Detecting B-cell lymphomas dysregulation modules based on molecular interaction network

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***Abstract*—Identifying dysregulation modules for complex diseases, such as B-cell lymphomas, can provide insights into the mechanisms of diseases and help to identify novel drug targets. In this work, based on molecular interaction network, we applied a network flow model to identify the dysregulation modules for three subtypes of non-Hodgkin's lymphomas, including Burkitt's lymphoma (BL), follicular lymphoma (FL), and mantle cell lymphoma (MCL). In our identified dysregulation modules, there are multiple genes that were reported in literature to be related to B-cell lymphomas, which demonstrate that our presented method is really effective for identifying dysregulation modules related to diseases.**

***Keywords*: B-Cell Lymphomas, network flow model, dysregulation modules**

I. Introduction

Complex diseases, such as cancer, are caused by multiple factors, involving dysregulation of distinct biological processes, which make it difficult to understand the pathogenic procedure underlying the diseases. Recently, a large amount of high-throughput data, e.g. protein-protein interaction and gene expression, are available, which provides a chance to identify oncogenes and dysregulated pathways for certain diseases. For example, based on protein interactome map, Wachi et al. found that the differentially expressed genes in lung squamous cancer tissues tend to be well connected in the protein interaction network [1]. Chen et al. presented a computational method to predict AD-related proteins based on protein interaction data [2]. Mani et al. introduced the interactome dysregulation enrichment analysis (IDEA) algorithm to predict oncogenes in B-cell lymphomas [4]. At the same time, gene expression data were widely used to detect disease-related genes based on differential expression analysis [3–8]. For instance, Ergun et al. constructed a gene network, and with expression profiles they found that the androgen-receptor (AR) can be used as the top candidate marker to detect the aggressiveness of prostate cancers [3].

Despite the success made by above mentioned methods, most of them focus on detecting single disease-related genes, which cannot give a global map of the processes affected by disease. Furthermore, candidate genes provided by these methods based on one dataset sometimes do not work on another dataset. In this paper, based on molecular interaction network, we applied our previously developed network flow model [9, 10] to identify the dysregulation modules for three subtypes of non-Hodgkin's lymphomas, including Burkitt's lymphoma (BL), follicular lymphoma (FL), and mantle cell lymphoma (MCL). In our identified dysregulation modules, there are multiple genes that were reported in literature to be related to B-cell lymphomas, which demonstrate that our presented method is really effective for identifying dysregulation modules related to diseases. In particular, we found that 7 genes (i.e. ABL1, BRCA1, CDC2, JAK3, LYN, MYC, and POU2F1) occurred in the dysregulation modules for all three distinct non-Hodgkin's lymphomas, which implies that these 7 genes may be important for the pathogenic procedure of B-cell lymphomas.

II. Materials and methods

A. B cell Interactome

In this work, B cell interactome was obtained from the B cell Interactome database (http://amdec-bioinfo. cu-genome.org/html/BCellInteractome.html) which includes 5737 proteins and 64649 unique pairwise interactions. The BCI is a mixed-interaction network which is composed of three types of interactions [4], including protein-protein interactions (PPI) [4], protein-DNA interactions (PDI) [11], and transcription factor-modulator interactions (TFMI) [12]. The three different data were integrated with a Bayesian evidence integration approach [4].

According to the interactome dysregulation enrichment analysis (IDEA) algorithm [4], the dysregulated interactions in three distinct non-Hodgkin's lymphomas were identified based on gene expression profiles from normal, tumor-related, and experimentally manipulated B cells. For the three distinct non-Hodgkins lymphomas, there are 722 dysregulated interactions and 573 proteins in BL, 192 dysregulated interactions and 207 proteins in FL, and 406 dysregulated interactions and 419 proteins in MCL. However, the dysregulated interactions identified by IDEA are independent with each other, which cannot provide a global map of the dysregulation pathways or modules underlying diseases considering that diseases generally require multiple genes to work in concert. Towards this end, we reconstructed the interactome by integrating all the dysregulation interactions with the interactions between those genes involved in dysregulation interactions, where the

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newly added interactions were further required to have a score large than 0.9 to reduce possible false positives. The biggest connected component was used for further analysis. As a result, the BL interactome includes 540 proteins and 1580 interactions, FL interactome includes 188 proteins and 326 interactions, and MCL interactome contains 383 proteins and 882 interactions.

B. Identification of B-cell lymphomas dysregulation modules

In this part, we applied our previously developed network flow model to detect dysregulation modules for B-cell lymphomas based on the interactome map. The interactome map is represented as a weighted undirected graph $G(V, E, W)$, where the vertex $v_i \in V$ represents a protein and the edge $E(i, j)$ denotes the interaction between proteins i and j. The weight $w_{ij} \in W$ accompanying edge $E(i, j)$ represents the confidence score of the interaction based on the likelihood ratio calculated by Bayesian evidence integration approach [4]. Given the weighted undirected graph $G(V, E, W)$ and some known disease genes, we aim to detect the dysregulation modules based on the assumption that genes in the dysregulation modules tend to interact with each other. Furthermore, we formalized the problem as identifying a compact connected subnetwork with maximum weight, where the genes in the subnetwork interact intensively with known disease gene. In brief, the model is formulated as following.

$$\underset{\{x_i, y_{ij}, z_{ij}\}}{Maximize} \sum_{i \in V} \sum_{j \in V} w_{ij} y_{ij} - \lambda \sum_{i \in V} \sum_{j \in V} y_{ij} \tag{1}$$

Subject to

$$y_{ij} \leq x_i, \tag{2}$$

$$y_{ij} \leq x_j, \tag{3}$$

$$\sum_{j \in V} y_{ij} \geq 1, \text{if } i \in \{S\}, \tag{4}$$

$$\sum_{j \in V} y_{ij} \geq 2x_i, \text{if } i \notin \{S\}, \tag{5}$$

$$\sum_{i \in V'} Z_{s_i} = R - 1, \tag{6}$$

$$\sum_{i \in V} Z_{ij} - \sum_{k \in V'} Z_{jk} = 1, j \in H, \tag{7}$$

$$\sum_{i \in V} Z_{ij} - \sum_{k \in V'} Z_{jk} = x_j, j \in V'', \tag{8}$$

$$\sum_{i \in V} Z_{ij} \leq (R - 1)\, x_j, j \in V', \tag{9}$$

$$x_i = 1, i \in \overline{H}, \tag{10}$$

$$Z_{ij} \in \{0, ..., R - 1\}, i \in V, j \in V', \tag{11}$$

$$x_i \in \{0, 1\}, i \in V'', \tag{12}$$

$$y_{ij} \in \{0, 1\}, i, j \in V, \tag{13}$$

where S is the source of the network flow, i.e. the known disease gene, $V' = V - \{S\}$, H is the set of the known nodes except the source node S, $V'' = V - \{H\}$, $\overline{H} = H \bigcup \{S\}$, x_i is a binary variable for protein $i \in V$ to denote whether protein i is selected as a component of the module, y_{ij} is also a binary variable to denote whether the interaction represented by $E(i, j)$ is a part of the module. The constraint $\sum_{j \in V} y_{ij} \geq 2x_i$ is to make ensure that x_i has at least two linking edges once it is selected in the obtained module, while the constraint $\sum_{j \in V} y_{ij} \geq 1$ means that the source protein S has at least one link to other proteins. The constraints $y_{ij} \leq x_i$ and $y_{ij} \leq x_j$ ensure that only when proteins i and j are both selected as components of the module, the corresponding reaction denoted by the edge E_{ij} would be considered. The constraint (6) means that there are $R - 1$ units of flow entering the network from the source S. The constraint (7) ensures that one unit of flow will leave the network for the known protein. The constraint (8) means that one unit of flow will leave the network when one protein is selected. The constraint (9) means that once a protein is selected, the maximum flow entering this protein is no more than $R - 1$.

The first term of the cost function means that we aim at finding a module with maximum weight, while the second term controls the size of the module. The parameter λ can be tuned in an easy manner. This model is a standard ILP problem which is difficult to find optimal solutions since ILP is an NP-hard problem. To make the model suit for large-scale interaction networks, we relax the the constrains $x_i \in \{0, 1\}$, $y_{ij} \in \{0, 1\}$ to $x_i \in [0, 1]$, $y_{ij} \in [0, 1]$, and $Z_{ij} \in \{0, ..., R - 1\}$ to $Z_{ij} \in [0, R - 1]$. With these relaxations, we can apply mixed integer linear programming (MILP) algorithms to solve the problem.

III. Results

A. Identification of dysregulation module for Burkitt's lymphoma

Burkitt's lymphoma (BL) is a type of B-cell non-Hodgkin's lymphoma (NHL) that mostly occurs in young people between the ages of 12 and 30. It is found that Burkitt's lymphoma is associated with a chromosomal translocation of the MYC gene [13]. Therefore, MYC was used as the source node in our network flow model to identify the dysregulation module for BL. With the interactome map consisting of 540 proteins and 1580 interactions, a BL dysregulation module was identified as shown in Fig. 1, which takes MYC as source node of the module with $R = 40$ and $\lambda = 0.95$ and contains 74 proteins and 269 interactions.

Among the 74 genes in our predicted BL dysregulation module, we found that 27 genes are reported to be related to lymphoma. Table I lists the 27 genes and the papers' corresponding PubMed IDs that report the relationship between the genes and lymphoma. Especially, four genes in our identified modules were reported to be associated with Burkitt's lymphoma, including DOK1, E2F1, NR4A1 and BCR. DOK1 was found to be affected at both expression and structure levels in a subset of Burkitt's lymphoma samples [15], which indicates that it may play an important role in

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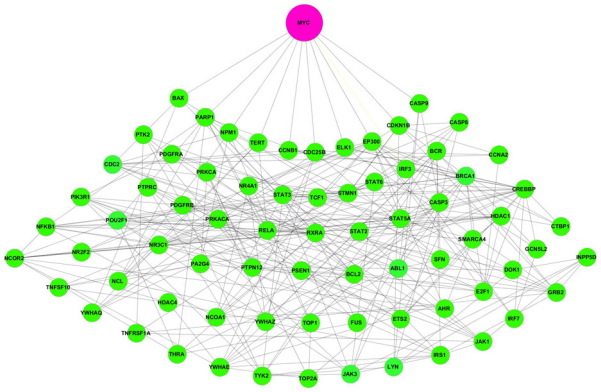

Fig. 1. BL dysregulation module, where MYC was used as the source node in the network flow model and shown as a pink circle while other proteins as green circles.

BL. However, DOK1 was not even in the top 500 genes identified by IDEA algorithm [4]. E2F1 is a member of the E2F family of transcription factors that play a crucial role in the control of cell cycle. It was found that E2F1 is involved in the formation of most sporadic Burkitt's lymphoma (sBL) tumors according to the study by Privado [16]. They showed that the reduction of this gene in sBL cells will inhibit tumor formation and decrease their proliferation rate, and proved that E2F1 collaborates with MYC in sBL formation. E2F1 was only ranked 139 by IDEA algorithm. NR4A1 encodes a member of the steroid-thyroid hormone-retinoid receptor superfamily. When the encoded protein is translocated from the nucleus to mitochondria, it will induce apoptosis. It was found that Burkitt's lymphoma is related to NR4A1 gene [17]. BCR displays serine/threonine kinase activity. Tyrosine phosphorylation of a number of proteins will rapidly increase when one stimulates B lymphocytes through their antigen receptor (BCR) resulting in a cascade of biochemical changes that will initiate B-cell proliferation and differentiation or growth inhibition. Tuscano et al. showed that BCR ligation leads to apoptosis of several Burkitt's lymphoma cell lines, and BCR and CD22 signaling can co-stimulate B-cell proliferation and induce apoptosis in Burkitt's lymphoma cell lines [18]. BCR was only ranked 96 by IDEA algorithm.

In addition, pathway enrichment analysis [19, 20] on our identified dysregulation module showed that cell cycle (P=1.05E-10), Fc epsilon RI signaling pathway (P=4.43E-08), ErbB signaling pathway (P=1.17E-07), Jak-STAT signaling pathway (P=1.98E-07), pathways in cancer (P=2.88E-07), focal adhesion (P=1.05E-10), and B cell receptor signaling pathway (P=6.88E-06) are significantly enriched.

The evidence from literature and pathway enrichment analysis demonstrates that our identified dysregulation module is indeed related to Burkitt's lymphoma and our method is effective to identify dysregulation module from molecular interaction network. In addition, the four genes we identified related to BL were not ranked high by IDEA method, implying that our method can complement with IDEA to identify dysregulation processes.

TABLE I
THE GENES THAT ARE REPORTED TO BE RELATED TO LYMPHOMA IN THE PREDICTED BL DYSREGULATION MODULE IN LITERATURE WITH CORRESPONDING PUBMED IDS [22].

Gene	PMID
AHR	19821039; 16985026
BAX	12749011; 15073604
BCR	10438726; 11027651; 9233773; 9533441; 12384401; 15380345; 12594826; 7947283; 19332026; 9052872
CASP3	11866986; 20450729; 14657946
CASP8	19414860
CASP9	19414860
CDC2	12068134; 14533937
CDC25B	14767575
CDKN1B	16122798
CTBP	18212045
DOK1	16338067
E2F1	19406837
GRB2	19716163
INPP5D	10382761
IRF7	15492278; 17393359
JAK3	12934099; 16554750
LYN	8264235; 18070987; 20043832; 17640867; 8688094; 7513431
MYC	7558417; 2307371; 1945409; 10713166; 7923569; 7958890 (top 6 among all 99)
NCOR2	15930272; 9753732
NPM1	8187071; 17488663; 8859196; 15233906; 11280786; 9121481 (top 6 among all 64)
NR4A1	7589118
PARP1	20196871
PDGFRA	18950958
PTPRC	1829834; 1845482; 1669003
STAT3	17439836; 14506160; 15161657; 18509351
STAT5A	16502315
STAT6	19423726; 1840141; 17210636; 15044251

B. Identification of dysregulation module for follicular lymphoma

Follicular lymphoma (FL) is another type of non-Hodgkin's lymphoma (NHL), which is characterized by translocation between chromosome 14 and 18 that results in the overexpression of the BCL2 gene. Therefore, BCL2 was used as the source node in our network flow model to identify the dysregulation module for FL. Based on the interactome map consisting of 188 proteins and 326 interactions, a FL dysregulation module was identified as shown in Fig. 2 with $R = 40$ and $\lambda = 0.95$, and contains 40 proteins and 90 interactions. There are 20 genes that are reported to be related to lymphoma among the 40 genes in our predicted FL dysregulation module. Table II lists the 20 genes and the papers' corresponding PubMed IDs that report the relationship between the genes and lymphoma. In particular, SYK has been reported to be associated with follicular lymphoma (FL) [21]. SYK encodes a

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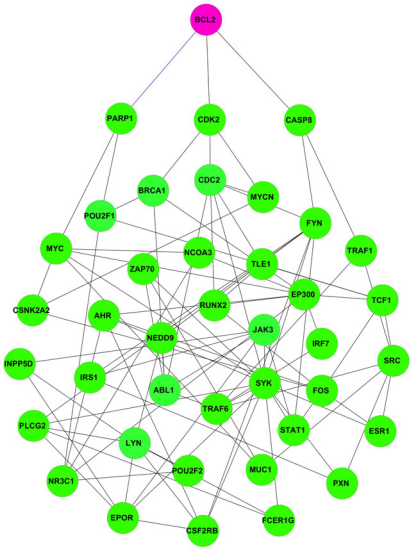

Fig. 2. FL dysregulation module, where BCL2 was used as the source node in the network flow model and shown as a pink circle while other proteins as green circles.

member of the family of non-receptor type Tyr protein kinases which are involved in diverse cellular dysregulations, including proliferation, differentiation, and phagocytosis. Leseux et al. suggested that SYK-mTOR pathway has played an important role in FL survival, and SYK could be a promising new target for B-cell lymphoma therapy [21]. In the results by IDEA algorithm, SYK was ranked 17 [4].

Furthermore, pathway enrichment analysis on our identified dysregulation module showed that pathways in cancer (P=5.89E-16), cell cycle (P=2.96E-10), apoptosis (P=2.38E-08), Jak-STAT signaling pathway (P=6.75E-07), MAPK signaling pathway (P=4.26E-06), Notch signaling pathway (P=1.46E-04), and B cell receptor signaling pathway (P=1.30E-03) are significantly enriched. These results make it clear that our identified dysregulation module is indeed related to follicular lymphoma and our method is effective to identify dysregulation module from molecular interaction network.

C. Identification of dysregulation module for mantle cell lymphoma

Mantle cell lymphoma (MCL) is an uncommon type of non-Hodgkin's lymphoma (NHL). MCL cells generally overexpress cyclin D1/BCL1 (CCND1) due to a t(11:14) chromosomal translocation in the DNA [14]. Therefore, CCND1 was used as the source node in our network flow model to identify the dysregulation module for MCL. Based on the interactome map consisting of 383 proteins and 882, a MCL dysregulation module was identified as shown in Fig. 3 with $R = 40$ and $\lambda = 0.95$, which contains 62 proteins and 208 interactions.

Among the 62 genes in our predicted MCL dysregulation module, we found that 27 genes are reported to be related to lymphoma. Table III lists the 27 genes and the papers' corresponding PubMed IDs that report the relationship between the genes and lymphoma. Specially, two genes in our identified modules were reported to be associated with mantle cell lymphoma (MCL), including CDC6 and CDK6. CDC6 plays a key role in DNA replication, and Pinyol et al. suggested that deregulation of the licensing factors CDC6 may play a

TABLE II
THE GENES THAT ARE REPORTED TO BE RELATED TO LYMPHOMA IN THE PREDICTED FL DYSREGULATION MODULE IN LITERATURE WITH CORRESPONDING PUBMED IDS [22].

Gene	PMID
AHR	19821039; 16985026
BCL2	18945749; 2223650; 18925696; 9349233; 8623759; 19120369 (top 6 among all 99)
CASP8	19414860
CDC2	12068134; 14533937
CDK2	16765349; 16150942
FOS	15507668
FYN	11453661
INPP5D	1989047; 12885297
IRF7	15542650; 15492278; 17393359
JAK3	12934099; 16554750
LYN	8264235; 18070987; 20043832; 17640867; 8688094; 7513431
MUC1	11729213; 12796388; 14555387; 11493472
MYC	7558417; 2307371; 1945409; 10713166; 7923569; 7958890 (top 6 among all 99)
MYCN	18391076
PARP1	20196871
PLCG2	9575194; 9865907
POU2F2	11904338; 14608905; 904338; 16778825
SYK	16912221; 19092849; 19296913; 19965662; 9865907; 19333898; 19608873
TRAF1	17197926; 15644776; 11046039
ZAP70	19575876; 15133473; 20029467; 16280661; 16426914; 18348159; 15487457

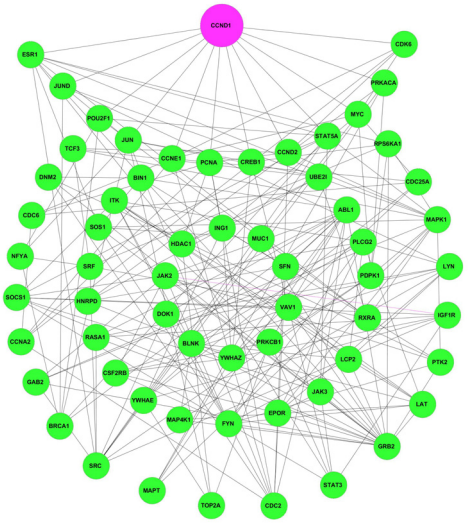

Fig. 3. MCL dysregulation module, where CCND1 was used as the source node in the network flow model and shown as a pink circle while other proteins as green circles.

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role in the pathogenesis of the chromosomal instability of a subset of MCL [23]. The protein encoding by CDK6 is a member of the cyclin-dependent protein kinase (CDK) family which are known to be important regulators of cell cycle progression. Zhao et al. showed that miR-29 is a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma [24]. In the results by IDEA algorithm, CDC6 was ranked 457 while CDK6 was ranked 30.

TABLE III
THE GENES THAT ARE REPORTED TO BE RELATED TO LYMPHOMA IN THE PREDICTED MCL DYSREGULATION MODULE IN LITERATURE WITH CORRESPONDING PUBMED IDS [22].

Gene	PMID
CCND1	20062012; 9846986; 8204893; 7772515; 9010577; 9209645 (top 6 among all 13)
CCND2	8455931; 8045261
CCNE1	19454496
CDC2	12068134; 14533937
CDC25A	12745652; 19305144; 14767575
CDC6	19101572
CDK6	11940479; 20086245; 10879740
DOK1	16338067
FYN	11453661
GAB2	14530346
GRB2	19716163
IGF1R	19423729
ITK	19535334
JAK3	12934099; 16554750
JUN	15507668
JUND	15507668; 12907453
LCP2	14984504
LYN	8264235; 18070987; 20043832; 17640867; 8688094; 7513431
MAPK1	17065146
MUC1	11729213; 12796388; 14555387; 11493472
MYC	7558417; 2307371; 1945409; 10713166; 7923569; 7958890 (top 6 among all 99)
PLCG2	18596745; 9575194; 9865907
SOCS1	19734449; 16287070; 16598306; 17867599; 16532038
SOS1	9374522
STAT3	17439836; 14506160; 15161657; 18509351
STAT5A	16502315
VAV1	15964830; 9178638; 14586401

Furthermore, pathway enrichment analysis on our identified dysregulation module showed that cell cycle (P=1.05E-10), ErbB signaling pathway (P=1.17E-07), Jak-STAT signaling pathway (P=1.98E-07), pathways in cancer (P=2.88E-07), focal adhesion (P=2.70E-06), and B cell receptor signaling pathway (P=6.88E-06) are significantly enriched. These results demonstrate that our identified dysregulation module is indeed related to mantle cell lymphoma.

D. Common markers for three distinct non-Hodgkin's lymphomas

Although BL, FL and MCL are three different non-Hodgkin's lymphomas, they may share some common marker genes. We compared the predicted dysregulation modules for the three lymphomas. Figure 4 shows the venn diagram of the genes in the three modules. There are 7 genes (i.e. ABL1, BRCA1, CDC2, JAK3, LYN, MYC, and POU2F1) that are contained in all of the three modules. The protein encoded by ABL1 has been involved in processes of cell differentiation, cell division, cell adhesion, and stress response. ABL1 is found important to chronic myelogenous leukaemia (CML). At the same time, CML is associated with extranodal B-cell lymphoma [26]. Therefore, ABL1 is possibly associated with B-cell lymphoma. The dysregulation of BRCA1 pathway has the risk for a subset of lymphomas [28]. Jin et al. proved that CDC2 is involved in the genesis or progression of malignant lymphoma, and they suggested that CDC2 can be a useful marker for response to chemotherapy [27]. Nagy et al. reported that specific inhibition of janus tyrosine kinase (JAK3) via NC1153 induces apoptosis of certain lymphoma cell lines [29]. LYN can control proliferation and survival in most B-cell NHLs and can be a therapeutic target [30]. MYC has been reported that its rearrangements are seen not only in BL, but also in FL, MCL and other lymphomas [25]. POU2F1 is a member of the POU transcription factor family, whose deficiency may play a role in B-cell lymphoma. All these evidence from literature indicates that these 7 genes may be important for the pathogenic procedure of B-cell lymphomas and used as markers for B-cell lymphomas.

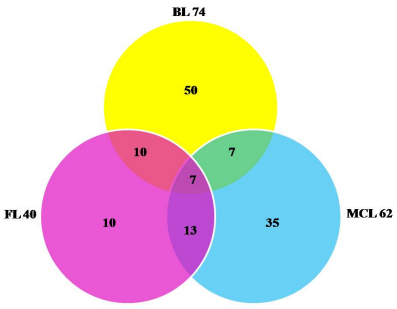

Fig. 4. Venn diagram for the genes shared among the three predicted dysregulation modules.

IV. CONCLUSION

In this paper, we applied a network flow model to detect the dysregulation modules for three distinct non-Hodgkin's lymphomas (Burkitt's (BL), follicular (FL), and mantle cell lymphoma (MCL)). In our identified dysregulation modules, a lot of genes are reported to be related to lymphoma in literature. In detail, the ratios are 27/74, 20/40 and 27/62 for BL, FL and MCL, respectively. In particular, we found 7 genes (i.e. ABL1, BRCA1, CDC2, JAK3, LYN, MYC, and POU2F1) that are contained in all three dysregulation modules, and they are also found to be associated with lymphomas, which imply that these 7 genes are important for pathogenic procedure of lymphomas.

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