Many students experience difficulty in making the connection between the microscopic structure of chromosomes to the molecular perspective of chromosomes as sequences of A-T and G-C nucleotide base pairs. This becomes especially apparent when students construct Punnett squares to investigate modes of inheritance. A typical representation of a Punnett square demonstrating a recessive mode of inheritance is shown below.

If both parents are heterozygous (Ss) for sickle cell disease, each child’s chances are:

- 25% chance of not having the disease (SS)
- 50% chance of carrying the disease (Ss)
- 25% chance of having the disease (ss)

Explore your students’ thinking by asking them to explain what the lowercase and uppercase letters represent in the Punnett square.

Have your students construct a Punnett square using a DNA sequence instead! Sickle cell anemia is a recessively inherited condition due to a single point mutation, from A (adenine) to T (thymine), in the gene for beta-globin protein found on chromosome 11. The mutation results in a change from the beta-globin protein amino acid glutamic acid to valine. People with the condition have atypical hemoglobin molecules which can distort red blood cells into a sickle shape. Painful episodes can occur when the sickled red blood cells get stuck in the capillaries depriving tissues and organs of oxygen-rich blood. If both parents are carriers of sickle cell anemia, the Punnett square can be constructed as:

<table>
<thead>
<tr>
<th>Normal beta-globin gene sequence</th>
<th>Sickle cell beta-globin gene sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’ G A G 3’</td>
<td>5’ G T G 3’</td>
</tr>
<tr>
<td>3’ C T C 5’</td>
<td>3’ C A C 5’</td>
</tr>
</tbody>
</table>
Students can also model an example of a condition that is inherited in a **dominant pattern**, typically represented in a Punnett square as shown below.

If one parent does not have Huntington disease (hh) and one parent has the Huntington gene mutation (Hh), each child’s chances are:

- 50% chance of not having the disease (hh)
- 50% chance of having the disease (Hh)

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of cognition. The most common form of this disorder usually appears in a person’s thirties or forties. Mutations in the HTT gene, found on chromosome 4, cause Huntington disease. The HTT gene provides instructions for synthesizing a protein called huntingtin whose role appears to affect nerve cell function. The mutation involves a DNA segment known as a CAG trinucleotide repeat. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people affected with Huntington disease the CAG segment is repeated 36 to more than 120 times. In the example below, one segment CAG would represent a repeat of 25 times. Two segments of CAG would represent a trinucleotide repeat of 50 times.

**Normal Huntington sequence (25 repeats) Huntington sequence (50 repeats)**

\[
\begin{array}{ccc}
5' & C & A & G & 3' \\
3' & G & T & C & 5'
\end{array}
\]

\[
\begin{array}{ccc}
5' & C & A & G & C & A & G & 3' \\
3' & G & T & C & G & T & C & 5'
\end{array}
\]

Have your students research and model additional heritable conditions using DNA sequences!