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# DNA-REPAIR

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# DNA-REPAIR MECHANISMS

- DNA-repair mechanisms exist to **correct DNA damage** due to:
  1. Environmental mutagens.
  2. Accidental base misincorporation at the time of DNA replication.



# DNA-REPAIR MECHANISMS

- There are four different types of DNA-repair mechanisms:
  - Excision repair
  - Mismatch repair
  - Recombination repair system
  - Double-strand repair

# EXCISION REPAIR SYSTEM

- Excision repair system : removing one strand with damage DNA site.
- Excision repair can be
  - Base-excision repair
  - Nucleotide-excision repair
- The system recognise the damaged site which caused by UV and radiation.
- Three protein are important in this process (XPA, XPB, and XPC).
- Theses protein detect the damaged site and form which is known as repair protein complex.



# EXCISION REPAIR SYSTEM

- The process start by the action of exonuclease which cleaves the damage strand at two site (27 nucleotides before the damaged site and 29 nucleotides after the damaged site) and removed
- Then, DNA synthesis will restore the missing strand and DNA ligase close the gap.

# MISMATCH REPAIR SYSTEM

- Mismatch repair system corrects the errors of replication
- Eight gene loci have been identified:
  - MSH2 (2p16).
  - MSH3 (5q3).
  - MSH4 (6p21.3).
  - MSH6 (2p16).
  - MLH1 (3p21).
  - MLH3 (14q24.3).
  - PMS1 (2q31-33).
  - PMS2 (7p22).



# Mismatch repair system

- The process begin by removing the strand which have an error bases
- DNA synthesis start by DNA polymerase III, which replace the damages strand.
- With somatic loss of the second normal allele the cell will accumulate genetic mutations and as a result of this, the pattern of microsatellite repeats at a polymorphic locus can differ from the surrounding normal tissue (also called RER<sup>+</sup>, replication error positive).

# DNA Repair

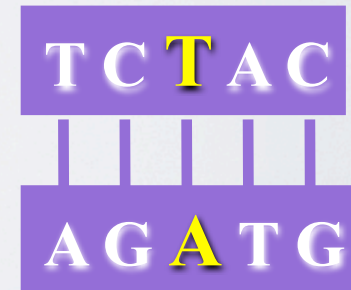
Base pair mismatch



Normal DNA repair



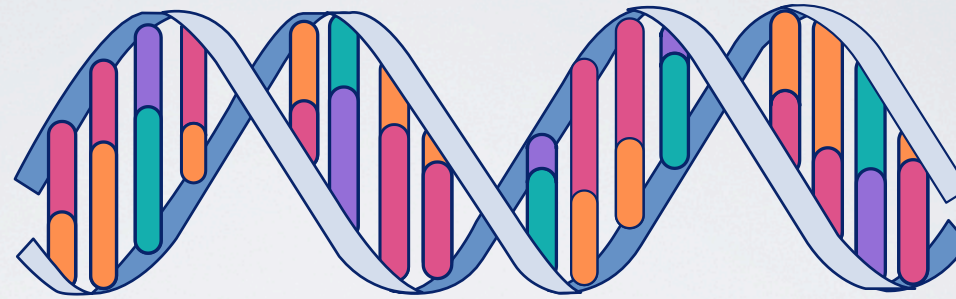
Mutation introduced by unrepaired DNA



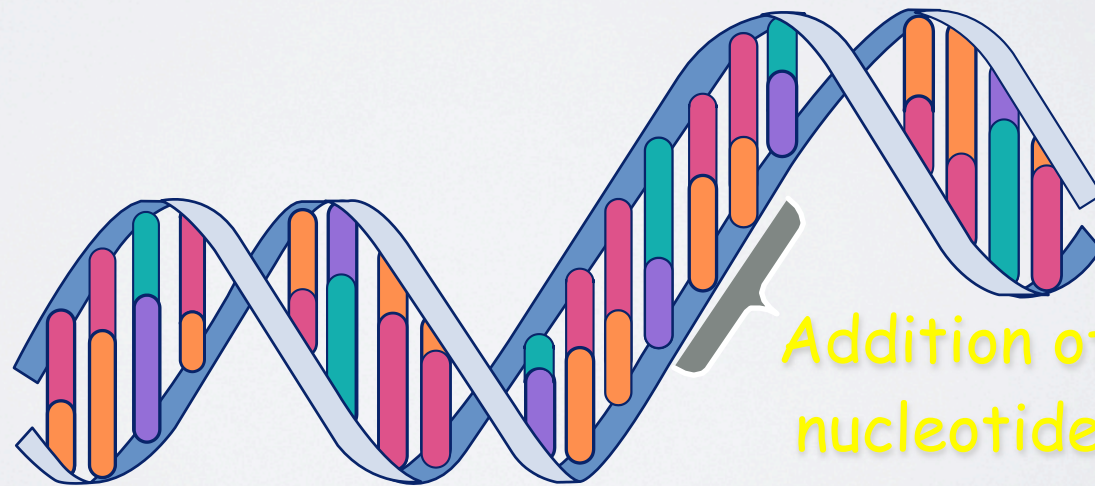


# Mismatch Repair Failure Leads to Microsatellite Instability (MSI)

Normal



Microsatellite instability



Addition of nucleotide repeats

# Microsatellite Instability (MSI)

- 10%-15% of sporadic tumors have MSI.
- 95% of HNPCC tumors have MSI at multiple loci.



# Replication repair system

- DNA damage interfere with replication and transcription.
- In replication: DNA damaged will affect the leading strand
- In transcription: DNA damage will affect the process due to RNA polymerase cannot use the leading strand as a template.

# Double-strand repair system

- Double-strand damage is a common consequence of gamma radiation.
- The process require three important genes
  - ATM (ataxia telangiectasia)
  - BRCA1
  - BRCA2