TEACHING THE GENOME GENERATION

Final Reflection and Bioethics

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Guiding Questions Final Reflection

Revisit the following guiding questions and update your answers to include everything you've learned from completing the activities in this module.

Given what you know about genome sequencing and genetic variation:

1. What can we learn from comparing genetic information across individuals and species?

Given what you know about (a) how DNA codes for proteins and (b) the connection between protein structure and function:

2. How might a DNA variant affect protein sequence, structure, or function?

Bioethics

Outcomes of Rare Disease Research

At the beginning of this module, you were asked to imagine that you were the parent of two daughters with a rare disorder. This scenario was based on a true story of a family searching for a medical diagnosis for their daughters so that they could connect with other patients and families. However, after many doctors' visits, the family still had not been able to receive a diagnosis.

They decided to participate in a research study and have the daughters' genomes sequenced. Using the sequencing data, researchers were able to identify variants in the gene Autophagy related 7 (*ATG7*) as the genetic cause of the daughters' disorder. They also connected the family with ten other individuals who had similar symptoms and genetic variants and who ranged in age from 5 years old to 71 years old.

3. Once again, imagine you are the parents in this family. How do you think you would feel after learning for the first time that there were other people, both kids and adults, who had the same disorder as your daughters? What would be going through your mind?

4. How do you think you would feel as one of the daughters? What would be going through your mind?

After the research study, the family finally received a medical diagnosis for their daughters: *Spinocerebellar ataxia, autosomal recessive 31 (SCAR31)*.

Although researchers identified genetic variants and established a diagnosis of SCAR31, there is still no treatment available for the disorder. The researchers know that the daughters' *ATG7* variants affect their Autophagy related 7 (ATG7) protein structure, which in turn affects ATG7 protein function in their cells. However, the researchers still do not fully understand how the loss of ATG7 protein function produces the daughters' specific symptoms.

5. Is there value in knowing the genetic cause of a disorder when there is no treatment available yet? How might having a diagnosis impact the patients and their families even without an available treatment?

As part of the study, the researchers performed **gene editing** on the patients' cells in the laboratory, replacing the patients' *ATG7* gene with a functioning copy of the *ATG7* gene. They found that the gene edited cells had normal ATG7 protein function.

These promising results in the lab are an important first step in the lengthy process for therapy research and development. After this discovery phase, all potential treatments must undergo preclinical testing in human cells or animal models in the laboratory to make sure they are safe and effective. Treatments must then go through **clinical trials**, where they are evaluated for safety and efficacy in groups of patients, before they can be made widely available. The entire treatment research and development process typically takes several years to complete.

6. If you were a patient or a family member, how would you want the researchers to proceed?

7. Would you want to participate in a clinical trial for gene editing? Why or why not?

8. Considering the time and resources needed to develop new therapies, what might be some barriers to future research on a treatment for this disorder?

Access to Researchers and Therapies

After identifying *ATG7* variants in the two daughters of the first family, the researchers used GeneMatcher to identify additional patients with mutations in *ATG7* for their study.

GeneMatcher is a freely accessible site designed to help connect doctors, researchers, and patients who are interested in the same genes. The site enabled the researchers to connect with other patients with *ATG7* variants from the UK, France, Germany, Switzerland, and Saudi Arabia.

1. Most of the families included in this study are from Europe. What are some possible explanations for this?

Even if a therapy was developed for treating SCAR31, patients would first need to obtain a diagnosis before they could be treated. From the story of the first family in this research study, we know that finding a diagnosis for a rare disorder can be a long, difficult process. Rare diseases are often overlooked as a possibility, because doctors are typically trained to consider more common diagnoses first. It can be challenging to find a doctor who is willing to consider a rare disease diagnosis.

Additionally, a patient's ability to access doctors, researchers, genome sequencing, and therapies can vary significantly depending on factors such as health insurance status, socioeconomic status, age, race, and geographic location.

2. How might limited access to health care impact this already challenging endeavor of obtaining a diagnosis? Who is likely to be most impacted?

References:

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