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Lesson

Fragile States: A Case Study Exploring Genetics, Molecular Biology, and Biochemistry Through the Lens of Fragile X Syndrome

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Abstract

This case aims to strengthen students' understanding of molecular biology concepts through study of Fragile X Syndrome (FXS). Students begin by learning the cause and phenotypes of FXS and related conditions. Students then apply genetics knowledge to describe the inheritance of FXS. Knowledge of the central dogma of molecular biology helps students understand the impact of genetic and epigenetic changes on expression of the *Fragile X mental retardation gene 1* and the impacts of the loss of the Fragile X Mental Retardation Protein on other protein production. As one example of the latter, students look at alterations in metabolic enzymes and consider ways to mitigate the phenotype, proposing treatments for FXS. Throughout the case, students are pointed to a clinical website and scientific literature to build their understanding. This case study also engages students in consideration of diversity and inclusion in conveying, interpreting, and acting on scientific information. Overall, this case can help students connect biological concepts to a real-world application while developing their abilities to think critically and comprehend scientific information.

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Learning Goals

Students will be able to integrate course content from undergraduate introductory courses that cover genetics, molecular biology, and biochemistry along with new information to interpret research and clinical scenarios. Specifically, following engagement with this case, students should:

◊ know the cause and inheritance pattern of Fragile X syndrome.

◊ understand that the process of gene expression can be regulated at multiple levels, including by changes outside the coding region and due to epigenetic effects.

◊ appreciate that the language we use and the clinical approaches we take can promote or hinder inclusion.

◊ consider that molecular knowledge can be used in developing treatments for human conditions.

◊ use web-based resources and primary literature to learn more about molecular mechanisms.

From the Genetics Society of America Core Competencies:

◊ Students should be able to identify and critique scientific issues relating to society or ethics.

Learning Objectives

Students will be able to:

Part 1:

a. determine the cause and conditions associated with Fragile X Syndrome from a patient-centered website. (Questions 1–3)

b. apply knowledge of genetics to describe what it means to be a carrier for Fragile X Syndrome. (Question 4)

c. consider the impacts of the language we use to describe genetic variation and resulting phenotypes. (Question 5)

Part 2:

a. construct and interpret a pedigree chart to determine the inheritance pattern of Fragile X Syndrome. (Questions 1, 3)

b. apply knowledge of sex-linked disorders to explain why Fragile X Syndrome is more prevalent in biological males. (Question 2)

c. consider how we ascertain and represent sex chromosomes and gender identity of individuals. (Question 4)

Part 3:

a. describe the cellular processes involved in going from genetic information to functional products. (Question 1)

b. explain how genomic sequences outside of the coding regions can impact gene regulation. (Question 2)

c. recognize the role that epigenetic factors play in turning genes on and off. (Questions 3, 4)

Learning Goals

From the Biochemistry and Molecular Biology Framework:

◊ How are genomes maintained?

◊ What skills are needed to access, comprehend and communicate science?

◊ What constitutes a scientific community of practice?

◊ What is the molecular basis of evolution?

From the Genetics Learning Framework:

◊ How is DNA organized?

◊ How can one deduce information about genes, alleles, and gene functions from analysis of genetic crosses and patterns of inheritance?

◊ How is genetic information expressed so it affects an organism's structure and function?

Learning Objectives

Part 4:

a. obtain information from a review article when directed to specific sections. (Question 1; Optional Question 5)

b. apply knowledge of translation to analyze the function of FMRP. (Question 2)

c. predict treatments for Fragile X Syndrome that can regulate translation in the absence of FMRP. (Question 3)

d. consider benefits and costs to individuals, communities, and society when deciding whether to treat a human disorder or syndrome. (Question 4)

Part 5:

a. obtain information from a primary article when directed to specific sections. (Question 1–3)

b. connect alterations in metabolism to changes in cellular function and disease states. (Questions 1–3)

c. discuss how alterations in enzyme action can affect concentration of reactants and products. (Question 2)

d. propose molecular and cellular treatment options to treat enzyme deficiencies. (Question 4)

From the Biochemistry and Molecular Biology Learning Framework:

◊ explain how mutations and epigenetic changes influence gene expression, structure and function of gene products and the fitness of an organism.

◊ explain what a mutation is at the molecular level, how it arises, and how it could potentially affect the organism from gene expression to fitness.

◊ given a case study, identify both scientific and societal ethical aspects.

◊ identify, locate and use the primary literature.

◊ use visual and verbal tools to explain concepts and data.

◊ explain the big picture aspects of current challenges in the molecular life sciences.

From the Genetics Learning Framework:

◊ describe the types of DNA regions that do not encode proteins: the general organization, possible function, and frequency of genes and non-gene DNA sequences in a typical eukaryotic genome.

◊ differentiate between a gene and an allele, including the recognition that genes may have many alleles.

◊ draw a pedigree based on information in a story problem.

◊ explain how the genetic code relates transcription to translation

◊ describe how expansion or retraction of triplet repeats can alter gene function and create a phenotype

◊ discuss how DNA is packaged in the chromosomes in terms of histones, nucleosomes, and chromatin

◊ locate, read, and comprehend primary literature research papers on genetics topics.

INTRODUCTION

Active learning and "real world" applications have been highlighted as key pedagogical strategies for today's students. In learning the invisible underpinnings of genetics and molecular biology, opportunities to work collaboratively and make connections to tangible phenotypes can be particularly important. This case was developed to complement introductory undergraduate coursework in the areas of genetics, molecular biology, and biochemistry. The five parts develop a story about Casey, a psychiatrist, as she learns and shares knowledge about Fragile X Syndrome (FXS). By engaging in the case, students can see how genetic variation affects gene expression and impacts metabolism among other biological functions in the context of Fragile X and related disorders.

FXS is a genetic disorder that impacts the nervous system, resulting in an array of phenotypes. It was originally named for its chromosomal level effect, the creation of an apparent disruption in the DNA or "fragile site" (see Primary Image). The underlying gene, *Fragile X mental retardation gene 1*, or *Fmr1*, is located on the X chromosome and has been shown to undergo silencing if there is an expansion in the array of CGG repeats within the 5′ untranslated region. The phenotype of an individual is generally related to the number of repeats and in turn, how much of the Fmr1 protein (FMRP) is expressed (1). Complete silencing of the *Fmr1* gene can result in Autism Spectrum Disorder as well as other neurological impairments. Partial repression of *Fmr1* has been shown to result in Primary Ovarian Insufficiency and Ataxia Syndrome (2). This lesson takes students through a case study where one of Casey's patients was found to have the Fragile X premutation, one of a number of known genetic variants of the *Fmr1* locus.

When exploring the molecular nature of the *Fmr1* gene in *Drosophila* species for a scientific research project, we realized that the nature of CGG expansion alleles and the resulting phenotypes could provide a clinical scenario that connects to fundamental knowledge in genetics, molecular biology, and metabolism. These topics are expected to be part of undergraduate curricula in the life sciences and basic understanding of the associated principles is a precursor for clinical education. However, existing case studies of Fragile X have an explicit clinical training orientation (e.g., 3). We developed and deployed this case study to provide an additional way for undergraduate students (mostly sophomores) to build their knowledge of challenging topics, an approach that has been shown to be effective (e.g., 4). We also wanted to support students in applying that knowledge to clinical and research scenarios, as these are the career interests of the majority of students in our introductory molecular biology class, and we suspect in many like it. In these ways and given that one author (L.E.W.) is an undergraduate student herself, we feel this case contributes to experiential learning, a current priority in education (5).

This case study (Supporting File S1) asks students to apply prior course knowledge and interpret specific sections of scientific websites and reports. The case is divided into five parts that were designed to be used following review of underlying background in a course. Parts 1 and 2 were employed after Mendelian genetics and more complex modes of inheritance were covered. Parts 3 and 4 of the case provided another way for students to think about the central dogma of molecular biology and gene regulation after these topics were covered in class. Part 5 builds on students' understanding of enzymes and metabolic pathways. For each part of the case, students were assigned to read the case and complete some questions as a pre-class assignment, while other questions were discussed in class.

Intended Audience

This case study is intended for students enrolled in intermediate-level undergraduate biology courses. We deployed it with students at a small, private liberal arts college, the majority of whom are planning a major in biology or related fields and many of whom are preparing for careers in health care. These mostly second-year students had completed at least one semester of biology and chemistry coursework prior to the start of this course.

As indicated below in the Prerequisite Knowledge section, Parts 1 and 2 focus on genetics, Parts 3 and 4 on molecular biology, and Part 5 on biochemistry (metabolic pathways). Our students were developing the required basic knowledge during the same semester in which we deployed the case to assess their success in learning and applying these concepts. We think it would also be possible to use this case as a review in more advanced classes. Additionally, we have tried to design the case such that only certain sections could be used based on the course topics and focus. Learning goals are given for each part to aid instructors in deciding what will be most useful for their students.

Required Learning Time

We split this case study into three sections, with each part estimated to require ~45 minutes of student preparation outside of class (Table 1). For class discussion, we recommend allotting 30–45 minutes for each section. This will of course vary between student populations and course constraints.

Prerequisite Student Knowledge

Knowledge that should be developed at least concurrently with this case includes Mendelian and sex-linked inheritance (Parts 1 and 2), transcription/translation and gene regulation including epigenetic controls (Parts 3 and 4; links to some supporting animations are provided), and enzyme function in the context of metabolic pathways (Part 5). The concept of orthologous genes would be helpful in discussion of mouse and fly models in Part 5 of the case (Supporting File S1).

Prerequisite Teacher Knowledge

Instructors with basic knowledge of the topics above should be comfortable deploying this case. The Cleveland Clinic resource on Fragile X (2) and the primary articles to which the students are referred (1, 6) should be understandable, but teachers will likely wish to review them in advance of discussing them with students. A National Institutes of Health resource for genetics vocabulary, available in English and Spanish, may be helpful (7).

As instructors seek to support students' learning of prerequisite and related knowledge, a more introductory level case offered by Ricks and Katzman (8) could help students learn about the Central Dogma of molecular biology. The basics of epigenetics could be explored at Learn Genetics from the University of Utah; an animation that shows how epigenetics impacts DNA structure and transcription (9) may be especially helpful for beginning students and is linked in Part 3 of the case. Other case studies (10–12) that focus on DNA methylation of specific regions and how it affects the human condition contain parallel resources and approaches that may also be of interest.

SCIENTIFIC TEACHING THEMES

Active Learning

Problem solving in the context of case studies is one recognized active learning strategy (13), and has been shown to support achievement of all students with particular benefits for science students who identify with historically underrepresented groups (14). We point students to two websites, one review article, and one scientific report and ask students to use these resources in addition to information in the case to address questions. Combining independent work outside of class with collaboration during class discussions was intended to help all students engage with the case in productive ways.

Formation of discussion groups establishes collaborative learning that has been identified as a high impact practice (15). In their introduction to a study focused on "When Group Work Doesn't Work," Cheng and Brickman (16) highlight and reference many considerations to make group work engaging and inclusive.

Finally, Driessen *et al.* (17) include case studies as one way to practice the *Vision and Change* (18) core competency of relating science to society. This connects to our goals of helping students to engage with complex and detailed course material through application to a clinical disorder and to reflect on ethical considerations when identifying and treating aspects of the human condition.

Assessment

Students' work on the case was assessed in two primary ways. Their understanding of and ability to apply material was reflected in their answers to some case study questions as a pre-class assignment. The approach of asking the students to review the case and answer some questions as homework was also used to ensure that students were prepared for class discussion of the case, with a focus on the remaining questions. Here, informal assessment of group conversation and answers shared with the class were used as measures of engagement. In addition to these two methods, a few exam questions were connected to considerations raised in the case study.

To enhance learning and also in preparation for submission of this case, students were asked to complete a brief reflective survey after each in-class discussion. In general, students agreed that engaging with the case helped them better understand concepts introduced in lecture and increased their ability to apply scientific knowledge (Table 2).

Inclusive Teaching

It was important to us that this case study provides opportunities to consider diversity and inclusion in addition to scientific content.

Two questions within the case study (Part 1, Question 5 and Part 2, Question 4) directly prompt students to reflect on the impacts of language and visual representations we use to describe aspects of the human condition:

1. *How does the language we use to describe a human phenotype (e.g., disease, disability, disorder, condition) reveal or impact our thinking about it?*
2. *In constructing a pedigree, we may find ourselves making assumptions about individuals' gender and/or biological sex. How does this influence how we understand inheritance of a condition such as FXS in a pedigree? How might clinicians and researchers better represent those identifying as gender fluid or those for whom their gender identity differs from their chromosomal makeup at birth?*

Given that genetics has had a difficult history with respect to inclusion, we wanted to embed these considerations in these sections of the case. The importance of this has been supported by previous studies. For example, Hales (19) highlights considerations and provides resources for instructors related to pedigree charts, gender identity, and inclusive language in general. One of the authors (A.T.H.) often draws attention to the word "mutation" when discussing genetics with students. Most people agree the term has a negative connotation, but may not have fully considered the impacts when this term is used to describe a human allele.

Question 5 in Part 4 asks students to consider the implications of developing clinical treatments for various human conditions, *i.e.,* what is seen as within the range of "normal" human phenotypes and what "needs" to be treated. We thought this was important given that two other questions ask students to propose possible treatments for Fragile X and related conditions. The case design and class discussions were influenced by a powerful op-ed (20) among other resources.

The importance of gender inclusivity in science has been highlighted in recent essays (21, 22). In Part 5, we deliberately introduce a character Sloane who uses 'they/them' pronouns, to help more students see themselves in scientific and medical fields (Sloane has an M.D./Ph.D. degree and is a neurologist). We deliberately mention various scientific careers, research sites, and a research program for undergraduates to help raise awareness of opportunities for all students, especially those who are first generation college students or members of communities historically underrepresented in the sciences. To help increase access, we have provided links to more information about Research Experiences for Undergraduates (REU) programs and MD/PhD degrees within the discussion notes for Parts 3 and 5.

Finally, following a suggestion from our IRB review, we embedded a statement that might be characterized as a trigger warning at the beginning of each case section distributed, along with contact resources for individuals struggling with any aspect of mental or physical health.

LESSON PLAN

The Supporting File S1 represents the full text of the case (with minor revisions detailed below) that we provided to students over the course of a semester. We shared the case via a learning management system in three sections (Parts 1 and 2, Parts 3 and 4, and Part 5), each time including the relevant learning goals, the trigger warning and resource note, and the case sections with associated questions. Case sections were made available approximately one week before a short written assignment was due followed by class discussion (see Table 1). We provided simple, similar instructions each time (*e.g.,* "Before class on Friday, please read through Parts 1 and 2 of the case study and associated questions. Then answer questions 1–4 of Part 1 in one sentence each as your pre-class assignment."). Sample answers and discussion points are included in Supporting File S2.

The questions assigned as homework that were judged to be those that students could most readily answer on their own, based on course content are marked by asterisks in Supporting File S1. Student submissions were due just before the class period in which the case sections were discussed. Instructors reviewed early submissions before class and any assigned questions that seemed to be challenging or confusing to students were discussed in class, in addition to questions not yet explored. When grading the pre-class assignment, one of us (A.T.H.) judged the quality of student's answers based on their ability to use information in the case and previously covered course content. This was a low-stakes assignment within our course, so we did not develop a formal rubric, although students could receive partial credit. We hope the sample answers provided in Supporting File S2 will be of help to other instructors as they decide on grading schema for their classes.

We held in-class discussions of the case in part of three Friday classes. We engaged students in an interactive lecture for about half of the class period, with the remainder of the time being used for work with the case study. Given the scope of the case, that day's lecture connected with some but not all aspects of the case sections, with some relevant course material having been presented in previous class sessions. In general, we spread out engagement with the case across the semester to align with coverage of related course material, which students seemed to appreciate (Table 3).

We assigned students to groups of 3 or 4 people for discussions, with groups changing for each case study section. We gave students time to talk about the questions before further discussion as an entire class, facilitated by the instructor. Our primary focus here was to assess student engagement, as was done throughout the course (see Supporting File S3). In addition to assessing student engagement in class discussions and students' pre-class assignments, we used case study material as a basis for some exam questions.

TEACHING DISCUSSION

Student reflection data (Table 2) indicates that engagement with the case supported student learning in our course. Students' rating of the effectiveness of the case in supporting learning in specific areas varied slightly. It was highest for genetics content ("how information is inherited according to Mendel's laws and their extensions and revisions"), followed by molecular biology ("transcription and translation, and regulation thereof"), and lowest for biochemistry ("metabolic pathways [enzymes and intermediates]"). We did use these data to inform changes to the resources provided and question structure in the molecular biology and biochemistry sections as detailed below. However, it is also important to remember that case study sections were deployed throughout the semester and we sense that student fatigue from a demanding course may have also played a role in their evaluation of Part 5 in particular.

We also reflected on our and our students' experience using the case by looking at the five main learning goals listed in the Scientific Teaching Context section. Student reflection data and assignment averages in the 'A' range support strong student learning with the genetics and molecular biology sections of the case. This directly connects to the first two learning goals:

- Know the cause and inheritance pattern of Fragile X syndrome
- Understand that the process of gene expression can be regulated at multiple levels, including by changes outside the coding region and due to epigenetic effects

Questions in Parts 1 and 2 designed to directly support the third learning goal ("Appreciate that the language we use and the clinical approaches we take can promote or hinder inclusion") were appreciated by students during class discussion. Learning goals 4 and 5 (below) presented the most challenge to students:

- Consider that molecular knowledge can be used in developing treatments for human conditions
- Use web-based resources and primary literature to learn more about molecular mechanisms

Students in this course were likely being introduced to molecular concepts in detail for the first time. This naturally makes understanding literature in this area and applying this understanding to propose clinical treatments more challenging. This was reflected by a lower average grade (low 'B') on the Part 5 assignment.

The approach of asking students to begin engagement with each case study section outside of class and then continue with discussion in class in general seemed effective and efficient. There were, however, a couple of specific aspects that we suggest should be considered and that we would alter in future course offerings. First, and perhaps not surprisingly, we typically found that we were able to offer only about 20 minutes for discussion, when the conversations could have gone on longer to deepen understanding of the case and underlying course content. This limitation likely also impacted students' reflection on their learning in the case (Tables 2, 3).

Second, in sharing this case with students in Muhlenberg College's BIO 175 *From Organisms to Molecules* courses in Fall 2022, case study learning objectives were matched with course objectives in the written materials provided. This was not drawn out in class discussions and perhaps doing so would have increased student awareness of tangible case study benefits. It also seems that this case challenges students in that there is a degree of ambiguity and in some cases not "one right

answer." For example, in Part 2, we deliberately incorporated a number of phenotypes in the family history, some of which can overlap with Fragile X-related conditions but also have other causes. While comments about questions being unclear were rare, we revised questions that were flagged as having less clear objectives on the student reflections (in open-ended comments). In Part 3, we also incorporated links to several animations (9, 23, 24), to assist students in answering questions 1, 3, and 4, which require knowledge of the central dogma of molecular biology and epigenetic mechanisms that control gene expression.

We re-considered the degree of difficulty of one of the questions in Part 4 specifically. This asks students to interpret a paragraph of the Richter and Zhao review (1) that describes many technical approaches that may be unfamiliar to students. Depending on the background of students enrolled in a given course, it may be preferable to look at this section of the paper together, so that the instructor can remind students of the purpose of various approaches and model looking up unfamiliar terms and techniques when reading the scientific literature. We have moved this question to the end of this section and labeled it as an optional extension, which would provide practice in dissecting the scientific literature.

Question 2 in Part 4 also points students to the Richter and Zhao review, but students were able to interpret this diagram of cellular processes. Questions 2 and 3 in Part 5 also involve looking at the scientific literature, in this case a primary report published in the journal *Human Molecular Genetics* (6). We had made some revisions to help students focus on main takeaways from the 'box and whiskers' style plot referred to in the question. For question 3 focused on a *Drosophila* model of a Fragile X-related condition, we provided a brief explanation of the various transgenic lines, but unpacking this with an instructor or teaching assistant may be helpful for some students, as a precursor to interpreting the data itself.

With these perspectives in mind, we encourage instructors to assign questions as homework or discuss the entire case section in class, based on their course and student population.

SUPPORTING MATERIALS

- S1. Fragile States – Case study
- S2. Fragile States – Sample answers and discussion notes
- S3. Fragile States – Sample syllabus language around engagement

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Table 1. Teaching timeline with a sample schedule. The same structure was used in deploying each of the three parts: Parts 1 and 2 (genetics) in week 3 of a fifteen-week semester, Parts 3 and 4 in week 8, and Part 5 in week 11.

Timing	Instructor Action	Student Activity	Estimaed Times
Friday before assignment due and discussion	Case sections made available		
Throughout the week (asynchronous)		Reading case sections and prepare answers to assigned questions	45 min
Friday class	Divide students into groups of 3 or 4	Discuss selected case study questions	~ 10 min
	Discussion with class as a whole	Discussion with class as a whole	~ 10 min
		Brief assessment (formative, not graded)	< 5 min

Table 2. Student reflections on genetics (Parts 1 & 2), molecular biology (Parts 3 & 4), and biochemistry (Part 5) portions of the case study. Question 1–4 data are reported as the average of Likert scale responses (1 = strongly disagree to 5 = strongly agree). Question 5 data is reported as the average on a scale of 1–10, with 10 being the most effective. Standard deviation is also shown for each response average. The second statement and Likert scale was directly provided by this statement to solicit open-ended reflection: *"If you disagree with the above statement, please indicate which question(s) were confusing and why on the reverse side. [circle your choice]."*

Survey Item	Parts 1 & 2	Parts 3 & 4	Part 5
1. Engaging in this case study helped me better understand the concepts introduced in lectures.	4.1 +/- 0.65	4.0 +/- 0.79	3.5 +/- 0.96
2. The objective of each question was clear.	4.3 +/- 0.57	3.5 +/- 0.85	3.5 +/- 0.86
3. This assignment increased my ability to comprehend scientific literature.	3.8 +/- 0.88	3.7 +/- 0.74	3.8 +/- 0.88
4. This assignment increased my ability to think critically and apply scientific knowledge.	4.2 +/- 0.71	4.0 +/- 0.74	3.7 +/- 0.98
5. How effective was this assignment in bettering your understanding of (genetics, the central dogma of molecular biology, metabolic pathways)?	7.7 +/- 1.4	7.0 +/- 1.8	6.4 +/- 2.0

Table 3. Summative student reflection. These cumulative questions were provided to students at the same time as they were reflecting on Part 5 but students were asked to evaluate these statements using a Likert scale (1 = strongly disagree to 5 = strongly agree) with respect to the case as a whole.

Survey Item	Mean Responses With Standard Deviation
The Fragile States case study provided a way to connect underlying course concepts to "real world" scenarios.	3.9 +/- 0.78
The Fragile States case study increased my enthusiasm for course concepts.	3.2 +/- 0.94
Engaging in the Fragile States case study increased my understanding of course concepts.	3.5 +/- 0.99
I like that the case was presented in sections tied to the course material we had been engaging with most recently.	3.8 +/- 0.73
I would have preferred to engage with all parts of the case at the same time.	2.5 +/- 0.75

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