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RiboSNitches reveal heredity in RNA secondary structure

RNA structure is known to affect gene expression but the mechanisms behind this phenomenon are unclear. Wan *et al.* determined how heritable changes in RNA structure affect gene expression by examining the RNA secondary structure (RSS) across the genome of each member of a family trio that consists of a mother, a father and their child.

The authors determined the genome-wide RSS patterns by comparing the deep sequencing reads of RNA samples that have been treated with RNase V1 and S1 nuclease, which are specific to double-stranded and single-stranded RNA, respectively. They also used methods to analyse the familial RSS under native deproteinized conditions and contrasted the information obtained with that found in *in vitro* renatured RNA samples. Overall, native and renatured mRNAs show similar RSS features, which suggests that sequence is a strong determinant of structure but that there are also notable deviations. In addition, they also found that 5.7% of regions consistently differed between native and renatured profiles, which suggests that they contain sites for RSS regulation *in vivo*. They also identified unique RSS signatures for post-transcriptional regulation, including a signature that marks exon–exon boundaries, which may contribute to RNA splicing, and defined binding sites for microRNAs (miRNAs).

Armed with this genome-wide map of the RSS landscape, the authors then asked, how does it change in related individuals? To address this, the authors determined which single-nucleotide variants (SNVs) affected RSS by calculating structural changes between pairs of alternative SNVs at the same site. The SNVs that affected RSS — dubbed ‘riboSNitches’ — constitute ~15% of all transcribed SNVs in the family trio, which is far more than expected. Moreover, allele-specific mapping in the child validated 61% of all homozygous riboSNitches and showed that these were found in native deproteinized samples, which suggests that they are biologically relevant *in vivo*.

Given this surprisingly high number of riboSNitches, the authors then determined whether they influence disease-related gene expression. Correlating their riboSNitch data with expression quantitative trait locus data, they found that 211 riboSNitches were positively correlated with changes in gene expression and identified 22 unique riboSNitches that are associated with human diseases, including asthma and Parkinson’s disease. As not all SNVs are associated with coding regions, this suggests that changes in non-coding regions that affect RNA structure have consequences on gene expression.

Finally, the authors looked at the distribution of riboSNitches throughout the genome. They rationalized that a riboSNitch will be selected against if it disrupts function and found that riboSNitches are significantly depleted both in the 3’ untranslated regions of mRNAs and around predicted miRNA-binding sites. In addition, riboSNitches that are located near splice junctions are associated with greater alternative splicing changes, which suggests that RSS could also regulate gene expression through splicing.

Collectively, these results offer a genome-wide view of the landscape and variation of RSSs and give insights into the role of RNA structure in gene regulation, thus providing a basis for future study into the importance of RSS across the transcriptome.

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ORIGINAL RESEARCH PAPER Wan, Y. *et al.* Landscape and variation of RNA secondary structure across the human transcriptome. *Nature* **505**, 706–709 (2014)