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A Standardized Ontology for Naming tRNA-derived RNAs Based on Molecular Origin

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Transfer RNA (tRNA), well-studied as the key adapter molecule in protein translation, is now known to be processed into a large collection of smaller stable RNAs. High-throughput small-RNA sequencing methods, including those specialized for tRNAs such as ARM-Seq¹, Pandora-seq², and others, have led to the identification of these tRNA-derived RNAs (tDRs) across all domains of life^{3,4}. Functional studies have revealed a plethora of regulatory roles associated with these small noncoding RNAs, including modulation of ribosome biogenesis, protein synthesis, gene silencing, stress response and plant nodulation⁵. Moreover, differential abundance of tDRs observed across tissues and cellular conditions suggests the possibility of leveraging tDRs as biomarkers for early diagnosis of cancer, heart disease, neurological disorders and other diseases⁶. Historically, they have been rudimentarily categorized by their positions in source tRNAs: namely, 5' or 3' fragments, 5' or 3' halves, internal fragments, 5' leaders or 3' trailers⁷. A constellation of diverse yet often overlapping names and acronyms has emerged, including “tRFs”, “tsRNAs”, “tiRNAs”, “SHOT-RNAs” and “tRNA halves”, among others. Several

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Author contributions

A.H. and P.C. designed and developed tDRnamer standalone software. P.C. designed and developed tDRnamer web server. P.C. and T.L. wrote the manuscript. All authors contributed to the design of tDR naming convention and the feature requirements of tDRnamer.

Code availability

The source code of tDRnamer and its web server is available at <https://github.com/UCSC-LoweLab/tDRnamer> and <https://github.com/UCSC-LoweLab/tDRnamer-web> respectively, both under the GNU General Public License v3.0.

Competing interests

The authors declare no competing interests.

databases^{3,8} have created their own independent serial or hexadecimal numbering systems, but, for various reasons, these names have not been widely adopted. Here we propose a consistent, uniform naming system (Fig. 1a) that is biologically informative and builds upon an existing, widely accepted naming scheme for full-length tRNAs⁹. To make the naming system readily accessible, we have also developed tDRnamer (Supplementary Fig. 1 and Supplementary Table 1), a resource providing a user-friendly, web-based interface, as well as a downloadable software version for efficient bulk processing. Given one or more sequences, the tool deterministically generates standardized tDR names within an information-rich display; alternatively, if given tDRnamer-generated names, it can produce the exact corresponding sequences. Additional graphical visualizations (Fig. 1c,d and Supplementary Figs. 2 and 3) are provided to further highlight the relatedness of similar tDRs and their positions within source tRNA(s).

The tDR naming system (Fig. 1a) consists of three required components, plus up to two supplemental notations in special cases. First, each name starts with the general prefix “tDR”, which is neutral to any functional role. If the tDR is derived from mitochondrial or plastid tRNAs, “mtDR” and “ptDR” is used. Second, the tDR’s precise start and end positions, relative to its source tRNA, are specified using the standardized Sprinzl tRNA position numbering¹⁰ (for example, “tDR-4:33”). This gives stems and loops consistent base numbers across all tRNAs (for example, the anticodon in every tRNA is at position 34–36). Third, the identifier of the most similar source tRNA found in the Genomic tRNA Database (GtRNAdb)⁹ is appended to the tDR name (for example, “Val-AAC-1”). Because some portions of different tRNAs may be identical, tDRs can often be derived from multiple indistinguishable parent tRNAs. In this case, a fourth component is added to the tDR name to indicate the number of potential source tRNAs (for example, “M7”). Finally, nucleotide differences may exist between tDRs and the reference tRNA set due to natural genetic variation, or may also be caused by misincorporation by reverse transcriptase at certain RNA modifications. To describe these tDRs succinctly, a name component can be added consisting of the original and substituted bases with their relative positions (for example, “U10A”).

To demonstrate the application of this new naming system with tDRnamer, we created systematic names for existing entries in tRFdb³ (Supplementary Data 1), immediately yielding useful observations. One notable case involves a group of seven tDRs potentially derived from multiple unique transcripts of tRNA^{Pro} (Fig. 1b). For tDR-1:31-Pro-AGG-1-M5 (tRFdb ID: 5013c), one can see five possible synonyms corresponding to five matching source tRNAs (Fig. 1c–d and Supplementary Table 2). In comparison to prior nomenclatures^{3,8}, this information is necessarily absent. The graphic (Fig. 1b) and alignment (Fig. 1d) show most of these tDRs are anchored to the 5′ end of source tRNAs (for example, “1:15”, “1:18”) while the remaining two align to the 3′ end (“59:76”, “55:76”). The alignment further shows that the longest tDR (5013c) exactly matches five potential source tRNAs, precisely enumerated by numbers in brackets following tDR sequences. Additional examples of complex tDR relationships showcase the unique functionality of the tDRnamer web analysis interface (Supplementary Figs. 2 and 3). For instance, three different regions of human tRNA-Gly-GCC-1 are processed into distinct tDRs of multiple lengths (Supplementary Fig. 2), whereas a tDR derived from 3′ trailer sequence of tRNA-

Arg-ACG-1-3 includes multiple single-nucleotide variants (Supplementary Fig. 3). These examples demonstrate the breadth and descriptive capabilities of the proposed tDR naming system. As such, tDRnamer should become a valuable analytic tool for recognizing the biological relatedness among tDRs, enabling more focused study of their biogenesis from source tRNAs. The new system will also provide a ready means for detailed comparisons of tDR sequencing results between studies, both retrospectively and prospectively, facilitating advances in this blossoming field of noncoding RNA research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The tDRnamer web server is available at <http://trna.ucsc.edu/tDRnamer/>. Standalone software can be obtained from GitHub at <https://github.com/UCSC-LoweLab/tDRnamer> and Docker image at <https://hub.docker.com/r/ucsclovelab/tDRnamer>. Example data can be downloaded from <http://trna.ucsc.edu/tDRnamer/data/examples/>. Pre-built reference databases for model organisms are available at <http://trna.ucsc.edu/tDRnamer/docs/refdb/>. The complete set of tRFdb³ data re-annotations by tDRnamer is available at http://trna.ucsc.edu/tDRnamer/data/tRFdb_reannotations/.

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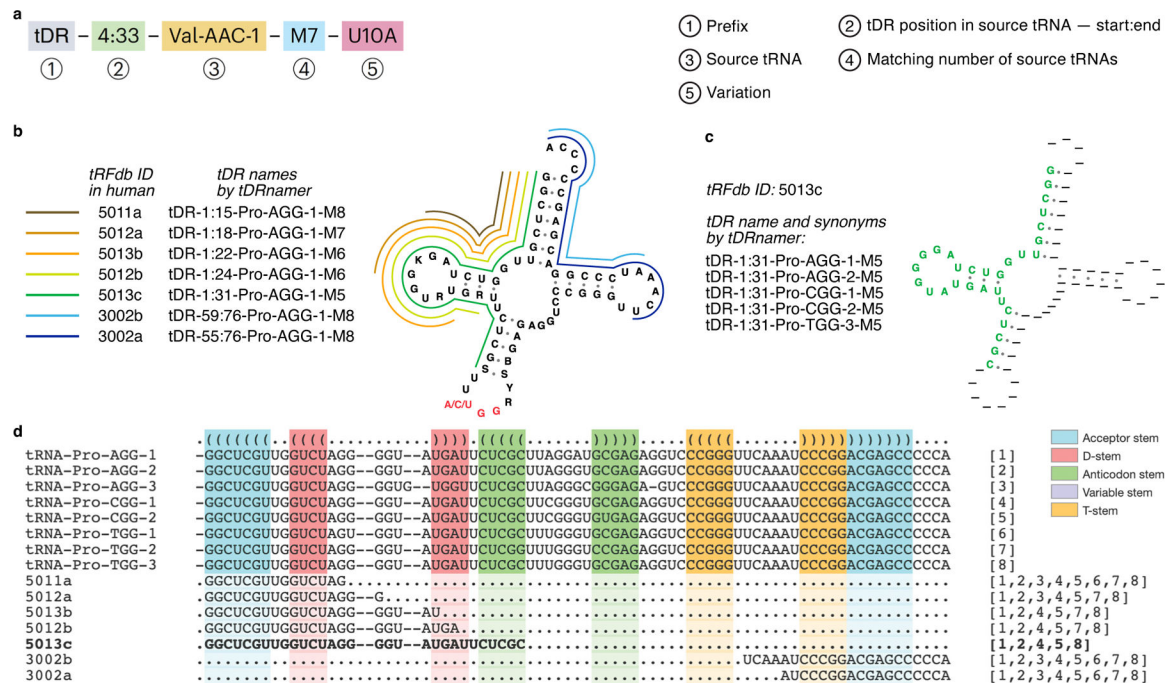


Fig. 1. Standardized naming for tRNA-derived RNAs (tDRs) illustrated by seven tDRs potentially derived from up to eight human tRNA^{Pro} transcripts.

a. The standardized tDR name contains three required components, plus up to two optional notations: (1) the “tDR” prefix; (2) start and end positions of the tDR relative to its source tRNA in Sprinzl numbering¹⁰ (if present, 5′ leader and 3′ trailer positions are preceded with “L” or “T” respectively); (3) the source tRNA name from GtRNAdb⁹; (4) “M” with the total number of matching source tRNA transcripts, when more than one exists; and (5) nucleotide variation annotation, if the tDR does not precisely match a reference source tRNA – it consists of the reference source tRNA nucleotide, followed by the relative position in tDR, and finally the substituted nucleotide found in the tDR. **b.** The tDR names for seven tRFdb entries with tRNA^{Pro(AGG)} as the source tRNA are listed. Colored lines around the tRNA^{Pro} secondary structure represent the positions of the derived tDRs. **c.** An example tDR (tRFdb ID 5013c) is located at the 5′ end of tRNA^{Pro} from position 1 to 31, as illustrated in green within the full tRNA secondary structure, generated by tDRnamer. The tDR name and synonyms show that its source tRNAs may include two different transcripts of tRNA^{Pro(AGG)}, two different transcripts of tRNA^{Pro(CGG)} and/or one tRNA^{Pro(UGG)}. **d.** tDRs are grouped and aligned with all potential source tRNA^{Pro} by tDRnamer. Color blocks represent stems in tRNA secondary structure. Bracketed numbers at the end of each tDR (for example, “[1,2,4,5,8]” for 5013c) refer to the five possible source tRNAs shown at the top of the alignment.