NONCODEV6: an updated database dedicated to long non-coding RNA annotation in both animals and plants

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ABSTRACT

NONCODE (http://www.noncode.org/) is a comprehensive database of collection and annotation of noncoding RNAs, especially long non-coding RNAs (lncRNAs) in animals. NONCODEV6 is dedicated to providing the full scope of lncRNAs across plants and animals. The number of lncRNAs in NONCODEV6 has increased from 548 640 to 644 510 since the last update in 2017. The number of human lncRNAs has increased from 172 216 to 173 112. The number of mouse IncRNAs increased from 131 697 to 131 974. The number of plant IncRNAs is 94 697. The relationship between lncRNAs in human and cancer were updated with transcriptome sequencing profiles. Three important new features were also introduced in NONCODEV6: (i) updated human lncRNA-disease relationships, especially cancer; (ii) lncRNA annotations with tissue expression profiles and predicted function in five common plants; iii) lncRNAs conservation annotation at transcript level for 23 plant species. NONCODEV6 is accessible through http://www.noncode.org/.

INTRODUCTION

There are vast majority of transcribed sequences that do not encode proteins called non-coding RNAs (ncRNAs). Long non-coding RNAs (lncRNAs) are ncRNAs that are >200 nt in length (1–3). Many types of research showed that lncRNAs play key roles in different kinds of biological processes in animals, such as circuity controlling pluripotency and differentiation, imprinting control, immune responses and chromosome dynamics (4–7). LncRNAs are also implicated in human diseases, with much attention focused on their involvement in cancer progression and development (8–9).

Of the articles retrieved from PubMed (10) about lncRNAs, we found that a large number of studies focused on lncRNA functions, especially the relationships between lncRNAs and cancers (11). It is increasingly evident that many genomic variations related to cancer reside inside regions that do not encode proteins. However, these regions are often transcribed into lncRNAs (12). The last version of NONCODE collected relationships between lncRNAs and cancers through literature mining and mutation analyses from public genome-wide association study (GWAS) data (13). NONCODEV6 obtains relationships between lncRNAs and cancers from known databases like Lnc2Cancer (14) and literature mining. Recently, studies on
transcriptome sequencing profiles revealed that IncRNAs may involve in cancer by interaction with cancer-related genes, such as RAS family (15). The recent application of next-generation sequencing to a growing number of cancer transcriptomes has indeed revealed thousands of IncRNAs whose aberrant expression is associated with different cancer types (16).

The numbers of IncRNAs found in plants are usually an order of magnitude lower than in animals, but they still constitute an important component of their transcriptomes (17). Since great importance has been attached to IncRNAs, large-scale identification and deep analysis on plant IncRNAs are in need (18). To this end, we took advantage of publicly available RNA-seq datasets for calculating their expression values and identifying homologs of IncRNAs. We then aimed to explore their potential functions (19).

In this update of NONCODE database, we collected high-confidence datasets of plant IncRNA and developed a pipeline to annotate IncRNAs in plants. The pipeline was applied to 23 plant species. NONCODEV6 provides information including sequence, genome position, CNIT score, conservation, tissue expression profiles and functional prediction for five common plant species. The goal of NONCODEV6 is to be a meeting point for IncRNA research in both plants and animals. NONCODEV6 is freely available at http://www.noncode.org/.

Data collection and processing

Similar to the former update, the current release incorporates data sources of the previous versions of NONCODE (13,20–24), public literature and other IncRNA databases. We used ‘ncrna’, ‘noncoding’, ‘non-coding’, ‘non-code’, ‘LncRNA’ and ‘lincRNA’ as keywords to retrieve literature related to IncRNAs in PubMed. We found 57872 articles in the last 10 years about IncRNAs in plants and 51771 new articles since 22 June 2017 (the last update of NONCODE) about IncRNAs in human and mice. The newly identified IncRNAs and their annotations were retrieved from the supplementary material or corresponding websites. The related IncRNA databases include Ensembl (25), RefSeq (26), lncRNAdb (27), LNCipedia (28), CANTATAdb (29), GREENC (30) and the old versions of NONCODE. All of the collected data were processed through a standard pipeline, which includes the following steps:

(i) Format normalization. All input data were processed into bed or gtf formats based on one assembly version. For example, TAIR 10 and TAIR 9 are two different assembly versions of Arabidopsis thaliana. All of the related data were converted into the TAIR 10 version.

(ii) Multi-source data combination. All of the normalized data files were combined using the Cuffcompare program in the Cufflinks suite (31).

(iii) Protein-coding RNA filtration. We filtered out protein-coding RNA using two methods. First, all RNAs were compared with the coding RNAs in RefSeq and Ensembl. Second, CNIT (Coding-NonCoding Identifying Tool) (32) was used to filter the RNAs and only the RNAs considered noncoding by CNIT were kept.

(iv) General information presentation. Location, exons, length, assembly sequence, source are listed in each transcript.

(v) Expression profiles and functional prediction in plants. Corresponding information in five common plants out of 23 is shown. Their expression profiles were curated from multiple tissues. Detailed data sources were listed in Supplementary Table S1. Functions for IncRNAs were predicted based on their co-expressed coding genes (34).

(vi) Conservation analysis at transcript level. The conservation of plant IncRNAs analysis was conducted with BLAST (35,36). The E-value cut-off was 1e-10. Each transcript in a plant species was blasted against each transcript in other 22 plant species.

(vii) Web presentation. New web pages, especially for plants, were constructed in NONCODEV6. More annotation information has been updated (52).

Statistical analysis of NONCODEV6

NONCODEV6 contains 644510 IncRNA transcripts from 39 species including 16 animals and 23 plants. A total of 96411 and 87890 genes were generated from 173112 and 131974 transcripts in human and mouse transcripts, respectively. Corresponding expression profiles and predicted functions were provided.

A total of 94697 IncRNAs from 23 plant species (A. thaliana, Cucumis sativus, Brassica napus, Brassica rapa, Chenopodium quinoa, Chlamydomonas reinhardtii, Glycine max, Gossypium raimondii, Malus domestica, Manihot esculenta, Medicago truncatula, Musa acuminata, Oryza rufipogon, Oryza sativa Japonica Group, Physcomitrella patens, Populus trichocarpa, Solanum lycopersicum, Solanum tuberosum, Triticum aestivum, Theobroma cacao, Trifolium pratense, Vitis vinifera, Zea mays) are included. The number of IncRNAs and long non-coding RNA genes (IncGenes) in plants are shown in Figure 1. The total number of plant IncGenes was 68808. IncRNAs in plants were annotated using strict standards for assurance of high confidence. NONCODEV6 follows the nomenclature of the last version (13). Both IncRNA transcripts and genes are designated systematically: NON + three characters (representing a species) + T (transcript) or G (gene) + six sequential numbers.

The addition of IncRNAs in plants is a very important update in NONCODEV6. Figure 2 shows the distribution of IncRNAs in 23 plant species. In Figure 2A, the average length of IncRNAs in plants ranged from 462 bp of C. reinhardtii to 1033 bp of C. quinoa. Most IncRNAs in plants have two or three exons and the distribution of exon number was shown in Figure 2B. The average number of exons per IncRNA in plants ranged from 1.3 of C. reinhardtii to 2.3 of B. napus in Figure 2C.

LncRNAs in human and mouse

We used a set of keywords to search in PubMed and proceeded data collection from other databases. After data collection and filtration, the number of IncRNAs in human increased from 172216 to 173112. The number of IncRNAs...
in mouse increased from 131,697 to 131,974. LncRNAs in human and mouse were updated using the last version of NONCODE pipeline.

Recently, researches have been focusing on the relationships between lncRNAs and cancers in human. There is a strong need to collect high-quality lncRNA profiles in cancers, which will help to explore the function and mechanism of lncRNAs in cancer. We summarized lncRNA-cancer associated information from related databases and literature mining. Information from six databases (LncSpA (37), LncTarD (38), Lnc2Cancer (14), LncRNADisease (39), LncRNAWiki (40) and MNDR (41)) was collected. Lnc2Cancer is a manually curated database that provides comprehensive experimentally supported associations between lncRNA and human cancer. LncSpA is a lncRNA spatial atlas of expression across normal and cancer tissues. LncTarD provides key lncRNA-target regulations, their functions and lncRNA-mediated regulatory mechanisms in human diseases.

LncRNA-disease associations predicted by computational methods are not included in NONCODEV6 due to the uncertainty; only experimentally supported relationships are integrated into NONCODEV6. In summary, we obtained 13,749 records of lncRNA and disease related information. The basic statistics about lncRNAs related to different cancer types were shown in Figure 3.

### Plant lncRNAs expression profiles in tissues

RNA-seq data of different tissues in five common plants were collected, including *A. thaliana*, *Z. mays*, *S. lycopersicum*, *C. sativus* and *O. sativa* (Table 1). Tissue expression profiles were analyzed using STAR (42) and StringTie (43). Clean reads were mapped to the corresponding genome by STAR with the parameters ‘-outSAMtype BAM SortedByCoordinate -outSAMattributes All’. Then, the expression levels of all lncRNAs and mRNAs were quantified as transcripts per kilobase million (TPM) using StringTie. The detailed expression information can be queried by searching for specific lncRNAs in NONCODEV6 (Figure 4).

### Plant lncRNAs and function annotation

Functional annotation analysis was conducted on five plants, including *A. thaliana*, *Z. mays*, *S. lycopersicum*, *C. sativus* and *O. sativa*. To investigate the potential functions of lncRNAs, the RNA-seq data collected from different tissues were used to analyze the co-expression between coding genes and lncRNAs.

Genes with the expression of variance ranked in the top 75% were retained, then the expression was used to calculated Pearson’s correlation coefficient (Pcc) and *P*-value.
Figure 2. Distribution of lncRNAs in 23 plant species

Plant lncRNAs conservation at transcript level

NONCODE provided the human IncRNA conservation analysis in previous versions. Therefore, when we added IncRNA annotation for plant species in NONCODEv6, plant IncRNA conservation analysis was provided, as well. With sequence homology and conservation accepted as indicators of biological function, more attention has been paid to understanding the evolutionary dynamics of IncRNAs. The evolutionary history of IncRNAs can provide insights into their functionality (44), but the absence of IncRNA annotations in plants has precluded comparative analyses. To understand the biological significance and evolution of IncRNAs in plants, we conducted transcript level assessments of the conservation of IncRNAs across the 23 plant species (46). To assess the primary sequence conservation of the plant IncRNAs, we performed a multi-species comparison. The IncRNA sequences of each plant species were aligned against the other 22 plant species by BLASTn (35) with parameter \(-E\)-value \(1 \times 10^{-10}\) (47). The genomes of all plant species were downloaded from plant Ensembl and GenBank database (48). Our study provides the first step to understand the evolutionary conservation of IncRNAs in plants for further functional studies.

We calculated the IncRNA sequence similarity at the transcript level to facilitate IncRNAs study across species. Pair-wise conservation comparisons of IncRNAs in 23 plant species were conducted by BLAST. Same as previous plant conservation study (35), reciprocal best hits for each pair were extracted with a matched query proportion \(\geq 50\%\) and \(E\)-value \(\leq 1 \times 10^{-10}\). Only 122 orthologous IncRNAs were found to meet the thresholds. Most of the plant species show...
limited conserved orthologs at transcript level filtered by E-value and coverage. Three plant pairs have more orthologous lncRNAs at the transcript level, including *B. napus* and *B. rapa*; *O. rufipogon* and *O. sativa*; *S. lycopersicum* and *S. tuberosum*. Generally speaking, there is low sequence conservation among the majority of lncRNAs at the transcript level. The cut-off values can be customized according to users’ specific needs, and the output results could be further investigated at genome or other level analysis.

**DISCUSSION**

Determining the protein-coding ability of a transcript is a critical part of the identification of lncRNAs, yet it represents quite a challenging task. CNIT, as a newly updated version of CNCI (51), shows 99.3% accuracy when tested on plant protein-coding and long non-coding transcripts (29). CNIT can provide the confidence of lncRNAs noncoding status. The standard for lncRNAs in NONCODEv6 is very high compared with other methods.

The focus has shifted from novel lncRNAs detection to more in-depth research on lncRNAs including function and multiple annotations, along with the progress of related studies. Therefore, in the update of human lncRNA, we focused on the relationship between lncRNAs and cancer. NONCODEv6 is a comprehensive database dedicated to lncRNA annotation in both animals and plants. We provide complete annotations of lncRNAs and detailed information, including function prediction and expression profiles.

For plants, there are not comprehensive tissue RNA-seq data due to difficulties in genome alignment and scarce annotation data for lncRNAs. In consideration of the limited resources, tissue RNA-seq data were collected for only five plant species. Data from other species still needs to be collected. We will follow up with the latest released datasets to enrich the annotation of lncRNAs in plants continuously. The lncRNA conservation analysis in plants was difficult without comprehensive construction tools and datasets. In the future, we will add more levels of analysis for plant lncRNAs conservation.

**Table 1.** The tissue RNA-seq data used in NONCODEv6

| Species            | Tissue                                                                 | No. of tissues$^a$ |
|--------------------|------------------------------------------------------------------------|-------------------|
| *Arabidopsis thaliana* | flower receptacles, flower, root, whole seedlings, cotyledons, leaf, stems, sperm cells, mature pollen, seed | 10                |
| *Cucumis sativus*   | ovary, root, stem, leaf, male flower, tendril, tendril base, female flower | 8                 |
| *Solanum lycopersicum* | stem, floral, leaf, root, vegetative meristem, seedling             | 6                 |
| *Zea mays*          | seedling, root, shoot, ovule, pollen, embryo sac, leaf, immature tassel, endosperm | 9                 |
| *Oryza sativa*      | shoot, caryopsis, crown root, egg, embryonic root, endosperm, lateral root, leaves, pistil, seedling root, unicellular zygote | 11                |

$^a$ Detailed data sources were listed in Supplementary Table S1.
Figure 4. An example of tissue expression profiles for one lncRNA of *A. thaliana* with id NONATH000001.1.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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