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Identifying MicroRNA and Gene Expression Networks Using Graph Communities

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Abstract: Integrative network analysis is powerful in helping understand the underlying mechanisms of genetic and epigenetic perturbations for disease studies. Although it becomes clear that microRNAs, one type of epigenetic factors, have direct effect on target genes, it is unclear how microRNAs perturb downstream genetic neighborhood. Hence, we propose a network community approach to integrate microRNA and gene expression profiles, to construct an integrative genetic network perturbed by microRNAs. We apply this approach to an ovarian cancer dataset from The Cancer Genome Atlas project to identify the fluctuation of microRNA expression and its effects on gene expression. First, we perform expression quantitative loci analysis between microRNA and gene expression profiles via both a classical regression framework and a sparse learning model. Then, we apply the spin glass community detection algorithm to find genetic neighborhoods of the microRNAs and their associated genes. Finally, we construct an integrated network between microRNA and gene expression based on their community structure. Various disease related microRNAs and genes, particularly related to ovarian cancer, are identified in this network. Such an integrative network allows us to investigate the genetic neighborhood affected by microRNA expression that may lead to disease manifestation and progression.

Key words: network integration; graph community detection; spin glass algorithm; microRNA networks

1 Introduction

Integrating various types of biological data has been increasingly powerful for analyzing biological systems. Particularly, integrative methods provide a useful outlook into understanding how epigenetic factors, including microRNAs (miRNAs), affect human health and disease. Recently, the functional influence of miRNAs on gene expression has become an important part of disease studies. Previous studies have shown that Single Nucleotide Polymorphisms (SNPs) affect miRNA expression[1–3] through the technique of expression Quantitative Trait Loci (eQTL) mapping[4]. These miRNA eQTL studies integrated SNP genotype data with miRNA expression by finding significant associations among SNPs and miRNA expression.

Recent studies demonstrate that integrating multi-dimensional data provides invaluable findings in various traits and diseases[5, 6]. While there has been much success with the current eQTL mapping methods, there are some critical factors hinder our understanding of how these loci contribute to diseases at a system level. For instance, these studies integrate only two layers of data that are available, assuming that individual SNPs and miRNAs are independent on each other. Since genes do not act in isolation, we should investigate downstream effects caused by eQTLs and then perturbed genes. miRNAs have been shown before

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that they fine tune gene expression through post-transcriptional processes, albeit a lack of systematic analysis. With the availability of multiple layers of data, we should design methods to integrate these data together for a more systematic view of how miRNAs perturb gene expression.

In this paper, we integrate data from various sources such as miRNA expression profiles, gene expression quantifications, miRNA targets, and protein-protein interactions. Using these data sources, we propose a network integration approach to expand eQTL associations based on interactome networks. We believe that by extending an eQTL network we can observe direct and indirect downstream effects of eQTLs. Particularly, we applied our approach to study how miRNAs affect gene expression and their downstream genes in their neighborhood in ovarian cancer. Our results show that our extended miRNA eQTL network covers miRNAs and genes related to disease or cancers, such as ovarian cancer.

Although focused on integrating miRNA and gene expression in this paper, our approach is applicable to study the genetic neighborhood perturbed by other factors like genetic variants. The code for our approach is freely accessible from https://github.com/shilab/community-detection/.

2 Methods

As shown in Fig. 1, our approach is composed of six steps as follows: (1) Data Collection: We collected and pre-processed miRNA/gene expression data and interactions. (2) eQTL Analysis: We performed an eQTL analysis between miRNA and gene expression profiles using two complementary methods, Matrix eQTL[7] and MTLasso2[8]. (3) Network Integration: We merged the eQTL associations, miRNA targets, and protein-protein interaction networks into a baseline network that captures the relationship among miRNAs and genes, much like our previous work[9]. Specifically, we performed database searches to identify direct miRNA targets. We then overlapped those results with a protein-protein interaction network. (4) Community Detection: We performed community detection on the merged network in order to identify communities within an effective propagation distance from our miRNA eQTL genes. (5) Statistical Significance: We used the Wilcoxon-Rank Sum test to determine the statistical significance of each community in the network. (6) Network Visualization: Significant communities were visualized in Cytoscape[10].

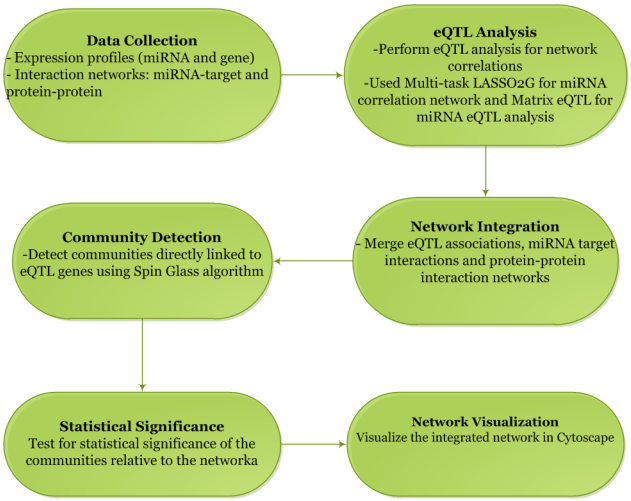

Fig. 1 The overall workflow of our approach.

2.1 Analysis of miRNA eQTL associations

The Cancer Genome Atlas (TCGA)[11] data set provides rich data across different layers for many cancer types. With an aim of constructing an integrative network of miRNA and gene expression in ovarian cancer, we used TCGA data including miRNA expression profiles, gene expression quantifications, miRNA interaction networks, and protein-protein networks. In total we integrated 964 miRNAs and gene targets, and 349 663 interactions from a protein-protein network. We combined these data to construct a network which extends from miRNA eQTL perturbations on particular genes in the TCGA data set. Our goal in this study is to integrate large-scale data in order to exploit the indirect effects of miRNA expression on gene expression in interaction networks in ovarian cancer.

Prior to data integration, we performed an eQTL analysis between the miRNA expression and gene expression profiles. The eQTL analysis was performed using Matrix eQTL[7], an R package that uses matrix operations to perform eQTL mapping based on the assumption that miRNAs and genes are independent respectively. After quantile normalization of miRNA and gene expression data respectively, we performed *cis* eQTL analysis, whereby we only tested miRNAs which were within 1 Mb of a gene. To identify associations between the miRNA and genes, we used a linear regression model provided by Matrix eQTL. We used multi-test correction based on False Discovery Rate (FDR) and chose the significant eQTLs with an FDR cutoff at <0.01 for further analysis.

To capture the relationships among miRNA and gene expression, in addition to Matrix eQTL, we used an orthologous approach, namely two-graph guided multitask Lasso model (MtLasso2G)[8]. MtLasso2G performs eQTL analysis with consideration of correlations among miRNAs and genes. MtLasso2G uses a sparse learning model that incorporates the relationships among miRNAs and genes respectively. We used a correlation expression network among miRNAs, and another co-expressed network among genes that potentially captured the structure of co-regulation networks. MtLasso2G accomplishes eQTL analysis by adding two regularization terms based on the two graphs on features (i.e., miRNA expression) and labels (i.e., gene expression), which are encoded as miRNA co-expression network and gene co-expression network in our analysis respectively.

We then merged the eQTLs identified from these two orthologous approaches and used the miRNA target genes identified from mirDB[12] to extend the eQTL network. The merged miRNA eQTL genes were considered as directly effected genes by miRNAs, and were used as seed genes to expand the network for an indirect effect analysis. We then used a human protein interaction network, namely InWeb[13], that combines protein interaction networks from various resources and across diverse organisms. We first overlapped the matching genes from our miRNA eQTL analysis with the InWeb network. Then we kept InWeb interactions with an edge weight greater than or equal to 0.10.

2.2 Network integration

The initial network was created from the miRNAs and eQTL associations. Using the miRNAs from eQTL analysis, we gathered known targets of these miRNAs to add to our network. With the known targets and eQTL associations, we overlapped this network with protein-protein interactions collected from the InWeb network[13]. We overlapped these two resulted networks by common genes shared in the networks, and generated a merged edge list to represent our integrated network. This allowed us to link the miRNAs to downstream targets by genes they share in common initially.

After generating this extended network, we performed community detection to identify downstream genes that interact directly with target genes affected by miRNAs. In particular, we used the spin glass community detection algorithm from igraph[14], which is primarily based on thermodynamics[15–17]. The semi-supervised spin glass algorithm is coupled with simulated annealing and is less computationally intensive compared to other methods based on optimizing the modularity of a network. The computational efficiency makes it attractive for large-scale networks. The communities provide a scope of interactions directly affected by genotypic perturbations on the miRNA level.

Using the spin model, the problem of community detection is mapped as identifying the spin states, which are the community indexes. The model is based on optimizing the qualifying energy function, known as the Hamiltonian, in Eq. (1) such that it minimizes the energy and maximizes the modularity of the system.

$$H(\sigma) = \boldsymbol{A}_{i,j}\gamma p_{i,j}\delta(\sigma_i, \sigma_j) \tag{1}$$

Here, $\boldsymbol{A}_{i,j}$ is the adjacency matrix consisting of nodes i and j and the edges between them; γ represents the weights and σ_i and σ_j represent the spin states or community indices which nodes i and j belong to in the network. In this function, $p_{i,j}$ represents the probability of an edge between nodes i and j. Thus, the adjacency matrix represents the relationships between nodes and edges based on the weights determined by γ. In reference to σ, i and j represent each community index. The Kronecker delta function has a binary value of 1 if the nodes represented by σ_i and σ_j are in the same community, otherwise it is 0. This function is optimized throughout the community detection process. An advantage of this algorithm is that it can detect overlapping communities without the network being affected by the degeneracy of the Hamiltonian.

Once the community detection process was completed, we selected those detected communities with nodes overlapping with miRNA associated genes from eQTL analysis. We used the network communities constructed here to expand the miRNA-gene associations by including genetic neighborhood encoded as protein-protein interactions from the InWeb network. Nevertheless, the community detection algorithm can be used on any genetic network as a guide. For example, we can perform community detection on a genetic regulatory network and find communities extended from miRNA associated genes.

In this study, we selected the direct and indirect

genes within an effective propagation distance[18] of the miRNAs in the ovarian cancer data set, generally at most six nodes. Nodes further from the source may not receive the perturbation signal, thus not being affected. Focusing on targets within close proximity, we chose to only visualize those genes that are within two neighbors away. The downstream effect can include downstream genes further than two neighbors, creating a larger community of downstream targets.

For selected communities, we used the Wilcoxon Rank-Sum test to determine the statistical significance. The Wilcoxon Rank-Sum tests the significance of the internal and external degrees of the vertices in the graph. This allowed us to measure the significance of the community relative to the graph. Then we visualized in Cytoscape[10] for further analysis.

3 Results and Discussion

3.1 Integrated network

We constructed an extended network consisting of miRNA eQTL genes as seed nodes, immediate target genes from the miRNA eQTL mapping results, and the indirect genes from the communities in the protein-protein interaction network. The edges of the constructed network include the miRNA eQTL associations between miRNAs and their affected genes and the interactions among miRNA directly affected genes and their downstream genes in a neighborhood.

The final integrated network consisted of miRNAs, their associated genes, protein-protein interactions, and targets from miRNA associated genes. The spin glass algorithm detected 25 communities. Of these 25 communities, we were only interested in communities that were linked to our miRNAs and associated genes, thus giving us 12 communities to further analyze. We used the Wilcoxon Rank-Sum test to determine the statistical significance. We found that all genetic communities affected miRNAs had considerably low p-values, thus being statistically significant in our network. This leads us to believe that the miRNAs significantly impact gene expression in the extended network. We can analyze the communities further to understand their impact in a biological system.

The integrated network is essentially composed of genes that are directly or indirectly affected by miRNA expression in ovarian cancer using TCGA datasets. Using the miRNA associated genes as seed genes, we extended the miRNA-gene associations through the communities detected from the spin glass algorithm. For our network analysis, we viewed specific communities from the InWeb network that were linked to these miRNAs and their downstream genes within an effective propagation distance (e.g., within two neighbors of miRNA associated genes). By including these neighbor genes, we captured both direct genes and indirect genes in a genetic neighborhood that were affected by miRNA expression. As an example of our extended network, please view Fig. 2.

3.2 Disease associations

In efforts to understand any disease associations in our network, we queried the miRNA associated genes in the Online Mendelian Inheritance in Man (OMIM) Disease database[19]. We found 59 genes were associated with diseases in OMIM. For example, *NUMA*1 is a nuclear mitotic asparatus protein found to be over-expressed in epithelial ovarian cancer, contributing to chromosomal instability[20]. Our integrated network shows that *NUMA*1 is indirectly linked to *mir*-15*b*. Please see Table 1 for other disease genes in our results. A visualization of the community containing known miRNAs can be seen in Fig. 3. Shown in this figure is *mir*-200*c* and its immediate targets within an effective propagation distance. *mir*-200*c* is a prognostic marker in ovarian cancer and is often associated with metastasis in other cancers. More examples of the miRNAs are shown in Table 2.

4 Conclusion

In this study, we developed a method based on community detection to construct an integrative view of the miRNA and gene expression network. Specifically, We used miRNA expression, gene expression, miRNA targets, and protein-protein interactions. We integrated this data to create a community-based network affected by miRNA perturbations. Hence, our resulted miRNA gene expression network includes the direct and indirect genetic neighborhood that are affected by miRNAs and their target genes.

In the future, we will include other types of biological networks such as regulatory networks to capture other types of relationships among genes. Our method is also applicable to build other biological

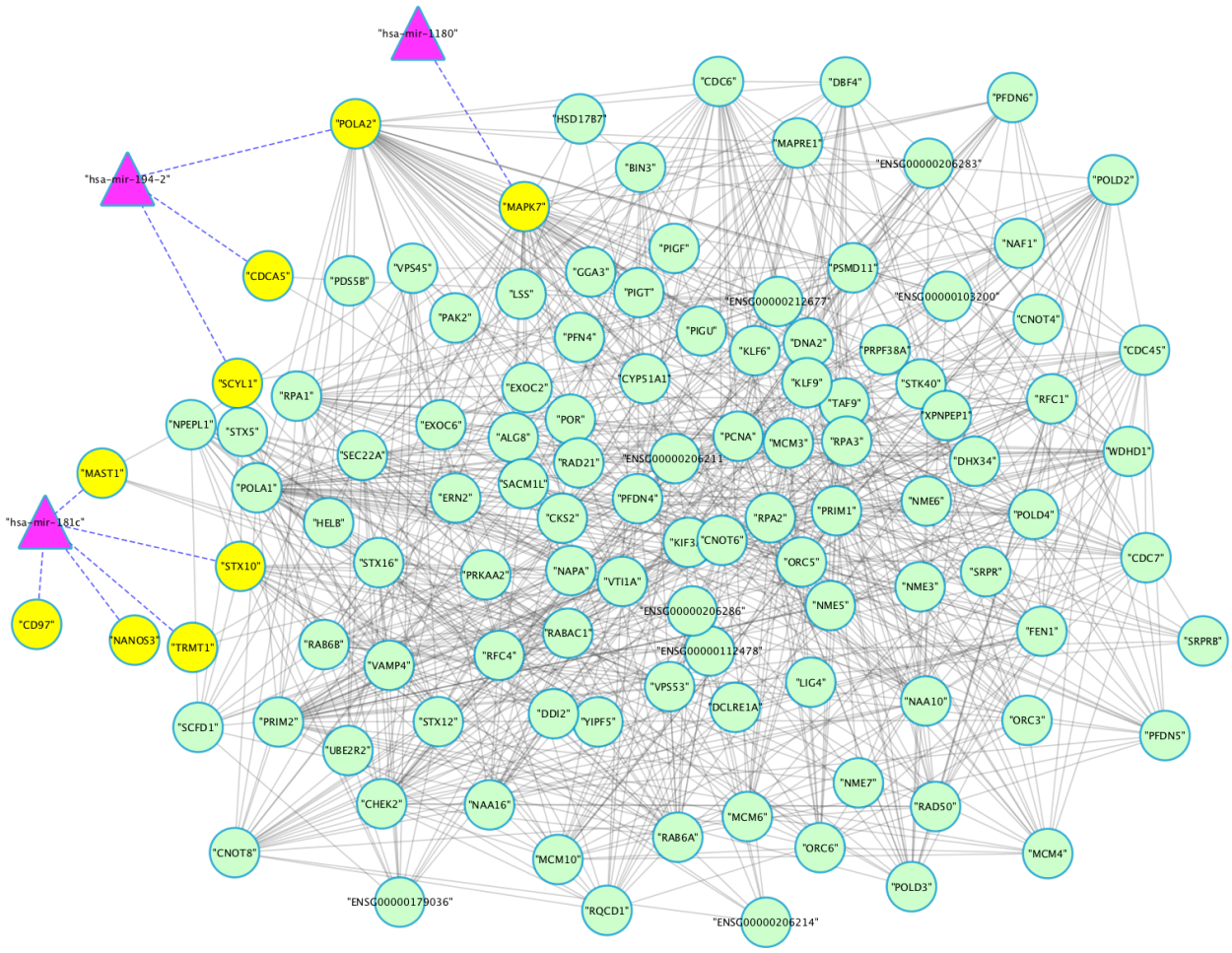

Fig. 2 An example of a community in the miRNA interaction network that contained miRNAs, their associated genes, and downstream genes that are indirectly affected by the miRNAs. The miRNAs are denoted by purple triangles and their immediate targets are represented by dashed blue lines while the indirect targets are shown as a solid gray line. All downstream targets from OMIM database are green nodes. Yellow nodes have yet to be directly associated with a disease of phenotype.

Table 1 A summary table showing the genes affected by eQTLs that are OMIM disease genes.

Gene	Description	Disease/Phenotype
CDKN1C, *KIP2*, *BWS*, *IMAGE*	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	IMAGE syndrome
CDKN1C, *KIP2*, *BWS*, *IMAGE*	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	Beckwith-Wiedemann syndrome
DGCR2, *DGS2*	The DiGeorge syndrome chromosome region-2	DiGeorge syndrome/velocardiofacial syndrome complex-2
HNRNPA1, *IBMPFD3*, *ALS20*	Heterogeneous nuclear ribonucleoprotein A1	Inclusion body myopathy wtih early-onset Paget disease without frontotemporal dementia 3
HNRNPA1, *IBMPFD3*, *ALS20*	Heterogeneous nuclear ribonucleoprotein A1	Amyotrophic lateral sclerosis 20
KIAA1279	*KIAA1279* gene	Goldberg-Shprintzen megacolon syndrome
KIF1A, *ATSV*, *UNC104*, *SPG30*, *HSN2C*, *MRD9*	Kinesin family member 1A	Spastic paraplegia 30, autosomal recessive
KIF1A, *ATSV*, *UNC104*, *SPG30*, *HSN2C*, *MRD9*	Kinesin family member 1A	Neuropathy, hereditary sensory, type IIC
KIF1A, *ATSV*, *UNC104*, *SPG30*, *HSN2C*, *MRD9*	Kinesin family member 1A	Mental retardation, autosomal dominant 9
LDLRAP1, *ARH*, *FHCB2*, *FHCB1*	Low density lipoprotein receptor adaptor protein 1	Hypercholesterolemia, familial, autosomal recessive
NUMA1	Nuclear mitotic apparatus protein-1	Leukemia, acute promyelocytic, NUMA/RARA type
POMC	Proopiomelanocortin (adrenocorticotropin/beta-lipotropin)	Obesity, adrenal insufficiency, and red hair due to POMC deficiency
POMC	Proopiomelanocortin (adrenocortic'otropin/beta-lipotropin)	Obesity, early-onset, susceptibility to
RECQL4, *RTS*, *RECQ4*	DNA helicase, RecQ-like 4	Rothmund-Thomson syndrome
RECQL4, *RTS*, *RECQ4*	DNA helicase, RecQ-like 4	RAPADILINO syndrome
RECQL4, *RTS*, *RECQ4*	DNA helicase, RecQ-like 4	Baller-Gerold syndrome
SLC25A3, *PHC*	Solute carrier family 25 (mitochondrial carrier), member 3	Mitochondrial phosphate carrier deficiency
TUBB, *TUBB5*, *M40*, *CDCBM6*	Tubulin, beta polypeptide	Cortical dysplasia, complex, with other brain malformations 6

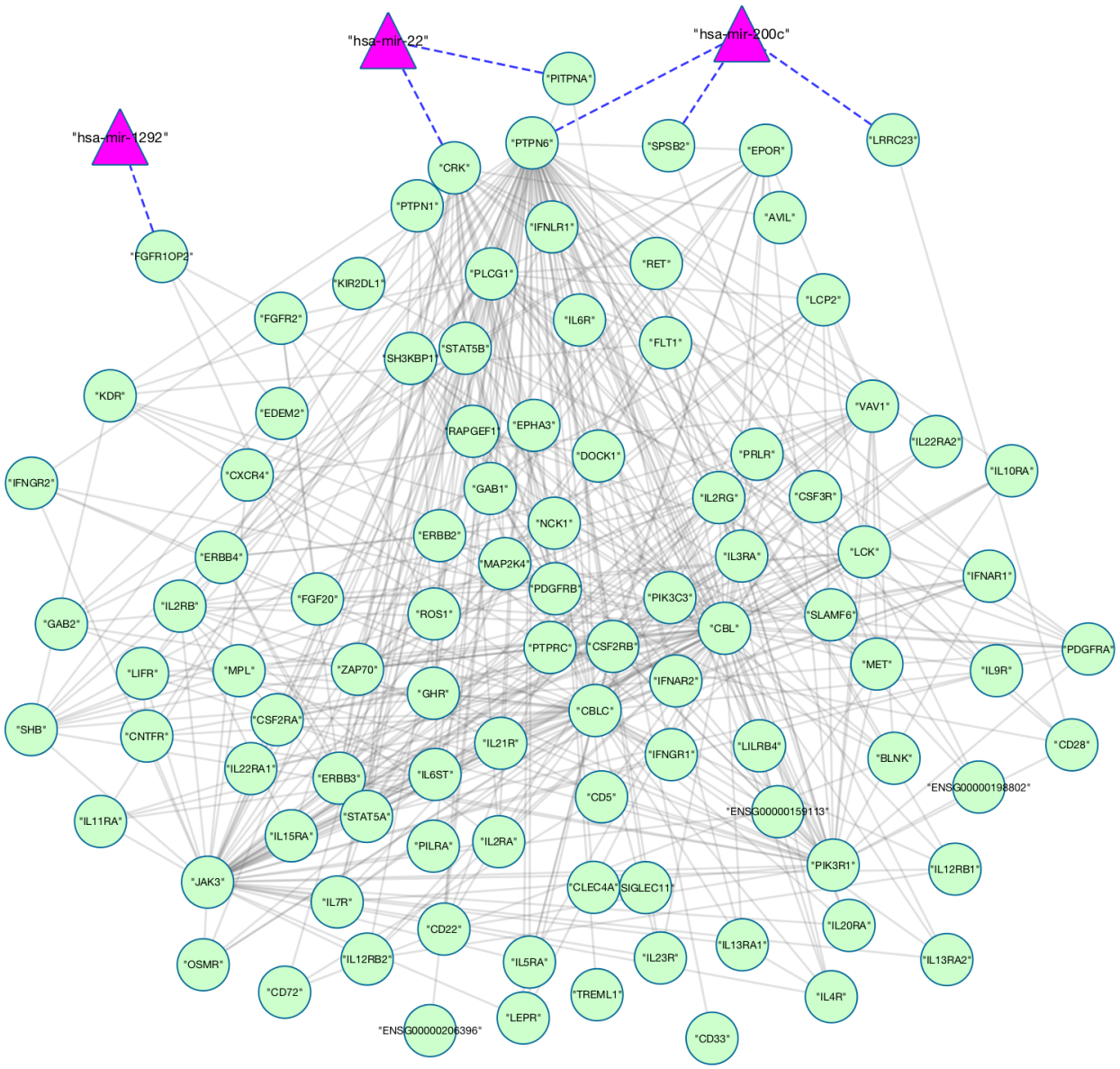

Fig. 3 Visualization of a community in our extended network with known miRNAs in ovarian cancer.

Table 2 List of miRNAs matched with the mirCancer database.

SNP/miRNA	Cancer	Profile	PubMed
hsa-let-7f-2	Breast cancer	Down	Breast cancer-specific TRAIL expression mediated by miRNA response elements of let-7 and miR-122.
	Bronchioloalveolar carcinoma	Down	let-7 microRNA expression is reduced in bronchioloalveolar carcinoma, a non-invasive carcinoma, and is not correlated with prognosis.
	Colon cancer	Down	let-7 microRNA functions as a potential growth suppressor in human colon cancer cells.
	Esophageal squamous cell carcinoma	Down	Role of microRNA let-7 and effect to HMGA2 in esophageal squamous cell carcinoma.
	Hepatocellular carcinoma	Down	MicroRNAs in Hepatobiliary and Pancreatic Cancers.
	Lung cancer	Down	Reduced expression of Dicer associated with poor prognosis in lung cancer patients.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-let-7f-2	Nasopharyngeal carcinoma	Down	MicroRNA let-7 suppresses nasopharyngeal carcinoma cells proliferation through downregulating c-Myc expression.
	Neuroblastoma	Down	LIN28B induces neuroblastoma and enhances MYCN levels via let-7 suppression.
	Pancreatic ductal adenocarcinoma	Down	let-7 MicroRNA transfer in pancreatic cancer-derived cells inhibits in vitro cell proliferation but fails to alter tumor progression.
hsa-mir-106b	Gastric cancer	Up	Circulating microRNAs in plasma of patients with gastric cancers.
	Glioma	Up	Down-regulation of miR-106b suppresses the growth of human glioma cells.
	Head and neck squamous cell carcinoma	Up	Comprehensive MicroRNA profiling for head and neck squamous cell carcinomas.
	Hepatocellular carcinoma	Up	Upregulation of microRNA-106b is associated with poor prognosis in hepatocellular carcinoma.
	Laryngeal carcinoma	Up	MiR-106b promotes cell proliferation via targeting RB in laryngeal carcinoma.
	Medulloblastoma	Up	miR-106b is overexpressed in medulloblastomas and interacts directly with PTEN.
hsa-mir-1180	Bladder cancer	Down	Up-regulation of p21(WAF1/CIP1) by miRNAs and its implications in bladder cancer cells.
hsa-mir-1228	Hepatocellular carcinoma	Up	miR-1228 promotes the proliferation and metastasis of hepatoma cells through a p53 forward feedback loop.
	Gastric cancer	Down	Restoration of miR-1228* expression suppresses epithelial-mesenchymal transition in gastric cancer.
hsa-mir-125b	Acute myeloid leukemia	Up	[miR-125b promotes proliferation of human acute myeloid leukemia cells by targeting Bak1].
	Bladder cancer	Down	MicroRNA-125b suppresses the development of bladder cancer by targeting E2F3.
	Breast cancer	Down	miR-125b is methylated and functions as a tumor suppressor by regulating the ETS1 proto-oncogene in human invasive breast cancer.
	Chronic lymphocytic leukemia	Down	The down-regulation of miR-125b in chronic lymphocytic leukemias leads to metabolic adaptation of cells to a transformed state.
	Follicular cancer	Up	MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer.
	Gastric cancer	Up	MiR-125b promotes cell migration and invasion by targeting PPP1CA-Rb signal pathways in gastric cancer, resulting in a poor prognosis.
	Glioblastoma	Down	Myc-associated zinc finger protein (MAZ) is regulated by miR-125b and mediates VEGF-induced angiogenesis in glioblastoma.
	Glioma	Up	MiR-125b expression affects the proliferation and apoptosis of human glioma cells by targeting Bmf.
	Hepatocellular carcinoma	Down	Histone lysine methyltransferase, SUV39H1, promotes HCC progression and is negatively regulated by microRNA-125b.
	Malignant melanoma	Down	miR-125b induces cellular senescence in malignant melanoma.
	Neuroblastoma	Up	MicroRNA-125b is a novel negative regulator of p53.
	Oral squamous cell carcinoma	Down	Decreased expression of miR-125b and miR-100 in oral cancer cells contributes to malignancy.
	Osteosarcoma	Down	miR-125b suppresses the proliferation and migration of osteosarcoma cells through down-regulation of STAT3.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-125b	Ovarian cancer	Down	Micro-RNAs and ovarian cancer: the state of art and perspectives of clinical research.
	Prostate cancer	Up	Oncomir miR-125b suppresses p14(ARF) to modulate p53-dependent and p53-independent apoptosis in prostate cancer.
hsa-mir-128	Acute lymphoblastic leukemia	Up	Distinctive microRNA signature is associated with the diagnosis and prognosis of acute leukemia.
	Acute myeloid leukemia	Up	Distinctive microRNA signature is associated with the diagnosis and prognosis of acute leukemia.
	Glioblastoma	Down	PDGF-B-mediated downregulation of miR-21: new insights into PDGF signaling in glioblastoma.
	Glioma	Down	Targeting of the Bmi-1 oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal.
	Osteosarcoma	Up	MicroRNA-128 promotes proliferation in osteosarcoma cells by downregulating PTEN.
	Prostate cancer	Down	MicroRNA-128 downregulates Bax and induces apoptosis in human embryonic kidney cells.
hsa-mir-1301	Liver cancer	Up	Identification of miRNAs that specifically target tumor suppressive KLF6-FL rather than oncogenic KLF6-SV1 isoform.
hsa-mir-149	Breast cancer	Down	MicroRNA-149 targets GIT1 to suppress integrin signaling and breast cancer metastasis.
	Colorectal cancer	Down	MicroRNA-149 Suppresses Colorectal Cancer Cell Migration and Invasion by Directly Targeting Forkhead Box Transcription Factor FOXM1.
	Gastric cancer	Down	MicroRNA-149 inhibits proliferation and cell cycle progression through the targeting of ZBTB2 in human gastric cancer.
	Glioblastoma	Down	miR-128 and miR-149 enhance the chemosensitivity of temozolomide by Rap1B-mediated cytoskeletal remodeling in glioblastoma.
	Head and neck squamous cell carcinoma	Down	The association between genetic polymorphism and the processing efficiency of miR-149 affects the prognosis of patients with head and neck squamous cell carcinoma.
	Nasopharyngeal carcinoma	Up	miR-149 promotes epithelial-mesenchymal transition and invasion in nasopharyngeal carcinoma cells.
	Non-small cell lung cancer	Down	miR-149 Inhibits Non-Small-Cell Lung Cancer Cells EMT by Targeting FOXM1.
hsa-mir-150	Breast cancer	Up	miR-150 promotes human breast cancer growth and malignant behavior by targeting the pro-apoptotic purinergic P2X7 receptor.
	Chronic lymphocytic leukemia	Up	Opposite prognostic significance of cellular and serum circulating microRNA-150 in Chronic Lymphocytic Leukemia patients.
	Chronic myelogenous leukemia	Down	Down-regulation of hsa-miR-10a in chronic myeloid leukemia CD34+ cells increases USF2-mediated cell growth.
	Colorectal cancer	Up	Circulating Exosomal microRNAs as Biomarkers of Colon Cancer.
	Esophageal squamous cell carcinoma	Down	MiR-150 is associated with poor prognosis in esophageal squamous cell carcinoma via targeting the EMT inducers ZEB1.
	Gastric cancer	Up	MiR-150 promotes gastric cancer proliferation by negatively regulating the pro-apoptotic gene EGR2.
	Lung adenocarcinoma	Up	Altered miR-143 and miR-150 expressions in peripheral blood mononuclear cells for diagnosis of non-small cell lung cancer.
	Lung cancer	Up	miR-150 promotes the proliferation and migration of lung cancer cells by targeting SRC kinase signalling inhibitor 1.
	Mantle cell lymphoma	Down	microRNA expression profile and identification of miR-29 as a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-150	Pancreatic ductal adenocarcinoma	Down	A Decrease in miR-150 Regulates the Malignancy of Pancreatic Cancer by Targeting c-Myb and MUC4.
	Colorectal cancer	Up	MicroRNA expression profiles in human colorectal cancers with liver metastases.
	Pancreatic cancer	Down	Upregulation of miR-150* and miR-630 Induces Apoptosis in Pancreatic Cancer Cells by Targeting IGF-1R.
hsa-mir-181a-1	Glioma	Down	MicroRNA-181 inhibits glioma cell proliferation by targeting cyclin B1.
	Hepatocellular carcinoma	Up	Identification of microRNA-181 by genome-wide screening as a critical player in EpCAM-positive hepatic cancer stem cells.
	Non-small cell lung cancer	Down	MicroRNA-181 functions as a tumor suppressor in non-small cell lung cancer (NSCLC) by targeting Bcl-2.
	Papillary thyroid carcinoma	Up	Expression of miRNAs in Papillary Thyroid Carcinomas Is Associated with BRAF Mutation and Clinicopathological Features in Chinese Patients.
	Prostate cancer	Up	microRNA-181 promotes prostate cancer cell proliferation by regulating DAX-1 expression.
hsa-mir-181c	Gastric cancer	Up	Upregulation of MicroRNA 181c Expression in Gastric Cancer Tissues and Plasma.
	Glioma	Down	MicroRNA-181 inhibits glioma cell proliferation by targeting cyclin B1.
	Hepatocellular carcinoma	Up	Identification of microRNA-181 by genome-wide screening as a critical player in EpCAM-positive hepatic cancer stem cells.
	Neuroblastoma	Down	MiR-181c modulates the proliferation, migration, and invasion of neuroblastoma cells by targeting Smad7.
	Non-small cell lung cancer	Down	MicroRNA-181 functions as a tumor suppressor in non-small cell lung cancer (NSCLC) by targeting Bcl-2.
	Osteosarcoma	Up	MicroRNA signatures associate with pathogenesis and progression of osteosarcoma.
	Papillary thyroid carcinoma	Up	Expression of miRNAs in Papillary Thyroid Carcinomas Is Associated with BRAF Mutation and Clinicopathological Features in Chinese Patients.
	Prostate cancer	Up	microRNA-181 promotes prostate cancer cell proliferation by regulating DAX-1 expression.
hsa-mir-192	Bladder cancer	Down	Expression of microRNAs in the Urine of Patients With Bladder Cancer.
	Colon cancer	Down	Prognostic significance of miR-215 in colon cancer.
	Colorectal cancer	Down	Association of microRNA expression with microsatellite instability status in colorectal adenocarcinoma.
	Epithelial ovarian cancer	Down	Gain-of-function microRNA screens identify miR-193a regulating proliferation and apoptosis in epithelial ovarian cancer cells.
	Gastric cancer	Up	MicroRNA-192 and -215 are upregulated in human gastric cancer in vivo and suppress ALCAM expression in vitro.
	Lung cancer	Down	MicroRNA-192 targeting retinoblastoma 1 inhibits cell proliferation and induces cell apoptosis in lung cancer cells.
	Pancreatic ductal adenocarcinoma	Up	Diagnostic and biological significance of microRNA-192 in pancreatic ductal adenocarcinoma.
hsa-mir-199b	Choriocarcinoma	Down	Decreased expression of microRNA-199b increases protein levels of SET (protein phosphatase 2A inhibitor) in human choriocarcinoma.
	Follicular thyroid carcinoma	Down	Differential miRNA expression defines migration and reduced apoptosis in follicular thyroid carcinomas.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-199b	Hepatocellular carcinoma	Down	[MicroRNA profiling in patients with hepatocellular carcinoma].
	Prostate cancer	Down	MiR199b Suppresses Expression of Hypoxia-Inducible Factor 1α (HIF-1α) in Prostate Cancer Cells.
hsa-mir-200c	Bladder cancer	Down	Expression of microRNAs in the Urine of Patients With Bladder Cancer.
	Breast cancer	Up	Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization.
	Cholangiocarcinoma	Down	Direct targeting of SUZ12/ROCK2 by miR-200b/c inhibits cholangiocarcinoma tumourigenesis and metastasis.
	Colon cancer	Down	miR-200c inhibits invasion and migration in human colon cancer cells SW480/620 by targeting ZEB1.
	Colorectal cancer	Down	miR-200c inhibits invasion and migration in human colon cancer cells SW480/620 by targeting ZEB1.
	Colorectal cancer	Up	MicroRNA-200c modulates epithelial-to-mesenchymal transition (EMT) in human colorectal cancer metastasis.
	Colorectal cancer	Up	Plasma miR-200c and miR-18a as potential biomarkers for the detection of colorectal carcinoma.
	Endometrial cancer	Up	The interactions between MicroRNA-200c and BRD7 in endometrial carcinoma.
	Gastric cancer	Down	The downregulation of miR-200c/141 promotes ZEB1/2 expression and gastric cancer progression.
	Head and neck squamous cell carcinoma	Down	MicroRNA-200c attenuates tumour growth and metastasis of presumptive head and neck squamous cell carcinoma stem cells.
	Hepatocellular carcinoma	Down	Expression of microRNAs, miR-21, miR-31, miR-122, miR-145, miR-146a, miR-200c, miR-221, miR-222, and miR-223 in patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma and its progno
	Lung adenocarcinoma	Down	miR-200 Inhibits lung adenocarcinoma cell invasion and metastasis by targeting Flt1/VEGFR1.
	Malignant melanoma	Down	miR-200c Inhibits Melanoma Progression and Drug Resistance throughDown-Regulation of Bmi-1.
	Mesenchymal cancer	Down	MicroRNA Expression Profiles in Kaposi's Sarcoma.
	Non-small cell lung cancer	Up	High expression of serum miR-21 and tumor miR-200c associated with poor prognosis in patients with lung cancer.
	Ovarian cancer	Up	Differential microRNA expression signatures and cell type-specific association with Taxol resistance in ovarian cancer cells.
	Pancreatic ductal adenocarcinoma	Down	XMD8-92 Inhibits Pancreatic Tumor Xenograft Growth via DCLK1-Dependent Mechanism.
	Rectal cancer	Up	The quantitative analysis by stem-loop real-time PCR revealed the microRNA-34a, microRNA-155 and microRNA-200c overexpression in human colorectal cancer.
	Renal clear cell carcinoma	Down	miRNA profiling for clear cell renal cell carcinoma: biomarker discovery and identification of potential controls and consequences of miRNA dysregulation.
hsa-mir-205	Bladder cancer	Down	Expression of microRNAs in the Urine of Patients With Bladder Cancer.
	Breast cancer	Up	Role of microRNAs-29b-2, -155, -197 and -205 as diagnostic biomarkers in serum of breast cancer females.
	Cervical cancer	Up	miR-205 Expression Promotes Cell Proliferation and Migration of Human Cervical Cancer Cells.
	Cervical squamous cell carcinoma	Up	miRNAs expression profiling to distinguish lung squamous-cell carcinoma from adenocarcinoma subtypes.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-205	Endometrial cancer	Up	miR-205 promotes tumor proliferation and invasion through targeting ESRRG in endometrial carcinoma.
	Esophageal cancer	Up	Alteration of miRNA Expression Correlates with Lifestyle, Social and Environmental Determinants in Esophageal Carcinoma.
	Gastric cancer	Down	Down-regulation of MicroRNA-205 promotes gastric cancer cell proliferation.
	Glioma	Down	MicroRNA-205 functions as a tumor suppressor in human glioblastoma cells by targeting VEGF-A.
	Head and neck squamous cell carcinoma	Down	Low-level expression of microRNAs let-7d and miR-205 are prognostic markers of head and neck squamous cell carcinoma.
	Hepatocellular carcinoma	Down	Hepatitis B virus X protein inhibits tumor suppressor miR-205 through inducing hypermethylation of miR-205 promoter to enhance carcinogenesis.
	Kidney cancer	Down	MicroRNA-205 inhibits Src-mediated oncogenic pathways in renal cancer.
	Laryngeal squamous cell carcinoma	Down	MicroRNA-205 suppresses proliferation and promotes apoptosis in laryngeal squamous cell carcinoma.
	Lung cancer	Up	Evaluation of dynamic change of serum miR-21 and miR-24 in pre- and post- operative lung carcinoma patients.
	Malignant melanoma	Down	Differential expression of microRNAs during melanoma progression: miR-200c, miR-205 and miR-211 are downregulated in melanoma and act as tumour suppressors.
	Non-small cell lung cancer	Up	miR-205 promotes the growth, metastasis and chemoresistance of NSCLC cells by targeting PTEN.
	Ovarian cancer	Up	The role of miR-205 in the VEGF-mediated promotion of human ovarian cancer cell invasion.
	Prostate cancer	Down	Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells.
	Renal cell carcinoma	Down	miRNA-205 Is a Candidate Tumor Suppressor that Targets ZEB2 in Renal Cell Carcinoma.
	Squamous carcinoma	Down	MicroRNA expression profiles of esophageal cancer.
hsa-mir-20a	Acute myeloid leukemia	Down	HIF-1α downregulates miR-17/20a directly targeting p21 and STAT3: a role in myeloid leukemic cell differentiation.
	B-cell lymphoma	Up	MicroRNA miR-17-5p is overexpressed in pancreatic cancer, associated with a poor prognosis, and involved in cancer cell proliferation and invasion.
	Breast cancer	Up	MicroRNA expression profiles in human breast cancer cells after multifraction and single-dose radiation treatment.
	Cervical cancer	Up	miR-20a promotes migration and invasion by regulating TNKS2 in human cervical cancer cells.
	Cholangiocarcinoma	Up	miR-17-92 cluster promotes cholangiocarcinoma growth: evidence for PTEN as downstream target and IL-6/Stat3 as upstream activator.
	Colorectal cancer	Up	MicroRNA signatures: novel biomarker for colorectal cancer?
	Esophageal squamous cell carcinoma	Up	TNF-β is a novel target of miR-19a.
	Gastric cancer	Up	Involvement of miR-20a in Promoting Gastric Cancer Progression by Targeting Early Growth Response 2 (EGR2).
	Glioma	Up	[Expression of hsa-miR-20a in human glioma tissues and its effect on the proliferation of human glioma cells *in vitro*].
	Hepatocellular carcinoma	Down	Decrease expression of microRNA-20a promotes cancer cell proliferation and predicts poor survival of hepatocellular carcinoma.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-20a	Lung cancer	Up	A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation.
	Malignant melanoma	Down	Differential regulation of aggressive features in melanoma cells by members of the miR-17-92 complex.
	Mantle cell lymphoma	Up	The miRNA-17-92 cluster mediates chemoresistance and enhances tumor growth in mantle cell lymphoma via PI3K/AKT pathway activation.
	Medulloblastoma	Up	The miR-17/92 polycistron is up-regulated in sonic hedgehog-driven medulloblastomas and induced by N-myc in sonic hedgehog-treated cerebellar neural precursors.
	Nasopharyngeal cancer	Up	Circulating miR-17, miR-20a, miR-29c, and miR-223 Combined as Non-Invasive Biomarkers in Nasopharyngeal Carcinoma.
	Osteosarcoma	Up	Upregulation of microRNA-17-92 cluster associates with tumor progression and prognosis in osteosarcoma.
	Ovarian cancer	Up	miR-20a promotes proliferation and invasion by targeting APP in human ovarian cancer cells.
	Prostate cancer	Up	miR-20a promotes Prostate cancer invasion and migration through targeting ABL2.
hsa-mir-20a-5p	Colorectal cancer	Up	Association of microRNA expression with microsatellite instability status in colorectal adenocarcinoma.
hsa-mir-22	Breast cancer	Down	A regulatory loop involving miR-22, Sp1, and c-Myc modulates CD147 expression in breast cancer invasion and metastasis.
	Colon cancer	Down	miRNA-22 suppresses colon cancer cell migration and invasion by inhibiting the expression of T-cell lymphoma invasion and metastasis 1 and matrix metalloproteinases 2 and 9.
	Colorectal cancer	Down	Clinical significance of miR-22 expression in patients with colorectal cancer.
	Esophageal squamous cell carcinoma	Down	Increased miRNA-22 expression sensitizes esophageal squamous cell carcinoma to irradiation.
	Gastric cancer	Down	microRNA-22 acts as a metastasis suppressor by targeting metadherin in gastric cancer.
	Hepatocellular carcinoma	Down	microRNA-22, downregulated in hepatocellular carcinoma and correlated with prognosis, suppresses cell proliferation and tumourigenicity.
	Lung cancer	Down	Tumor suppressor miR-22 suppresses lung cancer cell progression through post-transcriptional regulation of ErbB3.
	Medulloblastoma	Down	MiR-22 is Frequently Down-regulated in Medulloblastomas, and Inhibits Cell Proliferation via the Novel Target PAPST1.
	Non-small cell lung cancer	Up	Circulating miR-22, miR-24 and miR-34a as novel predictive biomarkers to pemetrexed-based chemotherapy in advanced non small cell lung cancer.
	Osteosarcoma	Down	miR-22 inhibits osteosarcoma cell proliferation and migration by targeting HMGB1 and inhibiting HMGB1-mediated autophagy.
	T-cell lymphoma	Down	miRNA-22 suppresses colon cancer cell migration and invasion by inhibiting the expression of T-cell lymphoma invasion and metastasis 1 and matrix metalloproteinases 2 and 9.
hsa-mir-223	Acute myeloid leukemia	Down	Cell-cycle regulator E2F1 and microRNA-223 comprise an autoregulatory negative feedback loop in acute myeloid leukemia.
	Bladder cancer	Up	Micro-RNA profiling in kidney and bladder cancers.
	Chronic lymphocytic leukemia	Down	MicroRNA-223 expression is uniformly down-regulated in B cell lymphoproliferative disorders and is associated with poor survival in patients with chronic lymphocytic leukemia.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-223	Colorectal cancer	Up	Overexpression of miR-223 correlates with tumor metastasis and poor prognosis in patients with colorectal cancer.
	Endometrial cancer	Down	MiR-223 suppresses endometrial carcinoma cells proliferation by targeting IGF-1R.
	Esophageal adenocarcinoma	Up	MicroRNA 223 is Up-regulated in the Multistep Progression of Barrett's Esophagus and Modulates Sensitivity to Chemotherapy by Targeting PARP1.
	Esophageal cancer	Down	Differential expression of miRNAs in esophageal cancer tissue.
	Esophageal squamous cell carcinoma	Up	Clinical significance of serum miR-223, miR-25 and miR-375 in patients with esophageal squamous cell carcinoma.
	Gastric cancer	Up	MicroRNA profiling of human gastric cancer.
	Glioblastoma	Up	microRNA-223 promotes the growth and invasion of glioblastoma cells by targeting tumor suppressor PAX6.
	Hepatocellular carcinoma	Up	Circulating microRNAs, miR-21, miR-122, and miR-223, in patients with hepatocellular carcinoma or chronic hepatitis.
	Lung cancer	Down	miR-223 functions as a potent tumor suppressor of the Lewis lung carcinoma cell line by targeting insulin-like growth factor-1 receptor and cyclin-dependent kinase 2.
	Mantle cell lymphoma	Down	MicroRNA-223 expression is uniformlyDown-regulated in B cell lymphoproliferative disorders and is associated with poor survival in patients with chronic lymphocytic leukemia.
	Nasopharyngeal cancer	Down	Circulating miR-17, miR-20a, miR-29c, and miR-223 Combined as Non-Invasive Biomarkers in Nasopharyngeal Carcinoma.
	Splenic marginal zone lymphoma	Down	MicroRNA-223 expression is uniformly down-regulated in B cell lymphoproliferative disorders and is associated with poor survival in patients with chronic lymphocytic leukemia.
hsa-mir-223-3p	Prostate cancer	Up	MiR-223-3p targeting SEPT6 promotes the biological behavior of prostate cancer.
hsa-mir-23b	Bladder cancer	Down	MicroRNA-23b functions as a tumor suppressor by regulating Zeb1 in bladder cancer.
	Gastric cancer	Up	miRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3.
	Glioma	Down	miRNA expression profiling in migrating glioblastoma cells: regulation of cell migration and invasion by miR-23b via targeting of Pyk2.
	Ovarian cancer	Up	MicroRNAs overexpressed in ovarian ALDH1-positive cells are associated with chemoresistance.
	Prostate cancer	Down	miR-23b represses proto-oncogene Src kinase and functions as methylation-silenced tumor suppressor with diagnostic and prognostic significance in prostate cancer.
hsa-mir-26b	Bladder cancer	Up	Micro-RNA profiling in kidney and bladder cancers.
	Breast cancer	Down	MiRNA-26b inhibits cellular proliferation by targeting CDK8 in breast cancer.
	Colorectal cancer	Down	Association of microRNA expression with microsatellite instability status in colorectal adenocarcinoma.
	Glioma	Down	Role of microRNA-26b in glioma development and its mediated regulation on EphA2.
	Hepatocellular carcinoma	Down	MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-26b	Lung cancer	Down	MicroRNA-26a/b Regulate DNA Replication Licensing, Tumorigenesis and Prognosis by Targeting CDC6 in Lung Cancer.
	Oral squamous cell carcinoma	Down	MicroRNA expression signature of oral squamous cell carcinoma: functional role of microRNA-26a/b in the modulation of novel cancer pathways.
	Osteosarcoma	Down	miR-26b inhibits proliferation, migration, invasion and apoptosis induction via the downregulation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 driven glycolysis in osteosarcoma cells.
	Prostate cancer	Down	Myc enforces overexpression of EZH2 in early prostatic neoplasia via transcriptional and post-transcriptional mechanisms.
hsa-mir-29b-2	Breast cancer	Up	microRNA-29 negatively regulates EMT regulator N-myc interactor in breast cancer.
	Gastric cancer	Down	Effects of microRNA-29 family members on proliferation and invasion of gastric cancer cell lines.
	Head and neck squamous cell carcinoma	Down	Tumour-suppressive microRNA-29s inhibit cancer cell migration and invasion by targeting laminin-integrin signalling in head and neck squamous cell carcinoma.
	Hepatocellular carcinoma	Down	Negative feedback of miR-29 family TET1 involves in hepatocellular cancer.
	Mesenchymal cancer	Down	miR-29 Acts as a Decoy in Sarcomas to Protect the Tumor Suppressor A20 mRNA from Degradation by HuR.
hsa-mir-30d	Hepatocellular carcinoma	Up	MicroRNA-30d promotes tumor invasion and metastasis by targeting Galphai2 in hepatocellular carcinoma.
	Lung cancer	Up	Evaluation of dynamic change of serum miR-21 and miR-24 in pre- and post- operative lung carcinoma patients.
	Medulloblastoma	Up	Amplification and overexpression ofhsa-miR-30b, Hsa-miR-30d and KHDRBS3 at 8q24.22-q24.23 in medulloblastoma.
	Non-small cell lung cancer	Down	Clinical evaluation of microRNA expression profiling in non small cell lung cancer.
	Prostate cancer	Down	miR-30 as a tumor suppressor connects EGF/Src signal to ERG and EMT.
	Renal cell carcinoma	Down	Proliferation inhibition and the underlying molecular mechanisms of microRNA-30d in renal carcinoma cells.
hsa-mir-30e	Chronic myelogenous leukemia	Down	MiR-30e induces apoptosis and sensitizes K562 cells to imatinib treatment via regulation of the BCR-ABL protein.
	Glioma	Up	Ionizing radiation-inducible miR-30e promotes glioma cell invasion through EGFR stabilization by directly targeting CBL-B.
	Prostate cancer	Down	miR-30 as a tumor suppressor connects EGF/Src signal to ERG and EMT.
	Glioma	Up	MicroRNA-30e* promotes human glioma cell invasiveness in an orthotopic xenotransplantation model by disrupting the NF-κB/IκBα negative feedback loop.
hsa-mir-320a	Colon cancer	Down	MicroRNA-320a suppresses human colon cancer cell proliferation by directly targeting β-catenin.
	Colorectal cancer	Down	[Corrigendum] microRNA-320a inhibits tumor invasion by targeting neuropilin 1 and is associated with liver metastasis in colorectal cancer.
	Glioblastoma	Down	MicroRNA-320a suppresses in GBM patients and modulates glioma cell functions by targeting IGF-1R.
	Nasopharyngeal carcinoma	Down	MicroRNA-320a inhibits cell proliferation, migration and invasion by targeting BMI-1 in nasopharyngeal carcinoma.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-320b	Colorectal cancer	Up	MicroRNA-320b promotes colorectal cancer proliferation and invasion by competing with its homologous microRNA-320a.
hsa-mir-328	Gastric cancer	Down	Macrophage-derived reactive oxygen species suppress miR-328 targeting CD44 in cancer cells and promote redox adaptation.
	Glioma	Down	microRNA-328 is a favorable prognostic marker in human glioma via suppressing invasive and proliferative phenotypes of malignant cells.
	Non-small cell lung cancer	Up	Peripheral Blood miR-328 Expression as a Potential Biomarker for the Early Diagnosis of NSCLC.
hsa-mir-34a	B-cell lymphoma	Down	The Epstein-Barr virus (EBV)-induced tumor suppressor microRNA MiR-34a is growth promoting in EBV-infected B cells.
	Bladder cancer	Down	MicroRNA-34a functions as an anti-metastatic microRNA and suppresses angiogenesis in bladder cancer by directly targeting CD44.
	Breast cancer	Down	MicroRNA-34a Suppresses Cell Proliferation by Targeting LMTK3 in Human Breast Cancer MCF-7 Cell Line.
	Cervical carcinoma	Down	MicroRNA-34a suppresses invasion through downregulation of Notch1 and Jagged1 in cervical carcinoma and choriocarcinoma cells.
	Chordoma	Down	MicroRNA-608 and microRNA-34a regulate chordoma malignancy by targeting EGFR, Bcl-xL and MET.
	Choriocarcinoma	Down	MicroRNA-34a suppresses invasion through downregulation of Notch1 and Jagged1 in cervical carcinoma and choriocarcinoma cells.
	Colon cancer	Down	MicroRNA-34a inhibits migration and invasion of colon cancer cells via targeting to Fra-1.
	Colorectal cancer	Down	Novel evidence for curcumin and boswellic acid induced chemoprevention through regulation of miR-34a and miR-27a in colorectal cancer.
	Endometrial cancer	Down	Role of miR-34a as a suppressor of L1CAM in endometrial carcinoma.
	Gastric cancer	Down	Evaluation of MicroRNA Expression Pattern of Gastric Adenocarcinoma Associated with Socioeconomic, Environmental and Lifestyle Factors in Northwestern Hungary.
	Glioblastoma	Down	MicroRNA-34a targets notch1 and inhibits cell proliferation in glioblastoma multiforme.
	Glioma	Down	MicroRNA-34a induces apoptosis in the human glioma cell line, A172, through enhanced ROS production and NOX2 expression.
	Head and neck squamous cell carcinoma	Down	Dysregulation of microRNA-34a expression in head and neck squamous cell carcinoma promotes tumor growth and tumor angiogenesis.
	Hepatocellular carcinoma	Down	Methylation-associated silencing of microRNA-34b in hepatocellular carcinoma cancer.
	Lung cancer	Down	Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34.
	Malignant melanoma	Down	Overexpression of the miR-34 family suppresses invasive growth of malignant melanoma with the wild-type p53 gene.
	Neuroblastoma	Down	A functional screen identifies miR-34a as a candidate neuroblastoma tumor suppressor gene.
	Non-small cell lung cancer	Down	Restoration of p53/miR-34a regulatory axis decreases survival advantage and ensures Bax-dependent apoptosis of non-small cell lung carcinoma cells.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
	Osteosarcoma	Down	Tumor necrosis factor-related apoptosis inducing ligand induces cytotoxicity specific to osteosarcoma by microRNA response elements.
	Ovarian cancer	Down	Frequent downregulation of miR-34 family in human ovarian cancers.
	Pancreatic cancer	Down	MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells.
	Papillary thyroid carcinoma	Up	MiR-34a targets GAS1 to promote cell proliferation and inhibit apoptosis in papillary thyroid carcinoma via PI3K/Akt/Bad pathway.
hsa-mir-34a	Prostate cancer	Down	MicroRNA-34a modulates c-Myc transcriptional complexes to suppress malignancy in human prostate cancer cells.
	Prostate cancer	Down	The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44.
	Rectal cancer	Up	The quantitative analysis by stem-loop real-time PCR revealed the microRNA-34a, microRNA-155 and microRNA-200c overexpression in human colorectal cancer.
	Renal cell carcinoma	Down	MicroRNA-34a suppresses malignant transformation by targeting c-Myc transcriptional complexes in human renal cell carcinoma.
	Retinoblastoma	Down	Differential microRNA-34a expression and tumor suppressor function in retinoblastoma cells.
	Squamous carcinoma	Up	Unique MicroRNA Expression Profiles in Cervical Cancer.
	Uveal melanoma	Down	MicroRNA-34a inhibits uveal melanoma cell proliferation and migration throughDownregulation of c-Met.
	Cervical squamous cell carcinoma	Down	miR-375 is down-regulated in squamous cervical cancer and inhibits cell migration and invasion via targeting transcription factor SP1.
	Colorectal cancer	Down	Expression levels of microRNA-375 in colorectal carcinoma.
	Esophageal cancer	Down	Epigenetic silencing of microRNA-375 regulates PDK1 expression in esophageal cancer.
	Esophageal squamous cell carcinoma	Down	Cell-specific detection of miR-375 Downregulation for predicting the prognosis of esophageal squamous cell carcinoma by miRNA in situ hybridization.
	Gastric cancer	Down	Snail-regulated MiR-375 inhibits migration and invasion of gastric cancer cells by targeting JAK2.
	Glioma	Down	Correlation of microRNA-375 Downregulation with unfavorable clinical outcome of patients with glioma.
hsa-mir-375	Head and neck squamous cell carcinoma	Down	Comprehensive MicroRNA profiling for head and neck squamous cell carcinomas.
	Hepatocellular carcinoma	Down	miR-375 inhibits autophagy and reduces viability of hepatocellular carcinoma cells under hypoxic conditions.
	Laryngeal squamous cell carcinoma	Down	miR-375 Suppresses IGF1R Expression and Contributes to Inhibition of Cell Progression in Laryngeal Squamous Cell Carcinoma.
	Nasopharyngeal carcinoma	Down	Significance of dysregulated metadherin and microRNA-375 in head and neck cancer.
	Non-small cell lung cancer	Down	Decreased expression of microRNA-375 in nonsmall cell lung cancer and its clinical significance.
	Oral cancer	Down	Anti-Cancer Drugs Reactivate Tumor Suppressor miR-375 Expression in Tongue Cancer Cells.
	Oral carcinoma	Down	Dysregulation of miR-31 and miR-375 expression is associated with clinical outcomes in oral carcinoma.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-375	Pancreatic cancer	Down	Expression levels of microRNA-375 in pancreatic cancer.
	Pancreatic carcinoma	Down	MicroRNA-375 targets PDK1 in pancreatic carcinoma and suppresses cell growth through the Akt signaling pathway.
	Pancreatic ductal adenocarcinoma	Down	Circulating MicroRNAs in Serum of Human K-ras Oncogene Transgenic Rats With Pancreatic Ductal Adenocarcinomas.
	Pancreatic ductal adenocarcinoma	Down	Knockdown of microRNA-21 inhibits proliferation and increases cell death by targeting programmed cell death 4 (PDCD4) in pancreatic ductal adenocarcinoma.
	Squamous carcinoma	Down	Tumor suppressive microRNA-375 regulates lactate dehydrogenase B in maxillary sinus squamous cell carcinoma.
hsa-mir-382	Osteosarcoma	Down	miR-382 inhibits tumor growth and enhance chemosensitivity in osteosarcoma.
hsa-mir-423	Breast cancer	Up	Genetic analysis and preliminary function study of miR-423 in breast cancer.
	Hepatocellular carcinoma	Up	MicroRNA-423 promotes cell growth and regulates G(1)/S transition by targeting p21Cip1/Waf1 in hepatocellular carcinoma.
hsa-mir-423-3p	Laryngeal carcinoma	Up	microRNA-423-3p promotes tumor progression via modulation of AdipoR2 in laryngeal carcinoma.
hsa-mir-425	Breast cancer	Down	Estrogen mediated-activation of miR-191/425 cluster modulates tumorigenicity of breast cancer cells depending on estrogen receptor status.
	Gastric cancer	Up	NF-kappaB-dependent MicroRNA-425Upregulation promotes gastric cancer cell growth by targeting PTEN upon IL-1? induction.
hsa-mir-501	Hepatocellular carcinoma	Up	MicroRNA-501 promotes HBV replication by targeting HBXIP.
hsa-mir-503	Colon cancer	Down	MiR-424/503-Mediated RictorUpregulation Promotes Tumor Progression.
	Gastric cancer	Down	microRNA-503 inhibits gastric cancer cell growth and epithelial-to-mesenchymal transition.
	Glioblastoma	Down	MicroRNA-503 acts as a tumor suppressor in glioblastoma for multiple antitumor effects by targeting IGF-1R.
	Hepatocellular carcinoma	Down	MicroRNA-503 inhibits the G1/S transition by downregulating cyclin D3 and E2F3 in hepatocellular carcinoma.
	Non-small cell lung cancer	Down	Epigenetic silencing of MicroRNA-503 regulates FANCA expression in non-small cell lung cancer cell.
	Oral squamous cell carcinoma	Down	Genomewide Study of Salivary MicroRNAs for Detection of Oral Cancer.
	Osteosarcoma	Down	MicroRNA-503 acts as a tumor suppressor in osteosarcoma by targeting L1CAM.
	Ovarian cancer	Up	MicroRNAs overexpressed in ovarian ALDH1-positive cells are associated with chemoresistance.
hsa-mir-625	Colorectal cancer	Down	Decreased expression of microRNA-625 is associated with tumor metastasis and poor prognosis in patients with colorectal cancer.
	Gastric cancer	Down	Down-regulated miR-625 suppresses invasion and metastasis of gastric cancer by targeting ILK.
	Hepatocellular carcinoma	Down	miR-625 suppresses tumour migration and invasion by targeting IGF2BP1 in hepatocellular carcinoma.
	Non-small cell lung cancer	Down	Low levels of cell-free circulating miR-361-3p and miR-625* as blood-based markers for discriminating malignant from benign lung tumors.
hsa-mir-675	Colon cancer	Up	Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer.

Table 2 List of miRNAs matched with the mirCancer database. (Continued)

SNP/miRNA	Cancer	Profile	PubMed
hsa-mir-675	Glioma	Up	Long Non-Coding RNA H19 Promotes Glioma Cell Invasion by Deriving miR-675.
	Hepatocellular carcinoma	Down	Downregulation of LncRNAH19 and MiR-675 promotes migration and invasion of human hepatocellular carcinoma cells through AKT/GSK-3/Cdc25A signaling pathway.
hsa-mir-874	Breast cancer	Down	MicroRNA-874 inhibits cell proliferation and induces apoptosis in human breast cancer by targeting CDK9.
	Gastric cancer	Down	miR-874 functions as a tumor suppressor by inhibiting angiogenesis through STAT3/VEGF-A pathway in gastric cancer.
	Head and neck squamous cell carcinoma	Down	Tumour-suppressive microRNA-874 contributes to cell proliferation through targeting of histone deacetylase 1 in head and neck squamous cell carcinoma.
hsa-mir-877	Oral squamous cell carcinoma	Down	Genomewide Study of Salivary MicroRNAs for Detection of Oral Cancer.
hsa-mir-92b	Glioblastoma	Up	The miR-92b functions as a potential oncogene by targeting on Smad3 in glioblastomas.
	Glioma	Up	MiR-92b inhibitor promoted glioma cell apoptosis via targeting DKK3 and blocking the Wnt/beta-catenin signaling pathway.
	Non-small cell lung cancer	Up	Inhibition of miR-92b suppresses nonsmall cell lung cancer cells growth and motility by targeting RECK.
hsa-mir-940	Prostate cancer	Down	MicroRNA-940 suppresses prostate cancer migration and invasion by regulating MIEN1.
hsa-mir-96-5p	Colorectal cancer	Down	MiR-96-5p influences cellular growth and is associated with poor survival in colorectal cancer patients.
hsa-mir-98	Breast cancer	Down	Breast cancer-specific TRAIL expression mediated by miRNA response elements of let-7 and miR-122.
	Bronchioloalveolar carcinoma	Down	let-7 microRNA expression is reduced in bronchioloalveolar carcinoma, a non-invasive carcinoma, and is not correlated with prognosis.
	Colon cancer	Down	let-7 microRNA functions as a potential growth suppressor in human colon cancer cells.
	Esophageal squamous cell carcinoma	Down	MicroRNA-98 and microRNA-214 post-transcriptionally regulate enhancer of zeste homolog 2 and inhibit migration and invasion in human esophageal squamous cell carcinoma.
	Gastric cancer	Up	MicroRNA profiling of human gastric cancer.
	Glioma	Down	Overexpression of RKIP inhibits cell invasion in glioma cell lines throughUpregulation of miR-98.
	Hepatocellular carcinoma	Down	MicroRNAs in Hepatobiliary and Pancreatic Cancers.
	Lung cancer	Down	Let-7a elevates p21(WAF1) levels by targeting of NIRF and suppresses the growth of A549 lung cancer cells.
	Malignant melanoma	Down	miR-98 suppresses melanoma metastasis through a negative feedback loop with its target gene IL-6.
	Nasopharyngeal carcinoma	Down	MicroRNA let-7 suppresses nasopharyngeal carcinoma cells proliferation through downregulating c-Myc expression.
	Neuroblastoma	Down	LIN28B induces neuroblastoma and enhances MYCN levels via let-7 suppression.
	Ovarian cancer	Down	EZH2-specific microRNA-98 inhibits human ovarian cancer stem cell proliferation via regulating the pRb-E2F pathway.
	Pancreatic ductal adenocarcinoma	Down	let-7 MicroRNA transfer in pancreatic cancer-derived cells inhibits in vitro cell proliferation but fails to alter tumor progression.

networks by integrating many other types of genomic and epigenomic data sets. Although we used ovarian cancer data to demonstrate the usage of our method, our approach can be applied to identify genetic neighborhood in any disease with similar genomic data available. Such an integrative network constructed from integrating diverse data layers will be more informative for understanding the propagation of perturbation signals and the underlying mechanisms of complex diseases.

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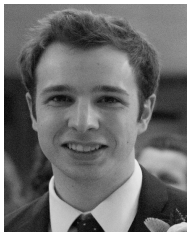

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