

# **Barbara McClintock**

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# Barbara McClintock Geneticist 1902-1992



Unit developed by April L. Gardner University of Northern Colorado, Greeley, Colorado

## Barbara McClintock's childhood

Barbara McClintock was born on June 16, 1902, to Sara and Thomas McClintock. They had four children within eight years and Sara's privileged background did little to prepare her for raising a family. Perhaps because her mother was so stressed by her growing family, Barbara, the third child, learned to entertain herself almost from infancy. This characteristic was so strong that her parents renamed her when she was only four months old. She had been named Eleanor, but her parents decided that "Barbara" was a more appropriate name for a child who showed as much strength and independence as she did.

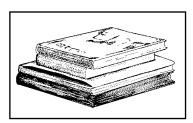
When Barbara's younger brother was born, the strain of raising so many young children became too much for Sara. Barbara was sent to live for a time with her aunt and uncle in Massachusetts. Her uncle was a fish dealer and Barbara enjoyed going with him to sell fish in the country. Her uncle bought a truck and Barbara believes her interest in motors came from watching him struggle with the constant breakdowns of his truck. When Barbara was only five years old, she asked for and received a set of tools.

Although Barbara was never close to her mother, both parents supported any of their children's interests. The McClintocks believed school was only a small part of growing up. Thomas told school officials that his children were not to be given homework — six hours of school was more than enough. When Barbara became interested in ice skating, her parents bought her the best skates and skating outfit they could afford. Every good day Barbara went skating, rather than to school.

## **Discovering science and pursuing an education**

In high school Barbara discovered science and the joy of problem solving. She decided to pursue science in college. Each of the McClintock children's individuality had been supported and encouraged — at least until adolescence. Then Barbara's mother became concerned that her children fit into adult society. By this time World War I had begun and Thomas was serving overseas as a military surgeon. Career guidance for their children was left to Sara. Barbara's older sisters followed their mother's advice that college would make them less likely to marry. They experimented with careers in music and acting and later married.

When it came to Barbara and Tom, her younger brother, Sara's influence was unsuccessful. Tom, like his grandfather, ran off to sea in his teens. Barbara was determined to go to Cornell University in New York. In addition to her mother's objections, however, there was little money



to support her venture. Barbara graduated from high school early and began working at an employment agency. After work, she went to the library to study on her own. When Thomas returned from the war, he apparently convinced Sara to support Barbara's continued education. Barbara enrolled in Cornell University in 1919.

From the beginning, Barbara loved college. She loved the lectures, especially in science, and was delighted at the opportunity to meet

a variety of people. She was quite popular and was elected president of the women's freshmen class. She also dated quite a bit during her first few years of college but soon realized that those emotional attachments could not last for her. She said, "There was not that strong necessity for a personal attachment to anybody. I just didn't feel it. And I could never understand marriage. I really do not even now....I never went through the experience of requiring it."

#### A career as a research scientist

Although marriage was most certainly not Barbara's goal, neither was a career. She simply lived for the joy of doing what she liked. She says that not until her mid-30s did she suddenly

realize that what she had was a woman's career as a research scientist. By the time of her official graduation from Cornell, she was working with Lester Sharp in the botany department. Since the genetics department would not take women graduate students, Barbara pursued graduate studies with Sharp in the botany department.

It was then that Barbara began her lifelong work with maize. Using a new staining technique, she was able to identify the individual chromosomes of the corn plant by their length, shapes, and patterns. In 1927, at age 25, Barbara received a Ph.D. in botany. She remained at Cornell as an instructor, intent on pursuing her research.

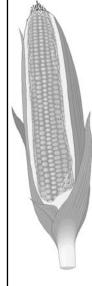
During the years from 1927 to 1931, Dr. McClintock worked with a motivated group of young scientists at Cornell. They spent many hours discussing the problems of maize genetics. In 1931, Dr. McClintock and a graduate student named Harriet Creighton published a cornerstone paper on the chromosomal basis of genetics. After her money at Cornell ran out, Dr. McClintock received a fellowship for continued research. This allowed her to visit and work with her colleagues in various parts of the country.

## What obstacles did Dr. McClintock face?

In 1933, Dr. McClintock received a Guggenheim Fellowship to go to Germany. Although this was an exciting opportunity, pre-World War II Germany was a grim experience. She returned very depressed and without a job. Jobs for research scientists during the Depression were almost nonexistent, especially for women. Dr. McClintock's former employer at Cornell explained her situation to the eminent geneticist T. H. Morgan. Morgan appealed to the Rockefeller Foundation to support her continued research. While he acknowledged her genius, he also spoke of her "personality difficulties," saying, "...she is sore at the world because of her conviction that she would have a much freer scientific opportunity if she were a man."

Dr. McClintock's friend and supporter, Lewis Stadler, at the University of Missouri in Columbia, was eager to have her as a colleague at the genetics center he was building. He persuaded the administration to offer her a position as assistant professor in 1936. Dr. McClintock accepted that position and spent the next five years in Missouri. She continued her very successful research program, but, when it became clear that she would not be promoted and probably would lose her position when Stadler retired, she resigned. She was disenchanted with university life: "It just meant that there was no hope for a maverick like me to ever be at a university."

In 1942, she was offered a one-year position at the Carnegie Institute at Cold Spring Harbor in New York. The position later became permanent. Although it would appear to be the perfect situation for Dr. McClintock — freedom to pursue her research with no teaching duties or administrative hassles — she was unsure of it for some time. Although Cold Spring Harbor buzzed with activity and excitement during the summer months, few people remained for the long, cold winter. Although Dr. McClintock worked alone in her research, she had not worked in intellectual isolation. She wanted to discuss ideas and strategies with research scientists in



her field. Nevertheless, she accepted the position and remained there for the rest of her life.

## Maize genetics and jumping genes

During the next decade Dr. McClintock applied herself to a unique phenomenon in maize. It appeared that certain regions of a chromosome moved, or *transposed*, to other positions.



When this happened, there was a corresponding change in pigment (color) production in the corn. The interpretation of her data was very complicated and Dr. McClintock, who now had few people with whom she could discuss her work, was concerned that it would not be understood.

In 1951, she presented a paper on transposition in maize chromosomes at the Cold Spring Harbor Symposium. As she feared, few scientists understood her work. However, she had not anticipated that her work would be rejected. This bitter disappointment led her even further into intellectual and professional isolation. Although her work was later vindicated, she never again presented a lecture at Cold Spring Harbor.

Thirty years after Dr. McClintock's pioneering work with maize, the transposition phenomenon was noticed in bacteria. In the mid-1970s, microbial geneticists noted a unique class of mutations. These mutations reverted, or mutated back to "normal," at a much higher frequency than would be expected. Further studies revealed that significant amounts of DNA had been added, or inserted, at the site of mutation. When the mutation reverted, the inserted DNA was removed. The inserted DNA is

often called a "jumping gene" because of its ability to "jump" into random regions of a chromosome and later "jump" back out. The inserted DNA caused genes near the site of the insertion to turn "on" or "off" — exactly the phenomenon Barbara McClintock had first noticed thirty years earlier.

These "jumping genes" are called *transposons*, borrowing from Dr. McClintock's own terminology. Transposons have now been found in every organism studied for them, including bacteria, maize, fruit flies, and yeast. They are believed to be a universal way in which genes are rearranged. In recognition of her pioneering work, Barbara McClintock was awarded the Nobel Prize in 1983. She continued her research at Cold Spring Harbor until her death in 1992 at the age of 89.

## SUGGESTIONS FOR TEACHERS ACTIVITY #1: What Is a Transposon? ACTIVITY #2: What Do You Know About DNA Structure? ACTIVITY #3: Thinking About Transposons

#### Purpose

To recognize some characteristics of transposons and to learn about the effects of transposons on gene expression.

#### Objectives

- 1) To explain what transposons are and typical characteristics of transposons.
- 2) To explain how transposons can be detected in genomes.
- 3) To note and discuss the consequences of transposition events.

#### Materials

Activity #1

- copies of "DNA Sequences" on page 318 (1 per student or student group)
- colored pencils or crayons (optional)

#### Activity #2

• 12 paper clips in each of 4 different colors for each group of students

#### Activity #3

• reference materials (several on transposons are listed at the end of this module in "References and Resources")

#### **Before You Begin**

Activity #1

- 1) This activity is most appropriate for an advanced or honors biology class. It assumes that students are familiar with genetics concepts such as DNA structure and base-pairing, chromosomes, genes, and crossing over and that they have a general understanding of gene expression.
- Students will need some background about transposons. Some information is provided in Resource Sheet #1, "Transposons," on pages 315-316; see "References and Resources" for further information.
- 3) Students should work individually or in groups of two to four for this activity.
- 4) Make copies of "DNA Sequences" on page

318 to give to students/groups.

- 5) Explain to students that the sequence given shows only the ends of a possible transposon and that the entire internal sequence is not given, since transposons are typically hundreds to thousands of base pairs long. (These sequences are "made up," but are so short that not even an entire DTR is shown; only ITRs can be found). Students may find it helpful to "color code" the bases to help them identify inverted repeat sequences.
- 6) As they continue working, tell students that ITRs must be at least five base pairs long. (Several of the sequences include three- or four-base inverted repeats; those do not count as transposon features.)
- 7) See "Activity #1: Key" on page 319.

#### Activity #2

- 1) Students should work in groups of two to four people for this activity.
- 2) Students will discover and prepare paper clip models of the structures explained in Resource Sheet #2, "DNA," on page 317.
- 3) See "Activity #2: Answers to Discussion Questions" on page 320.

#### Activity #3

1) This is a discussion activity for the whole class or student groups. See "Activity #3: Answers to Discussion Questions" on page 320.

#### **Safety Considerations**

None.

#### **Questions to Ask**

- See questions in student activity pages.
- How can you tell when a mutation has occurred? What kinds of things could have happened to the DNA when a mutation occurs?

Activity #1

• Why is it important to consider the polarity

(3'/5' orientation) of the DNA strands when looking for ITRs?

#### Activity #2

• What part of the transposon does the "stem" region represent?

#### Activity #3

- Can bacteria that have normal *gal* genes use galactose as a food source? Why/why not? How about those with a mutant *gal* gene?
- How could "superbugs," bacteria that are resistant to all antibiotics used to treat the infections they cause, have come about?

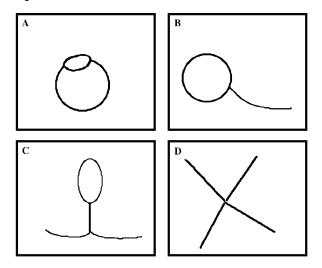
#### Where to Go From Here

- Have students read Evelyn Fox Keller's biography of Barbara McClintock (see "References and Resources") and report on it. Discuss the following questions: What was unique about the way Dr. McClintock approached research problems? What barriers did she face as a woman in science? What things do you most admire about her? What things do you least admire?
- Study other review articles about transposons. Several such references are included in "References and Resources."
- If you live near a college or university, call the biology, chemistry, or biochemistry department. They should have a list of faculty members and a synopsis of their research programs. Search among the list for a woman who is doing work with transposons or other molecular genetics problems. Invite her to be a guest lecturer in your class. Students could generate a list of questions to ask her about her work. All students will enjoy this, and your female students may discover that science is a career for someone like themselves.
- If there is no university nearby, check local agricultural, pharmaceutical, or similar industries, especially if they include a research division. Again, ask for the name of a woman on staff who is working in molecular genetics and invite her to speak to your class.
- If neither of these options is available to you, your class could write to a biology department at the nearest university to dis-

cover the types of research programs in their biology department.

#### **Ideas for Assessment**

- Suppose you are examining a pigmentforming trait in a species of bacteria. Normal ("wild type") bacteria form a pink pigment when they grow in colonies. Mutant bacteria are unable to form this pigment and produce creamy-white colonies. What phenomena would you expect to observe if the gene for producing this pigment is part of a transposon? Explain why.
- Examine the representations of electron micrographs of various DNA molecules in the diagram below. A thin line represents single-stranded DNA and a thick line represents double-stranded DNA. Which of the pictures shows how a segment of DNA that contains a transposon would appear? Explain.



• In addition, some of the suggestions listed in "Where to Go From Here" may be suitable for project-type assessments for students working individually or in teams.

#### **References and Resources**

✓ About Barbara McClintock:

Keller, E. F. (1983). *A Feeling for the Organism*. New York: W. H. Freeman and Company.

#### ✓ About women in science:

Herzenberg, C. (1986). *Women Scientists from Antiquity to the Present: An Index.* West Cornwall, CT: Locust Hill Press. O'Hern, E. M. (1985). *Profiles of Pioneer Women Scientists.* Washington, DC: Acropolis Books.

Rossiter, M. W. (1982). *Women Scientists in America: Struggles and Strategies to 1940.* Baltimore, MD: The Johns Hopkins University Press.

#### ✓ On transposons:

Berg, D., & Howe, M. (eds). (1989). *Mobile DNA*. Washington, DC: American Society of Microbiology.

Caldwell, M. (1994). Prokaryotes at the gate. *Discover, 15 (8)*, p. 45-50. (Note: This article does not discuss transposons specifically; however, it does describe how bacteria have developed resistance to many antibiotics over the last several decades, a phenomenon in part related to the ability of transposons to insert themselves into unrelated DNA sequences.)

Cohen, S. N., & Shapiro, J. A. (1980). Transposable genetic elements. *Scientific American*, 242, p. 40-49.

Doring, H. P., & Starlinger, P. (1984). Barbara McClintock's controlling elements: Now at the DNA level. *Cell*, *39*, p. 253-59.

Fedoroff, N. V. (1984). Transposable genetic elements in maize. *Scientific American, 250*, p. 84-98.

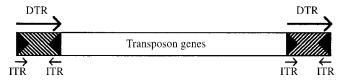
#### ✓ Photo credit:

Photos on pages 307 and 311 courtesy of Cold Spring Harbor Laboratory Archives, Cold Spring Harbor, NY.

## Resource Sheet #1 Transposons

*Transposons* are segments of DNA that are capable of moving, or transposing, from one region in a chromosome to another. Unlike previously studied genetic rearrangements, transposition depends neither on recombination between homologous DNA sequences nor on the enzymes that assist in that recombination. The so-called "illegitimate" recombination events of transposons occur at unrelated, apparently random sites.

More recent studies of transposons have revealed the following general structure:



Transposons that have been characterized in bacteria, yeast, fruit flies, and corn all have this same general structure. The transposon genes are flanked by direct terminal repeats (DTR) of several hundred bases — the DNA base sequence is repeated in the same order at either end of the transposon. (However, sometimes the terminal repeats are inverted with respect to their sequence.) The ends of the DTRs within the transposons are flanked by shorter inverted repeat sequences (ITRs) of 5 to 30 base pairs. For example, the left end may include the sequence:

#### 5' TAGGCTATGC 3' 3' ATCCGATACG 5'

The sequence of the right end would be reversed:

#### 5' GCATAGCCTA 3' 3' CGTATCGGAT 5'

An element is not transposable if these ITRs are not present. However, transposition also requires the activity of an enzyme known as a *transposase*. Most DTRs also include a gene for such a transposase enzyme. A gene for a protein that controls the transcription of the transposase gene (the repressor) is also usually present. A transposon which does not include a transposase gene will not "jump" unless another transposition requires that both a functional transposase gene and the ITRs are present.

Between the flanking DTRs, a transposon may include one or more genes for other proteins. For example, most bacterial transposons studied carry one or more genes which make the bacteria resistant to specific antibiotics. Some transposons include regulatory regions of DNA (e.g., promoters). These DNA sequences may cause a nearby chromosomal gene to be expressed, that is, they will "turn on" genes.

(continued)

#### (continued)

Transposons may "jump" in several different ways. Some transpose only by replication. In this case, the original transposon remains at its site in the genome, while the new transposon inserts into another genomic site. This may interrupt another gene, causing a phenotypic change. The organism now has an additional transposon in its genome. Other transposons are excised from their site in a particular chromosome and insert into another site in the same or a different chromosome. In some cases, excision leads to breakage of the original chromosome and loss of some genes, causing a phenotypic change. In other cases, excision restores the original (pre-transposon) DNA sequence, resulting in restoration of gene function and the corresponding phenotype.

*Drosophila melanogaster* (fruit fly) genomes have a family of similar transposable elements called *copia* (because they were originally detected as genes that produced a copious amount of RNA). These elements are 5,000 to 8,000 base pairs long, including 276-base pair DTRs. Within the DTRs are 17-base-pair ITRs. The white-apricot eye-color phenotype is due to the insertion of a copia transposon in the white gene. Yeast DNA contains *Ty* transposable elements, which are about 6,000 base pairs long and include 334-base-pair DTRs. Some yeast strains include as many as 35 copies of the *Ty* transposon. Finally, mammals contain a family of DNA sequences known as the *Alu* family. They are flanked by directly repeating sequences, a characteristic of transposons.

## Resource Sheet #2 DNA

- When DNA is heated, the hydrogen bonds which hold the two strands together are broken and the strands separate from each other.
- Typically, there are different proportions of purines and pyrimidines in the two complementary strands, which permit them to be isolated from each other using cesium chloride density gradient centrifugation. The strand with the greater proportion of purines is more dense and will form a band of DNA nearer the bottom of the centrifuge tube than the other strand.
- Each band of DNA can be removed separately, yielding purified DNA strands. If these strands are cooled, the bases will begin to form hydrogen bonds with bases within the same strand.
- Alternatively, DNA that has been heat denatured can be rapidly cooled so that base pairing can occur only within a DNA strand and not between two different strands. This is a dynamic equilibrium process; however, runs of five bases or more in a row that can hydrogen bond with each other tend to form a fairly stable structure.
- Inverted repeat sequences create such an opportunity. These DNA sequences form what are called "stem and loop" structures: the "stem" is the based-paired, double-strand region and the loop is the non-base-paired, single-strand region. Electron micrographs of such DNA sequences show these lollipop-like structures.

## Activity #1: DNA Sequences

1

5' A G T T C C A T C C T A A A A A G G G G G C C T A T G C T A C T A A T G A C T G A G 3' 3' G C A A G G T A G G A T T T T T C C C C G G G A T A C G A T G A T T A C T G A C T C 5'

<u>2</u>

5' T G T G C C A T G C T A C C A T G G C C A C C T T T G A T A C T A C T A A T T G G C A C A 3' 3' A C A C G G T A C G A T G G T A C C G G T G G A A A C T A T G A T G A T T A A C C G T G T 5'

<u>3</u>

5' A G A C T A C T A G A G A G C A C T A G A G G G C G C G A C T A G C G T C A G C T A G C T 3' T C T G A T G A T C T C T C G T G A T C T C C C G C G C T G A T C G C A G T C G A T C G A 5'

<u>4</u>

5' A G T C A G G T A T C G C G A A T T A A G G C C T T A C G A C C G C G A T A T A T T A A 3' 3' T C A G T C C A T A G C G C T T A A T T C C G G A A T G C T G G C G C T A T A T A A T 5'

<u>5</u>

5' A G T C G A T A C G T A C G A G A A G G G A C T A C C A G G C T A C T A C G C G T A G A 3' 3' T C A G C T A T G C A T G C T C T T C C C T G A T G G T C C G A T G A T G C G C A T C T 5'

## Activity #1: Key

| 1(No inverted repeats apparent)5'AGTTCCATCCT3'TCAAGGTAGGA3'TCAAGGTAGGA                       |
|--|
| <b>2</b><br>5' <u>TGTGCCA</u> TGCT ===================================                       |
| <b><u>3</u></b><br>5' <u>AGACTA</u> CTAGA ===================================                |
| <u>4</u> 5'GGTATCGCGAA3'CCATAGCGCTT  |
| 5(No inverted repeats apparent)5'AGTCGATACGT3'TCAGCTATGCA=================================== |

## Activity #2: Answers to Discussion Questions

- **1.** The structure has a stem and a loop; it looks like a lollipop.
- **2.** The loop region is the single-strand, non-base-paired region of the DNA sequence.
- **3.** Geneticists could heat the suspected DNA sequence to denature it into single strands, separate the strands, and allow the separated strands to cool and form base pairs. If there is a transposon, a stem and loop structure should be formed that could be observed with the help of an electron microscope and appropriate staining and preparation techniques. (Students may also suggest that they could wait to see if mutations occurred in the organism which contains the suspected DNA region. However, they should explain how they could differentiate a mutation due to a transposon insertion or deletion from a mutation due to a single base-pair change or deletion or insertion of just a few bases).

## Activity #3: Answers to Discussion Questions

- 1. Since the transposon is probably several thousand base pairs long, it is almost certain that the *gal* gene will no longer produce a functional enzyme for breaking down galactose. Thus the bacteria would no longer be able to use galactose as a food source it would be mutant for galactose use. (Microbiologists would call this bacteria a *galactose auxotroph*.)
- **2.** There could be several indications of this. One is that the ability to use galactose as a food source would most likely be restored in the bacteria because the transpose would excise precisely from the gene. A second indication might be that the bacteria would no longer be resistant to penicillin. However, if the transposon inserted itself into another gene in the same bacteria (which is not unlikely), it would still be resistant to penicillin. Another way to determine this would be if restriction markers on either side of the *gal* gene are known and the size of the DNA fragment produced in the "normal" (non-transposon-containing) bacteria is known. When a transposon inserts into the gene, that fragment size will increase considerably. If it "jumps" from the gene, the smaller fragment characteristic of the normal bacterial DNA should be observed.
- **3.** Corn that lost the ability to form pigment may have experienced a transposon insertion into a gene for pigment. The transposon insertion would result in production of a nonfunctional product, like the *gal* insertion in the bacteria above. Corn that regained the ability to form pigment may have had a transposon that excised itself from a pigment-production gene and inserted itself elsewhere in the genome. Thus pigment production was restored.
- **4.** If cattle are constantly taking in antibiotics in their feed, the bacteria that live in their stomachs and intestines and that are resistant to the antibiotics will survive and pass the resistance trait on to their offspring. Thus many bacteria that carry antibiotic-resistant genes are excreted in cattle feees. Because antibiotic-resistant genes are often part of bacterial transposons and because transposons can "jump" to DNA of other species, the antibiotic-resistant genes may be carried into other bacteria. Some cause diseases in cattle, humans, and other organisms. Infections caused by these bacteria would be difficult to treat, since the bacteria that causes them may become resistant to antibiotics typically used.

## ACTIVITY #1: What Is a Transposon?

**Questions to Answer** 

**1.** Examine the DNA sequences given below. Which one(s) do you suspect include transposons?

|   | С Т А А Т G А С Т G А 3'<br>G А Т Т А С Т G А С Т 5' |
|---|--|
| <b>2</b><br>5'TGTGCCATGCT =================================== |  |
| <u>3</u> 5'AGACTACTAGA   3'TCTGATGATCT                        |  |
| <u>4</u> 5'GGTATCGCGAA   3'CCATAGCGCTT                        |  |
|   | C T A C G C G T A G A 3'<br>G A T G C G C A T C T 5' |

**2.** Draw a box around the transposon(s) in the box above. Explain what characteristic makes you believe these represent transposons.

**3.** In the box above, underline the inverted repeats of the transposon(s).

## ACTIVITY #2: How is DNA Structured?

Work through the following "thought experiment" with your teammates:

- Suppose you take a solution of one of the transposon-containing DNA fragments from *Activity* #1 and heat it.
- You heat the solution enough that the hydrogen bonds holding the two DNA strands together break and the strands come apart.
- Next, you separate the "top" and "bottom" strands into separate solutions and then allow the separate solutions to cool down slowly.
- The single DNA strands will begin to *anneal*, or form hydrogen bonds, with complementary bases within each strand.

# Simulate the above process using colored paper clips to represent DNA bases:

- **1.** Use the paper clips and the code your teacher gives you to construct a chain for one of the strands of the transposon-containing DNA fragments from *Activity* #1. Use as many regular metal paper clips as you want (and have available) for the internal bases represented by "====." This represents a single DNA strand after the solution has been heated and the strands came apart.
- **2.** Now comes the tough part! As the solution cools down, the individual DNA strands will try to base pair within themselves. See if you can find regions where base pairing could occur within your DNA strand. At least five base pairs in a row must form in order to make a stable structure.
- **3.** Connect the region of base pairing using paper clips across the region.



#### **Questions to Answer**

**1.** How would you describe the structure that results? Draw it below:

- **2.** What part of the transposon does the "loop" region represent?
- **3.** How might geneticists be able to determine whether or not there is a transposon in a particular DNA fragment?



## **ACTIVITY #3: Thinking About Transposons**

