Mutations can change the meaning of genes

• Mutations are permanent changes in the DNA base sequence

• Simplest mutation is a point mutation or a change in a single nucleotide that affects one codon

• The triplet code has some flexibility because several different codons code for the same aa, so some changes have no effect at all
MUTATIONS

• This acts as a defense mechanism against mutations because most of the time mutations would destroy proteins or they would result in the inability to make a protein.

• If a mutation produces a codon that specifies a different aa it will change the structure of the completed protein.
  – Sickle cell anemia is due to a single point mutation.
4 types of mutations

- Missense mutation
- Nonsense mutation
- Frame-shift mutation
- Silent mutations
A missense mutation

\[ \text{GGUCACUGGGCGGUUCUUAAUGAAA...} \]
\[ \text{gly \ his \ trp \ arg \ phe \ leu \ met \ lys} \]

\[ \text{GGUCUCUCUGGGCGGUUCUUAAUGAAA...} \]
\[ \text{gly \ leu \ trp \ arg \ phe \ leu \ met \ lys} \]

A single base change in the mRNA, due to a base change mutation in the DNA, results in the incorporation of a different amino acid.
Figure 10.16A

Normal hemoglobin DNA

mRNA

Glu

Mutant hemoglobin DNA

mRNA

Val

Normal hemoglobin

Sickle-cell hemoglobin
FIGURE 14.22
The molecular basis of a hereditary disease. Sickle cell anemia is produced by a recessive allele of the gene that encodes the hemoglobin \( \beta \) chains. It represents a change in a single amino acid, from glutamic acid to valine at the sixth position in the chains, which consequently alters the tertiary structure of the hemoglobin molecule, reducing its ability to carry oxygen.
Affects 1/500 black Americans
1/10 is heterozygous for the sickle cell gene
Sickle cell allele is even more common among West African Blacks
In some parts of Africa the birth rate of individuals with this disease is 1/25
Individuals homozygous for this condition have normal looking RBC when there is plenty of oxygen present.

If they exert themselves and deplete oxygen in their blood the RBC change from a disc shape to a crescent shape.

They can not fit through the capillaries.

They clog up blood vessels and starve parts of the body for blood.

They cause internal bleeding and pain.

These sickled cells are fragile and rupture and cause anemia.
SICKLE CELL ANEMIA

Under normal conditions heterozygotes are fine
Heterozygotes may show some symptoms at high altitude when oxygen concentrations are low
They have 1 normal gene that produces normal hemoglobin and 1 sickle cell gene with valine instead of glutamic acid at position 6
A NONSENSE MUTATION

GGUCACUGGCGGGUUCUUAAUGAAAA.....
gly his trp arg phe leu met lys

GGUCACCUAAGCGGGUUCUUAAUGAAAA.....
gly his STOP

A single base change in the mRNA, due to a base change mutation in the DNA, creates a STOP codon.
Size of a genetic code word (codon)

Original sequence  
GAC GAC GAC GAC GAC GAC GAC GAC ...

One base added
Sequence disrupted  
GAC UGA CGA CGA CGA CGA CGA CGA ...

Two bases added
Sequence disrupted  
GAC UUG ACG ACG ACG ACG ACG ACG ...

Three bases added
Sequence restored  
GAC UUU GAC GAC GAC GAC GAC GAC ...

= Wrong triplet
Figure 3.6  Alternate reading frames in a messenger RNA.
• Types of mutations

NORMAL GENE

mRNA

Protein

Met Lys Phe Gly Ala

BASE SUBSTITUTION

mRNA

Protein

Met Lys Phe Ser Ala Met Lys Leu Ala His

BASE DELETION

mRNA

Protein

Met Lys Leu Ala His

Figure 10.16B
**Wild Type**

mRNA: AUG AAG UUU UGG CUA AA
Protein: Met Lys Phe Gly Stop

**Base-Pair Insertion or Deletion**
Frameshift causing extensive missense

mRNA: AUG AAG GGG CUA AA
Protein: Met Lys Leu Ala ...

Frameshift causing immediate nonsense

mRNA: AUG AUG UUU UGG CUA A
Protein: Met Stop

Insertion or deletion of 3 nucleotides: no extensive frameshift

mRNA: AUG UUU UGG CUA A
Protein: Met Phe Gly Stop

**Base-Pair Substitution**
No effect on amino acid sequence

mRNA: AUG AAG UUU UGG CUA AA
Protein: Met Lys Phe Gly Stop

Missense

mRNA: AUG AAG UUU UGG CUA A
Protein: Met Lys Phe Ser Stop

Nonsense

mRNA: AUG UUG UGG CUA A
Protein: Met Stop
# Table 11.6

## Types of Mutations

A sentence comprised of three-letter words can provide an analogy to the effect of mutations on a gene’s sequence:

<table>
<thead>
<tr>
<th>Type</th>
<th>Mutation Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>THE ONE BIG FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Missense</td>
<td>THQ ONE BIG FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Nonsense</td>
<td>THE ONE BIG QBI GFL YHA DON ERE DEY</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>Insertion</td>
<td>THE ONE BIG WET FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Duplication</td>
<td>THE ONE BIG FLY FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>Expanding mutation</td>
<td></td>
</tr>
<tr>
<td>generation 1</td>
<td>THE ONE BIG FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>generation 2</td>
<td>THE ONE BIG FLY FLY FLY HAD ONE RED EYE</td>
</tr>
<tr>
<td>generation 3</td>
<td>THE ONE BIG FLY FLY FLY FLY FLY HAD ONE RED EYE</td>
</tr>
</tbody>
</table>
Gene Disorders

- **Tay-Sachs disease**
  - Autosomal recessive disorder that destroys the nervous system
  - Affected children are normal at birth
  - Begin to lose skills at about 6 months of age
  - Gradually lose sight and hearing and the ability to move
  - Often blind by age 1
  - Typically die before the age of 3
TAY-SACHS DISEASE

Caused by a deficiency of an enzyme that breaks down lipids in the cells that surround nerve cells, so the nervous system gets buried in lipids

- Being a carrier for Tay-Sachs may protect against tuberculosis
- During WWII TB was rampant in eastern European Jewish settlements
TAY-SACHS DISEASE

- Often healthy relatives of children who had Tay-Sachs disease did not contract TB even though they were repeatedly exposed.

- The mutant Tay-Sachs allele increased in frequency as TB selectively killed those who did not carry it.

- Frequency of the allele rose in Ashkenazi Jewish populations of Eastern and Central Europe.
Tay Sachs Disease

- Rare in most populations
  - 1/300,000 births in US

- Frequent in Ashkenazi Jewish populations of Eastern and Central Europe and US
  - 1/3,500 births
  - 1/28 individuals heterozygous