New techniques better determine how ancient viral DNA influences human genes

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New laboratory techniques can identify which of our genes are influenced by DNA snippets that are left behind in our genetic code by viruses, a new study finds.

Viruses have long been known to reproduce by using the genetic machinery of the cells they invade. As part of that process over time,

these microorganisms have left behind thousands of DNA sequences, called transposons, throughout the genetic material (genomes) in many lifeforms, including mice and humans, say the study authors. Studies established decades ago the idea that a few of these viral insertions have come to play a role in the action of genes.

Determining which transposons regulate which genes, however, has proven to be a challenge, as transposons may influence a nearby gene or one that is located far away in the DNA molecular chain.

Published online December 13 in *Genome Biology*, the new study describes methods that capture more information on the location and influence of viral insertions in genomes, identifying genes potentially controlled by active transposons (most are silenced by our cells' defense mechanisms).

"One of the interesting findings from our study is that a single transposon may control more than one gene and that one gene can be regulated by more than one transposon, increasing the complexity of the potential impact of transposons on health and disease," says senior study author Jane Skok, Ph.D., the Sandra and Edward H. Meyer Professor of Radiation Oncology at NYU Langone Health's Perlmutter Cancer Center. "Furthermore, viral insertions from the same family preferentially interact with each other, possibly reinforcing their impact on genetic activity."

View of Genetic Reality

For decades after the discovery of DNA, researchers mostly thought of genetics in terms of genes, the pieces or sequences of DNA that encode instructions for building proteins in cells. Then scientists discovered that genes make up just 2 percent of our DNA and that most genetic complexity stems from the vast non-gene code, which influences when

genes are turned on or off. Further, half of that non-gene code was found to come from insertions of viral DNA. Consequently, say the authors, genetic variation, and the potential for disease-causing mistakes, occurs in transposons as well as in genes.

The current results are based on the discovery that pieces of DNA, called enhancers, control gene activity. These enhancers may be separated from their target genes by a long distance on a linear DNA chain but can curl around in 3-D space to interact with another section of the chain by forming loops. Evidence then emerged that some of these looping enhancers may be parts of viral transposon sequences.

But those trying to understand the role of these enhancers faced a problem.

Transposon insertions occur at many sites and are therefore repeats of the same DNA code (not unique). However, popular genome-wide association studies rely on finding a link between a single, unique piece of DNA and risk for a disease. Thus, repeat sequences are typically ignored because it is not clear which of these multiple insertion sites is interacting with a particular disease-related gene.

Experimental evidence supports the idea that to exert influence, enhancers must make physical contact with their target genes through loop formation. Identifying such interactions between different pieces of DNA became possible in 2002 with the development of a technique called chromosome conformation capture.

The current study describes two variations on this technology, collectively called 4TRAN, which take advantage of the repetitive nature of transposons to capture their interactions. The techniques provide direct evidence that some transposons exert long-range control of genes by looping.

One of the new techniques, 4TRAN-PCR, proved to be capable of finding all interactions involving members of a transposon family that contain a particular DNA sequence, enabling the researchers to count the hundreds or thousands of places where such transposons occur. The method demonstrated that transposons are more likely to interact with DNA within local neighborhoods (topologically associating domains), but also that they take part in long-range interactions determined by the activation status of the compartments they are in.

The second technique, Capture 4TRAN, attached probes to each member of a viral family that, in combination with other tricks, enabled the team to determine the influence of any single transposon copy on a specific gene or genes. For example, the study showed that a few of the 7,200 copies of repetitive DNA left behind by the viral MER41 family, which infected our primate ancestors 60 million years ago, now serve as enhancers that turn on immune system genes via long-range DNA contacts by looping. Ironically the target genes in this case act to combat, of all things, viruses.

Moving forward, the team has already begun experiments seeking to identify networks of interactions between transposons and genes that are different in cancer cells than in healthy cells.

More information: Ramya Raviram et al, Analysis of 3D genomic interactions identifies candidate host genes that transposable elements potentially regulate, *Genome Biology* (2018). DOI: 10.1186/s13059-018-1598-7

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