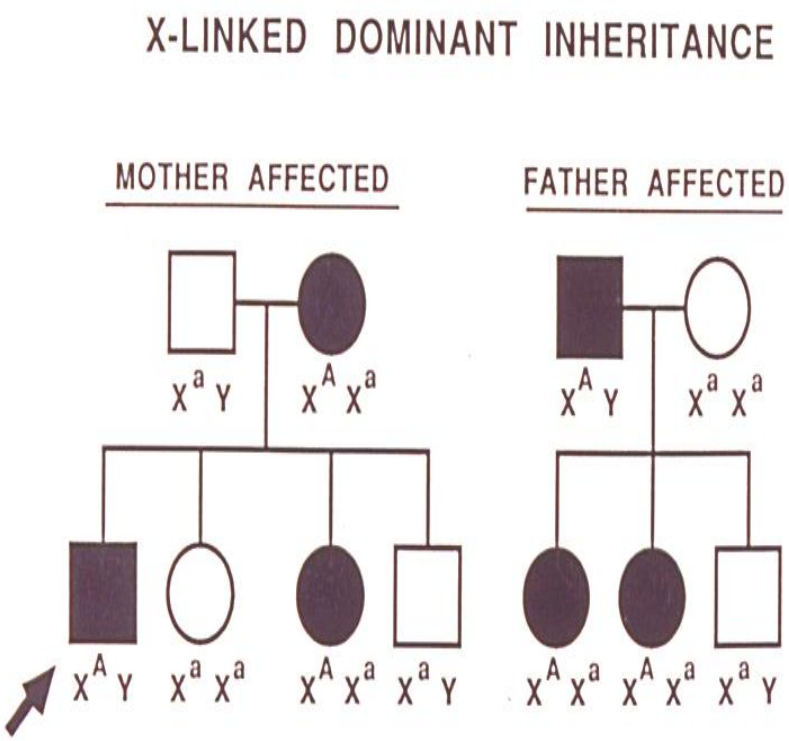
$X^a X^a$ Normal mother

$X^A Y$ Affected father

F / M	X^a	X^a
X^A	X^AX^a affected	X^AX^a affected
Y	X^aY normal	X^aY normal

- For heterozygous affected females:
  - 25% risk for affected son
  - 25% risk for affected daughter
  - 50% chance for an affected offspring
- For hemizygous affected males:
  - 100 % risk for affected daughter
  - 0 % risk for affected son (all sons will be normal)
  - 50% chance for an affected offspring

X-linked Dominant Pedigree



- Homozygous females often more severely affected than hemizygous males
- Affected females risk affected sons and affected daughters
- Affected males risk affected daughters
- No male to male transmission
- Difficult to distinguish from autosomal dominant

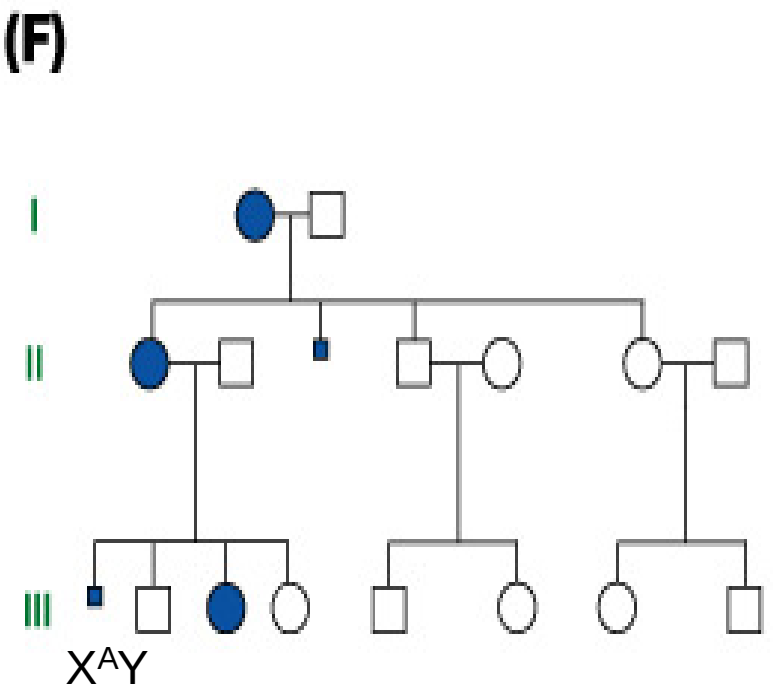
- Browning of the enamel of the teeth
- Albright's hereditary osteodystrophy
- Taybi Syndrome

Lethalitv

- The expression of trait in the heterozygous female may be variable.
- Often, the clinical expression is more consistent and severe in hemizygous males than in heterozygous females, with some conditions causing lethality in males.

- Male lethality in X-linked dominant conditions; absence of the normal allele is lethal before birth

- Affected males are not born (example: Aicardi syndrome)



Deviations from simple Mendelian inheritance

Exceptions/deviations to clear cut Medelian inheritance

- New mutation
- Non penetrance: failure of a dominant condition to manifest (other genes/environment/just chance)
- Reduced penetrance
- Lethal alleles
- Anticipation
- Multiple allele inheritance
- Co-dominance
- Incomplete dominance
- Epistasis
- Pleiotropy

New Mutation

- Gene transmitted by one of the parents underwent a change in DNA resulting in a mutation from a normal to a disease bearing gene
- Frequent cause of appearance of genetic disease in individual with no prior family history of disorder
- recurrence risk for individual's siblings is very low
- may be substantially elevated for individual's offspring
- Example: 7/8 of all cases of achondroplasia are due to new mutations ; 1/8 transmitted from achondroplastic parents
- must know adequate family history to distinguish

Reduced Penetrance

- an individual who has the genotype for a disease may not exhibit the disease phenotype at all, even though he or she can transmit the disease gene to the next generation

- Retinoblastoma – Autosomal Dominant malignant eye tumor is a good example of reduced penetrance

- About 10% of the **heterozygotes** of the RB susceptibility gene ***do not have the disease***

Anticipation

Some genetic diseases seem to display an earlier age of onset and/or more severe expression in more recent generations

- In genetics, **anticipation** is a phenomenon whereby the symptoms of a genetic disorder become apparent at an earlier age as it is passed on to the next generation.
- In most cases, an increase of severity of symptoms is also noted.
- Anticipation is common in trinucleotide repeat disorders such as Huntington's disease and myotonic dystrophy where a dynamic mutation in DNA occurs.
- All of these diseases have neurological symptoms.

Some examples of diseases showing anticipation

Autosomal Dominant
Huntington's Disease - CAG
Myotonic Dystrophy - CTG

Autosomal Recessive
Friedreich Ataxia - GAA

X-Linked
Fragile X syndrome - CGG

Anticipation - Myotonic Dystrophy

- gene is expanded in CTG trinucleotide repeat

- # repeats - strongly correlated with severity of disease
  - 5-30 copies - unaffected
  - 50-100 copies - mildly affected
  - 100 to several thousand - full blown MD

- # of repeats often increases with succeeding generations

Multiple-allele inheritance

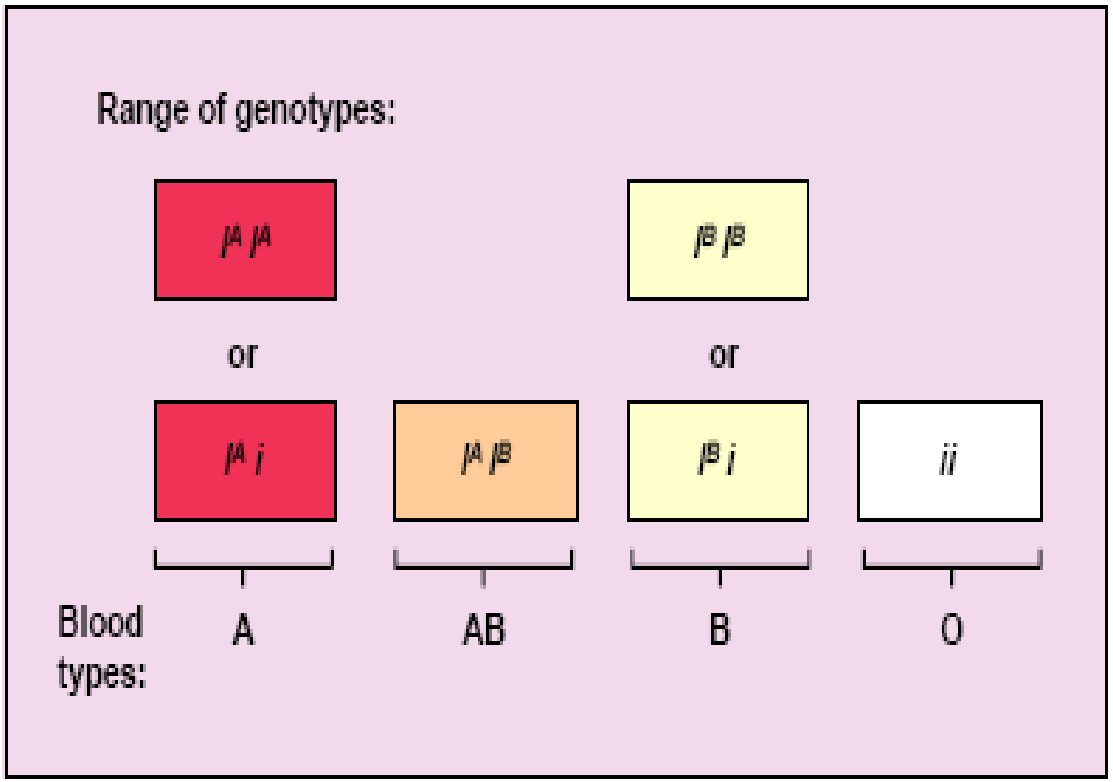
- Genes that exhibit more than two alternate alleles
- ABO blood grouping is an example

- Three alleles (I^A, I^B, i) determine the ABO blood type in humans

- I^A and I^B are codominant (both are expressed if present); “i” is recessive to the others

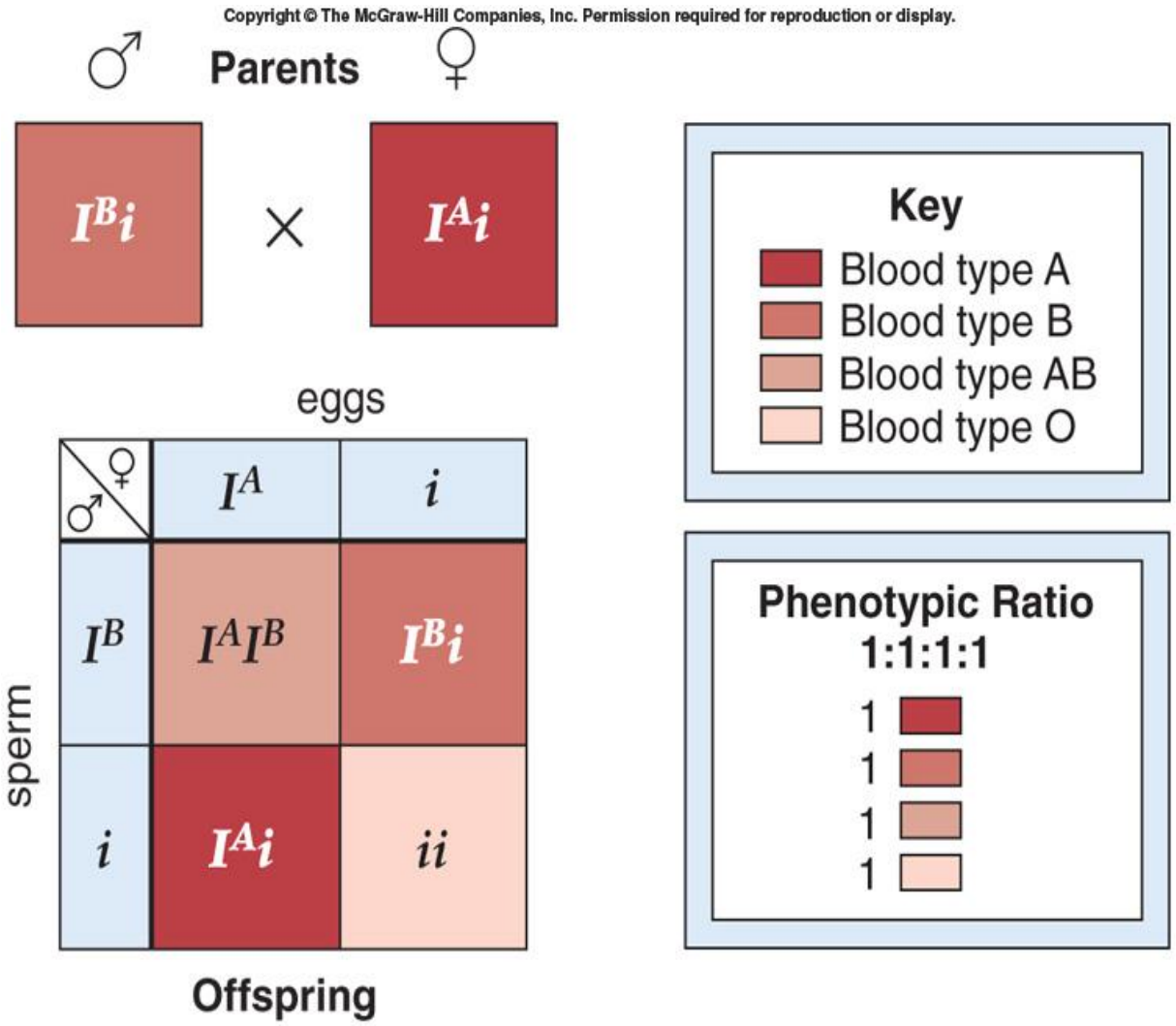
Co-dominance

- Co- dominance: Two alleles are equally expressed in a heterozygote
  - Neither allele is dominant or recessive
  - Both influence the phenotype



ABO Blood Type:Allele Combinations

- What are the possible blood types of children from a mother with type A blood and a father with type B blood(both heterozygous)?



Incomplete Dominance: Sickle cell trait

- Heterozygous individuals have a phenotype intermediate between homozygous dominant and homozygous recessive

- Sickling gene is a human example when aberrant hemoglobin(Hb) is made due to a mutation in the beta globin gene (recessive trait)
  - Long rod-like molecules
  - Stretches RBC into sickle (cresent) shape

- SS = normal Hb is made

- Ss = sickle-cell trait (both aberrant and normal Hb are made)

Commonly found in African - American population

- ss = sickle-cell anemia (only aberrant Hb is made)

Pleiotropy and Epistasis

- Pleiotropy: Genes that exert effects on multiple aspects of physiology or anatomy are pleiotropic

  – Eg: Marfan syndrome - a mutation in the gene for fibrillin (an elastic connective tissue protein) affects the skeleton, cardiovascular system, lungs, eyes and skin.

- Epistasis:

  Epistasis is the phenomenon where the effects of one gene are modified by one or several other genes, which are sometimes called **modifier genes**.

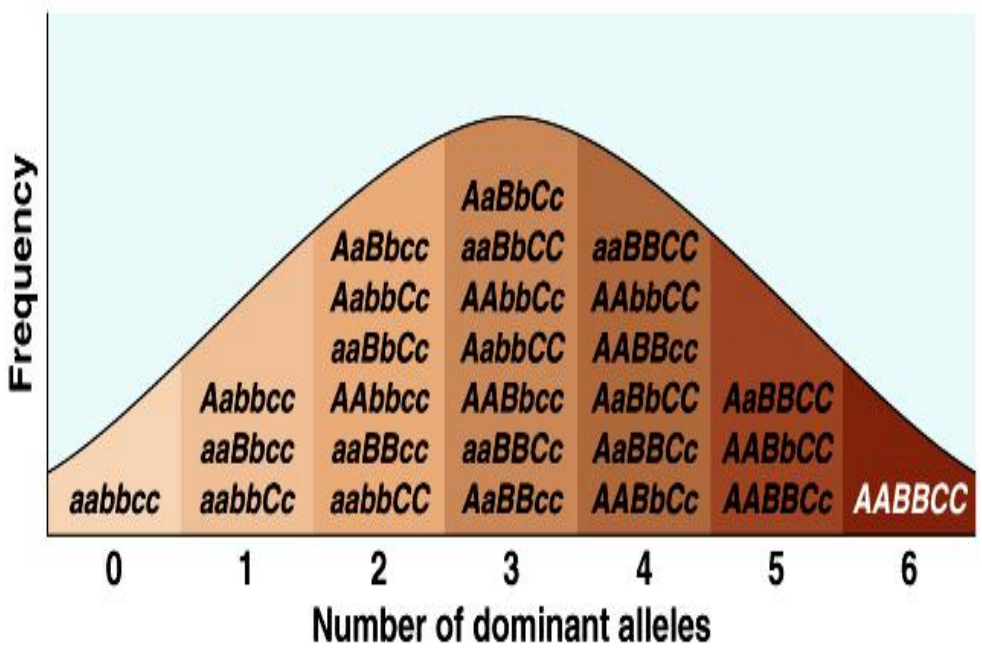
Influence on Environmental factors on gene expression

- Environmental factors influence genetic expression
  - Drugs taken during pregnancy
  - Poor Nutrition after birth can affect brain development and height
  - Hormonal deficits during childhood can lead to abnormal skeletal growth

Non-Mendelian Inheritance

Polygenic Inheritance

- Polygenic inheritance is the result of the additive effect of a large number of individual alleles (in different loci) and this results in a normal distribution in the population.
- Eg; skin color controlled by three separately inherited genes each with 2 alleles
- Other eg: eye color, intelligence, height



Alleles for dark skin (*ABC*) are incompletely dominant over those for light skin (*abc*)

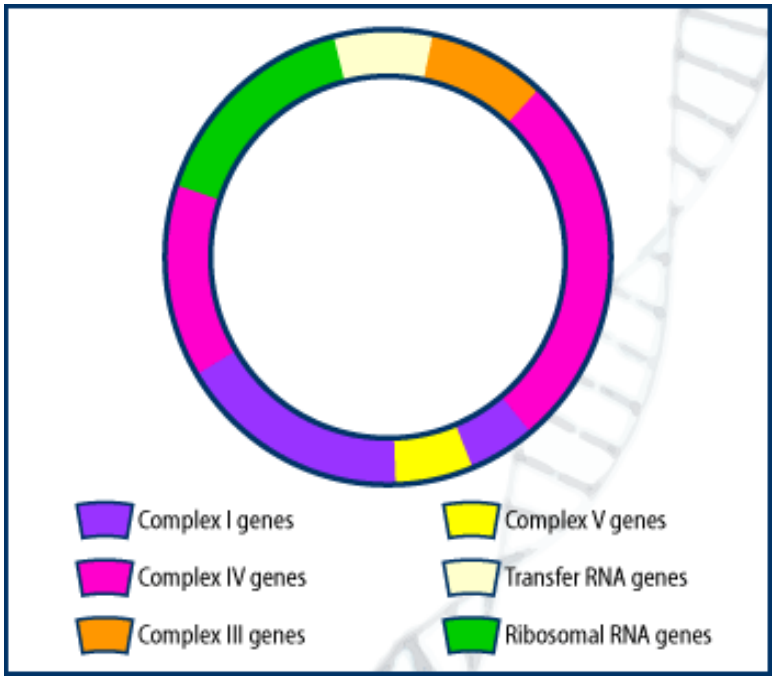
Mitochondria and its DNA

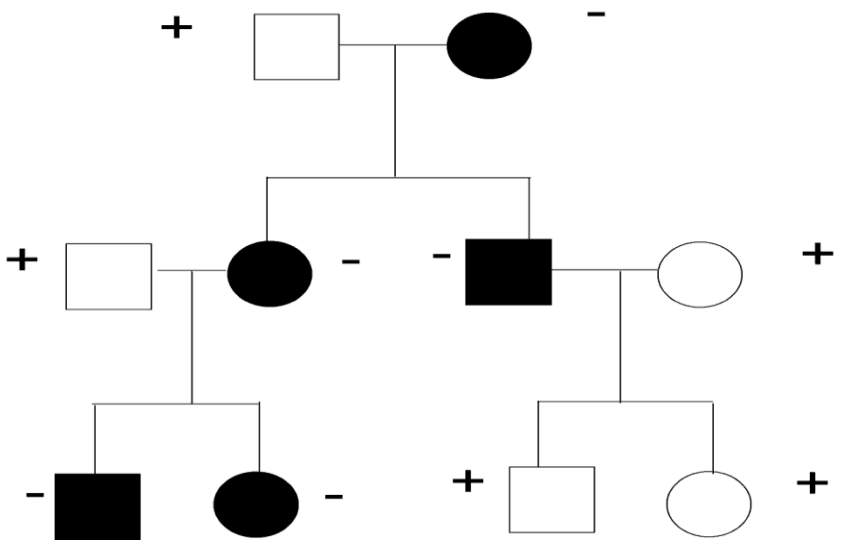
- The cytoplasm of each cell contains several hundred mitochondria.
- Through the oxidative phosphorylation process (OXPHOS), these essential organelles produce ATP.
- Mitochondria have their own distinct DNA called mtDNA, which is comprised of a small double stranded circular molecule.
- The mtDNA molecule contains only 37 genes.

  These include
  - ribosomal RNA genes and
  - genes that code for enzymes used in the mitochondria
- The mutation rate in mtDNA is ten times higher than in nuclear DNA because mtDNA are subject to damage from reactive oxygen molecules released as a byproduct during OXPHOS.
- In addition, the mtDNA also lacks the DNA repair mechanisms found in the nucleus.

Mitochondrial Inheritance

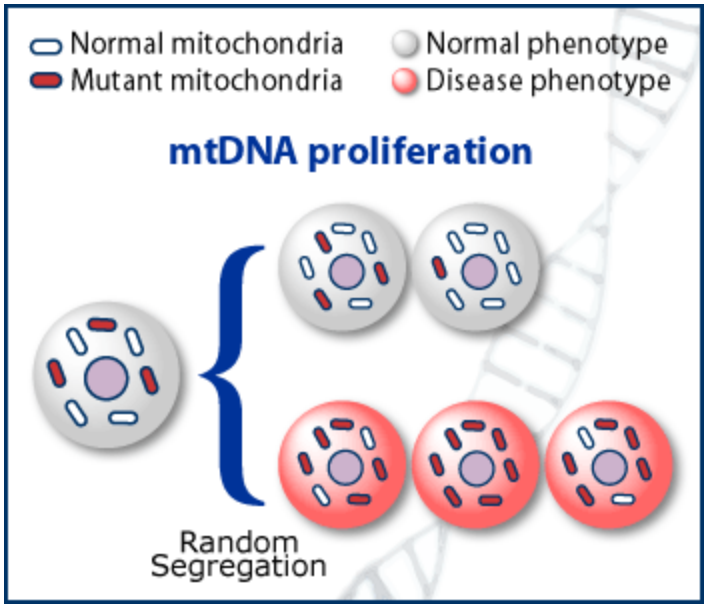
- Mitochondria are only inherited from the mother thru the ovum.
- If a female has a mitochondrial trait, all of her offspring inherit it.
- If a male has a mitochondrial trait, none of his offspring inherit it.
- Note that only 1 allele is present in each individual, so dominance is not an issue.





Heteroplasmy vs. Homoplasmy

- A cell can have some mitochondria that have a mutation in the mtDNA and some that do not.
- This is termed ***heteroplasmy***.
- The proportion of mutant mtDNA molecules determines both the penetrance and severity of expression of some diseases.



- ***Homoplasmy*** refers to a cell that has a uniform collection of mtDNA: either completely normal mtDNA or completely mutant mtDNA.
- A unique feature of mtDNA is that, at cell division, the mtDNA replicates and sorts randomly among mitochondria. In turn, the mitochondria sort randomly among daughter cells.
- Therefore, in cells where heteroplasmy is present, each daughter cell may receive different proportions of mitochondria carrying normal and mutant mtDNA.
- More than one copy of mtDNA are passed to daughter cells

Mitochondrial DNA disorders

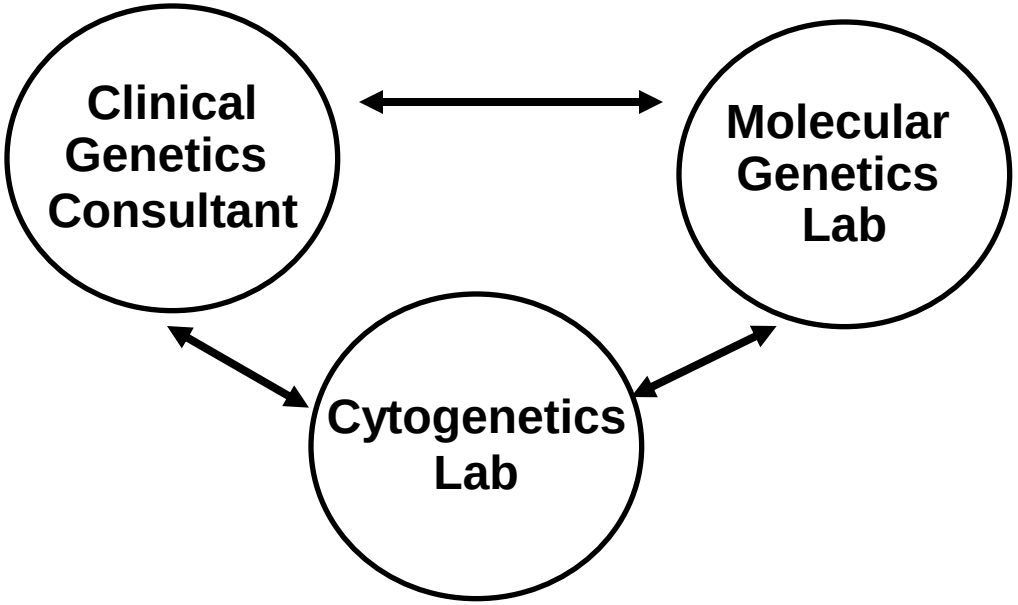
- Many of the disorders caused by mutations in mtDNA affect tissues that have a high energy demand, such as the central nervous system, the heart, and muscle.

- Therefore, mitochondrial disorders often involve the neuromuscular system and may include encephalopathy, myopathy, ataxia, retinal degeneration, and loss of function of the external ocular muscles.

- Some examples of conditions caused by mtDNA mutations include LHON (**L**eber's **H**ereditary **O**ptic **N**europathy) and MELAS (**M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis, and **S**troke-like episodes).

Medical genetics in the health service

A Medical Genetics Unit



- Is the disease worth testing for
  - Can we predict the course of the disease?
  - Can we improve treatment?
  - Can we affect outcome?
  - Is termination of pregnancy justified?

Functions

- Clinical diagnosis
- Risk assessment
- Prenatal & presymptomatic diagnosis
- Counselling

- Do we have an appropriate test
  - Has the genetic change been identified?
  - In the condition?
  - In the family?
  - Is the test accurate and reproducible?
  - Is there a lab that will perform the test?

Genetic Testing

Genetic Testing: Types

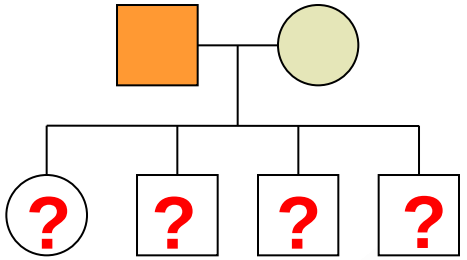
- Predictive testing
- New born screening
- Carrier screening

Should be a voluntary process and counseling should be available to both to the patient and to the family

Genetic Testing

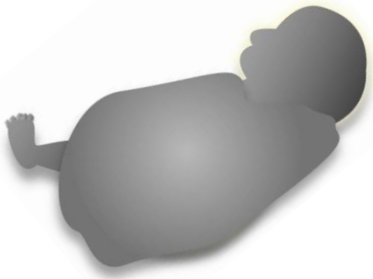
Predictive testing

Tells a person if she carries a mutation that will cause, or put her at higher risk for, a disease later in life.



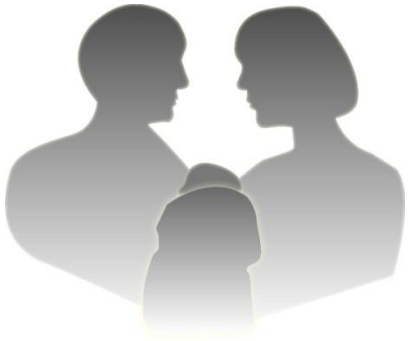
Newborn screening

Detects common disorders in newborns, where immediate treatment can prevent dangerous symptoms



Carrier testing

Tells a person whether or not he carries a mutation that could be passed on to his offspring. One can be a carrier, but not be at risk for a disease (as in recessive genes)



New born screening

- purpose: to find newborns who will benefit from early diagnosis and treatment

- criteria for inclusion of a disorder in a newborn screening program:
  - if it involves a preventable damage
  - High frequency in a population
  - screening needed to recognize/detect the disorder
  - mandated by state law (eg. Illinios, USA)
    - Phenylketouria, galactosemia, hemoglobinopathies

Carrier screening

- Identification of a heterozygote state of a given trait; to assess risk of having affected children
  - Autosomal recessive = 25% risk
  - X-linked recessive = son of a female carrier has 50% of being affected

- Important:
  - For reproductive decisions when there is family history (Tay-sachs, cystic fibrosis, sicklecell, phenylketouria)
  - Population screening for certain ethnic groups (tay sachs, sickle cell)
  - For late onset disorders (hungtington, breast cancer, hemochromatosis)

- Two major ways of identification: pedigrees & blood or DNA tests
  - Blood tests and DNA probes can detect the presence of recessive genes
    - Thalassaemia, Tay-Sachs, Cystic fibrosis

Predictive diagnosis

- Available for late onset conditions (pre-symptomatic)
  - Untreatable neurodegenerative diseases
  - Familial cancers (mutations in BRCA 1 gene are associated with breast and ovarian cancer)
  - offers preventive therapy
  - Enables reproductive choices

Available Predictive Tests

Cystic Fibrosis

Tay Sachs Disease

Huntington's Disease

Catastrophically high cholesterol

Inherited susceptibility to cancer

- Breast Cancer
- Colon Cancer
- Thyroid Cancer

Pros and Cons of genetic testing

Positives:

- Clarify diagnosis
- Allow parents to determine and evaluate risk of passing on genetic disorders
- Help develop treatment or prevention of genetic disorders

Negatives

- Some tests are only able to provide probability for passing on traits
- Large margin of error-Karyotyping
- High cost

.

Genetic Counseling

Genetic Counseling

- The process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it, and of the ways in which this may be prevented or avoided.

- The process:
  - Determine the facts: diagnosis, etiology and inheritance patterns, natural history, treatment available, and recurrence risk
  - Draw a pedigree
  - Transmitting the Information: To those requesting it in a sensitive, understandable and culturally appropriate way
  - Supporting the decision making process : Non directive

Genetic Counseling contd

- Who and when you need genetic counselling ?
  - Possible problem detected during prenatal testing
  - Birth of an affected child
  - Family history or diagnosis of a genetic disorder
  - Repeated unexplained loss of pregnancy

- What is discussed with patients and their family members
  - About the disease and its outcomes
  - How it is inherited
  - Significance of the test result
  - Treatment available to cure or prevent
  - Risks that other children might have

- There has to be signed consent before testing

- The process is non directive (especially with regard to reproductive decisions) and confidential

Features that support the single gene or Mendelian inheritence Summary

- Autosomal dominant
  - Males and females affected in equal proportions
  - Affected individuals in multiple generations
  - Transmission by individuals of both sexes (male to male, female to female, male to female and female to male)
- Autosomal recessive
  - Males and females equally affected
  - Affected individuals usually only in a single generation
  - Parents can be related

- X linked recessive
  - Usually males only affected
  - Transmitted through unaffected females
  - Males cannot transmit the disorder to their sons
- X linked dominant
  - Males and females affected but often with an excess of females
  - Females less severely affected than males
  - Affected males can transmit the disorder to their daughters but not to sons
- Y linked inheritance
  - Affected males only
  - Affected males must transmit it to their sons

Objectives

- You should be able to
  - Outline the special features of the following patterns of inheritance
    - Autosomal recessive
    - Autosomal dominant
    - X linked recessive
    - X linked dominant
  - Calculate the recurrence risk and risk of being a carrier
  - List genetic disorders in each of the above categories
  - Draw a pedigree using standard symbols
- Outline the principles of genetic counseling
- Give an outline of the types of genetic testing