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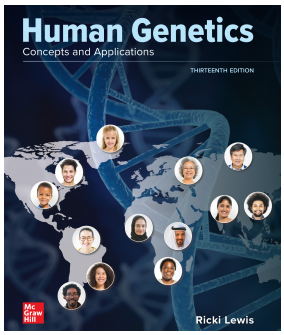

Chapter 12

Gene Mutation

Thirteenth Edition

Ricki Lewis

1

Learning Outcomes 1

1. Distinguish between mutation and mutant.
2. Define *polymorphism*.
3. Distinguish between germline and somatic mutations.
4. Describe mutations in the genes that encode beta globin and collagen.
5. Provide examples of how mutations in a single gene can cause more than one illness.
6. Explain how mutations arise spontaneously and how they may be induced.
7. Describe the two types of single-base mutations.

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Learning Outcomes 2

8. Explain the consequences of a splice-site mutation.
9. Discuss mutations that add, remove, or move DNA nucleotides.
10. Describe how pseudogenes and transposons can cause mutations.
11. Give examples of how the location of a mutation in a gene affects the phenotype.
12. Describe a conditional mutation.
13. List the types of damage that DNA repair mechanisms fix.
14. Describe the types of DNA repair.

3

The Nature of Gene Variants 1

The terms mutation and polymorphism each denote a genetic change from the wild type (most common form).

A **mutation** is change in a DNA sequence is rare in a population and typically affects the phenotype.

A **polymorphism** simply means many forms.

- It is a change in a gene that is less rare than a mutation and more prevalent in a population.

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The Nature of Gene Variants 2

- The sequencing of many genomes shows that a DNA base change that is a mutation in one population may be a harmless polymorphism in another, due to the effects of other genes and different environments.
- The distinction between the two terms reflects gene function as well as frequency.
- Because of the confusion between the terms mutation and polymorphism, the term "**gene variant**" is being used for both terms.

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The Nature of Gene Variants 3

The effect of mutations vary.

- "Loss-of-function" mutations—Recessive
- "Gain-of-function" mutations—Dominant

The term **mutant** refers to phenotype.

- Usually connotes an abnormal or unusual, or even uncommon variant that is nevertheless "normal"

Mutations are important to evolution.

Our evolutionary relatedness to other species allows us to study many mutations in nonhuman species.

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Germline and Somatic Mutation

Germline mutation

- Change occurs during the DNA replication that precedes meiosis
- Transmitted to the next generation of individuals

Somatic mutation

- Happens during DNA replication before a mitotic cell division
- Affect only cells that descend from changed cell
- A person with a somatic mutation has **somatic mosaicism**

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Somatic Mutation

A dog with genotype *e/e* of the *MC1R* color gene is golden or cream-colored, whereas a dog who is genotype *E/e* is black or chocolate.

- A somatic mutation before birth can cause a pigment patch

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Somatic Mosaicism 1

When somatic cells mutate in an individual, not all the cells in that individual have that mutation.

Because not all the cells are affected by the mutation, the individual has somatic mosaicism.

- Patterns arise as affected cells migrate during development.

This is what happens in Proteus syndrome

- The few hundred patients have overgrowth of skin and bone, but only in the body parts that bear a mutation in the gene *AKT1*

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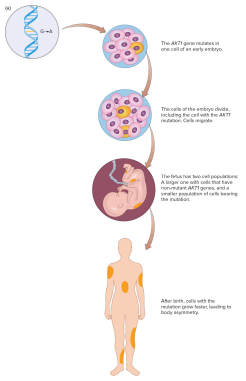
Somatic Mosaicism 2



a: Source: The Proteus Syndrome Foundation, UK

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Somatic Mosaicism 3

(b)

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Mutations Alter Proteins

Identifying how a mutation causes symptoms has clinical applications, and also reveals the workings of biology

Examples of mutations that cause disease are those of the:

- Beta globin gene
- Collagen genes

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Sickle Cell Disease 1

First inherited illness understood at the molecular level

Results from a single DNA base change in the β-globin gene, which replaces glutamic acid (6th position) with valine

- Hemoglobin molecules aggregate into long, curved rods, that deform the red blood cell
  - Sickled RBCs lodge in narrow blood vessels, cutting off local blood supplies
    - Cause great pain in the blocked body parts
  - Sickled RBCs are destroyed in the liver and spleen
    - Cause anemia

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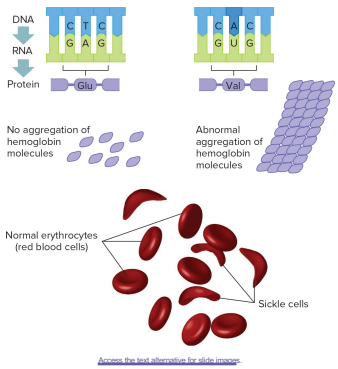
Sickle Cell Disease 2



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Thalassemia

- Caused by another beta hemoglobin mutation
- Too few beta globin chains
- Excess of alpha globin prevents formation of hemoglobin molecules
- Liberated iron slowly damages heart, liver, and endocrine glands
- Thalassemia minor (heterozygous)
- Thalassemia major (homozygous for mutation and more severe)

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Collagen

A major component of connective tissue

- Bone, cartilage, skin, ligament, tendon, and tooth dentin

More than 35 collagen genes encode more than 20 types of collagen molecules

- Other genes affect collagen too

Mutations in these genes, not surprisingly, lead to a variety of medical problems

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Collagen Disorders

Table 12.1 Some Collagen Disorders

Disorder	Mutations (Genotype)	Signs and Symptoms (Phenotype)
Alport syndrome	Mutations in any of three genes (*COL4A3, COL4A4, COL4A5*) affect type IV collagen, which disrupts tissue boundaries.	Deafness and inflamed kidneys
Chondrodysplasia	Deletion, insertion, or missense mutation replaces Gly with bulky amino acids in *COL2A1* type II collagen gene.	Stunted growth, deformed joints
Dystrophic epidermolysis bullosa	Mutation in *COL7A1* gene that encodes type VII collagen breaks down fibrils that attach epidermis to dermis.	Skin blisters upon any touch
Ehlers-Danlos syndrome	Diverse mutations in at least a dozen genes affect collagens or the molecules to which they bind.	Stretchy, easily scarred skin, lax joints
Osteoarthritis	Missense mutation in α1 collagen gene (*COL1A1*) substitutes Cys for Arg.	Painful joints
Osteogenesis imperfecta type I	Inactivation of α1 collagen gene (*COL1A1 or COL1A2*) reduces number of collagen triple helices by 50%.	Easily broken bones; blue eye whites; deafness
Stickler syndrome	Nonsense mutations in type II procollagen gene (*COL2A1 or COL11A1*) reduce number of collagen molecules.	Joint pain, degeneration of vitreous gel and retina

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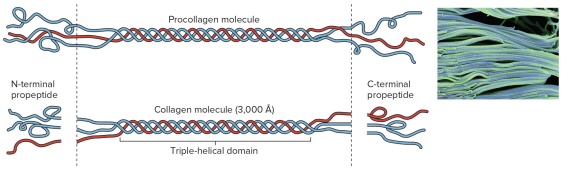
Collagen Has a Precise Structure

Longer precursor, procollagen is trimmed to form collagen.



 (photo): Science Photo Library RF/Getty Images 18

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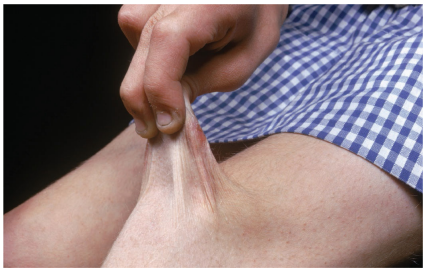
Ehlers-Danlos Syndrome

A mutation prevents procollagen chains from being cut.

- Collagen molecules cannot assemble, and so skin becomes stretchy.



 Biophoto Associates/Science Source

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How Mutations Cause Disease

Disease	Protein	Mutations (Genotype)	Signs and Symptoms (Phenotype)
Cystic fibrosis	Cystic fibrosis transmembrane regulator (CFTR)	Missing amino acid or other variant alters conformation of chloride channels in certain epithelial cell plasma membranes. Water enters cells, drying out secretions.	Frequent lung infection, pancreatic insufficiency
Duchenne muscular dystrophy	Dystrophin	Deletion eliminates dystrophin, which normally binds inner face of muscle cell to plasma membrane. Muscles weaken.	Gradual loss of muscle function
Familial hypercholesterolemia	LDL receptor	Deficient LDL receptors cause cholesterol to accumulate in blood.	High blood cholesterol, early heart disease
Hemophilia B	Factor IX	Absent or deficient clotting factor causes hard-to-control bleeding.	Slow or absent blood clotting
Huntington disease	Huntingtin	Extra bases add amino acids to the protein, which impairs certain transcription factors and proteasomes.	Uncontrollable movements, personality changes
Marfan syndrome	Fibrillin or transforming growth factor β receptor	Deficient proteins in lenses cause cataracts and in the wall of the aorta cause aneurysm (bursting).	Long limbs, weakened aorta, spindly fingers, sunken chest, lens dislocation
Neurofibromatosis type 1	Neurofibromin	Defect in protein that normally suppresses activity of a gene that causes cell division, leading to abnormal growths.	Pigmented skin patches and benign tumors of nervous tissue beneath skin

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Allelic Diseases 1

Different disease phenotypes caused by mutations in the same gene

Result from mutations in different parts of the gene

- Be localized (a single base change)
- Catastrophic (a missing gene)
- Alter the protein in ways that affect its interactions with other proteins

Allelic diseases may arise from a mutation that affects a protein that is used in different tissues.

- Some researchers are reclassifying cystic fibrosis as two allelic diseases, based on whether the lungs are affected.

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Allelic Diseases 2

Gene	Function	Associated Diseases
ATP7A	Copper transport	Menkes ("kinky hair") disease; peripheral neuropathy
DMD	Dystrophin muscle protein	Duchenne and Becker muscular dystrophy
FBN1	Encodes fibrillin-1, which forms tiny fibrils outside cells; a connective tissue protein	Marfan syndrome; systemic sclerosis (scleroderma; "stiff skin syndrome")
FGFR3	Fibroblast growth factor	Two types of dwarfism
GBA	Glucocerebrosidase	Gaucher disease; Parkinson disease
PSEN1	Presenilin 1 (enzyme part that trims membrane proteins)	Acne inversa; Alzheimer disease
RET	Oncogene (causes cancer)	Multiple endocrine neoplasia; Hirschsprung disease
TRPV4	Calcium channel	Peripheral neuropathy; spinal muscular atrophy

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Causes of Mutations

Mutations may occur spontaneously or by exposure to a chemical or radiation.

An agent that causes a mutation is called a **mutagen.**

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Spontaneous Mutation 1

De novo or new mutations

Not caused by exposure to known mutagen

Result from errors in DNA replication

DNA bases have slight chemical instability

- Exist in alternating forms called tautomers
- As replication fork encounters unstable tautomers, mispairing can occur

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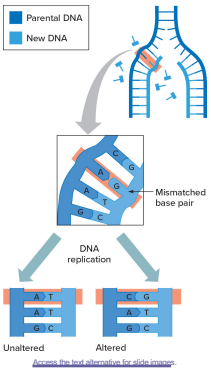
Spontaneous Mutation 2



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Spontaneous Mutation Rate

Rate differs between genes.

- Larger genes usually have higher mutation rates.

Each individual has multiple new mutations.

Spontaneous mutation also manifests as **gonadal mosaicism**.

- A parent has a mutation in some sperm or oocytes, because a spontaneous mutation occurred in the developing testis or ovary

Mitochondrial genes mutate at a higher rate than nuclear genes because they can't repair their DNA.

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Determining Mutation Rate

Estimates of spontaneous mutation rate can be derived from observation of new, dominant traits

For autosomal genes:

- Mutation rate = # of new cases/2*X*, where *X* = # of individuals examined
- The denominator has a factor of 2 to account for the nonmutated homologous chromosome.

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Mutational Hot Spots

In some genes, mutations are more likely to occur in regions called hot spots

Short repetitive sequences

- Pairing of repeats may interfere with replication or repair enzymes

Palindromes

- These sequences read the same, in a 5′ to 3′ direction, on complementary strands
- Often associated with insertions or deletions

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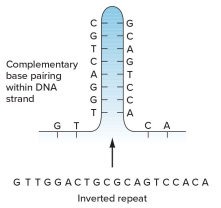
DNA Symmetry Increases the Likelihood of Mutation

Repeat of a nucleotide A A A A A A A A A

Direct repeat of a dinucleotide G C G C G C G C

Direct repeat of a trinucleotide T A C T A C T A C



Palindrome G A A T T C / C T T A A G

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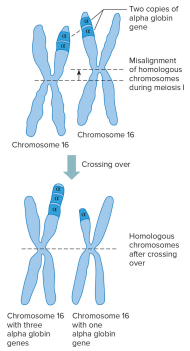
Gene Duplication and Deletion

The blood disease alpha thalassemia illustrates the confusing effect of direct (as opposed to inverted) repeats of an entire gene.

- The repeated alpha globin genes are prone to mutation by mispairing during meiosis.



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Induced Mutations

Caused by **mutagens**, many are also **carcinogens** and cause cancer

Examples:

- Alkylating agents—Remove a base
- Acridine dyes—Add or remove base
- X rays—Break chromosomes
- UV radiation—Creates thymine dimers

Site-directed mutagenesis—Changes a gene in a desired way

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Ames Test

An *in vitro* test of the mutagenicity of a substance

One version uses *Salmonella* bacteria with mutation in gene for histidine

- Bacteria are exposed to test substance
- Growth on media without histidine is recorded
- Bacteria only grow if mutations have occurred

Because many mutagens are also carcinogens, the substances that the Ames test identifies as mutagens may also cause cancer.

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Exposure to Mutagens

An organism may be exposed to a mutagen intentionally, accidentally, or naturally.

- Workplace
- Industrial accidents
  - Chernobyl Nuclear Power Station in Ukraine
- Medical treatments
  - X-rays
- Weapons
- Natural sources
  - Cosmic rays, sunlight, and radioactive substances in the earth's crust

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Types of Mutations 1

Mutations can be classified in several ways

- By whether they remove, alter, or add a function
- By exactly how they structurally alter DNA

The same single-gene disease can result from different types of mutations.

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Types of Mutations 2

Table 12.4
A sentence comprised of three-letter words analogies to the effects of mutations on a gene's DNA sequence:

Normal	THE ONE BIG FLY HAD ONE RED EYE
Missense	THQ ONE BIG FLY HAD ONE RED EYE
Nonsense	THE ONE BIG
Frameshift	THE ONE QBI GFL YHA DON ERE DEY
Deletion	THE ONE BIG HAD ONE RED EYE
Insertion	THE ONE BIG FLY WET HAD ONE RED EYE
Duplication	THE ONE BIG FLY FLY HAD ONE RED EYE
Expanding mutation	
Generation 1	THE ONE BIG FLY HAD ONE RED EYE
Generation 2	THE ONE BIG FLY FLY FLY HAD ONE RED EYE
Generation 3	THE ONE BIG FLY FLY FLY FLY FLY HAD ONE RED EYE

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Point Mutations

A change of in a single DNA base

Transition = Purine replaces purine or pyrimidine replaces pyrimidine

- A to G or G to A
- C to T or T to C

Transversion = Purine replaces pyrimidine or pyrimidine replaces purine

- A or G to T or C
- T or C to A or G

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Consequences of Point Mutations

Missense mutation = Replaces one amino acid with another

Nonsense mutation = Changes a codon for an amino acid into a stop codon

- Creates truncated proteins that are often nonfunctional
- Cells have a response to shortened proteins called **nonsense-mediated decay**

A stop codon that is changed to a coding codon lengthens the protein

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Splice Site Mutations 1

Alters a site where an intron is normally removed from mRNA

Can affect the phenotype if:

- Intron is translated into amino acids
  - Example: One cystic fibrosis mutation
- Exon is skipped
  - Phenomenon is called **exon skipping**
  - Example: Familial dysautonomia (FD)

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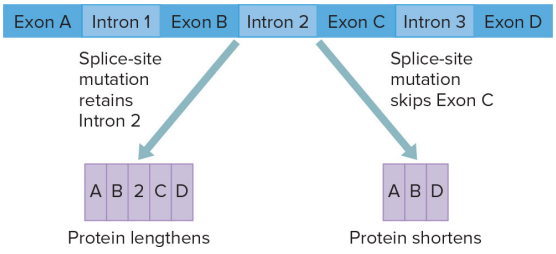
Splice Site Mutations 2



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Deletions and Insertions 1

The genetic code is read in triplets

Nucleotides changes not in multiples of three lead to disruptions of the reading frame

Cause a **frameshift mutation** and alter amino acids after mutation

Nucleotide changes in multiples of three will *not* cause a frameshift

- But they can still alter the phenotype

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Deletions and Insertions 2

A **deletion** removes genetic material

- Male infertility: Tiny deletions in the Y

An **insertion** adds genetic material

- Gaucher disease: Insertion of one base

A **tandem duplication** is an insertion of identical sequences side by side

- Charcot-Marie-Tooth disease: Tandem duplication of 1.5 million bases

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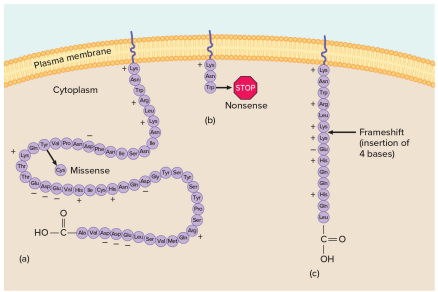
Different Mutations in a Gene Can Cause the Same Disease.

Example: Familial hypercholesterolemia



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Pseudogenes 1

A DNA sequence similar to a gene but which is not translated

May have evolved from original gene by duplication and acquired mutation

Crossing over between a pseudogene and functional gene can disrupt gene expression

- Some cases of Gaucher disease result from a crossover between the working gene that encodes the enzyme glucocerebrosidase and its pseudogene, which is 96% similar in sequence and is located 16,000 bases away

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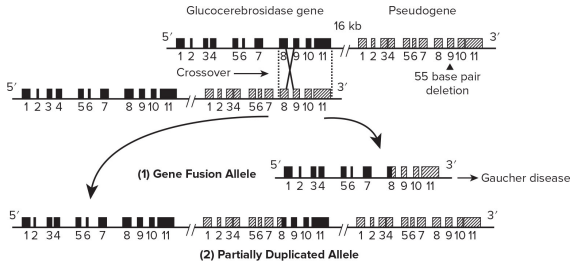
Pseudogenes 2



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Transposons

These “jumping genes” can alter gene function in several ways:

- They can disrupt the site they jump from
- They can shut off transcription of the gene they jump into
- They can alter the reading frame if they are not a multiple of three bases.

One example is a case of hemophilia A

- A transposon jumped from chromosome 22 into the factor VIII gene on the X chromosome

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Expanding Repeats 1

In an **expanding repeat**, a gene actually grows as a small part of the DNA sequence is copied and added

- If insertion is in coding sequence, the triplet repeats lead to extra amino acids, and the longer protein will harm the cells
  - Example: Huntington disease
- If insertion is in non-coding sequences, gene expression is blocked *before* a protein is even made
  - Example: Myotonic dystrophy type 1

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Expanding Repeats 2

- Some genes are particularly prone to expansion of repeats.
- Number of repeats correlates with earlier onset and more severe phenotype.
- **Anticipation** is the expansion of the triplet repeat with an increase in severity of phenotype with subsequent generations.

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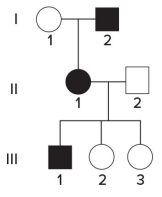
Expanding Repeats 3

Myotonic Dystrophy



Pedigree	Age of onset	Phenotype	Number of copies of GAC mRNA repeat
I	Older adulthood	Mild forearm weakness, cataracts	50–80
II	Mid-adulthood	Moderate limb weakness	80–700
III	Childhood	Severe muscle impairment, respiratory distress, early death	700+

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Copy Number Variants (CNV)

- Are sequences that vary in number of copies from person to person
- CNVs called **short tandem repeats (STRs)**
- CNVs may have no effect on the phenotype or they can disrupt a gene's function and harm health
- CNVs are particularly common among people who have behavioral disorders, such as attention deficit hyperactivity disorder (ADHD), autism, and schizophrenia.

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The Importance of Position

The degree that a mutation alters phenotype depends on:

- Where in the gene the change occurs
- How it affects conformation or expression of encoded protein

Examples—Hemoglobin and prions

- Certain mutations exert effects while other do not

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Globin Mutations

Associated Phenotype	Name	Mutation
Clinically silent	Hemoglobin (Hb) Wayne	Single-base deletion in alpha globin gene causes frameshift, changing amino acids 139 to 141 and adding amino acids
	Hb Grady	Nine extra bases add three amino acids between amino acids 118 and 119 of alpha chain
Oxygen binding	Hb Chesapeake	Change from arginine to leucine at amino acid 92 of beta chain
	Hb McKees Rocks	Change from tyrosine to STOP codon at amino acid 145 in beta chain
Anemia	Hb Constant Spring	Change from STOP codon to glutamine elongates alpha chain
	Hb S	Change from glutamic acid to valine at amino acid 6 in beta chain causes sickling
	Hb Leiden	Amino acid 6 deleted from beta chain
Protection against malaria	Hb C	Change from glutamic acid to lysine at amino acid 6 in beta chain causes mild sickling

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Factors That Lessen the Effects of Mutation 1

Silent mutations are mutations that do not alter the encoded amino acid

Example:

- A mutation from CAA to CAG alters the DNA, but the protein sequence remains unchanged
- CAA and CAG both code for glutamine
- These are called **synonymous codons**

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Factors That Lessen the Effects of Mutation 2

A **missense mutation** alters the encoded amino acid to another amino acid.

- Creates a nonsynonymous codon

Some nonsynonymous mutations are conservative

- Encode a chemically similar amino acid and may not alter function.

The impact of a missense mutation is not predictable from protein sequence alone.

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Factors That Lessen the Effects of Mutation 3

A **conditional mutation** produces a phenotype under particular conditions or environments.

Glucose-6-phosphate dehydrogenase deficiency

- Caused by 200 known mutations in the X-linked gene
- Glucose 6-phosphate dehydrogenase enzyme responds to oxidants, chemicals that strip electrons from other molecules.
  - High levels of oxidants occur when eating fava beans or taking certain antimalarial drugs.

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DNA Repair

Fortunately, DNA replication is very accurate—only 1 in 100 million or so bases is incorrectly incorporated.

Errors in DNA replication or damage to DNA create mutations.

- May result in cancer

Most errors and damage are repaired.

Type of repair depends upon the type of damage or error.

Organisms vary in their ability to repair DNA.

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Types of DNA Repair

In many modern species, three types of DNA repair mechanisms check the genetic material for mismatched base pairs.

- Photoreactivation repair
- Excision repair
- Mismatch repair

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Photoreactivation Repair

Enzymes called photolyases absorb energy from visible light and use it to detect and bind to pyrimidine dimers

- The extra bonds are then broken

Enables UV-damaged fungi to recover from exposure to sunlight

Humans do not have this type of repair

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Excision Repair 1

Pyrimidine dimers and surrounding bases are removed and replaced

Humans have two types of excision repair

Nucleotide excision repair

- Replaces up to 30 bases
- Corrects mutations caused by different insults

Base excision repair

- Replaces 1 to 5 bases
- Specific to oxidative damage

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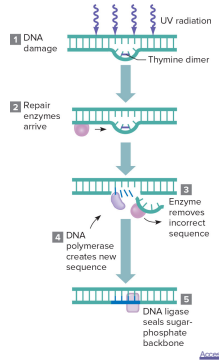
Excision Repair 2



1. DNA damage
2. Repair enzymes arrive
3. Enzyme removes incorrect sequence
4. DNA polymerase creates new sequence
5. DNA ligase seals sugar-phosphate backbone

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Mismatch Repair 1

Enzymes check newly replicated DNA for small loops that emerge from the double helix.

- Caused by nucleotides that do not base pair properly

The incorrect base is excised and replaced.

Proofreading is the detection of mismatches.

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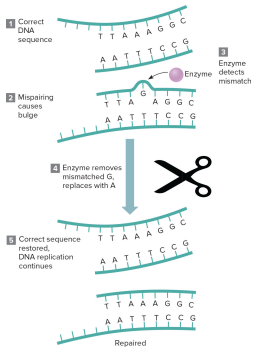
Mismatch Repair 2



1. Correct DNA sequence
2. Mispairing causes bulge
3. Enzyme detects mismatch
4. Enzyme removes mismatched G, replaces with A
5. Correct sequence restored, DNA replication continues

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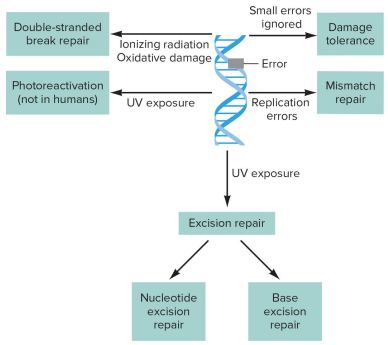
DNA Repair Mechanisms



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Failure of DNA Repair

If both copies of a repair gene are mutant, a disorder can result

The protein p53 monitors repair of DNA

- If damage is too severe, the p53 protein promotes programmed cell death or **apoptosis**

In DNA repair disorders, mutations and chromosome breaks persist.

- Mutations in repair genes greatly increase susceptibility to certain types of cancer following exposure to mutagens.

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DNA Repair Disorders

DNA repair disorders include:

- Trichothiodystrophy
- A form of inherited colon cancer
- Xeroderma pigmentosum
- Ataxia telangiectasia

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Trichothiodystrophy

At least five genes are involved

- At its worst, this condition causes dwarfism, intellectual disability, and brittle hair and scaly skin

Symptoms reflect accumulating oxidative damage

Faulty nucleotide excision repair or base excision repair or both

The trichothiodystrophies are unusual in that they do not increase cancer risk.

Only about 100 cases are known worldwide.

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Inherited Colon Cancer

Hereditary nonpolyposis colon cancer is a group of seven disorders also known as Lynch syndrome

- Affects 1/200 individuals and accounts for 3% of newly diagnosed colorectal cancers

Defect in mismatch repair which normally keeps a person's microsatellites all the same length.

HNPCC gene is on chromosome 2

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Xeroderma Pigmentosum 1

Autosomal recessive disorder

Results from mutations in any of seven genes

- It can reflect malfunction of nucleotide excision repair or deficient "sloppy" DNA polymerase
  - Thymine dimers remain and block replication

Only 250 cases worldwide

Affected individuals must avoid sunlight

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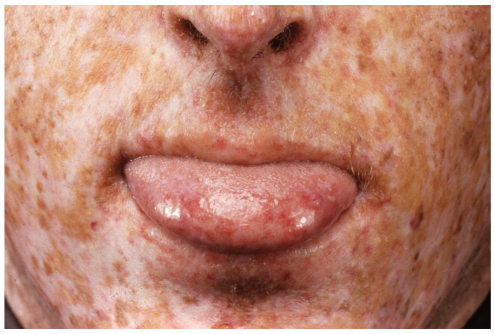
Xeroderma Pigmentosum 2



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Ataxia Telangiectasia

Autosomal recessive disorder

Results from defect in cell cycle checkpoint kinase

- Cells continue through cell cycle without pausing to inspect the new DNA

Individuals with AT have 50 times the risk of developing cancer over general population

AT is rare, but heterozygotes are not.

- They have a two- to sixfold increase in cancer risk

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