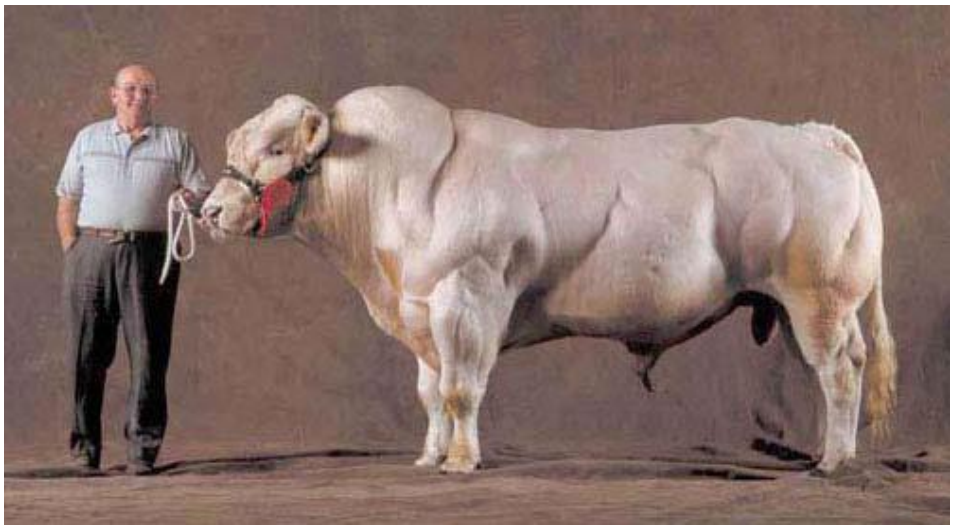
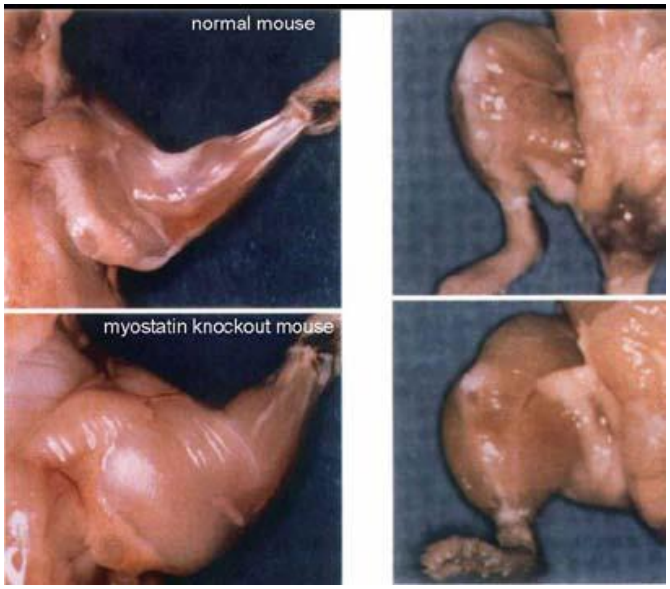
The Effects of Mutations

Part A: The Belgian Blue Mound of Beef is a breed of cattle that is extremely muscular. At two years of age, males can weigh over 1700 pounds, and females over 1100 pounds! This breed originated in the 1850s in Belgium as a result of breeding two different types of cattle. Biologists have discovered that the excessive muscle development is caused by a mutation.



Myostatin (which is also called growth and differentiation factor-8) is a protein found in the skeletal muscle of mammals. It is a growth factor - a molecule that plays a part in controlling cell division, cell growth, and cell development. Experimenters at Johns Hopkins University discovered the role of the gene first in mice. Mice were engineered that had the myostatin knockoutmice. The resulting mice developed two to three times more muscle than mice with a normal version of the gene. The mice were described as looking "like Schwarzenegger mice" by the experimenters. Analysis of the muscle tissue of the mice showed that the number of muscle cells and size of muscle cells was two to three times greater in the muscle tissue of the knockout mice than in normal mice.



There are three general types of mutations that can occur:
i) Point mutation: A change in any single nucleotide of a DNA sequence.
ii) Deletions: The loss of one or more nucleotides in a DNA sequence.
iii) Insertions: The addition of one or more extra nucleotides in a DNA sequence.

There are 3 possible results from a point mutation, deletion, or insertion occurring:

i) Silent mutation: The mutation does not result in a change the amino acid sequence.
ii) Missense mutation: A mutation that causes one amino acid in the protein sequence to be changed to a different one.
iii) Nonsense mutation: A mutation that results in a stop codon where there used to be a codon for an amino acid. This results in translation being stopped before the primary structure of the protein is complete.

1. Use the section of the normal myostatin gene below to determine the amino acid sequence for normal myostatin. You are looking amino acids 273 - 288 of the 375 amino acids in the protein.

2. Now determine the amino acid sequence for Belgian Blue myostatin.

3. Indicate the location of the mutation in the DNA sequence for Belgian Blue myostatin.

Normal myostatin

273 288

DNA	TGT	GAT	GAA	CAC	TCC	ACA	GAA	TCT	CGA	TGC	TGT	CGC	TAC	CCC	CTC	ACG
mRNA																
Amino acid																

Belgian Blue myostatin

273 288

DNA	TGT	GAC	AGA	ATC	TCG	ATG	CTG	TCG	CTA	CCC	CCT	CAC	GGT	GGA	TTT	TGA
mRNA																
Amino acid																

Questions (Part A)

1. Define the terms growth factor and "knockout mouse."

2. Predict which type of mutation would have the most serious effect on an individual. Justify your answer.

3. Where is myostatin found?

4. Based on the appearance of the organisms that have a mutated version of the myostatin gene, suggest the function of myostatin in mammals.

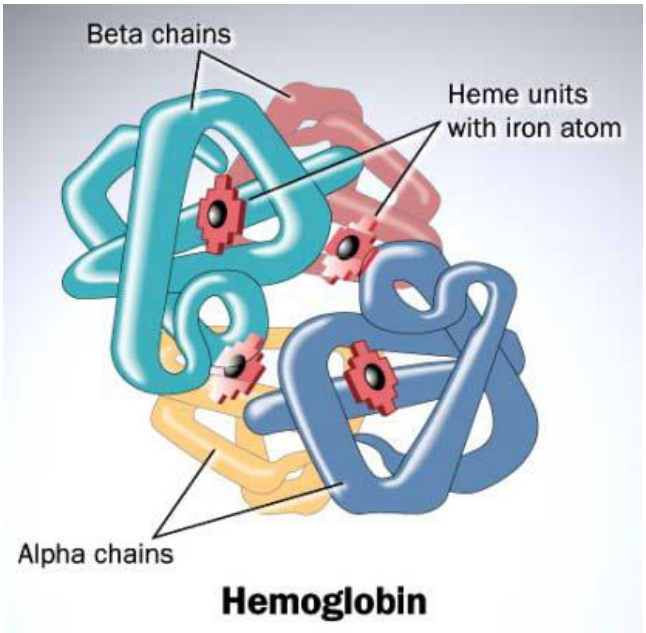
5. Which type of mutation occurred in the Belgian Blue myostatin? Justify your response.

6. What was the result of the mutation that occurred?

7. A breed of cattle called the Piedmontese cattle has the same type of extra muscle as the Belgian Blue cattle; however, the mutation to the myostatin gene is different. It is caused by a point mutation that changes a guanine to an adenine at DNA nucleotide number 941. This causes cysteine to be replaced with tyrosine in the amino acid sequence. What type of mutation is caused by this point mutation?

8. In both the Belgian Blue cattle and the Piedmontese cattle, describe the change(s) to protein structure that might be responsible for the changed appearance of these animals.

Part B: Hemoglobin is a protein found in the erythrocytes (red blood cells) of mammals. Its function is to carry oxygen in the blood to be delivered to all cells of the body. (It also carries some carbon dioxide from cells of the body to the lungs.) The protein consists of 574 amino acids that are arranged into 4 subunits. 2 of the subunits are identical to each other and called alpha-globin subunits. The other 2 subunits are also identical to one another, but are called beta-globin subunits.



In an individual with sickle cell anemia, the red blood cells, are sickle-shaped. Normal red blood cells, on the other hand, are shaped like a doughnut without a hole in the middle. The reason for the misshapen cell in individuals with sickle cell anemia is the hemoglobin protein in the red blood cells is abnormal. The sickle-shaped red blood cells don't pass through blood vessels easily, and tend to clump and stick together. This can lead to severe pain, serious infections, and organ damage. The red blood cells in individuals with sickle cell anemia only live 10-20 days, whereas a normal red blood cell lives for 120 days.

Repeat the steps you completed for the myostatin gene using the sequence for the normal and mutated hemoglobin gene, below.

Normal Hemoglobin

1 7

DNA	CAC	GTG	GAC	TGA	GGA	CTC	CTC
mRNA							
Amino acid							

Mutated hemoglobin

1 7

DNA	CAC	GTG	GAC	TGA	GGA	CAC	CTC
mRNA							
Amino acid							

Questions (Part A)

9. What is anemia, and why do people with sickle cell anemia have anemia?

10. Describe the mutation as silent, missense, or nonsense. Justify your response.

11. Only people who have inherited 2 copies of the mutated gene (one from each parent) for hemoglobin actually have sickle cell anemia. The average life expectancy of someone with sickle cell anemia is around 45 years. If someone inherits one bad gene for hemoglobin and one good gene, they are said to have sickle cell trait. Individuals with sickle cell trait are less susceptible to malaria than individuals who inherit two normal versions of the hemoglobin gene. Suggest a reason why sickle cell trait and sickle-cell anemia are much more prevalent in the African-American population than in any other race of humans.

12. Sickle cell anemia is more common in our modern population than in the past, and individuals with sickle cell anemia are living much longer lives than they used to. Why do you suppose this is the case?