Scientists discover distant DNA working together to affect disease risk

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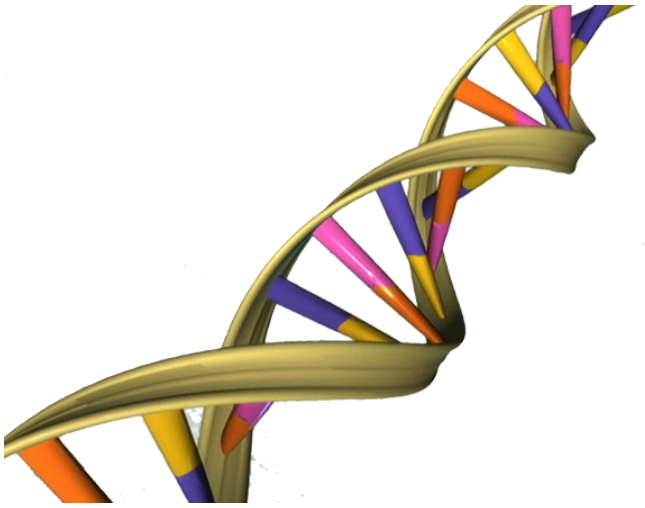

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A person's DNA sequence can provide a lot of information about how genes are turned on and off, but new research out of Case Western Reserve University School of Medicine suggests the 3-D structure DNA forms as it crams into cells may provide an additional layer of gene control. As long strands of DNA twist and fold, regions far away from each other suddenly find themselves in close proximity. The revolutionary study suggests interactions between distant regions may affect how genes are expressed in certain diseases.

Peter Scacheri, PhD, Associate Professor of Genetics and Genome Sciences at Case Western Reserve University School of Medicine has been studying how specific regions of DNA physically interact with disease genes. His most recent study, published in *Nature Genetics*, discovered regions of DNA he termed "outside variants" that physically interact with high-risk mutations in a person's DNA sequence called single nucleotide polymorphisms, or SNPs. The outside variants suggest a new level of gene regulation and may help explain how identical SNPs can lead to different clinical outcomes.

"Our previous work showed that there was more to the expression of a disease gene than just the nearby regulatory elements on the DNA strand, and it seemed logical to look at variants that are brought in close physical proximity to the gene when DNA is packaged in the cell," said Scacheri. "By looking at these 'outside variants,' we can determine the risk associated with disease with better precision than by just looking at the known variants."

The study investigated SNPs associated with six autoimmune diseases, rheumatoid arthritis, systemic lupus, Crohn's disease, multiple sclerosis, ulcerative colitis, and celiac disease. The SNPs were previously identified through genome-wide association studies, increasingly popular research tools that search DNA sequence data for regions associated with disease. The large-scale studies tend to zero in on SNPs in "enhancer clusters" of DNA, regions known to contort and interact with disease genes. The researchers identified outside variant DNA regions that seemed to be dependent on known disease SNPs, but were found far beyond enhancer clusters normally associated with the diseases.

Olivia Corradin, PhD, Fellow and Principal Investigator at Whitehead Institute for Biomedical Research, former graduate student in Scacheri's laboratory and lead author of the study explained, "New technologies and DNA sequencing now enable us to evaluate the 3-dimensional organization of DNA within a cell. This gave us the opportunity to assess our hypothesis that multiple DNA variants that are in physical contact with the same gene may help to explain genetic predisposition to disease."

Once the researchers discovered outside variants,

they studied DNA samples to determine the impact of the regions on disease gene levels. The team used computer models to compare gene levels associated with their newly identified outside variants to those associated with previously identified SNPs. The team discovered outside variants physically interacted with known SNPs within the DNA samples and both genetic elements joined forces to mediate disease risk. Through the models, Scacheri's team was able to use outside variants to better predict disease risk.

According to Scacheri, "The big surprise was when we crunched the numbers and compared the risk associated with the amount of heritability that could be explained by the outside variants. By our calculations, outside variants accounted for a whopping 2-3 times more of the heritability than explained by the current models. That was far more than we had expected."

Further characterization of outside variants revealed they have much in common with enhancer clusters. Proteins that help activate disease genes commonly attach to both regions. In fact, 77% of outside variants identified by the researchers were located near protein attachment sites similar to those found in enhancer clusters. The similarities between outside variants and enhancer clusters support the team's conclusion that multiple elements work together to control disease genes.

Said Corradin, "Imagine you have a light bulb hooked up to multiple dimmer switches in different places in a room. Instead of studying the effect of each switch, one at a time, we studied the light bulb, and asked 'how do the multiple switches combine to control the room's light?' This perspective allowed us to better determine the genetic risk associated with disease."

The study provides a better understanding of how folded DNA employs distant genetic regions to control how genes are turned on or off. Three dimensional models of DNA may therefore reveal other genetic elements that can help explain the complex processes of gene control, and ultimately disease heritability. The outside variants identified in the study may also provide additional biomarkers to assess a person's risk of disease.

"We found outside variants associated with several autoimmune-related disorders, including multiple sclerosis, Crohn's disease, and arthritis. The next step is to see if this extends to other common diseases, like heart disease and diabetes," said Scacheri, indicating his research team plans to "determine whether we can use outside variants in a diagnostic or preventive medicine setting to better identify individuals who are most at risk for developing these diseases."

More information: Modeling disease risk through analysis of physical interactions between genetic variants within chromatin regulatory circuitry, *Nature Genetics*, DOI: 10.1038/ng.3674

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