THE MOLECULAR EVOLUTION OF GENE BIRTH AND DEATH

OVERVIEW

This advanced lesson describes how mutation is a key element in both the birth and death of genes. Students proceed through a series of presentation slides that include background information, examples, and embedded video, and animation links. Questions challenge students to synthesize information and apply what they learn regarding how genes are gained and lost through evolutionary time.

KEY CONCEPTS AND LEARNING OBJECTIVES

- Mutations are changes in an organism's DNA. They occur at random.
- Whether or not a mutation has an effect on an organism's traits depends on the type of mutation and its location.
- Mutations can result in both the appearance of new genes and the loss of existing genes.
- One way that a new gene can arise is when a gene is duplicated and one copy (or both copies) of the gene accumulates mutations, which change the function of the gene.
- One way that a gene can be lost is when one or more mutations accumulate that destroy its function.

Students will be able to

- analyze gene sequences and transcribe DNA into messenger RNA (mRNA);
- translate mRNA into a sequence of amino acids by using a genetic code chart; and
- compare wild-type and mutated DNA sequences to determine the type of mutation present.

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.LS3.A, HS.LS3.B, HS.LS4.B, HS.LS4.C
Common Core (2010)	ELA-Literacy.RST.9-10.1, ELA-Literacy.RH.9-10.4, ELA-Literacy.RST.9-10.7, ELA-Literacy RST.11-12.1, ELA-Literacy.RST.11-12.7, ELA-Literacy.RST.11-12.9
AP Biology (2012–13)	1.A.1, 1.A.2, 1.A.4, 2.E.1, 3.A.3, 3.C.1, 3.C.2, 4.A.1, 4.B.1, 4.C.1
IB Biology (2009)	3.4, 3.5, 3.6, 4.1, 5.4, 7.2, 7.3, 7.4, 7.5, 7.6, C.1, C.2

KEY TERMS

chromosomal alteration, deletion, duplication, evolution, gene mutation, insertion, mutation, natural selection, point mutation, pseudogene, substitution mutation, translocation

TIME REQUIREMENTS

This lesson was designed to be completed within two 50-minute class periods and one night of homework; alternatively, this lesson can be assigned completely as homework if computers and the Internet are available to all students.

SUGGESTED AUDIENCE

This lesson is appropriate for high school biology (second year, AP, and IB), advanced high school genetics elective, introductory college biology, and college-level genetics.

PRIOR KNOWLEDGE

Students should know the definition of "gene" and be familiar with the structure of a eukaryotic chromosome. Students should understand protein structure and the processes of meiosis, the cell cycle, transcription, translation, gene regulation, and X inactivation. Finally, they should also understand the concepts of natural selection and evolution.

MATERIALS

- student presentation slides
- Internet connection for hyperlinks
- genetic code chart

TEACHING TIPS

- Because the presentation slides for this lesson are on the BioInteractive website, you can use a number of different strategies for implementing this lesson in the classroom:
  - You can proceed through the slides in front of the class. If you choose this option, either pause to let students complete the student handout or complete the lesson questions as a class.
  - Students can work in pairs if a computer lab (or laptop cart) is available. Each student pair can proceed through the slides on its own computer, answering questions as it goes along.
  - Students can complete the student handout in class or as an individual take-home assignment, assuming students have access to the presentation slides, a computer, and the Internet.
- You can download the presentation slide file from the BioInteractive website and save it to a collaborative space for student use.
- Note that this lesson focuses on mutations that affect chromosome structure, not chromosome number (trisomy, monosomy, etc.).
- If you are interested in learning more about the sickle cell mutation and its connection to malaria discussed in this lesson, watch the third short film in the short film *The Making of the Fittest* series: *Natural Selection in Humans* at http://www.hhmi.org/biointeractive/making-fittest-natural-selection-humans.
- All video clips and animations are hyperlinked, but hyperlinks only work if the slides are in slide-show mode.

ANSWER KEY

1. *What drives the evolution of new genes? Define "mutation." Are mutations random?*

Mutations drive the evolution of new genes. A mutation is a change in an organism's genetic information, or DNA. Yes, mutations are random.

2. *Which of the following has a greater potential effect on the evolution of a population: mutations in somatic (body) cells or mutations in gametes (egg and sperm)? Explain.*

Mutations that occur in gametes (egg and sperm) have a greater potential to affect the course of evolution because they can be passed on to the next generation.

3. *What is a point mutation?*

A point mutation is a change in a single nucleotide of a DNA sequence.

4. *When can an insertion or deletion be something other than a point mutation?*

This can happen when the mutation involves two or more nucleotides that are inserted into or deleted from the DNA sequence.

5. *DNA is transcribed to messenger RNA (mRNA), which is translated into a sequence of amino acids that fold to form a protein.*

a. *Complete the tables below by first transcribing the DNA triplets to mRNA codons and then translating them to amino acids by using a genetic code chart (see page 8 of this handout).*

Wild-Type DNA Sequence

DNA	GAC	TCT	GGA	CAC	CTC
mRNA	**CUG**	**AGA**	**CCU**	**GUG**	**GAG**
Amino Acid	**Leu**	**Arg**	**Pro**	**Val**	**Glu**

Mutant DNA Sequence 1

DNA	GAC	TCT	GGA	CGC	CTC
mRNA	**CUG**	**AGA**	**CCU**	**GCG**	**GAG**
Amino Acid	**Leu**	**Arg**	**Pro**	**Ala**	**Glu**

Mutant DNA Sequence 2

DNA	GAC	ACT	GGA	CAC	CTC
mRNA	**CUG**	**UGA**	**CCU**	**GUG**	**GAG**
Amino Acid	**Leu**	**(stop)**			

b. *Which mutant sequence contains a missense mutation? Explain your answer.*

Mutant DNA sequence 1 has a missense mutation, because only one amino acid changed.

c. *Which mutant sequence contains a nonsense mutation? Explain your answer.*

Mutant DNA sequence 2 has a nonsense mutation, because translation of the protein stopped prematurely.

6. *Which type of substitution mutation has the greatest chance of leading to a nonfunctional protein? Explain your answer.*

A nonsense mutation has the greatest chance of producing a fully nonfunctional protein because it prematurely stops translation, thereby truncating the protein.

7. *Describe the cause of sickle cell anemia.*

Sickle cell anemia is caused by a point (missense) mutation in the hemoglobin protein. Glutamic acid is replaced by valine, causing hemoglobin molecules to clump together and change the shape of red blood cells.

8. *Rett syndrome occurs almost exclusively in girls, but there are a few male patients. The right side of* ***slide 10*** *depicts the normal protein (A) and the proteins produced by three different* MECP2 *mutations (B, C, and D), along with the resulting phenotypes of the male Rett syndrome patients. The top illustration (A) shows the healthy protein with the most important domains highlighted in light blue and pink. The orange band in the bottom illustration (D) indicates the presence of a different amino acid in the protein sequence compared to the normal protein.*

a. *What type of substitution mutation would result in the protein structures shown in B and C?*

A nonsense mutation, as both mutations produce truncated proteins

b. *Even though the proteins depicted in B and C are caused by the same type of mutation, patients with the mutation depicted in C have less-severe symptoms. Develop a hypothesis to explain why.*

Translation of the protein in B is halted sooner than that of the protein in C, resulting in a much shorter protein. The symptoms of individuals with the mutation shown in B are likely more severe because the protein is unable to perform most, if any, of its functions. Perhaps proteins translated from the gene in C,

which are truncated later in translation, can still perform some or most of their functions due to the intact protein domains, though probably not as well as the normal protein (A).

c. *What type of substitution mutation causes the protein depicted in D?*

Point mutation

d. *Form a hypothesis to explain why patients with the mutation depicted in D have less-severe symptoms than patients with the other type of mutation.*

The sequence of amino acids in the protein shown in D differs from that of a normal protein (A) in only one amino acid position. The symptoms are probably mild in individuals with the protein shown in D because the protein has a complete sequence, including the functional domains, and can likely perform most of its functions. Individuals with the proteins shown in B and C, however, have truncated proteins that are unlikely to perform as well as the normal protein, or not at all.

e. *There are many more female patients with Rett syndrome than males; furthermore, female patients exhibit a much wider range of symptoms than males do. Explain both observations. (Hint: Think about what you know about the X chromosome; you may also watch the* X Inactivation *animation at http://www.hhmi.org/biointeractive/neuroscience/x_inactivation.html.)*

Human males have one X chromosome, so if the *MECP2* mutation occurs in a male, he will express the mutation. Females possess two X chromosomes, one of which undergoes X inactivation in each cell. If the *MECP2* mutation is in only one of the X chromosomes, some cells will express the normal gene while others will express the mutant gene. As a result, females with the *MECP2* mutation are more likely to survive than males; this explains why Rett syndrome is almost exclusively seen in girls. Females with Rett syndrome express a wider spectrum of symptoms than those seen in the few male patients that have been identified, due to the differential expression of the two X chromosomes.

9. *The following sequence contains an insertion mutation, shown in the larger, red font.*

a. *Use the genetic code chart to complete the table below.*

Mutant DNA Sequence 3

DNA	GAC	**C**TC	TGG	ACA	CCT
mRNA	**CUG**	**GAG**	**ACC**	**UGU**	**GGA**
Amino Acid	**Leu**	**Glu**	**Thr**	**Cys**	**Gly**

b*. Compare this amino acid sequence to the wild-type sequence in Question 5. Explain why frameshift mutations can have such major consequences on a protein's function.*

A frameshift mutation is especially detrimental because it alters the reading frame of the DNA and therefore how all of the mRNA downstream of the mutation is translated. Since a protein's structure, and therefore its function, is determined by its sequence of amino acids, any protein translated from DNA that has a frameshift mutation is unlikely to be functional unless the mutation occurs toward the C terminal end of the protein.

10. *What is a trinucleotide repeat?*

A trinucleotide repeat is a sequence of three nucleotides, repeated several times. In spinocerebellar ataxia type 1 that sequence is CAG.

11. *After watching the 14-minute lecture clip regarding spinocerebellar ataxia type 1 (SCA1) on* ***slide13****, answer the following questions.*

a. *What type of mutation causes SCA1, and how does the mutation occur?*

SCA1 is caused by the expansion of a trinucleotide (CAG) repeat. This mutation occurs during DNA replication as a result of slippage of the DNA polymerase enzyme during the replication process.

b*. Explain how the number of CAG repeats relates the severity of the disease.*

The greater the number of repeats in the DNA, the earlier the onset of the disease and the more severe the symptoms.

c. *What is another human disease caused by a trinucleotide repeat expansion?*

The most well-known example is Huntington disease, but students may also mention other spinocerebellar ataxias or spinobulbar muscular atrophy.

12. *Many people mistakenly think that "all mutations are bad."*

a. *Explain how it is possible for a mutation to have no effect on an organism.*

Silent point mutations change the sequence of DNA, but due to redundancy in the genetic code, there is no effect on translation. Scientists consider these mutations to be neutral, causing no change in the protein's amino acid sequence.

b. *Use the example of rock pocket mice to explain how a mutation can have a positive effect on an organism.*

The mutation that causes dark coat color in rock pocket mice is an advantage to individuals that live on dark rocks. In this habitat, a mouse with dark-colored fur would blend in and not be seen as easily by predators as mice with light-colored coats.

13. *When in the cell cycle do most chromosomal alterations that affect chromosome structure occur?*

Chromosomal alterations most often occur during the S phase of interphase, when DNA is replicating, or during prophase I of meiosis when crossing-over occurs.

14. *List and describe the four types of alterations that affect chromosome structure.*

The four types of chromosomal mutations that affect chromosomal structure are (1) deletions (part or all of a chromosome is lost); (2) inversions (a segment of a chromosome is inverted during the process of crossing-over); (3) translocations (a part of a chromosome attaches to a nonhomologous chromosome); and (4) duplications (part or all of a chromosome is repeated, resulting in multiple copies of a gene or genes).

15. *How might these chromosomal alterations affect gene expression? (Hint: Watch the* Gene Switch *animation at http://www.hhmi.org/biointeractive/evolution/gene_switch.html.)*

Eukaryotic gene expression depends on enhancers and promoters, which are regulatory regions involved in transcription. These sequences can be located near the genes they regulate (for example, promoters), but enhancer regions can also be quite far away, sometimes even on a different chromosome. Chromosomal alterations can change the position of genes relative to their enhancer and promoter sequences, thus affecting how gene expression is regulated.

16. *What type of chromosomal alteration causes cri-du-chat syndrome? How do you know?*

Cri-du-chat syndrome is caused by a chromosomal deletion on chromosome 5. The chromosome diagram on slide 17 shows a portion of chromosome 5 missing.

17. *View the four-minute lecture clip and animation on* ***slide 18****. (Note: Gleevec is a pharmaceutical drug developed to help treat chronic myelogenous leukemia, or CML.)*

a. *What type of chromosomal alteration causes CML?*

Translocation

b. *Which chromosomes are affected by this meiotic error?*

Chromosomes 9 and 22

c. *What is the "Philadelphia chromosome"? It* **is an abnormal version of chromosome 22 caused by a translocation with chromosome 9. As a result of the translocation, a large segment of chromosome 22 is fused to a portion of chromosome 9.**

d*. Explain the mechanism by which Gleevec works to treat CML.*

Gleevec binds to the active site of the BCR-ABL protein and prevents phosphorylation of its target protein. This in turn prevents the abnormal cell growth associated with CML.

18. *Define "paralogous genes" and explain the evolutionary significance of gene duplication.*

Paralogous genes are pairs of genes within an organism's genome that have diverged from duplication events. Gene duplication is a common source of novel traits and has played a major role in the evolution and diversification of life.

19. *Describe the possible outcomes of gene duplication.*

The duplicated gene can (1) lose its function, (2) gain a novel function, or (3) split the function with the ancestral gene, resulting in a more-efficient function.

20. *Explain how gene duplication led to the evolution of a key mammalian trait.*

In mammals, the duplicated lysozyme gene took on a new function: milk production.

21*. What is a pseudogene?*

A noncoding gene, or pseudogene

22. *Explain how the accumulation of mutations could lead to gene death.*

If mutations cause a significant-enough change in the structure or expression of the resulting protein, then the protein will be nonfunctional. Assuming that there is no negative effect on the organism, and that the mutated gene does not develop a novel function, the mutations persist and continue to accumulate. Eventually, the gene may no longer be translated at all.

23. *Develop a hypothesis to explain the evolutionary significance of the gene death events for the examples listed below.*

a. *Olfactory receptor genes in humans and mice*

The relative rates of duplication and gene death in olfactory genes have resulted in mice having a better sense of smell than humans do.

b. *Myoglobin gene in some icefish species*

The loss of myoglobin genes from the muscles and hearts of some icefish suggests that they have a reduced ability to bind oxygen and deliver it throughout the body.

24. *Explain the evolutionary significance of icefish "antifreeze" proteins. What types of chromosomal rearrangements and gene mutations led to the development of the antifreeze protein? (Hint: Watch the animation about the ancestral and antifreeze gene in the film very closely. Three mutation events follow the initial gene duplication.)*

Antifreeze proteins enable icefish to survive in the Antarctic waters without their blood freezing by preventing the growth of ice crystals. A chromosomal duplication that resulted in a gene duplication was followed by a deletion within the duplicated gene, a replication of a repeated DNA sequence due to the slippage of DNA polymerase, and an insertion. The combination of these mutations gave rise to a gene that codes for antifreeze proteins in icefish.

25. *What "gene death" event occurred in icefish? How did it affect their ability to survive and reproduce?*

The event was the loss of genes for the globin polypeptides, which make up the hemoglobin molecule found in red blood cells. The loss of hemoglobin and red blood cells enhanced the ability of the fish to survive and reproduce, because it made the blood more fluid and therefore easier to pump through the body despite the frigid water temperatures.

26. *Explain how icefish serve as an example of both the birth and death of genes.*

In their evolutionary history, icefish have both gained and lost genes that have enhanced their ability to survive in their environment. Genes were "born" that code for antifreeze proteins that prevent their blood from freezing solid. Genes for hemoglobin molecules "died," which resulted in increased blood fluidity.

27. *Using what you know about the icefish genome, explain this statement: "Genes tell the story of evolution."*

Sample answer: "By looking at the DNA sequences of organisms in a particular species and comparing these sequences to those of other existing and extinct species, scientists can determine the sequence of mutations that have played important roles in the evolution of that species. For example, they can determine that a gene duplication led to the evolution of antifreeze proteins in icefish and to the loss of the hemoglobin protein."

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