Lesson
The Making of the Fittest
Natural Selection and Adaptation

hhmi | BioInteractive
Educator Materials

INTRODUCTION TO THE MOLECULAR GENETICS OF THE COLOR MUTATIONS IN ROCK POCKET MICE

OVERVIEW

These lessons serve as an extension to the Howard Hughes Medical Institute short film *The Making of the Fittest: Natural Selection and Adaptation*. Students will transcribe and translate portions of the wild-type and mutant rock pocket mouse *Mc1r* gene. By comparing DNA sequences, students identify the locations and types of mutations responsible for the coat-color change described in the film. Students will answer a series of questions to explain how a change in amino acid sequence affects the functionality of the MC1R protein, and how that change might directly affect the coat color of the rock pocket mouse populations and the survival of that population.

KEY CONCEPTS AND LEARNING OBJECTIVES

- A mutation is a random change to an organism's DNA sequence.
- Most mutations have no effect on traits, but some mutations affect the expression of a gene and/or the gene product.
- The environment contributes to determining whether a mutation is advantageous, deleterious, or neutral.
- Natural selection preserves favorable traits.
- Variation, selection, and time fuel the process of evolution.
- Both the type of the mutation and its location determine whether or not it will have an effect on phenotype (advanced version only).

Students will be able to:

- transcribe and translate a DNA sequence.
- connect DNA changes to phenotype.
- analyze and organize data.

CURRICULUM CONNECTIONS

Curriculum	Standards
NGSS (April 2013)	HS-LS1-1, HS-LS3-1, HS-LS3-2, HS-LS4-2, HS-LS4-4, HS-LS4-5 HS.LS1.A, HS.LS4.B, HS.LS4.C
Common Core (2010)	CCSS.ELA-Literacy.RST.9-10.3, CCSS.ELA-Literacy.RST.9-10.4, CCSS.ELA-Literacy.RST.9-10.7
AP Biology (2012–13)	1.A.1, 1.A.2, 3.A.1, 3.C.1, 4.B.1
IB Biology (2009)	3.5, 4.1, 4.3, 5.4, 7.3, 7.4, D.2, G.1

KEY TERMS

evolution, natural selection, variation, trait, mutation, adaptation

TIME REQUIREMENT

These activities are designed for one 50-minute class period including showing the film. Additional time for the analysis questions might be required for homework depending on students' pace. Both activities cover the same material, but activity 2 has additional material covering intracellular, transmembrane, and extracellular domains.

SUGGESTED AUDIENCE

Activity 1: The activity is designed for high school biology (primarily first-year biology, both regular and honors).
Activity 2: The activity is designed for AP and IB high school biology and introductory college biology.

PRIOR KNOWLEDGE

Students should be familiar with the definitions of "gene" and "protein." They should also be comfortable with basic molecular genetics, including a familiarity with the processes of transcription and translation. Finally, students should understand that a protein's amino acid sequence determines its structure, which determines its function.

MATERIALS

Students will need:

genetic code chart (provided in student materials)
blue, red, and green colored pencils

TEACHING TIPS

- If you do not have access to a color printer to print the chart on page 2 of this document, you should compare students' work to how the charts below appear on your computer screen.
- You could assign analysis questions as homework to reduce the amount of class time required for this lesson.

ANSWER KEY ACTIVITY 1

GENE TABLE 1: WILD-TYPE *MC1R* GENE (LIGHT COAT-COLOR PHENOTYPE)

	015							***022***
DNA	TTG	AGG	TGG	GCG	TGT	CCG	CAA	GGA
mRNA	**AAC**	**UCC**	**ACC**	**CGC**	**ACA**	**GGC**	**GUU**	**CCU**
Amino Acid	**Asn**	**Ser**	**Thr**	**Arg**	**Thr**	**Gly**	**Val**	**Pro**

	105							***112***
DNA	CGG	GAC	CGG	TGG	GCC	CAC	TGA	CAC
mRNA	**GCC**	**CUG**	**GCC**	**ACC**	**CGG**	**GUG**	**ACU**	**GUG**
Amino Acid	**Ala**	**Leu**	**Ala**	**Thr**	**Arg**	**Val**	**Thr**	**Val**

	154							***161***
DNA	TCA	TAA	CAC	TGT	GAC	GGG	GCC	CGA
mRNA	**AGU**	**AUU**	**GUG**	**ACA**	**CUG**	**CCC**	**CGG**	**GCU**
Amino Acid	**Ser**	**Ile**	**Val**	**Thr**	**Leu**	**Pro**	**Arg**	**Ala**

	209			***212***
DNA	GTG	TAC	GAA	CGT
mRNA	**CAC**	**AUG**	**CUU**	**GCA**
Amino Acid	**His**	**Met**	**Leu**	**Ala**

	230							*237*
DNA	GAA	CAG	GTG	GTT	CCA	AAG	GCT	GAG
mRNA	**CUU**	**GUC**	**CAC**	**CAA**	**GGU**	**UUC**	**CGA**	**CUC**
Amino Acid	**Leu**	**Val**	**His**	**Gln**	**Gly**	**Phe**	**Arg**	**Leu**

GENE TABLE 2: MUTANT *MC1R* GENE (DARK COAT-COLOR PHENOTYPE)

	015							*022*
DNA	TTG	AGG	TGG	ACG	TGT	CCG	CAA	GGA
mRNA	**AAC**	**UCC**	**ACC**	**UGC**	**ACA**	**GGC**	**GUU**	**CCU**
Amino Acid	**Asn**	**Ser**	**Thr**	**Cys**	**Thr**	**Gly**	**Val**	**Pro**

	105							*112*
DNA	CGG	GAC	CGG	TGG	ACC	CAC	TGA	CAC
mRNA	**GCC**	**CUG**	**GCC**	**ACC**	**UGG**	**GUG**	**ACU**	**GUG**
Amino Acid	**Ala**	**Leu**	**Ala**	**Thr**	**Trp**	**Val**	**Thr**	**Val**

	154							*161*
DNA	TCA	TAA	CAC	TGT	GAC	GGG	ACC	CGA
mRNA	**AGU**	**AUU**	**GUG**	**ACA**	**CUG**	**CCC**	**UGG**	**GCU**
Amino Acid	**Ser**	**Ile**	**Val**	**Thr**	**Leu**	**Pro**	**Trp**	**Ala**

	209			*212*
DNA	GTG	TAC	GAG	CGT
mRNA	**CAC**	**AUG**	**CUC**	**GCA**
Amino Acid	**His**	**Met**	**Leu**	**Ala**

	230							*237*
DNA	GAA	CAG	GTG	GTG	CCA	AAG	GCT	GAG
mRNA	**CUU**	**GUC**	**CAC**	**CAC**	**GGU**	**UUC**	**CGA**	**CUC**
Amino Acid	**Leu**	**Val**	**His**	**His**	**Gly**	**Phe**	**Arg**	**Leu**

QUESTIONS ANSWER KEY

1. *In gene expression, which enzyme is responsible for transcribing the DNA sequence into mRNA by adding complementary RNA nucleotides?* **RNA polymerase**

2. *In a eukaryotic cell, where does transcription occur?* **In the nucleus**

3. *Describe the process of translation.*

Translation is the process of turning instructions from mRNA into chains of amino acids. It occurs in the cytoplasm with the help of ribosomes and tRNA.

4. *In a eukaryotic cell, what main organelle is involved in translation?* **Ribosome**

5. *Explain the relationship between DNA sequence, amino acid sequence, and protein structure and function.*

Students may simply relate DNA sequence to amino acid sequence, and amino acid sequence to the three-dimensional shape of the protein. An example of a student response may be: "DNA sequence provides the code for the amino acid sequence. The amino acid sequence determines the structure of the protein, which affects the function of the protein."

6. *The Mc1r gene codes for the* **melanocortin 1 receptor (MC1R)** *protein.*

7. *If the MC1R protein is 317 amino acids long, why are there 954 base pairs in the coding region of the gene?*

Each of the amino acids has a corresponding mRNA codon and DNA triplet consisting of a three-base sequence. A protein that has 317 amino acids therefore has a DNA base sequence consisting of 951 base pairs (317 × 3 = 951 base pairs). The three additional base pairs correspond to a stop codon for which there is no complementary amino acid. The stop codon signals the termination of translation.

8. *Of the five mutations you identified in the Mc1r gene, how many are:*

5 substitutions; **0** insertions; **0** deletions

9. *Of the five mutations you identified in the Mc1r gene, how many are:*

1 silent; **4** missense; **0** nonsense

10. *Mice with the wild-type (nonmutant) Mc1r gene have light-colored fur. Which pigment is responsible for this coloration?* **Pheomelanin**

11. *Using the information in the introduction on mutations and your knowledge of proteins, develop a hypothesis to explain how the changes in the MC1R protein's amino acid sequence might affect its function.*

Sample answer: The four missense mutations in the *Mc1r* gene change the amino acid sequence of the MC1R protein, which changes the structure of the protein. The change in protein structure will affect the protein function.

12. *Explain how silent mutations affect the structure and function of the protein.*

Silent mutations do not change the amino acid, and therefore will not change the structure of the protein. Because a protein's structure is related to its function, silent mutations do not affect the function of the protein.

13. *Using the information provided in the introduction under "MC1R Gene," explain how the mutant MC1R protein directly affects a rock pocket mouse's coat color.*

The amino acid changes in the MC1R protein may change the structure and function of the protein. This leads to increased production of eumelanin, which results in the dark color.

14. *Mutations are a source of genetic variation. In the film, Dr. Carroll says that mutations occur randomly. What does that mean?*

Sample answer: It means that mutations do not occur for a purpose or for any predetermined result.

15. *It is a common misconception that "all mutations are bad." Use the example of rock pocket mice to explain why this is not true. In your answer, explain how the dark coat color mutation can be an advantage to some mice and a disadvantage to others.*

Sample answer: Mutations can result in new traits. The selective advantage provided by a trait depends on the environment. For example, on a light substrate, individuals with dark-colored coats would be at a disadvantage

because they would stand out more than individuals with light-colored coats, making them easier for predators to spot. However, in the dark lava flow habitat, those same dark-colored individuals would have a selective advantage because they would be better camouflaged than light-colored individuals. So, the statement that "all mutations are bad" is incorrect, because there are different selective pressures on the traits produced by mutations depending on the habitat. There are also silent mutations that do not change the resulting protein; these are neutral, neither good nor bad.

16. *Use your understanding of evolution and the information in the film to explain how the dark-colored mutation came to be so common in some populations of rock pocket mice. Be specific.*

Sample answer: The dark-colored mouse has a selective advantage in a habitat such as the Pinacate lava flow, which has a dark-colored substrate. Since rock pocket mice reproduce quickly and often, the frequency of this favored trait would spread rapidly through the population. Any light-colored mice in the dark-colored habitat would be at a selective disadvantage, thus decreasing their gene frequency in future generations. In this way, favorable traits accumulate and increase in frequency—just as Darwin explained.

ANSWER KEY ACTIVITY 2

GENE TABLES

WILD-TYPE *MC1R* GENE (LIGHT-COLORED COAT PHENOTYPE)

	015									024	
DNA	TTG	AGG	TGG	GCG	TGT	CCG	CAA	GGA	GTG	GAG	EXTRACELLULAR DOMAIN I
mRNA	**AAC**	**UCC**	**ACC**	**CGC**	**ACA**	**GGC**	**GUU**	**CCU**	**CAC**	**CUC**	
Amino Acid	**Asn**	**Ser**	**Thr**	**Arg**	**Thr**	**Gly**	**Val**	**Pro**	**His**	**Leu**	

MUTANT *MC1R* GENE (DARK-COLORED COAT PHENOTYPE)

	015									024	
DNA	TTG	AGG	TGG	ACG	TGT	CCG	CAA	GGA	GTG	GAG	EXTRACELLULAR DOMAIN I
mRNA	**AAC**	**UCC**	**ACC**	**UGC**	**ACA**	**GGC**	**GUU**	**CCU**	**CAC**	**CUC**	
Amino Acid	**Asn**	**Ser**	**Thr**	**Cys**	**Thr**	**Gly**	**Val**	**Pro**	**His**	**Leu**	

WILD-TYPE *MC1R* GENE (LIGHT-COLORED COAT PHENOTYPE)

	105									114	
DNA	CGG	GAC	CGG	TGG	GCC	CAC	TGA	CAC	CAT	GTC	EXTRACELLULAR DOMAIN III
mRNA	**GCC**	**CUG**	**GCC**	**ACC**	**CGG**	**GUG**	**ACU**	**GUG**	**GUA**	**CAG**	
Amino Acid	**Ala**	**Leu**	**Ala**	**Thr**	**Arg**	**Val**	**Thr**	**Val**	**Val**	**Gln**	

MUTANT *MC1R* GENE (DARK-COLORED COAT PHENOTYPE)

	105									114	
DNA	CGG	GAC	CGG	TGG	ACC	CAC	TGA	CAC	CAT	GTC	EXTRACELLULAR DOMAIN III
mRNA	**GCC**	**CUG**	**GCC**	**ACC**	**UGG**	**GUG**	**ACU**	**GUG**	**GUA**	**CAG**	
Amino Acid	**Ala**	**Leu**	**Ala**	**Thr**	**Trp**	**Val**	**Thr**	**Val**	**Val**	**Gln**	

WILD-TYPE *MC1R* GENE (LIGHT-COLORED COAT PHENOTYPE)

	154									163	
DNA	TCA	TAA	CAC	TGT	GAC	GGG	GCC	CGA	GCC	ACC	INTRACELLULAR DOMAIN I
mRNA	**AGU**	**AUU**	**GUG**	**ACA**	**CUG**	**CCC**	**CGG**	**GCU**	**CGG**	**UGG**	
Amino Acid	**Ser**	**Ile**	**Val**	**Thr**	**Leu**	**Pro**	**Arg**	**Ala**	**Arg**	**Trp**	

MUTANT *MC1R* GENE (DARK-COLORED COAT PHENOTYPE)

	154									163	
DNA	TCA	TAA	CAC	TGT	GAC	GGG	ACC	CGA	GCC	ACC	INTRACELLULAR DOMAIN I
mRNA	**AGU**	**AUU**	**GUG**	**ACA**	**CUG**	**CCC**	**UGG**	**GCU**	**CGG**	**UGG**	
Amino Acid	**Ser**	**Ile**	**Val**	**Thr**	**Leu**	**Pro**	**Trp**	**Ala**	**Arg**	**Trp**	

WILD-TYPE *MC1R* GENE (LIGHT-COLORED COAT PHENOTYPE)

	208				212	
DNA	CAC	GTG	TAC	GAA	CGT	TRANSMEMBRANE V
mRNA	**GUG**	**CAC**	**AUG**	**CUU**	**GCA**	
Amino Acid	**Val**	**His**	**Met**	**Leu**	**Ala**	

MUTANT *MC1R* GENE (DARK-COLORED COAT PHENOTYPE)

	208				212	
DNA	CAC	GTG	TAC	GAG	CGT	TRANSMEMBRANE V
mRNA	**GUG**	**CAC**	**AUG**	**CUC**	**GCA**	
Amino Acid	**Val**	**His**	**Met**	**Leu**	**Ala**	

WILD-TYPE *MC1R* GENE (LIGHT-COLORED COAT PHENOTYPE)

	230									239	
DNA	GAA	CAG	GTG	GTT	CCA	AAG	GCT	GAG	TTT	CCG	INTRACELLULAR DOMAIN III
mRNA	**CUU**	**GUC**	**CAC**	**CAA**	**GGU**	**UUC**	**CGA**	**CUC**	**AAA**	**GGC**	
Amino Acid	**Leu**	**Val**	**His**	**Gln**	**Gly**	**Phe**	**Arg**	**Leu**	**Lys**	**Gly**	

MUTANT *MC1R* GENE (DARK-COLORED COAT PHENOTYPE)

	230									239	
DNA	GAA	CAG	GTG	GTG	CCA	AAG	GCT	GAG	TTT	CCG	INTRACELLULAR DOMAIN III
mRNA	**CUU**	**GUC**	**CAC**	**CAC**	**GGU**	**UUC**	**CGA**	**CUC**	**AAA**	**GGC**	
Amino Acid	**Leu**	**Val**	**His**	**His**	**Gly**	**Phe**	**Arg**	**Leu**	**Lys**	**Gly**	

QUESTIONS ANSWER KEY

1. *Using the amino acid location numbers provided above the first and last column of each table, list the locations of the five amino acids that contain a mutation.*

The amino acid locations are 018, 109, 160, 211, and 233.

2. *Of the five mutations you identified in the Mc1r gene, how many are the following:*

5 substitutions, **0** insertions, **0** deletions

3. *Of the five mutations you identified in the Mc1r gene, how many are the following:*

1 silent, **4** missense, **0** nonsense

4.

a. *Which four amino acid locations (see Question 1 above) contain the missense mutations?*

The amino acids are 018, 109, 160, and 233.

b. *Explain the link between DNA sequence and protein structure and function.*

Students may simply relate DNA sequence to amino acid sequence, and amino acid sequence to the three-dimensional shape of the protein. More-advanced students should be able to link the mutation to a change in the protein's primary structure, which affects other levels of structure (secondary and tertiary). All student responses should demonstrate an understanding of the link between DNA and the sequence of amino acids that determines the structure, and therefore function, of a protein.

5. *Using the information on mutations in the introduction and your knowledge of proteins, develop a hypothesis to explain how the changes in the MC1R protein's amino acid sequence might affect its function.*

Students might suggest that since the four missense mutations in the *Mc1r* gene change the amino acid sequence of the MC1R protein, the protein will not function properly, as a protein's function is determined by its structure.

6. *Many proteins, including MC1R, contain several structural domains that can fold and function independently from the rest. The domain names were provided for each portion of DNA sequence you translated earlier. Answer the following questions.*

a. *Where is the MC1R protein found, and what is its function? Be specific.*

It is a receptor protein embedded in the membrane of melanocytes. It is specialized for pigment production.

b. *Which protein domains contain the four Mc1r missense mutations? (Refer to the gene tables you completed earlier.)*

The mutation at 018 is in Extracellular Domain I, the mutation at 109 is in Extracellular Domain III, the mutation at 160 is in Intracellular Domain I, and the mutation at 233 is in Intracellular Domain III.

c. *Define "extracellular."*

Extracellular means "something outside of a cell."

d. *Define "intracellular."*

Intracellular means "something inside of a cell."

e. *Why is it significant that the four missense mutations are found in the extracellular and intracellular domains of the protein? Explain your answer. (Hint: Think about MC1R's function.)*

Specific answers will vary, but students should have the idea that a protein that spans a cell membrane has a portion that projects out of the cell (extracellular) and a portion that projects into the cell (intracellular). This type of receptor protein usually functions in either cell transport or cell signaling. Changes in the structure of extracellular and intracellular portions can change the function of the protein in the signaling pathway or the transport mechanism. (Note: See the lesson "The Biochemistry and Cell Signaling Pathway of the *Mc1r* Gene" for more detail on this concept.)

7. *Using the information on the Mc1r gene in the introduction and your knowledge of proteins, develop a hypothesis to explain how the change in MC1R protein function might directly affect a rock pocket mouse's coat color. Be specific and consider both the light-colored and dark-colored phenotypes.*

Specific answers will vary, but students should suggest that the normal MC1R receptor protein will produce relative amounts of eumelanin and pheomelanin that will result in the light coat color. In addition, the dark-colored mouse population contains the mutant *Mc1r* gene, which results in a different receptor protein. This change in structure might lead to increased production of eumelanin, which results in the dark color.

8. *Explain why the mutation at amino acid location 211 is not as significant as the other four mutations.*

It is a silent mutation, so the amino acid in that position does not change, nor does the structure of the specific domain. This is important because a protein's structure relates to its function. No change in the structure suggests that there is no change in the function of this particular domain of the protein.

9. *Mutations are a source of genetic variation. In the film, Dr. Sean Carroll says that mutations occur randomly. What does this mean?*

Sample answer: "It means that mutations do not occur for a purpose or for any predetermined result."

10. *It is a common misconception that "all mutations are bad." Use the example of rock pocket mice to explain why this statement is not true. In your answer, explain how the dark coat-color mutation can be an advantage to some mice and a disadvantage to others.*

Sample answer: "Mutations can result in new traits. The selective advantage provided by a trait depends on the environment. For example, on a light substrate, individuals with dark-colored coats would be at a disadvantage because they would stand out more than individuals with light-colored coats, making them easier for predators to spot. However, in the dark lava flow habitat, those same dark-colored individuals would have a selective advantage because they would be better camouflaged than light-colored individuals. So the statement that "all mutations are bad" is incorrect, because there are different selective pressures on the traits produced by mutations depending on the habitat. There are also silent mutations that do not change the resulting protein; these are neutral, neither good nor bad."

11. *Use your understanding of evolution and the information in the film to explain how the dark-colored mutation came to be so common in some populations of rock pocket mice. Be specific.*

Sample answer: "The dark-colored mouse has a selective advantage in a habitat such as the Pinacate lava flow, which has a dark-colored substrate. Since rock pocket mice reproduce quickly and often, the frequency of this favored trait would spread rapidly through the population. Any light-colored mice in the dark-colored habitat would be at a selective disadvantage, thus decreasing their gene frequency in future generations. In this way, favorable traits accumulate and increase in frequency—just as Charles Darwin explained."

AUTHOR
Ann Brokaw
AP Biology Teacher
Rocky River High School
Rocky River, Ohio