doi:10.4149/neo_2016_408

Significant prognostic values of nuclear genes encoding mitochondrial complex I subunits in tumor patients

L. D. LI[1,2,‡], H. F. SUN[1,2,‡], Y. BAI[3,‡], S. P. GAO[1,2], H. L. JIANG[1,2], W. JIN[1,2,*]

[1]Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Collaborative Innovation Center of Cancer Medicine, Fudan University Shanghai Cancer Center, Shanghai, 200030, China; [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200030, China; [3]Department of Obstetrics and Gynecology of Shanghai Medical College, Fudan University, Shanghai 200032

**Correspondence: weijin7207@126.com*
‡Contributed equally to this work.

Received December 15, 2015 / Accepted February 5, 2016

In cancer biology, it remains still open question concerning the oncogenic versus oncosuppressor behavior of metabolic genes, which includes those encoding mitochondrial complex I (CI) subunits. The prognostic value of nuclear genome mRNAs expression of CI subunits is to be evaluated in the tumor patients. We used the Kaplan Meier plotter database, the cBio Cancer Genomics Portal, and the Oncomine in which gene expression data and survival information were from thousands of tumor patients to assess the relevance of nuclear genome mRNAs level of CI subunits to patients' survival, as well as their alterations in gene and expression level in tumors. We presented that the relative expression level of overwhelming majority of the nuclear genes of CI subunits with survival significance (overall survival, relapse free survival, progression free survival, distant metastasis free survival, post progression survival, and first progression), had consistent effects for patients in each type of four tumors separately, including breast cancer, ovarian cancer, lung cancer, and gastric cancer. However, in gene level, frequent cumulative or individual alteration of these genes could not significantly affect patients' survival and the overexpression of the individual gene was not ubiquitous in tumors versus normal tissues. Given that reprogrammed energy metabolism was viewed as an emerging hallmark of tumor, thus tumor patients' survival might potentially to be evaluated by certain threshold for overall expression of CI subunits. Comprehensive understanding of the nuclear genome encoded CI subunits may have guiding significance for the diagnosis and prognosis in tumor patients.

Key words: mitochondrial complex I, genes, tumor, prognosis, KM plotter

According to the United States Cancer Statistics, as the second leading cause of death in the United States, cancer is expected to be the leading cause of death in the next few years [1].

With high heterogeneity and complexity, despite advances in basic and clinical research, prognosis of malignant tumors remains discouraging due to the high postoperative recurrence rate and metastasis [2]. Therefore, the mechanism investigation for tumor incidence and progression, as well as tumor biomarkers identification are imperative and will help to provide better prognostic prediction and individualized treatments for patients.

As was indicated in an analysis of mitochondrial DNA (mtDNA) mutations in the literatures scanned in Medline from 1998 to 2011, in 921 tumor cases where the entire mitochondrial genome had been sequenced, about 56% of all tumors contained at least one mutation, with 28% being in mitochondrial complex I (CI) and 35% in the Dloop [3]. Lu and colleagues reported similar results of mutations in mtDNA encoding CI subunits in a wide range of cancers [4].

Albeit frequent mtDNA mutations being documented in cancer, [5] it is still elusive as to what a role they play in tumorigenesis, and how mitochondrial function can be affected by a specific mtDNA mutation type. Notably, none of the known pathogenic point mutations causing

Abbreviations: NADH – Nicotinamide Adenine Dinucleotide Hydrogen; OXPHOS – Oxidative Phosphorylation; OS – Overall Survival; ROS – Reactive Oxygen Species; CI – Mitochondrial Complex I; mtDNA: mitochondrial DNA; nDNA – nuclear DNA

primary mitochondrial disease is demonstrably associated with tumor [6]. Only recently the concept of heteroplasmy and threshold effect has been introduced to investigate the mtDNA mutations' functional consequences during cancer progression [7, 8].

Pelicano et al hold the view that mtDNA mutations result in downregulation of oxidative phosphorylation (OXPHOS) function, and thus promote tumor survival [9]. As the first and crucial component of mitochondrial respiratory chain, human CI comprises forty nine subunits. Forty two of them are encoded by the nuclear genome and assembled within both the hydrophilic and the hydrophobic arms [10]. While the remaining seven are encoded by mtDNA and constitute the hydrophobic arm, and together with the other seven nuclear gene-encoded ones, they constitute the evolutionarily conserved "core subunits" of CI, which are involved in the electron transfer and proton pumping. Whereas the rest "accessory" subunits may participate in stabilizing CI, regulating the enzymatic activity, preventing the generation of reactive oxygen species (ROS) or protecting the CI from oxidative damage [11, 12].

Unlike the mtDNA, being affected by their distinct structure, replication and hereditary mode, as well as the hazardous environment, nuclear DNA (nDNA) encoding the mitochondria components are more stable. And far few studies had specially focused on mitochondria nDNA in tumor prognosis.

In the current study, for the first time we investigated the prognostic value of individual nuclear genes encoding CI subunits ('all genes' for short where appears following the passage), especially focusing on the seven core subunits genes ('core genes' for short where appears following the passage) as the representative, in different four types of tumor patients, using Kaplan Meier plotter (KM plotter) database. Then the gene-level and expression-level alterations of the 'all genes' and 'core genes' were explored through the cBio Cancer Genomics Portal and Oncomine. Furthermore, the relationship among their survival significances, alterations in gene and expression levels and the tumor reprogrammed energy metabolism was discussed.

Materials and methods

The Kaplan Meier plotter. The Kaplan Meier plotter (http://kmplot.com/analysis/) was capable to assess the effect of 54675/22277 genes on survival using 10188 cancer samples, which included 4142 breast, 1648 ovarian, 2437 lung and 1065 gastric cancer patients with a mean follow-up of 69/40/49/33 months. The background database was established using gene expression data and patients survival information from the Cancer Biomedical Informatics Grid (caBIG, http://cabig.cancer.gov/), Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/), Cancer Genome Atlas (TCGA, http://cancergenome.nih.gov), and the European genome–phenome archive (EGA, https://www.ebi.ac.uk/ega/), which was handled by a MySQL server and integrates gene expression and clinical data simultaneously [13-16].

In order to analyze the prognostic value of a particular gene, the cohorts were divided into two groups according to the median (or upper/lower quartile) expression of the gene. The two groups could be compared in terms of overall survival (OS), and relapse free survival (RFS), and so on [14].

Briefly, the forty-two 'all genes' (NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA13, NDUFA2, NDUFA3, NDUFA4, NDUFA5, NDUFA6, NDUFA7, NDUFA8, NDUFA9, NDUFAB1, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFB1, NDUFB10, NDUFB11, NDUFB2, NDUFB3, NDUFB4, NDUFB5, NDUFB6, NDUFB7, NDUFB8, NDUFB9, NDUFC1, NDUFC2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, and NDUFV3) were individually entered into the database (http://kmplot.com/analysis/) respectively to obtain Kaplan-Meier survival plots in which the number-at-risk was indicated below the main plot. Hazard ratio (and 95 % confidence intervals) and log rank *P* value were calculated and displayed on the webpage.

The cBio Cancer Genomics Portal. The cBio Cancer Genomics Portal (http://cbioportal.org), developed at Memorial Sloan-Kettering Cancer Center (MSKCC), was specifically designed to address the unique data integration issues posed by large-scale cancer genomics projects, including the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) [17]. It provided a web resource for exploring, visualizing, and analyzing multidimensional cancer genomics data, and presents us with graphical summaries of gene-level data from multiple platforms, network visualization and analysis, survival analysis, patient-centric queries, and software programmatic access.

We queried cross-cancer alteration summary for multigene cumulative alteration as well as individual gene changes in 105 cancer studies through the cBio Cancer Genomics Portal (www.cbioportal.org) to investigate the gene-level alterations of CI subunits in cancers.

Oncomine analysis. Oncomine, a cancer microarray database and web-based data-mining platform aimed at facilitating discovery from genome-wide expression analyses, in which differential expression analyses comparing most major types of cancer with respective normal tissues as well as a variety of cancer subtypes and clinical-based and pathology-based analyses were available for exploration [18].

The individual gene of 'all genes' expression level was analyzed using Oncomine. We compared mRNA levels of cancer vs. normal patient datasets. We selected 1.5 fold change, *P* value=0.05, and top 10% gene rank as thresholds.

Results

Significant and consistent prognostic value of individual nuclear genes encoding CI core subunits in different cancer patients' survival. The CI was divided into six sub-complexes,

and their 49 subunits were grouped to comprise their corresponding parts. The characteristics of the seven core subunits encoded by nDNA were shown in (S-Table1 and S-Table2) [9].

Among all the 49 Mitochondrial CI subunits' genes, only the 7 mitochondrial genes were not found in the Kaplan Meier plotter (http://kmplot.com/), probably due to the lack of mtDNA data compared to the nDNA.

We first examined the OS of the seven 'core genes' mRNA expression in www.kmplot.com, for breast cancer, ovarian cancer, lung cancer and gastric cancer respectively. Survival curves were plotted for all patients (Figures 1-3). The desired Affymetrix ID, Cases Number, Hazard Ratio (HR; and 95% confidence intervals) and Log Rank *P* were summarized in Table1.

For breast cancer, high expression of the 'core genes' mRNA except for NDUFS3 and NDUFV2 was found to be correlated to worse OS in all breast cancer patients followed for 25 years (Figure 1A, 1B, Figure 2A, 2B, 2C). While high level of NDUFV2 mRNA was found to be in relation with better OS, and NDUFS3 expression level had no significant OS for all breast cancer patients (Figure 1C; 3A). Integrated with the other 'all genes' in S-Table4, it could be indicated that 24 out of the 42 'all genes' had worse, and 2 better OS for all breast cancer patients (Figure 3E). Moreover, most of the "core genes" had worse OS in luminal B breast cancer patients (S-Table3.1). And, for pathology grade I and/or II patients, majority of the "core genes" predicted worse OS (S-Table3.2).

For ovarian cancer, high expression of NDUFS3, NDUFS7, NDUFS8 and NDUFV1 mRNA were found to be correlated to better OS in all ovarian cancer patients (Figure 1C; Figure 2A-C) However, NDUFS1 and NDUFS2 had the opposite effect. The Figure 3B showed that NDUFV2 expression had no significant OS for all ovarian cancer patients. Together with the other 'all genes' in S-Table4, it could be found that 15 out of the 42 'all genes' had worse, and 6 better OS for ovarian cancer patients (Figure 3E). Additionally, for the pathology grade I and/or II ovarian cancer patients, most of the "core genes" had significant prognostic values, better or worse (S-Table3.3). For serous ovarian cancer patients, almost all the "core genes" expression level could predicted better OS (S-Table3.4).

Table 1. The summary of desired Affymetrix ID, Cases Number, Hazard Ratio (HR; and 95% confidence intervals) and Log Rank P of the individual core gene's OS curves for the four different tumors.

Cancer	Subunits	Affymetrix ID	Survival	Cases-low	Cases-high	HR	95% CI	P-value
Breast cancer	**NDUFS1**	203039_s_at	OS	306	811	1.44	1.09-2.01	0.011
	NDUFS2	208969_at	OS	547	570	1.3	1.03-1.65	0.029
	NDUFS3	201740_at	OS	724	393	1.2	0.94-1.52	0.15
	NDUFS7	211752_s_at	OS	519	598	1.35	1.06-1.72	0.014
	NDUFS8	203190_at	OS	408	709	1.31	1.01-1.68	0.039
	NDUFV1	208714_at	OS	527	590	1.38	1.08-1.76	0.0096
	NDUFV2	202941_at	OS	417	700	0.73	0.57-0.93	0.0097
Ovarian cancer	**NDUFS1**	203039_s_at	OS	503	1079	1.24	1.07-1.43	0.004
	NDUFS2	201966_at	OS	1182	400	1.26	1.09-1.46	0.0023
	NDUFS3	201740_at	OS	934	648	0.84	0.73-0.97	0.014
	NDUFS7	211752_s_at	OS	459	1123	0.85	0.73-0.98	0.025
	NDUFS8	203189_s_at	OS	609	973	0.85	0.75-0.98	0.021
	NDUFV1	208714_at	OS	491	1091	0.84	0.73-0.97	0.017
	NDUFV2	202941_at	OS	428	1154	0.88	0.77-1.02	0.098
Lung cancer	**NDUFS1**	203039_s_at	OS	1339	587	0.88	0.77-1.01	0.069
	NDUFS2	201966_at	OS	1304	622	1.21	1.07-1.38	0.036
	NDUFS3	201740_at	OS	524	1402	1.52	1.3-1.77	1.10E-07
	NDUFS7	211752_s_at	OS	624	1302	1.27	1.1-1.47	0.00093
	NDUFS8	203189_s_at	OS	482	1444	1.76	1.48-2.09	6.90E-11
	NDUFV1	208714_at	OS	1441	485	1.28	1.12-1.48	0.0047
	NDUFV2	202941_at	OS	623	1303	1.64	1.41-1.9	6.90E-11
Stomach cancer	**NDUFS1**	203039_s_at	OS	623	253	0.5	0.4-0.61	4.00E-11
	NDUFS2	201966_at	OS	325	551	0.69	0.58-0.82	1.70E-05
	NDUFS3	201740_at	OS	538	348	0.66	0.55-0.78	3.40E-06
	NDUFS7	211752_s_at	OS	539	337	0.62	0.52-0.74	1.80E-07
	NDUFS8	203189_s_at	OS	588	288	0.74	0.61-0.89	0.0015
	NDUFV1	208714_at	OS	553	323	1.53	1.29-1.82	9.40E-07
	NDUFV2	202941_at	OS	457	419	0.56	0.47-0.67	3.70E-11

Abbreviation: OS: overall survival; HR: hazard ratio; CI: confidence interval; Cases-low/high: patient number of low/high expression of the corresponding gene;

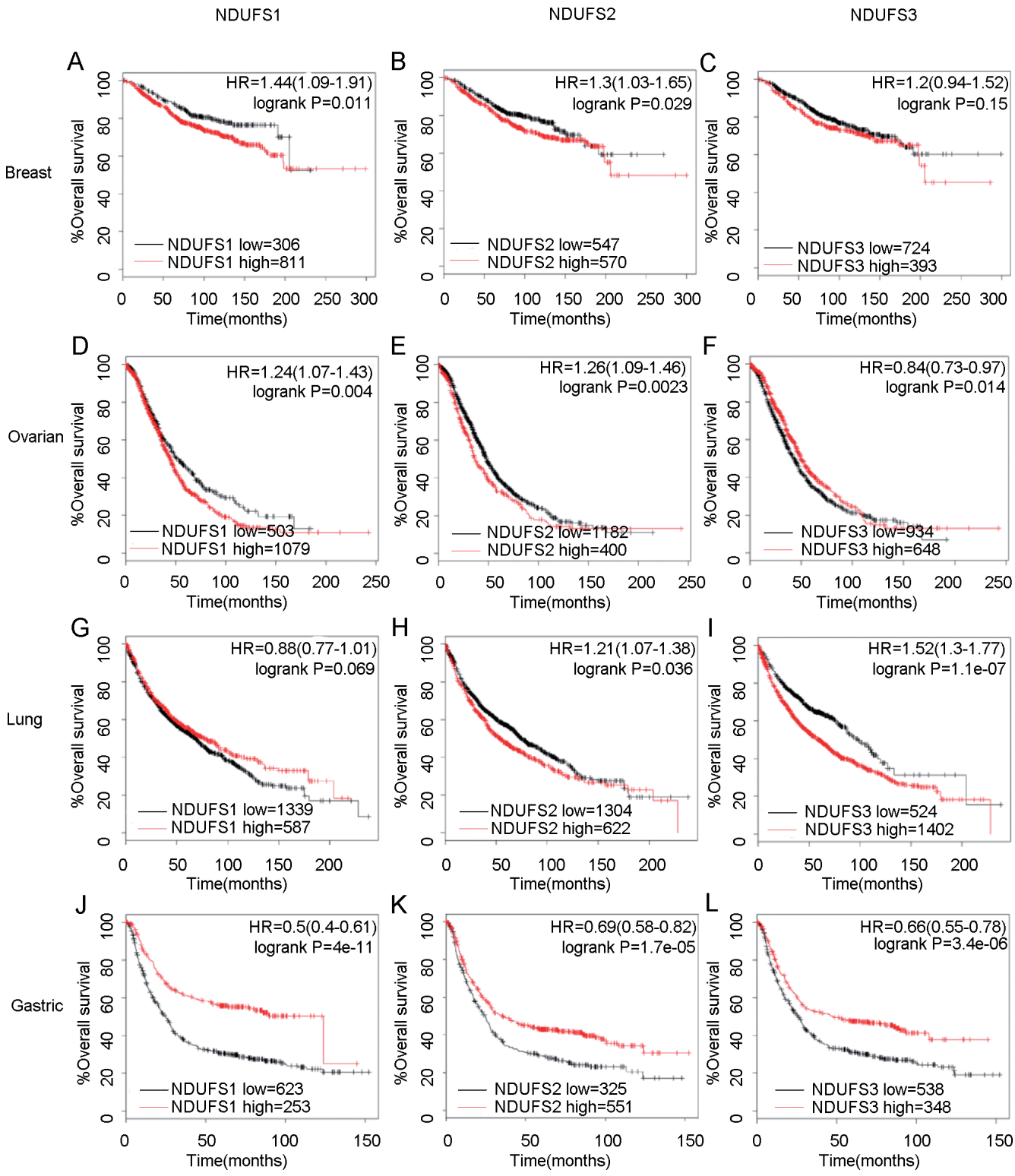


Figure 1. The prognostic value of NDUFS1, NDUFS2, and NDUFS3 expression in four tumor patients

Notes: The desired Affymetrix ID of each gene in each tumor is valid, summarized in Table1; (A-C): Survival curves are plotted for all breast cancer patients (n=1117). (D-F): Survival curves are plotted for all ovarian cancer patients (n=1582). (G-I): Survival curves are plotted for lung cancer patients (n=1926). (J-L): Survival curves are plotted for gastric cancer patients (n=876). Data was analyzed using Kaplan Meier Plotter (www.kmplot.com). Abbreviation: HR: hazard ratio

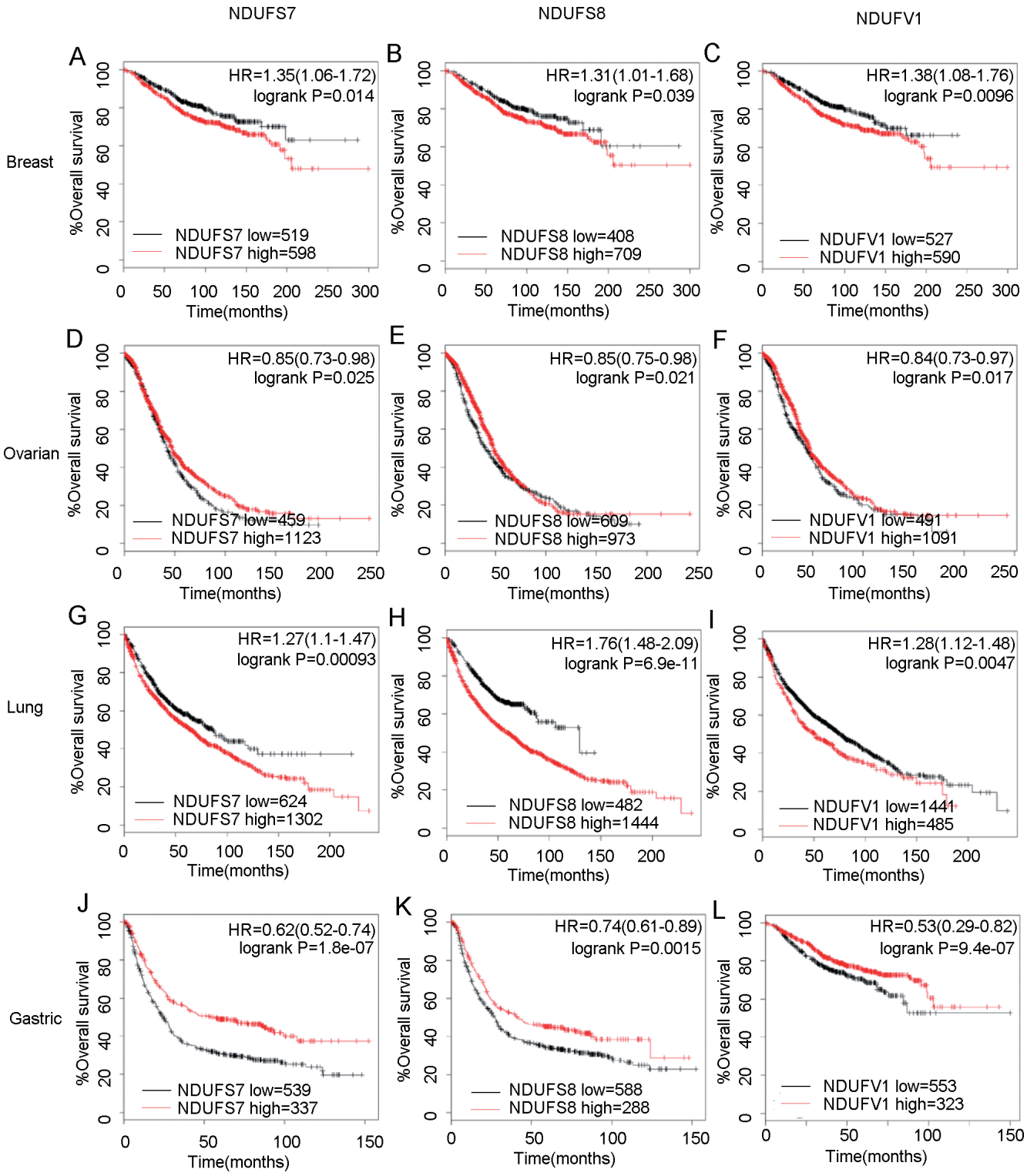


Figure 2. The prognostic value of NDUFS7, NDUFS8, and NDUFV1 expression in four tumor patients

Notes: The desired Affymetrix ID of each gene in each tumor is valid, summarized in Table1; (A-C): Survival curves are plotted for all breast cancer patients (n=1117). (D-F): Survival curves are plotted for all ovarian cancer patients (n=1582). (G-I): Survival curves are plotted for lung cancer patients (n=1926). (J-L): Survival curves are plotted for gastric cancer patients (n=876). Data was analyzed using Kaplan Meier Plotter (www.kmplot.com). Abbreviation: HR: hazard ratio

For lung cancer, the curves showed that high level of the seven 'core genes' apart from NDUFS1, contributed to worse OS in all lung patients (Figures 1B, 1C, 2A-C, 3C). Although NDUFS1 expression above or below the median separated the patients into two groups, the Log Rank *P* value, however, was 0.069. Integrated with the other 'all genes' in S-Table4, it could be indicated that 29 out of the 42 'all genes' had worse, and 2 better OS for lung cancer patients (Figure 3E). Additionally, it could be indicated that, except for NDUFS1 predicting better OS, the other members of the "core genes" could predict

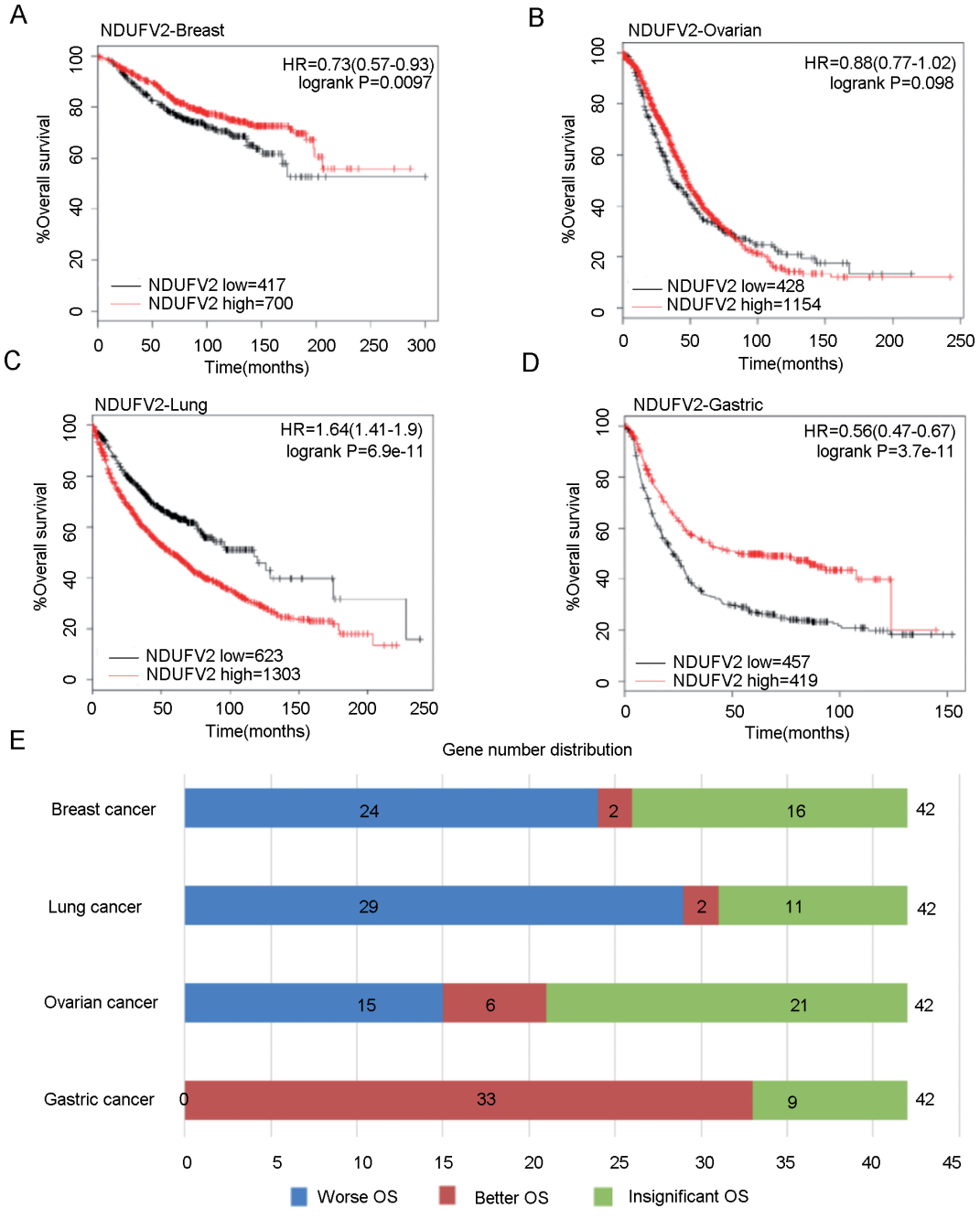


Figure 3. The prognostic value of NDUFV2 expression in four tumor patients and data distribution
Notes: The desired Affymetrix ID of NDUFV2 in each tumor is valid, summarized in Table1; (A-D): Survival curve is plotted for all breast cancer patients (n=1117), all ovarian cancer patients (n=1582), for lung cancer patients (n=1926), and for gastric cancer patients (n=876). Data was analyzed using Kaplan Meier Plotter (www.kmplot.com). (E): Gene number distribution of "all genes" in their prognostic effects in different four types of tumors. The desired Affymetrix ID of each gene in each tumor is valid, summarized in S-Table4. Abbreviation: HR: hazard ratio; OS: overall survival.

worse OS, especially for adenocarcinoma or clinical stage I and II patients, which was in accordance with the NDUFS1 good and others worse for all patients (S-Table3.5 and S-Table3.6). While, whether the patients had smoking history or not, female or male, the "core genes" exhibited similar results as for all patients (S-Table3.7 and S-Table3.8).

What was more meaningful was that, for gastric tumor, the high expression of seven 'core genes', apart from NDUFV1 with worse OS, had identically significant better OS in all gastric cancer patients (Figure 1, 2A-C; 3D). Together with the other 'all genes' in S-Table4, we amazingly found that 33 out of the 42 'all genes' had better OS for gastric cancer patients, none with worse OS (Figure 3E). Furthermore, for well differentiated or clinical stage III and IV patients, the "core genes" could predict better OS, except for NDUFV1 predicting worse OS, which was in accordance with the NDUFV1 worse and others good for all patients (S-Table3.9, S-Table3.10). While, whether the patients were intestinal type or diffuse type according to Lauren Classification, female or male, the "core genes" exhibited similar results as for all patients (S-Table3.11, S-Table3.12).

Additionally, we further queried the 'core genes' for other prognostic indicators in the four tumors, including relapse free survival (RFS), post progression survival (PPS) and distant metastasis survival (DMFS) for breast cancer; progression free survival (PFS), and PPS for ovarian cancer; first progression (FP) and PPS for lung cancer; FP for gastric cancer. Survival curves are plotted for all patients (S-Figure 2-5). The desired Affymetrix ID, Cases Number, Hazard Ratio (HR; and 95% confidence intervals) and Log Rank *P* were summarized in S-Table5**.** For breast cancer, as was shown in S-Figure 1, apart from the genes with no prognostic significance (data not shown) and two (NDUFS8 and NDUFV2) with the opposite prognostic effect, the high expression of all the individual "core genes" was correlated with patients' worse survival, in accordance with the effect of them in the OS**.** For ovarian cancer, as was indicated in S-Figure 2**,** the majority of the 'core genes' high expression had a good prognostic effect for all patients, only with NDUFS1 the opposite effect on FP. For both lung and gastric cancers, apart from the genes with no prognostic significance (not shown), high expression of the 'core genes' had identical prognostic significance to the OS respectively, as was shown in S-Figure 3 and 4.

Briefly, for overwhelming majority of the 'all genes' with significant OS of the CI, relative expression level of the individual gene had consistent prognostic effect for patients in each of the four tumor separately (Figure 3E).

While from another perspective, it could be demonstrated that for the individual gene, its influence on the four type of different tumor patients' survival were inconsistent, as was indicated in Figure 1 (A, D, G, J) for NDUFS1, Figure 1 (B, E, H, K) for NDUFS2, Figure 1 (C, F, I, L) for NDUFS3, Figure 2 (A, D, G, J) for NDUFS7, Figure 2 (B, E, H, K) for NDUFS8, Figure 2 (C, F, I, L) for NDUFV1, and Figure 3 (A-D) for NDUFV2.

Frequent cumulative alterations of the 'all genes' in various cancers while limited influence in patients' survival. Given that the expression level of individual 'all genes' of the CI had significant and identical influence on patients' survival, then we were interested in investigating the genes' alterations between normal and cancer patients in gene and expression-levels.

From the cross-cancer alteration summary for the 'all genes' in 105 studies including various tumors (Figure 4A, 4B), it could be found that 86 of all the studies exhibited gene changes, among which almost half of them manifested that more than 30% of cancer patients burdened alterations of the genes in each of the study. Some individual studies even found that more than 80% patients held abnormal genes**.** Then we tested the 'core genes' in the same 105 studies. From the cross-cancer alteration summary (Figure 4C, 4D), we found that 26 of the 79 studies showing genetic changes exhibited more than 15% of patients bearing gene alterations in each study**.**

Genetic alterations included four types, mutation, deletion, amplification, and multiple alteration, of which the amplification was prominent (Figure 4A, 4C). Additionally, the similar phenomenon occurred in the nuclear genes of the five CI subcomplexes respectively (http://cbioportal.org).

However, an interesting phenomenon was that, albeit significantly and widely amplification of the 'all genes' and 'core genes' in various tumors, only 5 out of the 86 studies for 'all genes' and 4 out of the 79 studies for 'core genes' exhibited that the cumulative alteration of genes had significant influence on the OS or disease free survival (DFS) of the patients, positive or negative (S-Figure 5A-I).

Furthermore, the alterations of individual gene occurred in only 0-15% of patients in each of the 105 studies, most of which less than 5%, and rarely was seen their significant influence on patients' survival (http://cbioportal.org).

In conclusion, cumulative or individual alteration of the 'all genes' in gene level could not significantly affect patients survival.

Overexpression of the individual CI subunits' gene was not ubiquitous in tumors versus normal tissues. From the perspective of molecular genetics, amplification is one of many ways in which a gene can be overexpressed [19].

Therefore, we extracted the summary data on transcript expression for the 'core genes' from the database Oncomine for different tumors, focusing on clinical specimens of cancer vs. normal patient datasets.

As was shown in Figure 5, for each of the seven 'core genes', overwhelming majority of the datasets eligible for the screening condition did not show any expression changes. Although limited, the number of overexpression datasets was more than the downregulation number for most genes. Similar results were demonstrated in the other individual gene of the 'all genes' (S-Table6). For gastric and lung tumors, the 'core genes' expression levels were in approximately accordant with their prognostic effects. While for breast and ovarian cancers, some paradoxical phenomena occurred between the 'core

genes' mRNA levels and their prognostic effects, probably due to some unknown mechanisms, which remained to be elucidated.

Thus we could concluded that it was not ubiquitous for the overexpression of the individual CI subunits' gene in tumors versus normal tissues.

Discussion

As an emerging hallmark of tumor, [20] reprogrammed energy metabolism can be caused by aberration of oncogene and tumor suppressor genes, [21] as well as can result from mutations in mtDNA [4]. Consequently OXPHOS function is disturbed, and ROS production elevated, then DNA damaged and oncogenic signaling pathways activated, which can further promote cancer cell metabolic reprogramming, hypoxia adaptation, uncontrolled growth and metastasis [3]. A vicious circle forms.

Eighty years ago, Warburg observed that tumor cells produced excess lactate in the presence of oxygen due to mitochondrial dysfunction, [22] which was known as the 'Warburg effect' or aerobic glycolysis. However, it is now clear that many tumor cells are capable of performing oxidative phosphorylation, and mitochondrial function is essential for cancer cell viability [23]. The 'reverse Warburg effect' presents that ROS produced from cancer cells can cause adjacent stromal fibroblasts cells mitophagy through inactivating caveolin-1, then lactate production increases in these stromal cells, which can further fuel cancer cell oxidative metabolism [24].

During tumor progression, cancer cells suffer various survival pressures, including the insufficient in nutrient and O_2 supplying, and the survivors must undergo processes

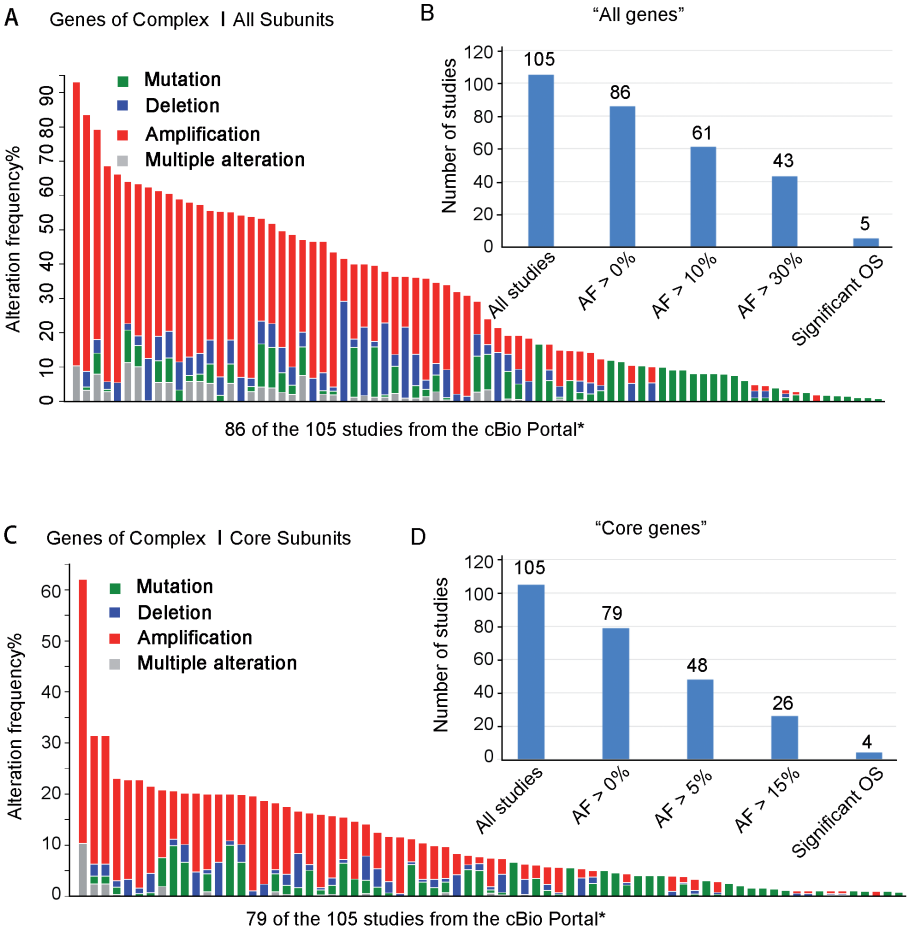


Figure 4. Cross-cancer alteration summary for the 42 "all genes" and 7 "core genes" in 105 studies.
Notes: *Order of the studies was seen in S-Table7; the alterations include mutation, deletion, amplification, and multiple alteration. (A): Cumulative alteration frequency of the "all genes" for each study was indicated. (B): Study number distribution of cumulative alteration frequency of the "all genes". (C): Cumulative alteration frequency of the "core genes" for each study was indicated. Data was analyzed using the cBio Cancer Genomics Portal (http://cbioportal.org). (D): Study number distribution of cumulative alteration frequency of the "core genes". Abbreviation: HR: hazard ratio; MSKCC: memorial sloan-kettering cancer center; TCGA: the cancer genome atlas; ICGC: international cancer genome consortium; AF: alteration frequency.

Figure 5. The "core genes" mRNA expression in different tumor types from Oncomine Notes: This graphic compares the number of datasets that had significant mRNA overexpression (left column, red) and underexpression (right column, blue) of the specified gene in cancer versus normal tissue. The datasets were obtained with the following parameters: *P* value threshold of 0.05, more than 1.5 fold change and top 10% of the gene rank.

of metabolic reprogramming and hypoxic adaptation [25]. In cancer biology, a still open question concerns whether metabolic genes including those encoding CI subunits play the oncogenic or oncosuppressor role [26].

As the first and crucial component of mitochondrial respiratory chain, CI plays a crucial role in several biochemical processes, such as the cellular redox status (NAD^+/NADH ratio and ROS levels) maintenance, mitochondrial membrane potential generation and finally for ATP production [27]. Moreover, for highly proliferating tumor cells, mitochondrial respiratory chain function is indispensable for the synthesis of the pyrimidines that cells used to divide [28]. Thus, disturbance in CI stability or activity not only undermine mitochondrial functions but also destruct cellular homeostasis, inducing widespread consequences such as activation of autophagy or apoptosis [29].

It seems that complete disassembly of CI caused by nucleotide alterations is disadvantageous for the tumor, i.e.

leading to HIF1α destabilization, with adverse effect on hypoxic adaptation [30]. Conversely, those less destructive somatic mutations, such as missense variants, may be maintained in tumor tissue, as they may instead positively promote HIF1α function and contribute to metabolic adaptation through decreasing, but not abrogating, CI function [30].

Oxygenation is actually not necessarily static in tumor cells but instead waves regionally and temporally, ranging from normoxia to hypoxia, due to the instability and chaotic organization of the tumor-associated neovasculature, [31] which exposes the mitochondria in variable oxygen conditions. Thus together with the "reverse Warburg effect", in which two subpopulations of cancer cells function symbiotically to fuel tumor growth, we can conclude that the OXPHOS may functions unstably in different tumors or in different stages or regions of one tumor. Additionally, it is well demonstrated that ROS plays a dose-dependent role in promoting cancer cells surviving or dying [32]. From the above, it is not difficult to understand the result that the relative expression level of the CI 'all genes' had reverse prognosis effect in different cancers, although the exact mechanisms are still to be elucidated. Due to tumor heterogeneity, the CI genes function might also vary, or even antipodal in the different subtypes or different stages of the same type of tumor. Thus precision medicine and individualized treatment were to be taken into account in their future clinical application.

Although the cumulative alterations of 'all genes' accounted for a large proportion in the thousands of patients populations, however, once specific to each person, maybe there were only partial or even individual gene alterations. Additionally, due to the diverse alterations, including mutation, deletion, amplification, and multiple alteration, it was hard to evaluate how the single amplification affect patients' survival.

Being programmed by proliferation-inducing oncogenes, reprogrammed energy metabolism was viewed as an emerging hallmark of tumor [20]. Thus it was proposed that function of the multi-subunits comprising CI might not be affected by only partial or individual subunits alterations, but the 'all genes' might be up or down regulated simultaneously in response to the respiratory chain activity. And the overall expression level and their threshold for survival evaluation of CI subunits for tumor patients were expected for investigation in large scale of population through the same platform by the uniform standards.

Although data from the three independent platforms were not comparative, while, all the three platforms contained as much as thousands of patients' information, to some extent, at least, they were illustrative enough to suggest the conclusions. And further investigation with more perfect design was still needed.

In this study, we presented that for overwhelming majority of the 'all genes' of the CI, relative expression level of the individual gene had consistent prognostic effect for patients in breast, ovarian, lung, and gastric tumors separately. However frequent cumulative or individual alterations of the 'all genes' in gene level could not significantly affect patients' survival. And the overexpression of the individual CI subunits' gene was not ubiquitous in tumors versus normal tissues. Given that reprogrammed energy metabolism was viewed as an emerging hallmark of tumor, thus tumor patients' survival might potentially to be evaluated by the overall expression level of CI subunits.

Comprehensive understanding of the nuclear genome encoded CI subunits may have guiding significance for the diagnosis and prognosis in tumor patients. Based on our study, the discovery of the systematic molecular mechanisms that how CI subunits reflect or lead to different outcomes of tumor patients can pave a way for more effective tumor diagnosis and treatment.

Acknowledgements: This work was supported by the grants from National Natural Science Foundation of China (81272923 and 81302299), Program for New Century Excellent Talents in University (NCET-12-0127).

Supplementary information is available in the online version of the paper.

Notes: All of the supplementary information (S-Tables and S-Figures) legends are indicated in S-legends. S-Table3.1-3.12 were indicated in S-Table3 file, and the other S-Tables were in the S-Tables file.

References

[1] SIEGEL R. L, MILLER K. D, JEMAL A. Cancer statistics, 2015. CA Cancer J Clin. (c) 2015 American Cancer Society. 2015; 1: 5–29.

[2] CHAFFER C. L, WEINBERG RAA. Perspective on cancer cell metastasis. Science. 2011; 6024: 1559–64. http://dx.doi.org/10.1126/science.1203543

[3] IOMMARINI L, CALVARUSO MA, KURELAC I, GASPARRE G, PORCELLI AM. Complex I impairment in mitochondrial diseases and cancer: parallel roads leading to different outcomes. Int J Biochem Cell Biol. Copyright (c) 2012 Elsevier Ltd. All rights reserved. 2013; 1: 47–63.

[4] LU J, SHARMA LK, BAI Y. Implications of mitochondrial DNA mutations and mitochondrial dysfunction in tumorigenesis. Cell Res. 2009; 7: 802–15. http://dx.doi.org/10.1038/cr.2009.69

[5] BRANDON M. and BALDI P. and WALLACE, D. C. Mitochondrial mutations in cancer. Oncogene. 2006; 34: 4647–62. http://dx.doi.org/10.1038/sj.onc.1209607

[6] SCHON EA, DIMAURO S, HIRANO M. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat Rev Genet. 2012; 12: 878–90. http://dx.doi.org/10.1038/nrg3275

[7] GASPARRE G, KURELAC I, CAPRISTO M, IOMMARINI L, and GHELLI A, et al. A mutation threshold distinguishes the antitumorigenic effects of the mitochondrial gene MTND1,

an oncogenes function. Cancer Res. 2011; 19: 6220–29. http://dx.doi.org/10.1158/0008-5472.CAN-11-1042

[8] PARK JS, SHARMA LK, LI H, XIANG R, HOLSTEIN D, et al. A heteroplasmic, not homoplasmic, mitochondrial DNA mutation promotes tumorigenesis via alteration in reactive oxygen species generation and apoptosis. Hum Mol Genet. 2009; 9: 1578–89. http://dx.doi.org/10.1093/hmg/ddp069

[9] PELICANO H, XU RH, DU M, FENG L, SASAKI R, et al. Mitochondrial respiration defects in cancer cells cause activation of Akt survival pathway through a redox-mediated mechanism. J Cell Biol. 2006; 6: 913–23. http://dx.doi.org/10.1083/jcb.200512100

[10] HIRST J. Mitochondrial complex I. Annu Rev Biochem. 2013; 551–75. http://dx.doi.org/10.1146/annurev-biochem-070511-103700

[11] CHEN R, FEARNLEY IM, PEAK-CHEW SY, WALKER JE. The phosphorylation of subunits of complex I from bovine heart mitochondria. J Biol Chem. 2004; 25: 26036–45. http://dx.doi.org/10.1074/jbc.M402710200

[12] HIRST J. Why does mitochondrial complex I have so many subunits? Biochem J. 2011; 2: e1–03. http://dx.doi.org/10.1042/BJ20110918

[13] MIHALY Z, KORMOS M, LANCZKY A, DANK M, BUDCZIES J, et al. A meta-analysis of gene expression-based biomarkers predicting outcome after tamoxifen treatment in breast cancer. Breast Cancer Res Treat. 2013; 2: 219–32. http://dx.doi.org/10.1007/s10549-013-2622-y

[14] GYORFFY B, LANCZKY A, EKLUND AC, et al. An online survival analysis tool to rapidly assess the effect of 22,277 genes on breast cancer prognosis using microarray data of 1,809 patients. Breast Cancer Res Treat. 2010; 3: 725–31. http://dx.doi.org/10.1007/s10549-009-0674-9

[15] GYORFFY B, LANCZKY A, SZALLASI Z. Implementing an online tool for genome-wide validation of survival-associated biomarkers in ovarian-cancer using microarray data from 1287 patients. Endocr Relat Cancer. 2012; 2: 197–208. http://dx.doi.org/10.1530/ERC-11-0329

[16] GYORFFY B, SUROWIAK P, BUDCZIES J, LANCZKY A. Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer. PLoS One. 2013; 12: e82241. http://dx.doi.org/10.1371/journal.pone.0082241

[17] CERAMI E, GAO J, DOGRUSOZ U, GROSS BE, SUMER SO, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. (c) 2012 AACR., 2012; 5: 401–04.

[18] RHODES DR, YU J, SHANKER K, DESHPANDE N, VARAMBALLY, R, et al. ONCOMINE: a cancer microarray database and integrated data-mining platform. Neoplasia. 2004; 1: 1–06. http://dx.doi.org/10.1016/S1476-5586(04)80047-2

[19] MYLLYKANGAS S, KNUUTILA S, MANIFESTATION, MECHANISMS AND MYSTERIES OF GENE AMPLIFICATIONS. Cancer Lett. 2006; 1: 79–89. http://dx.doi.org/10.1016/j.canlet.2005.07.045

[20] HANAHAN D, WEINBERG RA, Hallmarks of cancer: the next generation. Cell. Copyright (c) 2011 Elsevier Inc. All rights reserved. 2011; 5: 646–74.

[21] KOPPENOL WH, BOUNDS PL, DANG CV, Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer. 2011; 5: 325–37. http://dx.doi.org/10.1038/nrc3038

[22] WARBURG O, On the origin of cancer cells. Science. 1956; 3191: 309–14. http://dx.doi.org/10.1126/science.123.3191.309

[23] FREZZA C, GOTTLIEB E, Mitochondria in cancer: not just innocent bystanders. Semin Cancer Biol. 2009; 1: 4–11. http://dx.doi.org/10.1016/j.semcancer.2008.11.008

[24] BONUCCELLI G, WHITAKER-MENEZES D, CASTELLO-CROS R, PAVLIDES S, PESTELL RG, et al. The reverse Warburg effect: glycolysis inhibitors prevent the tumor promoting effects of caveolin-1 deficient cancer associated fibroblasts. Cell Cycle. 2010; 10: 1960–71. http://dx.doi.org/10.4161/cc.9.10.11601

[25] BERETTA S, WOOD JP, DERHAM B, SALA G, and TREMOLIZZO L, et al. Partial mitochondrial complex I inhibition induces oxidative damage and perturbs glutamate transport in primary retinal cultures. Relevance to Leber Hereditary Optic Neuropathy (LHON). Neurobiol Dis. 2006; 2: 308–17. http://dx.doi.org/10.1016/j.nbd.2006.07.016

[26] CAIRNS RA, HARRIS IS, MAK TW, Regulation of cancer cell metabolism. Nat Rev Cancer. 2011; 2: 85–95. http://dx.doi.org/10.1038/nrc2981

[27] ROESTENBERG P, MANJERI GR, VALSECCHI F, SMEITINK JA, WILLEMS PH, et al. Pharmacological targeting of mitochondrial complex I deficiency: the cellular level and beyond. Mitochondrion. Copyright (c) 2011 Elsevier B.V. and Mitochondria Research Society. All rights reserved. 2012; 1: 57–65.

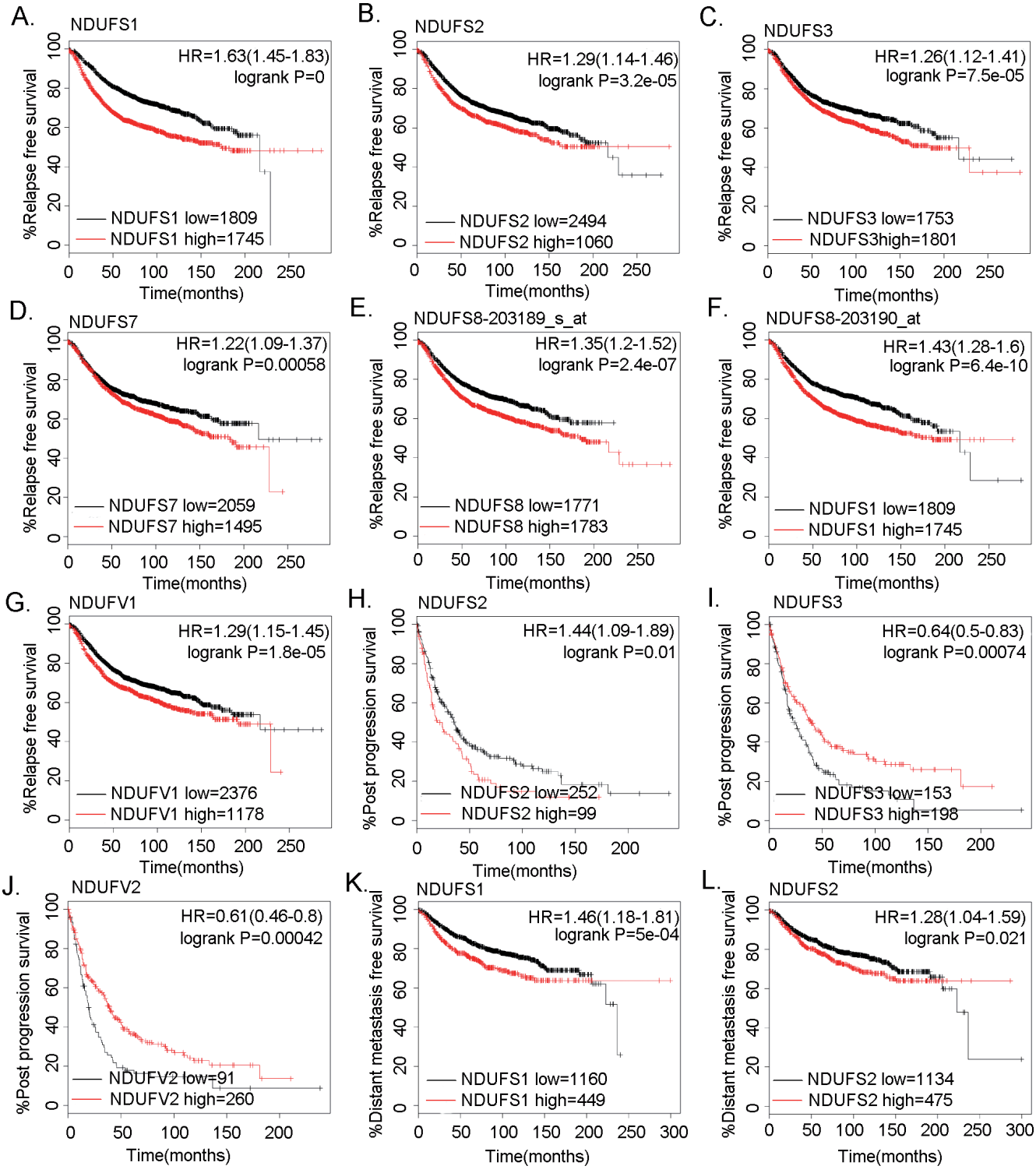
[28] KING MP, KOGA Y, DAVIDSON M, SCHON EA, Defects in mitochondrial protein synthesis and respiratory chain activity segregate with the tRNA(Leu(UUR)) mutation associated with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. Mol Cell Biol. 1992; 2: 480–90. http://dx.doi.org/10.1128/MCB.12.2.480

[29] THOMPSON CB, Metabolic enzymes as oncogenes or tumor suppressors. N Engl J Med. 2009; 8: 813–15. http://dx.doi.org/10.1056/NEJMe0810213

[30] PORCELLI AM, ANGELIN A, GHELLI A, MARIANI E, MARTINUZZI A, et al. Respiratory complex I dysfunction due to mitochondrial DNA mutations shifts the voltage threshold for opening of the permeability transition pore toward resting levels. J Biol Chem. 2009; 4: 2045–52. http://dx.doi.org/10.1074/jbc.M807321200

[31] HARDEE ME, DEWHIRST MW, AGARWAL N, SORG BS, Novel imaging provides new insights into mechanisms of oxygen transport in tumors. Curr Mol Med. 2009; 4: 435–41. http://dx.doi.org/10.2174/156652409788167122

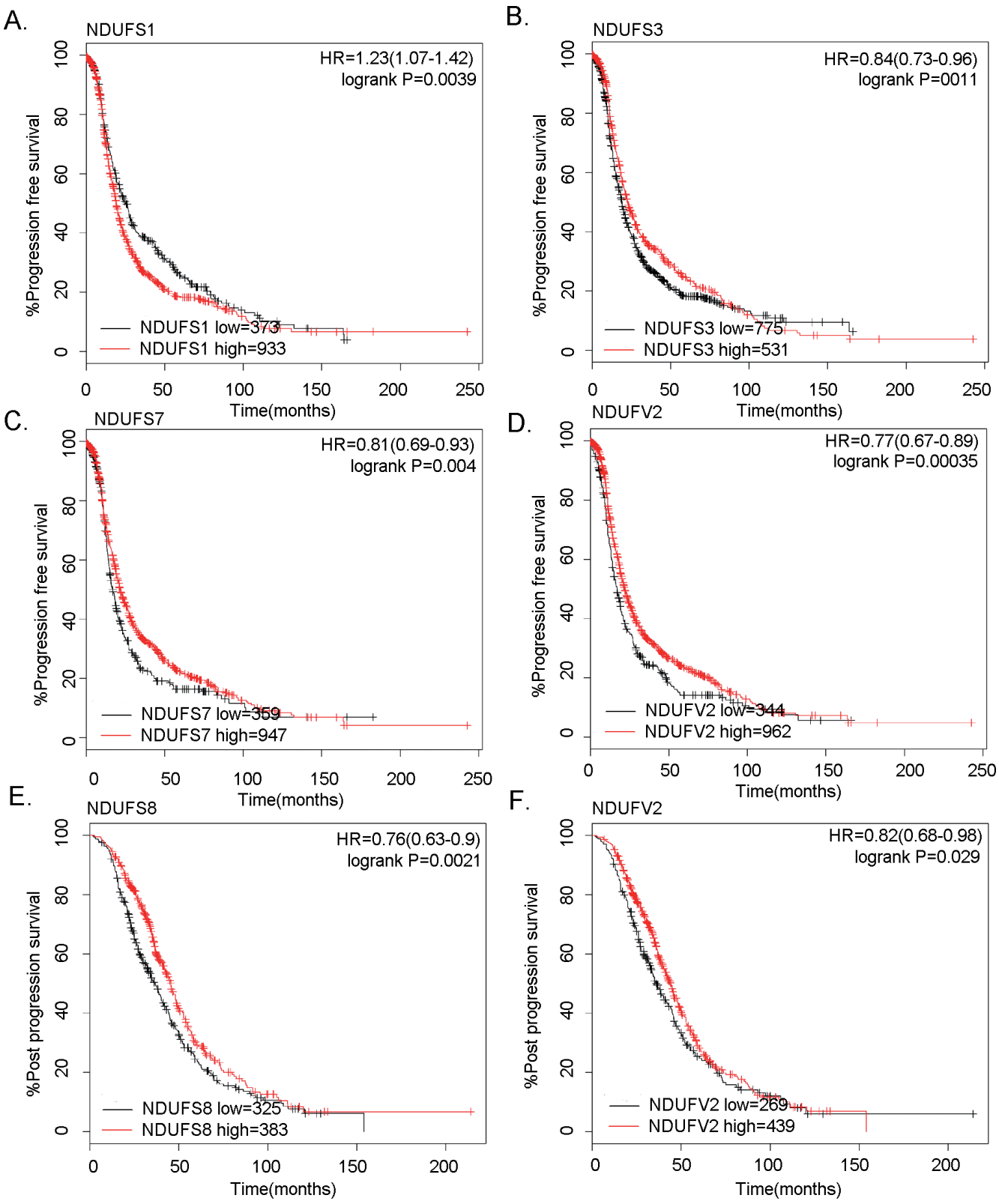
[32] LIOU GY, STORZ P, Reactive oxygen species in cancer. Free Radic Res. 2010; 5: 479–96. http://dx.doi.org/10.3109/10715761003667554



S-Figure 1. The prognostic value of the "core genes" expression in breast cancer patients

Notes: The desired Affymetrix ID of each gene in each tumor is valid, summarized in S-Table5. (a-l): Survival curves are plotted for all breast cancer patients of RFS (n=3554), DMFS (n=1609) and PPS (n=351). Data was analyzed using Kaplan Meier plotter (www.kmplot.com).

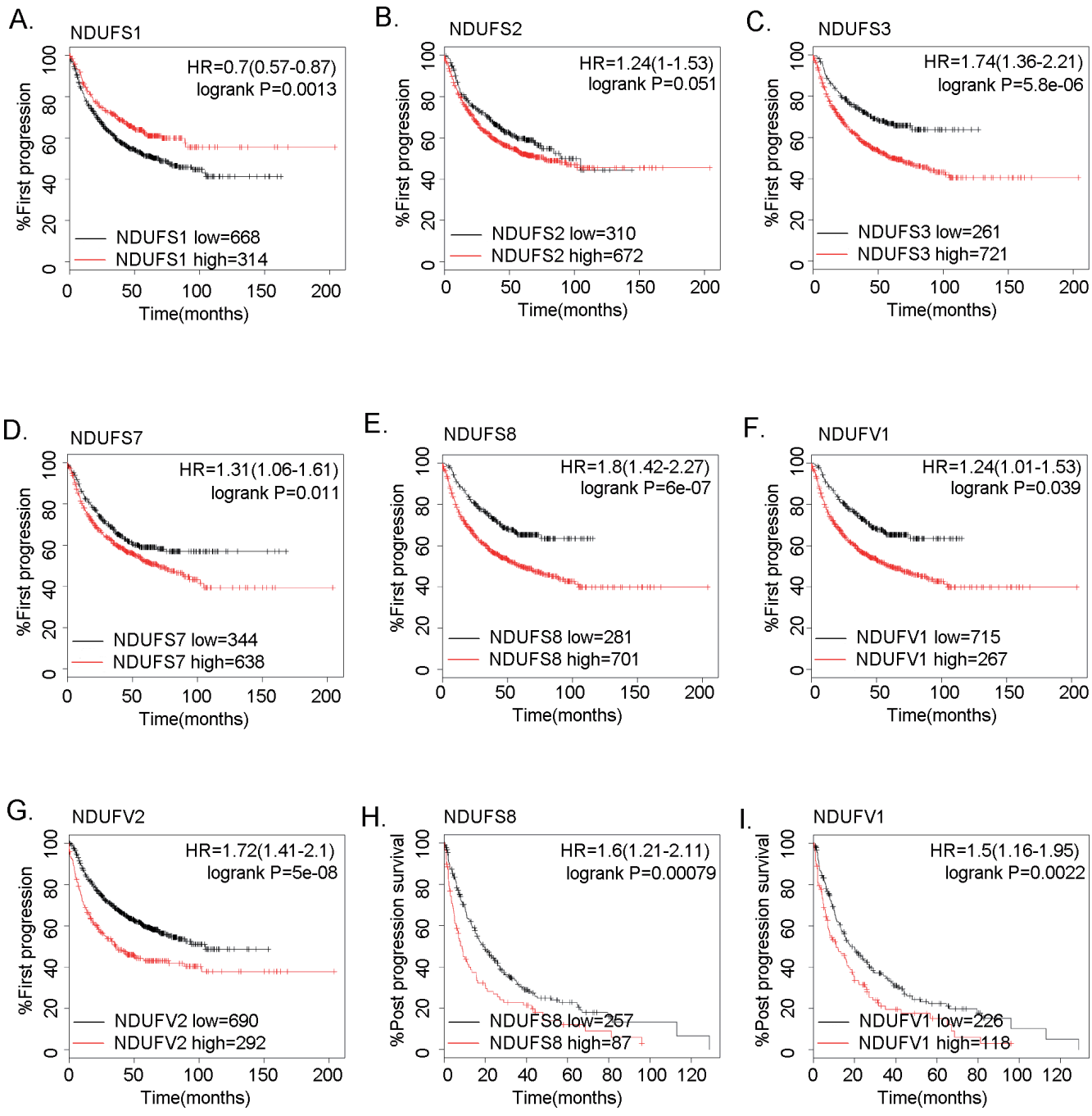
Abbreviation: HR: hazard ratio; RFS: relapse free survival; DMFS: distant metastasis survival; PPS: post progression survival.



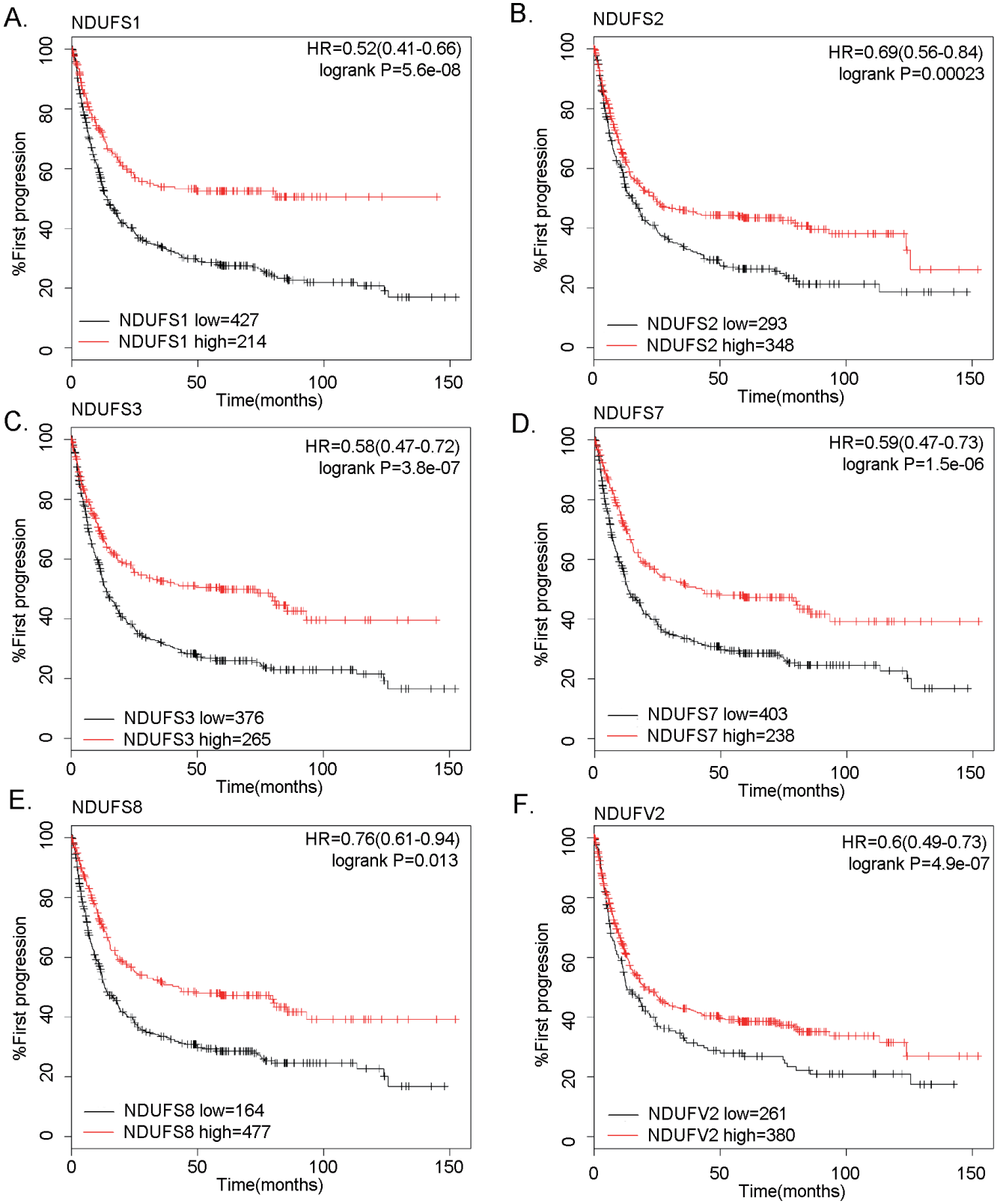
S-Figure 2. The prognostic value of the "core genes" expression in ovarian cancer patients

Notes: The desired Affymetrix ID of each gene in each tumor is valid, summarized in S-Table5. (a-f): Survival curves are plotted for all ovarian cancer patients of PFS (n=1306), and PPS (n=708). Data was analyzed using Kaplan Meier plotter (www.kmplot.com).

Abbreviation: HR: hazard ratio; PFS: progression free survival; PPS: post progression survival.



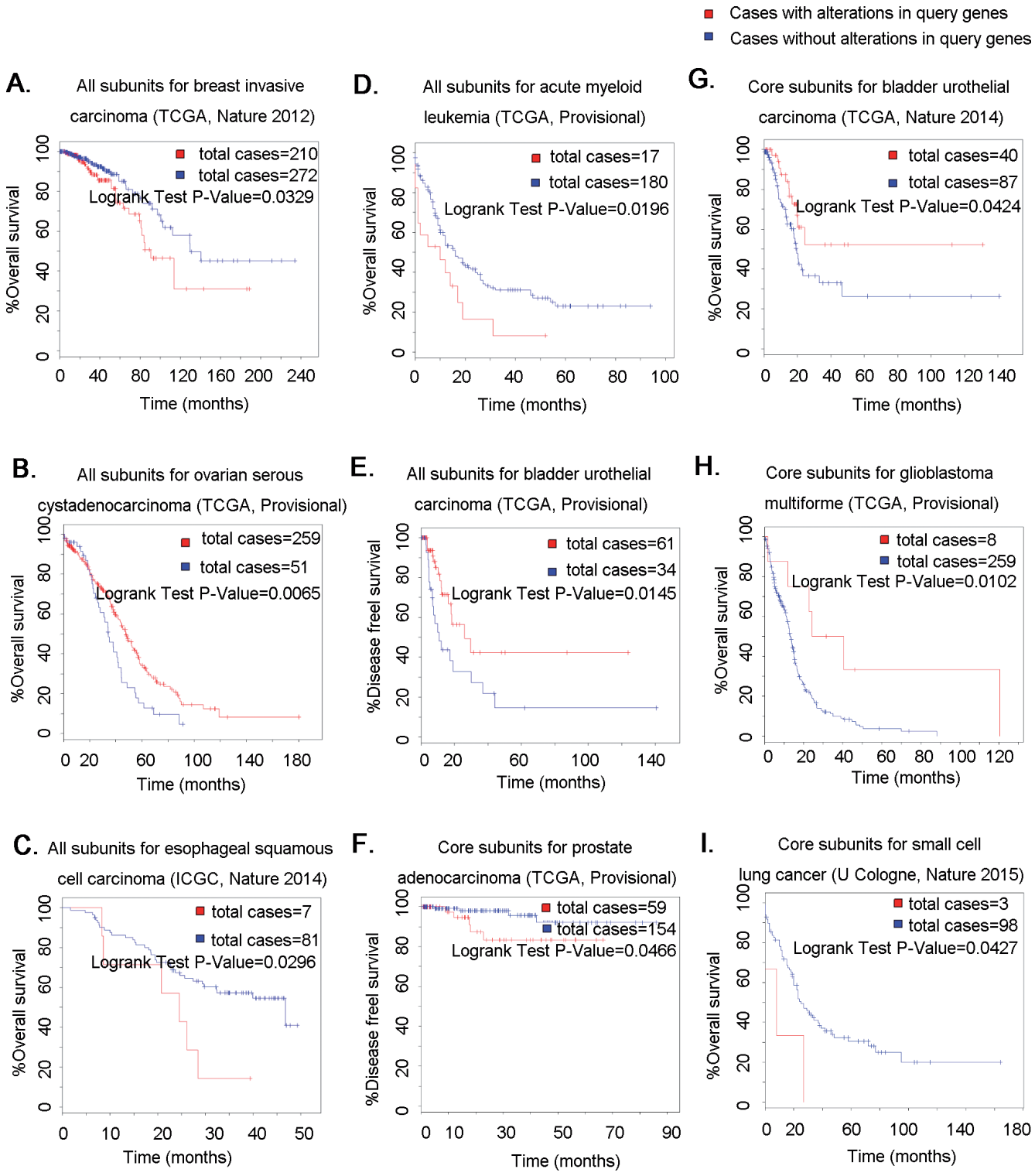
S-Figure 3. The prognostic value of the "core genes" expression in lung cancer patients
Notes: The desired Affymetrix ID of each gene in each tumor is valid, summarized in S-Table5. (a-i): Survival curves are plotted for all lung cancer patients of FP (n=982), and PPS (n=344). Data was analyzed using KM plotter (www.kmplot.com).
Abbreviation: HR: hazard ratio; FP: first progression; PPS: post progression survival.



S-Figure 4. The prognostic value of the "core genes" expression in gastric cancer patients

Notes: The desired Affymetrix ID of each gene in each tumor is valid, summarized in S-Table5. (a-i): Survival curves are plotted for all gastric cancer patients of FP (n=982). Data was analyzed using Kaplan Meier plotter (www.kmplot.com).

Abbreviation: HR: hazard ratio; FP: first progression.



S-Figure 5. The significant prognostic value of the cumulative alteration of "all genes" and "core genes" in limited cancer patients
Notes: Data was analyzed using cBio Cancer Genomics Portal (http://cbioportal.org).
Abbreviation: TCGA: the cancer genome atlas; ICGC: international cancer genome consortium.

S-Table 1. The characteristic of the 14 core subunits of CI

Domain	Homo sapiens	Protein description	Cofactors and TMHs
Nuclear genome, hydrophilic arm	NDUFS1	NADH-ubiquinone oxidoreductase 75 kD subunit, mitochondrial	[2Fe–2S], 2 × [4Fe–4S]
	NDUFV1	NADH-dehydrogenase [ubiquinone] flavoprotein-1, mitochondrial	Flavin, [4Fe–4S]
	NDUFS2	NADH-dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial	
	NDUFS3	NADH-dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial	
	NDUFV2	NADH-dehydrogenase [ubiquinone] flavoprotein-2, mitochondrial	[2Fe–2S]
	NDUFS7	NADH-dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial	[4Fe–4S] (cluster N2)
	NDUFS8	NADH-dehydrogenase	2 × [4Fe–4S]

		[ubiquinone] iron-sulfur protein 8, mitochondrial	
Mitochondri-al genome, hydrophobi-c arm	ND1	NADH-ubiquinone oxidoreductase chain 1	8 TMHs[a]
	ND2	NADH-ubiquinone oxidoreductase chain 2	14 TMHs[b]
	ND3	NADH-ubiquinone oxidoreductase chain 3	3 TMHs
	ND4	NADH-ubiquinone oxidoreductase chain 4	14 TMHs
	ND4L	NADH-ubiquinone oxidoreductase chain 4L	3 TMHs
	ND5	NADH-ubiquinone oxidoreductase chain 5	16 TMHs
	ND6	NADH-ubiquinone oxidoreductase chain 6	5 TMHs

[a]An extra C-terminal TMH is present in T. thermophilus.

[b]Three TMHs are absent from the mammalian enzyme.

S-Table 2. The six sub-complexes of total 49 mitochondrial complex I subunits.

Sub-complex	Subunits
Alpha sub complex	NDUFA1, NDUFA2, NDUFA3, NDUFA4, NDUFA5, NDUFA6, NDUFA7, NDUFA8, NDUFA9, NDUFA10, NDUFA11, NDUFA12, NDUFA13; NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4；NDUFAB1
Beta sub complex	NDUFB1 NDUFB2 NDUFB3 NDUFB4 NDUFB5 NDUFB6 NDUFB7 NDUFB8 NDUFB9 NDUFB10 NDUFB11
Sub complex unknown	NDUFC1, NDUFC2
Flavoprotein 1	NDUFV1, NDUFV2, NDUFV3
Fe-S protein	NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6, NDUFS7, NDUFS8
Mitochondrial encoded NADH dehydrogenase subunit	MT-ND1 MT-ND2 MT-ND3 MT-ND4 MT-ND4L MT-ND5 MT-ND6

S-Table3.1-3.12 were indicated in the S-Table3 file.

S-Table3.1 Correlation of “core genes” with intrinsic subtypes of breast cancer patients.

Gene	Intrinsic Subtypes	Case Number	HR(95%CI)	*P* value
NDUFS1	Basal	668	0.63 (0.28 − 1.42)	0.26
	Luminal A	2069	0.66 (0.36 − 1.2)	0.17
	Luminal B	1166	2.15 (0.82 − 5.68)	0.11
	HER2+	239	1.75 (0.69 − 4.44)	0.24
NDUFS2	Basal	668	0.58 (0.33 − 1.01)	0.051
	Luminal A	2069	0.85 (0.58 − 1.25)	0.41
	Luminal B	1166	1.52 (0.99 − 2.32)	0.053
	HER2+	239	0.32 (0.1 − 1.07)	0.05
NDUFS3	Basal	668	0.33 (0.15 − 0.74)	0.005
	Luminal A	2069	1.26 (0.86 − 1.86)	0.24
	Luminal B	1166	1.6 (1.05 − 2.45)	0.029
	HER2+	239	1.41 (0.65 − 3.08)	0.39
NDUFS7	Basal	668	1.93 (1.11 − 3.36)	0.018
	Luminal A	2069	1.35 (0.87 − 2.1)	0.18
	Luminal B	1166	1.59(1.03 − 2.46)	0.033
	HER2+	239	1.85 (0.86 − 3.95)	0.11
NDUFS8	Basal	668	0.75 (0.43 − 1.31)	0.31
	Luminal A	2069	1.43 (0.95 − 2.15)	0.087
	Luminal B	1166	1.69 (1.07 − 2.67)	0.022
	HER2+	239	0.68 (0.32 − 1.47)	0.33
NDUFV1	Basal	668	0.76 (0.44 − 1.32)	0.33
	Luminal A	2069	1.5 (1.01 − 2.21)	0.042
	Luminal B	1166	1.52 (0.99 − 2.34)	0.056
	HER2+	239	4.51 (1.07 − 19.05	0.025
NDUFV2	Basal	668	1.43 (0.75 − 2.73)	0.28
	Luminal A	2069	0.51 (0.35 − 0.75)	0.00053
	Luminal B	1166	1.51 (0.97 − 2.35)	0.068
	HER2+	239	0.55 (0.25 − 1.21)	0.13

S-Table3.2 Correlation of “core genes” with pathology grades of breast cancer patients.

Gene	Grade	Case Number	HR(95%CI)	*P* value
NDUFS1	I	318	0 (0 − Inf)	0.28
	II	778	3.54(0.34 − 37.02)	0.27
	III	811	0.52 (0.22 − 1.24)	0.13
NDUFS2	I	318	1.69(0.64 − 4.45)	0.28
	II	778	1.64 (1.03 − 2.61)	0.034
	III	811	0.85 (0.57 − 1.27)	0.44
NDUFS3	I	318	3.48 (1.26 − 9.62)	0.01
	II	778	1.53 (0.9 − 2.58)	0.11
	III	811	0.69 (0.45 − 1.08)	0.1
NDUFS7	I	318	6.35(0.84 − 48.15)	0.041
	II	778	2.18 (1.28 − 3.73)	0.0033
	III	811	1.6 (1.06 − 2.42)	0.025
NDUFS8	I	318	4.55(1.75 − 11.81)	0.00066
	II	778	1.8 (1.05 − 3.11)	0.031
	III	811	1.4 (0.87 − 2.26)	0.16
NDUFV1	I	318	4.55(1.68 − 12.34)	0.0011
	II	778	2.09 (1.16 − 3.76)	0.012
	III	811	1.18 (0.78 − 1.79)	0.43
NDUFV2	I	318	1.71 (0.66 − 4.42)	0.26
	II	778	1.42 (0.88 − 2.27)	0.15
	III	811	0.67 (0.45 − 1.01)	0.055

S-Table3.3 Correlation of “core genes” with pathology grades of ovarian cancer patients.

Gene	Grade	Case Number	HR(95%CI)	*P* value
NDUFS1	I	56	0.43 (0.12 − 1.5)	0.17
	II	315	1.52(0.84 − 2.77)	0.16
	III	974	0.89 (0.66 − 1.19)	0.41
NDUFS2	I	56	2.7 (1.03 − 7.04)	0.035
	II	315	0.77(0.56 − 1.04)	0.09
	III	974	1.39 (1.15 − 1.66)	0.00045
NDUFS3	I	56	0.46 (0.18 − 1.18)	0.099
	II	315	0.65 (0.46 − 0.92)	0.015
	III	974	0.82 (0.69 − 0.97)	0.022
NDUFS7	I	56	0.38 (0.14 − 1.02)	0.045
	II	315	0.68 (0.49 − 0.96)	0.026
	III	974	0.88 (0.74 − 1.05)	0.14
NDUFS8	I	56	2.13 (0.84 − 5.41)	0.1
	II	315	0.64 (0.47 − 0.88)	0.0051
	III	974	0.88 (0.72 − 1.06)	0.18
NDUFV1	I	56	3.62 (1.33 − 9.83)	0.007
	II	315	0.69 (0.51 − 0.95)	0.023
	III	974	0.86 (0.71 − 1.02)	0.089
NDUFV2	I	56	0.7 (0.26 − 1.86)	0.47
	II	315	0.68 (0.5 − 0.93)	0.016
	III	974	0.85 (0.71 − 1.03)	0.093

S-Table3.4 Correlation of “core genes” with histologic types of ovarian cancer patients.

Gene	Histologic Type	Case Number	HR(95%CI)	*P* value
NDUFS1	Endometrioid	36	0 (0 − Inf)	0.085
	Serous	1144	1.12 (0.84 − 1.5)	0.43
NDUFS2	Endometrioid	36	0 (0 − Inf)	0.039
	Serous	1144	1.37(1.15 − 1.64)	0.00042
NDUFS3	Endometrioid	36	0 (0 − Inf)	0.11
	Serous	1144	0.84 (0.71 − 0.99)	0.038
NDUFS7	Endometrioid	36	2.7(0.45 − 16.15)	0.26
	Serous	1144	0.88 (0.75 − 1.03)	0.11
NDUFS8	Endometrioid	36	0.36(0.06 − 2.18)	0.25
	Serous	1144	0.84 (0.71 − 1)	0.049
NDUFV1	Endometrioid	36	0 (0 − Inf)	0.15
	Serous	1144	0.86 (0.72 − 1.01)	0.071
NDUFV2	Endometrioid	36	2.62(0.44−15.68)	0.27
	Serous	1144	0.84 (0.71 − 0.99)	0.037

S-Table3.5 Correlation of “core genes” with histologic types of lung cancer patients.

Gene	Histologic Type	Case Number	HR(95%CI)	*P* value
NDUFS1	adenocarcinoma	866	0.39 (0.3 − 0.51)	7.7e−13
	squamous cell carcinoma	675	0.7 (0.5 − 0.98)	0.035
NDUFS2	adenocarcinoma	866	1.35(1.05 − 1.74)	0.018
	squamous cell carcinoma	675	0.91 (0.71 − 1.17)	0.48
NDUFS3	adenocarcinoma	866	2.98 (2.09 − 4.26)	2.3e−10
	squamous cell carcinoma	675	1.29 (0.99 − 1.67)	0.056
NDUFS7	adenocarcinoma	866	1.52 (1.2 − 1.92)	0.00039
	squamous cell carcinoma	675	0.78 (0.6 − 1.03)	0.074
NDUFS8	adenocarcinoma	866	3.29 (2.31 − 4.67)	1.9e−12
	squamous cell carcinoma	675	1.49 (1.1 − 2.02)	0.0092
NDUFV1	adenocarcinoma	866	1.44 (1.14 − 1.82)	0.0018
	squamous cell carcinoma	675	1.31 (1.02 − 1.69)	0.034
NDUFV2	adenocarcinoma	866	2.77 (2.01 − 3.83)	1.1e−10
	squamous cell carcinoma	675	1.23 (0.97 − 1.57)	0.087

S-Table3.6 Correlation of “core genes” with clinical stage of lung cancer patients.

Gene	Clinical Stage	Case Number	HR(95%CI)	*P* value
NDUFS1	I	652	0.34(0.25 − 0.48)	2.8e−11
	II	320	0.58 (0.36 − 0.94)	0.025
	III	70	0.66 (0.31 − 1.39)	0.27
NDUFS2	I	652	1.78 (1.34 − 2.36)	4.9e−05
	II	320	0.7 (0.48 − 1.02)	0.061
	III	70	0.72 (0.39 − 1.32)	0.28
NDUFS3	I	652	2.91 (2.07 − 4.09)	1.4e−10
	II	320	1.53 (1.06 − 2.2)	0.023
	III	70	0.68 (0.37 − 1.26)	0.22
NDUFS7	I	652	3.06 (2.08 − 4.5)	2.6e−09
	II	320	1.64 (1.05 − 2.56)	0.027
	III	70	1.52 (0.86 − 2.7)	0.15
NDUFS8	I	652	3.68 (2.48 − 5.45)	3.4e−12
	II	320	2.28 (1.45 − 3.58)	0.00024
	III	70	1.64 (0.94 − 2.84)	0.076
NDUFV1	I	652	1.97 (1.46 − 2.66)	6.5e−06
	II	320	1.45 (1 − 2.1)	0.046
	III	70	0.71 (0.4 − 1.28)	0.25
NDUFV2	I	652	2.98 (2.21 − 4)	4.2e−14
	II	320	1.77 (1.2 − 2.6)	0.0032
	III	70	1.39 (0.78 − 2.46)	0.26

S-Table3.7 Correlation of “core genes” with gender of lung cancer patients.

Gene	Gender	Case Number	HR(95%CI)	*P* value
NDUFS1	Female	818	0.34 (0.24 − 0.48)	1.4e−10
	Male	1387	0.51 (0.41 − 0.65)	1e−08
NDUFS2	Female	818	1.43 (1.12 − 1.84)	0.0041
	Male	1387	1.08 (0.92 − 1.26)	0.36
NDUFS3	Female	818	1.56 (1.16 − 2.09)	0.0031
	Male	1387	1.54 (1.27 − 1.88)	1.2e−05
NDUFS7	Female	818	1.56(1.19−2.04)	0.0012
	Male	1387	1.26 (1.04 − 1.52)	0.016
NDUFS8	Female	818	1.97(1.43 − 2.72)	2.7e−05
	Male	1387	1.67 (1.35 − 2.05)	1.3e−06
NDUFV1	Female	818	1.41 (1.1 − 1.8)	0.0065
	Male	1387	1.22 (1.04 − 1.43)	0.014
NDUFV2	Female	818	2.18 (1.58 − 3)	1e−06
	Male	1387	1.64 (1.35 − 2)	4.8e−07

S-Table3.8 Correlation of “core genes” with smoking history of lung cancer patients.

Gene	Smoking History	Case Number	HR(95%CI)	*P* value
NDUFS1	Smokers	970	0.62 (0.41 − 0.95)	0.026
	Non-smokers	247	0.34 (0.1 − 1.16)	0.071
NDUFS2	Smokers	970	1.47 (1.19 − 1.81)	0.00032
	Non-smokers	247	1.65 (0.84 − 3.23)	0.14
NDUFS3	Smokers	970	1.58 (1.2 − 2.07)	0.0011
	Non-smokers	247	3.26 (1.84 − 5.78)	1.9e−05
NDUFS7	Smokers	970	0.83 (0.67 − 1.04)	0.099
	Non-smokers	247	3.89 (2.15 − 7.06)	1.5e−06
NDUFS8	Smokers	970	1.61 (1.25 − 2.08)	0.00023
	Non-smokers	247	4.37 (2.28 − 8.38)	1.2e−06
NDUFV1	Smokers	970	1.27 (1.03 − 1.57)	0.027
	Non-smokers	247	2.33 (1.31 − 4.14)	0.0029
NDUFV2	Smokers	970	1.67 (1.33 − 2.09)	7.5e−06
	Non-smokers	247	3.74 (2.06 − 6.79)	3.2e−06

S-Table3.9 Correlation of “core genes” with clinical stage of gastric cancer patients.

Gene	Clinical Stage	Case Number	HR(95%CI)	*P* value
NDUFS1	I	69	0.16 (0.05 − 0.57)	0.0014
	II	145	0.69 (0.36 − 1.36)	0.28
	III	319	0.57 (0.42 − 0.76)	9.3e−05
	IV	152	0.63 (0.43 − 0.93)	0.019
NDUFS2	I	69	0.46 (0.17 − 1.26)	0.12
	II	145	0.62 (0.34 − 1.13)	0.11
	III	319	0.57 (0.42 − 0.77)	0.00024
	IV	152	0.67 (0.46 − 1)	0.047
NDUFS3	I	69	1.68 (0.54 − 5.27)	0.37
	II	145	0.44 (0.24 − 0.8)	0.0062
	III	319	0.72 (0.52 − 0.99)	0.043
	IV	152	0.51 (0.34 − 0.77)	0.001
NDUFS7	I	69	0.36 (0.12 − 1.04)	0.048
	II	145	0.41 (0.2 − 0.84)	0.011
	III	319	0.62 (0.46 − 0.83)	0.0013
	IV	152	0.63 (0.41 − 0.98)	0.038
NDUFS8	I	69	0.45 (0.17 − 1.24)	0.11
	II	145	1.7 (0.94 − 3.08)	0.075
	III	319	0.67 (0.5 − 0.91)	0.011
	IV	152	0.65 (0.43 − 0.98)	0.036
NDUFV1	I	69	2.6 (0.92 − 7.37)	0.064
	II	145	1.9 (0.88 − 4.11)	0.097
	III	319	1.83 (1.37 − 2.44)	2.8e−05
	IV	152	0.71 (0.45 − 1.12)	0.14
NDUFV2	I	69	0.35 (0.12 − 1.03)	0.047
	II	145	0.31 (0.14 − 0.69)	0.0025
	III	319	0.54 (0.39 − 0.74)	0.00011
	IV	152	0.59 (0.4 − 0.87	0.0068

S-Table3.10 Correlation of “core genes” with differentiated degree of gastric cancer patients.

Gene	Differentiation	Case Number	HR(95%CI)	*P* value
NDUFS1	poorly	166	1.4 (0.93 − 2.11)	0.1
	moderately	67	0.73 (0.37 − 1.43)	0.35
	well	32	0.23 (0.08 − 0.7)	0.0047
NDUFS2	poorly	166	1.59 (0.97 − 2.6)	0.065
	moderately	67	0.73 (0.36 − 1.48)	0.38
	well	32	0.39 (0.16 − 0.98)	0.037
NDUFS3	poorly	166	1.46 (0.98 − 2.18)	0.064
	moderately	67	0.46 (0.2 − 1.05)	0.059
	well	32	0.47 (0.19 − 1.21)	0.11
NDUFS7	poorly	166	1.3 (0.81 − 2.07)	0.27
	moderately	67	0.46 (0.24 − 0.9)	0.02
	well	32	0.61 (0.22 − 1.69)	0.34
NDUFS8	poorly	166	0.66 (0.4 − 1.1)	0.11
	moderately	67	0.41 (0.73 − 2.72)	0.3
	well	32	0.25 (0.1 − 0.65)	0.0023
NDUFV1	poorly	166	1.39 (0.93 − 2.08)	0.11
	moderately	67	0.5 (0.26 − 0.96)	0.034
	well	32	2.24 (0.75 − 6.66)	0.14
NDUFV2	poorly	166	0.64 (0.39 − 1.08)	0.091
	moderately	67	0.65 (0.33 − 1.31)	0.23
	well	32	1.93 (0.8 − 4.66)	0.14

S-Table3.11 Correlation of “core genes” with gender of gastric cancer patients.

Gene	Gender	Case Number	HR(95%CI)	*P* value
NDUFS1	Female	244	0.35 (0.22 − 0.58)	1.3e−05
	Male	567	0.49 (0.38 −0.64)	3.2e−08
NDUFS2	Female	244	0.65 (0.46 − 0.93)	0.017
	Male	567	0.65 (0.52 − 0.8)	6.9e−05
NDUFS3	Female	244	0.64 (0.45 − 0.92)	0.016
	Male	567	0.64 (0.52 − 0.8)	9.7e−05
NDUFS7	Female	244	0.44 (0.28 − 0.67)	0.00013
	Male	567	0.65 (0.52 − 0.8)	5.7e−05
NDUFS8	Female	244	0.58 (0.4 − 0.84)	0.0036
	Male	567	0.71 (0.56 − 0. 9)	0.0037
NDUFV1	Female	244	1.53 (1.07 − 2.18)	0.018
	Male	567	1.63 (1.31 − 2.03)	7.6e−06
NDUFV2	Female	244	0.5 (0.34 − 0.74)	0.00038
	Male	567	0.54 (0.44 − 0.67)	2.4e−08

S-Table3.12 Correlation of “core genes” with Lauren Classification of gastric cancer patients.

Gene	Lauren Classification	Case Number	HR(95%CI)	*P* value
NDUFS1	Intestinal	336	0.41 (0.28 − 0.58)	2.5e−07
	Diffuse	248	0.59 (0.42 − 0.84)	0.0026
	Mixed	33	0.5 (0.16 − 1.56)	0.22
NDUFS2	Intestinal	336	0.56 (0.41 − 0.77)	0.00026
	Diffuse	248	0.56 (0.4 − 0.79)	0.00075
	Mixed	33	0.52 (0.17 − 1.54)	0.23
NDUFS3	Intestinal	336	0.52 (0.38 − 0.71)	4.2e−05
	Diffuse	248	0.61 (0.4 − 0.93)	0.021
	Mixed	33	0.39 (0.14 − 1.12)	0.071
NDUFS7	Intestinal	336	0.59 (0.42 − 0.83)	0.0019
	Diffuse	248	0.61 (0.43 − 0.87)	0.0054
	Mixed	33	2.41 (0.67 − 8.61)	0.16
NDUFS8	Intestinal	336	0.65 (0.46 − 0.9)	0.0089
	Diffuse	248	0.8 (0.55 − 1.17)	0.26
	Mixed	33	0.22 (0.06 − 0.8)	0.012
NDUFV1	Intestinal	336	1.93 (1.36 − 2.75)	2e−04
	Diffuse	248	1.31 (0.93 − 1.84)	0.12
	Mixed	33	2.03 (0.73 − 5.62)	0.17
NDUFV2	Intestinal	336	0.41 (0.3 − 0.56)	1.2e−08
	Diffuse	248	0.59 (0.42 − 0.83)	0.0023
	Mixed	33	0.39 (0.12 − 1.24)	0.098

S-Table 4. The summary of desired Affymetrix ID, Cases Number, Hazard Ratio (HR; and 95% confidence intervals) and Log Rank P of the individual all gene's OS curves for the four different tumors.

Cancer	Subunits	Affymetrix ID	Survival	Cases -low	Cases -high	HR	95% CI	P-value
Breast	**NDUFA2**	209223_at	OS	341	776	**1.33**	1.02− 1.47	**0.0368**
cancer	**NDUFA4**	217773_s_at	OS	820	297	**1.54**	1.19 − 1.99	**0.00083**
	NDUFA6	202001_s_at	OS	456	661	**1.51**	1.17 − 2.93	**0.0012**
	NDUFA8	218160_at	OS	354	763	**1.33**	1.02 − 1.74	**0.038**
	NDUFA9	208969_at	OS	547	570	**1.3**	1.03 − 1.65	**0.029**
	NDUFAF2	228355_s_at	OS	361	161	**1.59**	1.09 − 2.32	**0.014**
	NDUFAF4	219006_at	OS	632	485	**1.6**	1.26 − 2.04	**0.0001**
	NDUFAB1	202077_at	OS	685	432	**1.41**	1.11 − 1.78	**0.0049**
	NDUFB2	218200_s_at	OS	444	673	**1.36**	1.06 − 1.74	**0.015**
	NDUFB3	203371_s_at	OS	329	788	**1.33**	1.02 − 1.74	**0.036**
	NDUFB4	218226_s_at	OS	737	380	**1.38**	1.09 − 1.76	**0.0082**
	NDUFB5	203621_at	OS	825	292	**1.33**	1.02 − 1.74	**0.035**
	NDUFB6	203613_s_at	OS	461	656	**1.49**	1.16 − 1.91	**0.0016**
	NDUFB7	211407_at	OS	570	547	**1.32**	1.04 − 1.67	**0.023**
	NDUFB9	222992_s_at	OS	227	295	**1.46**	1.02 − 2.11	**0.04**
	NDUFB11	218320_s_at	OS	516	601	**1.35**	1.06 − 1.72	**0.015**
	NDUFC2	218101_s_at	OS	815	302	**1.34**	1.04 − 1.73	**0.024**

	NDUFS6	203606_at	OS	458	659	**1.8**	1.39 − 2.32	**6.2E−06**
	NDUFV3	226209_at	OS	171	351	**1.59**	1.06 − 2.39	**0.024**
	NDUFB8	201227_s_at	OS	278	839	0.71	0.55 − 0.91	**0.0073**
	NDUFA1	202298_at	OS	532	585	1.26	0.99 − 1.6	0.06
	NDUFA3	218563_at	OS	405	712	1.16	0.9 − 1.5	0.25
	NDUFA11	228690_s_at	OS	309	213	1.39	0.97 − 1.98	0.069
	NDUFA12	223244_s_at	OS	273	249	1.42	0.99 − 2.03	0.052
	NDUFA13	220864_s_at	OS	836	281	1.27	0.98 − 1.65	0.068
	NDUFB10	223112_s_at	OS	338	184	1.22	0.85 − 1.76	0.28
	NDUFC1	203478_at	OS	732	385	1.07	0.84 − 1.37	0.58
	NDUFS5	201757_at	OS	430	687	1.28	0.99 − 1.64	0.057
	NDUFA5	215850_s_at	OS	305	812	0.82	0.63 − 1.06	0.12
	NDUFA7	1557532_at	OS	151	371	0.7	0.48 − 1.01	0.057
	NDUFA10	217860_at	OS	580	537	0.82	0.64 − 1.04	0.093
	NDUFAF1	204125_at	OS	305	812	0.78	0.6 − 1	0.053
	NDUFAF3	209177_at	OS	305	812	0.83	0.64 − 1.07	0.15
	NDUFB1	206790_s_at	OS	836	281	0.85	0.64 − 1.12	0.25
	NDUFS4	209303_at	OS	333	784	0.82	0.64 − 1.05	0.12
Ovarian	**NDUFA1**	202298_at	OS	837	734	1.59	1.3 − 1.94	6.4E−06
cancer	**NDUFA3**	218563_at	OS	1147	435	**1.25**	1.08 − 1.45	**0.0028**
	NDUFA4	217773_s_at	OS	1067	515	**1.25**	1.08 − 1.44	**0.002**
	NDUFA6	202000_at	OS	881	701	**1.18**	1.03 − 1.35	**0.016**

NDUFA9	208969_at	OS	748	834	**1.23**	1.08 − 1.41	**0.0022**
NDUFA13	220864_s_at	OS	949	633	**1.17**	1.03 − 1.34	**0.02**
NDUFAF3	209177_at	OS	1173	409	**1.18**	1.01 − 1.37	**0.034**
NDUFB2	218201_at	OS	500	1082	**1.21**	1.04 − 1.4	**0.011**
NDUFB3	203371_s_at	OS	1184	398	**1.27**	1.1 − 1.48	**0.0015**
NDUFB4	218226_s_at	OS	803	779	**1.15**	1 − 1.31	**0.044**
NDUFB8	201227_s_at	OS	780	802	**1.23**	1.07 − 1.4	**0.0027**
NDUFS4	209303_at	OS	1164	418	**1.21**	1.04 − 1.41	**0.016**
NDUFS6	203606_at	OS	462	1120	**1.17**	1 − 1.36	**0.045**
NDUFA8	218160_at	OS	401	1181	0.81	0.7 − 0.94	**0.0059**
NDUFB6	203613_s_at	OS	298	840	0.82	0.69 − 0.98	**0.028**
NDUFA2	209224_s_at	OS	1071	511	1.13	0.98 − 1.3	0.084
NDUFAF4	219006_at	OS	1163	419	1.14	0.98 − 1.33	0.081
NDUFB5	203621_at	OS	286	852	1.12	0.93 − 1.35	0.22
NDUFB7	202839_s_at	OS	704	878	1.11	0.97 − 1.27	0.13
NDUFA5	201304_at	OS	1175	407	1.12	0.96 − 1.3	0.14
NDUFA7	202785_at	OS	395	1187	0.9	0.77 − 1.04	0.15
NDUFA10	217860_at	OS	1135	447	0.9	0.77 − 1.05	0.18
NDUFAF1	204125_at	OS	437	1145	0.93	0.81 − 1.08	0.36
NDUFB11	218320_s_at	OS	1125	457	0.9	0.77 − 1.05	0.17
NDUFC1	203478_at	OS	587	995	0.91	0.8 − 1.04	0.18
NDUFC2	218101_s_at	OS	941	641	0.92	0.8 − 1.06	0.23

	NDUFS5	201757_at	OS	740	842	0.9	0.79 − 1.03	0.12
	NDUFAB1	202077_at	OS	592	990	1.06	0.92 − 1.21	0.42
	NDUFB1	206790_s_at	OS	643	939	0.89	0.78 − 1.02	0.081
	NDUFA11	no available	OS					
	NDUFA12		OS					
	NDUFAF2		OS					
	NDUFB9		OS					
	NDUFB10		OS					
	NDUFV3		OS					
Lung	**NDUFA1**	202298_at	OS	904	1022	**1.24**	1.09 − 1.41	**0.00093**
cancer	**NDUFA2**	209223_at	OS	671	1255	**1.16**	1.01 − 1.32	**0.032**
	NDUFA3	218563_at	OS	511	1415	**1.57**	1.34 − 1.84	**1.9E−08**
	NDUFA5	215850_s_at	OS	1257	669	**1.29**	1.13 − 1.47	**1.4E−10**
	NDUFA7	202785_at	OS	499	1427	**1.38**	1.18 − 1.62	**5.6E−05**
	NDUFA9	208969_at	OS	1238	688	**1.36**	1.2 − 1.55	**2.3E−06**
	NDUFA10	217860_at	OS	768	1158	**1.55**	1.35 − 1.78	**2.7E−10**
	NDUFA13	220864_s_at	OS	500	1426	**1.55**	1.31 − 1.82	**1.8E−07**
	NDUFAF3	209177_at	OS	540	1386	**1.51**	1.29 − 1.76	**1.9E−07**
	NDUFAF4	219006_at	OS	1257	669	**1.48**	1.3 − 1.68	**1.4E−09**
	NDUFB1	206790_s_at	OS	1369	557	**1.17**	1.02 − 1.34	**0.024**
	NDUFB2	218201_at	OS	645	1281	**1.44**	1.25 − 1.66	**5.30E-07**
	NDUFB3	203371_s_at	OS	485	1441	**1.86**	1.57 − 2.21	**7.1E−13**

NDUFB4	218226_s_at	OS	484	1442	**1.85**	1.55 − 2.2	**2.9E−12**
NDUFB5	203621_at	OS	1342	584	**1.19**	1.04 − 1.36	**0.0095**
NDUFB6	203613_s_at	OS	1144	782	**1.31**	1.15 − 1.49	**2.9E−05**
NDUFB7	202839_s_at	OS	1007	919	**1.31**	1.15 − 1.48	**3.9E−05**
NDUFB8	214241_at	OS	1163	763	**1.23**	1.08 − 1.4	**0.0016**
NDUFB11	218320_s_at	OS	939	987	**1.24**	1.09 − 1.41	**0.00089**
NDUFC1	203478_at	OS	771	1155	**1.22**	1.07 − 1.39	**0.0034**
NDUFC2	218101_s_at	OS	871	1055	**1.43**	1.25 − 1.63	**8.20E-08**
NDUFS4	209303_at	OS	544	1382	**1.95**	1.65 − 2.31	**2.6E−15**
NDUFS5	201757_at	OS	1239	687	**1.25**	1.1 − 1.42	**0.00064**
NDUFAF1	204125_at	OS	1426	500	0.58	0.5 − 0.68	**9.1E−12**
NDUFS6	203606_at	OS	1309	617	0.76	0.66 − 0.88	**0.00014**
NDUFA4	217773_s_at	OS	1442	484	1.09	0.95 − 1.26	0.22
NDUFA6	202001_s_at	OS	1328	598	1.08	0.95 − 1.24	0.24
NDUFAB1	202077_at	OS	592	990	1.06	0.92 − 1.21	0.42
NDUFA8	218160_at	OS	487	1439	0.92	0.79 − 1.06	0.24
NDUFA11	no available	OS					
NDUFA12		OS					
NDUFAF2		OS					
NDUFB9		OS					
NDUFB10		OS					
NDUFV3		OS					

Gastric	**NDUFA1**	202298_at	OS	334	542	**0.63**	0.54 − 0.75	**1.5E−07**
cancer	**NDUFA2**	209224_s_at	OS	336	540	**0.69**	0.58 − 0.82	**2E−05**
	NDUFA3	218563_at	OS	437	439	**0.8**	0.68 − 0.95	**0.012**
	NDUFA4	217773_s_at	OS	237	639	**0.76**	0.63 − 0.92	**0.0039**
	NDUFA5	201304_at	OS	486	390	**0.5**	0.42 − 0.6	**1.6E−14**
	NDUFA6	202001_s_at	OS	623	253	**0.69**	0.57 − 0.84	**0.00018**
	NDUFA7	202785_at	OS	587	289	**0.5**	0.41 − 0.61	**2.2E−12**
	NDUFA8	218160_at	OS	352	524	**0.6**	0.51 − 0.71	**3.8E−09**
	NDUFA13	220864_s_at	OS	454	422	**0.64**	0.54 − 0.76	**3.3E−07**
	NDUFAF1	204125_at	OS	651	225	**0.5**	0.41 − 0.63	**2.1E−10**
	NDUFAF3	209177_at	OS	242	634	**0.75**	0.62 − 0.9	**0.0022**
	NDUFAF4	219006_at	OS	600	276	**0.6**	0.49 − 0.73	**2.20E-07**
	NDUFAB1	202077_at	OS	564	312	**0.67**	0.56 − 0.81	**2.2E−05**
	NDUFB1	206790_s_at	OS	417	459	**0.73**	0.62 − 0.87	**0.00029**
	NDUFB2	218200_s_at	OS	346	530	**0.66**	0.56 − 0.78	**1.7E−06**
	NDUFB3	203371_s_at	OS	656	220	**0.65**	0.53 − 0.81	**0.0001**
	NDUFB4	218226_s_at	OS	496	380	**0.75**	0.63 − 0.89	**0.0011**
	NDUFB5	203621_at	OS	515	361	**0.61**	0.51 − 0.73	**6.4E−08**
	NDUFB6	203613_s_at	OS	551	325	**0.49**	0.41 − 0.6	**8.5E−14**
	NDUFB7	202839_s_at	OS	473	403	**0.56**	0.47 − 0.66	**3E−11**
	NDUFB8	201226_at	OS	250	626	**0.71**	0.59 − 0.85	**0.00022**
	NDUFB11	218320_s_at	OS	428	448	**0.73**	0.62 − 0.86	**0.00026**

NDUFC1	203478_at	OS	472	472	**0.55**	0.46 − 0.66	**1.1E−11**
NDUFC2	218101_s_at	OS	652	224	**0.79**	0.64 − 0.97	**0.021**
NDUFS4	209303_at	OS	457	419	**0.65**	0.55 − 0.77	**5.2E−07**
NDUFS6	203606_at	OS	429	447	**0.78**	0.66 − 0.92	**0.0037**
NDUFA10	217860_at	OS	305	571	0.93	0.78 − 1.11	0.4
NDUFS5	201757_at	OS	628	248	1.26	1.05 − 1.51	0.014
NDUFA9	208969_at	OS	367	509	1.12	0.94 − 1.33	0.19
NDUFA11	no available	OS					
NDUFA12		OS					
NDUFAF2		OS					
NDUFB9		OS					
NDUFB10		OS					
NDUFV3		OS					

S-Table 5. The summary of desired Affymetrix ID, Cases Number, Hazard Ratio (HR; and 95% confidence intervals) and Log Rank P of the individual core gene's other survival curves for the four different tumors.

	Subunits	Affymetrix ID	Survival	Cases-low	Cases-high	HR	95% CI	P-value
Breast cancer	**NDUFS1**	203039_s_at	RFS	1809	1745	1.63	1.45-1.83	0
	NDUFS2	208969_at	RFS	2494	1060	1.29	1.14-1.46	3.20E-05
	NDUFS3	201740_at	RFS	1753	1801	1.26	1.12-1.41	7.50E-05
	NDUFS7	211752_s_at	RFS	2059	1495	1.22	1.09-1.37	0.00058
	NDUFS8	203189_s_at	RFS	1771	1783	1.35	1.2-1.52	2.40E-07
	NDUFS8	203190_at	RFS	1809	1745	1.43	1.28-1.6	6.40E-10
	NDUFV1	208714_at	RFS	2376	1178	1.29	1.15-1.45	1.80E-05
	NDUFS2	208969_at	PPS	252	99	1.44	1.09-1.89	1.00E-02
	NDUFS3	201740_at	PPS	153	198	0.64	0.5-0.83	0.00074
	NDUFV2	202941_at	PPS	91	260	0.61	0.46-0.8	0.00042
	NDUFS1	203039_s_at	DMFS	1160	449	1.46	1.18-1.81	5.00E-04
	NDUFS2	208969_at	DMFS	1134	475	1.28	1.04-1.59	0.021
Ovarian cancer	**NDUFS1**	203039_s_at	PFS	373	933	1.23	1.07-1.42	0.0039
	NDUFS3	201740_at	PFS	775	531	0.84	0.73-0.96	0.011
	NDUFS7	211752_s_at	PFS	359	947	0.81	0.69-0.93	0.004
	NDUFV2	202941_at	PFS	344	962	0.77	0.67-0.89	0.00035
	NDUFS8	203189_s_at	PPS	325	383	0.76	0.63-0.9	0.76

	NDUFV2	202941_at	PPS	269	439	0.82	0.68-0.98	0.029
Lung	**NDUFS1**	203039_s_at	FP	668	314	0.7	0.57-0.87	0.0013
cancer	**NDUFS2**	201966_at	FP	310	672	1.24	1-1.53	0.051
	NDUFS3	201740_at	FP	261	721	1.74	1.36-2.21	5.80E-06
	NDUFS7	211752_s_at	FP	344	638	1.31	1.06-1.61	0.011
	NDUFS8	203189_s_at	FP	281	701	1.8	1.42-2.27	6.00E-07
	NDUFV1	208714_at	FP	715	267	1.24	1.01-1.53	0.039
	NDUFV2	202941_at	FP	690	292	1.72	1.41-2.1	5.00E-08
	NDUFS8	203189_s_at	PPS	257	87	1.6	1.21-2.11	0.00079
	NDUFV1	208714_at	PPS	226	118	1.5	1.16-1.95	0.0022
Gastric	**NDUFS1**	203039_s_at	FP	427	214	0.52	0.41-0.66	5.60E-08
cancer	**NDUFS2**	201966_at	FP	293	348	0.69	0.56-0.84	0.00023
	NDUFS3	201740_at	FP	376	265	0.58	0.47-0.72	3.80E-07
	NDUFS7	211752_s_at	FP	403	238	0.59	0.47-0.73	1.50E-06
	NDUFS8	203189_s_at	FP	164	477	0.76	0.61-0.94	0.013
	NDUFV2	202941_at	FP	261	380	0.6	0.49-0.73	4.90E-07

S-Table 6. The "all genes" mRNA expression in different tumor types from Oncomine.

	Screening conditions							
Subunits	**Analysis Type**	**Data type**	**P-value threshold**	**Gene rank (top%)**	**Fold change threshold**	**Total number of Datasets**	**Number of overexpression-datasets**	**Number of underexp-ression datasets**
NDUFA1	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	327	10	6
NDUFA2	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	292	20	2
NDUFA3	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	301	17	5
NDUFA4	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	316	11	13
NDUFA5	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	351	10	9
NDUFA6	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	280	17	6
NDUFA7	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	336	14	5
NDUFA8	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	250	14	5
NDUFA9	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	351	18	1
NDUFA10	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	293	8	5
NDUFA11	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	194	11	2
NDUFA12	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	199	10	0
NDUFA13	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	295	16	4
NDUFAF1	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	325	6	11

NDUFAF2	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	181	12	2
NDUFAF3	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	295	9	10
NDUFAF4	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	283	8	7
NDUFAB1	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	296	8	0
NDUFB1	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	294	13	3
NDUFB2	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	295	14	3
NDUFB3	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	304	7	1
NDUFB4	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	267	7	4
NDUFB5	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	331	13	0
NDUFB6	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	333	6	2
NDUFB7	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	363	19	4
NDUFB8	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	305	11	10
NDUFB9	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	162	18	2
NDUFB10	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	220	6	4
NDUFB11	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	268	20	2
NDUFC1	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	322	12	7
NDUFC2	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	270	11	1
NDUFS4	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	338	5	5
NDUFS5	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	333	17	2
NDUFS6	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	315	18	3
NDUFV3	**cancer VS normal**	**mRNA**	**0.01**	**10%**	**2**	237	6	6

S-Table 7. Order of the studies in Fig4A and Fig4C (from left to right)

Order	ALL genes	Core genes
1	Breast(BCCRC Xenograft)	Breast(BCCRC Xenograft)
2	Ovarian(TCGA)	Pancreas（UTSW）
3	Lung squ(TCGA)	Bladder(TCGA pub)
4	Pancreas（UTSW）	Bladder(TCGA)
5	Ovarian(TCGA pub)	Breast(TCGA)
6	Esophagus(TCGA)	Esophagus(TCGA)
7	NCI-60	Liver(TCGA)
8	Lung squ(TCGA pub)	Ovarian(TCGA)
9	CCLE(Novartis/Broad 2012)	NCI-60
10	Bladder(TCGA)	Uterine(TCGA)
11	Bladder(TCGA pub)	Gastric(TCGA)
12	Prostate(MICH)	CCLE(Novartis/Broad 2012)
13	Head & neck(TCGA pub)	Lung adeno(TCGA)
14	Head & neck(TCGA)	MPNST(MSKCC)
15	Lung adeno(TCGA pub)	Uterine(TCGA)
16	Uterine CS(TCGA)	Gastric(TCGA pub)
17	Lung adeno(TCGA)	Bladder(MSKCC 2012)
18	Breast（TCGA pub2015）	Sarcoma(TCGA)
19	Sarcoma(TCGA)	Lung adeno(TCGA pub)
20	Breast(TCGA)	Head & neck(TCGA pub)

21	Gastric(TCGA pub)	ACyCle(MSKCC)
22	Gastric(TCGA)	Lung squ(TCGA)
23	Cervical(TCGA)	Breast(TCGA pub)
24	Prostate(SU2C)	Head & neck(TCGA)
25	Melanoma(TCGA)	Melanoma(TCGA)
26	MPNST(MSKCC)	Prostate(SU2C)
27	Liver(TCGA)	ucs（Johns Hopkins 2014）
28	Breast(TCGA pub)	Cervical(TCGA)
29	DLBC(TCGA)	Uterine CS(TCGA)
30	Uterine(TCGA)	Ovarian(TCGA pub)
31	ACyCle(MSKCC)	Sarcoma(MSKCC)
32	Uterine(TCGA pub)	Lung squ(TCGA pub)
33	Prostate(TCGA)	Lung adeno(Broad)
34	ACC(TCGA)	Prostate(MICH)
35	Prostate(TCGA 2015)	Pancrease(TCGA)
36	ccRCC(TCGA)	DLBC(TCGA)
37	Pancrease(TCGA)	Colorectal(TCGA pub)
38	Lung adeno(Broad)	Colorectal(TCGA)
39	Glioma(TCGA)	PCPG(TCGA)
40	Uveal Melanoma（TCGA）	Prostate(TCGA)
41	Bladder(MSKCC 2012)	Melanoma(Yale)
42	Sarcoma(MSKCC)	Prostate(TCGA 2015)

43	Colorectal(TCGA)	Liver(AMC)
44	Colorectal(TCGA pub)	ACC(TCGA)
45	Prostate(Broad/Cornell 2013)	Glioma(TCGA)
46	pRCC(TCGA)	Colorectal(Genentech)
47	ccRCC(TCGA pub)	Prostate(Broad/Cornell 2013)
48	Prostate(MSKCC 2010)	pRCC(TCGA)
49	ucs（Johns Hopkins 2014）	Melanoma(Broad)
50	Colorectal(Genentech)	Gastric(UHK)
51	chRCC(TCGA)	ccRCC(TCGA)
52	PCPG(TCGA)	Bladder(BGI)
53	Liver(AMC)	Melanoma(Broad/DFCI)
54	GBM(TCGA)	Gastric(Pfizer UHK)
55	GBM(TCGA 2013)	Prostate(MSKCC 2010)
56	chRCC(TCGA)	ccRCC(TCGA pub)
57	Lung SC(JHU)	GBM(TCGA)
58	Melanoma(Broad)	chRCC(TCGA)
59	Lung SC(CLCGP)	GBM(TCGA 2013)
60	AML(TCGA pub)	Lung SC（UCOLOGNE）
61	AML(TCGA)	Uveal Melanoma（TCGA）
62	Melanoma(Yale)	Cholangiocarcinoma(JHU)
63	Bladder(BGI)	Esophagus(Broad)
64	Gastric(UHK)	Breast(BCCRC)

65	Head & neck(Broad)	chRCC(TCGA)
66	Melanoma(Broad/DFCI)	Head & neck(Broad)
67	Gastric(Pfizer UHK)	Esophagus(ICGC)
68	Esophagus(ICGC)	AML(TCGA)
69	Esophagus(Broad)	AML(TCGA pub)
70	Lung SC（UCOLOGNE）	ccRCC(BGI)
71	Ewing sarcoma（DFCI）	Thyriod(TCGA pub)
72	Breast(Sanger)	Thyriod(TCGA)
73	Thyriod(TCGA pub)	Breast(Broad)
74	Thyriod(TCGA)	Prostate(MSKCC 2014)
75	Breast(Broad)	Ewing sarcoma（DFCI）
76	GBM(TCGA 2008)	Prostate(Broad/Cornell 2012)
77	Prostate(Broad/Cornell 2012)	MBL(ICGC)
78	Cholangiocarcinoma(JHU)	nccRCC（genentech 2014）
79	Prostate(MSKCC 2014)	Breast(sanger)
80	NPC(Singapore)	
81	Breast(BCCRC)	
82	MM(Broad)	
83	nccRCC（genentech 2014）	
84	ccRCC(BGI)	
85	Pancreas(ICGC)	
86	MBL(ICGC)	