

Barbara McClintock and the discovery of jumping genes

For much of the 20th century, genes were considered to be stable entities arranged in an orderly linear pattern on chromosomes, like beads on a string (1). In the late 1940s, Barbara McClintock challenged existing concepts of what genes were capable of when she discovered that some genes could be mobile. Her studies of chromosome breakage in maize led her to discover a chromosome-breaking locus that could change its position within a chromosome. McClintock went on to discover other such mobile elements, now known as transposons. She also found that depending on where they inserted into a chromosome these mobile elements could reversibly alter the expression of other genes. She summarized her data on the first transposable elements she discovered, *Ac* and *Ds*, in a 1950 PNAS Classic Article, “The origin and behavior of mutable loci in maize” (2). Although their existence was accepted relatively soon after by maize geneticists, the widespread nature of mobile genetic elements and the implications of McClintock’s discovery took decades to be widely recognized.

By the 1970s the great strides made in molecular biology led to the discovery of transposons in other organisms, starting with viruses and bacteria. We now know that transposons constitute more than 65% of our genomes and approximately 85% of the maize genome. “Transposons are astonishingly abundant, comprising a majority of the DNA in some species,” said Nina Fedoroff, a professor at Penn State University and King Abdullah University of Science and Technology and author of the PNAS Classic Perspective on McClintock’s article, “McClintock’s challenge in the 21st century” (3). Confirmation that transposons were widespread among eukaryotes eventually led to the wider appreciation of her original discovery. McClintock received a number of prestigious awards, including the 1970 National Medal of Science and culminating in an unshared Nobel Prize in Physiology or Medicine in 1983. In her press statement about the Nobel Prize, McClintock noted, “It might seem unfair to reward a person for having so much pleasure, over the years, asking the maize plant to solve specific problems and then watching its responses” (4).

McClintock started asking questions of maize well before she identified transposition. Her early contributions to the field of maize cytogenetics—a combination of classic genetic techniques and microscopic examination of stained maize



Barbara McClintock at her laboratory desk, 1971.

Photo by Ross Meurer. Image courtesy of the Barbara McClintock Collection, Cold Spring Harbor Laboratory Library and Archives.

chromosomes—set the stage for her later discovery.

A Closer Look at Maize Chromosomes

Gregor Mendel’s work on inheritance in pea plants was rediscovered in the early 1900s, and many researchers began using maize and fruit flies to study genetics. Thomas Hunt Morgan’s group conducted many pioneering genetic studies in the fruit fly model during this period, and Morgan’s student Alfred Sturtevant published the first genetic map of a chromosome in 1913 (5). It was in this milieu that Barbara McClintock began her life-long study of maize. She would soon help extend to maize some of the classic genetic work done previously in fruit flies, confirming Morgan’s ideas about the role played by the chromosome in heredity.

After receiving her BSc from Cornell’s College of Agriculture in 1923, McClintock stayed on and completed a PhD in botany in 1927, then continued her research as an instructor at Cornell. During this time, McClintock developed staining techniques to visualize maize chromosomes, techniques that would later help her discover transposition. By 1929, she

had refined these techniques sufficiently to discriminate between each of the 10 maize chromosomes, allowing researchers to link genetic data to the behavior of chromosomes. McClintock also helped identify all of the maize linkage groups, genes that are inherited together because of their proximity on the same chromosome.

By 1932, McClintock had published nine articles on maize chromosomes, including studies of the centromere and the nucleolus, and a landmark 1931 PNAS article in which she and graduate student Harriet Creighton demonstrated genetic crossing-over at the chromosomal level and showed that genetic recombination involved the physical exchange of chromosome segments, a major contribution to the field of genetics (6). McClintock was elected to the National Academy of Sciences in 1944 at the age of 42, and in 1945 she was elected the first woman president of the Genetics Society of America. “Had she done no more,

See Classic Article “The origin and behavior of mutable loci in maize” on page 344 in issue 6 of volume 36.

See Classic Perspective on page 20200.

McClintock would have become a major figure in the history of genetics,” Fedoroff wrote of McClintock’s early work, in a book presented to McClintock on her 90th birthday (7). In 1941 she was appointed to a full-time research position at the Carnegie Institution of Washington’s Department of Genetics at Cold Spring Harbor, and it was here that she would discover transposition.

Chromosome Breakage and Transposons

At the Carnegie Institution, McClintock continued previous studies on the mechanisms of chromosome breakage and fusion in maize. She identified a particular chromosome breakage event that always occurred at the same locus on maize chromosome 9, which she named the “*Ds*” or “dissociation” locus. McClintock spent several years studying the *Ds* locus and discovered that *Ds* could change position within the chromosome, a finding that she described in the 1947–1948 Carnegie Yearbook. Additional experiments with the *Ds* locus revealed that chromosome breakage at this locus required a second dominant locus, which could also initiate its own transposition. McClintock named this locus *Activator*, or *Ac*, and found that *Ds* chromosome breakage could be activated by an *Ac* element at a different site or even on a different chromosome.

McClintock’s 1950 PNAS Classic Article summarized years of experimental data in support of *Ds* and *Ac* transposition (2). In the article, McClintock noted that *Ac* and *Ds* could transpose, that their insertion could lead to unstable mutations, and that the movement of transposons from the mutated loci could restore a gene’s function. McClintock followed up her Classic Article with a talk at the 1951 Cold Spring Harbor Symposium describing her discovery of transposition. When she finished, geneticist Evelyn Witkin recalls, there was dead silence—a foretaste of the initial reception her findings would receive (4).

Muted Reaction

McClintock described the initial reaction to her discovery as “puzzlement, even hostility” (8). Speaking of the scientific community at large she said “I was startled when I found they didn’t understand it; didn’t take it seriously” (4). The concept of transposition did not fit easily within the framework of genetics at the time. McClintock’s description of mutations that switched genes on and off was at odds with the existing idea that mutations permanently inactivated genes. Furthermore, decades of genetic mapping data had shown that genes were arranged linearly in fixed positions relative to each other, which made it hard for researchers to accept that genes could move within the genome.

McClintock did not let the scientific community’s reaction discourage her. “It didn’t bother me, I just knew I was right. Anybody who had had that evidence thrown at them with such abandon couldn’t help but come to the conclusions I did about it,” McClintock said (4). In the 1950s McClintock described a novel mobile element, *Suppressor-Mutator (Spm)*, and its complex regulation. She discovered that *Spm* could switch back and forth between an “inactive” form and an active form—what she called “changes of phase,” now known to be a result of methylation. Some forms of *Spm* cycled between inactive and active phases during development, whereas others showed specific patterns of expression and were only active in certain plant parts. These pioneering studies foreshadowed later work showing the importance of epigenetics, heritable changes not caused by changes to the DNA sequence, in development.

Delayed Recognition

By the mid-1960s, the steps leading from DNA transcription into mRNA and the translation of the RNA messenger into the amino acid sequences that make proteins were well established. The ge-

netic code was broken. Genes were no longer abstract concepts but discrete molecular entities that could be manipulated in a test tube. A little before McClintock’s formal retirement in 1967, mobile genetic elements were discovered in bacteriophages—viruses that infect bacteria (9). They would soon be discovered in bacteria themselves, and eventually in *Drosophila* as well (10, 11). The scientific community gradually recognized that transposons were not just peculiar to maize but were in fact widespread across species.

It was not until the 1980s that *Ac* and *Ds* transposons were molecularly cloned and isolated (12). The *Ac* element was found to be a small transposon that encoded a single protein, its transposase enzyme. *Ds* elements were often internally deleted derivatives of an *Ac* element, although they could also be considerably different from *Ac* (13).

In 1983, 35 years after her first published report of transposition and 33 years after the publication of her PNAS Classic Article, McClintock was awarded the Nobel Prize. “You just know sooner or later, it will come out in the wash, but you may have to wait some time,” McClintock said after receiving the prize (4).

McClintock remained active in science well after her retirement from active research. She remained at Cold Spring Harbor as a Distinguished Service Member of the Carnegie Institution of Washington (now the Carnegie Institution for Science) and attended the annual Cold Spring Harbor Symposia and seminars until she died in 1992 at the age of 90. McClintock’s own words best describe what sustained her life-long enthusiasm for research: “I just have been so interested in what I was doing and it’s been such a pleasure, such a deep pleasure, that I never thought of stopping... I’ve had a very, very, satisfying and interesting life.” (4).

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