Teacher Notes for "A mistake in copying DNA can result in dwarfism."[1]

In this minds-on activity, students analyze evidence about achondroplasia to learn how a mistake in DNA replication can result in a new mutation that affects a child's characteristics. This analysis and discussion activity reviews several basic genetics principles and helps to counteract several common misconceptions about genetics.

Before beginning this activity, your students should have a basic understanding of DNA, cell division and genetics. For this purpose, I recommend either:
– the analysis and discussion activity, "Introduction to Genetics – Similarities and Differences between Family Members" (https://serendipstudio.org/exchange/bioactivities/geneticsFR) *or*
– the hands-on activity, "Genetics" (https://serendipstudio.org/sci_edu/waldron/#genetics).[2]

Learning Goals

In accord with the Next Generation Science Standards:[3]

- Students will gain understanding of the Disciplinary Core Idea:
  - LS3.B: Variation of Traits – "Although DNA replication is highly regulated and remarkably accurate, errors do occur and result in mutations, which are also a source of genetic variation."
- This activity helps to prepare students for the Performance Expectation:
  - HS-LS3-2, "Make and defend a claim based on evidence that inheritable genetic variations may result from… viable errors occurring during replication…"
- Students will engage in the Scientific Practice:
  - Constructing Explanations: "Apply scientific ideas, principles, and/or evidence to provide an explanation of phenomena…, taking into account possible unanticipated effects."
- This activity provides the opportunity to discuss the Crosscutting Concept:
  - Cause and Effect: "Cause and effect relationships can be suggested and predicted for complex natural… systems by examining what is known about smaller scale mechanisms within the system."

This activity will help to counteract the following common misconceptions.[4]

- Each gene influences only one trait (not recognizing how common pleiotropy is).
- A person who doesn't have a characteristic lacks the gene for this characteristic (not recognizing that the person has other alleles for this gene).
- Dominant traits are the most common traits (which is true for some genes, but not all).
- All genetic conditions are inherited (not recognizing the role of new mutations or mistakes in meiosis in causing some genetic conditions).

Instructional Suggestions and Background Information

To maximize student learning and participation, I recommend that you have students work in pairs to answer each group of related questions. Student learning is increased when students

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[1] By Dr. Ingrid Waldron, Dept Biology, Univ Pennsylvania, 2023. These Teacher Notes and the related Student Handout are available at https://serendipstudio.org/exchange/bioactivities/geneticsdwarf.

[2] As additional background, I recommend "DNA Function, Structure and Replication", "Mitosis and the Cell Cycle – How the Trillions of Cells in a Human Body Developed from a Single Cell", and "Understanding How Genes Are Inherited via Meiosis and Fertilization".

[3] http://www.nextgenscience.org/sites/default/files/HS%20LS%20topics%20combined%206.13.13.pdf and http://www.nextgenscience.org/sites/default/files/Appendix%20G%20-%20Crosscutting%20Concepts%20FINAL%20edited%204.10.13.pdf

[4] These misconceptions are taken primarily from http://knowgenetics.org/common_misconceptions/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2278104/ (especially tables 5 and 6).

discuss scientific concepts to develop answers to challenging questions. After pairs of students have worked together to answer a group of related questions, I recommend that you have a class discussion to probe student thinking and help students develop a sound understanding of the concepts and information covered.

If your students are learning online, I recommend that they use the Google Doc version of the Student Handout available at https://serendipstudio.org/exchange/bioactivities/geneticsdwarf. To answer question 4b, students can either print page 2 of the Student Handout, draw on it and send pictures to you, or they will need to know how to modify a drawing online. To answer online, they can double-click on the drawing in the Google Doc to open a drawing window. Then, they can use the editing tools to answer the questions.[5]

If you prepare a revised version of the Student Handout Word document, please check the format by viewing the PDF.

If you would like to have a key with the answers to the questions in the Student Handout, please send a message to iwaldron@upenn.edu. The following paragraphs provide additional background information and instructional suggestions.

You may want to introduce this topic by referring to examples of people with achondroplasia in popular culture, e.g. Peter Dinklage, who played the dwarf in the TV series, "Game of Thrones", and the mother and one of the children (Zach) in the TV series, "Little People, Big World". The average height of an adult male with achondroplasia is 132 cm (4'4"), and the average height of an adult female is 124 cm (4'1") (https://www.achondroplasia-growthcharts.com/height-development/).

Question 1 introduces the driving question for most of this learning activity. This question should stimulate students to begin thinking about the driving question. Information in the rest of the activity will help the students to understand the answer to the driving question.

The table in the middle of page 1 of the Student Handout reinforces student understanding that genotype determines which version or versions of a protein are made, and the proteins in turn influence the person's characteristics. The allele responsible for achondroplasia results in a protein that is overactive in inhibiting bone growth, which results in short arms and legs. The protein is Fibroblast Growth Factor Receptor 3; when Fibroblast Growth Factors bind to this receptor molecule, the paradoxical result is inhibition of long bone growth. The single nucleotide difference between the **D** and **d** alleles results in a single amino acid difference out of hundreds of amino acids. The **D** allele provides instructions to make a version of the Fibroblast Growth Factor Receptor 3 that results in overactivity of this inhibitory receptor molecule (https://www.omim.org/entry/100800).[6]

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[5] To insert text, click Insert at the top of the page, click Insert, then click Text Box and drag it to where you want it and type your text. When you are done, click Save and Close.

[6] Different mutations of the same gene can result in hypochondroplasia, which typically has milder symptoms than achondroplasia. Most people with hypochondroplasia have parents with average height, and the hypochondroplasia is due to a new mutation. Hypochondroplasia and achondroplasia each occur in approximately 1 in 20,000 to 30,000 newborns. (https://medlineplus.gov/genetics/condition/hypochondroplasia/)
The gene for Fibroblast Growth Factor Receptor 3 is one of the multiple genes that influence height (see pages 5-6 of the Student Handout for "Introduction to Genetics – Similarities and Differences between Family Members"; https://serendipstudio.org/exchange/bioactivities/geneticsFR). For students who have completed this introductory genetics activity, you may want to point out that the **D** allele discussed in this activity on dwarfism is rarer and has a bigger effect than the alleles discussed in the introductory genetics activity.

The **D** allele for achondroplasia is considered dominant because a heterozygous **Dd** person has the dwarf phenotype. However, there are important differences between a heterozygous individual (~7% risk of infant death) and an individual who is homozygous for the **D** allele (~100% early mortality). A major cause of mortality and morbidity is brainstem compression due to a narrower opening at the base of the skull where the brainstem exits down toward the spinal cord. Thus, achondroplasia illustrates how a single gene can affect multiple phenotypic traits (called pleiotropy). (This point will be discussed in question 10.)

As explained on page 2 of the Student Handout, sperm stem cells continuously replace themselves by mitosis; the continuous production of new sperm stem cells allows a man's testes to keep producing several million sperm a day for many years. For general information about stem cells, see https://medlineplus.gov/stemcells.html.

The importance of highly accurate DNA replication is illustrated by the example of achondroplasia, where a change in a single nucleotide has a dramatic effect on phenotype. Similarly, a difference in a single nucleotide in the hemoglobin gene results in sickle cell anemia (see "The Genetics of Sickle Cell Anemia and Sickle Cell Trait"; https://serendipstudio.org/exchange/bioactivities/geneticsSCA). It should be noted that most changes in a single nucleotide do not result in major changes in phenotype, either because there is no change in the amino acid due to redundancy in the genetic code or because the change in amino acid does not significantly change the function of the protein.

You may want to suggest that, as students answer question 5, they should check off each term specified for inclusion so they can keep track of all the concepts they should include in their answer.

As discussed in question 6, a new mutation that causes achondroplasia is more common in the sperm of older fathers. One reason why is that the sperm stem cells of older fathers have gone through more mitotic cell divisions, which has provided more opportunities for mistakes in copying DNA (additional unidentified factors also contribute; https://pubmed.ncbi.nlm.nih.gov/26975491/).

In ~80% of cases of achondroplasia, neither parent has the allele for achondroplasia; instead, achondroplasia is due to a new mutation which occurred during production of one of the gametes**.** Mistakes in DNA replication can cause a disease that is genetic, but not hereditary. Another example of a condition that is genetic, but not hereditary occurs when nondisjunction of chromosomes or chromatids results in Down syndrome ("How Mistakes in Meiosis Can Result in Down Syndrome or Death of an Embryo"; https://serendipstudio.org/exchange/bioactivities/mmfmistakes). It should be noted that, despite these examples, DNA replication and meiosis are highly accurate, so most of a person's alleles are inherited from his/her parents.

As discussed in question 9, achondroplasia is an example of a condition caused by an allele that is partially dominant, but rare in the population. 99.99% of the population is homozygous for the recessive **d** allele for this gene. Achondroplasia is rare because there is substantial selection against inheritance of the achondroplasia allele and the mutation rate is low.

At the end of this activity, you can ask students to give examples that illustrate the Cause and Effect Crosscutting Concept: "Cause and effect relationships can be suggested and predicted for

complex natural… systems by examining what is known about smaller scale mechanisms within the system.”.

Additional information about achondroplasia is available at:

- https://rarediseases.info.nih.gov/diseases/8173/achondroplasia
- https://medlineplus.gov/genetics/condition/achondroplasia/

Sources for Student Handout Figures

● Figure on page 1 from https://www.intouchweekly.com/wp-content/uploads/2019/09/lpbw-star-amy-roloffs-mother-patricia-knight-dies-at-age-86.jpg?fit=400%2C400&quality=86&strip=all&resize=400%2C400

● Figure on page 2 adapted from OpenStax College - Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30132982.

● Figure on page 3 from https://i.pinimg.com/originals/19/e5/66/19e566a4bea2846e7068f599461db969.jpg.

Additional Genetics and Molecular Biology Learning Activities

Genetics – Major Concepts and Learning Activities
(https://serendipstudio.org/exchange/bioactivities/GeneticsConcepts)
Part I summarizes key concepts in genetics. Part II presents common misconceptions. Part III recommends an integrated sequence of learning activities on the biological basis of genetics, plus seven human genetics learning activities. These learning activities develop student understanding of key concepts and counteract common misconceptions. Each of these recommended learning activities supports the Next Generation Science Standards (NGSS; https://www.nextgenscience.org/).

Molecular Biology: Major Concepts and Learning Activities
(https://serendipstudio.org/exchange/bioactivities/MolBio)
This overview reviews key concepts and learning activities to help students understand how genes influence our traits by molecular processes. Topics covered include basic understanding of the important roles of proteins and DNA; DNA structure, function and replication; the molecular biology of how genes influence traits, including transcription and translation; the molecular biology of mutations; and genetic engineering. To help students understand the relevance of these molecular processes, the suggested learning activities link alleles of specific genes to human characteristics such as albinism, hemophilia, sickle cell anemia and muscular dystrophy. Suggested activities include analysis and discussion activities, hands-on laboratory and simulation activities, web-based simulations, and a vocabulary review game.