Lost in translation: Researchers discover translator gene may play a role in disease

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In this animation, the research team indicates where they observed variants in the tRNA structure. The blue represents areas that were found to be less frequently mutated and red represents areas more frequently mutated. Credit: University of Western Ontario

A molecule called tRNA, or transfer ribonucleic acid, is an essential component of the human genome that acts as a translator. It reads the genetic code and translates it into proteins—one of the key building blocks of the human body.

When researchers and clinicians investigate the genome's relation to disease, they have traditionally focused on mutations in the code for proteins. But now researchers at Western University have shown that the genes encoding tRNAs can also have mutations that cause the code to be misread, and in greater numbers than previously thought.

Think of it like a translator app on your phone—if it has errors in its software, the output is going to be all wrong, even if the original text is correct.

"This actually changes the way we think about the genetic code," said lead author Mathew Berg, a Ph.D. Candidate at Western's Schulich School of Medicine & Dentistry. "We have shown that variation in tRNA has the potential to lead to a protein being made improperly, which can lead to misfolding and malfunction of the protein."

The research team, led by Schulich Medicine & Dentistry Professors Christopher Brandl, Robert Hegele and Patrick O'Donoghue, say this is significant because many human diseases like Alzheimer's disease and diseases of the heart muscle are linked to misfolded proteins.

The work was published online today in the journal *RNA Biology*.

"Genetic variation is one of the major reasons why some people acquire a disease while others do not and we expect that an individual with 10 abnormal tRNAs might be more likely to acquire a disease than someone with one," said Brandl. "Another interesting aspect of what we saw is that the profile of tRNAs in even the limited group we looked at was very diverse. No two individuals were the same."

The researchers point out that all previous evidence suggested that there were minimal variations in the tRNA genes, likely attributed to the fact that it hadn't been looked at this closely before. Based on previous

evidence, the team only expected to find one or two mutants in the tRNA.

The group, including Ph.D. Candidate Dan Giguere, came up with a new way to sequence and read the tRNA to get a better picture of the variation that exists between individuals. This deep sequencing data gathered at Western showed that human tRNA variation was previously underestimated by more than 30-fold.

In a group of 84 people in London, Ontario they found that individuals contain on average 66 variants in their tRNA genes.

"Because tRNA variation has been hard to analyze, it has largely been overlooked in genetic association studies. Our work suggests that it is important to look at the tRNA genes and we also provide the tools to do so," said Brandl.

Next, the group wants to get a better understanding of exactly how these genes are contributing to disease and determine whether it can be reversed. They also expect that they'll find even greater variation by looking at more diverse populations from other areas around the world.

More information: Matthew D. Berg et al, Targeted sequencing reveals expanded genetic diversity of human transfer RNAs, *RNA Biology* (2019). DOI: 10.1080/15476286.2019.1646079

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