GENE MUTATION

A ***mutation*** is a heritable change in genetic information. Mutations are both the sustainer of life and the cause of great suffering. On the one hand, mutation is the source of all genetic variation, the raw material of evolution. The ability of organisms to adapt to environmental change depends on the presence of genetic variation in natural populations, and genetic variation is produced by mutation. On the other hand, many mutations have detrimental effects, and mutation is the source of many diseases and disorders.

Categories of Mutations

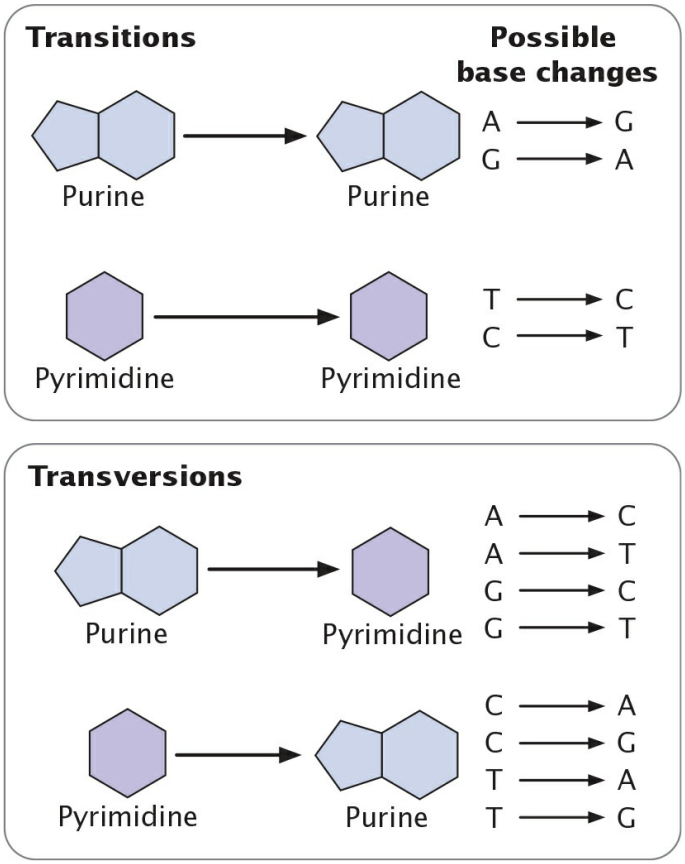
In multicellular organisms, we can distinguish between two broad categories of mutations: somatic mutations and germ-line mutations. ***Somatic mutations*** arise in somatic tissues, which do not produce gametes. When a somatic cell with a mutation divides (by mitosis), the mutation is passed on to the daughter cells, leading to a population of genetically identical cells (a clone). The earlier in development that a somatic mutation takes place, the larger the clone of cells that contain the mutation will be.

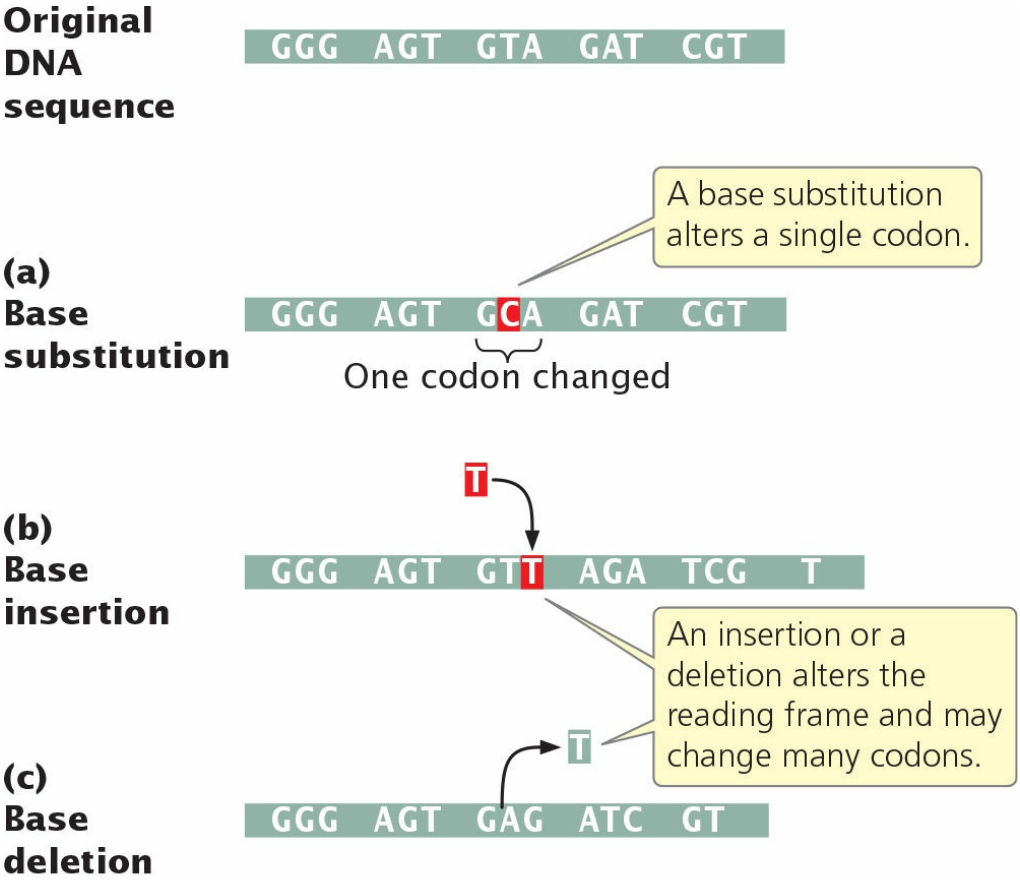
Germ-line mutations arise in cells that ultimately produce gametes. A germ-line mutation can be passed to future generations, producing offspring that carry the mutation in all their somatic and germ-line cells.

Types of Gene Mutations

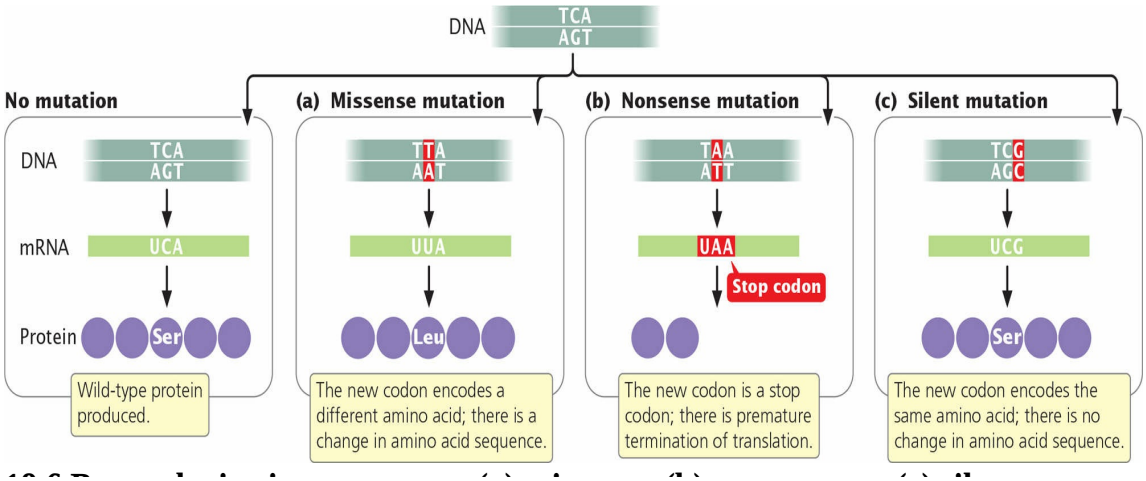
Based on the molecular nature, mutation can be classified into -

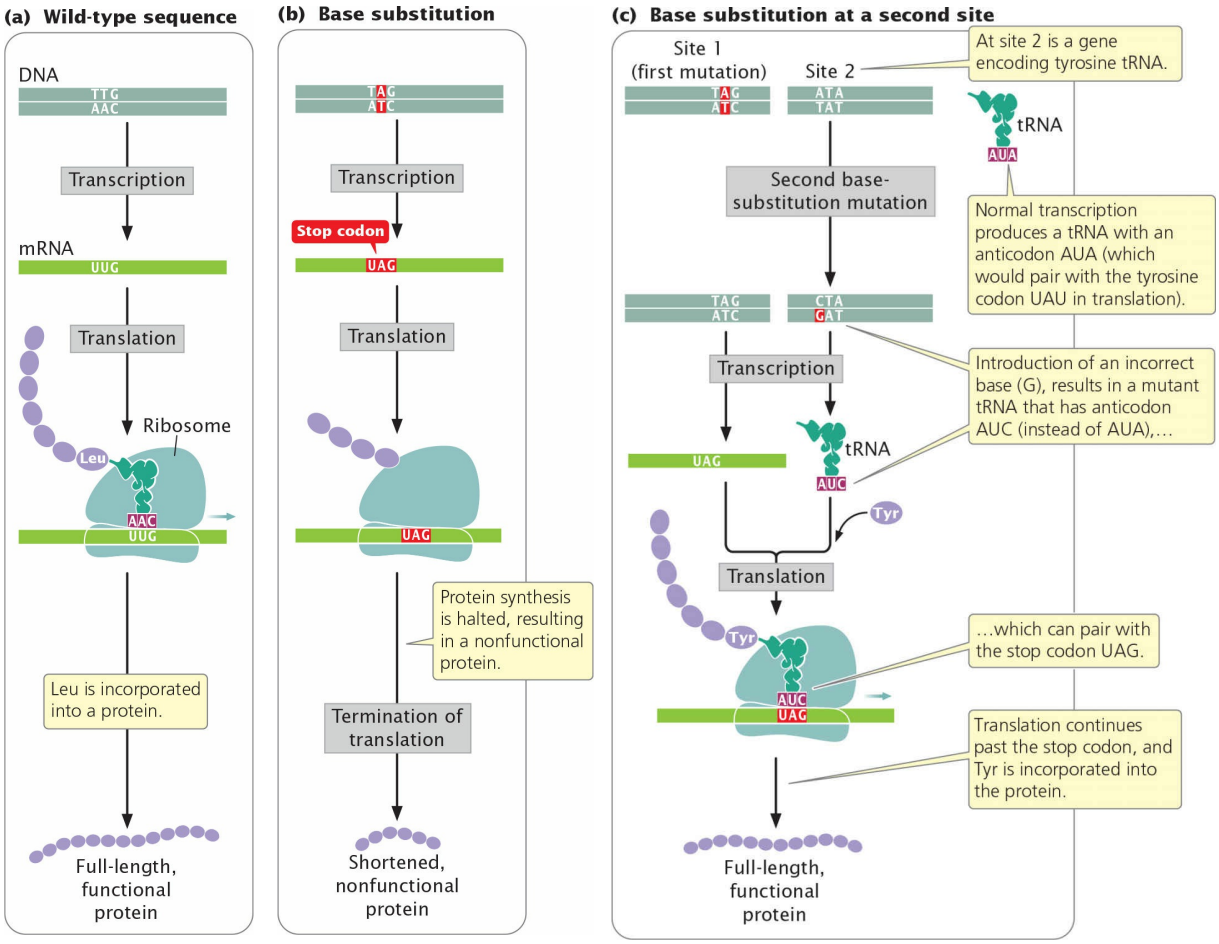
BASE SUBSTITUTIONS The simplest type of gene mutation is a ***base substitution***, the alteration of a single nucleotide in the DNA. There are two types of base substitutions. In a ***transition***, a purine is replaced by a different purine or, alternatively, a pyrimidine is replaced by a different pyrimidine. In a ***transversion***, a purine is replaced by a pyrimidine or a pyrimidine is replaced by a purine. The number of possible transversions is twice the number of possible transitions, but transitions arise more frequently because transforming a purine into a different purine or a pyrimidine into a different pyrimidine is easier than transforming a purine into a pyrimidine, or vice versa.


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


Original DNA sequence
GGG AGT GTA GAT CGT
(a) Base substitution
A base substitution alters a single codon.
GGG AGT GCA GAT CGT
One codon changed
(b) Base insertion
T
GGG AGT GTT AGA TCG T
An insertion or a deletion alters the reading frame and may change many codons.
(c) Base deletion
T
GGG AGT GAG ATC GT

INSERTIONS AND DELETIONS Another class of gene mutations contains ***insertions*** and ***deletions*** (collectively called *indels*): the addition or removal, respectively, of one or more nucleotide pairs. Although base substitutions are often assumed to be the most common type of mutation, molecular analysis has revealed that insertions and deletions are often more frequent. Insertions and deletions within sequences that encode proteins may lead to ***frameshift mutations***: changes in the reading frame of the gene. Frameshift mutations usually alter all amino acids encoded by the nucleotides following the mutation, so they generally have drastic effects on the phenotype. Some frameshifts also introduce premature stop codons, terminating protein synthesis early and resulting in a shortened (truncated) protein. Not all insertions and deletions lead to frameshifts, however; insertions and deletions consisting of any multiple of three nucleotides leave the reading frame intact, although the addition or removal of one or more amino acids may still affect the phenotype. Indels that do not affect the reading frame are called ***in-frame insertions*** and ***in-frame deletions***.




(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
At site 2 is a gene encoding tyrosine tRNA.
TAG
ATC
ATA
TAT
tRNA
AUA
Second base-substitution mutation
Normal transcription produces a tRNA with an anticodon AUA (which would pair with the tyrosine codon UAU in translation).
TAG
ATC
CTA
GAT
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, and Tyr is incorporated into the protein.
Full-length, functional protein