ENCODE: the rough guide to the human genome

Back in 2001, the **Human Genome Project** gave us a near complete readout of our **DNA**. Somehow, those As, Gs, Cs, and Ts contained the full instructions for making one of us, but they were hardly a simple blueprint or recipe book. The **genome** was there, but we had little idea about how it was used, controlled or organized, much less how it led to a living, breathing human.

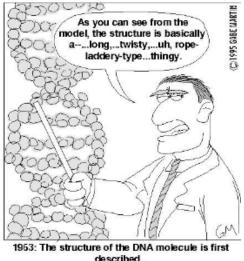
That gap has just got a little smaller. A massive international project called **ENCODE** – the Encyclopedia Of **DNA** Elements – has moved us from "Here's the **genome**" towards "Here's what the **genome** does". Over the last 10 years, an international team of 442 scientists have assailed 147 different types of cells with 24 types of experiments. Their goal: catalogue every letter (**nucleotide**) within the **genome** that does something.

For years, we've known that only 1.5 percent of the **genome** actually contains instructions for making **proteins**, the molecular workhorses of our cells. But ENCODE has shown that the rest of the **genome** – the non-**coding** majority – is still rife with "functional elements". That is, it's doing *something*. According to **ENCODE's** analysis, 80 percent of the **genome** has a "**biochemical** function", but the key point is: It's not "junk".

And what's in the remaining 20 percent? Possibly not junk either, according to Ewan Birney, the project's Lead Analysis Coordinator and self-described "cat-herder-in-chief". He explains that **ENCODE** only (!) looked at 147 types of cells, and the human body has a few thousand. A given part of the **genome** might control a **gene** in one cell type, but not others.

That the **genome** is complex will come as no surprise to scientists, but **ENCODE** does two fresh things: it catalogues the **DNA** elements for scientists to pore over; and it reveals just how *many* there are. "The **genome** is no longer an empty vastness – it is densely packed with peaks and wiggles of **biochemical** activity," says Shyam Prabhakar

Think of the human **genome** as a city. The basic layout, tallest buildings and most famous sights are visible from a distance. That's where we got to in 2001. Now, we've zoomed in. We can see the players that make the city tick: the cleaners and security guards who maintain the buildings, the sewers and power lines connecting distant parts, the police and politicians who oversee the rest. That's where we are now: a comprehensive 3-D portrait of a dynamic, changing entity, rather than a static, 2-D map.



And just as London is not New York, different types of cells rely on different **DNA** elements. For example, of the roughly 3 million locations where **proteins** stick to **DNA**, just 3,700 are commonly used in every cell examined. Liver cells, skin cells, **neurons**, **embryonic stem cells**... all of them use different suites of switches to control their lives. Again, we knew this would be so. Again, it's the scale and the comprehensiveness that matter.

Where will it lead us? It's easy to get carried away, and **ENCODE's** scientists seem wary of the hypeand-backlash cycle that befell the **Human Genome Project**. Much was promised at its unveiling, by both the media and the scientists involved, including medical breakthroughs and a clearer understanding of our humanity. The **ENCODE** team is being more cautious. "This idea that it will lead to new treatments for cancer or provide answers that were previously unknown is at least partially true," says Gingeras, "but the degree to which it will successfully address those issues is unknown.

"We are the most complex things we know about. It's not surprising that the manual is huge," says Birney.

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