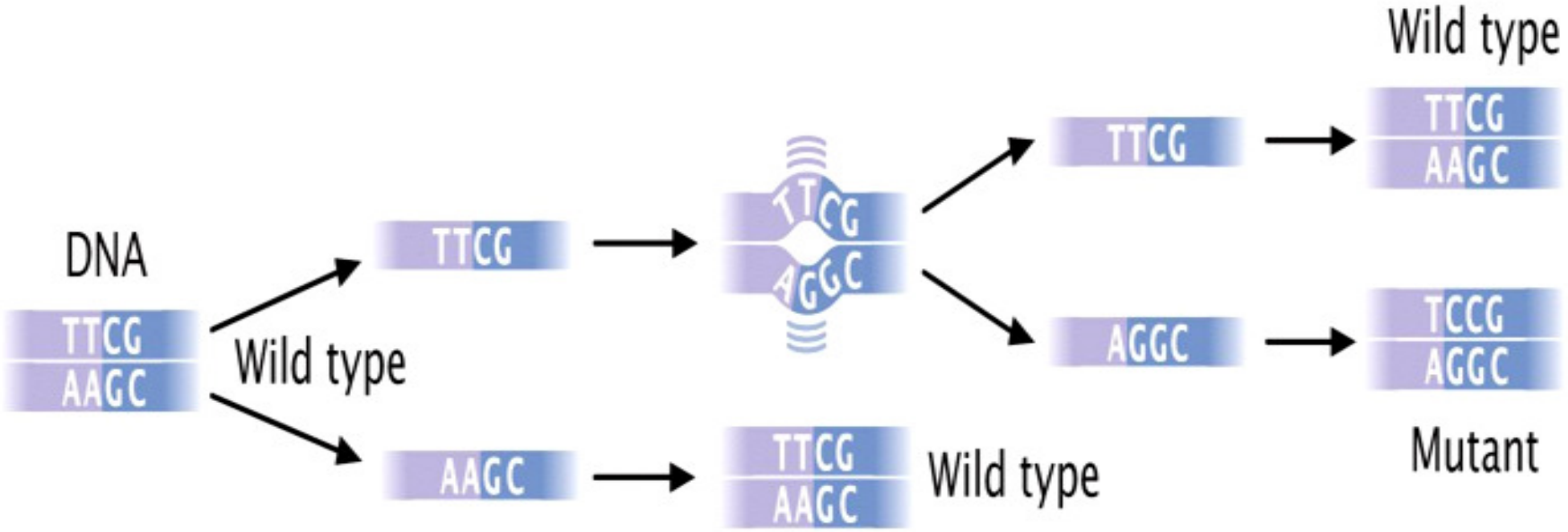
Mutation

- **Mutation is a permanent change in base sequence or rearrangement in DNA .**
  Mutations are NOT "fixed" until replication



Three classes of mutations :

Genome mutations – involve loss or gain of whole chromosomes (giving rise to monosomy or trisomy)

Chromosome mutations – abnormatily in chromosome structure .

Gene mutations – may result in partial or complete deletion of a gene or, more often, affect a single base.

Site of mutation:

- **In germ cells**

  Mutations that affect the germ cells are transmitted to the progeny and may give rise to inherited diseases.

- **In somatic cells**

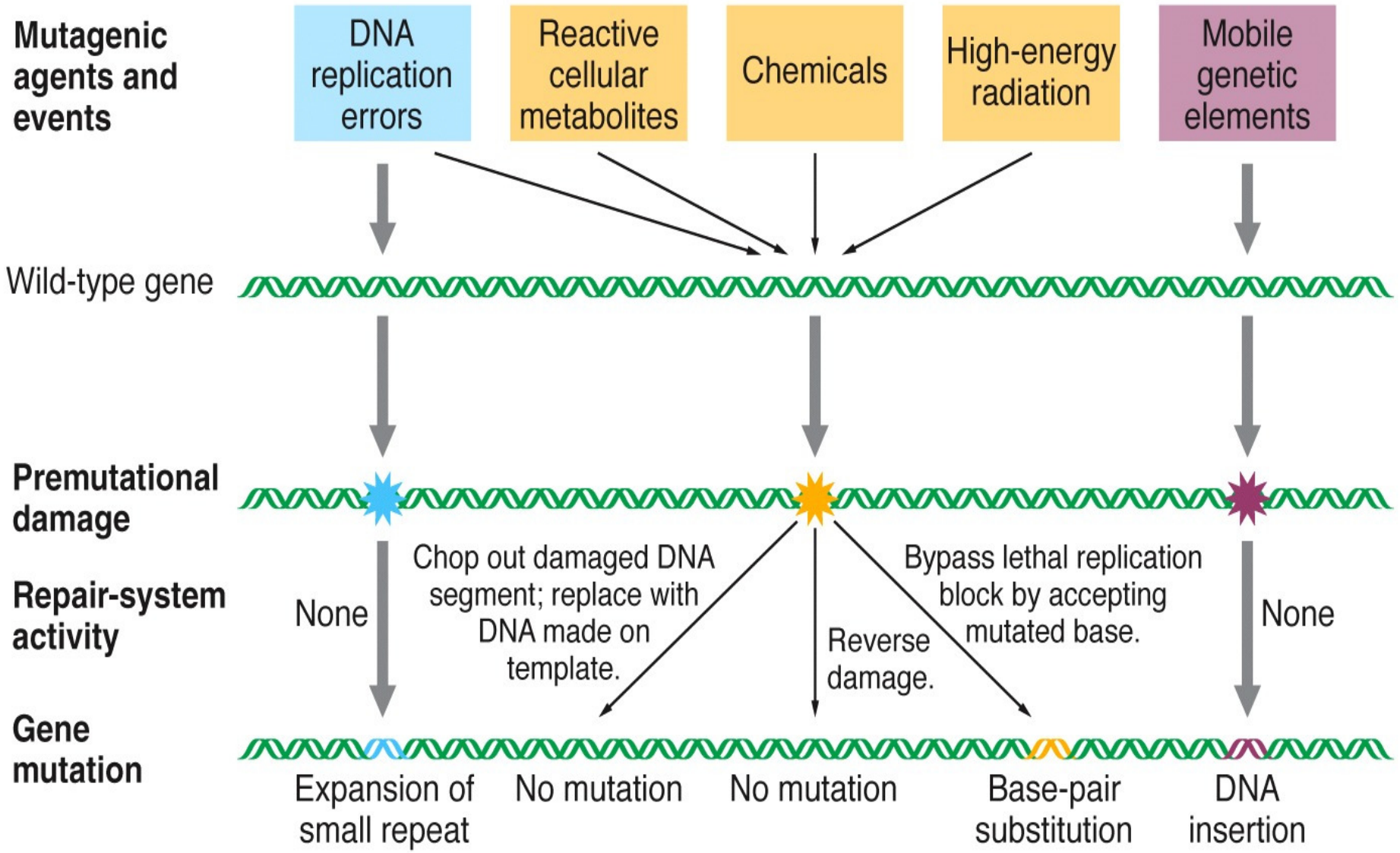
  Mutations in somatic cells are important in the genesis of cancers and some congeital malformations.

Causes of Mutation

- Spontaneous mutations
  - Arise naturally during DNA replication
- Induced mutations

  Mutations that result from the the influence of an extraneous factor (mutagenes) . Occur in higher rate
  - Ionizing radiation (X-rays)
  - Non-ionizing radiation (UV)
  - Chemical mutagens

Causes of gene mutations



Effects of mutations on Proteins

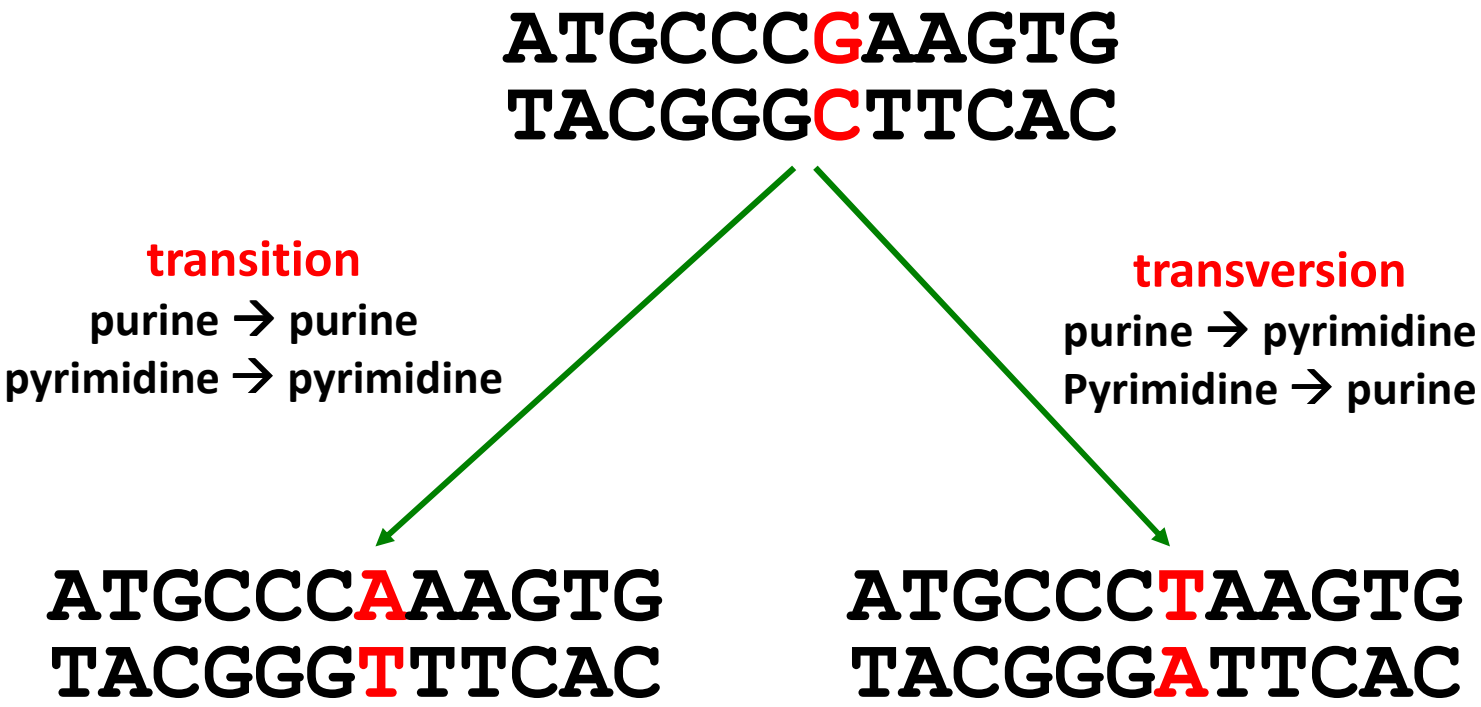
- **Positive** – causes the protein to be have an better function (this will allow for natural selection and evolution)
- **Negative** – reduce or eliminate the protein function (loss of function)
- **Neutral** –no significant change in protein function

Gene mutation

I – Point Mutation

- Involve a single base pair.
- May be :
  1- Base substitution .
  2- Base insertion .
  3- Base deletion .

Point Mutations
(Base Substitutions)



1 – Base substitutuion

a- Silent mutation

Normal gene

3`GGT CTC CTC ACG CCA 5`

(DNA)

↓

CCA GAG GAG UGC GGU

Codons (mRNA)

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

Substitution mutation

GGT CT**T** CTC ACG CCA

↓

CCA GA**A** GAG UGC GGU

↓

Pro-**Glu**-Glu-Cys-Gly

- **No change in the amino acid (degenerate code)**
- **change in the 2nd or 3rd codon position**
- **no change in protein sequence or phenotype**

b- Missense mutation

Normal gene

GGT CTC CTC ACG CCA

↓

CCA GAG GAG UGC GGU

Codons

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

Substitution mutation

GGT C**A**C CTC ACG CCA

↓

CCA G**U**G GAG UGC GGU

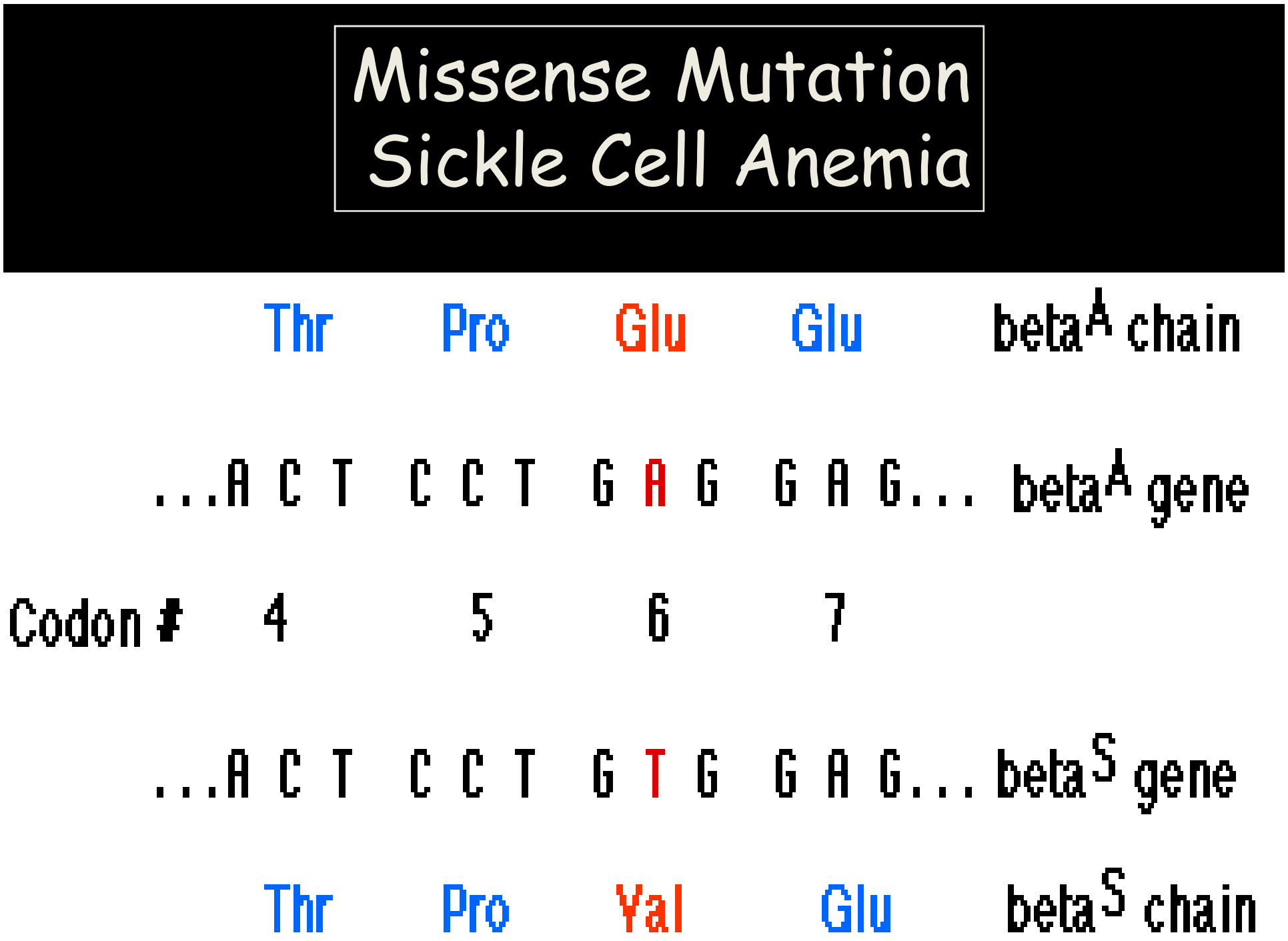
↓

Pro-**Arg**-Glu-Cys-Gly

*** Substitutions will only affect a single codon and change one amino acid in the polypeptide chain .**

***Their effects may not be serious unless they affect an amino acid that is essential for the structure and function of the protein molecule (e.g. sickle cell anaemia)**

Missense Mutation
Sickle Cell Anemia



Neutral mutation

- Triplet codes for different but functionally equivalent amino acid :

AAA → A**G**A

Lys **Arg**

(at many positions, will not alter protein function)

- Protein shape determines how a protein will function. A change in one amino acid may change the shape enough to distort the protein (as in sickle cell disease).
- Thus, change in one base could potentially distort a whole protein.
- It is more likely that a frame shift mutation will change several triplets and distort a protein's structure.

c -Nonsense mutation

Normal gene

GGT CTC CTC ACG CCA

↓

CCA GAG GAG UGC GGU

Codons

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

Substitution mutation

GGT CTC CTC ACT CCA

↓

CCA GAA GAG UGA GGU

↓

Pro-Glu-Glu-**STOP**

-Base substitution is leading to the change of a.a codon to a stop codon (premature stop codon)

-This will give a shrot polypeptide chain according to the point of mutation .

Nonsense mutations

ATGTCTTCCTCATCGAGTTCA**TAA**
MetSerSerSerSerSerSerSer**END**

ATGTCTTCC**TGA**TCGAGTTCATAA
MetSerSer**END**serserserend

non-sense mutation near 5' end

ATGTCTTCCTCATCGAGT**TGA**TAA
MetSerSerSerSerSerSer**END**end

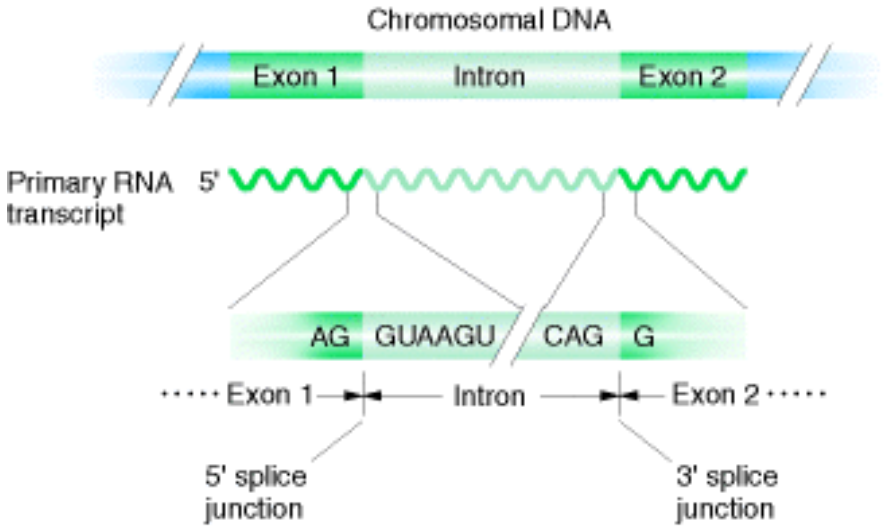
non-sense mutation at 3' end

d- RNA splicing mutation

- Base substitution in the splicing sites of the intron gives abnormal polypeptide chain (longer) containing a.a sequence corresponding to the non-splicing intron .

Splice Sites

- Conserved splice sites are shared by both the exon and the intron.
- Different signals on the donor site (3') and on the acceptor site (5').



2- Base insertion

A frame shift mutation

Normal gene

CTC CTC ACG CCA GGT

↓

CCA GAG GAG UGC GGU

Codons

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

Insertion of one base

GGT **G**CT CCT CAC GCC A

↓

CCA **C**GA GGA GUG CGG U

↓

Pro-**Arg-Gly-Val-Arg**

3- Base deletion

A frame shift mutation

Normal gene

GGTCTCCTCACGCCA

↓

CCAGAGGAGUGCGGU

Codons

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

one base deletion

GGT**C/C**CTCACGCCA

↓

CCA**GG**GAGUGCGGU

↓

Pro-**Gly-Ser-Ala-Val**

Frame Shift mutations

- A frame shift mutation results from a base deletion or insertion.
  It will changes the triplets (codon) that follow the mutation.

  CGG CCC AAT to CGG C**G**C **CAA T**
- Frame shift mutations have greater effects than a point mutation because they involve more triplets (recall how important triplets are to protein synthesis)
- It will give a mutant polypeptide chain with different a.a sequence after the point of mutation .

Frame shift mutations•

ATGTCTTCCTCATCGAGTTCA**TAA**
MetSerSerSerSerSerSerSer**END**

- Small insertions or deletions in the DNA sequence that results in a shift in the reading frame
- often results in shorter proteins
- may also result in longer proteins

ATG**C**TCTTCCTCATCGAGTTCATAA
Met**LeuPheLeuIleGluPheIle.**

frameshift mutation near 5' end (insertion of a C)

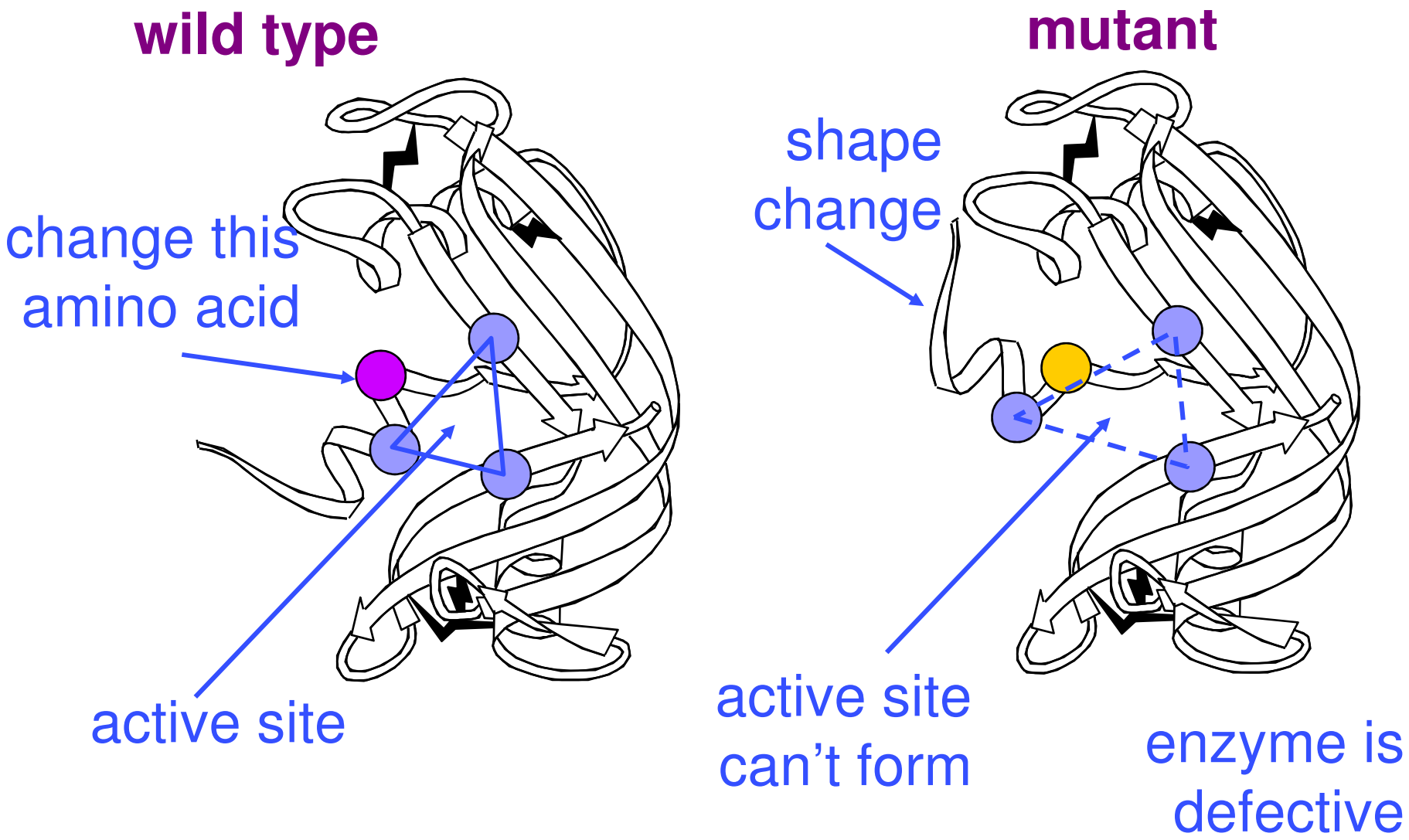
Frame shift mutation at 3' end (insertion of a C)

ATGTCTTCCTCATCGAGT**C**TCATAA
MetSerSerSerSerSerSer**LeuIle.**

Consequences of mutations

- **Missense mutations differ in severity**
  - conservative amino acid substitution substitutes chemically similar amino acid (eg. neutral a.a with another neutral a. a), less likely to alter function
  - nonconservative amino acid substitution substitutes chemically different amino acid, more likely to alter function
- **Nonsense mutation results in premature termination of translation**
  - truncated polypeptides often are nonfunctional
- **Point mutation in non-coding region may affect transcription, RNA splicing, and protein assembling**

Changes in the primary structure of proteins can change folding and alter function of a protein



II- Mutations involved more than one base

1 – Insertion or deletion of more than one base

- If the bases involved are 3 or multiple of 3 :

the polypeptide chain will increased or decreased in a number of a.a according to the bases involved .

e.g **9 bases** inserted → **3 a.a** increased .

- If the bases involved are not 3 or multiple of 3 → **Frame shift mutation** .

2- Inversion

- **Inversion mutations may involved a few bases or large number of bases . So it will change one or meny amino acids in the polypeptide chain .**

Normal gene

CTC CTC ACG CCA GGT

↓

CCA GAG GAG UGC GGU

Codons

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

Inversion mutation

GGT C**CT** CTC ACG CCA

↓

CCA G**GA** GAG UGC GGU

↓

Pro-**Gly**-Glu-Cys-Gly

III Gene deletion or gene duplication

- Absence or presence of more than one copy of the gene on the chromosome .
- Results in the absence or increase of the gene product .
- Mainly result from unequal crossing over .e.g. Thalassemias (gene deletion).

Mutagenic factors

- Biological factors : parental age
- DNA damaging agents

Effect of parental age :

- 1 – Old maternal age may give a birth to a child with genomic mutation e.g Down syndrome . The cause is non-disjunction in ovogenesis .
- 2- old paternal age cause dominant gene mutations . The cause is defective DNA repair enzyme system because of aging .

DNA damaging agents

- **High energy sources**
  - UV-light, X-rays,
  - Radioactive material
- **Chemical agents**
  - benzenes (cigarette smoke)
  - alkylating agents (ethylmethane sulfonate = EMS)
  - N-nitroso compounds, nitrosamines (food additives)
  - PAHs and HAs (agents formed by heating food)
    - PAH = polycyclic aromatic hydrocarbon
    - HAs = heterocyclic amines
  - numerous pesticides, insecticides, fungicides
- **Natural mutagens**
  - Viruses
  - plant alkaloids, plant toxins, aflatoxin B_1 (AFB_1)

Radiation :

- High energy radiation as X-ray , UV can cause damage in DNA as fragmentation ,base opening , dimer formation .
- E.g Thymine dimer formation result from exposure to UV . Accumulation of thymine dimer without repair lead to Xeroderma pigmentusm .

wavelengths of radiation:

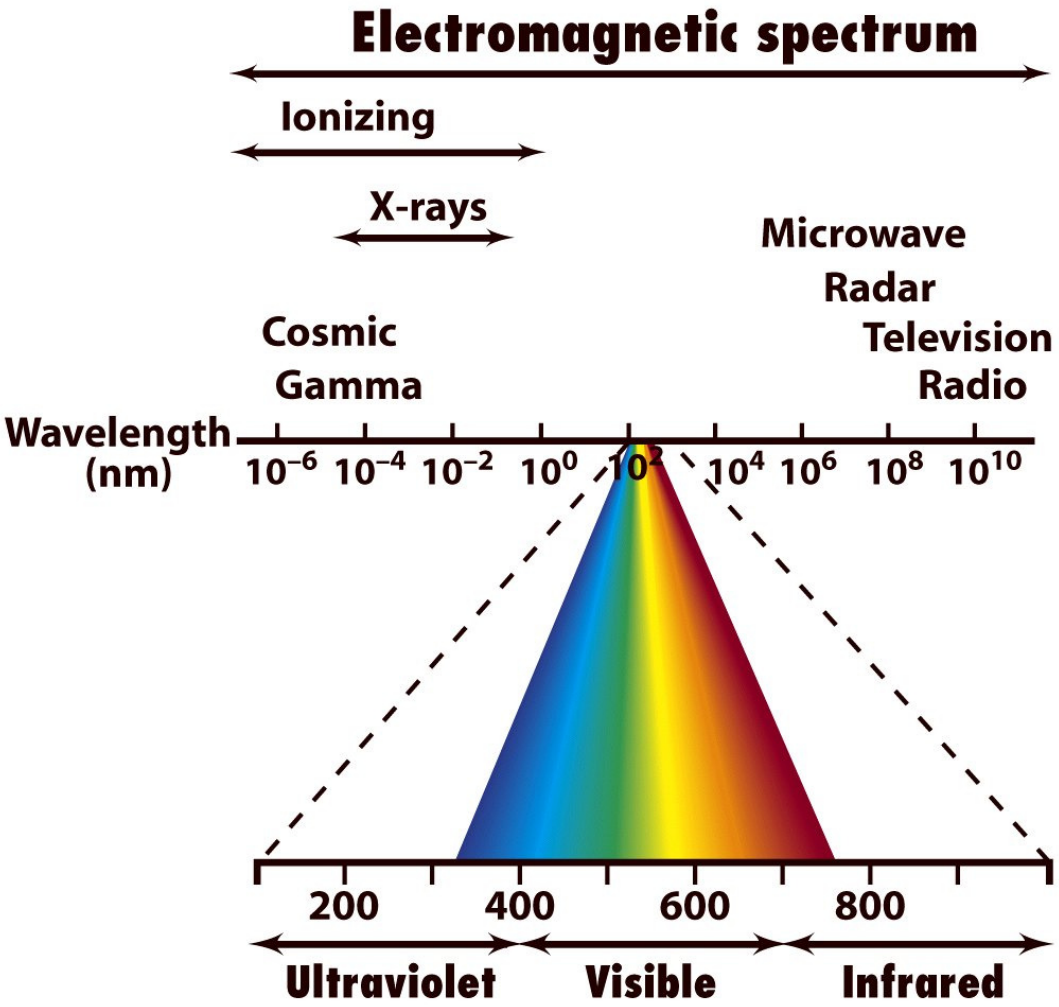


Figure 10-6 Brock Biology of Microorganisms 11/e

ionizing (e.g., X-rays):

- hydroxyl radicals (OH•)

UV (nonionizing):

- pyrimidine dimers

Radiation: ionising

- α, β particles, γ, χ rays
- Free radicals formed
- React with and damage DNA
  - ssDNA breaks
  - dsDNA breaks
  - nt substitutions
- hard to repair

Radiation: ultraviolet

- UV energy absorbed by base
- Chemical modification of base
- Adjacent pyrimidines covalently bond
  - Pyrimidine dimers
- DNA helix distorted
  - Replication & transcription blocked

Exposure to UV light (for example in sunlight) causes formation of linked Thymines, which lead to errors during replication