Naming system for transfer RNA fragments to increase research productivity, standardization

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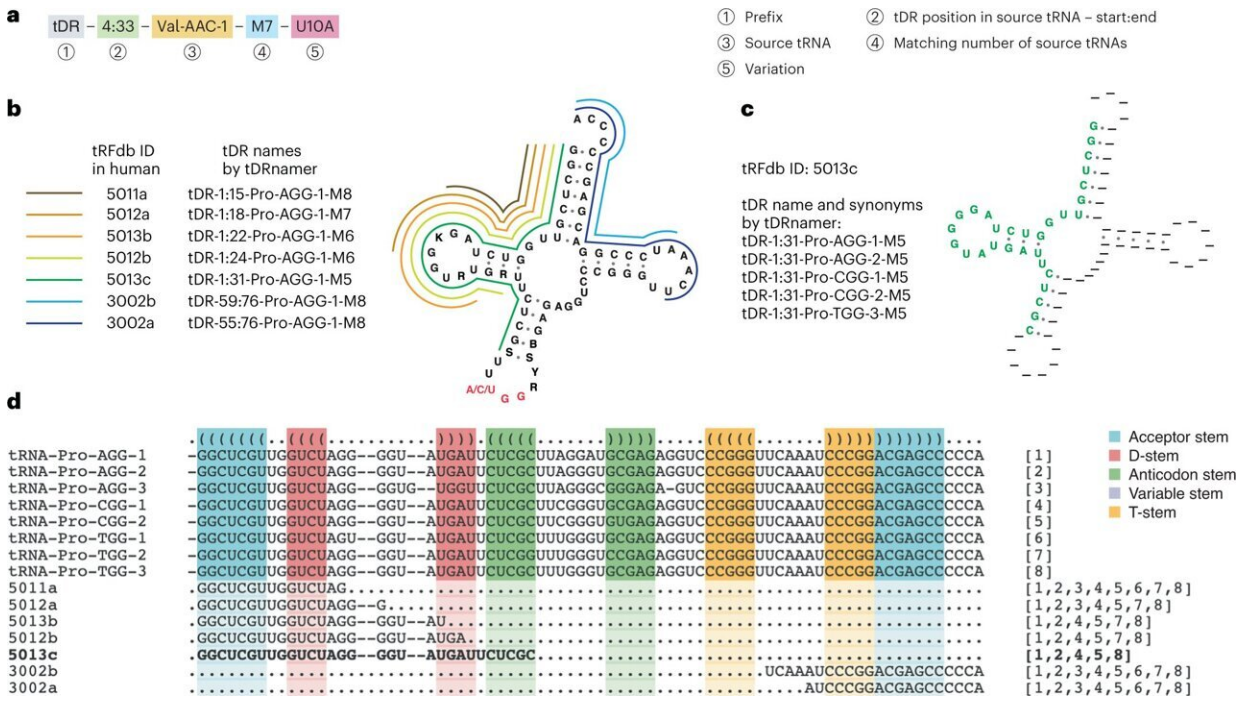

Standardized naming for tRNA-derived RNAs (tDRs) illustrated by seven tDRs potentially derived from up to eight human tRNAPro transcripts. Credit: *Nature Methods* (2023). DOI: 10.1038/s41592-023-01813-2

Transfer RNA, more commonly referred to as tRNA, is well known for its key role in translating genetic material into protein. Recent

discoveries about fragments of tRNA, which scientists had previously thought of as simply waste products in the cell ecosystem, has led to an increase in attention to these elements and the diverse functions they serve across all domains of life. These tRNA fragments, or tRNA-derived RNAs, are now an active area of interest for scientists studying topics such as Parkinson's, cancer research, and more.

Until now the scientific community has not had a clear, standardized system for identifying and naming tRNA fragments. As a result, scientists across the world have been creating their own names for these functional molecules, making it difficult to compare and reproduce work in this field.

To address this issue, UC Santa Cruz Professor of Biomolecular Engineering Todd Lowe and his group created a new naming scheme for tRNA fragments aimed at standardizing this research. The inspiration and final standard grew from consensus and collaboration, co-led with Professor of Pediatrics and Genetics Mark Kay at Stanford, along with other leaders in tRNA research from around the world, all co-authors on the paper.

To promote adoption of the new naming system, the Lowe lab made a free, open source web server which enables researchers to simply paste in their tRNA fragment sequences to receive a consistent, biologically informative name with additional annotations and graphic displays. The server also allows researchers to input a sequence name and receive the exact sequence of bases to which it belongs. A new correspondence paper in the journal *Nature Methods* details these contributions.

"Hopefully now the field will be required to name tRNA fragments in a uniform way, and compare results," Lowe said. "Right now, there's almost no requirement for reproducibility in this field—it's awful."

Postdoctoral Scholar Andrew Holmes and Project Scientist Patricia Chan, both in Lowe's group, were lead authors on the paper and key in creating the new web server.

As a graduate student, Lowe wrote a software tool—tRNAscan-SE—to improve upon the existing methods for identifying tRNA genes in DNA sequences. This tool is still the main method used by scientists to identify and annotate tRNA genes, and it continues to be maintained and improved upon by Lowe's group. This history, and their expertise in both RNA biology—specifically tRNAs—and computational work, makes Lowe's group a natural fit for addressing the issue of naming tRNA fragments.

Research on tRNA fragments is a relatively new field, as they started gaining recognition and interest only about a decade ago. These fragments are widely varied and perform a myriad of roles in the cell ecosystem, many of which are still being discovered and explored. For example, some tRNA fragments have been recognized to promote cell growth by enabling assembly of ribosomes, the protein factories, whereas other fragments can gum up that same machinery, halting protein production. Other fragments bind key proteins that can enhance or prevent programmed cell death, and still others get exported in extracellular microvesicles that can communicate information across cells. Together, this mix of many hundreds of types of tRNA fragments add another layer of fine-tuning control to cells, and show promise as a new class of biomarkers for early detection of disease.

The particularities of the chemical bonds in tRNAs had made these molecules difficult to sequence. New sequencing methods have been developed to address these challenges, which has also led to an acceleration of research in this field.

The current lack of a naming system for tRNA fragments makes it very

difficult for researchers to compare their discoveries. It also makes it nearly impossible to determine which tRNA the fragment originates from. In humans alone, there are more than 500 different tRNA genes, and understanding which one or more the fragment is derived from is crucial for understanding the role that the fragments play.

"When someone publishes something, you often don't know what its significance is in the context of everything else that's been done in the field of tRNA fragments," Lowe said. "That's unheard of—it's frustrating, and it's not a robust way to do science."

The new naming scheme makes it easy to locate where in a genome the tRNA fragment comes from and if it is derived from multiple tRNAs or just one. It also identifies if there is variance between the sequenced fragment and the reference tRNA.

Lowe hopes that journal editors will require this new naming system in order to accelerate the process of comparing and integrating findings across the wide range of research that involves tRNA fragments.

Lowe believes some researchers may be hesitant to stop using the original names they've assigned to tRNA fragments discovered in their labs, but suggests researchers can use their chosen identifiers in papers as long as they give reference to the systematic name as well. The many collaborating co-authors on the paper who helped shape the standard will be important in getting the word out about this new system and encouraging other scientists to adopt it.

"We were thrilled to work with a group of scientists who had a vested interest in putting away individual preferences for the good of the field and produced a naming scheme that will make it easier to advance this growing field," Kay said.

In the future, Lowe and his group intend to merge the naming software with another of their programs, which maps misincorporation-inferred modifications in tRNA sequencing reads. They will also apply the new naming system to publicly available data sets, and incorporate these into the Genomic tRNA Database (GtRNAdb), which is maintained by Lowe's group.

Lowe is excited to see what discoveries will be enabled by the adaption of this naming system.

"There's a ton more of these tRNA fragments," Lowe said. "We've just seen the tip of the iceberg, which is why this is so important."

More information: Andrew D. Holmes et al, A standardized ontology for naming tRNA-derived RNAs based on molecular origin, *Nature Methods* (2023). DOI: 10.1038/s41592-023-01813-2

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