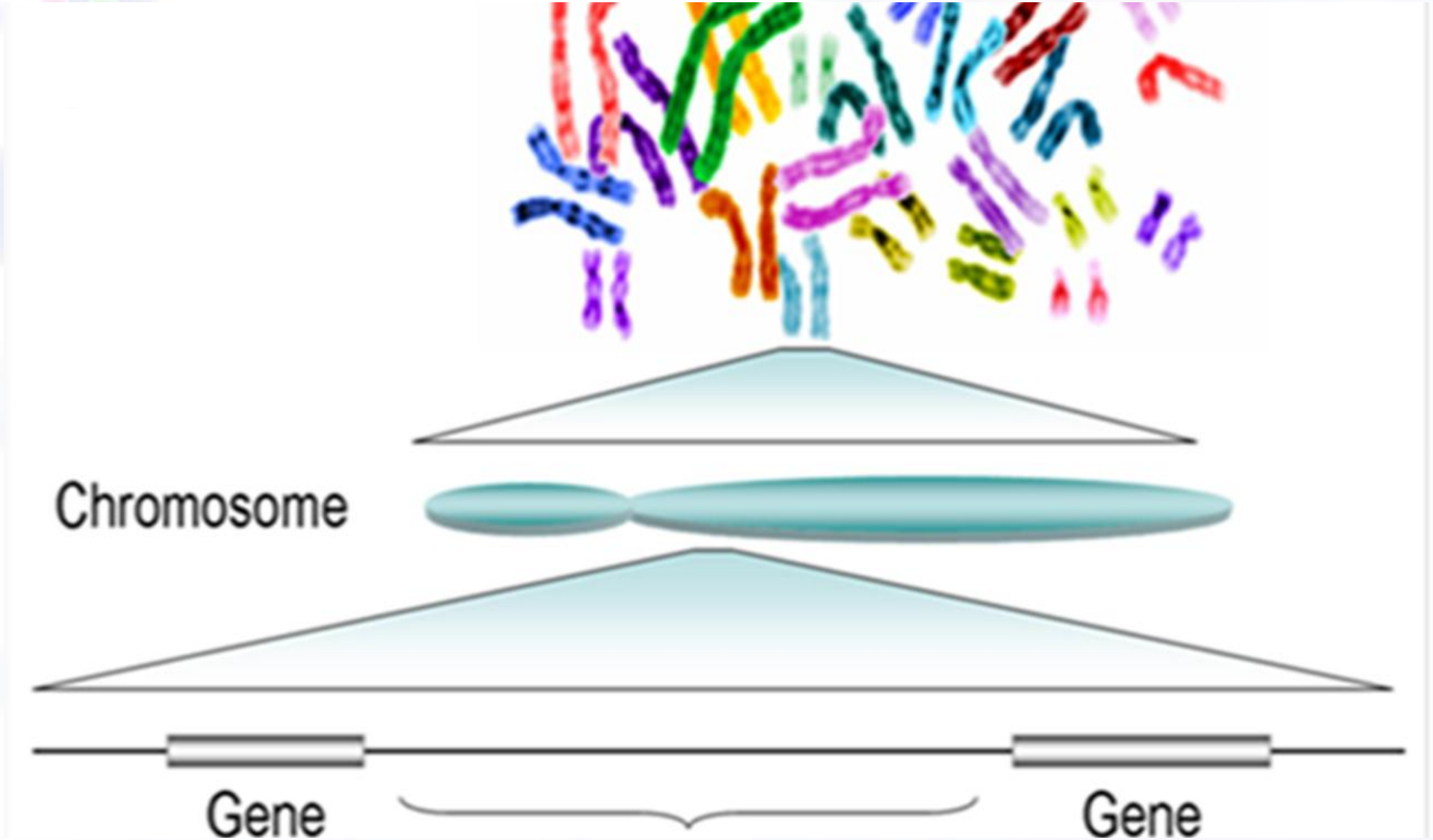
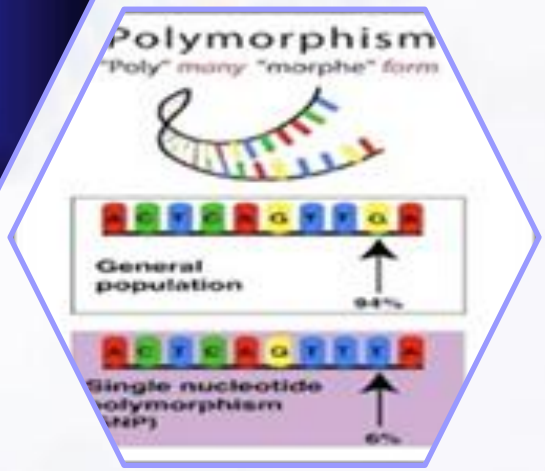
Basic Genetics

SALWA HASSAN TEAMA



GENETICS

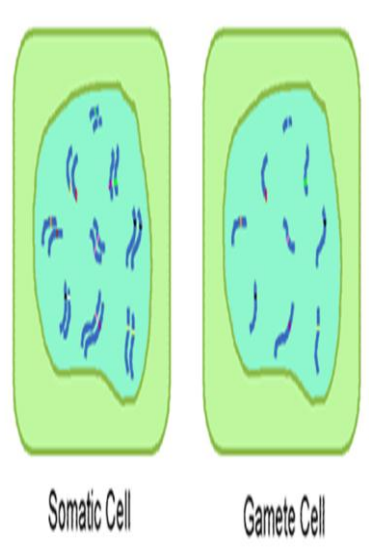
GENETICS IN MEDICINE



GENETICS/ GENOMICS

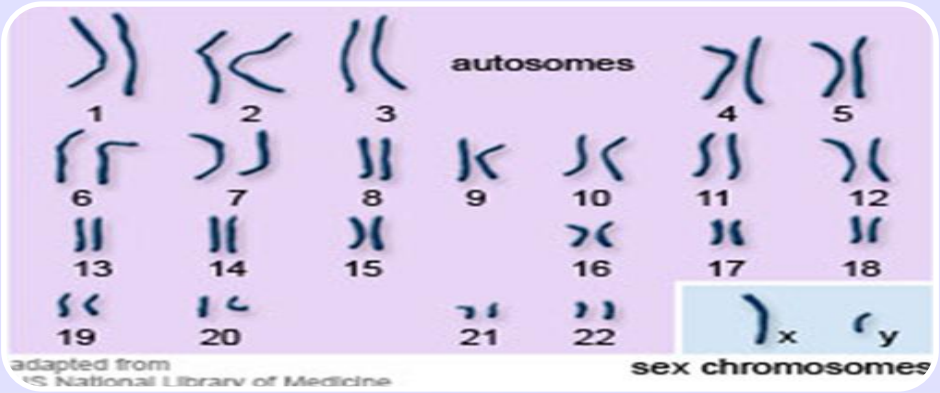
- A discipline of biology.
- The **new genetics/ genomics** is changing the face of health care. In the past, genetics encountered as extremely rare disorders caused by single gene defect. Nowadays, the genes play not only in many common conditions, but also in how people react to medication.
- Many disease is beginning to be seen as the consequence of interactions among genes and environmental factors. It has important application to public health and medical research and clinical medicine; diagnosis, treatment and management of hereditary disorders and medical diseases.

SOMATIC CELL / GAMETE CELL



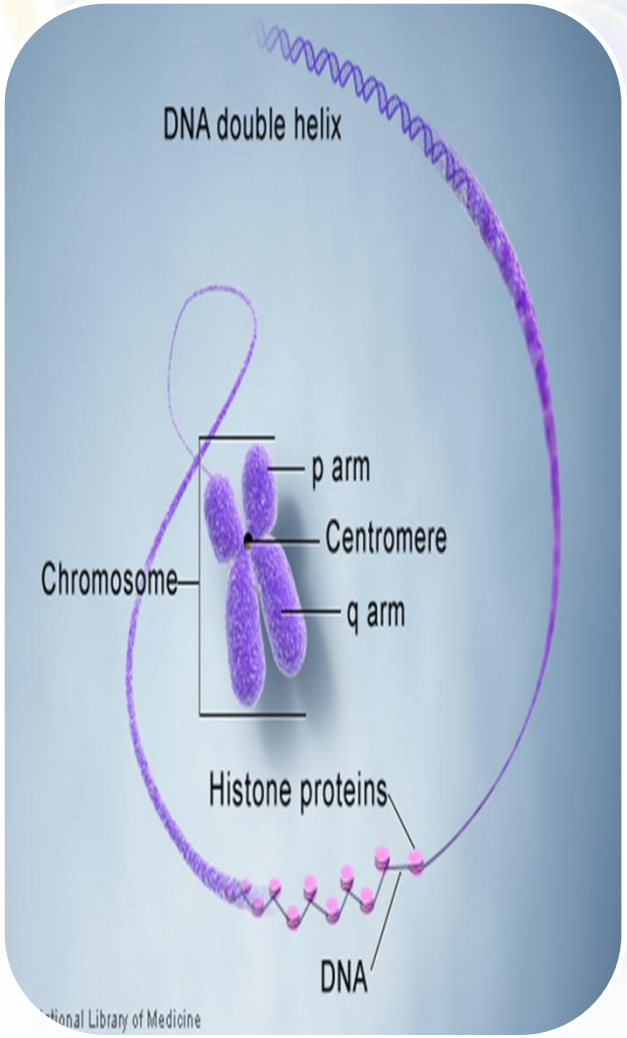
Somatic cells are said to have a diploid complement consisting of 46 chromosomes

Somatic cell containing two of each chromosome and thus two copies of every gene. Gamete cell (ova/ sperm) has a haploid complement of 23 chromosomes



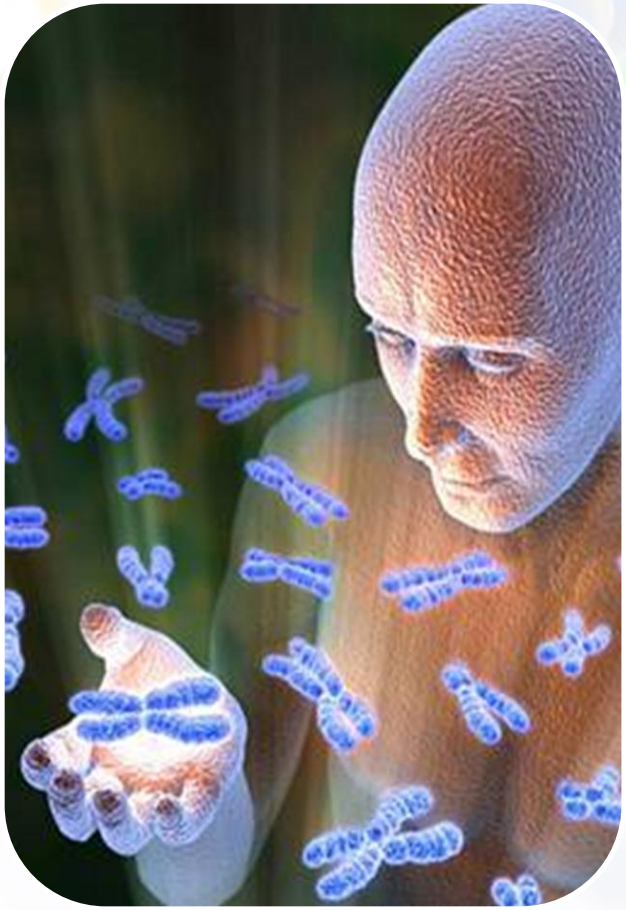
In <u>normal human cell DNA</u> contained in the nucleus, arranged in 23 pairs of chromosomes; 22 pairs of chromosomes (autosomes); the 23 chromosome pair determines the sex of individual and is composed of either (xx) (female) or an (xy) (male).

THE DNA



- The genetic material of all cellular organisms and most viruses.
- The gigantic molecule which is used to encode genetic information for all life on Earth.
- The 30.000 or more protein encoding genes are scattered among 3 billion DNA bases among each set of 23 chromosomes.

THE CHROMOSOME/ GENE



- The storage place for all genetic information.
- The number of chromosomes varies from one species to another.
- The complete set of chromosomes in the cells of an organism is its karyotype.
- The normal human karyotype is made up of 46 chromosomes.
- The study of chromosome and cell division is referred to as cytogenetics.
- The gene; Located on chromosome on its place or locus.

LOCUS

Locus is the specific location of a gene or DNA sequence on a chromosome.

- The ordered list of loci known for a particular genome is called a genetic map.
- Gene mapping is the process of determining the locus for a particular biological trait.

ALLELE

Allele: A variant of the DNA sequence at a given locus. Each allele inherited from a different parent.

- Cells whose chromosomes have the same allele of given gene at some locus are called homozygous with respect to that gene.
- Cells those that have different alleles of a given gene at a locus, heterozygous with respect to that gene.

THE MITOCHONDRIAL DNA

Human cells have hundreds of mitochondria, each containing a number of copies of a small circular molecule, mitochondrial chromosome.

The mitochondrial DNA is only 16 kb in length (less than 0.03 % of the length of the smallest nuclear chromosome) and encodes only a few dozen genes. Although the products of these genes function in mitochondria, the majority of proteins found in mitochondria is the product of nuclear genes.

Mitochondrial genes exhibit exclusively maternal inheritance.

CLASSIFICATION OF GENETIC DISEASES

Single Gene Disorders: e.g. Cystic fibrosis is caused by mutations in a single gene called CFTR and is inherited as a recessive trait.

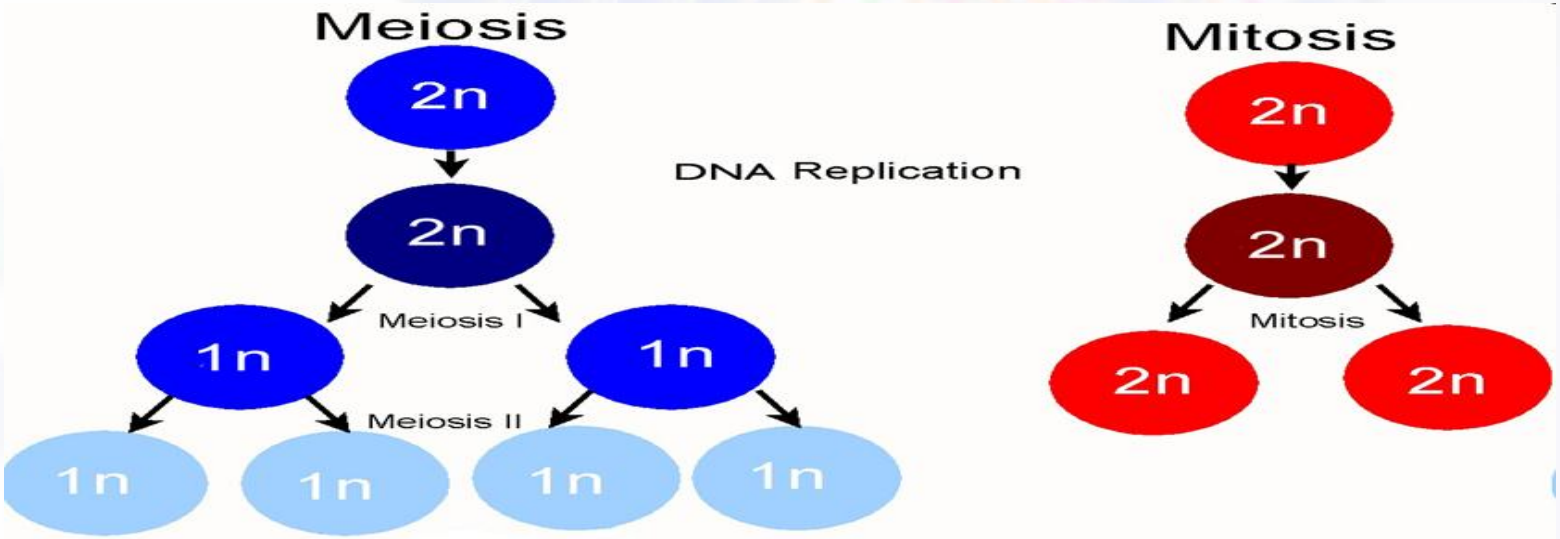
Non Mendelian Genetics and Multifactorial inheritance.

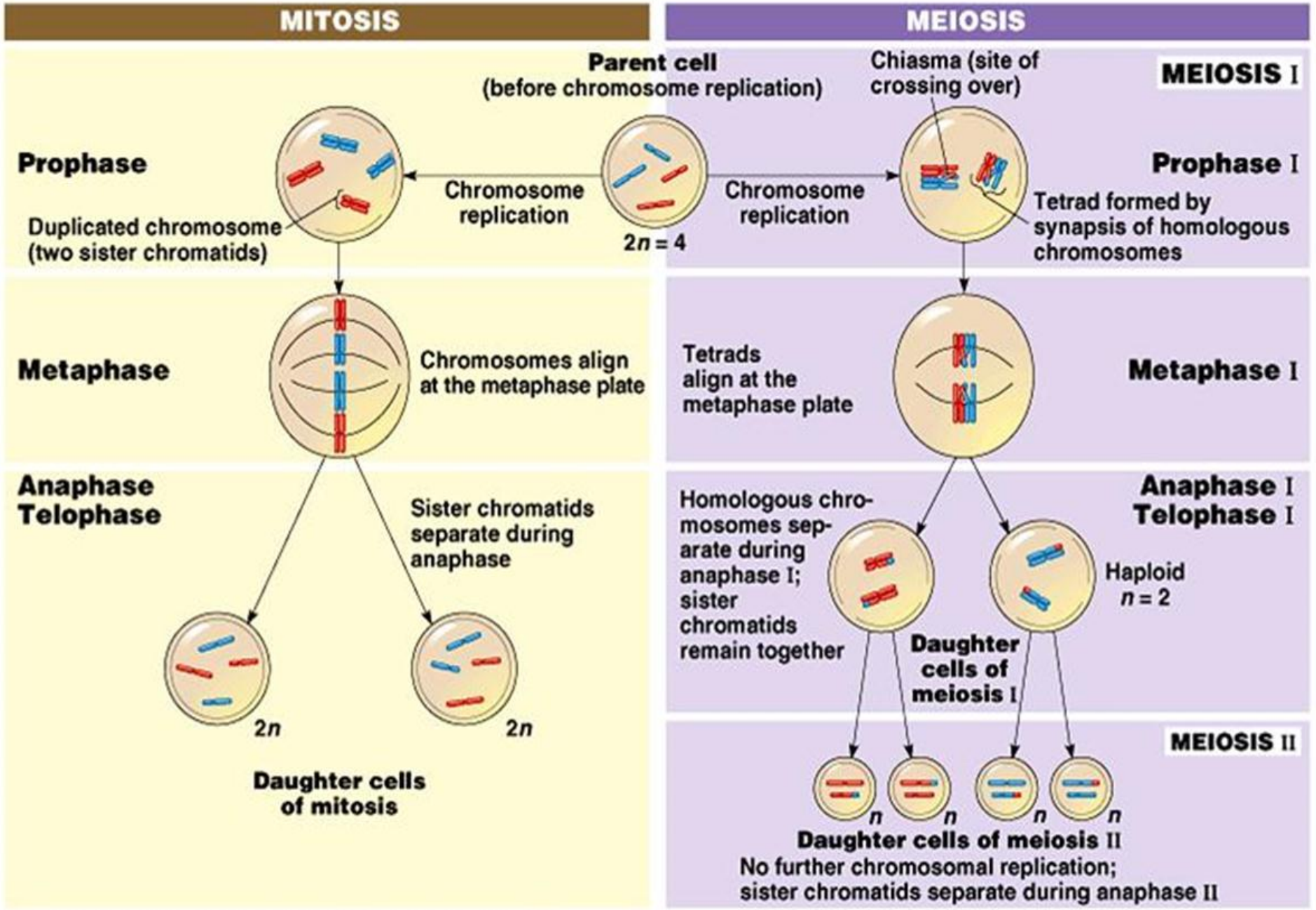
Multifactorial Disorders: Common condition includes common congenital malformation such as cleft lip and palate and acquired disorders such as diabetes mellitus and schizophrenia.

Chromsomal Abnormalities: e.g. Down syndrome.

Medical Relevance of Mitosis and Meiosis

The biological significance of mitosis and meiosis lies in ensuring the constancy of chromosome number from one cell to its progeny and from one generation to the next. The medical relevance of these processes lies in errors of one or the other mechanism of cell division leading to formation of an individual or of a cell lineage with an abnormal number of chromosomes





PATTERN OF INHERITANCE

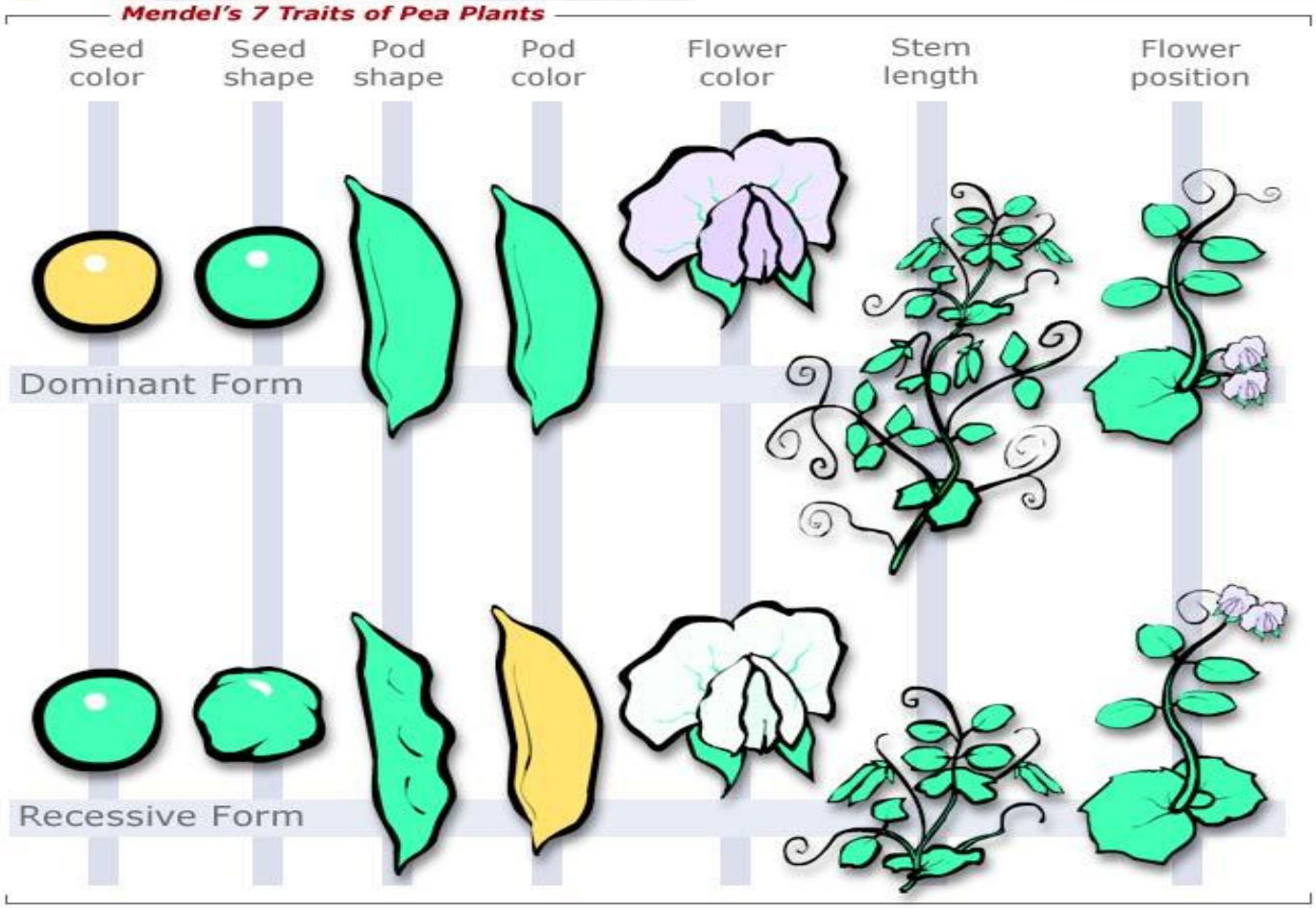
Mendelian genetics

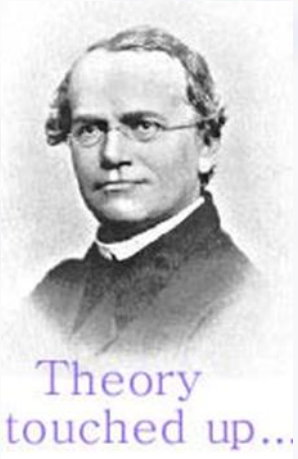
Non-Mendelian inheritance

Multifactorial inheritance

Over 6000 traits or disorders in humans exhibit simple single gene **unifactorial or mandelian inheritance**.

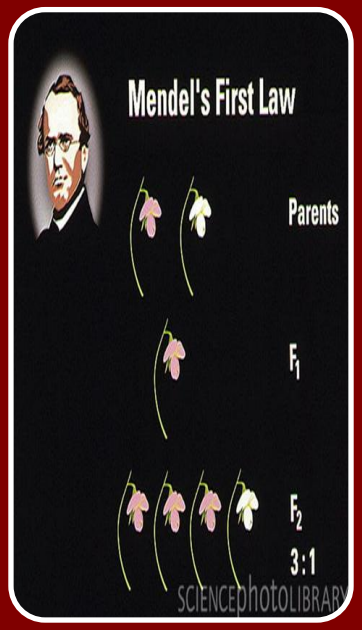
However, characteristics such as **height**, and many common familial disorders do not usually follow a simple pattern of inheritance.





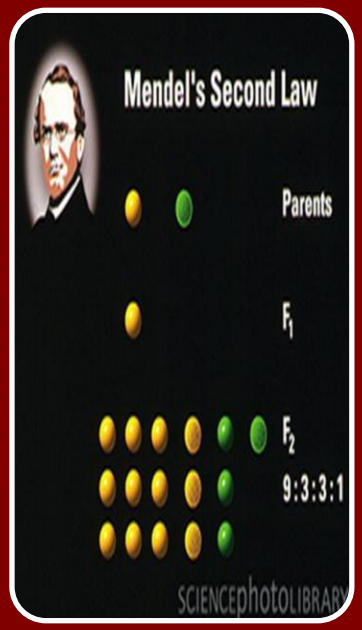
Source: http://www.personal.psu.edu/staff/d/r/drs18/bisciImages/index.html

MENDEL'S LAW OF UNIFORMITY

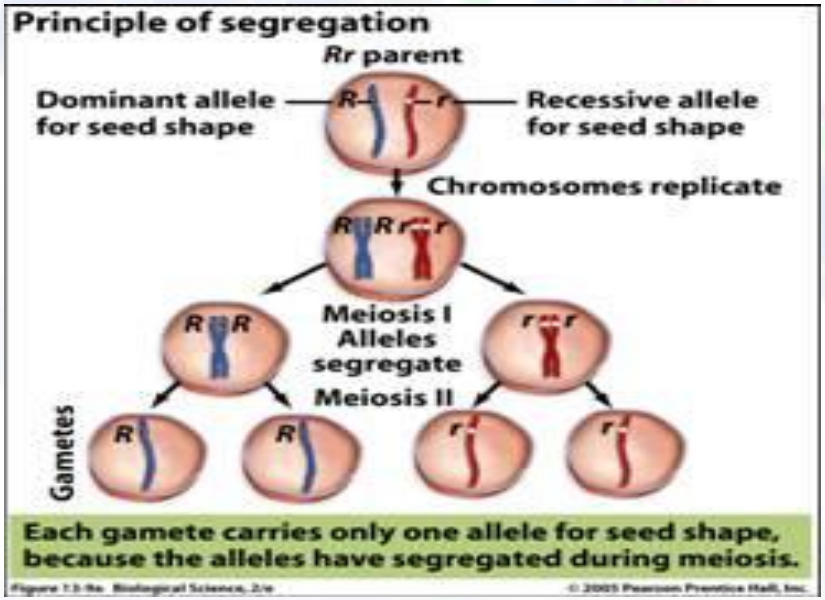


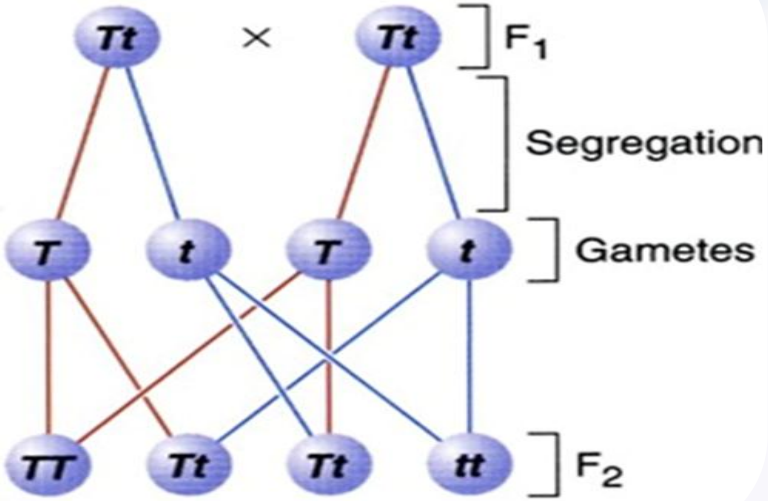
- ″The law of uniformity refers when two homozygotes with different alleles are crossed, all offsprings in the F1 generation are identical and heterozygous‟ 6

MENDEL'S LAW OF SEGREGATION



"During gamete formation, each member of the allelic pair separate from the other member to form the genetic constitution of the gamete. Only one of which can be transmitted at any one time. Rare exception to this rule can occur when two allelic genes fail to separate due to the chromosome non-disjunction in meiosis I" 6

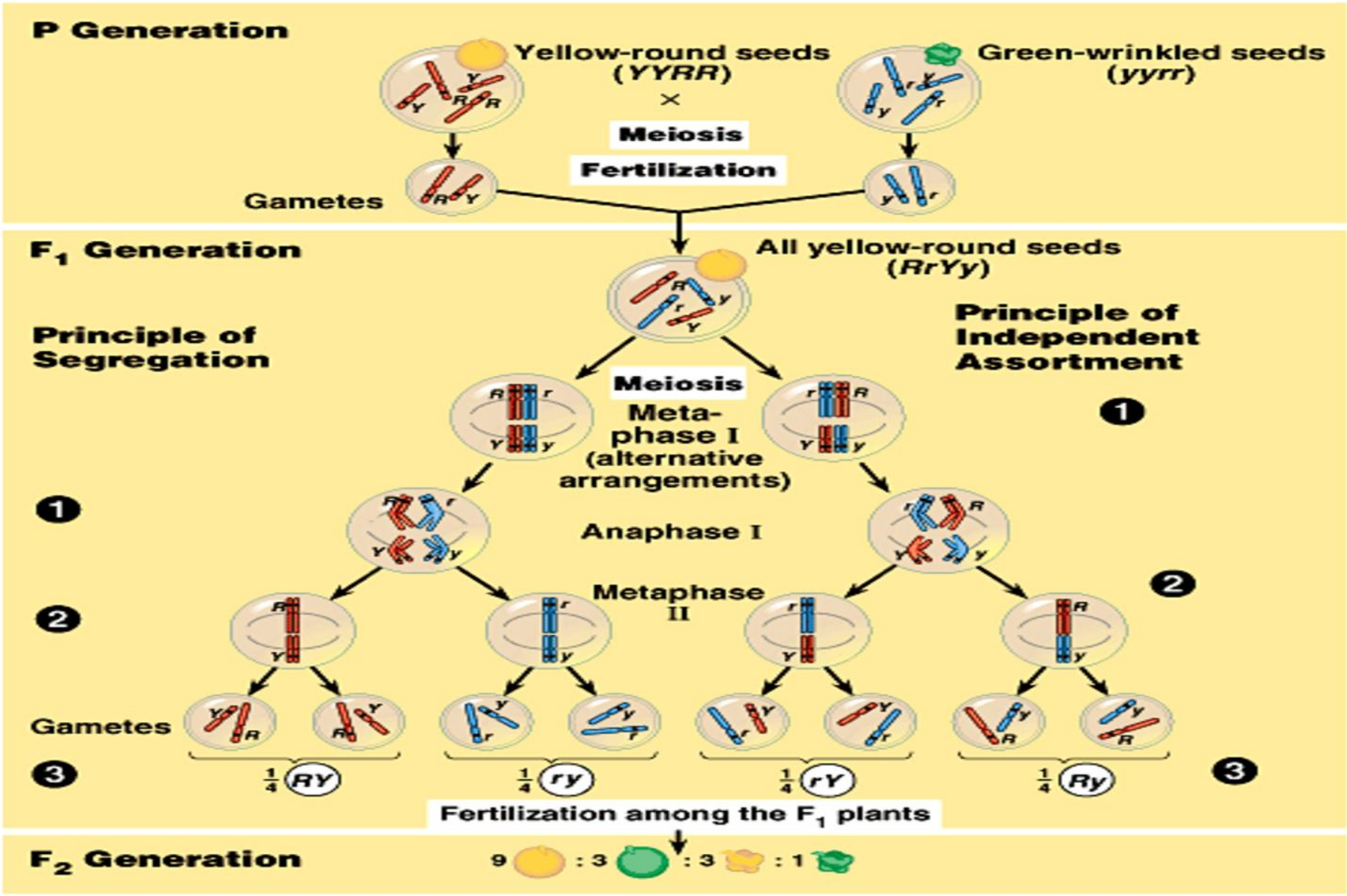

Principle of segregation
Rr parent
Dominant allele for seed shape
Recessive allele for seed shape
Chromosomes replicate
Meiosis I
Alleles segregate
Meiosis II
Gametes
Each gamete carries only one allele for seed shape, because the alleles have segregated during meiosis.


Tt
×
Tt
F1
Segregation
T
t
T
t
Gametes
TT
Tt
Tt
tt
F2

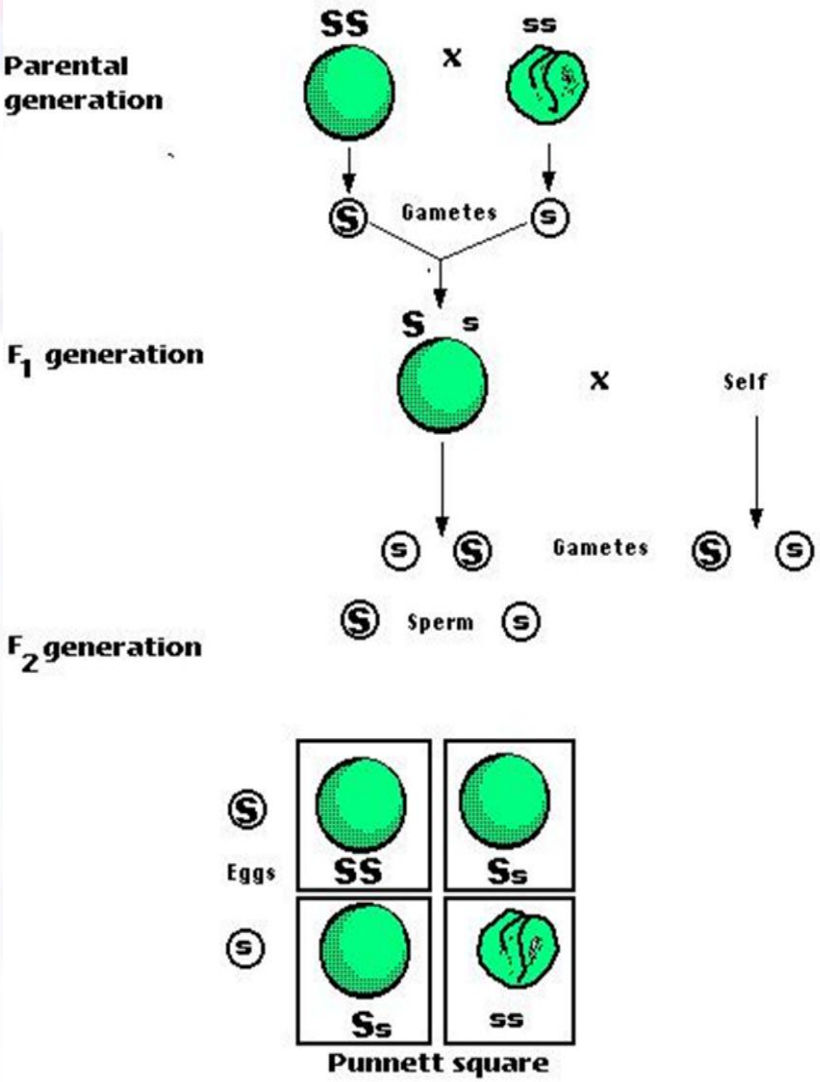
MENDEL'S LAW OF INDEPENDENT ASSORTMENT

"Every trait inherited independently of one another; members of different gene pairs segregate to offspring independently of one another, this is not always true as genes, which are close together on the same chromosome tend to be inherited together; they are linked"[6].

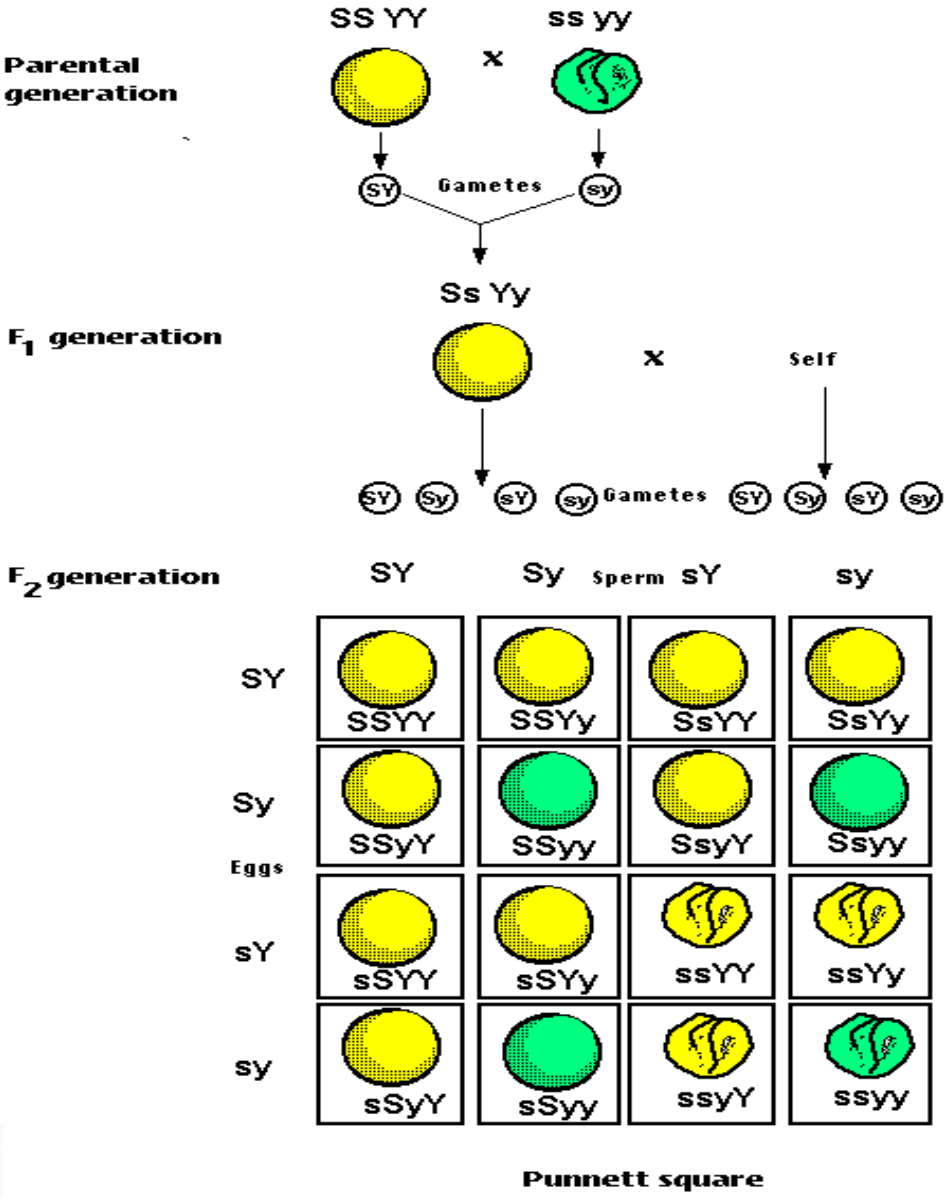
The Chromosomal Basis of Mendel's Laws



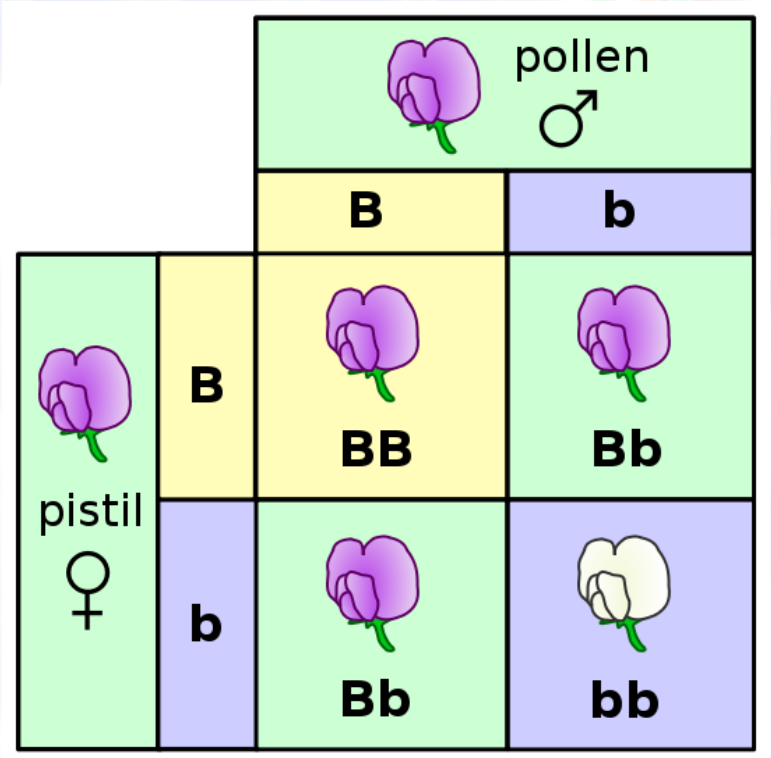
Mendel: Monohybrid cross



Mendel: dihybrid cross



Punnetts Square



A punnetts square showing the different ways in which genes can segregate and combine in the second filial cross.

Construction of a punnetts square provides a simple method for showing the possible gamete combination in different mating.

MODE OF INHERITANCE

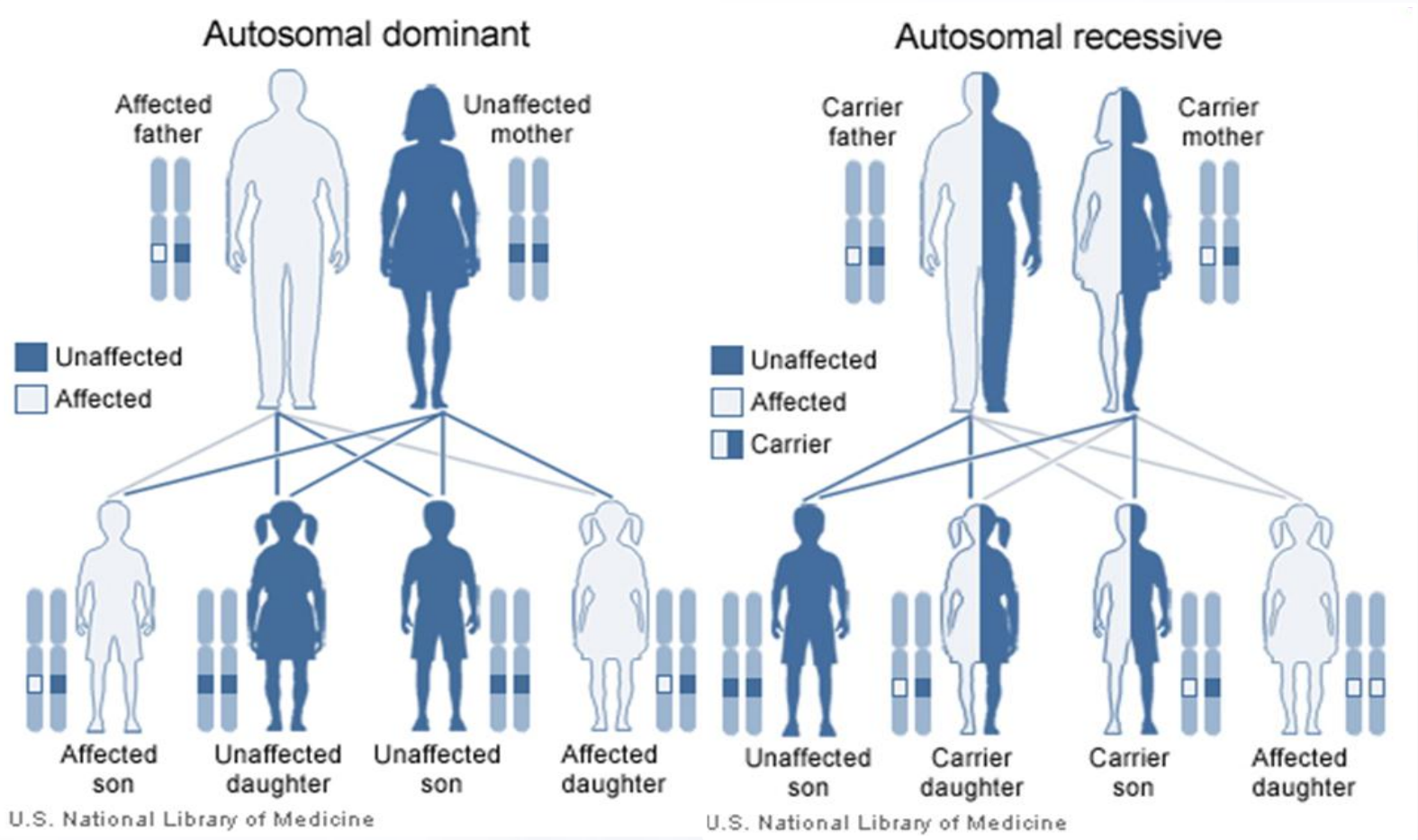
Autosomal Inheritance

- **Autosomal Dominant Inheritance**
- **Autosomal Recessive Inheritance**

Sex Linked Inheritance

- **X Linked Inheritance**
- **Y Linked Inheritance**

AUTOSOMAL INHERITANCE



Autosomal Dominant Inheritance

Male and female can be affected.

Manifest in the heterozygous state.

No skipped generation.

Vertical transmission.

Each child has 50% chance of inheriting the mutation.

Occasionally arise as a new mutation.

Autosomal Recessive Inheritance

Male and female can be affected

Manifest in the homozygous state

All affected individuals in a family are usually in a

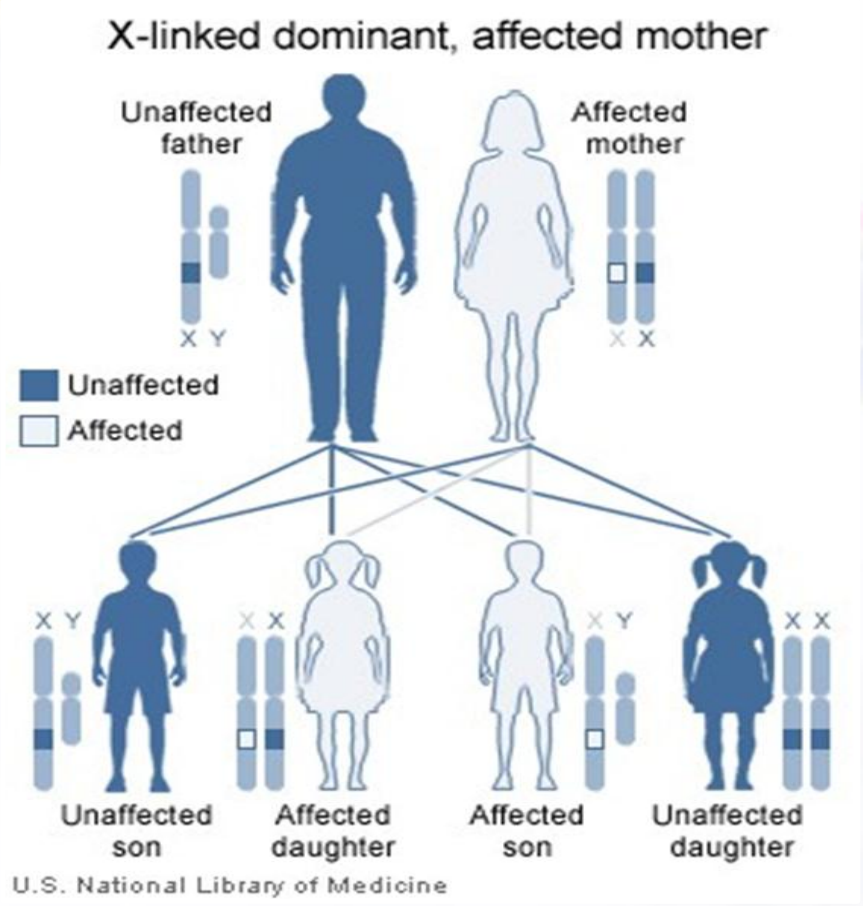
single sibship, that is they are brothers and sisters.

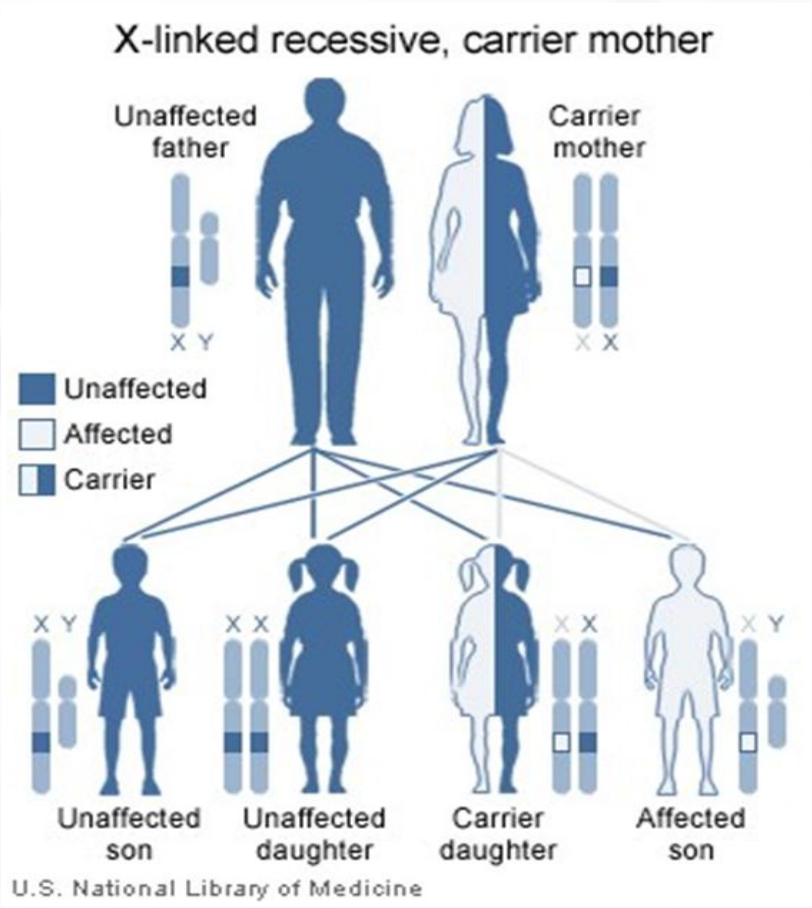
Horizontal inheritance

Parents of an affected individual are heterozygous

Consanguinity in parents provides further support for autosomal recessive inheritance.

SEX-LINKED INHERITANCE





X-linked Dominant

Uncommon

Manifest in heterozygous female as well as in male who has

the mutant allele on his x chromosome.

Each child has 50% chance of inheriting the mutation.

Affected female can transmit the disorder to male and female children.

Affected male transmits the trait to all his daughters but to non of his son.

X Linked Recessive

Disorder should affect males exclusively;

Passed from heterozygote or homozygote mother to affected son.

Male with a mutant allele on a single x chromosome is said to be hemizygous for that allele.

Carrier female; each son has a 50% chance of being affected and each daughter has 50% chance of being the carrier.

Affected male ; all of his daughters will be carriers, but non of his sons will be affected.

Some x linked disorders are not compatible with survival to reproductive age and are not, therefore transmitted by affected males; e.g. Duchenne muscular dystrophy.

Y Linked Inheritance

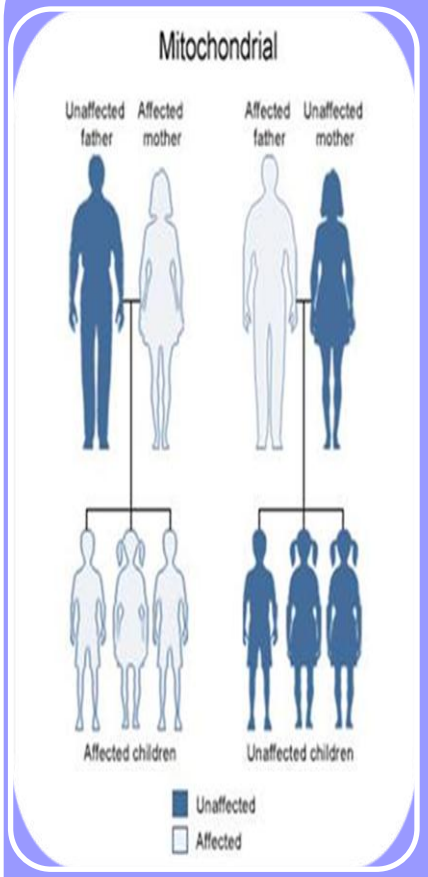
Only males are affected and that an affected male transmits the trait to all of his sons but non of his daughters.

Non-mendelian Inheritance is a general term that refers to any pattern of inheritance in which traits do not segregate in accordance with mendel's laws.

- Mosaicism
- Triplet Repeat Disorders
- Extranuclear inheritance
- Gene conversion
- Infectious heredity
- Genetic Imprinting
- Genetic heterogeneity
- Uniparental Disomy
- ….

Mosaicism

- Mosaics Individuals who possess cells with genetic differences from the other cells in their body.
- Mosaicism of either somatic or germ cells:
  - Somatic mosaicism; if a mutation happens in the non-gamete forming tissues.
  - Germline mosaicism; mutations occur in the egg or sperm cells and can be passed on to offspring.



Extranuclear inheritance; The phenotype of traits linked to genes found in mitochondria are determined exclusively by the maternal parent.

Trinucleotide repeat disorders: These diseases are all caused by the expansion of microsatellite tandem repeats consisting of a stretch of three nucleotides. E.g. Fragile X syndrome and Huntington's disease.

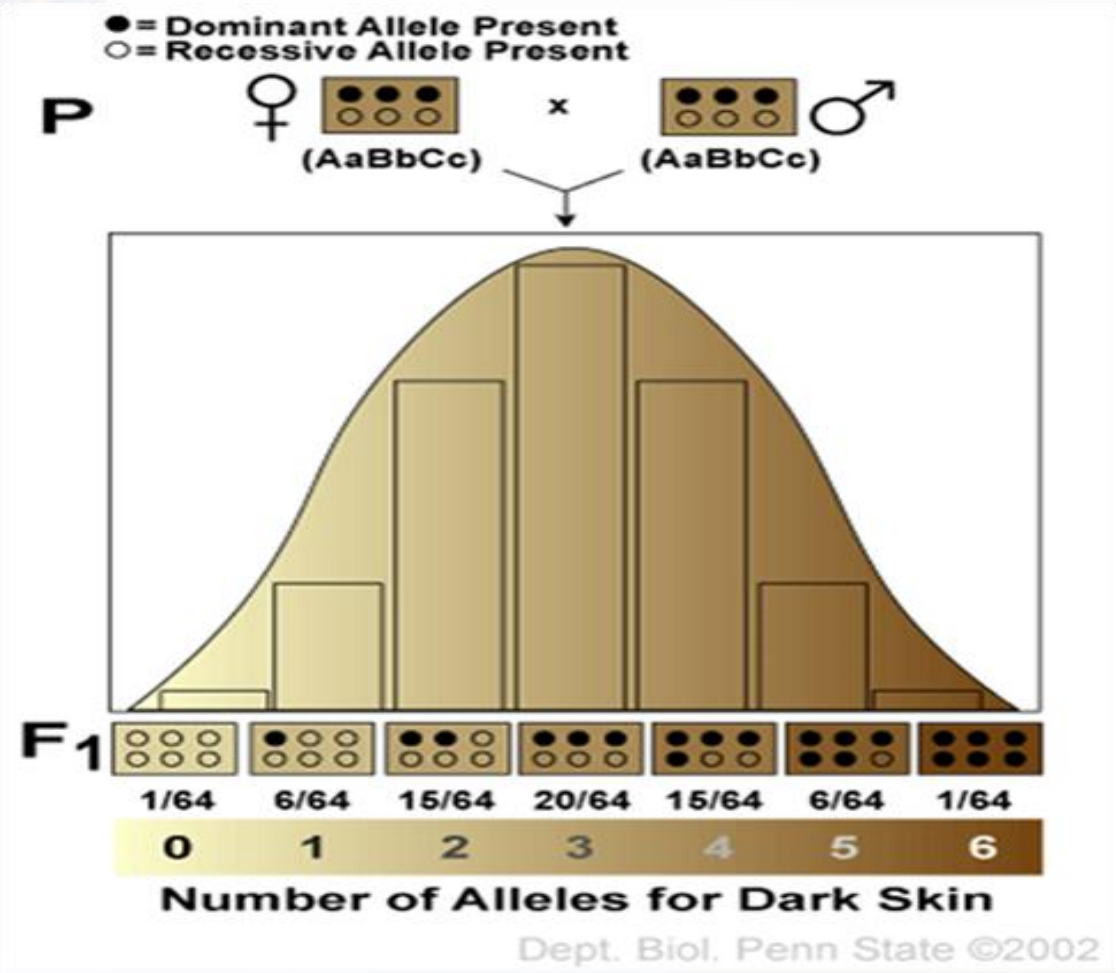
Gene conversion: A piece of DNA sequence information is the crossover from one DNA helix to another DNA helix, whose sequence is altered.

Infectious heredity

Infectious particles such as viruses which infect host cells and continue to reside in the cytoplasm of these cells. If the presence of these particles results in an altered phenotype, then this phenotype may be subsequently transmitted to progeny, inheritance will be determined only by the infected status of the maternal parent.

Genomic imprinting

POLYGENIC (MULTIFACTORIAL) INHERITANCE



Polygenic (Multifactorial) Inheritance

Some traits were previously believed to be Mendelian, but their inheritance is (probably) based on more complex genetic models;

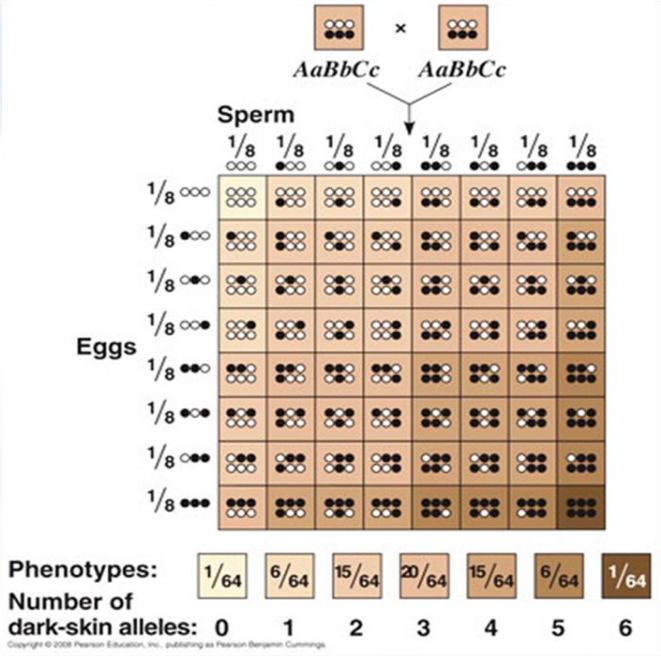
Skin color
Hair color
Morton's toe
Tongue rolling
Blood type
……..

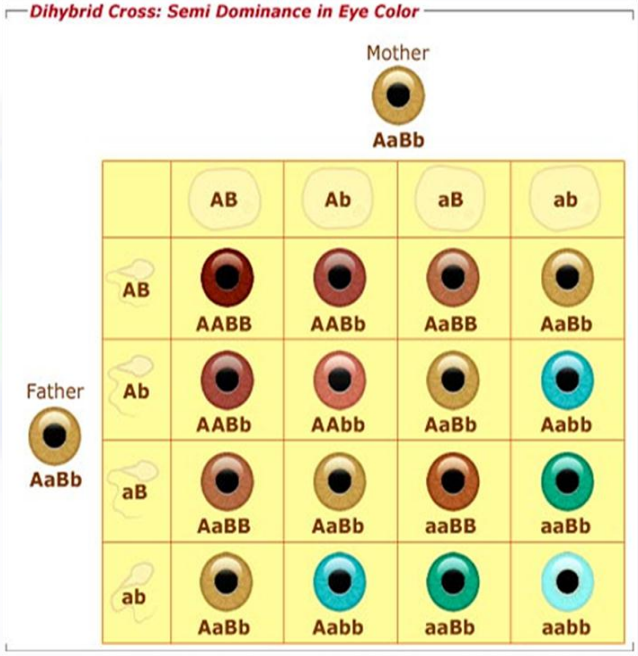
Polygenic (Multifactorial) Inheritance

Normal traits

- Height
- Eye Color
- Intelligence
- ……..

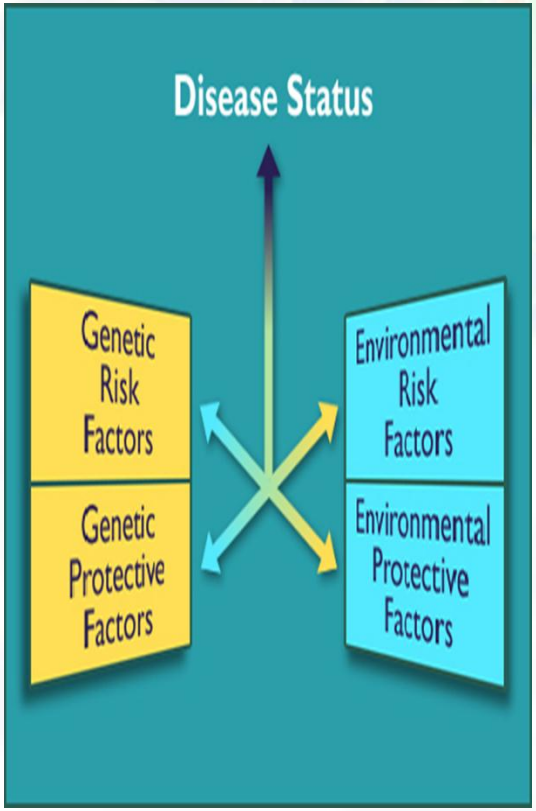
Abnormalities based on more complex genetic models;
regulated by protein products of two or more genes.


AaBbCc
AaBbCc
Sperm
1/8
Eggs
Phenotypes:
Number of dark-skin alleles:
1/64
6/64
15/64
20/64
15/64
6/64
1/64
0
1
2
3
4
5
6


Dihybrid Cross: Semi Dominance in Eye Color
Mother
AaBb
Father
AaBb
AB
Ab
aB
ab
AABB
AABb
AaBB
AaBb
AABb
AAbb
AaBb
Aabb
AaBB
AaBb
aaBB
aaBb
AaBb
Aabb
aaBb
aabb

MULTIFACTORIAL DISEASES AND DISORDERS

Environmental factors also play an important role in the modulation of the genetic defects.



- Diabetes mellitus
- Hypertension
- Ischemic heart disease
- Gout
- Schizophrenia
- Bipolar disorder
- Neural tube defect
- Dwarfism
- Cleft lip/palate
- Peripheral disease and
- Some cancer
- .....

CHROMOSOME ABNORMALITY

Numerical	
Aneuploidy	Monosomy Trisomy Tetrasomy
Polyploidy	Triploidy Tetraploidy
Structural	
Translocations Deletions Inversions Rings isochromosomes	Reciprocal Robertsonian Paracentric Pericentric
Different cell lines	Mosaicism Chimaerism

Robert F. Mueller, Ian D. Young. Emery's Elements of Medical Genetics

Are chromosomal disorders inherited?

most chromosomal disorders (such as down syndrome and turner syndrome) are not passed from one generation to the next; although it is possible to inherit some types of chromosomal abnormalities.

Numerical Abnormalities: these changes are not inherited, but occur as random events during the formation of reproductive cells (eggs and sperm).

Structural Abnormalities: some changes in chromosome structure can be inherited, while others occur as random accidents during the formation of reproductive cells or in early fetal development.

GENETICS IN MEDICINE

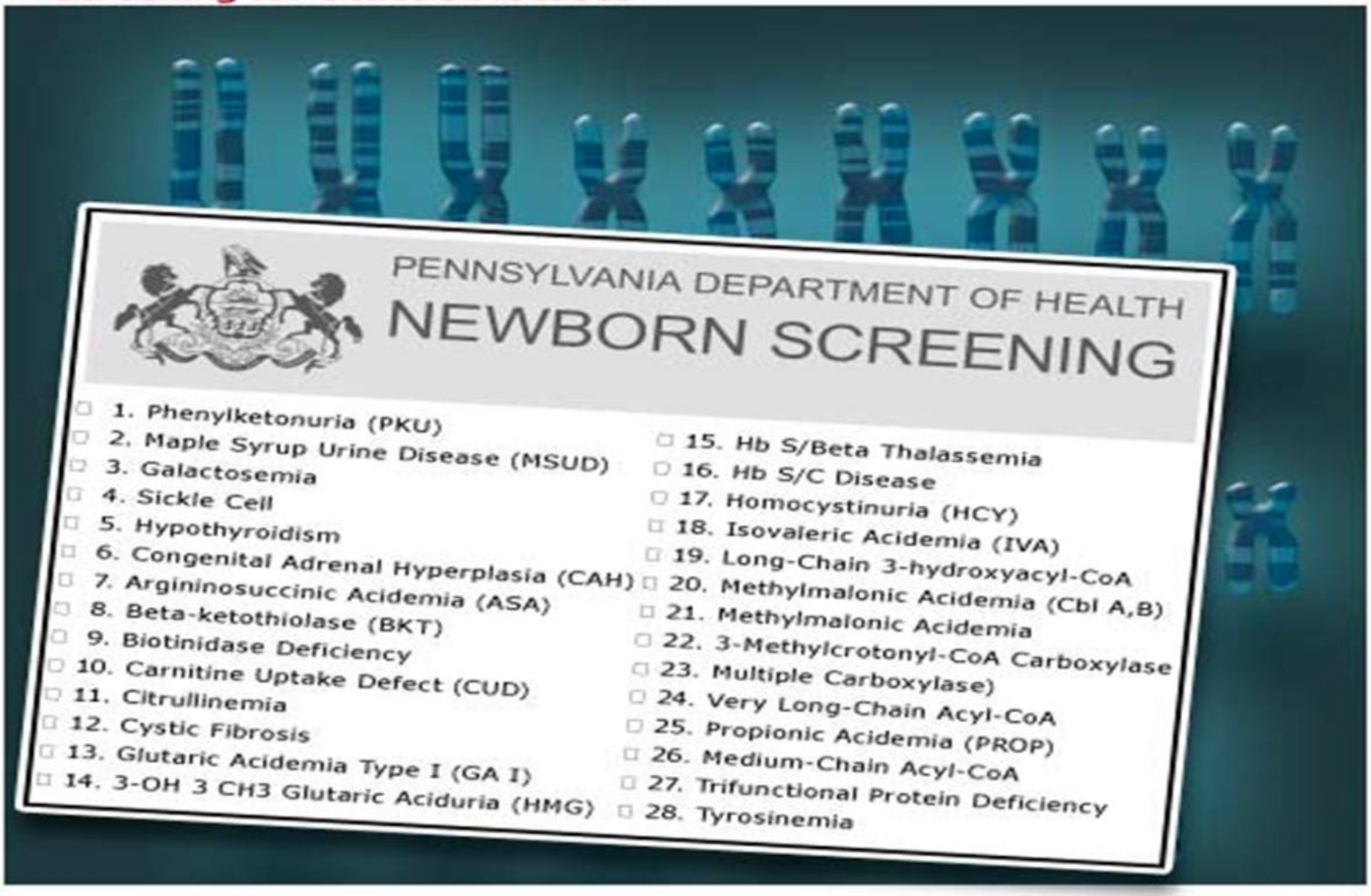
- **Diagnosing and Predicting Disease and Disease Susceptibility**, inherited genetic diseases, cancer,…
- **Gene tests** to detect genes in people suspected of having particular diseases or of being at risk for developing them.
- **Drug design**
- **Gene Therapy**
- **……**

GENETIC TESTS

TYPES OF GENETIC TESTS	
DIAGNOSTIC TESTS:	establish or confirm the diagnosis for an individual already affected.
PRE-SYMPTOMATIC TESTS:	tell with certainty if someone will develop some disease in the future. This category includes the test for Huntigton's disease.
PREDICTIVE TESTS:	can indicate an increased risk for a disease but cannot tell if and when a person will be affected.

- Predictive testing (to estimate the risk to a patients without any symptoms)
- Presymptomatic testing
- Diagnostic testing for diseases
- Carrier testing
- Prenatal testing
- Preimplantation genetic diagnosis
- Genetic screening
- Pharmacogenetic testing
- Forensic testing

Screening for Genetic Diseases




hope.
it's in our
genes.™

REFERENCES AND ONLINE FURTHER READING

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TEAMA 2017


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