Disease phenotype similarity improves the prediction of novel disease-associated microRNAs

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***Abstract*—Many studies have shown roles of miRNAs (microRNAs) on human disease and a number of computational methods have been proposed to predict such associations by ranking candidate microRNAs according to their relevance to a disease. Among them, network-based methods are becoming dominant since they well exploit the "disease module" principle in miRNA functional similarity networks. Of which, Random Walk with Restart (RWR) algorithm-based method on a miRNA functional similarity network, namely RWRMDA, is state-of-the-art one. The use of this algorithm was inspired from its success in predicting disease gene because "disease module" principle also exists in protein interaction networks. Besides, many other algorithms were also designed for prediction of disease genes. However, they have not yet been utilized for disease microRNA prediction. In this study, we proposed a method, namely RWRHMDA, for prediction of disease-associated miRNAs. This method was based on RWRH algorithm, which was successfully proposed for disease gene prediction on a heterogeneous network of genes and disease phenotypes. In particular, we used this algorithm to rank disease candidate miRNAs on a heterogeneous network of phenotypes and miRNAs, which was constructed by integrating a shared target gene-based microRNA functional similarity network and a disease phenotype similarity network. Comparing the prediction performance of RWRHMDA with that of RWRMDA on a set of 35 disease phenotypes, we found that RWRHMDA significantly outperformed RWRMDA irrespective of parameter settings since it better exploited "disease module" principle. In addition, using RWRHMDA method, we identified eight novel Alzheimer's disease-associated miRNAs.**

Keywords—disease-associated miRNA; Random walk with restart algorithm; RWRH; Alzheimer's disease.

I. INTRODUCTION

Finding underlying molecular mechanisms of diseases is one of the important goals in biomedical research. Many methods have been proposed to identify genetic factors of diseases. In which, prediction of disease-associated genes have been taken much attention in last decades [1, 2]. Recently, studies on the molecular mechanisms of diseases have been extended to microRNA (shortly called miRNA) which is a class of small non-coding regulatory RNAs that play an important role in the post-transcriptional regulation of gene expression [3, 4]. More importantly, many studies have shown role of miRNAs in both common [5-9] and rare diseases [10]. For instance, miRNAs have been related to metabolic diseases [11], obesity, diabetes and cancer [12].

To predict novel disease-associated miRNAs, a number of network-based methods have been proposed to associate miRNAs to diseases. Depending on how the network is represented, different approaches can be envisaged. For instance, study [13] built a heterogeneous miRNA target-dysregulated network based on physical miRNA-target interactions, then analyzed topological features of the network to prioritize candidate disease miRNAs. However, most network-based methods exploit "disease module" principle (i.e., functionally related miRNAs tend to be associated with phenotypically similar diseases [14, 15]) in homogeneous miRNA functional similarity networks (i.e., nodes represent miRNAs and edges represent the degree of functional relatedness between the miRNAs) for prediction of disease-associated miRNAs [16-19]. For instance, local similarity measure-based methods only assessed direct neighbors of known disease-associated miRNAs [13, 16]. Meanwhile, global similarity measure-based methods such as Random Walk with Restart (shortly called RWR) algorithm, have been recently proposed and shown to outperform local similarity measure-based ones [19-21]. The application of RWR algorithm on miRNA functional similarity networks to predict disease-associated miRNAs is inspired from its success in disease gene prediction on protein interaction networks. Indeed, this algorithm has been successfully applied in a number of studies for disease gene prediction [22-24] and also considered a state-of-the-art method in that field compared to other network-based methods [25]. The success of RWR in both prediction of disease-associated genes and miRNAs is because it well exploits "disease module" principle, which appears in both protein interaction networks (i.e., proteins associated to the same or similar disease tends to form functional/physical module in protein interaction networks [26-28]) and miRNA functional similarity networks (i.e., functionally related miRNAs tend to be associated with phenotypically similar diseases [14, 15]). However, these methods just used the RWR algorithm for disease miRNA prediction on homogeneous networks (i.e., all nodes in the miRNA functional similarity networks are miRNAs). Recently, a variant of RWR algorithm, namely RWRH, was proposed for a heterogeneous network. This algorithm was then applied to

978-1-4673-6640-3/15/$31.00 ©2015 IEEE

predict disease-associated genes on a heterogeneous network of genes and disease phenotypes [29]. That study showed that RWRH better exploit "disease module" principle than RWR [22] since a disease phenotype similarity network was additionally integrated with a protein interaction network for disease gene prediction [29].

Inspired from the success of RWR-based methods on a miRNA functional similarity network for disease miRNA prediction (i.e., RWRMDA [20] and ours [19]), we proposed a method, RWRHMDA, which was based on the RWRH algorithm, for disease miRNA prediction in this study. To test the performance of RWRHMDA, we constructed a heterogeneous network of miRNAs and disease phenotypes. To this end, we constructed a homogeneous miRNA network by integrating an existing miRNA functional synergistic network collected from [30] and miRNA functional similarity networks constructed based on shared target genes of miRNAs. Then, we integrated this network with a disease phenotype similarity network by known disease phenotype-miRNA associations to construct a heterogeneous network of miRNAs and disease phenotypes. The performance of RWRHMDA was assessed based on average AUC (area under ROC curve) over a set of disease phenotypes. Experimental results showed that the performance RWRHMDA is better than that of RWRMDA, which run only on the homogeneous miRNA, for prediction of disease-associated miRNAs irrespective of parameter settings. This is because RWRHMDA better exploited "disease module" principle with the integration of disease phenotype similarity information. In addition, we used RWRHMDA to find novel miRNAs associated to Alzheimer's disease. The evidence search from literature about the associations between 100 highly ranked candidate miRNAs and Alzheimer's disease confirmed eight of them, which are not yet recorded in public disease-miRNA association database.

II. Methods

A. Construction of a homogeneous miRNA network

To construct a homogeneous miRNA network, we integrated a miRNA functional synergistic network collected from [30] and miRNA functional similarity networks constructed based on shared target genes of miRNAs. More specifically, we collected a network consisting of 3,872 functional interactions among 692 miRNAs from [30]. To construct shared target gene-based miRNA functional similarity interactions, we used 143,596 miRNA-target gene associations of human from PITA [32] and 520,526 miRNA-target associations of human from TargetScan [33], then followed the same procedure as in [16] to construct miRNA functional similarity interactions. Particularly, two miRNAs were defined to functionally interact if they share at least one target gene and the weight of that interaction was defined by the number of shared target genes divided by the number of target genes of miRNA which targets to a smaller number of genes. This definition resulted in a network containing 1,526 functional interactions among 331 miRNAs collected from PITA and a network consisting of 46,118 functional interactions among 1,428 miRNAs collected from TargetScan. Final, to integrate these different miRNA functional networks,

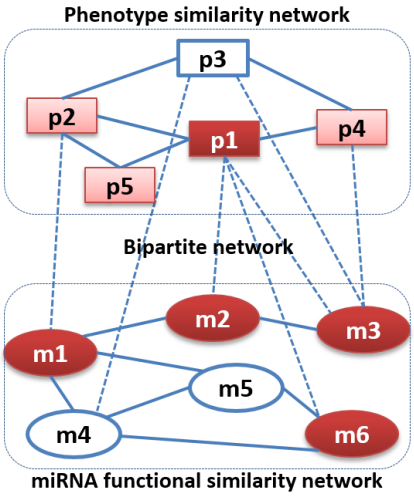

Fig. 1. Construction of a heterogeneous network of miRNAs and disease phenotypes. Phenotype similarity and homogeneous miRNA networks are connected by bipartite network.

we normalized the weight of each interaction in these networks in a range of [0, 1] as follow:

$$w'_{ij} = \frac{w_{ij} - min}{max - min}$$

where w_{ij} is weight of interaction between miRNA i and j, min and max are the smallest and largest values of interaction weights of each miRNA functional network, respectively.

Then, these three miRNA functional networks were combined using "per-edge average" method as follow:

$$\overline{w}_{ij} = \frac{1}{M}\sum_{k=1}^{M}(w'_{ij})_k$$

where M is number of networks containing interaction between miRNA i and j.

As a result, a comprehensive homogeneous miRNA network consisting of 1,521 miRNAs and 51,362 functional interactions was constructed.

B. Database of known phenotype-miRNA associations

miR2Disease [34] is a comprehensive resource of miRNA and human disease which is manually curated. In this study, we obtained 270 experimentally verified disease phenotype–miRNAs associations from this database. This can be considered a bipartite network connecting a total of 53 disease phenotypes and 118 miRNAs.

C. Construction of a heterogeneous network of disease phenotypes and miRNAs

To construct a heterogeneous network of disease phenotypes and miRNAs, we collected a disease phenotype similarity matrix from [31], where an element of the matrix represents degree of similarity between two phenotypes. By selecting only five neighbors which have largest similarities for each node, we constructed a disease phenotype similarity

network consisting of 19,791 interactions among 5080 phenotypes. Then, we connected this network with the homogeneous miRNA network by the bipartite network of known disease phenotype-miRNA associations. Figure 1 shows illustrative sample of such the heterogeneous network.

D. Network-based ranking algorithms

Given a connected weighted graph G(V, E) with a set of nodes V=$\{v_1, v_2, \ldots, v_N\}$ and a set of links E=$\{(v_i, v_j)|\ v_i, v_j \in V\}$, a set of source/seed nodes $S \subseteq V$ and a $N \times N$ adjacency matrix W of link weights. Here, we are going to introduce algorithms for measuring relative importance of node v_i to S. By modeling the miRNA networks (i.e., the homogeneous/heterogeneous miRNA networks) as a graph, ranking/prioritization of candidate miRNAs is to predict novel miRNAs associated to a disease phenotype of interest (d). The rankings of candidate miRNAs are based on their relative importance to a set of known d-associated miRNAs and d. This value also measures how much relevant to d a candidate miRNA is.

Random Walk with Restart on a homogenous miRNA network

RWR is a variant of the random walk and it mimics a walker that moves from a current node to a randomly selected adjacent node or goes back to source nodes with a back-probability $\gamma \in (0, 1)$. RWR can be formally described as follows:

$$P^{t+1} = (1-\gamma)W'P^t + \gamma P^0$$

where P^t is a $N \times 1$ probability vector of $|V|$ nodes at a time step t of which the ith element represents the probability of the walker being at node $v_i \in V$, and P^0 is the $N \times 1$ initial probability vector. W' is the transition matrix of the graph, the (i, j) element in W', denotes a probability with which a walker at v_i moves to v_j among $V \backslash \{v_i\}$. All nodes in the network are eventually ranked according to the steady-state probability vector P^∞. The steady-state of each node represents its relative importance to the set of source nodes S.

Inspired from the success of this algorithm for disease gene prediction [22], study [20] proposed the RWR-based method, RWRMDA, for disease miRNA prediction on a homogeneous miRNA network. In which, the transition matrix $W'$is defined as follow:

$$(W'_M)_{ij} = \frac{(W_M)_{ij}}{\sum_j (W_M)_{ij}}$$

where W_M is adjacency matrix of the homogeneous miRNA network.

In addition, the set of source nodes (S) was specified by miRNAs known to be associated with d. Therefore, the initial probability vector was defined as follow:

$$P^0 = \begin{cases} \frac{1}{|S|} & if\ v_i \in S \\ 0 & otherwise \end{cases}$$

Random Walk with Restart on a heterogeneous miRNA network

RWRH algorithm was first proposed for disease gene prediction on a heterogeneous network of genes and disease phenotypes [29]. This can be considered a variant of the RWR algorithm, since it was defined in the same formula as for RWR. The difference is construction of transition matrix W'.

Based on the RWRH algorithm, in this study, we proposed a method, RWRHMDA, for disease miRNA prediction on the heterogeneous network of miRNAs and disease phenotypes. More specifically, W' was defined as follow:

$$W' = \begin{bmatrix} W'_M & W'_{MP} \\ W'_{PM} & W'_P \end{bmatrix}$$

where W'_M and W'_P are intra-subnetwork transition matrices of the homogeneous miRNA network and the phenotype similarity network, respectively. W'_{MP}, W'_{PM} are inter-subnetwork transition matrices. Let λ be the jumping probability the random walker jumps from the miRNA network to the phenotype network or vice versa. Then, these matrices were defined as follow:

$$(W'_{MP})_{i,j} = p(p_j|m_i) = \begin{cases} \frac{\lambda (W_{MP})_{ij}}{\sum_j (W_{MP})_{ij}} & if \sum_j (W_{MP})_{ij} \neq 0 \\ 0 & otherwise \end{cases}$$

$$(W'_{PM})_{i,j} = p(m_j|p_i) = \begin{cases} \frac{\lambda (W_{MP})_{ji}}{\sum_j (W_{MP})_{ji}} & if \sum_j (W_{MP})_{ji} \neq 0 \\ 0 & otherwise \end{cases}$$

$$(W'_M)_{i,j} = \begin{cases} \frac{(W_M)_{ij}}{\sum_j (W_M)_{ij}} & if \sum_j (W_{MP})_{ij} = 0 \\ \frac{(1-\lambda)(W_M)_{ij}}{\sum_j (W_M)_{ij}} & otherwise \end{cases}$$

$$(W'_P)_{i,j} = \begin{cases} \frac{(W_P)_{ij}}{\sum_j (W_P)_{ij}} & if \sum_j (W_{MP})_{ji} = 0 \\ \frac{(1-\lambda)(W_P)_{ij}}{\sum_j (W_P)_{ij}} & otherwise \end{cases}$$

where W_P and W_{MP} are adjacency matrices of the phenotype similarity and bipartite networks.

By letting η be the parameter to weight the importance of each network, the initial probability vector was defined as follow:

$$P^0 = \begin{cases} (1-\eta)\frac{1}{|S|} & if\ v_i \in S \\ \eta & if\ v_i \equiv d \\ 0 & otherwise \end{cases}$$

For these two algorithms, all remaining miRNAs in the networks, which are not known to be associated to d, were selected as candidates for ranking.

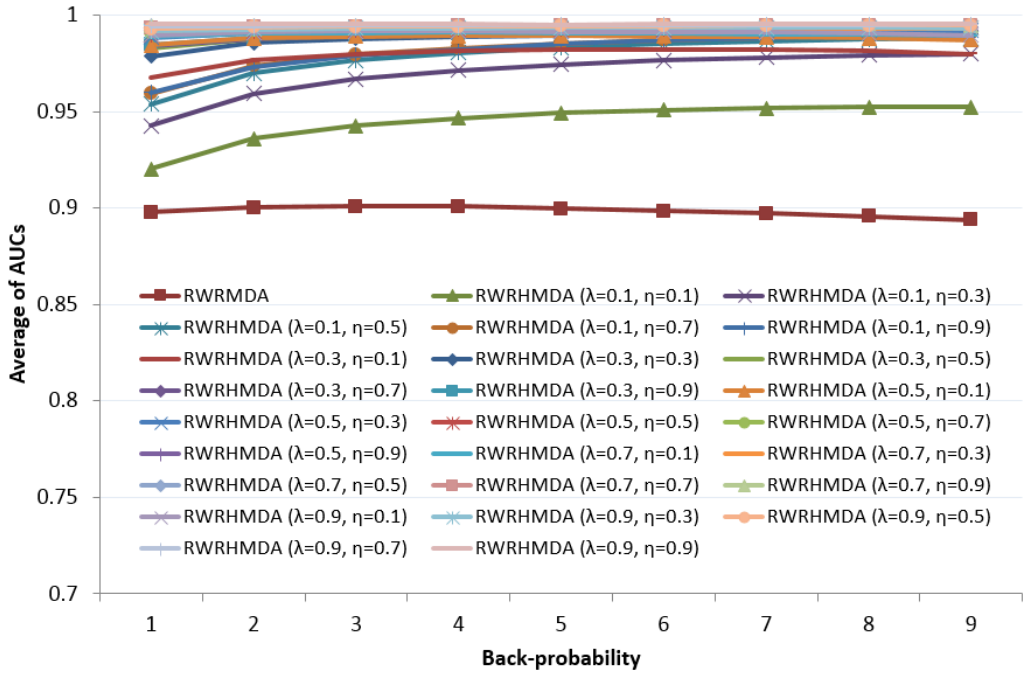

Fig. 2. Performance comparison between RWRHMDA and RWRMDA

III. Results and Discussion

A. Performance comparison

To compare the performance of RWRHMDA with that of RWRMDA, we used leave-one-out cross-validation (LOOCV) method for each disease phenotype in a set of disease phenotypes. Due to using LOOCV, only 35 of 53 disease phenotypes associating to at least two miRNAs were finally selected for assessment. For each disease phenotype (*d*), in each round of LOOCV, we held out one known *d*-associated miRNA. The rest of known *d*-associated miRNAs and *d* were used as seed nodes. The held-out miRNA and remaining miRNAs in the homogeneous miRNA network, which were not known to be associated to *d*, were ranked by RWRHMDA and RWRMDA methods. Then, we plotted the receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) to compare the performance of these two methods. This curve represents the relationship between *sensitivity* and (1-*specificity*), where *sensitivity* refers to the percentage of known *d*-associated miRNAs that were ranked above a particular threshold and *specificity* refers to the percentage of miRNAs which were not known to be associated to *d* ranked below this threshold. Consequently, the performance of each method was an average of AUC values over the set of 35 disease phenotypes. For fair comparison, we varied the back-probability (γ) in a range of [0.1, 0.9]. Two other parameters (i.e., λ and η) of RWRHMDA were also varied in {0.1, 0.3, 0.5, 0.7, 0.9}. Figure 2 shows that the performance of RWRHMDA was better than that of RWRMDA statistically significantly for all combinations of λ and η (All P-values < 0.05, using two-sample t-Test for means). In addition, the performance of RWRHMDA was getting better when γ increased, whereas that of RWRMDA slightly changed. This indicated "disease module" principle is better exploited when the disease phenotype similarity information is taken together. Indeed, when γ is high, the random walker tends to assign miRNAs located near seed nodes (i.e., remaining known disease miRNAs) higher scores; therefore, the held-out miRNA, which is still closely connected to remaining known disease miRNAs, was given a higher rank. In addition, Figure 2 also shows that when λ and η increase the performance of RWRHMDA increased. This indicated that disease phenotype similarity information is more important than miRNA functional similarity information.

B. Case study: Alzheimer's disease

In this experiment, we tried to predict novel miRNAs associated to Alzheimer's disease (MIM ID is 104300). Alzheimer's disease is a multi-factorial and fatal neurodegenerative disorder for which the mechanisms leading to profound neuronal loss are incompletely recognized. According to the database of disease-miRNA associations, miR2Disease [34], six miRNAs are known to be associated with Alzheimer's disease. To predict novel miRNAs associated to this disease, we used those known associated miRNAs and the MIM ID of Alzheimer's disease as source nodes, and other miRNAs in the homogeneous miRNA network as candidates. We set $\gamma = \eta = \lambda = 0.9$, since RWRHMDA achieved best performance with these values. After all candidate miRNAs were ranked, we selected 100 highly ranked candidates for evidence search about the association between miRNA and Alzheimer's disease from literature on PubMed using Entrez Programming Utilites [35]. Table 1 shows eight evidenced candidate miRNAs. For instance, study [36] (PubMed ID: 23585551) showed de-repression of FOXO3a death axis by

hsa-miR-132 and *hsa-miR-212* causes neuronal apoptosis in Alzheimer's disease. In addition, it was reported that *hsa-miR-132* may contribute to disease progression through aberrant regulation of mRNA targets in the Tau network [37] (PubMed ID: 24014289). Also, *hsa-miR-181b* regulates serine palmitoyltransferase and in turn amyloid β, novel targets in sporadic Alzheimer's disease [38] (PubMed ID: 21994399). Other not yet evidenced miRNAs in the top 100 miRNAs can be good candidates for biologists for further investigation (This list will be provided upon request).

TABLE I. Eight evidenced Alzheimer's disease-associated miRNAs among top 100 ranked candidates

Rank	miRNA	PubMed ID
1	*hsa-miR-132*	23585551, 24014289
6	*hsa-miR-181b*	21720722, 21994399
15	*hsa-miR-27a*	24212398
20	*hsa-miR-339*	24352696
28	*hsa-let-7g*	23922807
72	*hsa-miR-590-3p*	21548758
75	*hsa-miR-545*	23922807
93	*hsa-miR-206*	22926857, 24465270

IV. Conclusions

The identification of novel disease-associated miRNAs is an important task in biomedical research. In this study, we proposed a method, RWRHMDA, which was based on a state-of-the-art algorithm for disease gene prediction problem, for disease miRNA prediction. Experiment results showed that the performance of RWRHMDA was better than that of a state-of-the-art method, RWRMDA, irrespective of parameter settings. In addition, RWRHMDA better exploited the "disease module" principle since it achieved better performance when the back-probability increases. Moreover, the performance of RWRHMDA was more superior when the jumping and weight parameters increase. This indicated that disease phenotype similarity information is more important than miRNA functional similarity information for prediction of disease-associated miRNAs. Finally, using RWRHMDA, we predicted eight novel miRNAs, including *hsa-miR-132, hsa-miR-181b, hsa-miR-27a, hsa-miR-339, hsa-let-7g, hsa-miR-590-3p, hsa-miR-545* and *hsa-miR-206*, associated to Alzheimer's disease, those are not yet recorded in the database of disease-miRNA associations, miR2Disease.

Acknowledgment

This research is funded by Ministry of Education and Training (MOET) under grant number B2014-01-84.

References

[1] M. G. Kann, "Advances in translational bioinformatics: computational approaches for the hunting of disease genes," *Briefings in Bioinformatics,* vol. 11, pp. 96-110, January 1, 2010 2009.

[2] L.-C. Tranchevent, F. B. Capdevila, D. Nitsch, B. De Moor, P. De Causmaecker, and Y. Moreau, "A guide to web tools to prioritize candidate genes," *Briefings in Bioinformatics,* vol. 12, pp. 22-32, January 1, 2011 2010.

[3] L. He and G. J. Hannon, "MicroRNAs: small RNAs with a big role in gene regulation," *Nature Reviews Genetics,* vol. 5, pp. 522-531, 2004.

[4] Z. Yang, F. Ren, C. Liu, S. He, G. Sun, Q. Gao*, et al.*, "dbDEMC: a database of differentially expressed miRNAs in human cancers," *BMC Genomics,* vol. 11, p. S5, 2010.

[5] R. Conrad, M. Barrier, and L. P. Ford, "Role of miRNA and miRNA processing factors in development and disease," *Birth Defects Research Part C: Embryo Today: Reviews,* vol. 78, pp. 107-117, 2006.

[6] Y. Li and K. V. Kowdley, "MicroRNAs in Common Human Diseases," *Genomics, Proteomics & Bioinformatics,* vol. 10, pp. 246-253, 2012.

[7] Joshua T. Mendell and Eric N. Olson, "MicroRNAs in Stress Signaling and Human Disease," *Cell,* vol. 148, pp. 1172-1187, 2012.

[8] M. Esteller, "Non-coding RNAs in human disease," *Nat Rev Genet,* vol. 12, pp. 861-874, 2011.

[9] I. Steinfeld, R. Navon, R. Ach, and Z. Yakhini, "miRNA target enrichment analysis reveals directly active miRNAs in health and disease," *Nucleic acids research,* vol. 41, p. e45, February 1, 2013 2013.

[10] M. Salvatore, A. Magrelli, and D. Taruscio, "The Role of microRNAs in the Biology of Rare Diseases," *International Journal of Molecular Sciences,* vol. 12, pp. 6733-6742, 2011.

[11] V. Rottiers and A. M. Näär, "MicroRNAs in metabolism and metabolic disorders," *Nat Rev Mol Cell Biol,* vol. 13, pp. 239-250, 2012.

[12] A. S. Ali, S. Ali, A. Ahmad, B. Bao, P. A. Philip, and F. H. Sarkar, "Expression of microRNAs: potential molecular link between obesity, diabetes and cancer," *Obesity Reviews,* vol. 12, pp. 1050-1062, 2011.

[13] J. Xu, C.-X. Li, J.-Y. Lv, Y.-S. Li, Y. Xiao, T.-T. Shao*, et al.*, "Prioritizing Candidate Disease miRNAs by Topological Features in the miRNA Target-Dysregulated Network: Case Study of Prostate Cancer," *Molecular Cancer Therapeutics,* vol. 10, pp. 1857-1866, October 1, 2011 2011.

[14] D. P. Bartel, "MicroRNAs: Genomics, Biogenesis, Mechanism, and Function," *Cell,* vol. 116, pp. 281-297, 2004.

[15] M. Lu, Q. Zhang, M. Deng, J. Miao, Y. Guo, W. Gao*, et al.*, "An Analysis of Human MicroRNA and Disease Associations," *PLoS ONE,* vol. 3, p. e3420, 2008.

[16] Q. Jiang, Y. Hao, G. Wang, L. Juan, T. Zhang, M. Teng*, et al.*, "Prioritization of disease microRNAs through a human phenome-microRNAome network," *BMC Systems Biology,* vol. 4, p. S2, 2010.

[17] J. Qinghua, H. Yangyang, W. Guohua, Z. Tianjiao, and W. Yadong, "Weighted Network-Based Inference of Human MicroRNA-Disease Associations," in *Frontier of Computer Science and Technology (FCST), 2010 Fifth International Conference on*, 2010, pp. 431-435.

[18] D. Wang, J. Wang, M. Lu, F. Song, and Q. Cui, "Inferring the human microRNA functional similarity and functional network based on microRNA-associated diseases," *Bioinformatics,* vol. 26, pp. 1644-1650, July 1, 2010 2010.

[19] D.-H. Le and K. Marchal, "Integration of miRNA-miRNA networks improves the prediction of novel disease associated miRNAs," in *The First NAFOSTED Conference on Information and Computer Science*, 2014, pp. 438-448.

[20] X. Chen, M.-X. Liu, and G.-Y. Yan, "RWRMDA: predicting novel human microRNA-disease associations," *Molecular BioSystems,* vol. 8, pp. 2792-2798, 2012.

[21] H. Chen and Z. Zhang, "Prediction of Associations between OMIM Diseases and MicroRNAs by Random Walk on OMIM Disease Similarity Network," *The Scientific World Journal,* vol. 2013, p. 6, 2013.

[22] S. Kohler, S. Bauer, D. Horn, and P. Robinson, "Walking the Interactome for Prioritization of Candidate Disease Genes," *The American Journal of Human Genetics,* vol. 82, pp. 949-958, 2008.

[23] D.-H. Le and Y.-K. Kwon, "GPEC: A Cytoscape plug-in for random walk-based gene prioritization and biomedical evidence collection," *Computational Biology and Chemistry,* vol. 37, pp. 17-23, 2012.

[24] D.-H. Le and Y.-K. Kwon, "Neighbor-favoring weight reinforcement to improve random walk-based disease gene prioritization," *Computational Biology and Chemistry,* vol. 44, pp. 1-8, 2013.

[25] S. Navlakha and C. Kingsford, "The power of protein interaction networks for associating genes with diseases," *Bioinformatics,* vol. 26, pp. 1057-1063, April 15, 2010 2010.

[26] I. Feldman, A. Rzhetsky, and D. Vitkup, "Network properties of genes harboring inherited disease mutations," *Proceedings of the National Academy of Sciences,* vol. 105, pp. 4323-4328, March 18, 2008 2008.
[27] K.-I. Goh, M. E. Cusick, D. Valle, B. Childs, M. Vidal, and A.-L. Barabási, "The human disease network," *Proceedings of the National Academy of Sciences,* vol. 104, pp. 8685-8690, May 22, 2007 2007.
[28] M. Oti and H. G. Brunner, "The modular nature of genetic diseases," *Clinical Genetics,* vol. 71, pp. 1-11, 2007.
[29] Y. Li and J. C. Patra, "Genome-wide inferring gene-phenotype relationship by walking on the heterogeneous network," *Bioinformatics,* vol. 26, pp. 1219-1224, May 1, 2010 2010.
[30] J. Xu, C.-X. Li, Y.-S. Li, J.-Y. Lv, Y. Ma, T.-T. Shao*, et al.*, "MiRNA-miRNA synergistic network: construction via co-regulating functional modules and disease miRNA topological features," *Nucleic acids research,* vol. 39, pp. 825-836, February 1, 2011 2011.
[31] M. A. van Driel, J. Bruggeman, G. Vriend, H. G. Brunner, and J. A. M. Leunissen, "A text-mining analysis of the human phenome," *Eur J Hum Genet,* vol. 14, pp. 535-542, 2006.
[32] M. Kertesz, N. Iovino, U. Unnerstall, U. Gaul, and E. Segal, "The role of site accessibility in microRNA target recognition," *Nat Genet,* vol. 39, pp. 1278-1284, 2007.
[33] B. P. Lewis, I. h. Shih, M. W. Jones-Rhoades, D. P. Bartel, and C. B. Burge, "Prediction of Mammalian MicroRNA Targets," *Cell,* vol. 115, pp. 787-798, 2003.
[34] Q. Jiang, Y. Wang, Y. Hao, L. Juan, M. Teng, X. Zhang*, et al.*, "miR2Disease: a manually curated database for microRNA deregulation in human disease," *Nucleic acids research,* vol. 37, pp. D98-D104, January 1, 2009 2009.
[35] S. Volinia and C. M. Croce, "Prognostic microRNA/mRNA signature from the integrated analysis of patients with invasive breast cancer," *Proceedings of the National Academy of Sciences,* vol. 110, pp. 7413-7417, April 30, 2013 2013.
[36] Y. Chen, T. Jacquemin, S. Zhang, and R. Jiang, "Prioritizing protein complexes implicated in human diseases by network optimization," *BMC Systems Biology,* vol. 8, p. S2, 2014.
[37] T. Jacquemin and R. Jiang, "Walking on a tissue-specific disease-protein-complex heterogeneous network for the discovery of disease-related protein complexes," *BioMed research international,* vol. 2013, 2013.
[38] Q. Wang, J. Sun, M. Zhou, H. Yang, Y. Li, X. Li*, et al.*, "A novel network-based method for measuring the functional relationship between gene sets," *Bioinformatics,* vol. 27, pp. 1521-1528, 2011.