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Primate-specific microRNAs found

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Israeli scientists have identified what may be the first microRNAs specific to primates, in research published online June 19 in *Nature Genetics*. They suggest these new microRNAs might mean that hundreds remain to be found in the human genome.

"Finding a group of genes that is specific to primates is very important for understanding our evolution, and bears significant diagnostic and therapeutic potential," lead researcher Isaac Bentwich, at Rosetta Genomics in Rehovot, told *The Scientist*.

MicroRNAs are single-stranded RNAs roughly 22 nucleotides long that regulate gene expression by binding to target gene mRNAs. The DNA sequence that codes for a microRNA gene includes the microRNA sequence and a nearby complementary sequence that, when transcribed, form a double-stranded RNA hairpin loop.

Past studies have identified 222 human microRNAs, of which scientists had confirmed the sequences of only 86 in humans. To uncover more, Bentwich and colleagues computationally folded the entire human genome into hairpins 55 nucleotides or longer. Of 11 million potential hairpins, 434,239 appeared to be viable microRNA candidates.

"Conventional approaches start with genome comparisons, to identify sequences important enough to be conserved across species. This new approach doesn't start with genome alignments. This allows them to find microRNAs not conserved beyond primates," Victor Ambros of Dartmouth Medical School in Hanover, N.H., who did not participate in this study, told *The Scientist.*

Of the initial candidates, Bentwich and colleagues selected a representative sample of 5,300 as a manageable amount for high-throughput microarray experiments in placenta, testis, thymus, brain and prostate—revealing 886 that were expressed. Using 359 of these for cloning and sequencing, the researchers confirmed 89 new microRNAs.

"Given the thousands of predictions they generate, of which many are false positives, the high-throughput validation procedure they have developed is essential," Chris Burge at the Massachusetts Institute of Technology (MIT) in Cambridge, who did not participate in this study, told *The Scientist*.

Extrapolating from their findings, Bentwich and colleagues estimate the human genome contains at least 800 microRNAs. The first estimate of human microRNA number from the labs of Burge and David Bartel of the Whitehead Institute and MIT in 2003 was no more than 255, but since then they and others have acknowledged that figure as low.

Fifty-three of the new microRNAs are located in two large clusters apparently unique to primates, unlike all other known human microRNA clusters, which are found in all mammals. One cluster, located on chromosome 19 and expressed only in placenta, is the largest ever reported and comprises 54 new microRNAs. The second cluster is located on the X chromosome and includes 10 microRNAs expressed only in testis.

Burge noted the 5' ends of the sequences in the larger cluster in many cases match those of sequences in a cluster of roughly 90 zebrafish microRNAs described in the May 6 issue of *Science*, where the microRNAs are also quite similar to one another and are conserved in other fish but not to mammals. The 5' end of a microRNA is believed to be of primary importance in specifying which mRNAs it regulates.

"Perhaps there are two different types of microRNA cluster—ones that are conserved with a small number of copies, and those that are not conserved in recent evolution that are present in many copies," Burge suggested.

He noted that the two clusters described by Bentwich's group are in tissues that need to proliferate rapidly, while the zebrafish cluster is expressed in the first 48 hours of development. "So perhaps if you're a regulatory molecule like a microRNA that may regulate a very large number of mRNAs, in order to have an impact on a rapidly proliferating cell type that is churning out mRNAs, maybe you need lots of gene copies, because every time you divide, you dilute out microRNAs."

A future challenge, Burge noted, is predicting the targets of nonconserved microRNAs. "For the conserved microRNAs, we have lists of thousands of conserved mRNA targets they're likely to regulate. But for these nonconserved microRNAs, we don't know yet."

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