

Mechanisms of Genetic Variation

Gene mutation

Recombination

Transposable elements

Chromosomal rearrangements

DNA methylation / Imprinting

Molecular Basis of Gene Mutations

I. Forward Mutations (+ to m)

A. Effect at DNA Level

1. Transitions: A \leftrightarrow G; T \leftrightarrow C
2. Transversions: Other bp substitutions
3. Deletions: Loss of 1 or more bp
Small: One gene disrupted
Large: Multiple genes disrupted
4. Insertions: Addition of 1 or more bp
Transposons; viruses
5. Duplications: Repeated sequences
Unequal crossing over
Duplications within a gene
Duplications of adjacent genes

B. Effect at Protein Level

1. Silent: Altered codon: Same AA
Example: AGG (Arg) to CGG (Arg)
2. Neutral: Altered codon: Equivalent AA
Minimal effect on protein structure
No loss of protein function
3. Missense: Altered codon: Different AA
Protein function altered
4. Nonsense: Premature termination of translation
Inappropriate stop codon in frame
5. Frameshift: Small additions or deletions
Not multiple of 3 bp
Alters reading frame during translation

II. Reverse Mutations

- A. Exact Reversions: Original codon restored
- B. Equivalent Reversions: Redundant codon formed
- C. Excision of Transposon: Responsible for apparent instability of mutant allele
 - 1. Perfect: Original genomic sequence restored
Mutant allele becomes wild type
 - 2. Imperfect: Small piece of transposon remains
Footprint – Evidence of excision
May or may not alter protein function

III. Suppressor Mutations

- A. Intragenic: Second site mutation within same gene
- B. Extragenic: Second site mutation in different gene
 - 1. Suppressors of nonsense mutations
 - 2. Suppressors of missense mutations
 - 3. Physiological/biochemical suppressors

Other Classifications Systems for Mutations:

- I. *Spontaneous:* Occur in nature; often replication defect
Induced: Generated in lab; exposure to mutagen
- II. *Germ Line:* Gametic; Transmitted to sexual progeny
Somatic: Not gametic; Not transmitted to progeny
- III. *Dominant:* Phenotype apparent in heterozygote
Recessive: Phenotype not apparent in heterozygote
- IV. *Lethal:* Mutant dies; Essential gene disrupted
Viable: Mutant survives

Mutagenic Agents: Factors that Modify DNA Structure

- I. Ionizing Radiation: X-rays; Gamma rays; cosmic rays
Major structural damage to DNA
Deletions; Rearrangements
- II. Ultraviolet Light: Crosslinked pyrimidine dimers
Interfere with replication processes
Repair mechanism activated in light
- III. Base Analogs: Chemicals that resemble normal bases
Incorporation alters base pairing

- IV. Alkylating Agents: Chemicals that modify normal bases
Ethyl methanesulfonate (EMS)

Detection of Mutations:

- I. Screen Population for Individuals with Visible Defects

Traditional Forward Genetics

- II. Devise Effective Strategies to Simplify Screening Process

Selection: Eliminate wild-types; Only mutants survive

Reverse Genetics: Examine DNA samples taken from
large population; Look for disruption of known gene.