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REVIEW OF POSTGRADUATE PATHOLOGY

GENERAL PATHOLOGY

HIGHLIGHTS

- Easy to understand and memorize general pathology for both MD and DNB postgraduate students.
- Assured success with high scoring in theory examination as well as viva voce.
- Contains usually asked questions in general pathology for postgraduate students.
- Includes topics that are not covered by usual textbooks of pathology.
- Keypoints are highlighted.



Ramadas Nayak
Rakshatha Nayak

JAYPEE

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CHAPTER 12

Genetic Disorders and Molecular Diagnosis

12.1 Genetic Disorders

CHAPTER OUTLINE

- Introduction
- Mutations
  - Causes
  - Classification of mutations
  - Structural chromosomal mutations
  - Major types of mutations
  - Functional effects of mutations on the protein
  - Alterations in protein-coding genes other than mutations
  - Alterations in noncoding RNAs
- Genetic disorders
  - Mendelian disorders/single-gene or monogenic disorders
  - Biochemical and molecular basis of single gene (mendelian) disorders
  - Disorders associated with defects in structural proteins
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- Complex multigenic disorders
- Chromosomal disorders
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  - Conventional (traditional) cytogenetics
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  - Cytogenetic disorders involving autosomes
  - Cytogenetic disorders involving sex chromosomes
- Single-gene disorders with nonclassic inheritance
  - Diseases due to trinucleotide repeat mutations
  - Mutations in mitochondrial genes
  - Disorders associated with genomic imprinting
  - Disorders associated with gonadal mosaicism

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INTRODUCTION

Gene is defined as a **segment of deoxyribonucleic acid** (DNA) which **carries the genetic information**. Gene is the basic physical and functional unit that is regulated by transcription and encodes an ribonucleic acid (RNA) product, which is most commonly, but not always, translated into a protein that produces its activity within or outside the cell. Genetics is the study of heredity, or how the characteristics of living organisms are transmitted from one generation to the next via DNA (consists of genes that are the basic unit of heredity). Thus, **genetics is the study which deals with the science of genes, heredity, and its variation in living organisms**. **Human genetics** deals with the study of individual genes, their role and function in disease, and their mode of inheritance.

A **genome** is an **organism's complete set of genetic instructions. Genomics**, in contrast, is the **study of the entire genetic information of organism's genes**—called the genome. Each genome contains all of the information needed to build that organism and allow it to grow and develop. Thus, genomics includes the study of function and interaction of DNA within the genome, as well as with environmental or nongenetic factors, such as a person's lifestyle. With the characterization of the human genome, genomics not only complements traditional genetics in understanding the etiology and pathogenesis of disease, but also plays a prominent role in diagnostics, prevention, and therapy of disease.

Human genome project (HGP) was initiated in the mid-1980s as an effort to characterize the entire human genome and completed the DNA sequence for the last of the human chromosomes in 2006. HGP provided the first draft of the about 3 billion base pairs (bp)/nucleotides of DNA per haploid human genome. This has dramatically increased our understanding regarding the developmental and genetic

disorders. The human genome contains about 20,000 protein-coding genes comprising 1.5% of the whole genome. Each gene varies in size. It is interesting to note that most of the protein-coding genes in the human genome are also found in genomes of other organisms including lower life forms (e.g., yeast). It is the remaining 98.5% of the human genome that is responsible for the remarkable complexity that ultimately determines the human species. This remaining 98.5% includes many non-protein-coding genes. These nonprotein-coding genes are transcribed into RNA molecules such as microRNAs and long noncoding RNAs. These are increasingly being recognized to play important regulatory functions. Recent advances in molecular genetics and cytogenetics technologies have greatly improved the understanding of the genetic basis of human disease including neoplasms.

Hereditary, familial, and congenital: Hereditary disorders are derived from one's parents and are transmitted in the germline through the generations. Hence, hereditary disorders are familial. Congenital means "born with" and some congenital diseases are not genetic (e.g., congenital syphilis). Not all genetic diseases are congenital. For example, Huntington disease is a genetic disease that begins to manifest only after 20s or 30s.

Genomic medicine, personalized medicine, or precision medicine is the study of our genes (DNA) and their interaction with our health. It aims at customizing medical decisions to an individual patient. The modern field of pharmacogenomics consists of study of how genes affect an individual's response to drugs. Now, it is possible to target drugs to specific genetic loci that are responsible for susceptibility to disease as well their prevention. This has created new classes of medicines targeting specific variants in gene and protein structure. This provides highly specific therapies with fewer side effects. Gene therapies also have great potential for treating genetic and many acquired diseases. Pharmacogenomics can be used to optimize drug therapy and predict efficacy, adverse events, and drug dosage of selected medications.

Diseases that manifest during the perinatal period may be caused due to factors in the fetal environment, genomic abnormalities or by combinations of genetic defects and environmental influences. For example, phenylketonuria (PKU) is disorder due to genetic deficiency of phenylalanine hydroxylase (refer pages 934 and 935). It produces mental retardation only if an infant with this disorder is exposed to dietary phenylalanine.

Genetic disorders are far more common than these are acknowledged. This is mainly because the genetic diseases diagnosed usually represent the tip of the iceberg and these remain hidden. Most of the time, genetic disorders with less extreme genotypic errors allow full development of embryonic and live birth.

Fetal death: About 50% of fetuses spontaneously aborted during the early months of gestation show a demonstrable chromosomal abnormality. The incidence of specific numerical chromosomal abnormalities in abortuses is several times more than in term infants. This indicates that most such chromosomal defects are lethal for survival of fetus and only a small number of fetuses with cytogenetic abnormalities are born alive. About 1% of all newborn infants reveal a gross chromosomal abnormality, and serious disease develops in about 5% of individuals younger than age of 25 years. Presently, advances in DNA sequencing have helped in detection of numerous smaller genetic errors. Probably the genomes contain at least 400 protein-damaging sequence variants and at least two bona fide disease mutations even in so-called healthy individuals. Thus, a potential disease-causing mutation need not produce disease. The expression of disease depends on complex interactions between genetic, epigenetic, and environmental factors.

Birth defects: A specific cause cannot be identified in more than two-thirds of all birth defects.

- **No known cause:** Presently in about 70% of birth defects, no known genetic or other cause is identifiable.
- **Genetic causes:** Genomic defects that cause birth defects include inherited traits or spontaneous mutations. Only small number due to chromosomal abnormalities.
- **Other causes:** Uterine factors, maternal disorders (e.g., metabolic imbalances or infections during pregnancy) or environmental exposures (e.g., drugs, chemicals, radiation) constitute not >6% of birth defects.

Reductions in the incidence of birth anomalies can be brought out by—(1) genetic counseling, (2) early prenatal diagnosis, (3) identifying high-risk pregnancies, (4) avoiding potential teratogens, and (5) implementation of preventive measures. For example, prenatal dietary supplement of folic acid can significantly reduce the incidence of congenital neural tube defects.

Infant mortality: In advanced countries, developmental and genetic birth defects are responsible for 50% of deaths during infancy and childhood. By contrast, in less developed countries, 95% of infant mortality is due to environmental causes (e.g., infectious diseases and malnutrition).

MUTATIONS

Q. Write short essay on principles and effects of gene mutations.

For synthesis of proteins, DNA is transcribed into RNA, which is processed into mRNA (messenger RNA). This, in turn, is translated into protein by ribosomes. Any changes in DNA can lead to corresponding changes in the amino acid sequence of its encoded protein or interfere with its synthesis.

The term mutation was coined by Müller in 1927. A **mutation is a permanent or stable change in the DNA** (genetic material) which can result in a disease. The term mutation is used to indicate the process to bring out genetic variations as well as the outcome of these alterations. It is to be noted that epigenetic events may also influence gene expression or facilitate genetic damage.

Definition: Mutation is defined as any permanent change in the primary nucleotide sequence of DNA regardless of its functional consequences though generally it has a negative significance.

Variation: This is a more neutral term and is now increasingly used to describe sequence changes in DNA and is recommended by many instead of mutation. Some variations may be lethal, others can be less injurious, and some may benefit as an evolutionary advantage.

Causes

Mutations drive evolution but can also be pathogenic.

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- **Spontaneous mutation:** Majority of mutations occur spontaneously due to errors in DNA replication and repair.
- **Induced mutation:** Mutations can be caused due to exposure to mutagenic agents such as chemicals, viruses, and ultraviolet or ionizing radiation.
- **Polymorphism:** If the genetic material change/variant (sequence variations) does not cause obvious effect upon phenotype (i.e., it is not appreciable or perceptible), it is termed as polymorphism. A **polymorphism is defined as genetic variation that exists in population with a frequency of at least 1%** (or >1%). The allele frequency and functional consequences of polymorphism are usually not known, the term variation is now increasingly recommended to describe these sequence changes. Generally, polymorphism consists of single base-pair substitutions that do not alter the protein coding sequence because of the degenerate nature of the genetic code. In the human genome, about 1 in 1,000 base pairs is polymorphic. Evolution is based on the accumulation over time of such nonlethal variation/mutations that alter the ability of a species to adapt to its environment.

Consequences of mutations (or variations): These are highly variable.

- Some mutations have no functional consequences.
- Some are lethal. Hence, they are not transmitted to the next generation.
- Some may confer an evolutionary advantage (i.e., polymorphism). This is in between the above two extremes. This consists of a broad range of DNA changes that account for the genetic diversity of any species.

With the exception of triplet nucleotide repeats, which can expand, variations are usually stable.

Classification of Mutations

Depending on the cell affected, mutations can affect either somatic cells or germ cells.

- **Germ cell mutations:** Mutations that affect the germ cells or germline (sperm or oocytes) are transmitted to the progeny/descendants and can produce inherited/hereditary diseases.
- **Somatic cell mutations:** Mutations can occur during embryogenesis or in somatic tissues (i.e., somatic cells). They can produce some congenital malformations and cancers. The mutations that are not inherited and do not **cause hereditary diseases are known as de novo mutations.** Mutations that occur during development can lead to **mosaicism**. In this, tissues are composed of cells with different genetic constitutions. If the germline is mosaic, a mutation can be transmitted to some progeny but not others. Sometimes, somatic mutations that do not affect cell survival can be detected because of variable phenotypic effects in tissues. For example, café-au-lait skin pigmentations in McCune–Albright syndrome (characterized by mutation during early embryogenesis). Other somatic mutations are associated with neoplasia because they confer a growth advantage to cells.

Structural Chromosomal Mutations

The rearrangement of genetic material during mutation causes structural changes. Mutations structurally vary.

- Mutations can involve the entire genome. For example, triploidy characterized by one extra set of chromosomes.
- Gross numerical or structural alterations in chromosomes or individual genes.

Structural mutations may be—(1) visible during karyotyping or (2) submicroscopic (minute/subtle changes). The submicroscopic gene mutations can result in partial or complete deletion of a gene or more often, a single nucleotide base. Few examples of genetic mutations are discussed below.

Major Types of Mutations

Mutations cause rearrangement of genetic material. The changes in the genetic material can range from single base substitutions, through insertions and deletions of single or multiple bases to loss or gain of entire chromosomes. Thus, structural changes can be divided into—(1) visible during karyotyping or (2) submicroscopic (minute/subtle changes).

Submicroscopic (minute/subtle changes): The submicroscopic gene mutations can result in partial or complete deletion of a gene or more often, a single nucleotide base.

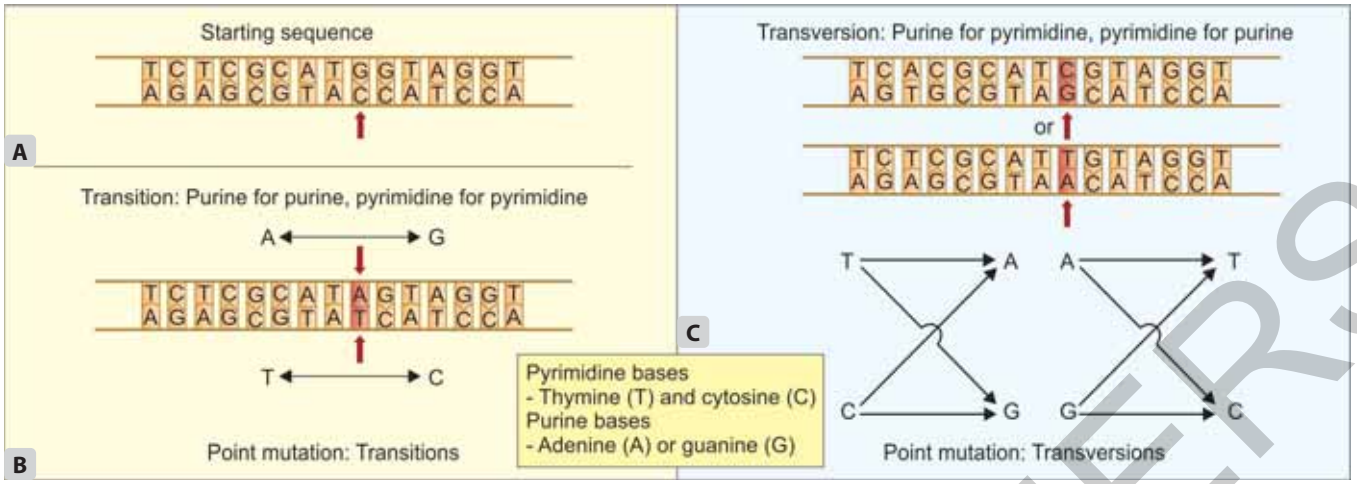
Point Mutation within Coding Sequences

Point mutation (single-base changes or base substitution or substitution mutation) is the replacement of one single **nucleotide base** (at a certain position in one strand of the DNA) **by another different nucleotide base within a gene.** Thus, one base pair in the DNA is altered. After DNA replication, a new base pair will appear in the daughter double helix. It may change the code in a triplet of bases and lead to the replacement of one amino acid by another in the gene product. These are the most common types of mutation and **point mutation is a common mechanism of oncogene activation.** Examples: Point mutations in one of the ***RAS*** genes (***HRAS, KRAS,*** or ***NRAS***) are observed in ~85% of pancreatic cancers and 45% of colon cancer, point mutations of ***RET*** in leukemia, and ***BRAF*** in melanoma. Point mutations (substitution) may be of two types—transition mutations and transversion mutations.

1. **Transition mutations (Figs. 1A and B):** It is a type of substitution in which the base of nucleotide is substituted by the same type of base in the nucleotide. Thus, a pyrimidine base [i.e., thymine (T) or cytosine (C)] is substituted by another pyrimidine (C for T or vice versa) or a purine base [i.e., adenine (A) or guanine (G)] is changed to another purine base (A for G or vice versa). Transition is more frequent than transversion (discussed below). Relatively high frequency of C to T transitions known as CpG dinucleotides (p represents the phosphate). This is because the methylated base in genomic DNA undergoes spontaneous deamination of methylcytosine converting them to thymine. CpG dinucleotides are termed as "hotspots" for mutation.
2. **Transversion mutations (Figs. 1A and C):** In this type, there is a substitution of a pyrimidine base by a purine base or vice versa. Thus, there are changes from a purine to either of the two pyrimidines or the change of a pyrimidine into either of the two purines. For example, TA or CG pair replaces the wild-type AT pair. It may occur in the coding region (the part of the gene that is translated into a protein) or noncoding region of the gene.

Functional groupings for point mutations: Majority of point mutations occur in the coding region of a gene. When the nucleotide sequence of a protein-coding gene containing the point mutation is transcribed into an mRNA molecule,

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FIGS. 1A TO C: Schematic representation of transition and transversion mutations. (A) Starting sequence of DNA; (B) Transition is a type of substitution in which the base of nucleotide is substituted by the same type of base in the nucleotide, i.e., pyrimidine base by another pyrimidine or a purine base is changed to another purine base; (C) Transversion mutations.

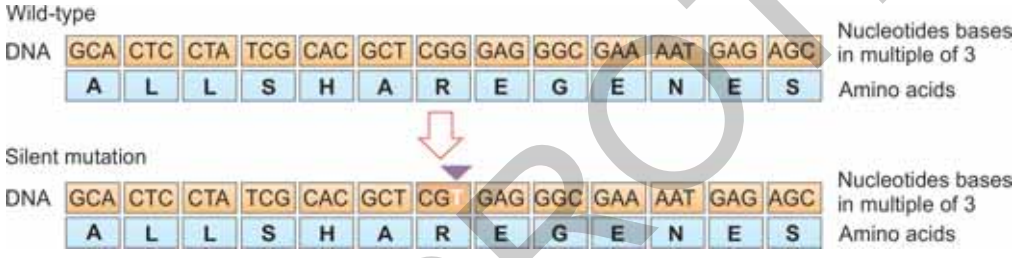
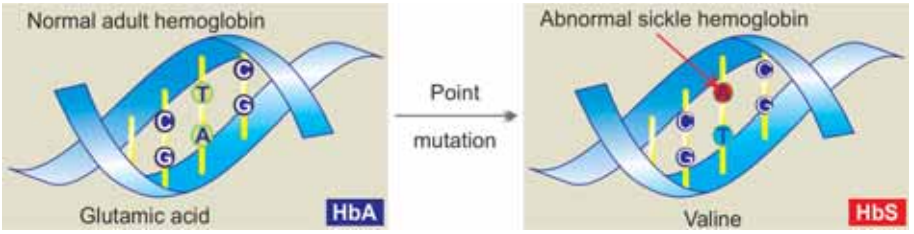


FIG. 2: Silent mutation. They do not change the primary structure of protein. In this example, CGG and CGT (point mutation where guanine is replaced by thymidine and vice versa) both encode amino acid arginine (one letter abbreviation for arginine is R).

then the RNA molecule will also show the base change at the corresponding location. Single-base changes in the mRNA are converted into a string of amino acids and may have one of the several effects when translated into protein. Thus, mutations often result as functional changes in the final protein product. Depending on the functional effect, point mutations can be divided into silent mutations, missense mutations, and nonsense mutations.

- **Silent (synonymous) mutations:** These occur when the point mutation causes altering of codon (produces a new genetic code) but still exactly encodes for the same amino acid as the original amino acid. For example, CGG and CGT (point mutation where guanine is replaced by thymidine and vice versa) both encoded amino acid arginine (one letter abbreviation for arginine is R) (**Fig. 2**). In some silent mutations, the new genetic code, codes for a different amino acid that has the same properties as the original amino acid. These point mutations do no show detectable effect.
- **Missense mutations:** It is a point mutation within coding sequences that changes the genetic code (change in the DNA sequence in a coding region) in a triplet of bases. If so, it alters an amino acid and leads to the replacement of one amino acid by another different amino acid in the gene product. Because these mutations alter the meaning of the sequence of the encoded protein, they are usually termed missense mutations (three-fourths of base changes in the coding region). In this type of point mutation change, the base substitution generates a genetic code that may code for a different amino acid. This results in incorporation of a different amino acid at the corresponding site in the protein molecule. This mistaken amino acid (or missense), depending on its location in the specific protein, may be acceptable, partially acceptable, or unacceptable to the function of that protein molecule.
  - **Conservative missense mutation:** In this type, the substituted amino acid has biochemical properties similar to the one it replaces (i.e., original). This change may have only little change or no effect on the function of the protein product.
  - **Nonconservative missense mutation:** In this type of missense mutations, new codon codes for a different amino acid and protein. The normal amino acid is replaced by biochemically a very different amino acid with very different properties. Thus, the result is change or loss of protein function. **Example, sickle cell anemia in which missense mutation affects the β-globin chain of hemoglobin** (**Fig. 3**). In this, the nucleotide triplet CTC (or GAG in mRNA), which encodes glutamic acid, is changed to CAC (or GUG in mRNA), which encodes valine. This single amino acid substitution (point mutation) changes the properties of hemoglobin and gives rise to sickle cell anemia.

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(HBA: hemoglobin A; HbS: hemoglobin S)

FIG. 3: Nonconservative missense point mutation in sickle cell anemia. When adenine replaces thymidine, the amino acid valine replaces glutamic acid in the sixth position of β-globin chain of hemoglobin and gives rise to abnormal sickle hemoglobin.

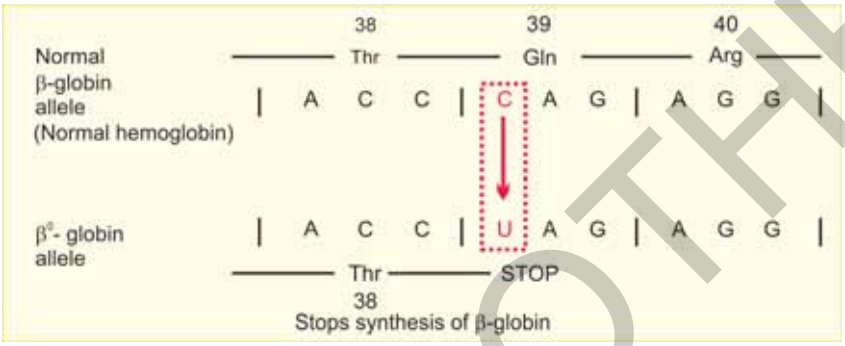


FIG. 4: Nonsense mutations shorten a polypeptide by replacing a codon with a stop signal leading to premature chain termination. In this example, a point mutation (C replaced by U) in codon 39 changes glutamine (Gln) codon to a stop codon. This stops the synthesis of protein at amino acid 38.

- **Nonsense mutation (stop codon):** It is a severe type of point mutation in which base substitution causes a stop (nonsense) codon resulting in the **premature termination**. There will be a premature termination codon (chain terminator or stop codon) of translation and the production of only a fragment of the intended protein molecule. The premature termination of protein synthesis leads to complete loss of function in the finished protein. Example, in β-globin chain, a point mutation affecting the codon for glutamine (CAG) creates a stop codon (UAG) if U replaces C (**Fig. 4**). This change leads to premature termination of β-globin gene translation. The short peptide produced due to this is rapidly degraded. It leads to deficiency of β-globin chains, thereby there is no synthesis of hemoglobin A. It produces a severe form of anemia called β_0-thalassemia.

Deletions and Insertions

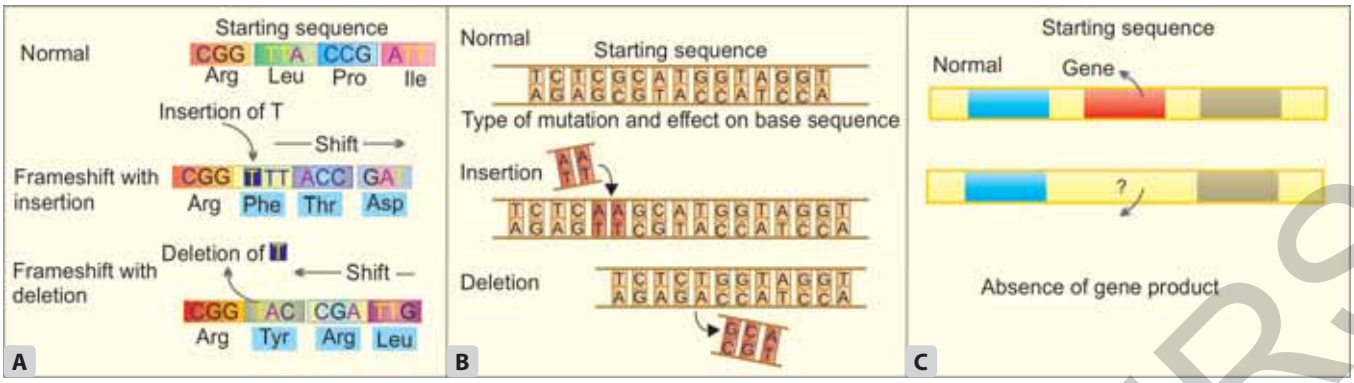
Q. Write short essay on frameshift mutation.

In deletion, there is loss of one or more nucleotide pairs from a DNA molecule. In insertion, there is addition of one or more nucleotides into a gene. Deletions and insertions may be as small as a single base pair or as large as megabases (i.e., millions of base pairs).

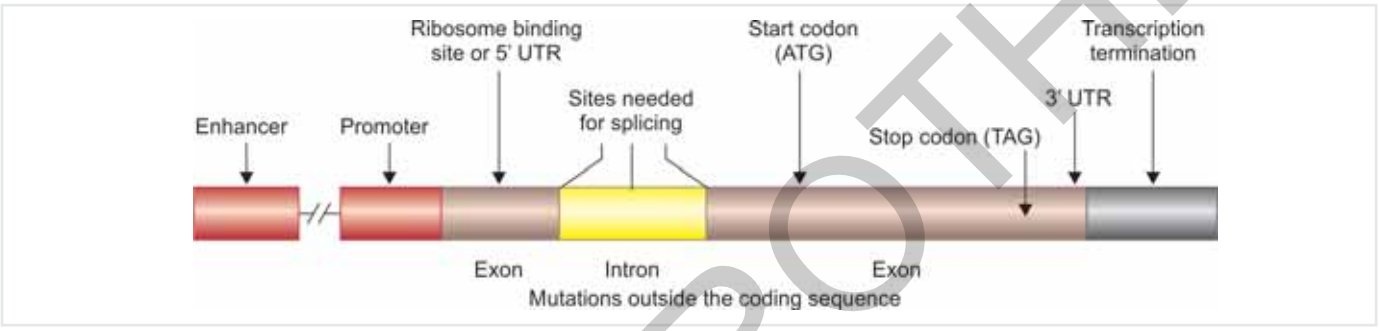
Consequences of small deletions or insertions: If they involve the coding sequence, it can have three possible effects on the encoded protein.

1. **Intact reading frame:** If the number of base pairs involved is three or a multiple of three, the reading frame will remain intact. There will be synthesis of an abnormal protein lacking or gaining one or more amino acids.
2. **Frameshift mutation:** Amino acids are encoded by trinucleotide sequences. Frameshift mutation may occur due to small insertion or deletion of one or more nucleotides in the coding regions.
   i. If the number of nucleotide bases inserted or deleted is not a multiple of 3, the reading frame [is a way of dividing the sequence of nucleotides in a nucleic acid (DNA or RNA) molecule into a set of consecutive, nonoverlapping triplets] of the message is changed (**Fig. 5A**). This leads to alterations in the reading frame of the DNA strand; hence they are known as frameshift mutations. This changes the genetic the code (**Fig. 5A**). Frameshift mutations can also alter transcription, splicing or mRNA processing.
   ii. If the number of base pairs involved is three (**Fig. 5B**) or a multiple of three, frameshift does not occur. This may synthesize an abnormal protein lacking or gaining one or more amino acids followed by truncation resulting from a premature stop codon. Usually, the result is the incorporation of a variable number of incorrect amino acids.
3. **Large deletions:** Large deletions may affect a portion of a gene or an entire gene, or several genes. When deletions involve a large segment of DNA, the part or entire coding region of a gene may be entirely removed (**Fig. 5C**). There will be no protein product. Large deletions and insertions can reorganize genomes by changing either the order of genes along a chromosome, the number of genes in the genome, or even the number of chromosomes. A large deletion may also bring together coding regions of nearby

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FIGS. 5A TO C: Frameshift mutations change the reading frame either by insertion or deletion. (A) Insertion or deletion of single nucleotide bases (not a multiple of 3), the code will be changed; (B) Insertion or deletion of more than one nucleotide bases; (C) Deletions involving a large segment of DNA in the coding region may entirely remove the gene.



(ATG: translation initiation/start codon which codes for the aminoacid methionine; TAG: stop or termination codon; UTRs: untranslated regions)

FIG. 6: The exons (coding region) carry the code for the production of proteins. Mutations outside the coding region (includes promoter sequences, enhancers or other regulatory regions) can also disrupt gene expression.

genes. This can give rise to a fused gene that generates a hybrid protein in which part or all of one protein is followed by part or all of another.

Mutations within Noncoding Sequences

Mutations may also involve the noncoding regions (**Fig. 6**) of gene. Gene expression depends on several signals other than the actual coding sequence. Mutations in promoter sequences, enhancers or other regulatory regions can affect the level of gene expression. Hence, point mutations or deletions involving these regulatory regions may lead to either marked reduction in or total lack of transcription. Example, certain hereditary anemias. Mutations in miRNA or siRNA binding sites within untranslated regions (UTRs) can also result in disease.

Trinucleotide Repeat Mutation

The DNA contains several repeat sequences of three nucleotides (trinucleotide). Trinucleotide-repeat mutations belong to a special category of genetic anomaly. Many distinct trinucleotide repeats/expansions have been associated (and are identified) in human disease (**Table 1**). The number of copies of some such repeats varies among individuals. They represent allelic polymorphism of the genes in which they are found. When they are repeated directly adjacent to each other (one right after the other), they are known as tandem repeats (**Fig. 7**). As a rule, the number of repeats below a particular threshold does not change during mitosis or meiosis. When the repetitive trinucleotide sequences reach above this particular threshold, the number of repeats can expand or contract. Mutations characterized by amplification of a

Table 1: Examples of diseases associated with trinucleotide repeats.

Disease	*Normal length of sequence*	*Length of sequence in full mutation*	*Location of trinucleotide repeats sequence*
CAG sequence			
• Huntington disease	10–30	40–100	4p16.3
• Kennedy disease	15–25	40–55	Xq21
• Spinocerebellar ataxia	20–35	45–80	6p23
CGG sequence			
• Fragile X syndrome	5–44	200–1,000	Xq27.3
CTG sequence			
• Myotonic dystrophy	5–35	50–2,000	19q13
GAA sequence			
• Friedreich ataxia	7–30	120–1,700	9q13

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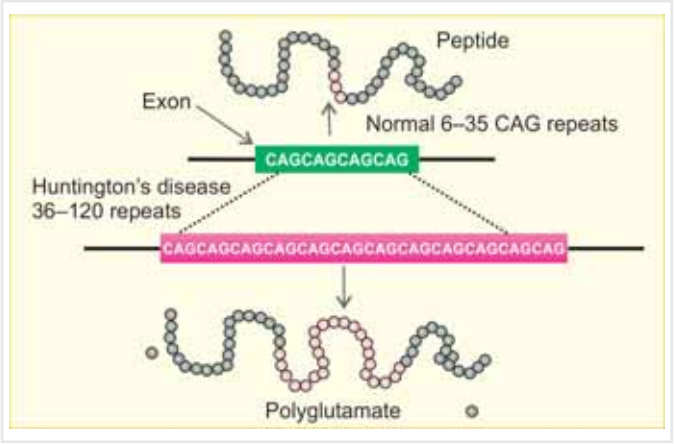


FIG. 7: Trinucleotide repeat disorder, e.g., Huntington's diseases. It results from expansion of a CAG (C is a pyrimidine base. A and G are purine bases) triplet repeat from a normal number of 6 to 35 repeats to greater than 36 repeats. This results in expansion of a polyglutamine sequence in the corresponding protein.

sequence of three nucleotides are more common. The specific nucleotide sequence that undergoes amplification differs in various disorders. However, almost all affected sequences share the nucleotides guanine (G) and cytosine (C) [G is a purine base and C is a pyrimidine base]. Fragile X syndrome (FXS) is a classic example of this category of disorders. In normal population, the number of tandem repeats of the sequence CGG within the regulatory region of a gene called familial mental retardation 1 *(FMR1)* is small with an average of 29. In FXS, there are 250–4,000 of these tandem repeats in *FMR1*. This expansion of the trinucleotide sequences prevents normal expression of the *FMR1* gene and gives rise to intellectual disability. One of the distinguishing features of these trinucleotide-repeat mutation is dynamic (i.e., the degree of amplification increases during gametogenesis). The number of these trinucleotide-repeat increases with each successive generation. This is also associated with increase in the severity of the disease and presents at younger age in successive generations. This mechanism is termed as genetic anticipation. Most trinucleotide repeat diseases are associated with expansions of a CAG (C is a pyrimidine base. A and G are purine bases) codon. This CAG encodes glutamine in the open reading frame of the gene. The tandem repeats of CAG result in polyglutamine tracts in the protein product. Hence, these disorders are associated with degeneration of neurons.

Functional Effects of Mutations on the Protein

Mutations in DNA can lead to either change in the amino acid sequence of a specific protein or may interfere with its synthesis. The consequences vary from those without any functional effect to those which have serious effects.

Loss-of-function (LOF) mutations: These mutations cause the reduction or complete loss of normal function of a protein (gene product). It is usually due to deletion of the whole gene but may also occur with a nonsense or frameshift mutation. LOF mutations involving enzymes are usually inherited in an autosomal or X-linked recessive manner. This is because the catalytic activity of the product of the normal allele is enough to carry out the reactions of most metabolic pathways.

- **Haploinsufficiency:** LOF mutations in the heterozygous state in which half normal levels of the gene product produce effect on phenotype, are called as haploinsufficiency mutations.

Gain-of-function mutations: These mutations result in either increased levels of gene expression or the development of a new function(s) of the gene product. These are usually due to missense mutations. In gain-of-function mutation, the protein function is altered in a manner that results in a change in the original function of the gene. The expanded triplet repeats mutations in the Huntington (*HTT*) gene cause qualitative changes in the gene product. These products aggregate in the central nervous system (CNS) causing its classic clinical features.

Lethal mutations: These lead to death of the fetus.

Alterations in Protein-coding Genes Other than Mutations

Apart from alterations in DNA sequence, coding genes also can undergo structural variations. These are copy number changes and include **amplifications or deletions—or translocations**. It may lead to aberrant gain or loss of protein function. Similar to mutations, structural changes may occur in the germline, or be acquired in somatic tissues. Many pathogenic germline changes involve a contiguous portion of a chromosome rather than a single gene (e.g., 22q microdeletion syndrome). Next-generation sequencing (NGS) technology is used for assessing genome-wide DNA copy number variation (CNV) at very high resolution Somatically acquired structural alterations (e.g., amplifications, deletions, and translocations) are often seen in cancers. For example, "Philadelphia chromosome"—translocation t (9;22) between the *BCR* and *ABL* genes in chronic myeloid leukemia (refer Fig. 25 of Chapter 10).

Alterations in Noncoding RNAs

There are very large number of genes that do not encode proteins but produce transcripts. The nonencoded products of these genes, so-called "noncoding RNAs (ncRNAs)", play important regulatory functions [e.g., small RNA molecules called microRNAs (miRNAs) and long noncoding RNAs (lncRNAs)].

Mutations can interfere with gene expression at various levels. Deletions and point mutations involving promoter sequences in a gene may suppress transcription. Mutations involving introns or splice junctions or both, may lead to abnormal mRNA processing. Translation can be affected if a nonsense mutation produces a stop codon (chain termination mutation) within an exon. Mutations may lead to expression of normal amounts of a dysfunctional protein (e.g., amyloidosis).

GENETIC DISORDERS

There are many types of genetic abnormalities that affect the structure and function of proteins. This may disrupt the cellular homeostasis and produce disease. The mode of inheritance for a given phenotypic trait or disease is determined by pedigree analysis using standard symbols. Definition of symbols in a standard pedigree is presented in **Figure 8**.

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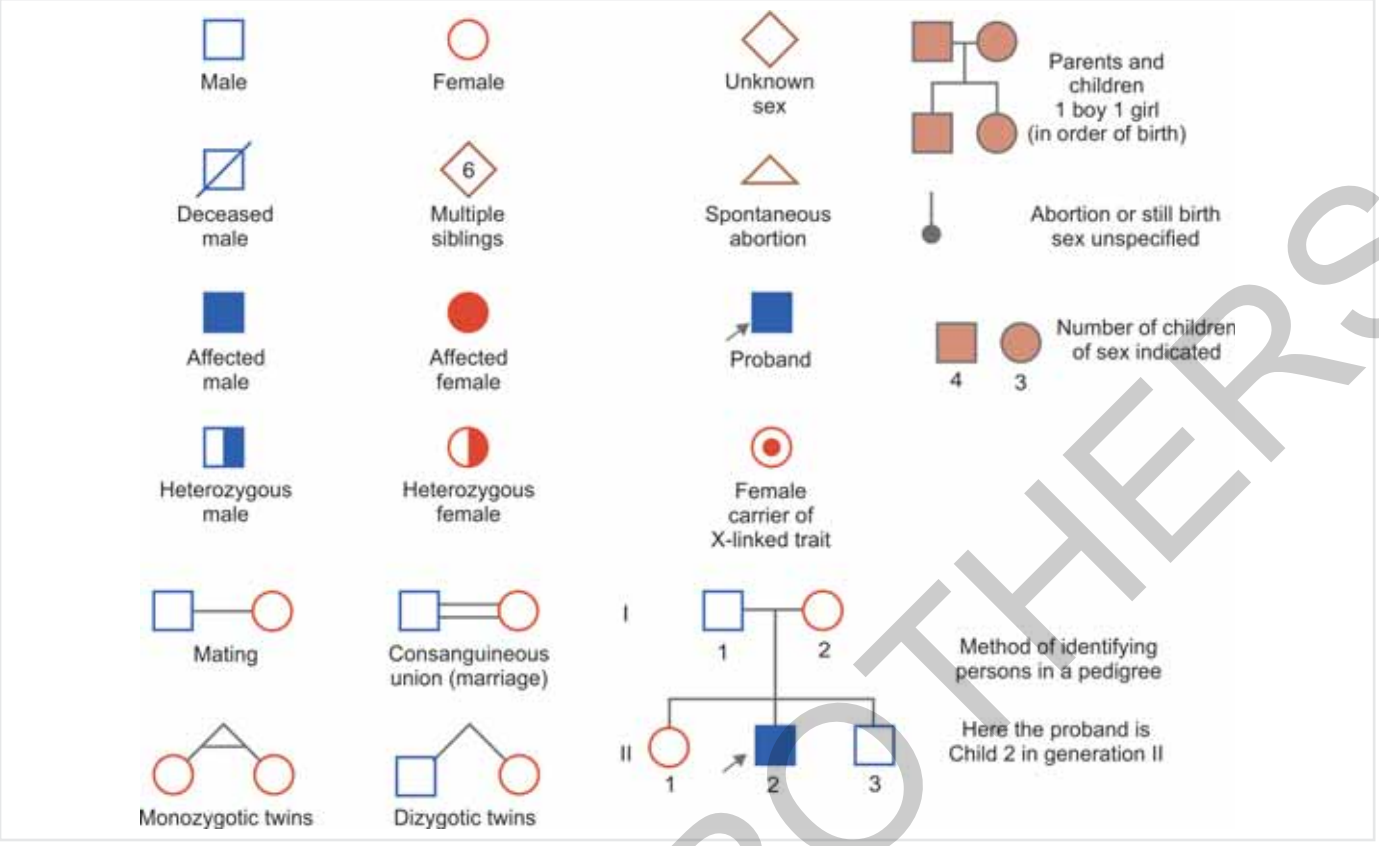


FIG. 8: Definition of symbols in a standard pedigree. Males = squares; females = circles. A line drawn between a square and a circle indicates a mating of that male and female. Two lines drawn between a square and a circle indicate a consanguineous mating in which the two individuals are related (usually as second cousins). Children of a mating are connected to a horizontal line, called the sibship line represented by short vertical lines. The children of a sibship are always listed in order of birth (the oldest on the left). Others are indicated in the figure.

Classification of genetic disorders: Genetic disorders are classified into different categories (**Box 1**).

Mendelian Disorders/Single-gene or Monogenic Disorders

Q. Write short essay on molecular and biochemical basis of Mendelian disorders/single gene disorders.

Disorders related to mutations in single genes with large effects: Single gene disorders result from mutations in single gene and are called as **monogenic human diseases**. They usually follow the principles of classic Mendelian pattern of inheritance (genetic transmission) originally put forth by Gregor Mendel. Hence, they are frequently termed as **Mendelian disorders**. The classic laws of mendelian inheritance are:

- **Mendelian trait:** It is determined by **two copies of the same gene called as alleles**. These alleles are present at the same locus on two homologous chromosomes. In the case of the X and Y chromosomes in males, a mendelian trait is determined by one allele only.
- **Location of defective gene**
  - In autosomal disorders (both dominant and recessive), the defective gene is on autosomes (autosomal inheritance) and is present on one of the 22 autosomes.
  - **Sex-linked traits:** These are encoded by loci on the X chromosome. In sex-linked disorders, it is on the sex chromosomes (sex-linked inheritance).
- **Dominant phenotypic trait:** Genes are inherited in pairs—one gene from each parent. However, the inheritance may not be equal, and one gene may overpower the other in their coded characteristic. The **gene that overshadows the other is called the dominant gene;** the **overshadowed gene is the recessive one. Dominant phenotype needs only one allele of a homologous gene pair**. The phenotype is expressed irrespective whether the allelic genes are homozygous or heterozygous.
- **Recessive phenotypic trait:** It **needs both alleles to be identical** (i.e., homozygous) for the expression of the phenotype.
- **Codominant inheritance:** Though mendelian traits are usually described as dominant or recessive, sometimes **both of the alleles in a heterozygous gene pair are fully expressed and contribute to the expression of phenotype**. It is called codominance. One of the classical examples for codominance is the AB blood group genes.
- **Homozygous versus heterozygous:** Most of the mutations occurring in autosomal genes produce partial expression in the heterozygote and full expression in the homozygote. For example, in sickle cell anemia, the normal hemoglobin A (HbA) is replaced by abnormal hemoglobin S (HbS). If an individual is homozygous for the mutant gene (i.e., sickle cell anemia), all the hemoglobin will be abnormal, HbS, type. Even with normal saturation of oxygen, this disorder is fully

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Ramadas Nayak MBBS MD graduated from Mysore Medical College, Mysuru, Karnataka, India and completed his postgraduation in Pathology from Kasturba Medical College, Mangaluru, Karnataka, India. Presently, he is working as a Professor, Department of Pathology, Yenepoya Medical College, Yenepoya (Deemed to be University), Mangaluru, Karnataka, India. In his illustrious teaching career of 38 years, he was the Head, Department of Pathology, Kasturba Medical College, Mangaluru, Manipal Academy of Higher Ed ucation, Karnataka, India. He has published over 83 scientific papers in both national and international journals. He serves as an Examiner for both undergraduate and postgraduate examinations in several universities. He has worked as a Project Officer for Development of an Atlas of Cancer in India—a project conducted by Indian Council of Medical Research (ICMR) sponsored by WHO. He was the Editorial Committee Member of South Asia Edition of British Medical Journal. He authored 9 books entitled *Essentials in Hematology and Clinical Pathology (second edition), Textbook ofPathology and Genetics for Nurses (second edition), Rapid Review of Hematology, Exam Preparatory Manual for Undergraduates: Pathology (fourth edition), Exam Preparatory Manual for Undergraduates: Pathology for Dental Students, Textbook ofPathology for BPTStudents, Textbook of Pathology for Allied Health Sciences, Histopathology Techniques and their Management,* and *Manual of Transfusion Medicine*. Twice he secured "Good Teacher Award" and eight times "Best Audio-visual Award" in Kasturba Medical College, Mangaluru, Karnataka, India.

Rakshatha Nayak MBBS MD DNB graduated from KS Medical Academy, Mangaluru, Karnataka, India and completed her postgraduation in Pathology from Yenepoya Medical College, Yenepoya (Deemed to be University), Mangaluru, Karnataka, India. Presently, she is working as an Assistant Professor, Department of Pathology, Kasturba Medical College, Mangaluru. She has worked as a tutor in the Department of Forensic Medicine, Kasturba Medical College, Manipal Academy of Higher Education (Manipal), Mangaluru for 1 year (2014-2015) and a tutor in pathology, Department of Pathology, Yenepoya Medical College, Mangaluru. She has attended and successfully completed International Society of Nephrology (ISN)/the American Nephrologists of Indian Origin (ANIO) Clinical Nephropathology Certificate Program conducted by International Society of Nephropathology in 2018. She has also cleared the Diplomat of National Board examination in Pathology in 2018. She has published and presented various scientific papers in national and international journals and conferences. She was awarded Short Term Studentship (STS) by Indian Council of Medical Research (ICMR), New Delhi during 2011. She has been awarded for being the highest scorer in Pathology in KS Medical Academy, Mangaluru and has secured 3rd rank in Phase-II MBBS (Pathology) Examination held in 2010 by Rajiv Gandhi University of Health Sciences (RGUHS), Bengaluru. She is also the highest scorer in KS Medical Academy, Mangaluru in General Medicine in the Final Year MBBS examination conducted by RGUHS, Bengaluru in 2012. She is the highest scorer in Pathology and the University topper in Postgraduate Examination conducted by Yenepoya (Deemed to be University) in 2018. She has 5 years of teaching experience and has taught students of Medical, Dental, and Allied Health Sciences. She is a coauthor of *Exam Preparatory Manual for Undergraduates: Pathology* (fourth edition) and *Manual of Transfusion Medicine.*

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