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Article

Deepening Undergraduate Students' Thinking about Central Dogma through Problem-Based Learning

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Abstract: A common belief among pre-medical and medical students is that biochemistry is not relevant to practicing medicine. The problem-based approach of case studies has been used in medical education to scaffold the application of content to clinical cases, but few studies report on a similar use in undergraduate biochemistry. Case studies in biochemistry and related disciplines have been previously reported as increasing learning motivation and supporting depth of knowledge. Additionally, students engaging in case studies outperform students in traditional instruction. The objective of this qualitative case study was to find how the timing of a medical case study within the instructional sequence in an undergraduate biochemistry course supported students in applying the central dogma of molecular biology to explain the transfer of Huntington's disease from parent to child. The CBL+ group reviewed the case study before class while the CBL− group was presented with the case study during class. Analysis of open response tasks added to the pre- and post-surveys suggested that the case study supported both groups in applying the central dogma to the case, but the earlier presentation of the case to the CBL+ group promoted deeper thinking about the mechanistic causation of the transfer of the disease.

Keywords: undergraduate biochemistry; case-based learning; central dogma



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1. Introduction

Problem-based learning (PBL) is a learner-centered curricular approach where learners conduct research, apply knowledge and skills, and integrate theory and practice to construct and evaluate viable solutions to an ill-structured problem [1]. PBL commonly includes case studies that contextualize learning in real-world scenarios and simulations [2–5]. One of several types of PBL is case-based learning (CBL), which is a pedagogical strategy that utilizes cases from the field to contextualize learning while applying scientific skills and knowledge to explain the case [2,3,5]. Constructing explanations or solutions in CBL initiates learners' prior knowledge and hones skills in research, analysis, interpretation, and creative thinking [6]. Further, the use of case studies in CBL promotes critical thinking and the re-organization of scientific knowledge so it can be utilized in field-based simulations [3].

Case studies have been implemented in undergraduate biology and biochemistry education to inspire interest, create relevancy, and apply knowledge to situations from the field (i.e., Kulak & Newton [4]; Cornely [7]; Harfield [8]; Knight [9]; Kulak et al. [10]; Porzecanski [11]; Rybarczyk [12]). Previous studies have demonstrated that students enjoy learning through CBL because of the connection the case studies make to real-world situations; thus, piquing student interest and creating relevance for learning and applying content [7,13]. Similarly, studies have reported that CBL interventions have increased students' learning motivation [9,10,14] and depth of knowledge [15]. Learning gains of students participating in CBL have been reported to outperform those of students engaging

in traditional instruction [8,12,16]. Further, students' participation in CBL tends to initiate students' selection of in-depth learning strategies in place of surface-level learning strategies such as memorization or the use of mnemonics [4].

An essential topic for understanding biology at the secondary and undergraduate levels is the central dogma of molecular biology (Central Dogma throughout this manuscript). It is a major focus of K-12 science standards and undergraduate biology education [17,18] and is a key pathway for understanding processes in biochemistry. Moreover, medical clinicians and educators have identified the Central Dogma as one of the most important and relevant topics to teach in biochemistry [19]. However, undergraduates and medical students frequently do not share this sentiment, but rather perceive biochemistry as irrelevant and having little application to their future careers in medicine or other health care fields [20–22]. And yet, biochemistry courses often include pathways inherent to understanding the Central Dogma that directly relates to inheritable genetic diseases. Planning CBL interventions around medical cases involving inheritable genetic disease may support students in recognizing the relevance and importance of the Central Dogma in scientific and health care fields, and its applicability to understanding inherited diseases.

The purpose of this paper is to report on the qualitative outcomes of a CBL instructional intervention in an advanced undergraduate genetics course developed around a medical case involving a genetically inherited disease. The Central Dogma creates an explanatory model for genetically inherited diseases that can be applied to making predictions about the probability of the transfer of a genetic disease from parent to child. The model also can be used in explaining to patients and their loved ones the underlying causes of inherited disease.

However, it appears that little consideration has been given to exploring how case studies have been implemented and the learning outcomes resulting from the timing of the case study within the target learning sequence [4]. Further, it also appears that little consideration has been given to how implementation can support students' content learning gains (e.g., Rhodes et al. [23]).

Given this information, the objective of this study was to determine how a medical case study can be used to support learning the Central Dogma in an advanced undergraduate genetics course. More specifically, this study delves into how the placement of the case study in the learning sequence influences the students' abilities to apply the Central Dogma as an explanatory cause for a genetic disease. The rationale of this study is that by understanding how case studies support and deepen student learning, future recommendations can be developed on how to implement case studies to support students learning the Central Dogma in the context of real-world medical cases. Within this study, students in an advanced undergraduate genetics course participated in a problem-based case study about juvenile onset Huntington disease (HD) diagnosed in a 14 year-old child. Students were able to select whether they reviewed the case study prior to the class, allowing for guided advance preparation, or whether they reviewed the case study for the first time during class, which was typical for the course. The study focused on attending to the completeness of scientific explanations and how learning was impacted if students were given the opportunity to solve the case prior to class in addition to reviewing the research articles assigned in preparation for the in-class case discussion. The research question that guided this study was: *How do learning outcomes differ between students engaging in a case-based method versus case-based lecture while applying the Central Dogma of Molecular Biology in the context of Huntington Disease?*

2. Background

2.1. Overview of Problem-Based and Case-Based Learning

A traditional CBL unit is considered to be a collaborative, open inquiry experience [2,24,25] that incorporates case studies to anchor instruction, cultivate interest, and promote application of knowledge. However, it can be presented with significant scaffolding to mitigate frustration and guide learners through the problem-solving process [1].

Traditionally, a PBL experience begins with the instructor presenting an ill-structured, complex, and relevant problem [1]. The loose nature of the problem creates opportunities for multiple solutions because there are a multitude of pathways to arrive at the solution. In many forms of CBL, students are introduced to the problem before they are exposed to any relevant content so that the problem anchors learning in a relevant and engaging situation or case [1,2]. After the problem is presented to the class, students work individually or in small groups to review the problem and apply prior knowledge to generate tentative hypotheses and solutions. It is at this point that students determine the additional information that is required to solve the problem. Then, student groups engage in collaborative learning as each group member individually seeks the required and relevant information to solve the problem. The group reconvenes to share and discuss the information. They decide on what information is relevant and useful to solving the case, and then synthesize that information to construct a solution. Student groups present their findings and solutions to the entire class after which the class embarks in a discussion about the most likely or efficient solution while considering the alternatives. Throughout the process, the instructor serves as a facilitator, rather than the provider of knowledge through direct instruction. Further, students engage in self-regulation across the problem-solving experience as they consider relevant and important information from the research they have gathered and presented [1,26].

Like PBL, CBL appears across a continuum with a teacher-centered approach at one end and an open inquiry-oriented student-centered approach at the other. As the student learning experience moves from a teacher-centered toward a more student-centered approach, learning increases in complexity. For example, at the far end of the teacher-centered approach, Barrows [2] identified the lecture-based case method where the instructor incorporates a vignette as a strategy to present the case and its history in the context of the lecture. The case-based lecture method is a similar strategy with the exception that the students are given time to study the case in class and make connections to the target content. Through the ensuing discussion, the teacher presents the problem and guides students to identify the problem, missing information, and solution criteria. Then the students are prompted to explain the causes using the target content for support. Meanwhile, in a more student-centered approach, such as the case-based learning method, students would work individually or in collaborative groups to review the problem and identify required and missing information, and solution criteria. They would develop hypothesized solutions and conduct the inquiry. Thus, moving toward a student-centered approach develops a more meaningful context while also increasing the complexity of problem solving, level of challenge, utilization of prior knowledge, and necessity for discovery learning [3].

According to Barrows [2], an example of PBL includes the case-based method, where “Students are given a complete case for study and research in preparation for a subsequent class discussion”, (p. 483). This type of problem-based learning combines student- and teacher-directed learning. The case method tends to be more structured, but supports hypothesis development, analysis, motivation, and cultivation of interest [2]. Similar to the case-based method, the modified case-based method requires more clinical reasoning and inquiry as students review their solutions and seek to identify more efficient reasoning patterns they could have followed in the problem-solving process. The modified case-based method tends to have a stronger clinical context, which is often more motivating to students [2]. The level of scaffolding for inquiry and teacher-directed learning presented in the problem context is dependent upon students’ prior knowledge and higher order thinking skills [24,27]. Regardless, a benefit of utilizing CBL includes situating students in relevant problem contexts analogous to those they would encounter upon entering their respective career fields [3].

Studies of medical students and undergraduates in STEM courses have reported positive student perceptions toward CBL in particular. For example, in their study of the CBL (case method) implemented at two medical schools, Srinivasan et al. [24] reported that students prefer case-based learning over the traditional problem-based format. Reported

reasons for this preference included fewer tangents, decreased work outside class, and less work that they perceived to be unbeneficial. Moreover, in case-based learning, students reported having more time with problem-solving [24].

Similarly, undergraduate students studying metabolic pathways of glycogen (i.e., (metabolism, regulation, integration) through CBL reported that a greater amount of work prior to problem solving was required [16]. They also indicated that they worked harder than required from a traditional lecture course. Even so, 85% of the biochemistry students and 75% of the biology students participating in CBL reported that they were satisfied or very satisfied with the experience. It is also noteworthy that undergraduate engineering students' perceptions of their learning did not predict their actual learning outcomes, whereas their perceptions of engagement predicted conceptual understanding [28]. Further, students' preference for guided inquiry experiences have also been reported in other disciplines (i.e., Hyland, et al. [29]).

2.2. Overall Trends in General Biochemistry Undergraduate Education Case-Based Learning

Central Dogma education is a narrow discipline that seems to be not often addressed in the research literature. Understanding CBL in general biochemistry and biology education provides insights into potential directions of Central Dogma education. CBL and PBL are beginning to gain momentum in biochemistry and biology education. CBL studies within these contexts focus on improving students' disposition towards learning. Overall themes in general biochemistry CBL include improving students' motivation and sense of self-efficacy, students identifying real-world applications, and students' preference for guided inquiry.

Several CBL implementation models have emerged in the literature, and the most common trend is CBL integrated within traditional lectures (e.g., Hartfield et al. [8], Kulak et al. [10], Yadav et al. [28], Cresswell & Loughlin [30]). Traditional university lectures, while efficient in transferring information to students, tend to promote surface-level learning strategies in students [4,31]. CBL creates opportunities for guided inquiry in a traditional lecture course with relative ease while minimizing content removal [10,27]. CBL integrated within lectures also has been shown to increase students' perceived motivation [10]. Similarly, student outcomes from fully implemented CBL models incorporated into medical biochemistry education have demonstrated higher levels of solving problems with a molecular perspective, increased motivation, and increased motivation to continue studying biochemistry [32].

Improved outcomes may be explained by a study, completed by Kulak and Newton [4], that investigated how CBL influences student learning approaches in biochemistry courses and how students perceive course experiences. In a lecture course that implemented CBL, students engaged in deeper learning study approaches. In contrast, students who were engaged in a lecture course without CBL increased surface-level learning approaches throughout the semester. Students in the CBL group outperformed those who were not participating in a CBL class with respect to overall grade comparison and grade distribution [4]. A positive relationship among biochemistry cases, deep-level learning, and memory retention has also been reported [4]. Yadav et al. [28] reported similar findings in their study, noting that engineering students' perceived engagement in CBL correlated to their improved conceptual understanding. In contrast, the researchers did not find a significant difference between rote learning outcomes of the students in the CBL lecture course and students taught through traditional lectures.

3. Theoretical Framework: Situated Learning

Situated learning provides a theoretical foundation to explain how CBL, and PBL more broadly, can influence learning motivation and foster the relevancy of science topics. Situated learning theory posits that learning is a goal-directed activity situated within sociocultural contexts that are influenced by community norms and assumptions inherent to the field. Embedded within the sociocultural norms are the practices, materials, and tasks

that are used to construct knowledge and apply it to the work of the discipline [33–37]. As such, apprenticeship is the instructional strategy often employed to integrate new members into the field [34,38,39]. Lave and Wenger [33] highlight how new members to the community engage in legitimate peripheral participation as apprentices, learning from the more knowing others in the community. Their inculcation often begins as onlookers, observing and learning through imitation and guidance from more knowing others. As they gain knowledge and skills and learn the beliefs and practices shared by the community, they gain confidence and slowly assume more active roles in the community until they, too, become leaders, sharing their knowledge and expertise with new, less experienced members.

However, learning does not occur in a vacuum, nor in just one sociocultural community [35,40]. Drawing from the work of Vygotsky [37], Brown et al. [38,39], Palincsar [41], and others, Hedegaard [35] argues that in the community of the formal school classroom (and the undergraduate classroom in the current case), students often bring to their learning understanding or funds of knowledge [40] they have constructed through, and applied to activities from, their everyday lives. This everyday knowledge is often used as an organizing frame and foundation for learning scientific knowledge even though there is often a stark difference in the meaning and organization of scientific knowledge compared to knowledge students use every day in their personal lives [42,43]. As a result, it is not uncommon for students to construct fragmented and incomplete understandings that do not reflect the knowledge and accepted norms of the wider scientific community (e.g., Vosniadou [42,43], Inagaki & Hatano [44]).

Moreover, difficulty learning the subject matter can lead to decreased self-efficacy, negative views toward learning, and, thus, decreased motivation to learn [45]. Conversely, observing a more knowing other (e.g., instructor) successfully reason through a problem, or guiding the student in doing so, can lead to positive views toward the subject matter. In addition, creating relevance of the content also can increase learning motivation [45]. Further, when learning does not occur within real-world contexts and does not create relevance, the value of the learning diminishes [46,47].

Drawing from the work of other education theorists (e.g., Brown [38,39]; Palincsar [41]; Vygotsky [37]), Hedegaard [35] argues that situated learning theory needs to be “anchored in three places: (a) everyday life situations that are characteristic of children’s community, (b) subject-matter areas, and (c) the learning subjects and their development”, (p. 117). Hedegaard clarifies that subject-matter knowledge includes “problem areas that are relevant for societal life, that have dominated the different sciences through time, and have developed into central concepts and procedures of science”, (p. 117). Thus, implementing a case study on an inherited genetic disease can potentially foster interest for students, illustrate a relevant articulation of Central Dogma to real world issues, and articulate the recommendations Hedegaard posits for anchoring science instruction.

In the current investigation, a case study was developed around an unusual medical case involving a male child who develops symptoms that eventually led to a diagnosis of Huntington’s disease (HD). Although this case does not reflect the typical age of diagnosis for HD (generally at midlife—ages 40s to 50s), it was selected because of its direct manifestation of the Central Dogma, the unusual nature of the case, and the focus on a juvenile patient. Further, the case demonstrates the challenges of diagnosing the cause of symptoms that also are observed in more common diseases, such as depression and anxiety. The focus of the current study was to explore how participating in unpacking and explaining the cause of HD might cultivate in students a deeper understanding of Central Dogma.

4. Methods

Presented here are the methods detailing a case study approach [48] using a constant comparative method [49] that investigated learning outcomes related to the Central Dogma as students solved a directed case study on HD. The objective of this study was to determine how a medical case study derived from a real medical case can situate learning to support the development of students’ understanding of the Central Dogma and its use as an

explanatory model for HD. Qualitative data were collected from pre- and post-surveys in the form of written explanations, recorded small group discussions collected during in-class activities, and the accompanying field notes. The following sections outline the details of the study.

4.1. Course Context and Participants

This study was conducted in an undergraduate Human Genetics course during the Spring 2021 semester at a large research university in the southeastern United States. Human Genetics is an upper-division course within the Department of Biology. Due to University guidelines developed in response to the pandemic, this course, typically offered in a traditional in-person lecture format, was offered as a synchronous online lecture course via Zoom. The course addressed topics related to the complexities of human genetics and disease including gene expression and regulation, etiology of commonly inherited diseases, genome structure, methods to identify genes that underlie disease, and to support students in forming opinions about genetics testing and personalized medicine. CBL in the form of three case lectures [2] was incorporated into the course for the application of genetic knowledge to specific disease examples. The case studies embedded within the spring 2021 semester occurred in the following order: HD, Cystic Fibrosis, and Cancer Genetics. The first author designed the case study about HD, while the other two case studies were available for instructional use from the National Center for Case Study Teaching in Science. Before the pre-survey for the HD case study, students learned the following topics: history of human genetics, meiosis, chromosome structure, gene expression and epigenetics, and molecular pathology.

Typically, within the course, students solve two case studies a semester through a case lecture model. Case studies were typically completed in a single class-meeting time and were selected to encourage students to articulate content previously taught in the course. In a typical case study session, students complete background reading as homework prior to the case lecture class. Readings typically included reviewing research articles about the topic. Once in class, the instructor guided students in reading the case study as a class, and then divided students into groups to discuss the case study questions. The HD case study was developed for the current study to explore differences in learning outcomes when students completed the case study as a case lecture (CBL— group within this study; [2]) or as a CBL intervention (known as CBL+ within this study; [2]).

All 28 students enrolled in the spring 2021 course were invited to participate in the study. Twenty-three consenting students completed the pre-survey, and twenty-six consenting students completed the post-survey. However, matched responses on pre- and post-surveys were collected from only 19 of the 26 consenting students. The other seven students either did not consent to complete the post-survey or their responses were not identifiable to match their surveys. Tables 1 and 2 summarize the demographics for the 19 students.

Table 1. Summary of Study Participants' Gender and Race.

Gender	Number of Students (Out of $n = 19$)	Percentage of Students
Female	11	57.9%
Male	8	42.1%
Race	Number of Students (Out of $n = 19$)	Percentage of Students
White	16	84.2%
Asian	2	10.5%
Other or unknown	1	5.2%

Table 2. Summary of Study Participants' Academic Standing.

Year	Number of Students (Out of $n = 19$)	Percentage of Students
Second Year	6	31.6%
Third Year	5	26.3%
Fourth Year	7	36.8%
Graduate Student	1	5.3%

4.2. Intervention

4.2.1. The Case Study

The intervention developed for this study was derived from an unusual published medical case involving an early adolescent male who was diagnosed at age fourteen with juvenile onset HD using molecular genetic testing [50]. HD is “an autosomal, dominantly transmitted progressive neurodegenerative disease involving the basal ganglia and cerebral cortex”, ([51], p. 153) and is typically diagnosed around middle age (40s and 50s; [50–53]). HD manifests with the repeat of the trinucleotide CAG (cytosine-arginine-guanine) that codes for the amino acid glutamine and appears within the region of the gene that codes for a protein [50,54]. The trinucleotide expansion (CAG) codes for an extended polyglutamate tract in the Huntington protein [54]. Statistically, the length of the extended polyglutamate tract correlates inversely with the age at onset of symptoms but does not reliably predict for an expected age of onset [50,53]). Common symptoms of HD include chorea—uncontrollable dance-like movements [55], and stiff postures, and psychiatric symptoms including irritability and dementia. Further, depression often appears before other symptoms emerge [50,53,54].

When constructing the case study, a biochemistry expert suggested situating the students in the context of HD as the condition is classified as a trinucleotide disorder. Trinucleotide repeats (TNR) is a type of mutation not typically discussed in general biology and genetics courses, and we believed this unusual mutation would elicit interest from students. Several trinucleotide disorders were considered as the focus of the case study, such as myotonic dystrophy. However, we selected HD because the mutation is located within the coding region, whereas the mutation for myotonic dystrophy is found within the non-coding region. Our concern about using a case such as myotonic dystrophy was that it would likely be too challenging for many of the students learning about trinucleotide repeats for the first time. Additionally, it was expected that many students would have heard of HD, creating a level of familiarity that could serve as foundational knowledge for learning about TNR.

The juvenile case was selected for the intervention because of its fit with Central Dogma as an explanatory model, and its unusual nature. As noted earlier, the HD trinucleotide expansion codes CAG occur within the coding region of the gene and lead to ubiquitous polyglutamate [56]. Although it is generally an adult-onset disease that appears around middle age, onset of symptoms can appear in the early years between the ages of 3 and 20 [50,51,53,56]. Specifically, HD appears in 5 to 10 per 100,000 persons and appears in only about 5–7% of HD cases. Even though such cases are rare, introducing undergraduate pre-medical students to such cases illustrates the chameleon-like symptoms [53] that can complicate diagnosing a disease and the usefulness of diagnostic genetic testing even in minors. Another reason for selecting the case was the information needed to differentiate juvenile onset from typical adult onset of HD. Juvenile cases are most often attributed (about 80%) to paternal genetic transmission, which can affect both sons and daughters ([51,54]. Further, HD has been observed in all ethnicities, although, it is more prevalent in White populations [51]. For these reasons, the case was considered relevant to a heterogenous college population enrolled in the advanced genetics course with many students interested in pursuing advanced degrees in health care fields.

Although there was not sufficient class time in the current study to conduct a deep discussion about the bioethics of genetic testing in minors, the case presents opportunities

to explore this topic. American College of Medical Genetics and many others strongly recommend deferring predictive genetic testing of minors until they reach the age of 18 when they have the greater intellectual and social maturity to understand the benefits and drawbacks of genetic testing and the potential psychological effects on the patient and family members, particularly family members that have not been tested but could be carriers of a genetic disease [52,53,57,58]. However, diagnostic genetic testing of minors as used in the selected case is recommended following the checklist reported in Nance and Myers [51] and Craufurd et al. [56]. Further, Botkin et al. [59] underscored the importance of including juvenile patients in the decision-making process for genetic testing because of their history and experiences with the symptoms. They also recommend considering the psychological benefits to adolescents who request genetic testing. Finally, whether juvenile or adult, all patients are expected to be provided with sufficient information about genetic testing along with high-quality genetic counseling [52,53,57,58,60]. A class discussion about possible inequities in health care today and the potential solutions could be added to the HD case study to explore issues surrounding access to high quality genetic testing resources and counseling. Some topics might include doctor–patient communication, access to high quality health care in urban or rural settings, and limited access to health care professionals that represent persons of color who might create a safe space for a patient of color when discussing such complex and often frightening topics.

4.2.2. Implementation

The implementation progressed in a sequence of four steps, including (1) the pre-survey, (2) homework preparation, (3) class discussion on Zoom, and (4) the post-survey. The implementation began approximately one week before the in-class case study activity when a two-day window was offered to students to complete the pre-survey on Qualtrics. The pre-survey was provided through the course learning management system (LMS) and was designed to be completed in one sitting. Once the pre-survey closed, students had five days to complete one of the two assignment options: they could either (1) review the case study and answer the questions, or (2) complete a problem set on the Central Dogma. They earned extra credit for submitting their completed work for either option before the day of the class discussion. In addition, all students regardless of whether they consented, were required as part of the course to review three assigned background readings and view a video clip in preparation for the case study discussion. The preliminary background readings included: (1) the original published medical case report that served as the foundation for this intervention [50], (2) the original article about the chorea observed in HD by George Huntington [61,62], and (3) the original article that first reported the gene expansion [63]. The video demonstrated DNA slippage and the incorporation of trinucleotides into the RNA strand. Consenting students who selected to complete the case study and submitted responses to the case study questions prior to the class discussion self-selected into the CBL+ group. Consenting students who submitted the completed problem set prior to the discussion or that consented but did not submit answers to the case study questions or problem set self-selected into the CBL– group. The class discussion occurred in one class session. Finally, students were given one week following the class discussion to complete the post-survey on Qualtrics in a similar manner to the pre-survey administration.

The case study discussion was presented in three parts. This included an introduction of the case, followed by small group discussions in Zoom breakout rooms and then as a whole class discussion on Zoom. The instructor introduced the case study by asking students to read the case aloud so that students could participate in both reading and listening to the case. The duration of the small group discussion was twenty minutes, followed by a large class discussion. Consenting students were organized into Zoom breakout rooms in groups of approximately six to seven students by their self-selected group (i.e., CBL+ group, CBL– group). Students not consenting to the study were included in an unidentified group. The case study consisted of five questions (Figure 1) and each

breakout group was assigned a single question. The CBL– and CBL+ groups were assigned to breakout rooms five and six. Each of the assigned questions was then presented in the large group setting for the third part of the discussion. Due to limitations with Zoom recording and IRB protocol, only the students in breakout room five and six were from the CBL– and CBL+ groups (see Figure 1) were recorded. The CBL+ group consisted of seven students and the CBL– discussion group consisted of six students. These two breakout rooms were selected because they discussed the culminating questions that required synthesizing aspects of Central Dogma to construct explanations to account for the development of HD in the case and the underlying mechanisms that can lead to this disease. Thus, demonstrating the target goal for the intervention: to identify differences in student thinking resulting from case lecture versus case-based instruction [2].

Answer the following questions using peer-reviewed articles from your own literature search, when possible, in addition to the articles provided.

Breakout Room 1: *What is Huntington disease? What is the normal age onset for Huntington disease? How is Huntington disease diagnosed?*

Breakout Room 2: *What are triple expansion repeats (TNR?) What role does TNR play in Huntington disease?*

Breakout Room 3: *What happens during DNA replication under normal conditions? What happened during DNA replication when there is a TNR in the gene? How does TNR influence protein folding?*

Breakout Room 4: *What is gene anticipation and what role does it play in Huntington disease? Using gene anticipation and data from the case report, why did Thomas develop symptoms of Huntington disease at a young age? Discuss gene anticipation in terms of both inheritance and DNA replication.*

Breakout Rooms 5 & 6: *Explain the compounded effects TNR creates in the processes of the Central Dogma of Molecular Biology, including: transcription, transcriptional regulation, and translation. How do these effects lead to Huntington disease? How do each of the processes affected by TNR differ from the normal processes of DNA replication, transcription, translation, and/or transcriptional regulation? Provide details and evidence to support your reasoning.*

Figure 1. Questions Assigned to Each Breakout Room to Guide Small Group Discussions.

Not all student groups were selected to be recorded because the number of consenting students exceeded the desired capacity of each discussion group, and the limited availability of necessary resources for doing so. Other groups were not recorded due to equipment and human subject confidentiality limitations. However, narrowing a focus on the two groups created an opportunity to closely focus on student thinking reflected in the responses from the two groups. Following the approved IRB protocol, informed consent was provided separately for pre- and post-surveys, respectively, and the small group discussion. All students were de-identified upon data collection. As such, students in the recorded small discussion groups may or may not have provided matched pre- and post-surveys and vice versa. In addition, students were offered extra credit in the class if they completed the case

study, problem sets, pre-survey, and post-survey, regardless of their decision to participate in the research study.

4.3. Data Collection

Data were collected from the pre- and post-surveys, responses to submitted assignments (i.e., case study questions and problem sets), and recorded discussions collected during small group work on Zoom, and field notes collected during the whole class discussion on Zoom.

The pre- and post-surveys consisted of the same two open-response tasks. These were designed to identify a foundational understanding of the Central Dogma (task 1), and the ability to apply the Central Dogma to explain the genetic downstream effects of Huntington's disease (task 2). The two open response tasks were as follows:

1. How would you describe the relationship between gene, genotype, gene mutations, phenotype, and disease?
2. Think about the Central Dogma and Huntington's disease. Which processes within the Central Dogma are involved in Huntington's disease? How are they involved in Huntington's disease?

The first question was designed to assess students' foundational understanding of the Central Dogma. The second question was designed to assess students' ability to apply their knowledge of the Central Dogma in the context of HD.

4.4. Analysis

In this case study [48], an interactive process using the constant comparative method [64] was utilized to analyze student responses from the two open response tasks. Deductive and inductive codes [65] were created in the first round of analysis. Deductive codes were created to reflect tenets of the Central Dogma related to HD and the case. Inductive codes were developed organically to represent ideas reflected in student responses that were not included in the deductive codes. In some cases, inductive codes highlighted student conceptions about the Central Dogma that are not congruent with currently accepted scientific views. We refer to these misunderstandings as alternative conceptions [66]. Codes were then grouped together into categories based on their relatedness to the topic and larger themes observed within the data [67]. Analysis was divided to identify students' foundational knowledge and how students applied their knowledge of the Central Dogma to account for the cause of HD.

Interrater reliability was determined in a two-step process. First, the researcher (first author) and a second coder with expertise in biology (third author) met to score the responses to the foundation question. They then individually coded responses, reconvening to compare responses. They followed this cyclic approach until reaching agreement on the codes at a level of 80% or higher [68]. When the agreement was less than 80%, they discussed codes and made modifications to the code book until reaching consensus. The researchers then scored all the responses independently before reconvening to discuss any code disagreements.

A second level of analysis was conducted to determine the accuracy of responses and how students used the Central Dogma to explain Huntington's disease. In this process, each of the pre- and post-survey responses was scored using a framework modified from Trundle et al. [69]. Students' responses were scored as one of the following: No Response/I don't know, Incorrect/alternative conception (where students provided an incorrect statement), a Scientific Fragment (where students provided a response that was partially correct or demonstrated a partial understanding), or a Scientific Explanation (where students provided a correct and complete explanation). A similar constant comparative method [64] for establishing interrater reliability was conducted as described above. Responses were categorized based on score, trends in students' understandings and conceptions. Data from the preparation assignments (i.e., case study questions and problem sets) and small group discussion were used to triangulate themes that emerged from the pre- and post-surveys.

5. Findings

5.1. Trends within Foundational Knowledge about the Central Dogma

Students in both the CBL– and CBL+ groups were asked the following question on their pre- and post-surveys to assess their foundational knowledge of the Central Dogma: How would you describe the relationship between gene, genotype, gene mutations, phenotype, and disease? The following sections detail the overall trends in students' pre- and post-survey responses for this foundation question. Additionally, trends within the findings in students' conceptions based on their depth of understanding are presented. Each section is demarcated by CBL– or CBL+ groups for the pre- and then post-survey responses.

5.1.1. Pre-Survey Responses

Central Dogma Terms and Relationships: CBL– Group Pre-Survey Responses

In this section, we present three categories of responses that were most often represented in the CBL– group's data. These include genotype, phenotype, and mutations. Additionally, we present trends in students' level of knowledge of the Central Dogma observed across the responses.

Overall, pre-survey responses from the six students in the CBL– group demonstrated superficial knowledge about the relationship between gene, genotype, gene mutation, phenotype, and disease. In general, responses from five of the CBL– students were presented as definitions of the terms where relationships between two or more terms were briefly described. The responses commonly defined genotype in relation to genes and DNA sequence. All responses indicated some understanding of genotype by explaining that genes code for or make up a genotype or noting that genotype is the DNA sequence of the organism. Responses also indicated that genotype consists of all genes, and/or is determined by the gene. CBL– responses generally suggested the understanding that a genotype consists of genes and genes code for a phenotype or that the phenotype is the reflection of gene expression. A representative quote from one of the CBL– students follows:

"A gene codes for a genotype which is presented in physical appearance as a phenotype. A gene mutation can result in a switched up genotype or a new phenotype, and a disease can result in a larger issue depending on what it affects."

In this example, the student relates the physical appearance to genotype, while also elaborating that a genetic mutation can change the genotype and therefore produce a new phenotype. The student seems to suggest a connection between the mutation and disease. One of the six students did not provide a definition for the term genotype, but rather connected genotype to phenotype and disease. This student's response follows:

"...If a particular gene carries a disease, it can be found in the genotype after mitosis and meiosis in the offspring. This genotype can display the phenotype of the gene in some cases. Gene mutations can be the cause of disease."

This response also appears to state that mitosis and meiosis must occur in the offspring before a gene mutation becomes apparent in a phenotype. This might be a simple case of a dangling modifier, but it also illustrates challenges students might have in explaining their understanding. Even so, this response appears to describe a relationship between gene, genotype, phenotype, and disease. All CBL– students' responses described a relationship among genotype, phenotype, and mutations. The responses also connected genotype to phenotype and mutations. Gene mutations were used to describe the downstream consequences of alternations within the genotype. All students mentioned that mutations will affect the genotype, and related phenotype to gene expression. Meanwhile, phenotype was described as a reflection of gene expression and/or the genotype. More specifically, students described that a genotype would determine the physiological expression in the offspring, whereas phenotype was defined as a display of the genotype. All except for one of the CBL– students' responses described phenotype as the reflection of a genotype, and a change in the genotype is expected to change the phenotype. For example, as noted below, one student asserted that the change in genotype will change the phenotype:

“Gene is a region coded that will determine the genotype (sequence) and determine the physiological expression of the sequence (phenotype).”

The remaining student did not connect gene mutations and phenotype.

Only two CBL– students’ pre-survey responses established relationships between phenotype and disease. One student described that phenotypic changes cause disease, as described in the following response:

“Gene mutations affect the gene itself, which can result in altered genotypes. Phenotypes are the physical trait observed from a genotype; if a mutant genotype is present and represents through a phenotype, this can result in disease.”

In contrast, the other CBL– student stated that phenotypic change is the disease itself, as represented in the following quote:

“Gene is a region coded that will determine the genotype (sequence) and determine the physiological expression of the sequence (phenotype). A disease has symptoms that are the phenotype of the mutated gene.”

Although the two examples illustrate a relationship between disease and phenotype, both examples suggest an alternative conception that phenotype rather than genotype causes disease.

Although proteins were not often noted in the responses, two students in the CBL– group explained that proteins create the phenotype. These students referenced proteins, stating that DNA or genes code for a protein that is expressed phenotypically. However, as illustrated in the two students’ responses that follow, these students did not specifically connect proteins to disease or phenotype:

“Genotypes are comprised of all the genes in an organism. Genes code for proteins that create the phenotype of an organism. Gene mutations can change the phenotype of an organism. Mutations can create certain phenotypic conditions that lead to a disease state.”

“A gene is a sequence of DNA that codes for a protein that can be expressed phenotypically. Genotype is the DNA sequence of an organism. Gene mutations are mutations in the genotype that may or may not be expressed phenotypically. Disease is the result of many possible errors in the central dogma and more, including, but not limited to, mutations occurring in replication, transcription, translation, RNA processing, and mitotic or meiotic mutations.”

Responses connected genes to phenotype by stating that genes code for proteins and proteins are expressed in the phenotype. The students’ responses also discussed how mutations change the genotype and that the mutation may appear in the phenotype. The second student recognized that disease is a result of errors within the Central Dogma. However, the student did not recognize how mutation alters protein structure and function, which then influences the downstream metabolism and causes disease. The students’ responses were analyzed to assess their level of understanding by utilizing a framework derived from Trundle et al. [69]. In general, the six students in the CBL– group presented a partial understanding of the genes, genotype, phenotype, mutations, and disease.

Central Dogma Terms and Relationships: CBL+ Group Pre-Survey Responses

Three categories emerged from the CBL+ group’s pre-survey responses. These included: genotype, phenotype, and mutations. Overall, students within the CBL+ group provided brief and superficial responses. However, a brief explanation of proteins and the Central Dogma were observed.

Nine of the thirteen CBL+ students provided a definition for genotype. The genotype definitions were varied and students characterized genotype as a term to identify specific genes or all the genes of an organism, or a term to describe a set of genes. Students’ conceptions about genotype included using the term as a label to describe the alleles for the specific gene. Additionally, students utilized the term genotype to describe how

genes are a way to determine the genotype. Lastly, students used the term genotype to describe what a gene looks like. Within the CBL+ pre-survey responses, a Central Dogma connection emerged as a new theme. Five students within the CBL+ group provided some sort of Central Dogma connection, which all relationships described related to genes. Three students provided a partial Central Dogma explanation, while two students provided a complete explanation about the Central Dogma.

The students who provided a partial explanation of the Central Dogma described the following connections: a gene is a specific section of DNA that performs a certain function; mutations can alter the protein; and genes contain all the information of DNA. Two students provided a brief, but a more holistic perspective of the Central Dogma. For example, one student described that “Genes code for a string of amino acids which form proteins. These proteins are used to carry out biological functions. . .”. The other student connected the Central Dogma to the formation of gene mutations: “Gene mutations can occur from improperly replicated/transcribed/translated/spliced genes which can alter the phenotype of an organism. . .”. Regardless of the extent that the Central Dogma was discussed within the responses of the CBL+ group, genes appeared to be the starting point when discussing downstream processes and/or the downstream effects of mutations.

In addition to genotype, another theme that emerged from the data included phenotype. Students discussed phenotype in three different contexts that were often connected: gene expression, physical characteristics, and disease. Phenotype in the context of gene expression appeared to be used to support discussions of mutations and/or physical traits. Of the thirteen students who self-selected into the CBL+ group, eight students provided a phenotype definition that related to gene expression. These students described phenotype as the outward appearance or the physical characteristics of a genotype. Similarly, these students defined phenotype as the collective term for all observable traits or as the reflection of a genotype, and discussed that genes contribute to a phenotype. Furthermore, nine of the thirteen students appeared to understand that a mutation may change the phenotype. Two students demonstrated an alternative conception that a mutation will change the phenotype. The remaining two students provided an ambiguous relationship between disease and phenotype.

A point of difference within the CBL+ group on their pre-survey responses is their discussion of phenotype in relation to disease, where various conceptions emerged from nine students. Six of these students discussed within their responses that disease is a phenotype. A representative response from the group follows:

“A disease is when that changed phenotype is deleterious and affects some normal function/structure.”

In this example, the student recognized that disease is an abnormal phenotype but also suggests the phenotype and not the genotype is the underlying cause of the disease. The conception that disease may influence phenotype was observed in another response where the student describes, “. . .Genetic disease can arise from gene mutations and the disease may or may not influence the phenotype”. This example suggests the student understands that mutations may cause a genetic disease while also holding the alternative conception that disease influences a phenotype rather than the disease as the phenotype. A trend observed in the CBL+ students’ responses was the close linkage between phenotype and mutations, and mutations and disease. Specifically, students’ discussions of mutations were used as a foundation for their discussions of disease and phenotype. Lastly, two students described that phenotype causes disease. For example, one student stated, “This phenotypic changes [sic] can be [a] disease cause for the organism. . .”. Thus, suggesting an alternative conception that disease leads to the outcome of a phenotype, rather than disease as a phenotype.

Overall, the level of understanding demonstrated by the CBL+ students pre-survey responses demonstrated greater partial understandings in their pre-survey responses in comparison to the CBL– group. Rather than providing a complete explanation, their responses tended to consist of fragmented ideas. An alternative conception that emerged in

the pre-survey responses was the relationship between phenotype and disease. In the CBL+ group, there were six students who discussed disease is a phenotype and demonstrated an accurate scientific understanding. However, two of the CBL+ students shared the alternative conception that phenotype *will* cause disease and two additional students suggested that phenotype *may* cause disease. Unlike the responses from the students in the CBL− group who tended not to include the relationship between disease and protein, the CBL+ students' responses often included discussions relating to the role of proteins within the Central Dogma. However, like the CBL− responses, the CBL+ responses reflected a partial understanding with scientific fragments rather than complete explanations.

5.1.2. Post-Survey Responses

Persistent Trends in Students' Conceptions and Depth of Understanding: CBL− Post-Survey Responses

Within the responses of the CBL− group, three categories emerged: genotype, phenotype, and mutations. Overall, the six students in the CBL− group demonstrated similar trends in their post-survey responses of the foundation question as in the pre-survey. Responses from the CBL− group were brief and superficial. A noteworthy finding is that four of the students in the CBL− group elected to complete the Central Dogma alternative pre-class assignment, while only two students did not complete a pre-class assignment. The completion of the assignment suggests students were motivated to prepare for the in-class discussion and in doing so, reviewed content that was addressed in the foundation question in the pre-and post-survey. However, upon analysis, there are no apparent differences between the responses of the students who completed the pre-class alternative assignment and those who did not.

The first theme that emerged from the CBL− post-survey responses included genotype. Students provided similar genotype definitions on the pre- and post-survey. Like the pre-survey, students discussed within their post-survey responses that a gene is made up of genotypes or a genotype includes all the genes within an organism. Students also described that genes give rise to genotype. Additionally, CBL− students defined genotype in relation to DNA. Definitions related to DNA included defining genotype as the sequence of a gene, a genotype is the DNA sequence, and the DNA sequence has regions that code for specific genes. This consistency in the definitions of genotype illustrated in the pre-and post-survey responses is represented in the following student's responses:

Pre-survey Response: "A gene codes for a genotype which is presented in physical appearance as a phenotype. A gene mutation can result in a switched up genotype or a new phenotype, and a disease can result in a larger issue depending on what it affects."

Post-survey Response: "A gene is made up of genotypes which physically appear as a phenotype. A gene mutation could alter the genotype to change the phenotype, and if the mutation is bad enough can cause a disease."

Consistent with the pre-survey response, the student provided a nearly identical definition of genotype and description of how genotype is related to phenotype in terms of physical appearance. Likewise, the student describes a similar relationship between mutation and disease. However, in the pre-survey response, the student described that disease depends on what the mutation affects, while the post-survey response focuses on the severity of the mutation. Another subtle difference is that the pre-survey response focuses on how mutations may cause changes in the genotype or phenotype. In contrast, the student understands in the post-survey response that a change in genotype may alter the phenotype, connecting the two ideas. The pre- and post-survey examples above also illustrate the close relationship between the themes of genotype and phenotype. This relationship was consistent in the post-survey responses across the CBL− group. Like the pre-survey, five of six students discussed phenotype in the context of gene expression, explaining that phenotype is the physical appearance of the genotype or the physical expression. Other similar explanations included that genes produce an observable phenotype, are expressed

phenotypically, or the phenotype is what is expressed of the genotype. The following CBL—students' quote exemplifies the relationship between genotype and phenotype most often described in the responses:

"Genotype is the sequence of DNA which has regions that code for specific genes, which specific regions of DNA sequence. These regions, after Central Dogma, are expressed and produce an observable phenotype. Gene mutations are any abnormal sequence of DNA within a gene encoding region and the product of such disease."

In this example, the student identifies that a section of a DNA sequence codes for a gene and builds upon the knowledge by describing that genes are expressed to produce a phenotype via the Central Dogma. One student did not discuss phenotype in relation to gene expression focused on how mutations cause changes in the phenotype and disease. The student responded as follows:

"[T]hey are all related. genes code for traits and can rise to genotypes, these genes can mutate and lead to changes in phenotype and disease."

Although the student may understand the relationship between gene expression and phenotype, the response did not explicitly identify this relationship, so we cannot conclude if the student had this understanding. Interestingly, students' discussion of phenotype did shift away from the conception that changes within the gene or genotype will cause a phenotypic change. Rather, students appeared to have realized that a mutation does not always result in a phenotypic change. Five students used terms such as "may", "can", or "could" when describing changes leading to a phenotypic change, indicating that the students understand that a mutation does not always lead to an observable change in phenotype. In comparison, only two students on the pre-survey demonstrated knowledge that a mutation does not always lead to a phenotypic change. While four of the students on the post-survey discussed that mutations may change the phenotype and lead to disease, only two of those students explicitly recognized that disease is a phenotype. The remaining student did not provide a clear indication that a phenotypic change may be observed in association with explaining that, "...If a gene mutation is expressed, you end up with a disease". One other theme that was observed within the CBL— post-survey responses included mutations. Students' understanding of mutations also remained relatively unchanged. All students in the CBL— group discussed that mutations could alter the genotype or gene, and phenotype. Additionally, one student described mutations as an abnormal DNA sequence within the gene, as represented in the following example:

"Genotypes are comprised of all of the genes present in an organism. Mutations can occur within these genes that may lead to a mutant phenotype. These mutant phenotypes may cause adverse reactions within the organism, leading to the disease condition."

This student's response also illustrates the practice of CBL— students on the pre-survey for CBL— to explain how mutations create a phenotype that causes disease or create a disease-like phenotype.

In addition to the overall trends in the CBL— group on the post-survey, students' responses were analyzed to determine trends based on their depth of understanding. Overall, the CBL— responses illustrated partial understanding of the Central Dogma. Most of the students' responses (four of six students) showed no change in their depth of understanding between pre- and post-survey, which was partial and fragmented. One of the two remaining students provided an incorrect response. The sixth student, however, submitted a scientific response regarding the relationship among genes, genotype, mutation, phenotype, and disease as illustrated in the following quotation:

"A gene is what is encoded to make a protein, and a gene can be expressed phenotypically. The sequence of the gene is the genotype. The genotype can give a phenotype. When a mutation occurs, the sequence of the genotype is altered and could lead to a different phenotype like a disease."

This student demonstrated an understanding that changes in the genotype can produce a disease phenotype but lacked some evidence regarding proteins. The student knew that genes code for proteins. However, the student did not connect proteins to a disease phenotype. One student in the CBL– group provided an incorrect statement that also was too brief to determine their understanding. Within this study, statements that were too brief to evaluate were categorized as incorrect responses as there was not enough information to determine students' understanding. For example:

“They are all related. Genes code for traits and can rise to genotypes, these genes can mutate and lead to changes in phenotype and disease.”

In the provided example, the student vaguely describes how the components of the Central Dogma are related. The student also provided an incorrect relationship between traits and genotype, along with an alternative conception about the relationship between phenotype and disease. For the four students in the CBL– group who demonstrated a partial understanding, their responses reflected the responses they submitted on the pre-survey. Students generally described that phenotype is the reflection of gene expression or of a gene, and a mutation can change the respective genotype and phenotype.

The following example illustrates this trend:

“Genotypes are comprised of all the genes present in an organism. Mutations can occur within these genes that may lead to a mutant phenotype. The mutant phenotypes may cause adverse reactions within the organism, leading to the disease condition.”

In this example, the student demonstrated an understanding that mutations may lead to changes within the phenotype. The student presented an alternative conception that phenotype may lead to “adverse reactions in the organism”, rather than a mechanistic view relating the mutation to changes in the phenotype that may manifest as a disease. Thus, they demonstrated a fragmented understanding through their discussion of phenotype causing a disease. Only one student held an alternative conception about genotype, which was that a gene consists of genotype:

“A gene is made up of genotypes which physically appear as a phenotype. . .”

Lastly, CBL– responses suggested these students understood that mutations may result in disease but did not relate this to phenotype. For example, one student responded by stating, “Genes determine genotype, a gene mutation affects the gene which affects the genotype. A phenotype is what is expressed of a genotype. If a mutation is expressed, you end up with a disease”. This student's response is indicative of the nature of the CBL– responses. Although the phenotype is described as the reflection of gene expression, the response excludes the relationship to phenotype and genotype when incorporating disease into their response.

Gains in Deep-Level Learning: CBL+ Post-Survey Responses

Three major categories emerged from the CBL+ post-survey responses that included genotype, phenotype, and mutations. Within this section, we review overall trends within the CBL+ post-survey responses and trends in students' depth of knowledge. Overall, the responses were brief, but demonstrated foundational knowledge related to the Central Dogma and disease.

The first theme observed within the CBL+ responses was the similarity between their descriptions of genotype portrayed on the pre- and post-survey. Like the pre-survey, ten of the thirteen students provided a genotype definition. Similar to their pre-survey responses, eight of these students defined genotype as all the genes within an organism or genes that correspond to the genotype. These students also explained that the genotype codes for genes or they defined genotype as the alleles of a gene. However, two students provided new definitions of genotype, that were not previously observed in the CBL+ pre-survey responses. One of these students described the genotype as the gene code that is transferred from one organism to another. Another student described the genotype as the molecular

structure of the gene. Eleven students within the CBL+ group provided a description of gene or genotype, which created a context for students' discussion for mutation and phenotype. Furthermore, responses between the pre- and post-survey were consistent, as represented in the following example:

Pre-survey Response: "...The genotype is a label for what kind of genes you have, while phenotype is the outward appearance of your genotype. Mutations in a gene can result in different genotypes that could lead to different phenotypes that are categorized as a disease."

Post-survey Response: "An individual has genes that correspond to their genotype. Genes can have mutations that result in a change in genotype that may or may not result in a new phenotype. Phenotypes are the [sic] visual characteristics of a genotype. Genetic mutations can lead to phenotypes that are harmful and can be categorized as diseases."

This student presents two major ideas: (1) phenotype is the observable outcome of a genotype; and (2) mutations may lead to a phenotypic change that can be considered a disease. Another theme that re-emerged within the post-survey responses included phenotype. Like the CBL+ pre-survey responses, phenotype appeared to have a strong connection to genotype. Phenotype was often described in the context of gene expression. Ten students established this connection. Among the ten responses, six students had referenced phenotype as an observable trait or physical characteristic. Furthermore, the nine students in the CBL+ group described phenotype as gene expression and discussed that mutations can change the genotype and phenotype. The third theme that was observed included mutations, which was often connected to discussion of phenotype. Three trends emerged from students' discussion about the relationship between mutations and phenotype, which related to their discussion of disease: (1) disease is a phenotype; (2) disease may or may not influence the phenotype; and (3) phenotype causes disease. Six students discussed that disease is a phenotype, while two students discussed that phenotype may or may not influence disease, and two students discussed that phenotype causes disease within their responses. Only one student did not connect phenotype and disease. Instead, this student provided a superficial response that provided definitions and statements, but did not connect genes, genotype, phenotype, mutations and disease.

A noteworthy finding within the CBL+ post-survey was the emergence of protein folding within three responses. These students discussed that a mutation can impact protein production or function, an incorrectly folded protein (as a result of a mutation) may not function or function in an inappropriate manner, or a mutation can cause a protein to take a different form. Within all three responses, students described that the protein with an alternative form will alter the phenotype. Two of these students described that the alternative protein is what created the disease phenotype. For example:

"Gene mutations can occur in a cell when the DNA for a gene has a mutation or in the process of expressing that gene. When a mutation is present in a person's genotype that greatly impacts a person's protein production or function, especially one that is necessary, it can result in a specific phenotype that is different than what is considered normal and can even present itself as a disease."

Within this example, the student utilized their discussion of proteins to describe how mutations may lead to an abnormal or disease phenotype. Furthermore, the student incorporates a discussion of protein production and function to explain why an abnormal phenotype may be present. More specifically, these students in the CBL+ group recognized that mutations influence protein structure or function, leading to an abnormal phenotype. Students also began to elaborate on this knowledge by explaining that changes in protein folding will disrupt protein function, which causes disease. The remaining student did not connect alternative proteins, phenotype, and disease as provided within the following example:

“All the genes in an organism make up the organism’s genotype. The genes code for proteins which are expressed in the organism. This expression is the phenotype. When there is mutation in genes, proteins sometimes fold incorrectly and don’t function or function in an inappropriate way. This can cause disease.”

It is possible that the student had a more complete understanding of this relationship, but the written response indicated conceptual gaps. For example, the student implies that protein expression is the phenotype, rather than the role of protein within various biological processes that may be attributed to the phenotype. The student understood that protein folding can contribute to disease but did not connect disease back to phenotype.

In addition to the overall trends in students’ understanding of their knowledge of gene expression and the Central Dogma, we were also interested in their depth of understanding. Overall, students in the CBL+ group demonstrated similar levels of knowledge about gene, genotype, phenotype, mutation, and disease on the pre- and post-survey, which reflected partial understandings with scientific fragments. However, the CBL+ group’s post-survey responses illustrated subtle changes in their depth of understanding of proteins. Their responses reflected the downstream effects of mutations that manifest as changes in protein folding, which changes the structure of the protein.

Also noteworthy is the fact that four of the thirteen CBL+ students provided complete scientific statements within their post-survey responses. The four students’ explanations tended to be in the context of mutations and served a functional purpose. Others stated that genes make up the genotype or that the genotype is the molecular structure of the genes. An example of genotype used in context of mutations follows:

“Different genes are related to genotypes by different alleles on that gene. Gene mutations are a change in a specific allele on the gene such that a nucleotide or more than one nucleotide is changed. . .”

Within this example, the student utilizes their genotype definition about alleles to support their discussion of mutations. Specifically, the student identified that mutations are changes at the nucleotide level within an allele. Additionally, students in the CBL+ group who provided scientific explanations tended to connect that proteins are produced by gene expression, which contributes to a disease phenotype. An example of a student’s response follows:

“Gene mutations can occur in a cell when the DNA for a gene has a mutation or in the process of expressing that gene. When a mutation is present in a person’s genotype that greatly impacts a person’s protein production or function, especially one that is necessary, it can result in a specific phenotype that is different then what is considered normal and can even present itself as a disease.”

As described within this student’s example, when a mutation occurs, protein function is altered or the protein is somehow different, which creates a disease phenotype. This example is representative of how students tended to describe the impact of mutations on protein production and function, which results in phenotype. One student took the same concept a step forward by describing that mutations impact protein folding, which influences the function and creates a disease. This concept is represented by revisiting the following example:

“All the genes in an organism make up the organism’s genotype. The genes code for proteins which are expressed in the organism. This expression is the phenotype. When there is mutation in genes, proteins sometimes fold incorrectly and don’t function or function in an inappropriate way. This can cause disease.”

The other nine students in the CBL+ group who demonstrated a partial understanding with fragmented ideas generally mirrored their pre-survey responses and lacked any discussion about proteins. Most of the nine students provided a definition that genes make up the genotype, although a few alternative conceptions about genotype coding for

proteins persisted. The primary focus within this group was that mutations within the genotype influence changes in the phenotype that lead to presentation of the disease:

“Genotype refers to the genes of an organism. Phenotype is reflective of how the genes are expressed. Gene mutations can change the phenotype in a way that may or may not cause disease.”

An alternative conception about phenotype causing disease emerged once within the dataset:

“Our genes are what cause us to have a specific genotype which is simply just our genetic makeup. Gene mutation alter our genotype and can have effects on our phenotype due to the mutations, there are many diseases that are a results of gene mutations that also cause a phenotype.”

5.2. Trends in Students’ Application of Content Knowledge in the Context of Huntington Disease

Students in both the CBL– and CBL+ groups were asked the following question on their pre- and post-surveys to assess how students connect their understanding of the Central Dogma to explain HD: Think about the Central Dogma and Huntington disease. Which processes within the Central Dogma are involved in Huntington disease? How are they involved in Huntington disease? The following sections detail the overall trends in students’ pre- and post-survey responses for the application question followed by trends based on the students’ depth of understanding. Each section is demarcated by CBL– and CBL+ groups for the pre- and then post-survey responses.

5.2.1. Pre-Survey Responses

Limited Understanding of the Connection between the Central Dogma and HD: CBL– Pre-Survey Responses

Overall, a majority of the six CBL– students’ pre-survey responses indicated that they did not know the relationship between the Central Dogma and HD. All except for one student (five students) in the CBL– group stated that they did not know but provided some sort of guess with an explanation. The guesses that students provided include translation, ineffective proteins, and splicing. Three students suggested mutations, with one student briefly expanding that mutation is associated with a nonfunctional phenotype. One student suggested ineffective protein production, while the other suggested an error in translation.

Discussion of gene mutations were observed in three responses: one student discussed general gene mutations, one student discussed a general mutation with a “nonfunctional phenotype”, and the other student discussed allelic mutations. The student who referenced the allelic mutation referenced the mutation, but could not connect the mutation to HD:

“I do not have any knowledge of the pathogenetic nature of Huntington disease. I guess there is an allelic mutation, but I do not how that is incorporated into the onset of disease.”

In respect to translation, one student simply guessed translation and another student guessed that ineffective proteins are related but lacked detail. Similarly, a student recognized that a mutation caused the disease but forgot which mutation was associated with HD.

Among the six CBL– students, five included an incorrect statement on their pre-survey regarding HD. However, one student presented a partial understanding. This student did not indicate that they did not know the answer. The student described that HD is caused by a gene mutation that impacts transcription and translation:

“Huntington Disease is a disease caused by gene mutation resulting in a non-functional phenotype which relates perfectly to the central dogma.”

The CBL– students who provided incorrect information about HD indicated that they did not know but provided a guess. Such guesses were related to the Central Dogma or mutations but were too vague to evaluate. The students who guessed that some aspect of the Central Dogma was involved most often referenced translations or ineffective protein

production in their reasoning. In the following example, the student describes that they did not know about the connection between HD and the Central Dogma, but guessed that ineffective protein production serves a role:

"I'm not sure which part of the central dogma is involved in Huntington's disease. I know that occurs later in life, and it likely deals with the ineffective production of proteins in some capacity."

Limited Understanding of the Connection between the Central Dogma and HD: CBL+ Pre-Survey Responses

Among the thirteen students, three students reported that they could not describe the relationship between the Central Dogma and HD and did not attempt an explanation. Three additional students in the CBL+ did report that they also did not know, but attempted to provide a tentative explanation of the relationship between the Central Dogma and HD. One student's attempt stated that they were not sure whether mutations in replication, transcription, or translation impacts HD. This student also lacked an explanation. Another student guessed that a mutation is passed from one generation to the next. The remaining student stated that they did not know, but explained that an error in replication, transcription, and translation would create a "wrong" protein and that would lead to the disease.

The remaining seven students provided a response without stating any uncertainty. Six of these responses were brief explanations with varying responses, while another student provided a correct detailed response (reported later in this section). Among the six students who provided a brief explanation, these responses included: (1) mistakes in transcription, translation, and nondisjunction; (2) mutations; (3) a mistake in mRNA; (4) a certain genotype leads to an incorrectly folded protein that causes the protein to improperly function; and (5) a mutation alters transcription and translation.

In addition to overall trends within the pre-survey responses of the CBL+ group, we were interested in trends within responses based on their level of understanding. Of the thirteen students self-selected into the CBL+ group, one student presented a scientific explanation. Six students presented a partial understanding on their pre-survey responses. Three students presented incorrect statements and four students did not know.

A range of responses were observed by the CBL+ students who demonstrated a partial understanding in their pre-survey responses. Two students referenced errors in replication, which creates errors in transcription and translation. As a result, a disease-causing protein is formed:

"I am not sure but I would guess an error occurred during replication that leads to the transcription and translation that creates a protein that is wrong and that causes the disease."

In this example, the student understood that proteins contribute to disease. The student also understood that error in replication would impact transcription and translation, contributing to a "wrong" protein. However, the response is vague; the student named the steps within the process, rather than describing the Central Dogma and the relation to disease. Another student who provided a partial response even presented knowledge about TNRs, which also causes the incorrect RNA and protein to be synthesized.

"The Central Dogma states that DNA makes RNA makes protein. Huntington's disease is caused by errors in DNA replication when a specific repetitive region of the genome is incorrectly replicated. Extra repeats are added. Because the DNA is incorrect, the wrong RNA and protein will be synthesized because of a cascade effect."

Within this example, the student provided a brief overview of the Central Dogma. The student was also able to expand on the idea that an error occurs during replication by the addition of a repetitive region, ultimately leading to an incorrect protein. Missing from the response was how the alternative protein contributed to disease. Other students

generally referenced mistakes in transcription and translation. This is illustrated in the following example:

“Huntington disease is a genetic disease, and a mutation in the DNA causes the transcription and translation to be altered.”

Finally, a few students vaguely discussed that incorrect protein synthesis was involved:

“A certain genotype causes a protein to be formed incorrectly so that it doesn’t function properly. This causes Huntington’s disease.”

Within these examples, while the students included elements within their responses that would be considered correct, the responses are vague. The vagueness within the response indicated a surface-level of understanding, rather than a depth of knowledge. Incorrect responses provided by students related to mutations, among other conceptions not related to HD. For the CBL+ students who provided incorrect statements related to mutations and inheritance, one student vaguely described that mutations lead to disease:

“There are specific mutations in the genome that lead to this disease.”

Similarly, another student stated that the mutation is inherited:

“Huntington’s disease is one gene mutation that is passed on from either parent. I’m not quite sure how they relate in scientific terms, I’d have to do more research.”

While these students understood that HD is inherited, their responses were too brief to determine a level of understanding. Lastly, one student provided incorrect information about chromosome separation (HD is not a nondisjunction disorder):

“Transcription and translation are processes within the Central Dogma that are involved in Huntington disease. Mistakes made during transcription and translation as well as other problems such as nondisjunction can result in Huntington disease.”

5.2.2. Post-Survey Responses

A Focus on Inheritance to Support Students’ Understanding: CBL– Post-Survey Responses

Three categories of data emerged from the coding: Central Dogma and related processes, mutations, and downstream effects. Herein, we begin providing overall findings and trends within the six post-survey responses of the CBL– group. Responses of the CBL– group were more detailed in the post-survey. A clear delineation between pre-survey and post-survey responses was the movement away from students’ uncertainty about the relationships. None of the six students noted omission of knowledge on the post-survey.

The first major theme that was observed within the data included discussions related to the Central Dogma. During such discussion, students in the CBL– most often described the following concepts: errors in replication, trinucleotide repeats, inheritance, and alternative proteins. When the CBL– group discussed the role of replication, it was in the context of TNR production. Replication appeared in five of the six responses. Replication and TNR appeared together in all instances, and they described that replication causes the expansion, except for one instance when the student stated that replication is involved in HD because it is a hereditary disease. An example of how students connect TNR and replication include:

“...DNA replication produces multiple copies of TNRs that exacerbate the mutation and severity of the HD phenotype.”

Within this example, the student appeared to understand that the production of TNR accumulates during replication, which impacts the severity of disease. The relationship described between replication and TNR was general, except for one student who stated that extra repeats are added by DNA polymerase.

Replication was the only conception within the Central Dogma and related processes theme that was frequently observed within the CBL– post-survey responses, although alternative protein discussions were observed within three responses. The discussions

about proteins involved a mutant gene resulting in a mutant protein, a phenotypic change due to the proteins expressed, and translation into a malformed protein. For example:

“Replication and translation are both deeply involved in Huntington disease. Replication is where the disease starts with the TNR expansion, then translation into a malformed protein that results in the disease.”

In the provided example, the student describes that the addition of TNR occurs during translation, when a malformed protein is formed after translation. The student uses translation to connect replication and protein production. In addition to replication, transcription and translation were briefly discussed and observed separately in different responses. The only discussion of transcription included the conception that when expanded DNA is transcribed, the reading frame with RNA changes.

An additional theme that emerged from the data included mutations. Discussion around mutations was frequently observed and appeared in four responses of the CBL—post-survey. Despite its frequency among the CBL—, these discussions remained brief. One response was as brief as “any sort of mutation can give rise to disease”. Three students mentioned that the mutation can be inherited, as illustrated in the following example:

“Huntington’s disease is the result of the production of an abnormal protein from a genetic mutation that was inherited from either parent. DNA replication produces multiple copies of TNRs that exacerbate the mutation and severity of the HD phenotype.”

Discussions around mutations and inheritance seemed characteristic to the CBL—group and appeared within four students’ responses, although this example involving inheritance were brief and only described that a mutation is inherited. In a similar response, another student elaborated that the mutation associated with HD is inheritable as a dominant gene:

“...This trinucleotide expansion then becomes heritable as a dominant gene. This mutant gene causes the creation of mutant Huntingtin, a protein that can cause severe damage in the cells of the body, especially nerve cells...”

This student provides more detail by describing the type of mutation that is located on a dominant gene. Inheritance was observed in three responses. However, in two examples provided, inheritance was used to support discussion of mutations.

The last theme that was observed included downstream effects. However, there was minimal discussion of systematic applications, and it was only described by one student. When describing the downstream effects, this student describes the effect of mutant Huntingtin gene on nerve cells and other proteins:

“...This mutant gene causes the creation of mutant Huntingtin, a protein that can cause severe damage in the cells of the body, especially nerve cells. In addition to this mutant protein, Huntington disease can have adverse effects on protein folding in chaperonins, and other effects on normal protein function within the cell.”

Like the other responses, the student described the formation of the mutant form of huntingtin, the protein involved in HD. The student described that this protein, once formed, acts on nerve cells and impacts the folding of other proteins. This is the first time that discussion beyond a mutant protein causing disease was observed. In addition to overall trends, students’ responses were analyzed for trends related to their depth of understanding. For the CBL—group on the post-survey, one student presented a scientific explanation, three students presented partial understandings, and two students provided incorrect responses. The CBL—student who presented a scientific explanation discussed errors in replication and the role of TNR in the dominant gene. This person also discussed TNR about the Central Dogma with the formation of mutant huntingtin and how it impacts nerve cells. This can be observed by revisiting the example previously discussed:

“Several aspects of the Central Dogma are involved in Huntington disease. Huntington disease can be caused by errors in DNA replication of the germline cell, causing a

trinucleotide repeat expansion to occur. This trinucleotide expansion then becomes heritable as a dominant gene. This mutant gene causes the creation of mutant Huntingtin, a protein that can cause severe damage in the cells of the body, especially nerve cells. In addition to this mutant protein, Huntington disease can have adverse effects on protein folding in chaperonins, and other effects on normal protein function within the cell."

This student correctly summarized the specific type of mutation (TNR) that accumulates during replication and causes the gene to expand. Additionally, the student described that TNRs are also inherited. In addition to inheritance, the student names the specific protein involved in HD and the downstream effects previously discussed: implications on nerve cells and folding of additional proteins. This student was able to describe how the Central Dogma was impacted from the gene level to protein interactions involved in HD. CBL— students who demonstrated partial understandings included more detail compared to the pre-survey responses, but still presented fragmented explanations. All students described the role of TNR in HD, but their responses varied. For example, one student related that TNRs are inherited, and, as they replicate, the expansion increases (along with severity of the disease). We revisit the following example:

"Huntington's disease is the result of the production of an abnormal protein from a genetic mutation that was inherited from either parent. DNA replication produces multiple copies of TNRs that exacerbate the mutation and severity of the HD phenotype."

In this example, the student described that TNRs are inherited and impact the severity of the disease phenotype. This example was considered a partial understanding as TNRs were not connected with proteins. Another student understood that HD relates to DNA polymerase slippage, which changes the reading frame of the mRNA. The student then stated that the type and number of proteins expressed determines the phenotype:

"During DNA replication, the DNA polymerase adds on extra repeated nucleotides which will cause an expansion in the DNA. When this expanded DNA gets transcribed, the reading frame of the mRNA changes. Therefore, there is a phenotypic change in terms of proteins expressed and how many."

This student expands on the idea of TNRs contributing to HD by describing how they are formed. The student connected proteins to phenotypic change and possibly demonstrating an implicit understanding of protein production and disease phenotype, but the student did not provide an explicit connection to HD. Finally, the last student provided a generic response that TNRs expand with replication, which is then translated into a mutated protein that leads to disease. We revisit the following example:

"Replication and translation are both deeply involved in Huntington disease. Replication is where the disease starts with the TNR expansion, then translation into a malformed protein that results in the disease."

Within this example, the student described that TNR are involved in disease, but otherwise provided a vague description of replication, translation, mutations, and disease. Ultimately, this indicated a surface-level understanding. While all information was correct, there appears to be limited detail that explicitly describes how the Central Dogma is impacted by HD. The two CBL— students who stated incorrect responses did not provide enough detail to determine their understanding. Responses included, "DNA replication is involved in HD because it is a hereditary disease that can be passed on to offspring" and "any sort of mutation can give rise to disease".

Downstream Effects of the Central Dogma and Huntington Disease: CBL+ Post-Survey Responses

Three themes emerged from the data of the CBL+ post-survey responses: Central Dogma and related processes, mutations, and downstream effects. Herein, we begin providing overall findings and trends within the post-survey responses of the CBL+ group.

We present our findings on the trends that were observed in the responses on the CBL+ post-survey.

The first theme that was observed was related to processes of the Central Dogma. In the post-survey, responses related to Central Dogma and related processes for students in the CBL+ group became more detailed and discussed a range of topics. Students mostly discussed TNRs, alternative proteins, transcription, replication, and translation. DNA slippage was also discussed to a lesser extent.

A common conception related to the Central Dogma included students' understandings of TNR. Eleven of thirteen students incorporated information about TNRs within their responses. Several students discussed TNR in the context of DNA replication and/or hairpin loops. Discussions about TNRs, replication, and hairpin loops appeared together within six responses. These students discussed that DNA slippage creates a hairpin loop, which results in the creation of TNRs. However, two of these students suggested that transcription is also involved as the extra repeats will be on mRNA, and one student had the alternative conception that the hairpin loop would be located on RNA. A third student connected transcription to TNR by describing that repeats are due to a transcriptional error, but does not include discussion on replication. Another student discusses TNRs and replication together without adding information on DNA slippage, describing that repeats increase with replication and disease severity is dependent on the number of repeats. The remaining response of the six students described that DNA slippage is responsible for the accumulation of repeats, and the severity of disease increases as the number of repeats increases.

Other responses were more generic and stated that HD is associated with trinucleotide repeats, which was observed in two responses. One student provided a brief explanation that a mutation is created by an expansion, which causes the protein to not "work" and forms toxic aggregates:

A gene is mutated by an expansion of a trinucleotide repeat. This causes the protein to not work and to form aggregates that are toxic.

Within this example, the student describes TNR and expansions as the type of mutations involved in HD; the student also vaguely describes a nonfunctional protein that promotes aggregation. The other student describes that the TNR is a mutation of a specific region of the genome, which causes repeats of the CAG sequence. This student also briefly explained that the increased number of TNR is associated with an increased severity of HD:

"Huntington's disease is caused by TNR mutations in a specific region of the genome. They cause repeats of the CAG sequence and with more TNR, the worse HD is for the patient."

Like the previous example, the student describes TNR as the type of mutation associated with HD and provided additional information by describing the relationship between the number of repeats and disease severity. A closely related theme included mutations. The discussion related to mutations heavily centered around TNRs, although TNRs were classified under the Central Dogma and related processes category for analysis purposes. In addition to TNRs, additional discussions about mutations were a theme that was minimally observed and only appeared within two responses. One student briefly discussed a mutation that occurs in transcription. The other student discussed gene anticipation, which was linked to the student's discussion of TNR. Proteins were also frequently discussed within the Central Dogma theme. The CBL+ group also frequently discussed proteins and was observed within the responses of six students, in which students' protein discussion ranged in complexity. Three responses included (1) a surface-level description involving the synthesis of disease-causing proteins; (2) the TNR causing the protein to "not work" and aggregate; and (3) the extra amino acids "mess up" protein function. A single response indicated an intermediate depth of knowledge. With the student's response, it was described that extra glutamines would create an "abnormal/toxic protein folding in a gain of function mutation". This was considered an intermediate response as the participant

knew that extra glutamines impacted the protein structure, but did not provide the depth of detail relating to structural biology observed in other responses. Two students provided more complex responses as they included the role of beta sheets in HD:

“All of the processes are involved because as the gene is replicated, there is a slippage in the DNA polymerase that creates TNRs, or trinucleotide repeats, of CAG in a hairpin loop. This hairpin loop when transcribed is incorporated into the mRNA as large amounts of repeats (from the 40s to 70s or even higher when ‘normal’ is considered under 34 repeats). This mRNA is then translated into a protein that has extra amino acids in the protein which leads to misfolding of the protein as extra beta sheets that change the structure enough to form aggregates which in bulk are toxic in the brain and destroy neuron function in the brain.”

This example is representative of the two students who discussed that the excess amino acids create structural differences in the protein, mainly through the presence of beta-sheets, which cause protein aggregation. Additionally, in five of the six responses that discussed alternative proteins, discussion of translation was also observed. Discussion about translation was also associated with students’ discussion of proteins. Discussion of proteins served a functional purpose in students’ responses concerning RNA and the mutant protein. Lastly, within the Central Dogma theme, various descriptions about transcription were observed. One student asserted that transcriptional regulation is involved with the onset of HD, but provided no explanation. Three students discussed errors or mutations in transcription, but only two of those students extended their ideas to include that such errors cause TNRs. Three students described that the hairpin loop or extra repeats will be incorporated into the RNA (this includes an alternative conception of one student, that hairpin loops form in the RNA). One student held the alternative conception that slippage creates hairpin loops during transcription. Several levels of understanding and alternative conceptions were observed in relation to transcription and HD. However, they generally seem to serve the purpose of supporting discussions of expansions and repeats.

Of particular interest was the theme of downstream effects. Discussions relating to systematic applications were minimal and only appeared within three post-survey responses of the CBL+ group. All three students discussed how mutated proteins aggregate, and two students elaborated that these aggregates cause neural toxicity. These students discussed that protein aggregation is associated with neural toxicity.

In addition to the general overall trends of the thirteen students in the CBL+ group, we were also interested in specific trends related to depth of knowledge. In the post-survey, three students in the CBL+ group provided complete scientific explanations. Nine students presented partial understandings, and one student presented an incorrect response. The students who presented scientific explanations discussed that most aspects of the Central Dogma were involved in HD. These students generally discussed that DNA polymerase slippage creates hairpin loops, which then creates the TNR and the repeats become incorporated into the DNA. Regarding protein structure, students described the addition of extra glutamines or formation of beta-sheets. The new structural additions cause protein fragmentation and aggregation. All students discussed neural toxicity within their responses. Two of the students related the beta-sheets and aggregation to neural toxicity. The remaining student stated that an abnormal protein product creates a toxic gain-of-function mutation. An example is as follows:

“The process that are involved in Huntington disease are translation, DNA replication, and possible transcriptional regulation. During DNA replication, DNA polymerase slips off of the DNA template strand causing a hairpin loop that is incorporated into the DNA causing triple nucleotide repeats. These regions are unstable and in the IR-15 gene are the cause of Huntington Disease. It is speculated that these regions are worsened by DNA mismatch repair inaccurately correcting the error. This causes the repeat area to get even longer leading to earlier onset of worse symptoms of Huntington Disease. When this area is translated as it is found in the exons, it produces proteins that have a different

Beta-sheet that causes them to fragment and then come back together in huge groups. These groups are toxic to neural cells and could be the result of cognitive impairment in individuals with Huntington's disease."

Another noteworthy finding within the responses of the CBL+ students who provided scientific explanations, as represented in the example, is the discussion of specific structural features within the protein and how such structures promote aggregation. This is in addition to the implications of the protein aggregates. Such detail within these responses indicates a deep-level of learning. Nine students in the CBL+ group presented partial understandings within their responses. Three major themes appeared within the responses of the student who held a partial understanding: (1) inheritance and disease severity; (2) excess glutamines; and (3) formation of hairpin loops. Students commonly discussed that TNR is the mutation that causes HD, which increases with transcription accumulates overtime:

"Transcription and translation are definitely involved in Huntington's disease. Huntington's results from trinucleotide expansions, which can cause slippage and hairpin loops during transcription. These repeats can accumulate over time as more slippage occurs and the repeats are continuously transcribed/translated. When a certain threshold of repeats is reached, an individual is said to have Huntington disease. The more repeats present, the earlier the onset of Huntington's."

Related to this topic, students also stated that severity also increases per generation in addition to disease progression within an individual.

"The central dogma is involved in HD because as the person's DNA is replicated, and as people with the disease reproduce, the more repeats there are in the DNA. These repeats are what is causing the problem in people with HD, so increasing the number of repeats just increases the severity of the disease."

Within these examples, the students provide accurate information about DNA slippage and TNR, but lack discussion related to proteins and how the mutation contributed to HD. Other students focused on the extra glutamines found within the mutant protein. Students described that the gene mutation is transcribed into RNA, which is then translated into a mutated protein with excess glutamine. The student described that "All processes within the Central Dogma are involved in Huntington's Disease. The cause of the disease stems from a DNA mutation, which is the beginning of the DNA → RNA → protein process. The DNA mutation gets transcribed into RNA, and the RNA is translated into a protein product with excess glutamine". Within the student response, the student states the steps of the Central Dogma instead of describing the processes. While the student recognized that the mutated protein product contains excess glutamine, there was no discussion on how the mutation was formed or any explanation on how the Central Dogma contributes to HD.

6. Discussion

This study sought to address the following question: How do learning outcomes differ between students engaging in a case-based method versus case-based lecture while applying the Central Dogma of molecular biology in the context of Huntington Disease? Within this study, students selected to engage in a case study either through a case-based lecture (CBL−) or a case-based intervention (CBL+).

Previous studies have reported that students enjoy learning with real-world connections provided by case studies [7,13]. Further, case studies have been shown to elicit interest and to create relevant contexts where students can apply their knowledge in undergraduate biology and biochemistry courses (i.e., Kulak & Newton [4]; Hartfield [8]; Knight et al. [9]; Kulak et al. [10]; Porzecanski et al. [11]; Rybarczyk et al. [12]; Cornely [7]). However, it appears that little consideration has been given to how case studies have been implemented and how learning sequence supports learning outcomes [4]. It also appears that a gap in the literature includes how certain CBL implementations support content learning gains (e.g.,

Rhodes et al. [23]). Related to this study includes the findings of Garcia-Ponce et al. [18], who reported a greater amount of work was required before a problem-solving experience.

CBL is a form of PBL. Even so, methods for implementing PBL and CBL range across a continuum from a teacher-centered approach to a student-centered approach. One such approach to CBL includes case-based lecture, where students solve a case in class that is embedded into the lecture [3]. An alternative student-centered example includes a case-based method, in which students are given time to conduct research and complete the case before class discussion [2]. Case-based lectures appear to be most frequently utilized (e.g., Cresswell & Loughlin [30]; Hartfield [8]; Kulak et al. [10]; Yadav, et al. [28]). Given the trends relating to the frequent use of case-based lectures and the need to understand the learning sequence with case studies, this study sought to identify how different modes of implementation can support students' learning. By understanding how different forms of case study implementations can support student learning, instructors can begin targeting different learning outcomes.

The foundation for situated learning needs to be found in three areas: relevancy of the problem, interest, and content [35]. Situated learning includes subject-matter areas [35] which are of particular interest in this study. The subject-matter area within situated learning should include problems that are relevant [35]. Therefore, the objective of this study was to implement a case study on HD to elicit interest among students and illustrate a relevant articulation of Central Dogma to real world issues. Although the relevancy of HD to the undergraduate students participating in the study might be argued, HD has relevance to the many students interested in pursuing careers in health care. The case creates relevance for learning the Central Dogma and inspires its application to explain the transference of HD from parent to offspring and the underlying downstream effects of the gene mutation that cause the disease.

Prior to this case study, students were assessed in two areas: their foundational knowledge related to the Central Dogma and applying their knowledge of the Central Dogma to explain HD. Students within the CBL− and CBL+ groups were asked the following question prior to engagement with pre-class activities: How would you describe the relationship between gene, genotype, gene mutations, phenotype, and disease? The objective of this question was to determine students' baseline understanding and conceptions related to the Central Dogma. Six students self-selected in the CBL− group and thirteen students self-selected into the CBL+ group.

The CBL− and CBL+ shared several similarities within their pre-survey responses. Specifically, both groups discussed that the genotype consists of genes and genes code for a phenotype, or the phenotype is the reflection of gene expression. Themes were observed within the descriptions about genotype by students within the CBL− and CBL+ groups. Both broadly defined genotype as a genetic sequence, all genes within the genome or organism.

Both groups also described a strong relationship between phenotype and gene expression. They most often discussed phenotype as the outward expression of genotype. Students also commonly referenced phenotype as the physical appearance upon gene expression. Furthermore, students in the CBL+ group connected mutations to a change in phenotype, and some students identified disease as a phenotype.

The connection of disease and phenotype is the primary difference between the pre-survey responses for the CBL− and CBL+ groups. The CBL+ group referenced that disease is a phenotype to a relatively larger extent compared to the CBL− group. Eleven students in the CBL+ group connected disease to phenotype, and two students in the CBL− made this connection on their pre-survey responses. A particular point of interest is the relationship students established among protein, phenotype, and disease. Both groups referenced protein within their responses, but the students in the CBL+ group connected proteins to phenotype and disease. One such example includes:

"Genes codes for proteins which affect the phenotype of an organism. Gene mutations can change the protein produced by the gene and, therefore, change the phenotype of the

organism. This phenotypic changes can be disease cause for the organism. The genotype is the specific alleles an organism has for a particular gene."

The student in the CBL– group provided a similar response. The student used protein to connect genes and phenotype. However, the student did not describe how mutations impact proteins, creating a conceptual gap between phenotype and disease. We revisit the following example as represented:

"Genotypes are comprised of all the genes in an organism. Genes code for proteins that create the phenotype of an organism. Gene mutations can change the phenotype of an organism. Mutations can create certain phenotypic conditions that lead to a disease state."

Lastly, another distinction between the CBL– and CBL+ groups include students' conceptions related to phenotype and disease. The CBL+ group tended to describe the relationship between phenotype and disease to a greater extent, but these students also emphasized that disease is a phenotype.

Students responded to the same question upon completion of the case study. Students' foundational knowledge remained relatively consistent for both groups on the pre- and post-surveys. Learning gaining in terms of acquiring knowledge did not appear to substantially improve. Discussions between genotype, mutations, and phenotype remained consistent between the pre- and post-survey. The CBL– group provided details on how mutations will impact the genotype, which may change the phenotype. CBL– students on the post-survey provided a fragmented explanation of the Central Dogma, as represented:

"Genotype is the sequence of DNA which has regions that code for specific genes, which specific regions of DNA sequence. These regions, after central dogma, are expressed and produce an observable phenotype. Gene mutations are any abnormal sequence of DNA within a gene encoding region and the product of such can be diseases."

Like the CBL– group, the CBL+ group was also consistent with their discussions about genotype, mutations, proteins, and phenotype. However, students in the CBL+ group also explained how mutations impact protein folding and would create an abnormal phenotype:

"Gene mutations can occur in a cell when the DNA for a gene has a mutation or in the process of expressing that gene. When a mutation is present in a person's genotype that greatly impacts a person's protein production or function, especially one that is necessary, it can result in a specific phenotype that is different then [sic] what is considered normal and can even present itself as a disease."

All students in the CBL– group presented a partial understanding with scientific fragments on their pre-survey responses. In the post-survey, all except for two students in the CBL– group demonstrated a partial understanding with scientific fragments. One student provided a scientific explanation, and one student provided an incomplete response. While many students in the CBL+ group did not demonstrate changes within their foundational knowledge, it appears they gained a deep level of learning as demonstrated through their discussion of protein folding.

To assess students' in applying the Central Dogma to explain HD, students were asked the following questions before pre-class activities and after the case study: Think about the Central Dogma and Huntington disease. Which processes within the Central Dogma are involved in Huntington's disease? How are they involved in Huntington's disease? Students appeared to experience more growth with the application of the Central Dogma to a clinical case.

On the pre-survey and post-survey, students in the CBL– group largely demonstrated partial understandings with scientific fragments. The CBL+ group appeared to demonstrate a similar trend. However, minimal scientific explanations were observed in the post-survey responses in both groups. On the pre-survey, students in both groups tended to state that they did not know how the Central Dogma and HD are related, but also suggested that mutations cause disease, and protein errors and translation errors were involved. Students

in the CBL– group also discussed mutations within the gene and the impact on phenotype. While the CBL+ group stated less often that they did not know the connection of the Central Dogma and HD, in comparison to the CBL– group, these students in the CBL+ group also discussed mutations causing disease and transcription, possibly indicating a better understanding on how more processes of the Central Dogma are involved.

In the post-survey responses, students in the CBL– group discussed replication, TNR, inheritance, and alternative proteins. We revisit the following example:

“Huntington’s disease is the result of the production of an abnormal protein from a genetic mutation that was inherited from either parent. DNA replication produces multiple copies of TNRs that exacerbate the mutation and severity of the HD phenotype.”

Students in the CBL+ group also discussed alternative proteins and TNR, but they also focused on transcription, translation, and DNA slippage. For example:

“Replication is involved in HD because of errors during replication by slippage of DNA polymerase. Transcription is involved because the extra CAG repeats will be included in the RNA product forming a hairpin loop. The translation is involved because the extra CAG repeats will code for extra glutamines which will, in turn, cause different abnormal/toxic protein folding in a gain of function mutation.”

Post-survey responses within the CBL– group remained vague and typically connected TNRs to replication and inheritance. In contrast, responses from students in the CBL+ group were more detailed and sophisticated. Students in the CBL+ group also discussed TNR in relation to DNA slippage that creates hairpin loops and eventually creating TNRs, along with accumulation of TNRs by transcription.

Discussion of proteins was a point of interest within our findings. The CBL– pre-survey responses lacked reference to proteins, while general descriptions of misfolding proteins were observed in the post-survey data. We revisit an example of protein discussion in a CBL– post-survey discussion:

“During DNA replication, the DNA polymerase adds on extra repeated nucleotides which will cause an expansion in the DNA. When this expanded DNA gets transcribed, the reading frame of the mRNA changes. Therefore, there is a phenotypic change in terms of proteins expressed and how many.”

The CBL+ group referenced proteins in a few responses in the pre-survey but tended to provide detail around the discussion proteins in their post-survey response. Often, such discussion included structural motifs, aggregation, and the downstream effects of the Central Dogma. Provided is an example of a post-survey response in the CBL+ group:

“All of the processes are involved because as the gene is replicated, there is a slippage in the DNA polymerase that creates TNRs, or trinucleotide repeats, of CAG in a hairpin loop. This hairpin loop when transcribed is incorporated into the mRNA as large amounts of repeats (from the 40s to 70s or even higher when “normal” is considered under 34 repeats). This mRNA is then translated into a protein that has extra amino acids in the protein which leads to misfolding of the protein as extra beta sheets that change the structure enough to form aggregates which in bulk are toxic in the brain and destroy neuron function in the brain.”

There are two particular points of interest within our findings. First, is the consistency of responses to the question assessing students’ foundational knowledge on the Central Dogma between pre- and post-surveys for both groups. At the surface, there appears to be no apparent learning gains. These findings are consistent with the data we also collected and analyzed from the same students using the Central Dogma Concept Inventory (CDCI) developed by Newman et al. [70]. Using a concept inventory to measure learning gains, we did not see a statistically significant difference between the increase between the two groups. This may have been due to the small sample size, the level of questions included on the CDCI, or a misalignment of questions on the CDCI in comparison to the analysis of Central

Dogma that was required for explaining the cause of HD in the patient presented in the case. Previous studies highlight how CBL students show no statistically significant differences from traditional lecture taught students on rote learning tasks, and after completing CBL instruction throughout an undergraduate genetics course (e.g., Murray-Nseula [71]). It also could be that the tasks in the CDCI were not uncovering nuances in Central Dogma that the CBL students learned by completing the concept inventory.

A second point of interest was how CBL+ students responded to each question, despite our consistent findings between the pre- and post-surveys. Students in the CBL+ appeared to have a foundational understanding about the relationship between proteins and phenotype on the foundational pre-survey questions. While the general themes in the post-survey responses paralleled CBL+ students' pre-survey responses, a point of difference was the depth of discussion relation to proteins. Specifically, discussion around an incorrectly folded protein that creates an abnormal phenotype. Additionally, students in the CBL+ group discussed beta sheets in relation to aggregation and neural toxicity. Such discussions were absent in the post-survey responses of the CBL– group. Both groups on the post-survey referenced alternative forms of proteins, but the CBL+ group referenced specific terms related to protein structure. Given these observations, we suggest that the learning sequence of cases may not support content learning gains. However, the learning sequence of a case study may support a deeper level of learning.

It has been previously reported that students struggle to associate phenotype with disease and understanding how proteins contribute to phenotype (i.e., Shaw et al. [72]). Students in the CBL+ group had a stronger tendency to connect protein structure with physiological effects, such as aggregation and neural toxicity. In addition, the CBL+ group's discussion about proteins and the level of detail provided by the students suggests the development of a deeper level of learning according to the characteristics of expertise outlined by Persky and Robinson [73]. Additionally, our findings suggest similar trends to those reported by Kulak and Newton [4] that deep-level learning is associated with case-based methods.

A final consideration of this study is the use of case studies in an online setting, of which conflicting results have been reported in the literature. A study completed by Nicklen et al. [74] did not observe a significant difference in learning outcomes between students working through a case study in an in-person versus an online format. This is also consistent with Raupach [75], where no significant difference was observed between a face-to-face and an online PBL when assessing clinical reasoning skills. However, significant differences have been observed when comparing online (along with hybrid) and in-person PBL environments where online learning demonstrated stronger learning gains (e.g., Dennis [76]; Taradi et al. [77]). This study adds to this body of the literature by suggesting a case-study learning sequence that supports deep-level learning in an online setting.

It appeared that learning sequences with case-based learning had yet to be investigated. This study compares two types of problem-based learning as characterized by Barrows [2]. In this study, we compare learning outcomes of two different learning sequences: case-based lecture versus case-based method. It has been previously reported that there are no significant differences between knowledge level, rote learning outcomes of the students in the CBL lecture course and students taught through traditional lecture [28,78]. On the surface, our findings also suggested minimal apparent differences. However, previous studies have reported that the use of case studies support deeper level learning approaches [5]. It appears that our findings are consistent with Kulak & Newton [4], that students in the CBL+ group gained a deeper-level of understanding of how the Central Dogma can be used to explain HD. In conclusion, we assert that the differences in learning sequences in case-based learning can support deep-level learning, rather than content gains as observed using qualitative methodology.

7. Limitations

Students were able to self-select into the CBL– and CBL+ groups, resulting in the CBL+ group being roughly twice the size of the CBL– group. Sample size created difficulties in making direct comparisons between the CBL– groups. Instead, general observed trends served as the basis for developing inferences between the two modes of implementation between the two groups. Furthermore, it is possible that self-selection into intervention groups may have induced a bias within the findings. An additional limitation of the study is that it was conducted during the COVID-19 pandemic. Due to university and state recommendations, the course was offered in a synchronous, online modality rather than the typical traditional in-person lecture format utilized pre-pandemic. Nicklen et al. (2017) reported that students were not as comfortable completing their course in an online modality in comparison to a traditional in-person lecture modality, and believed it detracted from their learning. Students in the current study might have shared similar views.

8. Conclusions

It appears that there are apparent learning differences in terms of content learning gains when comparing case-based lecture and case-based method. Our findings support the hypothesis that case-based methods promote a deeper level of learning. In a case study on Huntington's Disease, students who engaged in case-based methods (represented as the CBL+ group within this study) demonstrated a deeper-level of learning based on the detail they provided in their discussions of proteins. To our knowledge, this study appears to articulate how case-based lectures versus case-based methods support learning by utilizing a constant comparative approach.

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