

# A Muscular Dystrophy Case Study Illustrating the Phenotypic Effects of Mutation

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## Abstract

Mutations in genes can lead to a variety of phenotypes, including various human diseases. Students often understand that a particular mutation in a single gene causes a disease phenotype, but it is more challenging to illustrate complex genetic concepts such as that similar mutations in the same gene cause very different phenotypes or that mutations in *different* genes cause similar phenotypes. We originally designed this lesson to build off of the CourseSource lesson “A clicker-based case study that untangles student thinking about the processes in the central dogma,” but it can also stand alone. In our lesson, students read or listen to a real-life case study featuring a patient who doggedly pursues the underlying genetic cause of her own disease—muscular dystrophy—and stumbles upon a similar mutation in the same gene that gives an athlete the seemingly opposite phenotype: pronounced muscles. The lesson also leads the students to overlay their understanding of the central dogma and mutation on protein function and disease, compares muscular dystrophy to the disease progeria, and concludes with an ethical challenge. We tested the lesson as both an independent homework assignment, as well as a small group in-class worksheet and both formats were successful.

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## Learning Goals

Students will:

- ◊ understand how one mutation affects all steps of the central dogma.
- ◊ understand how mutations in a gene affect the protein structure and function.
- ◊ learn that “similar” mutations in *the same* gene can lead to seemingly opposite phenotypes or very different disease states.
- ◊ learn that mutations in *different* genes can lead to similar phenotypes.
- ◊ consider the ethics around choosing to have children when affected with a known heritable disease.

From Genetics Society of America Genetics Learning Framework:

- ◊ How is genetic information expressed so it affects an organism’s structure and function?
- ◊ How do different types of mutations affect genes and the corresponding mRNAs and proteins?
- ◊ How does genetics impact society and society impact genetics?

## Learning Objectives

Students will be able to:

- ◊ explain how DNA mutations affect protein function and phenotype.
- ◊ predict the relative phenotypic consequences of different types of mutations.
- ◊ explain why “similar” mutations in the same gene lead to different phenotypes, and why mutations in different genes lead to similar phenotypes.

## INTRODUCTION

We designed this lesson as a follow-up to the popular CourseSource lesson “A clicker-based case study that untangles student thinking about the processes in the central dogma” (1), in which students examine the genotypes and phenotypes of fictitious brothers Liam and Elijah. Liam has Duchenne muscular dystrophy due to a mutation in his dystrophin gene, while Elijah is healthy and has a wild-type dystrophin allele. In this lesson, students follow Liam’s mutation through the steps of the central dogma, and evaluate the effects of the mutation on protein sequence, size, and expression levels. This lesson does an excellent job of reinforcing how mutations affect cellular processes, including DNA replication, transcription, translation, and protein function. However, it focuses exclusively on a set of symptoms due to *one* mutation in *one* gene, which does not capture the complexity of the human disease landscape.

Many excellent lessons teach one gene/trait by focusing on Mendelian inheritance (e.g., 2, 3). These lessons are an important introduction to the consequences of mutation. Yet, one gene is often the cause of multiple diseases due to allele, locus, and phenotypic heterogeneity. This genetic complexity is especially common in human diseases (4). In order to better educate both students and the public, it is critical to integrate lessons that expand on the simple one gene-one disease concept (5).

We wanted to take advantage of a memorable case study featuring a real muscular dystrophy patient, Jill Viles (6). Unlike the fictitious Liam, real Jill suffers from Emery-Dreifuss muscular dystrophy. Students therefore learn that there are mutations in different genes that can lead to similar phenotypes, in this case, muscle loss. In contrast to Liam, who has a mutation in his dystrophin gene, Jill has a mutation in her lamin a/c (*LMNA*) gene, leading students to consider how mutations in *different* genes can give rise to *similar* phenotypes. Finally, Jill, an amateur genetic sleuth, successfully diagnoses Olympian Priscilla Lopes-Schliep with a mutation in *her LMNA* gene. The nature of Priscilla and Jill’s mutations are seemingly extremely similar: both mutations are missense mutations and they are located within three codons of each other. Students consider how similar mutations in the same gene can lead to such different phenotypes. Remarkably, mutations in the same region of *LMNA* can also cause progeria, a disease of premature aging. By including progeria in the lesson, students learn that mutations in a single gene can cause diverse symptoms and diagnosis of very different diseases.

### Intended Audience

We first taught this lesson in 2017 to an introductory genetics class of mixed science and non-science majors, mostly juniors and seniors, at Bryant University, a historically business school with a Science and Technology department. Many of our twenty-eight students informed us at the beginning of the course that they were interested in careers in the health sector, so as the class progressed, we illustrated the most important concepts with specific disease case studies. We adapted the lesson in 2019 for an introductory human genetics class (36 students) at Emory University, an R1 research institution, in which the students were mostly pre-medical juniors and seniors. We taught the lesson again in 2021 to a class of 64 students at Emory. In all cases, we taught “A clicker-based case study that untangles

student thinking about the processes in the central dogma” (1) in class and followed the in-class discussion with the current lesson as independent homework (2017, 2019) or in-class assignment (2021).

### Required Learning Time

We originally designed this lesson as a homework assignment that students completed in their own time (they were given four days). We estimate that reading the ProPublica piece (6) should take students, on average, 30-60 minutes. If students choose to listen to the *This American Life* podcast “Something only I can see,” which covers the same material in less depth, the entire podcast is 57 minutes, while the relevant segment (Act 1: “Do these genes make me look fatless?”) is 36 minutes. Students will not have time to read or listen to these resources during class. However, the worksheet (S1. Phenotypic effects of mutation - Worksheet) may be easily adapted to an in-class lesson—as we did in 2021—if the students complete the reading and/or listening assignments ahead of time. When the students work through the worksheet questions during class, they have completed it in one 50 minute class period. A longer class (e.g., 75 minutes) would leave time for an optional in-class ethical discussion or debate, which we include in the worksheet. Please see Table 1 for the lesson plan timeline.

### Prerequisite Student Knowledge

Students should understand the steps of the central dogma and types of mutations and their consequences. Therefore, this lesson on *LMNA* works well as a follow up to the CourseSource lesson entitled “A clicker-based case study that untangles student thinking about the processes in the central dogma” (1). This lesson by Pelletreau *et al.* (1) focuses on X-linked Duchenne muscular dystrophy due to mutations in the dystrophin gene, while the current lesson begins with mutations in the autosomal lamin a/c gene that result in non-sex-linked Emery-Dreifuss muscular dystrophy. Using these lessons sequentially reinforces the important concept that mutations in *different* genes can lead to *similar* phenotypes (Table 2). However, even without the prior in-class lesson (1), the current lesson emphasizes that mutations in the *same* gene can lead to *different* phenotypes. Students should be familiar with codon tables and classes of amino acids (if only in passing) and with the basics of somatic vs. germline mutations. To complete the worksheet (S1. Phenotypic effects of mutation - Worksheet), teachers should provide students with a codon table that includes amino acid properties (e.g., basic, polar, etc.).

### Prerequisite Teacher Knowledge

Instructors do *not* need a deep understanding of muscular dystrophy or progeria to teach this lesson. However, an excellent resource for learning about these diseases is the [National Institutes of Health National Center for Advancing Translational Sciences Genetic and Rare Diseases Information Center](#), which has articles on Muscular Dystrophy, Duchenne Muscular Dystrophy, Emery-Dreifuss Muscular Dystrophy, and Progeria. [The Online Mendelian Inheritance in Man \(OMIM\) website](#) also includes additional details on the nature of *LMNA* mutations. Instructors should have a foundation in genetics and the central dogma, which can be augmented by free online resources on [Scitable by Nature Education](#). Useful articles include those on the central dogma and mutation (7).

## SCIENTIFIC TEACHING THEMES

### Active Learning

Case studies are an excellent way to develop critical thinking and promote active learning (8, 9). They are especially relevant for science students seeking a career in health or medicine in which they will interact directly with patients. In this lesson, students independently read and/or listen to a fascinating case study of a citizen scientist researching her own disease. They then consider questions related to the reading. We tested this lesson as a homework assignment (2017, 2019) as well as part of a flipped classroom: students performed the background reading and listening as homework, and worked through the worksheet (S1. Phenotypic effects of mutation - Worksheet) in class in small groups (2021). The questions can also be adapted for in-class clicker questions. We suggest using the ethical questions at the end of the worksheet for a short in-class debate.

### Assessment

Our goal was to emphasize that: 1) The same phenotype can result from mutations in different genes; 2) Mutations in the same gene can lead to different phenotypes. The worksheet supplied with the current lesson (S1. Phenotypic effects of mutation - Worksheet) involves short answer questions that are each assigned a suggested point value (3-6 pts) for a total of 50 points. Because our classes were relatively small, we were able to consider each answer and therefore awarded partial credit for partially correct answers. We have also included several “extra credit” questions that involve ethical considerations rather than “correct” or “incorrect” answers, and so we awarded extra credit points simply for well thought out answers. The point system is flexible and the instructor can choose to evaluate however they believe is appropriate. The questions are currently formatted as short answer, but most may be converted to multiple choice. In addition, choosing to flip the lesson so that students complete the worksheet in-class or use the questions as the foundation for an in-class discussion negates the need for worksheet grading (S2. Phenotypic effects of mutation - Worksheet Key), and teachers can instead assess students based on participation.

### Inclusive Teaching

Quite often, students think of scientists as “other people.” In this lesson, they learn about a real patient, Jill Viles, who searches for the mutation that underlies her own muscular dystrophy. Jill does not have formal scientific or medical training, and not only does she successfully determine the genetic cause of her own disease, but she also correctly hypothesizes that an Olympic athlete, Priscilla Lopes-Schliep, has a mutation in the same gene (6). Jill’s journey includes interactions with doctors and researchers, and demonstrates that anybody can be a scientist if they question and pursue information. In addition, diverse students learn well from illustrative case studies (8) and we find that students from all backgrounds are acutely interested in human diseases. To expand the ethical discussion beyond muscular dystrophy, we included optional debate questions that challenge students to think about the definition of a disability and how disabilities can build communities. Engaging students in large group discussion and small group work is extremely beneficial; it increases student achievement and persistence, develops communication and teamwork skills, and generates more favorable attitudes toward science (reviewed

in 10). Students perceive that group work facilitates learning and strengthens the link between empirical and theoretical learning (11). Groups of students that are ethnically diverse, mixed gender, and include students with different approaches to problem solving collaborate better than more homogenous groups (reviewed in 10).

## LESSON PLAN

We taught the lesson “A clicker-based case study that untangles student thinking about the processes in the central dogma” (1) in class. A month later, we assigned the current lesson worksheet (S1. Phenotypic effects of mutation - Worksheet) and posted links to the relevant background material, both as a reading (“The DIY Scientist, the Olympian, and the Mutated Gene”), and as a podcast from *This American Life* (“Something Only I Can See/Act 1: Do these genes make me look fatless?”). We suggested students choose which background media to review, as the podcast and article have similar content. A thorough understanding of the podcast or article is not necessary to complete the worksheet, but provides both background and context for the worksheet questions. We did not review the pre-work at the start of the lesson.

We assigned the current lesson worksheet to pairs of students during an hour-long discussion period, encouraged students to ask questions of each other, and asked leading questions when they seemed off-track. For example, students sometimes struggled with one of the most difficult questions on the worksheet: *Is it possible that Jill’s mutation (G to C point mutation) causes a nonsense mutation?* Some students automatically assume that a point mutation can have any type of consequence: silent, missense, or nonsense. When students struggled, we asked them: “What are possible stop codons?” After consulting the codon table and answering: “UAA, UAG, UGA,” students realized that no stop codon includes a “C.” They then correctly answered that there is no way that Jill’s point mutation results in a nonsense mutation. In addition, students were sometimes confused about the double-stranded nature of DNA: if the coding strand has the sequence 5’-TAG-3’ (stop codon), then the template strand has the sequence 5’-CTA-3’. Therefore, they reasoned, Jill’s G to C point mutation could alter a coding sequence into a stop codon. Here, we found it helpful to ask them: *What is the convention for writing DNA?* They should answer that the standard is 5’ to 3’. When discussing a mutation, we use conventional terminology and refer to the coding strand, written 5’ to 3’.

We believe students need about 4 days for this assignment if it is assigned as homework; you may encourage them to work alone at first and then allow them to consult in small groups to tackle the more difficult questions. When assigned in class, the students completed the worksheet within a 50-minute period while the instructor(s) circulated to address questions. However, if desired, students may work through blocks of themed questions and convene as a whole group to discuss several times during class. We have also included optional discussion questions that require additional time, but can be used during a subsequent class period (S1. Phenotypic effects of mutation - Worksheet).

We scored the worksheet out of 50 points (S2. Phenotypic effects of mutation - Worksheet Key), but this may work best for smaller classes, as grading short answers is time consuming.



Instructors might instead elect to have the students bring the completed worksheets to class and discuss their answers together, either grading the assignment as “completed” or not, or employing peer grading.

## TEACHING DISCUSSION

The main goal of the *LMNA* lesson was for students to understand that: 1) similar symptoms can be caused by very different genetic causes, and 2) opposite symptoms can be caused by seemingly similar genetic causes. We often brought up these themes throughout the semester-long genetics course. For example, when we discussed the concept of epistasis in lecture, students learned that loss-of-function mutations in any one player in a related pathway can lead to identical phenotypes. When we taught the students about genetic screens, they learned that mutations in one gene can rescue the phenotype generated by mutations in a different gene, thereby linking genes into pathways. A running theme throughout our genetics lectures was the relationship between mutation, protein structure, protein function, and phenotype, and this concept was revisited in some form in almost every class.

Students reacted positively to the *LMNA* lesson; we received many questions about the diseases in particular. Students were especially concerned because we had discussed classes of mutations in coding sequence (e.g., silent, missense, nonsense) several times, including during the Duchenne muscular dystrophy in-class lesson “A clicker-based case study that untangles student thinking about the processes in the central dogma” (1) (Table 1). From the discussions that stemmed from the Duchenne muscular dystrophy lesson, students learned the general genetics rules, including 1) silent mutations are unlikely to affect protein structure or function and therefore less likely to underlie disease, 2) missense mutations are more likely to change protein function—and therefore cause disease symptoms—if the amino acid properties are drastically changed, and 3) nonsense mutations are the most likely disease-causing candidates. While these rules hold true generally, even seemingly benign mutations can lead to severe disease. The current lesson focuses on three missense mutations in the *LMNA* gene that all cause different phenotypes: Priscilla’s (L530P), Jill’s (R527P) and a mutation that causes progeria (R527L). Students are at first uncomfortable with “breaking” previously defined rules, but soon learn that this is an important part of critical evaluation. By pairing the Duchenne muscular dystrophy lesson (1) with the current *LMNA* lesson, students learned that mutations in *different* genes (dystrophin and *LMNA*) can lead to similar phenotypes (muscular dystrophy), and that “similar” mutations in *the same* gene (the three missense mutations in *LMNA*) can lead to seemingly opposite phenotypes or very different disease states. These observations challenge the rule that phenotype severity is due to the “severity” of the mutation, with silent as the least and nonsense as the most severe.

When Jill chose to publicly tell her story, she was concerned that she would elicit criticism for her personal decision to have a child with a significant chance of inheriting muscular dystrophy (6). We therefore chose to conclude the *LMNA* lesson with an ethics-based discussion. Just as Jill and Priscilla’s similar *LMNA* missense mutations cause dramatically different phenotypes, their phenotypes may also elicit dramatically different judgements. During our ethics discussion about both

Jill and Priscilla’s choices to have children, students were surprised when they struggled to define the concept of “disease.” They openly wondered why as a society we value certain phenotypes and disvalue others. To emphasize the modern relevance of this dichotomy, we also challenged students’ own preconceptions of dwarfism and deafness. We hope that by concluding our lesson with this ethical discussion we emphasized the extension of critical thinking beyond traditional classroom concepts and into real world scenarios.

## SUPPORTING MATERIALS

- S1. Phenotypic effects of mutation - Worksheet
- S2. Phenotypic effects of mutation - Worksheet Key

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**Table 1. Lesson Timeline.** You may choose to first teach an in-class lesson that illustrates the central dogma with a muscular dystrophy case study (1). The current lesson requires a short amount of student pre-work. You may choose to assign the worksheet as homework or in-class as a small group activity.

Activity	Description	Estimated Time	Notes
"A clicker-based case study that untangles student thinking about the processes in the central dogma" (1)	In-class active learning activity.	55 min	Optional
Copy included worksheet (1 per student)	Worksheet is provided as Word document and may be altered if desired.	5 min	May also be distributed electronically
Identify/copy codon table	Table should include amino acid properties (basic, polar, etc.). It may be helpful to choose a DNA codon table (with T) rather than an RNA table (with U), depending on students' prior knowledge.	5 min	May also be distributed electronically
Listening to the podcast: <a href="#">This American Life: Something Only I Can See/Act 1: Do these genes make me look fatless?</a>	Pre-work. Students may listen to the podcast (here), read the article (below), or both. Most of the information is included in both resources.	36 min (Act 1 only)	Students should be given a clickable hyperlink
Reading the ProPublica story: <a href="#">The DIY Scientist, the Olympian, and the Mutated Gene</a>	Pre-work. Students may listen to the podcast (above), read the article (here), or both. Most of the information is included in both resources.	20-45 min, depending on reading speed	Students should be given a clickable hyperlink
Distribution and completion of included worksheet		At least 4 days if used as homework or one 50-minute class period	Recommended as take-home self-guided lesson OR In-class small group discussion
Optional ethical discussion	Optional ethics discussion questions are provided at the end of the worksheet.	10 min	May also be assigned in a subsequent lesson

**Table 2. Overview of the topics covered in both CourseSource lessons.** We suggest using this lesson in conjunction with “A clicker-based case study that untangles student thinking about the processes in the central dogma” (1); however, the lesson may also stand alone.

Activity	“A clicker-based case study that untangles student thinking about the processes in the central dogma” (1)	“A muscular dystrophy case study illustrating the phenotypic effects of mutation” (this lesson)
Genetic condition	- Duchenne muscular dystrophy	- Emery-Dreifuss muscular dystrophy - Lipodystrophy - Pronounced muscles - Progeria
Affected gene	- Dystrophin ( <i>DMD</i> ) gene on chromosome X (sex-linked)	- Lamin a/c ( <i>LMNA</i> ) gene on chromosome 1 (not sex-linked)
Type of inheritance observed	- X-linked recessive (loss of function)	- Autosomal dominant (gain of function) or autosomal recessive, depending on the condition
Types of mutations discussed	- Promoter - Intron - Silent - Missense - Nonsense	- Missense