

Molecular Genetics IV

Mutation



All genetic variation arises from change in the nucleotide sequences of DNA.

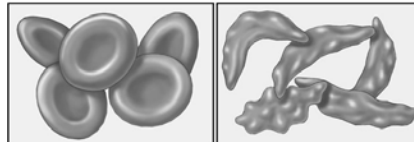
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Alleles of a gene commonly differ by only a single nucleotide pair in DNA. The nucleotide change results in an amino acid change in the protein and a change in the properties of the protein.

Sickle-cell anemia

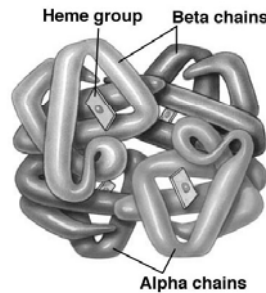
Sickle-cell anemia is due to a recessive gene. Homozygotes for the sickle-cell allele have sickle-cell anemia. They have problems delivering oxygen to their tissues when they are stressed and oxygen levels in their blood start to drop.

The gene codes for β -Hb, one of the two proteins that make up the hemoglobin molecule.



Normal red blood cells

Sickled red blood cells



β-Hb has an amino acid sequence containing 146 amino acids

In normal β-Hb, the sixth amino acid is GLU

In sickle-cell β-Hb, the sixth amino acid is VAL

In mRNA

GLU is coded by either GAA or GAG,

VAL is coded by GU-

A single base-pair change in DNA can account for the amino acid change

template: CTT → CAT
 coding: GAA → GTA
 codon: GAA → GUA
 amino acid: GLU → VAL

		Codon Chart				
		Second Letter		Letter		
		U	C	A	G	
F	U	UUU-Phe	UCU-Ser	UAU-Tyr	UGU-Cys	U
	U	UUC-Phe	UCC-Ser	UAC-Tyr	UGC-Cys	C
	A	UUA-Leu	UCA-Ser	UAA-Stop	UGA-Stop	A
	A	UUG-Leu	UCG-Ser	UAG-Stop	UGG-Trp	T
i	r	CUU-Leu	CCU-Pro	CAU-His	CGU-Arg	h
	r	CUC-Leu	CCC-Pro	CAC-His	CGC-Arg	i
	s	CUA-Leu	CCA-Pro	CAA-Gln	CGA-Arg	r
	s	CUG-Leu	CCG-Pro	CAG-Gln	CGG-Arg	d
L	e	AUU-Ile	ACU-Thr	AAU-Asn	AGU-Ser	U
	e	AUC-Ile	ACC-Thr	AAC-Asn	AGC-Ser	L
	t	AUA-Ile	ACA-Thr	AAA-Lys	AGA-Arg	e
	t	AUG-Met	ACG-Thr	AAG-Lys	AGG-Arg	A
e	r	GUU-Val	GCU-Ala	GAU-Asp	GGU-Gly	t
	r	GUC-Val	GCC-Ala	GAC-Asp	GGC-Gly	e
	G	GUA-Val	GCA-Ala	GAA-Glu	GGA-Gly	r
	G	GUG-Val	GCG-Ala	GAG-Glu	GGG-Gly	A

A single base pair change in DNA is called a **point mutation**

There are several different types of point mutations

missense - a change that results in a substitution of one amino acid for another (e.g. β-Hb for sickle-cell)

nonsense - a change that results in a stop codon replacing a normal amino acid codon

silent - a change in a base pair that results in no change in an amino acid

frameshift - due to an insertion or deletion of one or more base pairs in DNA

Frameshift mutations result in a change in the reading frame of the mRNA that is transcribed from them

Frameshift mutations result in a change in the reading frame of the mRNA that is transcribed from them. This results in a change in many amino acids in the protein.







↓

DNA: AAT TCC GGA ATTC- AAT CCG GAA TTC-
 mRNA: UUA AGG CCU UAA → UUA GGC CUU AAG
 protein: LEU ARG PRO STOP LEU GLY LEU LYS etc.

Frameshift mutations have disastrous effects on the structure and function of proteins.

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		Second Letter		Letter		
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	U	UUC-Phe	UCC-Ser	UAC-Tyr	UGC-Cys	C
	i	UUA-Leu	UCA-Ser	UAA-Stop	UGA-Stop	A
	U	UUG-Leu	UCG-Ser	UAG-Stop	UGG-Trp	T
r	C	CUU-Leu	CCU-Pro	CAU-His	CGU-Arg	U
	C	CUC-Leu	CCC-Pro	CAC-His	CGC-Arg	i
	t	CUA-Leu	CCA-Pro	CAA-Gln	CGA-Arg	r
	C	CUG-Leu	CCG-Pro	CAG-Gln	CGG-Arg	d
L	A	AUU-Ile	ACU-Thr	AAU-Asn	AGU-Ser	U
	e	AUC-Ile	ACC-Thr	AAC-Asn	AGC-Ser	L
	t	AUA-Ile	ACA-Thr	AAA-Lys	AGA-Arg	e
	A	AUG-Met	ACG-Thr	AAG-Lys	AGG-Arg	C
e	r	GUU-Val	GCU-Ala	GAU-Asp	GGU-Gly	U
	r	GUC-Val	GCC-Ala	GAC-Asp	GGC-Gly	e
	G	GUA-Val	GCA-Ala	GAA-Glu	GGA-Gly	r
	G	GUG-Val	GCG-Ala	GAG-Glu	GGG-Gly	A

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Mutation	Example result
NO MUTATION 	Normal B protein is produced by the B gene.
POINT MUTATION Base substitution Substitution of one or a few bases 	B protein is inactive because changed amino acid disrupts function.
Insertion Addition of one or a few bases 	B protein is inactive because inserted material disrupts proper shape.
Deletion Loss of one or a few bases 	B protein is inactive because portion of protein is missing.
CHANGES IN GENE POSITION Transposition 	B gene or B protein may be regulated differently because of change in gene position.
Chromosomal rearrangement 	B gene may be inactivated or regulated differently in its new location on chromosome.

In addition to point mutations, rearrangements of the DNA can result in a change in the expression of genes.

Transpositions - movement of genes from one position in the genome to another.

Chromosomal rearrangements - inversions of whole sets of genes or translocations of genes from one chromosome to another.

Major rearrangements may or may not have phenotypic consequences.

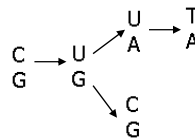
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What causes mutations?

DNA replication is very accurate, but DNA polymerase is not 100% accurate. Mutations that are not due to external factors are called **spontaneous mutations**.

Our body temperature (37C) increases the rate of spontaneous mutation. The base C spontaneously converts to the base U readily at high temperatures.

A CG base pair can become a UG base pair. If the mismatch is not detected and repaired before DNA replication begins, the U will be paired with an A during replication. The UG will thus become an UA and a CG base pair. Replacement of the U or further replication will result in the UA becoming an TA base pair. So, heat causes CG base pairs to become TA base pairs.



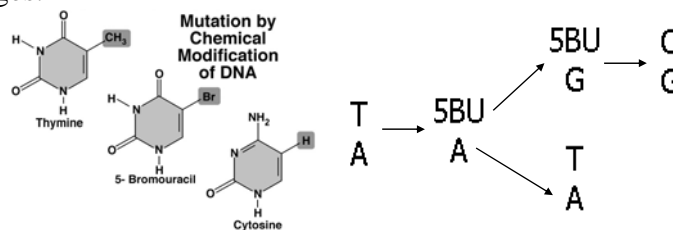
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Environmental factors also influence the rate of mutation.

Many chemicals cause mutations. Some are very powerful mutagens:

Nitrous acid - HNO_2 - causes GC base pairs to become AT base pairs, and AT base pairs to become GC base pairs. The salt of nitrous acid (nitrite) can be found in preserved meats and is mutagenic.

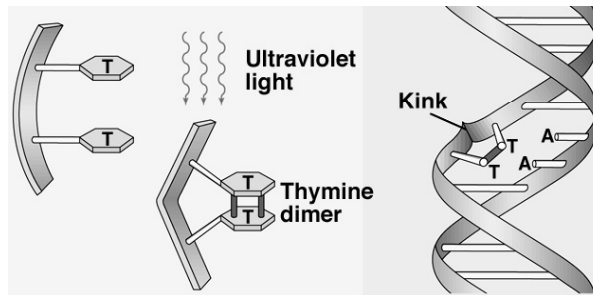
5-Bromouracil is a **base analog**. It can be incorporated into DNA and pair with A or G. It results in AT to GC changes or GC to AT changes.



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ionizing radiation - X-rays, nuclear radiation
 cause mutations by creating highly reactive free radicals
 can cause minor or major mutations
 Can react with DNA and cause breaks in the DNA backbone
 This may destroy individual genes, or result in loss of whole
 sets of genes through loss of pieces of chromosomes

UV rays from sunlight result in the formation of TT dimers



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T-T dimers can be repaired, but if they remain unrepaired until replication, the opposite strand will be replicated incorrectly. DNA polymerase will skip the bases included in the dimer, and a 2 nucleotides will be lost from the DNA.



A loss of two bases results in a frameshift mutation.

The human genetic disease Xeroderma pigmentosa results from the inability to repair TT dimers. Affected individuals are extremely sensitive to sunlight and very liable to develop skin cancer.

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