Mutations & DNA Repair

• Types of Mutations
• Mutations: Molecular level/Protein Level
• Mutagens
• DNA repair

\[ a^+ \rightarrow a \quad \{ \text{forward mutation} \}\]
\[ D^+ \rightarrow D \]
\[ a \leftarrow a^+ \quad \{ \text{reverse mutation} \}\]
\[ D \rightarrow D^+ \]
Garrod & Bateson: Inborn errors of metabolism

One gene-one polypeptide
Gene mutation

- somatic
- germinal
- study process of mutation
- dissect a biological process
Mutations: Molecular level

- **Point Mutations:**
- **Base Pair substitution**
- **transitions**
- **transversions**

<table>
<thead>
<tr>
<th>Sequence of part of a normal gene</th>
<th>Sequence of mutated gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Transition mutation (AT to GC in this example)</td>
<td></td>
</tr>
<tr>
<td>5’ TCTCAAAATTTGCG 3’</td>
<td>5’ TCTCAAAATTTGCG 3’</td>
</tr>
<tr>
<td>3’ TGAATTCTCAAA 3’</td>
<td>3’ TGAATTCTCAAA 3’</td>
</tr>
<tr>
<td>b) Transversion mutation (CG to GC in this example)</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>c) Missense mutation (change from one amino acid to another; here, a transition mutation from AT to GC changes the codon from lysine to glutamic acid)</td>
<td></td>
</tr>
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</tr>
<tr>
<td>--- Ser. Gin Lys Pro Thr---</td>
<td>--- Ser. Gin Lys Pro Thr---</td>
</tr>
<tr>
<td>d) Nonsense mutation (change from an amino acid to a stop codon; here, a transversion mutation from AT to TA changes the codon from lysine to UAA stop codon)</td>
<td></td>
</tr>
<tr>
<td>5’ TCTCAAAATTTGCG 3’</td>
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</tr>
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</tr>
<tr>
<td>--- Ser. Gin Lys Pro Thr---</td>
<td>--- Ser. Gin Lys Pro Thr---</td>
</tr>
<tr>
<td>e) Neutral mutation (change from an amino acid to another amino acid with similar chemical properties; here, an AT-to-GC transition mutation changes the codon from lysine to arginine)</td>
<td></td>
</tr>
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<td>5’ TCTCAAAATTTGCG 3’</td>
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</tr>
<tr>
<td>3’ TGAATTCTCAAA 3’</td>
<td>3’ TGAATTCTCAAA 3’</td>
</tr>
<tr>
<td>--- Ser. Gin Lys Pro Thr---</td>
<td>--- Ser. Gin Arg Pro Thr---</td>
</tr>
<tr>
<td>f) Silent mutation (change in codon such that the same amino acid is specified; here, an AT-to-GC transition in the third position of the codon gives a codon that still encodes lysine)</td>
<td></td>
</tr>
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<td>--- Ser. Gin Lys Pro Thr---</td>
</tr>
<tr>
<td>g) Frameshift mutation (addition or deletion of one or a few base pairs leads to a change in reading frame; here, the insertion of a GG base pair scrambles the message after glutamine)</td>
<td></td>
</tr>
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Mutations: Protein Level

- 4 groups of amino acids
- silent mutation
- Missense mutation & examples
- neutral
- non-functional
- nonsense mutation
- anti-nonsense
- Frameshift mutation
Frameshift mutation

- Occur at Hot spots
- Highly repetitive areas

![Diagram showing examples of substitutions, deletions, and insertions leading to frameshift mutation.](image_url)
Spontaneous mutations

a) Normal Watson-Crick base pairing

b) Non-Watson-Crick base pairing between normal pyrimidines and rare purines

c) Non-Watson-Crick base pairing between rare pyrimidines and normal purines
Spontaneous mutations: Tautomers
Mutagens

- Can be physical or chemical agents
- Use Ames Test for mutagens
- Mutagens are potential carcinogens
Physical Mutagens: UV light and X-rays Radiation

![Visible spectrum (wavelength) diagram]

- 750 nm to 380 nm
- Radio waves, Microwaves, Infrared, UV, X-rays, Gamma rays, Cosmic rays

- Decreasing wavelength = Increasing energy

![Graph: % X-Linked recessive lethals vs X-ray dose (roentgens)]

- Linear relationship:
  - % X-Linked recessive lethals: 0, 5, 10, 15, 20
  - X-ray dose (roentgens): 1000, 2000, 3000, 4000, 5000, 6000

![Diagram: Dimer formed between adjacent thymidine residues along a DNA strand]

- UV exposure
- Dimer formation
Chemical Mutagens

intercalating agents  structural analogs

[Diagram of chemical mutagens with structures and reactions]
Chemical Mutagens

Figure 17.13. Alkylation-induced specific mispairing. The alkylation (in this case, ethylation generated by EMS) of the O-6 position of guanine and also the O-4 position of thymine can lead to direct mispairing with thymine and guanine, respectively, as shown here. In bacteria, where mutations have been analyzed in great detail, the principal mutations detected are GC → AT transitions, indicating that the O-6 alkylation of guanine is most relevant to mutagenesis.
Chemical mutagens

- oxygen, ozone, superoxide
DNA repair

- detoxification
- alkyltransferases
- General Excision
  - Specific excision
    - AP endonuclease
    - DNA glycosylase
- photoreactivation
- SOS response
- mismatch repair
  - methylation of adenine
Base Excision Repair

**Base excision repair**

5' ACUGT
3' TGGTCA

Duplex with U-G mismatch

Uracil DNA glycosylase recognizes and excises incorrect base

5' ACAGT
3' TGGTCA

AP endonuclease recognizes lesion and nicks DNA strand

5' ACAGT
3' TGGTCA

DNA polymerase and DNA ligase

ACCAGT
TGGTCA

Mismatch repaired
Nucleotide Excision Repair

- Xeroderma pigmentosum (XP)
- 29 bases in eukaryotic cells
- UVR genes
- DNA lesions
Pyrimidine Dimer repair

Excision repair of pyrimidine dimer and other damage-induced distortions of DNA initiated by the UvrABC endonuclease.

- Enzyme detects distortion due to dimer
- Uvr ABC endonuclease enzyme bound to DNA
- Nuclease activity cuts damaged DNA strand, 8 nucleotides to 5' side of the dimer and 4 or 5 nucleotides to 3' side.
- Excised segment diffuses away and is broken down by exonucleases
- DNA polymerase I fills gap and DNA ligase seals remaining nick.
SOS response

mismatch repair methylation of adenine

Post replication repair
1. Lesion present in DNA unwound prior to replication

3. Undamaged complementary region of parental strand is recombined

Recombined complement

New gap formed

4. New gap is filled by DNA polymerase and DNA ligase
Outline of the SOS response. (a) The SOS system in the uninduced state; (b) The SOS system when induced by DNA damage. The details of the SOS response are given in the text.

(a) Uninduced state

- **lexA** gene
  - LexA protein
  - Represses transcription of genes involved in various DNA repair processes

(b) Induced state

- **lexA** gene
  - Active RecA protein
  - Stimulates LexA to cleave itself
  - No repression; transcription of repair genes takes place

- **recA** gene
  - RecA protein becomes activated by DNA damage