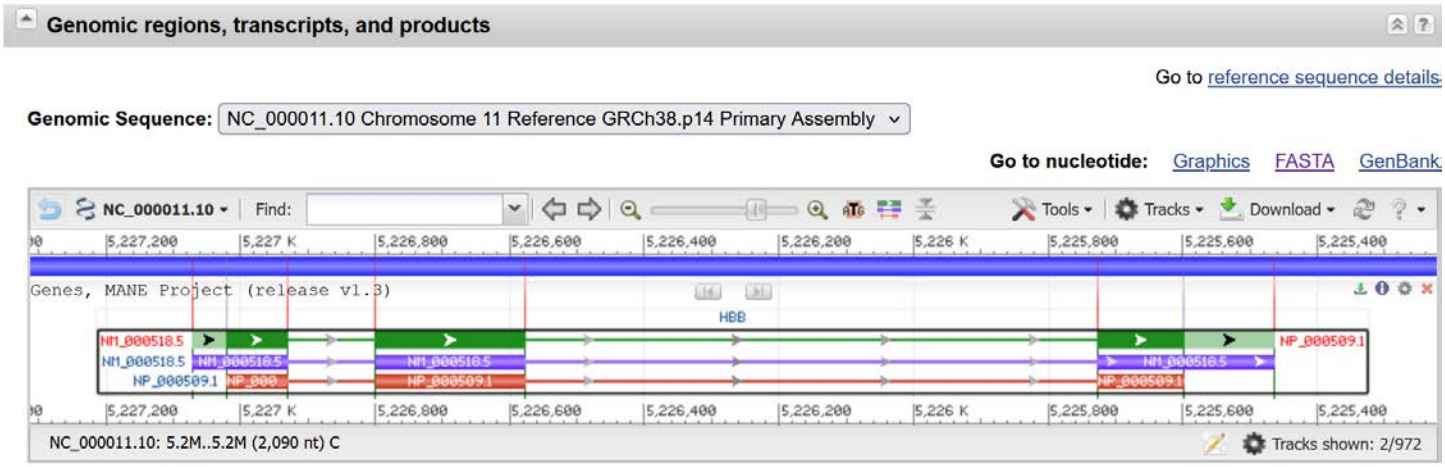
Teacher Information
Introductory Biology (HS)

The purpose of this assignment is to provide students with an opportunity to investigate the impacts of various types of mutations on the human HBB gene (the one that causes Sickle Cell Anemia). Prior to this assignment, students should be familiar with HOW to transcribe and translate DNA codons into mRNA codons, and they should be able to identify the different types of mutations (missense, nonsense, silent, frameshift) and the basic impact each of those mutations have on the resulting amino acid sequence.

To show students what happens with the hemoglobin when the sickle cell mutation is present:
https://www.wehi.edu.au/wehi-tv/haemoglobin-and-sickle-cell-anaemia/

To show students what the symptoms of sickle cell disease are, along with the impact of another mutation in a second gene, and why that might be an option for gene therapy (HHMI):
https://www.biointeractive.org/classroom-resources/genetic-treatment-sickle-cell-disease

TEACHER KEY:
https://www.ncbi.nlm.nih.gov/gene/3043



Focusing in on DNA corresponding to the amino acid sequence found in (Wild Type) Exon 1:

							20		25 27			36
DNA	TAC	CAC	GTA	GAC	TGA	GGA	CTC	CTC	TTC	AGA	CGG	CAA
RNA	AUG	GUG	CAU	CUG	ACU	CCU	GAG	GAG	AAG	UCU	GCC	GUU
AA	Met	Val	His	Leu	Thr	Pro	Glu	Glu	Lys	Ser	Ala	Val

The example of a missense mutation in the HBB gene that causes Sickle-Cell Disease is the substitution of adenine (A) with thymine (T) at the sixth codon of the HBB gene.

Specific Example:

HGVS Nomenclature:

- **c.20A>T**
- **NM_000518.5(HBB):c.20A>T (p.Glu7Val)**

Protein Change:

- **p.Glu6Val** or **E6V**

Description:

- This notation indicates that at nucleotide position 20 in the coding DNA sequence of the HBB gene, adenine (A) is replaced by thymine (T).
- This change results in the substitution of the amino acid glutamic acid (Glu) with valine (Val) at the sixth position of the beta-globin protein.

Missense Mutation (Sickle Cell Mutation)

							20		25	27		36
DNA	TAC	CAC	GTA	GAC	TGA	GGA	CAC	CTC	TTC	AGA	CGG	CAA
RNA	AUG	GUG	CAU	CUG	ACU	CCU	GUG	GAG	AAG	UCU	GCC	GUU
AA	Met	Val	His	Leu	Thr	Pro	Val	Glu	Lys	Ser	Ala	Val

A nonsense mutation in the HBB gene introduces a premature stop codon, leading to a truncated and usually nonfunctional protein. Here's an example of a nonsense mutation in exon 1 of the HBB gene:

Specific Example:

HGVS Nomenclature:

- **c.22C>A**

Protein Change:

- **p.Glu8Ter** or **Q8X**

Description:

- This notation indicates that at nucleotide position 22 in the coding DNA sequence of the HBB gene, cytosine (C) is replaced by Adenine (A).
- This change results in the substitution of the amino acid glutamic acid(Glu)** at position 8** with a stop codon (Ter), leading to a premature termination of the protein.

							20	22	27			36
DNA	TAC	CAC	GTA	GAC	TGA	GGA	CTC	ATC	TTC	AGA	CGG	CAA
RNA	AUG	GUG	CAU	CUG	ACU	CCU	GAG	UAG	AAG	UCU	GCC	GUU
AA	Met	Val	His	Leu	Thr	Pro	Glu	STOP				

A silent mutation in a gene is one that changes a nucleotide sequence without altering the amino acid sequence of the protein it encodes. In the HBB gene, an example of a silent mutation in exon 1 is:

Specific Example:

HGVS Nomenclature:

- **c.27C>T**

Description:

- This notation indicates that at nucleotide position 27 in the coding DNA sequence of the HBB gene, cytosine (C) is replaced by thymine (T).
- Despite this change, the amino acid sequence remains unchanged because the new codon still codes for the same amino acid.

Focusing in on DNA corresponding to Exon 1

							20		25 27			36
DNA	TAC	CAC	GTA	GAC	TGA	GGA	CTC	CTC	TTT	AGA	CGG	CAA
RNA	AUG	GUG	CAU	CUG	ACU	CCU	GAG	GAG	AAA	UCU	GCC	GUU

Deletion Mutation that results in a frameshift mutation

NM_000518.5:c.25_26del

Description of the Mutation:

- **Position**: Nucleotide positions 25 and 26 in the coding sequence of the HBB gene.
- **Type of Mutation**: Deletion of two nucleotides.

Deletion (Frameshift)
Deletion of 25 and 26

Focusing in on DNA corresponding to the amino acid sequence found in Exon 1

							20		25 27			36
DNA	TAC	CAC	GTA	GAC	TGA	GGA	CTC	CTC	TTC	AGA	CGG	CAA
RNA	AUG	GUG	CAU	CUG	ACU	CCU	GAG	GAG	AAG	UCU	GCC	GUU
AA	Met	Val	His	Leu	Thr	Pro	Glu	Glu	Lys	Ser	Ala	Val

NEW DNA

							20		25 27			36
DNA	TAC	CAC	GTA	GAC	TGA	GGA	CTC	CTC	CAG	ACG	GCA	ACG
RNA	AUG	GUG	CAU	CUG	ACU	CCU	GAG	GAG	GUC	UGC	CGU	UGC
AA	Met	Val	His	Leu	Thr	Pro	Glu	Glu	Val	Cys	Arg	Cys

For an extension / higher level biology, students can be asked to identify the impact of the mutations on the physical structure of the resulting protein (based on the properties of the amino acid chain, etc.)