CHAPTER 20

TO THE BITTER END
The Genetics of PTC Sensitivity

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Abstract

This case dramatizes the discovery of a Mendelian trait in humans, namely the variation in the ability to taste the chemical phenylthiocarbamide (PTC). By examining data and questions related to this trait, students draw connections between Mendel's principles of inheritance and variation at the DNA level by learning about the phenotypic differences due to the single nucleotide polymorphisms in a major gene influencing the ability to taste PTC.

Learning Objectives

- Understand how Mendelian traits are inherited and studied in humans.
- Explain the role of DNA sequences and mutations in determining protein structure and function.
- Understand how DNA mutations that compromise protein function may be inherited as a recessive allele.
- Understand the connection between Mendelian and molecular genetics by generalizing the specific facts learned in this case to other examples.

Quantitative Reasoning Skills/Concepts

- Carry out basic mathematical operations.
- Use numerical evidence to formulate null and alternative hypotheses.
- Articulate complete and correct claims based on numerical data.
- Use appropriate reasoning to support the validity of data-based claims.
- Create and interpret Punnett squares (Author's note: Although this is one possible way to obtain answers to some of the questions in this case, I encourage my students to use probability rules instead.)
- Perform DNA analysis.

The Case Study

Part I: Discovery

"Arthur," said C. R. Noller in an irritated voice. "What the heck are you doing over there? Why did you let that awful-tasting stuff get into the air? It's so bitter that I want to vomit!"

Drs. Arthur Fox and C.R. Noller were working separately in a lab at the DuPont Chemical Company's facilities in Wilmington, Delaware.

"What do you mean, C.R.?" snapped Arthur. "I don't taste anything, and I'm right on top of this stuff."

"It's got to be that powder you've got there," retorted C.R. "I'm not working with anything bitter, and I'm too far from the door for it to be coming from outside the lab."

Arthur was transferring some phenylthiocarbamide (PTC) into a bottle. During the transfer, some of the white powder had dispersed into the air.

"Look," said Arthur as he licked his finger, picked up a few PTC crystals, and licked his finger again. "I don't taste anything."

"Arthur," said C. R., "give me some of that stuff. I really don't want to taste it, but I'll do it just to prove you're wrong!"

Arthur Fox brought the bottle of PTC over to C. R. Noller, who picked up a few crystals. As soon as the crystals touched his tongue, C. R. exclaimed, "Yuck! Quick—get me something to rinse out my mouth! That stuff is just too bitter!"

After C. R. rinsed out his mouth with some water, Arthur said, "Let's see if we can find some other folks to taste this PTC to see if they taste anything."

For several days Arthur asked all his co-workers, friends, and acquaintances to taste his PTC powder and found that neither he nor C. R. were unique. Regardless of gender, age, or ethnicity, about 60% of people tasted PTC as bitter, like C. R. The other 40% were, like Arthur himself, taste blind: PTC had no taste to them. Arthur also tested closely related chemicals with the same results.

News of Arthur's discovery was published in *Science*, the premier American science journal (Anonymous 1931). Shortly thereafter Arthur received the following letter:

Dear Dr. Fox,

I read the news of your discovery of variation in the ability to taste phenylthiocarbamide (PTC) and related compounds with great excitement. I am studying Mendelian markers in human populations. Unfortunately, we have few examples of such traits in humans, as you can see from my article recently published in the *Eugenical News* (1931b), which I have enclosed. Would you please send me some PTC? I would like to study this variation in tasting ability to see if it is inherited and, therefore, can be used as a Mendelian marker.

Sincerely yours,

L. H. Snyder, PhD

Professor of Genetics

Ohio State University

Questions

1. What does L. H. Snyder mean by the term "Mendelian marker"?
2. What question(s) will Dr. Snyder address in his study?
3. What is his hypothesis?

Part II: Mendelian Genetics

After obtaining some PTC from Arthur Fox, L. H. Snyder determined the PTC phenotype (can taste or cannot taste) for the members of 100 nuclear families. He first verified that gender was not a factor by comparing the number of male tasters and non-tasters to the number of female tasters and non-tasters. Because there was essentially no difference between sexes, Snyder grouped families by the phenotypes of the parents, disregarding the gender of each parent, and tabulated his data (see Table 20.1, p. 204; Snyder 1931a):

TABLE 20.1.

PTC phenotypes of children from 100 nuclear families grouped by parent phenotype combinations (from Snyder 1931a).

		Phenotypes of Children	
Parent-Phenotype Combinations	**No. of families**	**Can taste**	**Cannot taste**
Both parents can taste	40	90	16
One parent can taste, the other cannot	51	80	37
Neither parent can taste	9	0	17

Questions

1. What kind of evidence would indicate that the ability to taste PTC is inherited?
2. Why was it important for Snyder to verify that males and females had similar proportions of tasters and non-tasters?
3. Why do couples who can taste PTC have children who cannot?
4. What is the significance of the fact that couples who cannot taste PTC never have children who can?
5. Based on these data, what can you conclude about PTC taste blindness? What is your evidence?
6. The second parent-phenotype combination would appear to represent a group of testcrosses. What ratios are expected from testcrosses and what does each ratio represent? These data don't seem to fit either of these expected ratios. How can you explain this?

Part III: Molecular Genetics

More than 70 years after Arthur Fox serendipitously discovered that humans vary in their sensitivity to PTC and related chemicals, researchers from the National Institutes of Health, Stanford University, and the University of Utah together discovered the main gene for PTC sensitivity in humans. This gene is a member of a gene family that encodes bitter taste receptors in the mouth called the *TAS2R* gene family (Kim et al. 2003).

TAS2R38, the gene responsible for PTC taste sensitivity, is on chromosome 7 and codes for a receptor protein responsible for bitter taste perception that binds PTC. The two common alleles differ by three SNPs, causing three amino acid changes. One common allele or haplotype has proline (P), alanine (A), and valine (V) for these three amino acids and therefore is called PAV. The other common allele is called AVI because the amino acids are alanine (A), valine (V), and isoleucine (I). The PAV allele codes for a form of the receptor protein that binds PTC, conferring the ability to taste this chemical. The protein product

of the AVI allele cannot bind PTC, and thus this allele confers the inability to taste PTC. However, the fact that the AVI and PAV alleles are expressed equally at the RNA level and that the AVI allele contains no frameshifts or other mutations that would result in early termination of the protein suggests that the AVI-coded receptor protein binds another bitter chemical that has not yet been identified (reviewed in Wooding 2006). Other haplotypes, presumably due to recombination between the three SNPs, occur but are rare. These rare haplotypes also showed functional responses in *in vivo* studies and, thus, these alleles appear to code for functional proteins (Bufe et al. 2005).

Questions

1. What is a gene family? What mechanism generates them?
2. What is a SNP? What is a haplotype? How can SNP haplotypes be determined?
3. Assuming the PAV allele is the original one, what types of mutations (silent, missense, nonsense, and so on) have changed the PAV allele into the AVI allele? Explain. Based on the information given, how do these changes fit with what you have learned about the "functional enzyme hypothesis"?
4. You repeat Snyder's experiment, but instead of determining the ability of each family member to taste PTC, you determine what alleles they carry: 2 PAV (PAV/PAV), 2 AVI (AVI/AVI), or 1 PAV and 1 AVI (PAV/AVI). Using Table 20.2, what are the possible outcomes for offspring if the parents have the genotypes described in the first column? Below the genotype, write the phenotype (taster or non-taster) of each kind of individual.

TABLE 20.2.

Possible genotypes and phenotypes of children from parents of different genotype combinations. (to be filled in by students)

Parent Genotype Combinations	Possible Genotypes / Phenotypes of Children
Both parents PAV/PAV	
Both parents PAV/AVI	
One PAV/PAV, the other PAV/AVI	
One PAV/PAV, the other AVI/AVI	
One PAV/AVI, the other AVI/AVI	
Both parents AVI/AVI	

1. Go back to Snyder's results in Table 20.1 and give all the possible genotypes for the phenotypes listed in that table.
2. For each step of gene expression, explain how DNA differences lead to phenotypic differences in the ability to taste PTC.
3. Generalizing from this example, what can you say about the connection between Mendelian and molecular genetics? What type of reasoning are you using here?
4. Hypothesize about some consequences of PTC-tasting ability in the daily lives of tasters and non-tasters.

Web Version

Detailed teaching notes, the case PDF, and an answer key are available on the NCCSTS website at *sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=595&id=595.*

References

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