Transposable Elements
(or, Jumping Genes)
Barbara McClintock (1902-1992)

She and Marie Curie are the only sole female recipients of the Nobel Prize.

She discovered and described the principles of transposable elements in maize.
Barbara McClintock (1902-1992)

Her first contribution was built on the idea that genes were located on chromosomes. She took the ten linkage groups of maize and connected each with a specific chromosome. Her microscopic observations were so exact that she was able to observe recombination events and show that they corresponded with recombination events in the next generation of corn.
Barbara McClintock (1902-1992)

These careful observations gave rise to one of the first cornerstones of modern genetics:

**Genes have fixed positions on chromosomes.**
Well, mostly, maybe.
Barbara McClintock (1902-1992)

Dr. McClintock noticed some unusual characteristics in a strain of corn.

The plants showed streaks and spots of color, an indication that mutations had taken place in the developing body of the plant.

Interestingly, these plants contained a broken chromosome 9.
Characteristics of the Corn

The patches were arranged in a way that suggested that the rate of mutation was constant for each plant.

In other words, something must be “regulating” the rate of mutation in the pigment genes.

Hmm.
Characteristics of the Corn

In a few of the plants, she noticed another interesting phenomenon.
Here and there, small portions of the plant would show greatly increased or decreased rates of mutation.

Dr. McClintock concluded that these portions arose from a single cell in which the gene regulating the mutation rate had itself changed.
Dr. McClintock’s Conclusions

There must be two elements to the process:

1) An element that actually caused the mutation,
2) An additional element that controlled the activity of the first element.
The Pieces

1) An element that actually caused the mutation: The dissociator (Ds), located on the short arm of chromosome 9 (where the breaks occurred)

2) An additional element that controlled the activity of the first element: the activator (Ac)
Transposition

- The most important finding was that these elements sometimes appeared in other locations on the chromosome!

In fact, she developed convincing evidence that Ac could remove itself from one place on a chromosome and reinsert itself in a different place.
Transposition, 2nd example: the suppressor-mutator system

This involves a series of transposable elements often located near pigment genes that suppress their function, and produce a white kernel.

When the element moves, the pigment gene function is restored, producing a reddish splotch of color on the skin of the kernel.
Transposition

For the first time, McClintock had shown that genes did not occupy fixed positions on chromosomes.

She concluded that transposition could be a key events controlling development and growth of large organisms.

As so often happens with landmark observations, her work was almost completely disregarded as important for over 20 years.
Transposition in other systems

Bacteriophage DNA: inserts itself into a chromosome, then removes itself.

Antibiotic resistance in bacteria: Genes that confer antibiotic resistance reside on moveable genetic elements.

Antibody specificity in higher animals: The genes that allow formation of highly specific antibodies have a variable region that is “shuffled.”
Antibodies

The immune system is capable of producing an incredible variety of antibodies when confronted with foreign substance or antigen.

This is the key factor that defines the ability of the immune system to fight off disease, *even diseases to which it has never been exposed*.

The number of unique antibodies produced by the mammalian immune system: estimated 100,000 to 1,000,000.
Antibodies

Given what you’ve been taught so far, to generate the lower number, 100,000, you’d need 100,000 different genes, right?

In fact, the TOTAL number of genes estimated in the ENTIRE genome is only about 30,000.
In 1976, a Japanese researcher working at MIT demonstrated the importance of McClintock’s moveable DNA in mammals. Tonegawa demonstrated that the “mature” antibody gene of the adult does not exist in the embryo. In fact, embryonic cells contain hundreds of alternate antibody gene parts that must be moved together to assemble the mature, functional gene product.
In each of the millions of mature immune cells, there are variable regions on chromosome 14 in which bits and pieces are moved from place to place, each encoding slightly different functional genes.

The key is that the bits and pieces are selected at random. In effect, in each cell the “deck” of antibody part “cards” is shuffled in a different way.
Immuoglobulin Gene Shuffling

The result is that the millions of immune cells each encode a slightly different immunoglobulin, which will have a specific recognition site at the end. The sheer number of possibilities ensures the likelihood that virtually any foreign antigen will have an antibody that recognizes it.

Further, the immune system can be “educated” such that it will recognize repeat visitors and will mount a more vigorous and rapid response on subsequent interactions.
Genome Projects
The Human Genome Project

In 1990, the Department of Energy proposed the importance of understanding the biological effects of radiation, and spearheaded a massive, international project to sequence every base in the 3.1 billion base pair human genome. The plan was to accomplish this goal in 15 years.
The Human Genome Project Goals

1.) Identify the ~30,000 genes in human DNA
2.) Determine the sequences of the 3 billion bases of the human genome
3.) Develop databases to store and access this information
4.) Improve tools for data analysis
5.) Transfer related technologies to the private sector
6.) Address the ethical, legal and social issues that would arise from the project
The Human Genome Project

The project officially ended in 2003, two years ahead of schedule, with the entire genome sequenced. A working draft had been completed in 2000.

The cost: $3.8 billion over 13 years, including associated research projects in addition to direct sequencing.
The Human Genome Project

By licensing technologies to the private sector and awarding grants for innovative research, the project not only moved forward more rapidly, but also catalyzed the multibillion-dollar US biotechnology industry, fostered the development of new medical, industrial, environmental and agricultural applications.
International Cooperation

At least 18 countries have established genome research programs. Some of the larger programs are in Australia, Brazil, Canada, China, Denmark, European Union, France, Germany, Israel, Italy, Japan, Korea, Mexico, Netherlands, Russia, Sweden, United Kingdom, and the United States.
DNA Sequencing

DNA sequencing involves:

1) Isolation and purification of DNA from individuals
2) Chemical sequencing to establish the order of nucleotides
3) Arranging the DNA sequences into the proper order
Reducing Costs and Speeding Up Sequencing

Technological developments dramatically decreased DNA sequencing's cost while increasing its speed and efficiency. For example, it took 4 years for the international Human Genome Project to produce the first billion base pairs of sequence and less than 4 months to produce the second billion base pairs. In the month of January 2003, the DOE team sequenced 1.5 billion bases. The cost of sequencing has dropped dramatically since the project began and is still dropping rapidly.
Reducing Costs and Speeding Up Sequencing

![Graph showing decreasing cost and increasing number of bases sequenced over time.](image)

- **Cost per base (dollars)**
- **Quality bases sequenced (billions)**: 0, 2, 12, 16, 20
Source DNA

For the publicly funded HGP, human DNA was isolated from blood (female) and sperm (male) collected from a large number of donors.

For the work privately funded by Celera Genomics, DNA resources used for these studies came from anonymous donors of European, African, American (North, Central, South), and Asian ancestry.
Research Challenges

- Gene number, exact locations, and functions
- Gene regulation
- DNA sequence organization
- Chromosomal structure and organization
- Noncoding DNA types, amount, distribution, information content, and functions
- Coordination of gene expression, protein synthesis, and post-translational events
- Interaction of proteins in complex molecular machines
- Predicted vs experimentally determined gene function
Research Challenges

- Conservation among organisms
- Protein conservation (structure and function)
- Proteomes (total protein content and function) in organisms
- Correlation of SNPs (single-base DNA variations among individuals) with health and disease
- Disease-susceptibility prediction based on gene sequence variation
- Genes involved in complex traits and multigene diseases
- Complex systems biology including microbes useful for environmental restoration
- Developmental genetics, genomics
Other Genome Projects Underway or Completed

Agriculturally important species: chicken, cow (Bos taurus with Bos indicus planned), honeybee

Related organisms: mouse, rat, dog, chimpanzee, macaque, laboratory opossum, duckbilled platypus

Lower animals: Fruit fly, roundworm, sea squirt, sea urchin, planarian, puffer fish, red flour beetle

Single-celled species: *E. coli* and other bacteria, multiple fungi species.