Advanced sequencing technology provides new insights into human mitochondrial diseases

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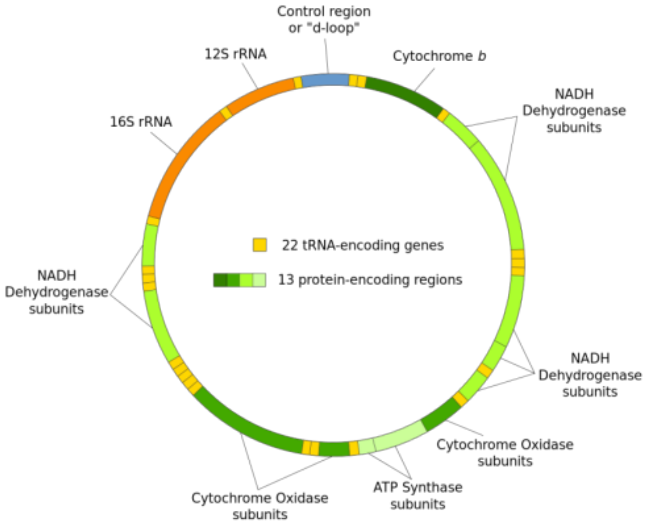

Structure of the human mitochondrial genome. Credit: Wikipedia/CC BY-SA 3.0

The ability to translate the genetic code into proteins is an essential step in all living organisms. A cornerstone of this molecular process is the ability of transfer RNA (tRNA) molecules to couple recognition of the genetic code with the cognate amino acid, which are the building blocks of proteins. Chemical modification of individual tRNAs is a critical step for the decoding process during protein synthesis.

Mitochondria are known as the powerhouse of the cell and an essential organelle that have a unique maternally-inherited genome and protein synthesis machinery devoted to aerobic energy production. Mutations in the tRNA genes encoded in the mitochondrial genome are the most frequent cause of human mitochondrial disorders.

Despite the fact that all mitochondrial DNA mutations disrupt energy production within the cell, specific mutations have distinct clinical symptoms. The molecular basis by which these disorders develop into diseases remains poorly understood.

One major deficit has been the lack of understanding of how primary genetic mutations in the mitochondrial genome affect all of the tRNAs and their respective chemical modifications. Past investigations into this topic have been hampered by technological limitations and the requirement for large amounts of patient material.

University of Helsinki researchers led by post-doctoral fellow Uwe Richter in the laboratory of Dr. Brendan Battersby at the Institute of Biotechnology, in collaboration with Tao Pan from the University of Chicago, overcame these limitations using the latest advances in methodological development of next-generation RNA sequencing to investigate the entire pool of mitochondrial tRNAs at single nucleotide resolution. The results of the study were published in the journal *Nature Communications*.

The approach allowed researchers for the first time to investigate the abundance and methyl modifications of all mitochondrial tRNAs in patients suffering from one of the most common inherited mitochondrial tRNA mutations, MERRF, or myoclonic epilepsy with ragged red fibers.

The analysis pipeline revealed quantitative changes in tRNA abundance and methyl modifications that had dramatic effects on protein synthesis within mitochondria. By restoring the modification, the group was able to delineate specific roles for the synthesis and also the stability of mitochondrial proteins. Collectively, the report sheds new light on the molecular mechanism in the development of human mitochondrial disorders.

More information: Uwe Richter et al, RNA modification landscape of the human mitochondrial tRNALys regulates protein synthesis, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06471-z

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