The Century of the Gene: Crash Course History of Science #42

Crash Course: History of Science
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With the question “what is life?” largely addressed at the molecular level—and with companies setting up labs to test how thousands of chemicals affect living things—and with new technologies like immortalized cell lines and somatic-cell “cloning”—humanity could finally cure all disease and live forever… Except that didn’t happen, because—as usual—the natural world is a lot more complicated than humans first thought.

Today, we’ll tell the story of the Human Genome Project. It’s really cool, you guys! [Intro Music Plays] Epistemically, the amount of information contained within even the smallest organism is simply mind-boggling.

There is lots and lots of DNA. Molecular biologists had figured out some genetic sequences in bacteria and the viruses that hijack them. But mapping the human genome?

That seemed like mapping every star in the universe. Technologically, scientists in the 1950s and 60s could barely sequence DNA and RNA at all. One major breakthrough came in 1977, when British biochemist and double Nobel Prize winner Frederick Sanger developed a new, reliable way of decoding DNA that became known as Sanger sequencing.

Sanger’s method became the standard way to sequence DNA until the late 1990s, when “next-gen,” high-throughput sequencers became available. It’s complicated, but Sanger sequencing cleverly works by chopping up an unknown sequence of DNA, tagging them with four different fluorescent dyes that bond to the four different nucleic bases, and then sorting out the segments by length. You can repeat the process many times to decode an entire genome.

One of the main issues is that decoding one sequence of DNA requires lots of copies of that sequence. And copying DNA, up until the 1980s, took lots of time. Like… weeks to months, and it was expensive… and, even then, it didn’t always work!

Enter American biochemist and avid surfer Kary Mullis. In 1983, while working at the biotech firm Cetus in California, Mullis developed polymerase chain reaction, or PCR. This was an automated way of taking advantage of a natural process for copying DNA.

In PCR, cycles of heating and cooling alternate between melting DNA and copying it using enzymes. PCR can make billions of copies every hour, helping scientists quickly replicate strands of DNA for study. Mullis and his bosses published a paper on PCR in 1985, and he went on to win the Nobel Prize.

You could say Mullis didn’t fit the mold of a traditional Nobelist. For one, he admitted to using LSD frequently in his youth. And—for a really weird two—in 1998, Mullis wrote an autobiography denying AIDS is a thing.

Which is just… really? That’s like “denying” pigeons! Anyway.

Modern science doesn’t rely on individuals. It’s a team sport. And the teams keep getting bigger.

By the late 1980s, some biologists began to discuss what had seemed impossible a decade before: completely decoding the human genome. The stated idea was to understand the different versions of genes that seem linked to cancers in order to develop better cancer-fighting drugs. Another goal was political: this would be the Manhattan Project of biology.

The U. S. would fund the future of medicine and attract the top biologists… hopefully no bombs, though. Planning began in 1988, when the U. S. National Institutes of Health, or NIH, and the Department of Energy agreed to work together. And the federal government created the Office, later the Center, for Human Genome Research.

The Center’s first director was the famous James Watson. But he resigned early on, and physician and geneticist Francis S. Collins took over.

Collins, by the way, has a rock band called The Directors! The Human Genome Project officially began on October 1st, 1990, with the goal of sequencing a representative “working draft” of ninety percent of a human genome—a model blueprint for a human body. There was no central hub: instead, many labs participated, all over the world.

So planning the project took years. But in 1996, DNA sequencing for the draft genome finally began at six U. S. universities.

ThoughtBubble, prime us. Humans are complicated. So many geneticists began by sequencing related organisms.

In 1996, an international team finished a draft sequence of Saccharomyces cerevisiae , the yeast humans use to make beer, bread, and bio-technologies. Although Saccharomyces is a microbe, it was still the first eukaryotic organism—with a membrane-bound nucleus, like humans!—to have its genome sequenced. Also in 1996, scientists revealed a “map” of sixteen thousand human genes.

Critics thought HGP would be a gargantuan waste of money. But the project was moving much faster than predicted. In 1997, the Center became the National Human Genome Research Institute, or NHGRI.

And then, in 1998, American bio-technologist J. Craig Venter, entered the competition. Earlier, Venter had worked at NIH, where he became an expert in making short synthetic bits of DNA called "Expressed Sequence Tags." These were useful for identifying genes… And Venter and the NIH controversially tried to patent them.

The U. S. Patent and Trademark Office said no in 1992, but this battle introduced Venter to the scientific limelight.

So later, when Venter disagreed with the manner in which HGP was being managed, he decided to compete with it—privately. That’s right: one dude said, I’ll beat the entire United States government at science! Venter believed that HGP should switch from reliable but slow Sanger sequencing to a much faster but more expensive new method called shotgun sequencing.!

Sanger sequencing only works on DNA strands up to ten thousand base pairs, which is very small. “Shotgunning” a genome involves fragmenting it into bits, several times in a row, and then letting a computer try to piece the blueprint back together. Each pass is flawed, but collectively, they add up to a whole sequence. Thanks, ThoughtBubble.

Venter wasn’t shy about letting the other HGP leaders know they were doing their job wrong. He officially quit HGP and started a for-profit company, Celera Genomics, that planned to use shotgunning and automation to sequence the human genome in three years—seven years faster than HGP. He would pay for this by holding the sequenced genes as intellectual property.

That is, he’d continue his decade-long fight over whether or not human genes can be owned. This rush to make money from human genes paralleled the pre-HGP rush to patent cell lines, like the University of California’s ownership of Mo, from last episode. And other companies followed suit.

In 1998, the government of Iceland controversially licensed the health data of all 275,000 Icelanders to a private U. S.–Icelandic company called deCODE Genetics, who were looking for genes linked to illnesses. deCODE declared bankruptcy in 2009 and has since been acquired by different companies. In early 1999, sequencing of the human genome at a large scale began, about a decade after the project started.

This was slow compared to the rapid development of the atomic bomb, but arguably that's like comparing one dangerous apple to billions and billions of oranges. And HGP had effects even before it finished. In 2000, President Clinton signed an Executive Order to prevent genetic discrimination in federal workplaces.

The same year, both a public group and Celera released the genetic sequence of the fruit fly—one of biology's rockstar model organisms. And then, also in 2000, with Venter about to scoop them, the leaders at the National Human Genome Research Institute called a truce. President Clinton, British Prime Minister Tony Blair, Venter, and Collins collectively announced the completion of eighty-five percent of a draft human genome.

Collins and Clinton both invoked religion. In Collins' words: "We have caught the first glimpses of our instruction book, previously known only to God." The complete draft was finished in 2003. Everybody was a winner.

Private industry had fought the government to a stalemate and secured serious investment. The government had spent less than three billion 1991 dollars. Which, if you think about, really is not much!

And medical researchers, evolutionary biologists, and bio-engineers now had more data than they knew what to do with! Within thirteen years, hundreds of scientists around the world had mapped the roughly three billion base pairs of DNA that code for a single human body. But they understood very little of it.

Originally, they predicted there would be about one hundred thousands genes, or regions that code for proteins, in a human genome. But there are only twenty thousand to twenty-five thousand. In fact, most DNA doesn't "code for" anything!

Some DNA serves important regulatory functions, turning coding genes on and off. Some may be "junk." So in 2003, NHGRI launched ENCODE—The Encyclopedia of DNA Elements Project—in order to understand all "functional elements" in human DNA. ENCODE published results in 2012.

On the technology side, the race to map the human genome drove the price of sequencing DNA way down. Sequencing cost continues to fall exponentially: The first human genome cost three billion dollars. Today, sequencing one human genome only costs about a thousand.

Lots of companies are doing just that. There are over fifteen hundred biotech companies in the U. S. today and more than ten thousand labs that conduct genetic sequencing.

And since 2009, community biology labs have supported the rise of "DIY bio," a movement wherein amateurs can sequence DNA and practice bioengineering in nonprofit labs. So what has all this DNA discovery led to? Immortality?

Flying cats? I don't... I don't want flying cats.

Sadly, human genetics remain really, really complicated today. Medical researchers are still working out ways to reprogram certain genes to, say, not give rise to cancer, or to reprogram immune cells to fight cancer better, without the need for toxic drugs. One day, healthcare may be specifically tailored to your unique genome and we'll talk about this vision for personalized medicine in two episodes.

What HGP and cheap genome sequencing did in the 1990s and 2000s, however, was change criminal law and not-change popular understandings of race. At first, defense lawyers were suspicious of DNA evidence. What if the lab made an error and sent the wrong person to jail?

But they soon realized that DNA evidence could be used to exonerate the wrongfully convicted. Today, DNA is a cornerstone of forensics. It's seen as more reliable than fingerprint evidence.

Of course, some people find it super creepy that authorities can "profile" someone using their DNA… Outside of the courtroom, the Human Genome Diversity Project, or HGDP, was organized at Stanford in the 1990s. Its mission: to collect DNA samples from thousands of different populations to understand human diversity. Its founder, Luca Cavalli-Sforza, was a prominent geneticist who thought HGDP would fight racism and celebrate different cultures.

Yet some critics accused HGDP of being racist by exploiting indigenous people for potential commercial gain: the World Council of Indigenous People's called it "the Vampire Project." Ouch. Recently, genetic ancestry testing has become commonplace. These could have highlighted how incredibly similar all humans are, and how artificial groupings based on so-called "races" are: they are the products of imperial census-taking, not science.

But instead, many ancestry tests reinforce census race terms. According to pioneering historian of biology Evelyn Fox Keller, the twentieth was the "century of the gene": the concept was born, explored, and finally understood to be much more complex than anyone had first thought. "Genes" aren't necessarily the best or even very good ways of thinking about traits in the blueprints of organisms. DNA isn't a computer language; it's a kind of molecule.

And knowing more about it may lead to better medicine one day, but it's going to take a long time. Next time—we're headed back to the world of data. It's time for the birth of everyone's absolute favoritest place, the Internet!

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