Ministry of Higher Education
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Lecture : 8

Chromosomal Mutations

Introduction to Gene Mutation:

Inheritance is based on genes that are faithfully transmitted from parents to offspring's during reproduction. Different mechanisms have evolved to facilitate the faithful transmission of genetic materials (information) from generation to generation. Nevertheless, 'mistakes' or changes in the genetic material do occur. Such sudden, heritable changes in the genetic material are called mutations.

Hugo de Vries used the term 'mutation' to describe phenotypic changes which were inheritable. The term 'mutation' refers both to the, change in the genetic material and to the process by which the change occurs.

An organism exhibiting a novel phenotype as a result of the presence of mutation is referred to as mutant. However, the term mutation is often used in a rather strict sense to cover only those changes which alter the chemical structure of the gene at the molecular level.

These are commonly called gene mutations or point mutations. A gene which represents a particular segment of DNA with characteristic base sequence transcribes m-RNA with particular code sequence, codon is triplet to be translated into protein of definite amino acid sequence. Mutation involves the change in the base sequence of DNA which is reflected in amino acid sequence of protein through RNA.

Origin of Gene Mutation:

A. Spontaneous mutation — mutation occurs during normal celjular activities, primarily DNA replication and repair.

B. Induced mutation — mutation occurs as a result of treatment with a mutagenic agent or environment; mutation rate is usually higher than background levels.

i. Ionizing radiation — α-, β-, γ- or X-rays; usually results in deletions or insertions of DNA.

ii. Non-ionizing radiation — UV light; causes adjacent thymines on one DNA strand to bond together (thymine dimer) resulting in a structure that must be repaired in order for DNA replication to proceed; inefficient repair can lead to point mutations.

iii. Chemicals — chemical substances that interact with DNA to create base changes.

(a) Base analogues — chemicals that are structurally similar to bases in DNA, but may have different base pairing properties; bromouracil (BU) is structurally similar to thymine so will be incorporated in a growing DNA strand in place of T, but due to its properties it base pairs more frequently with G than with A. The mutagenic effect is mostly due to incorrect base pairing with G, leading to GC-AT transitions.

(b) Base modifiers — chemicals that make changes to a specific base changing its ability to base pair properly; e.g., deamination of cytosine creates a uracil base that will pair with an A instead of the G previously designated by the original C, or alkylating agents that add a methyl group causing guanine to mispair with thymine.

(c) Intercalating agents — chemicals that insert themselves into the DNA helix causing DNA replication and transcription problems; usually results in deletions or insertions.

C. Mutator mutations — mutations that influence the mutability of other genes.

i. Specific mutators — limited to one locus.

ii. Nonspecific mutators — effect is not specific to one locus; these mutations are generally in genes that control DNA repair.

Effects on Gene Mutation:

i. Effect on Protein (codons):

A. Silent mutation — change in a codon (usually in the third position) that does not change the amino acid coded for.

B. Nonsense mutation — change in a codon from amino acid specificity to a stop codon; results in premature amino acid chain termination during translation.

C. Missense mutation — change in a codon that changes the specificity to a different amino acid; changes the primary sequence of the polypeptide chain and alters the function of the protein.

D. Neutral mutation — change in the codon such that a different amino acid is specified how-ever, the new amino acid behaves similarly to the original one (e.g., has a similar functional group) and does not alter the function of the protein.

E. Frame shift mutation — a shift of the reading frame caused by a deletion or insertion of one or a few nucleotides; creates numerous missense and nonsense codons downstream of the mutational event.

ii. Effect on Gene Function:

A. Loss-of-function mutation — a mutation that results in a lack of gene function, this can result from a number of different types of mutations and is recessive in nature.

B. Gain-of-function mutation — a mutation that results in a new or different gene function; this can result from a number of different types of mutations and is dominant in nature.

iii. Effect on DNA:

A. Structural mutations — changes in the nucleotide content of the gene.

1. Base substitution mutations — substitution of one nucleotide for another.

(a) Transition mutations substitute one purine for another purine or one pyrimidine for another pyrimidine.

(b) Transversion mutations substitute one purine for a pyrimidine or vice versa.

2. Deletion mutations — loss of some portion of DNA.

3. Insertion mutations — addition of one or more extra nucleotides.

B. Chromosomal rearrangements — changing the location of a piece of DNA within the genome can result in large structural changes (translocations or inversions) in

genes or may change the expression of a gene by placing it under the control of a different promoter (called a “position effect”).

1. Translocations — movement of DNA to a nonhomologous chromosome; usually an exchange occurs between two nonhomologous chromosomes.

2. Inversions — movement of DNA within the same chromosome; a 180° rotation or “flip”.

iv. Magnitude of phenotypic effect:

A. Change in mutation rate — alleles mutate at different rates; some can be distinguished based on their rate of mutation.

B. Isoalleles — produce identical phenotypes in homozygous or heterozygous combinations with each other, but prove to be distinguishable when in combination with other alleles.

C. Mutants affecting viability

1. Subvitals — relative viability is greater than 10% but less than 100% compared with wild type.

2. Semilethals — cause more than 90% but less than 100% mortality.

3. Lethals — kill all individuals before adult stage.

Direction of Gene Mutation:

A. Forward mutation — creates a change from wild type to abnormal phenotype.

B. Reverse or back mutation — changes an altered nucleotide sequence back to its original sequence.

C. Suppressor mutations — produces a change from abnormal (i.e., mutated) phenotypes back to wild type. There are two types of suppressor mutations.

1. Intragenic suppressor — a mutation in the same gene as was originally mutated, but at a different site, that results in restoration of wild-type function (e.g., if an arginine codon CGU was originally mutated to serine codon-, AGU, the suppression causes a change back to an arginine codon, AGA; also, restoration of a reading frame by additions or deletions)

2. Intergenic suppressor — a mutation in another gene that results in restoration of wild- type function (e.g., a nonsense mutation may be suppressed by a mutation in the tRNA for that codon so that it now inserts an amino acid). These are sometimes referred to as suppressor genes or extragenic suppressors.

Types of Gene Mutation:

i. Morphological Mutation:

This involves changes in morphology including colour, shape, size, etc., e.g., albino ascospores in Neurospora, kernel colour in corn, curly wings in Drosophila, and dwarfism in pea.

ii. Lethal Mutation:

This involves genotypic changes leading to death of an individual. Example includes albino mutation resulting from chlorophyll deficiency in plants.

iii. Biochemical Mutation:

Biochemical mutations are identified by a deficiency, so that the defect can be overcome by supplying the nutrient or any other chemical compound, for which the mutant is deficient. Such mutation has been studied in bacteria and fungi, as well as blood disorders in human.

iv. Resistant Mutation:

Resistant mutations are identified by their ability to grow in presence of an antibiotic (e.g., streptomycin, ampicillin, cycloheximide) or a pathogen, to which wild type is susceptible.

v. Conditional Mutation:

Conditional mutations are those which permit the mutant phenotype to be expressed only under certain restrictive conditions (e.g., high temp.). Under normal condition termed as permissive condition the mutants express normal phenotype.

vi. Somatic and Germinal Mutation:

During development of organisms, mutation may occur in any cell at any stage of the cell cycle. If a mutation occurs in the somatic cell of the organism, it immediately reproduces other cells like itself resulting chimera, but not the whole organism being mutated. When the new individual develops from such cells through vegetative means, it is said to be somatic mutation.

When, however, mutation occurs in the germ cells, it can produce entirely a new organism and the type of mutation is known as germinal mutation.

vii. Missense Mutation:

A missense mutation is one which results in replacement of one amino acid in a polypeptide chain by another. As a result of mutation, one base of a codon may be substituted by another base. The changed codon may then code for another amino acid.

viii. Nonsense Mutation:

Of the 64 codons 61 code for amino acids, while three are termination codons which do not specify any amino acid. The three termination codons are UAA, UGA and UAG. Any mutation resulting in the alteration of a codon specifying an amino acid to a termination codon is called nonsense mutation. Thus if the codon UAC (for tyrosine) undergoes a one base substitution (C G) it becomes UAG, a termination codon.

A nonsense mutation leads to termination of polypeptide synthesis. As a result the polypeptide is incomplete. Such chains are likely to be biologically inactive. A nonsense mutation causes a relatively drastic change in the enzyme synthesized and as such likely to have a deleterious effect on the phenotype.

ix. Silent Mutation:

A mutation which does not result in phenotypic change is called a silent mutation. Silent mutations are of different types.

(a) The genetic code is degenerate, i.e., more than one codon may specify an amino acid. Therefore, when a mutated codon codes for the same amino acid as the original, there is no change in amino acid.

(b) The codon change may result in one amino acid substitution but this is not sufficient to modify the function of protein appreciably.

(c) The mutation may occur in a nonfunctional gene.

x. Suppressor Mutation:

The effect of a mutation on the phenotype can be reversed so that original wild type phenotype is brought back. A second mutation at a different site neutralizes the effects of the first mutation.

xi. Spontaneous and Induced Mutation:

Mutations may arise spontaneously in nature. They may be artificially induced, or may be caused by environment agents. Induced mutations are thus resulting from exposure of organisms to mutagenic agents such as ionizing irradiation, ultraviolet light or various chemicals which react with genes. Mutations can be classified on the basis of several criteria (Table 13.1).

Induction of Gene Mutation:

Mutagens:

Mutations can be artificially induced with the help of mutagenic agents or mutagens which can be broadly grouped into physical mutagens and chemical mutagens

Physical mutagens	Chemical mutagens	
I. Non-ionizing radiation	I. Aziridines	1. Ethyleneimine (EI)
Ultraviolet (UV) rays	II. Mustards	2. Nitrogen mustard
II. Ionizing radiation		3. Sulphur mustard
(a) Electromagnetic rays	III. Nitrosamines	4. Dimethyl nitrosamine (DMN)
X-rays		5. Nitrosoguanidine (NG)
Gamma rays		6. Nitrosomethyl urea (NMU)
(b) Corpuscular rays	IV. Epoxides	7. Ethylene oxide (EO)
Beta rays (electrons)		8. Diepoxybutane (DEB)
Protons (H-nuclei)	V. Alkyl sulphonates	9. Diethyl sulphonate (DES)
Neutrons		10. Methyl methane sulphonate (MMS)
Alpha rays (He particles)		11. Ethyl methane sulphonate (EMS)
Other heavy particles	VI. Miscellaneous	12. Nitrous acid
		13. Maleic hydrazide
		14. Hydrazine
		15. Hydroxylamine

Physical Mutagens:

These include various kinds of radiations including X-rays whose mutagenic effect was first demonstrated by Muller and Stadler. Radiations may be ionizing or non-ionizing. Ionizing radiations will cause ionization and will force ejection of an electron from the atom it attacks. X-rays, gamma rays, beta rays and neutrons are common ionizing radiations used for inducing mutations.

Non-ionizing radiations like UV do not cause ionization, but cause excitation through energy transfer.

Chemical Mutagens:

Auerbach in Drosophila was the first to demonstrate that mutation can be induced by certain chemicals. Later Oehelkers demonstrated the same effect in plants. At present, there are a variety of chemical substances known which cause mutations in plants and animals.

Majority of chemicals, even water from certain sources may cause dis-balance in metabolism and mutation. As such, any commercial or medical products, before being released, are tested for the mutagenic effects. Mustard gas, EMS have been most extensively used for induction of mutation.

Other Mutagens:

In addition, low pH as well as high temperature may cause mutation. Mutation rate is also influenced by aging of the organism.

Clastogens, Carcinogens and Teratogens:

Clastogens are agents causing effects include chromosomal alterations — breaks, gaps, fragments, lagging, sticky bridge, pulverization, stickiness, waviness, wooliness, polyploidy, inversion, translocation, sister chromatid exchanges and associated aberrations. Clastogens include both chemical (gammexene) and physical (X-ray) agents.

The clastogenic effects are often used as parameters of genotoxicity. The end points for the test of genotoxicity at the microscopic level are chromosomal changes, fragments and micronuclei, mostly observed at the metaphase and later stages.

The standard test system used in higher plants are Allium cepa, Tradescantia virginiana, Vicia faba, Hordeum vulgare and Zea mays. All clastogens, in general, are mutagens as well, but all mutagens are not necessarily clastogens. Specially those which cause point mutation like X-rays in low dosage is a mutagen whereas in high dosage it may be clastogen.

Carcinogens are a group of chemicals which causeancer in animals and humans. The carcinogens affect DNA, preventing it from giving the necessary directions for the synthesis of substances which control cell growth. Most carcinogens act as mutagens and both kinds of effects are related to DNA damage.

Radiation and many chemical carcinogens act by damaging DNA and inducing mutations. Most common carcinogens are aflatoxin, dimethyl nitrosamine, nickel-carbonyl, benzo (α-) pyrene, α-naphthylamine, vinyl chloride, etc.

Teratoma are considered as abnormal body developments in early embryogenesis. The agents either physical (X-ray) or chemical (cocaine) which cause such abnormalities are termed as teratogens. The susceptibility to teratogens is also a factor controlled by individual genetic system.

Chromosome mutation

A chromosome mutation is a change in the structure or arrangement of the structure or arrangement of the chromosome**.** Mutations are caused by

- Physical agents e.g. X-rays and ultraviolet light
- Chemical mutagens such as nitrous acid
- spontaneous way by unequal crossing way by unequal crossing over.over.

Alterations in Chromosome

Structural changes

- DELETIONDELETION
- DUPLICATIONDUPLICATION
- TRANSLOCATIONTRANSLOCATION
- INVERSIONSINVERSIONS
- NUMERICAL CHANGES

Aneuploidy :- Excess or Deficiency in a single chromosome

EUPLOIDY. Excess or Deficiency complete one or more sets of chromosomes

TYPES OFTYPES OF Aneuploidy

- Monosomy (2n-1)
- Nullisomy
- Trisomy(2n+1)
- Tetrasomy (2n+2)

Human Chromosomal Aneuploids

Autosomal Aneuploids

- Down Syndrome Trisomy 21
- Edward Syndrome Trisomy 18
- Patau Syndrome Trisomy 13

* **Trisomy**: three copies of one chromosome Trisomy: three copies of one chromosome

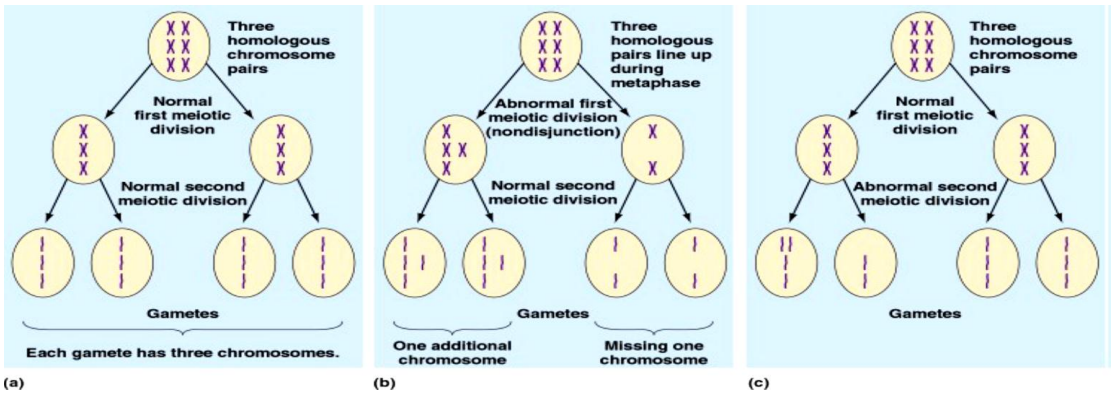
TABLE 8.1

Terminology for Variation in Chromosome Numbers

Term	Explanation
Aneuploidy	$2n \pm x$ chromosomes
Monosomy	$2n - 1$
Disomy	$2n$
Trisomy	$2n + 1$
Tetrasomy, pentasomy, etc.	$2n + 2$, $2n + 3$, etc.
Euploidy	Multiples of n
Diploidy	$2n$
Polyploidy	$3n$, $4n$, $5n$, . . .
Triploidy	$3n$
Tetraploidy, pentaploidy, etc.	$4n$, $5n$, etc.
Autopolyploidy	Multiples of the same genome
Allopolyploidy (Amphidiploidy)	Multiples of closely related genomes

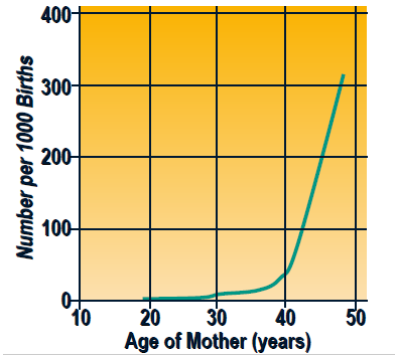
Aneuploidy

1. Arises by Non-disjunction
2. Non-disjunction = failure of homologues or chromatids to separate during meiosis



Normal Meiosis **Non-disjunction in Meiosis I** **Non-disjunction in Meiosis II**

Incidence of Down Syndrome Increases with Maternal Age



Human Chromosomal Aneuploids

Sex Chromosome Aneuploids

- Turner Syndrome 45, XO Sterile female
- Triplo-X 47, XXX Fertile female
- Klinefelter Syndrome 47, XXY Fertile female
- XYY Syndrome 47, XYY Fertile male

Applying Knowledge

Lets determine how many Barr bodies would be found in each cell of someone with

- Turner Syndrome 45, XO 0
- Triplo-X 47, XXX 2
- Klinefelter Syndrome 47, XXY 1
- XYY Syndrome 47, XYY 0

Euploidy: - Excess or Deficiency in the numberof the entire chromomosomal complement

- Monoploid
- Diploid
- Triploid
- Tetraploid

Chromosome Structure Changes

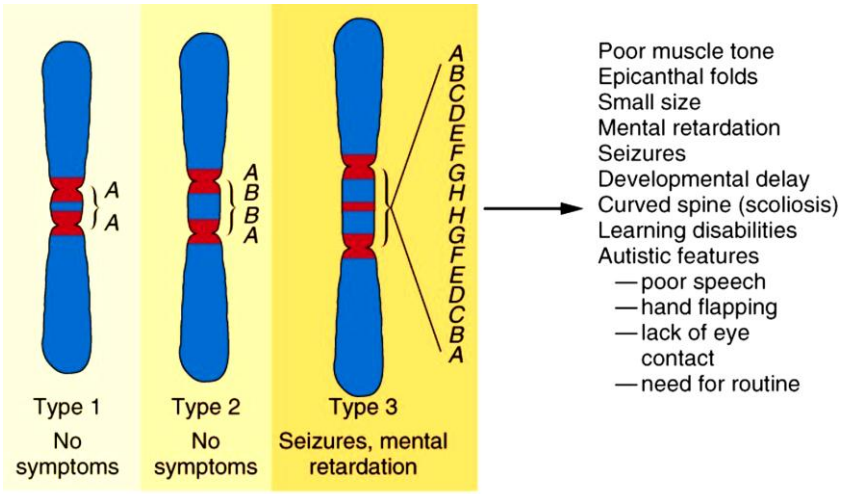
Change	Description
Deletion	Loss of a chromosomal segment can occur terminally or internally
Duplication	Repeat of a chromosomal segment
Translocation	Movement of chromosomal segment to non-homologous chromosome or genes from one linkage group transferred to another
Inversion	Reversal of a chromosomal segment (rotated 180)

Chromosome Deletion in Humans

- Cri-du-chat syndrome is correlated with is correlated with a deletion at the end of chromosome 5
- Deleterious effects pseudosominance,, absence of crossing over etc

Chromosome Duplication in Humans

- Small duplications in chromosome 15 cause no symptoms and no deleterious effects
- Large duplication (with inversion) causes mental retardation



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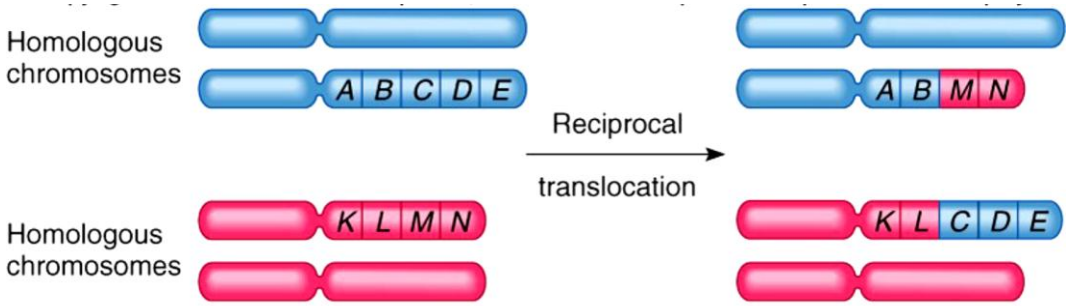
Chromosome Translocation in Humans

- Reciprocal Translocation involves exchange between two non -homologous chromosomes

- Reciprocal translocation between chromosomes 2 and 20 causes Alagille Syndrome
- Effects heart, liver, kidneys etc



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SIGNIFICANCE OF INVERSION

- ORIGIN OF NEW SPECIES
- PROOF FOR THE OCCURANCE OF CROSSING OVEROF
- INVERSION IS CONSIDERED ASINVERSION IS CONSIDERED AS CROSSING OVER REPRESSORS.

Ass. Prof. Dr. Naer Alkaabi