MOLECULAR MUTATIONS

TAUTOMERIC SHIFT

TRANSITIONS

TRANSVERSIONS

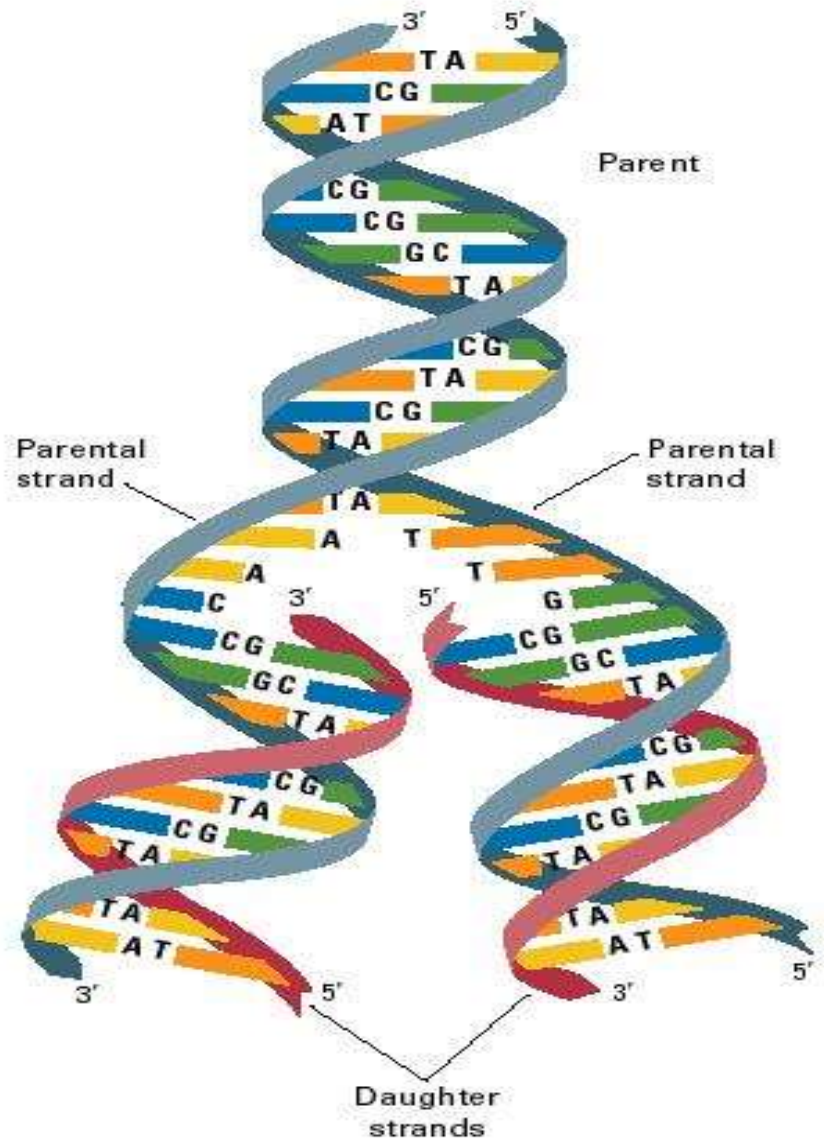
BACK MUTATION

AND

SUPPRESSOR MUTATION

INTRODUCTION

- **Watson and Crick described the double helical structure of DNA**
- **Semi conservative replication based on specific base pairing**
- **Accurate transmission of genetic information from generation to generation.**



MUTATION

- **Mutation**
- Mutations are permanent, heritable changes in genetic information
- **Chromosome mutations** –alter number or structure of chromosomes- so affect many genes
- **Gene mutation**- genetic information of a single gene
- Source of genetic variation, the raw material for evolution
- Also have deleterious effects like diseases

TAUTOMERIC SHIFTS

- **Tautomeric shift comes under spontaneous mutations because they may occur infrequently without involvement of an external agent.**

- Each of the bases in DNA can appear in one of several forms, called tautomers, which are isomers that differ in the positions of their atoms and in the bonds between the atoms.

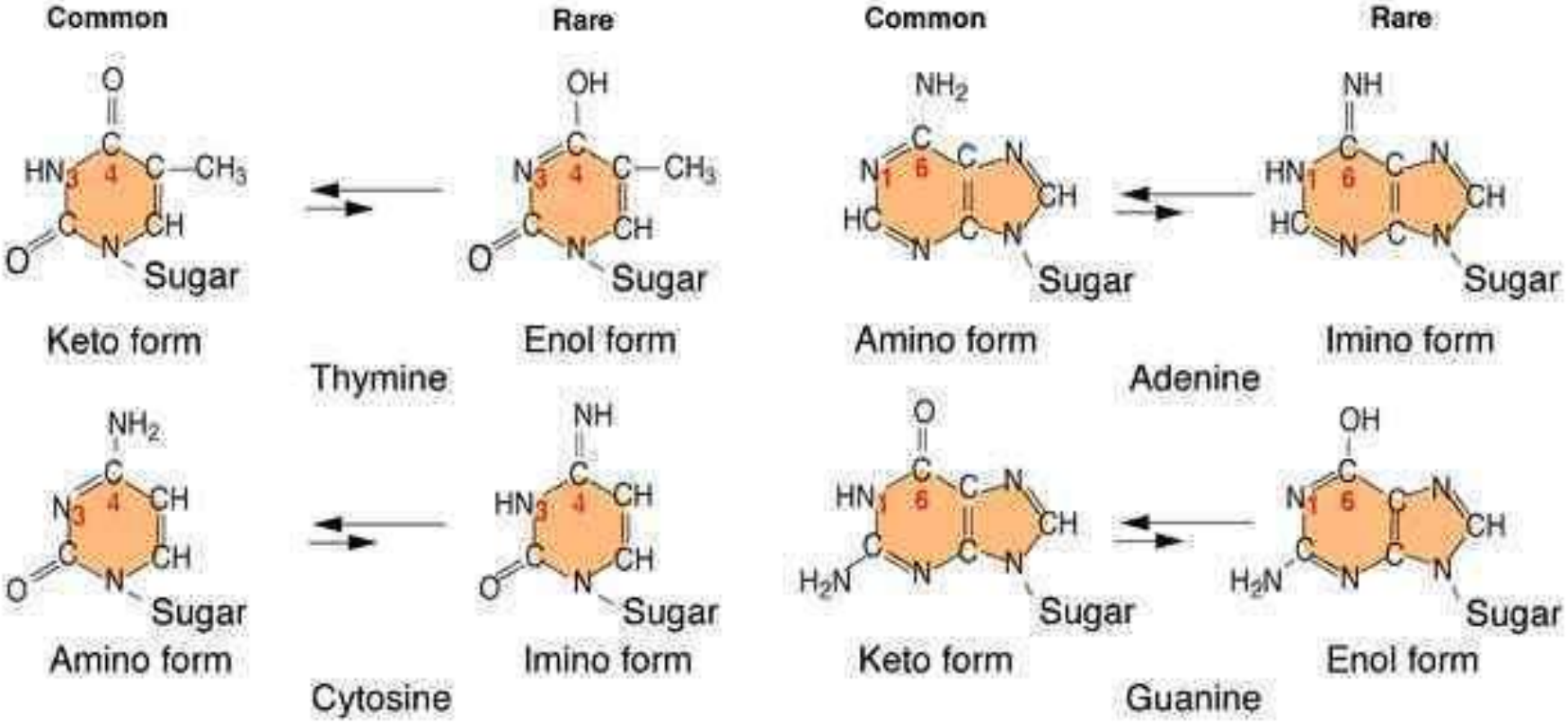
- **Tautomeric shifts are reversible shifts of proton position in a molecule.**

- **Hydrogen atoms can move from one position to another in a base, such chemical fluctuations are called tautomeric shifts.**

- **When tautomeric shifts occur in DNA bases, they may miss - pair during DNA replication.**

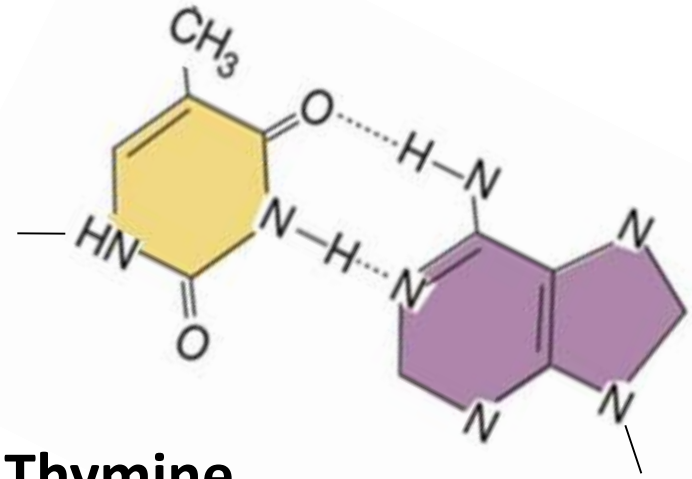
- **If not repaired, they become mutations.**

- **Results in the synthesis of nonfunctional protein or gene products .**


Common
Rare
Keto form
Enol form
Thymine
Common
Rare
Amino form
Imino form
Adenine
Amino form
Imino form
Cytosine
Keto form
Enol form
Guanine

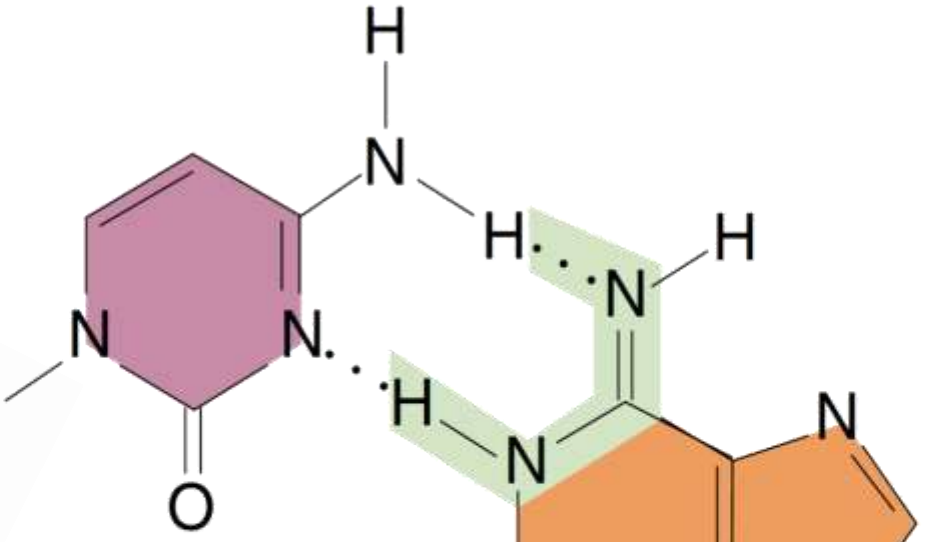
Tautomeric forms of adenine

- **In the common amino form, adenine does not base-pair with cytosine; in the tautomeric imino form, it can.**



Thymine

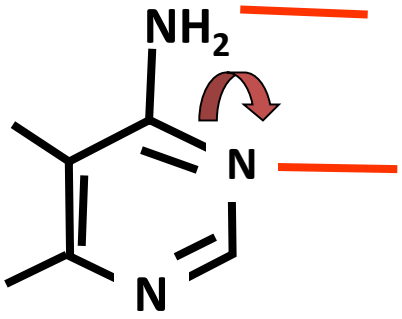
Adenines



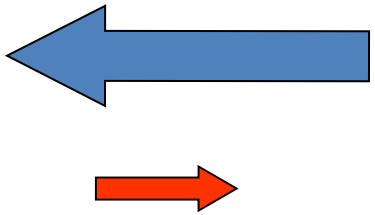
Cytosine

Rare imino form of adenine (A*)

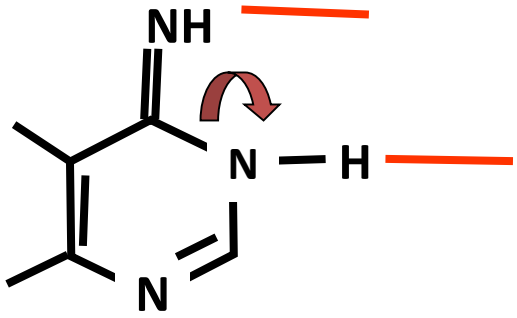
2 x H Bonds



Adenine in its AMINO form
Will bind to Thymine.
TA pairing as expected.



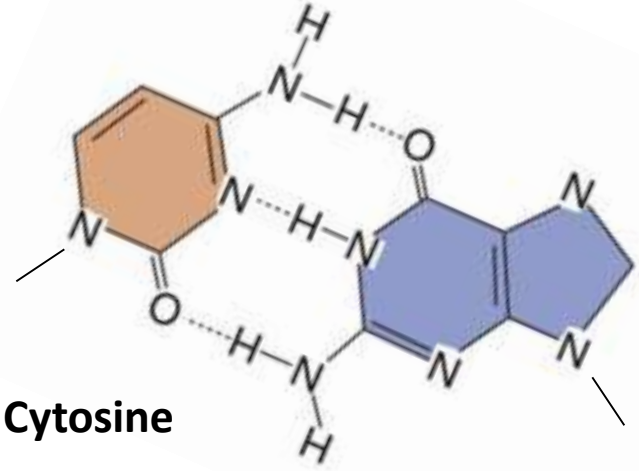
Still 2 x H Bonds

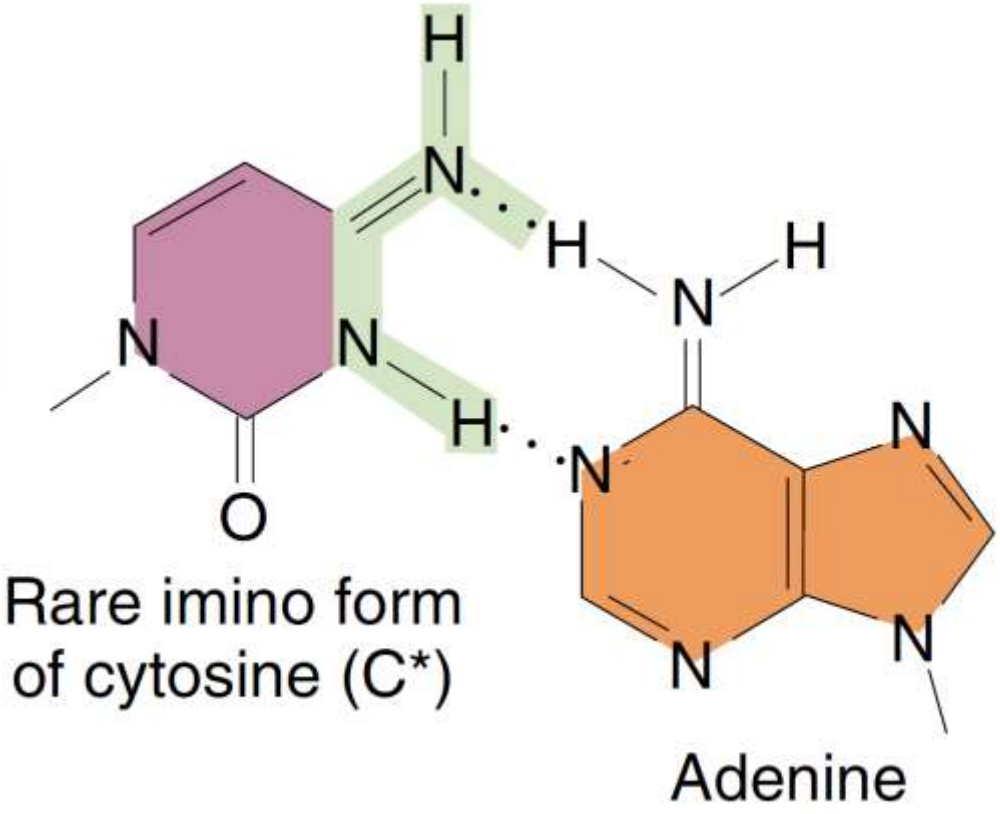


Adenine in its IMINO form. Binds Cytosine.
AC pairing.

Tautomeric form of cytosine

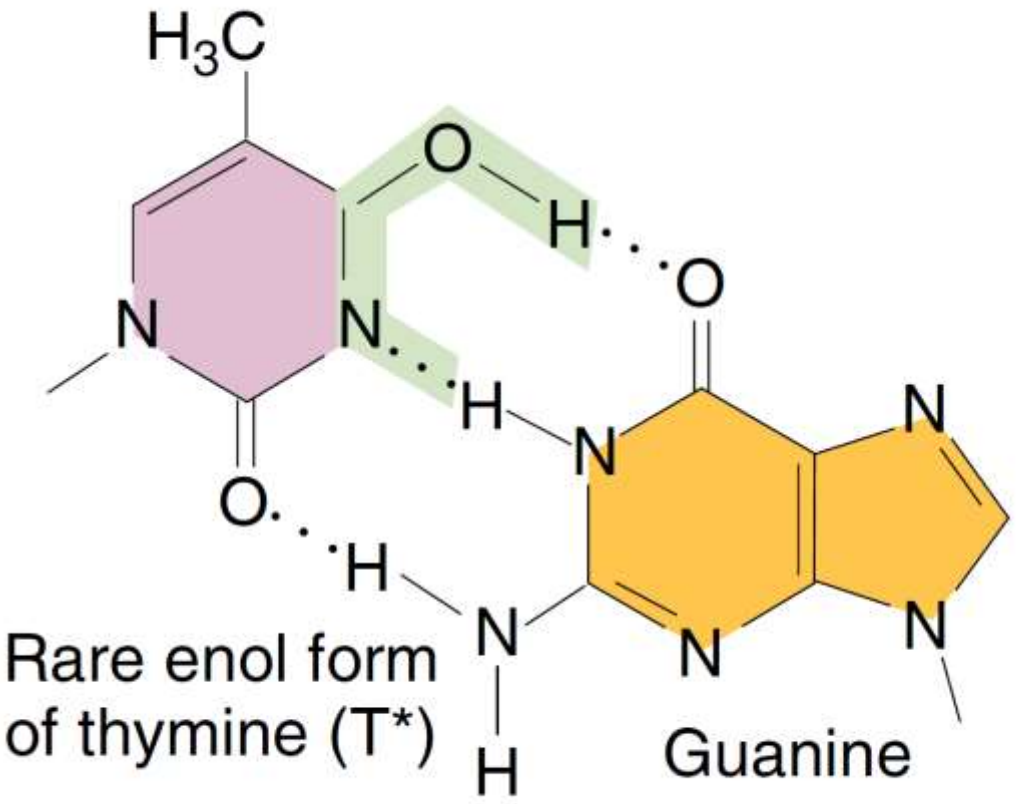
Pairs with adenine instead of guanine



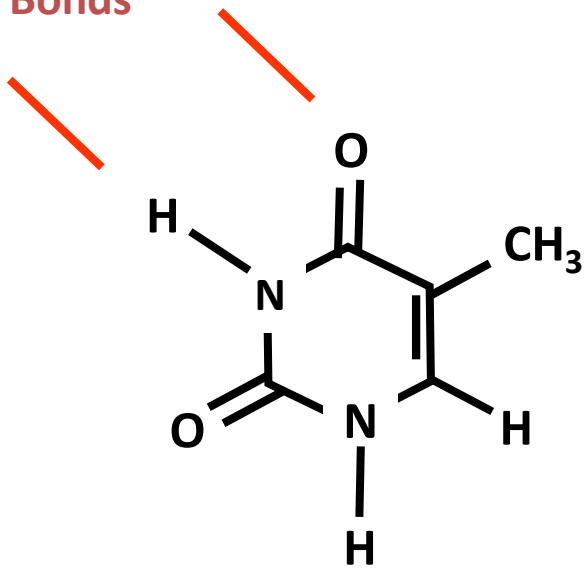


Tautomeric form of thymine

Pairs with cytosine instead of adenine

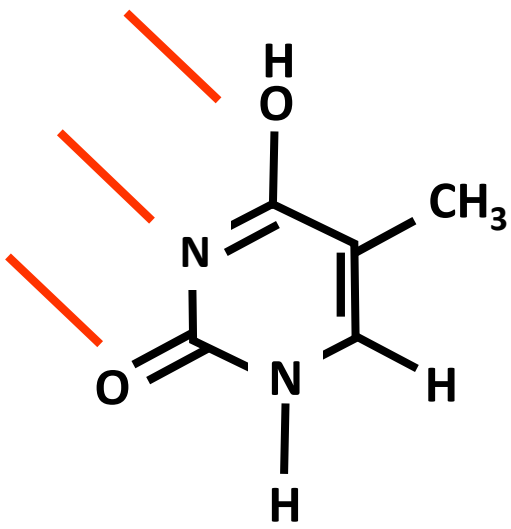


2 x H Bonds



Thymine in its KETO form
Will bind to Adenine
TA pairing as expected during replication

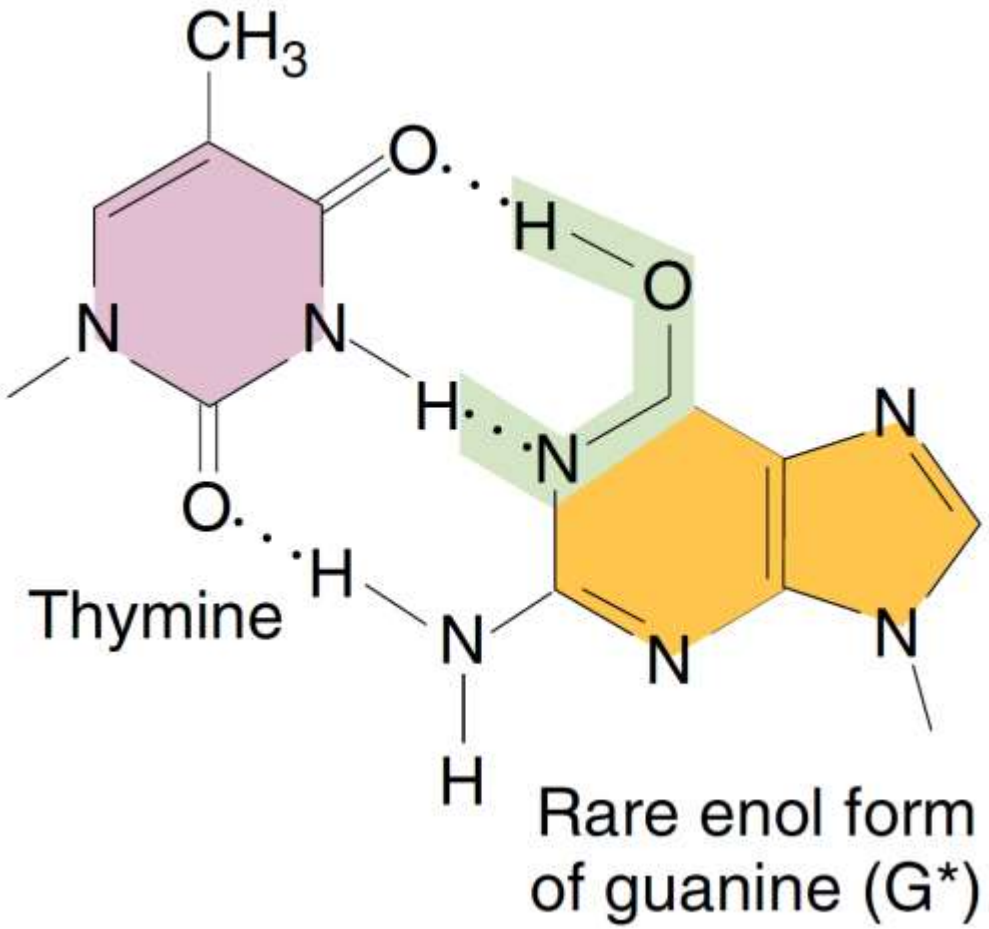
3 x H Bonds



Thymine in its ENOL form. Binds Guanine.
TG pairing during replication

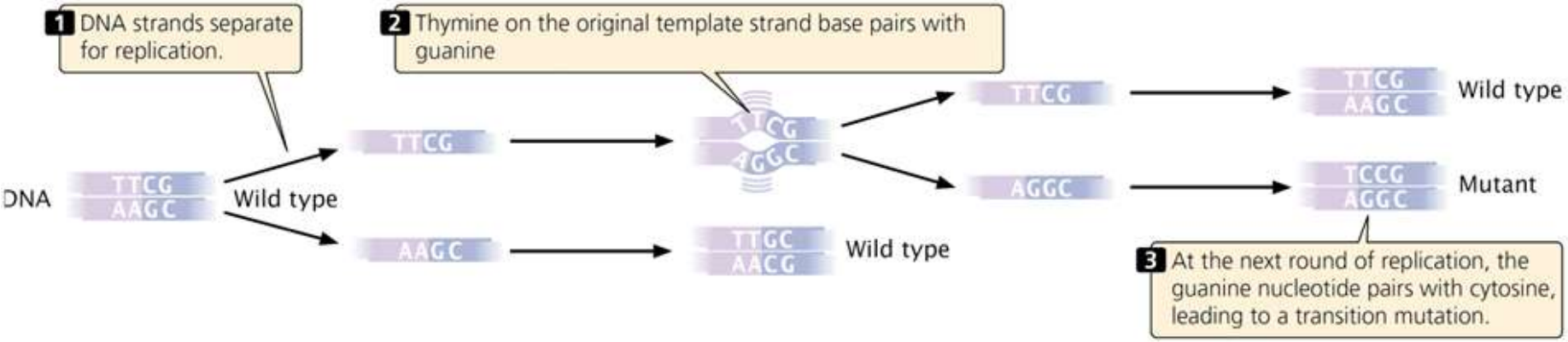
Tautomeric form of guanine

- Pairs with thymine instead of cytosine



HOW IT BECOMES A MUTATION

- In replication T which normally pairs with adenine mispairs with G
- In the next round of replication T pairs with A producing copy of original sequence
- And G pairs with C- thus creates error

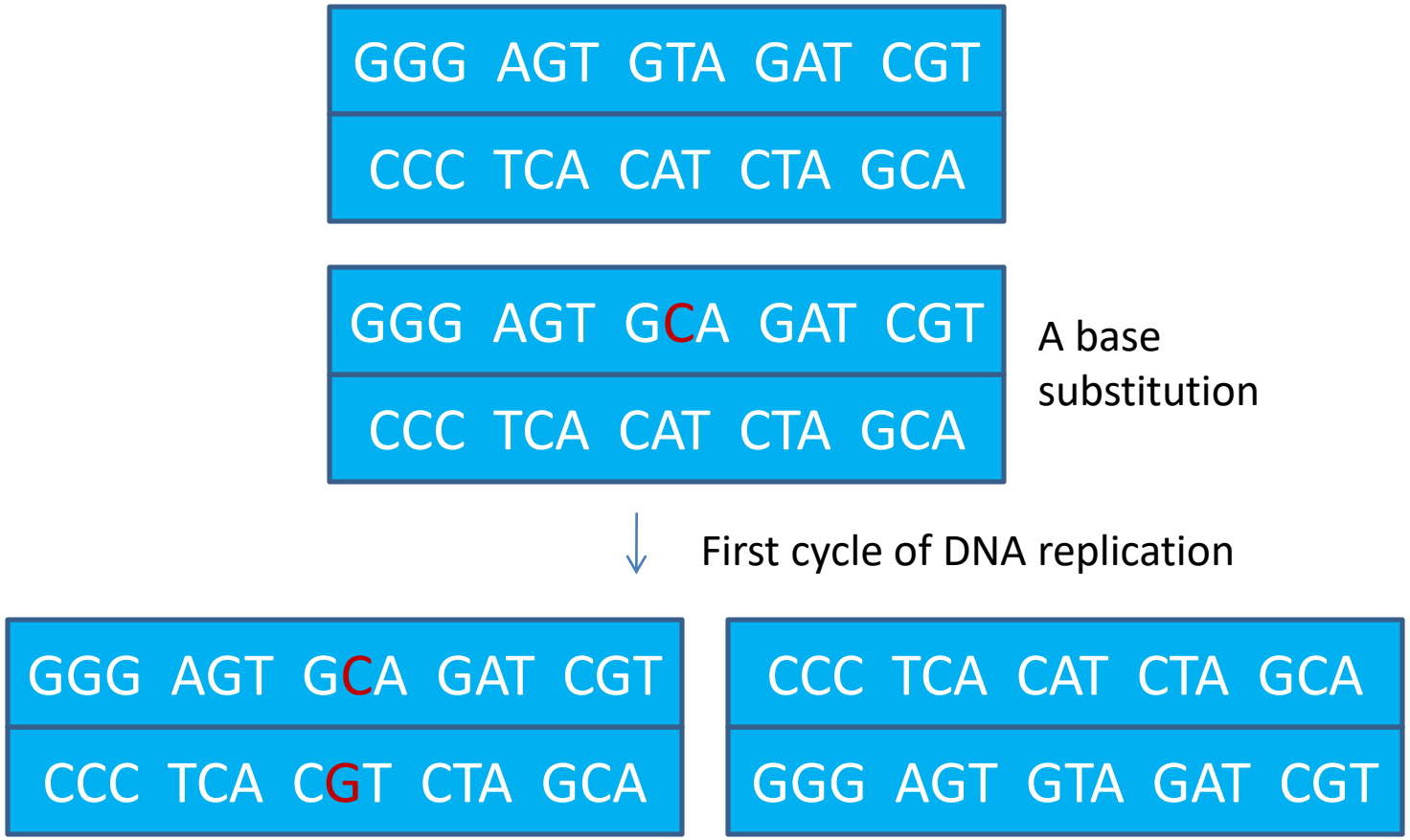


- **C-G** pair in place of original **T-A** pair
- Because all the pairings are correct repair systems fail to detect the error

BASE SUBSTITUTIONS

- Alteration of single nucleotide in the DNA
- Because of complementary nature of the two strands results in base pair substitution in the next round of replication

A base substitution usually leads to base pair substitution



BASE SUBSTITUTIONS ARE OF TWO TYPES

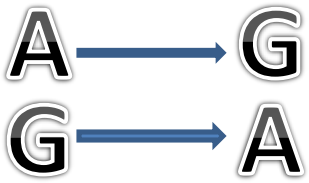
Transitions

And

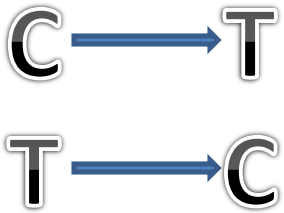
Transversions

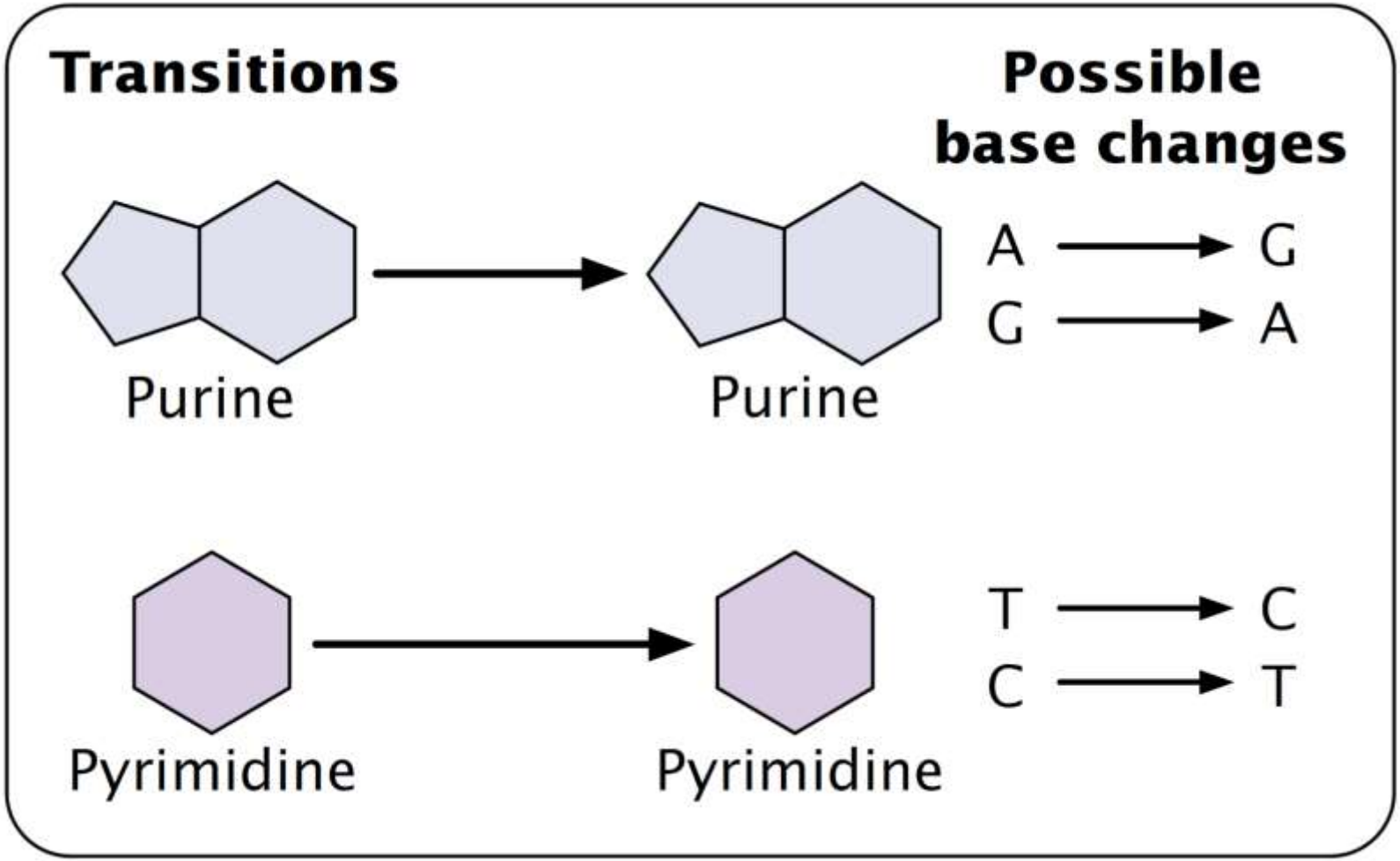
Transition:

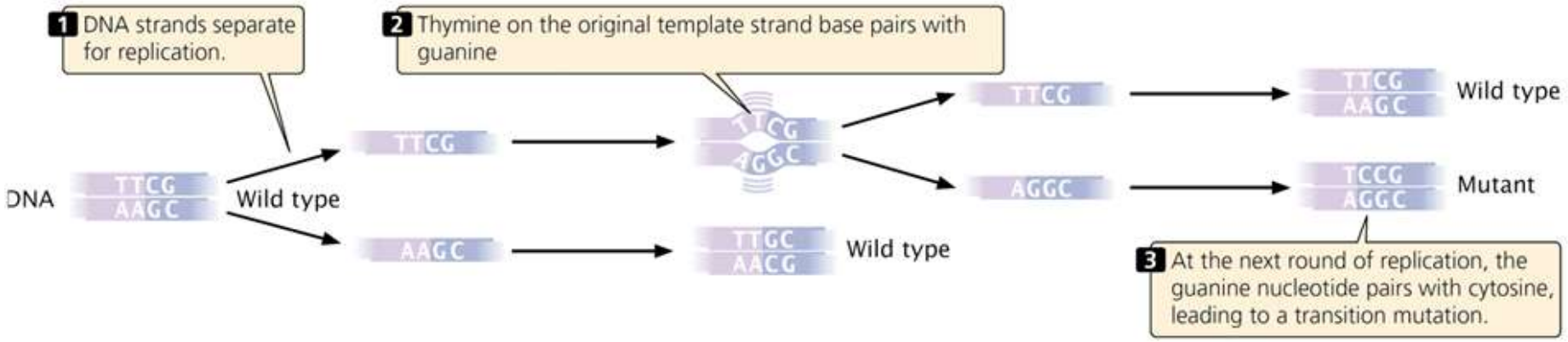
Purine is replaced with a purine



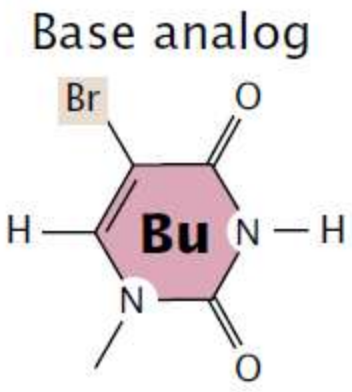
Pyrimidine is replaced with a pyrimidine



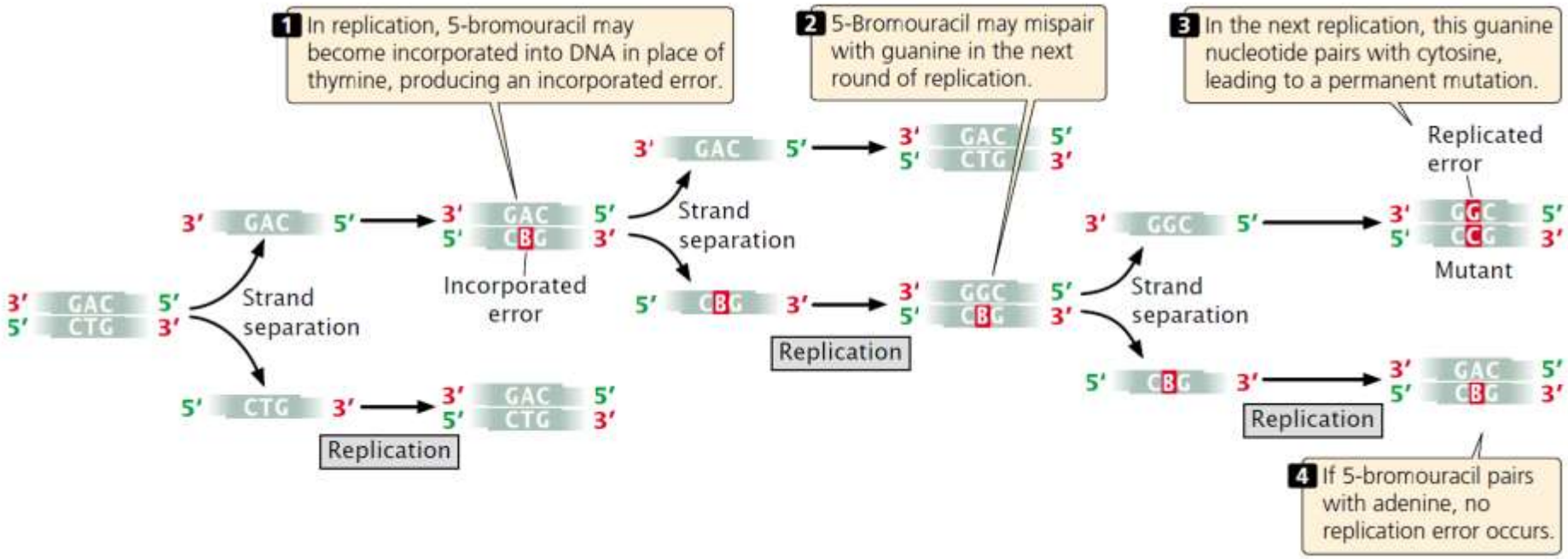

Transitions
Possible base changes
Purine
Purine
A → G
G → A
Pyrimidine
Pyrimidine
T → C
C → T


1 DNA strands separate for replication.
2 Thymine on the original template strand base pairs with guanine
DNA
TTCG
AAGC
Wild type
TTCG
AAGC
TTCG
AGGC
TTCG
AAGC
Wild type
TTGC
AACG
Wild type
AGGC
TCCG
AGGC
Mutant
3 At the next round of replication, the guanine nucleotide pairs with cytosine, leading to a transition mutation.

- 5- Bromouracil, a base analogue of thymine
- Pairs with guanine instead of adenine
- Creates A→T to G→C transition



5-Bromouracil

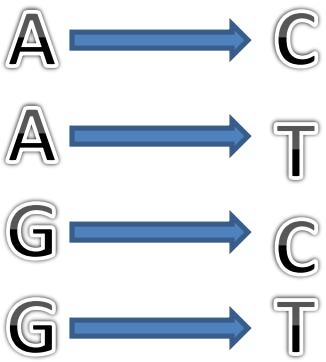

1 In replication, 5-bromouracil may become incorporated into DNA in place of thymine, producing an incorporated error.
2 5-Bromouracil may mispair with guanine in the next round of replication.
3 In the next replication, this guanine nucleotide pairs with cytosine, leading to a permanent mutation.
4 If 5-bromouracil pairs with adenine, no replication error occurs.
Strand separation
Incorporated error
Replication
Replicated error
Mutant

- The adenine analog **2-aminopurine (2AP),**
- Normally base pairs with thymine but occasionally forms base pair with cytosine

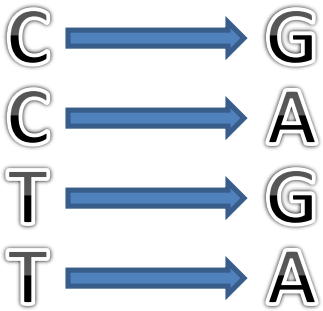
- Thus 2AP generates A→T to G→C transitions.

Transversions:

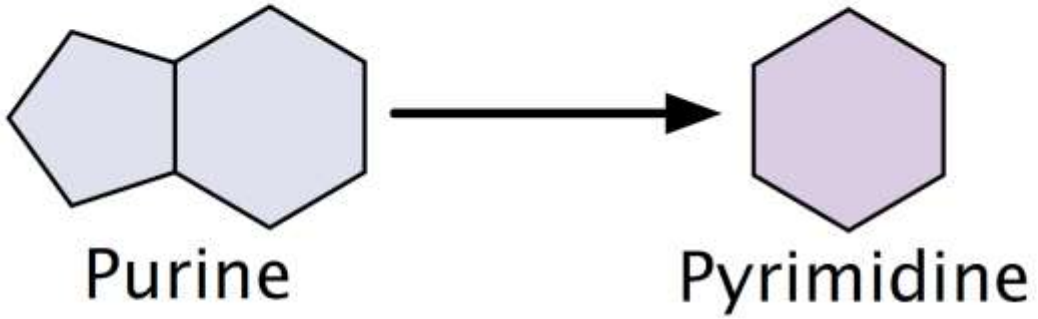
A purine is replaced by a pyrimidine



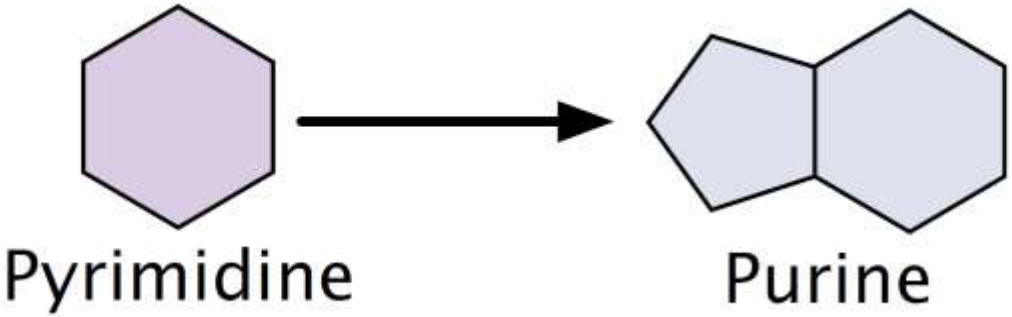
or a pyrimidine is replaced by a purine



Transversions

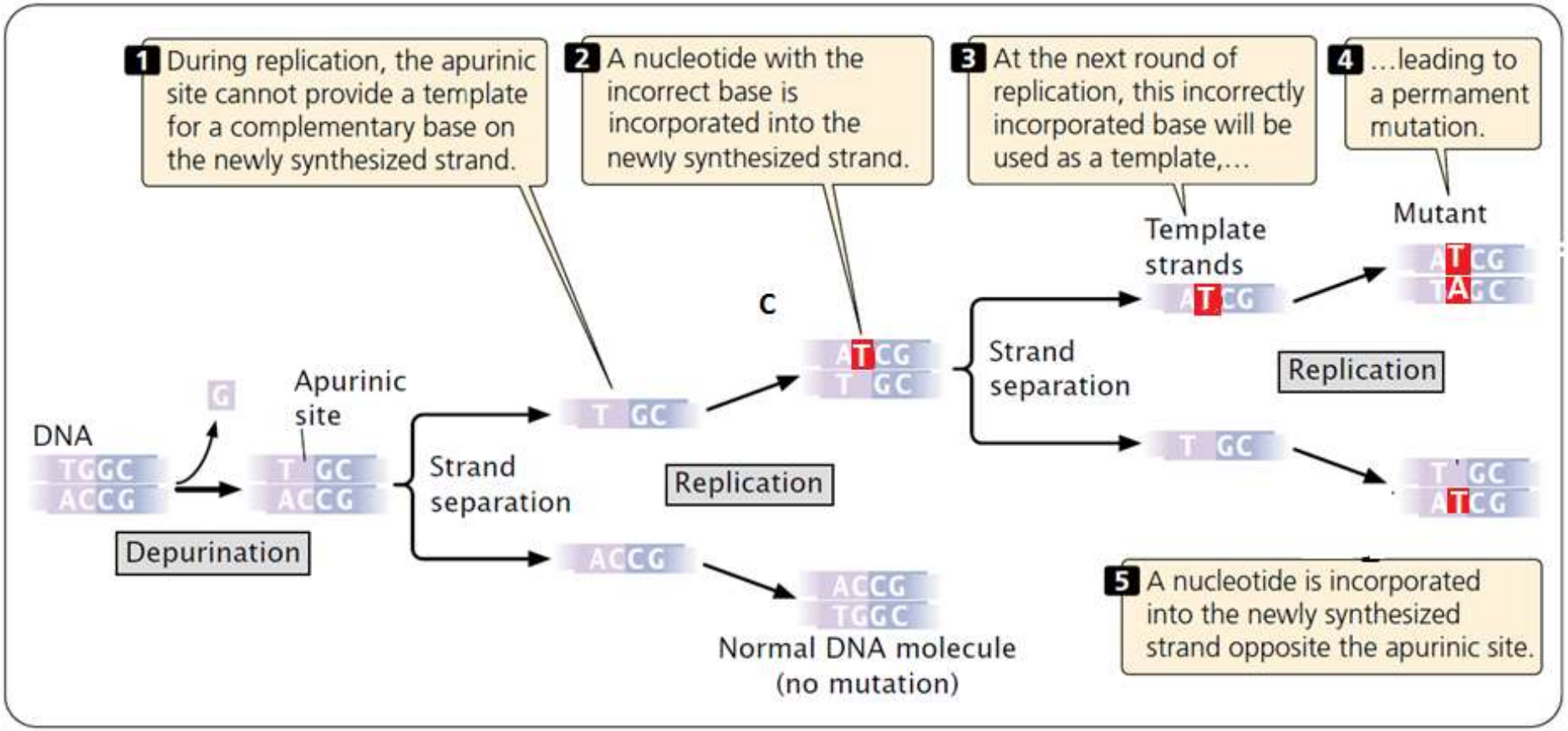


A → C
A → T
G → C
G → T

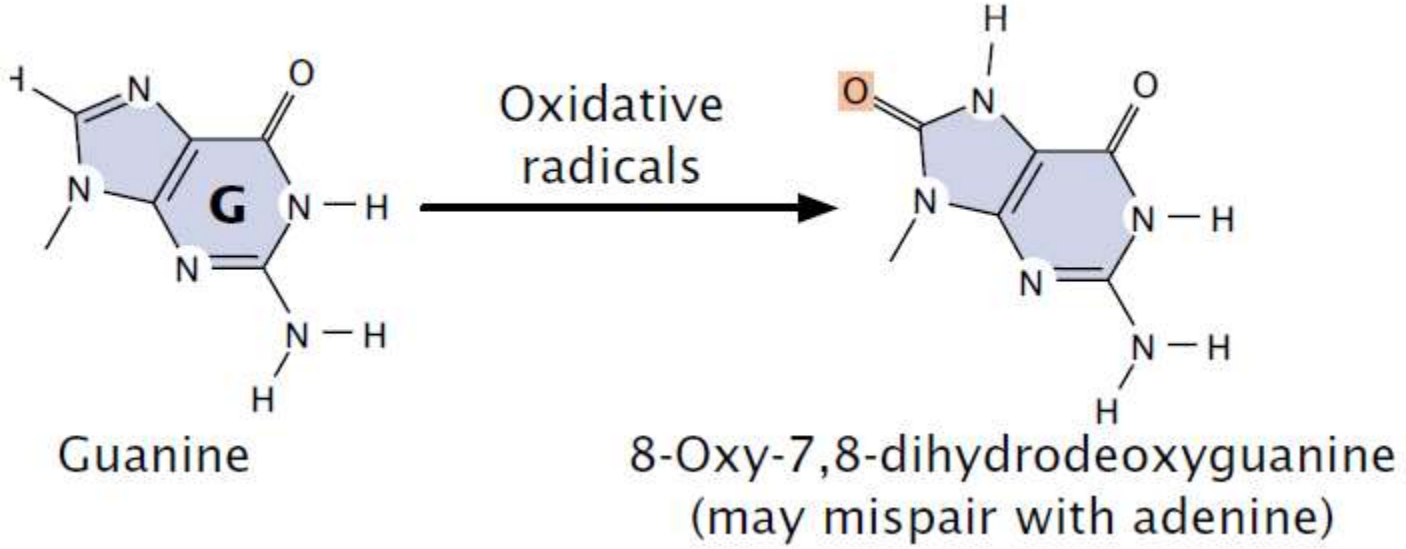


C → A
C → G
T → A
T → G

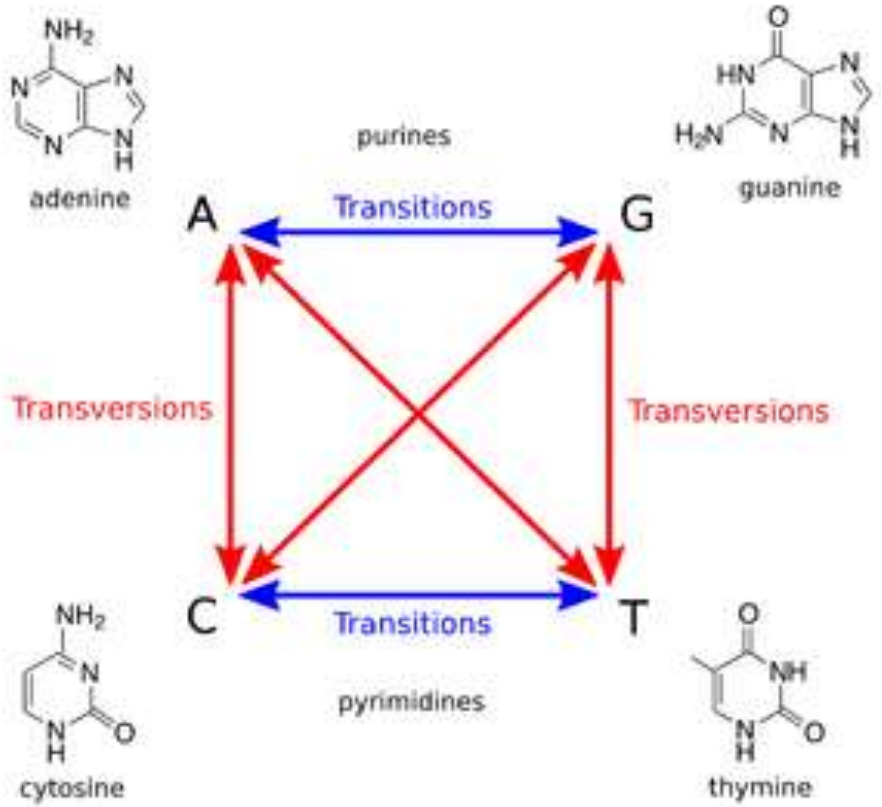
- Alkylating agents such as dimethyl sulfate, **nitrogen mustard,** and **ethylnitrosourea** often generates transversions.
- The alkylation of the N7 position of a purine nucleotide causes its subsequent depurination.
- The resulting gap in the sequence is filled in by an error-prone repair system
- Transversions arise when the missing purine is replaced by a pyrimdine


1 During replication, the apurinic site cannot provide a template for a complementary base on the newly synthesized strand.
2 A nucleotide with the incorrect base is incorporated into the newly synthesized strand.
3 At the next round of replication, this incorrectly incorporated base will be used as a template,…
4 …leading to a permament mutation.
Mutant
Template strands
C
DNA
Apurinic site
Depurination
Strand separation
Replication
Strand separation
Replication
Normal DNA molecule (no mutation)
5 A nucleotide is incorporated into the newly synthesized strand opposite the apurinic site.

- Reactive forms of oxygen damage DNA and induce mutations
- Causes chemical changes to DNA.
- For e.g.-oxidation converts guanine into 8-oxy-7,8-dihydrodeoxyguanine which mispairs with adenine instead of cytosine,
- Causing a G-C→TA transversion mutation.



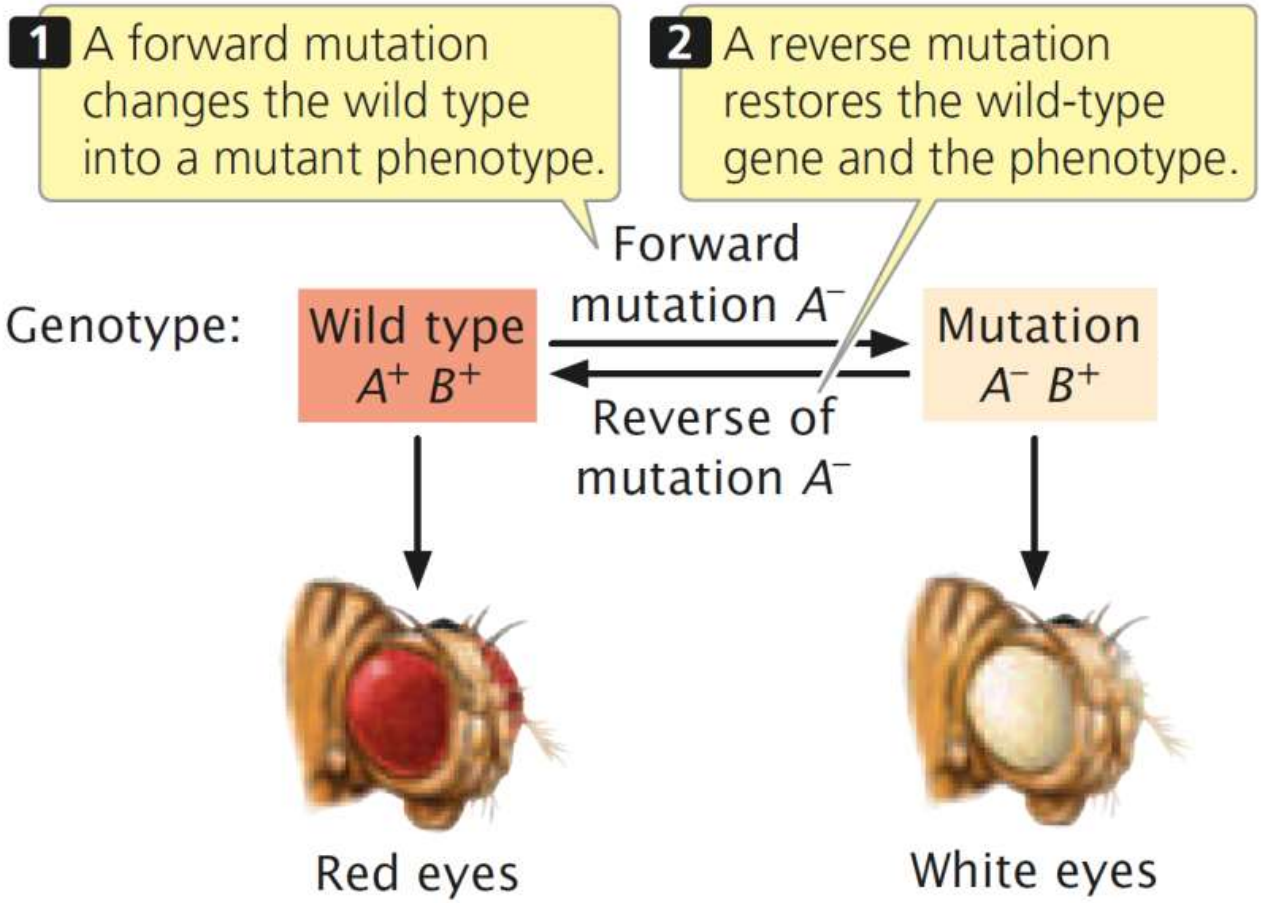
- The number of possible transversions is twice the number of possible transitions



BACK MUTATIONS

- Forward mutation:
  - ❖ A mutation that alters the wild type phenotype

- Back or Reverse mutation (reversion):
  - ❖ A mutation that changes a mutant phenotype back in to the wild type
  - ❖ **Back mutation to original sequence**
  - ❖ Mutation happens at the site of earlier mutation


1 A forward mutation changes the wild type into a mutant phenotype.
2 A reverse mutation restores the wild-type gene and the phenotype.
Genotype:
Wild type
A^+ B^+
Forward mutation A^-
Reverse of mutation A^-
Mutation
A^- B^+
Red eyes
White eyes

BACK MUTATIONS

- Mutagens which produces both A-T→G-C and G-C→A-T transitions are able reverse its mutations
- E.g.ethylmethanesulphonate

Suppressor mutation

- Suppresses the effect of other mutation
- Occurs at a site different from the site of original mutation
- Mask or compensate for the initial mutation without reversing it.
- Organism with a suppressor mutation is a double mutant but exhibits the phenotype of unmutated wild type
- Different from reverse mutation in which mutated site is reverted back into the wild type sequence

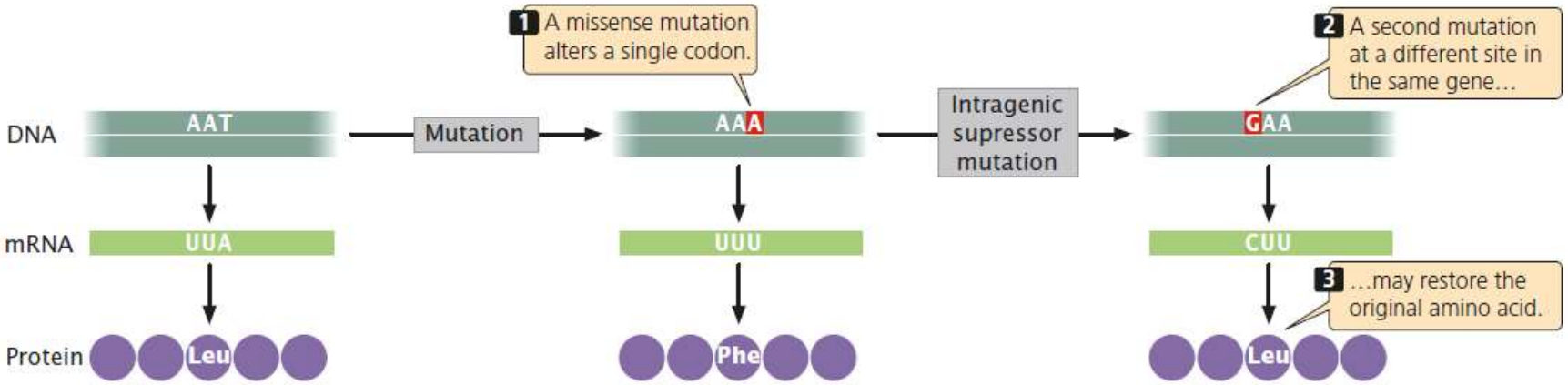
Are of two types

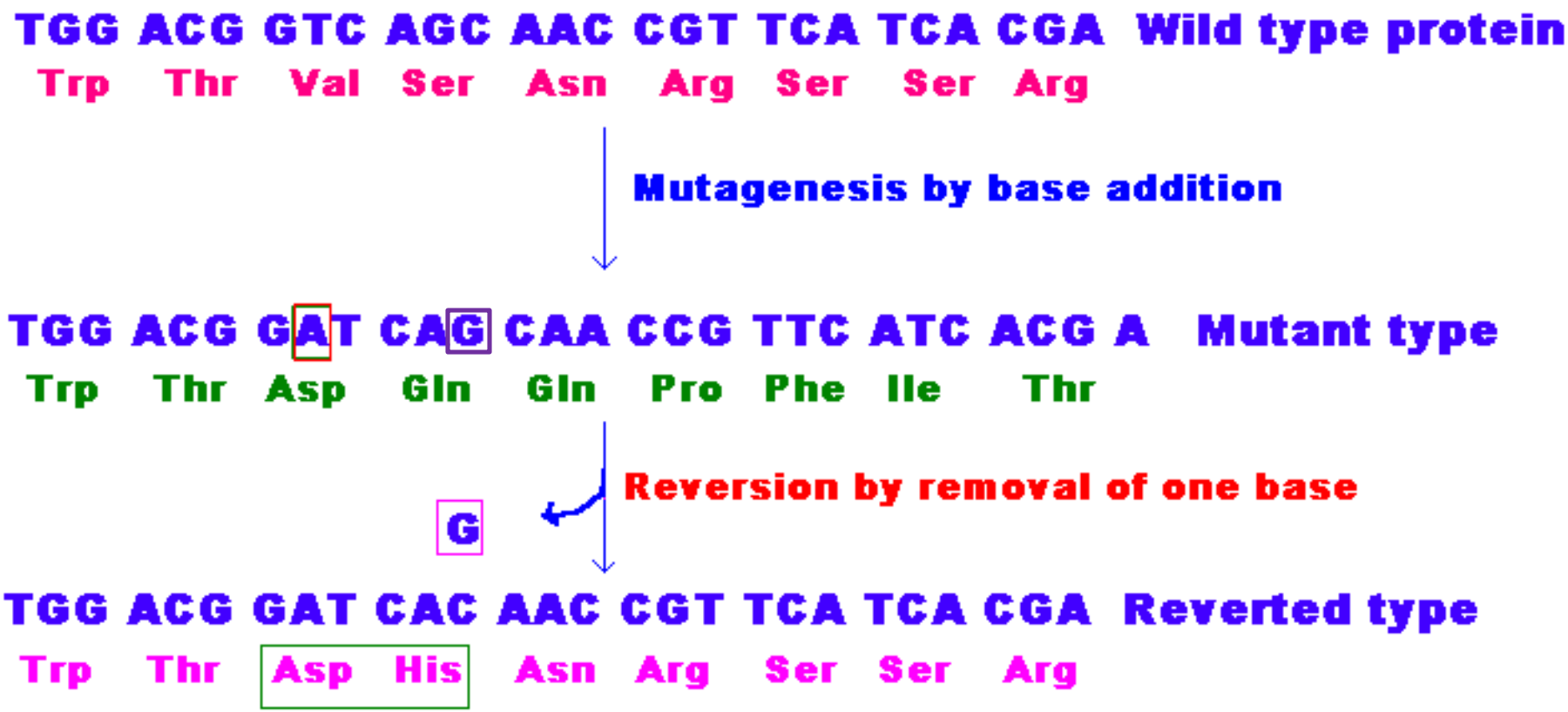
- Intragenic suppression
- Intergenic suppression

INTRAGENIC SUPPRESSION

- Intragenic suppression occurs when a second mutation in the same gene masks the occurrence of the original mutation.

- The original sequence actually is not restored.


1 A missense mutation alters a single codon.
2 A second mutation at a different site in the same gene…
3 …may restore the original amino acid.
DNA
AAT
Mutation
AAA
Intragenic supressor mutation
GAA
mRNA
UUA
UUU
CUU
Protein
Leu
Phe
Leu

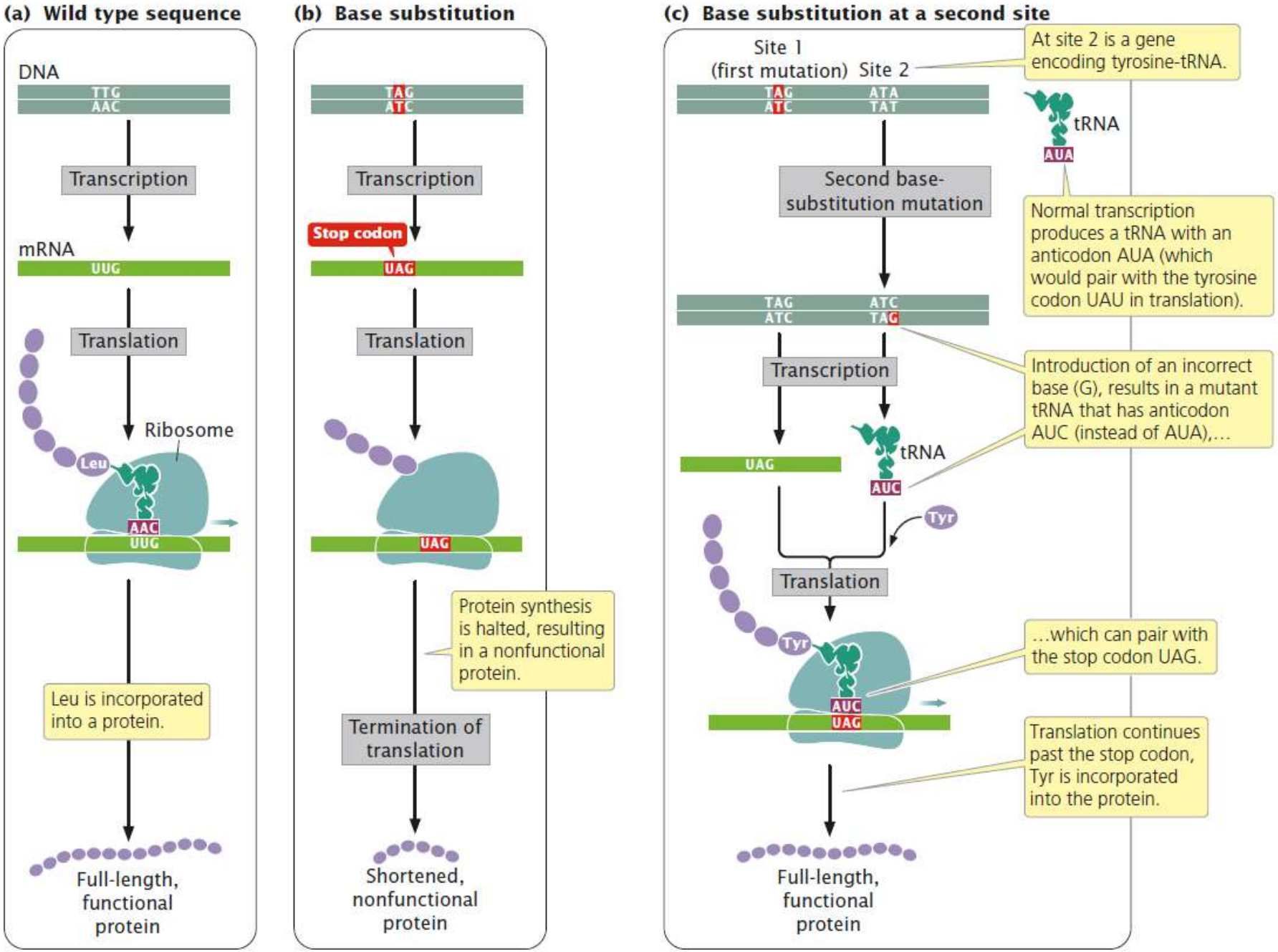


Apart from these two amino acids,
others are same in protein

INTERGENIC SUPPRESSIONS

- Occur in a gene that is different from the one bearing the original mutation.

- These suppressors sometimes work by changing the way that the mRNA is translated – nonsense suppression.


(a) Wild type sequence
DNA
TTG
AAC
Transcription
mRNA
UUG
Translation
Ribosome
Leu
AAC
UUG
Leu is incorporated into a protein.
Full-length, functional protein
(b) Base substitution
TAG
ATC
Transcription
Stop codon
UAG
Translation
UAG
Protein synthesis is halted, resulting in a nonfunctional protein.
Termination of translation
Shortened, nonfunctional protein
(c) Base substitution at a second site
Site 1 (first mutation)
Site 2
TAG ATA
ATC TAT
At site 2 is a gene encoding tyrosine-tRNA.
tRNA
AUA
Normal transcription produces a tRNA with an anticodon AUA (which would pair with the tyrosine codon UAU in translation).
Second base-substitution mutation
TAG ATC
ATC TAG
Transcription
Introduction of an incorrect base (G), results in a mutant tRNA that has anticodon AUC (instead of AUA),…
UAG
tRNA
AUC
Tyr
Translation
Tyr
AUC
UAG
…which can pair with the stop codon UAG.
Translation continues past the stop codon, Tyr is incorporated into the protein.
Full-length, functional protein

- Intergenic suppressors can also work through genic interactions

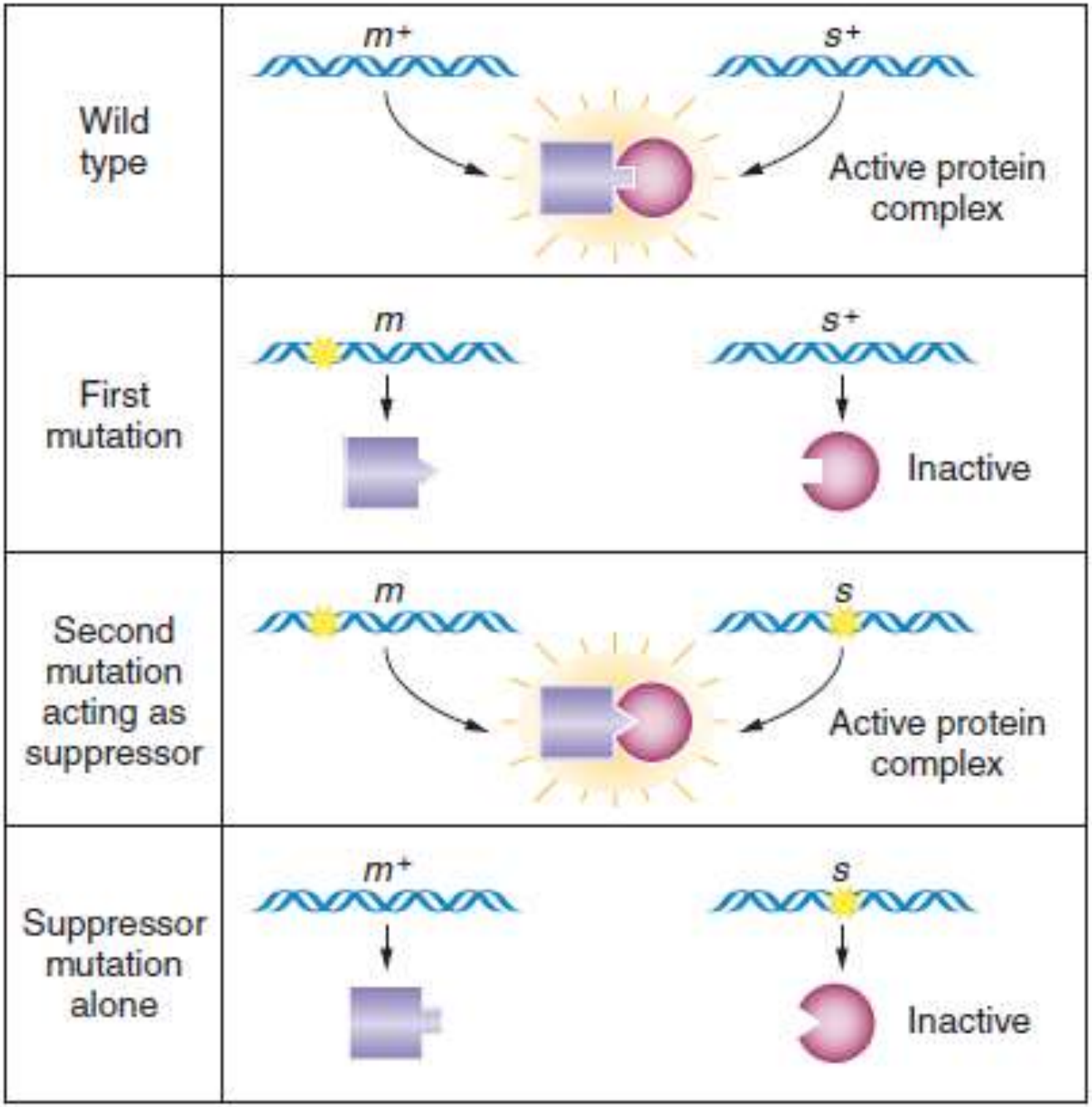
- Polypeptide chains that are produced by two genes may interact to produce a functional protein

- A mutation in one gene may alter the encoded polypeptide so that the interaction is destroyed

- Then a functional protein is no longer produced.

- A suppressor mutation in the second gene may produce a compensatory change in its polypeptide therefore restoring the original interaction.

- An example is seen in proteins that bind to each other
- A mutation causing shape change- lead to malfunction because it cannot bind to its partner protein.
- A mutation in gene for partner protein- may cause a shape change
- Now it could bind to the abnormal protein of the first gene, hence restoring an active complex.


Wild type
m+
s+
Active protein complex
First mutation
m
s+
Inactive
Second mutation acting as suppressor
m
s
Active protein complex
Suppressor mutation alone
m+
s
Inactive

THANK YOU…….