COLUMBIA | Zuckerman Institute

BRAIN STEM | Bringing Neuroscience to the Classroom

DNA Sequencing and Precision Medicine

Supported by: ΙΣΝ SNF ΙΔΡΥΜΑ ΣΤΑΥΡΟΣ ΝΙΑΡΧΟΣ STAVROS NIARCHOS FOUNDATION

DNA Sequencing and Precision Medicine

Students learn the basics of DNA sequencing and use imaginary data to diagnose a rare genetic disorder. Students also evaluate the pros and cons of sequencing individual genomes.

Suggested duration

- 2 x 45 min class periods

Essential questions

- What is precision medicine?
- How does DNA sequencing work?
- How can DNA sequences inform medicine?
- Who should/should not get their DNA sequenced?

Objectives

All students will...

- Define what precision medicine is
- Understand what a genome is and what we can learn from it
- Learn how genome sequencing works

Advanced students will...

- Identify key parts of a scientific study
- Understand how genome sequencing can be used to treat diseases such as ALS or epilepsy

Materials

- Projector

Supplementary materials

- DNA Sequencing and Precision Medicine slides
- Student sheet1
- Student sheet 2
- Sequencing activity 1 sheet: printed in color
- Sequencing activity 2 sheet
- Extension sheet

Based on

The Stavros Niarchos Brain Insight Lecture, "Finding the Right Medicine One Patient at a Time: Developing Targeted Treatments to Combat Neurological Disease." By David Goldstein, PhD

https://www.youtube.com/watch?v=bKTnjEx4Zj8&feature=youtu.be

Instructional Activities

Class 1

1. Introduction to Precision Medicine | 10min

Use DNA Sequencing and Precision Medicine slides

Use student sheet 1

- Ask students to write their initial thoughts on what they think precision medicine is in the left-hand "Before" box.

Show students the video clip: *"What is Precision Medicine?" (slide 3)*

- Ask students to discuss the clip with their table group, then record their revised thinking in the right-hand "After" box.
- Discuss students' responses with the class, generating a class discussion.

2. Figure Analysis Template 1: The Cost of Genome Sequencing | 15-20min

Use student sheet 1

- Ask students to use Figure Analysis Template 1 to derive meaning from the graph showing how the cost of sequencing a genome has changed over time.
- Ask students to answer each of the questions on the Figure Analysis Template.

3. What is a Genome and What Can we Learn from it? | 5min

Use student sheet 1

- Students will write their initial thoughts on what they think a genome is and what we can learn by sequencing it in the "Before" box."

Show students the video clip: *"What is Precision Medicine?" from* ***8:38-11:14***

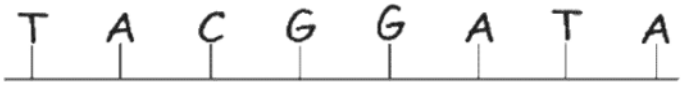
- Ask students to discuss the clip with their table group, then record their revised thinking in the "After" box.
- Individuals or tables can share out, generating a class discussion.

4. Sequencing Activity 1 | 15-20min

Use slides 6-13

Use sequencing activity 1 sheet

1. Groups of 2-4 students arrange the color-coded DNA strips from largest to smallest. This is to model the concept that gel electrophoresis uses electrical charge to move DNA fragments through a gel. As DNA fragments move, smaller pieces are able to move through the gel faster. As such, the DNA fragments are separated by size.
2. Students organize the DNA pieces according to which "Terminator" produced them. In effect, they will put the pieces on the tubes that match the color of the DNA pieces. This is meant to model the fact that each "terminator" (A, C, T, and G) produces fragments that end with that letter. For example, the tube with ATP dideoxynucleotide will produce copies that end in A.
3. To further illustrate this point before moving on to the next step, a sequence of DNA is provided and students are asked to determine what sequences would be produced by each of the four "terminators."



- "Terminator" A would produce A and ATGCCTA
- C would produce ATGC and ATGCC
- G would produce ATG
- T would produce AT, ATGCCT, and ATGCCTAT

(This is done by matching complementary base pairs and STOPPING whenever the complementary base is the same as the "terminator").

4. Students organize their DNA fragments by size (smallest going farthest) AND by which "Terminator" was used to produce them. This step again uses the concept that gel electrophoresis separates DNA fragments based on size. This time, instead of all the fragments occupying one lane as they did in Step 1, they are in separate lanes based on the "terminator" that was used to produce them. As such, all of the fragments in the left lane will end in A. All of the pieces of DNA in the second lane will end in C. All of the DNA sequences in the third lane will end with T. All of the DNA fragments in the far right lane will end in G.
5. Ask students to use the arrangement by size and "terminator" to write the sequence. Starting with the piece that traveled the furthest, the students will write the name of the "Terminator" used to produce each fragment. This will give them the sequence of the DNA they are analyzing.
6. Students write the DNA sequence on their Student Sheets. The sequence should be:

   CGATACTGGTG

   This is done by writing the "terminator" bases in order from the smallest to largest. This step also explains that you would not actually see DNA letters or individual fragments, but bands that are comprised of thousands of copies of the same fragment of DNA. Slide 13 shows a diagram of what this would look like as well as an actual Sanger Sequencing gel for comparison.

EXTENSION

Use student sheet 1

- Now that students have some conceptual understanding of how DNA sequencing works, ask them what this could teach us about disease.
- Ask them to fill out the left hand side of the box ("Before") individually.

Show students the video clip: "What Can Sequencing the Genome Teach Us About Disease?" (slide 14)

- Ask students to discuss the clip with their table group, and then share out with the class.
- Ask them to use the left hand side of the box ("After") to record their revised thinking.

Class 2

Use DNA Sequencing and Precision Medicine slides

Use student sheet 2

1. Case Study: Cara Greene | 5-10min

Show students the video clip: "Cara Greene: Good Morning, America" (slide 16)

Ask them to think about how DNA sequencing and precision medicine have affected this family's life.

2. Sequencing Activity 2 | 10-15min

Use slides 17-20

Use sequencing activity 2 sheet

1. Each table group should receive the sanger sequencing results from one of the imaginary patients. The context of the activity is to imagine that each patient is suffering from an unknown genetic disorder, and that their DNA will be compared to Cara Greene's to see if they also have Brown-Violetto-Van Laere Syndrome. The specific gene being compared is SLC52A2, a gene which codes for a vitamin transporter protein. In people who do not have a mutated gene, this protein helps vitamins enter into cells. Without the functioning protein, cells cannot take in enough vitamins. Each table should use the picture of the sanger sequencing gel to determine the imaginary sequence of the gene.

Show students the video clip: "Cara Greene" from the lecture (slide 17) from ***14:33-17:18***

2. As they watch this brief section of the lecture, students should listen for the normal job of the protein coded for by the SLC52A2 gene, the symptoms, and the treatment.

3. Ask students to enter their sequences into a class data table on overhead, projector, whiteboard, chalkboard, or chart paper. Each student should then copy the class data table into the data table on their student sheet.

4. Based on the sequencing data, have students make a diagnosis and prognosis for each patient.

3. Figure Analysis Template 2: Who Should be Sequenced? | 15-20min

Use student sheet 2

The final section of this class asks students to think about who should have their DNA sequenced and why as they watch two clips from Dr. Goldstein's lecture and analyze a graph.The causes of stroke

- Initial thoughts: Students should write down who they think should/should not be sequenced and why. Encourage students to take more nuanced stances than "nobody" or "everybody" and to explain their reasoning.

Show students the video clip: "Should everyone be sequenced?" from ***1:04:00-1:06:00***

Students will watch a clip from the lecture outlining several areas of research that Dr. Goldstein is pursuing through sequencing.

- Ask students to use Figure Analysis Template 2 to analyze a graph from Dr. Goldstein's lecture.

Show students the video clip: "The challenges of sequencing" from ***1:07:58-1:09:09***

Students will watch a brief clip from the Q&A session after the lecture. In the clip, Dr. Goldstein expresses concern that sequencing and identifying variants will lead to overreactions by individual patients and by the health care system as a whole.

4. Final thoughts | 5min

- After incorporating the information from the graph and video clips, ask students to articulate who they think should and should not have their genome sequenced and why.

EXTENSION

Use extension sheet

- Ask students to analyze the abstracts of the following papers:
- Epi4k Consortium (2017) Ultra-rare genetic variation in common epilepsies: a case-control sequencing study. Lancet Neurology

  https://www.ncbi.nlm.nih.gov/pubmed/28102150
- Cirulli et al. (2015) Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science

  https://www.ncbi.nlm.nih.gov/pubmed/25700176
- In their analysis, they can identify and paraphrase the following aspects of each study: 1) Background and purpose, 2) Methodology, 3) Results, and 4) Conclusions.
- Then they can identify how sequencing contributed to understanding and/or treatment of ALS and/or epilepsy.

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Vocabulary

Exome	The portion of the genome that codes for proteins.
Gel electrophoresis	A technique that uses an electrical charge to pass DNA pieces through a gel, separating them by size.
Genome	An organism's complete set of DNA.
Next Gen Sequencing	DNA sequencing techniques that combine the basic principles of Sanger sequencing with technologies that allow sequencing to be done quickly and at a much lower price.
Sanger sequencing	A DNA sequencing technique that uses "terminator" dideoxynucleotides and gel electrophoresis to determine the sequence of DNA.
"Terminator" dideoxynucleotide	Nucleotides (sugar, phosphate, base) that attach to their complementary base and then STOP further nucleotides from attaching, terminating the DNA.
Variation	Differences in traits of individuals that exist because of differences in the genomes and environments of those individuals.

Sources

The Stavros Niarchos Brain Insight Lecture, “Finding the Right Medicine One Patient at a Time: Developing Targeted Treatments to Combat Neurological Disease.” By David Goldstein, PhD

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