Mutations

Lecture 15
Objectives 1: Mutation

Define **mutation**.

Describe the **types** of mutations and their **effects** on the protein that is produced.

Distinguishing between **spontaneous** and **induced** mutations.

Distinguish between **somatic** and **germinal** mutations.

Explain why mutations are **not all harmful**.

Terms: **missense** mutation, **nonsense** mutation, **frameshift** mutation, **silent** mutation, **mutagen**
Objectives 2: Gene Expression

Explain how cells in all the different parts of your body develop such **different characteristics and functions.**

Contrast the roles of the **promoter** and **protein encoding** (structural) portions of a gene.

Describe the interactions of the **promoter** region of a gene, **transcription** factors, and **RNA polymerase** in the expression of a gene.
What are Mutations?

A mutation is any physical change in the genetic material (such as a gene or a chromosome).

More than 4,000 diseases are thought to stem from mutated genes inherited from our parents.
What are Mutations?

A mutation may or may not affect the amino acid sequence.

A mutation may or may not affect the phenotype.

Some specific mutations in a gene may have more adverse affects than other mutations in the same gene.

A mutation is not necessarily bad.
General Types of Mutations

Chromosomal Mutations

Changes in chromosome structure
- Deletion, duplication, inversion, or translocation.

Changes in chromosome number
- Polyploidy, aneuploidy

Point Mutations

Substitution of a single base with another
Addition or deletion of one or more nucleotides.
Mutations of Chromosomes
Genetic Mutations and their Effects on Proteins
### Table 12.2 The Genetic Code

<table>
<thead>
<tr>
<th>First Letter in Codon</th>
<th>Second Letter in Codon</th>
<th>Third Letter in Codon</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>UUU: Phenylalanine (Phe; F)</td>
<td>UCU: Serine (Ser; S)</td>
</tr>
<tr>
<td></td>
<td>UUC</td>
<td>UCC</td>
</tr>
<tr>
<td></td>
<td>UUA</td>
<td>UCA</td>
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<tr>
<td></td>
<td>UUG</td>
<td>UCG</td>
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<tr>
<td>C</td>
<td>CUU: Leucine (Leu; L)</td>
<td>CCU: Proline (Pro; P)</td>
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<tr>
<td></td>
<td>CUC</td>
<td>CCC</td>
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<td></td>
<td>CUA</td>
<td>CCA</td>
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<tr>
<td></td>
<td>CUG</td>
<td>CCG</td>
</tr>
<tr>
<td>A</td>
<td>AUU: Isoleucine (Ile; I)</td>
<td>ACU: Threonine (Thr; T)</td>
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<td></td>
<td>AUC</td>
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<td>AUG</td>
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<tr>
<td>G</td>
<td>GUU: Valine (Val; V)</td>
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<td>GUG</td>
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</table>

**U** | **C** | **A** | **G** |
--- | --- | --- | --- |
Phenylalanine (Phe; F) | Serine (Ser; S) | Tyrosine (Tyr; Y) | Cysteine (Cys; C) |
Leucine (Leu; L) | Proline (Pro; P) | Histidine (His; H) | Arginine (Arg; R) |
Isoleucine (Ile; I) | Threonine (Thr; T) | Asparagine (Asn; N) | Serine (Ser; S) |
Methionine (Met; M) | Alanine (Ala; A) | Aspartic acid (Asp; D) | Glycine (Gly; G) |
Valine (Val; V) | Alanine (Ala; A) | Glutamic acid (Glu; E) | Glycine (Gly; G) |

See Appendix C for chemical structures of amino acids.
Missense mutation

Substitutes a different amino acid

Original
TEMPLATE DNA code CTC (Glutamine - glu)

Mutation
TEMPLATE DNA code CAC (Valine - val)
Nonsense mutation

Inserts a stop codon before the end of the gene.

Original
TEMPLATE DNA code ATG (tyrosine - tyr)

Mutation
TEMPLATE DNA code ATT (STOP)
Silent mutations

Do not change the amino acid sequence

GAA and GAG code for Glutamic Acid (Glu).

GCU, GCC, GCA, and GCG all code for Alanine (Ala).

GGU, GGC, GGA, and GGG all code for Glycine (Gly)


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- Phenylalanine (Phe; F)
- Leucine (Leu; L)
- Leucine (Leu; L)
- Isoleucine (Ile; I)
- Methionine (Met; M) and “start”
- Valine (Val; V)

- Serine (Ser; S)
- Proline (Pro; P)
- Threonine (Thr; T)
- Alanine (Ala; A)

- Tyrosine (Tyr; Y)
- Cysteine (Cys; C)
- “Stop”
- “Stop”

- Histidine (His; H)
- Arginine (Arg; R)
- Asparagine (Asn; N)
- Serine (Ser; S)

- Glutamine (Gln; Q)
- Lysine (Lys; K)
- Aspartic acid (Asp; D)
- Glycine (Gly; G)

- Tryptophan (Trp; W)

See Appendix C for chemical structures of amino acids.
Percent of Mutations that are Silent

Expected: 

Observed: 25
a. Normal red blood cells

DNA → TRANSCRIPTION → mRNA → TRANSLATION → Protein

No aggregation of hemoglobin molecules

b. Sickled red blood cells

DNA → TRANSCRIPTION → mRNA → TRANSLATION → Protein

Abnormal aggregation of hemoglobin molecules

© Dr. Gopal Murli/Science Photo Library
Frameshift Mutations:

Additions or deletions of one or more nucleotides

Original
GAC-UAU-ACA codes for Asp-Tyr-Thr

Insertion
GAA-CUA-UAC-A codes for Glu-Leu-Tyr

Deletion
GAU-AUA-CA codes for Asp-Ile
Frameshift Mutations

Ribosomes have a "reading frame" that decodes mRNA in sets of three nucleotides (one codon) at a time.

There are no "punctuation marks" to delineate the codons, so adding or deleting one or more nucleotides in the DNA changes the "reading frame" of the codon.

The amino acid sequence in the protein from that point will all be changed, radically changing the shape and function of the protein.
Frameshift Mutations:

Adding or deleting **triplets** (three or multiples of three nucleotides) will add or delete one or more amino acids.

If the triplet(s) is/are added or deleted **between** two codons, there will be no disruption of the reading frame.

If the triplet(s) is/are are added or deleted **within** a codon, there will be a **temporary disruption** of the reading frame.
Frameshift Mutations:

Original
GAC-UAU-ACA codes for Asp-Tyr-Thr

Insert triplet between frame
GAC-AAA-UAU-ACA codes Asp-Lys-Tyr-Thr

Insert triplet within frame
GAA-AAC-UAU-ACA codes Glu-Asn-Tyr-Thr
Hemoglobin Mutants: Missense, Nonsense, and Frameshift

**Normal beta chain**
ATG GTG CAC CTG ACT CCT GAG GAG AAG TCT GCC GTT ACT GCC CTG TGG GCC AAG GTG AAC GTG GAT GAA GTT GGT GTT GGT GAG GCC CTG GGC
Val His Leu Thr Pro Glu Glu Lys Ser Ala Val Thr Ala Leu Trp Gly Lys Val Asn Val Asp Glu Val Gly Gly Glu Ala Leu Gly

**HbS Sickle cell (missense)**
ATG GTG CAC CTG ACT CCT GTG GAG AAG TCT GCC GTT ACT GCC CTG TGG GCC AAG GTG AAC GTG GAT GAA GTT GGT GTT GGT GAG GCC CTG GGC
Val His Leu Thr Pro Val Glu Lys Ser Ala Val Thr Ala Leu Trp Gly Lys Val Asn Val Asp Glu Val Gly Gly Glu Ala Leu Gly

**HbC (missense)**
ATG GTG CAC CTG ACT CCT AAG GAG AAC TCT GCC GTT ACT GCC CTG TGG GCC AAG GTG AAC GTG GAT GAA GTT GGT GTT GGT GAG GCC CTG GGC
Val His Leu Thr Pro Lys Glu Lys Ser Ala Val Thr Ala Leu Trp Gly Lys Val Asn Val Asp Glu Val Gly Gly Glu Ala Leu Gly

**HbThalassemia (nonsense)**
ATG GTG CAC CTG ACT CCT GAG GAG AAG TCT GCC GTT ACT GCC CTG TGG GCC TAG GTG AAC GTG GAT GAA GTT GGT GTT GGT GAG GCC CTG GGC
Val His Leu Thr Pro Glu Glu Lys Ser Ala Val Thr Ala Leu Trp Gly Stop

**HbThalassemia (frameshift) -AA**
ATG GTG CAC CTG ACT CCT GAG GAG GTC TGC CCT GTG GGC TAG TTG TAAG GGT GAA GGT GGA GTA AGT TGG TGA GGC CTG GGG C
Val His Leu Thr Pro Glu Glu Val Cys Arg Tyr Cys Pro Val Gly Glu Gly Glu Arg Ala Stop
Expanding Genes

Some genes have repeated base sequences, and the number of these may increase each generation.

Responsible for myotonic muscular dystrophy (AGC/CTG repeats), Huntington disease (CAG repeats), and Fragile X syndrome (CGG repeats).

Expansion is caused by slippage during DNA replication.

Fragile X Syndrome:

- 6-50 CGG repeats in an unaffected individual
- 50-200 CGG repeats in a carrier
- >200 CGG repeats in an affected individual

The concept of expanding genes is the foundation of the current method of DNA profiling (DNA fingerprinting).
<table>
<thead>
<tr>
<th>Wild type &quot;Normal Gene&quot;</th>
<th>THE ONE BIG FLY HAD ONE RED EYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>THQ ONE BIG FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Nonsense</td>
<td>THE ONE BIG</td>
</tr>
<tr>
<td>Frameshift</td>
<td>THE ONE QBI GFL YHA DON ERE DEY</td>
</tr>
<tr>
<td>Deletion</td>
<td>THE ONE BIG HAD ONE RED EYE</td>
</tr>
<tr>
<td>Duplication</td>
<td>THE ONE BIG FLY FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Insertion</td>
<td>THE ONE BIG WET FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Expanding</td>
<td>(P) THE ONE BIG FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Expanding</td>
<td>(F1) THE ONE BIG FLY FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Expanding</td>
<td>(F2) THE ONE BIG FLY FLY FLY FLY FLY FLY HAD ONE RED EYE</td>
</tr>
</tbody>
</table>
### Mutation Lecture Activity

**Point mutations** - changes in single DNA nucleotides.

- **Part of gene to be transcribed**: CTG / TTA / CGC
- **Mutation 1**: CTG / TTG / CGC Silent
- **Mutation 2**: CTG / TTT / CGC Missense
- **Mutation 3**: ATT / TTA / CGC Nonsense

What is the mRNA sequence without mutation?
With mutation 1, 2, and 3?

What is the amino acid sequence without mutation?
With mutations 1, 2, and 3?

### Frameshift mutations: Additions or Deletions

- **Part of gene to be transcribed**: CTG / TTA / CGC
- **Mutation 1**: CTA / GTT / ACG / C Addition
- **Mutation 2**: CT_T / TAC / GC Deletion
- **Mutation 3**: CTG / CTG / TTA / CGC Expansion

What is the mRNA sequence without mutation?
With mutation 1, 2, and 3?

What is the amino acid sequence without mutation?
With mutations 1, 2, and 3?
<table>
<thead>
<tr>
<th></th>
<th>DNA</th>
<th>RNA</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orig</td>
<td>CTG/TTA/CGC</td>
<td>GAC/AAU/GCG</td>
<td>Asp-Asn-Ala</td>
</tr>
<tr>
<td>1</td>
<td>CTG/TTG/CGC</td>
<td>GAC/AAC/GCG</td>
<td>Asp-Asn-Ala</td>
</tr>
<tr>
<td>2</td>
<td>CTG/TTT/CGC</td>
<td>GAC/AAA/GCG</td>
<td>Asp-Lys-Ala</td>
</tr>
<tr>
<td>3</td>
<td>ATT/TTA/CGC</td>
<td>UAA/AAU/GCG</td>
<td></td>
</tr>
</tbody>
</table>

Point Mutation

![Codon Table]

The table on the right side illustrates the relationship between DNA, RNA, and protein sequences. Each row represents a change in the DNA sequence, which results in a change in the RNA sequence and subsequently in the protein sequence. For example, the first mutation from CTG/TTA/CGC to CTG/TTG/CGC results in the amino acid sequence changing from Asp-Asn-Ala to Asp-Asn-Ala. The third mutation from ATT/TTA/CGC to ATT/TTT/CGC results in the amino acid sequence changing from Asp-Asn-Ala to Asp-Lys-Ala. The UAA/AAU/GCG sequence indicates a stop codon, which terminates protein synthesis.
Frameshift Mutation

<table>
<thead>
<tr>
<th>Orig</th>
<th>DNA</th>
<th>RNA</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG/TTA/CGC</td>
<td>GAC/AAU/GCG</td>
<td>Asp-Asn-Ala</td>
<td></td>
</tr>
<tr>
<td>¹</td>
<td>CTA/GTT/ACG/C</td>
<td>GAU/CAA/UGC/G</td>
<td>Asp-Gln-Cys</td>
</tr>
<tr>
<td>²</td>
<td>CTT/TAC/GC</td>
<td>GAA/AUG/CG</td>
<td>Glu-Met</td>
</tr>
<tr>
<td>³</td>
<td>CTG/CTG/TTA/CGC</td>
<td>GAC/GAC/AAU/GCG</td>
<td>Asp-Asp-Asn-Ala</td>
</tr>
</tbody>
</table>

![2nd base in codon]

![3rd base in codon]
Causes of Mutations

Spontaneous mutations

Damage may occur at any time in any cell.

Errors during \textit{chromosome replication} happen only about once in 100,000 bases.

Given that the human genome has about 6 billion bases, this means each replication cycle will have 60,000 errors associated with it.

Cells contain several complex systems to fix damage before, during, and after DNA replication.

Such mutations occur more frequently in organisms with very short generation times, such as viruses and bacteria.
Causes of Mutations

Induced Mutations

DNA sequences are altered as a result of exposure to **mutagens** (agents that increase the rate of mutation).

Mutations may be purposely induced for research purposes (chemicals, gamma rays, x-rays).

Natural mutagens include radon, cosmic rays, and UV light.

Human-created mutagens include cigarette smoke, pollution, pesticides, chemicals, nuclear radiation, and biological warfare. Also, exposure in utero to alcohol, cocaine, carbon monoxide, German measles, lead, mercury, and many others.
Somatic vs. Germinal Mutations

Somatic Mutations (Greek Soma= body)

Mutations in the body cells of an organism, including any cell type **EXCEPT** the cell lines destined to produce eggs or sperms by meiosis.

Somatic Mutations can **NOT** be passed on to one's children.

Somatic mutations may result in unusual cell growth (such as cancer).
Mosaicism

Somatic mutations that occur early in development may result in the cells of an individual not being entirely genetically uniform.

Mosaicism may occur with aneuploid situations as well.
Somatic vs. Germinal Mutations

Germinal Mutations (Latin germinare= to sprout)

Mutations in cells destined to produce gametes (eggs and sperm).

Germinal mutations result in genetically altered gametes that may be passed on to the individual's offspring. This means that these mutations may not affect the individuals in which they occur, but may result in genetic disorders in their offspring.
Mutations are Not All Bad

Mutations may occur in non-coding regions of DNA.

The vast majority of your DNA is not involved in protein coding.

Within an allele, as much as 95% of the DNA is non-coding. Introns get spliced out before protein synthesis starts.

Mutations in non-coding regions usually do nothing to the phenotype of the individual.

Even within coding regions of alleles, some mutations have no effect on the resulting protein.
Mutations and Evolution

Mutations introduce new alleles & increase the genetic variability of a population.

Alleles are formed by mutations of pre-existing alleles. For some genes, there may be hundreds of different alleles.

Some mutations increase the efficiency of the protein produced or change its function.

Genetic variability is essential to the survival of a species and even the formation of new species.

Mutations make evolution possible.
Overview of the Control of Gene Expression

All of the living cells in our body have the same genetic information.

Cells develop very different structures and functions (skin, nerves, muscles, bone, fat, kidney, etc.).

Cells develop different structures and functions because different genes are "turned on" or "turned off" in different parts of your body.

Cells produce different types and quantities of proteins.

Organisms respond to the environmental changes by turning on (or off) specific genes or groups of genes.
Developmental Genes

Genes must be turned on or off in the correct sequence within a particular group of cells.

**Homeotic genes** control proper embryo developmental sequence.

"Master genes" whose products "turn on" a sequence of coordinated events.
Homeotic mutants

*Drosophila* homeotic mutant

The appendage on segment T3 of *Drosophila* is normally a haltere -- a small balancing organ.

Mutant deficient in Ubx expression grows a second wing instead of a haltere.
Controlling Gene Expression

A gene consists of two main parts:

**The Protein Encoding Region** - This is the section of DNA that is transcribed.

**The Promoter Region** - This is a section of DNA at the beginning of the gene that acts as an on/off switch for the protein encoding region.
DNA

Promoter

Gene sequence to be transcribed

\[ \text{GGTATACCCGCCATATG} \]

\[ \text{GGTATAACCGGGG} \]

- a.

- b.

TATA binding protein

Transcription factor

RNA polymerase

\[ \text{GGTATACCCGCCATATG} \]

\[ \text{GGTATAACCGGGG} \]

Transcription

\[ \text{mRNA} \]
Transcription factors

Proteins that bind to specific base sequences on the Promoter Region of a gene.

Each gene locus has its own specific set of transcription factor proteins.
RNA Polymerase

The enzyme that constructs the RNA from the base sequence in the protein encoding region of the Gene
Role of Transcription Factors

**General transcription factors** are necessary for transcription to occur

Activators are transcription factors that turn genes **on** or increase their rate

Repressors are transcription factors that turn genes **off** or decrease their rate

Activators and repressors interact with other cell signals (e.g. one gene can turn another on or off) and with external environmental signals.
RNA Polymerase will not bind to the DNA and initiate transcription until all the required Transcription Factors are properly bound to the Promoter Region of the gene or the RNA Polymerase itself.

If a transcription factor gene is mutated the proper transcription factor protein will not be produced and the gene that the transcription factor helps turn on or off will not function properly.