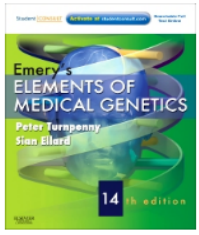
Lecture-1

Brief History of Genetics and Mode of Inheritance

Suggested Book



Emery's Elements of Medical Genetics

14th Edition

With STUDENT CONSULT Online Access

Medical Genetics

- Genetics in medicine had its start at the beginning of 20th century.
- Garrod (1857-1936) and others recognized that Mendel's (1822-1884) law of inheritance could explain the recurrence of certain diseases in families.
- At the beginning of 21st century, with the completion of Human Genome Project (1990-2003), medical genetics grew as a special branch for the diagnosis and management of common and rare genetic diseases.
- Medical genetics focuses not only on the patient but also on the entire family. A family history is important to understand the mode of inheritance.

Historical Background

- Early Greek philosophers and physicians such as Aristotle (384-322 BC) and Hippocrates (460-370 BC) concluded that important human characteristics were determined by semen.
- Semen was thought to be produced by whole body; hence bald-headed fathers would have bald-headed sons.
- Menstrual blood was regarded a culture medium and the uterus as an incubator.

Historical Background

- Engravings in Chaldea in Babylonia (modern-day Iraq) dating back 6000 years show pedigrees documenting the transmission of certain characteristics of horse's mane.
- However, any early attempts to unravel the mysteries of genetics would have been severely hampered by a total lack of knowledge and understanding of basic processes such as conception and reproduction.
- These ideas prevailed until the 17th century, when Dutch scientists Leeuwenhoek (1632-1723) and de Graaf (1641-1673) recognized the existence of sperm and ova, thus explaining how the female could also transmit characteristics to her offspring.

Technology Development

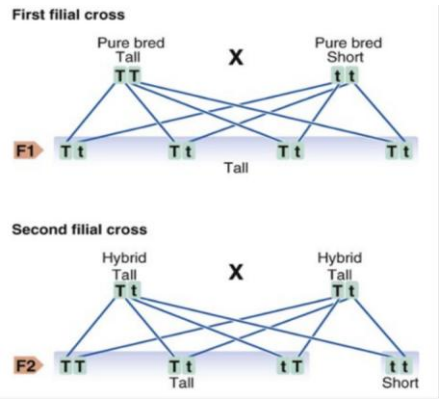
Year 1900	Now
Chromosomes were barely visible	Chromosomes can be rapidly analyzed
DNA sequencing was not possible	Sequence of entire genome has been published

Current Understanding of Genetics

- Mainly based on the work of the Austrian monk Gregor Mendel (1822–1884).
- In 1865, he presented the results of his breeding experiments on garden peas.
- Mendel's observations remained unnoticed until 1900, 16 years after his death.
- Mendel's work can be considered as the discovery of genes and how they are inherited.
- In recognition of Mendel's enormous contribution, the term **Mendelian** is commonly used to different patterns of inheritance by single-gene characteristics and to disorders result from defects in a single gene.

Mendel's Experiments

- Mendel studied contrasting characters in the garden pea.
- When strains bred for a feature such as tallness were crossed with plants bred to be short all of the offspring in the first filial or F1 generation were tall.
- When plants in F1 generation were interbred, this led to both tall and short plants in a ratio of **3 : 1**



Pea Traits studies by Mendel

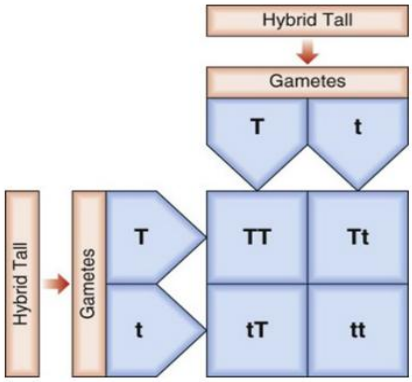
Pea trait	Dominant trait		Recessive trait		Numbers in second generation (F2)	Ratio
Seeds						
Seed shape	Round		Wrinkled		5474:1850	2.96:1
Seed colour	Yellow		Green		6002:2001	2.99:1
Whole plants						
Flower colour	Purple		White		705:224	3.15:1
Flower position	Axial		Terminal		651:207	3.14:1
Plant height	Tall		Short		787:277	2.84:1
Pod shape	Inflated		Constricted		882:299	2.95:1
Pod colour	Green		Yellow		428:152	2.82:1

Mendel's Observation

- Characteristics that were manifest in the F1 hybrids were referred to as **dominant**.
- Those that reappeared in the F2 generation were described as being **recessive**.
- Mendel proposed that the plant characteristics were controlled by a pair of factors, one of which was inherited from each parent.
- The pure-bred plants, with two identical genes, used in the initial cross are referred to as **homozygous**.
- The hybrid F1 plants, each of which has one gene for tallness and one for shortness, is referred to as **heterozygous**.
- The genes responsible for these contrasting characteristics are referred to as **allelomorphs** or **alleles**.

Punnett Square

- An alternative method for determining **genotypes** in offspring involves the construction of a Punnett square.

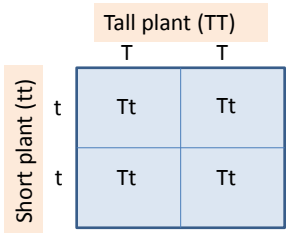


Mendel's Laws of Inheritance

- Law of Uniformity (Law of Dominance)
- Law of Segregation
- Law of Independent Assortment

Law of Uniformity

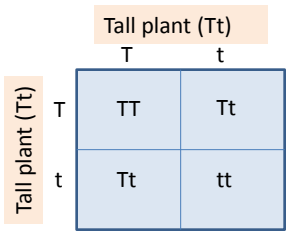
- When two homozygotes with different alleles are crossed, all of the offspring in the F1 generation are identical and heterozygous.
- Offspring will have only the dominant trait in the phenotype.
- In other words, the characteristics do not blend and can reappear in later generations.



Parent plants (P generation)		Offspring (F1 generation)	
Genotype	Phenotype	Genotype	Phenotype
TT x tt	Tall x Short	100% Tt	100% Tall

Law of Segregation

- Each person possesses two genes for a particular characteristic, only one of which can be transmitted at any one time.
- During the formation of gametes (eggs or sperm), the two alleles responsible for a trait separate from each other.
- Alleles for a trait are then "recombined" at fertilization, producing the genotype for the traits of the offspring.



Parent plants (hybrid) (F1 generation)		Offspring (F2 generation)	
Genotype	Phenotype	Genotype	Phenotype
Tt x Tt	Tall x Tall	25% TT 50% Tt 25% tt	75% Tall 25% Short

Law of Independent Assortment

- The members of different gene pairs segregate to offspring independently of one another.
- Mendel noticed that the height of the plant, shape of the seeds and color of the pods had no impact on one another.

- A green pod can have round or wrinkled seeds.
- A yellow pod can also have round or wrinkled seeds.
- Different traits do not influence the inheritance of each other. They are inherited independently.

R- dominant allele for round seeds

r- recessive allege for wrinkle seeds

G- dominant allele for green pods

g- recessive allele for yellow pods

	RG	Rg	rG	rg
RG	RRGG ○	RRGg ○	RrGG ○	RrGg ○
Rg	RRgG ○	RRgg ○	RrGg ○	RRgg ○
rG	RrGG ○	RrGg ○	rrGG ✡	rrGg ✡
rg	RrGg ○	Rrgg ○	rrGg ✡	rrgg ✡

Dihybrid Cross

- Dominant phenotypes for both traits = 9
- Dominant for first, recessive for second = 3
- Dominant for second, recessive for first = 3
- Recessive for both traits = 1

Single hybrid Cross

- Color- 12 green:4 yellow (3:1)
- Shape- 12 round:4 wrinkle (3:1)

As seen in law of segregation

Lecture-2

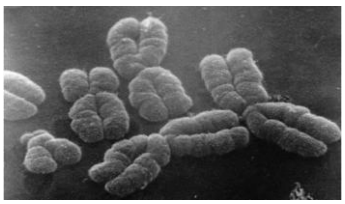
Chromosomes and Cell Division

Chromosomes

- DNA is packaged into **chromosomes** and can be considered as being made up of tightly coiled long chains of genes.
- Unlike DNA, chromosomes can be visualized during cell division using a light microscope, under which they appear as threadlike structures or 'colored bodies'.
- The word *chromosome* is derived from the Greek *chroma* (= color) and *soma* (= body).
- Chromosomes are the factors that distinguish one species from another and that enable the transmission of genetic information from one generation to the next.
- Their behavior at somatic cell division in mitosis ensures that each daughter cell retains its own complete genetic complement.
- Similarly, their behavior during gamete formation in meiosis enables each mature ovum and sperm to contain a unique single set of parental genes.

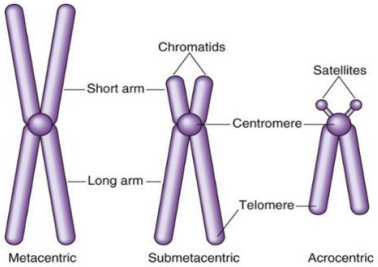
Morphology of Chromosomes

- At the submicroscopic level, chromosomes consist of an extremely elaborate complex, made up of supercoils of DNA.
- Under the electron microscope chromosomes can be seen to have a rounded and rather irregular morphology.
- However, most of our knowledge of chromosome structure has been gained using light microscopy.
- Special stains selectively taken up by DNA have enabled each individual chromosome to be identified.



Morphology of Chromosomes

- Morphologically chromosomes are classified according to the position of the centromere.
- If this is located centrally, the chromosome is **metacentric**.
- If located in an intermediate position the chromosome is **submetacentric**.
- If located terminally, it is **acrocentric**.
- Acrocentric chromosomes sometimes have stalk-like appendages called **satellites** that form the nucleolus of the resting interphase cell and contain multiple repeat copies of the genes for ribosomal RNA.



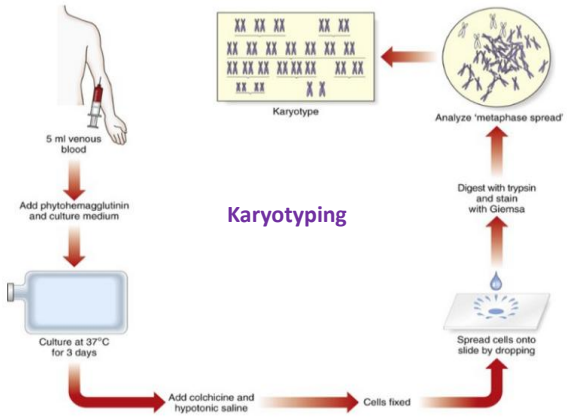
- Chromosomes are best seen when they are maximally contracted and genes are not being transcribed (Metaphase).
- Chromosome can be seen to consist of two identical strands known as **chromatids** or **sister chromatids**, which are the result of DNA replication having taken place during the S (synthesis) phase of the cell cycle.
- These sister chromatids are joined at a primary constriction known as the **centromere**. Centromeres are responsible for the movement of chromosomes at cell division.
- Each centromere divides the chromosome into short and long arms, designated p (= petite) and q ('g' = grande), respectively.
- The tip of each chromosome arm is known as **telomere**.
- Telomeres play a crucial role in sealing the ends of chromosomes and maintaining their structural integrity.
- Telomeres consist of many tandem repeats of a TTAGGG sequence.
- During DNA replication, an enzyme known as **telomerase** replaces the 5' end of the long strand, which would otherwise become progressively shorter until a critical length was reached when the cell could no longer divide and thus became senescent.
- This is in fact part of the normal cellular aging process, with most cells being unable to undergo more than 50 to 60 divisions. However, in some tumors increased telomerase activity has been implicated as a cause of abnormally prolonged cell survival.

Classification of Chromosomes

- Individual chromosomes differ not only in the position of the centromere, but also in their overall length.
- Based on the three parameters of length, position of the centromere, and the presence or absence of satellites, chromosomes are subdivided into groups labeled A to G.
- A, 1–3; B, 4–5; C, 6–12 and X; D, 13–15; E, 16–18; F, 19–20; G, 21–22 and 1 Y.
- In humans the normal cell nucleus contains 46 chromosomes, made up of 22 pairs of **autosomes** and a single pair of sex chromosomes.
- XX in the female and XY in the male. One member of each of these pairs is derived from each parent.
- Somatic cells are **diploid** having 46 chromosomes.
- Gametes (ova and sperm) have **haploid**, with 23 chromosomes.
- In female each ovum carries an X chromosome, whereas in the male each sperm carries either an X or a Y chromosome.
- Members of a pair of chromosomes are known as **homologs**.
- **Chromatin** (DNA + histone proteins) exists in two main forms. **Euchromatin** stains lightly and consists of genes that are actively expressed. **Heterochromatin** stains darkly and is made up largely of inactive, unexpressed, repetitive DNA.

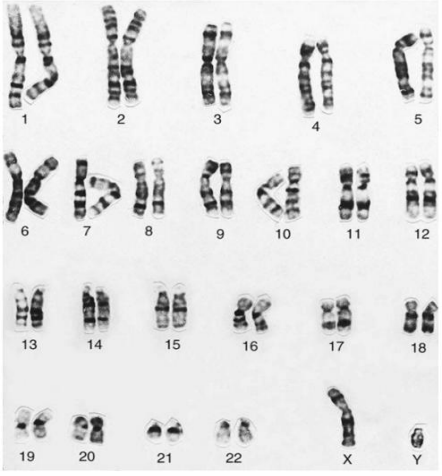
Methods of Chromosomes Analysis

- Lymphocytes from peripheral blood.
- Nutrient medium containing phytohemagglutinin, which stimulates T lymphocytes division, is added.
- Cells are cultured at 37°C for about 3 days.
- Colchicine (inhibitor of spindle formation) is added to arrest cell division during metaphase.
- Hypotonic saline is then added to lyse RBCs.
- Chromosomes are then spread, fixed, mounted on a slide and stained for analysis.



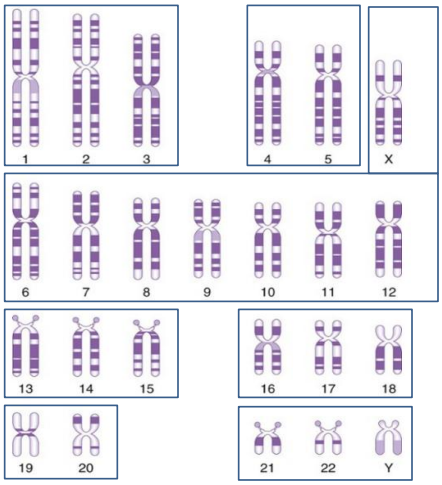
Chromosome Banding

- G (**Giemsa**) banding is used most commonly for staining.
- The chromosomes are treated with trypsin, which denatures their protein, and then stained with a DNA-binding dye (Giemsa) that gives each chromosome a characteristic pattern of light and dark bands.
- G banding provides chromosome analysis with approximately 400 to 500 bands per haploid set.
- Each of these bands corresponds to approximately 6000 to 8000 kilobases (kb) or 6 to 8 megabases (mb) of DNA.



Karyotype Analysis

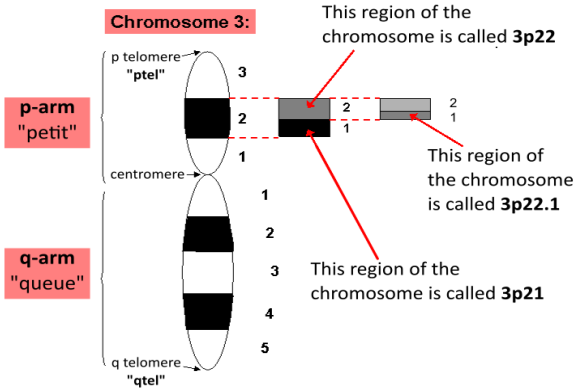
- Counting the number of chromosomes present in a specified cell, sometimes referred to as **metaphase spreads**, followed by careful analysis of the banding pattern of each individual chromosome.
- The banding pattern of each chromosome is specific and can be shown in the form of a stylized karyotype known as an **idiogram**.
- The cytogeneticist analyzes each pair of homologous chromosomes, either directly by looking down the microscope or using an image capture system to photograph and arrange chromosomes in the form of a **karyogram**.



Chromosome Nomenclature

- Chromosome number
- Arm (p or q)
- Region
- Band
- Sub-band

- Example: The chromosomal locus ***3p22.1***
  3 = chromosome 3
  p = p-arm
  22 = region 2, band 2
  1 = sub-band 1



Chromosome Nomenclature

- A normal female karyotype is written as **46,XX**
- A normal male karyotype as **46,XY**
- Sex chromosome abnormalities are described first, followed by autosomal changes in numerical order.
- Numerical changes (gain or loss of chromosome) are listed before structural abnormalities (insertion, translocation, etc).
- **45,X (**classical monosomy X or Turner syndrome)
- **47,XXX (**a female with three X chromosomes)
- **47,XY,+18 (**male with trisomy18)
- **48,XX,+18+21 (**female with both trisomy18 and trisomy21)
- **45,XY,-21 (**male with monosomy21)