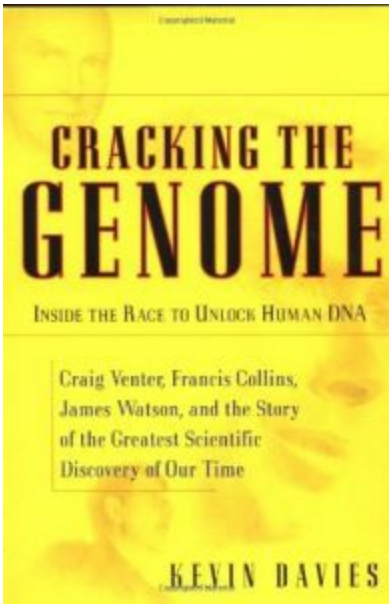

Book Cracking the Genome

Inside the Race to Unlock Human DNA

Kevin Davies
Free Press, 2001

Recommendation

Ken Davies has written an informed observer's account of the passionate race to solve what some believe to be the most profound scientific riddle of our era: decoding the human genome. His book is an undertaking of ambitious scope: He aims to paint the personalities in all their human colors and offer an accurate historical account, while also drilling deep enough into the research to do justice to the science. He does a beautiful job of suggesting the profound personal motivations of the two protagonists of the drama, scientists Francis Crick and maverick scientist J. Craig Venter. Short of earning your Ph.D. in molecular science, this may be as close as you ever get to understanding what the hoopla was really all about. *BooksInShort* recommends Davies' book as a must for savvy thinkers in the biotech business, and an enlightening read for the rest of us mere (genetically flawed) mortals.

Take-Aways

- Mapping the human genome is arguably the greatest scientific accomplishment of the 1900s.
- Bureaucratic institutions and private enterprise raced to decode the human genome.
- Key researchers included Francis Crick of the U.S. National Institute of Health and J. Craig Venter of Celera Genomics. Both had deep personal motivations.
- Perkin Elmer Corp.'s automatic gene splicing machines were pivotal to Venter's accelerated work.
- Frustrated by bureaucratic resistance, Venter quit his post as a government scientist.
- Within a few years of starting his own company, he was a successful entrepreneur.
- French, English, American and Japanese scientists played crucial roles in uncovering gene-based diseases.
- People share 99.9% of their genes; we are very similar.
- The next big research challenge is mapping the human proteome - through which genes are translated into proteins that determine body function.
- Physicist Stephen Hawking warns that in time someone will try to create a "new and improved" version of a human being.

Summary

The Recipe of Life

In the spring of 1953, two promising young scientists submitted a brief manuscript to the editor of Nature magazine. The paper, which would alter the course of history and science, began with what would later be described as one of the greatest understatements of all time:

> “The human genome indubitably holds the key to our future, but perhaps even more significantly, it also carries the secrets of our past.”

"We wish to suggest a structure for the salt of deoxyribose nucleic acid (DNA). This structure has novel features which are of considerable biological interest."

With those unassuming words, James Watson and Francis Crick introduced perhaps the 20th century’s most important discovery: the double-helix structure of life. Crick later observed that while the United States was only 200 years old, and civilization itself scarcely 10,000 years old, DNA and RNA have performed their mysterious evolutionary work for billions and billions of years. Crick wrote, "All that time the double helix has been there, and active, and yet we are the first creatures on Earth to become aware of its existence."

> “Our great-grandchildren will have dominion over the generations to come, with the capability to engineer traits into the genetic material as easily as sewing a button on a shirt.”

Thirty-seven years after the discovery of the double helix, the $3 billion Human Genome Project began its mission - decoding the precise sequence of the three billion chemical bases (made from various combinations of four proteins represented by the letters A, C, G and T) of the human genome. The founder of the U.S. National Institute for Health (NIH) Human Genome initiative was none other than that same James Watson. This great work could one day yield untold medical treasures: a cure for cancer or cystic fibrosis, an end to muscular dystrophy and genetic birth defects.

> “We have the awesome potential - should we so desire - of rewriting the language of God and the responsibility of harnessing the genome to improve the human condition in an equitable and ethical manner.”

From the beginning, two powerful protagonists competed in the quest for genomic Holy Grail. The first was geneticist Francis Collins, a University of Michigan scientist who took over as head of NIH’s initiative when Watson stepped down. His rival, J. Craig Venter, left the Human Genome Project in May 1998, to form his own company. Venter’s Celera Genomics used the first commercial DNA sequencing machines to sequence the entire human genome years ahead of the established 2005 deadline. With enormous prestige on the line, the two teams traded insults and accusations for two years while racing to finish their work. In April 2000, Venter claimed that he had finished sequencing the DNA of a human being.

> “What upset Venter’s peers the most was that in just two years, Venter had been transformed from a solid, respectable scientist working for the federal government into a stunningly successful, fabulously wealthy entrepreneur.”

That summer, as their profound, elegant scientific achievement was about to devolve to the trash-talking level of a professional wrestling match, the two sides agreed to a joint announcement at the White House on June 26 that the human genome had been solved.

Venter and Collins stood beside President Bill Clinton as he declared, "Today we are learning the language in which God created life." British Prime Minister Tony Blair also recognized Venter and Collins’ achievement. Speaking live via satellite from London, Blair termed their breakthrough "the first great technological triumph of the 21st century." He also alluded to the fact that 99.9% of every person’s genetic code is essentially the same. "Modern science," Clinton responded, "has confirmed what we first learned from ancient faiths. The most important fact of life on this earth is our common humanity."

> “The human genome - also known as the Book of Life, the Manual of Man, the Code of Codes - contains riches of almost inestimable value. But it must be said that it is one utterly boring read. Then again, more than three billion letters

will do that to you."

Francis Collins concluded, alluding to the scientific competition, "I am happy that today, the only race we are talking about is the human race." In turn, Venter predicted several practical applications, expressing the hope that cancer deaths might be reduced to zero in our lifetime. He concluded, "The complexities and wonder of how the inanimate chemicals that are our genetic code give rise to the imponderables of the human spirit should keep poets and philosophers inspired for millennia."

J. Craig Venter

If J. Craig Venter had not offended the wrong people along the path of his meteoric success, he would probably be a cinch for a Nobel Prize. He was born on October 14, 1946 in Salt Lake City, to a tax accountant and his wife, an artist. By all accounts, Venter was a rebellious child who frequently skipped classes at Mills High School. He barely graduated in 1964 and, rather than attend college, he moved south to work evenings at a Sears Department Store so that he could hang out with the surfers all day. Venter was a surfer boy: sun-bleached hair, lean tan body. To him, responsibility and consequences were just adult myths. But bliss enjoys a short half-life, and the conflict in Vietnam loomed. In 1965, Venter joined the Navy, hoping to make the swim team and compete in the Olympics. But after he scored top marks in an intelligence test administered to more than 30,000 recruits, the Navy shipped him to San Diego to train as a hospital corpsman, a role he thought would be relatively safe.

> "It would take an entire lifetime to listen to an unexpurgated recital of the genome sequence."

In 1967, he found himself in Da Nang, triaging troops wounded in the Tet Offensive. Two deaths, in particular, moved him. The first was a soldier, unscathed but for a .22 bullet wound in his head, who died shortly after his arrival. The other was an 18-year-old boy with massive chest and stomach injuries who clung to life for several weeks, suffering morphine-induced dreams of going home. Vietnam shook Venter, who faced a sharp choice between continued escapism and growing up fast. As he watched thousands die, each hour of life became increasingly meaningful to him. Venter put his free-spirited days behind him forever.

> "The total amount of DNA in the 100 trillion cells in the human body laid end to end would run to the sun and back about 20 times."

Back home, he immersed himself in his studies at the University of California, San Diego. He earned a Ph.D. in physiology and pharmacology in only six years and graduated with a determination to contribute to scientific breakthroughs that would save lives. In 1984, he moved to the National Institute of Neurological Disorders and Stroke at the NIH. Venter's lab was given the job of identifying a specific protein on the surface of heart cells that senses adrenaline, the "fight-or-flight" hormone that makes your heart pound. He succeeded, but the search took years and $10 million. As a man who had watched comrades' lives bleed out in minutes, Venter felt outraged by the glacial pace of medical science.

> "If [Venter] had not stirred up so much controversy and resentment over the past decade, he would be a certainty for Stockholm's annual Nobel party."

His response was to fly to California in 1986 to meet with Michael Hunkapiller, one of the designers of a new DNA sequencing machine, manufactured by the Applied Biosystems (ABI) division of the Perkin Elmer Corporation (PE). Because the $100,000 machines used fluorescent dyes to tag the four genetic components (A,G, C and T), they could analyze 24 samples simultaneously, yielding about 12,000 letters of DNA daily. In February 1987, Venter's lab became one of the first alpha test sites for the ABI sequencer. Initially, however, the machines rendered too many false positives, which meant Venter's group had to conduct tedious experiments to confirm their results.

> "One of Venter's virtues is that he is an impatient man, and everything he had tried to that point simply took too long."

Venter conceived the solution 35,000 feet above the Pacific Ocean, flying back from a conference in Japan. He realized that he needed a system that would ignore the massive amounts of "junk DNA" in the human genome. The answer was genetic transcription, the natural process occurring in every human cell by which the body "reads" chromosomes to translate them into actual proteins to perform specific tasks - i.e. fighting infection, growing tissue or adjusting metabolism. Proteins only emerged from DNA that was actually functional within the cell, so this would provide the short cut that Venter desperately needed. Now he had the tools to accelerate the quest for the human genome. However, the bureaucratic resistance toward his new approach was stifling. Finally,

Venter accepted one of several offers to take his initiative private. On July 10, 1992, in a former ceramics factory, Venter opened the world's largest DNA sequencing operation with 30 ABI 373A automated DNA sequencers, a ship to sail to the finish line in the biggest race of 20th century science.

Francis Collins

When Francis Collins agreed to replace James Watson as director of the National Center for Human Genome Research, becoming the official leader of biology's version of the Manhattan Project, he said it was more important than landing on the moon or splitting the atom.

> "Craig Venter remains as controversial as he was nine years ago, when he burst onto the scientific stage, but even his detractors would acknowledge that his vision has brought the Human Genome Project to completion five years ahead of schedule."

Collins was born in April 1950, the fourth son in his family. His father, a teacher, and his mother, a playwright, had a small farm in Virginia's Shenandoah Valley. Collins' mother home-schooled him, nurturing his early interest in chemistry and math. At age 24, he earned his Ph.D. in physical chemistry from Yale. By the time he earned his M.D., he had become a born-again Christian. Finding disease-causing genes, he said, was akin to "appreciating something that up until then, no human had known, but God knew it." In 1981, after his residency, Collins returned to Yale to study at the knee of geneticist Sherman Weissman. By 1985, Collins discovered a mutation that caused a fetal blood disease. He had hit the fast track; cracking the genetic code was almost within reach.

The Genetic Endgame

Internationally, the pace of genetic discoveries began to accelerate in the 1990s. In 1993, a French team led by Jean-Louis Mandel isolated the gene for adrenoleukodystrophy. In 1994, John Wasmuth discovered the gene for the most common genetic form of dwarfism. A French team also discovered the gene for spinal muscular atrophy. A collaborative effort determined the gene causing polycystic kidney disease that, like Huntington's disease, manifests only in adulthood. Scientists uncovered several genes related to hereditary blindness, including retinitis pigmentosa. Mary-Claire King discovered the first deafness gene in an extended Costa Rican family. By 1995, researchers had isolated more than 50 disease genes. Around the globe, the race was on to uncover ancient genetic mysteries. Venter and Collins' joint announcement that they had sequenced human DNA kicked off the new century of research on June 26, 2000.

The Post-Genomic Era

In the wake of the sequencing of our genetic roadmap, the obvious question is "What next?" The next great challenge on the horizon is the proteome project. A month after the announcement at the White House, Venter announced, "It's only by understanding protein function that we can truly understand and predict medical outcomes." So the next step is to map how the various genes produce the vast array of proteins that affect the human body. What are the properties of those proteins and how do they affect human development. There are tens of thousands of scientists capable of studying the links between genes, proteins and disease. The work of the genome project provides the road map for getting there. Venter - who learned as he fought wounds in the rice paddies of Vietnam that there is never time enough - helped to push the project forward by several years. Meanwhile, Collins and the NIH succeeded in bringing together an unwieldy international consortium to produce a working draft of the sequence. They plan to continue their work until it is refined, accurate and comprehensive beyond question.

Some scientists, however, are concerned that the power of the genome may be misused. Japanese researchers have introduced two new base pairs - additions to A-T and C-G - into a gene, essentially creating new genetic material. Physicist Stephen Hawking warns that no matter what legislative regulations are put in place, "someone will improve humans somewhere," possibly genetically altering brain size, for example. The controversy erupting over the use of stem cells harvested from embryos is articulate testimony to the capacity of scientific advance to cause ethical dilemmas. Similarly, the 1996 birth of Dolly, the cloned sheep, provoked deeper questions about the sanctity of individual life. Future discoveries related to the human genome promise to provide nothing less than answers to the origins of life and the evolution of humanity. What we will do with that knowledge remains unknown.

About the Author

Kevin Davies was formally trained in the science of molecular genetics, and has hunted for genes that cause cystic fibrosis and muscular dystrophy. In 1990, he joined the prestigious British journal *Nature,* where Watson and Crick's revolutionary discovery was first published. He met repeatedly with the principal figures in the race to decode the human genome throughout the course of that heralded scientific effort. Davies previously co-authored a book on the race to find the gene that causes breast cancer.