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Protein Network and Functional Analysis of Human Leukemia Type's Interaction

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Abstract
Comorbid diseases occurring in an individual because of two reasons. First, the common diseases genes which are the common biological factors that cause comorbid diseases Gene interactions between leukemia and lung cancer indicate a more nuanced pathogenetic process or acquired resistance to cancerogenesis, as well as the existence of an unidentified constitutional feature. Aside from the combined impact of several etiologic risk factors including smoking, genetic vulnerability, and the form and dosage of other drugs administered,Therefore, it is important building a broad protein-protein interaction network to the understanding of molecular disease mechanisms and the evolution of targeted treatments. To date, no clear nominee interaction proteins have specified and the molecular interaction events still poorly understood, A comprehensive protein-protein interaction network and a complete mechanism of interaction between human leukemia types are also lacking.So in this study, the main purpose was having been done to improve a protein-protein interaction map that exhibits the possible protein interaction and major molecular functions in myeloid - lymphoid leukemia interaction protein network. LeGenD Leukemia gene literature database was used to find all leukemia types related gens in adult and many of fusion process have been utilized to construct myeloid - lymphoid leukemia interaction network. An analyzing network represented new interactions in binding and fusion of leukemia types.These new protein interactions include 52 proteins did not have any publications on it.disease-associated genes and the major molecular functions were identified by analyzing the network in myeloid- lymphoid interaction protein.Using functional analysis of the network the most proteins in the predicted functional network have participated in signal transduction, hemostasis, Neutrophil degranulation, DNA repair, Genetic transcription pathway, Immune system and gene expression (transcription). The analysis of disease associations indicated that myeloid - lymphoid leukemia interaction disorderpossesses a significant association with diseases such as cancer, Type 2 Diabetes and pulmonary disease.More research is needed to establish the significance of newly discovered computational interactions, as well as the genetic connections between irregular myeloid-lymphoid interactions and disease.
Keywords:myeloid; lymphoid, Leukemia; Protein-protein interactions

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Introduction

Chromosome translocations are acquired and recurrent in human leukemia. ALL is the most common and lethal form of leukemia in children, and it is the leading cause of death among children under the age of 20 in the United States. Approximately 6000 cases are diagnosed annually, half of them are children and adolescents[1]. 62% is the number that represents the number of deaths due to AML in the United States, more than 10,000 people according to the SEER database [2]. A patient with both chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) at the same time is extremely rare. Furthermore, the majority of these cases occurred as a result of chemotherapeutic agents being used to treat CLL patients. [3-5]. The protein-protein interaction is a biological network that has been commonly used to predict protein functions, identify essential genes or proteins, detect protein complexes, and discover network motifs[6, 7]. PPI can interact in a variety of ways, including direct physical interactions between proteins in complexes and passing interactions between members of specific protein pathways. The proteins involved in PPIs are engaged and interact spatially or temporally with other proteins within the process, also it is work as non-interacting members of the same pathway [8]. In addition to that, the development in computational and biochemical methods contributed to discovering and developing PPI[9-11].Diseases and biological networks are inextricably related, according to numerous studies. Furthermore, errors in biological networks, especially in differentiating critical nodes, are frequently the cause of a variety of diseases. As a result, research into biological networks and critical nodes could aid in the discovery of critical targets for disease treatment.[12]. Recently explaining the interrelationships between disease-related genes and proteins, also studying the protein-protein interactions in humans brought new insights into diseases' network biology.[13].

Methods

The initial collection of human leukemia types proteins

LeGenD Leukemia gene literature database(http://soft.bioinfo-minzhao.org/lgl/index.html). was used to find all leukemia types related gens in adult with keywords" AML mutation genes", "ALL mutation genes", "CML mutation genes" and "CLL mutation genes". Following that, the genes that are expressed in humans were chosen. and they were divided into two groups, myeloid and lymphoid group. However, all values were extracted from this databases statistics page. This site was planned to be easy to use, we can download the proteome easily. All data were extracted in the tab-delimited and XLSX format. In order to change ID of each gene, two of gene identifier (ID) were used in this study. First one is DAVID database (http://david.abcc.ncifcrf.gov/conversion.jsp) [14],

The second is UniProt ID mapping (http://www.uniprot.org/uploadlists/). [15]. The collected genes were submitted, and ID types of inputs and outputs were chosen.

The development of a network of protein-protein interactions (PPI).

The first step in creating the PPI network is to obtain a protein that has been designated. To accomplish this, each gene's UniProt ID was inserted into the STRING database (http://string-db.org/), and each protein-protein interaction was retrieved and shown in Table 1. The collected proteins- proteins interactions were loaded into Cytoscape 3.7.1 [15]. To proteins interaction network (PIN) were constructed, one for lymphoid associated proteins and the other for myeloid associated proteins type. Then, two types of leukemia interaction networks compared and

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Aunion overlapping network was computed in Cytoscape using the network modification plugin, which compares two networks. Table No. 2

Table 1: The names of the genes in each of the five clusters, as well as their groups

Leukemia type	Number of interactions
Lymphoid	13504
Myloid	2428

Analysis of biological function

Using the ClueGo plugin of Cytoscape, the major molecular functions were identified for the leukemia types interaction genes network. ClueGO is a bioinformatics method that enhances gene biological role understanding by using a simple Cytoscape plug-in. It analyses a cluster or compares two clusters in great detail, showing their community functions. GO, KEGG, BioCarta, REACTOME, and WikiPathways are among the databases used.[16].

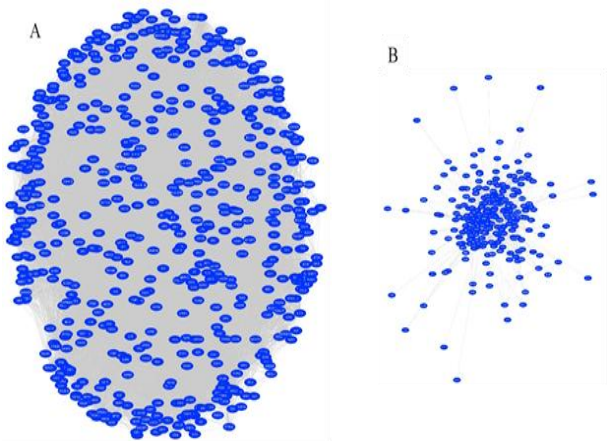
Disease association

The DAVID bioinformatics software used the GAD database to identify disease genes associated with myeloid-lymphocytic interaction. To restrict the interaction disease terminology, the Benjamini–Hochberg multiple testing correction p-value cutoff of 0.01 was used.

1. Discussion and Results

Construction of the PPI network

Cytoscape 3.7.1 was used to load the collected protein-protein interactions.[15]. To proteins interaction network (PIN) were constructed, one for lymphoid associated proteins and the other for myloid associated proteins type. The lympoid PIN contains 553 gene nodes and contain13504 interactions. While 246 gene nodes in mypoid PIN and 2428 interactions. Figure (1).



1st Illustration In cytoscape 3.7.1, build two networks: A and B, respectively, display the lymphoid type associated proteins network and the myeloid type associated proteins network. These protein interaction networks have 553 nodes and 13504 interactions in A and 246

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nodes and 2428 interactions in B.

.**Myeloid-lymphoid interaction network extraction**

The two types of leukemia interaction networks merged, union network was calculated. The union genes interaction network between the two types of leukemia consists of 719 nodes and 15402 interactions. Figure (2).

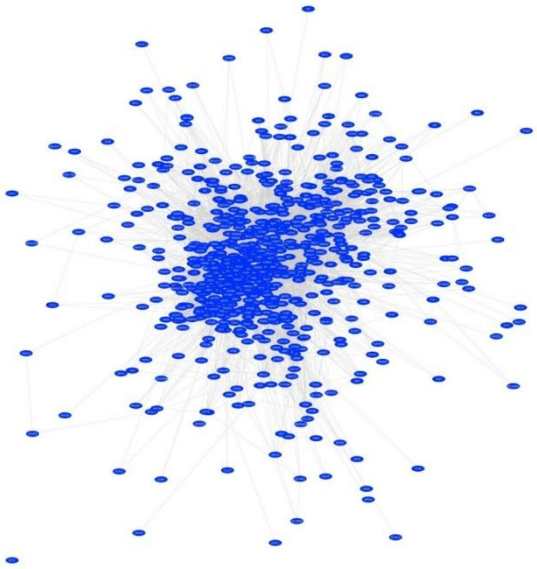

Figure 2: Leukemia types genes union interaction network (created by Cytoscape)

Table *2*:leukemia types union interaction network merged

Type of leukemia	Nodes	Interactions
Lymphoid	553	13504
Myeloid	246	2428
Lymphoid-myeloid merged	719	15402

The proteins and the interactions in the network are represented in appendix E. Some of these interactions have already been identified in some types of leukemia and in addition to their roles in human. Such as SOCS1- IRF3 interaction, SOCS-1 is a tumor suppressor involved in the best possible regulation of cytokine/growth factor responses in acute myeloid leukemia. In a SOCS-Box based manner, SOCS1 interacted directly with IRF3, facilitating its proteasomal degradation..[17].

HIF1A is a protein that is studied in leukemia. Levels of CITED2 (CBP/p300-interacting-transactivator-with-an-ED-rich-tail 2) are needed for leukemic stem cell survival and have recently been found to be upregulated in 70% of AML cases. The molecular role of CITED2 is to prevent HIF1 transactivation by interfering with the interaction of HIF1A's carboxy-terminus with EP300/CREBBP .[18, 19].Furthermore, the interaction of some of these nodes has been studied in the past in other diseases. HIF-1, like HIF1A linked to CITED2, is involved in the pathogenesis of life-threatening disorders and plays a significant role in cellular adaptation to hypoxia in epidermal keratinocytes. CITED2 (CBP/p300-

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interacting transactivator with an ED-rich tail 2) also inhibits [20].

New myeloid- lymphoid protein interacts

The identified leukemia types proteins by mass spectrometry (MS) proteomics data were categorized in two groups: Lymphoid and Myeloid leukemia protein group. The new interaction between two groups has finally been studied. Using STRING and MI scores, we calculated the "combined score" for any pair of proteins predicted. Consequently, it was filtered only the new interactions that did not As a result, only new interactions with high confidence PPIs (STRING scores 0.700 and MI scores 0.431) that had no publications were considered. The 25 proteins involved in the new protein interactions are involved in 15 high confidence interactions. table No (3).

Table 3 shows the new interactions discovered in the merged network between myeloid and lymphoid proteins.

myeloid proteins	lymphoid protein	Combined-score
AGPAT2	CD33	0.9
POU2F2	BCL2A1	0.905
ANXA1	CCR9	0.9
PICALM	CBL	0.9
PICALM	TACR1	0.902
PICALM	IL7R	0.902
PICALM	TPD52	0.900
MSLN	IGFBP7	0.902
MSLN	APOE	0.903
KLF5	TP53	0.782
BIRC2	DIABLO	1.00
SET	FOXO1	0.59
CBL	EGFR	0.96
HDAC6	HDAC6	0.902
HCK	CCL11	0.906

The first new interaction we discovered was that silencing AGPAT2 inhibits cancer cell proliferation and increases their sensitivity to chemotherapeutic drugs [151]. The CD33 antigen was found to be more frequently associated with B-lineage ALL (25%) than T-lineage ALL (12%), with MFI values reflecting the percentage of positive leukemic cells, similar to what was found for CD20 and CD22 antigens. Furthermore, the CD33 antigen was mostly expressed in the B-common subgroup, implying a connection between its expression and immunologic classification. [152]. The created protein network indicated that POU2F2 and ANXA1 proteins interact with BCL2A1 and CCR9 proteins with combined score 0.9 and 0.905 respectively. POU2F2, a POU domain family homeobox-containing transcription factor, has been found to have variations in expression in AML. The encoded protein binds to the octamer sequence 5'-ATTTGCAT-3', which is a typical transcription factor binding site, in the promoters of immunoglobulin genes.[21].

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Here we found the POU2F2 in myeloid leukemia play role in the myeloid –lymphoid interaction by interacting with BCL2A1 in lymphoid leukemia type. BCL2A1 is made up of three exons and is found on chromosome 15 at 8 sub-band 15q24.3. Its primary role is to prevent cell death caused by chemotherapeutic agents. In this case, t(14;15)(q32;q24)-induced overexpression of BCL2A1 is likely to have led to early relapse and resistance to salvage chemotherapy.[22, 23].

Also, CCR9 proteins interact with Annexin A1 (ANXA1) which is reported to involve in many biological processes like inflammation, cellular transduction, differentiation, apoptosis, proliferation and phagocytosis and these processes can relate to cancer. The expression of ANXA1 is induced by different drugs which leads to apoptosis in different types of cell. Because it can protect cancer cells from stress and cytotoxic agents, ANXA1 plays a role in drug resistance in leukemic cells. [24-26]. The signaling pathway has been shown to increase CCR9 expression, which is essential in T-lineage acute lymphoblastic leukemia (T-ALL) [28]. It is involved in tumor chemoresistance and metastasis, decreasing the efficacy of traditional surgery, radiotherapy, and chemotherapy. This approach showed that PICALM in myeloid type plays some roles in interaction between myeloid and lymphoid process by interacting with CBL, TACR1, IL7R and TPD52 in lymphoid. (TACR1) transcript is overexpressed in CLL patient cells to bind with myeloid type. Also, the PICALM is expressed in myeloid to bind with lymphoid leukemia types. The role of the tachykinin NK1 receptor (NK1R), also known as TACR1, in the pathogenesis of leukemia has been illustrated by a wide body of evidence.[27].

In humans, the PICALM gene (chromosome 11q14) has been related to a variety of clinical disorders. PICALM has been identified as a translocation partner for the AF10 transcription factor gene in leukemias and lymphomas (10p12). In 5–10% of T-cell acute lymphoblastic leukemias, the PICALM-AF10 translocation is found, as well as in 5–10% of T-cell acute lymphoblastic leukemias. *[28, 29]*.PICALM also has a relationship with CBL, an E3 ubiquitin ligase. [30]. In the development of human B-cell precursor leukemia, the activation of IL7RA is crucial. It induces a pre-leukemic condition that can lead to leukemia, resembling Ph-like leukemia in nature.[31]. TPD52 is a protein that supports membrane trafficking events and can play a role in cytokinesis. It is rarely expressed in children with high hyperdiploid ALL, but it is often upregulated in neoplasia.[32]. The created protein network indicated that the IGFBP7 and APOE in lymphoid leukemia has interaction with MSLN in myeloid leukemia type. It's a cell-surface glycoprotein found mostly in mesothelial cells that line the pleura, peritoneum, and pericardium, although it's frequently found in large concentrations in leukemia and other cancers.[33].In vitro, IGFBP7 improves ALL resistance to asparaginase by acting as a positive regulator of ALL and stromal cell development.[34]. A functional analysis of expressed APOE proteins revealed that it plays a role in cholesterol regulation and lipoprotein modeling [36].KLF5 interacts with TP53 in lymphoid leukemia, according to the findings. They're crucial in the relationship between myeloid and lymphoid leukemia. According to the results, BIRC2 in lymphoid cells interacts with DIABLO in myeloid cells to play a part in myeloid-lymphoid interactions. The protein BIRC2 belongs to the inhibitor of apoptosis (IAP) family.[35]. DIABLO, on the other hand, is a protein that binds to IAP directly and has a low PI. In AML, this protein appears to be one of the most effective inhibitors of IAPs. A good treatment outcome is linked to high Smac/DIABLO expression.[36]. From the other physical interactions between two main types of leukemia is SET in lymphoid interaction with FOXO1in myloid leukemia type. SET when interacted with FoxO1, play important role in the inhibition acetylation of FoxO1 and activated the transcriptional activity of it toward p21[37]. Forkhead box (FOX) is

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involved in leukemogenesis, relapse, and drug sensitivity in AML biology.[38]. CBL in myeloid interact with EGFR in lymphoid, Casitas B-lineage Lymphoma (CBL)are rare in AML but associated with inv (16)[39]. The epidermal growth factor receptor activates a number of pathways (EGFR). Because of its ability to mediate apoptosis, EGFR signaling, which is a transmembrane receptor tyrosine kinase (RTK), has become a good target in anticancer drug production, migration, and cell proliferation. Inhibiting the EGFR pathway induces cell death in T-ALL cells, according to new findings.[40].In our research, we discovered that HDAC6 interacts with himself, and we called this case HDAC6 (SIPs). Signal transduction, gene expression control, enzyme activation, and immune response are all regulated by Self-Interacting Proteins (SIPs).[41]. Histone deacetylases (HDACs) are enzymes that cause histone deacetylation. HDAC6 is well known for targeting nonhistone substrates such as tubulin and hsp90. One effect of this is that it has an effect on protein degradation via the aggresome pathway. Overexpression of it in leukemias may be a new way to diagnose leukemia and a new target for leukemia therapy. [42, 43].HCK, also known as Src family kinase (SFK), is a hematopoietic cell kinase found in high amounts in chronic myeloid leukemia and other hematologic tumors. HCK proteins are involved in the progression of acute myeloid leukemia.[44][45].

In current study, CCL11 interact with HCK and according to ToomitsuMiyagaki study and his olleagues, the interaction of CCL11 and CCR3 promotes CCR3 cell survival and proliferation in lymphoma cells.[46]

Molecular function analysis

To classify the main molecular function community involved in the protein network, the ClueGO software (a Cytoscape plugin) was used to investigate the myeloid-lymphoid interaction network. The majority of the proteins were found to be involved in metabolism process control, positive metabolism process regulation, negative biological process regulation, and cellular response to stimuli, according to the findings.

The myeloid-lymphoid interaction protein network was analyzed using ClueGO (Figure 3). (Created in Cytoscape with the ClueGO plugin)

Regulation of metabolism, negative regulation of biological processes, and gene expression regulation are all interesting related molecular functions.

To feed anabolic cell growth, the proliferation of leukemia cells necessitates the upregulation and reconnection of metabolic pathways. Oncogenes directly and indirectly regulate metabolic pathways, and abnormal metabolism is important not only for leukemia proliferation and survival, but also for oncogene addiction, which is important for the development of targeted therapies.[47]. As a result, activation of anabolic pathways, in addition to energy, is a critical component of oncogenic transformation. Otto Warburg was the first to recognize the abnormal metabolic nature of cancer. [48]A tumor metabolism is a druggable molecular space, which has sparked a lot of interest in targeting metabolic flaws in cancer. [47]. The findings suggest that metabolism process activity is an essential molecular mechanism for leukemia type interaction.

The other important molecular function is regulation of gene expression.Alterations in normal gene expression regulation are a key feature of hematopoietic malignancies and a hallmark of cancer. Transcription factors play a critical role in the regulation of gene expression in the hematopoiesis process. The study of gene expression profiling revealed the abnormally expressed genes linked to ALL relapse and allowed the identification of targe[49, 50].

Cellular response to stimulus, any process that causes a change in the state or activity of a cell in response to stimuli such as leukemia inhibitory factor (LIF).Which is a pleiotropic interleukin-6

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(IL-6) cytokine with multiple functions in health and disease and involvement in numerous biological processes. Furthermore, it interacts with the membrane glycoprotein 130. (gp130) [51]. Davis and colleagues discovered that injecting LIF into murine myeloid leukemia (M1) cells reduced cell proliferation. [52].

David analysis

The DAVID bioinformatics software used the GAD database to identify disease genes associated with myeloid-lymphocytic interaction. The Benjamin–Hochberg multiple testing correction p-value cutoff of 0.01 was used to restrict the association disease terms (Table 2).

Pathways ($P \leq 0.05$)	Count	Pvalue	Genes
null	140	7.78E-52	HIF1A , CP2E1 , CCL2 , IRF5 , MRP2 , VEGFA , SDF1 , CP1A1 , FLT3 , OSTP , GSK3B , HLAG , JAK3 , GLYAT , PPARA , TNR16 , ALEX , KIT , PA24A , S28A1 , TN13B , GNAS1 , PERM , PON1 , IGF1 , BRAF , NKX25 , SHH , TNR5 , NOS3 , BIRC5 , MRP3 , TLR9 , IL1RA , LEP , FGFR3 , GSTP1 , CX3C1 , CATA , FINC , TAU , ERCC1 , GTR1 , LRP6 , HGF , NFKB1 , BC11A , CD9 , SMAD3 , LPAR1 , UD11 , HMOX1 , IL8 , TNFB , NNMT , AHR , AURKA , OGG1 , XRCC3 , MTRR , HS71A , CP1B1 , KI3L1 , GGH , MEFV , NTRK3 , NOS2 , DQB1 , CP2B6 , ESR2 , HLAE , FAT1 , CD27 , IL7RA , NEP , HDAC1 , EPHB4 , TLR4 , RASK , F13A , PTPRC , HMGA2 , LYAM3 , TR13B , ADRB3 , POTE1 , GNAS2 , EGLN , MMP9 , KIBRA , CCR9 , CDN2A , S19A1 , TYK2 , PGFRA , ADIPO , STAT1 , IFNG , ITPA , MK01 , IL1A , IL6 , FOXP3 , TPMT , ARF , ITA2 , CREB1 , MTHR , PAI1 , IL10 , CSF2 , IL2 , GNAS3 , PREP , APC , C1TC , PK3C3 , MMP2 , XBP1 , MLH1 , UDB17 , PECA1 , DPB1 , LYAM2 , STAT6 , CP2D6 , CD70 , IL4RA , TYSY , NOTC3 , CCND1 , XRCC1 , PDCD1 , APOE , CD14 , ERCC2 , HPSE , XPA , MRP1 , XPC , GSTM1 , TGFB1 , ACES , ITAM
Lung Cancer	110	4.40E-49	HIF1A, PDCD5, CP2E1, CCL2, BLM, FANCA, FCER2, MRP2, VEGFA, CP1A1, SDF1, GSK3B, JAK3, PPARA, PERM, PON1, CASP8, IGF1, BRAF, FOLC, TNFL6, TNR5, NOS3, MRP3, BIRC5, PRDM2, IL1RA, LEP, GSTP1, CX3C1, CATA, FINC, RAD51, ERCC1, GTR1, LRP6, NFKB1, ARNT, UD11, HMOX1, IL1AP, IL8, TNFB, AHR, AURKA, OGG1, XIAP, XRCC3, MTRR, CD81, HS71A, CP1B1, GGH, NOS2, AKT2, ESR2, IL7RA, EZRI, RASK, MPIP3, POTE1, EGLN, MMP9, IKBE, CDN2A, S19A1, STAT1, IFNG, GSHR, IL1A, IL6, ARF, MPIP1, MTHR, PIM1, GPX3, IL10, CSF2, RAG1, DICER, APAF, IL2, P63, APC, C1TC, MMP2, XBP1, MLH1, UDB17, AGO2, LYAM2, CP2D6, IRF3, IL4RA, TYSY, IL15, UPAR, PTEN, CCND1, SEPP1, XRCC1, APOE, CD14,

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			ERCC2, MRP1, XPA, BIRC3, GSTM1, XPC, TGFB1, CHK1
lung cancer	97	1.96E-43	HIF1A, PDCD5, CCL2, CP2E1, BLM, FANCA, MRP2, VEGFA, CP1A1, GSK3B, JAK3, S28A1, PERM, CASP8, IGF1, BRAF, FOLC, TNFL6, TNR5, NOS3, MRP3, TLR9, IL1RA, LEP, GSTP1, CX3C1, RAD51, ERCC1, GTR1, LRP6, NFKB1, ARNT, UD11, IL8, TNFB, AHR, AURKA, OGG1, XRCC3, MTRR, CD81, CP1B1, GGH, NOS2, DQB1, ESR2, IL7RA, EZRI, RASK, MPIP3, GA45A, POTE1, EGLN, MMP9, IKBE, CDN2A, S19A1, STAT1, IFNG, IL1A, RFC1, IL6, ARF, MPIP1, MTHR, PIM1, GPX3, PAI1, IL10, CSF2, RAG1, APAF, IL2, P63, APC, MMP2, XBP1, MLH1, LYAM2, CP2D6, IRF3, IL4RA, TYSY, UPAR, IL15, PTEN, CCND1, SEPP1, XRCC1, APOE, ERCC2, MRP1, XPA, BIRC3, GSTM1, XPC, TGFB1, CHK1
Colorectal Cancer	87	1.12E-41	CDX2, HIF1A, CCL2, CP2E1, BLM, MRP2, VEGFA, CP1A1, SDF1, TLR4, RASK, LYAM3, ADRB3, GNAS2, MMP9, ALEX, CDN2A, S19A1, ADIPO, GNAS1, PERM, IFNG, CASP8, PON1, IGF1, BRAF, FOLC, TNFL6, IL1A, RFC1, OBF1, NOS3, VGFR1, MRP3, BIRC5, IL6, TPMT, PRDM2, ARF, IL1RA, ITA2, LEP, MTHR, GSTP1, CATA, PAI1, IL10, RAD51, ERCC1, GNAS3, BMP4, APC, C1TC, NFKB1, MMP2, MK, MLH1, UD11, IL8, TNFB, AHR, LYAM2, AURKA, CP2D6, OGG1, IL4RA, B2CL1, TYSY, XRCC3, MTRR, CSK21, WIF1, PTEN, CCND1, SEPP1, CP1B1, XRCC1, GGH, NOS2, APOE, CD14, DQB1, ERCC2, MRP1, XPA, NDRG1, GSTM1, XPC, TGFB1, CHK1, ESR2
chronic obstructive pulmonary disease	84	6.01E-40	CP2E1, BLM, FANCA, MRP2, IL7RA, VEGFA, CP1A1, EZRI, TLR4, RASK, GSK3B, JAK3, MPIP3, POTE1, EGLN, MMP9, IKBE, S19A1, CDN2A, STAT1, PERM, CASP8, IGF1, TNFL6, IL1A, TNR5, NOS3, ARF, IL1RA, LEP, MPIP1, PIM1, GSTP1, MTHR, CX3C1, GPX3, CATA, FINC, IL10, CSF2, RAD51, RAG1, APAF, ERCC1, IL2, GTR1, P63, LRP6, APC, NFKB1, MMP2, XBP1, MLH1, ARNT, HMOX1, IL8, TNFB, AHR, AURKA, CP2D6, OGG1, IRF3, IL4RA, TYSY, IL15, XRCC3, MTRR, PTEN, CD81, CCND1, SEPP1, CP1B1, XRCC1, GGH, NOS2, CD14, APOE, ERCC2, MRP1, BIRC3, GSTM1, XPC, TGFB1, ESR2, CHK1
Bladder Cancer	92	3.35E-38	CCL2, CP2E1, BLM, FANCA, MRP2, IL7RA, VEGFA, CP1A1, EZRI, TLR4, RASK, GSK3B, JAK3, MPIP3, POTE1, GNAS2, EGLN, MMP9, ALEX, IKBE, CDN2A, S19A1, STAT1, GNAS1, PERM, IFNG, CASP8, PON1, IGF1, TNFL6, IL1A, RFC1, TNR5, NOS3, IL6, ARF, IL1RA, LEP, MPIP1, PIM1, FGFR3, MTHR, GSTP1, CX3C1, GPX3, CATA, IL10, CSF2, RAD51, RAG1, APAF, ERCC1, IL2, GNAS3, GTR1, P63, LRP6, APC, NFKB1, MMP2, XBP1, MLH1, ARNT, HMOX1, IL8, TNFB, AHR, LYAM2, AURKA, CP2D6,

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			OGG1, IRF3, IL4RA, B2CL1, TYSY, IL15, XRCC3, MTRR, PTEN, CD81, CCND1, SEPP1, CP1B1, XRCC1, GGH, NOS2, APOE, CD14, ERCC2, XPA, BIRC3, GSTM1, XPC, TGFB1, ESR2, CHK1
esophageal adenocarcinoma	73	2.83E-35	HIF1A, PDCD5, CP2E1, FANCA, MRP2, VEGFA, CP1A1, OSTP, RASK, GSK3B, MPIP3, KPCA, MMP9, CDN2A, PGFRA, IFNG, CASP8, PON1, PK3CG, IGF1, MSLN, BRAF, FOLC, IL1A, NOS3, VGFR1, MRP3, BIRC5, IL6, ARF, IL1RA, ITA2, LEP, MPIP1, GSTP1, MTHR, CX3C1, IL10, RAD51, RAG1, APAF, ERCC1, IL2, C1TC, APC, NFKB1, PK3C3, MMP2, MLH1, ARNT, IL8, TNFB, AHR, AURKA, OGG1, IL4RA, B2CL1, TYSY, IL15, XRCC3, MTRR, PTEN, CCND1, CP1B1, XRCC1, GGH, NOS2, ERCC2, MRP1, XPA, BIRC3, XPC, TGFB1, CHK1
stomach cancer	41	4.87E-33	IL10, CP2E1, RAD51, VEGFA, ERCC1, IL2, CP1A1, APC, C1TC, TLR4, MMP2, RASK, GSK3B, MLH1, IL8, TNFB, MMP9, KIT, CDN2A, S19A1, OGG1, PGFRA, IL4RA, TYSY, XRCC3, PERM, IFNG, MTRR, CCND1, XRCC1, IL1A, NOS2, IL6, CD14, DQB1, ARF, ERCC2, IL1RA, GSTM1, MTHR, GSTP1, TGFB1
Type 2 Diabetes| edema | rosiglitazone	183	4.03E-32	KS6B1, HIF1A, BLM, CP2E1, CCL2, FANCA, IRF5, VEGFA, SDF1, CP1A1, FLT3, OSTP, WEE1, GLIP1, GSK3B, HLAG, JAK3, PPARA, SNF5, ALEX, NOTC2, PA24A, KPCT, GNAS1, PERM, CATG, PON1, CASP8, FOXP1, IL7, IGF1, LPXN, NKX25, PTHR, REL, B2LA1, STA5B, TNR5, NOS3, MRP3, TLR9, IL1RA, LEP, PBX3, GSTP1, CX3C1, FINC, ITB1, CATA, LRP6, HGF, NFKB1, PLF4, BC11A, MK13, SLIT2, LPAR1, ARNT, ROR1, HMOX1, UD11, IL1AP, IL8, TNFB, SETBP, OGG1, RON, BAG3, CCL18, TF65, XIAP, XRCC3, LYAM1, MTRR, CSK21, HS71A, CP1B1, MEFV, NOS2, PRTN3, AKT2, SIAE, SPRC, PPAC, ESR2, MDM4, MEF2C, CALC, CSK2B, NF1, IF2B3, BASI, CD166, AAPK1, B2L14, CTNA1, PER2, EZRI, TLR4, F13A, ANXA1, CALCA, HMGA2, LYAM3, ADRB3, GNAS2, DMD, EGLN, MMP9, CLTR1, IKZF2, CXCR5, MK14, IKBE, S19A1, ADIPO, UFO, PGFRA, JUN, RARA, STAT1, NCAM1, DPP4, AF10, IFNG, GSHR, MK01, PO2F2, IL1A, OBF1, RFC1, CCL11, VGFR1, IL9, IL6, TPMT, ETV6, AAKB1, PK3CD, ITA2, CREB1, ADA17, MTHR, GPX3, A4, PAI1, IL10, CSF2, RAG1, APAF, IL2, BMP4, GNAS3, C1TC, APC, MK12, MMP2, PDE3B, PDIA2, SIA8D, MEIS1, RAF1, BAG4, DPB1, LYAM2, STAT6, IRF3, IL4RA, TYSY, NOTC3, IL15, UPAR, PTEN, XRCC1, PGS2, RARB, CD14, APOE, CD79A, ERCC2, MRP1, DBLOH, BIRC3, GSTM1, TGFB1, ACES, ITAM

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ovarian cancer	71	6.01E-32	HIF1A, CALC, MRP2, VEGFA, OAS3, CP1A1, EZRI, OSTP, RASK, CALCA, MMP9, TYK2, CDN2A, JUN, STAT1, DPP4, KI67, PERM, CASP8, IGF1, MK01, BRAF, TNFL6, IL1A, CCL11, WNT5A, NOS3, IL6, NGAL, ARF, IL1RA, MPIP1, DKK1, GSTP1, MTHR, TNFL9, PAI1, FINC, ITB1, IL10, TAU, RAD51, ERCC1, BMP4, C1TC, MMP2, MLH1, UD11, GROA, IL8, AURKA, OGG1, CD70, B2CL1, TYSY, NOTC3, XRCC3, UPAR, PTEN, CCND1, CP1B1, XRCC1, PGS2, DQB1, ERCC2, MRP1, XPA, CD24, SPRC, GSTM1, XPC, ESR2, MDM4

According to **Error! Reference source not found.**, the achieved results from DAVID analysis represent that 183 genes of myeloid-lymphoid protein interaction network are involved in Type 2 Diabetes and edema disease, 41 genes in stomach cancer and 110 genes are involved in lung cancer disease. Qiong Liu and his workers found, the relationship between T2DM and CML. According to the findings, there are 13 genes that are duplicated, one module that is duplicated, four biological functions that are duplicated, and one pathway that is duplicated. The response to the glucose process has been shown to be linked to CML..[53]. According to the results, there are 183 genes that differ between leukemia and Edema disease. Edema-like optic nerve infiltration is an isolated symptom of a leukemia relapse before a hematological relapse. Furthermore, since leukemic optic neuropathy is a life-threatening symptom, treatment should begin as soon as possible before permanent optic neuropathy develops. [54]. 41genes of the network are related to gastric cancer. MayankMangal and his workers found, there is increased in incidence of gastric cancer in patients with CLL. Many factors responsible for the incidenceit's in the patient with leukemia. Such as, the initiators and promoters which caused the leukemia. The second one is the hereditary factor. The use of cytotoxic drugs and irradiation, which is especially important in cancer patients, is the third factor. An immunosuppressive condition brought on by cancer is the fourth element [55]. The result showed 110 genes are involved in lung cancer disease to myeloid- lymphoid interaction network. Interactions of genes between leukemia and lung cancer suggest a more complex pathogenetic mechanism or acquired susceptibility to cancerogenesis, as well as the presence of a constitutional trait that has yet to be identified. An immunosuppressive condition brought on by cancer is the fourth element [56].

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