Barbara McClintock, a 21st Century Biologist

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"…we that are young
Shall never see so much, nor live so long."
(*King Lear*)

The Maize Genetics Group at Cornell - Early Days of 20th Century Biology

20th Century Biology

- Mechanism rather than vitalism
- Atomistic genotype-phenotype relationship (one gene-one enzyme); the Central Dogma of Molecular Biology
- Gradual evolution with accidental random changes to the genome
- "In the period following the 'rediscovery' of Mendel's work biologists have extended and developed the gene theory to the point where it now seems clear genes are the basic units of all living things. They are the master molecules that guide the development and direct the vital activities of men and amoebas." (Beadle, G.W. 1948. The genes of men and molds. *Sci. Amer*. 179(3), 30)

21st Century Biology

- Cellular control networks, signal transduction and checkpoints
- Systems biology, redundancy, robustness, and precision
- Genome evolution by internal natural genetic engineering systems
- “A goal for the future would be to determine the extent of knowledge the cell has of itself, and how it utilizes this knowledge in a “thoughtful” manner when challenged.” (McClintock, B. 1984. The Significance Of Responses Of The Genome To Challenge. Science 226: 792-801.)

What Enabled McClintock To Be So Far Ahead of Her Time?

- Witnessing mechanism-vitalism debates and the major developments of 20th Century biology; understanding the limitations of the "now explanation"
- Intimate knowledge of maize plants and their chromosomes
- Experience with X-ray induced chromosome rearrangements
- Detailed analysis of chromosome breakage and its consequences
- 25 years studying changes induced by transposable controlling elements

Ring Chromosomes and Breakage I

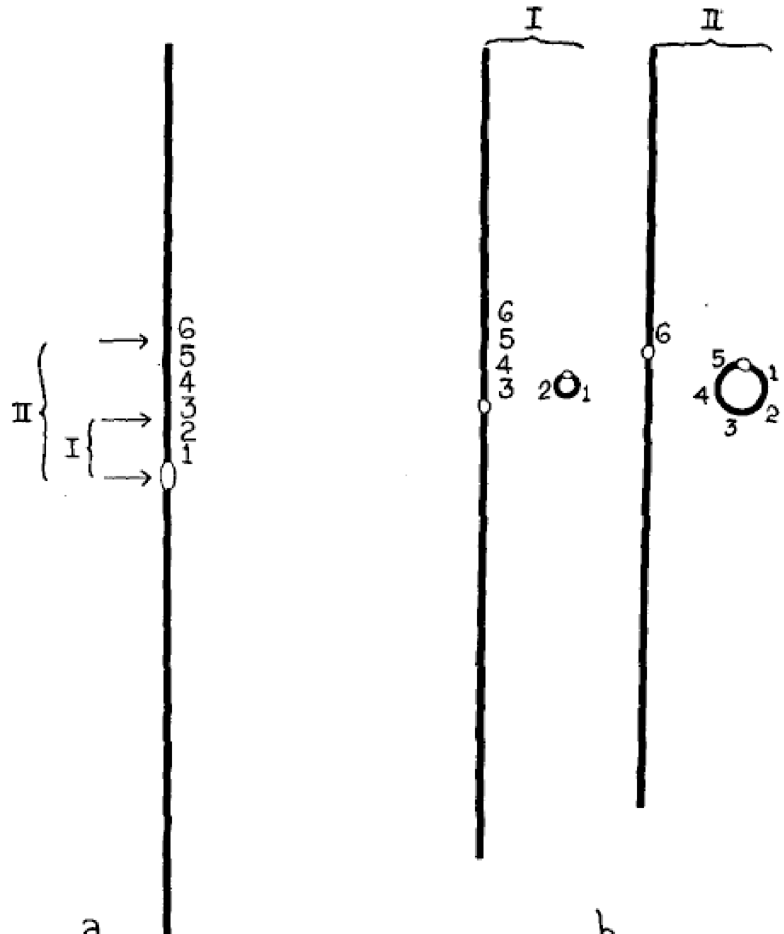
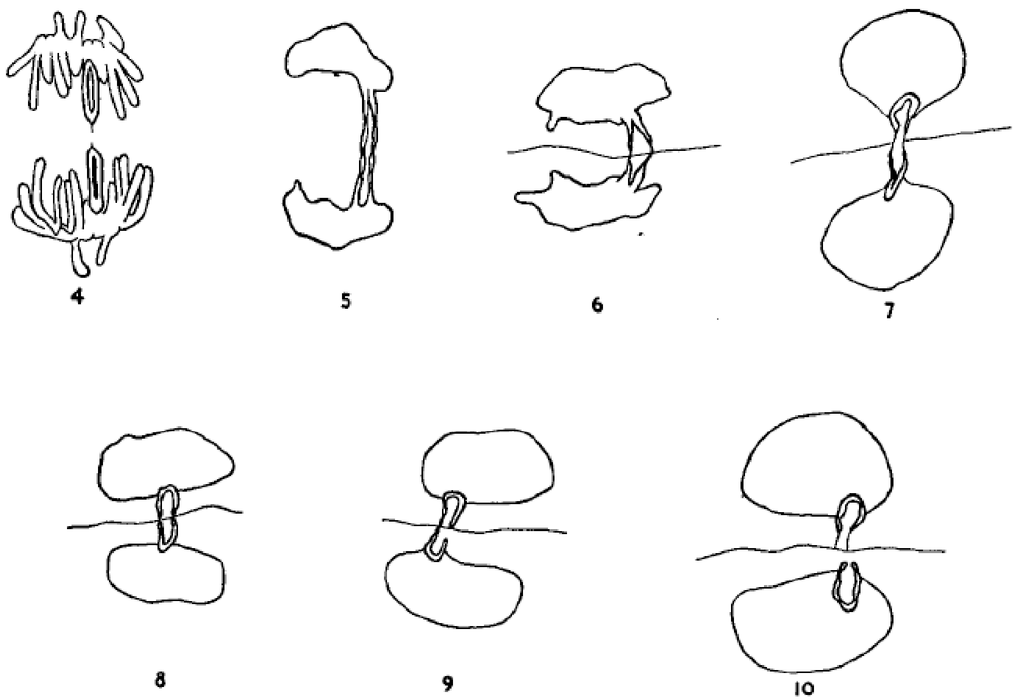
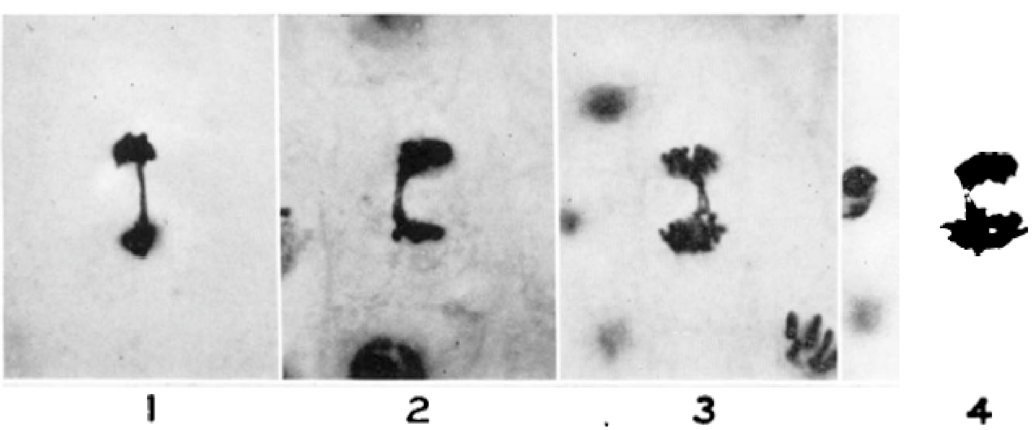


FIGURE 2.—a. Diagram of a normal chromosome V. The slightly bulging section represents the spindle fiber attachment region. The sets of arrows, I and II, point to the positions of breaks which gave rise to the two deficient rod chromosomes and their compensating ring chromosomes illustrated in I and II of b. The deficient rod and compensating ring chromosomes of I are referred to in the text as Def 1 and R 1 respectively, those of II as Def 2 and R 2 respectively

McClintock B. 1938. The production of homozygous deficient tissues with mutant characteristics by means of the aberrant mitotic behavior of ring-shaped chromosomes. Genetics 23: 315-376.



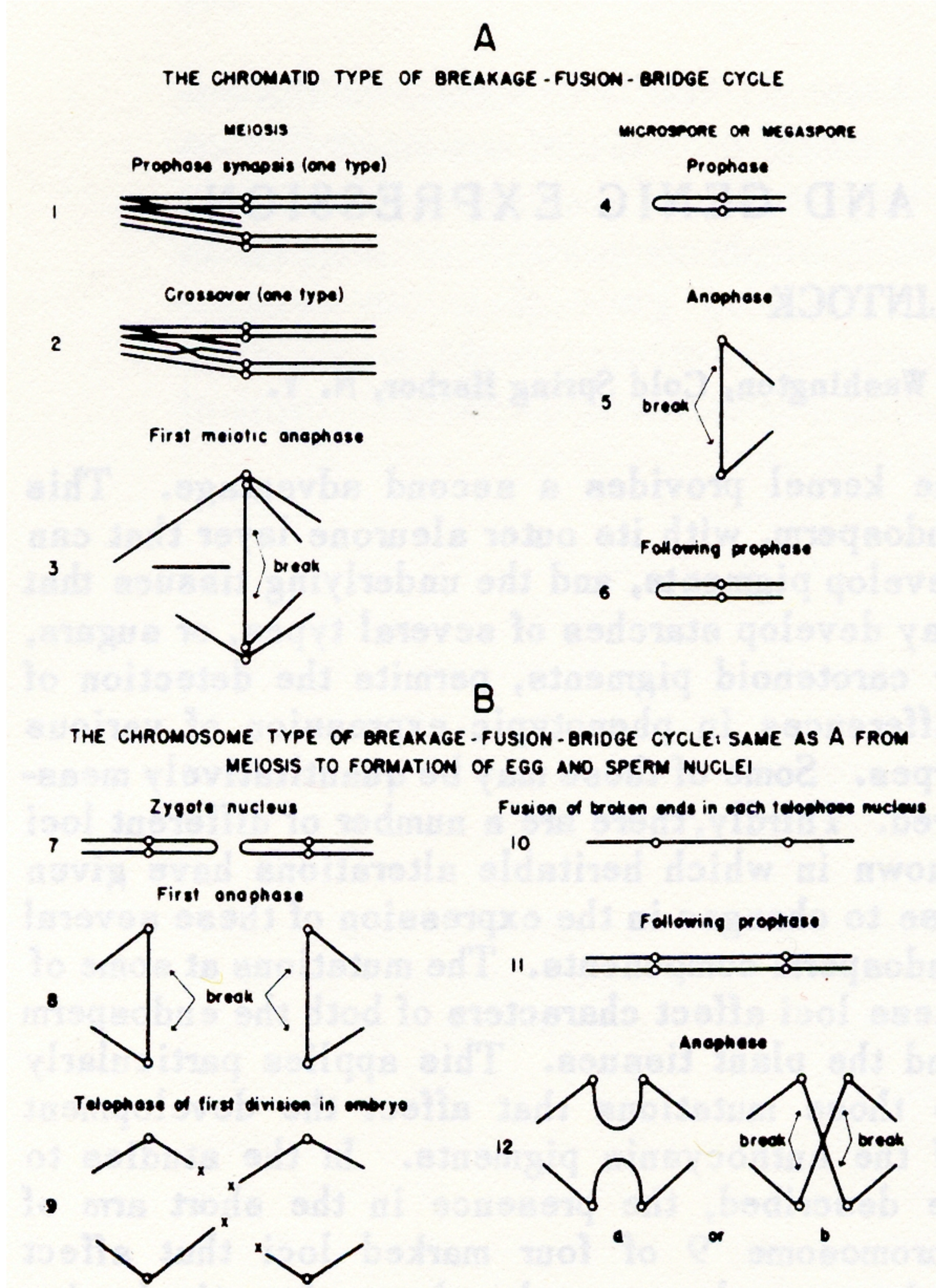
RING CHROMOSOMES IN MAIZE 325



Ring Chromosomes and Breakage II

McClintock B. 1938. The production of homozygous deficient tissues with mutant characteristics by means of the aberrant mitotic behavior of ring-shaped chromosomes. Genetics 23: 315-376.

Instigating Chromosome Breakage-Fusion-Bridge Cycles

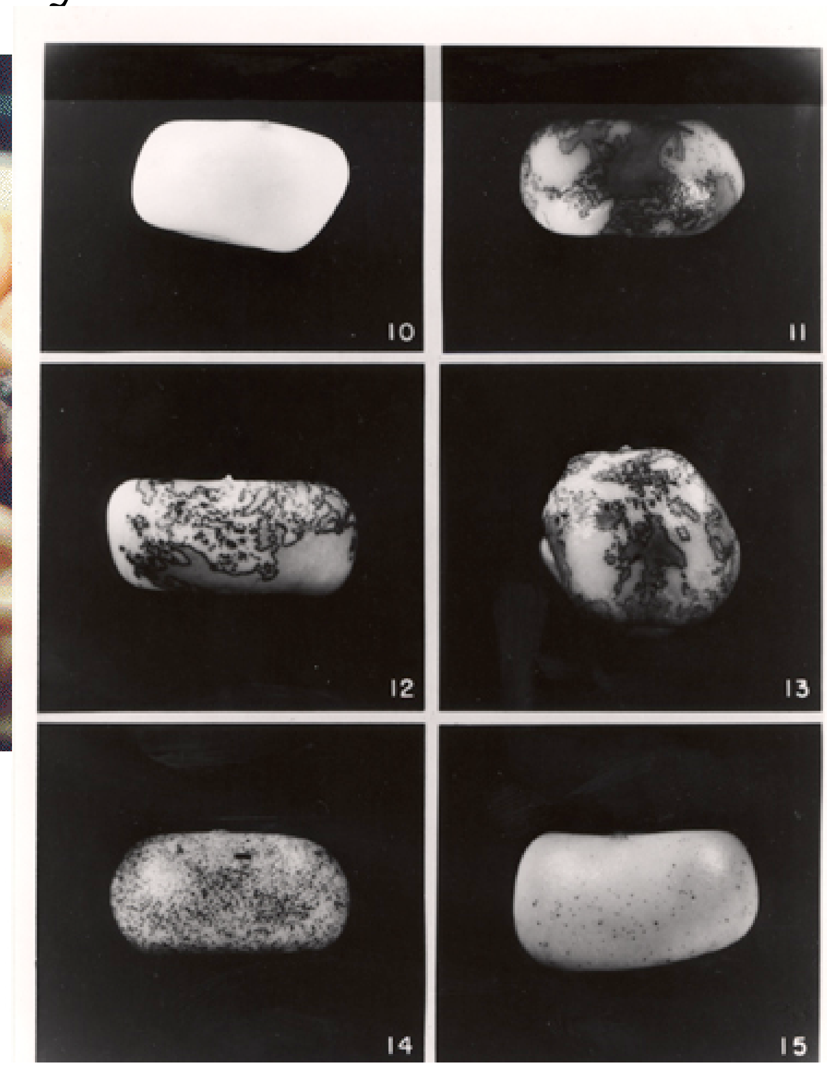


McClintock B.1951. Chromosome organization and genic expression. Cold Spring Harbor Symposia on Quantitative Biology 16: 13-47.)

The Significance of Chromosome Breakage and Fusion (NHEJ)

"The conclusion seems inescapable that cells are able to sense the presence in their nuclei of ruptured ends of chromosomes, and then to activate a mechanism that will bring together and then unite these ends, one with another. And this will occur regardless of the initial distance in a telophase nucleus that separated the ruptured ends. The ability of a cell to sense these broken ends, to direct them toward each other, and then to unite them so that the union of the two DNA strands is correctly oriented, is a particularly revealing example of the sensitivity of cells to all that is going on within them." (McClintock, B. 1984. The Significance Of Responses Of The Genome To Challenge. Science 226: 792-801.)

Unexpected Results of Chromosome Breakage ("Genome Shock"): Built-in Systems for Genome Restructuring, Combinatorial Control Regions, and Nuclear Regulatory Circuits



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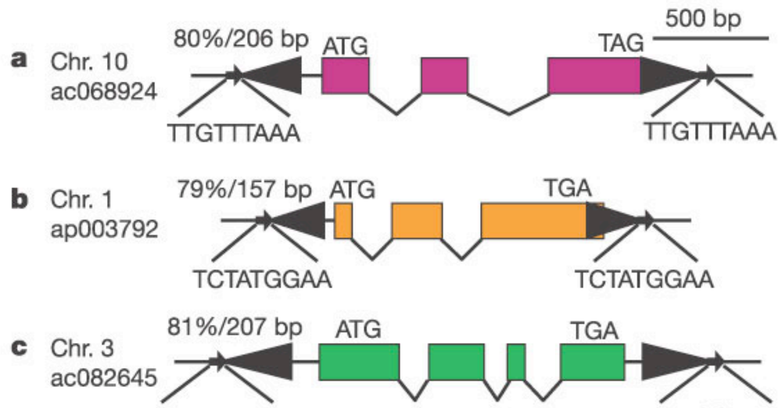
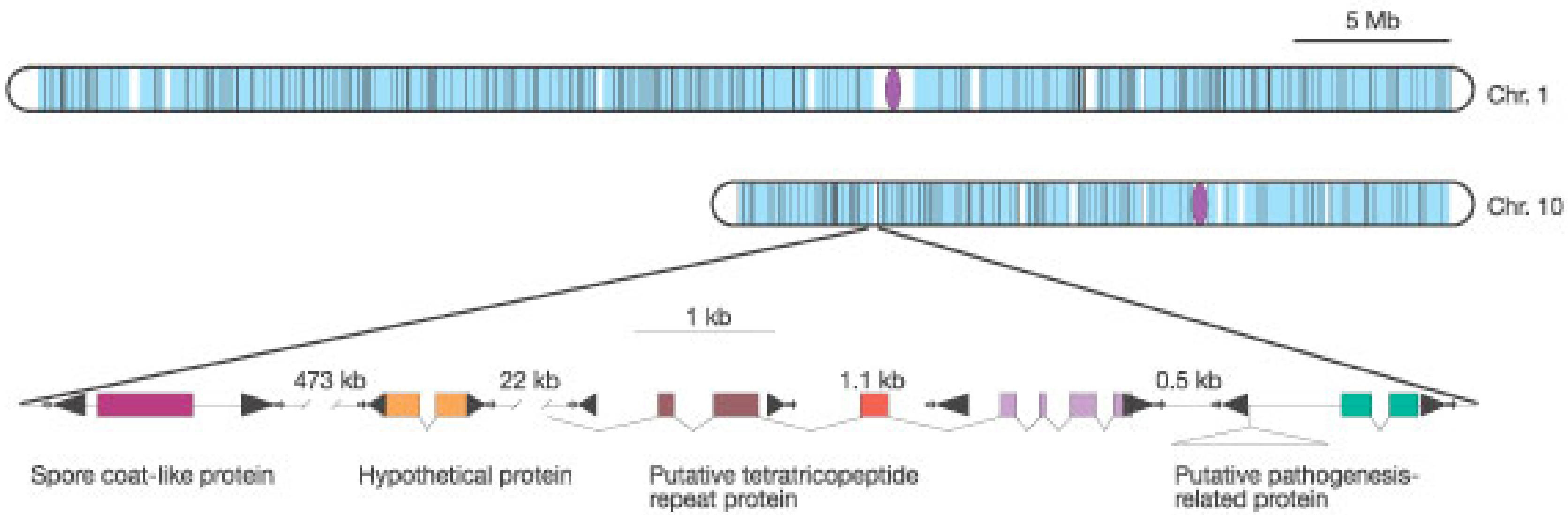
“Darwin has muddied our thinking about evolution” (Chicago, 1982)

“It was these various effects of an initial traumatic event that alerted me to anticipate unusual responses of a genome to various shocks it might receive, either produced by accidents occurring within the cell itself, or imposed from without, such as virus infections, species crosses, poisons of various sorts, or even altered surroundings such as those imposed by tissue culture. Time does not allow even a modest listing of known responses of genomes to stress that could or should be included in a discussion aimed at the significance of responses of genomes to challenge. The examples chosen illustrate the importance of stress in instigating genome modification by mobilizing available cell mechanisms that can restructure genomes, and in quite different ways. A few illustrations from nature are included because they support the conclusion that stress, and the genome’s reactions to it, may underlie many species formations.” (McClintock, B. 1984. The Significance Of Responses Of The Genome To Challenge. Science 226: 792-801.)

Natural genetic engineering of sequenced genomes - Pack-MULEs in the Rice Genome





Ning Jiang, Zhirong Bao, Xiaoyu Zhang, Sean R. Eddy and Susan R. Wessler. 2004. Pack-MULE transposable elements mediate gene evolution in plants. Nature 431, 569-573.

21st Century Research Agenda: Nuclear Reprogramming for Development

"In higher plants, each fertile flower has the equivalent of a "germline"in it. The flower makes the gametes and initiates embryo formation. In this regard, consider the many flowers that may be produced by a bush or a tree. Some system must operate to reprogram the genome in those cells of the flower that will produce the gametes and establish the zygote. This implies that the specific programming sequences, earlier initiated and required for flower production, must be "erased" in order to return the genome to its very early state. ... In these instances, however, the process of resetting is regulated, and the genome is not permanently restructured. This is not true for plants arising from many tissue cultures." (McClintock, B. 1984. The Significance Of Responses Of The Genome To Challenge. Science 226: 792-801.)