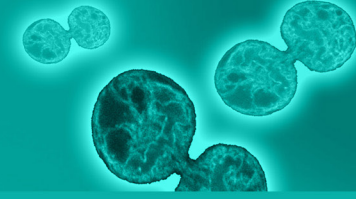# *BRAF*: from gene to cancer therapy
## Student worksheet

Your task

You are a team of scientists who have been asked to interpret data from the Cancer Genome Project at the Wellcome Trust Sanger Institute. You have been given sequence data from 10 patients diagnosed with malignant melanoma. Two samples have been taken from the patients, a sample of the tumour and a blood sample that will act as a control. You have specifically requested sequence data for the *BRAF* gene found on chromosome 7 as literature has shown that this gene is commonly associated with malignant melanoma.

Using your data, discuss the significance of the mutations you find and identify ways this genetic information could be used to develop practical solutions to the diagnosis and treatment of malignant melanoma.

Part 1: Interpreting the data (5–10 minutes)

Each sample sheet has two samples, one tumour sample and one healthy reference sample. Complete and compare the complementary sequences for the data sets to identify how the mutations affect the DNA sequence. Use the guide below to help you interpret your data sets.
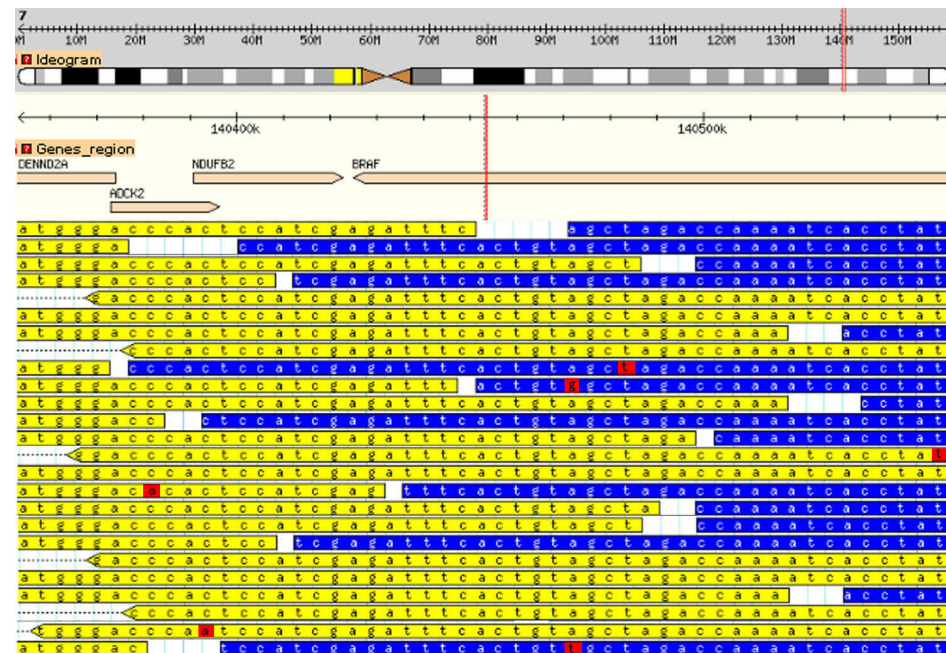
Ideogram: This represents the chromosome on which the *BRAF* gene is located. The red line indicates the location of the gene sequence.

Gene region: This represents the genes found in this region. The arrowhead represents the direction in which the gene is transcribed. This will give you a hint as to how to read the data.

Sequence reads: This section is the data produced by the sequencer.

Yellow sections represent DNA reads sequenced along the strand from 5' to 3' (right to left).

**Blue** sections represent DNA reads sequenced from 3' to 5' (left to right).

Red boxes indicate a base change in the DNA sequence compared to the reference human genome sequenced.

A mutation will be displayed as a base change occurring multiple times in the same location on both blue and yellow reads.

A single red box on its own can indicate that the sequencing machine has made an error when sequencing the DNA.

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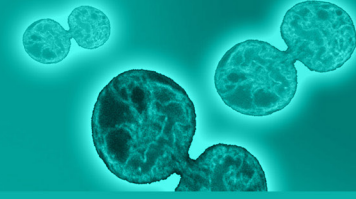
Data analysis

In your group analyse and interpret the 10 *BRAF* samples. Complete the table at the bottom of each data set. This process has three stages:

1. Write down the consensus gene sequence in the data set.
2. Write down the complementary strand to the gene sequence.
3. Using the complementary strand sequence, translate each codon into an amino acid using the codon wheel. Make sure that you do this in the 5' to 3' direction.

Once your group has completed all the data sheets collate your data into the table below:

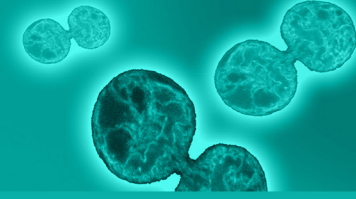| Sample	Mutation Yes / No	Codon number	Healthy codon	Tumour codon	Healthy amino acid	Tumour amino acid
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Mark **all** of the mutations on the *BRAF* gene banner or gene sheet.

Question 1

Is there a pattern in the distribution of the *BRAF* mutations?

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Part 2: Consult COSMIC (5–10 minutes)

Find out whether your findings correspond to the findings of other cancer researchers by consulting the COSMIC database:
http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/

Follow the instructions below to help you navigate the database:
1. On the homepage in the search box click on *By Gene*.
2. Type in *BRAF* and press the red *Go* button.
3. Select *BRAF* from the list of genes (please note that sometimes you may be taken straight to step 4 by the website).
4. In the *Mutation Analysis* box on the right of the screen, click on the *Histogram* button to see a graphical representation of the known mutations in the *BRAF* gene. Enter the amino acid range from the *BRAF* gene banner (581-621) into the boxes to the right of the histogram and press the red *Apply* button. This will display the region of the gene that you have been studying in more detail.
5. You should see a bar on the histogram that corresponds to the position where you have found mutations. You will see that the bar at this position is divided into sections depending on which mutation has occurred and the number of samples with the mutation. Hover over the bar to see the type of mutations and number of samples (mutation count) at position 600.
6. Click on the largest section of the bar to display more information about the mutation. This represents samples with the same substitution as seen in your samples.
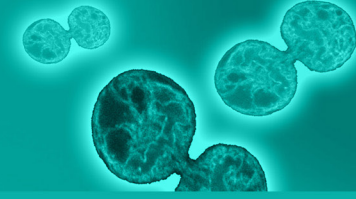
Question 2

Are there any mutations that match your findings? If so, how many samples have this mutation? Is it a common mutation?

Question 3

In which tissues are *BRAF* mutations commonly found? (Click on the *Tissue Distribution* tab to find out which tissues carry *BRAF* mutations. Hover the mouse over the tissue type to get figures for the number of samples with mutations.)

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Question 4

For malignant melanoma, what is the most relevant tissue type to investigate further? (Click on this tissue type, then click on the *Genes with Mutations* tab. Sort the data in the *Mutated samples* column from highest to lowest by clicking on the arrow at the top of the column twice).

Tissue type	

Gene	% samples with mutations

What are the three most commonly mutated genes in the table?
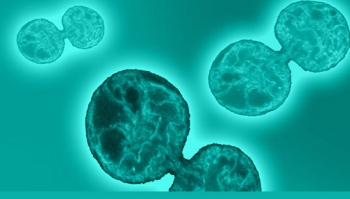
Part 3: Data discussion (20–30 minutes)

Using the *BRAF* information cards, discuss in groups the significance of your findings and consider the questions below. Be prepared to feed back your ideas to the rest of the class.

Question 5

How does the mutation have an impact on cell growth and division? What are the consequences of this?

Question 6
How can DNA sequence data be used by the research community to improve cancer treatment?

Question 7

a) How would you identify if an advanced melanoma patient carried the *BRAF* mutation and what treatment would you prescribe?
b) How would you treat an advanced melanoma patient without the *BRAF* mutation? Explain your reasons.

Base your ideas on the findings and evidence from the *BRAF* information cards.

Consider issues such as:

• What challenges could there be when treating metastatic melanoma and how could these be overcome?
• What happens if the patient suffers a relapse or develops resistance to a treatment?