Lec 6

The Mutation

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Mutation

Mutation: is a process that produces a gene or chromosome that differs from the wild type.

It is most commonly defined as a spontaneous permanent change in a gene or chromosome which usually produces a detectable effect in the organism concerned and is transmitted to the offsprings.

- Mutated gene or chromosome results from a mutational process while the organism or cell whose changed phenotype is attributed to a mutation is said to be a mutant.
- The mutation may result due to changes either on the gene or the chromosome itself. Thus, broadly mutation maybe:

1. Gene mutation where the allele of a gene changes.
2. Chromosome mutation where segments of chromosomes, whole chromosomes, or entire sets of chromosomes change.

Causes and Mechanisms of Mutation

1. Errors in DNA replication.
2. Errors in DNA repair.
3. Environmental **mutagen** causes DNA damage that is not repaired correctly.
4. Transposons and insertion sequences (a mobile DNA elements that can move from one location in the chromosome to another; the element may “jump” into a gene thereby mutating it).
5. External Causes: Mutagenic agents that damage DNA such as chemical mutagens, physical mutagens or biological mutagens.

Agents of Mutations

- The substances or agents which induce artificial mutations are called **mutagenes or mutagenic agents**.
- Mutagens may be of physical, chemical or biological origin.
- They may act directly on the DNA, causing direct damage to the DNA, and most often result in replication error.
- Some however may act on the replication mechanism and chromosomal partition.
- Many mutagens are not mutagenic by themselves, but can form mutagenic metabolites through cellular processes, for example: through the activity of the **cytochrome P450 system** and other **oxygenases such as cyclooxygenase**.

The mutagenic agents are of the following kinds:

1. Radiation and Radioactive Decays
2. Temperature
3. Chemical Agents
4. Biological agents

Radiation and Radioactive Decays

- **Ionizing radiations** such as X-rays, gamma rays and alpha particles cause DNA breakage and other damages. The most common lab sources include cobalt-60 and cesium-137. Ionizing radiations cause breaks in polysugar phosphate backbone of DNA and, thus, causing chromosomal mutations such as break, deletion, addition, inversion and translocation.
- **Ultraviolet radiations** with wavelength above 260 nm are absorbed strongly by bases, producing **pyrimidine dimers**, which can cause error in replication if left uncorrected.
- **Radioactive decay**, such as 14C in DNA which decays into nitrogen.

Temperature

- The rate of all chemical reactions are influenced by temperature. It is reported that the rate **of mutation is increased due to increase in temperature**.
- For example, an increase of 10°C temperature increases the mutation rate two or three-fold.
- Temperature probably affects both thermal stability of DNA and the rate of reaction of other substances with DNA.

Chemical Agents

- Many chemical substances have been responsible to increase the mutability of genes.
- Any chemical substance that affects the chemical environment of chromosomes is likely to influence, at leas indirectly, the stability of DNA and its ability to replicate without error.
- Some of the known chemical mutagens include:

1. **Reactive oxygen species (ROS)** These may be superoxide, hydroxyl radicals and hydrogen peroxide, and large number of these highly reactive species which are generated by normal cellular processes.
2. **Deaminating agents**, such as nitrous acid which can cause transition mutations by converting cytosine to uracil.
3. **Polycyclic aromatic hydrocarbon (PAH)**, when activated to diol-epoxides can bind to DNA and form adducts
4. **Nitrosamines**are an important group of mutagens found in tobacco, and may also be formed in smoked meats and fish via the interaction of amines in food with nitrites added as preservatives. Other **alkylating agents** include mustard gas and vinyl chloride.
5. **Alkaloid** from plants, such as those from Vinca species, may be converted by metabolic processes into the active mutagen or carcinogen.
6. **Benzene**, an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes.

Biological agents

- **Transposon** is a section of DNA that undergoes autonomous fragment relocation/multiplication. Its insertion into chromosomal DNA disrupts functional elements of the genes.
- **Virus**– Virus DNA may be inserted into the genome which disrupts genetic function. Infectious agents have been suggested to cause cancer as early as Peyton Rous 1911 who discovered the **Rous sarcoma virus.**
- **Bacteria**– some bacteria such as ***Helicobacter pylori*** cause inflammation during which oxidative species are produced, causing DNA damage and reducing efficiency of DNA repair systems, thereby increasing mutation.

Significance of Mutations

1. Variants in genes (which are caused by mutations) are needed to study the transmission of traits.
2. Mutations can tell the researcher about the function of a gene product in a biological system.
3. Mutations are the basis for cancer and other genetic diseases.
4. Gene mutations serve as the source for most alleles in a population and is therefore the origin of genetic variation within a population.
5. Mutations drive **evolution**: mutations are the raw material upon which natural selection acts.

Types of Mutations

- There are various schemes for classification of different kind of mutations. Depending on:
- A. The Type of Cell Involved
- B. Mode of Origin
- C. Direction of Mutation
- D. Size and Quality
- E. Phenotypic Effects
- F. Magnitude of Phenotypic Effect
- G. Loss of Function or Gain of Function

A. The Type of Cell Involved

1. **Somatic mutations**

- Mutations that are in the somatic tissues of the body.
- Mutations are not transmitted to progeny.
- The extent of the phenotypic effect depends upon whether the mutation is dominant or recessive (dominant mutations generally have a greater effect).
- The extent of the phenotypic effect depends upon whether it occurs early or late in development (early arising mutations have a greater effect).

2. **Germinal mutations**

- Mutations that are in the germ tissues of the body.
- Mutations may be transmitted to progeny
- Dominant mutations are seen in first generation after the mutation occurs
- If a female gamete containing an X-linked mutation is fertilized, the males will show the mutant phenotype
- Recessive mutations will only be seen upon the chance mating with an individual carrying the recessive allele too; thus, the recessive mutation may remain hidden for many generations

B. Mode of Origin

(1) Spontaneous mutations

- The spontaneous mutations occur suddenly in the nature and their origin is unknown. They are also called “background mutation” and have been reported in many organisms such as, Oenothera, maize, bread molds, microorganisms (bacteria and viruses), Drosophila, mice, man, etc.

(2) Induced mutations

- Besides naturally occurring spontaneous mutations, the mutations can be induced artificially in the living organisms by exposing them to abnormal environment such as radiation, certain physical conditions (i.e., temperature) and chemicals.

C. Direction of Mutation

- According to their mode of direction following types of mutations have been recognised:

1. Forward mutations

- In an organism when mutations create a change from wild type to abnormal phenotype, then that type of mutations are known as forward mutations. Most mutations are forward type.

2. Reverse or back mutations

- The forward mutations are often corrected by error correcting mechanism, so that an abnormal phenotype changes into wild type phenotype.

D. Size and Quality

According to size following two types of mutations have been recognized:

1. Point mutation

When heritable alterations occur in a very small segment of DNA molecule, i.e., a single nucleotide or nucleotide pair, then this type of mutations are called “point mutations”. The point mutations may occur due to following types of subnucleotide change in the DNA and RNA.

– Deletion mutations. The point mutation which is caused due to loss or deletion of some portion (single nucleotide pair) in a triplet codon of a cistron or gene is called deletion mutation.

– Insertion or addition mutation. The point mutations which occur due to addition of one or more extra nucleotides to a gene or cistron are called insertion mutations.

The mutations which arise from the insertion or deletion of individual nucleotides and cause the rest of the message downstream of the mutation to be read out of phase, are called **frameshift mutations.**

– Substitution mutation. A point mutation in which a nucleotide of a triplet is replaced by another nucleotide, is called substitution mutation.

D. Size and Quality

- **2. Multiple mutations or gross mutations.**
- When changes involving more than one nucleotide pair, or entire gene, then such mutations are called gross mutations. The gross mutations occur due to rearrangements of genes within the genome. It may be:
- The rearrangement of genes may occur within a gene. Two mutations within the same functional gene can produce different effects depending on gene whether they occur in the cis or trans position.
- The rearrangement of gene may occur in number of genes per chromosome. If the numbers of gene replicas are non-equivalent on the homologous chromosomes, they may cause different types of phenotypic effects over the organisms.
- Due to movement of a gene locus new types of phenotypes may be created, especially when the gene is relocated near heterochromatin. The movement of gene loci may take place due to following method:
- **(i) Translocation.** Movement of a gene may take place to a non-homologous chromosome and this is known as translocation.
- **(ii) Inversion.** The movement of a gene within the same chromosome is called inversion.

E. Phenotypic Effects

1. Morphological mutations are mutations that affect the outwardly visible properties of an organism.
2. Lethal mutations are mutations that affect the viability of the organism
3. Conditional mutations are mutations in which the mutant allele causes the mutant phenotype only in certain environments (called the restrictive condition).
4. Biochemical mutations are mutations that may not be visible or affect a specific morphological characteristic but may have a general affect on the ability to grow or proliferate.

F. Magnitude of Phenotypic Effect

According to their phenotypic effects following kinds of mutations may occur:

1. Dominant mutations

   The mutations which have dominant phenotypic expression are called dominant mutations.

2. Recessive mutations

   Most types of mutations are recessive in nature and so they are not expressed phenotypically immediately. The phenotypic effects of mutations of a recessive gene is seen only after one or more generations, when the mutant gene is able to recombine with another similar recessive gene.

3. Isoalleles

   Some mutations alter the phenotype of an organism so slightly that they can be detected only by special techniques. Mutant genes that give slightly modified phenotypes are called isoalleles. They produce identical phenotypes in homozygous or heterozygous combinations.

G. Loss of Function or Gain of Function

1. Loss of function mutation

- Loss of function mutation is also called inactivating mutations, result in the gene product having less or no function (being partially or wholly inactivated).

2. Gain of function mutations

- The gain of function mutations also called activating mutations, change the gene product such that its effect gets stronger (enhanced activation) or even is superseded by a different and abnormal function.

ANNY QUESTIONS

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