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Slight alterations in microRNA sequences hold more information than previously thought

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Researchers have encountered variants or isoforms in microRNAs (miRNAs) before, but assumed that these variants were accidental byproducts. A recent study, published in the journal *Oncotarget* this month, shows that certain so called isomiRs have abundances that depend on geographic subpopulations and gender and that the most prevalent variant of a given miRNA may not be the one typically listed in the public databases.

"This study shows that microRNA isoforms are much more common than we had previously assumed. The fact that some isoforms are shared by certain subpopulations or are more prominent in women than in men suggests that their presence likely serves a purpose and this warrants further study." says Isidore Rigoutsos, Director of the Center for Computational Medicine at Thomas Jefferson University (TJU).

MiRNAs are short non-coding RNAs approximately 22 nucleotides in length that were first discovered a little over 20 years ago. It was not long after their discovery that they began commanding the attention of many researchers worldwide thanks to their intimate involvement in many cellular events. We know now that miRNAs are regulators of protein-coding and also of non-protein-coding RNA transcripts and that they regulate the abundance of the affected transcripts, the miRNA "targets," in a sequence-dependent manner. What makes miRNAs so important is their involvement in fundamental processes such as development and

homeostasis. Not surprisingly, miRNAs and their dysregulation have also being linked to many human conditions, diseases, and syndromes.

MiRNAs, just like the messenger RNAs that code for proteins, have "isoforms" i.e. variants that arise from the same genomic locus and differ from one another by only 1-2 letters at either their left or right terminus. Different variants of a given miRNA typically have different abundances compared to that of the 'representative' isoform of the locus which is also the one that is generally listed in the public databases.

For many years, miRNA isoforms had been thought of as inconsequential. However, the advent of next generation sequencing, or deep sequencing, is now enabling scientists to take a higher-resolution look at these molecular events.

A TJU team led by Rigoutsos analyzed deep sequencing data from lymphoblastoid cell lines (LCLs) derived from 452 men and women from five different population groups capturing four European and one African ancestries. The team discovered that the isomiRs in these LCLs exhibit expression profiles that are population-dependent and gender-dependent with differences existing even among the European populations. By analyzing independently obtained experimental data, the team was able to generate additional evidence showing that many of the isomiRs they identified could also associate with the Argonaute silencing complex, suggesting that these miRNA variants participate in the RNA interference pathway and have functional roles just like the 'representative' miRNA from the corresponding locus. What these functional roles are and how they differ for each variant is only beginning to be understood. Even though the TJU team worked with LCLs, Dr. Rigoutsos states that "one can reasonably assume that analogous observations likely hold true for other cell types as well."

The team's findings have several implications: For researchers they

suggest that the assays currently in the market do not necessarily capture the variant that is prevalent in the cells with which a researcher works, instead measuring a less abundant isoform that is perhaps nonessential for the cell or tissue type at hand. The findings suggest that even cell lines from the same tissue could have more differences than they have similarities. For patients, the findings represent an opportunity for a potentially significant advantage: the knowledge that a given patient has a different molecular profile than another patient with the same disease is a very important piece of information that physicians can use to the patient's benefit when deciding which course of medical treatment to follow.

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