Conspicuous tRNA lookalikes riddle the human genome

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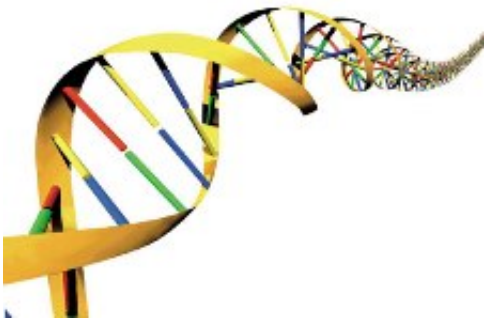

Transfer RNAs (tRNAs) are ancient workhorse molecules and part of the cellular process that creates the proteins, critical building blocks of life that keep a cell running smoothly. A new discovery suggests that the number of human genomic loci that might be coding for tRNAs is nearly double what is currently known. Most of the newly identified loci resemble the sequences of mitochondrial tRNAs suggesting unexpected new links between the human nuclear and mitochondrial genomes, links that are not currently understood.

Transfer RNAs (tRNAs) represent an integral component of the translation of a messenger RNA (mRNA) into an amino acid sequence. TRNAs are non-coding RNA molecules and can be found in all three kingdoms of life i.e., in archaea, bacteria and eukaryotes.

At the DNA level, a triplet of consecutive nucleotides known as the "codon" is used to encode an amino acid. Frequently, a given amino acid can be encoded by more than one codon: in fact, there are 61 distinct codons encoding the 20 standard human amino acids. During translation, each of the codons contained in the coding region of the mRNA at hand is recognized by its matching tRNA and the corresponding amino acid added to the nascent amino acid sequence. It has been known for many years that each of these 61 tRNAs has multiple copies spread throughout the genome that is found in the human nucleus. The presence of multiple genomic loci from which the same molecule can be made is a fairly standard trick of genomic organization: processing these loci in parallel can ensure that adequate amounts of each tRNA can be generated quickly enough to meet the high demand that the amino acid translation process imposes on the cell. In addition to the 61 tRNAs that are found in the human nuclear genome, 22 more tRNAs are encoded in the genome of the cellular organelle known as the mitochondrion: the mitochondrion, originally a bacterium itself, uses these 22 tRNAs to make proteins out of the just-over-a-dozen mRNAs that are encoded in its genome.

Recent research efforts have shown that tRNAs can have other roles, which go beyond their involvement in protein synthesis. For example, tRNAs can affect the physiology of a cell, they can modulate the abundance of important molecules, etc. These and other unexpected findings have revived interest in looking at tRNAs, this time under a different prism. But, how many tRNAs are actually encoded by the human genome and could be potentially involved in amino acid translation and other processes?

A team led by Isidore Rigoutsos, Director of the Computational Medicine Center at Thomas Jefferson University (TJU), set out to tackle this question and they have reported their findings in a study that was just published in the journal *Frontiers in Genetics*. "What we found,

frankly, surprised us," said Rigoutsos.

The team searched the 3 billion base pairs of the human genome for DNA sequences that resembled the 530 known nuclear and mitochondrial tRNAs. Even though they used very stringent criteria in their searches, they found 454 "lookalike" loci, i.e., sequences that look like tRNA, but haven't yet been experimentally confirmed as such. The researchers found nearly as many as the known ones with which they started: 81% of these tRNA-lookalikes had not been reported previously. Rather unexpectedly, the team found that most of these new loci resembled some of the 22 mitochondrial tRNAs.

Interestingly, the discovered tRNA lookalikes are not spread uniformly across the 24 chromosomes. Instead, they have penetrated preferentially some chromosomes and have avoided others. For example, chromosomes 1, 2, 7, 8 and 9 claim the lion's share of the discovered tRNA-lookalikes. On the other hand, chromosome 18 contains no lookalikes. Also, some of the codons are particularly over-represented among the lookalikes whereas other codons are absent.

The surprises did not stop there. The team also discovered that in the chromosomes where the tRNA-lookalikes are found their locations are not accidental either. Instead, the lookalikes are positioned in close proximity to known nuclear tRNAs. This of course begs the question whether the tRNA-lookalikes are transcribed, just like the known tRNAs. By examining public repositories, the team found evidence of transcription for more than 20% of the discovered tRNA-lookalikes: the transcriptional profiles appear to depend on cell type, which suggests that more of the look-alikes will be found to be transcribed as data from more cell types become available. On several occasions, the public data revealed evidence for molecules whose endpoints matched exactly the endpoints of the tRNA-lookalikes discovered by the team. "This is certainly exciting, but it is currently unclear whether these molecules

participate in translation as tRNAs, or have entirely different roles," said Rigoutsos.

More information: A.G. Telonis et al., "Nuclear and mitochondrial tRNA-lookalikes in the human genome," *Frontiers in Genetics*, DOI: 10.3389/fgene.2014.00344, 2014.

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