Systematic expression and bioinformatics analysis of fibrinogen-like protein 1 in human cancer and its co-expression network

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Research Article

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Abstract

Background

Fibrinogen-like protein 1 was initially found in a study on hepatocellular carcinoma and it is overexpressed in human cell lines and rats. Recently, investigations have focused on fibrinogen-like protein 1 dysfunction in carcinogenesis. Our study aims to determine the role of fibrinogen-like protein 1 and its possible role in human carcinoma.

Methods

Fibrinogen-like protein 1 expression in different neoplasms was assessed by Oncomine. Fibrinogen-like protein 1 coexpression networks in various cancers were established using Coexpedia. Finally, we investigated the potential functions of fibrinogen-like protein 1 with gene ontology and pathway enrichment analyses with the FunRich V3.

Results

Fibrinogen-like protein 1 was overexpressed in several kinds of neoplasms at the transcriptional level. Coexpression networks showed that fibrinogen-like protein 1 regulates immune response and lipid related pathways.

Conclusions

The present results offer the possibility that fibrinogen-like protein 1 acts as a therapeutic target for some types of cancers and may take part in carcinogenesis.

Introduction

Cancer is still the most important factor for increasing mortality in non-communicable diseases globally. According to the WHO (World Health Organization), with the population aging fast globally, by 2030, the number of new cancer cases will be more than doubled from the number today if the incidence of total cancer is at least not reduced [1]. Although research on cancer has been happening for years, effective therapy to decrease the incidence of cancer seems to be a challenge because of the heterogeneity of cancer causes, all of which are related to a specific class of genes called proto-oncogenes or oncogenes. New targets and chemotherapeutic strategies are needed[2–4]. The immune system shows a strong relationship with the progression of cancer[5–9]. Drugs that block the programmed cell death protein 1/ programmed death ligand 1 (PD-1/PD-L1) pathway increase survival rates in different types of cancer. Despite their valid therapeutic effects in some patients, these drugs are not panacea for all cancer patients. As such, much more research on the intricate mechanisms is needed.

Fibrinogen-like protein 1 (FGL1) was initially found in a study on hepatocellular carcinoma and it is overexpressed in human cell lines and rats [10]. It was also highly upregulated in regenerating rodent livers [11]. A recent study showed that FGL was upregulated in gastric carcinoma tissues and it may promote cell proliferation, invasion, and migration by affecting epithelial-mesenchymal transition[12]. A few studies have shown that FGL1 is related to metabolic diseases[13, 14]. Lymphocyte-activation gene 3 (LAG-3) is the major ligand that mediates immune suppressive functions and currently plays an important role in cancer therapy currently[15, 16]. A recent study found out that FGL1 was a major immune inhibitory ligand of LAG-3. Under physiological conditions, FGL1 protein contributes to the metabolic functions of LAG-3. However, the function of FGL1 in the immune system and cancer is still unknown.

Bioinformatics methods can be used to analyze and play a role in the analysis of gene and protein expression and regulation based on the raw data of biological databases. We characterized the expression of FGL1 in Oncomine, which is an online cancer database to facilitate discovery by genome-wide expression analysis. [17, 18]. We analyzed the data of possible coexpressed genes with FGL1 from the TCGA database to predict probable signaling pathways involved in various cancers.

In our research, we aimed to investigate the pathological roles of FGL1 in different types of cancers using publicly available bioinformatics datasets, including prostate, breast, and liver cancer dataseets and to offer new directions for mechanistic research.

Method

Oncomine database analysis

The expression level of FGL1 in different cancers was determined through analysis in the Oncomine database [17, 18]. “FGL1” and “Cancer vs. Normal Analysis” were used as the search parameters in our analysis. The conditions in our analysis were as follows: the thresholds were a fold change of 2 and a threshold p-value of 1E-4; and the top 10% of genes were analyzed (Fig. 1.). The specifics of our analysis are summarized in Table .

Co-expedia analysis

We constructed a coexpression network with genes related to FGL1 using Co-expedia (http://www.coexpedia. org/)[19]. Coexpedia currently contains approximately 8 million co-expressed genes, constructed from 384 Human Geo datasets and 248 mouse Geo datasets. The website constructs its reanalysis by integrating the data of several datasets on the GEO datasets. Co-expedia is a new database for exploring the possible related functions of genes based on co-expression and associated with MeSH terms.

GO and KEGG pathway enrichment analysis of differentially expressed genes

To explore the functional roles of the above differentially expressed genes, DAVID database (https://david.ncifcrf.gov/) was used to perform GO term enrichment analysis of molecular function (MF), biological process (BP), and cellular component (CC) and KEGG pathway enrichment analysis. P-value < 0.05 was considered as the cut-off criterion. Go and KEGG are two databases that contain information about the function of each gene, and enrichment analysis is a way to integrate these functions. KEGG (http://www.kegg.jp/ or http://www.genome.jp/kegg/) is an integrated database resource for biological interpretation of genome sequences and other high-throughput data. Molecular functions of genes and proteins are associated with ortholog groups and stored in the KEGG Orthology (KO) database.

Results

To investigate the function of FGL1 in various types of cancers, the expression of FGL1 was analyzed between cancer and normal tissues with data from the Oncomine database. The parameters were set as follows: thresholds were a p-value of 10^{-4}, fold change 2, the top 10% genes were selected. The FGL1 was overexpressed in a few types of neoplasms and downregulated in some others compared with the respective level in ordinary tissues (Fig. 1). These data show that FGL1 may play either an oncogenic or anti-oncogenic role within different types of cancer. Thus, a comprehensive analysis of FGL1 is described in detail.

FGL1 transcription expression in cancer

Our results indicated FGL1 was upregulated in prostate, lung, liver, and breast cancer, but was downregulated in pancreatic and breast cancers compared to the respective level in normal tissues (Fig. 2). These data correspond to the previous research on FGL1 expression. For example, our study showed that FGL1 was overexpressed in hepatocellular carcinoma which is proved to increase its expression in the same cancer[10].

Alternations of FGL1 in various neoplasms

The frequency and type of FGL1 alternations in neoplasms

The cBioPortal database was used to analyze the FGL1 gene alternations in of 151 cancer studies in the TCGA pipeline. Our analysis showed 18 different studies that used a > 5% alteration frequency in the datasets (Fig. 3 and Table □-□). The cancer datasets with the highest frequency of alternation was a prostate dataset(MICH), which included 61 samples and the overall rate of all alterations in FGL1 was shown to be 18.3%. Another dataset with a high frequency was the prostate cancer datasets from TCGA, which contained 499 samples from patients with prostate neoplasm, and the FGL1 alternation rate was 14.03%. Almost all the alternations from the two datasets were deep deletions. The third datasets, a pancreatic cancer datasets from UTSW, included 109 samples of microdissected pancreatic ductal adenocarcinoma, and the alternation rate of FGL1 was 9.17%. Thereafter, we regrouped the selected

studies above based on the primary organs or tissues of the tumors. The three types of cancer with the highest rate of alterations were prostate cancer (12.86%), pancreatic cancer (9.17%), and endometrial cancer (8.77%). Meanwhile, the most common alternation type of FGL1 in our analysis was deep deletion, especially in the first two datasets.

Mutated FGL1 loci in various types of cancers

Figure 4 outlines the characteristics of all mutations in the included cancer datasets. FGL1 mutations included 17 missense mutations and 1 truncating mutation, and 6 of these mutations occurred in the hotspot of S21L (substitution type: missense, position 21, S◊L) All the mutations achieved a level of 3 (the number of patients with the same mutation site) in the Catalogue Of Somatic Mutations In Cancer (COSMIC) database, indicating that the fragment with the mutation is important for its role in the pathological process of cancer. We also found mutations in breast invasive ductal carcinoma and cutaneous squamous cell carcinoma.

FGL1 coexpression network in cancer

We used the Coexpedia database to analyze the coexpression of genes with FGL1 to further explore the function and the involved signaling pathways of FGL1 in disease, especially in cancer. In our analysis, FGL1 was coexpressed with 251 genes (Fig. 5 and Table). GO terms analysis was conducted to identify the related cellular component, biological process, molecular function and biological pathway terms(Fig. 6). The biological pathway showed that the term ‘cell cycle’ was highly enriched among the genes that were coexpressed with FGL1, which were also closely related to the complement cascade, FOXA transcription factor networks and lipid transport (Fig. 6d). The ‘myocardial infarction’ and ‘cerebrovascular accident’ terms were the most closely diseases connected with FGL1 in the GO-DO enrichment analysis, with cancer, hepatocellular carcinoma and carcinoma being the first three cancer-related diseases (Fig. 7a).

The correlations of chemical and medical compounds with FGL1 can be assessed using the Coexpedia database, which is separate from other coexpression databases (Fig. 7b). The top MeSH terms associated with FGL1 in our analysis were organoplatinum compounds and colorectal neoplasms. The most related types of cancer in our results were neuroblastoma, breast neoplasms and bone neoplasms. The analysis of organoplatinum compounds and colorectal neoplasms was performed in two GEO datasets, a GEO datasets of CRC samples used for FOLFOX therapy prediction, and a GEO datasets from the study ‘Characterization of an Oxaliplatin Sensitivity Predictor in a preclinical Murine Model of Colorectal Cancer’.

Discussion

FGL1 is a secreted molecule with a fibrinogen-related domain in its C-terminal fragment and is highly expressed in the liver. This protein belongs to a family of proteins with a fibrinogen-related domain,

including members, such as fibrinogen b and c, as well as some other proteins including angiopoietins, fibroleukin, and tenascins. Despite the information on the detailed function of the proteins in this family, the research related to FGL1 is still scarce.

Although the function of FGL1in liver has been investigated[13], the specific role of FGL1 in hepatocellular carcinoma remains controversial. FGL1 was initially isolated and identified as a protein upregulated in liver carcinoma [10]. In one study, FGL1 was proven to promote hepatocyte proliferation via an autocrine mechanism in the L02 cell line. And FGL1 was shown to suppress hepatocellular carcinoma cell proliferation through an intracrine pathway[20]. In another study, it acted as a tumor suppressor in hepatocellular cancer through an Akt dependent pathway and showed its function as a possible target in the therapy of hepatocellular carcinoma [21].

However, in another study focused on the role of FGL1, the protein was shown to be downregulated in the hepatocellular carcinomas compared with normal liver tissue[22]. Although FGL1 has been studied in the liver, little research has been done in other fields. We hope that our findings will contribute to knowledge and provide possible research directions in the field of oncology. The differing mRNA level of FGL1 in different type of cancer show that this gene is regulated differently. FGL1 was upregulated in prostate cancer and downregulated in pancreatic cancer in several datasets which indicates that FGL1 may be involved in different mechanisms in disparate neoplasms.However, different studies focusing on the identical cancers also showed opposite results of FGL1 expression. New insights into the pathogenesis of such neoplasm are urgently needed.

Gene mutations generally cause phenotypic changes, which are closely associated with to DNA replication, DNA damage repair, tumorigenesis and aging [23]. Therefore, the detection of FGL1 mutations is significant in investigating the function of FGL1 in carcinogenesis and identifying potential therapeutic pathways. Based on our analysis [24], at least 5% of samples from cBioPortal database from cancers of the prostate, pancreas, breast, lung, liver and bladder were proven to have mutations in FGL1; deep deletions comprised the majority of alternations. It is notable that two datasets of prostate cancer shown mutations in more than 10% mutation of tumors; considering the notable expression variation in the prostate cancer, further research is needed to elucidated the mechanism and role of FGL1. Annotated mutations from cBioPortal showed that the most recurrent mutation in FGL1 was S21L, which was detected in breast invasive ductal carcinoma and cutaneous squamous cell carcinoma samples.

Analyzing gene coexpression networks is one way to elucidate the unknown mechanisms and potential pathways of the target genes. Coexpedia is unique for its analysis based on the functional connection of coexpression proteins and its focus on biomedical factors. Coexpedia is a coexpression database just based on MeSH terms that enables the acquisition of biomedical coexpression data [19]. Interestingly, the top MeSH term in the GO-DO analysis of FGL1 was myocardial infarction which is not related to neoplasms. The top 10 diseases were not strongly related to cancer, neither. The top ten terms were strongly linked to metabolic diseases, which indicates that FGL1 plays a role in diabetes mellitus and fatty liver disease. Further analysis of the top five terms related to neoplasms indicated that FGL1 was

most closely linked with ‘organoplatinum compounds’ and ‘colorectal neoplasms’. The results of the GO analysis for FGL1-related genes offer a potential FGL1-based targets. The analysis showed that FGL1 was related to the immune response, which is consistent with the previous research[25]. FGL1 is highly upregulated in human carcinoma, and increased FGL1 in the plasma of cancer patients is related to a poor prognosis and resistance to anti-PD-1/B7-H1 therapy. This study proved that FGL1 is a major immune inhibitory ligand of LAG-3, which is an immune inhibitory receptor, with major histocompatibility complex class II as a canonical ligand. Although the analysis in our study showed the strong relationship between metabolism of FGL1 implied in our research indicates a possible role of FGL1 in cancer field. It may be a link between obesity and cancer and mediate the impact of obesity on immune responses though PD-1[26]. More studies are needed to determine the possible mechanism.

In this systematic study we provided some evidence regarding altered expression of FGL1 and improved the understanding of large-scale genome-wide oncogenic data, which may facilitate translation of this genomic knowledge into clinical practice. A limitation still exists in our study: the research was based on the databases, and more progressive evidence should be developed in vivo and in vitro. The controversial finding related to the prognostic role of FGL1 mRNA might also be a result of the different databases, difference in samples and difference between groups. Our analysis may provide a foundation for determining the function of FGL1 in various cancer cells.

Abbreviations

PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; FGL1: Fibrinogen-like protein 1; WHO: World Health Organization; LAG-3: Lymphocyte-activation gene 3.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare that they do not have any potential conflict of interest with respect to this manuscript.

Availability of data and materials

All the datasets used and/or analyzed used in the present study are publicly available.

The datasets generated and/or analysed during the current study are available in the website sites below.

1. Oncomine database: https://www.oncomine.org/resource/login.html
2. Co-expedia: http://www.coexpedia. org/
3. DAVID database: https://david.ncifcrf.gov/
4. KEGG: http://www.kegg.jp/ or http://www.genome.jp/kegg/

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Author contributions

Study conception and design: Qian Wang, Literature search: Shu-Zhen Chen. Data collection and analysis: Qian Wang. Data interpretation: Qian Wang. Writing: Qian Wang and Hua-Wei Zhang. All authors read and approved the final manuscript.

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Tables

Table . the significant changes of FGL1 expression in cancers

cancer	Cancer typer	P-value	Fold-change	Rank (%)	sample
Prostate cancer	Prostate carcinoma	5.54E-5	3.499	1	19
	Prostate carcinoma	5.41E-7	2.904	3	122
Breast	Lobular breast carcinoma	5.42E-7	2.67	2	64
	Mucinous breast carcinoma	3.76E-6	-3.189	2	65
	Male breast carcinoma	4.05E-9	-2.257	2	64
Liver	Hepatocellular carcinoma	7.23E-10	-2.174	8	197
Lung	Lung Adenocarcinoma	1.32E-16	2.437	2	246
pancreas	Pancreatic Adenocarcinoma	7.87E-10	-64.287	6	27
	Pancreatic Adenocarcinoma	1.79E-5	-34.311	1	36
	Pancreatic Carcinoma	1.38E-6	-11.430	1	17

Table . the alternation frequency and type of FGL1 in cancer datasets

Type	Dataset	N	Alternation frequency (%)	Amplification	Deep deletion	Mutation	Fusion
Prostate	MICH	61	18.30	1.64(1)	16.39(10)	0	0
Prostate	TCGA	499	14.03	14.03(70)	0	0	0
Pancreas	UTSW	109	9.17	1.83(2)	7.34(8)	0	0
Neuroendocrine Prostate Cancer (NEPC)	Trento/Cornell/Broad 2016)	114	8.77	7.89(9)	0.88(1)	0	0
Uterine CS	TCGA	57	8.77	1.75(1)	7.02(4)	0	0
BLCA	TCGA 2017	413	8.23	0	7.51(31)	0.73(3)	0
Bladder	TCGA	413	7.75	0	7.51(31)	0.24(1)	0
cSCC	MD ANDERSON 2014	39	7.69	0	0	7.69(3)	0
Colorectal	TCGA	640	7.03	0.16(1)	6.41(41)	0.47(3)	0
Ovarian	TCGA	606	6.60	0.33(2)	6.27(38)	0	0
Lung adeno	Broad	183	6.56	0	6.01(11)	0.55(1)	0
DLBC	TCGA PanCan	48	6.25	0	6.25(3)	0	0
CCLE	Novartis/Broad 2012	1020	6.18	2.75(28)	3.43(35)	0	0
Liver	TCGA	442	6.11	0	6.11(27)	0	0
Lung adeno	TCGA PanCan	566	5.83	0	4.59(26)	0.88(5)	0.35(5)
Breast	TCGA	1105	5.79	0.63(7)	5.07(56)	0.09(1)	0
Lung squ	TCGA	511	5.48	0	5.48(28)	0	0
Prostate	Broad/Cornell 2013	57	5.26	0	5.26(3)	0	0

Table the alternation frequency and type of FGL1 in cancer type

type	N	Alternation frequency(%)	amplification	Deep deletion	mutation	fusion
Prostate	731	12.86	1.37(10)	11.49(84)	0	0
Pancreas	109	9.17	1.83(2)	7.34(8)	0	0
Endometrial cancer	57	8.77	1.75(1)	7.02(4)	0	0
Bladder cancer	826	7.99	0	7.51(31)	0.48(4)	0
Skin cancer	40	7.50	0	0	7.5(3)	0
Colorectal	640	7.03	0.16(1)	6.41(41)	0.47(3)	0
Ovarian	606	6.60	0.33(2)	6.27(38)	0	0
Mature B-Cell Neoplasms	48	6.25	0	6.25(3)	0	0
Cancer of Uknown Primary	1020	6.18	2.75(28)	3.43(35)	0	0
Hepatobiliary Cancer	442	6.11	0	6.11(27)	0	
Lung adeno	183	6.56	0	6.01(11)	0.55(1)	0
Breast cancer	1093	5.86	0.64(7)	5.12(56)	0.09(1)	0
Non-Small Cell Lung Cancer	1260	5.79	0	5.16(65)	0.48(6)	0.16(2)

Table The co-expression genes of FGL1 in Coexpedia database

Gene	Co-expression genes
FGL1	FGA, FGB, APOH, FGG, ALB, APOB, AMBP, SERPINC1, KNG1, HRG, APCS, CRP, PLG, ORM1, ITIH2, ARG1, TF, SLC2A2, HPX ITIH3, CFHR2, APOA1, CYP2C9, MAT1A, C8B, CYP2E1, GC, ALDOB, APOC3, APOA2, AHSG, CPB2, ITIH1, CYP2C8, F2, F9, SERPINA3, TTR, CP, HP, LECT2, C9, ANGPTL3, ERP27, SAA4 RBP4, LBP, SLC7A2, C8A, VTN, PON1, TDO2, CFHR5, AQP8, TEX11, UGT2B15, CFHR4, LIPC, ASGR2, C6, BHMT, SERPIND1, HPD, ITIH4, INSL4, C4BPA, SERPINI2, TM4SF20, MUC5B, IGFBP1, ADH4, UGT2B4, CYP8B1, HAMP, UGT2B28, A1CF, APOM, FABP1, FMO3, TM4SF4, HAO1, CUZD1, PAH, MUC5AC, CPS1, SERPINA5, MBL2, CYP3A4, PNLIPRP1, A1BG, ADH1A, HSD17B6, KLK1, SERPINA6, CTRL, AGXT, ADH1B, CTRC, SERPINA1, GATM, HGD, CPA2, SLC22A1, CELA2B, SYCN, ACSM2A, AGT, SERPINA10, GP2, CEACAM7, CYP2A6, SPP2, PLA2G1B, YBX1, SERPING1, CELA3B, CD14, SLC30A2, CLPS, NT5E, PPAP2A, AOX1, MS4A6A, SCAMP1, USH1C, OPTN, APOC4, C8G, PDPR, CDH18, GYS2, HAL, HPN, RPL41, TMEM97, GFRA4, CXCR4, CFB, CYP3A7, PAQR9, ACSM5, CPA1, HOMER2, CBS, PDIA2, AFM, NR1I2, RPL38, VNN1, SLC39A6, CELA3A, SOX15, KIRREL2, HSD11B1, C4BPB, GPX3, CPLX2, HABP2, JAK3, SLC10A1, ADH6, CYP4F2, PIPOX, AZGP1, KCNK3, RDH16, CD44, CACNA1I, APOC2, SULT2A1, CHI3L1, ZNF324, AADAC, PCK1, CEL, SLC51A, HOXB5, IMPA2, PON3, TFR2, NR5A2, GLS2, LEAP2, PRSS3, FTCD, APOA5, RBPJL, FXYD2, GATA2, CRYBB3, F13B, FAM133A, HMGCS2, C10orf10, CSRP3, OR1F1, EXPH5, HPR, G6PC, CCL20, SLC22A9, CCDC9, TMEM151B, TBX6, THBS4, ACADL, SERPINA7, CLDN2, CTNND2, MDK, CDH20, RPS15A, HGFAC, CCRN4L, KIAA1467, ALDH8A1, SLC28A3, ABCB4, EGF, SORD, CLDN1, CYP2B6, TRIM10, DIO1, SPEF1, HBQ1, DLX4, UPB1, TRIM45, VIM, NAT2, FMO5, NHA, COL11A2, OGDHL, F12, SLC1A2, DRD5, RPS24, PKHD1, GNMT, MUC15, GPR31, CPN2, NCR2, MUC3A, FTL, SFSWAP, SHBG, TMPRSS15, INHBE

Figures

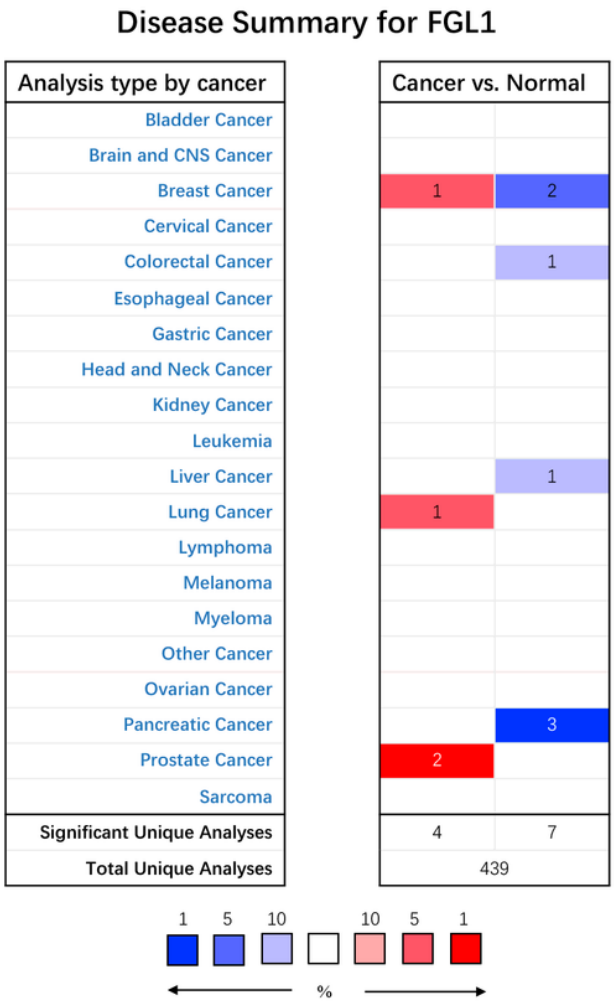


Figure 1

FGL1 mRNA expression in various cancer types The comparison indicated the number of datasets with FGL1 mRNA overexpression (right column, red) and under expression (left column, blue) in cancer versus normal tissue. The threshold was designed with the following parameters: p-value of 1E-4, fold change of 2, and gene ranking of 10%.

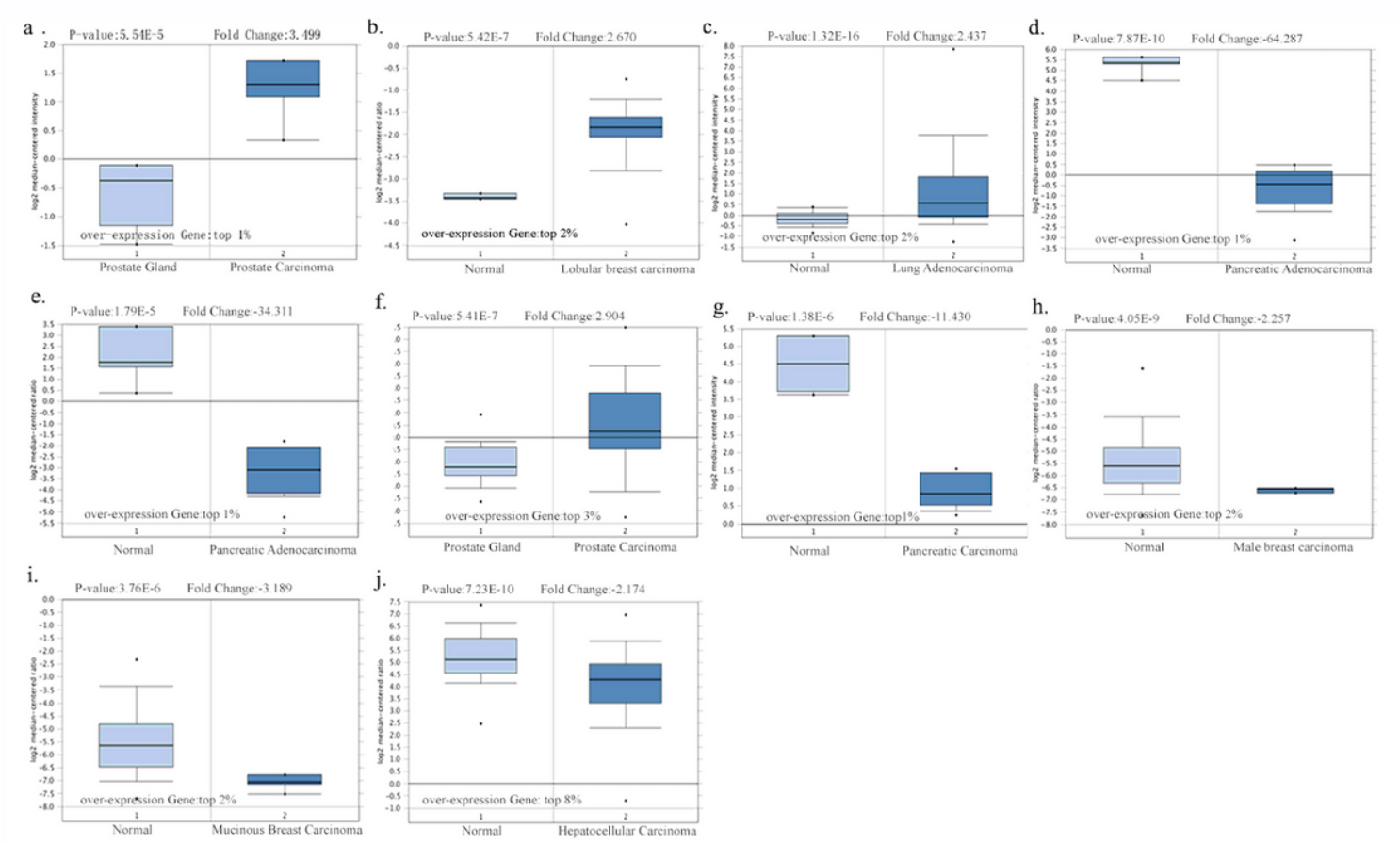


Figure 2

FGL1 analysis in different cancer types (Oncomine database). The data shows the contrast of FGL1 expression between cancer tissues (dark blue) and normal tissues (light blue). The results show FGL1 expression in prostate carcinoma vs prostate gland(A), in lobular breast carcinoma vs normal (B), in lung adenocarcinoma vs normal(C), in pancreatic carcinoma vs normal (D), in pancreatic adenocarcinoma vs normal (E), in prostate carcinoma vs prostate gland (F), in pancreatic carcinoma vs normal (G), in male breast carcinoma vs normal (H), in mucinous breast carcinoma vs normal (I), in hepatocellular carcinoma vs normal(J).

Figure 3.

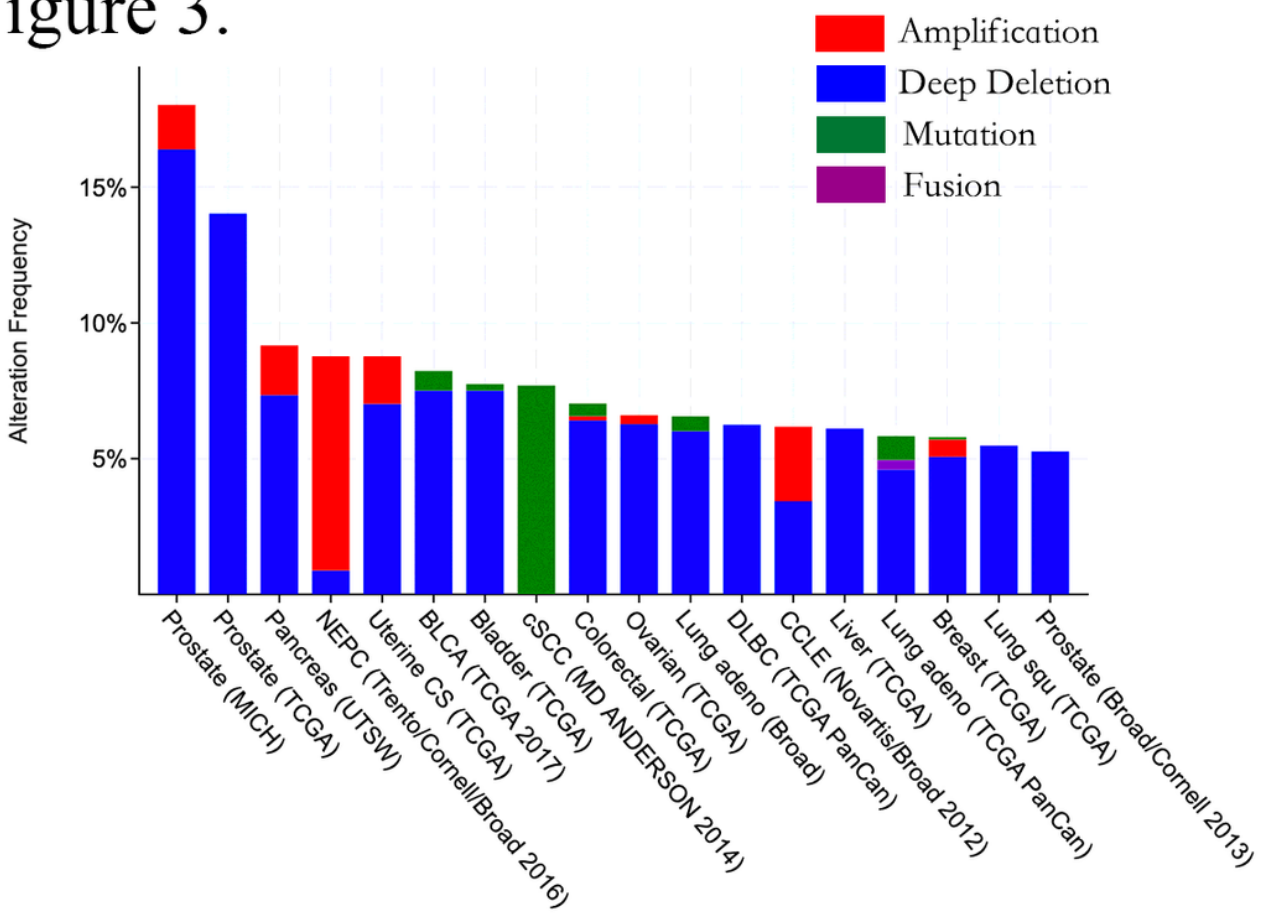
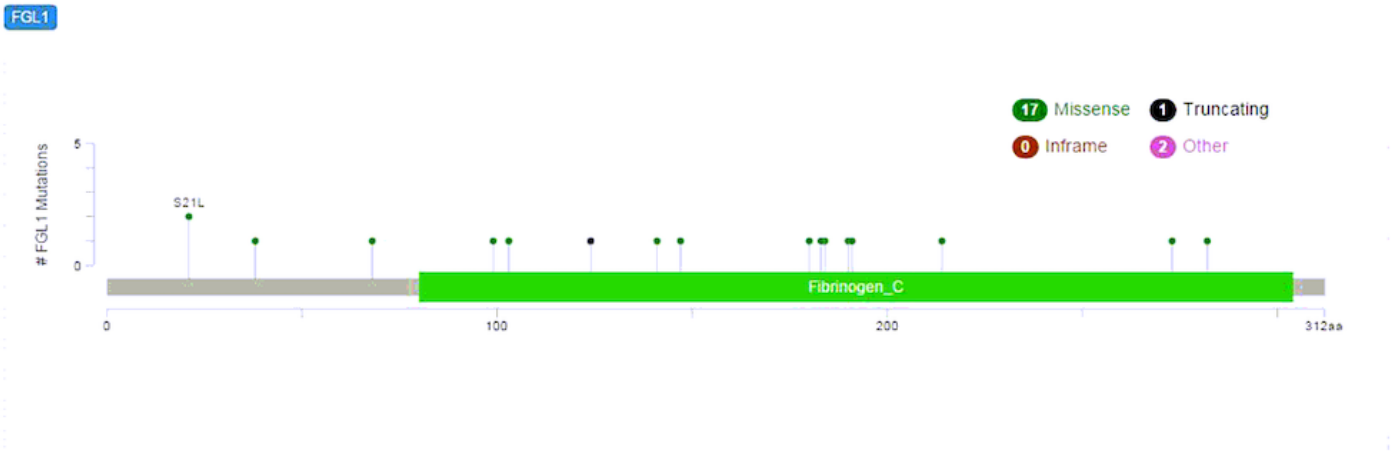


Figure 3

The frequency and type of FGL1 mutations in cancer (cBioPortal) only cancer types containing an alteration frequency of >5% are shown

a. Mutation diagram of FGL1 in cancer



b. Mutation annotation of FGL1 in cancer

Study	Sample ID	Cancer Type	Protein Change	Annotation ▼	Mutation Type	Copy #	COSMIC	Allele Freq (T)	# Mut in Sample
Breast Invasive ...	TCGA-AN-A046-01	Breast Invasive Ductal Carcinoma	*S21L*		Missense	Diploid	3	0.24	4274
Cutaneous Squamo...	CSCC-37-T	Cutaneous Squamous Cell Carcin...	*S21L*		Missense		3	0.09	945
Bladder Cancer (...	TCGA-ZF-AA4X-01	Bladder Urothelial Carcinoma	*Q124**		Nonsense	ShallowDel	2		595
Lung Adenocarcin...	LUAD-YINHD	Lung Adenocarcinoma	*S183C*		Missense	Diploid	1		2711
Lung Adenocarcin...	LUAD-YINHD	Lung Adenocarcinoma	*E180Q*		Missense	Diploid	1		2711
Lung Adenocarcin...	TCGA-55-6972-01	Lung Adenocarcinoma	*F147S*		Missense	Gain	1	0.41	264
Lung Adenocarcin...	TCGA-55-6982-01	Lung Adenocarcinoma	*E68K*		Missense	ShallowDel	1	0.14	215
Bladder Cancer (...	TCGA-DK-A1AC-01	Bladder Urothelial Carcinoma	*G282R*		Missense	ShallowDel	1		1259
Bladder Urotheli...	TCGA-DK-A1AC-01	Bladder Urothelial Carcinoma	*G282R*		Missense	ShallowDel	1	0.52	1230
Colorectal Adeno...	TCGA-AA-A010-01	Colon Adenocarcinoma	*R38C*		Missense	Diploid	4		6560
Colorectal Adeno...	TCGA-AG-3892-01	Rectal Adenocarcinoma	*F191V*		Missense	Diploid	1		1859
Lung Adenocarcin...	TCGA-44-5644-01	Lung Adenocarcinoma	*Q103K*		Missense	ShallowDel	1	0.79	908
Lung Adenocarcin...	TCGA-55-8208-01	Lung Adenocarcinoma	*I99M*		Missense	Diploid		0.03	319
Colorectal Adeno...	TCGA-AA-3984-01	Colon Adenocarcinoma	*S214F*		Missense	Diploid	1		3190
Bladder Cancer (...	TCGA-ZF-A9RG-01	Bladder Urothelial Carcinoma	*R184H*		Missense	Diploid			212
Lung Adenocarcin...	TCGA-55-8094-01	Lung Adenocarcinoma	*MTUS1-FGL1*		Fusion	Gain			395
Lung Adenocarcin...	TCGA-55-8508-01	Lung Adenocarcinoma	*MTUS1-FGL1*		Fusion	Diploid			165
Cutaneous Squamo...	CSCC-19-T	Cutaneous Squamous Cell Carcin...	*N190I*		Missense		1	0.13	1275
Cutaneous Squamo...	CSCC-60-T	Cutaneous Squamous Cell Carcin...	*E141K*		Missense			0.10	1375
Lung Adenocarcin...	TCGA-44-2655-01	Lung Adenocarcinoma	*G273C*		Missense	Diploid	1	0.09	164

Figure 4

FGL1 mutations in cancer studies (cBioPortal). This graphical view shows the positions of 20 mutations; the hotspot (S21L) represents the common founder mutation (A); the tabular view provides additional information about partial mutations. Hyperlinks to the COSMIC database show that mutations (S21L) (B)

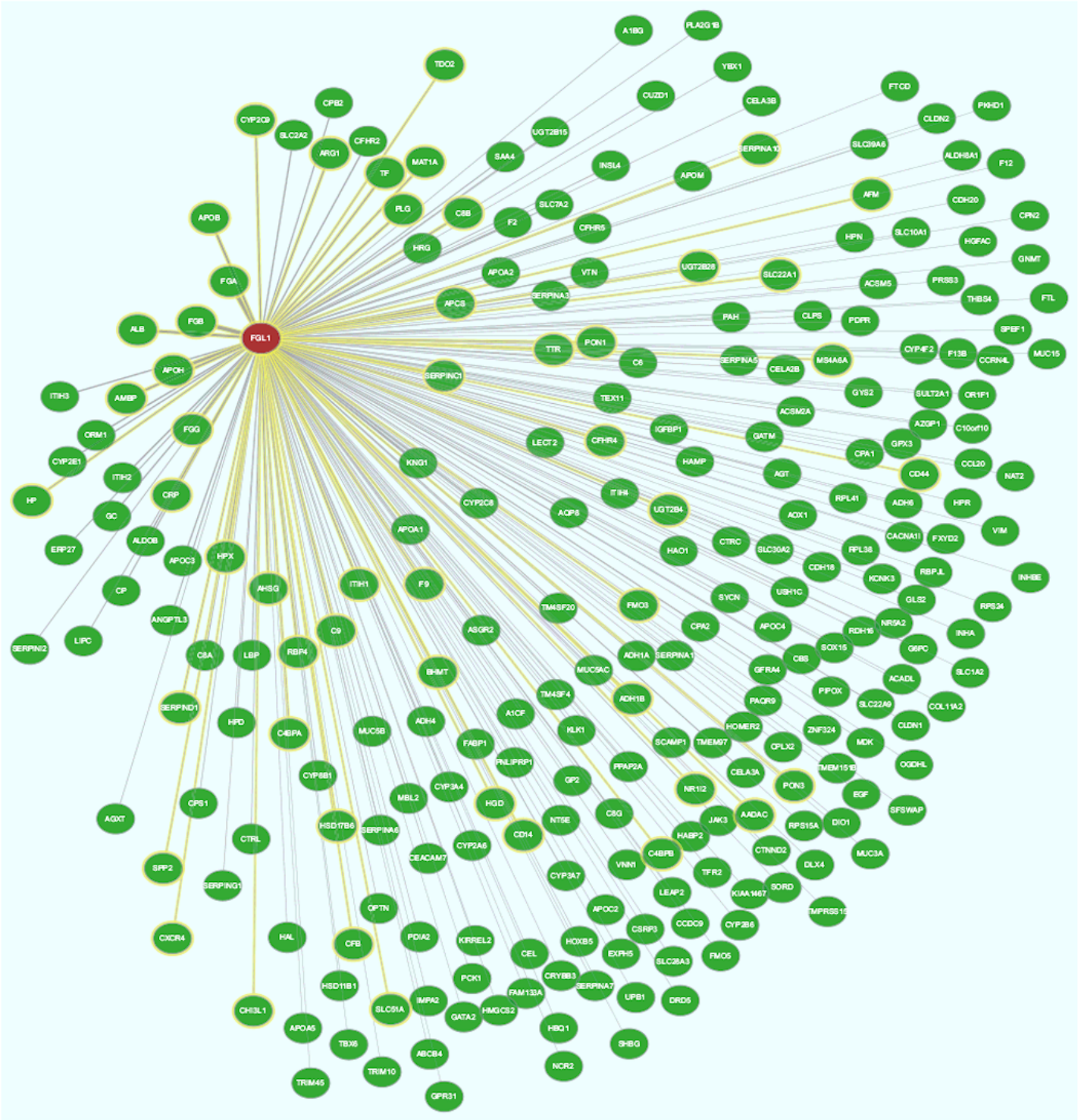


Figure 5

Co-expression network of FGL1 (Coexpedia) Co-expressed genes with FGL1 are ranked according to Coexpedia's online instructions.

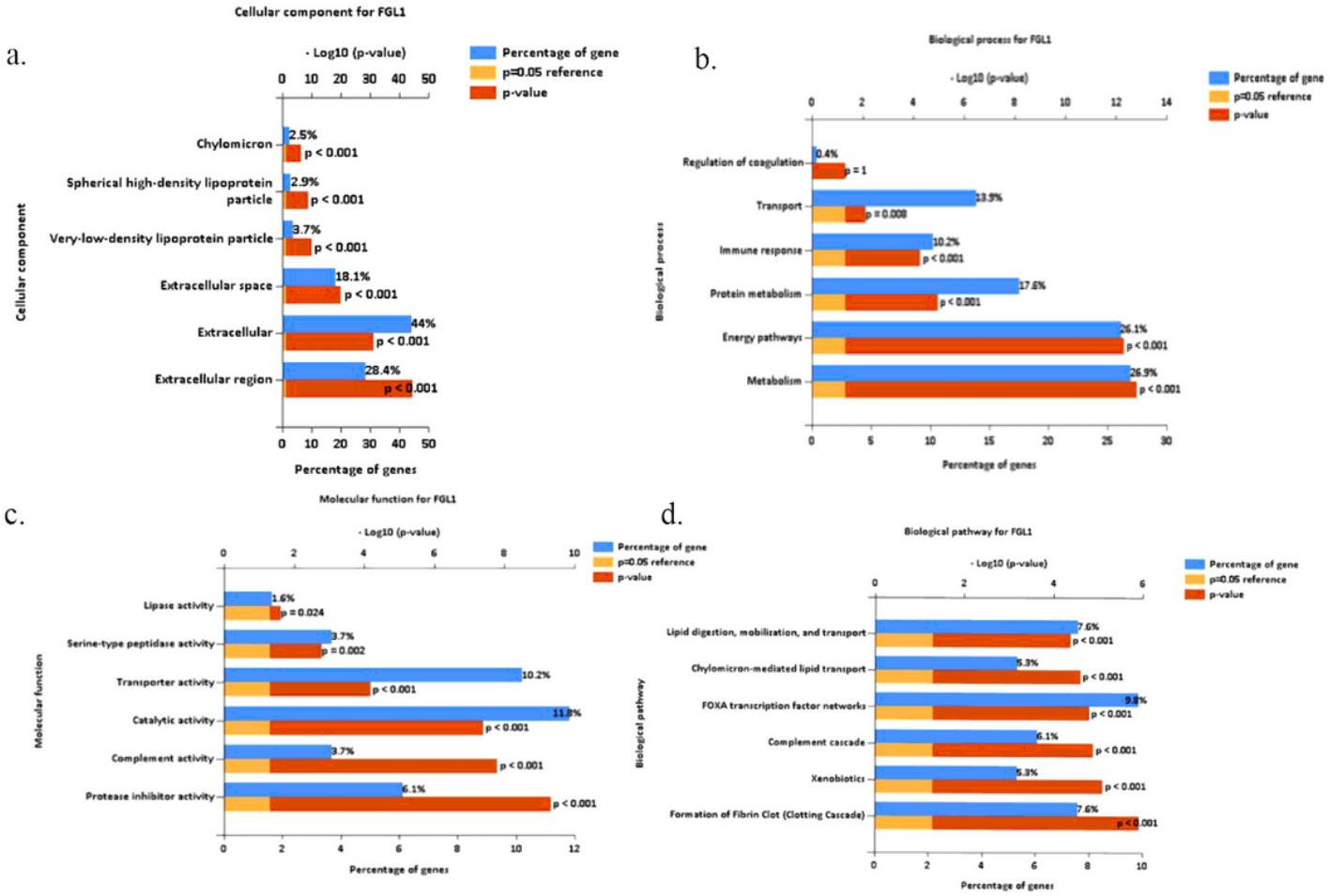
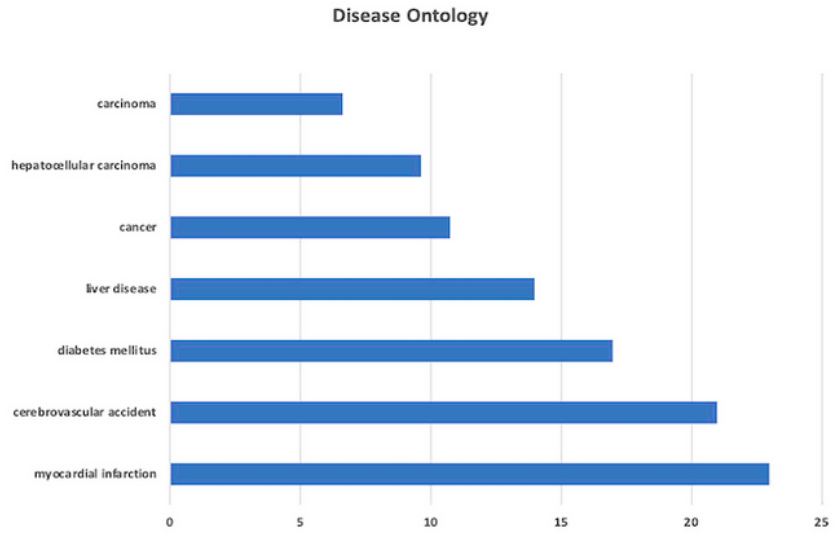


Figure 6

Significantly enriched Gene Ontology annotation of FGL1 including (A) cellular components, (B) biological process, and (C) molecular function. (D)biological pathway (FunRich V3).

a.



b.

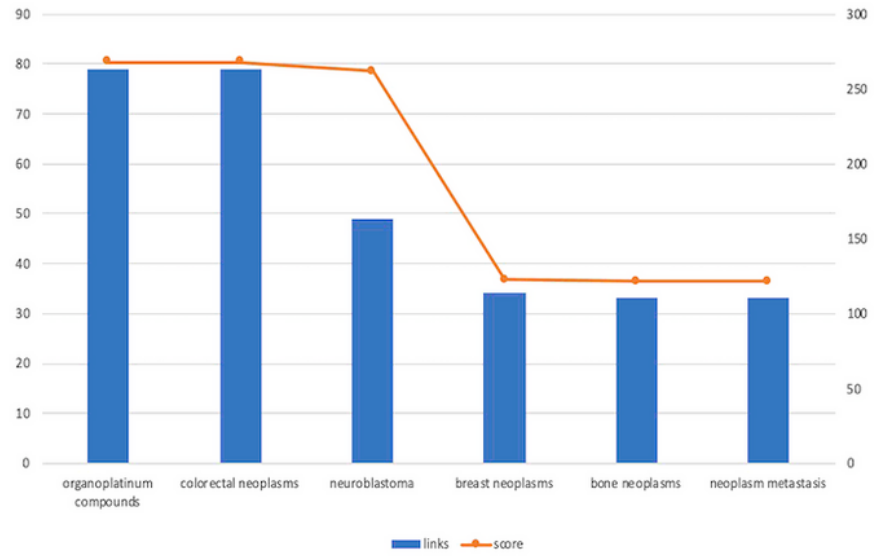


Figure 7

Disease Ontology annotation and Enrichment after including ‘neoplasm’as a MeSH term in the analysis of the FGL1 co-expression network (Coexpedia) The enriched GO-DO terms(A) and MeSH terms including ‘neoplasm’ (B) were ranked according to Coexpedia’s online instructions