Supplementary Material

Symmetry in Cancer networks Identified : Proposal for multi-cancer biomarkers

Supplementary Information

Data Collection

Various gene ontology and text search terms were used to list down protein names for seven tissues in both healthy and disease conditions. For instance, in order to search (1) Breast cancer data, we used *breast cancer AND organism:"Homo sapiens (Human) [9606]"* for UniprotKB and *(Breast cancer) AND Homo sapiens [porgn : txid9606]* for GenBank database, and (2) for healthy breast tissues data, we used *breast AND organism: "Homo sapiens (Human) [9606]"* for UniprotKB and *(Breast cancer) AND "Homo sapiens"[porgn : txid9606]* for GenBank database. Similar search methods were adapted to retrieve data for other tissues. Additionally, we explored other resources (cell-lines) to enrich our protein name collection. The various cell-line databases were used to obtain the list of proteins for different cancers are Human Mammary Epithelial Cells (HMEC) and Michigan Cancer Foundation - 7 (MCF-7) cell lines for were used for breast tissues. Protein 2D page and Cervical cancer database (CCDB) (http://crdd.osdd.net/raghava/ccdb/) for cervical tissues, ACTREC Oral Cancer Database and Head and Neck Oral Cancer Database (HNOCDB) for oral cancer, ATCC cell line database and Cancer Cell Line Encyclopedia for all considered cancers. In this way, we have now two protein sets for each tissues, *i.e.,* disease and healthy.

Furthermore, we found interactions among proteins in each protein set from STRING database. STRING database is a depository for the curated and experimentally verified protein-protein interactions those are direct (physical), indirect (functional) or both for a given list of proteins. The protein-protein interaction data of all the seven cancers for normal and disease states in the form of adjacency list are available for reuse on request to authors.

The detailed steps of Survival analysis

We have used biomarker validation tools available at SurvExpress for survival analysis. SurvExpress is a comprehensive gene expression database and web-based tool that provides survival multivariate analysis and risk assessment from a list of genes (biomarker) in human cancer datasets. The following simple steps were used to analyse TCGA gene expression values taken for each gene:

1. We acessed SurvExpress database at http://bioinformatica.mty. itesm.mx:8080/Biomatec/SurvivaX.jsp
2. We inserted details of Gene name, Tissue of interest in data field 2 and 3, respectively and chosen default entries for rest of the columns. Here, we selected TCGA database for data retrival (in following we have given details of TCGA database).
3. Clicked on 'Send (field 5) button in ordrer to retrive data from TCGA database.
4. On SurvivaXvalidator page, we used Bimarker: Cox Survival analysis function. Then, we selected available the outcome variable in Censored filed and kept rest of the fields as default.

All the detailed information regarding each field is accessed using SurvExpress tutorials available at http:bioinformatica.mty.itesm.mx/drupal /sites/default/ files/ SurvExpress%20Tutorial %20final-4.pdf
5. Results are generated in PDF files and further analysed.

Degeneracy at zero (0) eigenvalue

The eigenvalue distribution of many real networks, particularly technological and biological networks such as protein-protein interactions of diseases, exhibit high degeneracy at zero eigenvalues. Mathematically in a network, duplication of nodes yields the same neighbors for two nodes in the corresponding adjacency matrices. It has been shown that duplication of nodes leads to lowering of the rank of the corresponding matrix, hence contributing one additional zero eigenvalue in the spectra. For the adjacency matrix of size N and rank r, the matrix has exactly $N - r$ zero eigenvalues. We discuss here three possible cases when the rank can lower in an adjacency matrix:
(i) two rows (columns) have exactly same entries, it is termed as complete row (column) duplication $R_1 = R_2$,
(ii) the partial duplication of rows (columns) where $R_1 = R_2 + R_3$, where, R_i denotes ith row of the adjacency matrix (Fig.S1). This condition is computationally exhaustive as to find this state in the matrix has large possibilities,
(iii) if there is an isolated node in the network, the row and column corresponding to it has zero entries and thus the rank of the matrix is lowered by one. For a connected network, the number of zero eigenvalues (λ_0) provides an exact measure of (i) and (ii) conditions. Similarly, the calculations for identification of degenerate -1 eigenvalues is given in for $\mathbf{A} + \mathbf{I}$ matrices.

Hallmarks of Cancer

The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. These properties for 39 proteins are briefly given in (Table S6).

Supplementary Tables

Table S1: **Network structural properties of 39 proteins identified using degenerate eigenvalues.** Here, $\langle K \rangle$, $\langle C \rangle$, $\langle B_c \rangle$ represent average degree, average clustering coeficient and average betweeness centrality of 39 proteins, respectively.

$\langle K \rangle$	$\langle C \rangle$	$\langle B_c \rangle$
35.05	0.041	0.00035

Table S2: **Datasets used for survival analysis.** All datasets were taken from the TCGA database. Each cohort represents the set of high and low-risk patients prescribed by the TCGA database. It is to note that time-frame taken for each cohort is different such as survival months for BRCA whereas survival days for CESC, COAD, HNSC, LOAD, LUSC, OV and PRAD.

Cancer	**Cohort**	**Cohort full form**	**Total patients**	**Low risk**	**High Risk**
Breast	BRCA	Breast cancer adenocarcinoma	502	251	251
Cervical	CESC	Cervical squamous cell carcinoma	191	96	95
Colon	COAD	Colon adenocarcinoma	350	175	175
Oral	HNSC	Head and neck squamous cell carcinoma	502	251	251
Lung	LOAD	Lung adenocarcinoma	475	238	237
	LUSC	Lung squamous cell carcinoma	175	88	87
Ovarian	OV	Ovarian serous cystadenocarcinoma	247	124	123
Prostate	PRAD	Prostate adenocarcinoma	497	249	248

Table S3: **Datasets of seven cancers.** Protein-protein interactions of seven cancers have been considered for their healthy and disease states. N represents number of proteins and N_c represents number of interactions.

	Normal		**Cancer**	
Tissue	N	N_c	N	N_c
Breast	2464	15131	2096	14183
Oral	2105	21746	1542	26794
Ovarian	1869	6873	2085	8067
Cervical	3559	21081	2397	20040
Lung	3261	17805	3131	17407
Colon	4932	38967	3458	36355
Prostate	2357	11049	5180	18969

Table S4: **Top 10 degree nodes in weighted and weighted multi-cancer PPI network.** Here, k^w and k^{uw} stand for node-degree in the weighted and the unweighted network, respectively. It is observed that the lists of top 10 degree proteins are different in two networks. *CACNB2* and *BRD7* are hub proteins (shown in bold face) in weighted PPI network whereas *UBC* is hub protein in unweighted PPI network. Hub protein is characterized here by considering the highest degree nodes compared to other nodes in the network.

	Weighted		**Unweighted**	
Sr.No.	**Protein**	k^w	**Protein**	k^{uw}
1	**CACNB2**	1565	**UBC**	877
2	**BRD7**	1524	*TP53*	716
3	*BCL11B*	1122	*AKT1*	698
4	*FAM83D*	1074	*ALB*	660
5	*MMP3*	1061	*TSPO*	654
6	*AMY1A*	1028	*SRC*	510
7	*CTPS2*	997	*EGFR*	508
8	*CTNND1*	992	*ESR1*	499
9	*AGR3*	930	*GAPDH*	495
10	*SNAP25*	889	*VEGFA*	483

Table S5: **Gene Expressions by risk groups.** L represents low risk group and H represents high risk group.

Cohort	**BRCA**		**CESC**		**COAD**		**HNSC**		**LUAD**		**LUSC**		**OV**		**PRAD**	
Protein	L	H	L	H	L	H	L	H	L	H	L	H	L	H	L	H
APOL6	2.9	3.4	3.4	2.9	3.3	3	3.5	3	3.2	3.5	3	3.3	3	3.3	3.2	2.7
BMI1	0	0	2.7	2.9	0	0.5	2.9	2.7	2.9	2.9	3.2	3.2	3	3.3	3	3.2
BTBD7	2.7	3	2.7	2.9	2.8	2.6	2.7	3	2.7	3	2.7	3	2.7	3	2.6	2.8
CDKN2A	-1	-2	3.4	3.6	1.6	2.7	3	0.8	0.4	2.5	3	0.5	3.7	2.7	0.4	1.4
DDIT4	3.5	3	3.5	4	3.1	3.5	3.4	3.9	3.1	3.6	3.9	3.4	2.9	3.4	3	3.5
FYN	2.4	2.7	2.5	2	2	2.7	2.7	2.4	3	2.5	2.5	3	2.5	3	2.3	1.7
KIR2DL2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LPL	2	3	0.1	1	0	0	0.7	2	3.3	2	1.6	2.5	2	1	1	1.6
MAPK11	1.6	2.3	2.5	1.8	1.6	2.1	2.5	2	1.5	2	1.7	2.5	0.7	1.8	2.5	2
NLE1	2	2.5	2	2.5	2.8	2.5	2.3	2.5	2.1	2.5	2.6	2.2	2	2.5	2.4	2.7
UTP14A	2.7	2.5	2.8	2.5	3	2.6	2.5	2.8	2.4	2.7	2.7	2.5	2.7	2.5	2.4	2.6
PRAD	3.2	2	2.3	4	2.9	1.6	0.7	2.9	4	3.4	2.8	3.3	4.5	4	3	2

Table S6: Biological functions of proteins corresponding to λ_{-1} eigenvalue in weighted cancer PPI network.

Sr. No.	Protein	Biological function
1	GOLPH3L	GOLPH3, a paralog of GOLPH3L, is a conserved protein that localizes ubiquitously expressed at membrane of the Golgi apparatus. GOLPH3L is associated with cell cycle regulation and cisplatin sensitivity. GOLPH3L silencing is associated with a reduction in cell viability, induction of cell cycle arrest, and increased apoptosis rates and cisplatin sensitivity [10].
2	DDIT4	DDIT4 gene (for DNA-damage-inducible transcript 4) encodes a protein product that is induced by a variety of stress conditions and whose major function is to inhibit mTORC1 by stabilizing the TSC1-TSC2 inhibitory complex. Having apoptotic acrtivity, it is considered to be a driver in the aggressiveness of cancer cells [11].
3	CETN1	Recently its been learned that is a cancer testis antigen which is thought to be one of the atrractive targets in adult cancer tissues which is highly up-regulated therein [12].
4	ALPK3	
5	RALBP1	RALBP1 is a stress-responsive, multi-functional transporter protein. It is frequently over-expressed in malignant cells and functions to oppose apoptosis by limiting the accumulation of endogenous or exogenous toxic electrophilic compounds in cells [13].
6	MAP3K6	MAP3K6 acts as a tumor suppressor and activates the JNK and p38 cascades and promotes apoptosis [14].
7	PDCL3	PDCL3 participates in G protein signaling by interacting with the chaperons. It participates in angiogenesis of cancer cells [15]
8	PFDN1	PFDN1 is an indicator for colorectal cancer prognosis and enhances tumor cell proliferation and motility through cytoskeletal reorganization [16]
9	SLC7A5	SLC7A5 is overexpressed in many cancers and its expression levels are usually correlated to cancer progression and aggressiveness. It is one of the important agent in PI3K/Akt/mTOR network [17].
10	CR2	The complement receptor 2 (CR2) gene plays central roles during inflammatory and immune responses. The upregulation or downregulation of CR2 was found in different cases [18].
11	ASPSCR1	Sarcoma chromosome region candidate 1 (ASPSCR1) is involved in intracellular regulation of the glucose transportation. It is found to be mutated in many cancers, resulted into over-regulation of energy uptake of cancer cells [19].
12	SH3PXD2B	It involves in reactive oxygen species (ROS) generation and ROS localization. It is also involved in cell adhesion and migration of numerous cell types [20].
13	FYN	FYN is a SRC family kinase (SFK) that has been shown to be up-regulated in human prostate cancer. It demonstrated to have role in metastasis and progression in a xenograft tumor model [21].
14	Rufy1	It involves in cancer cell migration and invasion and have role in membrane trafficking, cytoskeleton remodeling and signal transduction [24]. Hence it supposed to performe role in metastatic potential of gastric cancer cell as Rufy3. [22].
15	FCGR2B	It is involved in the phagocytosis of immune complexes and in the regulation of antibody production by B-cells. It is often found to be disregulated in to the cancer cells [23].
16	OSTC	It involved in the pathway protein glycosylation, which is part of Protein modification and reported to involve in breast carcinoma [25].
17	NLE1	It plays a role in regulating the expression of CDKN1A and several members of the Wnt pathway, probably via its effects on Notch signalling pathway nle1.
18	MAPK11	MAPK11 is highly expressed in the metastatic breast cancer. Further, it is responsible to breast cancer-induced osteolytic bone destruction He.
19	FZD6	FZD6 is crucially involved in regulating tissue development and differentiation, and is often deregulated in cancer [28].
20	BCKDK	BCKDK promotes tumorigenesis whereas it is valuable and potential biomarker for diagnosis of colorectal cancer. It is negatively regulated [29].
21	EXOSC5	Exosome component 5 is intracellular protein which works in RNA processing and also involved in degradation of histone EXOSC5.
22	ASIP	ASIP gene is not only related to pigmentation traits but is also involved in the etiology of skin cancer [31].
23	BMI1	BMI1 is epigenetic regulator and it promotes oncogenesis with DNA damage response as it is the regulator of DNA damage response [32].
24	NAGK	It participates in preserving cell attachment and ER homeostasis where it primarily function as amino acid biosynthesis [33].
25	APOL6	It participates in programmed cell death and immunity. It is highly expressed in cancer cells [34].
26	CNOT1	CNOT1 promotes osteosarcoma cell growth as well as found to have role in tumor inhibition and Hedgehog signaling pathway inhibition [35].
27	TRIO	It is Rho guanine nucleotide exchange factor. It Promotes of Colorectal Cancer Invasion and Metastasis ny NOTCH signaling [36].
28	CDKN2A	CDKN2A also known as cyclin-dependent kinase Inhibitor 2A. The gene codes for two proteins, including the INK4 family member p16 (or p16INK4a) and p14arf both are tumour suprresors [37].
29	PRPF40A	It is RNA-binding and pre-mRNA Processing Factor participates in assembly of splicing machinery onto the pre-mRNAs. It acts upstream of hypoxia pathways in many cancers [38].
30	UTP14A	It participates into rRNA processing as well as ribosome biogenesis. It directly interacts to p53 for its degradation [39].
31	LPL	It often goes with the most common somatic deletions in prostate tumors [40]
32	DPAGT1	Its role affects intercellular adhesion and cytoskeletal dynamics drives tumorigenic phenotypes. DPAGT1 also regulates and is regulated by Wnt/-catenin signaling, impacting the balance between proliferation and adhesion in homeostatic tissues [41].
33	TET1	TET1 is a tumour suppressor that inhibits colon cancer growth by derepressing inhibitors of the WNT pathway. TET1 silencing in primary epithelial colon cells increase their cellular proliferation while its re-expression in colon cancer cells inhibits their proliferation and the growth of tumour xenografts even at later stage.
34	PTGES	It is oxido-reductase whose expression was associated with reduced overall and progression-free patient survival [43].
35	WFDC2	Its over-expression is corelated with cell growth as well as cell proliferation [44].
36	KIR2DL3	It is transmembrane glycoprotein expressed by natural killer cells and subsets of T cells. It is thought to play an important role in regulation of the immune response of tumor cells by lowering NK cell activation threshold leading to antitumor response [45].
37	YIPF6	It is overexpressed in cancer cells and has found to have effects on cell proliferation, colony formation, migration, and invasion [46].
38	BTBD7	Btbd7 expression was elevated in non-small cell lung cancer tissues compared to normal lung tissues. Further, it is significantly associated with lymph node metastasis, reduced E-cadherin expression and patients poor clinical outcome [47]
39	CDR2	CDR2 is termed to be tumor antigen and is highly expressed in tumour cells. It is involved in signal transduction and transcription [48].

Supplementary Figures

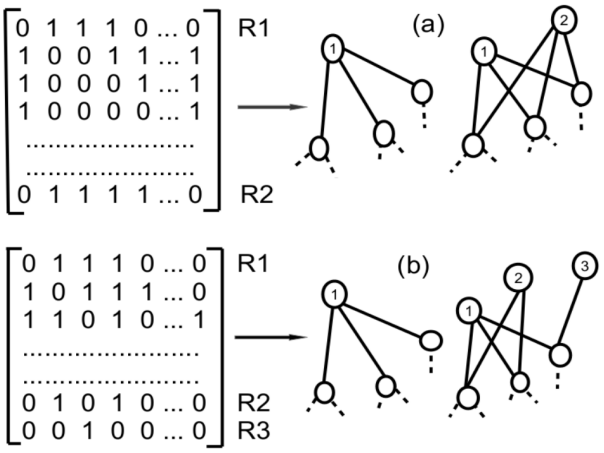

Figure S1: **Zero Degeneracy.** Schematic diagram representing (a) complete node duplication and (b) partial node duplication in networks. Biological networks know to posses a higher degeneracy at the zero eigenvalue than corresponding random networks. The degeneracy at the zero eigenvalue is signature of presence of node duplication in the network.

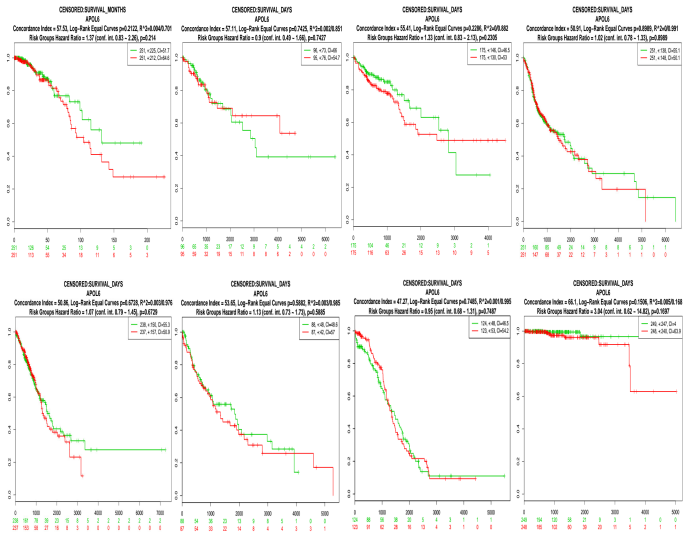

Figure S2: **Kaplan-Meier plots of APOL6 for different cancer types.**

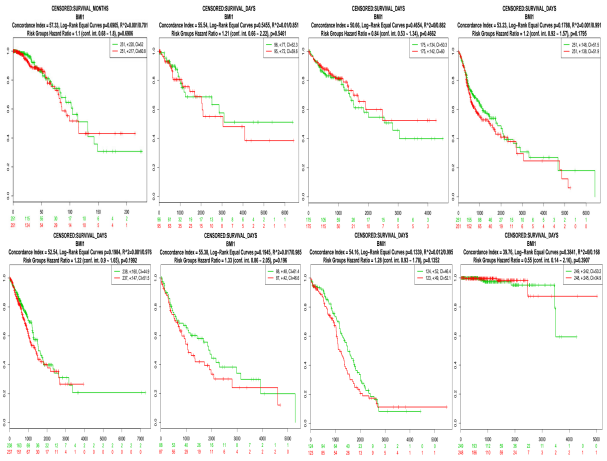

Figure S3: **Kaplan-Meier plots of BMI1 for different cancer types.**

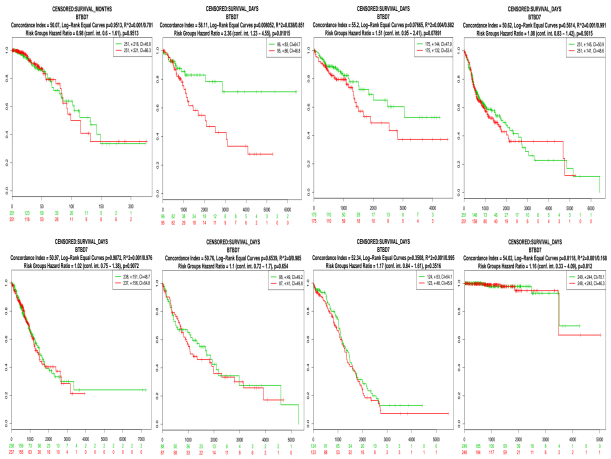

Figure S4: **Kaplan-Meier plots of BTBD7 for different cancer types.**

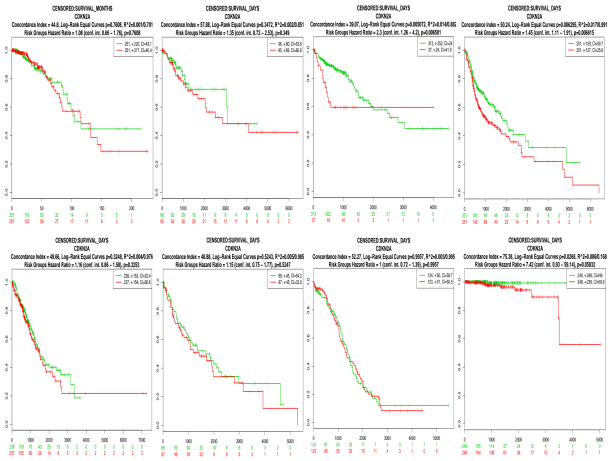

Figure S5: **Kaplan-Meier plots of CDKN2A for different cancer types.**

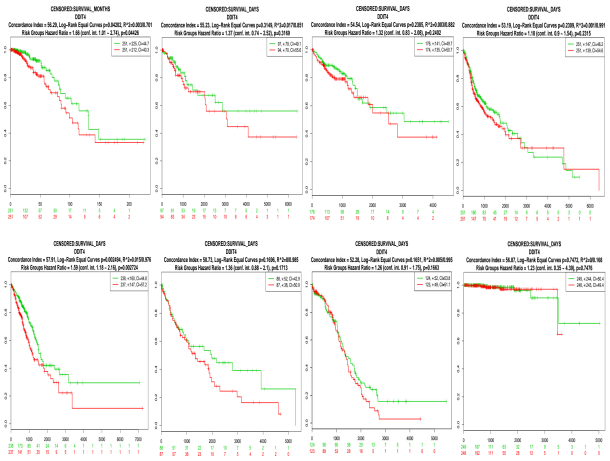

Figure S6: **Kaplan-Meier plots of DDI4T for different cancer types.**

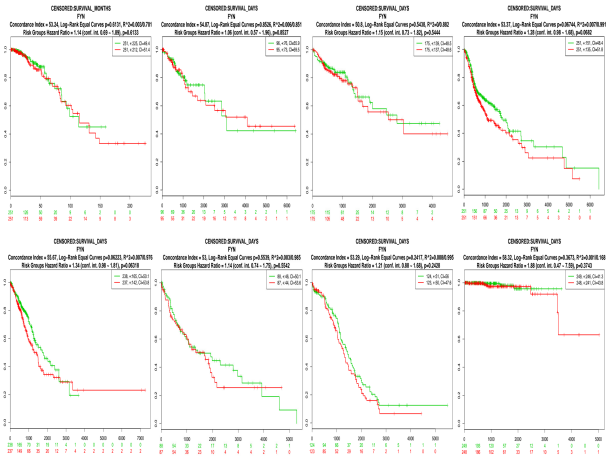

Figure S7: **Kaplan-Meier plots of FYN for different cancer types.**

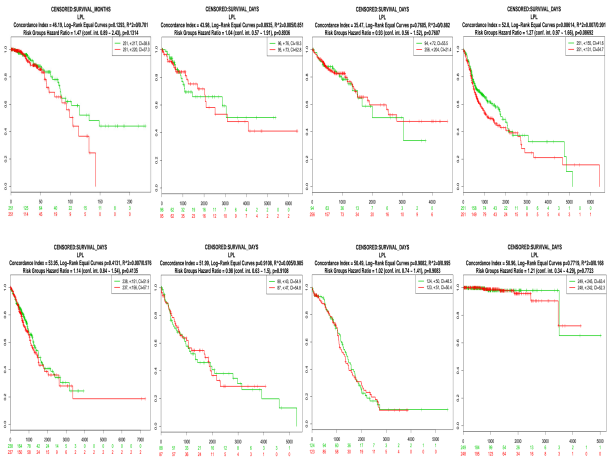

Figure S8: **Kaplan-Meier plots of LPL for different cancer types.**

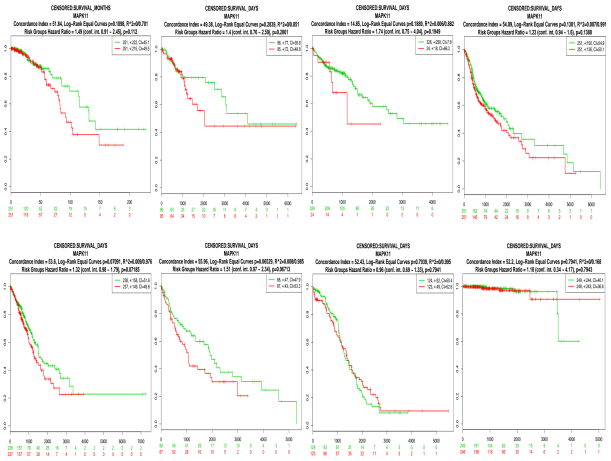

Figure S9: **Kaplan-Meier plots of MAPK11 for different cancer types.**

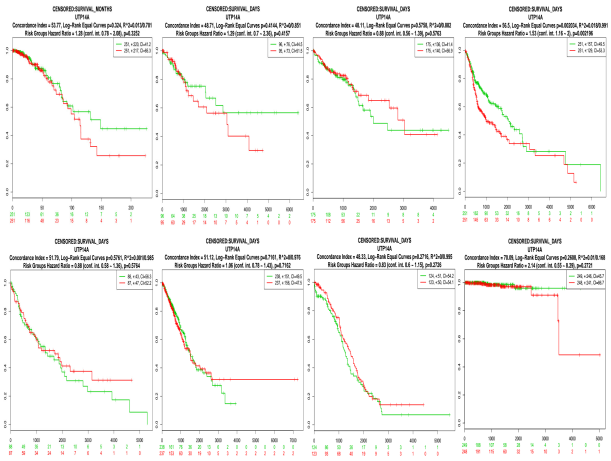

Figure S10: **Kaplan-Meier plots of UTP14A for different cancer types.**

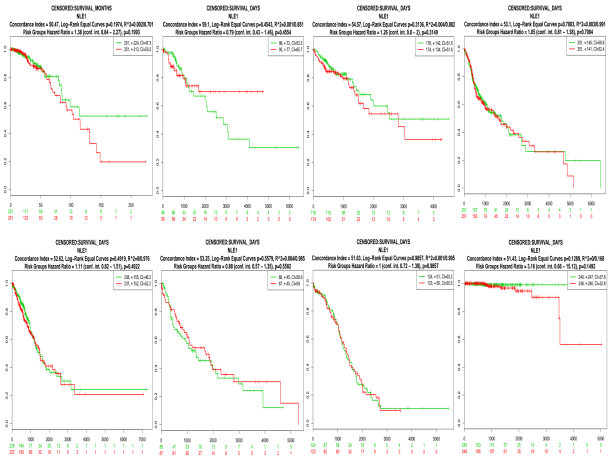

Figure S11: **Kaplan-Meier plots of NLE1 for different cancer types.**

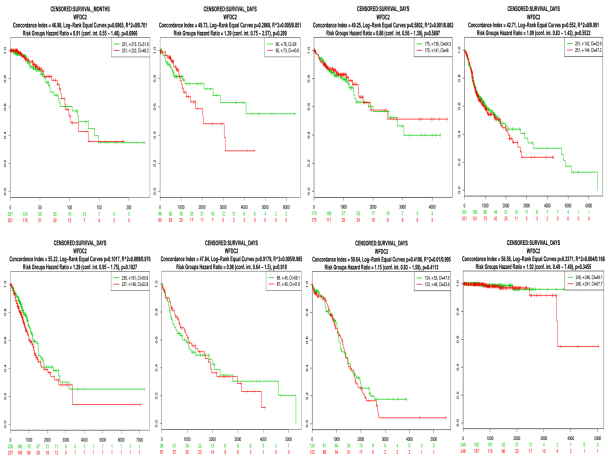

Figure S12: **Kaplan-Meier plots of WFDC2 for different cancer types.**

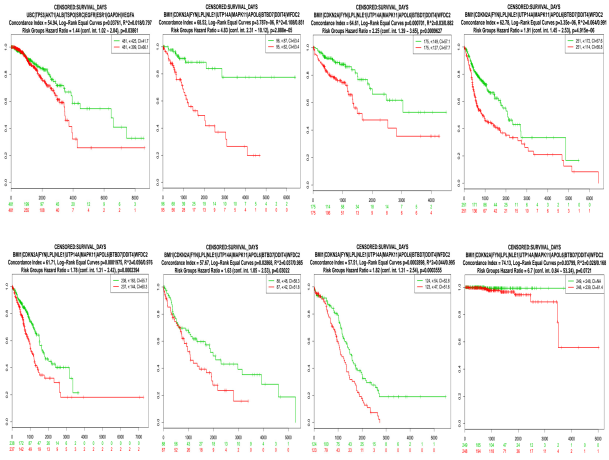

Figure S13: **Kaplan-Meier plots of multi-proteins for different cancer types.**

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