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Study nearly triples the locations in the human genome that harbor microRNAs

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According to the public databases, there are currently approximately 1,900 locations in the human genome that produce microRNAs (miRNAs), the small and powerful non-coding molecules that regulate numerous cellular processes by reducing the abundance of their targets. New research published in the *Proceedings of the National Academy of Sciences (PNAS)* this week adds another roughly 3,400 such locations to that list. Many of the miRNA molecules that are produced from these newly discovered locations are tissue-specific and also human-specific. The finding has big implications for research into how miRNAs drive disease.

"By analyzing human deep-sequencing data, we discovered many new locations in the human genome that produce miRNAs. Our findings effectively triple the number of miRNA-generating loci that are now known" says Isidore Rigoutsos, Ph.D., Director of the Computational Medicine Center at Thomas Jefferson University, who led the study. "This new collection will help researchers gain insights into the multiple roles that miRNAs play in various tissues and diseases."

For nearly three years, the team collected and sequenced RNA from dozens of healthy and diseased individuals. The samples came from pancreas, breast, platelets, blood, prostate, and brain. To their collection they also added publicly available data eventually reaching more than 1,300 analyzed samples representing 13 human tissue types. Their analyses uncovered 3,356 new locations in the human genome that generate over 3,700 previously undescribed miRNAs.

For a handful of the 13 tissues they studied, the team also had access to information describing miRNA association with Argonaute, an essential protein member of the regulatory complex that enables miRNA to interact with their targets. They found that 45 percent of the newly discovered miRNAs were in fact associated with Argonaute, a further indication that these molecules are involved in gene regulation. "We anticipate that many more of the newly discovered miRNAs will be found loaded on Argonaute as additional such data become available for the other tissues," says Eric Londin, Ph.D., an Assistant Professor and co-first author together with Phillipe Loher, M.S., a computational biologist and software engineer, both members of Jefferson's Computational Medicine Center.

One of the key design choices that the team made was to not limit their search to conserved genomic sequences, i.e. to only those sequences that are shared across multiple organisms. Instead the researchers scanned the genome much more broadly. "Advances in sequencing technology of the last several years made it easier to generate more data, from more tissues, and do so faster," says Dr. Rigoutsos who is also a researcher at the Sidney Kimmel Cancer Center at Jefferson. "Investigating the alluring possibility that miRNAs with important roles might exist only in humans was within reach. And this is what we set out to do."

Of the new molecules, 56.7 are specific to humans and most of them (94.4 percent) are found only in primates. Because of this organism-specificity these RNA molecules are involved in regulatory events that are absent from model organisms such as mouse and the fruit fly.

Tissue-specificity is another important characteristic of these new miRNAs. It means that these molecules are behind molecular events that are present in a single tissue, or in only a few tissues. Some of these molecules could potentially prove useful as novel tissue-specific disease biomarkers.

The tissue- and primate-specificity of the new molecules are expected to have important implications for the community's attempts to understand the causes of diseases. A first step in that direction requires the identification and validation of the targets for each of these 3,707 new miRNAs. To assist in these efforts, the team generated computational predictions of each miRNA's putative targets that are available from the Computational Medicine Center's website.

More information: *PNAS*
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