Barbara McClintock on Defining the Unstable Genome

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Induction of Instability at Selected Loci in Maize
Barbara McClintock
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From examination of instability of genic action at a number of known loci in maize, it is concluded that mutations need not express changes in genes, but may be the result of changes affecting the control of genic action. B. McClintock 1953.

It is with this prescient statement that Barbara McClintock began the discussion of her classic 1953 *GENETICS* article describing how so-called "extragenic" components, now known as transposons, could alter the function of nearby genes. Precisely 30 years later she would be the sole winner of the Nobel Prize in Physiology or Medicine for her scrupulous studies of unexpected phenotypic changes she observed in maize, and the insight that led to her discovery of mobile genetic elements.

While studying the behavior of broken chromosome ends during mitosis, McClintock came across a site on maize chromosome 9 that was sensitive to breakage. Breakage depended on an element that she named Dissociation, or Ds. She identified a second, independent region that was necessary to induce breakage at Ds, the so-called Activator or Ac element. The 1953 article was a follow up to earlier work defining the behavior of the Ac-Ds system (McClintock 1950, 1951), and provided evidence that its effect on the expressivity of traits was generalizable to many loci.

The study focused on pigmentation of the aleurone, the outermost layer of the endosperm, which surrounds and nourishes the maize embryo. McClintock specifically screened for transposition of Ds to two genes, *A1* and *A2*, which are required for the synthesis of the reddish-purple pigment anthocyanin. McClintock constructed tester stocks homozygous for endosperm markers affecting color, morphology, and amylose starch production and located in a chromosome region susceptible to breakage. Using these, she was able to deduce that new Ds mutations behaved in much the same way as Ds insertions at other loci. Because she found similar changes at multiple loci, McClintock concluded that mechanisms controlling gene activity could be independent of the genes themselves. This conclusion predated the characterization of regulatory genes in eukaryotes by several decades, a remarkable achievement. It was made possible through the elegance of McClintock's genetic schemes, the meticulous documentation of results, and an unflinching confidence in her interpretation of their significance.

Ironically, McClintock's conclusions about chromosomal instability were published the same year as reports describing the structure of DNA (Franklin and Gosling 1953; Watson and Crick 1953; Wilkins *et al.* 1953). It would take 30 more years and significant technological advances before the molecular structures of Ac and Ds were finally determined in bold experiments performed by Nina Fedoroff (Fedoroff *et al.* 1983). DNA sequence analyses verified that Ac encodes a transposase, the enzyme that mediates transposition, whereas the Ds transposon is a defective version of Ac that comes in many forms (Fedoroff 1989).

McClintock's findings precipitated the search for mobile elements throughout nature. Over half of the human genome consists of transposons. Some are the basis for genomic instability and disease (Hancks and Kazazian 2016), and others, through their influence on gene regulation, are potential mediators of evolutionary change (van't Hof *et al.* 2016), or lie dormant as targets for future remobilization. Even now, with genomes fully sequenced and many more tools available to study them, our understanding of their dynamic nature and the impact of transposons on gene function is far from complete.

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Image of Barbara McClintock courtesy of Cold Spring Harbor Laboratory Archives.
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Barbara McClintock (center) pictured in 1989 with Maxine Singer (left) and Nina Fedoroff (right). McClintock hypothesized the existence of transposons, Fedoroff was the first to characterize them molecularly, and Singer identified transposons in the human genome. Photo courtesy of the Carnegie Institution for Science.

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