ncRNA-disease association prediction based on sequence information and tripartite network

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Abstract

Background: Current technology has demonstrated that mutation and deregulation of non-coding RNAs (ncRNAs) are associated with diverse human diseases and important biological processes. Therefore, developing a novel computational method for predicting potential ncRNA-disease associations could benefit pathologists in understanding the correlation between ncRNAs and disease diagnosis, treatment, and prevention. However, only a few studies have investigated these associations in pathogenesis.

Results: This study utilizes a disease-target-ncRNA tripartite network, and computes prediction scores between each disease-ncRNA pair by integrating biological information derived from pairwise similarity based upon sequence expressions with weights obtained from a multi-layer resource allocation technique. Our proposed algorithm was evaluated based on a 5-fold-cross-validation with optimal kernel parameter tuning. In addition, we achieved an average AUC that varies from 0.75 without link cut to 0.57 with link cut methods, which outperforms a previous method using the same evaluation methodology. Furthermore, the algorithm predicted 23 ncRNA-disease associations supported by other independent biological experimental studies.

Conclusions: Taken together, these results demonstrate the capability and accuracy of predicting further biological significant associations between ncRNAs and diseases and highlight the importance of adding biological sequence information to enhance predictions.

Keywords: ncRNA-disease association predictions, Tripartite network, Resource allocation

Background

Recent studies have investigated the biological functions, transcriptome, and regulation of non-coding RNAs (ncRNAs) of all sizes in a wide range of organisms [1]. siRNA (short interfering RNA), miRNA (microRNA) and piRNA (piwi-interacting RNA) are the three main types of short ncRNAs (less than 30 nucleotides). They play an important role in histone modification, gene silencing, heterochromatin formation, and DNA methylation, targeting at the transcriptional and post-transcriptional levels. Long non-coding RNAs (lncRNAs), which are greater than 200 nucleotides, are relevant in fundamental processes of gene regulation, such as chromatin modification and transcriptional regulation [2]. Studies indicate that lncRNAs can be categorized in one or more of the four archetypes, which include signal archetype (molecular signal or transcriptional activity indicator), decoy archetype (measure and adjust the balance of RNA regulation), guide archetype (directs the localization of ribonucleoprotein complexes to their targets), and scaffold archetype (a structural role for relevant proteins or RNAs to resemble). However, the main functions, structures, and mechanisms of lncRNAs remain unknown [3].

Because of their categorization into the four archetypes, ncRNAs have been proposed to have strong...
connections with the development and pathophysiology of diseases. Computational and experimental studies have demonstrated that alteration and deregulation of both short ncRNAs and lncRNAs at the structural and expression levels, can cause various types of cancer, such as breast cancer, leukemia, hepatocellular, and colon cancer, as well as neurodegenerative disorders, cardiovascular diseases, and immune-mediated diseases [4].

X-inactive specific transcript (Xist) is a lncRNA located on the X chromosome of the placental mammals that plays an important role in the X inactivation process. Lee et al. [5] demonstrated that Xist is a potent suppressor of hematological cancer in mice. Xist is required for hematopoietic stem cell survival and function. Therefore, Xist deletion results in leukemia, marrow fibrosis, and histiocytic sarcoma.

Yang et al. [6] also demonstrated a strong correlation between lncRNAs in tumor tissues and hepatocellular carcinoma (HCC). According to their experimental results, Cox regression analysis showed that both lncRNAs H19 and UCA1 were serious risk factors for HCC. Furthermore, logistic regression also indicated that H19 was overexpressed in hepatitis B virus-infected individuals.

A study on lncRNA PRINS (Psoriasis susceptibility-related RNA Gene Induced by Stress) provides further evidence on an association between ncRNAs and diseases. PRINS is transcribed by RNA polymerase II and expressed at various levels of human tissues [7]. PRINS is believed to play a role in susceptibility to psoriasis and has been linked to autoimmune diseases [8].

These findings are representative of the small number of ncRNA-disease connections that have been functionally established. This poses a major obstacle for bio-physic...
To validate the performance of our proposed method, we conducted a 5-fold-cross-validation procedure to demonstrate its reliability, accuracy and efficiency, on a dataset reconstructed from Chen et al. (2013) [15]. In addition, by using a database of experimentally confirmed interactions between ncRNAs and miRNAs shown in Helwak et al. [16], we performed another validation of our proposed method. Our results demonstrate that our proposed method outperforms ncPred.

Methods
Data sources
In order to evaluate the performance of the approach, we prepared two kinds of data, ncRNA-target interaction matrix (LncRNADisease database (2015)) and target-disease interaction matrix (DisGeNET database) which are the same database sources used in Chen et al. (2013) [15], to form the tripartite network, as well as the sequence expression of those targets and ncRNAs (extracted from Uniprot and LncRNADisease databases, respectively). Since there are ncRNA sequence expressions and targets that are still unknown, we could only collect 76 ncRNAs, 109 targets, and 514 diseases (see Table 1). In Fig. 1, the degree distribution of the resulting network is shown. The results indicate that the entire network may follow a power law distribution. Moreover, we collected experimentally confirmed interactions between ncRNAs and miRNAs from the database shown in [16] and from Alaimo [13] Supplementary Information files and reconstructed another dataset composed on 151 ncNRAs, 179 targets and 134 diseases (see Helwak dataset in Table 1).

Computational approach
In our approach, disease-target and target-ncRNA interaction matrices are required to construct the tripartite network (See Fig. 2). Sequence expressions of both targets and ncRNAs are also needed to generate string-kernel features for the prediction method. The overall algorithm of our method is shown in Fig. 3.

Let \( D = \{d_1, d_2, ..., d_m\} \) be a set of diseases, let \( T = \{t_1, t_2, ..., t_n\} \) be a set of targets which refer to genes or microRNA, and let \( R = \{r_1, r_2, ..., r_p\} \) be a set of non-coding RNAs. Let \( SR^l = \{sr_1^l, sr_2^l, ..., sr_p^l\} \) and let \( ST^l = \{st_1^l, st_2^l, ..., st_n^l\} \) be sets of the sequence expressions of the targets and ncRNAs respectively.

L-gram-string kernel feature extraction and standardization
In our approach, the features of sequence expressions were extracted via the \( l\)-gram-string kernel method [17], in which each string is transformed into a vector consisting of the number of occurrences of each substring of length \( l \). In bioinformatics, string kernel is considered a function that measures the similarity of a pair of sequence expressions (strings) with finite length, for the purpose of generating real-value feature vectors. In our case, the method was evaluated experimentally using length \( l = 1, 2, 3 \) and 4.

| Table 1 Description of the datasets |
|-------------------------------------|
| Type of Data                  | Chen et al | Helwak et al. |
| Diseases                      | 514        | 134           |
| Targets                       | 109        | 179           |
| ncRNAs                        | 76         | 151           |
| Disease-target interactions    | 580        | 1572          |
| Target-ncRNA interactions      | 111        | 610           |
| Average degree                | 1,977      | 9,405         |
In order to improve the quality and reduce the redundancy of the computed features from the previous step, the standardization method below was applied [18].

\[
x' = \frac{x - \bar{x}}{\sigma},
\]

where \(x\) is the original feature vector, \(\bar{x}\) is the mean and \(\sigma\) is the standard deviation.

Thus, let \(SST^d = \{sst_1^d, sst_2^d, \ldots, sst_n^d\}\) and \(SSR^d = \{ssr_1^d, ssr_2^d, \ldots, ssr_p^d\}\) be sets of the normalized real-value feature vectors computed from the sequence expressions of the targets and ncRNAs respectively.

**RBF kernel similarity among ncRNAs and targets**

To effectively compute the similarity among each pair of ncRNA-ncRNA and target-target, the RBF kernel similarity technique was employed. In statistical learning, RBF kernel can be viewed as a common kernel function to measure the similarity [19].

Let \(k_{\text{rna}}(i, j)\) and \(k_{\text{target}}(i, j)\) be the RBF kernel similarity function of pair ncRNA-ncRNA and target-target respectively.

Thus, the RBF similarity of \(i^{th}\) ncRNA and \(j^{th}\) ncRNA can be computed as

\[
k_{\text{rna}}(i, j) = \exp\left(-\gamma_1 \| sst_i^d - sst_j^d \|^2 \right),
\]

where \(\gamma_1 = \frac{1}{2\sigma_1^2}\), \(\sigma_1\) is the parameter \(0 < \sigma_1 < 1\).

The RBF similarity of \(i^{th}\) target and \(j^{th}\) target can be computed as

\[
k_{\text{target}}(i, j) = \exp\left(-\gamma_2 \| sst_i^t - sst_j^t \|^2 \right),
\]

where \(\gamma_2 = \frac{1}{2\sigma_2^2}\), \(\sigma_2\) is the parameter \(0 < \sigma_2 < 1\).

**Constructing the tripartite network disease-target-ncRNA**

\(G(D, T, R, E)\), where \(E\) denotes a set of edges, is a tripartite network (Fig. 2) representing the disease-target interactions and target-ncRNA interactions. \(A^{DT} = \{a_{ij}^{DT}\}_{m \times n}\) denotes the adjacency matrix of the disease-target network, and \(A^{TR} = \{a_{ij}^{TR}\}_{n \times p}\) represents the adjacency matrix of target-ncRNA network.

Targets represent a group of biomolecules functionalized by non-coding RNAs. Targets can be genes, proteins, microRNAs, etc., whose activities include expression regulation, binding, and complex formation. In our method, targets function as a bridge allowing us to extract further biological information, for
enhancing the accuracy of disease-ncRNA association inference.

Our method integrates the resource-allocation algorithm in the network with pairwise similarity information derived from sequence expressions to produce scores showing the level of certainty of the interaction. Essentially, the resource-allocation algorithm carries prior understanding of the bipartite network, which can be employed to predict the interactions.

Multi-layer resource-allocation technique with sequence (MRAS) information
Since the tripartite network consists of two bipartite networks, two-layer resource-allocation techniques were applied. For the first-layer (disease-target bipartite network), the resource will be transferred from the nodes in T (targets) to the nodes in D (diseases) integrating with pairwise similarity information between each pair of the diseases, then move back to the nodes in T. For the second-layer (target-ncRNA bipartite network), the resource integrated with pairwise similarity information between each pair of the ncRNAs, is allocated from the nodes in R (ncRNAs) to the nodes in T, and then combined with the resource from the previous layer. Finally, the weights computed within the two layers were merged into one, called combined weight \( W_C \), indicating the likelihood that in case a disease associates with a target \( t_i \), it then possibly interacts with ncRNA \( r_j \). Prediction scores \( P \) can then be computed from the combined weight \( W_C \), and the higher the score, the greater the certainty that the ncRNA will associate with a particular disease.

Let \( \text{deg}(x) \) be the degree of node \( x \) in the disease-target network, and \( \text{deg}(y) \) be the degree of node \( y \) in the target-ncRNA network.

- **Layer 1**: disease-target bipartite network
  Let \( W^T = \{ w^T_{ij} \}_{n \times p} \) be the probability that the \( i \)-th target interacts with the \( j \)-th target when both of them interact with the same disease:

  \[
  w^T_{ij} = k_{\text{target}}(i, j) \cdot \frac{a^T_{ij}}{\text{deg}(t_i)}
  \]

  Hence, the combined weight \( W_C = \{ w^C_{ij} \}_{n \times p} \) of the two bipartite networks together with the similar neighborhood of both targets and ncRNAs can be obtained as follows. The formula assigned more weight to the path with higher frequency.

\[
W^C_{ij} = \sum_{l=1}^{n} \left[ W^T_{il} \sum_{r=1}^{p} \left( a^R_{lr} \cdot w^R_{rj} \right) \right]
\]

Finally, the prediction score matrix can be computed based on the following formula: \( P = [p_{ij}]_{m \times p} = A^{DT} \cdot W_C \)

Based on the above procedures, the prediction score matrix was produced via the integration of biological similarities of sequence expressions and the resource-allocation technique in the tripartite network. The score matrix thus predicted associations between ncRNAs and diseases. The higher the score, the higher the certainty of ncRNA-disease connectivity.

**Results**

**Algorithm prediction performance and evaluation**

As mentioned, the performance of our method was measured by applying a 5-fold-cross-validation procedure as well as other computational operations. The evaluation algorithm is described as follows:

1) First, we consider all pairs of ncRNA and disease \((N \text{ pairs})\) exiting in the tripartite network. These pairs are expected to be predicted by the algorithm in the score matrix \( P \).
2) Fix a pair of values for \( \sigma_1 \) and \( \sigma_2 \).
3) Consider k-fold cross validation with \( k = 5 \). Therefore, all \( N \) pairs are divided into 5 groups.
4) Each group of \( N/5 \) elements becomes a test data one time. The rest four groups are training data
5) From each test data group, we scan those pairs that are connected through targets and disconnect them (see Fig. 4b)
6) Run the algorithm and make predictions only for the pairs in the test group \( P_{test} \).
7) Construct a ROC curve for the test group based on \( N/5 \) scores for \( P_{test} \).
8) Repeat 3~7 for different folds. We average all five ROC curves.
9) Repeat 3~8 for randomization of test and training groups five more times and obtained an averaged ROC curve.
10) Repeat 2~9 for each \( \sigma_1 [0.1,0.12,0.14,0.16,0.18] \times \sigma_2 [0.1,0.2,0.3,0.4,0.5] \) and pick up the best AUROC among all results.

\[
w^R_{ij} = k_{\text{RNA}}(i, j) \cdot \frac{\sum_{l=1}^{n} a^T_{il} a^R_{lj}}{\text{deg}(r_j)}
\]
Evaluation results

We took into account the area under receiver operating characteristic (ROC) curve (AUC) values to assess the reliability, credibility, and accuracy of the prediction method. Table 2 demonstrates that our proposed method clearly outperforms ncPred in terms of the average values of AUC for the analysed datasets as shown in Table 1. These results emphasize the improved reliability and accuracy of predicting new ncRNA-disease associations or biological relevance using our approach, compared to that of Alaimo et al. which uses ncPred.

In our approach, the RBF kernel technique was selected to conduct the similarity measure. In order to prove that RBF kernel can interpret the similarity of biological significance more appropriately, we conducted comparison experiments on the dataset listed in Table 1 with three representative kernel functions: linear kernel, polynomial (degree = 2) kernel and RBF kernel. Table 3 clearly illustrates the prediction performance of our approach underlying each kernel function. The results demonstrate that RBF kernel successfully outperforms the other two kernel techniques, showing the highest average AUC values (see Fig. 5b).

The l-gram-string kernel technique was applied to extract biological features from the sequence data of ncRNAs and targets in the proposed method. In order to investigate which length of l can interpret and extract better information from the sequence data, we validated the performances underlying different lengths of l. We also compared the results of the proposed method under two assumptions. By using the cut link method described in algorithm performance evaluation section and without cut link. Table 4 shows the comparison for both methods and for l-gram-string kernel (when l = 1, 2, 3 and 4) in terms of AUC values using the dataset described in Table 1. The results show that link cut notably decreases the prediction of the algorithm as expected from 0.75 to 0.57 (see Fig. 6a and b). However, even though we perform this strict procedure, the algorithm is able to predict correctly interactions with an AUC above 0.5. The results also show that performance slightly improved at l = 3. Thus, l = 3 is the optimal parameter for the method (see Table 4 and Fig. 6b). Note that for Helwak dataset the optimal length is l = 1.

For parameter tuning of RBF kernel similarity function σ1 and σ2 we selected the optimal parameters as explained in the evaluation method procedure. Table 5 shows the optimal values identified in our computation.

Case studies

In order to demonstrate the credibility and functionality of the proposed method, we compared predicted disease-ncRNA pairs using Chen et al. dataset with recent experimental studies, as shown in Table 6, on six diseases, namely lung cancer, liver cancer, breast cancer,
urinary bladder neoplasms, prostatic neoplasms and stomach neoplasms.

**Lung cancer**
Lung Cancer (LC) is one of the most deadly diseases affecting both men and women worldwide. There are three types of lung cancer: non-small cell lung cancer, small cell lung cancer, and lung carcinoid tumor. In 2015 lung and bronchus cancer accounted for 13.3% of all cancer cases in the US. The proposed method predicted that seven ncRNAs, H19, HOTAIR, MALAT1, PVT1, WRAP53, XIST, CDKN2B-AS1 are associated with LC. Kondo et al. reported that the alteration and deregulation of H19 impacts lung cancer cell growth [20]. HOX transcript antisense RNA (HOTAIR) prevents gene expression via collection of chromatin modifiers. Loewen et al. demonstrated that HOTAIR plays an important role in the intervention of lung cancer [21]. lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) can impair in vitro cell motility of lung cancer cells and simultaneously influence a number of genes (Tano et al. & Tseng et al. [22, 23]). Yang et al. reported that an increased expression of the IncRNA PVT1 promotes tumorigenesis in non-small cell lung cancer [24]. Tantai et al. suggested a combined identification of long non-coding RNA XIST and HIF1A-AS1 in serum as an effective screening for non-small cell lung cancer [25]. Park et al., observed evidences for lung cancer with two variants located in cancer pleiotropic regions, namely TERT and risk of lung adenocarcinoma and CDKN2BAS1 with risk of lung squamous cell carcinoma [26].

**Liver cancer**
Liver cancer is the third most deadly cancer worldwide [27]. Very few patients receive curative treatments, while the majority do not recover since they are diagnosed at later stages. Our method predicted that ncRNAs H19, PCNA-AS1 and WRAP51 are correlated with liver cancer. H19 ncRNA expression was shown to result in high H19 protein expression in liver cancer whenever there is a loss of imprinting [28]. Iizuka et al. investigated further the epigenetic abnormalities in the insulin-like growth factor 2 (IGF2) and H19 genes observed in hepatocellular carcinoma (HCC) [29]. Yuan et al. reported that antisense long non-coding RNA PCNA-AS1 promotes tumor growth in hepatocellular carcinoma [30]. Several studies have also linked WRAP51 with HCC [31].

**Breast cancer**
Breast cancer is a ductal carcinoma beginning in the cells of lobules, ducts and other tissues of the breast. In the United States, breast cancer is the second most common cancer, just after skin cancer. Both women and

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**Table 4** Comparison of l-gram-string kernel in terms of average Area Under the Curve (AUC) values

|                  | l=1     | l=2     | l=3     | l=4     |
|------------------|---------|---------|---------|---------|
| Chen et al.(2013)| AUC     | 0.7507  | 0.7506  | 0.7513  | 0.7433  |
|                  | Cut link AUC | 0.5706  | 0.5644  | 0.5713  | 0.5476  |
| Helwak et al.(2013)| AUC     | 0.7854  | 0.7855  | 0.7338  | 0.7080  |
|                  | Cut link AUC | 0.7744  | 0.7098  | 0.6430  | 0.6441  |

The performance of the l-gram-string kernel for l=1, 2, 3 and 4 was examined using the AUC metric. The computation was done using the RBF kernel. Table also shows the prediction performance when the links between a disease and their associated ncRNAs are deleted (Cut link UAC). Italic numbers indicate the best performance.
men can suffer from this severe disease. Our method predicted that four ncRNAs, H19, PVT1, SRA1 and WRAP53 may be associated with this disease. Berteaux et al. found out that H19 transcript antisense RNA stabilize breast cancer cells and is overexpressed in breast tumors [32]. Others evidences were found across literature [33, 34]. Zhang et al. reported that the non-protein coding plasmacytoma variant translocation 1 (PVT1) has been implicated in human cancers [35, 36]. In addition, Hube et al. reported that alternative splicing of SRA1 could lead to the generation of coding and non-coding RNA isoforms in breast cancer cell lines [37]. Cao et al. recently reported about the association between the WRAP53 gene rs2287499 C > G polymorphism and cancer risk [38].

### Urinary bladder Neoplasms
Urinary bladder neoplasms are the result of abnormal growth of bladder cells, and are considered as one of the common cancers. Men are at higher risk for this disease than women. The predictive results derived from our method inferred that ncRNAs H19 and WRAP53 might be associated with urinary bladder cancer. Luo et al. demonstrated that the abnormal expression of H19, particularly its up-regulation, contributed to cell proliferation in bladder neoplasms [39]. Wrap53 is a multifunctional gene which is capable of regulating p53 levels in both normal and cancer cell lines [40].

### Prostatic Neoplasms
Prostatic neoplasm is caused by uncontrolled growth of cells located in the prostate causing tumors. Based upon our proposed method, prostate cancer was predicted to be associated with H19, MALAT1, CDKN2B-AS1, HOTAIR, PCAT1, SRA1, XIST. Zhu et al. demonstrated that H19 was significantly downregulated in the metastatic prostatic tumor cell line M12 [41]. Perez et al.

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**Table 5** Optimal values of $\sigma_1$ and $\sigma_2$ parameters

|                | $\sigma_1$ | $\sigma_2$ |
|----------------|------------|------------|
| Chen et al.(2013) | 0.6        | 0.7        |
| Helwak et al.(2013) | 0.9        | 0.1        |

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### Fig. 6 Illustration of the ROC curves for the proposed algorithm
ROC curves for the proposed algorithm MRAS using different values of l-gram string ($l = 1, 2, 3$ and $4$) and using RBF kernel (a) without link cut (AUC = 0.75) and (b) with link cut (AUC = 0.57) for the Chen dataset. The results for the Helwak dataset using RBF kernel (c) without link cut (AUC = 0.85) and (d) with link cut (AUC = 0.77)
showed that the antisense intronic transcript of MALAT1 is correlated with tumor differentiation in prostate cancer [42]. Fehringer reported the involvement of CDKBN2B-AS1 in Cross-cancer genome-wide analysis of lung, ovary, breast, prostate and colorectal cancer using a cross-cancer genome-wide analysis [43]. Zhang et al. discovered that LncRNA HOTAIR enhances the Androgen-Receptor-Mediated Transcriptional Program and Drives Castration-Resistant Prostate Cancer [44]. Ren et al. suggested the Long noncoding RNA MALAT-1 as a potential therapeutic target for castration resistant prostate cancer [45]. Presner et al. results implied that the Long Non-Coding RNA PCAT-1 Promotes Prostate Cancer Cell Proliferation through cMyc [46]. The same research group used a transcriptome sequencing across a prostate cancer cohort to identify PCAT-1 as an unannotated lincRNA implicated in disease progression [47]. Several works also reported on the involvement of SRA1 [48] and XIST [49] in prostatic neoplasm.

Stomach Neoplasms

Stomach neoplasms that occurs as a consequence of abnormal growth of stomach cells have also been associated to ncRNAs in several works. Our method predicted CDKN2B-AS1, HOTAIR and MALAT1 as main correlated molecules with stomach neoplasms. Zhang et al., reported that ANRIL (CDKN2B-AS1) which recruits and binds to PRC2 is usually observed upregulated in human gastric cancer (GC) tissues [50]. Lee et al. found that long non-coding RNA HOTAIR tends to promote not only carcinogenesis but also invasion of gastric adenocarcinoma [51]. Wang et al. also observed that MALAT1 promotes cell proliferation in gastric cancer by recruiting SF2/ASF [52].

Discussion

Our work has improved the prediction quality and performance of Alaimo et al.’s method ncPred by integrating a biological feature information derived from sequence data with weight calculated by the multi-layer resource allocation technique, throughout the whole disease-target-ncRNA tripartite network.

The proposed method is unique because involves three types of biological information, namely ncRNAs sequences, target sequences and diseases. This rich biological information is also organized in a complex tripartite network in which targets integrate information from ncRNAs and diseases. Our study extended Alaimo’s approach [13] because we integrated biological sequence information. The uniqueness of the datasets and the complexity of the networks structure make it difficult to perform a straightforward comparison of our predictions with other approaches besides ncPred algorithm [13]. Indeed, most of the previous works have been done using a more simple approach involving a bipartite network. For example, Yang et al. [12] constructed a bipartite network composed of only lncRNAs and diseases. On this network, a propagation algorithm

Table 6 The predicted ncRNAs related to the six diseases examined in this study

| Disease                   | ncRNA   | Evidence (PMID)                        |
|---------------------------|---------|----------------------------------------|
| Breast Neoplasms          | H19     | 15985428;27540977;9811352;24780616       |
| Breast Neoplasms          | PVT1    | 17908964;10485452;23907597              |
| Breast Neoplasms          | SRA1    | 17710122;26460974                       |
| Breast Neoplasms          | WRAP53  | 27525856;15736346                       |
| Carcinoma, Hepatocellular | H19     | 9570364                                 |
| Carcinoma, Hepatocellular | PCNA-AS1| 24704293                               |
| Carcinoma, Hepatocellular | WRAP53  | 23836507                                |
| Lung Neoplasms            | HOTAIR  | 25010625;22088988                       |
| Lung Neoplasms            | MALAT1  | 23243023;26490983                       |
| Lung Neoplasms            | PVT1    | 25400777                                |
| Lung Neoplasms            | XIST    | 26339353                                |
| Prostatic Neoplasms       | CDKN2B-AS1 | 27197191;24088946                      |
| Prostatic Neoplasms       | H19     | 19513555;25895025                       |
| Prostatic Neoplasms       | HOTAIR  | 26411689                                |
| Prostatic Neoplasms       | MALAT1  | 23845456                                |
| Prostatic Neoplasms       | PCAT1   | 21804560                                |
| Prostatic Neoplasms       | SRA1    | 16607388                                |
| Prostatic Neoplasms       | XIST    | 16261845                                |
| Stomach Neoplasms         | CDKN2B-AS1 | 24810364;26187665                      |
| Stomach Neoplasms         | HOTAIR  | 25063030;23890877                       |
| Stomach Neoplasms         | MALAT1  | 24857172                                |
| Urinary Bladder Neoplasms | H19     | 23354591                                |
| Urinary Bladder Neoplasms | WRAP53  | 27912092                                |

The predicted ncRNAs related to lung cancer, liver cancer, breast cancer, urinary bladder neoplasms, prostatic neoplasms and stomach neoplasms based upon our method. Each research article reporting on a specific ncRNA is shown with a unique ID (PMID) by PubMed.
navigated to infer lncRNAs implicated in diseases. Alaimo et al. [13] have already shown that their method outperformed the method by Yang et al. [12].

Our computational analyses indicate that our approach could result in more reliable and biologically efficient disease-lncRNA associations prediction than ncPred (See Tables 2 and 6). The prediction scores were obtained based on significant biological information, which provided useful suggestions of which lncRNA-disease associations have stronger interactions. This paves an easy path for pathologists to analyze and interpret lncRNA-disease associations. However, in order to accurately determine and confirm the associations, suitable patients and document cases are still needed.

The proposed method still has limitations that need to be considered. For instance, it lacks lncRNA-target interaction data and their particular sequence data. Those sequence data are required to extract the feature vector, which could extend the computational time. Furthermore, the lengths of lncRNAs and targets vary, ranging from less than 100 nucleotides to more than 10,000 nucleotides. This impacts the ranking of predicted lncRNA-disease associations. Accordingly, more related datasets are required to improve and expand the reliability and quality of lncRNA-disease association inference.

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Availability of data and materials
The datasets used in our study were downloaded from the publicly available databases mentioned in the text. The source code is available from the corresponding author on reasonable request.

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Authors’ contributions
TA and JCN made available computer programs and performed rigorous computational experiments by designing the algorithmic evaluation. HN designed the method and performed preliminary computational experiments. TM, JCN and MH contributed to the data acquisition, data analysis and interpretation of data. TA supervised HN’s work with giving various advices and comments. TM, HN and JCN wrote the draft. All of the authors have read and approved the final manuscript.

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References
1. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009;10:155–9.
2. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Mol Cell. 2011;43(6):904–14.
3. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 2012;22(9):1775–89.
4. Wapinski O, Chang HY. Long noncoding RNAs and human disease. Trends Cell Biol. 2011;21(6):354–61.
5. Lee JT, Bartolomei MS. X-inactivation, imprinting and long noncoding RNAs in health and disease. Cell. 2013;152:1308–23.
6. Yang Z, Lu Y, Xu Q, Tang B, Park C-K, Chen X. HULC and H19 played different roles in overall and disease-free survival from hepatocellular carcinoma after curative hepatectomy: a preliminary analysis from gene expression omnibus. Di Markers. 2015;2015:190129.
7. Scana V, Pasha A. Long non-coding RNAs in infection biology. Front Genet. 2012;3:3088.
8. Li J, Yuan Z, Liu C. Long non-coding RNAs and complex human diseases. Int J Mol Sci. 2013;14(9):18790–808. https://doi.org/10.3390/ijms140918790.
9. Chen X, Yan GY. Novel human IncRNA-disease association inference based onlncRNA expression profiles. Bioinformatics. 2013;29:2617–24.
10. Sun J, et al. Inferring novel IncRNA–disease associations based on a random walk model of a IncRNA functional similarity network. Mol BioSyst. 2014;10: 2074–81.
11. Li J, et al. A bioinformatics method for predicting long noncoding RNAs associated with vascular disease. Sci China Life Sci. 2014;57:852–7.
12. Yang X, Gao L, Guo X, et al. A network based method for analysis of lncRNA-disease associations and prediction of lncRNAs implicated in diseases. PLoS One. 2014;9(1):e87797.
13. Alaimo S, Giugno R, Pulvirenti A. ncPred: ncRNA-disease association prediction through tripartite network-based inference. Front Bioeng Biotechnol. 2014;2:71.
14. Chen X. Predicting IncRNA-disease associations and constructing IncRNA functional similarity network based on the information of miRNA. Sci Rep. 2015;5:13186.
15. Chen G, Wang Z, Wang D, Qiu C, Liu M, Chen X, et al. LncRNA: disease a database for long-non-coding RNA-associated diseases. Nucleic Acids Res. 2013;41:D983–5.
16. Helwak A, Kudla G, Dudnakova T, Tollervey D. Mapping the human miRNA interactome by CLASH reveals frequent noncanonical binding. Cell. 2013; 153(3):654–65.
17. Sören S, Gunnar R, Konrad R, Bottou L, Chapelle O, DeCoste D, Weston J. editors. In: Large-Scale Kernel Machines, chap. 4. Cambridge: MIT Press; 2007. p. 73–104.
18. Ismail B, Dauda U. Standardization and its effects on k-means clustering algorithm. Res J Appl Sci Eng Technol. 2013;6(17):3299–303.
19. Vert JP, Tsuda K, Scholkopf B. A primer on kernel methods. Kernel Methods in Comput Biol. 2004;35–707.
20. Kondo M, Suzuki H, Ueda R, Oda H, Takagi K, Takahashi T, Takahashi T. Frequent loss of imprinting of the H19 gene is often associated with its overexpression in human lung cancers. Oncogene. 1995;10(6):1193–8.
21. Loewen G, Jayawickramarajah J, Zhuo Y, Shan B. Functions of IncRNA HOTAIR in lung cancer. J Hematol Oncol. 2014;7:90.
22. Tano K, Akimitsu N. Long non-coding RNAs in cancer progression. Front Genet. 2012;3:219.
23. Tseng JJ, Hsieh YT, Hsu SL, Chou MM. Metastasis associated lung adenocarcinoma transcript 1 is up-regulated in placenta previa incerta/percreta and strongly associated with trophoblast-like cell invasion in vitro. Mol Hum Reprod. 2009;15(11):725–31.

24. Yang YR, Zang SZ, Zhong CL, Li YX, Zhao SS, Feng XJ. Increased expression of the IncRNA PVT1 promotes tumorigenesis in non-small cell lung cancer. Int J Clin Exp Pathol. 2014;7(10):6929–35.

25. Tantai J, Hu D, Yang Y, Geng J. Combined identification of long non-coding RNA XIST and HIF1A-AS1 in serum as an effective screening for non-small cell lung cancer. Int J Clin Exp Pathol. 2015;8(7):7887–91.

26. Park SL, et al. Pleiotropic associations of risk variants identified for other cancers with lung cancer risk: the PAGE and TRICL consortia. J Natl Cancer Inst. 2014;106(4):dju061.

27. Llovet JM, Lok A. Hepatitis B virus genotype and mutants: risk factors for hepatocellular carcinoma. JNCI J Natl Cancer Inst. 2008;100(16):1211–3.

28. Qi P, Du X. The long non-coding RNAs, a new cancer diagnostic and therapeutic gold mine. Mod Pathol. 2013;26:155–65.

29. Izuoka N, Oka M, Tamesa T, Hamamoto Y, Yamada-Okabe H. Imbalance in expression levels of insulin-like growth factor 2 and H19 transcripts linked to progression of hepatocellular carcinoma. Anticancer Res. 2004;24(6):4085–9.

30. Yuan SX, Tao QF, Wang J, Yang F, Liu L, Wang LL, Zhang J, Yang Y, Liu H, Wang F, Sun SH, Zhou WP. Antisense long non-coding RNA PCNA-AS1 promotes tumor growth by regulating proliferating cell nuclear antigen in hepatocellular carcinoma. Cancer Lett. 2014;349(1):87–94.

31. Ortiz-Cuaren S, Cox D, Villar S, Friens MD, Durand G, Chabrier A, Khuaprema T, Sangsrayang S, Ognjenovic S, Groopman JD, Hainaut P, Le Calvez-Kelso F. Association between TP53 R249S mutation and polymorphisms in TP53 intron 1 in hepatocellular carcinoma. Genes Chromosomes Cancer. 2013;52(10):912–9.

32. Bertaux N, Lottin S, Monte D, Pinte S, Quatannens B, Coll J, Hondermarck H, Curgy JJ, Dugimont T, Adriamens E. H19 miR-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. J Biol Chem. 2005;280(33):29625–26.

33. Zhang K, Luo Z, Zhang Y, Zhang L, Wu L, Liu L, Yang J, Song X, Liu J. Circulating IncRNA H19 in plasma as a novel biomarker for breast cancer. Cancer Biomark. 2016;17(2):187–94.

34. Adriamens E, Dumont L, Lottin S, Bolle D, Lepretre A, Delobelle A, Bouali F, Dugimont T, Coll J, Curgy JJ. H19 overexpression in breast adenocarcinoma stromal cells is associated with tumor values and steroid receptor status but independent of p53 and K-67 expression. Am J Pathol. 1998;153(5):1597–607.

35. Zhang Z, Zhu Z, Zhang B, Li W, Li X, Wu X, Wang L, Fu L, Fu L, Dong JT. Frequent mutation of rs13281615 and its association with PVT1 expression in breast cancer and promotes tumor growth by epigenetically silencing of miR-99a/miR-449a. Oncotarget. 2014;5(8):2276–92.

36. Qi P, Du X. The long non-coding RNAs, a new cancer diagnostic and therapeutic gold mine. Mod Pathol. 2013;26:155–65.

37. Kurisu T, Tanaka T, Ishi J, Matsumura K, Sugimura K, Nakatani T, Kawashima H. Expression and function of human steroid receptor RNA activator in prostate cancer cells: role of endogenous hSRA protein in androgen receptor-mediated transcription. Prostate Cancer Prostatic Dis. 2006;9(2):173–8.

38. Laner T, Schulz WA, Engers R, Muller M, Florl AR. Hypomethylation of the XIST gene promoter in prostate cancer. Oncol Res. 2005;15(5):257–64.

39. Zhang EB, Kong R, Yin DD, You LH, Sun M, Han L, Xu TP, Xie Y, Yang JS, De J, C. Long noncoding RNA ANRIL indicates a poor prognosis of gastric cancer and promotes tumor growth by epigenetically silencing of miR-99a. Oncotarget. 2014;5(8):2276–92.

40. Lee NK, Lee JH, Park CH, Yu D, Lee YC, Cheong JH, Noh SH, Lee SK. Long non-coding RNA HOTAIR promotes carcinogenesis and invasion of gastric adenocarcinoma. Biochem Biophys Res Commun. 2014;445(2):171–8.

41. Wang J, Su L, Chen X, Li F, Cai Q, Yu B, Liu E, Wu W, Zou Z. MALAT1 promotes cell proliferation in gastric cancer by recruiting SPZ2/ATF. Biomed Pharmacother. 2014;68(3):557–64.

42. Fehringer G, et al. Cross-cancer genome-wide analysis of lung, ovary, breast, prostate and colorectal cancer reveals novel pleiotropic associations. Cancer Res. 2016;76(17):5103–14.