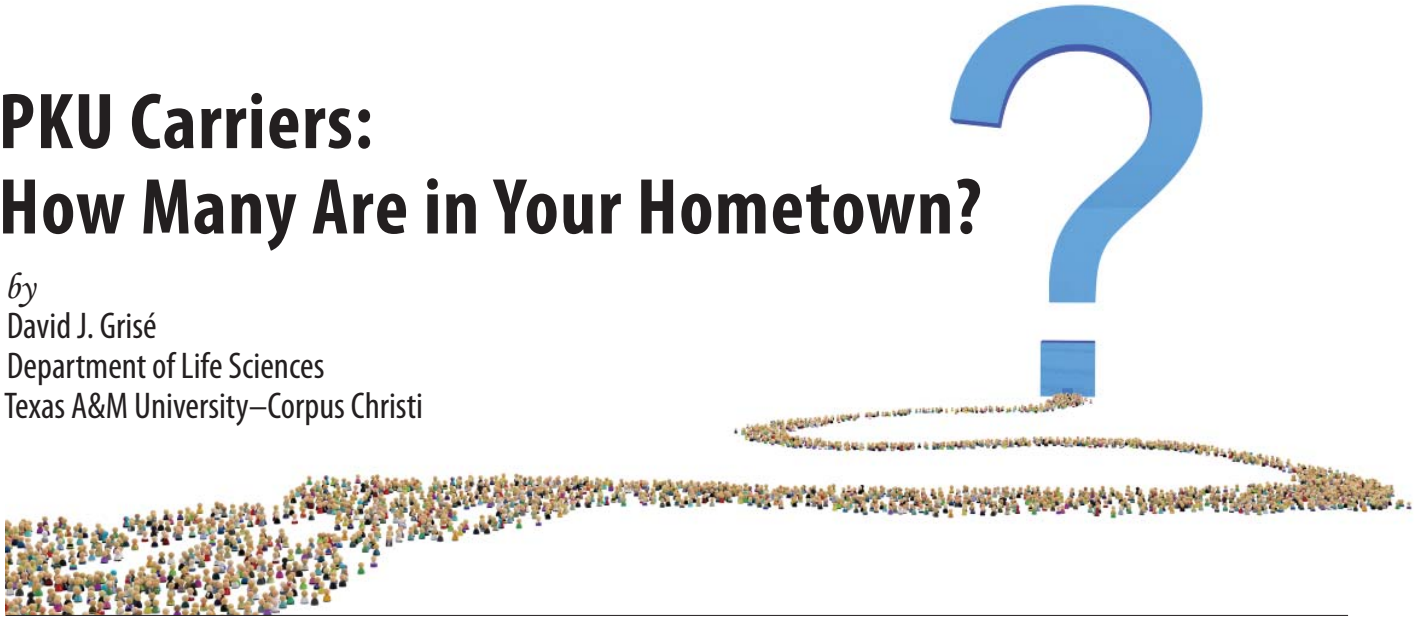
PKU Carriers: How Many Are in Your Hometown?



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Part I – PKU

Sitting in biology class one day, Jane was taking notes about traits determined by a single gene with a dominant and a recessive allele. She wasn't too interested because the example used in class was seed color in pea plants. Although she would have rather been texting her friends about going to the beach near Corpus Christi later in the day, she wrote down that yellow is the dominant allele, the allele for green seed color is recessive to the allele for yellow seed color, heterozygotes have yellow seeds, blah, blah, blah. Thankfully, the clock made its way to 11:50AM, and she was free.

After class, Jane met some of her friends for lunch. Anna asked, "Jane, didn't you have baked potato and broccoli yesterday and the day before that too? Hey, you also have the same drink that you had the past couple of days. What is going on with that?"

"Just after I was born I was diagnosed with a condition called phenylketonuria, or PKU for short," replied Jane. "I don't understand the condition very well. My parents made me follow a special diet the doctors gave them. My diet has very little of the amino acid phenylalanine. Some nutrients are missing in my diet so I drink a can of this nutrient drink every day. Caitlin, read the warning on the back of that diet soda you are drinking."

"Why would there be a warning on my diet soda can?" asked Caitlin. "Oh, here it is! It says, *Phenylketonurics: Contains phenylalanine*."

Jane replied, "If I have any of that stuff, I just can't think straight. When I first got here, I went off my diet. It was awful. I couldn't remember anything, I couldn't concentrate, and I couldn't pay attention. Biology was impossible when I was eating 'normal' foods. Now that I am back on my diet, biology is still a hard class, but it's not as bad as when I was eating 'normal' foods."

Mariela asked, "Jane, if you don't eat 'normal' foods, then what do you eat?"

"I eat things like I'm eating now," replied Jane. "I eat a lot of fruits, vegetables, low protein breads, and pasta. I have one of these phenylalanine-free formula drinks containing protein, vitamins, and minerals every day. My typical meal is a couple different types of vegetables and a baked potato."

"Does everybody in your family eat this diet?" asked Megan.

"No, my parents, brother, and sister don't have PKU, so they can eat 'normal' foods."

Amanda, Jane's best friend, said, "Hey, lab starts in 10 minutes, we better read the lab so we can answer the questions on the pre-lab quiz."

Later, Amanda called Jane and asked if Jane had started working on the questions they had to answer for class on Friday. Amanda normally didn't look at these questions until just before they were due, but because she was finding the course challenging, she took a look at the questions early. She read the first question to Jane:

> *Let's assume that earlobe shape in humans is determined by a single gene with two alleles. Two people with unattached earlobes have a child with attached earlobes. Which earlobe shape is determined by the dominant allele? Which earlobe shape is determined by the recessive allele?*

Hearing the question, Jane dropped everything she was doing and told Amanda she had to go do something and would call her back. It had suddenly occurred to Jane that maybe she was beginning to understand why she had PKU!

Questions

1. What are Jane's symptoms when she eats foods containing the amino acid phenylalanine?
2. Given these symptoms, what organ is most affected when a person with PKU consumes the amino acid phenylalanine in their diet?
3. A person without PKU does not have any symptoms when they consume foods with the amino acid phenylalanine. Why might Jane have the symptoms she does when she consumes foods with phenylalanine?

Later that evening, after spending considerable time reading the text and searching the internet for information about PKU, Jane called Amanda and asked her to come over to her apartment so they could work on the questions for biology class that were due on Friday.

"Hi Amanda, I think I finally understand why I can't eat 'normal' foods!"

"What are you talking about Jane? I still can't understand dominant and recessive alleles. I need help with this."

"Amanda, that's it! I have two recessive alleles and you have at least one dominant allele. Because I have two recessive alleles, I can't make the enzyme phenylalanine hydroxylase (PAH)."

"Phenyl-what?" replied Amanda. "What does phenyl-whatever do and how does that explain anything about dominant and recessive alleles?"

"My parents are heterozygous at the gene locus for PAH so they can make PAH, which is the enzyme that breaks down phenylalanine. They both gave me a recessive allele. Because I have two copies of the recessive allele at the gene locus for PAH, I can't make PAH or break down phenylalanine. That's why I have PKU. When I eat phenylalanine, it just builds up and causes me problems."

"Really? I think I understand this, but I'm not sure."

"It's simple, Amanda. You can think of PKU as being due to a single gene for which there is a dominant allele and a recessive allele. If a person has a least one dominant allele, they do not have PKU because they can make an enzyme that breaks down phenylalanine. If a person like me has two recessive alleles, they can't make the enzyme and they have PKU."

"Great work, Jane, now we can easily answer the questions for Friday."

After class on Friday, Amanda and Jane told their biology professor that understanding the genetics of PKU helped them answer the questions that were due that day. Their professor, Courtney Jones, told them that they would determine the number of carriers for PKU in Corpus Christi later in the semester when they covered the Hardy-Weinberg Principle (also referred to as Hardy-Weinberg Equilibrium).

Questions

Define symbols for the alleles at the gene locus for PAH and then answer the following questions:

4. What are the genotypes of Jane's parents?
5. What are the genotypes of Jane's brother and sister?
6. What is Jane's genotype?

Part II – Hardy-Weinberg

"Today we will start discussing the Hardy-Weinberg Principle or Equilibrium," Dr Jones said toward the end of class. "The Hardy-Weinberg Principle or Equilibrium is often used as a basis of comparison. It is a null hypothesis. The allele and genotype frequencies in a population will not change over time if no evolutionary forces are acting on that population. I am out of time today; please work on the Hardy-Weinberg question set for Friday."

Jane and Amanda got together on Thursday night to discuss the questions due the next day. The first question was about the data needed to determine the number of carriers in the population.

"Jane, what's a carrier?"

"My parents are carriers, Amanda. They don't have PKU because they have a dominant allele that produces PAH, but carry the recessive allele that doesn't make PAH."

"Hey, Jane, we know your parents are carriers. Can we count the number of carriers in the population and move on to the next question?"

"What are you thinking, Amanda? For most people, you can't know if they are a carrier or not."

"But, Jane, we do know if a person is a carrier or not. We know your parents are carriers. We can just count the number of carriers, and then divide by the number of people in the population to get the frequency of carriers and plug that number into the equation."

Questions

1. Who is correct? Can Jane and Amanda directly count the numbers of carriers in a population? Why or why not?
2. Can Jane and Amanda determine any of the allele and/or genotype frequencies in the population just by counting? If so, which one(s)?

Part III – Carriers

After determining that Jane is correct and that they cannot directly count carriers in the population, Amanda opened her notes from biology lecture. Dr. Jones had told them that the Hardy-Weinberg Equation, the mathematical expression of the Hardy-Weinberg Principle, can be stated as:

$(p+q)^2=1$ or as $(p^2 + 2pq + q^2)= 1$

"Jane, what the heck are p and q?"

After consulting the text, Jane said, "I think I figured it out, p and q are allele frequencies. I think that in the case of complete dominance with two alleles, p represents the frequency of the dominant allele, and q represents the frequency of the recessive allele."

"Right, so with only two alleles, then p + q = 1. I still don't understand how this is helpful because we can't determine p or q just by counting people in the population."

"Amanda, is there another form of the equation, the one for genotypes?"

"Yes, here it is. I think p^2 represents the frequency of homozygous dominant genotype, 2pq represents the frequency of the heterozygous genotype, and q^2 represents the frequency of homozygous recessive genotype."

"That sounds right," said Jane. "And they add up to one because there are only three genotypes.

"But what do we do now?" asked Amanda.

"I don't know," replied Jane. "But we might want to start by determining if we know any of these five values. We know q^2."

"Right!" said Amanda. "We could count people with the recessive phenotype in Corpus Christi and divide by the total number of people in Corpus Christi and we'd have q^2."

"Exactly!" said Jane. "And because we know q^2 we can determine q. And if we know q, we can determine p. We are just about done with these questions!"

Questions

1. Once Jane and Amanda know the frequency of the homozygous recessive genotype (q^2), how can they determine the frequency of the recessive allele (q)?
2. How can Jane and Amanda determine the frequency of the dominant allele (p)?
3. If 33 of the 300,000 people in Corpus Christi, TX, have PKU, how many people are carriers (heterozygous) for PKU?
4. Dr. Jones mentioned that the allele and genotype frequencies in a population will not change over time if no evolutionary forces are acting on that population. To determine the number of carriers in a population, you make the assumption that no evolutionary forces are acting on the population. What are these evolutionary forces?

"Well, Amanda, what can we do with this information?"

"Jane, didn't you tell me that you would like to know the chance that you will have a child with PKU?"

"I would, but unless I marry someone with PKU, I don't know how to figure that out."

"Can we use the number of carriers in Corpus Christi to answer this question?"

"I don't know," replied Jane. "I think so, but I'm not sure. I have a 100% chance of passing on the PKU allele to my child, but how do I figure out the chance that my husband will be a carrier?"

"For the Corpus Christi population, we know that!" exclaimed Amanda. "The chance that your husband will be a carrier is the frequency of carriers. The chance that you will pass on the PKU allele is 1, the chance that your future

husband will be a carrier is 2pq, and the chance that he will pass on the PKU allele if he is a carrier is ½. Multiply them together and you have it."

"That makes sense to me," said Jane. "But could we determine the chance that you will have a child with PKU?"

"I don't know," said Amanda. "No one in my family has PKU, but I guess I could be a carrier."

"Well, we know the chance that you are a carrier is 2pq. If you are a carrier, the chance that you pass on the PKU allele is ½. The same for your future husband: the chance he is a carrier is 2pq and the chance that he will pass on the PKU allele is ½. I think all we have to do is multiply all those together and we have an answer."

Questions

5. Is their reasoning sound? Did they correctly calculate their chance of having a child with PKU? If not, what should they include in their calculations?
6. If Jane marries somebody in Corpus Christi without symptoms of PKU, what is the chance that she and her husband will have a child with PKU?
7. If Amanda marries somebody in Corpus Christi without symptoms of PKU, what is the chance that she and her husband will have a child with PKU?

Further Reading

For more information about the detection and treatment of PKU, see "Issues in Newborn Screening for Phenylketonuria" by Richard K. Koch in *American Family Physician* 60:1462–6 (1999) (http://www.aafp.org/afp/991001ap/1462.html).

For an introduction to population genetics, including an application of Hardy-Weinberg Equilibrium, go to: http://courses.bio.psu.edu/fall2005/biol110/tutorials/tutorial9.htm.