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snoDB 2.0: an enhanced interactive database, specializing in human snoRNAs

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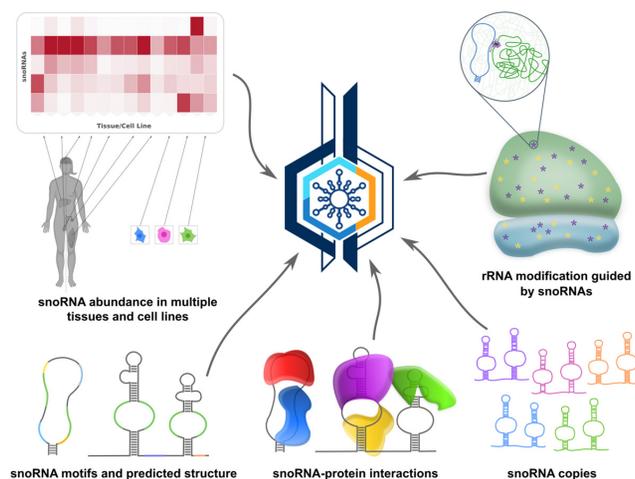
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ABSTRACT

snoDB is an interactive database of human small nucleolar RNAs (snoRNAs) that includes up-to-date information on snoRNA features, genomic location, conservation, host gene, snoRNA–RNA targets and snoRNA abundance and provides links to other resources. In the second edition of this database (snoDB 2.0), we added an entirely new section on ribosomal RNA (rRNA) chemical modifications guided by snoRNAs with easy navigation between the different rRNA versions used in the literature and experimentally measured levels of modification. We also included new layers of information, including snoRNA motifs, secondary structure prediction, snoRNA–protein interactions, copy annotations and low structure bias expression data in a wide panel of tissues and cell lines to bolster functional probing of snoRNA biology. Version 2.0 features updated identifiers, more links to external resources and duplicate entry resolution. As a result, snoDB 2.0, which is freely available at <https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/>, represents a one-stop shop for snoRNA features, rRNA modification targets, functional impact and potential regulators.

GRAPHICAL ABSTRACT



INTRODUCTION

Small nucleolar RNAs (snoRNAs) are small non-coding RNAs ranging in size from 60 to 300 nucleotides and encoded in all eukaryotic genomes annotated so far. Based on their characteristic RNA motifs and protein-binding partners, they are classified into two groups, the box C/D snoRNAs and the box H/ACA snoRNAs, best characterized for their role in guiding, respectively, the 2'-O-ribose methylation and the pseudouridylation of ribosomal RNAs (rRNAs) and small nuclear RNAs (snRNAs). However, in the last two decades, a handful of snoRNAs have been shown to be involved in the regulation of a multitude of other cellular processes such as alternative splicing (1–3), 3' end processing (4), exosome recruitment (5) and chromatin

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remodelling (6) through either RNA or protein interactions. Moreover, a plethora of studies found that snoRNAs are dysregulated in many cancer types and other diseases (7–11).

The study of snoRNAs and their complex family relationships involves several technical challenges. These include the very stable structure of snoRNAs and, more specific to mammals, their high copy numbers in genomes and their genomic location in introns of longer genes referred to as their host genes (12–14). These challenges are compounded by other factors related to our limited knowledge of these small RNAs and the few reliable datasets detecting them and their targets accurately. For example, the functions of chemical modification in rRNAs guided by snoRNAs, while being extensively studied, are not yet fully understood [e.g. (15–20)]. Indeed, for a long time, it was accepted that these chemical modifications are present on all rRNA molecules to maintain their conserved structures. However, with the emergence of advanced techniques to detect the level of chemical modification in rRNAs, such as RiboMethSeq (21) or HydraPsiSeq (22), it was recently shown that some positions are only partially modified and that the level of modification could vary in different cell lines, conditions or in certain pathologies (15,17,20,22–24). Furthermore, although there is currently a massive amount of publicly available RNA-seq datasets, few provide a reliable and realistic quantification for snoRNAs. TGIRT-seq, a sequencing method using a thermostable reverse transcriptase, is one such method that performs well for highly structured RNAs such as transfer RNAs and snoRNAs (12,25,26).

For the study of human snoRNAs, four dedicated databases are currently publicly available. snoRNABase (27), available since 2005, provides information about snoRNA sequences, rRNA and snRNA targets as well as their host genes, but is no longer regularly updated and is lacking many human snoRNAs present in other resources. snoRNA Atlas provides information about chromosomal location, conservation, average abundance and targets (28), while snOPY is focused on snoRNA orthology relationships across eukaryotes (29). As a complementary resource, we developed in 2018 snoDB (30), an interactive specialized human snoRNA database offering up-to-date information obtained from general and snoRNA-specific resources as well as our low structure bias TGIRT-seq datasets. We now provide snoDB 2.0, a second version with updated identifiers and updated links to other resources, correction for duplicate entries and most importantly diverse new data presented in an interactive format. snoDB now includes snoRNA–protein interaction data, information on the different copies of each snoRNA, snoRNA motifs and domains, secondary structure prediction, TGIRT-seq abundance data for 9 tissues and 5 cell lines (for a total of 37 samples) and a brand new section on rRNA modifications guided by snoRNAs.

DATABASE CONTENT

To ensure that the information is as up to date as possible, we obtained data from the latest versions of all the resources that were originally considered for the first version of snoDB. One of the problems we faced with the

original version was the redundancy of some entries (Supplementary Figure S1). Indeed, some overlapping snoRNAs having as few as one nucleotide difference in 5', 3' or both were present as two or more distinct entries in snoDB (as well as in other resources), with their own sets of IDs and missing information. To solve this problem in version 2.0, we merged overlapping entries, ensuring that one genomic location was associated with only one snoRNA. Because we had no way of knowing the true beginning and end of a snoRNA, we prioritized information (e.g. genomic location, gene name, etc.) from some resources over others. We arbitrarily prioritized, in the following order, Ensembl (V104) (31), RefSeq (V109) (32), snoRNA Atlas (July 2021) (28) and snOPY (July 2021) (29) annotations. Ensembl itself has duplicate entries for some snoRNAs in its annotation file. In these cases, we chose snoRNAs starting with 'SNOR' first; otherwise, we prioritized the longest of the entries. In all cases, we used a concatenation of the IDs (e.g. ENSG00000281910;ENSG00000206952) to help the user to easily identify their snoRNAs of interest. We also included links (all obtained in July 2021) from HGNC (33), NCBI (34), snoRNABase (27), RNACentral (35) and Rfam (36). When possible, we used the Infernal package to add missing Rfam IDs as recommended by Rfam (36). snoDB 2.0 now contains 2123 non-redundant entries.

Along with all the features that were originally included in the first version of snoDB (30), we now have additional evolutionary conservation information, sequence annotations, a predicted secondary structure, protein interaction data and copy information for all snoRNAs in snoDB as well as the level of abundance of snoRNAs and of their host gene. snoDB now presents a conservation score that was extracted from the UCSC Genome Browser, PhastCons track for 100 vertebrates (37,38) for each snoRNA. In addition, each entry now also features a secondary structure predicted using RNAfold and RNAplot from the Vienna package (39) in which the predicted snoRNA sequence motifs and guide regions can be highlighted. snoDB already contained information on RNA interacting partners of snoRNAs, to which we have added a section on snoRNA–protein interactions, extracted from eCLIP datasets of 150 RNA-binding proteins from the Encyclopedia of DNA Elements (ENCODE) Consortium (40). We also added a section on family members (based on Rfam classification), which is important when analysing snoRNAs by PCR, for example, since such snoRNAs often have very similar sequences. Finally, the abundance of snoRNAs and their host genes was obtained from 37 datasets that use the low structure bias TGIRT-seq approach (12,22,23) (GEO entries GSE126797, GSE157846, GSE99065 and GSE209924, and SRA entries SRX1426160 and SRX1426193). For all these newly added characteristics, more details are available in the About/Help section of the database.

To improve snoRNA quantification from RNA-seq datasets, we create a simple tool called snoRupdate. Indeed, to avoid biases due to the lack of some snoRNAs from current annotation files (e.g. gene transfer format), it is important to complete these annotations before performing RNA-seq analysis. For this purpose, snoRupdate, accessible from the main page or directly from GitHub (<https://github.com/scottgroup/snoRupdate>), is designed to

add all missing snoRNAs from snoDB to the provided annotation file.

Finally, in this second version of the database, we added a completely new section on chemical modifications of rRNAs, which includes snoRNA–rRNA interaction sites, widely used rRNA sequences with conversion between them and modification levels for known modified rRNA positions. The rRNA modification sites were taken from snoRNABase (27), snoRNA Atlas (28), Krogh *et al.* (41) and Kehr *et al.* (42). Modification site annotations are dependent on rRNA sequences, and several versions of rRNAs are used in the literature (Supplementary Table S1). Lastly, rRNA modification levels were extracted from four studies using RiboMethSeq (17,23), HydraPsiSeq (22) or SILNAS (24).

WEB INTERFACE

Main page

On the main page, we made changes taking care to keep the interface similar enough to allow a smooth transition for users of the previous version. The navigation bar, on the top right panel, now includes a change log page, which allows to track changes made in future versions and to have access to old versions, a new rRNA chemical modification section (discussed further below), a link to snoRupdate (described above) and finally a sequence search tool section embedding a widget designed by RNAcentral (35) that enables the comparison of an input sequence against a large collection of non-coding RNAs.

The bottom of the page presents the main snoRNA interactive table, the columns of which can be controlled using the ‘Column visibility’ button. In version 2.0, we generated unique snoDB identifiers and use them for navigation through the website. The table can be easily filtered using the multiple search fields (see the tutorial section for advanced usage). As in the previous version, all the information in the main table, or only a selection, can be exported in different formats (xlsx, tsv, bed and now in fasta). Individual rows can also be selected to export only a part of the visible data.

snoRNA abundance visualization page

snoDB now provides abundance data from a considerably larger number of samples (9 tissues and 5 cell lines consisting in total of 37 datasets). We thus dedicated an independent page to the visualization of abundance, accessible through a button at the top right of the table of the main page, employing the Clustergrammer-JS and Clustergrammer-PY libraries (43), to provide an interactive heatmap. From the main table, the abundance profiles for all entries, or only a subpart (filtered and/or selected), can be observed simultaneously. The abundance data of all 37 samples can also be easily downloaded from this page.

Individual snoRNA pages

Aside from the main page, snoDB also has an individual page dedicated to each snoRNA. In this detailed view, all the information contained in the table from the main page

on a particular snoRNA is recorded. In this updated version, it is possible to visualize important motifs (boxes and guide regions) of a snoRNA, and its predicted secondary structure by toggling two buttons in the first section. Furthermore, since snoRNA copies can often be a problem, as they are not so easy to find and are thus often overlooked, we included in this page a section listing all copies of a snoRNA. These copies can also be further investigated by clicking on ‘Inspect copies in main table’. When redirected, the information for the different entries can be exported in different formats and the level of abundance of all the snoRNA copies can be viewed in a heatmap. Next, in addition to snoRNA–RNA interactions, we also added a section dedicated to snoRNA–protein interactions. This section lists the RNA-binding proteins reported to bind to the snoRNA, the cell line in which the experiment was conducted, a *P*-value for the interaction and a score [obtained from ENCODE (40)]. Finally, instead of using a table for the level of abundance of the snoRNA and its host gene, they are now available as interactive box plots.

rRNA chemical modifications

One of the significant additions of the snoDB 2.0 new release is the rRNA modification section, which contains four subsections accessible via the different top tabs: rRNA modifications, rRNA sequences, conversion table and modification levels (Figure 1A). The rRNA modification subsection includes an interactive table of all listed snoRNA–rRNA interactions. The status of the modification (i.e. whether the modification site has been validated by one or more techniques) is also mentioned to avoid confusion due to some predicted sites not being modified. The whole, or only the desired part, can be copied or exported in csv or xlsx formats. Next, the rRNA sequence tab enables visualization of the most widely used rRNA sequences. Validated modified positions are annotated and color-coded [2′-*O*-ribose methylation (Nm), pseudouridylation (Ψ) or both], and clicking on any of these modified sites returns snoRNAs predicted to modify this position, as well as a clickable link to the detailed view for the snoRNAs. The third subsection is a conversion table between different versions of rRNAs used in different articles and references. Any position can be searched, and the table contains the position in each different rRNA reference sequence as well as the nucleotide at this specific position. The whole table or a part can also be copied or exported in csv or xlsx formats. The last tab refers to a section where one can visualize the level of modification observed by different techniques and independent groups, in different tissues and cell lines (Figure 1), with the provision that rigorous comparisons cannot be made between the datasets because different methods were employed. By selecting the modification type (2′-*O*-ribose methylation or pseudouridylation; Figure 1B), the rRNA molecule (18S, 28S or 5.8S; Figure 1C) and the study (all the studies or only a single one; Figure 1D), the user sees a box plot displaying a compilation of all the modification levels for each position (Figure 1E). From there, it is possible to search a position with the top left input field (or by clicking on the chart; Figure 1F), reorder the rRNA positions according to position, coefficient of variation or mean

rRNA chemical modifications

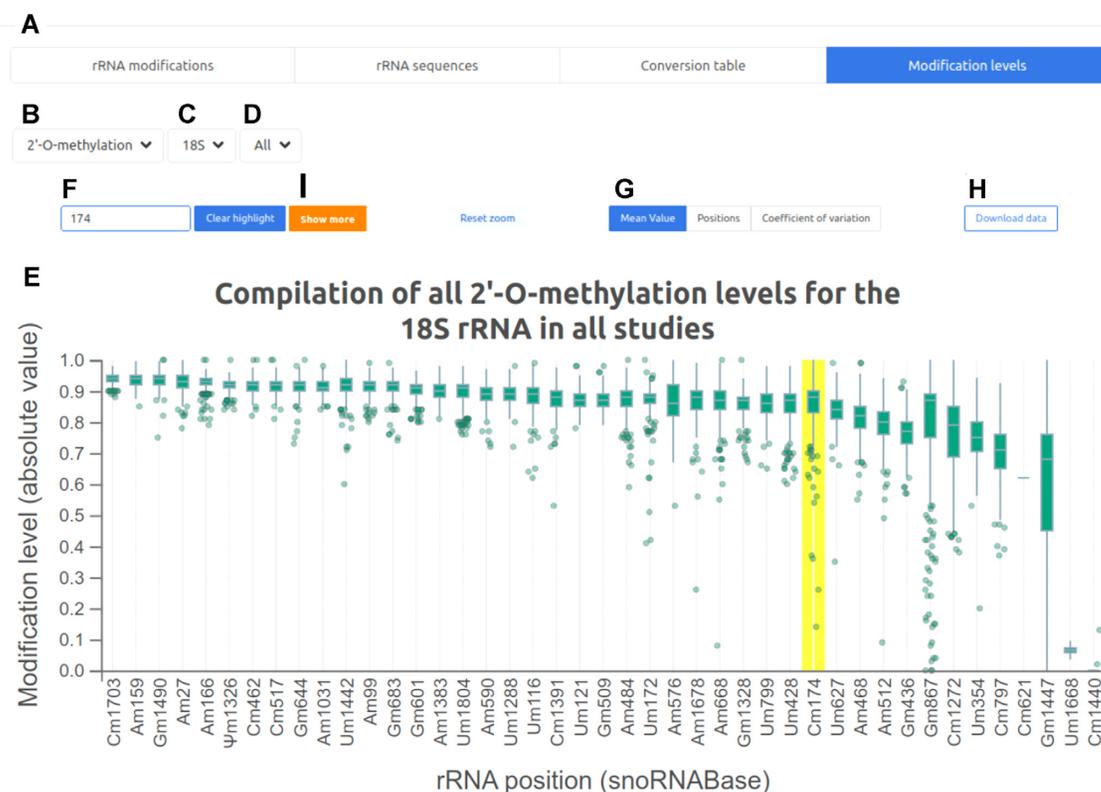


Figure 1. Screenshot of the ‘Modification levels’ tab, one of the four subsections of the new rRNA chemical modification section. (A) Four tabs corresponding to each of the new subsections: rRNA modifications, rRNA sequences, conversion table and modification levels. (B–D) Modification type (2'-O-ribose methylation or pseudouridylation), rRNA molecule (18S, 28S or 5.8S) and study (all the studies or only a single one) to choose from. (E) Box plot displaying a compilation of the levels of all modified positions. (F) Search field used to look for a specific modified position. (G) Buttons to reorder the box plot according to mean value, position or coefficient of variation. (H) ‘Download data’ button to download the raw data used to generate the chart. (I) ‘Show more’ button used to get a more detailed view of the level of modification of a single position (see Supplementary Figure S2).

value (default sorting) (Figure 1G) and change the zoom of the chart. The entire dataset used to generate the box plot can be exported using the ‘Download data’ button (Figure 1H). When a position is highlighted in the chart, an orange button appears (Figure 1I), which provides the user with a more detailed view of the level of modification, in a dot plot representation, of a single site across different previously selected cell lines and studies (Supplementary Figure S2).

CONCLUSION AND FUTURE PLANS

snoDB aims to provide the community with an efficient way to navigate through the most up-to-date snoRNA data. This second version of snoDB has kept its user-friendly interface with its main overview table and individual snoRNA pages, but on top of the consolidation and addition of missing snoRNAs, many more characteristics of snoRNAs are now available, including sequence motifs and structures, copy identification, considerably more abundance data and snoRNA–protein interactions. We also added a completely new section on rRNA modifications. Our future plans, in addition to periodic updates of the current information contained in the database, include providing the same level of information on snoRNAs from other species.

DATA AVAILABILITY

snoDB 2.0 is freely available at <https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/>.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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