



## DNA Wrap: Packaging Matters

*An Introduction to Epigenetics*  
UNC-Chapel Hill's Superfund Research Program

What causes the physical appearance and health status of identical twins to diverge with age? In this lesson, students learn that the environment can alter the way our genes are expressed, making even identical twins different. After watching a PBS video, *A Tale of Two Mice*, and reviewing data presented in the *Environmental Health Perspectives* article *Maternal Genistein Alters Coat Color and Protects Apy Mouse Offspring from Obesity by Modifying the Fetal Epigenome*, students learn about epigenetics and its role in regulating gene expression.

### **Author**

Dana Haine, MS  
University of North Carolina at Chapel Hill Superfund Research Program

### **Reviewers**

Dana Dolinoy, PhD  
University of Michigan

Rebecca Fry, PhD  
University of North Carolina at Chapel Hill Superfund Research Program

Banalata Sen, PhD, Audrey Pinto, PhD, Susan Booker, Dorothy Ritter  
Environmental Health Perspectives

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## Learning Objectives

By the end of this lesson students should be able to:

- define the term “epigenetics”
- describe DNA methylation as a mechanism for inhibiting gene transcription
- describe how gene expression can vary among genetically identical offspring

## Alignment to NC Essential Science Standards for Biology

### **Bio.3.1 Explain how traits are determined by the structure and function of DNA.**

- Bio.3.2.3 Explain how the environment can influence the expression of genetic traits.

### **Bio.4.1 Understand how biological molecules are essential to the survival of living organisms.**

- Bio.4.1.2 Summarize the relationship among DNA, proteins and amino acids in carrying out the work of cells and how this is similar in all organisms.

### **Bio.3.3 Understand the application of DNA technology.**

- Bio.3.3.1 Interpret how DNA is used for comparison and identification of organisms.

**Note to Teacher:** This lesson is best conducted after students have learned about general DNA structure and function; transcription and translation; general regulation of gene expression.

## Skills Used or Developed

- Communication (note-taking, oral, written – including summarization)
- Comprehension (listening, reading)
- Critical thinking and response
- Graph reading
- Figures (reading legends)

## Class Time Required

**45-60 minutes**

Depending on student proficiency level, this lesson can be completed as a homework assignment to encourage independent student work and/or to save class time.

## Materials

- Computer with Internet access and audio (sound) capabilities
- LCD Projector
- Accompanying Powerpoint slide library (optional)
- Student worksheet, one copy per student

## Teacher Preparation

- Ensure students have a basic understanding of DNA structure and function prior to introducing the concept of epigenetics. **Students should already be familiar with the following terminology:**
  - Chromatin
  - Chromosome
  - Deoxyribonucleic acid (DNA)
  - Gene
  - Gene expression/regulation
  - Histone proteins
  - Nitrogenous base
  - Nucleoprotein
  - Nucleotides
  - Phosphodiester bond
  - Promoter
  - Ribonucleic acid (RNA)
  - Transcription
  - Transcription factors
  - Translation
- Review the Background Information, Procedure and Student Instructions for this activity. Additional resources are listed in the *Resources* section.
- Make copies of the *Student Worksheet*, one per student.

## Background Information

**Deoxyribonucleic acid** (DNA) is a large, complex molecule (macromolecule) that contains the genetic code or the information needed to direct the activities of a cell and for transmission of this information to the next generation. A single DNA strand is made up of building blocks called **nucleotides** that are connected together like a chain. Each DNA nucleotide is composed of a **nitrogenous base**—either adenosine (A), guanine (G), thymine (T), or cytosine (C)—a five-carbon deoxyribose sugar (S), and a phosphate group (P). A **gene** is a specific sequence of nucleotides within a DNA strand that provides the instructions necessary to carry out a particular activity.

DNA exists as a double-stranded polymer of nucleotides that forms a helix in which two DNA strands run anti-parallel to one another and interact via **hydrogen bonds** between the nitrogenous bases. The hydrogen bonds between the nitrogenous bases can be broken to allow the DNA strands to separate during

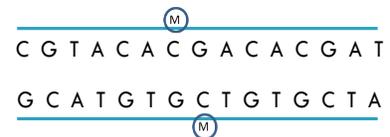
DNA replication and gene expression, which occurs when the nucleotide sequence of a gene is copied into **ribonucleic acid (RNA)** during a process called **transcription**. For genes that encode proteins, DNA is copied into messenger RNA (mRNA), which then directs the synthesis of proteins during the process known as **translation**. **Gene expression** is highly regulated in order to control a cell's activities; thus, the timing and amount of RNA and protein generated from a given gene varies depending on the cell's activities. Disruption of gene expression regulation leads to diseases such as cancer.

Inside cells, DNA is packaged around proteins called **histones**; this DNA–protein (**nucleoprotein**) complex is called **chromatin**. Histones act like “spools” around which DNA is wrapped. In humans, each cell contains approximately 2 meters of DNA; however, because of the wrapping of DNA around histones, the condensed DNA is approximately 120 micrometers long!

This DNA “packaging” in the form of chromatin plays a key role in the regulation of gene expression. The nucleoprotein inside cells serves as a docking site for the different proteins and enzymes and their interactions required for DNA replication, transcription, recombination, and repair.

This lesson introduces students to the emerging field of epigenetics. **Epigenetics** literally means “on top of or in addition to genetics,” and is the study of changes in gene expression not accompanied by alterations in DNA sequence. In parallel to the term genome, which defines the complete set of genetic information contained in the DNA of an organism, **epigenome** refers to the complete set of epigenetic pathways in an organism. Epigenetic modifications to DNA exert profound influences on gene activity. For example, studies suggest that epigenetic variation may be responsible for subtle differences in appearance and behavior of identical twins. Identical twins are more epigenetically similar early in life but show remarkable divergence with age.

Epigenetic pathways such as **DNA methylation** and histone modifications interact with each other to regulate expression of genes. One of the most common and well-characterized epigenetic pathways is DNA methylation. DNA methylation occurs when an enzyme called a **methyltransferase** covalently attaches a methyl (-CH<sub>3</sub>) group to a cytosine base that is adjacent to a guanine base (see Figure 1). Such sites where a cytosine is adjacent to guanine via a phosphodiester bond are called CpG sites. Scientists have observed that DNA methylation occurs predominately along places on the DNA strand that are rich in CpG pairs. One type of CpG-rich region is a CpG island. CpG islands are associated with approximately 60-70% of mammalian genes, and most CpG islands are unmethylated in normal mammalian cells. Thus, changes in methylation patterns at CpG islands can interfere with normal gene expression by altering the transcriptional competency of a gene's promoter. Genes that are essential for a cell's function are not methylated. In contrast, inactive genes are usually methylated to suppress their expression.

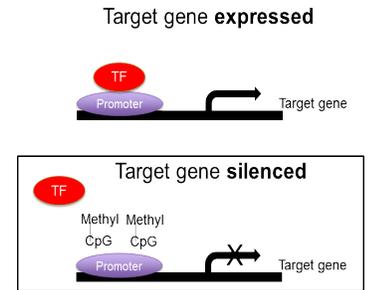


**Figure 1: This representative DNA helix depicts two methyl groups (M) covalently attached to two cytosine bases in DNA.**

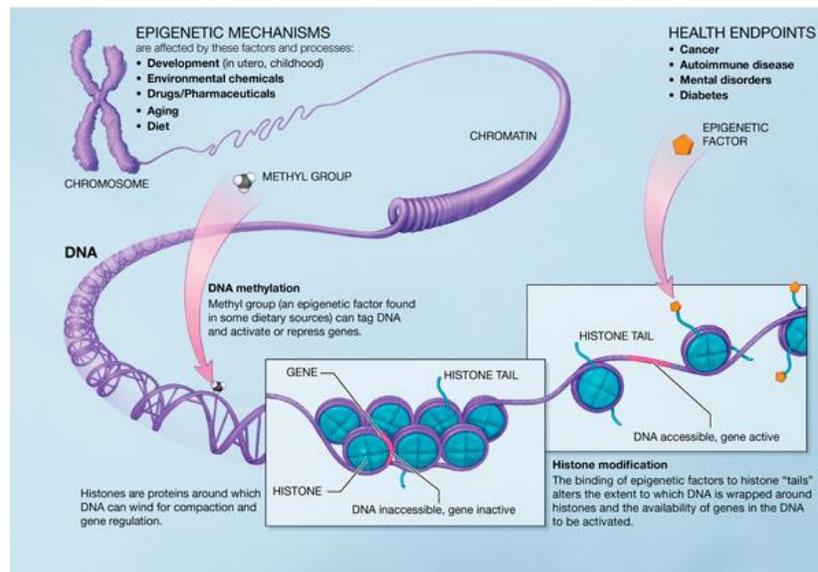
While DNA methylation is involved in normal control of gene expression, changes in the extent of DNA methylation can contribute to cancer or disease by silencing genes that that should otherwise be active or expressed or by causing expression of genes that are usually inactive. Methylation is one mechanism for suppressing (or silencing) gene transcription by preventing one or more **transcription factors (TF)** and thus **RNA polymerase** from accessing a gene's **promoter** which is required for transcribing DNA into RNA (see Figure 2).

The histone proteins that hold DNA tightly wound inside each cell can also be modified by methylation or other modifications such as acetylation or phosphorylation. When too much or too little of a given histone modification occurs, it affects a gene's expression and consequently its function, which causes unwanted alterations in the cell, potentially resulting in disease.

**Epigenetic modifications** can be maintained and inherited by daughter cells during mitosis and to a lesser extent during meiosis. Therefore, epigenetic modifications that occur *in utero* can be passed on to subsequent generations. Environmental factors such as exposure to heavy metals (arsenic, nickel) and cigarette smoke, and dietary factors such as vitamin and folate deficiencies have been linked to abnormal changes in epigenetic pathways, suggesting that an individual's environment plays an important role in shaping their epigenome. Epigenetic changes have been observed in different stages of cancer progression, in the process of aging, and in other human diseases such as Alzheimer's disease, diabetes and obesity.



**Figure 2: The addition of methyl groups to CpG islands common to promoters is one mechanism for suppressing (or silencing) gene transcription (Image: Fry, 2011).**



Source: <https://commonfund.nih.gov/epigenomics/figure>

In *A Tale of Two Mice* (<http://www.pbs.org/wgbh/nova/genes/mice.html>), the narrator discusses the difference in coat color between two genetically identical mice. The obese, yellow mouse has an unmethylated Agouti gene, which is constantly being expressed (when it normally should be “off” or silenced), while her sister, the brown mouse, has a methylated Agouti gene that has permanently been turned “off” and thus is not expressed. Although genetically identical in terms of the DNA sequences they've inherited from their mother and father (the mice are inbred), epigenetic modifications have led one mouse to be overweight and more susceptible to diabetes and cancer. This difference in gene expression between the genetically identical mice can be attributed to differential gene expression as a result of epigenetic modifications.

## Procedure

1. As an engagement activity, go to <http://www.pbs.org/wgbh/nova/body/epigenetic-mice.html> and launch the interactive slide show titled *A Tale of Two Mice*. Show students Chapter 1: *The Agouti Sisters* (50 seconds) to generate student interest.
2. Distribute copies of the *Student Worksheet* and ask students to work in pairs to complete Step 1.
3. Promote a brief class discussion by asking students to share their answers to Step 1, questions 1 and 2, with the class.
  - What does it mean to say that two individuals are genetically identical?
  - How can two genetically identical mice look so different?
4. Tell students that the answer to these questions lies in how DNA is packaged inside cells and then invite students to complete Step 2 on their worksheet. The amount of time students need for this step depends on the extent to which DNA and chromosome structure has already been covered in class.
5. Review student answers to Step 2 before proceeding to Step 3.
6. Next, introduce students to the concept that changes in gene expression can occur without changes in the DNA sequence of genes (mutation). Describe the process of DNA methylation as a means of silencing transcription of a gene (as described in the Background section).
7. To conclude this description of DNA methylation, return to the audio slide show *A Tale of Two Mice*. and show students Chapter 2: *The Epigenome* (1:06) and at least the first 15 seconds of the next chapter, *Switching on the Agouti Gene* – which explains that in the yellow, obese mouse, the agouti gene is unmethylated and turned on all of the time while in the brown mouse the gene is completely methylated and shut down.
8. Ask students to complete Step 3 by summarizing in their own words how DNA methylation affects DNA structure and function. Review student responses as a class before proceeding.
9. Next, ask students to read Step 4, examine Figures 4 and 5 from the featured *Environmental Health Perspectives* article and answer the corresponding questions. *Optional: Expose students to the original article and have them read and discuss all or part of this scientific publication.*
10. Review student responses as a class before allowing them to proceed to Step 5.
11. Ask students to read Step 5, and with a partner, discuss how the authors' conclusions are significant to them.
12. Discuss student responses as a class to conclude this lesson.
13. *Optional:* If time permits, you may choose to finish showing *A Tale of Two Mice* or the entire NOVA special *Epigenetics*, available at: <http://www.pbs.org/wgbh/nova/body/epigenetics.html>

## Assessment Options

- Ask students to turn in their completed worksheets (*Answer Key* provided).
- Ask student to summarize, in their words, what they learned during this activity.
- Ask students to construct a concept map using critical vocabulary terms (see below) along with vocabulary terms from page 2 to demonstrate they understand the concept of epigenetics in the context of DNA structure and function.

## Critical Vocabulary

Definitions for the terms below were obtained from the National Institute of Health, *Genetics Home Reference Handbook*  
<http://ghr.nlm.nih.gov/handbook/howgeneswork/epigenome>

**Epigenetics:** refers to heritable changes in the regulation of the expression of gene activity without alteration of genetic structure.

**Epigenetic modifications:** chemical compounds (e.g. methyl groups) that are added to single genes can regulate their activity; these modifications are known as epigenetic changes. These chemical “tags” can remain in place as cells divide and in some cases can be inherited through generations.

**Epigenome:** refers to all of the chemical compounds that have been added to the entirety of one’s DNA (genome) as a way to regulate the activity (expression) of all the genes within the genome. Environmental influences, such as a person’s diet and exposure to pollutants, can also impact the epigenome.

**Methylation:** small molecules called methyl groups, each consisting of one carbon atom and three hydrogen atoms, are covalently attached to segments of DNA by an enzyme known as a methyltransferase. When methyl groups are added to a particular gene, that gene is turned off or silenced, and no protein is produced from that gene.

**Methyltransferase:** refers the enzyme that covalently attaches a methyl group to DNA.

## Resources

Bob Weinhold. *Epigenetics: The Science of Change*. Environmental Health Perspectives. 2006.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392256/>

National Human Genome Research Institute, Epigenomics Fact Sheet.  
<http://www.genome.gov/27532724>

National Institute of Health, Genetics Home Reference, What is the Epigenome?  
<http://ghr.nlm.nih.gov/handbook/howgeneswork/epigenome>

National Institute of Health, A Scientific Illustration of How Epigenetic Mechanisms Can Affect Health  
<https://commonfund.nih.gov/epigenomics/figure>

NOVA, *Ghost in Your Genes*.  
<http://www.pbs.org/wgbh/nova/genes/>

Scitable by Nature Education, Epigenetic Influences and Disease. <http://www.nature.com/scitable/topicpage/Epigenetic-Influences-and-Disease-895>

University of Utah, Genetic Science Learning Center, Epigenetics.  
<http://learn.genetics.utah.edu/content/epigenetics/>

## Reference

Dana C. Dolinoy, Jennifer R. Weidman, Robert A. Waterland and Randy L. Jirtle. *Maternal Genistein Alters Coat Color and Protects Azy Mouse Offspring from Obesity by Modifying the Fetal Epigenome*. Environ Health Perspect.114: 567–572. 2006.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1440782/>

Paul Wade and Trevor Archer. *Epigenetics: Environmental Instructions for the Genome*. Environ Health Perspect.114:A140 –A141. 2006.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392246/>

## Step 1

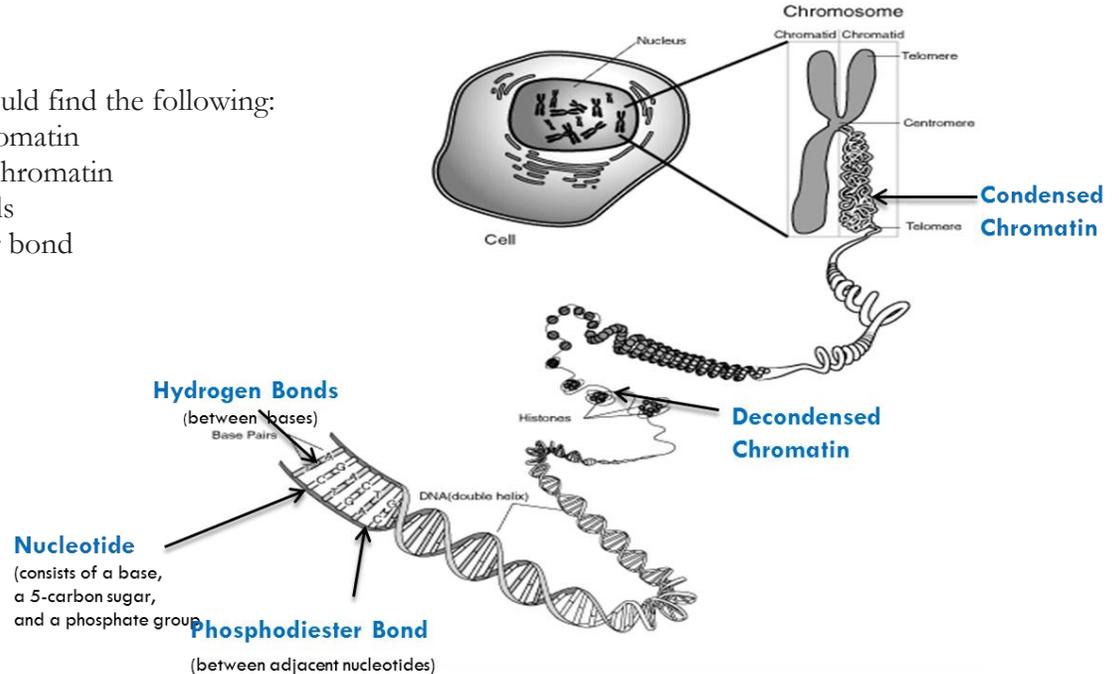
Watch Chapter 1 of the video “A Tale of Two Mice,” and be prepared to discuss these questions as a class:

1. What does it mean to say that two individuals are genetically identical?  
*Answers may vary, but will likely include some consensus about genetically identical offspring having the same sequences of DNA in their genes.*
2. How can two genetically identical mice look so different?  
*Answers may vary but do not tell students the answer. The genes of genetically identical individuals are not always expressed equally—this is known as differential gene expression.*

## Step 2

The figure below shows the location of chromosomes within a cell and the composition (i.e., DNA and structural proteins) and three-dimensional structure of chromosomes. Individually, or with a partner, use your textbook if necessary, to:

1. Indicate where you would find the following:
  - a. Condensed chromatin
  - b. Decondensed chromatin
  - c. Hydrogen bonds
  - d. Phosphodiester bond
  - e. Nucleotide



2. List the components of chromatin.  
*The main components are DNA and histone proteins but chromatin also includes RNA molecules and other associated proteins.*
3. Describe the role of histone proteins within a chromosome.  
*Histone proteins act as “spools” around which DNA winds to reduce the amount of space taken up by DNA in a cell. In this lesson, students learn that histones play both a structural and functional role in the cell since histones also play a role in gene regulation.*

### Step 3

Research suggests that the way DNA is “packaged” into chromatin plays an important role in genetic processes like DNA replication, recombination, repair, and transcription. This means that changes in gene expression (i.e., the yellow mouse versus the brown mouse in the video you saw) can occur without changes in the DNA structure itself (mutation).

Epigenetics is the study of other factors besides the DNA sequence that influence whether or not a gene is transcribed into mRNA and then translated (conversion of mRNA sequence into amino acids) into a protein. An individual’s environment, even in the womb, can influence these factors and permanently alter the expression of genes in the adult. Alterations in epigenetic mechanisms lead to development of diseases, such as some forms of cancer, including colorectal cancer and leukemia, neurodevelopmental disorders, obesity, and type 2 diabetes.

Your teacher provided you with an example of an epigenetic mechanism called **DNA methylation** that prevents a gene from being expressed (transcribed and translated into its protein product); this is also known as suppression of gene expression or gene silencing.

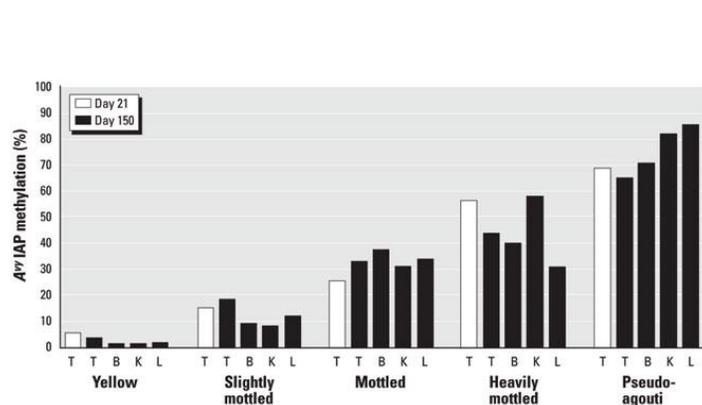
After learning about methylation and viewing Chapter 2 of “A Tale of Two Mice,” **summarize in your own words how this epigenetic modification affects DNA structure and function.**

*Answers will vary, but should indicate student understanding that methylation suppresses transcription of a gene by preventing the gene from being accessed by enzymes such as RNA polymerase that are essential for transcription to occur.*

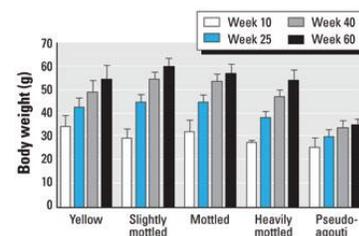
### Step 4

Below are the experimental results published in Figures 4 and 5 of the *Environmental Health Perspectives* article *Maternal Genistein Alters Coat Color and Protects  $A^y$  Mouse Offspring from Obesity by Modifying the Fetal Epigenome*.

In this study, pregnant mice were exposed to genistein, a component of soy, to determine if exposure to genistein influenced gene expression among genetically identical offspring.



**Figure 4.** Average  $A^y$  IAP methylation as a function of coat color, tissue type, and age. Abbreviations: B, brain; K, kidney; L, liver; T, tail. Average methylation across CpG sites 1–9 in day 150 tissues derived from ectodermal (B and T), mesodermal (K), and endodermal (L) tissues from five genistein-supplemented  $A^y/a$  animals representing the five coat-color phenotypes is correlated with that in day 21 tail tissue (Pearson’s  $r > 0.9$  and  $p < 0.05$  for each correlation).

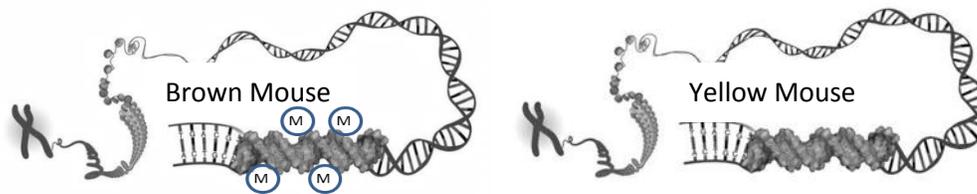


**Figure 5.** Variation of average body weight among animal coat-color class over time. Significant weight differences among coat-color classes start at week 25 and continue through adulthood. Pseudoagouti animals exhibit normal body weight compared with overweight yellow, slightly mottled, mottled, and heavily mottled animals due to hypermethylation in the  $A^y$  IAP region, which shuts off ectopic *Agouti* transcription. By shifting the offspring population coat-color distribution toward brown pseudoagouti animals, genistein supplementation significantly increases the incidence of normal-body-weight animals.

Look at the experimental results above (Figures 4 and 5) and complete the table on the next page before answering the questions that follow:

Mouse Coat Color	% Methylation in Tail Tissue (T) on day 21 (see Figure 4)	Body Weight (g) at week 60 (see Figure 5)
Yellow	~5%	~54g
Slightly Mottled	~15%	~60g
Mottled	~36%	~58g
Heavily Mottled	~58%	~54g
Pseudo-agouti (brown)	~70%	~38g

1. According to Figure 4, what is the relationship between percent methylation (y-axis) and coat color (x-axis)?  
*The greater the % methylation, the darker the coat color.*
2. According to Figure 5, what is the relationship between body weight (y-axis) and coat color (x-axis)?  
*The greater the % methylation, the more protected the mouse is from obesity (mice exhibit normal body weight).*
3. What explains the five different coat colors observed among offspring?  
*Each coat color corresponds to a different extent of methylation; the amount of methylation increases as coat color darkens.*
4. In which mouse population is the *Agouti* gene silenced? Active?  
*The *Agouti* gene is silenced in mice exhibiting the pseudo-agouti coat color and is most active in mice exhibiting a yellow coat.*
5. Assume the DNA diagrams below represent two *Agouti* genes, one in a brown mouse and one in a yellow mouse. Indicate which mouse would have a methylated *Agouti* gene by drawing methyl groups on the appropriate DNA strand.  
*The *Agouti* gene in the brown mouse is methylated.*



### Step 5

Read the authors' conclusions below, and with a partner discuss how these conclusions could be relevant for humans and summarize in your own words below.

“In the present study, we observed a statistically significant shift in coat-color phenotype and adult body weight distribution among genetically identical offspring whose mothers received a diet supplemented with 250 mg/kg diet of genistein. The shifts in coat color and body weight were mediated by increased methylation ... of the *Agouti* gene. Hypermethylation in the genistein-supplemented population results in decreased ectopic *Agouti* expression, which reduces yellow pheomelanin production and protects against adult-onset obesity. This is the first study to demonstrate that exposure to dietary genistein *in utero*, at levels present in human adult populations consuming high-soy diets, affects coat color and reduces population incidence of obesity by altering the epigenome in mice. Thus, an active ingredient in soy enhances the early establishment of DNA methylation.... [O]ur findings show that early nutritional and environmentally induced epigenetic modifications can provide an alternative mechanism for varying individual susceptibilities to environmental agents. Our results also suggest a plausible explanation for the lower incidence of certain cancers in Asians compared with Westerners (Chang et al. 2001; Lee et al. 1991) as well as the increased cancer incidence in Asians who immigrate to the United States (Ziegler et al. 1993).”

*Answers will vary, but students should conclude that these results may also apply to humans, and that diet, especially during pregnancy, can influence our epigenome and ultimately determine our susceptibility to cancer and disease. This example also clearly demonstrates that DNA methylation does not always lead to negative consequences for the individual.*

**Step 1**

Watch Chapter 1 of the video “A Tale of Two Mice,” and be prepared to discuss these questions as a class:

3. What does it mean to say that two individuals are genetically identical?
  
4. How can two genetically identical mice look so different?

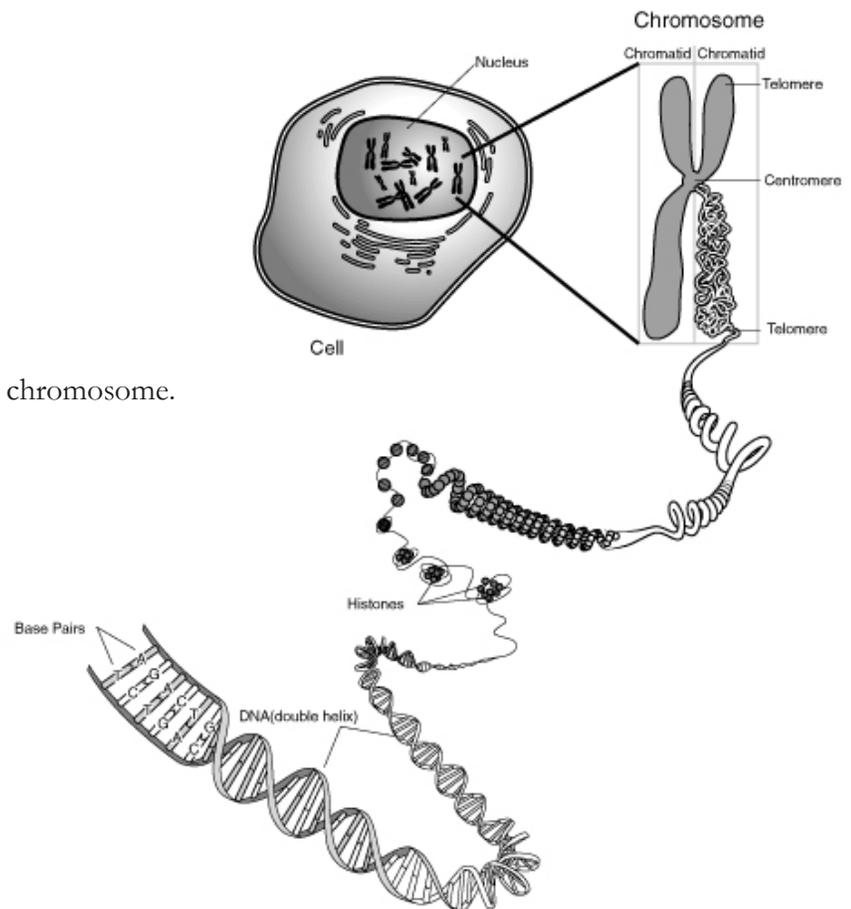
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3. List the components of chromatin.

3. Describe the role of histone proteins within a chromosome.



### Step 3

Research suggests that the way DNA is “packaged” into chromatin plays an important role in genetic processes like DNA replication, recombination, repair, and transcription. *This means that changes in gene expression (i.e., the yellow mouse versus the brown mouse in the video you saw) can occur without changes in the DNA structure itself (mutation).*

Epigenetics is the study of other factors besides the DNA sequence that influence whether or not a gene is transcribed into mRNA and then translated (conversion of mRNA sequence into amino acids) into a protein. An individual’s environment, even in the womb, can influence these factors and permanently alter the expression of genes in the adult. Alterations in epigenetic mechanisms lead to development of diseases, such as some forms of cancer, including colorectal cancer and leukemia, neurodevelopmental disorders, obesity, and type 2 diabetes.

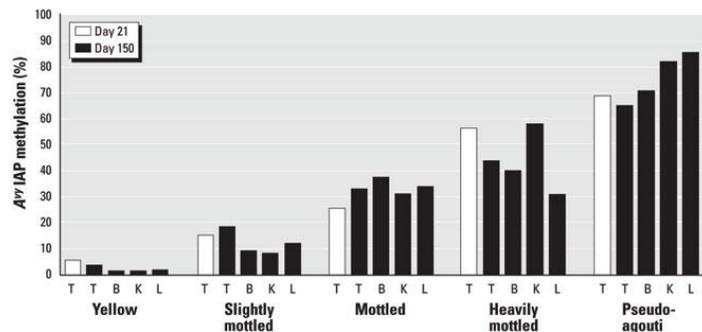
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After learning about methylation and viewing Chapter 2 of “A Tale of Two Mice,” **summarize in your own words how this epigenetic modification affects DNA structure and function.**

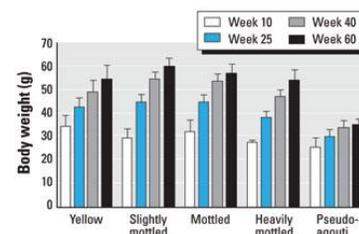
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**Figure 5.** Variation of average body weight among animal coat-color class over time. Significant weight differences among coat-color classes start at week 25 and continue through adulthood. Pseudoagouti animals exhibit normal body weight compared with overweight yellow, slightly mottled, mottled, and heavily mottled animals due to hypermethylation in the  $A^y$  IAP region, which shuts off ectopic *Agouti* transcription. By shifting the offspring population coat-color distribution toward brown pseudoagouti animals, genistein supplementation significantly increases the incidence of normal-body-weight animals.

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Yellow		
Slightly Mottled		
Mottled		
Heavily Mottled		
Pseudo-agouti (brown)		

1. According to Figure 4, what is the relationship between percent methylation (y-axis) and coat color (x-axis)?
2. According to Figure 5, what is the relationship between body weight (y-axis) and coat color (x-axis)?
3. What explains the five different coat colors observed among offspring?
4. In which mouse population is the *Agouti* gene silenced? Active?
6. Assume the DNA diagrams below represent two *Agouti* genes, one in a brown mouse and one in a yellow mouse. **Indicate which mouse would have a methylated *Agouti* gene by drawing methyl groups on the appropriate DNA molecule below.**



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