**Genes for Memory**

**Lesson Overview**

Students learn about the connections between genes and cognition by experimenting with knockout mice. By interacting with the animated experiments and interpreting results, students draw conclusions about the genes linked to learning and memory.

**Description of Activity**

In the first activity, *Genes for Memory Part 1*, students learn about the Morris water maze and knockout mice while recording data from an online experiment. After observing and recording the reactions of two groups, students work collaboratively to form hypotheses.

In the second set of activities, *Genes for Memory Part 2*, students construct graphs and analyze data from a related experiment. Students contrast the two experiments and form conclusions about learning and memory.

Following these activities, students can access a press release describing the Wellcome Trust Sanger Institute’s research report from the *Journal of Neuroscience* that reported findings from these experiments. Students are asked to compare their own findings with the findings of neuroscientists.

**Background**

This activity is based on research by Cuthbert and colleagues (2007) from the *Genes to Cognition* research group at the Wellcome Trust Sanger Institute in the United Kingdom.

With the knowledge that humans who lack the sap102 gene have severe learning difficulties, the group studied the behavioral and biochemical effects of knocking out sap102 in mice. The researchers examined spatial ability in mice, which was determined by the ability to remember a location in a water maze. The sap102 knockout mice showed impaired learning and were inefficient in their choice of strategy. Following extra training sessions, however, they improved. In other words, the genetic disadvantage could be overcome with training.

There are parallels between the behavioral changes observed in the knockouts and those seen in children with autism or Asperger syndrome. These children can perform extremely well on some psychological tests, perhaps because they adopt mental strategies that other people cannot.

The research group noted that the SAP102 protein binds to several proteins that have been linked to autism. This takes us a step closer toward understanding the biochemical basis of learning and learning deficits.
Goals and Objectives

Students will be able to:

- Observe an experiment in which learning and memory are studied in wild-type and mutant mice.
- Formulate and communicate hypotheses about observed cognitive phenomena.
- Record, interpret, analyze, and communicate scientific data.
- Graph and interpret the results of an experiment from a data table.
- Experience the way a research scientist investigated a phenomenon and the genes that led to it.

Assumptions of Prior Knowledge

Students should have a basic understanding of the scientific concepts of an introductory or general biology course, or of an introductory psychology course at the secondary or post-secondary levels.

Common Misconceptions/Difficulties

- Studying behavior and cognition has little to do with genes.
- Students often have problems connecting behavior with genes.
- The same gene mutation in a mouse and a human are unrelated.
- Repeating experiments leads to precisely the same conclusions.

Implementing the Lesson

Time Allotment

Part 1: 1 x 50-minute class
Part 2: 1 x 50-minute class

Before Class

Become familiar with Genes to Cognition Online (www.g2conline.org).
Photocopy student worksheets:
- Genes for Memory, Part 1
- Genes for Memory, Part 2
Prepare 1 sheet of graph paper per student

During Class

Use Genes for Memory, Part 1, to introduce students to the Morris water maze. The Morris water maze is used to test learning in rodents. In this experiment, two groups
of mice are tested on their ability to locate a hidden escape platform. The experimental group has had the sap102 gene knocked out and the control group consists of wild-type mice.

Ask students to conduct their experiments online and to record time (in seconds) of the swimming mice on their worksheet. Students should also pay attention to the route the mice take in searching for the platform.

Use *Genes for Memory, Part 2*, to introduce students to another type of knockout mice under investigation, called PSD-95. The results of the Morris water maze test are provided to students, who are expected to graph the results of experimental and control groups for locating a hidden escape platform.

After graphing and analyzing the data, ask students to hypothesize the meaning of the various experiments conducted. Following their conclusions, students will access a press release from the Wellcome Trust Sanger Institute that is relevant to the experiments. Students should compare their findings with the team of scientists and to summarize their opinions.

**Recommendations for Evaluation:**

Have students use the DNALC Simple Mapper to construct individual concept maps or ask students to build a concept map using the terms: cognition, memory, learning, gene mutation, knockout gene, sap102 mice, PSD-95 mice, Morris water maze (other concepts may be added by the students).

Use the G2C Online Test Items to construct an evaluation based on this lesson.

**Suggestions for Extended Learning**

Students who are interested can read more about the process of knocking out genes in mice. They can begin by listening to or reading along with Dr. Seth Grant on G2C Online. *Gene Knockout in Mice* (#897) is particularly instructive in this regard.

- Students can do research on the homolog DLG-3 gene in humans which is associated with mental retardation and learning disabilities.
- If a student has an interest in looking at Dr. Cuthbert and colleagues’ original paper, from which the data for these experiments was derived, they can access it by clicking on the media item sap102 – Sanger Institute Research (#1403) on the COGNITION level of model organisms.
- Mice are one of several model organisms used in science. Research some of the rules for using mice in a laboratory. Explain any ethical issues you may come across. Compare the rules for the use of animals in the laboratory in the United States versus the United Kingdom.
Glossary

**Chimera:** A chimera is an animal made up of two or more types of genetically different cells. For example, when the embryonic stem cells from a brown mouse are injected into the blastocyst of a donor mouse (white mouse) the offspring will be a combination of both types of mice and is called a chimera.

**Cognition:** Cognition is the collective term for “higher” mental processes including attention, judgment, language, learning, memory, and thinking.

**DNA:** DNA (deoxyribonucleic acid) is the nucleic acid located in the nucleus of a cell. It contains the genetic information which controls all cell activities. It has the unique ability to replicate itself.

**Gene:** Genes are the basic units of heredity. A gene is a section of DNA on a chromosome that codes for the production of a protein. It can also code for RNA.

**Gene expression:** Gene expression is the process by which a gene is translated into a protein.

**Gene mutation:** A gene mutation is any change in the genetic information.

**Knockout gene:** When a gene is prevented from functioning in an organism (when the gene is no longer expressed) it is known as a “knockout gene” or “gene knockout.” This technique can be used to study the unknown effects of a particular gene. A knockout mouse is a mouse that has had one or more genes “knocked out.”

**Morris water maze:** The Morris water maze is an apparatus used to investigate spatial learning and memory in laboratory rats and mice. It consists of a large circular pool filled with opaque water in which a small escape platform is hidden.

**Neuroscience:** Neuroscience is a field of science that studies the nervous system. This includes biochemistry, brain anatomy, cell biology, genetics physiology, and psychology.

**Protein:** A protein is a complex organic molecule composed of one or more chains of amino acids. The order of the amino acids is determined by the sequence of bases in DNA. Some examples include enzymes, structural proteins, transport proteins, and receptors.

**PSD-95:** Postsynaptic density protein 95 (PSD-95) is a gene that produces a protein that is a member-associated guanylate kinase (MAGUK). It is located in synaptic junctions and may contribute to learning and memory. In humans PSD-95 is known as DLG4.

**sap102:** sap102 is the synapse-associated protein 102 gene. sap102 produces a protein that is a member-associated guanylate kinase (MAGUK), located in synaptic junctions and may contribute to learning and memory. In humans, sap102 is known as DLG3.
**Synapse:** A synapse is the space between two nerve cells, where a nerve impulse moves from one neuron to another.

**Wild type:** Wild type refers to the typical form of an organism that we expect to find in nature. It refers to both genotype and phenotype. In laboratory experiments, wild types are often used as controls to measure normal responses.

**Resources**

*Related Readings:*


*Web Resources:*

1. *DNA Interactive* (www.dnai.org)

National Science Education Standards

**Content Standard A: Science as Inquiry**

- Identify questions and concepts that guide scientific investigations
- Formulate and revise scientific explanations and models using logic and evidence
- Use technology and mathematics to improve investigations and communications
- Communicate and defend a scientific argument

**Content Standard C: Life Science**

The Cell

- Cells store and use information to guide their functions. The genetic information stored in DNA is used to direct the synthesis of the thousands of proteins that each cell requires.

The Molecular Basis for Heredity

- In all organisms, the instructions for specifying the characteristics of the organism are carried in DNA.
- Changes in DNA (mutations) occur spontaneously at low rates. Some of these changes make no difference to the organism, whereas others can change cells and organisms.

The Behavior of Organisms

- Multicellular animals have nervous systems that generate behavior. Nervous systems are formed from specialized cells that conduct signals rapidly through the long cell extensions that make up nerves. The nerve cells communicate with each other by secreting specific excitatory and inhibitory molecules. In sense organs, specialized cells detect light, sound, and specific chemicals and enable animals to monitor what is going on in the world around them.
- Organisms have behavioral responses to internal changes and to external stimuli. Responses to external stimuli can result from interactions with the organism’s own species and others, as well as environmental changes; these responses either can be innate or learned. The broad patterns of behavior exhibited by animals have evolved to ensure reproductive success. Animals often live in unpredictable environments, and so their behavior must be flexible enough to deal with uncertainty and change.

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Like other aspects of an organism's biology, behaviors have evolved through natural selection. Behaviors often have an adaptive logic when viewed in terms of evolutionary principles.

Behavioral biology has implications for humans, as it provides links to psychology, sociology, and anthropology.

**Content Standard G: History and Nature of Science**

Nature of scientific knowledge

- Scientific explanations must meet certain criteria. First and foremost, they must be consistent with experimental and observational evidence about nature, and must make accurate predictions, when appropriate, about systems being studied. They should also be logical, respect the rules of evidence, be open to criticism, report methods and procedures, and make knowledge public. Explanations on how the natural world changes based on myths, personal beliefs, religious values, mystical inspiration, superstition, or authority may be personally useful and socially relevant, but they are not scientific.

- Because all scientific ideas depend on experimental and observational confirmation, all scientific knowledge is, in principle, subject to change as new evidence becomes available.

Science as a Human Endeavor

- Individuals and teams have contributed and will continue to contribute to the scientific enterprise.

- Scientists have ethical traditions. Scientists value peer review, truthful reporting about the methods and outcomes of investigations, and making public the results of work. Violations of such norms do occur, but scientists responsible for such violations are censured by their peers.
**Answer Key**

*Genes for Memory, Part 1*

1. Access *sap102 Swimming Mice* (#898, a COGNITION content section of *Learning & Memory*) and read the introduction about mouse behavior. Click **Start** to begin the experiment. Record the swim times for each of the mice in the space below.

<table>
<thead>
<tr>
<th></th>
<th>Hidden platform</th>
<th>Visible platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type mouse #1</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Wild-type mouse #2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Wild-type mouse #3</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Wild-type mouse #4</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>sap102 mouse #1</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>sap102 mouse #2</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>sap102 mouse #3</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>sap102 mouse #4</td>
<td>49</td>
<td>5</td>
</tr>
</tbody>
</table>

One a separate sheet, record your answers to the following questions...

2. What conclusions can you draw regarding the behavior of the two types of mice when the platform was hidden?

*The wild-type mice find the platform faster and in a more direct way. The sap102 knockouts take longer and swim in tiny circles as they look for the platform.***

3. What conclusions can you draw regarding the behavior of the two types of mice when the platform was visible?

*This is the critical question:*

*Both types of mice find the platform in approximately the same amount of time although the strategy used by the sap102 mice remains unchanged. Because the sap102 mice found the visible platform without difficulty, we can conclude that they do not have any deficits in swimming or in getting to the platform. This confirms that they have impaired memory – when they have to remember where the platform is (i.e. when it is hidden) they perform poorly.*
4. Other than the time taken to find the platform, what other measure could researchers use to compare the two groups?

The most obvious other measurement is to track the route the mice took toward finding the platform, and to measure the length or directness.

5. What other conditions must be controlled by the experimenters when doing this type of experiment. Think of at least three.

The mice must be introduced to the maze from the same position.
The water temperature must be the same.
The platform must be in the same place each time.

Other student answers may be acceptable
Genes for Memory, Part 2

1. Create a graph of this data. Use red to indicate the wild type points and black for the PSD-95 mice. Connect your data points with the appropriate color. Remember to label properly and use other known rules for graphing.

![Graph of Wild-Type vs. PSD-95 - Hidden Platform]

2. What do you conclude, regarding the behavior of the two types of mice, when the platform was hidden?
The wild-type mice took a shorter route to the hidden platform. This suggests that the PSD-95 mice may have impaired memory of the platform location.

3. Examine the graph below. What do you conclude, regarding the behavior of the two types of mice, when the platform was visible?
The PSD-95 mice were impaired at finding the visible platform. This shows that even when they can see the platform the PSD-95 mice take a longer route toward its location.
4. In Part 1, we learned that although sap102 mice have impairments in finding the hidden platform, they are not impaired in finding a visible platform. Using the above results, what do you conclude about the differences between the sap102 and PSD-95 knockout mice in terms of learning?

The PSD-95 mice are more impaired. This could be because they are severely learning impaired in that they have difficulty in locating even a visible platform. However, these results are also consistent with the hypothesis that the PSD-95 mice may have impairment other than in learning. For example, they may not have been able to coordinate their swimming.

5. Access the COGNITION section of Learning & Memory and again click on sap102 Swimming Mice (#898). In the related items, click on sap102 - Sanger Institute Research (#1403). Read the press release from the Wellcome Trust Sanger Institute and answer the following questions.

a. According to the article, what did investigators conclude when they compared the sap102 mice and wild-type mice?

Mice lacking the sap102 gene do poorly on learning tasks designed to test their ability to learn spatial information. They used an inefficient learning strategy and did not perform as well as wild-type mice in the learning experiment.
b. Was this conclusion similar to your own? Explain.
   Yes, the sap102 mice did not locate the platform as well as the wild-type mice.

c. Why do the investigators believe that genetic change in these sap102 mice can be overcome?
   The mice got better at finding the platform through repeated training. They benefit from the “extra lessons” or practice although they continued to use an inefficient strategy.

d. What surprising data resulted when the mice were tested in a different kind of learning task and not one that required spatial skills?
   The sap102 mutants were quicker than wild type animals. They again used different strategies but in this case the strategy gave above normal levels of performance.

e. How does Dr. Grant compare behavioral changes observed in mice to children with Asperger syndrome, a type of autism?
   These children are like the sap102 mutants. They often do especially well on some psychological tests because they are able to use mental strategies that other people cannot.

f. What is the proposed explanation of his findings?
   The proposal is that there is a biochemical foundation for this observation. The SAP102 protein binds to several other proteins that have been associated with autism.

6. Why did the scientists choose the sap102 and PSD-95 genes as the ones they chose to knockout and study?
   Both of these genes are expressed in the synapse and are associated with learning and memory.
Genes for Memory Assessment Items – Answer Sheet

1. Answer: c (Adapted from Achievement Test Form K-3JAC2, May 1988)


3. Answer: d (Adapted from the August 2007, New York State Regents Exam)

4. Answer: b (Adapted from the January 2008, New York State Regents Exam)

5. Answer: c (Adapted from the June 2007, New York State Regents Exam)

6. Allow a maximum of 3 credits, allocated as follows:

   a. Allow a maximum of 2 credits, 1 credit for each of two ways this knowledge has improved medicine and health care for humans.

      Acceptable responses include, but are not limited to:

      i) gene tests to diagnose disease
      ii) gene therapy
      iii) genetic engineering to produce hormones
      iv) understand causes of inherited disease
      v) prevent disease

   b. Allow 1 credit for identifying one specific concern that could result from the application of this knowledge. Acceptable responses include, but are not limited to:

      i) screening for genetic diseases may limit insurance coverage
      ii) gene therapy could result in overpopulation
      iii) may lead to discrimination