- Colour-blind women give birth to colour-blind daughters only when their husband is also colour-blind.
- Women who have normal vision but can transmit colour-blindness are called carriers.

CHROMOSOMAL ABERRATIONS

- Chromosomal aberrations are abnormalities in the structure or number of chromosomes.
- They are often responsible for genetic disorders.
- They may occur spontaneously or can be induced by environmental agents such as chemicals, radiations and ultraviolet light.
- Generally, chromosomal abnormalities occur when there is error in cell division (mitosis or meiosis).
- Chromosomal aberration involves breaking of chromosome segments, their loss or union with the same (intrachromosomal aberration) or different chromosomes (interchromosomal aberration).
- Chromosomal aberrations can be recognised with the use of karyotype.
- Structural changes in chromosomes are of the following four types:
  1. Deficiency or deletion
  2. Duplication
  3. Inversion
  4. Translocation

1. Deficiency

- Deficiency or deletion is the loss of chromosomal segments.
- The lost segment may be terminal (terminal deletion) or intercalary (intercalary deletion).

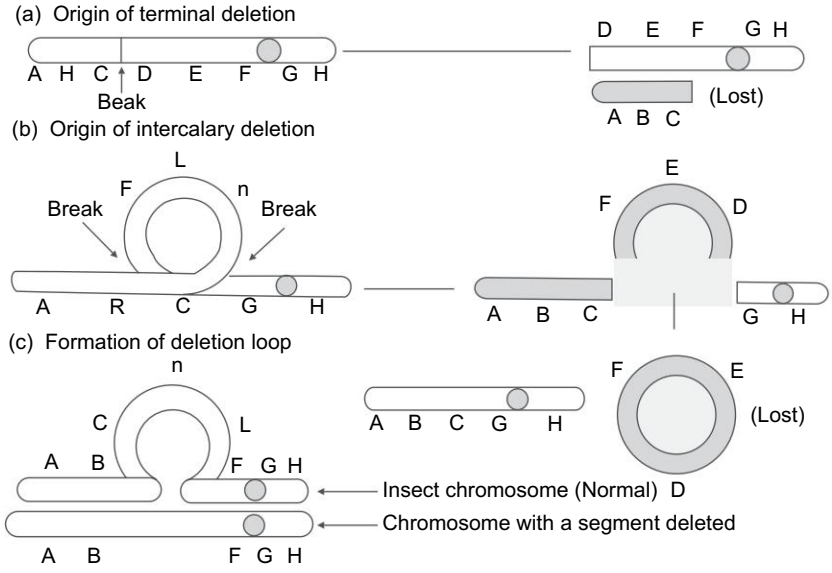


Fig. 16 Deletion: (a) Terminal deletion (b) Intercalary deletion (c) Formation of deletion loop

- Terminal deletion involves single break near the terminal end, while intercalary deletion involves two breaks; the separated segment is lost and there is reunion of the broken ends.
- In heterozygous deletion, the synapsed chromosome would show difference in length at one end (terminal deletion) or loop (intercalary deletion).
- Homozygous deletion may be lethal if some vital gene is involved.
- In the presence of deletion, a recessive allele behaves like a dominant allele. This phenomenon is known as pseudodominance.
- Heterozygous deficiencies lead to many genetical disorders such as retinoblastoma, myeloid leukaemia, cri-du-chat syndrome, etc.
- Deletion involves change in the amount of DNA.
- Genetically, deletion can be recognised by recessive lethality, pseudodominance and lack of revertability and cytologically by deletion loops.

2. Duplication

- When a set of genes are present twice in a chromosome, it is known as duplication.
- From evolutionary point of view, duplications are very important as they supply additional genetic material capable of evolving new functions.
- Duplication arises due to unequal crossing over.
- Adjacent duplicated segments may occur in tandem sequence with respect to each other (abcbcd) or in a reverse order (abccdb).
- Duplications are more frequent in nature and are less deleterious in comparison with deletions.
- Duplication involves change in the amount of genetic material.
- Repeated duplication of the same gene results in gene amplification as well as the formation of gene families.
- A small duplication is rarely lethal even when homozygous. However, sometimes it may be pathological.

3. Inversion

- Inversion involves two breaks in the chromosome followed by the reunion of the ends in a reverse manner, i.e., the broken segments rotate through 180°.
- Thus in inversion, only the arrangement of genes is changed and not the number.

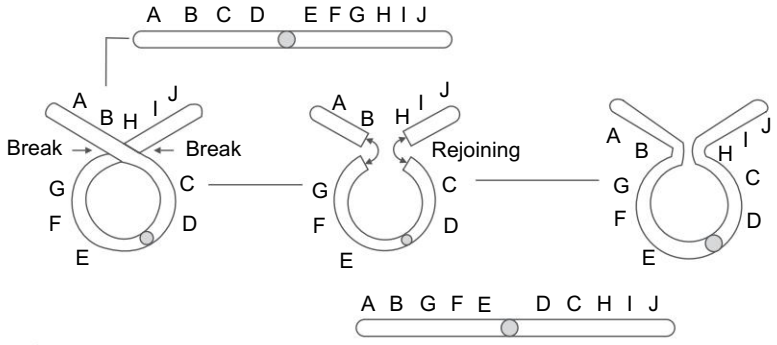


Fig. 17 Diagram showing the mechanism by which some of the inversion might occur

- Generally this change in the gene order does not produce clinical abnormality but it results in increased

risk of generating abnormal gametes.

- Organisms may be either homozygous or heterozygous for an inversion.
- Inversions are of the following two types:
  - Paracentric inversion – The inverted segment does not include centromeres.
  - Pericentric inversion – The inverted segment includes centromeres.
- If crossing over takes place within the inverted segment of a paracentric inversion, then it results in the formation of acentic and dicentric chromosomes.
- If crossing over occurs within the loop of a pericentric inversion, then the resulting chromatids have a duplication and a deficiency.

4. Translocation

- Translocation is the exchange of chromosomal segments between the nonhomologous chromosomes.
- Translocation is of the following three types:
  - Simple Translocation – The broken segment gets attached to one end of the nonhomologous chromosome.
  - Reciprocal Translocation – It involves the exchange of chromosomal segments between members of two different pairs.
  - Shift Translocation – The broken segment gets inserted interstitially in a nonhomologous chromosome.

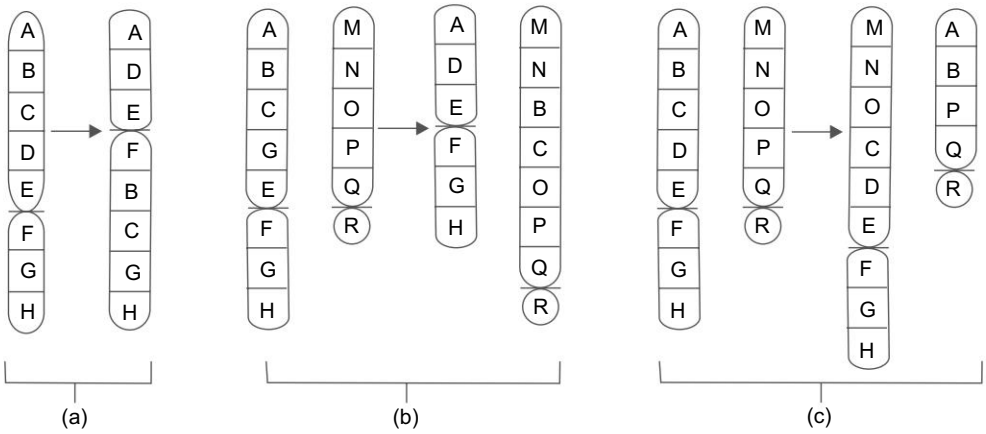


Fig. 18 Different types of translocation: (a) Simple translocation (b) Reciprocal translocation (c) Shift translocation

- Translocation occurs due to irregularities during crossing over.
- In translocation, there is no loss or addition of genetic material, only rearrangement of genes occurs. Thus, two new chromosomes are produced with an altered gene sequence.
- A balanced translocation carrier is at risk of producing chromosomally unbalanced offspring.
- Generally, translocation heterozygotes are less fertile in comparison with translocation homozygous. It is some of the gametes produced by them that give rise to unviable progeny due to deficiency or duplication of the chromosome segment.
- Translocation may alter the size of a chromosome as well as the position of the centromeres.

Changes in Chromosome Number

Variation in chromosome number is of the following two types:

1. Euploidy
2. Aneuploidy

1. Euploidy

- Euploidy involves variation of entire sets of chromosomes.
- It involves complete genomes.
- When one complete set of chromosome is present, it is called monoploidy (n). If two sets of chromosomes are present, it is called diploidy ($2n$) and if more than two sets of chromosomes are present, it is termed as polyploidy.

(a) Monoploidy

- Monoploidy is also termed as haploidy.
- Each chromosome is represented only once.
- Haploidy may arise as an abnormality in species which are diploid.
- It is common in plants but rare in animals.
- Among animals, haploidy occurs in male honeybees, ants and other insects which develop from unfertilised eggs (parthenogenesis).
- The chromosome behaviour differs in haploids from diploids.
- Monoploids are usually smaller in size and have less vigor in comparison with diploids.

(b) Polyploidy

Organisms having more than two sets of chromosomes are termed as polyploids and the phenomenon is known as polyploidy.

- Polyploid organisms may be classified as triploids ($3n$), tetraploids ($4n$), pentaploids ($5n$) and so on.
- A proportion of polyploidy cells occur normally in human bone marrow, because megakaryotes generally have 8–16 times the haploid number.
- Tetraploid cells are a normal feature of regenerating liver and many other tissues.
- Polyploidy is of two types, viz., autoploidy and alloploidy
- In autoploidy, there is multiplication of the same genome while in allopolyploidy, there is multiplication of chromosomes from two different ancestral stocks.
- Polyploidy arises due to error during meiosis or fertilisation. Sometimes abnormal mitosis also leads to polyploidy.
- Polyploidy is common in plants but rare in animals.
- Polyploidy is artificially induced with colchicine. Colchicine is an alkaloid derived from the autumn crocus (*Colchicum autumnale*) which disturbs spindle formation**.**

2. Aneuploidy

- Aneuploidy refers to variations in chromosome numbers involving individual chromosomes.
- Aneuploids have unbalanced chromosome sets, i.e., with extra or missing chromosomes.
- Aneuploids are generally produced by nondisjunction or some type of chromosome misdivision at either meiosis or mitosis.
- Aneuploids may be of the following types:

(a) Monosomics – Monosomics are individuals having one chromosome less than the diploid number ($2n-1$).
(b) Double Monosomics – There are two chromosomes less, that are different members of the chromosomal complement ($2n-1-1$).
(c) Nullisomics – They have two chromosomes less than the diploid complement ($2n-2$).
(d) Trisomics – Homolog of normal diploid complement is present three times ($2n+1$).
(e) Double Trisomics – There are two extra chromosomes, which are different members of the genome ($2n+1+1$).
(f) Tetrasomics – In a tetrasomy individual, one chromosome of the genome is present four times ($2n+2$).

GENE MUTATION

- Mutation is the sudden, discontinuous and inheritable change in genetic material.
- Mutation is the failure of the DNA repair mechanism.
- A mutation occurs when the DNA is damaged or changed in such a way as to alter the genetic message carried by that gene.
- Once the gene has been damaged or changed, the mRNA transcribed from that gene will carry an altered message.
- These changes could give rise to the following types of mutations:
  1. **Silent Mutation –** There is change in the nitrogenous base but there is no change in the amino acid.
  2. **Missense Mutation –** It involves changes in the nitrogenous base as well as in the amino acid sequence. Sickle cell anaemia is a good example of missense mutation, which is caused by the substitution of valine in place of glutamic acid in the haemoglobin chain.
  3. **Nonsense Mutation –** It changes the codon into terminating codon, resulting in the termination of the polypeptide chain. It results in the formation of short polypeptide chain which has little or no biological effect. Such mutations are also called terminator mutations.
- The term 'mutation' was coined by Hugo de Vries.
- Mutations may occur in somatic cells as well as germ cells.
- Mutations arising in somatic cells are not passed to the next generation, while those occurring in reproductive cells are passed onto the next generation.
- Mutations occurring in nature are called spontaneous mutations. They arise due to inherent errors in the DNA replication and transmission processes.
- Spontaneous mutation can occur at any point in the cell cycle.
- Mutation rate varies from 10^{-4} to 10^{-6} mutations per gene per generation. In humans, the mutation rate is 10^{-5} to 10^{-6} per gamete per generation.
- Mutations that occur due to or in response to some externally applied agents are called induced mutations.
- Depending upon the effect, mutation may be dominant or recessive.
- T H Morgan (1910) reported white eye mutation in *Drosophila melanogaster*.
- Mutations play a key role in speciation.
- A variety of agents cause mutations and they are called mutagens.
- Mutagens may be physical or chemical.

- Physical mutagens are X-rays, gamma rays, beta rays, ultraviolet rays, etc.
- There are varieties of chemical mutagens such as nitrogen mustard, sulfur mustard, dimethyl nitrosamine, ethylene oxide, di-ethyl sufonate, nitrous acid, hydroxyl amine, hydrazine, etc.

Molecular Basis of Mutations

There are two basic types of mutations.

1. **Substitution Mutations –** It involves replacement of one nitrogenous base of a triplet codon by another nitrogenous base. It may be of the following two types:
   - **Transition –** Transition is the replacement of a purine by another purine and replacement of one pyrimidine by another pyrimidine.
   - **Tranversion –** Transversion is the replacement of purine by pyrimidine and pyrimidine by purine.
2. **Frameshift Mutation –** Frameshift mutation is caused by the addition or deletion of a base pair in the gene, resulting in change in the reading frame of the DNA.
   - Addition or deletion of one or more nitrogenous bases results in a new codon sequence that code for quite different amino acids.
   - The change in amino acid sequence results in a change in the synthesised protein, which is generally nonfunctional.

Deletion

- Deletion is the removal of one or more nitrogenous bases from the DNA polynucleotide chain.
- Deletion results in the establishment of a new sequence which occurs by deletion of any number of bases, not divisible by three.
- Suppose the original reading frame is CAT GAT CAT GAT CAT GAT CAT, then deletion of C of the last codon will read as CAT GAT CAT GAT CAT GAT TA.

Insertion

- If one or more bases are added (provided it is not divisible by three), it will disturb the genetic message.
- +G CAT GAT GCA TGA TCA TGA TCA T
- If deletion and insertion take place simultaneously, then the message will be out of frame only in the triplet between the deletion and insertion.
- Deletion and insertion
- –C+C CAT GAT ATG ATC ATC GAT

Mechanism of Spontaneous Mutations

Spontaneous mutations arise by mutagens present in the environment, such as radiation, radioactive compounds, heat and naturally occurring base analogues like caffeine. Spontaneous mutations that arise by tautomerisation are described here.

Tautomerisation

- Isomerisation between tautomers is called tautomerisation.

- Tautomers are the two forms of the same compound.
- Normally, in a DNA molecule, adenine (purine) pairs with thymine (pyrimidine) while guanine (purine) pairs with cytosine (pyrimidine).
- All these four nitrogenous bases (adenine, thymine, cytosine and guanine) of DNA have rare tautomeric forms.
- These rare forms are called tautomers and are formed by the rearrangements of hydrogen atoms.
- The normal bases of DNA are generally present in the keto form and amino form.
- As a result of tautomeric arrangement, they can be transformed into rare enol form and imino form, in which distribution of electron is slightly different.
- In a tautomeric state, adenine pairs with cytosine and thymine pairs with guanine.
- The unusual pairing of adenine with cytosine results in G–C pairing in the next generation causing formation of mutant forms in some progeny.
- The rare base pairing result in misreplication of DNA leading to mutation.
- Ambiguity of base pairs during replication may also result in spontaneous mutations.

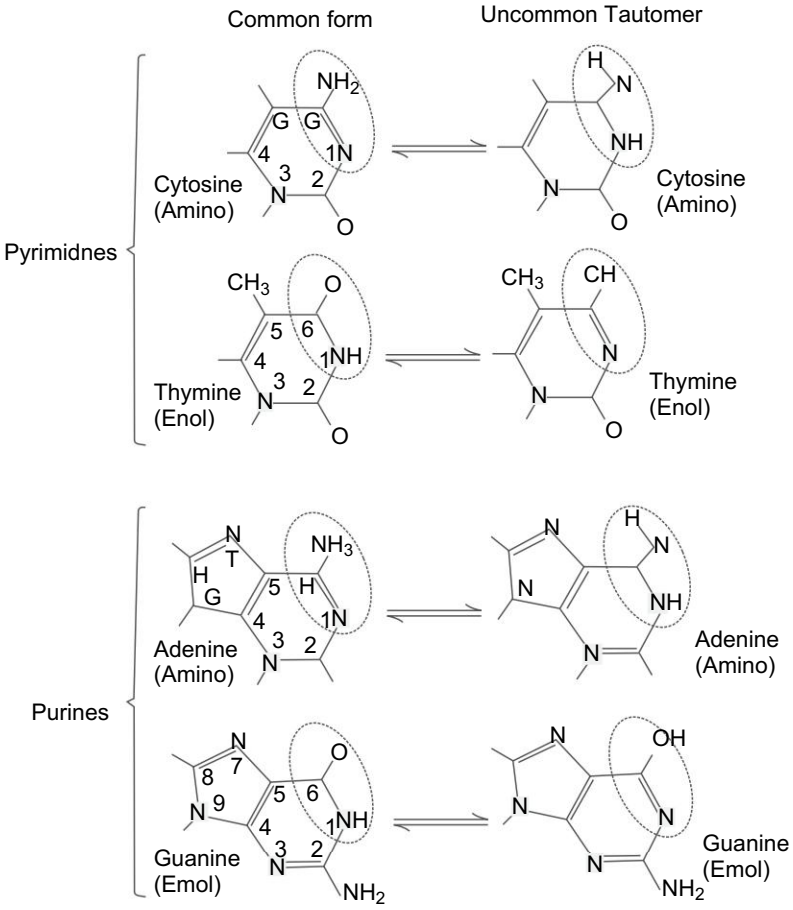


Fig. 19 The uncommon forms of bases

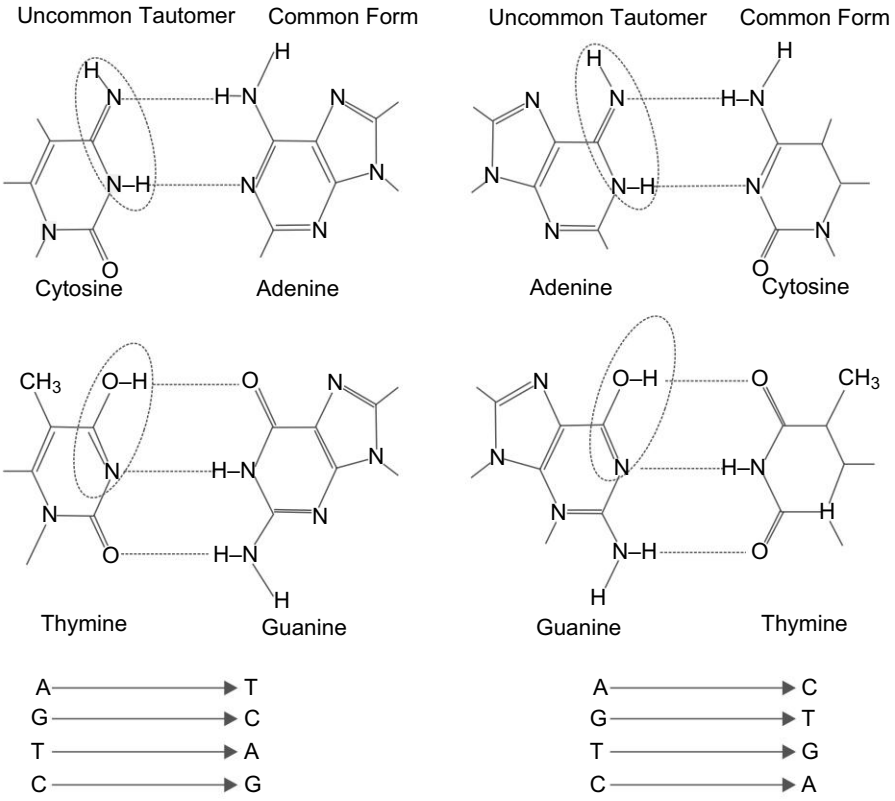


Fig. 20 Normal (I) and Tautomeric (II) pairing of four nitrogenous bases

Mechanism of Induced Mutations

- There are three general approaches to induce mutation, viz., radiations, chemicals and transposons.
- H J Muller pioneered in inducing mutation using X-ray radiation in *Drosophila* and developed a method of detecting mutations that are lethal.
- Besides X-ray, other types of radiation that have been used for inducing mutations are gamma rays and fast neutron bombardment.
- Chemical mutagens work mostly by inducing point mutations.
- Chemical mutagen can be classified into three groups on the basis of the way through which they bring about mutations. These are as follows:
  1. Base analogues, which become incorporated into the DNA instead of normal bases.
  2. Agents that cause modification in purine and pyrimidine bases.
  3. Agents that produce distortion in the DNA.
- Base analogues and agents producing distortion in the DNA need replication of the DNA for their incorporation, while agents modifying bases can bring about modification even in nonreplicating DNA.

1. Base Analogues

- Base analogues are chemicals having structures similar to nitrogenous bases.
- Base analogues sometimes become incorporated into the DNA in place of normal nitrogenous bases.
- 5-bromouracil (5-BU) is a pyrimidine analogue and is structurally very similar to thymine. It can pair with adenine or guanine.
- 2-aminopurine (2-AP) is a purine analogue that can pair with cytosine and thymine.
- Both 5-bromouracil and 2-aminopurine only mutate when they are incorporated in the replicating DNA.

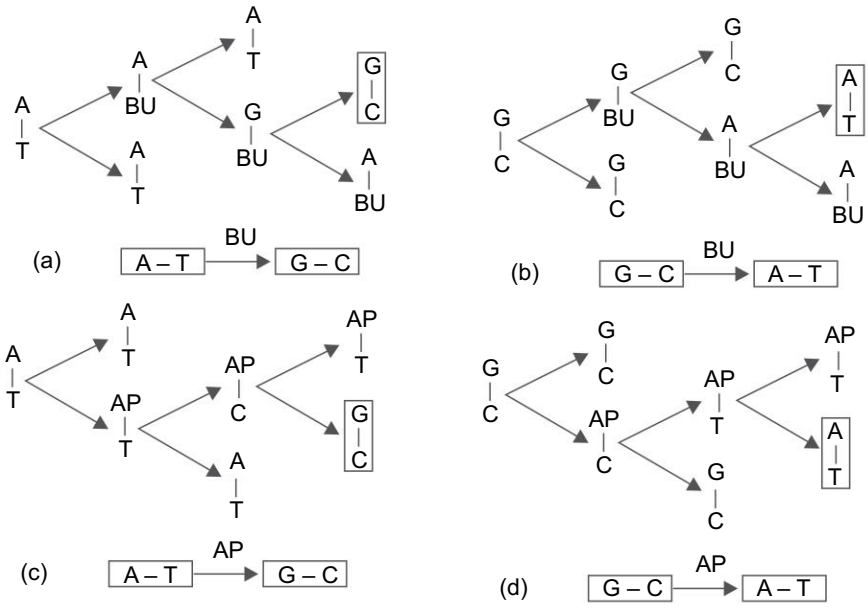


Fig. 21 Changes in base pairing due to the incorporation of base analogues

2. Base Modification

There are some mutagens which cause change in base pairing, resulting in incorrect pairing.

- Such modifications involve alkylation, hydroxylation, deamination, depurination, etc**.**

(a) Deamination

- Some of the chemicals (like nitrous acid and hydroxyl amine) cause deamination of nitrogenous bases. They replace amino group ($–NH_2$) group by hydroxyl group (–OH).
- Deamination of cytosine results in the formation of uracil; deamination of adenine leads to the formation of hypoxanthine (H); and that of guanine forms xanthine.
- Hypoxanthine shows similarity with guanine.
- During the course of DNA replication, uracil pairs with adenine while xanthine pairs with cytosine.
- Thus, it results in the substitution of A = T for G ≡ C and G ≡ C for A = T.

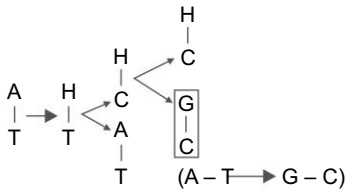
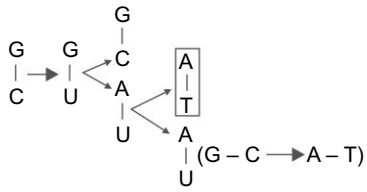
Normal base of DNA	Normal pairing	Altered base by deamination	Altered pairing
Adenine	A = T	Hypoxanthine (H)	
Cytosine	C≡G	Uracil	

Fig. 22 Deamination caused by nitrous acid and abnormal pairing

(b) Hydroxylation

- Hydroxyl amine complexes with cytosine and causes its hydroxylation, resulting in the formation of hydroxyl cytosine (HC).
- This hydroxyl cytosine pairs with adenine instead of guanine.
- At the time of DNA replication, this introduces thymine at this level.
- Thus, G–C pairing changes to A–T pairing.

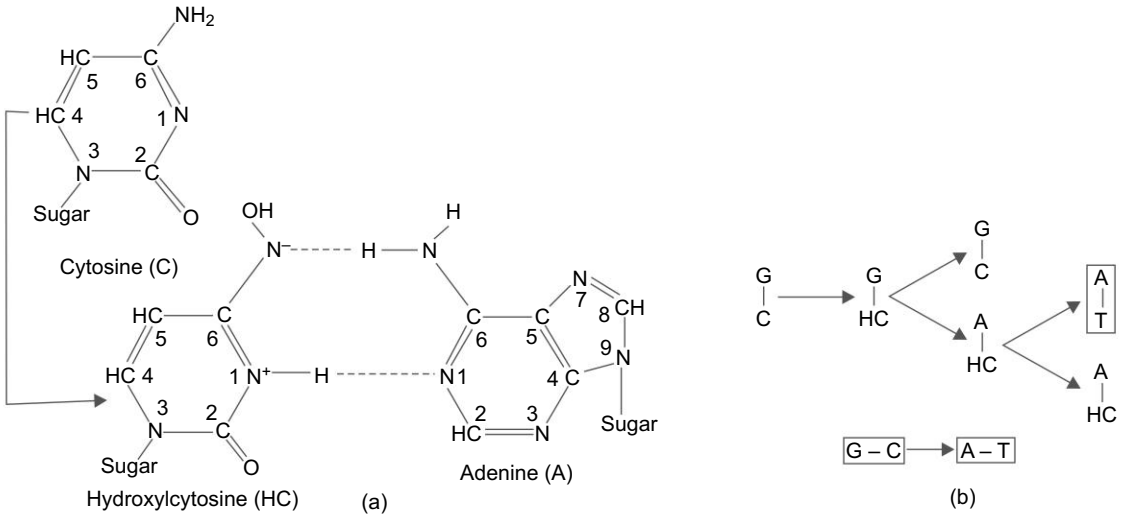


Fig. 23 Transition of C–G to A–T produced by hydroxyl amine due to conversion of cytosine to hydroxyl cytosine

(c) Alkylation

- Alkylation is caused by alkylating agents.
- Alkylating agents cause mutations by transitions, transversions, deletions and frameshifts.
- Alkylating agents (such as ethyl-methane sulfonate, ethyl-ethane sulfonate and mustard gas) can mutate both replicating and nonreplicating DNA.
- Alkylating agents bring about methylation and ethylation of nitrogenous bases.
- Alkylation of guanine results in mispairing with thymine and during the course of replication, it may result in G ≡ C ⟶A = T pairing.
- Ethyl methane sulfonate (EMS) removes guanine from the strand of the DNA and leaves a gap point.
- At the time of replication, any of the four nitrogenous bases become inserted in the gap.
- In the next replication, the gap is filled by a base, which is complementary to the inserted base.
- This may lead to transition or transversion.

3. Agents causing Distortion of DNA

There are certain acridine dyes (proflavin, acridine orange) that can be intercalated between bases of the DNA strand causing distortion in the DNA.

- This results in insertion or deletion of bases during replication, resulting in mutations.

Transposable Elements as Mutagens

- Scientists are now using transposable elements to create new mutations.
- Transposable elements are mobile pieces of DNA that can move from one location to another in a genome.
- Often when they move to a new location, the result is a new mutant.
- The mutant arises due to the presence of a new piece of DNA in a wild-type gene that disrupts the normal functioning of the gene.
- Thus, transposable elements are a powerful source of creating insertional mutations. This is known as insertional mutagenesis.
- Besides, prion replication has been shown to be subjected to mutation.

MODERN CONCEPT OF GENE

- The presence of genes was first proposed by Mendel in 1865. He called it factor. The term ‘gene’ was coined by Johannson in 1909.
- Gene is the basic fundamental unit of heredity and life.
- Genes control both structure and specific function of the cells and thus the entire organism.
- Genes are present in each and every cell of all organisms.
- Chemically, each gene consists of a specific sequence of DNA building blocks, called nucleotides. Each nucleotide is made up of pentose sugar, nitrogenous base and phosphoric acid.
- On an average, a gene consists of 1,500 nucleotide base pairs.
- The strands of DNA into which genes occur are organised into chromosomes.
- Each gene provides a blueprint for the synthesis of enzymes and other proteins.

- A gene expresses itself producing a specific protein through the process of transcription and translation.

$$\text{Gene} \xrightarrow{\text{Transcription}} \text{mRNA} \xrightarrow{\text{Translation}} \text{Protein}$$

- A single gene may occur in several forms called alleles. Generally a gene has two forms, viz., dominant and recessive. When a gene exits in more than two forms, it is known as multiple alleles.
- Sometimes two alleles of a character express equally. This is known as co-dominance.
- Genes can replicate and can produce its own copies.
- The expression of genes is influenced by environmental factors.
- The total set of genes of an organism is called a genome.
- Genes may vary in their make up from person to person.
- Each gene occupies a fixed position on the chromosome called locus.
- Genes are arranged in a single linear order on a chromosome.
- Alteration in the number and arrangement of genes may result in mutation.
- Changes that occur due to mutations in germ cells can be transmitted to the next generation.
- Mutations that affect somatic cells may result in various types of cancers.
- Many genes are present on each chromosome and they are inherited together. Such genes are called linked genes.
- Sometimes two or more genes interact to produce a particular trait. This is termed as 'interaction of genes'.
- Sometimes a single pair of genes produces two or more characters. This is known as pleiotropism.
- Transfer of alleles of genes occurs from one population to another, called gene flow, which leads to change in gene frequencies.
- The number of genes in a particular cell may be increased (by polyploidy or hyperploidy) or decreased (hypoploidy).
- Inbreeding leads to homozygosity while outbreeding results in heterozygosity within the gene pool.
- Fine structure of gene has revealed that a gene consists of cistron, recon and muton.
- Cistron is a portion of the DNA specifying a polypeptide chain.
- Recon is the smallest unit of DNA capable of recombination.
- Muton is the smallest unit of DNA capable of undergoing mutation.
- Some genes are naturally split. Such genes contain some sequences which do not code for amino acids (called introns) and some sequences that code for amino acid (called exons).
- Genes having only one intron are called monointron gene (RNA tyr gene) while genes having more than one introns are called multi-introns genes (rat muscle X-acting gene has six introns).
- There are certain genes, which code for more than one polypeptide. Such genes are called overlapping genes.
- Overlapping genes share some of the same sequences (In bacteriophage φX174, gene *E* lies entirely within gene *D*1, but they are translated in different reading frameworks).
- There are genes which move from one location to another on a chromosome.

Such genes are called jumping genes or transposons.

- A gene that produces two proteins simultaneously from a long transcript by changing the end point of protein synthesis is known as nested gene. The entire coding sequence of such a gene lies between the start codon and terminating codon of a larger external gene. Thus, the entire coding sequences are present in other genes.
- The genes that have lost their ability to perform a function due to mutations are called pseudogenes. They look like normal genes but do not express any RNA or protein. They are often termed as nonfunctional DNA and regarded as junk.

- Genes that lack well-defined exon or introns sequences, i.e., the exon in one instance might be introns in another case, are termed as complex genes. These genes manifest excessive rearrangement in sequence (mRNA), i.e., before post-transcriptional modifications.
- Genes that cause cancer are called oncogenes. Oncogenes are activated form of proto-oncogenes.
- The genes that code for proteins, which act as transcription factor, enhancing the rate at which certain DNA sequences are transcribed are termed as homeotic genes. Homeotic genes play a key role in the early development and differentiation of embryonic tissue in eukaryotic organisms. These genes were first identified in *Drosophila*.
- The group of genes showing similarity with each other is termed as gene family, arising by duplication. All genes in the family may occur on the same locus. For example, five members of growth hormone gene family are clustered on chromosome 17 in humans. Gene families provide information how new genes arise and diversify.

HUMAN GENETICS

- Human genetics is the branch of genetics that deals with the study of inheritance of human traits.
- Sir Archibald Garrod is generally described as the Father of Human Genetics.
- About 200 traits are known to be genetically transmitted in human beings. Some of these traits are transmitted through typical Mendelian pattern and some through non-Mendelian pattern.

Human Karyotype

- Karyotype refers to the complement of chromosomes, either at species level or at individual level.
- The correct number of human chromosomes (46) was given by Tijio and Levan (1956). Previously, the chromosome number of humans was considered to be 46.
- Normal human karyotype contains 22 pairs of autosomes and one pair of sex chromosomes.
- Karyotype of normal karyotype of men is 44+XY and that of women is 44+XX.
- The table given below shows the nomenclature of chromosome groups proposed by the *Denver Report and the London Report* (1963).

Table 4

S. No.	*Denver report*	*London report*	*Description*
1.	Group 1–3	Group 1–3 (A)	Large and metacentric chromosomes
2.	Group 4–5	Group 4–5 (B)	Large submetacentric chromosomes
3.	Group 6–12	Group X, 6–12 (C)	Medium-sized submetacentric chromosomes
4.	Group 13–15	Group 13–15 (D)	Large acrocentric chromosomes; all may have satellites
5.	Group 16–18	Group 16–18 (E)	Chromosome 16 is metacentric while 17 and 18 are submetacentric
6.	Group 19–20	Group 19–20 (F)	Small metacentric chromosomes
7.	Group 21–22	Group 21–22 +Y (G)	Short acrocentric chromosomes having satellites but Y chromosome lacks satellite