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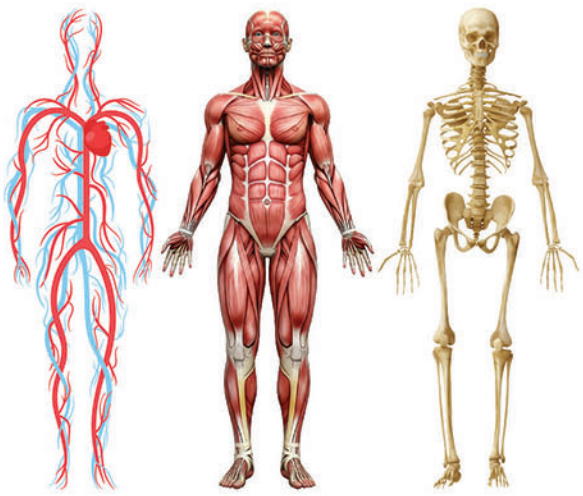

Textbook of General Anatomy

with Case Scenarios & Clinical Applications

3rd Edition



Clinically Integrated with
- **Systemic Anatomy**
- **Radiological Anatomy**
- **Dissection of Cadaver**



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As per the Revised Competency-based Medical Education Curriculum (NMC)

V Subhadra Devi

JAYPEE

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CHAPTER

14

Introduction to Genetics: Chromosomal Aberrations and Clinical Genetics

LEARNING OBJECTIVES

- Chromosome structure and classification
- Numerical and structural abnormalities with examples
- Modes of Inheritance with examples
- Lyon hypothesis
- Mosaicism
- Chimerism
- Pedigree chart

INTRODUCTION

Central dogma of molecular biology: It describes how genetic information flows within cells. It involves **three** main steps:

1. Transcription of DNA to messenger RNA in the nucleus.
2. Transportation of mRNA from the nucleus to the cytoplasm.
3. Translation of mRNA to proteins on ribosomes.

DEOXY RIBONUCLEIC ACID (DNA)

It is the molecule that contains the genetic blueprint for life.

Structure (Fig. 14.1)

- It is made up of two strands twisted like a spiral staircase (double helix).
- Each strand is made up of *nucleotides* the building blocks which include a deoxyribose sugar (S), a phosphate (P) group and a nitrogenous base the purines [(Adenine (A) Guanine (G)] and pyrimidines [Cytosine (C) or Thymine (T)] that shows perfect base pairing (A with T and G with C).
- The total amount of DNA in a cell is about 2 meters in length and fits into the nucleus

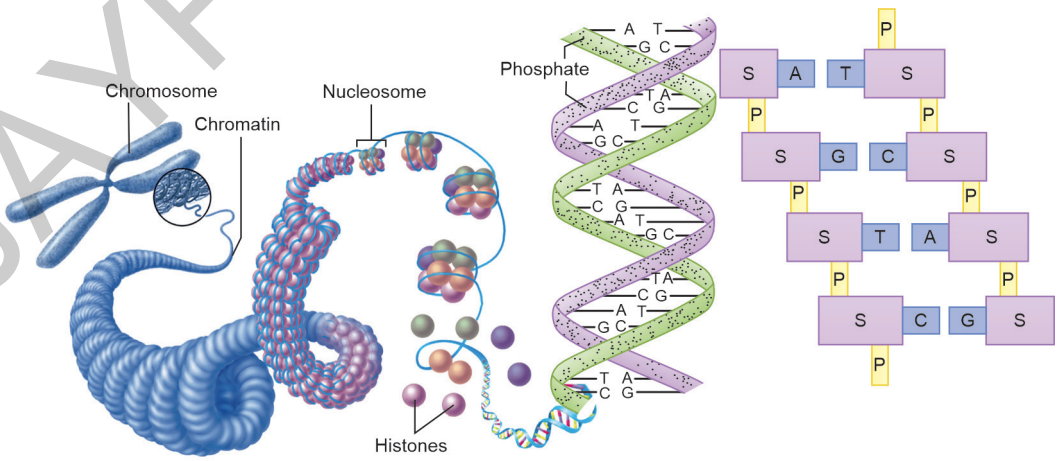

Fig. 14.1: DNA structure, chromatin and chromosome.

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in the form of 23 pairs of chromosomes with each containing a fragment of DNA.

Functions

- DNA stores instructions (genetic code) for making proteins required for working of the cells. It is transmitted from parents to offspring and determines the characters/traits.
- It copies itself before cell division for maintaining the same genetic information in the newly formed cells.

Hierarchy of Organization of DNA

- **DNA double helix:** The basic structure of DNA, containing paired nucleotide bases.
- **Nucleosomes:** DNA wrapped around histone proteins to form nucleosomes, resembling *"beads on a string."*
- **Chromatin:** A fiber formed by nucleosomes coiling and folding, which can be in a more relaxed (**euchromatin**) or tightly packed (**heterochromatin**) state.
- **Chromosome:** In the most condensed state, chromatin fibers further fold to form the chromosome, which is visible during cell division.

CHROMOSOMES: NUMBER, STRUCTURE AND CLASSIFICATION

AN73.1: Describe the structure of chromosomes with classification.
AN73.2: Describe technique of karyotyping with its applications.
AN73.3: Describe the Lyon's hypothesis.

- **Definition:** Deeply stained minute rod-like structures seen in the nucleus of a dividing cell.
- They may be rod-shaped or V-shaped, or J-shaped.
- Formed during cell division by condensation of chromatin.
- Chromosomes are composed of deoxyribonucleic acid (DNA) and proteins.
- Characters of parents are transmitted to offspring through codes borne on strands of DNA.
- Genes are made of such strands of DNA. They are located on chromosomes.

Chromosome Structure

- In a resting cell, chromosomes are not visible under a light microscope, as their chromatin material is highly dispersed. However, during cell division, the chromatin network in the nucleus becomes condensed into several chromosomes.
- Each chromosome consists of two parallel rod-like elements that are called ***chromatids*** **(Fig. 14.2)**.
- The two chromatids are joined to each other at a narrow area that is light staining and is called the ***centromere*** (or kinetochore). In this region, the chromatin of each chromatid is most highly coiled (heterochromatin). The chromatids appear to be a constricted here and this region is called the ***primary constriction***.
- Typically, the centromere is not midway between the two ends of the chromatids, but somewhat toward one end **(Fig. 14.2)**. As a result, each chromatid can be said to have a long arm (denoted by letter q) and a short arm (denoted by letter p).
- Individual chromosomes differ from one another in total length, in the relative length of the two arms, position of centromere and in various other characteristics.

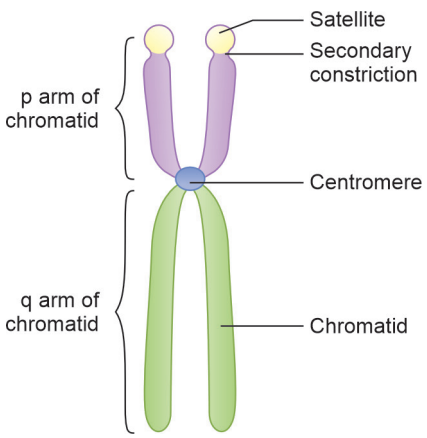

Fig. 14.2: Chromosome—structure.

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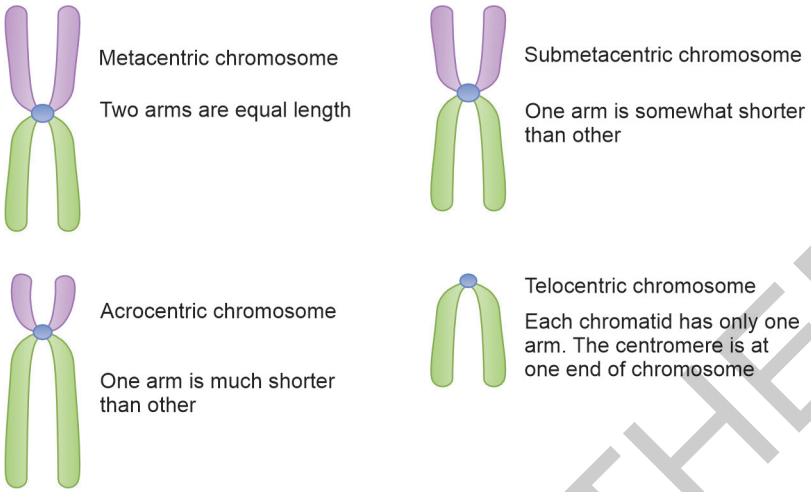

Fig. 14.3: Chromosome classification–based on centromere position and arm length.

- Based on the position of centromere the chromosomes **(Fig. 14.3)** are classified as:
  1. ***Metacentric:*** Centromere is centrally placed and the two arms are of equal length.
  2. ***Submetacentric:*** Centromere is slightly away from the center and the two arms are only slightly different in length.
  3. ***Acrocentric:*** Centromere is nearer to one end and the difference in length of arms is marked.
  4. ***Telocentric:*** Centromere lies at one end.
- These differences enable us to identify each chromosome individually. Classification of chromosomes in this way is called ***karyotyping***. Karyotyping makes it possible for us to detect abnormalities in chromosome number or in individual chromosomes.
- Additional help in identification is obtained by the presence of ***secondary constrictions*** in some chromosomes. Such constrictions lie near one end of the chromatid. The part of the chromatid distal to the constriction may appear to be a rounded body almost separate from the rest of the chromatid; such regions are called ***satellite bodies***.
- Secondary constrictions are concerned with the formation of nucleoli and are therefore, called ***nucleolar organizing centers***. Considerable help in identification of individual chromosomes can also be obtained using special staining procedures by which each chromatid can be seen to consist of a number of dark and light staining transverse bands.
- Chromosomes are distinguishable only during mitosis. In the interphase (between successive mitoses), the chromosomes elongate and assume the form of long threads. These threads are called ***chromatin***.

Haploid and Diploid Chromosomes

- The number of chromosomes in each cell is fixed for a given species and in human beings, it is 46. This is referred to as the ***diploid*** (or double) number.
- However, in spermatozoa and ova, the number of chromosomes is only half the diploid number, i.e., 23. This is called the ***haploid*** (or half) number.
- After fertilization, the resulting zygote has 23 chromosomes from the sperm (or father), and 23 from the ovum (or mother). The diploid number is thus restored.

Autosomes and Sex Chromosomes

- The 46 chromosomes in each cell can be divided into 44 ***autosomes*** and 2 ***sex***

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chromosomes. The sex chromosomes may be of two kinds, X or Y.

- In a male, there are 44 autosomes, one X-chromosome and one Y-chromosome; while in a woman, there are 44 autosomes and two X-chromosomes in each cell.
- When we study the 44 autosomes, we find that they really consist of 22 pairs, the two chromosomes forming a pair being exactly alike (***homologous chromosomes***).
- In a woman, the two X-chromosomes form another such pair; in a man, this pair is represented by one X- and one Y-chromosome.
- One chromosome of each pair is derived from the mother and the other from the father.

Duplication of Chromosomes (Fig. 14.4)

- The two strands of the DNA molecule separate exposing the bases (A, T, C, G).
- Each original strand acts as a template. New bases are added: **Adenine (A)** pairs with **Thymine (T) Cytosine (C)** pairs with **Guanine (G)**.

Each new strand joins with its matching original strand, forming two identical DNA molecules and now the cell is ready for division.

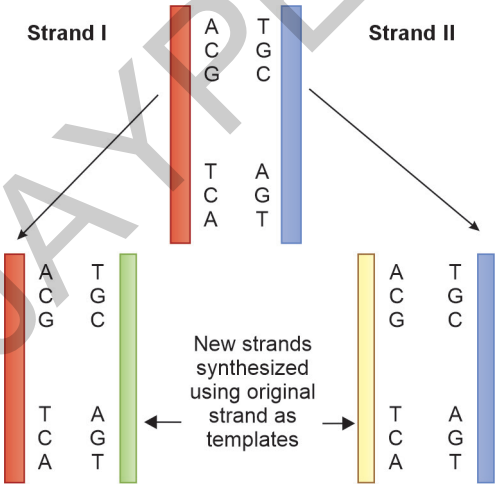

Fig.14.4: Duplication of DNA molecule.

KARYOTYPING

- It is the procedure by which chromosomes can be prepared, photographed, mapped and arranged individually in an individual by applying the criteria described above.
- The purpose of karyotyping is to detect chromosomal abnormalities. The procedure involves preparation from peripheral blood culture.

Procedure for peripheral blood culture: Various steps in karyotype are **(Fig. 14.5)**:

1. ***Collection of blood:*** A sample of 1–2 mL blood is collected by venipuncture in a sterile syringe containing heparin.
2. ***Planting:*** The heparinized blood is added to the 10 mL test tube containing karyotyping medium [RPMI medium

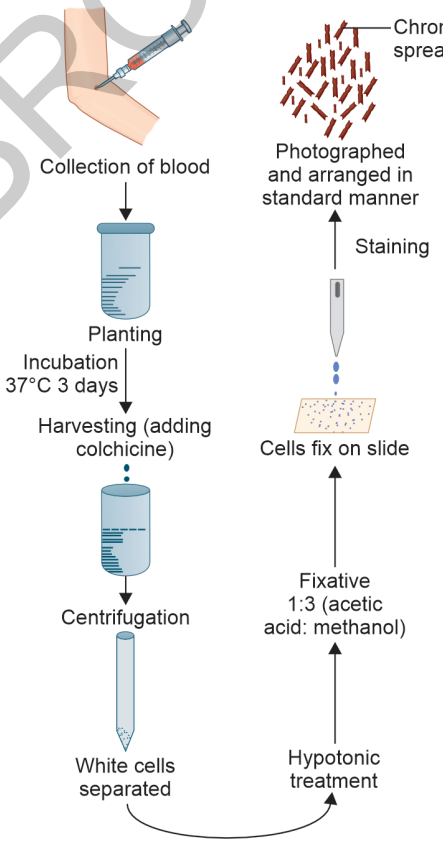

Fig.14.5: Karyotyping—procedure.

Source: IBS embryology, 13th edition.

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supplemented with calf/AB serum, L-glutamine, antibiotic (gentamicin) and phytohemagglutinin M (PHA-M)]. The serum provides nutrition, L-glutamine the amino acids. Gentamicin is an antibiotic to prevent contamination and phytohemagglutinin is a mitotic agent that allows multiplication of cells.

3. ***Incubation:*** For 72 hours at 37°C with shaking of the test tube in between.
4. ***Harvesting:*** At 70 hours colchicine is added to arrest mitosis at metaphase. It arrests cell division at a stage where chromosomes are most distinct.
5. ***Centrifugation:*** Spinning at the rate of 1,500 rpm for 7 minutes and removal of supernatant fluid. The cells will settle at the bottom of the test tube.
6. ***Treatment with hypotonic saline (sodium citrate):*** Addition hypotonic saline solution to rupture red blood cells, swelling of white blood cells and separation of chromatids.
7. ***Fixation of cells:*** By adding 1:3 glacial acetic acid: methanol.
8. ***Dropping of cells on a slide:*** Cell fixation on slide by dropping the cells from a pipette from a height for chromosomal spread (without overlapping).
9. ***Staining:*** The slide is treated with trypsin that partially digests the chromosomes. Later slide is subjected to Giemsa staining.
10. ***Microscopic observation and photography:*** Chromosomes to be observed under microscope and photomicrograph to be obtained.

Karyotype

- It is also known as **Idiogram**.
- It is standard arrangement of a photographed metaphase spread of chromosomes that are arranged in order of decreasing length. The photographs are cut, and the chromosomes are arranged in proper sequence.

TABLE 14.1: Classification of chromosomes.

Group	Pairs of chromosomes	Features
A.	1–3	Long, metacentric
B.	4, 5	Long, submetacentric
C.	6–12 + X Chromosome	Medium, submetacentric
D.	13–15	Medium, acrocentric, satellite bodies +
E.	16–18	Short, submetacentric
F.	19, 20	Short, metacentric
G.	21, 22 + Y Chromosome	Short, acrocentric, satellite bodies +

- In this way a map of chromosomes is obtained and abnormalities in their number, size and shape can be observed.
- In many cases specific chromosomal abnormalities can be correlated with specific diseases.
- According to **Denver system of classification**, the chromosomes including sex chromosomes are arranged into seven groups based on their length, position of centromere and presence of satellite bodies as shown in **Table 14.1**.
- Karyotypes of a normal male and a female are shown in **Figures 14.6 and 14.7**.

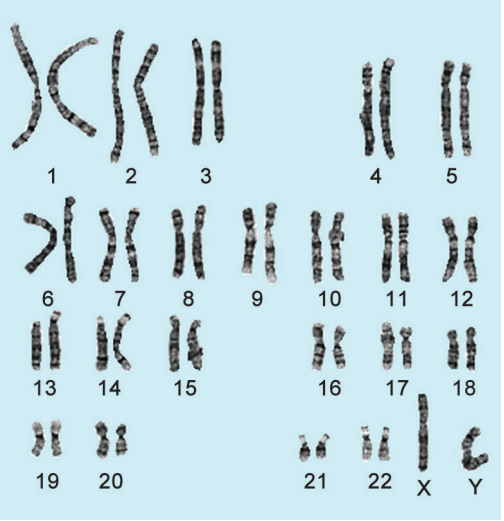

Fig. 14.6: Karyotype—normal male.

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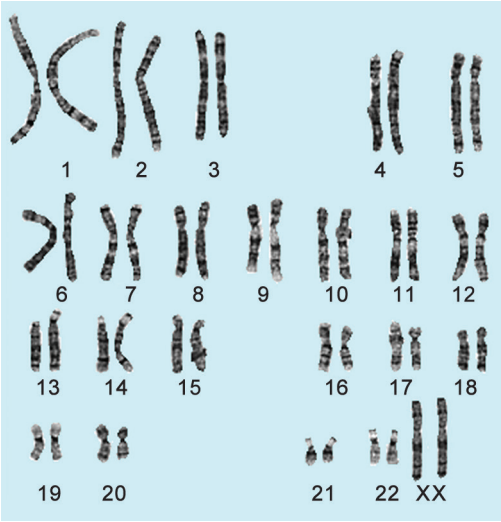

Fig. 14.7: Karyotype—normal female.

LYON HYPOTHESIS AND SEX CHROMATIN

Chromatin

- Chromosome (CHS) in interphase
- Highly extended filaments forming diffuse network

Euchromatin

- The uncoiled portion of CHS during interphase
- Genetically active

Heterochromatin

- The coiled portion of CHS in interphase
- Genetically inert

Lyon Hypothesis

- Dr Mary Lyon proposed that one of the two X chromosomes in normal female is functional, and the other is condensed and inactive in early developmental period. It is called ***Barr body*** or ***sex chromatin***.
- This condensed chromosome can be paternal or maternal in origin. Thereafter the same X chromosome is inactivated in all the daughter cells. This process of inactivation of X chromosomes are called ***lyonisation***.
- In the case of normal males there is no sex chromatin or Barr body as they have only one X chromosome which is active.
- The process of inactivation occurs around 15th day of gestation.
- The mechanism of inactivation is the methylation of DNA initiated by X-inactivation center located on the long arm of X chromosome close to centromere.
- Net effect of inactivation is to equalize the phenotypes in males and females for the genes carried on X chromosome. This phenomenon is called **dosage compensation**. In a female with 3 X chromosomes (Triple X syndrome/Trisomy X/Super female) the number of Barr bodies will be 2 and in a female with one X chromosome there will be no Barr body (Turner's syndrome with XO karyotype). A man of Klinefelter's syndrome with 47 XXY karyotype will have single Barr body. Hence, the number of Barr bodies visible at interphase are always one less than the total number of X chromosomes.

Sex Chromatin

- Small, dark-staining, condensed mass of inactivated X-chromosome within the nucleus of nondividing cell, i.e., during interphase. Usually located just inside the nuclear membrane of the interphase nucleus.
- Present in most female mammals in the nuclei of all cells except the germ cells.
- Inactive mammalian X-chromosome is always late-replicating, and in eutherian mammals, it is heterochromatic and hypermethylated.
- The term sex chromatin comprises two superficially dissimilar structures:
  1. ***Barr body***, present in epithelial (oral, skin, vaginal, urethral, corneal) and other tissue cells (placenta, dental pulp, skin fibroblasts)
  2. ***Drumstick/Davidson body*** in polymorphonuclear leukocytes.
- Study of sex chromatin is a relatively simple diagnostic test for certain genetic abnormalities.

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Barr Body (Fig. 14.8A)

- Barr bodies are mostly situated at the periphery of the nucleus.
- *Count*: Sex differences: Males 1–2%; females 20–80%.
- *Measurement*: Approximately 1 µm.
- *Barr bodies have several distinct shapes*: Planoconvex/wedge-shaped/rectangular.
- *Maximum no. of Barr bodies/nucleus* = 0 (or) 1.
- *Maximum no. of Barr bodies in diploid cells* = No. of X-chromosomes – 1. In tetraploids, it is two less than the no. of X-chromosomes, and in octaploids, it is four less than the no. of X-chromosomes. Patients with 4X-chromosomes have three Barr bodies.

Drumstick (Davidson Body) (Fig. 14.8B)

- Appears as a deeply stained body attached to the nucleus of the polymorphonuclear leukocytes.
- Appendage is attached to a lobe of nucleus by a filament of variable length and thickness.
- It consists of a head of about 1.5 µm in diameter.
- Seen in all types of polymorphonuclear leukocytes but only that in neutrophils to be considered.
- *Incidence*: 2–3% or 6/500 cells in normal females.
- It is a highly condensed X chromosome which, in the presence of another X chromosome, may be extruded from the main body of the nucleus of polymorphonuclear leukocytes.

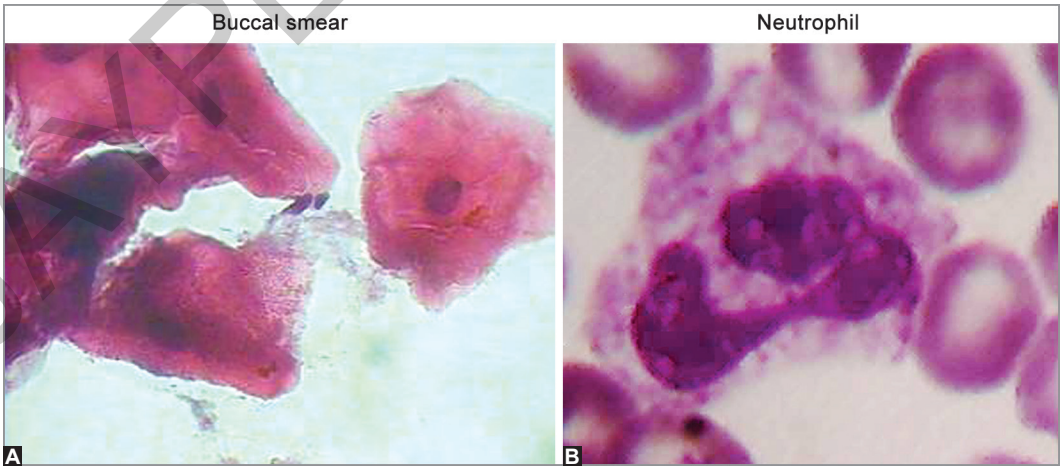
CHROMOSOMAL ABNORMALITIES

AN75.1: Describe the structural and numerical chromosomal aberrations.
AN75.2: Explain the terms mosaics and chimeras with example.
AN75.3: Describe the genetic basis and clinical features of Prader Willi syndrome, Edward syndrome, Patau syndrome, Down syndrome, Turner syndrome and Klinefelter syndrome.
AN75.4: Describe genetic basis of variation: polymorphism and mutation.
AN75.5: Describe in brief: genetic counseling, karyotyping, FISH, PCR and genetic sequencing.

Chromosomal abnormalities are classified broadly into numerical and structural. In each, those involving autosomes and those involving sex chromosomes are included **(Tables 14.2 and 14.3)**:

Patau's Syndrome

It is an autosomal abnormality with ***trisomy of chromosome 13*** or ***trisomy D***.



Figs. 14.8A and B: Sex Chromatin: (A) Barr body in buccal smear; (B) Drumstick (Davidson body) in neutrophil.

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TABLE 14.2: Structural abnormalities of chromosomes.

Abnormality	Feature	Clinical condition
Deletion	Loss of segments of a chromosome	▫ Wolf-Hirschhorn syndrome – 4p- ▫ Cri-du-chat syndrome – 5p-
Microdeletion	Deletion detected by high resolution banding	▫ Proximal part of long arm of 15 q ▫ If paternally inherited–Prader-Willi syndrome ▫ If maternally inherited–Angel man syndrome
Inversion	Detachment of a part of chromosome by 2 breaks	Rarely causes problem
Duplication	Abnormal splitting of chromosomes	Depends on location, size and genes involved in duplication. *Example:* PMP 22 gene duplication of CHS 17 in Charcot-Marie-Tooth disease
Isochromosome	▫ Duplication of one entire chromosome arm and deletion of another chromosome arm ▫ This results in a chromosome with two identical arms—either two short arms or two long arms	Duplication of genes
Ring chromosome	▫ Chromosomes are deleted at both ends ▫ Deleted sticky ends adhere to each other in the form of a ring	Clinical manifestations depend on deletion of specific genes
Translocation	Exchange of segments between non-homologous chromosomes	▫ May not always produce abnormal phenotype ▫ But it can lead to formation of unbalanced gametes ▫ Carries high risk of abnormal progeny

TABLE 14.3: Numerical abnormalities of chromosomes.

Name of the abnormality	Numerical anomaly	Autosomal/sex chromosomal
Down syndrome	Trisomy, 21	Autosomal
Edward's syndrome	Trisomy, 18	Autosomal
Patau's syndrome	Trisomy, 13	Autosomal
Turner syndrome	45, XO	Sex chromosomal
Klinefelter's syndrome	47, XXY	Sex chromosomal

Clinical Features

- There will be gross malformations of brain at birth.
- Microphthalmia, cleft lip or cleft palate
- Polydactyly and congenital heart disease
- The newborn will not survive for more than few weeks.

Edward's Syndrome

It is an autosomal abnormality with ***trisomy of chromosome 18*** or ***trisomy E***.

Clinical Features

- Elongated face with flat nose, low set ears, micrognathia
- Rocker bottom feet
- Usually, they will not survive beyond infancy.

Down Syndrome

It is also known as ***mongolism*** because of the facial features of a Mongolian.

- Down syndrome is the result of an error in meiosis where an egg or sperm cell gets an extra chromosome 21.
- The chances are more if the mother's age is >35 years (1 in 1,400 in <25 years to 1 in 100 if the age is 40 years).

Clinical Features (Fig. 14.9)

- Mentally retarded-IQ 25–75
- Poor growth- short stature

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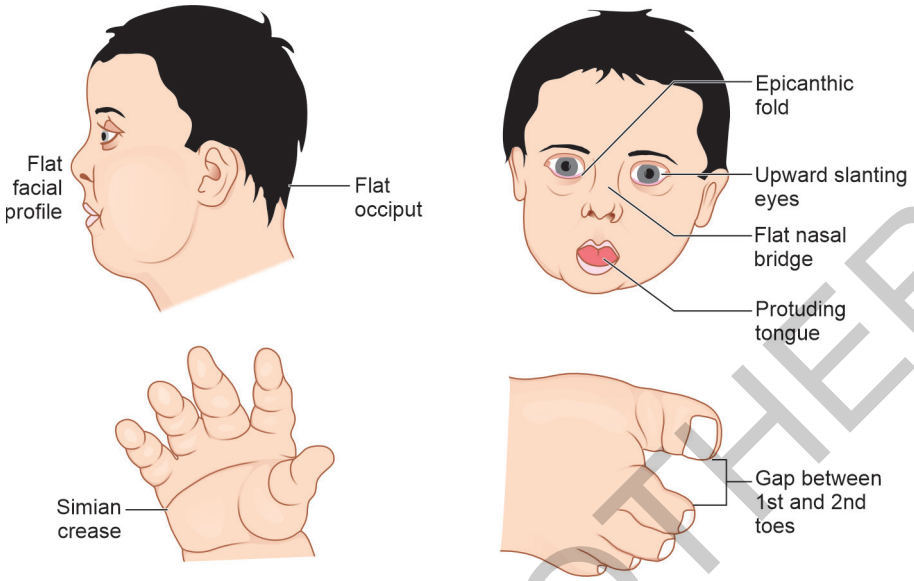

Fig. 14.9: Down syndrome–facial features.

Source: IBS embryology, 13th edition.

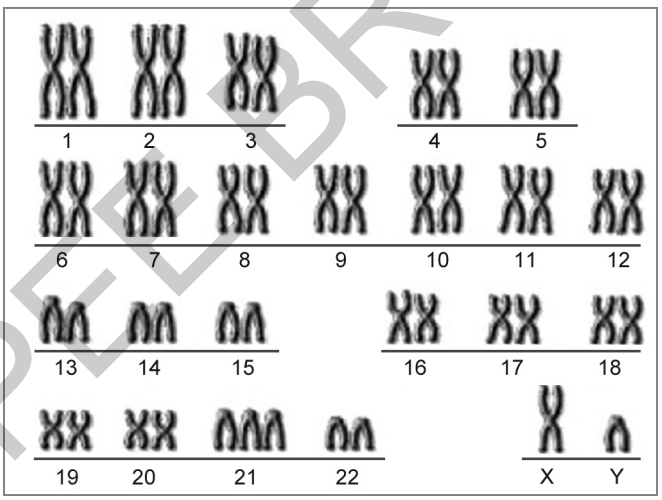

Fig. 14.10: Down syndrome–karyotype

Source: IBS embryology, 13th edition.

- Poor muscle tone
- Major heart defect—40% incidence
- *Facial features*—small head, round face, epicanthal fold, protruding tongue, small ears, sloping palpebral fissure.
- *Hands*—short and broad, and single palmar crease (Simian crease).
- Widely spaced great toe.

Chromosomal and genetic basis: Because of nondisjunction **extra chromosome 21(trisomy 21)** was present **(Fig. 14.10)**. Defect in the Down syndrome critical region 1 (DSCR1) on chromosome 21 is responsible for this condition.

Recurrence risk: Increases with increase in the age of mother.

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Counseling: Based on the results of the following prenatal diagnostic tests:

- Amniocentesis
- Triple test-maternal serum at 16 weeks gestation
  1. Alfa-fetoproteins-reduced
  2. Estriol-reduced
  3. Human chorionic gonadotropin-increased
- Inhibin (A level)—increased

Turner Syndrome

It is a sex chromosomal abnormality where there will be ***partial or complete absence of one X chromosome***.
Incidence: 1 in 5,000 to 1 in 10,000 live births.

Clinical Features (Fig. 14.11)

- Short stature
- Webbing of neck
- Cubitus valgus
- Low set ears
- Shield/broad chest with widely spaced nipples
- Brown nevi
- Normal or slightly retarded intelligence

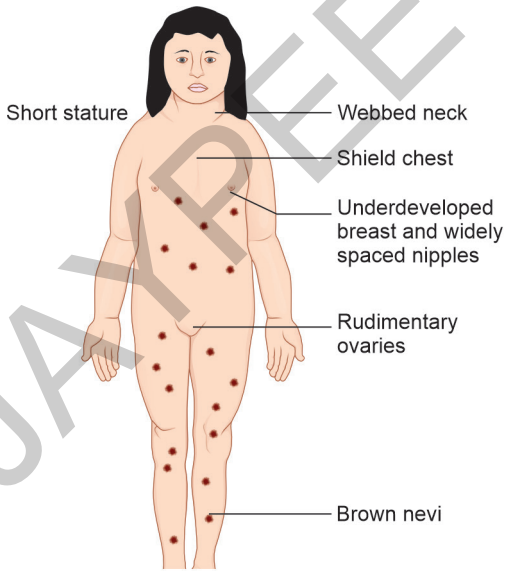

Fig. 14.11: Turner syndrome–facial features.
Source: IBS embryology, 13th edition.

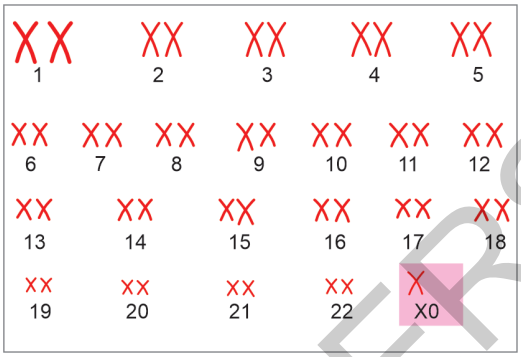

Fig. 14.12: Turner syndrome–karyotype.
Source: IBS embryology, 13th edition.

- Rudimentary ovaries or streak gonads
- Amenorrhea

Buccal smear: Barr body absent due to nondisjunction in gametogenesis.
Karyotype: Monosomy of X CHS - 45 XO **(Fig. 14.12)**.

Klinefelter Syndrome

It is also called ***XXY syndrome***. It affects physical and intellectual development in boys.
Incidence: 1 in 1,000 newborns.

Clinical Features (Fig. 14.13)

- At adolescence age the male comes with the complaint of infertility.
- The individual is tall with some degree of mental retardation.
- Small testes
- Normal penis and scrotum
- Scanty pubic and facial hair
- Gynecomastia

Genetic screening: Karyotype 47, XXY and Barr body positive **(Fig. 14.14)**. It is due to meiosis II nondisjunction.

ALLELE

A normal (somatic) cell has two variants (alleles) for a trait/character. A gamete (sperm, egg) contains one allele, randomly chosen from the two somatic alleles. *Example:* If you have one allele for brown eyes (represented as B) and one for blue eyes (represented as b),

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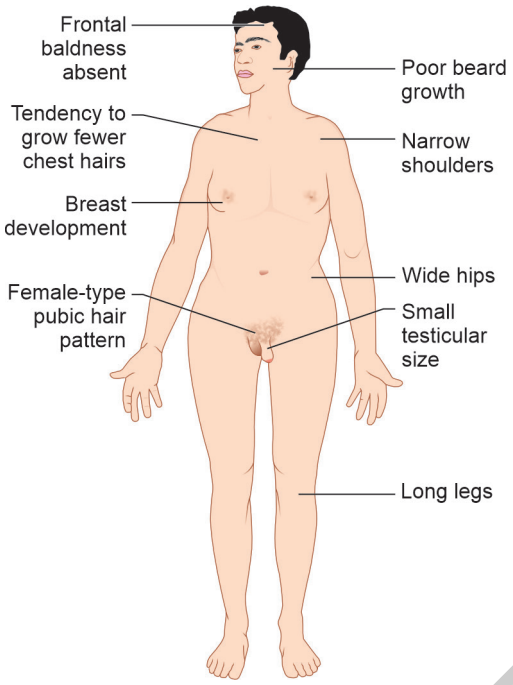

Fig. 14.13: Klinefelter syndrome–facial features.
Source: IBS embryology, 13th edition.

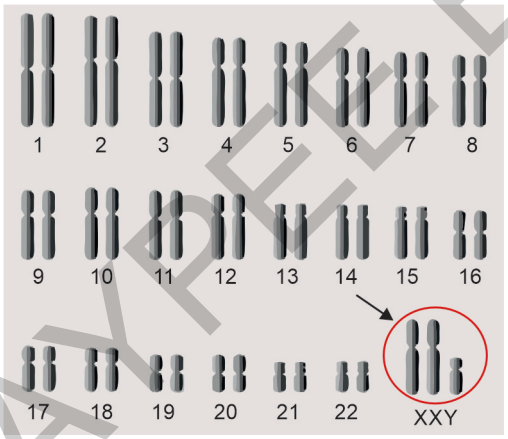

Fig. 14.14: Klinefelter syndrome–karyotype.
Source: IBS embryology, 13th edition.

somatic cells have alleles for both (Bb) and each gamete will carry one of it (B or b) chosen randomly.

If the two alleles are different (***heterozygous*, e.g., Bb**), the trait associated with only one of these will be visible (**dominant**) while the other will be hidden (**recessive**). *Example:* B is dominant, b is recessive. If two alleles are same (dominant/recessive) it is **homozygous (e.g., BB/bb).**

PUNNETT SQUARE (FIG. 14.15)

- It is a diagram used to predict the result of a genetic cross.
- Used to determine the probability of an offspring having a particular genotype.
- For the above example it can be shown as follows:
  - **Genotype:** The state of the two alleles at one or more locus associated with a trait/character.
  - **Phenotype:** The state of the observable trait/character.
- Genotype for brown and blue eyes have been shown in **Table 14.4.**

GENE POLYMORPHISM AND MUTATION

Polymorphism

- If more than one allele occupies a specific locus of a gene in a population that gene is polymorphic.

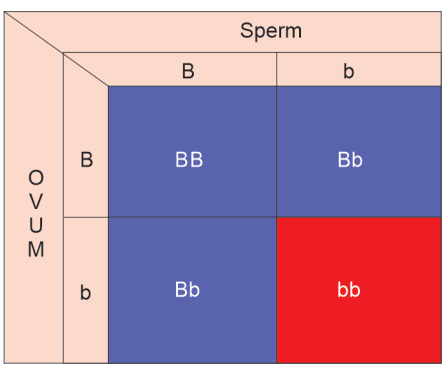

Fig. 14.15: Punnett square.

TABLE 14.4: Genotype for brown and blue eyes.

Genotype	Phenotype
BB (homozygous)	Brown eyes
Bb (heterozygous)	Brown eyes
bb (homozygous)	Blue eyes

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- In addition, there should be a minimum of 1% occurrence if each allele in the population to be considered for polymorphism. It is inheritance of genes in different forms called alleles that will have different DNA sequences.
- A polymorphic variant of a gene can lead to abnormal expressions of protein that may be associated with disease. *Examples*: Increased incidence of hypertension, ischemic stroke and coronary artery disease is linked to a polymorphic variant of the *CYP4A11* gene that reduces the enzyme activity for regulating blood pressure. Another common example is the genes coding for the major histocompatibility complex (MHC) located on chromosome 6.
- Polymorphisms can be identified in the laboratory using polymerase chain reaction (PCR) to amplify the sequence of a gene followed by DNA sequencing.
- Clinical importance of polymorphism is in lung cancer and asthma.
- Gene polymorphism has an important role in drug designing (pharmacogenetics).

Mutation

- Gene mutation is a permanent alteration in the DNA sequence. The size of mutations ranges from a single DNA base pair to a large segment of a chromosome involving multiple genes. The mutations can be germline (resulting from fertilization) or somatic.
- The causes of mutation can be radiation, UV rays, X-rays, exposures to chemicals, etc. The agents that cause mutation are *mutagens*.
- Germline mutations occur at the time of fertilization where if the DNA of one germ cell is showing mutation the cells resulting from fertilization with that show the mutation in all its cells.
- In *somatic cell mutation* as the changes are caused by environmental factors, for example, UV radiation affects only certain cells and is not passed on to the generations.
- The types of mutation are duplication, insertion, deletion if it is involving chromosomes.

MOSAICISM

- It is a condition where somatic cells of the body contain more than one genotype. This is due to nondisjunction during early mitosis resulting in loss of chromosomes from some of the trisomic cells.
- Examples include mosaic Down's syndrome where some of the cells show trisomy and some do not.

CHIMERISM

- The individual presents two or more genetically different cell lines derived from more than one zygote.
- There are two types of chimeras: Dispermic chimeras and blood chimeras.
- Dispermic chimeras result from fertilization of two ova by genetically different X and Y bearing sperms. This results in the formation of two zygotes that fuse to form a single embryo.
- Blood chimeras result when two nonidentical twins in utero exchange their cells through placental barrier. In such cases 90% of cells of one twin show one type of karyotype (XY) with one type of blood group (B), whereas other twin shows 90% of cells with a different karyotype (XX) with different blood group (A).

The difference between chimerism and mosaicism is that in mosaicism the cell lines are derived from single zygote whereas in chimerism different cell lines result from fusion of different zygotes.

GENETIC COUNSELING

Definition

It is a process where an individual affected or at risk for a genetic condition is clearly informed of the details for taking an informed decision.

The details that are provided are:

- Probability of suffering from the disorder

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- Probability of transmitting the disorder to the offspring
- Possible consequences of the disorder
- Potential means available for treating the disorder
- Potential means of avoiding occurrence of malformation or disease in question

The people who can provide these details are the:

- Family doctor for common genetic disorders
- Pediatrician
- Obstetrician
- Genetic counselor

Various aspects of genetic counseling are:

- Risk estimation of developing a disorder or its transmission to the offspring.
- Providing information about prenatal and other diagnostic tests.
- Psychological support to the family
- Information about specialized services, like speech or educational therapy.

People who need genetic counseling are:

- Maternal age >35 years
- History of recurrent miscarriages
- Birth of a fetus with anomalies
- Family history of genetic abnormalities

FLUORESCENCE IN SITU HYBRIDIZATION TECHNIQUE

- Fluorescence in situ hybridization (FISH) is a molecular cytogenetic technique for visualizing specific DNA or RNA sequences on chromosomes or within cells using fluorescently labeled probes that bind to complementary sequences in a sample.
- **Uses:** For detecting chromosomal deletions, duplications, translocations, gene localization or mutation and cancer diagnosis.

POLYMERASE CHAIN REACTION

- Polymerase chain reaction (PCR) is a technique in molecular biology that allows scientists to amplify tiny amounts of DNA into millions of copies
- It is used in genetic testing (mutations, gene editing) forensic laboratories (DNA finger printing, paternity testing, disaster victim identification), medical diagnostic labs (COVID-19 and HIV), and biotechnology research (cloning).

GENETIC/DNA SEQUENCING

- It is the process of determining the exact order of nucleotides (A, T, C, G) in a DNA molecule, i.e., genetic code.
- The sequencing can be observed in a single gene, a chromosome, or an entire genome.
- It is used for observing mutations, disease risk and in personalized medicine.
- The different types are: Sanger sequencing, next generation sequencing (NGS), whole genome sequencing (WGS), whole exome sequencing (WES).
- In the field of medicine, it is used for identification of genetic disorders, cancer mutations and in personalized medicine.

SYMBOLS USED FOR CHROMOSOMAL NOMENCLATURE

Symbols used in karyotypes have been shown in **Table 14.5**.

TABLE 14.5: Symbols used in karyotype.

Symbol	Karyotype
46 XX	Normal female
46 XY	Normal male
A – G	Chromosome groups
1 – 22	Autosome numbers
X, Y	Sex chromosomes
46/47	Mosaicism
del	**Deletion**
dup	**Duplication**
inv	**Inversion**
r	**Ring chromosome**

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INHERITANCE OF GENETIC DISORDERS

AN74.1: Describe Mendelian and non-Mendelian inheritance. Explain various modes of inheritance with examples.
AN74.2: Draw pedigree charts for the various types of inheritance and give examples of diseases of each mode of inheritance.
AN74.3: Describe multifactorial inheritance with examples.
AN74.4: Describe the genetic basis and clinical features of achondroplasia, cystic fibrosis, vitamin D resistant rickets, hemophilia, Duchenne's muscular dystrophy and sickle cell anemia.

- The pattern of inheritance of genetic disorders facilitates the diagnosis of the disorder, calculation of risk of the disorder in the present and future offspring and for counseling the parents.
- By obtaining family history, a ***pedigree chart*** is prepared to understand the pattern of occurrence (inheritance) of the disease in the families.
- By drawing a **Punnett square** the percentage risk can be interpreted.

Pedigree Chart

- It is a pictorial representation of generations of a family showing the information of family members and their relationship to one another, marriages among cousins(consanguineous) including details of live births, stillbirths and abortions, etc.
- A pedigree chart shows genetic connections among individuals using standardized symbols. For drawing pedigree charts certain standard symbols are used **(Fig. 14.16)**. Knowledge of probability and Mendelian patterns are required for understanding the basis for a trait.
- Conclusions are most accurate if they are drawn using large number of pedigrees (generations). A sample pedigree chart is presented in **Figure 14.17**.
- Importance of understanding the pattern of inheritance of genetic disorders is it facilitates:
  - Diagnosis of genetic disorders

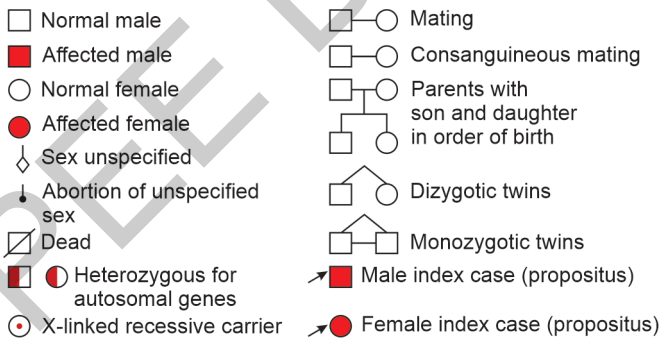

Fig. 14.16: Symbols used in pedigree chart.

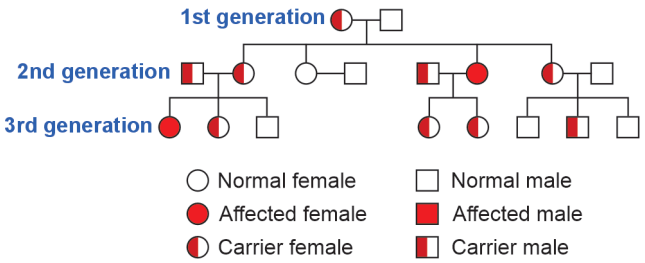

Fig. 14.17: Sample pedigree chart.

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- Calculation of the risk of getting a genetic disease in the present and future offspring
- Genetic counseling: Suggest preventive methods for genetic disorders.

According to the ***mode of transmission genetic disorders*** can be classified as follows:

Mendelian or single gene disorders:

1. Autosomal dominant inheritance
2. Autosomal recessive inheritance
3. X-linked dominant inheritance
4. X-linked recessive inheritance
5. Y-linked inheritance

Nonmendelian disorders: These result from:

1. **Incomplete dominance:** It is a heterozygous phenotype.
   Example: Familial hypercholesterolemia
2. **Codominance:** Both alleles are fully expressed in the phenotype.
   Example: AB blood group
3. **Mitochondrial inheritance:** It is passed from mother to offspring via mitochondrial DNA.
   Example: Leber's hereditary optic neuropathy (LHON)
4. **Genomic imprinting:** Expression depends on whether the gene is inherited from the mother or father.
   Examples: Prader-Willi syndrome (paternal deletion) and Angelman syndrome (maternal deletion)
5. **Anticipation:** Disorder worsens or appears earlier in successive generations.
   Examples: Huntington's disease, myotonic dystrophy
6. **Polygenic inheritance:** Multiple genes contribute to a trait.
   Examples: Type 2 diabetes, hypertension, schizophrenia

Autosomal Dominant Inheritance (Fig. 14.18)

- The mode of transmission is vertical. An affected person has an affected parent.
- There is 50% of chance of dominant trait being transmitted to offsprings.
- Both males and females are equally affected.

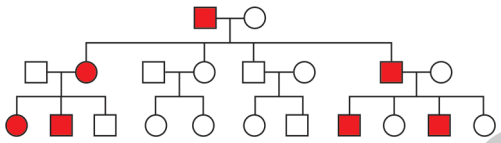

Fig. 14.18: Pedigree chart of autosomal dominant inheritance.

- Dominant genes are expressed in heterozygotes.
- Delayed age of onset.
- The trait appears in every generation without skipping. An unaffected offspring does not transmit the disease.
- *Examples:* Achondroplasia, angioneurotic edema, Huntington' s chorea, multiple neurofibromatosis, osteogenesis imperfecta

Achondroplasia

Incidence: 1 in 15,000 to 40,000

Features:

- Short stature (nonproportional)
- Rhizomelic shortening
- Midface hypoplasia
- Frontal bossing

Genetic basis: It is caused by a mutation in fibroblast growth factor receptor 3 (FGFR3) gene on CHS 4p.

Pattern of inheritance: It shows autosomal dominant inheritance. This condition can be detected by prenatal ultrasound examination.

Autosomal Recessive Inheritance (Fig. 14.19)

- **Horizontal transmission:** The trait appears in sibs and parents are normal.

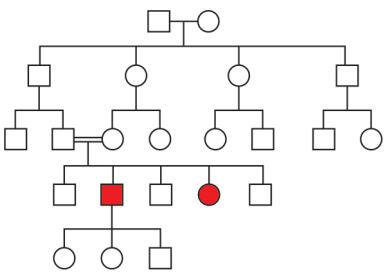

Fig. 14.19: Pedigree chart of autosomal recessive inheritance.

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- **History of consanguineous marriage:** The parents are blood related. The couple are carriers of abnormal genes.
- About 25% chance of having an affected child (double dose of abnormal gene) in a carrier couple.
- Early age of onset
- Both males and females have an equal chance of getting affected.
- *Examples:* Cystic fibrosis, Inborn errors of metabolism (albinism, phenylketonuria), hemoglobinopathies (sickle cell anemia, thalassemia).

Cystic fibrosis

Incidence: 1 in 2,500 people in the population

Clinical features:

- Breathing difficulty and respiratory infections.
- Over time, mucus buildup in the respiratory passages and infections can lead to permanent lung damage, formation of scar tissue (fibrosis) and cysts in the lungs.
- Mucus can also block the digestive tract and pancreas, leading to digestive problems—malnutrition, cirrhosis of liver. Small bowel obstruction in newborns because of thickened meconium (meconium ileus).

Genetic basis: Mutation in the cystic fibrosis transmembrane conductance (CFTR) gene on CHS 7 that controls the flow of salt and fluids in and out of cells. Defects in this gene affect the cells that produce mucus, sweat and digestive juices. Causes accumulation of thick, sticky mucus in the various ducts of the body especially lungs and pancreas. Seen only when both copies of the gene (inherited from each parent) are defective.

Pattern of inheritance: Autosomal recessive inheritance

Importance of genetic screening:

- Prenatal diagnosis of a fetus at risk
- Carrier testing for at-risk relatives and their reproductive partners
- Preimplantation genetic diagnosis for pregnancies at high risk for CF.

Sickle cell anemia

- Hemoglobinopathy due to change in the structure of hemoglobin chain
- **Sickling of RBC:** Some red blood cells become deformed—look like sickles used to cut wheat. Not enough red blood cells to carry oxygen throughout your body leads to hemolytic anemia.
- Obstruction of small arteries due to clumping of defective RBC resulting in thrombosis, ischemia, infarction. Autosomal recessive inheritance. Affected person is homozygous for mutant gene.
- Mutation in the gene responsible for coding beta polypeptide chain—hemoglobin beta gene on short arm of CHS 11.

Features:

- **Due to destruction of RBC:** Splenomegaly
- **Due to anemia:** Severe fatigue or tiredness
- **Bone marrow hypertrophy:** Frequent infections
- **Due to obstruction of small vessels (thrombosis):** Frequent episodes of pain in different parts of the body
  - Swelling of hands and feet with associated pain
  - Lung infarcts
  - Cerebrovascular accidents

X-linked Dominant Inheritance (Fig. 14.20A)

- Trait is more frequent in females than in males.
- Affected male transmit the trait to all his daughters not to his sons.
- Affected females if homozygote, transmit to all her children. If affected females are heterozygote, transmit the trait to half her children of either sex.
- *Example*: Vitamin D-resistant rickets, Xg blood groups

Vitamin D-resistant rickets

- It is a hereditary hypophosphatemic rickets due to low levels of phosphate in the blood. This mineral (phosphate) is essential for the normal formation of bones and teeth.

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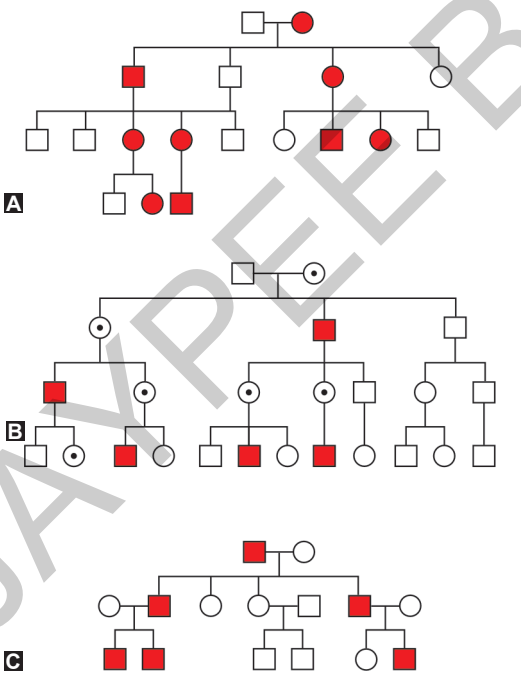
- Signs and symptoms begin in early childhood.

Features: Vary widely.

- Slow growth and the individual is shorter than his peers.
- Abnormalities that interfere with movement and bone pain.
- Characteristic features is bowed legs or knock knees.
- Craniosynostosis—premature fusion of skull bones
- Dental abnormalities
- Enthesopathy—abnormal bone growth with attachment of ligaments and tendons to the joints.

Pattern of inheritance: Most common is X-linked dominant. Less common is autosomal dominant. Autosomal recessive inheritance is rare.



Figs. 14.20A to C: Pedigree charts of sex-linked inheritance. (A) X-linked dominant inheritance; (B) X-linked recessive inheritance; (C) Y-linked inheritance.

X-linked Recessive Inheritance (Fig. 14.20B)

- Females (XX) are the carriers. One X chromosome contains abnormal genes. Allelic genes on other X chromosomes are normal.
- Males are the victims. When abnormal gene involves nonhomologous part of single X chromosome of male (XY) disease is expressed. Defective genes have no corresponding allele in Y chromosome to counteract.
- If mother is carrier and father is healthy, 50% of her sons are affected by the disease and 50% of her daughters are carriers.
- *Examples:* Hemophilia, partial color blindness, glucose-6-phosphate dehydrogenase (G6PD) deficiency, Duchenne muscular dystrophy

Hemophilia

- Inherited clotting disorder—X-linked recessive.
- Factor VIII and IX are blood coagulation factors—required for conversion of prothrombin to thrombin which in turn converts fibrinogen to fibrin.

Types:

- Hemophilia A (royal)—deficiency of factor VIII (antihemophilic globulin). Incidence: 1 in 5,000 males
- Hemophilia B (Christmas disease)—deficiency of factor IX (Christmas factor). Incidence: 1 in 40,000 males

Clinical features:

- Blood coagulation disorder-prolonged CT with normal BT
- Prolonged bleeding after injury/surgery. Spontaneous bleeding in joints and muscles

Genetic basis: Gene location-long arm of X chromosome near the distal end.

Duchenne muscular dystrophy

- Slow and progressive muscle weakness and wasting of muscles of lower limbs.
- Common muscular disorder in males. 1 in 3,500 incidence.

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- It begins around 3rd year and will be confined to wheelchair around teen age.

Diagnosis

- Elevated creation of kinase level
- Muscle biopsy—muscle tissue replaced with fat and connective tissue
- CHS - Xp21- microdeletion
- Protein-dystrophin link between extracellular laminin and intracellular actin. Absence of DMD gene on short arm of X chromosome results in muscle cell degeneration.

Y-linked Inheritance (Fig. 14.20C)

- Y-linked traits are present in all male descendants of affected male.
- The genes that are carried on the Y-chromosome are called ***holandric genes***.
- Dominant and recessive patterns will not apply as only one allele is present.
- *Example:* Hairy pinna.

Multifactorial Inheritance

Genetic and environmental factors:

- **Drugs:** Thalidomide and anticancer, antiepileptic and antimalarial drugs
- **Viral infections:** Rubella virus, papilloma virus
- **Ionizing radiation:** X-rays and radioactive substances like I131.
- *Examples:* Cleft lip and cleft palate, clubfoot, congenital heart disease, neural tube defects (anencephaly and spina bifida).

Clinical Applications

Nondisjunction

- Normally, chromosomes split at the centromere and move to the opposite polls of cells.
- In nondisjunction, one or more chromosomes fail to separate correctly because of improper functioning of spindle fibers.
- This causes one daughter cell to get an extra chromosome (trisomy) and the other to miss one (monosomy).
- Nondisjunction happens in both mitosis and meiosis and can involve both autosomes and sex chromosomes.
- Early mitotic nondisjunction can result in a mix of normal and abnormal cells (mosaicism).
- Nondisjunction in meiosis I results in 2 gametes with extra chromosome (disomic, 24 CHS), and 2 gametes lacking one chromosome (nullisomic, 22 CHS).
- Nondisjunction in meiosis II results in 2 gametes that are normal (monosomic, 23 CHS), 1 gamete with extra chromosome (disomic, 24 CHS), and 1 is with one missing chromosome (nullisomic, 22 CHS).
- Autosomal nondisjunction is the basis for Down syndrome, Edward syndrome and Patau syndrome.
- Sex chromosomal nondisjunction is the basis for Klinefelter syndrome, Turner syndrome and triple X syndrome.

Clinical Anatomy

Case Scenario

Problem: Radha aged 35 years and Ramu aged 38 years had a baby boy after a normal delivery at full term. The pediatrician noticed the following during routine neonatal screening:

- Flat face with upward slanting eyes

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- A single palmar crease (Simian crease)
- Hypotonia
- A heart murmur

Questions

1. What could be the case based on the above findings?
2. What genetic test you advise for the newborn for confirmation?

Anatomical Explanation

1. It is a case of Down syndrome based on the observations in the neonate and the age of the mother.
2. Karyotyping to confirm trisomy of 21 chromosome.

Key Concept

Take Home Message—Genetics: Chromosomal Aberrations and Clinical Genetics

- Chromosomes are composed of deoxyribonucleic acid (DNA) and proteins.
- Chromosomes are classified based on the position of centromere into metacentric, submetacentric, telocentric and acrocentric.
- Karyotyping is a laboratory technique used to visualize and analyze the complete set of chromosomes in a cell.
- A karyotype is a visual representation of an individual's complete set of chromosomes, arranged systematically (based on length of chromosome, position of centromere and length of p arm and q arm) to highlight structural features.
- The 23 pairs of chromosomes are organized into A-G groups.
- Lyon hypothesis proposes random inactivation of one X chromosome in females to ensure dosage compensation.
- Chromosomal abnormalities are classified into numerical (trisomies and monosomy) and structural (deletion, duplication, inversion, isochromosome, ring chromosome).
- Based on mode of inheritance the genetic disorders are classified into Mendelian and non-Mendelian disorders.

REVIEW QUESTIONS

1. Lyon hypothesis
2. Karyotyping
3. Karyotype
4. Genetic counseling
5. Numerical anomalies of chromosomes
6. Structural anomalies of chromosomes
7. Klinefelter syndrome
8. Down syndrome
9. Pedigree chart
10. Mutation
11. Mosaicism
12. Chimerism
13. Turner syndrome
14. Down syndrome
15. Punnett square
16. Autosomal dominant inheritance
17. Autosomal recessive inheritance
18. X-linked inheritance
19. Hemophilia
20. Sickle cell anemia
21. Cystic fibrosis
22. Achondroplasia
23. Multifactorial inheritance

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MULTIPLE CHOICE QUESTIONS

1. Cystic fibrosis is:

A. Autosomal dominant disorder
B. Autosomal recessive disorder
C. Mitochondrial disorder
D. Sex-linked recessive disorder

2. The number of chromosomes in a female somatic cell and in the ovum are:

A. 46; 23
B. 23; 46
C. 46; 46
D. 23; 23

3. The mechanism responsible for Angelman and Prader-Willi syndromes are:

A. Genomic imprinting
B. Lyonization
C. Methylation
D. Mutation

4. All the following are autosomal dominant disorders, *except*:

A. Achondroplasia
B. Angioneurotic edema
C. Huntington's chorea
D. Hemophilia

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Answers

1. B 2. A 3. A 4. D

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