Molecular Biology (4)

DNA mutations

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Resources

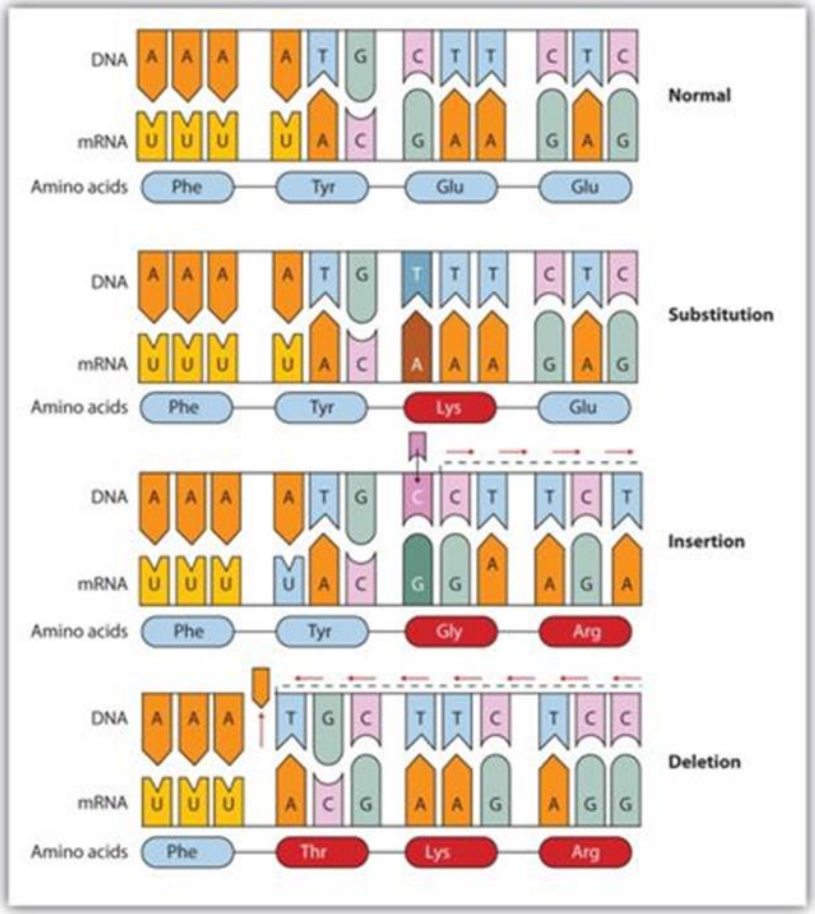
- This lecture
- Cooper, pp.207-219
- *http://www.ncbi.nlm.nih.gov/books/NBK21897/*
- *https://www.ncbi.nlm.nih.gov/books/NBK21936/*

Types of mutations

- Micromutation that involve small regions of the DNA
- Macromutations that involve the chromosomes as a whole

Review: Gene Mutations

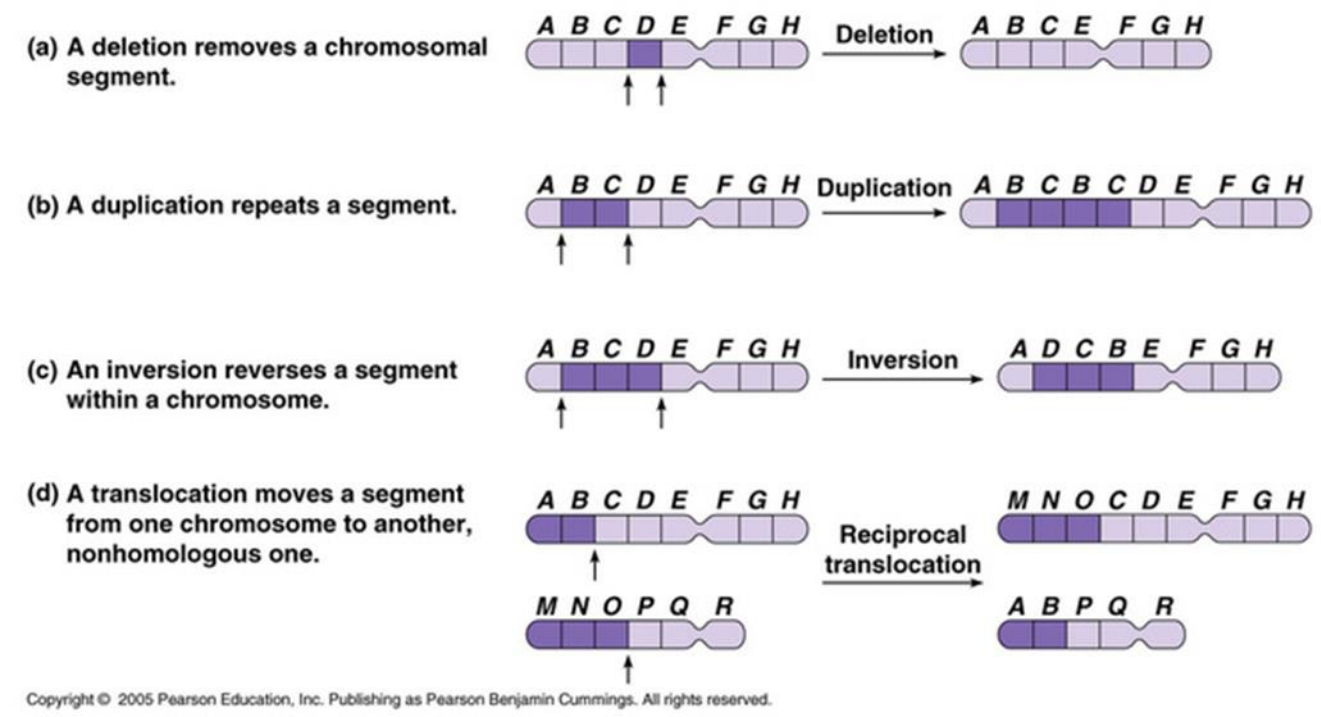
- "Micromutations"
- Small changes to DNA
  - One or several bases
  - Change can be positive, negative, or neutral
- Can be passed to offspring if in gametes

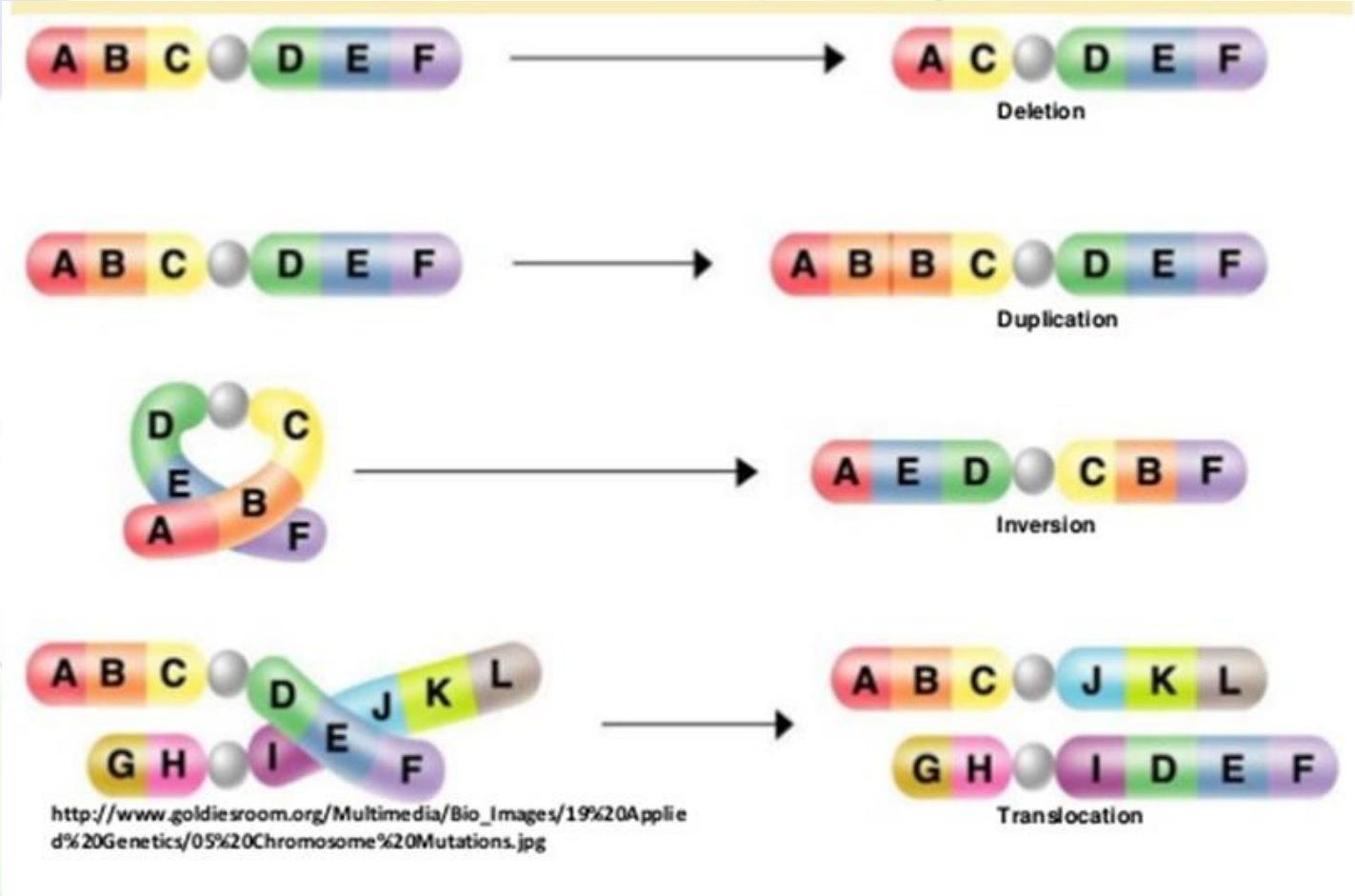


DNA macromutations

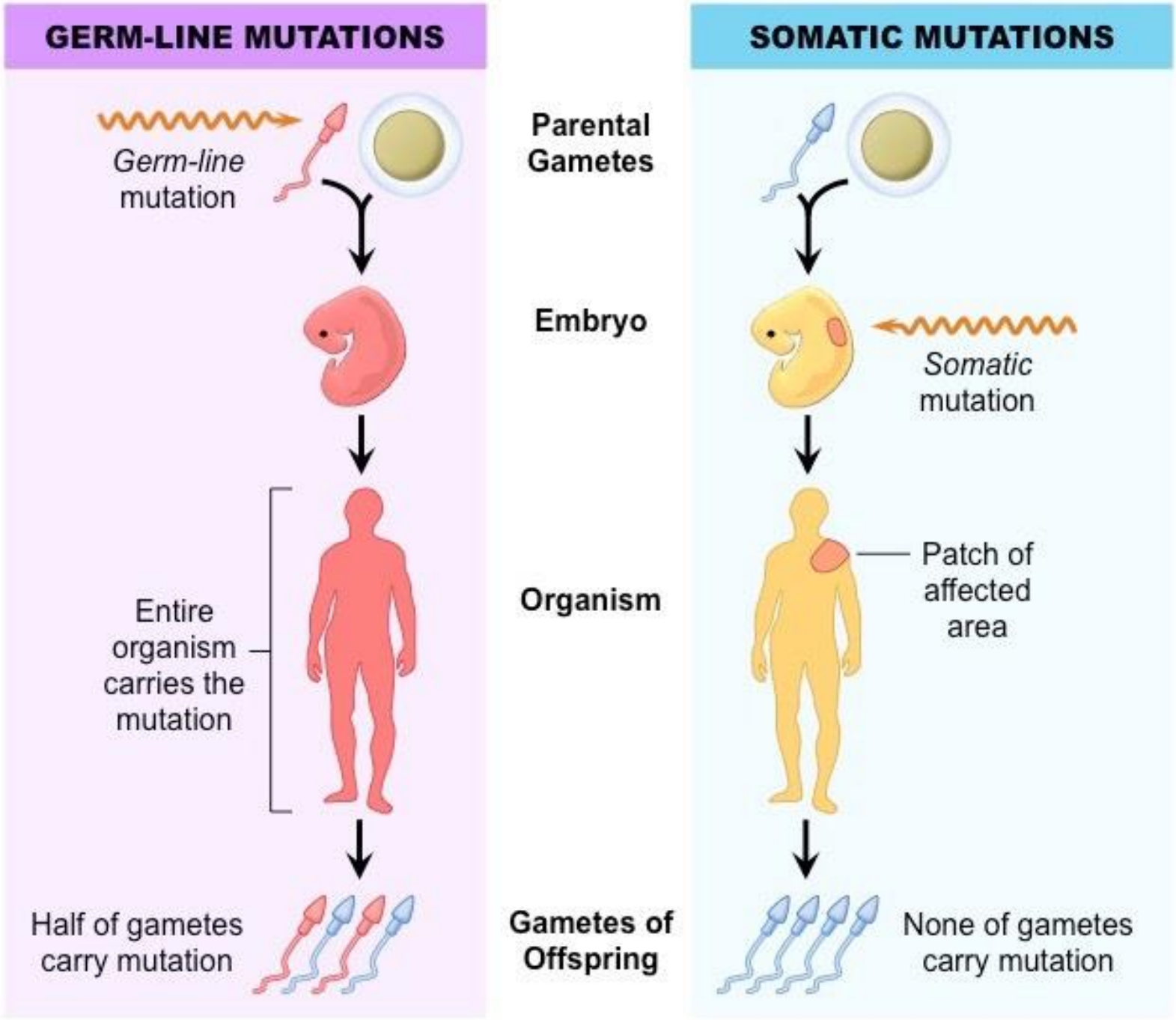
- Translocations, that bring different regions of gene segments together
- Deletions of a few nucleotides to long stretches of DNA,
- Insertions and duplications of nucleotides or long stretches of DNA
- Inversion of

DNA segments





http://www.goldiesroom.org/Multimedia/Bio_Images/19%20Applied%20Genetics/05%20Chromosome%20Mutations.jpg


GERM-LINE MUTATIONS
SOMATIC MUTATIONS
Parental Gametes
Embryo
Organism
Gametes of Offspring
Germ-line mutation
Somatic mutation
Entire organism carries the mutation
Patch of affected area
Half of gametes carry mutation
None of gametes carry mutation

Causes of DNA mutations

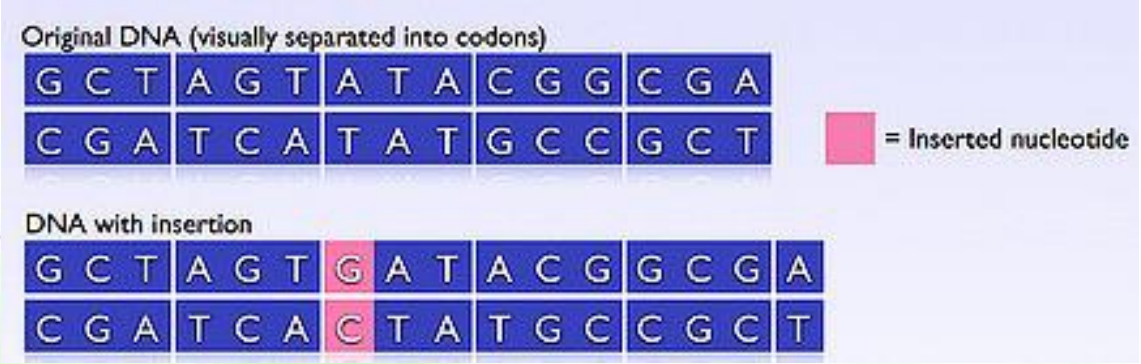
- DNA mutations can arise spontaneously or induced.
- Spontaneous mutations are naturally occurring mutations and arise in all cells.
  - They arise from a variety of sources, including errors in DNA replication and spontaneous lesions
- Induced mutations are produced when an organism is exposed to a mutagenic agent, or mutagen.

Induced Mutations

- Mutations those that result from changes caused by environmental chemicals or radiation are called as **induced mutations.**
- A number of environmental agents are capable of damaging DNA including certain chemicals and radiation.
- Mutagen: Any environmental agent that significantly increases the rate of mutation above the spontaneous rate.

Sources of errors of DNA replication

- Formation of inaccurate nucleotide pairs (A-C or G-T) leading to base substitution.
- Frameshift mutations
  - Insertion and deletion of one or a few bases can change the reading "frame" of codons and can lead to changes in the amino acid sequence of the produced protein.
  - These mutations often occur at repeated sequences.



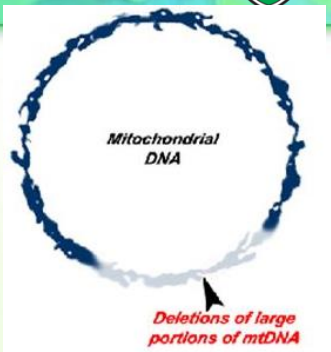
- Large deletions and duplications
  - They also often occur at sequence repeats.

Spontaneous mutations and human diseases

- **Deletion due to a three-base-pair repeat**
- **Expansion of a three-base-pair repeat**

Spontaneous mutations and human diseases

- **Deletion due to a three-base-pair repeat**
  - Kearns-Sayre syndrome: mitochondrial encephalomyopathies.



KEARNS SAYRE SYNDROME

XpertDox Clinical, Education, Research

Condition characterized by progressive weakness of eye muscles

Affects 1 to 3 per 100,000 individuals

1st described in 1958 by Thomas P. Kearns & George Pomeroy Sayre

Onset before 20 years of age

Caused by genetic or acquired defect of mitochondria metabolism

Symptoms are unsteady gait, visual issues, deafness & cardiac rhythm abnormalities

Diagnosed by genetic testing

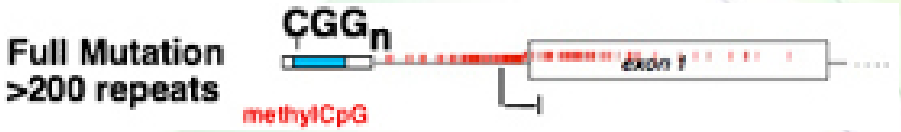
Treatment is symptomatic & supportive

Complications are retinal damage, dementia, kidney problems & loss of vision

Pacemakers, hearing aids & hormonal replacement needed for normal life expectancy

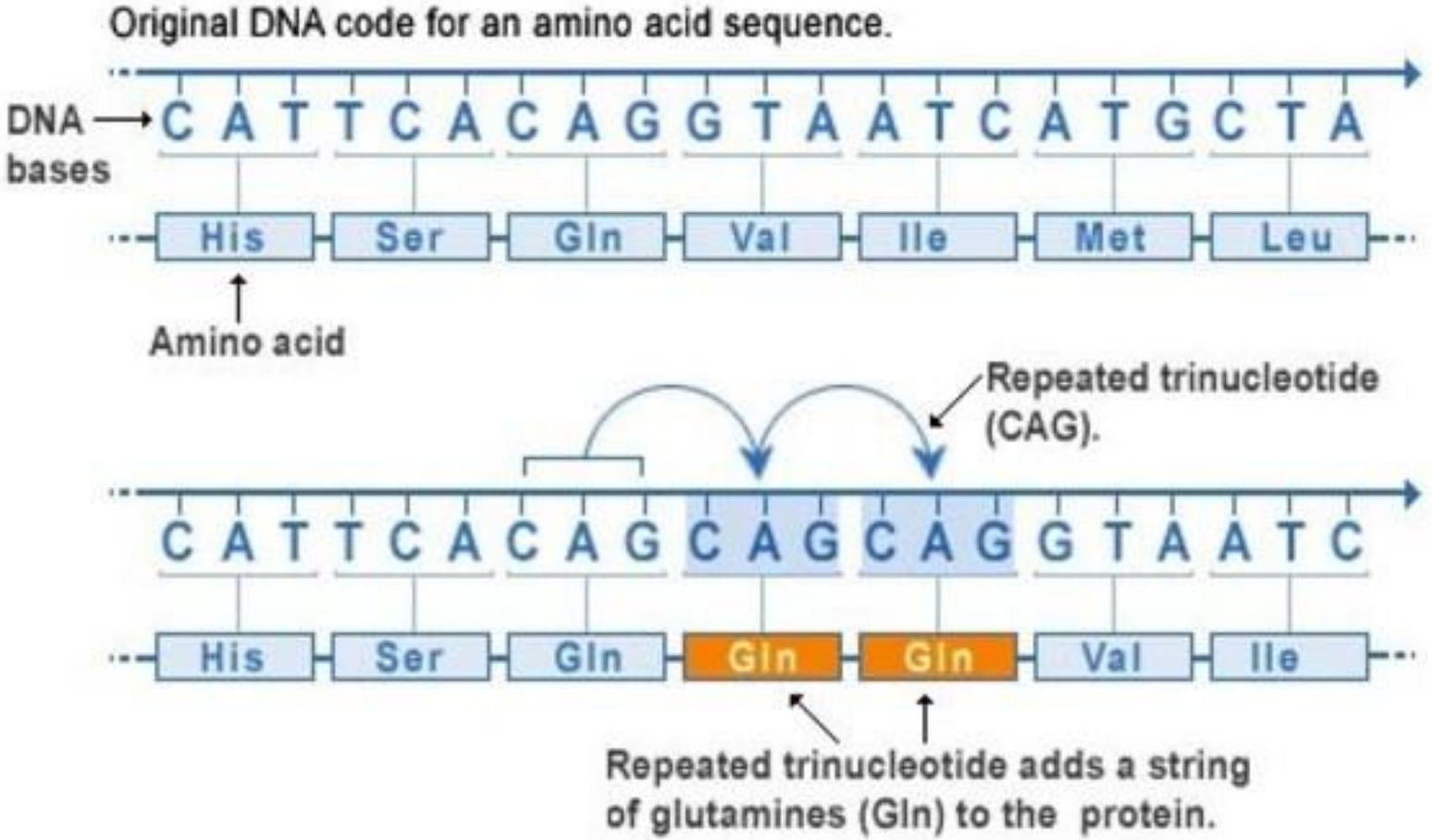
Spontaneous mutations and human diseases

- **Expansion of a three-base-pair repeat**
  - Fragile X syndrome (CGG repeats in the FMR-1 gene)



  - Kennedy disease (X-linked spinal and bulbar muscular atrophy (CAG repeats in the androgen receptor)
  - Myotonic dystrophy (CTG repeat in the non-coding region of a kinase gene)
  - Huntington disease (CAG repeats in HTT gene)

Repeat expansion mutation



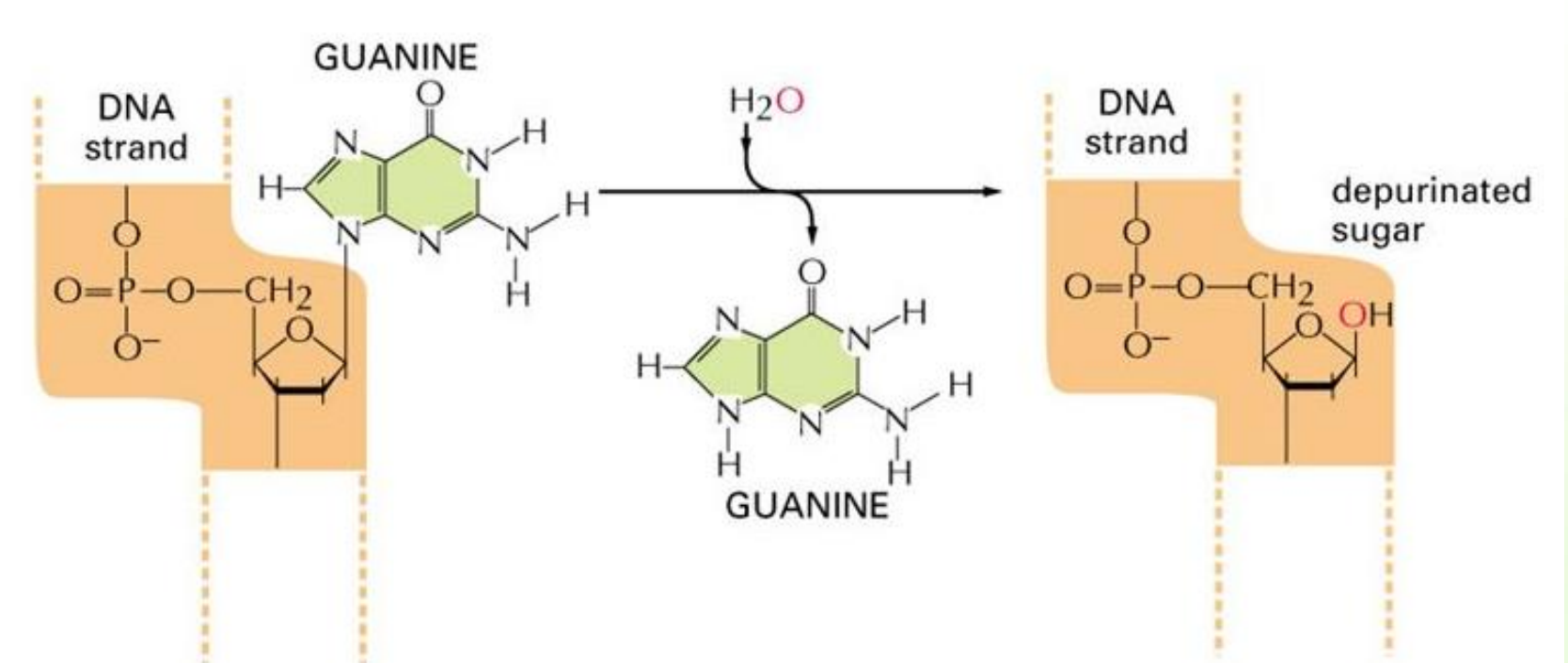
U.S. National Library of Medicine

Spontaneous lesions

- Spontaneous lesions are naturally occurring type of DNA damage that can generate mutations
  - Depurination
  - Deamination
  - Oxidatively damaged bases

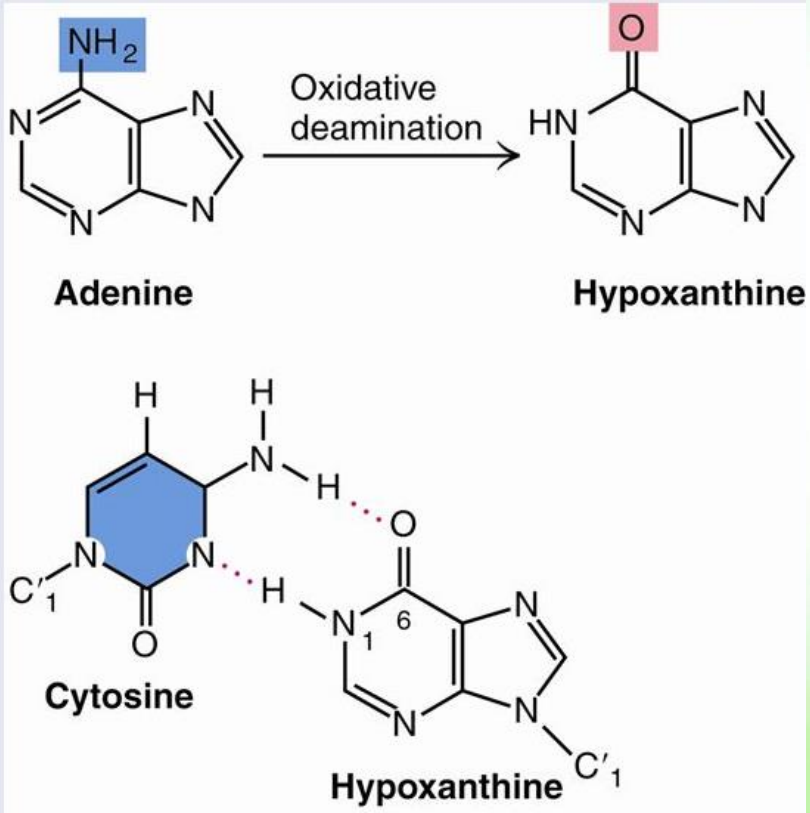
Depurination

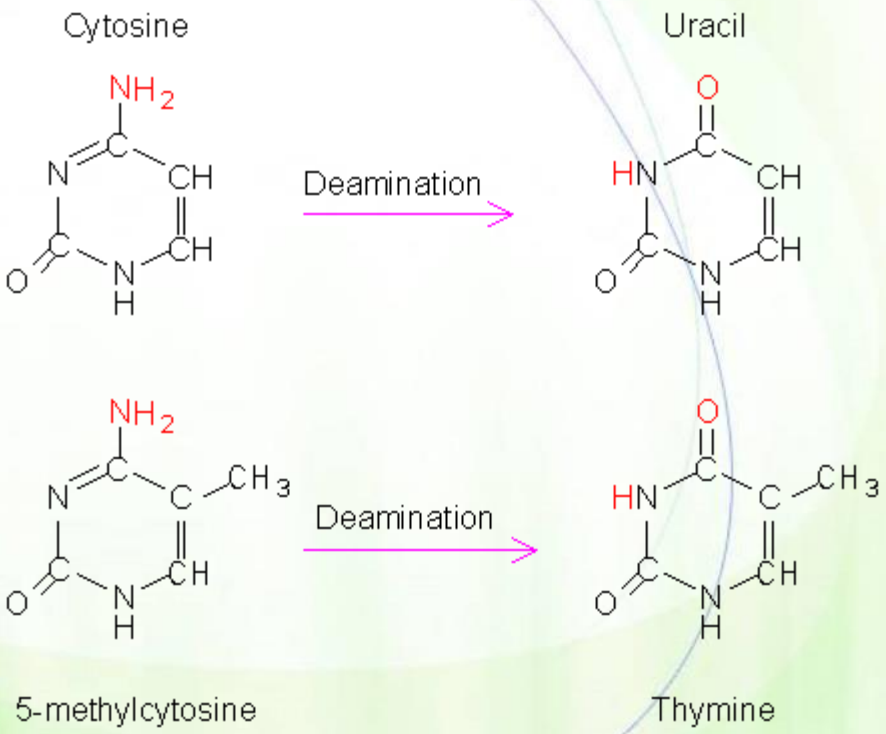
- Cleavage of the glycosidic bond between the base and deoxyribose creating apurinic sites (AP sites)
- During replication, a random base can be inserted across from an apurinic site resulting in a mutation.



Deamination

- The deamination of cytosine yields uracil.
- The deamination of methylated cytosine yields thymine.
- The deamination of adenine yields hypoxanthine.





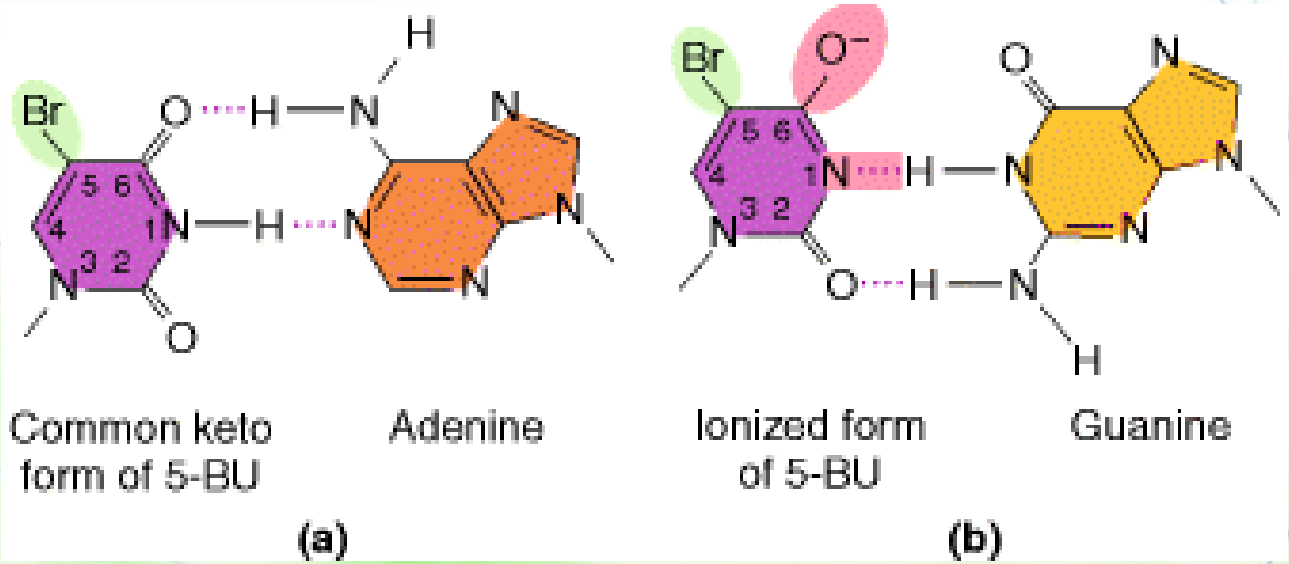
Induced mutations

Mechanisms of mutagenesis

- Mutagens induce mutations by at least three different mechanisms:
  - Add a base analog during DNA replication
  - Alter an existing base causing mispairing (alkylation)
  - Damage a base disabling pairing with any base

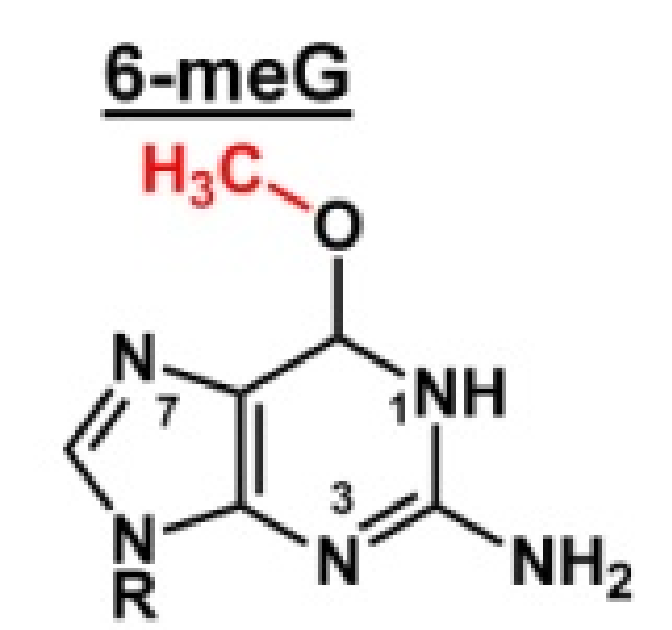
Incorporation of base analogs

- Base analogs have similar structure to normal nucleotides and are incorporated into DNA during replication.
- 5-bromouracil (5-BU), an analog of thymine, pairs with adenine, but, when ionized, it pairs with guanine.



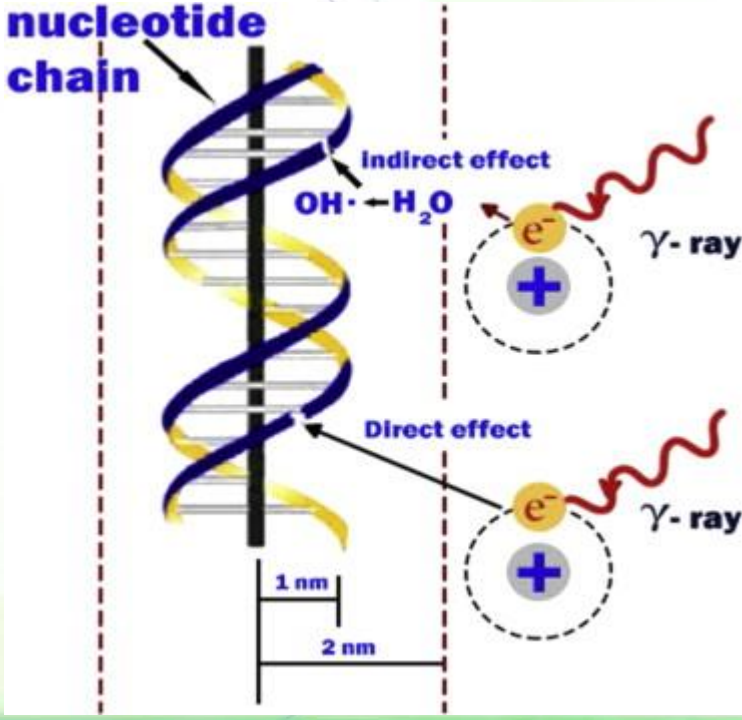
Specific mispairing

- Bases existing in DNA can be altered causing mispairing following replication.
  - Alkylating agents can transfer methyl group to guanine forming 6-methylguanine, which pairs with thymine.



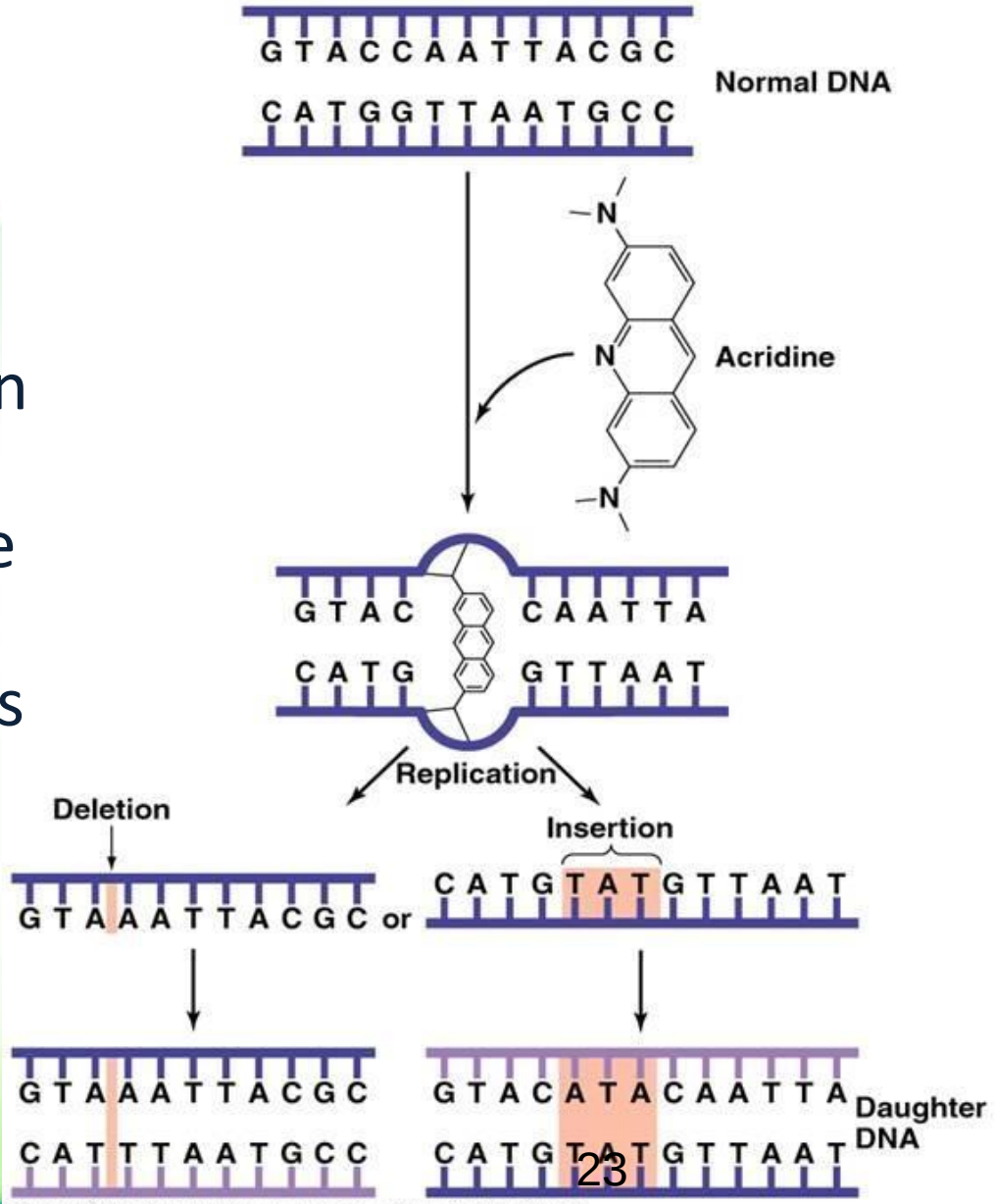
Base damage

- Ionizing radiation results in the formation of ionized and excited molecules that can cause damage to DNA including
  - Base damage,
  - Creation of AP sites (apurinic or apyrimidinic sites)
  - Strand breaks



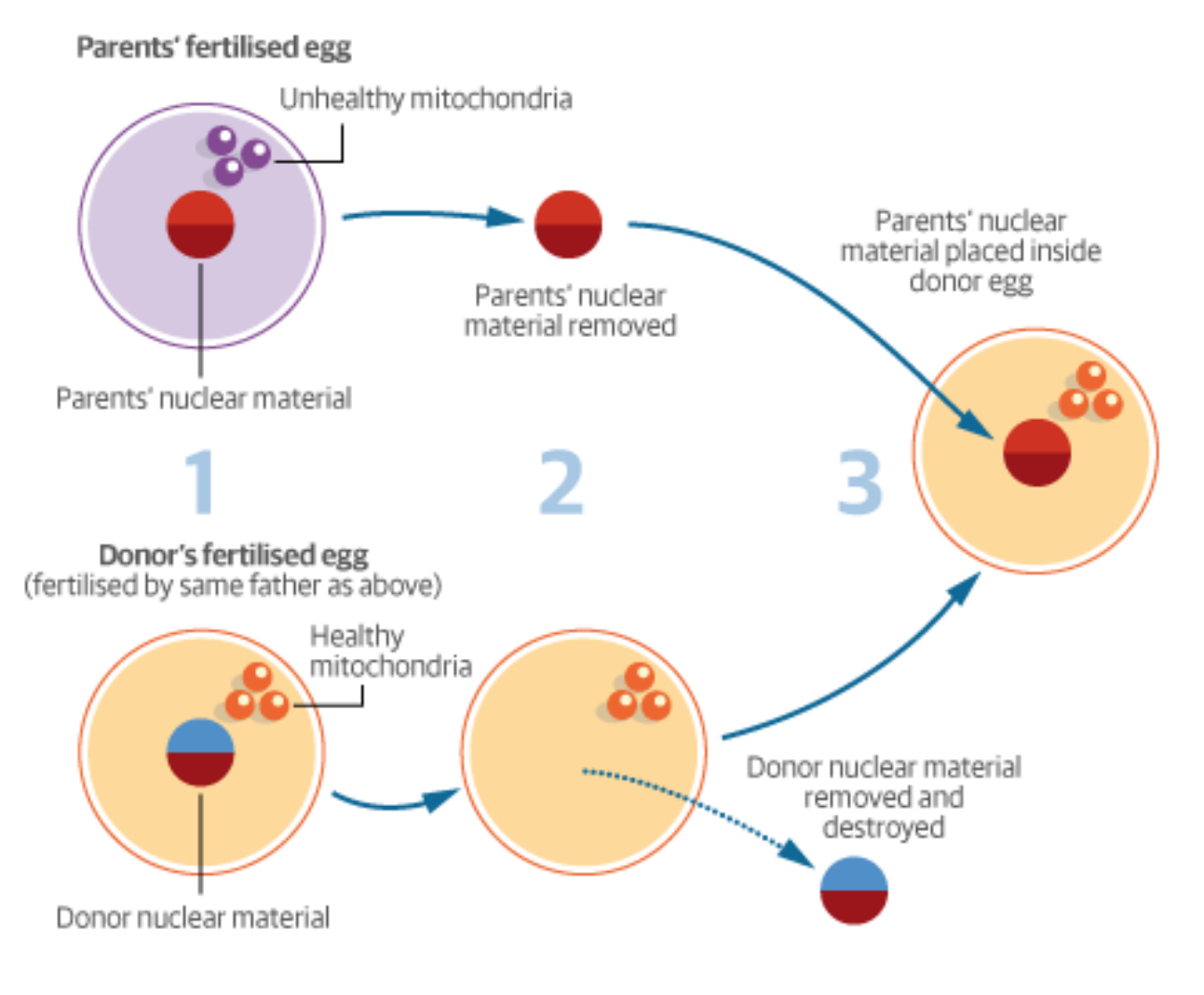
Intercalating agents

- The intercalating agents such as proflavin and ethidium bromide are planar molecules that can insert themselves (intercalate) between the bases and cause single-nucleotide-pair insertions or deletions.



Controversial issue

Three-parent babies



https://www.theguardian.com/science/2015/feb/02/three-parent-babies-explained