Human Chromosomes

The correct number of somatic chromosome in human being was determined to the 2N = 46 by **Tjio** and **Levan** in 1956. Each cell of human body has 23 pairs of chromosomes. Out of these, 22 pairs are similar in males and females. These are called **autosomes.** The chromosomes of twenty third pair are called **sex chromosomes** or **allosomes.**

In females (women) both the sex chromosomes are similar and are termed as **XX chromosomes.** But in males (men) one of the sex chromosomes is smaller in size and is known as **Y chromosome,** while the other is larger in size and is called **X chromosome.**

In a human karyotype the homologous chromosomes are paired and classified into seven groups, according to their length and location of centromere. The 22 pairs of autosomes are numbered 1 to 22. The sex chromosomes, *XX* or *XY* are not numbered. Individual chromosome pairs in a group, though similar in size, are further differentiated by their banding pattern using special fluorescent dyes, such as quanacrine mustard or geisma. The banding pattern of a particular chromosome always remain constant for a particular treatment.

In this manner, each one of the 22 pairs of autosomes and the sex chromosomes can be visually identified. Any defect in any chromosome such as deletion or translocation is identified. Any numerical abnormality such as monosomy (one chromosome less) or trisomy (one chromosome extra) can also be detected.

Human Genetic Disorders

Human genetic disorders can be grouped into two categories: 1. Human genetic disorders due to chromosomal abnormalities 2. Gene related human disorders.

1. Human Genetic Disorders due to Chromosomal Abnormalities

(*a*) ***Autosomal Abnormalities***

(*i*) **Down's syndrome or Mongolism** (Mongolian Idiocy)—Down's syndrome was first reported by **Longdon Down** in 1866. This disorder is caused due to trisomy of 21st chromosome. The patient has 47 chromosomes (*i.e.,* an extra 21st chromosome). Trisomy arises due to non-disjunction (non-separation) of 21st chromosomes during oogenesis (egg formation). Thus, the egg has 24 chromosomes instead of 23. Fertilization of such egg with a normal sperm results in trisomy of 21st chromosome. Such abnormal child may be born from the mothers of 45–50 years of age.

The affected child has a prominant forehead, flattened nasal bridge, habitually opened mouth, projecting lower lip with a large protruding tongue, skin folds at the corners of eyes, malformed heart and underdeveloped gonads and genitalia. (*Fig. 5.45*). Down's syndrome occurs almost once in every 600 births.

Alzheimer's Disease. This disease is characterised by the loss of memory and ability of judgement as well as a general physical impairment. It is caused due to accumulation of amyloid protein plaques in the brain resulting in the degradation of neurons. The protein containing amyloid peptide is produced and processed in a number of ways in the normal brain from a large amyloid precursor protein. This disease is common among Down's syndrome. This diseases is due to ageing involvement of the chromosome 21 or chromosome 19. Different genes have been linked to Alzheimer's disease but these genes only predict susceptibility to disease. This disease is characterised by dementia (mental deterioration) leading to loss of memory.

Fig. 5.45. A three year old girl who suffers from Down's syndrome.

(*ii*) **Edward's Syndrome** (18-Trisomy). It was described by **Edward** in 1960. This syndrome is due to an extra chromosome number 18. Thus, total number of chromosomes is 47. It occurs more often in females than in males. The frequency of this abnormality is about 1 per 3500 live births. The affected person keeps the fingers tightly clenched against the palm of the hand. Other symptoms are small jaws, deformed ears, small sternum and pelvis. The patient is mentally retarted.

(*iii*) **Patau's Syndrome** (13-Trisomy). It was described by **Patau** in 1960. This syndrome is due to an extra chromosome number 13. The affected person has small head and abnormalities of the face, eyes and forebrain, cleft lip and palate, low set deformed ears, small chin and the hands are often clenched in the manner described for Edward's syndrome. It occurs in about 1 in 5000 live births. The mean life span of the affected person is about 4 months.

(*iv*) **Cri du chat (Cat Cry) Syndrome.** The affected newborn cries like mewing of a cat, was first described by **Lejeune** in 1963 in France, hence it is named *Cri du chat* (Cat Cry). This condition is due to a deletion in the short arm of the chromosome number 5. It is very rare. The affected person has a small head, widely spaced eyes, receding chin and congenital heart disease.

(*v*) **Chronic Granulocytic Leukemia** (a type of blood cancer). It is caused due to deletion of a part of 22nd chromosome and its subsequent attachment with 9th chromosome (reciprocal translocation). The 22nd chromosome, from which a little segment from long arm is deleted, is called **Philadelphia chromosome**, as it was first reported in the city of Philadelphia in 1959. The reciprocal translocation brings about change in the conformation of C-A61 protein, causing transformation of proto oncogene into oncogene (c-onc). It results in excess production of granular leucocytes, hence called chronic granulocyte leukemia or chronic myloid leukemia (CML).

(*b*) ***Sex Chromosomal Abnormalities***

(*i*) **Turner's syndrome** (XO individual; Fig. 5.46). Such individuals are undeveloped female with single *X* chromosome. An *XO* individual is formed, when an *X*-carrying sperm fertilises an *O* egg. Such a female has rudimentary ovaries, shield shaped thorax (underdeveloped breasts), short stature and abnormal intelligence. She may not menstruate or ovulate.

An *YO* constitution (*Y* carrying sperm fertilizing an *O* egg) is non-viable.

(*ii*) **Klinefelters Syndrome** (XXY individual ; Fig. 5.47). Such an individual is a male in general appearance but has female characters. The person has long limbs, enlarged breasts (gynaecomastia), sparse body hair and underdeveloped testes. Such individual is often sterile and mentally defective. You may recall that an *XXY* constitution determines a female in

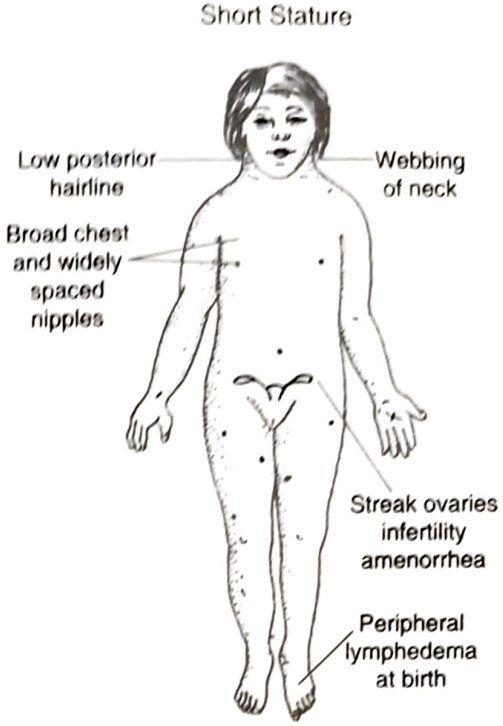

Fig. 5.46. Turner's Syndrome.

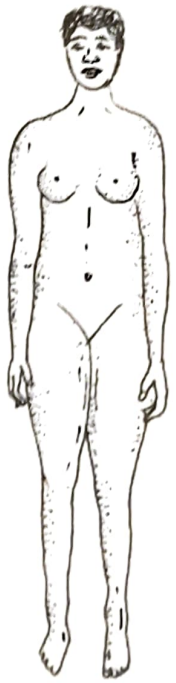

Fig. 5.47. Klinefelter's Syndrome.

Drosophila. In humans, however, the *Y* chromosome is male determinant. Even *XXXXY* individuals are males. However, they are greatly mentally retarded. Mental retardation increase with increased *X* complement.

(*iii*) **Super females** (XXX individuals). Such females have extra *X* chromosomes. They are characterised by abnormal sexual development and mental retardation.

(*iv*) **Super males** (XYY individuals). Such males are usually taller than normal males. They have reduced intelligence and tend to be more aggressive due to over production of male hormones. They have criminal bend of mind.

Identification of Syndromes. The number of *X* and *Y* chromosomes associated with various abnormalities or syndromes can be determined by counting the number or **barr bodies** and ***Y* spot** from buccal mucosa and epithelial cells from hair roots. On staining with orcein, one of the two *X* chromosomes of a normal female appears as a **chromatin body** (heterochromatic region) in the interphase nucleus. This body is called **barr body** (**M.L. Barr** and **E.C. Bertram,** 1949). The number of barr bodies is always one less than the number of *X* chromosomes. The interphase nuclei of males do not have this body because each cell of the males has only one *X* chromosome. In the cells with a higher number of *X* chromosomes, the number of barr bodies increases correspondingly. The number of *Y* chromosome can be determined by ***Y* spot analysis**. *Y* chromosome of the interphase nuclei stained with quinacrine dye has a bright fluorescent spot called *Y* spot on its long arm under ultraviolet light.

2. Gene Related Human Disorders

(*a*) **Disorders due to Defective Gene or Gene Mutation on Autosomes.** These are of two types—recessively inherited traits and dominantly inherited traits.

Recessively Inherited Traits. These are caused by recessive genes in homologous condition. Some common example of this type of disorders are following:

(*i*) **Alkaptonuria** (Black urine disease). This disorder is due to a recessive gene and appears only in homozygous recessive individuals. Alkaptonurics excrete alkapton (homogentisic acid) in their urine, which spontaneously combines with oxygen to form a black pigment. The pigment causes darkening of cartilages of ears and nose, and blackening of urine. People with dominant allele (both homozygous and heterozygous individuals) excrete normal urine, because their blood contain an enzyme called *alkapton oxidase* (homogentisate oxidase), which oxidises alkapton to carbon dioxide and water. Alkaptonurics

Table 5.7. Number of Barr Bodies and Y Spots, and Phenotypes of Human beings with Different Constitutions of Sex Chromosomes

Sex Chromosome	*Number of Barr Bodies*	*Number of Y Spots*	*Phenotypes*
FEMALE			
XO	0	0	Turner's syndrome
XX	1	0	Normal
XXX	2	0	Super female with mental abnormalities
XXXX	3	0	Super female with mental abnormalities
XXXXX	4	0	Super female with mental abnormalities
MALE			
XY	0	1	Normal
XYY	0	2	Super male
XXY	1	1	Klinefelter's syndrome
XXYY	1	2	Klinefelter's syndrome
XXXY	2	1	Extreme Klinefelter's syndrome
XXXXY	3	1	Extreme Klinefelter's syndrome

does not produce this enzyme because of the presence of recessive gene in homozygous condition.

(*ii*) **Phenylketonuria** (PKU). It is an inborn error in metabolism due to a defective recessive gene. The homozygous recessive lacks the enzyme *phenylalanine oxidase* needed to change one amino acid, phenylalanine, to another, tyrosine. Phenylalanine accumulates in the tissues and some of it changes into phenyl pyruvic acid which damages the brain and causes the reduction of colour of hair and skin. The heterozygous individuals are normal but carriers.

(*iii*) **Albinism.** Albinism is characterised by lack of dark pigment **melanin** in the skin, hair and iris. It is caused by the absence of the enzyme *tyrosinase* which is necessary for the synthesis of the pigment melanin from dihydroxyphenylalanine.

Albinism is also due to a recessive gene, which is in homozygous condition, block the formation of melanin pigment. Albinism by itself is not a disability, however, an albino is susceptible to eye disorders due to damaging effect of bright light.

(*iv*) **Tay Sach's Disease** (Infantile Amaurotic Idiocy). The child with Tay Sach's disease is born normal, but develop severe brain and spinal cord damage, later in a few months due to an error in fat metabolism. This results in mental retardation and paralysis. The victim dies in 3 or 4 years. There is no cure for this disease.

(*v*) **Gaucher's Disease.** This disorder is caused due to impairment of the breakdown of fatty acid substances which leads to the accumulation of lipid materials in body tissues and blood. It is caused by a recessive gene that inhibits the activity of the enzyme *glucocerebrosidase*. As a result there is accumulation of cerebroside (a sphingolipid). There is enlargement of the spleen and liver and expansion of some of the limb bones.

(*vi*) **Sickle Cell Anaemia.** This disorder is caused due to a defective recessive gene. The red blood corpuscles of the affected individuals become elongated and curved under low oxygen tension. The individuals suffer severe tissue damage due to aggregation of RBCs in the venous side of the capillary system under oxygen deficiency. It is known as **sickle cell crisis.** The sickled enythrocytes are destroyed more rapidly than the normal ones leading to anaemia. This disease is controlled by a single pair of alleles, Hb^A and Hb^S. Recessive homozygotes (Hb^S/Hb^S) die early in life due to severe anaemia. However, heterozygotes (Hb^A/Hb^S) are apparently unaffected, as they carry at least one normal allele. They are carriers of the defective gene

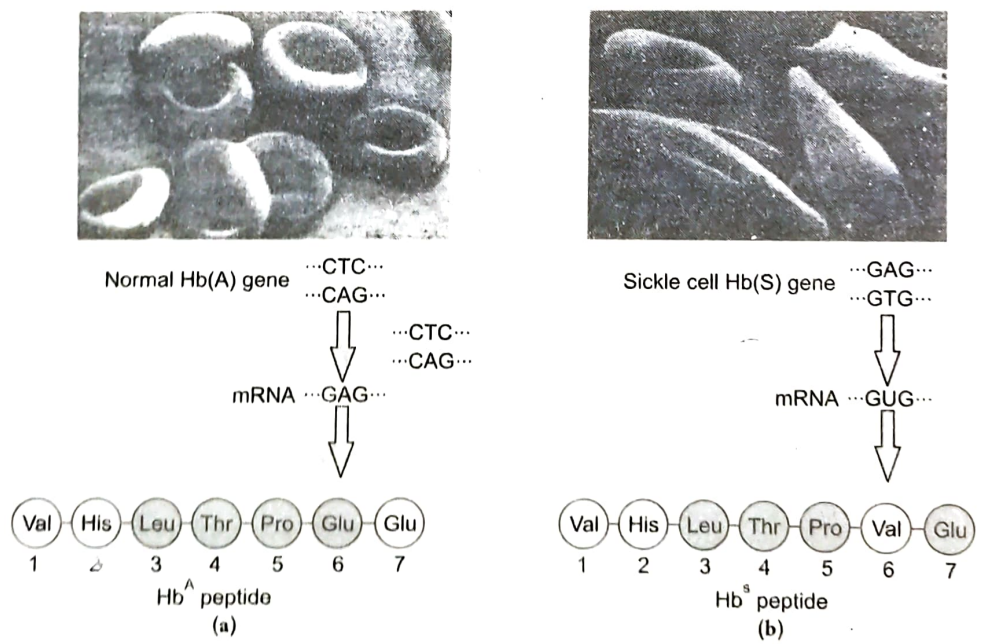

Fig. 5.48. Micrograph of the red blood cells and the amino acid composition of the relevant portion of b-peptide of haemoglobin: (*a*) From a normal individual and (*b*) From an individual with sickle cell anaemia.

and can transmit the same to 50 per cent of their offspring on an average. The inheritance of sickle cell anaemia has already been discussed in detail in chapter 12 (see pleiotropy).

This defect arises due to substitution of valine for glutanine at the sixth position in the *B* chain of globin molecule of haemoglobin (*Fig. 5.48*). This discovery has provided the direct evidence that genes specify proteins and also established the concept of inherited molecular diseases.

(*vii*) **Thalassaemia.** It is a genetic defect originated in mediterranean region and is also common in Middle East, Indian subcontinent and in South East Africa. Thalassaemia is characterised by reduced synthesis of either a or b chains, likewise designated as α- or β-thalassaemias. β-thalassaemia was first described by **Cooley,** hence it is also called **Cooley's anaemia** or **thalassaemia major.** The reduced synthesis of β-chains leads to accumulation of α-chains which cause damage to the precursors of red blood corpuscles in the bone marrow. Persons homozygous for the β-thalassaemia gene suffer from severe haemolytic anaemia. Heterozygous persons also not normal but show the defect in a less severe form (**thalassaemia minor**).

Thalassaemia is of three types: α, β, and δ thalassaemia.

- **Alpha (α) Thalassaemias** are caused due to mutations in HbA_1 and HbA_2 genes on chromosome 16, inherited in Mendelian recessive manner. There are two gene loci and so four alleles. α thalassaemias result in decreased alpha-globin production, therefore fewer alpha-globin chains are produced, leading to production of an excess β chains and excess of γ chains in new borns. The excess β chains form unstable tetramers (HbH of 4 β chains) that have abnormal oxygen dissociation curves.
- **Beta (β) Thalassaemias** are caused due to mutation in HbB gene on chromosome 11, inherited in an autosomal recessive manner. The severity of the disease depends on the nature of the mutation. Mutations are characterised as β^0 or β **Thalassaemia major** (if they prevent formation of any β-chains) and β^+ or **β-thalassaemia intermedia** (if they allow formation of some β-chain formation. In either case, there is a relative excess of α-chains, which bind to RBC membranes, leading to damage of the later. High concentration of α chains forms toxic aggregates.
- **Delta (δ) Thalassaemia** About 3 per cent of haemoglobin in adults is made of α-chains and δ chains. Delta (δ) is caused due to mutations in δ gene, decreasing its ability to synthesise δ chains.

(*viii*) **Cystic Fibrosis** (CF). This is caused by a single autosome recessive gene controlling an enzyme, which produces a unique glycoprotein resulting into the production of mucus of abnormally high viscosity. The over viscous mucus interferes in the normal functioning of many exocrine glands including sweat glands of skin, lungs, liver and pancreas. The symptom of the disease is related to the abnormal mucus. Mucus usually stagnate the tubules of the lungs making it susceptible to infection resulting into bronchitis. The secretory cell of liver and pancreas also show impaired function and less production of bile and digestive enzymes of pancreas.

Dominantly Inherited Traits. These disorders are caused by defective dominant genes. One parent carries the defective gene which is inherited by about half the children. The normal children do not have the defective gene and their children are all normal. This is in contrast to the recessively inherited disorders, in which the heterozygous (carrier) individuals, though normal, may pass on the defect to their children. Some dominant defective traits in humans are (*i*) **polydactyly** (extra digits), (*ii*) **brachydactyly** (abnormally short digits), (*iii*) **Achondroplasia** a form of dwarfism long bones do not grow, (*iv*) a disorder in which crowns of teeth wear down readily, and (*v*) **Huntington's chorea** (uncontrolled twitching of voluntary muscles and mental deterioration appearing between the age of 25 to 55). (*vi*) **Phenyl thio-carbamide (PCT)**tasting, (*vii*) **Neurofibromatrosis** tumor like growths on body (*viii*) **Wooly hairs** (*ix*) **Aniridia** absence of iris in eye. All the above mentioned disorders occur due to the defective (mutated) autosomal genes, which have dominant effect.

(*b*) **Disorders due to Defective Gene on Sex Chromosomes.** Some genetic disorders are produced by a defective gene on sex chromosomes. These are called sex linked disorders. **Haemophilia, red-green colour blindness,** and **muscular dystrophy** are well known sex linked disorders in humans. All these are caused by a recessive gene located on the X

chromosome, and affect the males more than the females. The Y chromosome mainly concerned with sex determination. Therefore, genes on the X chromosome in male always express themselves in respective of their dominant and recessive nature. The males are thus, **hemizygous** for these disorders.

In **muscular dystrophy**, the mutated gene on X chromosome is unable to produce a protein called **dystrophin**. The latter is believed to relay the nerve's signal to the calcium storage in the muscle cell. Due to it calcium is not released from the muscle cell. As a resul the muscle contraction does not occur at the very firs step. Abnormal rise in calcium level in the muscl release an enzyme that destroys actin and myosin. Thi causes deterioration of muscles at an early age. Th victim becomes invalid by the age of 10 and generall dies by the age of 20.

A summary of some human genetic disorders i given in table 5.8.

Table 5.8. A summary of some important human genetic disorders with their symptoms and effects

Disorder	*Dominant / Recessive*	*Autosomal / Sex linked*	*Symptom*	*Effect*
Sickle-cell anaemia	Recessive	Autosomal, gene on Chromosome 11	Aggregation of erythrocytes, more rapid destruction of erythrocytes leading to anaemia.	Abnormal haemoglobin in RBC's
Phenylketonuria	Recessive	Autosomal, gene on Chromosome 12	Failure of brain to develop in infancy, mental retardation, idiots	Defective form of enzyme phenylalanine hydroxylase.
Cystic fibrosis (CF)	Recessive	Autosomal, gene on Chromosome 7	Excessive thick mucus clogging in lungs, liver and pancreas anomalies.	Failure of chloride ion transport mechanism through cell membrane.
Huntington's disease (HD)/Huntington Chorea	Dominant	Autosomal, gene on Chromosome 4	Gradual degeneration of brain tissue in middle age, loss of motor control.	Production of an inhibitor of brain cell metabolism.
Haemophilia A/B	Recessive	Sex-linked, gene on X chromosome	Failure of blood to clot	Defective form of blood clotting factor VIII/IX.
Colour blindness	Recessive	Sex-linked, gene on X chromosome	Failure to discriminate between red and green colour.	Defect in either red or/and greed cone cell of retina.
Down's Syndrome	—	Autosomal, Aneuploidy (Trisomy, +21)	Mongolian eyefold (epicanthus) open mouth, protruded tongue projected lower lip, Many loops on finger tips, palm crease	Retarded mental development IQ below 40
Turner's Syndrome	—	Sex chromosomal Monosomy 44 + X0	Short stature females, (<5′) webbed neck, body hair absent menstrual cycle absent. Sparse pubic hair underdeveloped breasts narrow lips, puffy fingers.	Sterile, hearing problem
Klinefelter's syndrome	—	Sex chromosomal Aneuploidy (Tri/tetrasomy of X chr) 44 + XXY, 44 + XXXY	These males are tall with longs legs, testes small, sparse body hair, barr body present, breast enlargement.	Gynaecomastia Azospermia, sterile