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GCSE key words
Genes
Genetic diseases
DNA
Mutation

Fruit flies and Alzheimer's disease

Eye of Science/SPL

Left: *Coloured scanning electron micrograph (SEM) of the fruit fly* Drosophila melanogaster *on a leaf*

In this article we look at some basic aspects of GCSE genetics and then at how fruit flies are being used in novel ways to study genetic diseases.

The instructions for constructing a living organism are encoded in long molecules called **deoxyribonucleic acid (DNA)**. DNA is contained within the chromosomes in the nucleus of every cell in all organisms larger than bacteria.

DNA and genes

The DNA molecules look like tiny twisted ladders; each rung on the ladder is formed by a pair of chemicals called bases (Figure 1). There are four different bases, symbolised by the letters A, C, T and G, that can pair up (A with T and C with G) to make the rungs. The order in which the bases are stacked up in the DNA molecule determines what the DNA does.

The function of much of the DNA in an organism is rather mysterious; some may have no function at all while some is involved in controlling the cell. Only small fragments of the total DNA have a clear function and these parts are called **genes**. The DNA in a gene tells each cell how to make a particular **protein**.

What do proteins do?

Proteins have a wide range of roles in cells, but we can think of them either as tools or as building blocks for the organism:

- They can be thought of as tools when they perform an action such as digesting food (digestive enzymes), releasing energy from sugar (enzymes in respiration), carrying oxygen in blood (haemoglobin) or acting as hormones (insulin).
- They can be thought of as building blocks when they make up bones, tendons (collagen), nails and skin (keratin).

To remain healthy the genes in the body must produce the correct amount of the right proteins. Small differences in genes cause the characteristics in people that we recognise as running in families, such as eye colour, hair colour, baldness and height. In animals and plants these genetic differences cause the characteristics that we can alter by selective breeding, such as milk production in cows or stalk length in wheat.

Figure 1 *DNA is like a spiral ladder with a pair of bases for each rung*

In humans, the cells from males and females have 22 pairs of chromosomes; females have an additional pair of X chromosomes, while males have one X and one Y chromosome.

How do genes cause disease?

Random changes to a gene (**mutations**) may drastically disturb the activity of a gene. This can result in a marked imbalance in protein activity, which shows itself as a disease.

Alcaptonuria

The first genetic disease to be described, called alcaptonuria, was discovered by Archibald Garrod in 1908. Patients with this disease suffer with arthritis (pain and damage to joints) and Garrod noticed that their urine turned black when exposed to the air. The arthritis and the coloured urine are now known to be caused by the build-up of a chemical called homogentisic acid. Normally this chemical is removed by an enzyme (a specialised protein), but in sufferers the gene is mutated so that the enzyme is no longer active. If an individual inherits two copies of the mutant gene then he or she cannot remove homogentisic acid from the blood and develops the disease. Alcaptonuria is a rare disease.

Cystic fibrosis

One of the commonest genetic diseases in the UK is cystic fibrosis. This is caused by mutation in a gene involved in mucus production. Individuals with two copies of the mutant gene produce mucus that is too thick and sticks in the lungs, resulting in repeated lung infections. This thick mucus is also produced in the gut and from other internal surfaces of the body.

The average length of the DNA molecule in a human chromosome is about 5 cm and we have 46 chromosomes in each cell. There are approximately 10 000 000 000 000 cells in the body and so the length of DNA in your body in metres is $0.05 \times 46 \times 10^{13}$, which is about 23 000 000 000 km.

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Aβ is read 'Abeta'.

Right: *Flies with Alzheimer's disease (on the left) are less able to climb the test tube than normal active flies (on the right). Read Box 1 to find out how you can watch these flies climbing*

Box 1 Useful websites

You can listen to Damian Crowther talking about fruit flies and Alzheimer's disease and see for yourself the effect of the Alzheimer's gene on the flies' behaviour at:
http://flymodel.cimr.cam.ac.uk/questions.html
A series of short videos answer such questions as:

- What does a fruit fly have for breakfast?
- How long does a fruit fly live?
- How do we make a fruit fly get Alzheimer's disease?
- How do we know that a fruit fly has Alzheimer's disease?
- How can we use fruit flies to test medicines?
- How big is a fruit fly's brain?
- How do Alzheimer's fruit flies behave?
- Why do we study flies in medical research?

You can find out more about how Alzheimer's disease affects people at www.alzheimers.org.uk by clicking on > *Facts about dementia* > *What is dementia?* > *Alzheimer's disease*.

Haemochromatosis

Some genetic diseases are caused by mutations in genes that make their proteins overactive. Haemochromatosis, the most common genetic disease in the UK, is an example of this; in this case the mutant protein causes the body to absorb too much iron from the diet. Normally iron is required as part of haemoglobin, the protein that carries oxygen in red blood cells, but too much causes damage to many organs including the liver, heart and kidneys.

Alzheimer's disease

Alzheimer's disease is a common cause of memory loss in elderly people. About 5% of cases are caused by mutations that result in faulty forms of the enzymes that would normally remove a potentially toxic protein from the brain. Mutant forms of these enzymes allow the accumulation of toxic peptide fragments (called Aβ peptides). As these Aβ peptide fragments build up in the brain the nerve cells that are required for memory stop working and the patient becomes ill.

How do fruit flies get Alzheimer's disease?

Genetic diseases are the subject of much research as scientists try to work out better treatments for them. One line of research is to utilise fruit flies with the human gene involved in Alzheimer's disease

The fruit fly (*Drosophila melanogaster*) has been used in genetic experiments for 100 years (see 'A life in science', pages 20–21). Scientists are now able to make a lot of different transgenic flies by placing new DNA into their chromosomes (see Box 2 and Figure 3). If the DNA is a human gene then the flies can be made

Box 2 Creating a transgenic fly

The process outlined below is illustrated in Figure 3.

Step 1

The first step in creating a transgenic fly is to splice (clone) the DNA for the human gene into a plasmid that contains a second gene which makes a coloured protein that makes the fly's eyes red.

Step 2

This recombinant plasmid is mixed with another plasmid which has the gene for an enzyme called transposase.

Step 3

Transposase is able to insert the recombinant plasmid, containing our gene of interest, into the chromosome of an embryo that would normally develop with a white eye.

If the recombinant plasmid is incorporated into the fly's chromosome successfully then the offspring will have red rather than white eyes. The red eye is said to be a marker for the transgene.

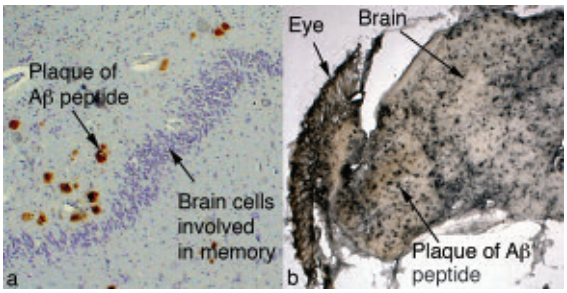

Figure 2 *The toxic Aβ peptide accumulates in the brains of patients with Alzheimer's disease as plaques (panel a, brown). These deposits damage nerves that are required for memory. In the transgenic fruit flies the same peptide accumulates as plaques (panel b, black) and damages the brain function. The true size of these images is 1 mm across*

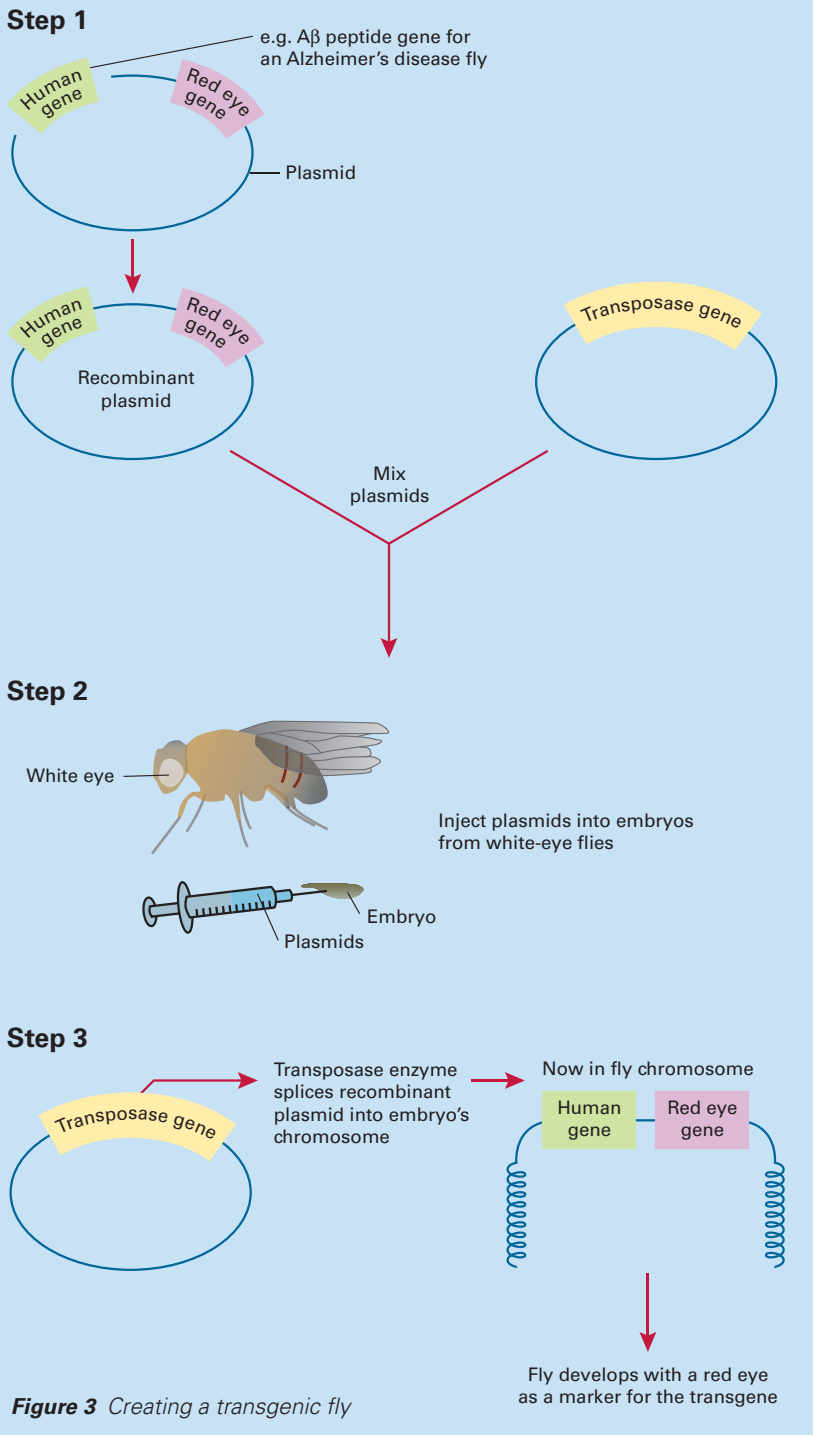

Figure 3 *Creating a transgenic fly*

to produce the corresponding human protein. If the human protein is involved in human disease we may find that the fly will suffer a similar disease. We can then use these flies to test new treatments that could be useful for human patients.

We want to find treatments for Alzheimer's disease, so we gave the fruit flies the human gene for the toxic Aβ peptides so that they produced the peptides in their brains. Using a microscope we looked carefully at the brains of the transgenic flies (Figure 2); we also measured their life-span and their walking abilities. We found that the Aβ peptides cause damage in the fly that is similar to the disease in the human brain.

Testing drugs for Alzheimer's disease

Because the fly develops the disease within a few days, rather than after 50–60 years as in human patients, we can do experiments much more rapidly. Importantly, we can test new drugs on the flies by putting the drugs in their food and testing whether the flies live longer or walk better. Since the genes in flies and humans are very similar we can start to think about new drugs for human patients by using the genetic information that we get from the flies.

Damian Crowther *qualified as a medical doctor and specialised in neurology (concerned with nerves and muscles). He now works on Alzheimer's disease in the Departments of Medicine and Genetics at the University of Cambridge.*

• You will probably learn in your science course about how transgenic bacteria are made. Check that you understand this and compare it with Figure 3. Two enzymes are needed to insert the human gene and the red eye gene into the plasmid — what are they called?