

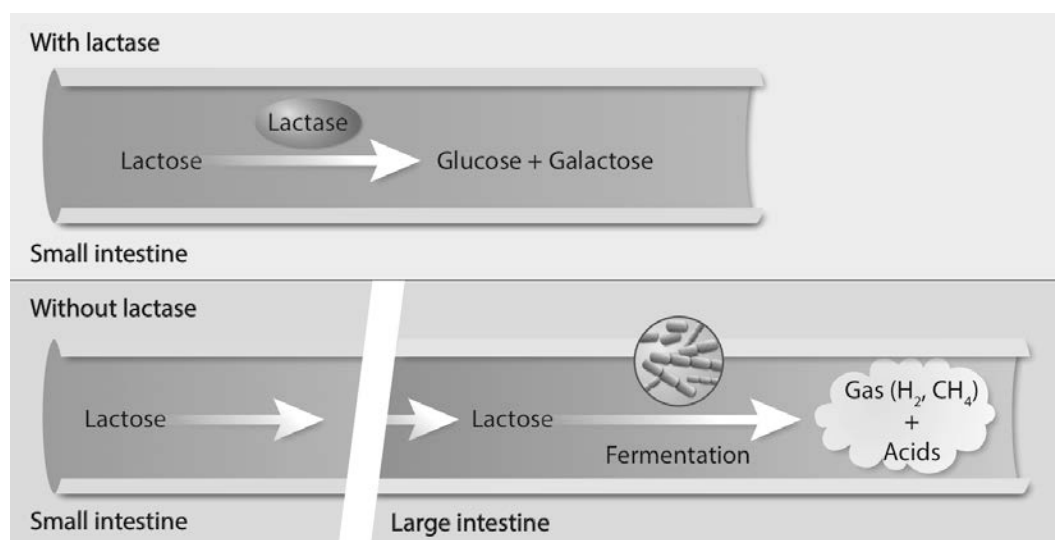
## PEDIGREES AND THE INHERITANCE OF LACTOSE INTOLERANCE

### INTRODUCTION

A defining characteristic of mammals is that mothers produce milk for their infants through a process called lactation. "Mother's milk" is packed with the proteins, fats, and carbohydrates that support the baby's growth and development. The main carbohydrate in milk is the sugar lactose, which is a disaccharide.

Infant mammals produce the enzyme lactase in their small intestines. Lactase breaks down lactose into glucose and galactose. These two simpler sugars, or monosaccharides, are easily absorbed through the small intestine and into the bloodstream. The blood delivers the sugars throughout the body to provide cells with a source of energy.

At around the time that children stop drinking their mother's milk, most of them also stop producing lactase. If lactase is not produced and a person drinks milk, undigested lactose travels from the small intestine to the large intestine, where it is digested by bacteria. When this happens, a person can have abdominal pain, bloating, flatulence, and diarrhea. Individuals with these symptoms are **lactose intolerant**.



**Figure 1.** If lactase is produced, the lactose in milk is digested into glucose and galactose in the small intestine. If lactase is not produced, undigested lactose goes from the small intestine to the large intestine, where it is digested by bacteria through fermentation. That process results in the production of various gases and acids that can cause discomfort and pain.

Only a minority of human adults—35% of the global human population—continues to produce lactase into adulthood and can drink milk without any problems. These individuals are **lactose tolerant**. They can also be referred to as being **lactase persistent**, meaning that lactase production persists beyond childhood. (People who no longer produce lactase as adults are called **lactase nonpersistent**.)

Genetic studies suggest that lactose tolerance arose among human populations in the last 7,000 to 9,000 years. This is also when humans began domesticating animals like cows, goats, and camels and started drinking their milk.

The film *Got Lactase? The Co-evolution of Genes and Culture* traces the evolution of lactose tolerance. It also describes how researchers analyzed the pedigrees of several Finnish families to identify the changes in the DNA, or mutations, responsible for lactose tolerance.

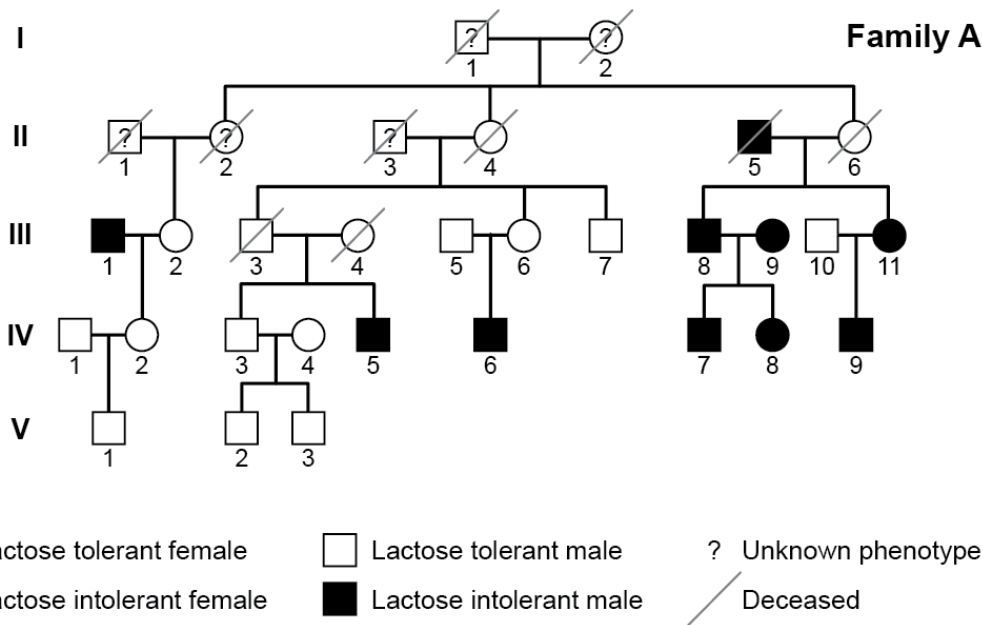
In this activity, you will analyze some of those pedigrees to determine how the lactose-tolerance/-intolerance trait is inherited. You will then analyze DNA sequences to identify mutations associated with the trait.

**PROCEDURE**

**Part 1: Determining the Pattern of Inheritance of Lactose Tolerance/Intolerance**

To determine how lactose tolerance/intolerance is inherited, researchers examined nine extended Finnish families for five generations.

Below is one of those pedigrees. The pedigree is shown exactly how it appeared in the original paper. Note that in this pedigree researchers were studying the inheritance of the lactose intolerance trait (filled-in symbols). For a refresher on pedigrees, refer to the chart on page 6.



**Figure 2.** Pedigree of Family A. (Adapted from a figure in Enattah, N. S., et al. 2002 *Nature Genetics* 30: 233-237.)

1. Based on the pedigree above, which of the following terms are appropriate for describing the inheritance of the lactose-intolerance trait (filled-in symbols)? Check all that apply.

- Recessive       Dominant
- Inherited       X-linked

2. Which of the following terms are appropriate for describing the inheritance of the lactose-tolerance trait (empty symbols)? Check all that apply.

- Recessive       Dominant
- Inherited       X-linked

3. Use the data in the pedigree and the terms listed in questions 1 and 2 to make a claim about how lactose intolerance is inherited. Provide at least two pieces of evidence in support of your claim.

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4. How comfortable are you with drawing a firm claim about the inheritance of lactose intolerance? What might you do next to increase your confidence in making this claim?

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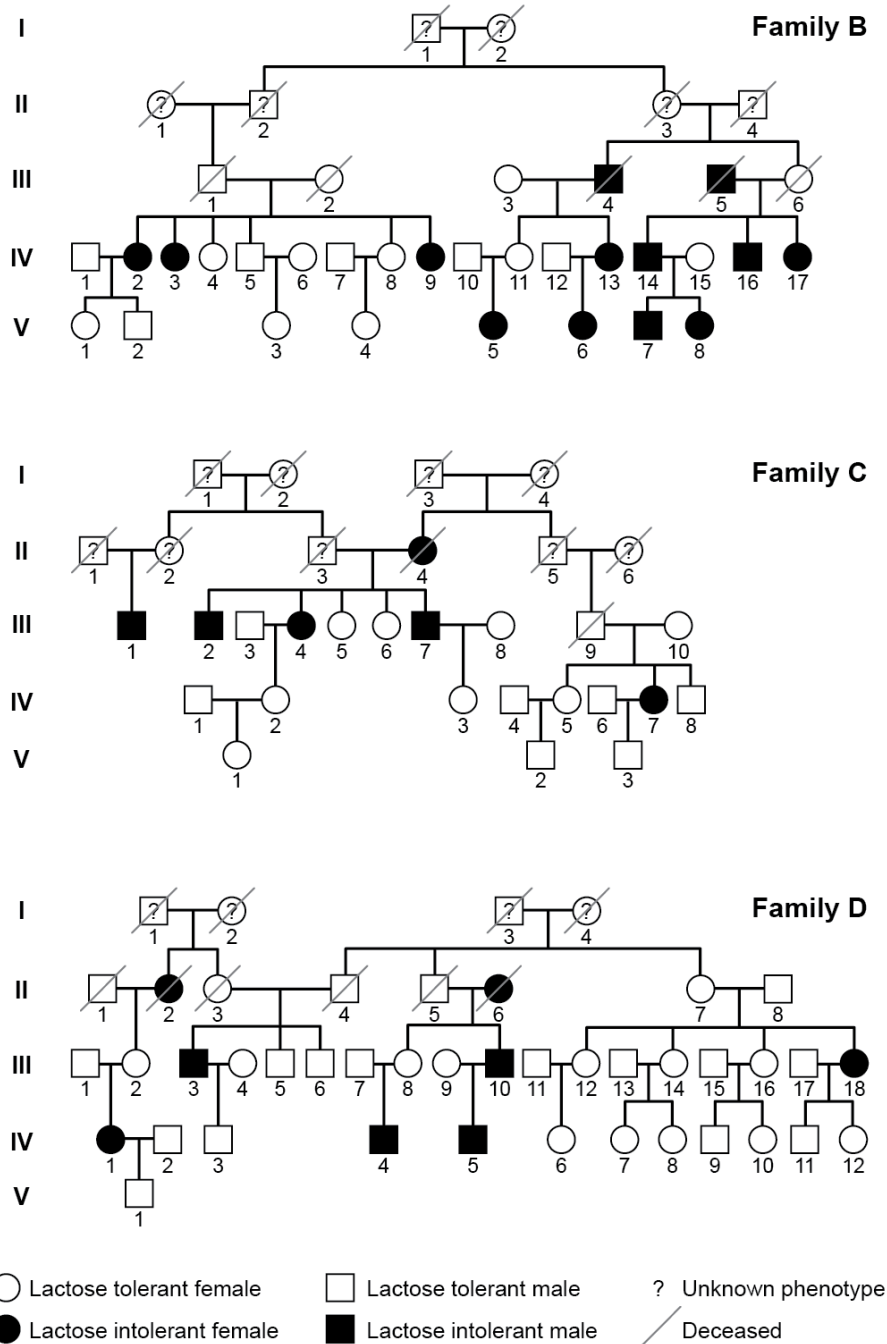
5. Study Individuals 5 and 6 of Generation III in Family A and their child. The two parents are lactose tolerant, yet their son is lactose intolerant. Are these data consistent or inconsistent with the claim you made in question 3? Explain your answer.

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You are now going to examine three additional pedigrees from the Finnish study. Again, these pedigrees are shown exactly how they appeared in the original publication.



**Figure 3.** Pedigrees of Families B, C, and D. (Adapted from a figure in Enattah, N. S., *et al.* 2002 *Nature Genetics* 30: 233-237.)

6. Do the data presented in these additional pedigrees support your claim in question 3 above? Explain your answer.

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7. Based on your claim, which symbols would you use to represent the genotype of an individual who is lactose tolerant?  
\_\_\_\_\_ Lactose intolerant? \_\_\_\_\_

8. Based on your claim, what is the genotype of Individual 3, Generation IV in Family C? Explain your answer.

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9. Based on the same claim, what is the genotype of the father of Individual 4, Generation IV in Family D? Explain your answer.

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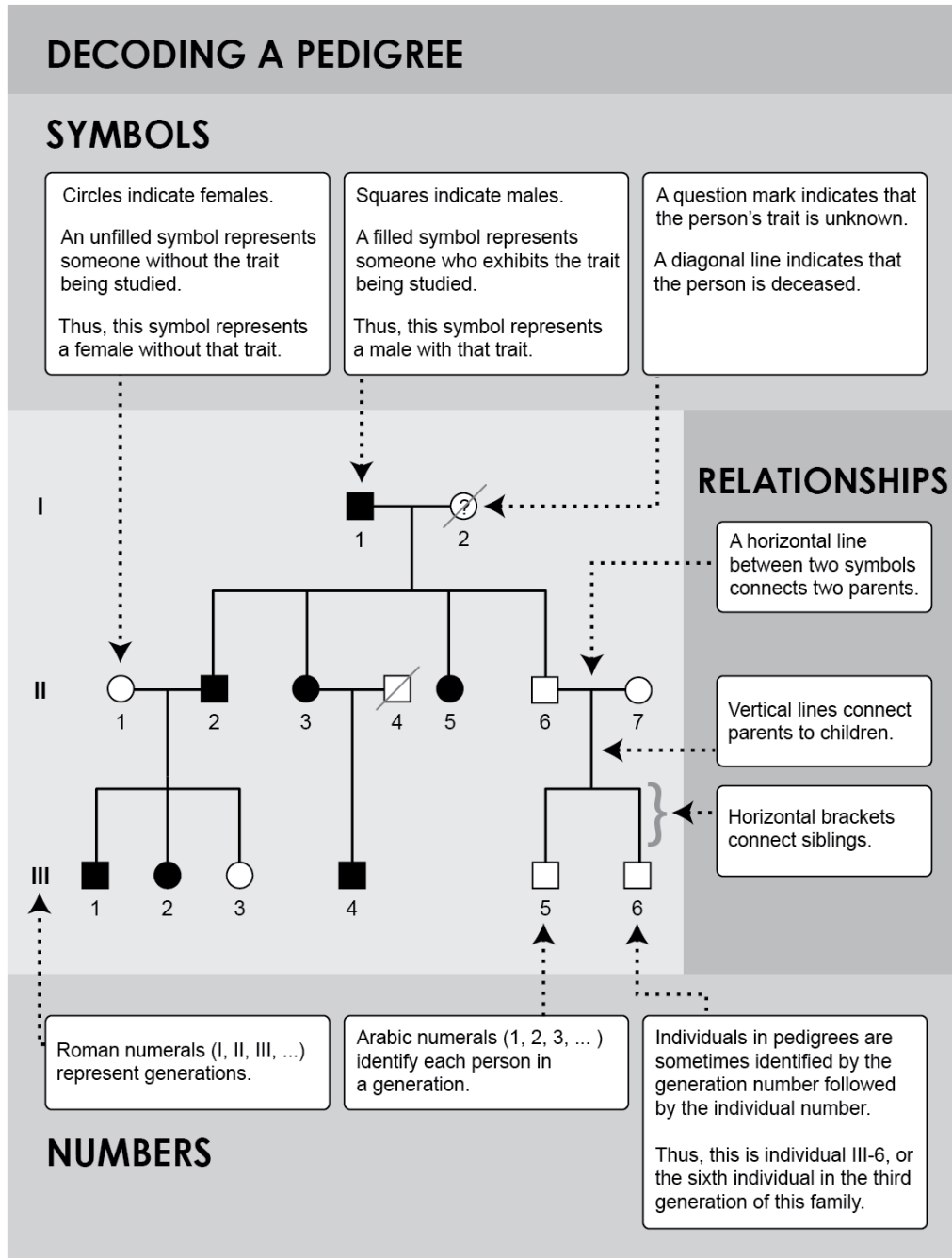
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10. Individuals 8 and 9, Generation IV in Family B are sisters. Based on your inheritance claims, what is/are the possible genotype(s) of:

- a. Individual 9? \_\_\_\_\_
- b. Individual 8? \_\_\_\_\_
- c. The parents of Individuals 8 and 9? \_\_\_\_\_

11. Individual 4, Generation IV in Family B is the sister of Individuals 8 and 9 in the question above. What is the probability that Individual 4 is homozygous? \_\_\_\_\_ Heterozygous? \_\_\_\_\_

A pedigree chart is a tool that helps illustrate how a trait is inherited from one generation to the next. Below is a pedigree chart that includes three generations of an extended family.

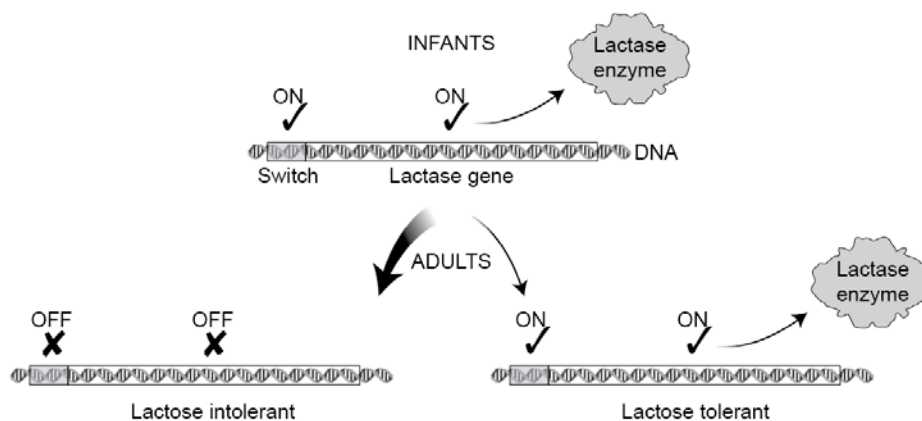


## Part 2. Finding the Responsible Mutation

In the film *Got Lactase? The Co-evolution of Genes and Culture* you learned that researchers did not find any changes in DNA sequence, or mutations, in the coding region of the lactase gene that were associated with lactose tolerance/intolerance. This finding suggested that the genetic change responsible for whether someone is lactose tolerant or intolerant is not in the coding region of the gene.

Could the change be in the regulatory region of the gene?

Genes are regulated, or turned on or off, by genetic elements called switches. When the lactase switch turns the lactase gene on, the lactase enzyme is produced. In babies, the lactase gene is turned on. But when babies grow into adults, the switch turns the lactase gene off in most people. In a minority of adults, a mutation in the lactase switch prevents the lactase gene from turning off. These adults are lactose tolerant.



**Figure 4.** The genetic switch that regulates the expression of the lactase gene is active in babies but not in most human adults. Individuals who are lactose tolerant (or lactase persistent) have a mutation in the lactase switch that keeps the switch turned on into adulthood.

To find the mutation that keeps the lactase gene on, researchers analyzed the DNA sequence of the lactase switch in several individuals. They found many differences. For example, at one particular position in the sequence of DNA, some individuals might have an adenine (A) nucleotide and others a thymine (T) nucleotide.

Most of the differences in DNA sequence have no effect on lactase production. To detect changes in DNA that are associated with lactose tolerance, researchers looked for variations that are consistently found in people who are lactose tolerant but not in people who are lactose intolerant, and vice versa.

You will now do the same.

Tables 1 and 2 show DNA sequences from two short regions of DNA on chromosome 2. Because each individual has two copies of chromosome 2 (one from each parent), each table includes two DNA sequences per person. Individuals are identified by generation number and individual number. For example, Individual B IV-4 is Individual 4, Generation IV in Family B.

**Table 1. DNA Sequence 1 from Lactose-Tolerant and -Intolerant Individuals**

Family	Generation	Individual	Phenotype	Sequence 1*
A	IV	3		<i>Copy 1, Chromosome 2:</i> TAAGATAATGTAGCCCTGG <i>Copy 2, Chromosome 2:</i> TAAGATAATGTAGCCCTGG
B	IV	4		<i>Copy 1, Chromosome 2:</i> TAAGATAATGTAGCCCTGG <i>Copy 2, Chromosome 2:</i> TAAGATAATGTAGCCCTGG
B	IV	8		<i>Copy 1, Chromosome 2:</i> TAAGATAATGTAGCCCTGG <i>Copy 2, Chromosome 2:</i> TAAGATAACGTAGCCCTGG
B	IV	9		<i>Copy 1, Chromosome 2:</i> TAAGATAATGTAGCCCTGG <i>Copy 2, Chromosome 2:</i> TAAGATAATGTAGCCCTGG
C	IV	3		<i>Copy 1, Chromosome 2:</i> TAAGATAATGTAGCCCTGG <i>Copy 2, Chromosome 2:</i> TAAGATAATGTAGCCCTGG
D	IV	4		<i>Copy 1, Chromosome 2:</i> TAAGATAATGTAGCCCTGG <i>Copy 2, Chromosome 2:</i> TAAGATAATGTAGCCCTGG

\*Sequence 1 is a nucleotide sequence corresponding to nucleotides 19923-13902 upstream from the start of the lactase gene.

**Table 2. DNA Sequence 2 from Lactose-Tolerant and -Intolerant Individuals**

Individual			Phenotype	Sequence 2*
A IV-3				<i>Copy 1, Chromosome 2:</i> ATAAAGGACTCTTGACAA <i>Copy 2, Chromosome 2:</i> ATAAAGGACTCTTGACAA
B IV-4				<i>Copy 1, Chromosome 2:</i> ATAAAGGACTCTTGACAA <i>Copy 2, Chromosome 2:</i> ATAAAGGACTCTTGACAA
B IV-8				<i>Copy 1, Chromosome 2:</i> ATAAAGGACTCTTGACAA <i>Copy 2, Chromosome 2:</i> ATAAAGGACGCTCTTGACAA
B IV-9				<i>Copy 1, Chromosome 2:</i> ATAAAGGACGCTCTTGACAA <i>Copy 2, Chromosome 2:</i> ATAAAGGACGCTCTTGACAA
C IV-3				<i>Copy 1, Chromosome 2:</i> ATAAAGGACTCTTGACAA <i>Copy 2, Chromosome 2:</i> ATAAAGGACTCTTGACAA
D IV-4				<i>Copy 1, Chromosome 2:</i> ATAAAGGACTCTTGACAA <i>Copy 2, Chromosome 2:</i> ATAAAGGACTCTTGACAA

\*Sequence 2 is a nucleotide sequence corresponding to nucleotides 30192-30173 upstream of the start of the lactase gene.

1. Study the two tables above. Fill in the phenotype (e.g., lactose tolerant or lactose intolerant) of each individual in the second column of the table. (You will need to look at the pedigrees in Part 1 to complete this step.)

2. Identify and circle all the nucleotides that differ between at least two sequences in each table.



3. Pretend that you are the researcher who discovered the variations and you are writing to a colleague describing what you found.

a. How would you describe the variation(s) you found in Sequence 1?

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b. How would you describe the variation(s) you found in Sequence 2?

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4. Based on the sequence data you analyzed, which variation is associated with lactose tolerance (lactase persistence)? Support your claim by providing at least three pieces of evidence.

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5. Is the variation associated with lactose tolerance (lactase persistence) found on one chromosome or both chromosomes in individuals with the trait? Explain your answer.

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6. From the pedigrees and the DNA sequencing data, what do you know about how the variation associated with lactose tolerance was inherited for Individuals B IV-4 and B IV-9?

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7. The mutation associated with lactose tolerance keeps the lactase gene turned on in adults. Based on the sequence and pedigree data, what can you infer about the regulation of the lactase gene in Individual A IV-3? Explain.

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**AUTHOR**

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