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Don't Trash These Genes

By Alice Park

Junk. Barren. Nonfunctioning. Dark matter. That's how scientists have described the vast majority of the human genome since it was first sequenced in 2000. The disappointment in those words involved more than just science. It was also about ego. Given our evolutionary sophistication, our genomes--the genetic blueprint that makes us the talking, empire-building, socially complex species we are--would certainly be stuffed with important and elegant genes, coding for critical proteins of unparalleled complexity. But when all was said and done, the 3 billion base pairs that line up to make our DNA coalesced into a paltry 22,000 genes. That's just 2% of the human genome. The rest, geneticists said with unconcealed embarrassment, didn't seem to do much.

Fortunately for our genetic pride, it turns out they were wrong. Most of that 98% of the genome is actually a buzzing universe of biochemical activity that is far from a molecular moonscape, according to the latest massive genome-sequencing effort led by the U.S. National Institutes of Health (NIH). And normally cautious scientists are shedding their reservations when they contemplate the opportunities emerging from the Encyclopedia of DNA Elements (ENCODE) project, possibilities that include finding cures for some of our most intractable diseases. "This is a powerful resource for exploring the fundamental question of how life is encoded," Dr. Eric Green, director of the NIH's National Human Genome Research Institute, told reporters when he announced the discovery. "It will help us understand the genomic basis of human disease."

That, of course, is the ultimate goal of gene-based research. If the Human Genome Project established the letters of the human code, ENCODE is providing the narrative of the genetic novel by fashioning those linear strings of DNA into meaningful molecular words. And in those words could be found cures.

Members of the ENCODE consortium, which includes 442 scientists in 32 labs around the world, say about 80% of the nongene portion of the human genome is a highly active live wire made up of 4

million constantly communicating switches of cross-talking DNA. (There's a small percentage that remains unexplained, but experts aren't quick to dismiss it as junk just yet.) Rather than being inert, the portions of DNA that do not code for genes are busy instructing those genes when to turn on or off and how much protein to make not just in different cells but also at different points in our lifetimes. Somewhere in that 80% of DNA, for example, lie the instructions that make an uncommitted cell in a growing embryo march off to form a brain neuron or that tell a cell in the pancreas to churn out insulin in response to a meal or that guide a skin cell to bud off and replace an old one.

From DNA to Disease

If those genetic traffic cops can keep the body functioning healthily, it stands to reason they must also be involved when things go awry. Research into the genetic roots of disease has been going on since long before the dark matter was mapped. Hundreds of so-called genomewide association studies, which compared healthy individuals with those who had specific diseases like schizophrenia, allowed scientists to pinpoint changes in affected individuals' genomes that did not appear in healthy participants'. If those differences did not happen to fall within a gene, the explanation given was either that scientists were failing to find them or that the problem didn't lie in the genome. Now it seems clear that what they were looking for might simply have been hidden in the black hole of the supposedly useless 98%. If you don't understand what that region does--or if you assume it does nothing--you'll never give it a good look.

By mapping that terra incognita, ENCODE opens up a whole new landscape of research. If a disease is indeed caused by a problem in one or more of the genetic on-off switches, which are properly known as regulatory regions, researchers should be able to trace it, study it and ultimately treat it. "Right now when people think of disease, they really zoom in on the protein-coding stuff because that's the only thing they know how to interpret," says Michael Snyder, director of the Center for Genomics and Personalized Medicine at Stanford University and one of the project's investigators. "But for the first time, ENCODE lets us look beyond just those parts."

And that could mean turning the talk about personalized medicine, and the hope of matching patients' unique forms of disease to the best care for them, into reality. Treatments for all the big killers--heart conditions, diabetes, Alzheimer's --are likely to benefit from this approach, and among the first patients to reap rewards may be those battling cancer. The disease takes many forms in many tissues but is ultimately driven by one thing: cells that grow out of control. In recent years, anticancer drugs have targeted specific pathways in the tumor-making process, and some, like Herceptin for breast cancer and Gleevec for stomach cancers, have led to dramatic boosts in survival rates. Now that ENCODE has exposed the entire network of circuits that keep cancer cells alive, doctors anticipate that they will find new uses for existing drugs. Breast and lung tumors, for

example, may turn out to rely on the same molecular circuit, so a drug used to treat one may help patients with the other.

Such payoffs will inevitably extend to the discovery of entirely new therapies. At Washington University in St. Louis, researchers have identified nearly two dozen transcription factors that transform raw DNA into RNA and then into functional proteins that 17 cancers have in common. Overactivation of these factors could fuel the growth of tumors. Find a way to bring them back under control and you tame a stunning 17 cancers--including ovarian, colon and breast--with a single treatment.

But even beyond the therapeutic applications, ENCODE is likely to become the navigation system of choice for patients who are simply trying to monitor and maintain their health. It won't be long before a checkup will mean getting your entire genome sequenced so your doctor can be better informed about your risk for disease. "This is the science for this century," says Ewan Birney of the U.K.'s European Bioinformatics Institute and ENCODE's lead analysis coordinator. "It's going to be really good fun to produce lots of insights into diseases over the next couple of years."

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