Molecular Biology

Lecture 7

Mutagenesis

- **Mutagenesis : is a process by which the genetic information of an organism is changed in a stable manner, resulting in a mutation. It may occur spontaneously in nature, or as a result of exposure to mutagens. It can also be achieved experimentally using laboratory procedures. In nature mutagenesis can lead to cancer and various heritable diseases.**
- **Mutation**
- **Mutations are permanent, heritable alterations in the base sequence of the DNA. They arise either through spontaneous errors in DNA replication or as a consequence of the damaging effects of physical or chemical agents on the DNA.**
- The simplest mutation is a **point mutation** (**a single base change)**. This can be either :
- a **transition**, in which one purine (or pyrimidine) is replaced by the other
- or a **transversion**, where a purine replaces a pyrimidine or vice versa.

- The **phenotypic effects** of such a mutation can be various.
- If it is in a noncoding or nonregulatory piece of DNA or in the position of a codon, which often has no effect on the amino acid incorporated into a protein , then it may be **silent.**
- If it results in an altered amino acid in a gene product then it is a **missense mutation** whose effect can vary from none to lethality, depending on the amino acid affected.
- Mutations which generate new stop codons are **nonsense mutations** and give rise to truncated protein products.

- **Insertions** or **deletions** involve the addition or loss of one or more bases. These can produce **frameshift mutations** in genes, where the translated protein sequence to the C-terminal side of the mutation is completely changed.
- Mutations that affect the processes of cell growth and cell death can result in tumorigenesis.
- The accumulation of many silent and other nonlethal mutations in populations produces **genetic polymorphisms** (acceptable variations in the 'normal' DNA and protein sequences)

- **Physical mutagens**
- Absorption of high-energy **ionizing radiation** such as **X-rays and γ-rays** causes the target molecules to lose electrons. These electrons can cause extensive chemical alterations to DNA,including **strand breaks and base and sugar destruction**.
- **Nonionizing radiation** causes molecular vibrations or promotion of electrons to higher energy levels within the target molecules. This can lead to the formation of new chemical bonds. The most important form causing DNA damage is **UV light** which produces pyrimidine dimers from adjacent pyrimidine bases.

- **Chemical mutagens**
- Base analogs are derivatives of the normal bases with altered base pairing properties and can cause direct mutagenesis. A wide range of other natural and synthetic organic and inorganic chemicals can react with DNA and alter its properties. **Nitrous acid deaminates cytosine to produce uracil (*Fig. 2), which*** base-pairs with adenine and causes GC→AT transitions upon subsequent replication. Deamination of adenine to the guanine analog hypoxanthine results in AT→GC transitions.
- **Alkylating agents, such as methylmethane sulfonate** (**MMS) and ethylnitrosourea (ENU) produce lesions** that usually have to be repaired to prevent serious disruption to the processes of transcription and replication. Processing of these lesions by the cell may give rise to mutations by **indirect mutagenesis. Intercalators** generate insertion and deletion mutations. Most chemical mutagens are **carcinogens and cause cancer.**

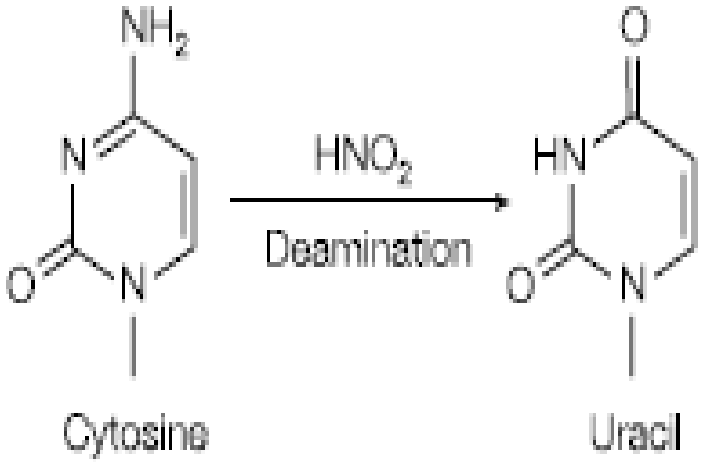


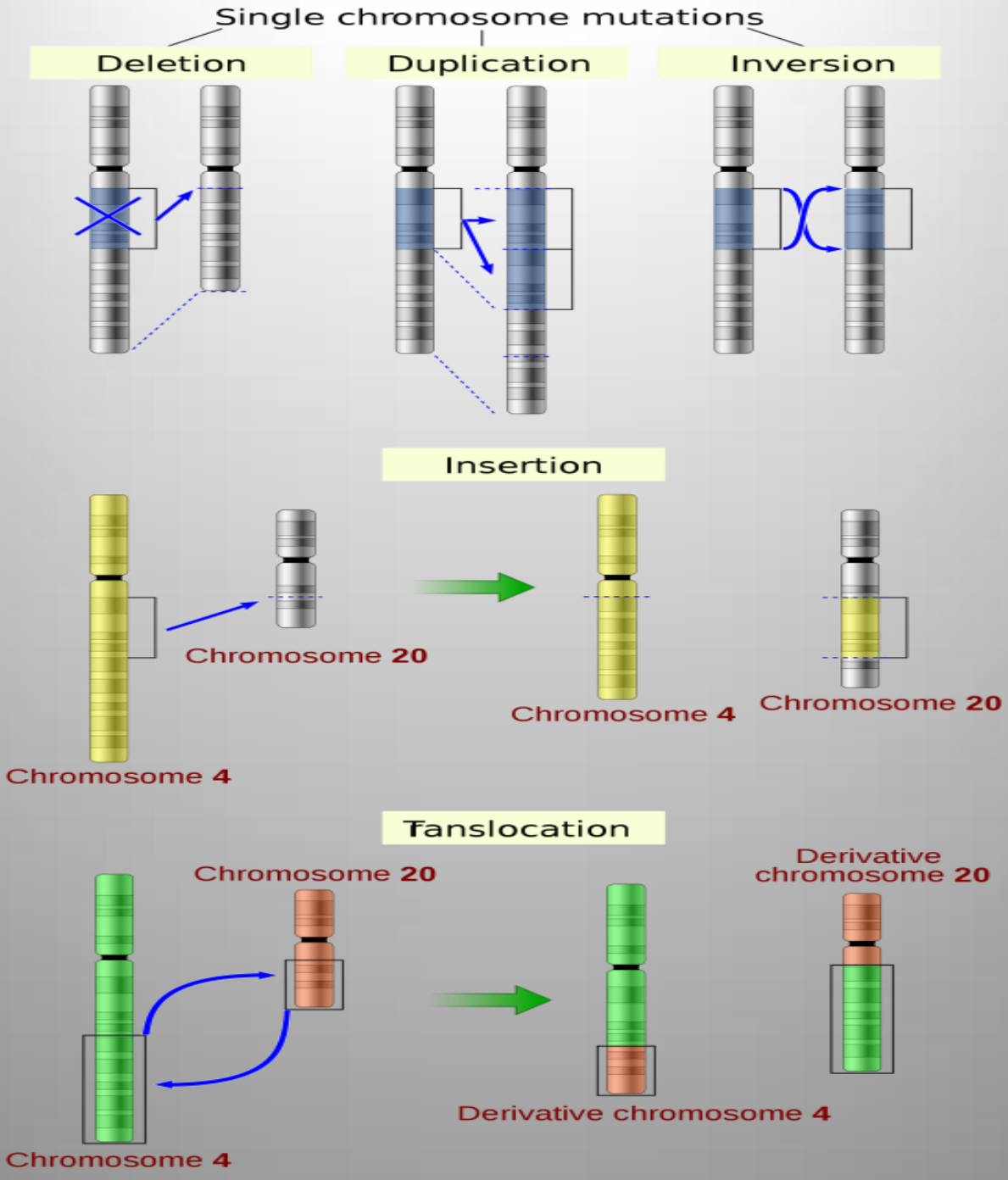
Fig. 2. Deamination of cytosine to uracil by nitrous acid.

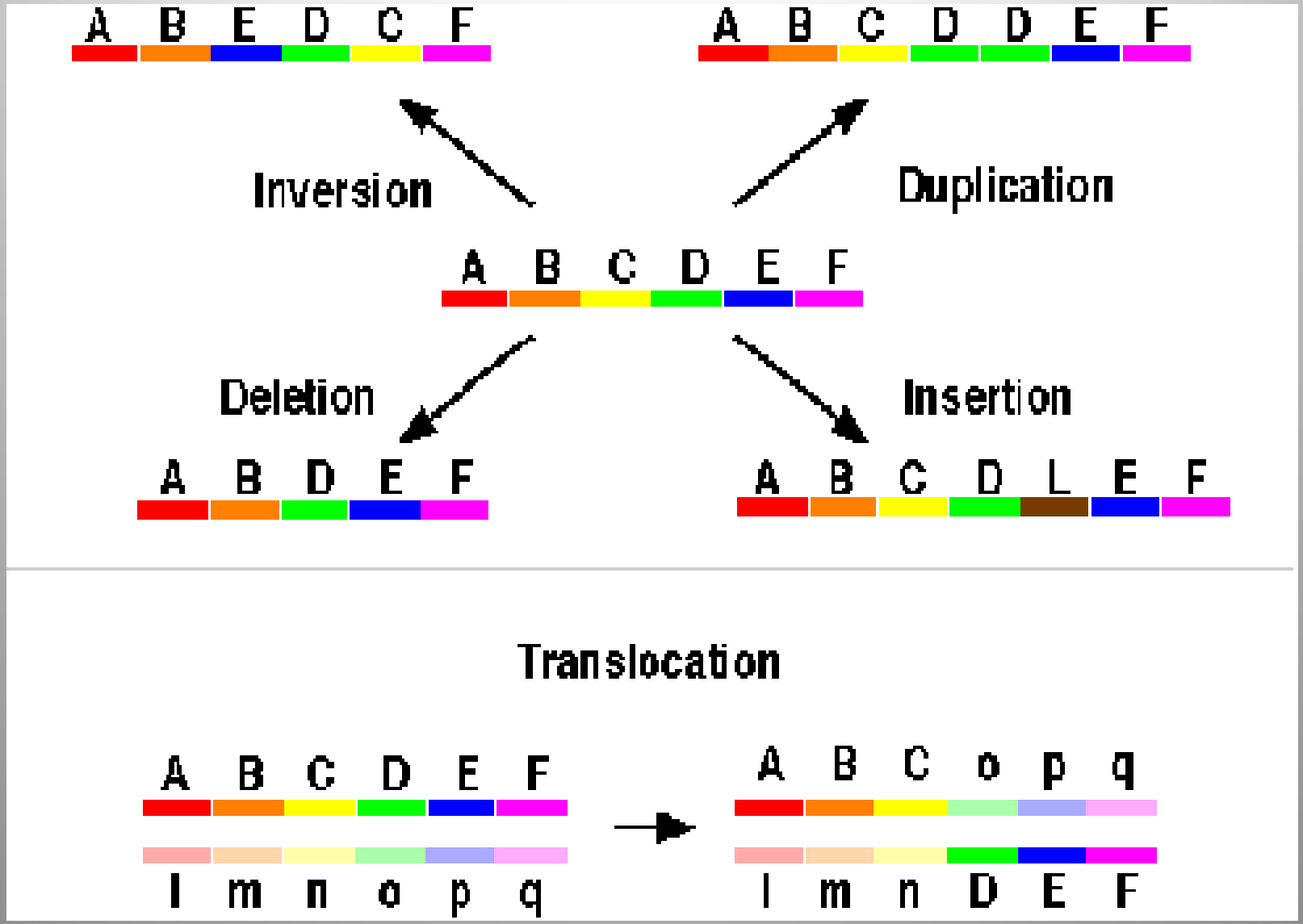
- **Chromosome abnormality**
- A **chromosome anomaly**, **abnormality**, **aberration**, or **mutation** is a missing, extra, or irregular portion of chromosomal DNA.It can be from an atypical number of chromosomes or a structural abnormality in one or more chromosomes. **Chromosome mutation** was formerly used in a strict sense to mean a change in a chromosomal segment, involving more than one gene.
- A **karyotype** refers to a full set of chromosomes from an individual that can be compared to a "normal" karyotype for the species via genetic testing. A chromosome anomaly may be detected or confirmed in this manner. Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis. There are many types of chromosome anomalies. They can be organized into two basic groups, numerical and structural anomalies.

- **Numerical disorders**
- This is called **aneuploidy** (an abnormal number of chromosomes), and occurs when an individual either is missing a chromosome from a pair (**monosomy**) or has more than two chromosomes of a pair (trisomy, tetrasomy, etc.).
- In humans, an example of a condition caused by a numerical anomaly is **Down Syndrome**, also known as Trisomy 21 (an individual with Down Syndrome has three copies of chromosome 21, rather than two).
- An example of monosomy is **Turner syndrome**, where the individual is born with only one sex chromosome, an X.

- **Structural abnormalities**
- When the chromosome's structure is altered, this can take several forms:
- Deletions: A portion of the chromosome is missing or deleted. Known disorders in humans include Wolf-Hirschhorn syndrome, which is caused by partial deletion of the short arm of chromosome 4.
- Duplications: A portion of the chromosome is duplicated, resulting in extra genetic material.
- Translocations: A portion of one chromosome is transferred to another chromosome. There are two main types of translocations:
  - Reciprocal translocation: Segments from two different chromosomes have been exchanged.
  - Robertsonian translocation: An entire chromosome has attached to another at the centromere

- Inversions: A portion of the chromosome has broken off, turned upside down, and reattached, therefore the genetic material is inverted.
- Insertions: A portion of one chromosome has been deleted from its normal place and inserted into another chromosome.
- Rings: A portion of a chromosome has broken off and formed a circle or ring. This can happen with or without loss of genetic material.
- Isochromosome: Formed by the mirror image copy of a chromosome segment including the centromere.
- Chromosome instability syndromes are a group of disorders characterized by chromosomal instability and breakage. They often lead to an increased tendency to develop certain types of malignancies.


Single chromosome mutations
Deletion
Duplication
Inversion
Insertion
Chromosome 20
Chromosome 4
Chromosome 4
Chromosome 20
Tanslocation
Chromosome 20
Derivative chromosome 20
Chromosome 4
Derivative chromosome 4


A B E D C F
A B C D D E F
Inversion
Duplication
A B C D E F
Deletion
Insertion
A B D E F
A B C D L E F
Translocation
A B C D E F
l m n o p q
A B C o p q
l m n D E F