All cancers result from changes to the DNA sequence in some of our cells. Because the genetic material within cells is exposed to mutagens such as UV radiation, it can accumulate mistakes during replication. Occasionally, one of these mutations alters the function of a critical gene, providing a growth advantage to the cell in which it has occurred and its offspring; these cells will divide at a faster rate than their neighbours. Gradually, the DNA acquires more mutations, which can lead to the disruption of other key genes, resulting in particularly fast-growing and invasive cells. The result is tumour formation, the invasion of the surrounding tissue and eventually metastasis – the spread of the cancer to other parts of the body.

Genes that lead to the development of cancer when mutated are known as ‘cancer genes’. Tumour suppressor genes (TSGs, Figure 1) encode the information for making proteins that normally slow down cell growth, preventing unnecessary division or promoting apoptosis (programmed cell death) if the cell’s DNA is damaged. Both copies of a TSG would have to be inactivated by mutation before this control of the cell cycle is lost. If one functional copy remains, there is still a ‘brake’ on the cell’s growth.

Proto-oncogenes (Figure 2), in contrast, encode proteins that promote cell division and differentiation (specialisation). When these genes acquire mutations that either make the proteins continually active or lead to the gene’s activity not being regulated anymore, they become oncogenes, promoting uncontrolled cell growth and division. For proto-oncogenes, a mutation in one copy of the gene can be enough to drive cancer development.

Can you spot a cancer mutation?

How does cancer develop, and how can geneticists tell that a cell is cancerous? This teaching activity developed by the Communication and Public Engagement team from the Wellcome Trust Sanger Institute, UK, answers these and other related questions.
Each individual case of cancer is caused by a unique set of mutations in proto-oncogenes and/or TSGs. Although the number is not yet known, it is thought that five or more mutations in cancer genes are needed for a cell (and its offspring) to become cancerous.

**KRAS** (pronounced kay-rass) is a proto-oncogene that encodes the protein KRAS, an intracellular signalling protein involved in promoting cell growth (to distinguish genes from proteins, gene names are conventionally written in italics). The following activity enables students to use real genomic data from the Cancer Genome Project to investigate common mutations in the **KRAS** gene that are associated with oncogenesis (cancer formation) and the development of pancreatic, colorectal, lung and other cancers. Originally developed for school visits to the Sanger Institute, the activity was then made available through the Yourgenome.org website. It recently formed part of the first course on bioinformatics for European teachers run by ELS at the European Bioinformatics Institute in Hinxton, UK. The full activity stimulates discussion about the causes of cancer, the function of gene mutations, protein structure and protein function.

**The KRAS activity**

Estimated duration: 45–60 minutes (with presentation and discussion)

**Materials**

All materials required to run the activity can be freely downloaded from the Yourgenome.org website either individually or as a compressed zip file:

- One set of 11 worksheets (KRAS_student_wsheet.pdf) – one worksheet per pair or group of students. An alternative version is available for black and white printers or for use with colour-blind stu-

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**Figure 1:** Tumour suppressor genes normally function to prevent cell growth and division. To lead to cancer, both copies of the gene would have to be mutated (marked in red)

**Figure 2:** Proto-oncogenes normally function to promote cell growth and division in a controlled manner. A mutation in one copy of the gene (marked in red) can be enough to drive cancer development

**Figure 3:** The KRAS gene sheet
For large groups (20 or more), use two sets of worksheets, providing double coverage of the gene.

- One KRAS gene sequence banner (KRAS_gene_banner.pdf; Figure 3) for the whole class, and one KRAS gene sheet (KRAS_genesheet_yg.pdf; Figure 3) per group of students. The gene sheet (printed on A3 or A4) requires little preparation time. The KRAS banner, printed on several sheets of paper that are then stuck together, enables the results from the whole class to be displayed simultaneously.
- One codon wheel sheet (KRAS_codon_wheel.pdf or any other codon table for sense DNA, 5’ to 3’) per group, see Figures 4 and 5
- One summary sheet (KRAS_data_sheet.pdf) per group
- Pens

To use the banner, you will also need large arrows for marking mutations on the gene sequence, squares for marking regions which have been checked (KRAS_annotations.pdf), and reusable adhesive (e.g. Blu Tack®) for sticking arrows and squares to the gene sequence banner. Find out more about how to use this method in the downloadable teacher notes.

In addition, you might find it helpful to have DNA, peptide and/or protein models to hand, and to use the Wellcome Trust Sanger Institute cancer animations (Cancer: Rogue cells and Role of cancer genes) on the KRAS activity website.

Introduction to the activity

The Investigating Cancer presentation (available online) provides students with an overview of cancer. It introduces the concept that cancer arises due to abnormalities in DNA sequence, explains the various causes of these mutations and introduces the worksheets and activity. Several sections of the presentation encourage student discussions (see the presentation notes).

In the first part of the activity, students identify differences between KRAS gene sequences in healthy and...
tumour cells on their worksheets, and mark these on the KRAS banner or gene sheet.

The worksheets have raw KRAS DNA sequencing traces from healthy and cancerous cell samples, represented as coloured line plots – one for each region of the gene. The four bases are represented on these plots by four different colours. Each coloured peak represents an individual DNA base:

- Red: T
- Green: A
- Blue: C
- Black: G (normally these peaks are yellow but this is not easy to read on paper)

There are 11 numbered worksheets in total, each showing two different regions of the KRAS gene. The six mutations in the KRAS gene are on worksheets one to six, so be sure to mix the sheets up before distributing them to the class. All must be completed to ensure full coverage of the gene. It is important to point out to the students that mutations are (relatively) rare, so not everyone will find one; this can be used to explore the importance of negative data and comprehensive coverage in scientific studies.

Identifying the mutations

Using the worksheets, the students will compare a section of DNA sequence from a healthy cell and a tumour cell from the same patient. The easiest way to identify whether a mutation has occurred is to write the DNA sequence below the coloured peaks (there is a colour key on the sheet to help) and to compare the written sequences.

If one of the letters is different (a peak has changed colour), this indicates a mutation in the sequence. In Figure 7, the A in the DNA sequence from the healthy cell has been replaced by G in the tumour cell.

If the students find a double peak at one base position, this should be recorded with the two alternative bases at that position, one above the other. In the example below, the healthy DNA sequence has a G, whereas the tumour sequence has both G and C. This is not an insertion: it represents a heterozygous mutation where only one copy of the gene has substituted a C for a G. In this case the tumour sequence has replaced G with a C.

All students should indicate the gene regions they have checked by ticking off the relevant region on the gene sheet (see Figure 9).

Students who find a mutation should indicate the specific base by circling it on the gene sheet (see Figure 9) and make a note of which codon this lies in (in this example, codon 12).

They should also fill in the table at the base of the worksheet, using the codon wheel to translate the DNA sequence into the amino acid, as shown in Table 1:

Table 1: Mutations as listed on the individual worksheets

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Healthy cell DNA sequence</th>
<th>Tumour cell DNA sequence</th>
<th>Healthy cell amino acid</th>
<th>Tumour cell amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>GGT</td>
<td>GTT</td>
<td>G(glycine)</td>
<td>V(valine)</td>
</tr>
</tbody>
</table>

Table 2: Mutations as recorded on the summary data sheet

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Healthy cell DNA sequence</th>
<th>Tumour cell DNA sequence</th>
<th>Healthy cell amino acid</th>
<th>Tumour cell amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>GGT</td>
<td>GTT</td>
<td>G(glycine)</td>
<td>V(valine)</td>
</tr>
<tr>
<td>13</td>
<td>GCC</td>
<td>GAC</td>
<td>G(glycine)</td>
<td>D(aspartic acid)</td>
</tr>
<tr>
<td>30</td>
<td>GAC</td>
<td>GAT</td>
<td>D(aspartic acid)</td>
<td>D(aspartic acid)</td>
</tr>
<tr>
<td>61</td>
<td>CAA</td>
<td>CGA</td>
<td>Q(glutamine)</td>
<td>R(arginine)</td>
</tr>
<tr>
<td>146</td>
<td>CCA</td>
<td>CCA</td>
<td>A(alanine)</td>
<td>P(proline)</td>
</tr>
<tr>
<td>173</td>
<td>GAT</td>
<td>GAC</td>
<td>D(aspartic acid)</td>
<td>D(aspartic acid)</td>
</tr>
</tbody>
</table>

Discussing the results

The results above are all single base substitutions. These mutations within the protein-coding region of the KRAS gene may be classified into one of three types, depending on the information encoded by the altered codon:

- Silent mutations code for the same amino acid.
- Missense mutations code for a different amino acid.
- Nonsense mutations code for a stop and can truncate the protein.

Images courtesy of the Wellcome Trust Sanger Institute Communication and Public Engagement team
Discuss whether the mutations are significant – will they have an impact on protein function or are they ‘silent’? In this activity, codons 30 and 173 are silent and therefore do not have a functional impact.

The presentation has a 3D space-fill image of the KRAS protein (Figure 10); slides 26–30 show where on the protein the significant mutations are, and you will notice they are all in the same region. Codons 12, 13 and 61 were the first mutations to be associated with oncogenic transformation in the KRAS protein; mutation 146 was only discovered in 2005. Use these slides to discuss the impact that the mutations could have on protein structure and KRAS’s function in growth signalling.

As an optional activity, the students can use RasMol, the molecular modelling software used to create the images on slides 26–30, to highlight the mutated amino acids in the protein structure. See the teacher notes for details.

How does information like this influence our approach to cancer?

The teacher notes contain a wealth of background information, using KRAS as an example, to stimulate discussion on how genomic information can be used to further our understanding of cancer and develop cancer treatments. Discussion points for students include:

- What experiments or approaches could be used to establish which cancers involve KRAS mutations?
- What could be the advantages of knowing this information?
- Cancer is a genetic disease: it is a result of changes in the DNA sequence. This is why many people believe that significant funding of research into cancer genetics is the best way of developing new cancer treatments and thus dealing with the disease. Cancer treatment and care for patients also requires large amounts of money (the UK National Health Service spent more than £2 billion on cancer care alone in 2000). Where and how do students think money should be spent?

### Web references

- w1 – Learn more about the Cancer Genome Project at the Wellcome Trust Sanger Institute here: [www.sanger.ac.uk/genetics/CGP](http://www.sanger.ac.uk/genetics/CGP)
- w2 – To learn more about the Wellcome Trust Sanger Institute in Hinxton, UK, a leader in the Human Genome Project, see: [www.sanger.ac.uk](http://www.sanger.ac.uk)
  The institute offers visits for school classes, teachers and the general public, as well as teacher support and further opportunities to get involved. See: [www.sanger.ac.uk/about/engagement](http://www.sanger.ac.uk/about/engagement)
- w3 – The Yourgenome.org website was launched by the Sanger Institute to stimulate interest in and discussion on genetic research. It includes a section of varied and well developed resources for teachers, including the activity presented in this article. See: [www.yourgenome.org](http://www.yourgenome.org)
- w4 – The European Learning Laboratory for the Life Sciences (ELLS) at the European Molecular Biology Laboratory provides continuing professional development courses (LearningLABs) in molecular biology for European secondary-school science teachers. In March

### Table 3: Type of mutation, as recorded on the summary data sheet

<table>
<thead>
<tr>
<th>Amino acid number</th>
<th>Healthy cell DNA sequence</th>
<th>Tumour cell DNA sequence</th>
<th>Healthy cell amino acid</th>
<th>Tumour cell amino acid</th>
<th>Type of mutation</th>
<th>Significant yes / no</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>GGT</td>
<td>GTT</td>
<td>G (glycine)</td>
<td>V (valine)</td>
<td>Point (missense)</td>
<td>yes</td>
</tr>
<tr>
<td>13</td>
<td>GCC</td>
<td>GAC</td>
<td>G (glycine)</td>
<td>D (aspartic acid)</td>
<td>Point (missense)</td>
<td>yes</td>
</tr>
<tr>
<td>30</td>
<td>GAC</td>
<td>CAT</td>
<td>D (aspartic acid)</td>
<td>D (aspartic acid)</td>
<td>Point (silent)</td>
<td>no</td>
</tr>
<tr>
<td>61</td>
<td>CAA</td>
<td>CGA</td>
<td>Q (glutamine)</td>
<td>R (arginine)</td>
<td>Point (missense)</td>
<td>yes</td>
</tr>
<tr>
<td>146</td>
<td>GCA</td>
<td>CCA</td>
<td>A (alanine)</td>
<td>P (proline)</td>
<td>Point (missense)</td>
<td>yes</td>
</tr>
<tr>
<td>173</td>
<td>GAT</td>
<td>GAC</td>
<td>D (aspartic acid)</td>
<td>D (aspartic acid)</td>
<td>Point (silent)</td>
<td>no</td>
</tr>
</tbody>
</table>

www.scienceinschool.org
2010. ELLS ran the first biinformatics LearningLAB for teachers at the European Bioinformatics Institute in the UK. For information on ELLS courses, please go to: www.embl.org/ells

w5 – To find out more about the European Bioinformatics Institute, see: www.ebi.ac.uk

w6 – To download all materials for the KRAS activity and for more background information, see: www.yourgenome.org/teachers/kras.shtml

Resources

Websites for student reference and discussion

The Cancer Research UK website offers accessible information on all the major cancers and current research. See: http://www.cancerresearchuk.org/cancerandresearch

The New Scientist website has an area focusing on cancer, featuring the latest articles on cancer research developments and interactive animations demonstrating targeted cancer drug functions. See: www.newscientist.com/topic/cancer

Nature Milestones in Cancer offers a collection of selected review-type articles and an online library of recent research papers from Nature Publishing Group, available for download as PDFs. It also has a cancer timeline showing major milestones in cancer research. See: www.nature.com/milestones/milecancer

The Inside Cancer multimedia website created by the DNA Learning Center offers a multimedia guide to cancer biology, diagnosis and treatment. See: www.insidecancer.org

Recent news articles

The BBC News website has published an interesting article on how newly discovered genetic hotspots for bowel cancer might help doctors to treat the disease better. See: http://news.bbc.co.uk or use the direct link: http://tinyurl.com/28o7zgl

Sample I (2009) First cancer genome sequences reveal how mutations lead to disease. The Guardian. See www.guardian.co.uk or use the direct link: http://tinyurl.com/yekvfx


This article includes a video interview with Professor Mike Stratton, leader of the Cancer Genome Project.

Further reading


The author version of this paper can be freely viewed online. See: www.ncbi.nlm.nih.gov/pmc or use the direct link: http://tinyurl.com/3x5ah6

For a full catalogue of somatic cancer genes (COSMIC) described in the above paper and created by the Cancer Genome Project, see: www.sanger.ac.uk


Download the article free of charge from the Science in School website (www.scienceinschool.org/2010/issue15/cancer#resources), or subscribe to Nature today: www.nature.com/subscribe.


For a classroom activity to discuss the ethics of knowing what your genes have in store for you, including the possibility of cancer, see: Strieth L et al. (2008) Meet the Gene Machine: stimulating bioethical discussions at school. Science in School 9: 34-38. www.scienceinschool.org/2008/issue9/genesismachine

If you enjoyed this article, why not take a look at other medicine-related articles previously published in Science in School? See: www.scienceinschool.org/medicine