CONTROL OF GENETIC INFORMATION

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MUTAGENESIS AND NATURE OF MUTATIONS

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Mutagenesis: Process which lead to mutations.

Mutation: A permanent alteration or change in the nucleotide sequence or arrangement in genetic material i.e. DNA.

- Two major classes:
  - Microscopically detected - gross structural chromosomal changes.
  - Sub-microscopic alterations - involving one or more nucleotide.

- Mutations are classified into:

  - Genome mutations
    - affect the whole genome
    - result from chromosome missegregation
    - frequency 10^{-2}/cell division
    - e.g. aneuploidy

  - Chromosome mutations:
    - Due to rearrangements in chromosome
    - Occur approx. $6x10^{-4}$/cell division
    - e.g. chromosomal translocations

  - Gene mutations
    - Results from base pair mutations
    - 10^{-10}/bp/cell division
      10^{-15} - 10^{-16}/locus/generation
    - e.g. point mutations

- Types of gene mutations (point mutations)

  _ Substitution: when one base is substituted for another
    - Transition: purine substituted for purine or pyrimidine for pyrimidine.
    - Transversion: purine substituted for pyrimidine or vice versa

    These may be:
    - Silent - Same amino acids, so no change in protein structure on function.
      - Approx. 20-25% of all single base changes are silent mutations.
    - Missense - Altered amino acid in protein.
      - Altered structure and function

- Approx. 70-75% of cases

❍ Nonsense - Produce stopcodon and hence premature termination of proteins. Possible loss of function and activity

- Approx 2-4% of single base changes

_ Deletion/insertion:

❍ Multiple of 3 (codon)
- Deletion/insertion of one or more amino acid in protein.

❍ Not multiples of 3
- Frameshift mutation. Altered amino acid sequence from the point of mutation, with loss of function and activity.

_ Dynamic:

❍ Recently identified group.
❍ Important and unexpected cause of mutation in inherited disease.
❍ Triplet repeat sequences which increase in copy number in affected individuals compared to the normal general populations.
❍ These are known as "triplet amplification or expansion"
❍ e.g. in Huntington's disease, Fragile X mental retardation and myotonic dystrophy.

<u>Causes of mutations:</u>

• Spontaneous

• Ionising radiations

❍ Natural
- cosmic radiation (UV rays, others)
- External gamma radiation
- Internal gamma radiation

❍ Artificial
- Medical radiology (X-rays, radiothreapy)
- Radioactive fall-out
- Occupational - nuclear plant workers

• Chemicals (base analogues, alkylating agents, intercelating agent, direct effect on DNA)
- Mustard gas
- Formaldehyde
- Benzene
- Some basic dyes
- Caffeine
- Azodyes
- Acroline dye

Location of Mutation:

- Mutations may occur in somatic or germ cells. Only germline mutations can be transferred from one generation to another.

- Somatic cell mutation are equally important. May give rise to significant proportion of cancer.

Effects of mutations:

- Several faults due to mutations occur in protein biosynthesis.

- Inborn errors of metabolism.
  - Enzyme defect or deficiency or absence.
  - Increased enzyme activity.

- Genetic disorders affecting various tissues, organs etc.

- Several mutations cause damage to the DNA. Mechanisms exist to correct these damages. However, if the defect is not corrected it has serious clinical consequences
  e.g. Xeroderma pigmentosum, ataxia telangiectasis and Fanconi anemia result from defect in DNA repair mechanisms.

The Frequency of New Mutations:

- Replication errors: 10^{-10} /bp/cell division

- Estimated cell division during lifetime of an adult = 10^{15} cell divisions.

- New mutations occur in thousands.

- Some rates of mutations are listed in Table 1

- Most mutations occur in somatic cells, but depending on the nature of mutation, its location in the genome, and the tissue involved, a given mutation may or may not lead to cancer or to phenotype variation.

- Small number of mutations occur in germline during mitotic division or meiosis.
  - Paternal new mutations are age-dependent. Approx. 1 in 10 sperms.
  - Carries a new deleterious mutation.
  - Maternal age also affects the chromosomal segregation and hence chromosomal non-disjunction and other abnormalities are more frequent in offsprings of older age females.

Table 1: Estimates of mutation rates for some human genes

Gene	Inheritance	Mutation Rate	New mutation per 10^6 gametes
Achondroplasia	AD	$0.6\text{-}4 \times 10^{-5}$	6-40
Duchenne Muscular Dystophy	XR	$0.4\text{-}1 \times 10^{-4}$	43-105
Hemophilia A	XR	$3\text{-}6 \times 10^{-5}$	32-57
Hemophilia B	XR	$2\text{-}3 \times 10^{-6}$	2-3
Neurofibromatosis Type 1	AD	$0.4\text{-}1 \times 10^{-4}$	44-100
Polycystic kidney disease	AD	$0.6\text{-}1.2 \times 10^{-4}$	60-120
Retinoblastoma	AD	$5\text{-}12 \times 10^{-6}$	5-12