

LACTASE PERSISTENCE: EVIDENCE FOR SELECTION

OVERVIEW

This activity focuses on the genetic changes that gave rise to lactase persistence—an example of recent human evolution. Students explore the evidence for lactase-persistence mutations that arose within the last 10,000 years in different populations and increased in frequency by natural selection. They watch three short video segments and answer questions about the scientific data presented in three figures. Students may work individually or in small groups. We designed this activity for introductory biology classes to teach students to analyze and interpret scientific figures.

Students may further explore the topic using the references provided at the end of this document.

KEY TERMS

adaptation, allele, fitness, mutation, natural selection, variant, trait

SUGGESTED AUDIENCE

This activity is appropriate for introductory biology classes. It provides an example of human evolution that connects genotype, phenotype, culture, and graphical analysis skills.

PRIOR KNOWLEDGE

Students should be familiar with basic concepts in evolutionary theory (such as adaptation, fitness, and natural selection) and understand the terms “alleles,” “genetic variations,” and “mutations.”

PROCEDURE

PART 1: WHAT IS LACTASE PERSISTENCE?

1. Show students the beginning of the HHMI film [Got Lactase? The Co-evolution of Genes and Culture](http://www.hhmi.org/biointeractive/making-fittest-got-lactase-co-evolution-genes-and-culture) (<http://www.hhmi.org/biointeractive/making-fittest-got-lactase-co-evolution-genes-and-culture>) from the start of the film to time stamp 4:26 minutes. This video segment will provide background about lactase persistence and lactose metabolism. The segment ends with an animated version of Figure 1.
2. Refer students to Figure 1 in their handouts. Discuss any questions students have about the video segment or the figure legend and then ask students to answer the questions after the figure (under the heading “Interpreting the Figure”).

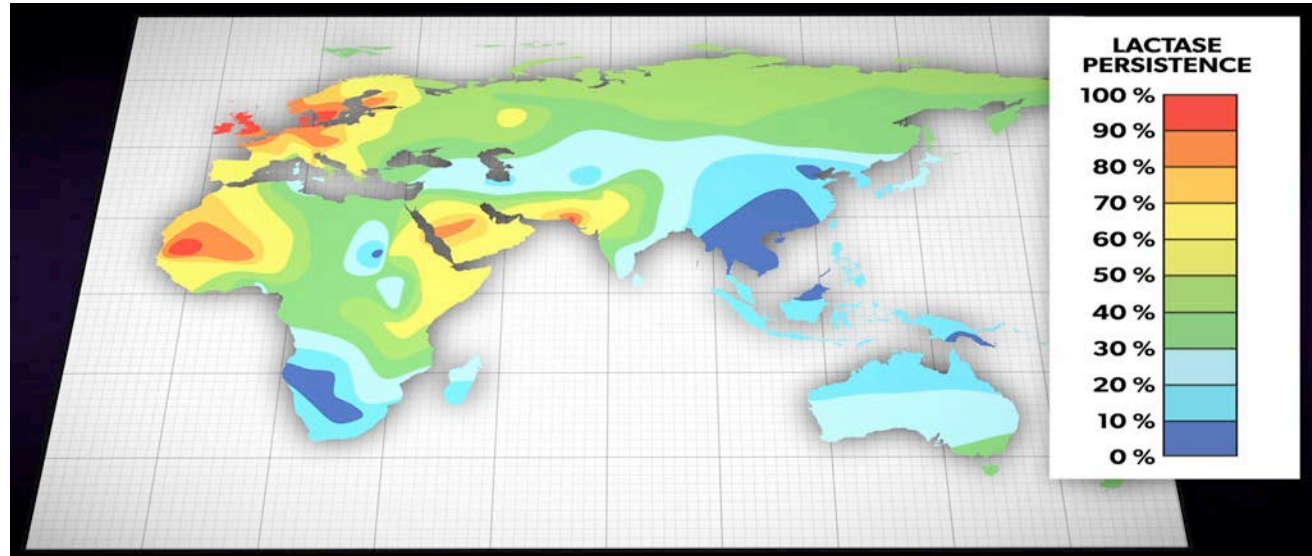
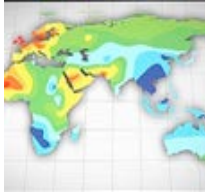


Figure 1. Global Distribution of Lactase Persistence. Worldwide, only about 35 percent of adults can digest lactose, and most are concentrated in particular geographic regions or “hot spots”: northern Europe, parts of east and west Africa, the Middle East, and South Asia. (Source: Adapted from Curry, Andrew. “The Milk Revolution.” *Nature* 500 (2013): 20–22. doi:10.1038/500020a. For an animated version of the map, see the HHMI film [Got Lactase? The Co-evolution of Genes and Culture](http://www.hhmi.org/biointeractive/making-fittest-got-lactase-co-evolution-genes-and-culture), <http://www.hhmi.org/biointeractive/making-fittest-got-lactase-co-evolution-genes-and-culture>, time stamp 4:12–4:26 minutes.)

Interpreting the Figure

1. *Why would a mutation leading to lactase persistence become common in a population?*

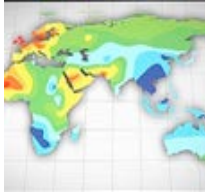
The lactase-persistence mutation would become common if it provided a survival and reproductive advantage in a particular environment. For example, in a population with domesticated cows, where milk is available, the ability to drink milk might have been advantageous in periods of drought or when food was limited. While possibly present in low frequencies, the change would not be advantageous in populations that do not consume milk.

2. *Use the map in Figure 1 to predict where you might find early evidence of dairying (i.e., using animal milk).*

The lactase-persistence hot spots are Europe, parts of Africa, the Middle East, and South Asia. That is where you would expect people began the cultural practice of dairying.

3. *Provide a scenario to explain how different global hot spots of lactase persistence could be caused by the same mutation.*

The mutation could originate in one population and spread to populations in other geographical locations as people with the lactase-persistence allele migrate to and settle in other places where there is the same selective pressure. Another possibility is that the same mutation could arise independently in four different populations.



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4. *Create a scenario to explain how different global hot spots of lactase persistence could be caused by different mutations.*

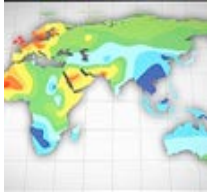
Each mutation could arise independently in a different population and increase in frequency because it offers the same selective advantage. Mutations could arise in the same gene and give rise to the same trait because many nucleotides contribute to controlling the expression of a gene. Mutations in a different gene could also give rise to the same trait. The latter scenario is an example of convergent evolution.

5. *Design an experiment to determine whether lactase persistence in the different global hot spots was caused by one or several mutations.*

Collect DNA from individuals who are lactase persistent and are from the global hot spot populations. Then look for genetic differences correlated with lactase persistence; the first place to look would be in and around the lactase gene. Compare the genetic differences to see if they are the same or different.

PART 2: EVIDENCE OF SELECTION

1. Show students a video clip from the 2011 Holiday Lecture by Dr. Sarah Tishkoff, titled [Genetics of Human Origins and Adaptation](http://media.hhmi.org/hl/11Lect2.html?start=50:42&end=51:47) at <http://media.hhmi.org/hl/11Lect2.html?start=50:42&end=51:47>. In it, she describes an animated version of Figure 2.
2. Following the video, discuss with students any questions they have about the content and then ask them to complete the questions following Figure 2 in their handouts.
3. Once students have completed their answers, discuss the two additional questions as a class discussion to lead into Part 3.



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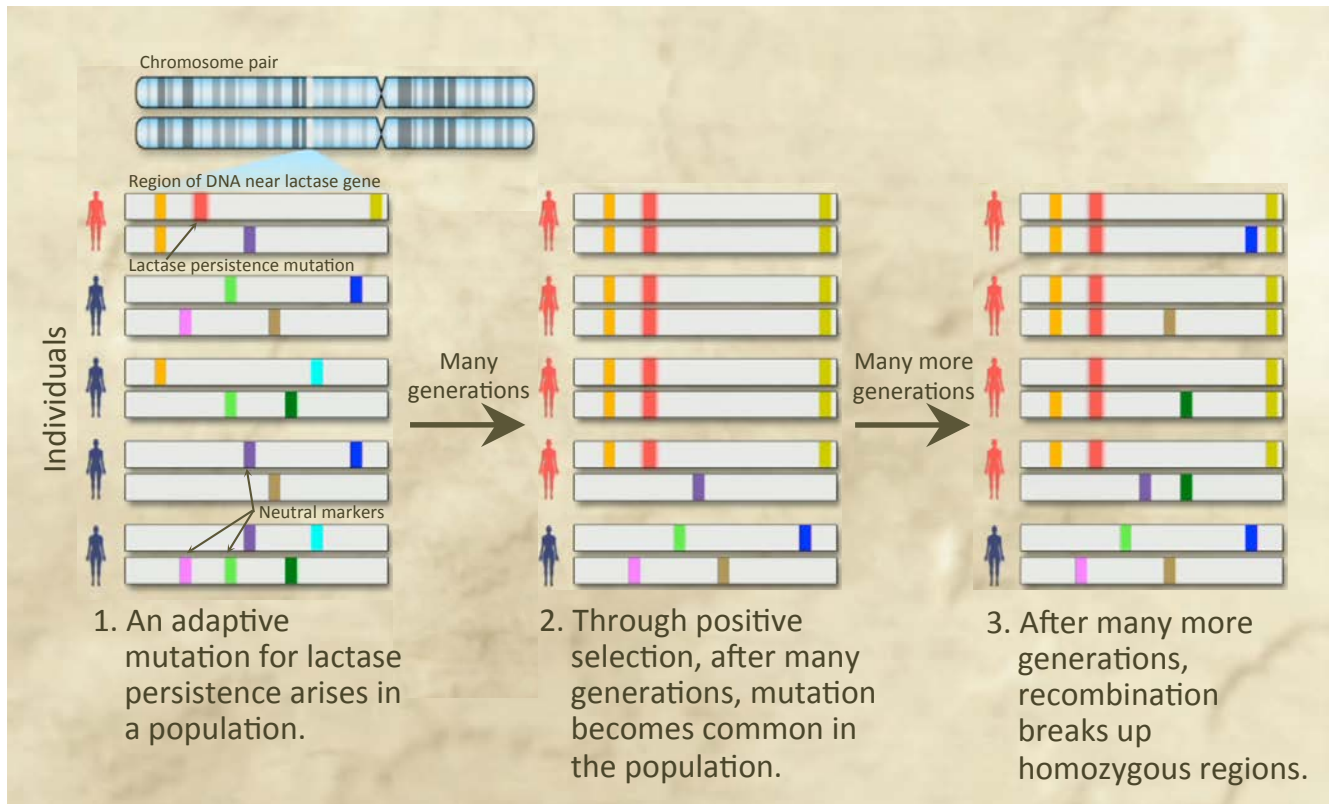
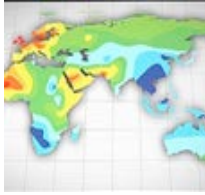


Figure 2. Evidence of a Selective Sweep for Lactase Persistence. Each individual has two copies of each chromosome, including the region around the lactase-persistence gene, shown as the white rectangles next to each individual. Lactase-persistent individuals have red silhouettes; lactase-nonpersistent individuals are blue. Comparing DNA sequences around the lactase gene in different individuals has revealed several neutral variations, or markers, which are denoted by different colored bands. In the first column, the red band indicates a genetic variant or mutation associated with lactase persistence—the lactase-persistence allele. When natural selection favors a beneficial allele, such as the lactase-persistence allele (red band), that allele is more likely to be passed on from one generation to the next. Over many generations, the beneficial allele increases in frequency. The frequencies of the nearby neutral markers (orange and yellow bands) also increase. These markers do not provide any selective advantage but are “swept” along with the beneficial allele. Column 2 shows evidence of this process as a reduction in genetic diversity in this particular region of chromosome 2. Over time, the association between the beneficial allele and neutral markers breaks down as a result of recombination, and the evidence for a selective sweep eventually disappears. (Source: Adapted from Tishkoff, Sarah A., [Lecture 2 – Genetics of Human Origins and Adaptation](#). 2011 Holiday Lectures on Science series Bones, Stones, and Genes: The Origin of Modern Humans. <http://media.hhmi.org/hl/11Lect2.html?start=50:42&end=51:47>.)

Interpreting the Figure

1. In column 1, the red band represents the lactase-persistence mutation. Why is it more prevalent in column 2, which shows the same DNA region in the same population after many generations?

The red band represents a beneficial allele favored by natural selection. Individuals with this allele have higher fitness and are more likely to reproduce and pass on their alleles to the next generation. As a result, the frequency of the allele increases in the population over many generations.



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2. In column 2, why do the orange and yellow bands always border the red band? What do the orange and yellow bands represent?

The orange and yellow bands are neutral variations in the DNA that happened to be nearby on the chromosome where the beneficial lactase persistence mutation arose. These variations are physically connected or linked to the red allele. Although they are not under selection, they are more likely to travel or hitchhike along with the beneficial red allele as it passes on from one generation to the next.

3. How many individuals in column 2 are homozygous for the lactase-persistence allele? How many are homozygous for the surrounding region (i.e., the white rectangle)?

In column 2, 3 of 5 individuals are homozygous for the red allele and for the surrounding region. We know this because these individuals are homozygous for two other variations near the lactase-persistence mutation.

4. Why would scientists want to identify regions in the genome that are homozygous in many individuals in a population (i.e., regions of homozygosity, or reduced diversity)?

Regions of homozygosity may contain genetic variants that have been under strong selection in recent evolutionary time. Thus, these regions may reveal the presence of genes that are evolutionarily important.

5. How many individuals in column 3 are homozygous for the lactase-persistence allele? How many are homozygous for the whole region?

In column 3, 3 of 5 individuals are homozygous for the red allele, but none is homozygous for the whole region. We know this because each individual has different variations (i.e., different-colored bands) in this genomic region.

6. How do you explain the differences between columns 2 and 3?

The region of homozygosity in column 3 is reduced compared to that in column 2. When chromosomes are passed on from parents to offspring, recombination shuffles extant variation among chromosomes each generation. Neutral mutations will also accumulate over thousands of generations in the homogeneous region. Over many generations, this reshuffling of DNA results in a smaller and smaller region of homozygosity.

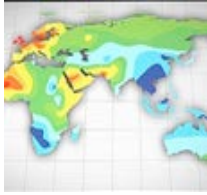
ADDITIONAL DISCUSSION QUESTIONS

1. Is lactase persistence a dominant or recessive trait? Use Figure 2 to explain your answer.

Dominant. Some lactase-persistent individuals, indicated by the red silhouettes, have only one copy of the lactase-persistence allele. A recessive trait would require two copies of the mutation. (Note: In Part 3, students will discover that the lactase-persistence allele is located in the regulatory region of the lactase gene and causes the gene to remain active in adulthood. One active version of the gene is sufficient to produce enough lactase enzyme to digest lactose.)

2. What does the length of the region of homozygosity around an allele reveal about its evolutionary history?

Mutations that were under selection more recently have larger regions of homozygosity than older mutations. This is because over time recombination breaks apart linked alleles or variants.



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Researchers can estimate when an advantageous mutation appeared and increased in frequency in a population by the length of homozygous stretches of DNA around it.

PART 3: LACTASE PERSISTENCE IN EAST AFRICA

1. Show students a two-minute video clip from the [Genetics of Human Origins and Adaptation](#) lecture by Sarah Tishkoff in which she discusses Figure 3 and explains its relationship to Figure 2: <http://media.hhmi.org/hl/11Lect2.html?start=51:47&end=53:51>. Note that Tishkoff conducted her research in East Africa, an area with both lactase-persistent and -nonpersistent individuals—a “yellow” region in the map in Figure 1.
2. Show students Figure 3 and ask them to answer the associated questions, working individually or in small groups.

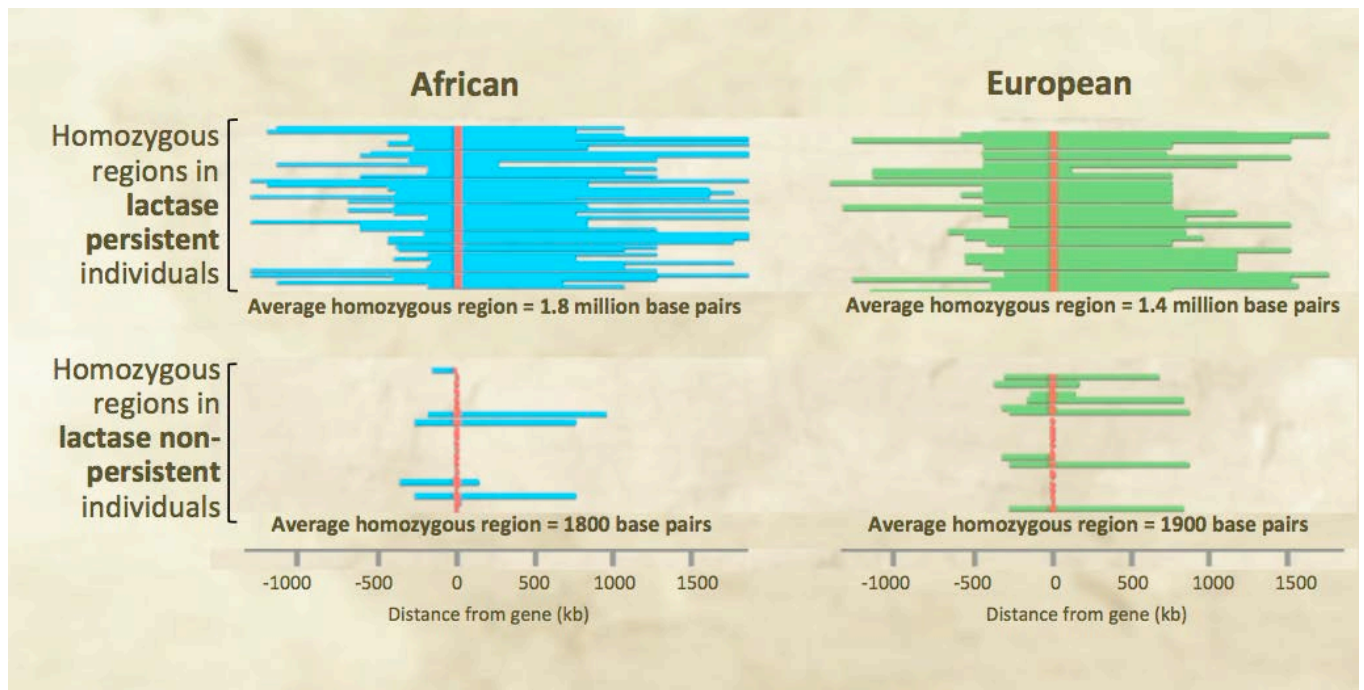
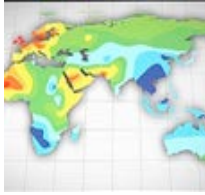


Figure 3. Evidence of Selection for Lactase Persistence in African and European Populations. Lactase-persistent individuals in African and European populations have large regions of homozygosity around the lactase-persistence alleles. Each blue and green bar represents a region of homozygosity in one individual; the lengths of these regions are shown at the bottom of the figure. Large areas of homozygosity indicate strong, recent selection. (Source: Adapted from Tishkoff, Sarah A., [Lecture 2 – Genetics of Human Origins and Adaptation](#). 2011 Holiday Lectures on Science series Bones, Stones, and Genes: The Origin of Modern Humans. <http://media.hhmi.org/hl/11Lect2.html?start=50:42&end=51:47>; and Figure 6 in Tishkoff, Sarah A., et al. “Convergent Adaptation of Human Lactase Persistence in Africa and Europe.” *Nature Genetics* 39 (2007): 31–40. doi:10.1038/ng1946.2007.)

Interpreting the Figure

1. In the African population, why do lactase-persistent individuals have large areas of homozygosity compared to individuals who are not lactase persistent?



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There was strong selection pressure for the lactase-persistence allele. This selection caused the allele (and surrounding DNA) to be passed on from one generation to the next. Evidence for this selective sweep can be seen as a large area of homozygosity in all lactase-persistent individuals. Because selection occurred recently, recombination has not had sufficient time to break up the linkage blocks. In lactase-nonpersistent individuals, there may have been selection for the allele that causes the lactase gene to be turned off, but this selection occurred so long ago that there is no evidence for it in the genome. Students may also say that the lactase-nonpersistence allele was not under selection in this population.

2. *Use evidence to explain whether either the African or European population shows evidence of strong, recent selection in the genome.*

Both populations show evidence of recent, strong selection for a beneficial allele. Lactase-persistent individuals have large blocks of homozygosity around the lactase gene—of 1.8 million base pairs and 1.4 million base pairs, respectively.

3. *The African and European populations have different lactase-persistence alleles. Use data from Figure 3 to formulate a hypothesis about which allele originated more recently.*

The data support the hypothesis that lactase persistence arose more recently in the African population. The average African homozygous region is 1.8 million base pairs, while the European average is 1.4 million base pairs. Assuming no difference in recombination rates among populations, longer regions of homozygosity indicate more recent selection.

4. *What additional evidence might support this hypothesis?*

Students' answers will vary, but one possible answer would be archaeological evidence of cattle domestication and dairying. This evidence exists and shows that dairying first occurred in Europe in a region that is now Hungary. Dairying was practiced slightly later in the African continent.

PART 4: SUMMARY DISCUSSION

1. *What is evolution?*

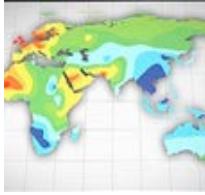
Evolution is the change in allele frequencies over time.

2. *Do the data on lactase persistence support the idea that humans are evolving? Use data to support your answer.*

The data on lactase persistence provides strong support that humans are evolving. In the last 10,000 years, different mutations that enable human adults to digest milk became prevalent in some human populations. In cultures that practiced dairying (in other words, consumed milk or milk products), the ability to digest milk as adults could provide a survival and reproductive advantage. In these populations, the lactase-persistence allele would have increased in frequency over time. This change in allele frequency is evidence for evolution.

3. *Does lactase persistence provide an example of a selective sweep? Use data to support your answer.*

Individuals of African and European ancestry who are lactase persistent have areas of reduced genetic diversity (homozygosity) around the lactase gene, providing evidence of a selective sweep for the mutation that gave rise to lactase persistence in these populations.



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RELATED RESOURCES AND REFERENCES

Check, Erika. "How Africa Learned to Love the Cow." *Nature* 444 (December 21, 2006): 994–996. doi:10.1038/444994a.

Evershed, Richard P., Sebastian Payne, Andrew G. Sherratt, Mark S. Copley, Jennifer Coolidge, Duska Urem-Kotsu, Kostas Kotsakis, et al. "Earliest Date for Milk Use in the Near East and Southeastern Europe Linked to Cattle Herding." *Nature* 455 (September 25, 2008): 528–531.

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Tishkoff, Sarah A. 2011. Lecture 2 – Genetics of Human Origins and Adaptation. 2011 Holiday Lectures on Science series Bones, Stones, and Genes: The Origin of Modern Humans. <http://media.hhmi.org/hl/11Lect2.html>.

Howard Hughes Medical Institute. *Regulation of the Lactase Gene* (Click and Learn activity and worksheet). <http://www.hhmi.org/biointeractive/regulation-lactase-gene>.

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