

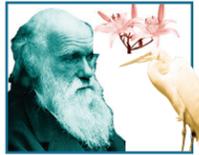


Cracking the Code of Life

Until the 19th Century most people, even such eminent scientists as Isaac Newton, believed that each new generation was a virtual replica of the parent generation—that within the parent was a tiny “preformed” version of the adult. No “seeds,” “codes,” or “hereditary material” were part of this early picture of inherited characteristics.

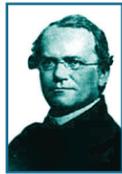
1859

Charles Darwin publishes *On The Origin of Species by Means of Natural Selection or The Preservation of Favoured Races in the Struggle for Life*. Although Darwin's landmark theory did not specify the means by which characteristics are inherited (because the mechanism of heredity had not been determined), his key premise was that evolution occurs through the selection of inherent and transmissible, rather than acquired, characteristics between individual members of a species.



1843–1868

Gregor Mendel, an Austrian monk now celebrated as “the father of genetics,” conducts his experiments breeding the garden pea. Mendel established two laws that anticipated modern genetic research. The *law of segregation* states that the “factors” (what we now call genes) that determine such traits as height and eye color come in pairs, and the pairs separate when sperm and egg cells reproduce in the process called *meiosis*. As a result, each offspring gets one form, or *allele*, of the pair from each parent, which explains why children exhibit traits of both their parents. Mendel's *law of independent assortment* states that the pairs of alleles separate independently of each other during meiosis. “My scientific labors have brought me a great deal of satisfaction,” Mendel wrote, “and I am convinced that before long the entire world will praise the result of these labors.” Mendel's work, however, was largely ignored for 30 years.

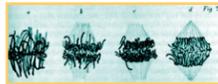


1869

Swiss physician **Frederick Miescher** isolates DNA from human white blood cells and the sperm of trout; he calls the substance “nuclein.”

1879

Walther Fleming, a German biologist, uses brightly colored dyes to help him observe long, thin threads in the nuclei of cells that appear to be dividing. These threads are later called *chromosomes*. In 1882, Fleming publishes a summary of the process, which he calls “mitosis.”



1883

Francis Galton of England, a cousin of Charles Darwin's, coins the word and helps popularize the notion of *eugenics*. Eugenics, the theory of improving human “stock” through “selective breeding,” ultimately leads to Nazi racial cleansing and forced sterilization laws in the United States, as well as modern prenatal testing and genetic counseling.

1900

Three European scientists, **Hugo de Vries**, **Karl Correns**, and **Erich von Tschermak** independently publish papers that confirm Mendel's Laws of Inheritance, giving Mendel's work its long-delayed recognition.

1902

Two cytologists, the American **Walter Sutton** and the German **Theodor Boveri**, reveal that genes are found on chromosomes, and that chromosomes come in pairs that are similar to each other.



1910

Thomas Hunt Morgan and his team at Columbia University, and later CalTech, begin studying hereditary traits in *Drosophila* fruit flies. Their research reveals how genes are arranged in a row on chromosomes, as well as a variety of other genetic phenomena including sex-linked traits (traits that are passed only to one sex and not the other), the effect of a gene's location on

its functioning, the existence of multiple alleles (gene forms), and chromosomal inversion (the reversal of a sequence of genes along part of a chromosome). Morgan's experiments also lead to *Drosophila's* unusual position as one of the best-studied organisms and most useful tools in genetic research to this day.

1926

Hermann Müller, a former member of Morgan's team, shows that exposure to X-rays can cause genetic mutations in *Drosophila*.

1941

While experimenting on bread mold, **George Beadle** and **Edward Tatum** show that genes regulate specific chemical events. They suggest that each gene directs the formation of one particular enzyme.

1944

Barbara McClintock, while studying the inheritance of color and pigment distribution in corn kernels at the Carnegie Institution Department of Genetics in Cold Spring Harbor, New York, discovers that genes can move from place to place on a chromosome and even jump from one chromosome to another. McClintock's discovery of *transposable*, or movable, genetic elements was greeted with initial skepticism but later recognized when, at age 81, she was awarded a 1983 Nobel Prize. Scientists now believe transposons may be linked to some genetic disorders such as hemophilia, leukemia, and breast cancer. They also believe that transposons may have played critical roles in human evolution.



Oswald Avery, **Colin MacLeod**, and **Maclyn McCarty** of the Rockefeller Institute show that a molecule in the cell nucleus called deoxyribonucleic acid, or DNA—and not proteins, as previously believed—contains the factors that determine heredity in most organisms.

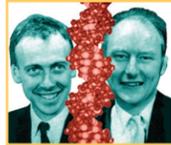
1952

Rosalind Franklin, a British chemist, uses a technique called X-ray diffraction to capture the first high-quality images of the DNA molecule.



1953

Franklin's colleague **Maurice Wilkins** shows the pictures to **James Watson**, an American zoologist, who has been working with **Francis Crick**, a British biophysicist, on the structure of the DNA molecule. After several false starts, Watson and Crick conclude that DNA is a *double helix*—two spiral strands that wind around each other like a twisted rope ladder.



1958

François Jacob and **Jacques Monod** predict the existence of *messenger RNA*, the molecule that carries information from the DNA in the cell's nucleus to the protein factories (the *ribsomes*) in the cytoplasm.

1962

Crick, **Watson**, and **Wilkins** share the Nobel Prize in medicine and physiology for the discovery that the DNA molecule has a double-helical structure. Rosalind Franklin, whose images of DNA helped lead to the discovery, died of cancer in 1958 and, under Nobel rules, was not eligible for the prize.

1966

Marshall Nirenberg and colleagues crack the *genetic code* by demonstrating that a specific sequence of three nucleotide bases (a *codon*, or nucleotide “word”) codes for, or specifies, each of the 20-some amino acids used by the cell to produce proteins.



Robert William Holley, an American biochemist, shows that *transfer RNA* is involved in the assembly of amino acids into proteins. In the process, Holley becomes the first person to determine the complete sequence of a nucleic acid.

1969

Scientists at **Harvard Medical School** are the first to isolate a single gene, a segment of bacterial DNA that assists in sugar metabolism.

Hamilton Smith discovers the first *restriction enzyme*, a kind of molecular “scissors” that cuts DNA at specific points, in *Haemophilus influenzae* bacteria.

1972

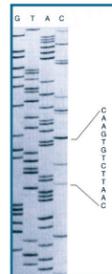
Paul Berg and colleagues combine DNA from different species and insert it into a host cell, creating the first *recombinant DNA* molecules.

1973

Stanley Cohen and **Herbert Boyer** “cut and paste” DNA from a frog into an *E. coli* cell where it is reproduced, marking the dawn of genetic engineering.

1974–1975

Allan Maxam and **Walter Gilbert** of Harvard University develop the method of DNA sequencing bearing their name. The Maxam-Gilbert method uses phosphorous labeling and four separate chemical reactions to determine the sequence of DNA nucleotides. At the same time, **Frederick Sanger** and colleagues at the Laboratory of Molecular Biology, Cambridge, England, develop the “chain termination” method of DNA sequencing, which becomes, with slight modifications, the standard sequencing method used today.



1975

Concerned about possible risks from genetic engineering, 150 molecular biologists meet at the **Asilomar Conference Center** in Pacific Grove, California to discuss ways to control genetic research until its hazards are better understood. Their recommendations lead to years of government supervision of recombinant DNA research until it is determined to be safe.

Robert Holley determines the complete sequence of the RNA of a bacteriophage called MS2 (a phage is a parasitic virus that attacks bacteria).



1976

Genentech, the first company devoted to genetic engineering, is founded in South San Francisco by **Herbert Boyer** and **Robert Swanson**.

1977

Frederick Sanger in England determines the entire sequence of the bacteriophage OX174.

1978

The gene for human insulin is cloned.

1980

Martin Cline and fellow scientists successfully transfer functional genes from one animal to another, creating the first transgenic mouse.

A human gene, coding for the protein *interferon*, is successfully introduced into and produced by bacteria.

After genetically engineering a bacterium capable of breaking down crude oil, **Ananda Chakrabarty** seeks to patent his creation under a provision of patent law providing patents for people who invent or discover any new and useful “manufacture” or “composition of matter.” A patent examiner and the Patent Office Board of Appeals reject the patent on the grounds that living things are not patentable. The decision, however, is reversed by the U.S. Supreme Court in a 5 to 4 decision. The Court rules that while natural laws, physical phenomena, abstract ideas, or newly discovered minerals are not patentable, a live artificially-engineered microorganism is.

1982



The **U.S. Food and Drug Administration** approves the first recombinant DNA medical product, bacterially produced human insulin.

The **National Flow Cytometry Resource (NFCR)** is established at Los Alamos National Laboratory in New Mexico to make state-of-the-art analytical instruments available to biomedical researchers.



1983

Kary Mullis and colleagues of the Cetus Corp., Emeryville, California invent *polymerase chain reaction* (PCR). This process, which allows the rapid reproduction of small samples of DNA, is applied within most facets of recombinant DNA technology, forensic analysis, and high-speed genome sequencing. Mullis received a 1993 Nobel Prize for his invention.



1984

A conference held by the **U.S. Department of Energy** (DOE) in Alta, Utah, discusses the possibility of using DNA research to detect tiny genetic mutations in the survivors of the Hiroshima and Nagasaki atomic bombs and their descendants. The conference sows the seeds for DOE's involvement in the Human Genome Project.



Francis Collins of the University of Michigan Medical Center devises a technique for “chromosome jumping” that allows researchers to skip over “uninformative” DNA regions and move rapidly up or down a chromosome in search of a particular gene.

“Genetic fingerprinting,” the technique of using sequences of DNA for identification, is developed by British geneticist **Sir Alec Jeffreys**.

The entire sequence of the HIV-1 genome is determined by **Chiron Corp.**

1986

The **Department of Energy** announces its Human Genome Initiative, the genesis of the International Human Genome Project.



The first genetically engineered vaccine, a vaccine for hepatitis B, is approved by the Food and Drug Administration.

1987



Advanced Genetic Sciences conducts the first field trial of a recombinant organism (a bacterium) on an agricultural product (strawberries).

1988

The **National Research Council** endorses a national effort to sequence the human genome, and the **National Institutes of Health** establishes its Office of Human Genome Research, with **James Watson** as its first director.



1990

W. French Anderson applies gene therapy for the first time. The recipient is a young girl with ADA deficiency, an immune system disorder.



1992

Researchers at **Lawrence Livermore National Laboratory** and **Lawrence Berkeley National Laboratory** in California discover a gene present in 25 to 30 percent of the population that predisposes individuals to increased heart attack risk. Discovery of this marker for heart disease on chromosome 19 may make possible the development of a simple test to screen humans for susceptibility to heart disease.

England's **Wellcome Trust** joins the Human Genome Project.

1994

The **Department of Energy** launches its Microbial Genome Program.



1995

Craig Venter and colleagues at The Institute for Genomic Research in Maryland decode the first whole genome of a free-living single-cell organism, the influenza microbe, using the whole genome shotgun sequencing method.

1996



Ian Wilmut and other researchers at Scotland's Roslin Institute clone a sheep from the cell of an adult ewe. This non-sexually produced animal is named “Dolly.”

The complete genome of the *E. coli* bacteria is sequenced.

1998

The first complete genome sequence of a multicellular organism, the round-worm *C. elegans*, is published.

1999

The **DOE Joint Genome Institute**, a genome-sequencing center formed by Lawrence Berkeley, Lawrence Livermore, and Los Alamos national laboratories, dedicates its new production sequencing facility in Walnut Creek, California.



The complete genome of the *Drosophila* fruit fly is sequenced.

2000

Working drafts of the human genome are completed by the public **International Human Genome Project** and by Craig Venter's **Celera Genomics**, a private company.

2001

The draft human genome sequence is published in the journals **Nature** and **Science**. Twenty sequencing centers in six countries—China, France, Germany, England, Japan, and the United States—contribute to the project. Most of the sequencing is done by five major centers: the Wellcome Trust's Sanger Center in England, the DOE Joint Genome Institute in California, and three NIH-funded centers at Baylor College of Medicine in Texas, Washington University School of Medicine in Missouri, and the Whitehead Institute in Massachusetts.

2001–2002

DOE launches its “Genomes to Life” program.



As rapid, highly accurate sequencing techniques become readily available, the complete genomes of a wide variety of microbes and model organisms, including the mouse, pufferfish, malaria mosquito, and sea squirt, are sequenced and analyzed. Genome comparisons yield significant new insights into the causes and progress of disease, biological evolution, and the relationship between organisms and the environment.

2003

The finished human genome is published concurrent with the 50th Anniversary of the discovery of the double helix.



For more information:

DOE Joint Genome Institute: www.jgi.doe.gov

DOE Human Genome Project: www.ornl.gov/hgmis

NIH Human Genome Project: www.genome.gov

Genomes to Life Program: <http://DOEGenomesToLife.org>

Microbial Genome Program: www.ornl.gov/microbialgenomes

Dolan DNA Learning Center: www.dnalc.org

Genetic Science Learning Center: <http://gslc.genetics.utah.edu>