# The dark side of 'junk' DNA: Repeating DNA sequences play a role in bone cancer

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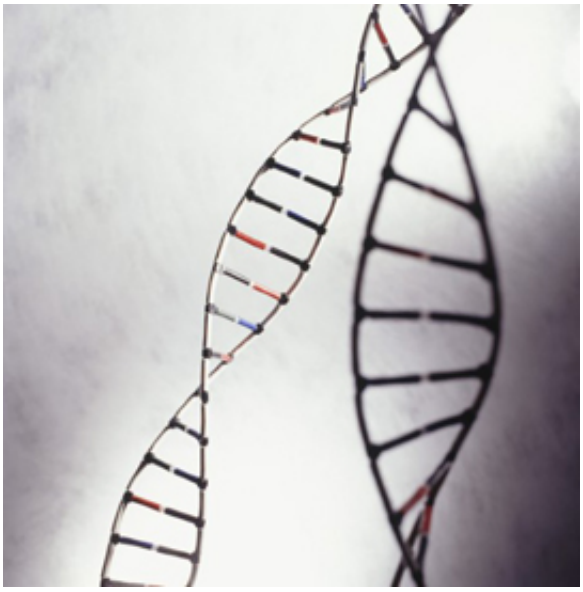

Credit: NIH

The stretches of DNA between genes, littered with repeating sequences, were once considered the "junk of the genome," but scientists are learning that some of this junk is far from harmless clutter.

Researchers at the University of North Carolina Lineberger Comprehensive Cancer Center report in the journal *Cell Reports* that certain short, repetitive sequences of DNA, or "junk," play an important role in the development of Ewing sarcoma, a rare bone and soft tissue cancer that occurs most commonly in children and adolescents.

"Some people may still think of these non-coding sequences as junk; that they don't really do anything but act as hangers-on to the more famous parts of the genome," said the study's senior author Ian J. Davis, MD, PHD, a pediatric oncologist and researcher at UNC Lineberger and the Denman Hammond Associate Professor in Childhood Cancer at the UNC School of Medicine. "But we found that repetitive elements contribute to cancer development for Ewing sarcoma based on traits that they share with immature cells."

For most people with Ewing sarcoma, their tumors have a mutation that creates a new gene called EWSR1-FLI1. This gene codes for a mutant protein, called an oncoprotein, that drives the cancer. But it turns out that the mutant protein does not work alone.

UNC Lineberger researchers found that specific states of DNA have enhanced susceptibility to the oncoprotein's attack. In particular, the way that repetitive DNA sequences interact with a class of proteins called histones, which act like a spool around which DNA is wrapped, offer an opportunistic environment for the oncoprotein. At certain sites, the DNA is more "open" or unwrapped around the histone spools, making them more accessible to the oncoprotein.

Davis and his collaborators discovered that the way certain repeat DNA sections interact with histones in Ewing sarcoma bore a striking similarity to that of stem cells, which are cells that haven't matured and can still become many types of cells. They believe that the looseness in the way that DNA and histones interact in stem cells and cancer cells at these repeat sites allows the oncoprotein to interact with the DNA, changing the way that many genes are expressed.

"We identified a new feature in the way the genome is organized in stem cells, and this ended up explaining a link between these immature cells and the development of Ewing sarcoma," Davis said. "This is one way

we think the oncogene capitalizes on a pre-existing environment and offers some insight into why the cancer might have a very specific window during which it could develop. It's kind of like a seed and soil relationship. The oncoprotein 'seed' can only form cancer in the correct stem cell 'soil.'"

The finding builds on previous research by Davis and others that showed the oncoprotein travels to certain non-coding, repeating sequences of DNA—repeating sections that have been a source of scientific and evolutionary debate, and at one time, were called "junk." At those sites, the oncoprotein helps to keep the DNA at those sites "open," allowing for nearby genes to be read and used as a blueprint for protein construction. Many genes implicated in tumor development are located near those repeat DNA sites.

While the oncoprotein's proclivity to travel was known, the researchers couldn't explain why it traveled to certain repeats and not to other similar regions, and why the oncoprotein seemed not to be able to act in any type of cell.

"Previous studies from our lab have demonstrated increased chromatin accessibility at these repeat DNA regions," said the study's first author Nicholas Gomez, PhD, who worked on the project as a doctoral student at UNC. "What we didn't know is the state of these regions in stem cells. Interestingly, we found that those repetitive regions with the highest accessibility in mesenchymal stem cells - the possible cell of origin in this cancer—predicted the regions that the oncoprotein would bind in the cancer."

Now, Davis and colleagues are focused on identifying treatments that can alter the chromatin targeted by the Ewing sarcoma oncoprotein. As a pediatric oncologist, Davis is motivated to better understand, and possibly to improve treatment for, this cancer and others through

research.

"I see children with difficult to treat and often incurable cancers in the clinic, as well as children with curable cancers that require months or sometimes years of toxic chemotherapy," he said. "The impact of these diseases and treatments on children and their families is profound. This appreciation gives me a special drive to tackle studies in the lab that to further our understanding of these diseases, and to use that information to try to advance treatments."

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