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A method of extracting disease-related microRNAs through the propagation algorithm using the environmental factor based global miRNA network

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Abstract. MicroRNAs (miRNA) are known to be involved in the development of various diseases. Hence various scientists in the field have been utilized computational analyses to determine the relationship between miRNA and diseases. However, the knowledge of miRNA and disease is still very limited. Therefore, we combined Environmental Factor (EF) data to a miRNA global network. Increasing research has shown that relationship between miRNAs and EFs play a significant role in classifying types of diseases. Environmental Factors consist of radiation, drugs, viruses, alcohol, cigarettes, and stress. Our global network considered all the interactions between every pair of miRNAs, which has led to precise analyses in comparison to local networks. As a result, our approaches' performance demonstrated its effectiveness in identifying disease-related miRNA and this is the area under the ROC curve (AUC) of 74.46%. Furthermore, comparative experiment has shown that our approach performs comparable to other existing methods with an accuracy of 94%, 90% and 96% for breast cancer, colonic cancer, and lung cancer respectively. In conclusion, these results support that our research has broadened new biological insights on identifying disease-related miRNAs.

Keywords: miRNA, disease, environmental factor, network, propagation algorithm

1. Introduction

MicroRNAs (miRNAs) are small non-coding RNAs that are composed of 19-22 nucleotides. They play an important role in the regulation of cell proliferation, growth, and apoptosis based on the base-pairing to the 3' untranslated-regions (UTRs) of their target mRNAs at post-transcriptional level. Growing evidence indicates that miRNAs have been associated with the pathogenesis of the disease. Therefore, discerning the relationship between miRNAs and diseases has become an important goal in the biological context. However, identifying disease-related miRNAs with existing experimental setup might be laborious and time-consuming. In addition, many researchers also face a difficult problem of limited knowledge on miRNA. Therefore a number of computational approaches have been developed

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lately to identify disease-related miRNAs.

Network approaches are widely utilized to determine miRNA-disease associations. Jiang at el. proposed a novel method by constructing a phenome-microRNAome network, which is composed of experimentally verified disease-miRNA associations [1]. Zhang developed a computational method based on a local miRNA network. This method is based on the assumption that functionally related miRNAs tend to be associated with phenotypically similar diseases. He also developed a MBSI (microRNA-based similarity inference), PBSI (phenotype-based similarity inference), and NetCBI (network-consistency-based inference) to identify disease-related miRNAs [2]. Gorodkin developed miRPD approach, where miRNA-Protein-Disease associations are inferred by the network analysis of known or predicted miRNA-protein associations and text-mined protein-disease associations [3]. Chen has proposed a Random Walk with Restart for MiRNA-Disease prediction (RWRMDA). He proposed that the accuracy to determine the disease-related miRNAs increases by using the global network [4]. Chen utilized a semi-supervised classifier based method (miREFScan) to predict novel disease-related interactions between miRNAs and EFs [5]. Here in this paper, we have applied environmental factors (EFs) on a global network. Further, we overcame the scarcity of information on miRNA and we propose a new method of calculating miRNA-miRNA similarity in biological context. Environmental factors (EFs) have recently been utilized as new means of inferring the relationship between diseases and miRNAs. The miREnvironment database contains information of EFs, such as drugs [6], cigarettes [7], alcohol [8], viruses [9], stress [10], and radiation [11], which plays a significant role in affecting various diseases. By applying the propagation algorithm on the miRNA-miRNA similarity network, we found hidden potential to identify association between disease-miRNA. To prove its superior performance, we applied our approach to 10 different diseases and obtained an area under the

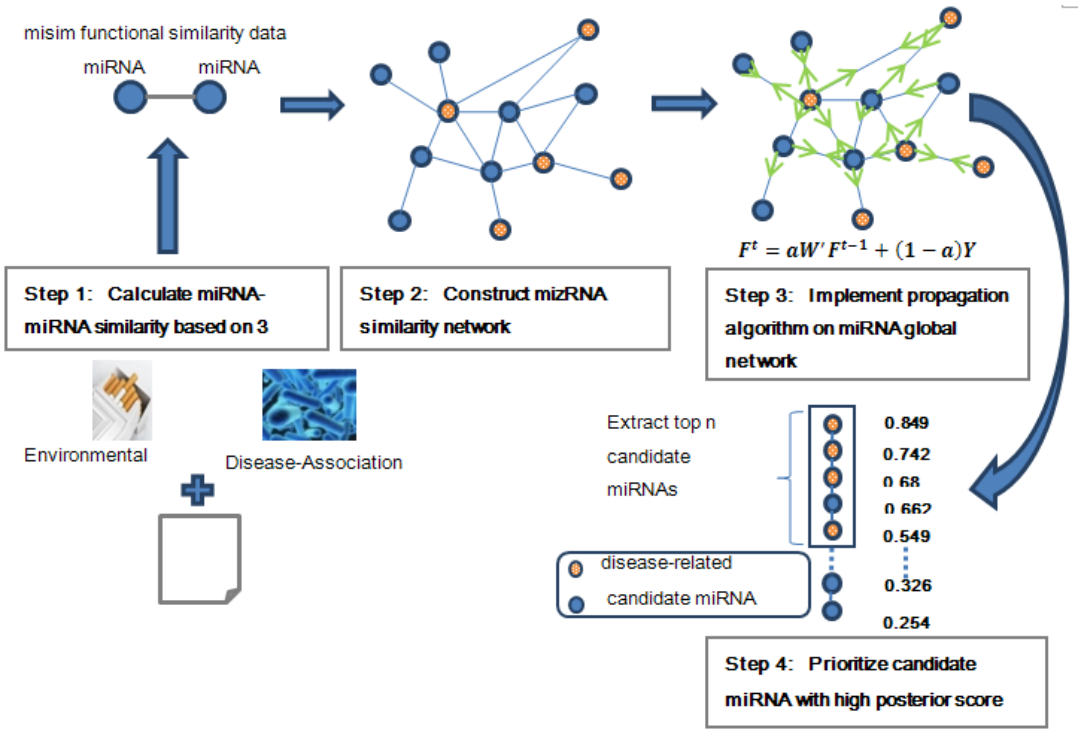

Fig. 1. The workflow of prioritizing candidate miRNAs.

ROC curve (AUC) at an average value of 74.46%, with the highest AUC (84.39%) for acute lymphoblastic leukemia. Furthermore, we selected the top 50 candidate miRNAs for breast cancer, colonic cancer, and lung cancer with an acquired accuracy of 94%, 90%, and 96% respectively.

2. Method and materials

In this Section, we described a method of determining disease- related miRNAs. Figure 1 briefly illustrates a workflow of our method. First, we calculated the similarities among miRNAs based on environmental factors, disease-associations, and the misim (miRNA-miRNA functional similarity score) similarity data. Secondly, we constructed miRNA similarity network based on similarities between each miRNA. Lastly, we implemented the propagation algorithm and extracted candidate miRNAs with high posterior scores. miRNAs with high posterior scores are expected to have a high relevance of disease-association. The answer datasets were downloaded from the HMDD and miR2Disease database.

2.1. Step 1: Calculate miRNA-miRNA similarity

To calculate the precise miRNA-miRNA similarity value, we applied three factors from different sources as described below.

2.1.1. The miRNA-miRNA functional similarity

The miRNA-miRNA functional similarity scores were downloaded from http://cmbi.bjmu.edu.cn/misim/ [12]. These similarities are calculated based on the assumption that genes with similar functions have a high possibility of relevance to phenotypically similar diseases. This data contains similarities among miRNAs in a matrix form. The functional similarity matrix, defined as S_F and $S_F(i,j)$, indicates the functional similarity between miRNAs in row i and miRNAs in column j. If a similarity score exists between two miRNAs, then miRNAs are linked by an edge with the value of a similarity score.

2.1.2. Environmental factor (EF)

The complex interactions between genetic factors (GFs) and environmental factors (EFs) determine phenotype of the organisms and diseases [13-17]. A recent study demonstrated that interactions between GF and EF provided an efficient way for understanding the pathogenesis of diseases [18-21]. Moreover, the analysis of interactions between drugs and genetic factors blazed a trail for discerning new indications of approved drugs [22, 23]. We obtained the experimentally verified miRNA-EF association data from the miREnvironment database [24]. This database contains more than 2500 entries, including 800 miRNAs, and 260 environmental factors, such as drugs, cigarettes, alcohol, viruses, stress, and radiation. In order to calculate a miRNA-miRNA similarities based on EFs, we constructed an EF similarity matrix S_E. Entry $S_E(i,j)$ contains the number of common EFs between miRNAs in row i and miRNAs in column j where $T(i,i)$ and $T(j,j)$ denote the total sum of common EFs in row i and the sum of common EFs in column j. Each similarity value is calculated as follows:

$$\overline{S_E(i,j)} = S_E(i,j) / \sqrt{T(i,i)}\sqrt{T(j,j)}.$$

2.1.3. Phenotype miRNA disease association

Based on the fact that miRNAs affecting a specific disease tend to share similar functions, a similarity between two miRNAs was calculated with their relevance of disease-association. We obtained a miRNA-disease association set from the HMDD [25] and miR2Disease [26] database respectively. By reviewing more than 600 published papers, HMDD provided 10368 entries that include 572 miRNA genes and 378 diseases from 3511 papers, and miR2Disease provided 1939 curated relationships between 299 human miRNAs and 94 human diseases. The same calculation was applied to the similar environmental factors, as mentioned above. Entry $S_D(i,j)$ denotes the number of shared diseases between miRNAs in row i and in column j in disease-similarity matrix S_D. Each similarity value is calculated as follows: $\overline{\mathrm{S_D}(i,j)} = \mathrm{S_D}(i,j) / \sqrt{\mathrm{T}(i,i)}\sqrt{\mathrm{T}(j,j)}$. As misim data is based on information of HMDD, we only considered the value of each similarity among miRNAs that does not appear in misim data.

2.1.4. Similarity combine

Each similarity calculated in the previous step was combined for a value of each edge in the miRNA global network. $\mathrm{S_M} = \frac{\mathrm{S_F}}{3} + \frac{\bar{\mathrm{S}}_\mathrm{E}}{3} + \frac{\bar{\mathrm{S}}_\mathrm{D}}{3}$, where $\mathrm{S_M}$ denotes the similarity among miRNAs.

2.2. Step 2: Construct a miRNA similarity network

Constructing a miRNA-miRNA global network consists of two steps: (1) Assigning initial scores for each node based on the miRNA expression data of specific diseases with the value of up-regulated expression. (2) Replacing the edge value with a similarity score that was calculated with environmental factors, disease-association, and misim data (miRNA-miRNA functional similarity score).

2.3. Step 3: Implementation of the propagation algorithm on the miRNA global network

In this paper, a hidden disease-miRNA association was inferred by performing the propagation algorithm on the global miRNA similarity network. The use of the global network has the advantage of considering the entire interactions of miRNAs. This improves the accuracy of finding disease-related miRNAs as compared to the only use of the information of neighbor. The miRNA-miRNA similarity based global network consists of 1395 miRNA-disease associations between 271 miRNAs and 137 diseases.

Performing propagation consists of three steps: (1) Assigning an initial score of each node based on the miRNA expression data of specific diseases and replacing the edge value with a similarity score that was calculated with environmental factors, disease-association, and misim data (miRNA-miRNA functional similarity score), (2) Conducting propagation algorithm on the global network (3) Extracting candidate disease-related miRNAs, according to the posterior scores of each node. The posterior score $\mathrm{F^t}$ is computed as follows: $F^t = \alpha W' F^{t-1} + (1-\alpha)Y$. $\alpha \in (0,1)$ denotes weights, amount of information received from neighbors, W' stands for weight of the edges, and Y implies the initial score of each nodes.

2.4. Step 4: Prioritize candidate miRNA with high posterior scores

In this paper, after implementation of multiple experiments, we found that performance of our

approach fits well with the value of α between 0.7 and 0.8. The propagation algorithm was performed until the posterior score was stabilized (until F^t - F^{t-1} $<10^{-6}$). The candidate miRNAs with high posterior scores are expected to have a high relevance of disease association.

3. Result

3.1. Prioritization of candidate miRNA on multiple cancers

In order to prioritize the candidate miRNAs, we obtained miRNA expression data either from The Cancer Genome Atlas (TCGA) or the Gene Expression Omnibus (GEO) database. Each node was placed with a miRNA value expression. Each edge was assigned by similarity value, which is calculated from environmental factors (EFs), disease association and miRNA-miRNA functional similarity (misim) as mentioned above. We applied the propagation algorithm to the global miRNA network and ranked the top 20 candidate miRNAs for 10 different diseases. We then confirmed them by using known disease-related miRNAs that were derived from the HMDD and miR2disease

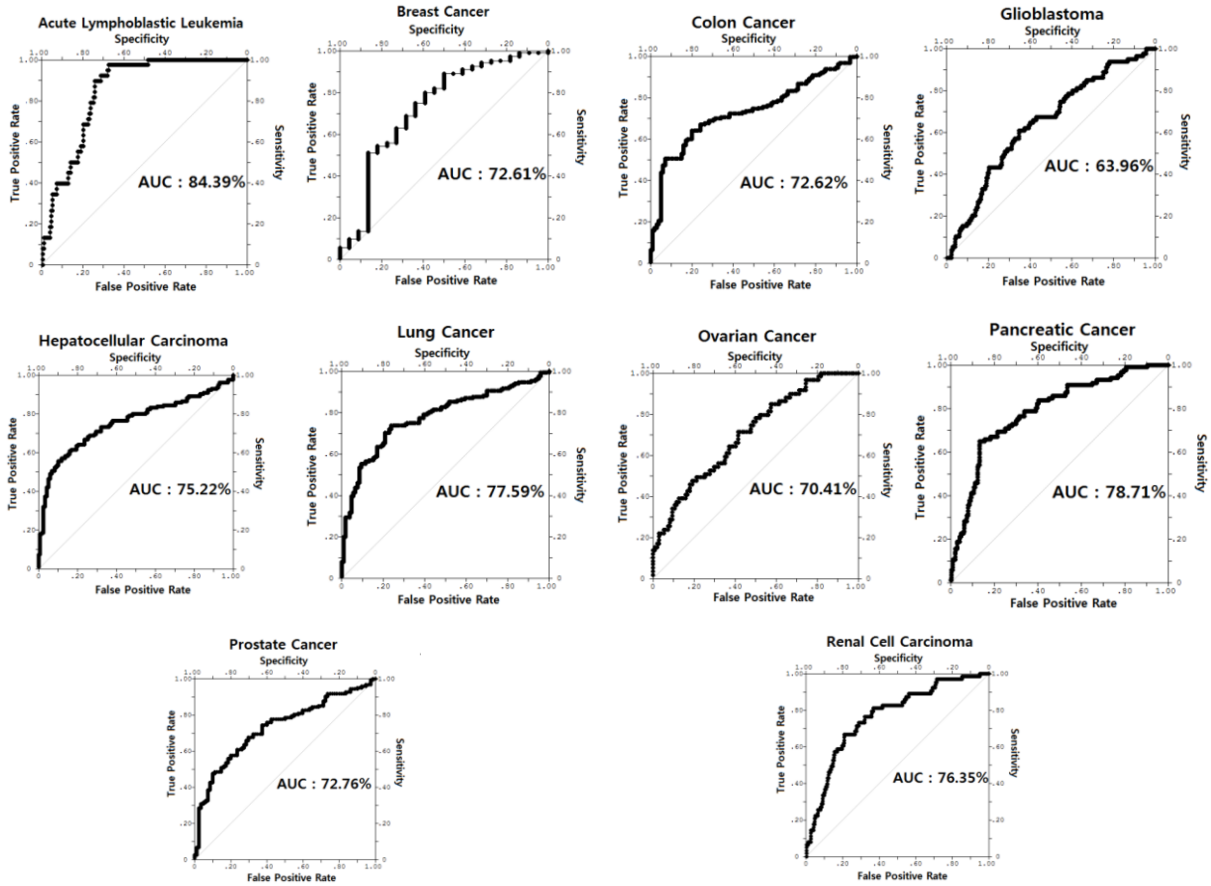

Fig. 2. Area Under the ROC curve (AUC) score for 10 different diseases. Average AUC score was 74.46% according to known miRNA- disease miRNAs from the HMDD and miR2disease databases.

databases. We studied the area under the ROC curve (AUC) to evaluate its performance. The ROC curve shows the tradeoff between sensitivity and specificity. Sensitivity denotes the percentage of disease-related miRNAs that are above the given threshold that is the ratio of correctly extracted disease-miRNAs to the total number of miRNAs. Specificity denotes the percentage of miRNAs that are below the given threshold. Figure 2 illustrates AUC for each disease. We achieved the highest AUC of 84.93% for acute lymphoblastic leukemia, the lowest AUC of 63.96 for glioblastoma, and an average AUC of 74.46%. In addition, we found that more than half of the candidate miRNAs were proven to be disease-related miRNAs, though glioblastoma was not (Figure 3).

Furthermore, we analysed the top 20 miRNA list of each disease to check their common functions. TAM (http://cmbi.bjmu.edu.cn/tam), which is an online miRNA functional enrichment tool that offers a list of biological meanings behind interested miRNAs, was used to find common functions of selected candidate miRNA lists of given diseases. To our amazement, the results showed that the functions of common miRNA lists were onco-tumors, tumor suppressors, cell proliferations, apoptoses, and cell cycle. It is well known that cancer is related to cell cycle dysregulation. In human beings, if cell cycle changes, cells can divide into malignant tumors and that may be the key factor of cancer incidence. Moreover, other enrichment functions, such as onco-tumors, tumor suppressors, cell proliferations, and apoptosis, are considered to be processes of cancer development.

3.2. Performance evaluation

Acute lymphoblastic leukemia — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-10a		
hsa-mir-21		O
hsa-mir-142	O	
hsa-mir-223	O	O
hsa-mir-148a		
hsa-let-7b	O	O
hsa-mir-22		O
hsa-mir-30e		
hsa-mir-25		
hsa-mir-93		
hsa-mir-191		
hsa-mir-30d		
hsa-mir-17	O	
hsa-mir-196b	O	O
hsa-mir-23a		O
hsa-mir-15b		
hsa-mir-29a	O	
hsa-mir-126	O	
hsa-mir-28		
hsa-mir-155	O	O

Breast cancer — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-21	O	O
hsa-mir-30a	O	
hsa-mir-99b		
hsa-mir-148a	O	O
hsa-let-7b	O	
hsa-mir-182	O	O
hsa-mir-25	O	
hsa-mir-22	O	O
hsa-mir-183	O	
hsa-mir-143	O	O
hsa-mir-30e		
hsa-mir-203	O	O
hsa-mir-200c	O	O
hsa-mir-93	O	
hsa-mir-10b	O	O
hsa-mir-30d	O	
hsa-mir-23a	O	
hsa-mir-375	O	
hsa-mir-29a	O	
hsa-mir-142		

Colon Cancer — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-192	O	O
hsa-mir-21	O	O
hsa-mir-148a	O	
hsa-mir-10a		O
hsa-mir-22	O	
hsa-mir-143	O	O
hsa-mir-203	O	O
hsa-mir-10b	O	O
hsa-mir-99b		
hsa-mir-182	O	O
hsa-mir-196b		
hsa-mir-30e		
hsa-mir-30d		
hsa-mir-375	O	
hsa-mir-183	O	O
hsa-mir-7b	O	O
hsa-mir-29a	O	O
hsa-mir-30a	O	
hsa-mir-199b	O	
hsa-mir-200c	O	O

Glioblastoma — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-let-7f		
hsa-mir-126		
hsa-mir-129		
hsa-let-7b		
hsa-mir-16		
hsa-mir-21	O	O
hsa-mir-29a	O	
hsa-mir-130a	O	O
hsa-mir-125b		
hsa-mir-195	O	
hsa-mir-15b		
hsa-let-7a		
hsa-mir-34a	O	O
hsa-mir-342	O	
hsa-mir-148a	O	
hsa-mir-338		
hsa-mir-23a		O
hsa-mir-26a		
hsa-mir-100		
hsa-mir-9		

Hepatocellular carcinoma — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-21	O	O
hsa-mir-22	O	
hsa-mir-143		O
hsa-mir-148a	O	O
hsa-mir-10b	O	
hsa-mir-192	O	
hsa-mir-10a	O	
hsa-mir-99b	O	
hsa-mir-30e		O
hsa-mir-25	O	O
hsa-mir-30d	O	
hsa-mir-28		
hsa-mir-30a	O	O
hsa-mir-39a	O	
hsa-let-7b	O	
hsa-mir-122	O	O
hsa-mir-100	O	
hsa-mir-210	O	
hsa-mir-93	O	O
hsa-mir-182	O	O

Lung cancer — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-21	O	O
hsa-mir-148a	O	
hsa-mir-22	O	O
hsa-mir-143	O	O
hsa-mir-203	O	O
hsa-mir-182	O	O
hsa-let-7b	O	O
hsa-mir-30e	O	
hsa-mir-30a	O	
hsa-mir-375	O	O
hsa-mir-29a	O	O
hsa-mir-30d	O	
hsa-mir-100	O	
hsa-mir-99b		
hsa-mir-142	O	
hsa-mir-10a		
hsa-mir-126		
hsa-mir-23a	O	
hsa-mir-141		O
hsa-mir-183	O	O

Ovarian cancer — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-let-7g	O	O
hsa-let-7f		O
hsa-let-7a		O
hsa-let-7e	O	O
hsa-let-7c	O	O
hsa-let-7b	O	
hsa-let-7i	O	O
hsa-let-7d	O	O
hsa-mir-217		
hsa-mir-140	O	
hsa-mir-520h		
hsa-mir-498		O
hsa-mir-149		
hsa-mir-34c	O	O
hsa-mir-433	O	
hsa-mir-22	O	
hsa-mir-612		
hsa-mir-379		
hsa-mir-206		O
hsa-mir-124		

Pancreatic cancer — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-21	O	O
hsa-mir-22		
hsa-let-7b	O	
hsa-mir-143	O	O
hsa-mir-192	O	
hsa-mir-10a	O	O
hsa-mir-99b		
hsa-mir-375	O	O
hsa-mir-148a	O	O
hsa-mir-203	O	O
hsa-mir-182	O	
hsa-mir-30d		
hsa-mir-30a		
hsa-mir-100		O
hsa-mir-183	O	
hsa-mir-200c	O	
hsa-mir-10b	O	O
hsa-mir-29a		
hsa-mir-23a	O	O
hsa-mir-199b	O	

Prostate cancer — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-143	O	O
hsa-mir-375	O	O
hsa-mir-10b		O
hsa-mir-21	O	O
hsa-mir-148a	O	O
hsa-mir-30a		
hsa-mir-22	O	O
hsa-mir-182	O	O
hsa-mir-200c	O	
hsa-let-7b	O	O
hsa-mir-30e		
hsa-let-7c	O	O
hsa-mir-183	O	O
hsa-mir-99b	O	O
hsa-mir-25	O	O
hsa-mir-29a	O	O
hsa-mir-30d	O	
hsa-mir-10a		O
hsa-mir-100	O	O
hsa-mir-29c		

Renal cell carcinoma — (1)HMDD (2)miR2Disease

	(1)	(2)
hsa-mir-30a		
hsa-mir-10b	O	
hsa-mir-143	O	
hsa-mir-21	O	O
hsa-mir-99b	O	
hsa-mir-22		
hsa-mir-126	O	
hsa-mir-148a		
hsa-mir-192		
hsa-mir-10a		
hsa-mir-30e		
hsa-mir-7b	O	
hsa-mir-30d	O	
hsa-mir-210	O	
hsa-mir-100	O	
hsa-mir-23a		
hsa-mir-29a		
hsa-mir-25		
hsa-mir-142a	O	
hsa-mir-23b	O	

Fig. 3. The top 20 candidate miRNA lists for 10 various diseases. Each miRNA's is confirmed by either the HMDD database or the miR2Disease database. Colored cells represent disease-related miRNA.

A comparative experiment was implemented to evaluate the performance of our method. We extracted the top 20 candidate miRNAs from 9 cancers to compare the results of other existing methods [27]. We found that this study extracted a larger number of disease-related miRNAs for most diseases (Figure 4). Furthermore, we compared the results with other miRNA prioritization methods [4]. We extracted the top 50 candidate miRNAs for breast cancer, colonic cancer, and lung cancer (Figure 5). We show that our method identified a larger number of disease-related miRNAs, except for breast cancer. However, additional analysis has shown that three miRNAs (hsa-mir-151 hsa-mir-30e, hsa-mir-142) that were not known to have relations with breast cancer were proved to have influence on breast cancer development. TAM, an online tool for annotations of microRNAs, has shown that hsa-mir-151 directly affects breast cancer, has-mir-30e is a key factor of neoplasm, and hsa-mir-142 has a relation with lung cancer, which is a phenotypically similar disease to breast cancer.

3.3. Case study: breast cancer

Breast cancer (BC) is considered to be one of the most commonly occurring female malignant cancers and accounts for approximately 22% of all the cancers in women. To evaluate the performance of our approach, we ranked the top 50 candidate miRNAs based on our method. We confirmed that 47 miRNAs were associated with breast cancer, demonstrating 94% accuracy. The known breast cancer related miRNA lists were downloaded from HMDD, miR2disease, and dbDEMC [28] respectively. To further investigate the functions of top 50 candidate miRNAs, we used TAM for the enrichment analysis. The majority of the miRNAs were related to lung cancer, colonic cancer, prostate cancer, and pancreatic cancer. These diseases are phenotypically similar diseases to breast cancer. The phenotypically similar diseases were downloaded from MimMiner [29], which provided information for a phenotypically similar disease list of specific diseases. Thus, we validated our assumption that phenotypically diseases tend to be functionally associated with miRNAs. We also checked the 3 other miRNAs that were not proven to be associated with breast cancer. Surprisingly, TAM has shown that one of the three miRNA proved to be breast cancer related miRNA and other miRNAs were related to lung cancer, which is a phenotypically similar disease to breast cancer. Therefore, our results showed that phenotypically diseases tend to be associated with functionally related miRNAs.

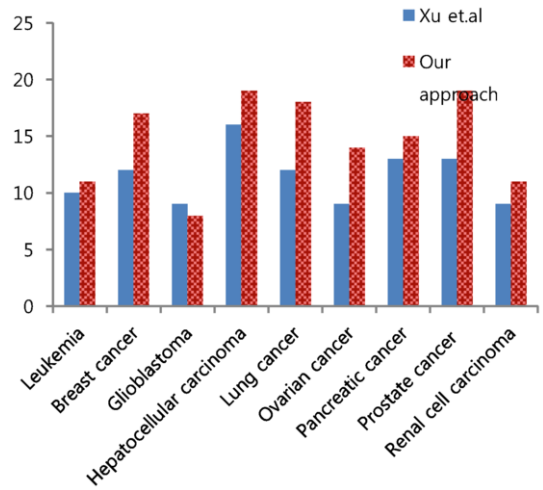

Fig. 4. Comparison with RWRMDA.

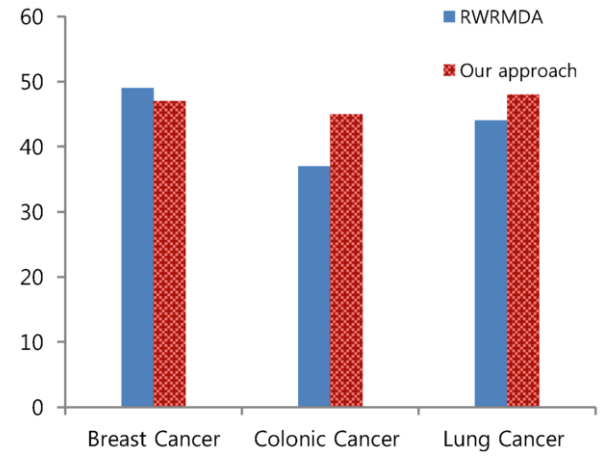

Fig. 5. Comparison with Xu, et al [4].

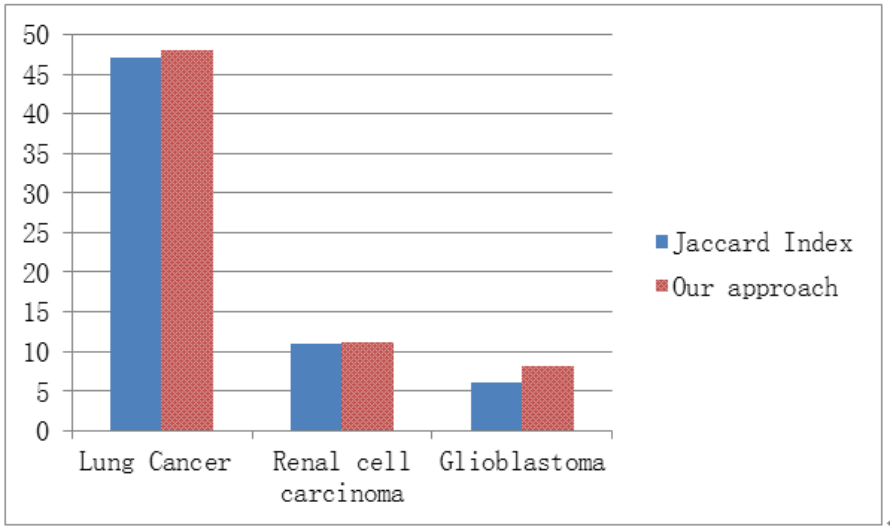

Fig. 6. The top 50 candidate miRNA lists for 3 different diseases when using similarity from our method and Jaccard index.

3.4. Comparing result with different similarity

Figure 6 above shows the number of confirmed disease-related miRNAs when using two different similarities; that is similarity calculated based on our method and Jaccard index. Although using Jaccard index showed meaningful result, calculation of similarity based on our method showed better performance. This proves that considering the total number of involving environmental factors and disease-association between two miRNAs gives better performance.

4. Discussion

In this study, we propose a method for inferring miRNA-disease association by using the miRNA global network constructed from environmental factors, disease-association, and misim data. The contribution of our approach relies on several main factors. First, by utilizing environmental factors, we broadened a new insight of determining disease-related miRNA and overcame the problem of limited knowledge that every miRNA researcher faces. Accumulated evidence from recent research showed that environmental factors, such as cigarettes, viruses, stress, alcohol, and radiation, play an important role in classifying disease types. Second advantage of using our method is that, compared to other existing methods, our approach does not depend on known disease-related miRNA. Lastly, the miRNA global network expanded the way of considering every interaction of miRNAs, which could efficiently reflect miRNA collaboration on the pathogenesis of specific diseases. By applying our miRNA prioritization method to 10 different diseases, we confirmed that top ranked miRNAs had a high relevance to disease-association. These results validate the propagation algorithm through global miRNA network's that efficiently extracted disease-miRNA associations.

Although our approach showed promising performances, some limitations do exist in our approach. First, additional information on known disease-related miRNA lists is needed to confirm the accuracy of finding disease-related miRNAs. The available knowledge of disease-miRNA association sets is too limited. Secondly, to improve the performance of the method and help understand the functions of

miRNA and to calculate the similarity score precisely we need to apply other sources of information.

5. Conclusion

Predicting disease-miRNA association is currently an important goal in bioinformatics. However, knowledge on the functions of miRNA is too limited and restricted. To overcome this problem, we propose a similarity based miRNA prioritization method that uses environmental factors, disease-association and misim data. Further by applying the propagation algorithm to the miRNA global network expanded a way to determine disease-related miRNAs. Experimental results not only proved that our prediction method performs well for identifying disease-related miRNAs, but also validated a strong relationship between miRNA and environmental factors on disease incidence. Furthermore, the method can help to understand disease pathogenesis mechanisms.

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