MUTATIONS

Introduction

Natures intention is that the exact genetic information from both parents will be seen in the offspring's DNA in the critical stages of fertilization. However, it is possible for this genetic information to mutate, which in most cases, can result in fatal or negative consequences in the outcome of the new organism.

Non-Disjunction and Down's Syndrome

One well known example of mutation is non-disjunction. Non-disjunction is when the spindle fibres fail to separate during meiosis, resulting in gametes with one extra chromosome and other gametes lacking a chromosome. If this non-disjunction occurs in chromosome 21 of a human egg cell, a condition called Down's syndrome occurs. This is because their cells possess 47 chromosomes as opposed to the normal chromosome compliment in humans of 46.

The fundamental structure of a chromosome is subject to mutation, which will most likely occur during crossing over at meiosis. There are a number of ways in which the chromosome structure can change, which will detrimentally change the genotype and phenotype of the organism. However, if the chromosome mutation effects an essential part of DNA, it is possible that the mutation will abort the offspring before it has the chance of being born.

Mutation

In most organisms genes are segments of DNA molecules. In the broad sense, the term 'mutation' refers to all the heritable changes in the genome, excluding those resulting from incorporation of genetic material from other organisms. A mutation is an abrupt qualitative or quantitative change in the genetic material of an organism. Mutations may be intragenic or intergenic. Intragenic mutations or point mutations include alterations in

the structure of the DNA molecule within a gene. In a point mutation there is a change in the normal base sequence of the DNA molecule.

This change results in a modification of the structural characteristics or enzymatic capacities of the individual. The unit of gene mutation is the muton. This may consist of one or many nucleotide pairs. Intergenic mutations, of which chromosomal changes in structure are examples, involve long regions of DNA, i.e. many genes. These include deletion or addition of segments of chromosomes, resulting in deficiency and duplication, respectively. In large deletions a base sequence corresponding to an entire polypeptide chain is sometimes lost. Such mutations are very useful in genetic mapping.

Germinal and Somatic Mutations

Eukaryotic organisms have two primary cell types - germ and somatic. Mutations can occur in either cell type. If a gene is altered in a germ cell, the mutation is termed a **germinal mutation**. Because germ cells give rise to gametes, some gametes will carry the mutation and it will be passed on to the next generation when the individual successfully mates. Typically germinal mutations are not expressed in the individual containing the mutation.

Somatic cells give rise to all non-germline tissues. Mutations in somatic cells are called **somatic mutations**. Because they do not occur in cells that give rise to gametes, the mutation is not passed along to the next generation by sexual means. To maintain this mutation, the individual containing the mutation must be cloned. Two example of somatic clones are navel oranges and red delicious apples.

Spontaneous and Induced Mutations

In general, the appearance of a new mutation is a rare event. Most mutations that were originally studied occurred spontaneously. This class of mutation is termed **spontaneous mutations**. But these mutations clearly

represent only a small number of all possible mutations. To genetically dissect a biological system further, new mutations were created by scientists by treating an organism with a mutagenizing agent. These mutations are called **induced mutations**.

The spontaneous mutation rate varies. Large gene provides a large target and tends to mutate more frequently. A study of the five coat color loci in mice showed that the rate of mutation ranged from 2×10^{-6} to 40×10^{-6} mutations per gamete per gene. Data from several studies on eukaryotic organisms shows that in general the spontaneous mutation rate is $2\text{-}12 \times 10^{-6}$ mutations per gamete per gene.

Mutations can be induced by several methods. The three general approaches used to generate mutations are **radiation**, **chemical** and **transposon insertion**. The first induced mutations were created by treating Drosophila with X-rays. In addition to X-rays, other types of radiation treatments that have proven useful include gamma rays and fast neutron bombardment. These treatments can induce point mutations (changes in a single nucleotide) or deletions (loss of a chromosomal segment).

Other Types of mutations

Morphological mutants affect the outward appearance of an individual. Plant height mutations could changes a tall plant to a short one, or from having smooth to round seeds. **Biochemical mutations** have a lesion in one specific step of an enzymatic pathway. For bacteria, biochemical mutants need to be grown on a media supplemented with a specific nutrient. Such mutants are called **auxotrophs**. Often though, morphological mutants are the direct result of a mutation in a biochemical pathway. In humans, albinism is the result of a mutation in the pathway which converts the amino acid tyrosine to the skin pigment melanin. Similarly, cretinism results when the tyrosine to thyroxine pathway is mutated. For some mutations to be expressed, the individual needs to be

placed in a specific environment. This is called the **restrictive condition**. But if the individual grow in any other environment (**permissive condition**), the wild type phenotype is expressed. These are called conditional mutations. Mutations that only expressed at a specific temperature (temperature sensitive mutants), usually elevated, can be considered to be **conditional mutations**. **Lethal mutations** are also possible. As the term implies, the mutations lead to the death of the individual. Death does not have to occur immediately, it may take several months or even years. But if the expected longevity of an individual is significantly reduced, the mutation is considered a lethal mutation. If a mutation occurs in that allele, the function for which it encodes is also lost. The general term for these mutations is **loss-of-function mutations**. The degree to which the function is lost can vary. If the function is entirely lost, the mutation is called a **null mutation**. If is also possible that some function may remain, but not at the level of the wild type allele. These are called **leaky mutations**.

Types of Mutations

I. Chromosome Mutations - gross changes in chromosomes.

Changes in the number of chromosomes.

1. Euploidy - variation in the number of sets of chromosomes.

a. Haploidy (Monoploidy) - one set of chromosomes (n) : ABC

b. Polyploidy-three or more sets of chromosomes.

c. Triploidy-3 sets of chromosomes (3n) : ABC, ABC, ABC.

d. Tetraploidy-4 sets of chromosomes (4n): ABC, ABC, ABC, ABC.

e. Pentaploidy-5 sets of chromosomes (5n) : ABC, ABC, ABC, ABC, ABC.

f. Hexaploidy (6n), **Septaploidy** (7n), **Octoploidy** (8n), etc

2. Aneuploidy - variation in the number of chromosomes of a set.

(Reduction in the normal number of chromosomes.)

a. Monosomics - Loss of one chromosome (2n-1) : ABC, AB.

b. Double monosomics - loss of 2 different chromosomes (2n-1-1): ABC, A.

b - loss of a pair of homologous chromosomes (2n-2) : AB, AB:

b. Increase in the number of chromosomes (polysomies).

Trisomies - presence of 1 extra chromosome (2n+ 1) : ABC, ABC, A.

Double trisomics - 2 different extra chromosomes (2n + 1 + 1) : ABC, ABC, AB.

Tetrasomics - an extra pair of homologous chromosomes (2n+2): ABC, ABC, AA.

pentasomics (2n+3), **Hexasomics** (2n+4), **Sepiasomics** (2n+5), etc.

B. Changes in the structure of chomosomes.

a. Loss or addition of segments of chromosomes.

Deletion (deficiency) - loss of a segment of a chromosome

Duplication - repetition of a segment of a chromosome.

b. Changes in the normal arrangement of genes in the chromosome.

Translocation – Exchange of segments between two non - homologous chromosomes, resulting in new chromosomes.

Inversion – Change in the linear order of genes by rotation of a section of a chromosome through 180 degrees.

C. Gene mutations or point mutations – changes in the nucleotide sequence of a gene.

a. Deletion
b. Insertion
c. Substitution

d. Inversion

Rate of Mutation

The frequency of spontaneous mutations is usually low, ranging form 10-7 to 10-12 per organism. The rate of detectable mutations in average gene is 1 in 106. It should be noted, however, that most methods for estimating the rate of mutations tend to under estimate their frequency due to many reasons. Firstly, lethal mutations which leave no progeny may be missed. Secondly, mutations which leave only a slight change in the phenotype may remain undetected. Mutations occur much more frequently in certain regions of the gene than in others. The favoured regions are called 'hot spots'. Mutations involving single nucleotides can revert to normal gene structure. Most single nucleotide mutations are reversible. In many cases the rate of reverse mutations is similar to the rate of forward mutations. In rare locations the rate of forward mutation is much greater than the rate of backward mutation.

Effects of Mutations on the Phenotype

According to their effects on the phenotype mutations may be classified as lethals, sub vitals and super vitals. Lethal mutations result in the death of the cells or organisms in which they occur. Sub vital mutations reduce the chances of survival of the organism in which they are found. Super vital mutations on the other hand may result in the improvement of biological fitness under certain conditions. There may also be mutations which are neither harmful nor beneficial to the organism in which they occur.

How Does a Mutation Act?

As mentioned in other sections, genes act by controlling the rate of production of specific proteins (enzymes). The scheme of protein synthesis in most organisms is as follows:

(1) The DNA (gene) produces a complementary mRNA strand which has codons consisting of nucleotide triplets.

(2) tRNA molecules, each forming a complex with a specific amino acid, have three free nuc1eotides which form the anticodon.

(3) The alignment of tRNA molecules on mRNA depends upon complementary codon-anticodon pairing

(4) Thus the sequence of amino acid molecules in an enzyme (and hence the structure and functions of the enzyme (depends upon the nucleotide sequence of mRNA. This in turn depends upon the nucleotide sequence in DNA. It will be seen that any change in the sequence of nucleotides of DNA will result in a corresponding change in the nucleotide sequence of mRNA. This may result in alignment of different tRNA molecules on mRNA. Thus the amino acid sequence and hence the structure and properties of the enzyme formed, will be changed. This may effect the traits controlled by the enzyme.

Molecular Basis of Mutations

Gene mutations at the molecular level involve modification of one base by another, or addition or deletion of one or more bases. Mutations may be spontaneous or induced **Spontaneous Mutations** - Mutations which occur under natural conditions are called spontaneous mutations. It should be noted that some spontaneous mutations arise by the action of mutagens present in the environment. These mutagens include cosmic radiation, radioactive compounds, heat, and such natural occurring base analogues like caffeine. These will be considered under 'induced mutations' as they are external agents bringing about mutations. Truly spontaneous mutations that will be dealt with here are those arising from tautomerism.

Tautomerism

The ability of a molecule to exist in more than one chemical form is called tautomerism .All the four common bases of DNA (adenine, guanine, cytosine and thymine) have unusual tautomeric forms, which are, however, rare. The normal bases of DNA are usually present in the keto form. As a result of tautomeric rearrangement they can be momentarily transformed

into the rare enol form in which the distribution of electrons is slightly different. Normal base pairing in DNA is A-T and G-C. The tautomeric forms are, however, capable of unusual ('forbidden') base pairing like T-G, G-T, C-A and A-C. This unusual base pairing results in misreplication of the DNA strand, giving rise to mutants in some of the progeny. Thus A*, a rare tautomer of adenine (a) pairs with cytosine. This leads to G-C pairing in the next generation. Spontaneous mutations can also arise as a result of ambiguity of base pairing during replication because of 'wobble'

Induced Mutations A variety of agents increase the frequency of mutation. Such agents are called mutagens. They include chemical mutagens, and radiations like X-rays, γ-rays and UV-light.

Chemical Mutagens The first chemical mutagen discovered was mustard 'gas'. In the 1950s chemical mutagens with more or less specific action were developed. Chemical mutagens can be classified according to the way in which they bring about mutations:

(1) Base analogues which are incorporated into DNA instead of normal bases
(2) Agents modifying purines and pyridines and agents labilizing bases, and
(3) agents producing distortions in DNA.

The agents in categories (1) and (3) require replication for their action, while agents in category (2) can modify even non replicating DNA.

Chemical mutagens work mostly by inducing **point mutations**. Two major classes of chemical mutagens are routinely used. These are **alkylating agents** and **base analogs**. Each has a specific effect on DNA. Alkylating agents [such as ethyl methane sulphonate (EMS), ethyl ethane sulphonate (EES) and musta rd gas] can mutate both replicating and non-replicating DNA. By contrast, a base analog (5-bromouracil and 2-aminopurine) only mutate DNA when the analog is incorporated into replicating DNA. Each class of chemical mutagen has specific effects that can lead to transitions, transversions or deletions.

Scientists are now using the power of transposable elements to create new mutations. Transposable elements are mobile pieces of DNA that can move from one location in a geneome to another. Often when they move to a new location, the result is a new mutant. The mutant arises because the presence of a piece of DNA in a wild type gene disrupts the normal function of that gene. As more and more is being learned about genes and genomes, it is becoming apparent that transposable elements are a power source for creating insertional mutants.