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Identification of Prognostic Gene Signatures for Survival of Patients With Phaeochromocytoma, Paraganglioma, and Other Tumor Types

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Abstract

Background/Aim: Tumor treatments remain unsatisfactory, as many patients continue to die despite therapy. There is an urgent need for novel drug targets, particularly for rare tumors. In this study, we sought to identify genes with prognostic significance for survival in patients with phaeochromocytoma or paraganglioma. We also examined whether these genes are relevant in other tumor entities.

Patients and Methods: We mined the TCGA-based KM Plotter and studied 186 risk genes for phaeochromocytoma and paraganglioma.

Results: Using Kaplan-Meier statistics, we performed 3,163 calculations based on 7,489 tumor biopsies and identified a 2-gene signature for phaeochromocytoma/paraganglioma (AQP4, FAM84H). Since the 186 risk genes are not exclusively related to the development of phaeochromocytoma/paraganglioma alone, we also investigated their prognostic relevance in 17 other tumor types. A clustered 12-gene signature has been found common in four other tumor entities (liver hepatocellular carcinoma, renal clear cell carcinoma, renal papillary cell carcinoma, lung adenocarcinoma). This signature consisted of *BUB1, BUB1B, CDK1, CENPA, CKAP2L, IQGAP3, MKI67, NDC80, PBK, RRM2, TOP2A*, and *TTK.*

Conclusion: Our analysis provides a basis for the development of a novel prognostic test to predict the survival time of patients.

Keywords: Kaplan-Meier analysis, paraganglioma, phaeochromocytoma, prognostic value, survival analysis, The Cancer Genome Atlas (TCGA).

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Introduction

Neuroendocrine tumors belong to the group of cancers that frequently metastasize and that are difficult to treat with anticancer drugs. They are derived from the neuroectoderm and some neuroendocrine tumor types of secret hormones (*e.g.*, adrenalin, noradrenalin). Phaeochromocytomas and paragangliomas are rare tumors mainly deriving from neuroectodermic adrenal tissue. Those deriving from sympathetic paraganglia are termed paragangliomas. While most phaeochromocytomas and paragangliomas represent benign adenomas, some are malignant carcinomas, indicating that these tumors may have specific genetic alterations determining some for more benign and some others for more malignant phenotypes. However, even benign tumors can exert detrimental effects, *e.g.*, paragangliomas closely located to cranial nerves and vasculature may lead to their compression or invasion (1). Phaeochromocytomas and paragangliomas are usually treated by surgery and radiotherapy rather than by drugs.

Gene signatures are in many cases used to select a group of patients for whom a particular treatment will be effective. The use of gene signatures to stratify tumors into prognostic and predictive subtypes is rapidly growing, and studies have shown increased numbers of gene signatures in the more common cancers, yet for rare and uncommon cancers gene signatures have not been studied in detail. Genetic profiling of phaeochromocytomas and paragangliomas revealed a considerably high genetic instability and quite a number of risk genes (2-7). In the present investigation, our study focused on identifying genes and gene signatures with prognostic relevance for patient survival as prognostic prediction models and tools could contribute significantly to the clinical treatment of patients. Current research is also focused on the identification of novel therapeutic targets and identifying subjects for optimal benefits of specific treatments.

The aim of the present study was to identify gene novel signatures that are useful as prognostic tools for the survival time of cancer patients. Therefore, we investigated the gene expressions deposited in the Cancer Genome Atlas (TCGA) database (8). We identified two gene signatures which have not been described before. In addition, the genes of these gene signatures may also serve as new targets for the development of novel targeted drugs in the future (9).

Patients and Methods

Compilation of risk genes. For the appropriate literature selection, we followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline (https://www.prisma-statement.org) (Figure 1). We screened the PubMed Literature database with the keywords "risk gene AND phaeochromocytoma AND review" as well as "risk gene AND paraganglioma AND review". At total of 174 publications were identified for phaeochromocytoma, and 145 articles for paraganglioma. These papers were visually inspected and 21 publications containing compilations of risk genes were selected for our own compilation of 186 genes (Table I). These genes are described in the literature to contribute to the development and progression of phaeochromocytoma. The expression of these genes was reported by the Cancer Genome Atlas (TCGA) (9).

Kaplan-Meier survival statistics. The Kaplan-Meier statistics is a standard technique to calculate the survival probability of cancer patients according to their clinical, biochemical, or molecular parameters. In the present study, we used the KM Plotter algorithm (https://komplot.com/analysis) as described (10, 11). To avoid type I errors of multiple comparisons, we used false discovery rate corrections (12) with a cut-off of 5%. The database of the KM Plotter consists of 7,489 biopsies from different tumor types from TCGA, including phaeochromocytoma and paraganglioma.

Our workflow is shown in Figure 2. We started by analyzing all 186 genes in patients with phaeochromocytoma/paraganglioma or 17 other tumor types, respectively, using Kaplan-Meier statistics. Two correlating genes in phaeochromocytoma/paraganglioma and 12 commonly correlating genes in four other tumor

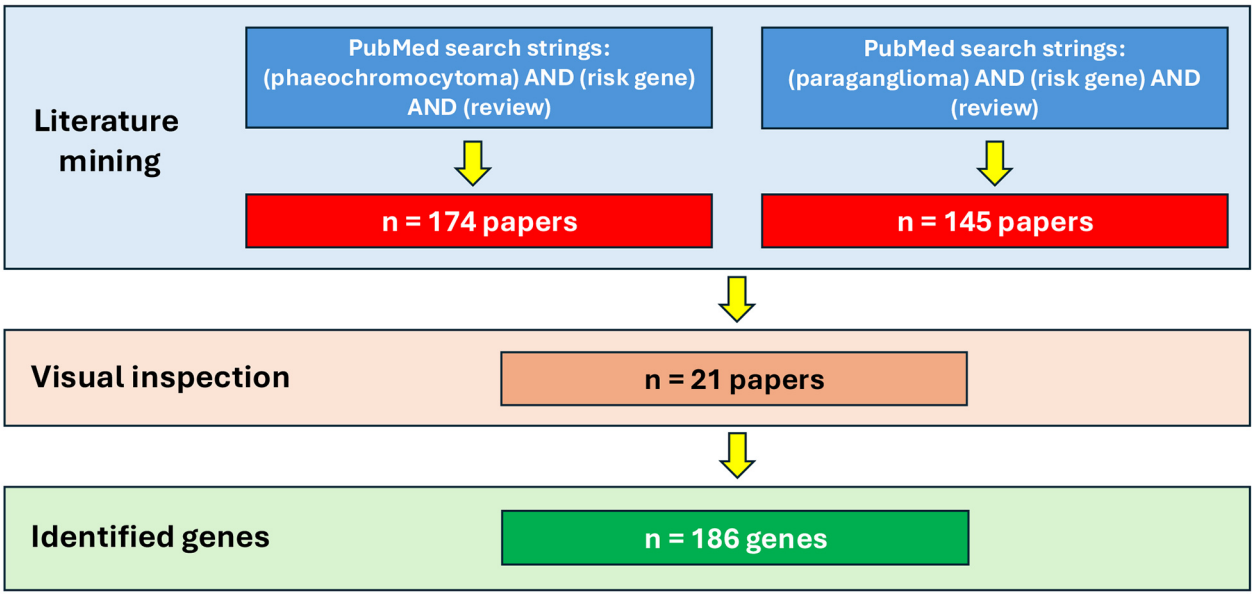

Figure 1. *Workflow to identify relevant risk genes for phaeochromocytoma and paraganglioma from PubMed according to the PRISMA guideline.*

types were subsequently subjected to combined Kaplan-Meier statistics. The prognostic relevance of these 2-gene and 12-gene signatures were determined for either all tumors or those subsets of tumors with high mutational rates. This was done to prove whether the gene signatures were also of prognostic value for survival in highly mutated tumors that are usually more aggressive than those with low mutational loads.

Results

Analyses of phaeochromocytoma- and paraganglioma-related risk genes with the survival times of patients. We performed Kaplan-Meier statistical calculations of 186 genes for 178 biopsies from phaeochromocytoma and paraganglioma (Table I). Surprisingly, the mRNA expression of only two genes (*AQP4* and *FAM83H*) significantly correlated with a worse prognosis of patients, *i.e.*, shorter overall survival times ($p<0.05$ and FDR<5%) (Figure 3A and C). Then, we used the mean mRNA expression profiles of both genes together for a combined Kaplan-Meier analysis. As expected, a significant correlation between high gene expression and short overall survival was found ($p=6.1\times10^{-5}$ and FDR=2%; Figure 3E), indicating the prognostic value of this 2-gene signature.

It is generally accepted that tumor mutations not only lead to carcinogenesis but also to tumor progression, and failure of therapy due to tumor heterogeneity and outgrowth of subpopulations with selection advantages in the tumor evolution (13). Therefore, we further compared subgroups of phaeochromocytoma and paraganglioma, *i.e.*, tumors with high and low mutation burden. Tumors with high mutation burden and high expression of *AQP4* alone, *FAM83H* alone, or the mean expression of both genes had significant shorter overall survival times than those with low expression of these genes (Figure 3B, D, and F). These correlations were not detectable in tumors with low mutation burden.

Analyses of phaeochromocytoma-and paraganglioma-related risk genes with the overall survival times of patients with 20 other tumor types. The 186 risk genes may not be specific exclusively for this tumor type but may also play a role in other tumor types. Therefore, we addressed the

Table I. *Prognostic significance of mRNA expression of 186 genes for overall survival of cancer patients.*

No.	Gene code	Name	Tumor type	Number	*p*-Value	FDR
1	*ADAMTS1*	ADAM metallopeptidase with thrombospondin-type motif	None			
2	*ADGRE1*	Adhesion G protein-coupled receptor E1	Head-neck squamous cell carcinoma	499	8.1×10^{-5}	2%
3	*AKR1B1*	Aldo-keto reductase family 1 member B	Stomach adenocarcinoma	371	1.9×10^{-5}	1%
4	*AK5*	Adenylate kinase 5	None			
5	*ALDH3A2*	Aldehyde dehydrogenase 3 family member A2	None			
6	*ALK*	Anaplastic lymphoma receptor tyrosine kinase	Uterine corpus endometrial carcinoma	542	1.1×10^{-6}	1%
7	*ANGPTL7*	Angiopoietin-like 7	None			
8	*APAF1*	Apoptotic peptidase activating factor 1	None			
9	*APOD*	Apolipoprotein D	None			
10	*APOE*	Apolipoprotein E	None			
11	*AQP4*	Aquaporin 4	Pheochromocytoma and paraganglioma	178	6.5×10^{-4}	5%
			Uterine corpus endometrial carcinoma	542	6.5×10^{-4}	1%
12	*ARNT*	Aryl hydrocarbon receptor nuclear translocator	None			
13	*ASCL1*	Achaete-scute family BHLH transcription factor 1	Kidney renal papillary cell carcinoma	287	6.4×10^{-6}	1%
14	*ATRX*	α-Thalassemia/mental retardation syndrome X-linked	None			
15	*BAP1*	BRCA2 DNA repair-associated protein 1	None			
16	*BMS1*	BMS1 ribosome biogenesis factor	Liver hepatocellular carcinoma	370	9.4×10^{-7}	1%
17	*BRAF*	B-Raf proto-oncogene, serine/threonine kinase	None			
18	*BUB1*	Budding uninhibited by benzimidazoles 1 homolog (yeast) mitotic checkpoint serine/threonine kinase	Kidney renal clear cell carcinoma	530	1.0×10^{-9}	1%
			Kidney renal papillary cell carcinoma	287	5.3×10^{-9}	1%
			Liver hepatocellular carcinoma	470	1.6×10^{-5}	1%
			Lung adenocarcinoma	504	1.6×10^{-5}	3%
			Pancreatic ductal adenocarcinoma	177	2.4×10^{-5}	1%
19	*BUB1B*	BUB1 mitotic checkpoint serine/threonine kinase B	Kidney renal clear cell carcinoma	530	1.8×10^{-5}	1%
			Kidney renal papillary cell carcinoma	287	9.0×10^{-9}	1%
			Liver hepatocellular carcinoma	370	4.3×10^{-5}	1%
			Lung adenocarcinoma	504	4.0×10^{-5}	1%
20	*CA12*	Carbonic anhydrase 12	Pancreatic ductal adenocarcinoma	177	3.8×10^{-6}	1%
21	*CA4*	Carbonic anhydrase 4	None			
22	*CARTPT*	Cocaine- and amphetamine-regulated transcript protein	Uterine corpus endometrial carcinoma	542	2.3×10^{-5}	1%
23	*CCL18*	C-C motif chemokine ligand 18	None			
24	*CCNB2*	Cyclin B2	Kidney renal clear cell carcinoma	530	2.6×10^{-11}	1%
			Kidney renal papillary cell carcinoma	287	2.2×10^{-10}	1%
			Lung adenocarcinoma	504	2.3×10^{-4}	5%
			Pancreatic ductal adenocarcinoma	177	1.7×10^{-5}	1%
25	*CD44 (= Hermes)*	Hematopoietic cell E- and L-selectin ligand	Kidney renal clear cell carcinoma	530	4.1×10^{-6}	1%
			Pancreatic ductal adenocarcinoma	177	8.3×10^{-4}	5%
26	*CD8A*	T-lymphocyte differentiation antigen T8/Leu-2 subunit α	None			
27	*CD8B*	T-lymphocyte differentiation antigen T8/Leu-2 subunit β	None			
28	*CD9*	Motility-related protein-1	Pancreatic ductal adenocarcinoma	177	1.7×10^{-4}	2%
29	*CDK1 (= CDC2)*	Cyclin-dependent kinase 1	Kidney renal clear cell carcinoma	530	2.7×10^{-8}	1%
			Kidney renal papillary cell carcinoma	287	1.9×10^{-11}	1%
			Liver hepatocellular carcinoma	370	1.2×10^{-5}	1%
			Lung adenocarcinoma	504	6.8×10^{-6}	1%
			pancreatic ductal adenocarcinoma	177	4.1×10^{-6}	1%
30	*CDCA7L*	Cell division cycle-associated 7-like	Liver hepatocellular carcinoma	370	3.3×10^{-5}	1%
31	*CDH19*	Cadherin 19	None			
32	*CDH9*	Cadherin 9	Breast cancer	1,089	4.7×10^{-7}	1%
			Ovarian cancer	373	1.6×10^{-5}	1%

Table I. *Continued*

Table I. *Continued*

No.	Gene code	Name	Tumor type	Number	*p*-Value	FDR
33	*CDT1*	Chromatin-licensing and DNA replication factor 1	Esophageal adenocarcinoma	80	8.4×10^{-4}	3%
			Liver hepatocellular carcinoma	370	1.9×10^{-5}	1%
			Lung adenocarcinoma	504	1.4×10^{-4}	3%
34	*CENPA*	Histone H3-like centromeric protein A	Kidney renal clear cell carcinoma	530	1.2×10^{-11}	1%
			Kidney renal papillary cell carcinoma	287	4.0×10^{-12}	1%
			Liver hepatocellular carcinoma	370	2.9×10^{-8}	1%
			Lung adenocarcinoma	504	1.2×10^{-4}	3%
			Pancreatic ductal adenocarcinoma	177	1.3×10^{-4}	1%
35	*CFC1*	Cripto, FRL-1, cryptic family 1	Breast cancer	1,089	1.6×10^{-5}	1%
36	*CITED1*	Cbp/P300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1	None			
37	*CKAP2L*	Cytoskeleton-associated protein 2-like	Kidney renal clear cell carcinoma	530	4.1×10^{-7}	1%
			Kidney renal papillary cell carcinoma	287	1.2×10^{-8}	1%
			Liver hepatocellular carcinoma	370	4.7×10^{-5}	1%
			Lung adenocarcinoma	504	6.1×10^{-5}	2%
			Pancreatic ductal adenocarcinoma	177	4.6×10^{-5}	1%
38	*COL1A1*	Collagen type I α 1 chain	Kidney renal clear cell carcinoma	530	2.7×10^{-4}	5%
			Kidney renal papillary cell carcinoma	287	5.1×10^{-8}	1%
39	*COL3A1*	Collagen type III α1 chain	Kidney renal papillary cell carcinoma	287	1.2×10^{-9}	1%
40	*COL5A2*	Collagen type V α2 chain	Kidney renal papillary cell carcinoma	287	4.9×10^{-9}	1%
41	*COL6A3*	Collagen type VI α3 chain	Kidney renal papillary cell carcinoma	287	1.0×10^{-9}	1%
42	*CRISPLD1*	Cysteine-rich secretory protein LCCL domain-containing 1	None			
43	*CSDE1*	Cold-shock domain-containing E1	None			
44	*CSMD2*	CUB and sushi multiple domains 2	Kidney renal papillary cell carcinoma	287	7.6×10^{-6}	1%
45	*CTGF*	Connective tissue growth factor	None			
46	*CYR61 (= CCN1)*	Cysteine-rich protein 61	None			
47	*DCHS2*	Dachsous cadherin-related 2	Kidney renal papillary cell carcinoma	287	3.4×10^{-4}	5%
			Liver hepatocellular carcinoma	370	2.6×10^{-4}	5%
48	*DLL4*	δ-Like canonical notch ligand 4	Cervical squamous cell carcinoma	304	4.0×10^{-4}	5%
			Kidney renal papillary cell carcinoma	287	3.8×10^{-4}	5%
49	*DLX2*	Distal-less homeobox 2	Sarcoma	279	4.5×10^{-5}	1%
50	*DNASE1L3*	Deoxyribonuclease 1-like 3	None			
51	*DNMT3A*	DNA methyltransferase 3 α	Liver hepatocellular carcinoma	370	1.6×10^{-4}	3%
			Uterine corpus endometrial carcinoma	542	7.3×10^{-5}	2%
52	*E2F4*	E2F transcription factor 4	Esophageal squamous cell carcinoma	81	1.1×10^{-5}	1%
			Kidney renal clear cell carcinoma	530	5.0×10^{-5}	1%
53	*EGFR*	Epidermal growth factor receptor	Bladder carcinoma	404	3.8×10^{-5}	1%
54	*HLF (= EPAS1, HIF2A)*	Endothelial PAS domain protein 1	None			
55	*ERBB2*	Erb-B2 receptor tyrosine kinase 2	Uterine corpus endometrial carcinoma	542	9.9×10^{-6}	1%
56	*ERBB3*	Erb-B2 receptor tyrosine kinase 3	None			
57	*ERBB4*	Erb-B2 receptor tyrosine kinase 4	None			
58	*MAPK1 (= ERK)*	Extracellular signal-regulated kinase 2	None			
59	*ESPL1*	Extra spindle pole bodies-like 1, separase	Kidney renal papillary cell carcinoma	287	1.0×10^{-10}	1%
			Liver hepatocellular carcinoma	370	2.6×10^{-5}	1%
			Lung adenocarcinoma	504	2.6×10^{-6}	1%
			Sarcoma	259	3.8×10^{-4}	5%
			Uterine corpus endometrial carcinoma	542	2.6×10^{-5}	1%
60	*ESR1*	Estrogen receptor 1	None			
61	*EZH2*	Enhancer of zeste 2 polycomb repressive complex 2 subunit	Kidney renal clear cell carcinoma	530	3.9×10^{-6}	1%
			Liver hepatocellular carcinoma	370	2.1×10^{-6}	1%

Table I. *Continued*

Table I. *Continued*

No.	Gene code	Name	Tumor type	Number	*p*-Value	FDR
62	*ESYT2 (= FAM62B)*	Extended synaptotagmin-like protein 2	Bladder carcinoma	404	1.3×10^{-5}	1%
			Pancreatic ductal adenocarcinoma	177	5.7×10^{-4}	5%
63	*FAM83H*	Family with sequence similarity 83 member H	Lung adenocarcinoma	504	2.9×10^{-4}	5%
			Pheochromocytoma and paraganglioma	178	1.7×10^{-4}	2%
64	*FCER1A*	Fc ε receptor Ia	None			
65	*FCGBP*	Fc fragment of IgG-binding protein	Liver hepatocellular carcinoma	370	2.8×10^{-4}	5%
			Ovarian cancer	373	$8.8.\times10^{-6}$	1%
66	*FGF18*	Fibroblast growth factor 18	Kidney renal papillary cell carcinoma	287	1.2×10^{-6}	1%
67	*FGFR1*	Fibroblast growth factor receptor 1	None			
68	*FH*	Fumarate hydrolase	None			
69	*FKBP9*	FK506-binding protein 9, 63 kDa	Bladder carcinoma	404	8.2×10^{-6}	1%
			Cervical squamous cell carcinoma	304	4.2×10^{-4}	5%
			Head-neck squamous cell carcinoma	499	1.4×10^{-4}	3%
70	*FLT1*	Fms-related receptor tyrosine kinase 1	Kidney renal papillary cell carcinoma	287	4.1×10^{-6}	1%
71	*GABRA1*	γ-Aminobutyric acid (GABA) A receptor, α1	Ovarian cancer	373	3.5×10^{-5}	1%
72	*GDNF*	Glial cell-derived neurotrophic factor	Kidney renal papillary cell carcinoma	287	1.3×10^{-5}	1%
73	*GFAP*	Glial fibrillary acidic protein	Uterine corpus endometrial carcinoma	542	5.7×10^{-5}	2%
74	*GJB6*	Gap junction protein, β 6, 30 kDa	Kidney renal clear cell carcinoma	530	1.9×10^{-7}	1%
75	*GJD2*	Gap junction protein δ 2	Breast cancer	1,089	2.6×10^{-6}	1%
			Ovarian cancer	373	1.3×10^{-4}	3%
76	*GNG4*	G-Protein subunit γ 4	Kidney renal papillary cell carcinoma	287	1.6×10^{-6}	1%
77	*GOT2*	Glutamic-oxaloacetic transaminase 2	Esophageal squamous cell carcinoma	81	1.5×10^{-3}	5%
			Head-neck squamous cell carcinoma	499	1.6×10^{-4}	5%
78	*H3F3A*	H3 histone family member 3A	None			
79	*HERC2*	HECT and RLD domain-containing E3 ubiquitin protein ligase 2	None			
80	*HES6*	Hes family BHLH transcription factor 6	Liver hepatocellular carcinoma	370	2.1×10^{-4}	3%
81	*HEY1*	Hes-related family BHLH transcription factor with YRPW motif 1	None			
82	*HK1*	Hexokinase 1	Head-neck squamous cell carcinoma	499	1.2×10^{-5}	1%
83	*HK2*	Hexokinase 2	None			
84	*HMGB3*	High mobility group box 3	Kidney renal clear cell carcinoma	530	1.2×10^{-4}	3%
			Sarcoma	259	4.3×10^{-5}	1%
85	*HOMER1*	Homer scaffold protein 1	Esophageal adenocarcinoma	80	1.3×10^{-3}	5%
86	*HRAS*	V-Ha-Ras Harvey rat sarcoma viral oncogene homolog	Liver hepatocellular carcinoma	370	2.3×10^{-4}	5%
87	*IDH1*	Isocitrate dehydrogenase ($NADP^+$) 1	Liver hepatocellular carcinoma	370	9.1×10^{-5}	2%
88	*IDH2*	Isocitrate dehydrogenase ($NADP^+$) 2	None			
89	*IGF1R*	Insulin-like growth factor 1 receptor	None			
90	*IL6*	Interleukin 6	Kidney renal clear cell carcinoma	530	5.3×10^{-8}	1%
91	*IQGAP3*	IQ motif-containing GTPase activating protein 3	Kidney renal clear cell carcinoma	530	1.9×10^{-10}	1%
			Kidney renal papillary cell carcinoma	287	1.4×10^{-7}	1%
			Liver hepatocellular carcinoma	370	8.9×10^{-6}	1%
			Lung adenocarcinoma	504	1.1×10^{-4}	3%
92	*ACO1 (= IRP1)*	Aconitase 1	None			
93	*KCNH2*	Potassium voltage-gated channel subfamily H member 2	Thymoma	118	8.3×10^{-3}	5%
			Uterine corpus endometrial carcinoma	542	5.4×10^{-5}	1%
94	*KIF1B*	Kinesin family member 1B	None			
95	*LEF1*	Lymphoid enhancer-binding factor 1	Kidney renal clear cell carcinoma	530	2.2×10^{-5}	1%
			Kidney renal papillary cell carcinoma	287	2.6×10^{-5}	1%
96	*LILRA6*	Leukocyte immunoglobulin-like receptor A6	None			
97	*LRRN3*	Leucine-rich repeat neuronal 3	None			
98	*MAML3*	Mastermind-like transcriptional coactivator 3	None			

Table I. *Continued*

Table I. *Continued*

No.	Gene code	Name	Tumor type	Number	*p*-Value	FDR
99	*MARCO*	Coactivator 3 mastermind-like	None			
100	*MAX*	MYC-associated factor X	None			
101	*MDH1*	Malate dehydrogenase 1	None			
102	*MDH2*	Malate dehydrogenase 2	None			
103	*MAP2K1 (= MEK1)*	Mitogen-activated protein kinase kinase 1	None			
104	*MEN1*	Menin 1	Liver hepatocellular carcinoma	370	3.5×10^{-4}	5%
105	*MKI67*	Marker of proliferation Ki-67	Kidney renal clear cell carcinoma	530	1.3×10^{-7}	1%
			Kidney renal papillary cell carcinoma	287	7.0×10^{-9}	1%
			Liver hepatocellular carcinoma	370	3.6×10^{-6}	1%
			Lung adenocarcinoma	504	9.3×10^{-5}	2%
			Pancreatic ductal adenocarcinoma	177	6.5×10^{-5}	1%
106	*MMP9*	Matrix metalloproteinase 9	Kidney renal clear cell carcinoma	530	2.3×10^{-4}	5%
107	*MMP12*	Matrix metalloproteinase 12	Kidney renal clear cell carcinoma	530	3.3×10^{-6}	1%
108	*MTOR*	mammalian target of rapamycin	None			
109	*MYC*	V-Myc avian myelocytomatosis viral oncogene homolog	Bladder carcinoma	504	5.8×10^{-5}	1%
			Kidney renal papillary cell carcinoma	287	4.1×10^{-4}	5%
110	*MYCN*	V-Myc avian myelocytomatosis viral oncogene neuroblastoma-derived homolog	None			
111	*MYO5B*	Myosin VB	Pancreatic ductal adenocarcinoma	177	7.3×10^{-5}	1%
112	*NDC80*	NDC80 kinetochore complex component	Kidney renal clear cell carcinoma	530	1.2×10^{-15}	1%
			Kidney renal papillary cell carcinoma	287	2.7×10^{-7}	1%
			Liver hepatocellular carcinoma	370	3.3×10^{-8}	1%
			Lung adenocarcinoma	504	1.8×10^{-4}	5%
113	*NEFH*	Neurofilament, heavy polypeptide	None			
114	*NEFM*	Neurofilament, medium polypeptide	None			
115	*NES*	Nestin	Kidney renal papillary cell carcinoma	277	1.6×10^{-4}	2%
116	*NETO2*	Neuropilin and tolloid-like 2	Kidney renal papillary cell carcinoma	287	9.1×10^{-6}	1%
			Sarcoma	259	3.2×10^{-7}	1%
117	*NF1*	Neurofibromatosis 1	None			
118	*NPY*	Neuropeptide Y	Uterine corpus endometrial carcinoma	542	1.4×10^{-4}	3%
119	*NRAS*	Neuroblastoma RAS ciral (V-Ras) oncogene homolog	Liver hepatocellular carcinoma	370	3.4×10^{-5}	1%
			Pancreatic ductal adenocarcinoma	177	3.3×10^{-4}	3%
			Sarcoma	259	4.8×10^{-4}	5%
120	*NRG3*	Neuregulin 3	Stomach adenocarcinoma	371	3.0×10^{-4}	5%
			Uterine corpus endometrial carcinoma	542	5.4×10^{-5}	1%
121	*NTRK3*	Neurotrophic receptor tyrosine kinase 3	Lung squamous cell carcinoma	495	1.8×10^{-4}	5%
122	*OLIG1*	Oligodendrocyte transcription factor 1	None			
123	*OLIG2*	Oligodendrocyte transcription factor 2	Breast cancer	1,089	3.8×10^{-5}	2%
124	*P2RY2*	Purinergic receptor P2Y2	Pancreatic ductal adenocarcinoma	177	8.5×10^{-5}	1%
125	*PBK*	PDZ-binding kinase	Kidney renal clear cell carcinoma	530	3.3×10^{-5}	1%
			Kidney renal papillary cell carcinoma	287	4.2×10^{-8}	1%
			Liver hepatocellular carcinoma	370	8.2×10^{-5}	2%
			Lung adenocarcinoma	504	2.9×10^{-4}	5%
126	*PCDHGA6*	Protocadherin γ subfamily A, 6	None			
127	*PCSK2*	Proprotein convertase subtilisin/kexin type 2	None			
128	*CD274 (= PD-L1)*	Programmed death-ligand 1	None			
129	*PENK*	Proenkephalin	Uterine corpus endometrial carcinoma	542	6.1×10^{-6}	1%
130	*EGLN2 (= PHD1)*	Prolyl hydroxylase 1	Kidney renal clear cell carcinoma	530	1.7×10^{-6}	1%
131	*PIK3AP1*	Phosphoinositide-3-kinase adaptor protein 1	None			
132	*PIK3C2A*	Phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 α	None			

Table I. *Continued*

Table I. *Continued*

No.	Gene code	Name	Tumor type	Number	*p*-Value	FDR
133	*PIK3C3*	Phosphatidylinositol 3-kinase catalytic subunit type 3	None			
134	*PIK3CA*	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α	None			
135	*PIK3CB*	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit β	Pancreatic ductal adenocarcinoma	177	4.5×10^{-4}	5%
136	*PIK3CD*	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ	None			
137	*PMAIP1*	Phorbol-12-myristate-13-acetate-induced protein 1	Esophageal adenocarcinoma	80	8.9×10^{-4}	3%
138	*PNMT*	Phenylethanolamine N-methyltransferase	Uterine corpus endometrial carcinoma	542	3.9×10^{-5}	1%
139	*PRKCB*	Protein kinase C β	None			
140	*PTGER4*	Prostaglandin E receptor 4	None			
141	*PTX3*	Pentraxin 3, long	Kidney renal clear cell carcinoma	530	5.9×10^{-5}	1%
142	*RBFOX1*	RNA-binding protein, fox-1 homolog (*C. elegans*) 1	None			
143	*RET*	Ret proto-oncogene	Kidney renal clear cell carcinoma	530	1.9×10^{-5}	1%
144	*RFC4*	Replication factor C subunit 4	Kidney renal clear cell carcinoma	530	5.4×10^{-10}	1%
			Kidney renal papillary cell carcinoma	287	9.1×10^{-7}	1%
			Liver hepatocellular carcinoma	370	4.7×10^{-5}	1%
145	*PRPF31 (= RP11)*	Pre-mRNA processing factor 31	None			
146	*RRM2*	Ribonucleotide reductase M2	Kidney renal clear cell carcinoma	530	3.4×10^{-8}	1%
			Kidney renal papillary cell carcinoma	287	4.7×10^{-11}	1%%
			Liver hepatocellular carcinoma	370	2.3×10^{-5}	1%
			Lung adenocarcinoma	504	1.1×10^{-6}	1%
			Pancreatic ductal adenocarcinoma	177	1.6×10^{-4}	1%
147	*RSPO2*	R-Spondin 2	None			
148	*SCG3*	Secretogranin III	Uterine corpus endometrial carcinoma	542	8.0×10^{-5}	2%
149	*SDCBP*	Syndecan-binding protein	None			
150	*SDHA*	Succinate dehydrogenase complex flavoprotein subunit A	None			
151	*SDHAF2*	Succinate dehydrogenase complex assembly factor 2	Kidney renal clear cell carcinoma	530	4.0×10^{-5}	1%
152	*SDHB*	Succinate dehydrogenase complex iron sulfur subunit B	None			
153	*SDHC*	Succinate dehydrogenase complex subunit C	None			
154	*SDHD*	Succinate dehydrogenase complex subunit D	None			
155	*SERPINE1*	Serpin family E member 1	Head-neck squamous cell carcinoma	499	3.7×10^{-5}	1%
			Stomach adenocarcinoma	371	2.2×10^{-6}	1%
156	*SETD2*	SET domain-containing 2, histone lysine methyltransferase	None			
157	*SFT2D3*	SFT2 domain-containing protein 3	Breast cancer	1,089	1.4×10^{-6}	1%
			Ovarian cancer	373	9.5×10^{-6}	1%
			Uterine corpus endometrial carcinoma	541	1.5×10^{-4}	5%
158	*SLC12A5*	Solute carrier family 12 (potassium/ chloride transporter), member 5	Kidney renal clear cell carcinoma	530	2.5×10^{-5}	1%
159	*SLC25A11*	Solute carrier family 25 member 11	None			
160	*SMC4*	Structural maintenance of chromosomes 4	Kidney renal papillary cell carcinoma	287	1.6×10^{-4}	2%
			Liver hepatocellular carcinoma	370	2.9×10^{-4}	5%
			Pancreatic ductal adenocarcinoma	177	4.2×10^{-5}	1%
161	*SMO*	Smoothened, frizzled class receptor	None			
162	*SOX10*	SRY-box transcription factor 10	Breast cancer	1,089	1.4×10^{-6}	1%
			Ovarian cancer	373	9.5×10^{-6}	1%
			Uterine corpus endometrial carcinoma	542	1.5×10^{-4}	5%

Table I. *Continued*

Table I. *Continued*

No.	Gene code	Name	Tumor type	Number	*p*-Value	FDR
163	*SOX4*	SRY-box transcription factor 4	Liver hepatocellular carcinoma	370	2.6×10^{-5}	1%
164	*STMN2*	Stathmin 2	Kidney renal clear cell carcinoma	530	5.9×10^{-5}	2%
			Kidney renal papillary cell carcinoma	287	4.5×10^{-12}	1%
165	*SYNPR*	Synaptoporin	Uterine corpus endometrial carcinoma	542	5.6×10^{-5}	2%
166	*TBX3*	T-Box transcription factor 3	Kidney renal papillary cell carcinoma	287	6.0×10^{-5}	1%
167	*TBXA2R*	Thromboxane A2 receptor	None			
168	*TCF4*	Transcription factor 4	None			
169	*TGDS*	TDP-glucose 4,6-dehydratase	None			
170	*TMEM127*	Transmembrane protein 127	None			
171	*TMEM130*	Transmembrane protein 130	None			
172	*TMEM45A*	Transmembrane protein 45A	Kidney renal clear cell carcinoma	530	1.2×10^{-5}	1%
			Thyroid carcinoma	502	1.1×10^{-5}	1%
173	*TOP2A*	DNA-topoisomerase 2A	Kidney renal clear cell carcinoma	530	1.9×10^{-9}	1%
			Kidney renal papillary cell carcinoma	287	1.0×10^{-9}	1%
			Liver hepatocellular carcinoma	370	1.3×10^{-5}	1%
			Lung adenocarcinoma	504	1.1×10^{-4}	3%
			Pancreatic ductal adenocarcinoma	177	4.9×10^{-5}	1%
			Sarcoma	259	5.2×10^{-4}	5%
174	*TRHDE*	Thyrotropin-releasing hormone-degrading enzyme	Uterine corpus endometrial carcinoma	542	1.1×10^{-6}	1%
175	*TTC9*	Tetratricopeptide repeat domain 9	None			
176	*TTK*	Phosphotyrosine-picked threonine protein kinase	Kidney renal clear cell carcinoma	530	4.8×10^{-8}	1%
			Kidney renal papillary cell carcinoma	287	1.1×10^{-8}	1%
			Liver hepatocellular carcinoma	370	6.5×10^{-9}	1%
			Lung adenocarcinoma	504	1.6×10^{-4}	3%
			Pancreatic ductal adenocarcinoma	177	1.3×10^{-4}	1%
			Uterine corpus endometrial carcinoma	542	1.8×10^{-5}	1%
177	*TWIST1*	Twist family BHLH transcription factor 1	Kidney renal clear cell carcinoma	530	2.7×10^{-4}	5%
			Kidney renal papillary cell carcinoma	287	4.2×10^{-7}	1%
178	*TYMS*	Thymidylate synthetase	Liver hepatocellular carcinoma	370	2.9×10^{-6}	1%
			Lung adenocarcinoma	504	2.6×10^{-4}	5%
179	*VCL*	Vinculin	Pancreatic ductal adenocarcinoma	177	4.4×10^{-4}	5%
180	*VEGFA*	Vascular endothelial growth factor A	Cervical squamous cell carcinoma	304	4.5×10^{-4}	5%
			Kidney renal papillary cell carcinoma	287	1.6×10^{-7}	1%
			Liver hepatocellular carcinoma	370	2.3×10^{-5}	1%
			Uterine corpus endometrial carcinoma	542	2.1×10^{-4}	5%
181	*VHL*	von Hippel Lindau gene	Liver hepatocellular carcinoma	370	3.6×10^{-5}	1%
182	*VIM*	Vimentin	None			
183	*VIPR2*	Vasoactive intestinal peptide receptor 2	Lung squamous cell carcinoma	495	1.0×10^{-4}	3%
184	*VWF*	Von Willebrand factor	None			
185	*WNT1*	Wingless-type MMTV integration site family, member 1 (oncogene INT1)	None			
186	*ZWINT*	ZW10-interacting kinetochore protein	Kidney renal papillary cell carcinoma	287	2.4×10^{-4}	3%
			Liver hepatocellular carcinoma	370	1.8×10^{-8}	1%

FDR: False discovery rate.

question whether these risk genes may also be related to the overall survival times of patients suffering from other tumor types. The TCGA-based data repository of the KMPlotter contained several other tumor types in addition to phaeochromocytoma and paraganglioma with a total number of 7,489 biopsies. We calculated the overall survival times of patients not only with phaeochromocytoma and paraganglioma but also with these other tumor types with a total number of 3,162 Kaplan-Meier statistics calculations. The plots shown in

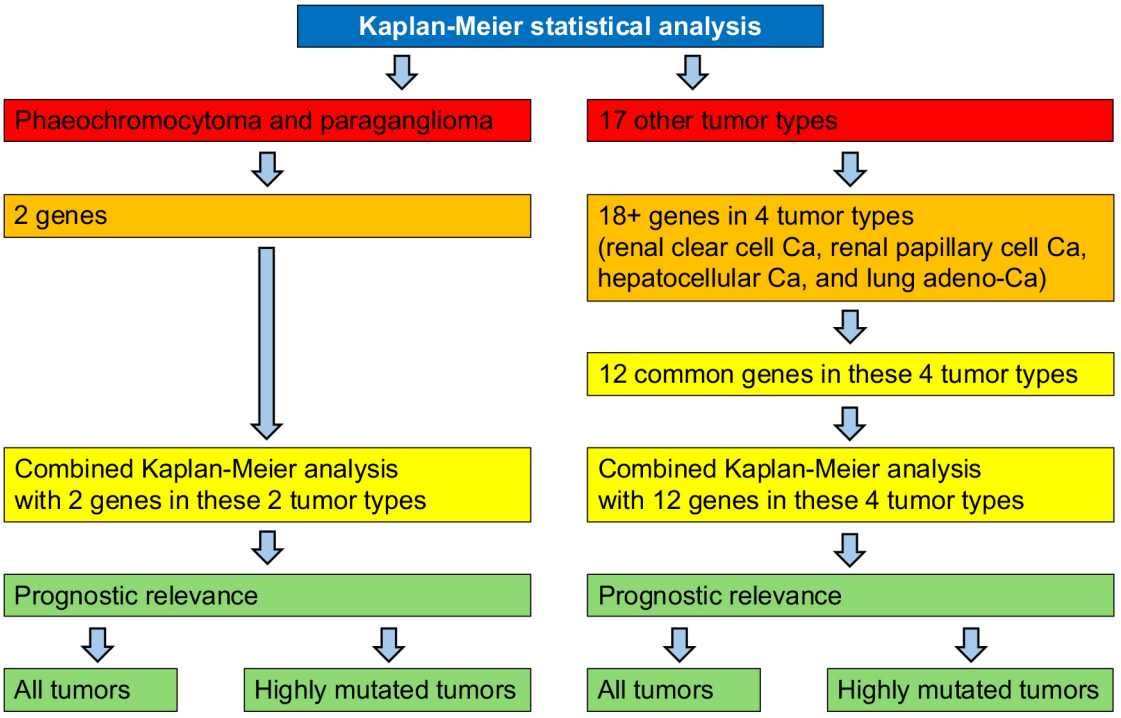

Figure 2. *Workflow to identify phaeochromocytoma-related risk gene signatures.*

Figure 4 and Figure 5 depict the 181 correlations which were statistically significant (yellow marked, $p<0.05$, FDR <5%). All others did not fulfill these criteria (blue marked). Of the 181 statistically significant correlations, 56 were associated with patient survival of one cancer entity, 22 with two cancer types, five with four and eight with five tumor types. The mRNA expression of one gene correlated with six tumor types.

We were interested to see which tumor types were most frequently associated with significant Kaplan-Meier correlations. As shown in Figure 6, renal papillary cell carcinoma, renal clear cell carcinoma, and hepatocellular carcinoma of the liver were the most frequently correlating tumor types with 27 or more significant associations, followed by lung adenocarcinoma, uterine corpus endometrial carcinoma and pancreatic ductal carcinoma (with 18 or more significant correlations). As also mentioned above, phaeochromocytoma and paraganglioma were only associated with two genes.

Based on the results shown in Figure 4, we investigated which tumor types correlated most frequently with the set of 186 genes. Out of the 18 tumor entities studied, the four most frequently appearing cancer types were renal papillary cell carcinoma, renal clear cell carcinoma, liver hepatocellular carcinoma, and lung adenocarcinoma (Figure 7). The expression of 18-32 genes correlated with worse overall survival of patients with these four tumor types. Therefore, we selected these four tumor types for our further analyses.

Overall survival analyses with a 12-gene signature. We investigated the accumulation of significant correlations in these tumor types in more detail. Renal papillary cell carcinoma, renal clear cell carcinoma, liver hepatocellular carcinoma, and lung adenocarcinoma showed significant correlations with 12 genes in common (*BUB1, BUB1B, CDK1, CENPA, CKAP2L, IQGAP3, MKI67, NDC80, PBK, RRM2, TOP2A,* and *TTK*) (Table II, Figure 4 and Figure 5). Then,

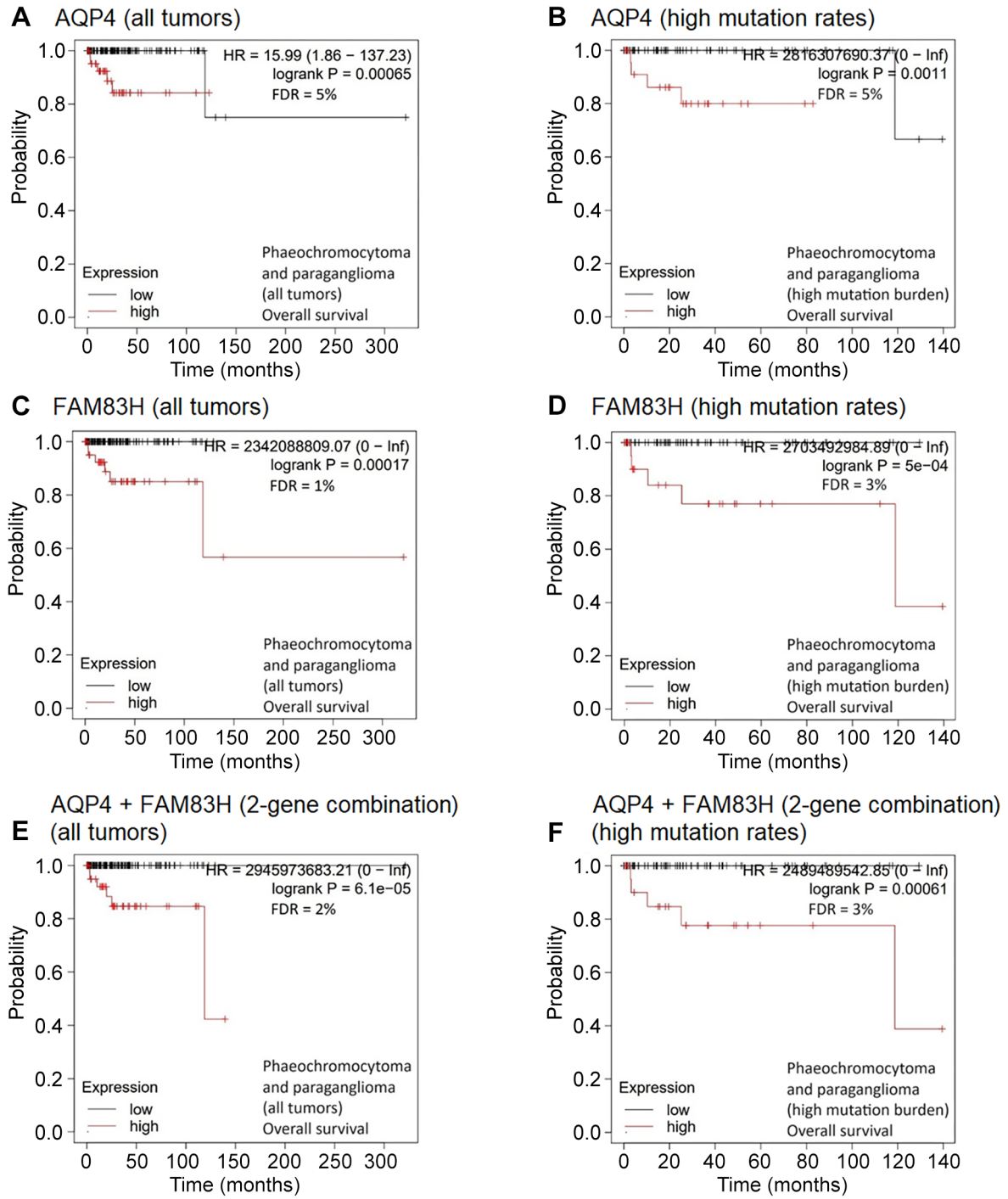

Figure 3. *Kaplan-Meier curves of overall survival time for patients with phaeochromocytoma or paraganglioma and mRNA expression of (A, B) AQP4 alone, (C, D) FAM83H alone, or (E, F) the mean RNA expression of both genes together. The panels A, C, and E show the survival analyses if tumors were subjected irrespective of whether they had high or low mutation rates, while the panels B, D, and F depict only those tumors with high mutation rates. Tumors with high mutation rates are considered as more aggressive than those with low numbers of mutations. Hence, it is relevant to know whether the identified candidate genes are also of prognostic significance in aggressive, highly mutated tumors.*

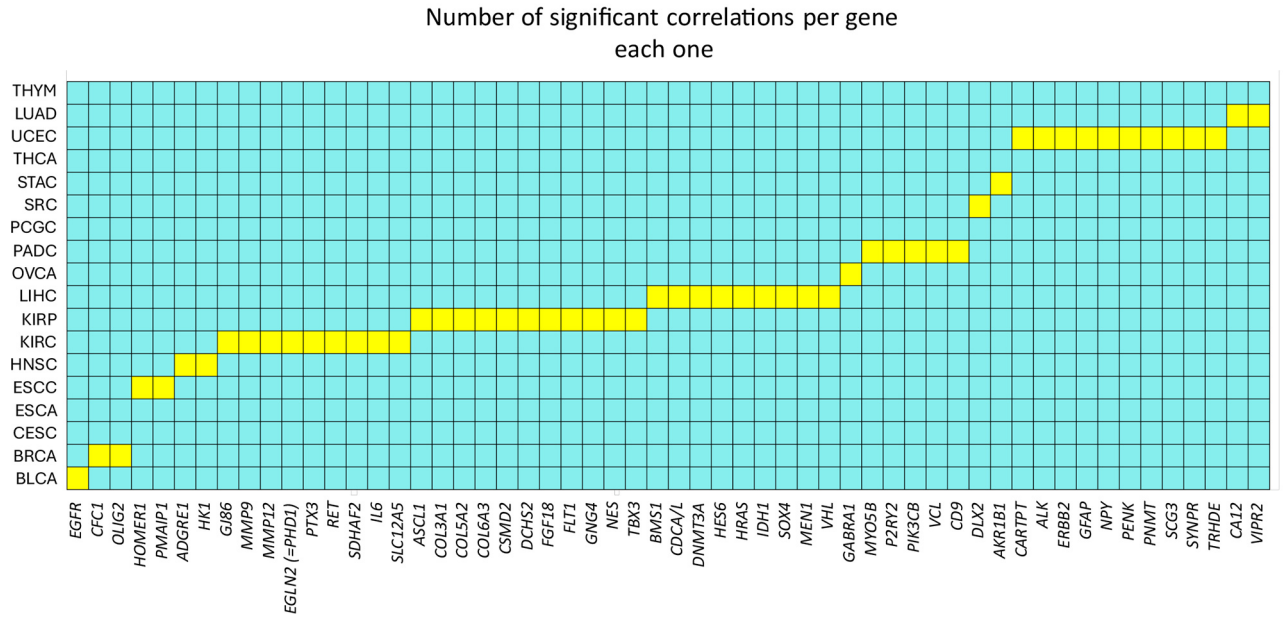

Figure 4. *Color-coded plot of Kaplan-Meier analyses of 186 genes for 18 tumor types. The yellow color indicates each one significant correlation between high mRNA expression in tumors and worse overall patient survival (p<0.05; FDR ≤5%). THYM, Thymoma; LUAD, lung adenocarcinoma; UCEC, uterine corpus endometrial carcinoma; THCA, thyroid carcinoma; STAC, stomach adenocarcinoma; SRC, sarcoma; PCGC, pheochromocytoma and paraganglioma; PADC, pancreatic ductal adenocarcinoma; OVCA, ovarian carcinoma; LIHC, liver hepatocellular carcinoma; KIRP, kidney renal papillary cell carcinoma; KIRC, kidney renal cell carcinoma; HNSC, head and neck squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; ESCA, esophageal adenocarcinoma; CESC, cervical squamous cell carcinoma; BRCA, breast cancer; BLCA, bladder cancer.*

we used the mean mRNA expression of these 12 genes and performed Kaplan-Meier analyses. As shown in Figure 7 A-D, the high expression of this 12-gene signature correlated with shorter overall survival in these four tumor entities compared to its low expression (p<0.0001; FDR=1%).

We also performed Kaplan-Meier statistics for high or low mutation burden and found a significant correlation for patients with highly mutated hepatocellular carcinoma. Their high mean expression of the 12-gene signature correlated with shorter survival, while low expression was associated with longer survival (p<0.00001; FDR=1%).

Refractory-free survival analyses with a 12-gene signature. While overall survival times are measured from initial diagnosis of the tumor to the death of the patient, it is also interesting to study the refractory-free survival, *i.e.*, the time from initial diagnosis to the reappearance of a tumor after therapy. Refractory-free survival is usually associated with better life quality of a patient compared to overall survival. Therefore, we performed Kaplan-Meier statistics of the four tumor types mentioned above (renal papillary cell carcinoma, renal clear cell carcinoma, liver hepatocellular carcinoma, and lung adenocarcinoma) regarding refractory-free survival times of the patients. As shown in Figure 8, the high mean mRNA expression of these 12 genes significantly correlated with shorter refractory-free survival times of patients with hepatocellular carcinoma (Figure 8A and B) or renal papillary cell carcinoma (Figure 8C and D). This was true if all tumors were subjected to survival analysis (Figure 8A and C) (p<0.001; FDR ≤2%). Tumors with many mutations are generally accepted as being more aggressive than those with fewer mutations. Therefore, we investigated whether this 12-gene signature is also predictive of shorter survival in tumors with high mutation rates. Indeed, high gene expression also

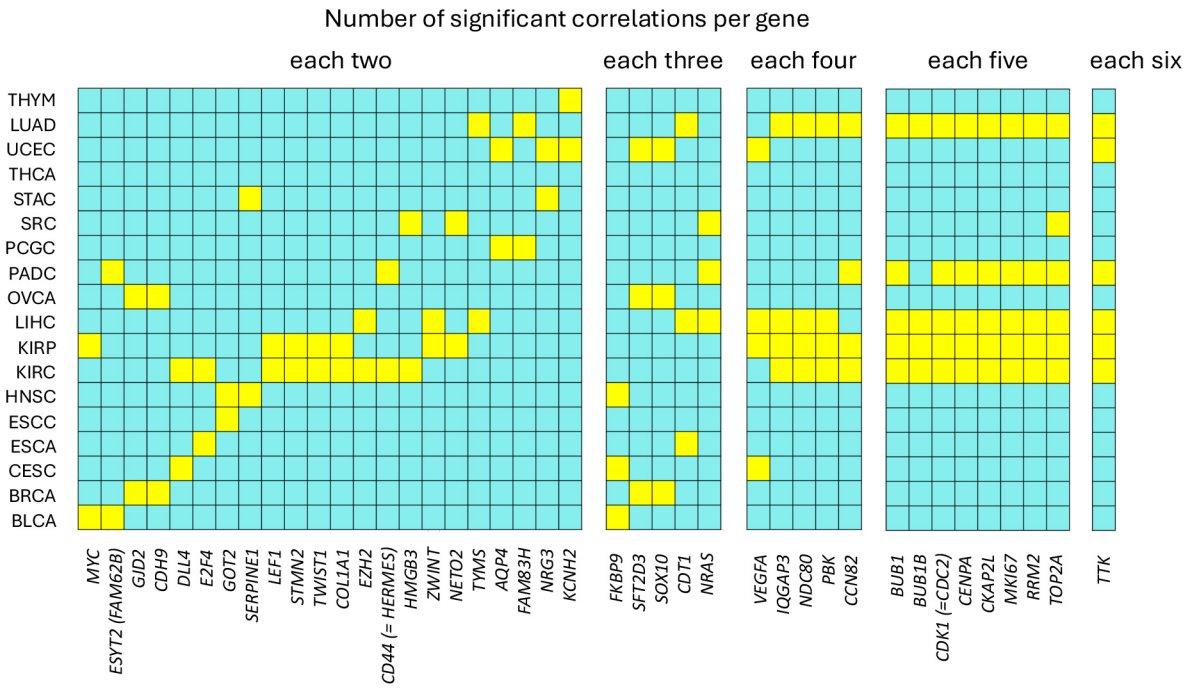

Figure 5. *Color-coded plot of Kaplan-Meier analyses of 186 genes for 18 tumor types. The yellow color indicates each two to six significant correlations between high mRNA expression in tumors and worse overall patient survival (p<0.05; FDR ≤5%). THYM, Thymoma; LUAD, lung adenocarcinoma; UCEC, uterine corpus endometrial carcinoma; THCA, thyroid carcinoma; STAC, stomach adenocarcinoma; SRC, sarcoma; PCGC, pheochromocytoma and paraganglioma; PADC, pancreatic ductal adenocarcinoma; OVCA, ovarian carcinoma; LIHC, liver hepatocellular carcinoma; KIRP, kidney renal papillary cell carcinoma; KIRC, kidney renal cell carcinoma; HNSC, head and neck squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; ESCA, esophageal adenocarcinoma; CESC, cervical squamous cell carcinoma; BRCA, breast cancer; BLCA, bladder cancer.*

indicated lower survival times of patients with high mutation rates (Figure 8B and D) (p<0.0001; FDR ≤1%).

Discussion

The aim of the present investigation was, first, to investigate whether genes whose expression has been correlated to the onset of phaeochromocytoma and paraganglioma may also be relevant for the outcome of this disease, *i.e.*, for the survival of patients. Since these genes are not exclusively specific for phaeochromocytoma/paraganglioma, we assumed that they might also be relevant for the survival of patients suffering from other tumor types than phaeochromocytoma/paraganglioma. Therefore, a second aim of his study was to see whether the genes with prognostic relevance for the survival of phaeochro-mocytoma or paraganglioma patients may also predict survival of patients with other tumor types. Based on literature mining, we compiled 186 risk genes for phaeochromocytoma/paraganglioma. As risk genes may contribute to carcinogenesis and tumor progression, their final role for the lifetime expectancy of cancer patients is not that well understood. To identify prognostic biomarkers for patient survival that may also serve as possible targets for future drug developments, we subjected the mRNA expression of these genes in 178 biopsies of phaeochromocytoma and paraganglioma deposited in the TCGA database to Kaplan-Meier survival analyses. Unexpectedly, the expression of only two genes (*AQP5* and *FAM83H*) significantly correlated with short survival times of patients. Since the 186 genes are not exclusively related to the development of phaeochro-

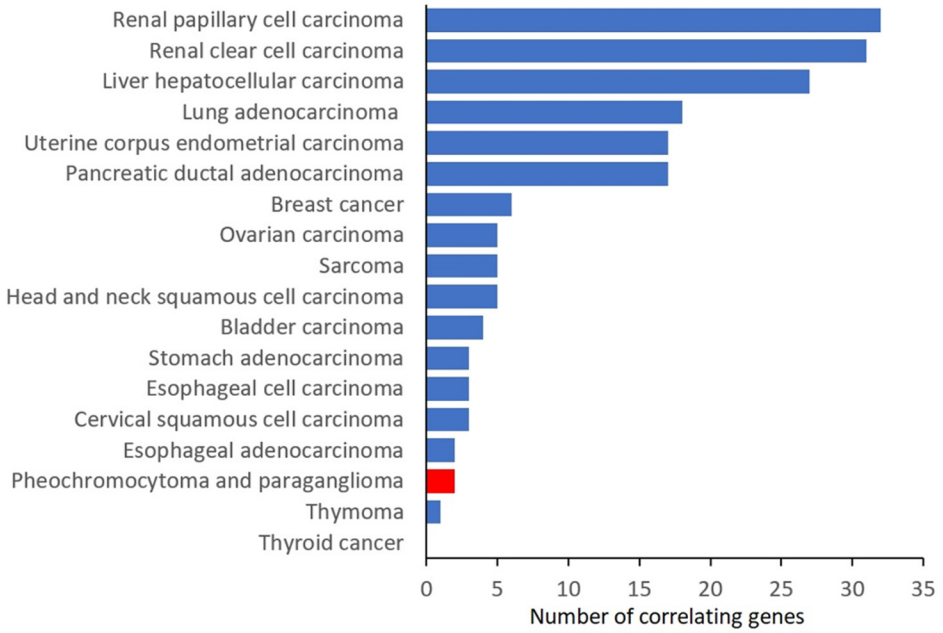

Figure 6. *Number of genes significantly correlating with survival of cancer patients. The expression of all 186 genes in patients with phaeochromocytoma (red bar) or patients with 17 other tumor types (blue bars) has been subjected to Kaplan Meier survival analyses. The number of genes whose mRNA expression significantly correlated with short survival times (p<0.05; FDR ≤5%) were represented as bar diagram.*

mocytoma/paraganglioma alone, we also investigated their prognostic value in 17 other tumor types. Interestingly, we observed a cluster of 12 genes that commonly appeared in four tumor types (renal papillary cell carcinoma, renal clear cell carcinoma, hepatocellular carcinoma, and lung carcinoma).

While most phaeochromocytomas and paragangliomas are benign and only a fraction exerts malignant features such as metastasis, the other four tumor types are malignant. Hence, it can be speculated that the two genes we identified in phaeochromocytoma and paraganglioma may be more associated with benign tumor growth, while the other 12 identified genes are related to malignant cancer growth. Interestingly, the majority of proteins encoded by these 12 genes have functions in mitosis or DNA metabolism, while the two genes with prognostic significance for phaeochromocytoma had other functions (water homeostasis, cell migration) (Table II). Aberrant mitosis and DNA metabolism are well-known characteristics of cancer, and it is plausible that genes related to these two biological processes have prognostic value for malignant rather than for benign tumor growth.

The *MKI-67* gene represents a surrogate marker to monitor the proliferative capacity of tumors. Its encoding protein Ki-67 is widely used as prognostic marker in many cancer types including the carcinoma types studied here (14). A high Ki-67 score is associated with high proliferation, and rapid proliferating tumor cells are generally more susceptible to chemotherapy than slowly growing ones.

On the other hand, *AQP4* and *FAM83H* may be valuable biomarkers to predict survival of phaeochromocytoma/paraganglioma with limited malignant potential. A role of *AQP4* has been described on other tumors of the brain such as low-grade glioma (15, 16). AQP4 aggregation influences plasma membrane dynamics to alter cell proliferation, invasiveness, migration, and apoptotic potential in glioma cells.

FAM83H has a role for cell migration. Hence, this gene may play a role in metastatic phaeochromocytoma. FAM83H and other members of the FAM83 family are involved in

Table II. *Prognostic significance of mRNA expression of selected genes for overall survival of patients with phaeochromocytoma/paraganglioma, renal clear cell carcinoma, renal papillary carcinoma, or lung adenocarcinoma.*

Gene code	Name	Function	Tumor type	No.	*p*-Value	FDR	Prognostic marker (Reference)
AQP4	Aquaporin 4	Water-selective channel, brain	PCPG	178	6.5×10^{-4}	5%	
BUB1	Budding uninhibited by benzimidazoles 1 homolog (yeast) mitotic checkpoint Serine/threonine kinase	water homeostasis	KIRC	530	1.0×10^{-9}	1%	(36, 37)
		Mitosis: mitotic spindle checkpoint; serine/threonine protein kinase; Other functions: DNA damage response, aneuploidy, cancer development	KIRP	287	5.3×10^{-9}	1%	(18, 38)
			LIHC	470	1.6×10^{-5}	1%	(39-42)
			LUAD	504	1.6×10^{-5}	3%	(43-48)
BUB1B	BUB1 mitotic checkpoint Serine/threonine kinase B	Mitosis: mitotic spindle checkpoint function and normal mitosis progression. Other functions: cancer development; proper chromosome segregation	KIRC	530	1.8×10^{-13}	1%	
			KIRP	287	9.0×10^{-9}	1%	
			LIHC	370	4.3×10^{-5}	1%	(49)
			LUAD	504	4.0×10^{-5}	1%	(37, 43, 45, 47, 50-52)
CDK1/CDC2	Cyclin-dependent kinase 1	Mitosis: essential for G_2/M transition. Serine/threonine protein kinase	KIRC	530	2.7×10^{-8}	1%	(10, 36, 53)
			KIRP	287	6.5×10^{-11}	1%	
			LIHC	370	1.2×10^{-5}	1%	(19, 40, 42-66)
			LUAD	504	6.8×10^{-6}	1%	(44, 47, 67-72)
CENPA	Histone H3-like centromeric protein A	Mitosis: assembly of kinetochore proteins andprogress through mitosis, chromosome segregation, and cytokines. Other functions: component of a modified nucleosome of nucleosome-like structure	KIRC	530	1.2×10^{-11}	1%	
			KIRP	287	4.0×10^{-12}	1%	(73)
			LIHC	370	2.9×10^{-8}	1%	(19, 55, 64, 74-76)
			LUAD	504	1.2×10^{-4}	3%	(69, 77, 78)
CKAP2L	Cytoskeleton-associated protein 2-like	Mitosis: mitotic spindle formation and cell cycle progression in neural progenitor cells	KIRC	530	4.1×10^{-7}	1%	(20, 79)
			KIRP	287	1.2×10^{-8}	1%	(80)
			LIHC	370	4.7×10^{-5}	1%	
			LUAD	504	61×10^{-5}	2%	(81)
FAM83H	Family with sequence similarity 83 member H	Keratin cytoskeleton disassembly; epithelial cellmigration; calcification of tooth enamel	PCPG	178	1.7×10^{-4}	2%	
			LUAD	504	2.9×10^{-4}	5%	
IQGAP3	IQ motif-containing GTPase activating protein 3	Regulation of actin cytoskeleton organization; signal transduction; cancer development	KIRC	530	1.9×10^{-10}	1%	(82, 83)
			KIRP	287	1.4×10^{-7}	1%	
			LIHC	370	8.9×10^{-6}	1%	(21, 84-86)
			LUAD	504	1.1×10^{-4}	3%	
MKI67	Marker of proliferation Ki-67	Mitosis: chromosome segregation and mitosis; chromosome dispersion following nuclear envelope disassembly	KIRC	530	1.3×10^{-7}	1%	
			KIRP	287	7.0×10^{-9}	1%	
			LIHC	370	3.6×10^{-6}	1%	(87-89)
			LUAD	504	9.3×10^{-5}	2%	(22, 90-93)
NDC80	NDC80 kinetochore complex component	Mitosis: contains microtubule-binding domain;stabilizes microtubule-kinetochore interactions; proper chromosome segregation	KIRC	530	1.2×10^{-15}	1%	(94)
			KIRP	287	2.7×10^{-7}	1%	
			LIHC	370	3.3×10^{-8}	1%	(65, 95-99)
			LUAD	504	1.8×10^{-4}	5%	(100)
PBK	PDZ-binding kinase	Mitosis: destabilizes TP53 and attenuates G_2/M checkpoint; Serine/threonine protein kinase; Other functions: tumor development; lymphoid cell activation and testicular functions	KIRC	530	3.3×10^{-5}	1%	(23)
			KIRP	287	4.2×10^{-8}	1%	(101)
			LIHC	370	8.2×10^{-5}	2%	(58, 102-109)
			LUAD	504	2.9×10^{-4}	5%	(110-113)
RRM2	Ribonucleotide reductase	DNA: catalyzes the formation of deoxyribonucleotides	KIRC	530	3.4×10^{-8}	1%	(114-118)

Table II. *Continued*

Table II. *Continued*

Gene code	Name M2	Function from ribonucleotides	Tumor type	No.	*p*-Value	FDR	Prognostic marker (Reference)
			KIRP	287	4.7×10^{-11}	1%	(101, 119)
			LIHC	370	2.3×10^{-5}	1%	(24, 25, 62, 104, 120-129)
			LUAD	504	1.1×10^{-6}	1%	(45, 46, 91, 131-139)
TOP2A	DNA-topoisomerase 2A	DNA: catalyzes breaking and rejoining of DNA strands to allow DNA strand passing; chromatin condensation, chromatid separation, and the relief of torsional stress during DNA replication	KIRC	530	1.9×10^{-9}	1%	(26, 27, 114, 118, 140-142)
			KIRP	287	1.0×10^{-9}	1%	
			LIHC	370	1.3×10^{-5}	1%	(45, 46, 91, 104, 105, 125, 126, 134, 143-151)
			LUAD	504	1.1×10^{-4}	3%	(45, 46, 91, 133, 152-159)
TTK	Phosphotyrosine-picked threonine protein kinase	Mitosis: chromosome alignment at the centromere during mitosis; centrosome duplication and proper chromosome segregation during mitosis	KIRC	530	4.8×10^{-8}	1%	
			KIRP	287	1.1×10^{-8}	1%	
			LIHC	370	6.5×10^{-9}	1%	(85, 160)
			LUAD	504	1.6×10^{-4}	3%	(157, 161, 162)

KIRC, Kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; PCPG, phaeochromocytoma and paraganglioma; FDR: false discovery rate.

diverse cancer types and play a role for poor survival prognosis (17). The 12 genes associated with shorter survival times of the four carcinoma types are partwise well-known for their prognostic role (*e.g.*, *BUB1, CDK1, RRM2, TOP2A*), partwise their prognostic value is not well studied yet (*e.g.*, *AQP4, FAM83H, CKAP2L, TTK*), and our investigation provides further evidence to consider them as valuable biomarkers in the future. As the majority of investigations come from Chinese authors, it comes as no surprise that tumor types that are very common in China (*i.e.*, hepatocellular carcinoma, lung adenocarcinoma) have been more frequently studied than others (*i.e.*, kidney cancers) (Table II).

We were not only interested identifying single prognostic markers but also studying entire gene signatures. The clustering of 12 genes in the four carcinoma types is remarkable, and forming the mean mRNA expression value of these 12 genes even improved the statistical significance in the Kaplan-Meier statistics making this gene signature a powerful tool to predict the survival probability of patients. Although other signatures have been reported in the literature related to several pathways and mechanisms (*e.g.*, ferroptosis, immune response, glycolysis, *etc.*) (18-27), the mitosis-related 12-gene signature described in the present study is novel and not described before.

We also investigated the mean mRNA expression of *AQP4* and *FAM83H* and found an improved statistical significance to predict survival of phaeochromocytoma and paraganglioma patients compared to the expression of both genes alone. Hence, this may serve as a novel 2-gene signature for these tumor types.

Novel biomarkers are not only valuable for the survival prognosis of patients but also for development of novel strategies for individualized treatment options. Mitosis and the DNA are also important treatment targets for classical anticancer drugs such as *Vinca* alkaloids, taxanes, alkylating agents, platin derivatives, and antimetabolites. Hence, the proteins encoded by the genes identified here may serve as novel targets for drug development.

During the past years, it became more and more clear that the current armamentarium of targeted drugs addressing the currently known drug targets can improve therapy success of cancer patients to some extent, but

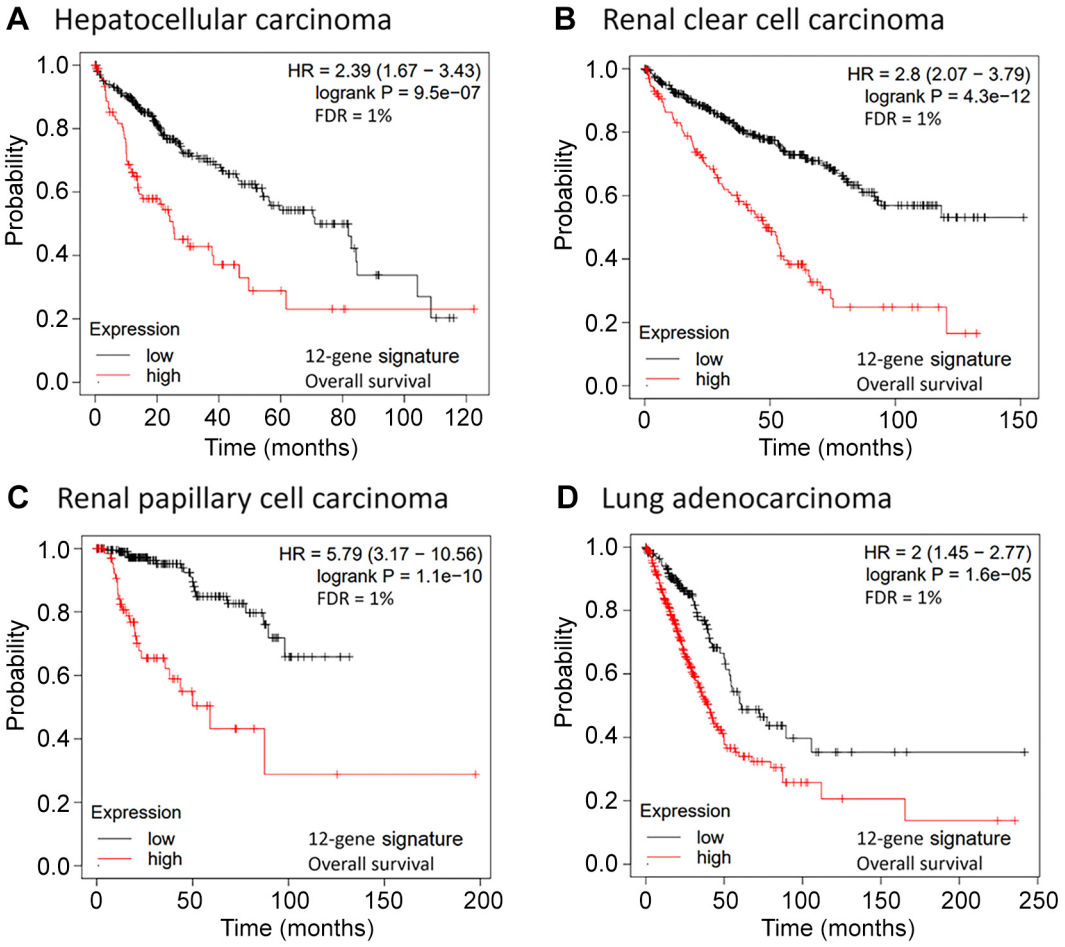

Figure 7. *Kaplan-Meier statistics of overall survival times of patients with (A) hepatocellular carcinoma, (B) renal clear cell carcinoma, (C) renal papillary cell carcinoma, or (D) lung adenocarcinoma and the mean mRNA expression of a 12-gene signature consisting of BUB1, BUB1B, CDK1, CENPA, CKAP2L, ISGAP3, MKI67, NDC80, PBK, RRM2, TOP2A, and TTK.*

satisfying long-term cures are not reachable in many cases. Therefore, new targets for new drugs are urgently required.

The biomarkers we found in our investigations were mainly related to the mitotic spindle and DNA metabolism. Mitosis and the DNA are also important treatment targets for classical anticancer drugs such as *Vinca* alkaloids, taxanes, alkylating agents, platin derivatives, and antimetabolites. However, the proteins identified in this study are novel candidates for targeted treatment. Some of the proteins encoded by the genes we identified are already used as drug targets (*e.g.*, TOP2A, CDK1) (28, 29), others are recognized but not yet largely exploited for drug discovery (30-35). Hence, there is considerable potential to identify novel inhibitors in the future for the proteins encoded by the genes identified in the present investigation.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, T.E.; methodology, E.O.; formal analysis, T.E.; investigation, E.O. and T.E.; data curation, E.O. and T.E.;

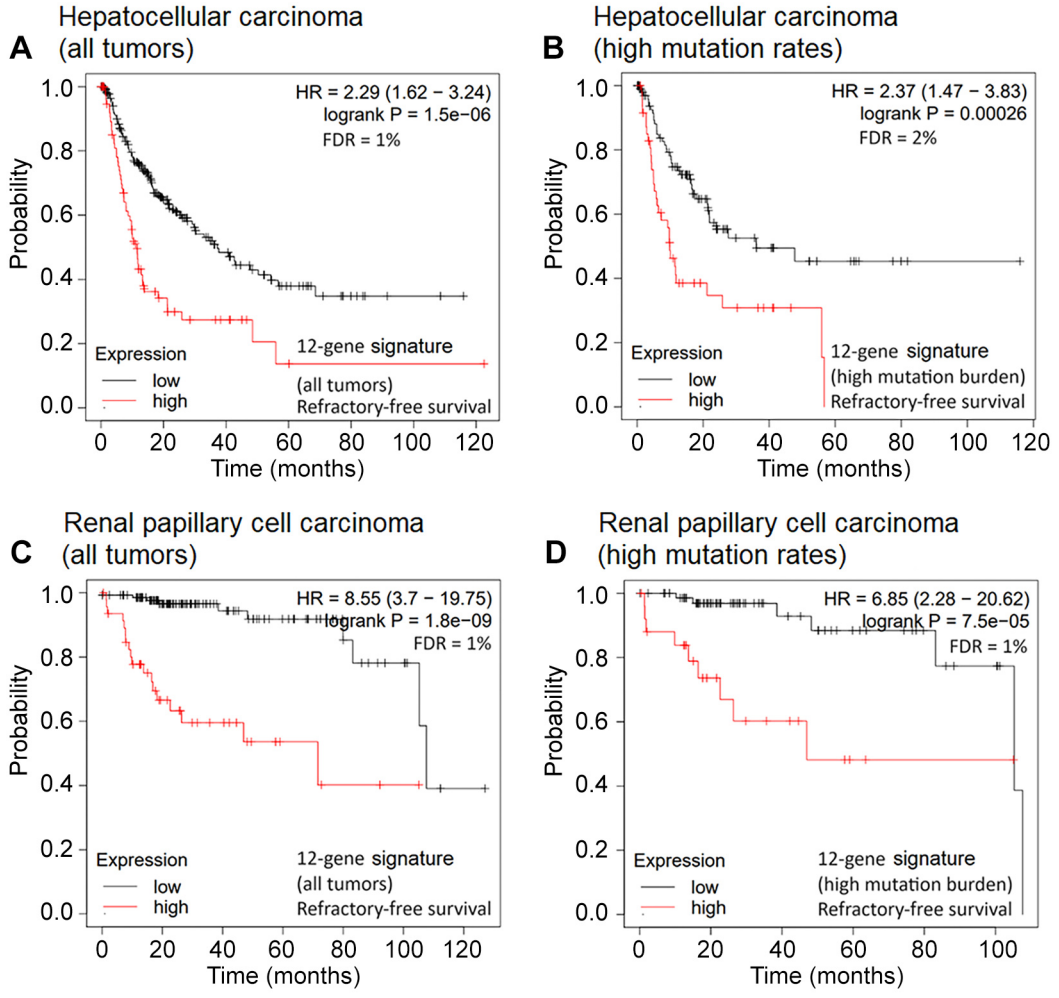

Figure 8. *Kaplan-Meier statistics of overall survival times of patients with (A, B) hepatocellular carcinoma or (C, D) renal papillary cell carcinoma. The panels A and B depict hepatocellular carcinomas and the panels C and D renal papillary cell carcinomas. The panels A and C show the survival irrespective of whether they had high or low mutation rates, while the panels B and D depict only those tumors with high mutation rates. Tumors with high mutation rates are considered as more aggressive than those with low numbers of mutations. Hence, it is relevant to know whether the identified candidate genes are also of prognostic significance in aggressive, highly mutated tumors.*

writing – original draft preparation, E.O. and T.E.; writing – review and editing, T.E.; supervision, T.E.; project administration, T.E. Both Authors have read and agreed to the published version of the manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 Corssmit EP, Romijn JA: Management of endocrine disease: Clinical management of paragangliomas. Eur J Endocrinol 171(6): R231-R243, 2014. DOI: 10.1530/EJE-14-0396

2 Brouwers FM, Elkahloun AG, Munson PJ, Eisenhofer G, Barb J, Linehan WM, Lenders JW, De Krijger R, Mannelli M,

Udelsman R, Ocal IT, Shulkin BL, Bornstein SR, Breza J, Ksinantova L, Pacak K: Gene expression profiling of benign and malignant pheochromocytoma. Ann N Y Acad Sci 1073: 541-556, 2006. DOI: 10.1196/annals.1353.058

3 Castro-Vega LJ, Lepoutre-Lussey C, Gimenez-Roqueplo A, Favier J: Rethinking pheochromocytomas and paragangliomas from a genomic perspective. Oncogene 35(9): 1080-1089, 2016. DOI: 10.1038/onc.2015.172

4 Alrezk R, Suarez A, Tena I, Pacak K: Update of pheochromocytoma syndromes: genetics, biochemical evaluation, and imaging. Front Endocrinol (Lausanne) 9: 515, 2018. DOI: 10.3389/fendo.2018.00515

5 Tang J, He D, Yang P, He J, Zhang Y: Genome-wide expression profiling of glioblastoma using a large combined cohort. Sci Rep 8(1): 15104, 2018. DOI: 10.1038/s41598-018-33323-z

6 Su Q, Ding Q, Zhang Z, Yang Z, Qiu Y, Li X, Mo W: Identification of genes associated with the metastasis of pheochromocytoma/paraganglioma based on weighted gene coexpression network analysis. Biomed Res Int 2020: 3876834, 2020. DOI: 10.1155/2020/3876834

7 Calsina B, Piñeiro-Yáñez E, Martínez-Montes ÁM, Caleiras E, Fernández-Sanromán Á, Monteagudo M, Torres-Pérez R, Fustero-Torre C, Pulgarín-Alfaro M, Gil E, Letón R, Jiménez S, García-Martín S, Martin MC, Roldán-Romero JM, Lanillos J, Mellid S, Santos M, Díaz-Talavera A, Rubio Á, González P, Hernando B, Bechmann N, Dona M, Calatayud M, Guadalix S, Álvarez-Escolá C, Regojo RM, Aller J, Del Olmo-Garcia MI, López-Fernández A, Fliedner SMJ, Rapizzi E, Fassnacht M, Beuschlein F, Quinkler M, Toledo RA, Mannelli M, Timmers HJ, Eisenhofer G, Rodríguez-Perales S, Domínguez O, Macintyre G, Currás-Freixes M, Rodríguez-Antona C, Cascón A, Leandro-García LJ, Montero-Conde C, Roncador G, García-García JF, Pacak K, Al-Shahrour F, Robledo M: Genomic and immune landscape of metastatic pheochromocytoma and paraganglioma. Nat Commun 14(1): 1122, 2023. DOI: 10.1038/s41467-023-36769-6

8 International Cancer Genome Consortium: International network of cancer genome projects. Nature 464(7291): 993-998, 2010. DOI: 10.1038/nature08987

9 Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, Mills GB, Shaw KR, Ozenberger BA, Ellrott K, Shmulevich I, Sander C, Stuart JM: The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet 45(10): 1113-1120, 2013. DOI: 10.1038/ng.2764

10 Nagy Á, Munkácsy G, Győrffy B: Pancancer survival analysis of cancer hallmark genes. Sci Rep 11(1): 6047, 2021. DOI: 10.1038/s41598-021-84787-5

11 Özenver N, Efferth T: Identification of prognostic and predictive biomarkers and druggable targets among 205 antioxidant genes in 21 different tumor types via data-mining. Pharmaceutics 15(2): 427, 2023. DOI: 10.3390/pharmaceutics15020427

12 Benjamini Y, Hochberg Y: Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Statistical Soc B (Methodological) 57(1): 289-300, 1995. DOI: 10.1111/j.2517-6161.1995.tb02031.x

13 Liggett LA, DeGregori J: Changing mutational and adaptive landscapes and the genesis of cancer. Biochim Biophys Acta Rev Cancer 1867(2): 84-94, 2017. DOI: 10.1016/j.bbcan.2017.01.005

14 Menon SS, Guruvayoorappan C, Sakthivel KM, Rasmi RR: Ki-67 protein as a tumour proliferation marker. Clin Chim Acta 491: 39-45, 2019. DOI: 10.1016/j.cca.2019.01.011

15 Simone L, Pisani F, Mola MG, De Bellis M, Merla G, Micale L, Frigeri A, Vescovi AL, Svelto M, Nicchia GP: AQP4 aggregation state is a determinant for glioma cell fate. Cancer Res 79(9): 2182-2194, 2019. DOI: 10.1158/0008-5472.CAN-18-2015

16 Zou S, Lan YL, Ren T, Li X, Zhang L, Wang H, Wang X: A bioinformatics analysis of the potential roles of aquaporin 4 in human brain tumors: an immune-related process. Front Pharmacol 12: 692175, 2021. DOI: 10.3389/fphar.2021.692175

17 Snijders AM, Lee SY, Hang B, Hao W, Bissell MJ, Mao JH: FAM83 family oncogenes are broadly involved in human cancers: an integrative multi-omics approach. Mol Oncol 11(2): 167-179, 2017. DOI: 10.1002/1878-0261.12016

18 Gao Z, Zhang D, Duan Y, Yan L, Fan Y, Fang Z, Liu Z: A five-gene signature predicts overall survival of patients with papillary renal cell carcinoma. PLoS One 14(3): e0211491, 2019. DOI: 10.1371/journal.pone.0211491

19 Jiang L, Zhao L, Bi J, Guan Q, Qi A, Wei Q, He M, Wei M, Zhao L: Glycolysis gene expression profilings screen for prognostic risk signature of hepatocellular carcinoma. Aging (Albany NY) 11(23): 10861-10882, 2019. DOI: 10.18632/aging.102489

20 Fu S, Liu Y, Zhang Z, Mei M, Chen Q, Wang S, Yang X, Sun T, Ma M, Xie W: Identification of a novel Myc-regulated gene signature for patients with kidney renal clear cell carcinoma. J Oncol 2022: 3487859, 2022. DOI: 10.1155/2022/3487859

21 Wu C, Luo Y, Chen Y, Qu H, Zheng L, Yao J: Development of a prognostic gene signature for hepatocellular carcinoma. Cancer Treat Res Commun 31: 100511, 2022. DOI: 10.1016/j.ctarc.2022.100511

22 Li Z, Qi F, Li F: Establishment of a gene signature to predict prognosis for patients with lung adenocarcinoma. Int J Mol Sci 21(22): 8479, 2020. DOI: 10.3390/ijms21228479

23 Wuttig D, Baier B, Fuessel S, Meinhardt M, Herr A, Hoefling C, Toma M, Grimm MO, Meye A, Rolle A, Wirth MP: Gene signatures of pulmonary metastases of renal cell carcinoma reflect the disease-free interval and the number of metastases per patient. Int J Cancer 125(2): 474-482, 2009. DOI: 10.1002/ijc.24353

24 Dai T, Li J, Lu X, Ye L, Yu H, Zhang L, Deng M, Zhu S, Liu W, Wang G, Yang Y: Prognostic role and potential mechanisms of the ferroptosis-related metabolic gene signature in

hepatocellular carcinoma. Pharmgenomics Pers Med 14: 927-945, 2021. DOI: 10.2147/PGPM.S319524
25 Zhang Y, Ren H, Zhang C, Li H, Guo Q, Xu H, Cui L: Development and validation of four ferroptosis-related gene signatures and their correlations with immune implication in hepatocellular carcinoma. Front Immunol 13: 1028054, 2022. DOI: 10.3389/fimmu.2022.1028054
26 Yin X, Wang Z, Wang J, Xu Y, Kong W, Zhang J: Development of a novel gene signature to predict prognosis and response to PD-1 blockade in clear cell renal cell carcinoma. Oncoimmunology 10(1): 1933332, 2021. DOI: 10.1080/2162402X.2021.1933332
27 Zhan C, Wang Z, Xu C, Huang X, Su J, Chen B, Wang M, Qi Z, Bai P: Development and validation of a prognostic gene signature in clear cell renal cell carcinoma. Front Mol Biosci 8: 609865, 2021. DOI: 10.3389/fmolb.2021.609865
28 Roskoski R Jr: Cyclin-dependent protein serine/threonine kinase inhibitors as anticancer drugs. Pharmacol Res 139: 471-488, 2019. DOI: 10.1016/j.phrs.2018.11.035
29 You F, Gao C: Topoisomerase inhibitors and targeted delivery in cancer therapy. Curr Top Med Chem 19(9): 713-729, 2019. DOI: 10.2174/1568026619666190401112948
30 Zhou B, Su L, Hu S, Hu W, Yip ML, Wu J, Gaur S, Smith DL, Yuan YC, Synold TW, Horne D, Yen Y: A small-molecule blocking ribonucleotide reductase holoenzyme formation inhibits cancer cell growth and overcomes drug resistance. Cancer Res 73(21): 6484-6493, 2013. DOI: 10.1158/0008-5472.CAN-13-1094
31 Abir-Awan M, Kitchen P, Salman MM, Conner MT, Conner AC, Bill RM: Inhibitors of mammalian aquaporin water channels. Int J Mol Sci 20(7): 1589, 2019. DOI: 10.3390/ijms20071589
32 Kar A, Zhang Y, Yacob BW, Saeed J, Tompkins KD, Bagby SM, Pitts TM, Somerset H, Leong S, Wierman ME, Kiseljak-Vassiliades K: Targeting PDZ-binding kinase is anti-tumorigenic in novel preclinical models of ACC. Endocr Relat Cancer 26(10): 765-778, 2019. DOI: 10.1530/ERC-19-0262
33 Wang S, Zhang M, Liang D, Sun W, Zhang C, Jiang M, Liu J, Li J, Li C, Yang X, Zhou X: Molecular design and anticancer activities of small-molecule monopolar spindle 1 inhibitors: A Medicinal chemistry perspective. Eur J Med Chem 175: 247-268, 2019. DOI: 10.1016/j.ejmech.2019.04.047
34 Martinez MJ, Lyles RDZ, Peinetti N, Grunfeld AM, Burnstein KL: Inhibition of the serine/threonine kinase BUB1 reverses taxane resistance in prostate cancer. iScience 26(9): 107681, 2023. DOI: 10.1016/j.isci.2023.107681
35 Mishra D, Mishra A, Rai SN, Singh SK, Vamanu E, Singh MP: In silico insight to identify potential inhibitors of BUB1B from mushroom bioactive compounds to prevent breast cancer metastasis. Front Biosci (Landmark Ed) 28(7): 151, 2023. DOI: 10.31083/j.fbl2807151
36 Jiang P, Sun TT, Chen CW, Huang RS, Zhong ZM, Lou XJ, Liu G, Wang L, Zuo RH: Identification of prognostic related hub genes in clear-cell renal cell carcinoma via bioinformatical analysis. Chin Med Sci J 36(2): 127-134, 2021. DOI: 10.24920/003651
37 Jiang W, Xu J, Liao Z, Li G, Zhang C, Feng Y: Prognostic signature for lung adenocarcinoma patients based on cell-cycle-related genes. Front Cell Dev Biol 9: 655950, 2021. DOI: 10.3389/fcell.2021.655950
38 Feng D, Zhang F, Liu L, Xiong Q, Xu H, Wei W, Liu Z, Yang L: SKA3 serves as a biomarker for poor prognosis in kidney renal papillary cell carcinoma. Int J Gen Med 14: 8591-8602, 2021. DOI: 10.2147/IJGM.S336799
39 Zhang L, Huang Y, Ling J, Zhuo W, Yu Z, Shao M, Luo Y, Zhu Y: Screening and function analysis of hub genes and pathways in hepatocellular carcinoma via bioinformatics approaches. Cancer Biomark 22(3): 511-521, 2018. DOI: 10.3233/CBM-171160
40 Li Z, Lin Y, Cheng B, Zhang Q, Cai Y: Identification and analysis of potential key genes associated with hepatocellular carcinoma based on integrated bioinformatics methods. Front Genet 12: 571231, 2021. DOI: 10.3389/fgene.2021.571231
41 Qi W, Bai Y, Wang Y, Liu L, Zhang Y, Yu Y, Chen H: BUB1 predicts poor prognosis and immune status in liver hepatocellular carcinoma. APMIS 130(7): 371-382, 2022. DOI: 10.1111/apm.13219
42 Shi Q, Meng Z, Tian XX, Wang YF, Wang WH: Identification and validation of a hub gene prognostic index for hepatocellular carcinoma. Future Oncol 17(17): 2193-2208, 2021. DOI: 10.2217/fon-2020-1112
43 Chen C, Guo Q, Song Y, Xu G, Liu L: SKA1/2/3 serves as a biomarker for poor prognosis in human lung adenocarcinoma. Transl Lung Cancer Res 9(2): 218-231, 2020. DOI: 10.21037/tlcr.2020.01.20
44 Zhang L, He M, Zhu W, Lv X, Zhao Y, Yan Y, Li X, Jiang L, Zhao L, Fan Y, Su P, Gao M, Ma H, Li K, Wei M: Identification of a panel of mitotic spindle-related genes as a signature predicting survival in lung adenocarcinoma. J Cell Physiol 235(5): 4361-4375, 2020. DOI: 10.1002/jcp.29312
45 Lin X, Zhou M, Xu Z, Chen Y, Lin F: Bioinformatics study on genes related to a high-risk postoperative recurrence of lung adenocarcinoma. Sci Prog 104(3): 368504211018053, 2021. DOI: 10.1177/00368504211018053
46 Song P, Chen J, Zhang X, Yin X: Construction of competitive endogenous RNA network related to circular RNA and prognostic nomogram model in lung adenocarcinoma. Math Biosci Eng 18(6): 9806-9821, 2021. DOI: 10.3934/mbe.2021481
47 Wang K, Zhang M, Wang J, Sun P, Luo J, Jin H, Li R, Pan C, Lu L: A systematic analysis identifies key regulators involved in cell proliferation and potential drugs for the treatment of human lung adenocarcinoma. Front Oncol 11: 737152, 2021. DOI: 10.3389/fonc.2021.737152
48 Chen R, Wang Z, Lu T, Liu Y, Ji Y, Yu Y, Tou F, Guo S: Budding uninhibited by benzimidazoles 1 overexpression is

associated with poor prognosis and malignant phenotype: A promising therapeutic target for lung adenocarcinoma. Thorac Cancer 14(10): 893-912, 2023. DOI: 10.1111/1759-7714.14822

49 Guo J, Li W, Cheng L, Gao X: Identification and validation of hub genes with poor prognosis in hepatocellular carcinoma by integrated bioinformatical analysis. Int J Gen Med 15: 3933-3941, 2022. DOI: 10.2147/IJGM.S353708

50 Song YJ, Tan J, Gao XH, Wang LX: Integrated analysis reveals key genes with prognostic value in lung adenocarcinoma. Cancer Manag Res 10: 6097-6108, 2018. DOI: 10.2147/CMAR.S168636

51 Qiu J, Zhang S, Wang P, Wang H, Sha B, Peng H, Ju Z, Rao J, Lu L: BUB1B promotes hepatocellular carcinoma progression via activation of the mTORC1 signaling pathway. Cancer Med 9(21): 8159-8172, 2020. DOI: 10.1002/cam4.3411

52 Chen J, Liao Y, Fan X: Prognostic and clinicopathological value of BUB1B expression in patients with lung adenocarcinoma: a meta-analysis. Expert Rev Anticancer Ther 21(7): 795-803, 2021. DOI: 10.1080/14737140.2021.1908132

53 Hongo F, Takaha N, Oishi M, Ueda T, Nakamura T, Naitoh Y, Naya Y, Kamoi K, Okihara K, Matsushima T, Nakayama S, Ishihara H, Sakai T, Miki T: CDK1 and CDK2 activity is a strong predictor of renal cell carcinoma recurrence. Urol Oncol 32(8): 1240-1246, 2014. DOI: 10.1016/j.urolonc.2014.05.006

54 Cai J, Li B, Zhu Y, Fang X, Zhu M, Wang M, Liu S, Jiang X, Zheng J, Zhang X, Chen P: Prognostic biomarker identification through integrating the gene signatures of hepatocellular carcinoma properties. EBioMedicine 19: 18-30, 2017. DOI: 10.1016/j.ebiom.2017.04.014

55 Li B, Pu K, Wu X: Identifying novel biomarkers in hepatocellular carcinoma by weighted gene co-expression network analysis. J Cell Biochem 120(7): 11418-11431, 2019. DOI: 10.1002/jcb.28420

56 Zhou Z, Li Y, Hao H, Wang Y, Zhou Z, Wang Z, Chu X: Screening hub genes as prognostic biomarkers of hepatocellular carcinoma by bioinformatics analysis. Cell Transplant 28(1_suppl): 76S-86S, 2019. DOI: 10.1177/0963689719893950

57 Liping X, Jia L, Qi C, Liang Y, Dongen L, Jianshuai J: Cell cycle genes are potential diagnostic and prognostic biomarkers in hepatocellular carcinoma. Biomed Res Int 2020: 6206157, 2020. DOI: 10.1155/2020/6206157

58 Meng Z, Wu J, Liu X, Zhou W, Ni M, Liu S, Guo S, Jia S, Zhang J: Identification of potential hub genes associated with the pathogenesis and prognosis of hepatocellular carcinoma via integrated bioinformatics analysis. J Int Med Res 48(7): 300060520910019, 2020. DOI: 10.1177/0300060520910019

59 Zou Y, Ruan S, Jin L, Chen Z, Han H, Zhang Y, Jian Z, Lin Y, Shi N, Jin H: CDK1, CCNB1, and CCNB2 are prognostic biomarkers and correlated with immune infiltration in hepatocellular carcinoma. Med Sci Monit 26: e925289, 2020. DOI: 10.12659/MSM.925289

60 Lei X, Zhang M, Guan B, Chen Q, Dong Z, Wang C: Identification of hub genes associated with prognosis, diagnosis, immune infiltration and therapeutic drug in liver cancer by integrated analysis. Hum Genomics 15(1): 39, 2021. DOI: 10.1186/s40246-021-00341-4

61 Liu J, Han F, Ding J, Liang X, Liu J, Huang D, Zhang C: Identification of multiple hub genes and pathways in hepatocellular carcinoma: a bioinformatics analysis. Biomed Res Int 2021: 8849415, 2021. DOI: 10.1155/2021/8849415

62 Nguyen TB, Do DN, Nguyen-Thanh T, Tatipamula VB, Nguyen HT: Identification of five hub genes as key prognostic biomarkers in liver cancer *via* integrated bioinformatics analysis. Biology (Basel) 10(10): 957, 2021. DOI: 10.3390/biology10100957

63 Zhang L, Li Y, Dai Y, Wang D, Wang X, Cao Y, Liu W, Tao Z: Glycolysis-related gene expression profiling serves as a novel prognosis risk predictor for human hepatocellular carcinoma. Sci Rep 11(1): 18875, 2021. DOI: 10.1038/s41598-021-98381-2

64 Kakar MU, Mehboob MZ, Akram M, Shah M, Shakir Y, Ijaz HW, Aziz U, Ullah Z, Ahmad S, Ali S, Yin Y: Identification of differentially expressed genes associated with the prognosis and diagnosis of hepatocellular carcinoma by integrated bioinformatics analysis. Biomed Res Int 2022: 4237633, 2022. DOI: 10.1155/2022/4237633

65 Chen S, Shen B, Wu Y, Shen L, Qi H, Cao F, Huang T, Tan H, Zhang G, Fan W: Identification of prognosis-related cyclin-dependent kinases and potential response drugs in hepatocellular carcinoma. J Cancer Res Ther 19(1): 108-116, 2023. DOI: 10.4103/jcrt.jcrt_1703_22

66 Islam B, Yu HY, Duan TQ, Pan J, Li M, Zhang RQ, Masroor M, Huang JF: Cell cycle kinases (AUKA, CDK1, PLK1) are prognostic biomarkers and correlated with tumor-infiltrating leukocytes in HBV related HCC. J Biomol Struct Dyn 41(21): 11845-11861, 2023. DOI: 10.1080/07391102.2022.2164056

67 Shi YX, Zhu T, Zou T, Zhuo W, Chen YX, Huang MS, Zheng W, Wang CJ, Li X, Mao XY, Zhang W, Zhou HH, Yin JY, Liu ZQ: Prognostic and predictive values of CDK1 and MAD2L1 in lung adenocarcinoma. Oncotarget 7(51): 85235-85243, 2016. DOI: 10.18632/oncotarget.13252

68 Liu WT, Wang Y, Zhang J, Ye F, Huang XH, Li B, He QY: A novel strategy of integrated microarray analysis identifies CENPA, CDK1 and CDC20 as a cluster of diagnostic biomarkers in lung adenocarcinoma. Cancer Lett 425: 43-53, 2018. DOI: 10.1016/j.canlet.2018.03.043

69 Cheng Y, Hou K, Wang Y, Chen Y, Zheng X, Qi J, Yang B, Tang S, Han X, Shi D, Wang X, Liu Y, Hu X, Che X: Identification of prognostic signature and gliclazide as candidate drugs in lung adenocarcinoma. Front Oncol 11: 665276, 2021. DOI: 10.3389/fonc.2021.665276

70 Feng C, Che W, Liang H, Zhang H, Lan C, Wu B, Lin W, Chen Y: Mining database to identify aging-related molecular subtype and prognostic signature in lung adenocarcinoma. J Oncol 2022: 9142903, 2022. DOI: 10.1155/2022/9142903

71 Du Q, Liu W, Mei T, Wang J, Qin T, Huang D: Prognostic and immunological characteristics of CDK1 in lung adenocarcinoma: A systematic analysis. Front Oncol 13: 1128443, 2023. DOI: 10.3389/fonc.2023.1128443
72 Li X, Xu C, Min Y, Zhai Z, Zhu Y: A prognostic signature for lung adenocarcinoma by five genes associated with chemotherapy in lung adenocarcinoma. Clin Respir J 17(12): 1349-1360, 2023. DOI: 10.1111/crj.13723
73 Li J, Li Q, Yuan Y, Xie Y, Zhang Y, Zhang R: High CENPA expression in papillary renal cell carcinoma tissues is associated with poor prognosis. BMC Urol 22(1): 157, 2022. DOI: 10.1186/s12894-022-01106-4
74 Long J, Zhang L, Wan X, Lin J, Bai Y, Xu W, Xiong J, Zhao H: A four-gene-based prognostic model predicts overall survival in patients with hepatocellular carcinoma. J Cell Mol Med 22(12): 5928-5938, 2018. DOI: 10.1111/jcmm.13863
75 Li C, Ding J, Mei J: Comprehensive analysis of epigenetic associated genes on differential gene expression and prognosis in hepatocellular carcinoma. J Environ Pathol Toxicol Oncol 41(1): 27-43, 2022. DOI: 10.1615/JEnvironPatholToxicolOncol.2021039641
76 Zhang S, Zheng Y, Li X, Zhang S, Hu H, Kuang W: Cellular senescence-related gene signature as a valuable predictor of prognosis in hepatocellular carcinoma. Aging (Albany NY) 15(8): 3064-3093, 2023. DOI: 10.18632/aging.204658
77 Wu Q, Qian YM, Zhao XL, Wang SM, Feng XJ, Chen XF, Zhang SH: Expression and prognostic significance of centromere protein A in human lung adenocarcinoma. Lung Cancer 77(2): 407-414, 2012. DOI: 10.1016/j.lungcan.2012.04.007
78 Zhou H, Bian T, Qian L, Zhao C, Zhang W, Zheng M, Zhou H, Liu L, Sun H, Li X, Zhang J, Liu Y: Prognostic model of lung adenocarcinoma constructed by the CENPA complex genes is closely related to immune infiltration. Pathol Res Pract 228: 153680, 2021. DOI: 10.1016/j.prp.2021.153680
79 Liu Z, Zhang J, Shen D, Hu X, Ke Z, Ehrich Lister IN, Sihombing B: Prognostic significance of CKAP2L expression in patients with clear cell renal cell carcinoma. Front Genet 13: 873884, 2023. DOI: 10.3389/fgene.2022.873884
80 Wang P, He X: Oncogenic and prognostic role of CKAP2L in hepatocellular carcinoma. Int J Clin Exp Pathol 13(5): 923-933, 2020.
81 Xiong G, Li L, Chen X, Song S, Zhao Y, Cai W, Peng J: Up-regulation of CKAP2L expression promotes lung adenocarcinoma invasion and is associated with poor prognosis. Onco Targets Ther 12: 1171-1180, 2019. DOI: 10.2147/OTT.S182242
82 Meng Q, Li CX, Long D, Lin X: IQGAP3 may serve as a promising biomarker in clear cell renal cell carcinoma. Int J Gen Med 14: 3469-3484, 2021. DOI: 10.2147/IJGM.S316280
83 Li W, Wang Z, Wang H, Zhang J, Wang X, Xing S, Chen S: IQGAP3 in clear cell renal cell carcinoma contributes to drug resistance and genome stability. PeerJ 10: e14201, 2022. DOI: 10.7717/peerj.14201
84 Shi Y, Qin N, Zhou Q, Chen Y, Huang S, Chen B, Shen G, Jia H: Role of IQGAP3 in metastasis and epithelial-mesenchymal transition in human hepatocellular carcinoma. J Transl Med 15(1): 176, 2017. DOI: 10.1186/s12967-017-1275-8
85 Wang J, Han K, Li Y, Zhang C, Cui WH, Zhu LH, Luo T, Bian CJ: Exploration and validation of the prognostic value of RNA-binding proteins in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 26(23): 8945-8958, 2022. DOI: 10.26355/eurrev_202212_30569
86 Dai Q, Song F, Li X, Huang F, Zhao H: Comprehensive analysis of the expression and prognosis for IQ motif-containing GTPase-activating proteins in hepatocellular carcinoma. BMC Cancer 22(1): 1121, 2022. DOI: 10.1186/s12885-022-10204-3
87 Wu SY, Liao P, Yan LY, Zhao QY, Xie ZY, Dong J, Sun HT: Correlation of MKI67 with prognosis, immune infiltration, and T cell exhaustion in hepatocellular carcinoma. BMC Gastroenterol 21(1): 416, 2021. DOI: 10.1186/s12876-021-01984-2
88 Duan S, Gao J, Lou W, Zhang Y, Deng Y, Wang C, Huang H, Xu H, Guo S, Lai S, Xi F, Li Z, Deng L, Zhong Y: Prognostic signature for hepatocellular carcinoma based on 4 pyroptosis-related genes. BMC Med Genomics 15(1): 166, 2022. DOI: 10.1186/s12920-022-01322-9
89 Li K, Yang Y, Ma M, Lu S, Li J: Hypoxia-based classification and prognostic signature for clinical management of hepatocellular carcinoma. World J Surg Oncol 21(1): 216, 2023. DOI: 10.1186/s12957-023-03090-x
90 Ghandili S, Oqueka T, Schmitz M, Janning M, Körbelin J, Westphalen CB, P Haen S, Loges S, Bokemeyer C, Klose H, Hennigs JK: Integrative public data-mining pipeline for the validation of novel independent prognostic biomarkers for lung adenocarcinoma. Biomark Med 14(17): 1651-1662, 2020. DOI: 10.2217/bmm-2020-0405
91 Li J, Liu X, Cui Z, Han G: Comprehensive analysis of candidate diagnostic and prognostic biomarkers associated with lung adenocarcinoma. Med Sci Monit 26: e922070, 2020. DOI: 10.12659/MSM.922070
92 Lin X, Zhou T, Hu S, Yang L, Yang Z, Pang H, Zhou X, Zhong R, Fang X, Yu Z, Hu K: Prognostic significance of pyroptosis-related factors in lung adenocarcinoma. J Thorac Dis 14(3): 654-667, 2022. DOI: 10.21037/jtd-22-86
93 Yang Y, Zhang S, Guo L: Characterization of cell cycle-related competing endogenous RNAs using robust rank aggregation as prognostic biomarker in lung adenocarcinoma. Front Oncol 12: 807367, 2022. DOI: 10.3389/fonc.2022.807367
94 Zhang B, Zhou Q, Xie Q, Lin X, Miao W, Wei Z, Zheng T, Pang Z, Liu H, Chen X: SPC25 overexpression promotes tumor proliferation and is prognostic of poor survival in hepatocellular carcinoma. Aging (Albany NY) 13(2): 2803-2821, 2020. DOI: 10.18632/aging.202329
95 Zhang H, Zou J, Yin Y, Zhang B, Hu Y, Wang J, Mu H: Bioinformatic analysis identifies potentially key differentially expressed genes

in oncogenesis and progression of clear cell renal cell carcinoma. PeerJ 7: e8096, 2019. DOI: 10.7717/peerj.8096
96 Xie W, Wang B, Wang X, Hou D, Su H, Huang H: Nine hub genes related to the prognosis of HBV-positive hepatocellular carcinoma identified by protein interaction analysis. Ann Transl Med 8(7): 478, 2020. DOI: 10.21037/atm.2020.03.94
97 Huang R, Liu J, Li H, Zheng L, Jin H, Zhang Y, Ma W, Su J, Wang M, Yang K: Identification of hub genes and their correlation with immune infiltration cells in hepatocellular carcinoma based on GEO and TCGA databases. Front Genet 12: 647353, 2021. DOI: 10.3389/fgene.2021.647353
98 Jiang SS, Ke SJ, Ke ZL, Li J, Li X, Xie XW: Cell division cycle associated genes as diagnostic and prognostic biomarkers in hepatocellular carcinoma. Front Mol Biosci 8: 657161, 2021. DOI: 10.3389/fmolb.2021.657161
99 Wang J, Li Y, Zhang C, Chen X, Zhu L, Luo T: Characterization of diagnostic and prognostic significance of cell cycle-linked genes in hepatocellular carcinoma. Transl Cancer Res 10(11): 4636-4651, 2021. DOI: 10.21037/tcr-21-1145
100 Sun ZY, Wang W, Gao H, Chen QF: Potential therapeutic targets of the nuclear division cycle 80 (NDC80) complexes genes in lung adenocarcinoma. J Cancer 11(10): 2921-2934, 2020. DOI: 10.7150/jca.41834
101 Deng R, Li J, Zhao H, Zou Z, Man J, Cao J, Yang L: Identification of potential biomarkers associated with immune infiltration in papillary renal cell carcinoma. J Clin Lab Anal 35(11): e24022, 2021. DOI: 10.1002/jcla.24022
102 Agarwal R, Narayan J, Bhattacharyya A, Saraswat M, Tomar AK: Gene expression profiling, pathway analysis and subtype classification reveal molecular heterogeneity in hepatocellular carcinoma and suggest subtype specific therapeutic targets. Cancer Genet 216-217: 37-51, 2017. DOI: 10.1016/j.cancergen.2017.06.002
103 Yan Y, Lu Y, Mao K, Zhang M, Liu H, Zhou Q, Lin J, Zhang J, Wang J, Xiao Z: Identification and validation of a prognostic four-genes signature for hepatocellular carcinoma: integrated ceRNA network analysis. Hepatol Int 13(5): 618-630, 2019. DOI: 10.1007/s12072-019-09962-3
104 Zhou Z, Li Y, Hao H, Wang Y, Zhou Z, Wang Z, Chu X: Screening hub genes as prognostic biomarkers of hepatocellular carcinoma by bioinformatics analysis. Cell Transplant 28(1_suppl): 76S-86S, 2019. DOI: 10.1177/0963689719893950
105 Wang J, Wang Y, Xu J, Song Q, Shangguan J, Xue M, Wang H, Gan J, Gao W: Global analysis of gene expression signature and diagnostic/prognostic biomarker identification of hepatocellular carcinoma. Sci Prog 104(3): 368504211029429, 2021. DOI: 10.1177/00368504211029429
106 Mu W, Xie Y, Li J, Yan R, Zhang J, Liu Y, Fan Y: High expression of PDZ-binding kinase is correlated with poor prognosis and immune infiltrates in hepatocellular carcinoma. World J Surg Oncol 20(1): 22, 2022. DOI: 10.1186/s12957-021-02479-w
107 Wang L, Qiu M, Wu L, Li Z, Meng X, He L, Yang B: Construction and validation of prognostic signature for hepatocellular carcinoma basing on hepatitis B virus related specific genes. Infect Agent Cancer 17(1): 60, 2022. DOI: 10.1186/s13027-022-00470-y
108 Chen Y, Huang W, Ouyang J, Wang J, Xie Z: Identification of anoikis-related subgroups and prognosis model in liver hepatocellular carcinoma. Int J Mol Sci 24(3): 2862, 2023. DOI: 10.3390/ijms24032862
109 Ding D, Wang D, Qin Y: Development and validation of multi-omic prognostic signature of anoikis-related genes in liver hepatocellular carcinoma. Medicine (Baltimore) 102(46): e36190, 2023. DOI: 10.1097/MD.0000000000036190
110 Lei B, Qi W, Zhao Y, Li Y, Liu S, Xu X, Zhi C, Wan L, Shen H: PBK/TOPK expression correlates with mutant p53 and affects patients' prognosis and cell proliferation and viability in lung adenocarcinoma. Hum Pathol 46(2): 217-224, 2015. DOI: 10.1016/j.humpath.2014.07.026
111 Abdel-Maksoud MA, Hassan F, Mubarik U, Mubarak A, Farrag MA, Alghamdi S, Atuahene SA, Almekhlafi S, Aufy M: An in-silico approach leads to explore six genes as a molecular signature of lung adenocarcinoma. Am J Cancer Res 13(3): 727-757, 2023.
112 Hu Z, Chen H, Li H, Xu S, Mu Y, Pan Q, Tong J, Xu G: Lysosome-related genes: A new prognostic marker for lung adenocarcinoma. Medicine (Baltimore) 102(35): e34844, 2023. DOI: 10.1097/MD.0000000000034844
113 Ma H, Zhang J, Shi Y, Wang Z, Nie W, Cai J, Huang Y, Liu B, Wang X, Lian C: PBK correlates with prognosis, immune escape and drug response in LUAD. Sci Rep 13(1): 20452, 2023. DOI: 10.1038/s41598-023-47781-7
114 Luo Y, Shen D, Chen L, Wang G, Liu X, Qian K, Xiao Y, Wang X, Ju L: Identification of 9 key genes and small molecule drugs in clear cell renal cell carcinoma. Aging (Albany NY) 11(16): 6029-6052, 2019. DOI: 10.18632/aging.102161
115 Guo X, Sun Z, Jiang S, Jin X, Wang H: Identification and validation of a two-gene metabolic signature for survival prediction in patients with kidney renal clear cell carcinoma. Aging (Albany NY) 13(6): 8276-8289, 2021. DOI: 10.18632/aging.202636
116 Huang S, Luo Q, Huang J, Wei J, Wang S, Hong C, Qiu P, Li C: A cluster of metabolic-related genes serve as potential prognostic biomarkers for renal cell carcinoma. Front Genet 13: 902064, 2022. DOI: 10.3389/fgene.2022.902064
117 Zhou Z, Yang Z, Cui Y, Lu S, Huang Y, Che X, Yang L, Zhang Y: Identification and validation of a ferroptosis-related long non-coding RNA (FRlncRNA) signature to predict survival outcomes and the immune microenvironment in patients with clear cell renal cell carcinoma. Front Genet 13: 787884, 2022. DOI: 10.3389/fgene.2022.787884
118 Zhu W, Ding M, Chang J, Liao H, Xiao G, Wang Q: A 9-gene prognostic signature for kidney renal clear cell carcinoma overall survival based on co-expression and regression

analyses. Chem Biol Drug Des 101(2): 422-437, 2023. DOI: 10.1111/cbdd.14141
119 Da Q, Ren M, Huang L, Qu J, Yang Q, Xu J, Ma Q, Mao X, Cai Y, Zhao D, Luo J, Yan Z, Sun L, Ouyang K, Zhang X, Han Z, Liu J, Wang T: Identification and validation of a ferroptosis-related signature for predicting prognosis and immune microenvironment in papillary renal cell carcinoma. Int J Gen Med 15: 2963-2977, 2022. DOI: 10.2147/IJGM.S354882
120 Lee B, Ha SY, Song DH, Lee HW, Cho SY, Park CK: High expression of ribonucleotide reductase subunit M2 correlates with poor prognosis of hepatocellular carcinoma. Gut Liver 8(6): 662-668, 2014. DOI: 10.5009/gnl13392
121 Chen D, Feng Z, Zhou M, Ren Z, Zhang F, Li Y: Bioinformatic evidence reveals that cell cycle correlated genes drive the communication between tumor cells and the tumor microenvironment and impact the outcomes of hepatocellular carcinoma. Biomed Res Int 2021: 4092635, 2021. DOI: 10.1155/2021/4092635
122 Gao S, Gang J, Yu M, Xin G, Tan H: Computational analysis for identification of early diagnostic biomarkers and prognostic biomarkers of liver cancer based on GEO and TCGA databases and studies on pathways and biological functions affecting the survival time of liver cancer. BMC Cancer 21(1): 791, 2021. DOI: 10.1186/s12885-021-08520-1
123 Huo J, Wu L, Zang Y: Development and validation of a metabolic-related prognostic model for hepatocellular carcinoma. J Clin Transl Hepatol 9(2): 169-179, 2021. DOI: 10.14218/JCTH.2020.00114
124 Su WJ, Lu PZ, Wu Y, Kalpana K, Yang CK, Lu GD: Identification of key genes in purine metabolism as prognostic biomarker for hepatocellular carcinoma. Front Oncol 10: 583053, 2021. DOI: 10.3389/fonc.2020.583053
125 Tian D, Yu Y, Zhang L, Sun J, Jiang W: A five-gene-based prognostic signature for hepatocellular carcinoma. Front Med (Lausanne) 8: 681388, 2021. DOI: 10.3389/fmed.2021.681388
126 Zhang L, Yuan L, Li D, Tian M, Sun S, Wang Q: Identification of potential prognostic biomarkers for hepatocellular carcinoma. J Gastrointest Oncol 13(2): 812-821, 2022. DOI: 10.21037/jgo-22-303
127 Weng W, Zhang D, Li S: Life span-associated ferroptosis-related genes identification and validation for hepatocellular carcinoma patients as hepatitis B virus carriers. J Clin Lab Anal 37(13-14): e24930, 2023. DOI: 10.1002/jcla.24930
128 Qin Z, Xie B, Qian J, Ma X, Zhang L, Wei J, Wang Z, Fan L, Zhu Z, Qian Z, Yin H, Zhu F, Tan Y: Over-expression of RRM2 predicts adverse prognosis correlated with immune infiltrates: A potential biomarker for hepatocellular carcinoma. Front Oncol 13: 1144269, 2023. DOI: 10.3389/fonc.2023.1144269
129 Yin X, Jiang K, Zhou Z, Yu H, Yan D, He X, Yan S: Prognostic and Immunological Potential of Ribonucleotide Reductase Subunits in Liver Cancer. Oxid Med Cell Longev 2023: 3878796, 2023. DOI: 10.1155/2023/3878796
130 Jin CY, Du L, Nuerlan AH, Wang XL, Yang YW, Guo R: High expression of RRM2 as an independent predictive factor of poor prognosis in patients with lung adenocarcinoma. Aging (Albany NY) 13(3): 3518-3535, 2020. DOI: 10.18632/aging.202292
131 Ma C, Luo H, Cao J, Gao C, Fa X, Wang G: Independent prognostic implications of RRM2 in lung adenocarcinoma. J Cancer 11(23): 7009-7022, 2020. DOI: 10.7150/jca.47895
132 Wang H, Wang X, Xu L, Zhang J, Cao H: High expression levels of pyrimidine metabolic rate-limiting enzymes are adverse prognostic factors in lung adenocarcinoma: a study based on The Cancer Genome Atlas and Gene Expression Omnibus datasets. Purinergic Signal 16(3): 347-366, 2020. DOI: 10.1007/s11302-020-09711-4
133 Zeng H, Ji J, Song X, Huang Y, Li H, Huang J, Ma X: Stemness related genes revealed by network analysis associated with tumor immune microenvironment and the clinical outcome in lung adenocarcinoma. Front Genet 11: 549213, 2020. DOI: 10.3389/fgene.2020.549213
134 Cheng WC, Chang CY, Lo CC, Hsieh CY, Kuo TT, Tseng GC, Wong SC, Chiang SF, Huang KC, Lai LC, Lu TP, Chao KSC, Sher YP: Identification of theranostic factors for patients developing metastasis after surgery for early-stage lung adenocarcinoma. Theranostics 11(8): 3661-3675, 2021. DOI: 10.7150/thno.53176
135 Li C, Wan Y, Deng W, Fei F, Wang L, Qi F, Zheng Z: Promising novel biomarkers and candidate small-molecule drugs for lung adenocarcinoma: Evidence from bioinformatics analysis of high-throughput data. Open Med (Wars) 17(1): 96-112, 2021. DOI: 10.1515/med-2021-0375
136 Tang B, Xu W, Wang Y, Zhu J, Wang H, Tu J, Weng Q, Kong C, Yang Y, Qiu R, Zhao Z, Xu M, Ji J: Identification of critical ferroptosis regulators in lung adenocarcinoma that RRM2 facilitates tumor immune infiltration by inhibiting ferroptotic death. Clin Immunol 232: 108872, 2021. DOI: 10.1016/j.clim.2021.108872
137 Zhang A, Yang J, Ma C, Li F, Luo H: Development and validation of a robust ferroptosis-related prognostic signature in lung adenocarcinoma. Front Cell Dev Biol 9: 616271, 2021. DOI: 10.3389/fcell.2021.616271
138 Deng B, Xiang J, Liang Z, Luo L: Identification and validation of a ferroptosis-related gene to predict survival outcomes and the immune microenvironment in lung adenocarcinoma. Cancer Cell Int 22(1): 292, 2022. DOI: 10.1186/s12935-022-02699-4
139 Li HL, Wang JX, Dai HW, Liu JJ, Liu ZY, Zou MY, Zhang L, Wang WR: Prognostic prediction value and biological functions of non-apoptotic regulated cell death genes in lung adenocarcinoma. Chin Med Sci J 38(3): 178-190, 2023. DOI: 10.24920/004222
140 Chen D, Maruschke M, Hakenberg O, Zimmermann W, Stief CG, Buchner A: TOP2A, HELLS, ATAD2, and TET3 are novel prognostic markers in renal cell carcinoma. Urology 102: 265.e1-265.e7, 2017. DOI: 10.1016/j.urology.2016.12.050

141 Gu Y, Lu L, Wu L, Chen H, Zhu W, He Y: Identification of prognostic genes in kidney renal clear cell carcinoma by RNA-seq data analysis. Mol Med Rep 15(4): 1661-1667, 2017. DOI: 10.3892/mmr.2017.6194
142 Berglund A, Amankwah EK, Kim YC, Spiess PE, Sexton WJ, Manley B, Park HY, Wang L, Chahoud J, Chakrabarti R, Yeo CD, Luu HN, Pietro GD, Parker A, Park JY: Influence of gene expression on survival of clear cell renal cell carcinoma. Cancer Med 9(22): 8662-8675, 2020. DOI: 10.1002/cam4.3475
143 Wong N, Yeo W, Wong WL, Wong NL, Chan KY, Mo FK, Koh J, Chan SL, Chan AT, Lai PB, Ching AK, Tong JH, Ng HK, Johnson PJ, To KF: TOP2A overexpression in hepatocellular carcinoma correlates with early age onset, shorter patients survival and chemoresistance. Int J Cancer 124(3): 644-652, 2009. DOI: 10.1002/ijc.23968
144 Chen PF, Li QH, Zeng LR, Yang XY, Peng PL, He JH, Fan B: A 4-gene prognostic signature predicting survival in hepatocellular carcinoma. J Cell Biochem 120(6): 9117-9124, 2019. DOI: 10.1002/jcb.28187
145 Cai H, Shao B, Zhou Y, Chen Z: High expression of TOP2A in hepatocellular carcinoma is associated with disease progression and poor prognosis. Oncol Lett 20(5): 232, 2020. DOI: 10.3892/ol.2020.12095
146 Liu R, Wang G, Zhang C, Bai D: A prognostic model for hepatocellular carcinoma based on apoptosis-related genes. World J Surg Oncol 19(1): 70, 2021. DOI: 10.1186/s12957-021-02175-9
147 Ma X, Zhou L, Zheng S: Transcriptome analysis revealed key prognostic genes and microRNAs in hepatocellular carcinoma. PeerJ 8: e8930, 2020. DOI: 10.7717/peerj.8930
148 Zeng Y, He H, Zhang Y, Wang X, Yang L, An Z: CCNB2, TOP2A, and ASPM reflect the prognosis of hepatocellular carcinoma, as determined by weighted gene coexpression network analysis. Biomed Res Int 2020: 4612158, 2020. DOI: 10.1155/2020/4612158
149 Meng J, Wei Y, Deng Q, Li L, Li X: Study on the expression of TOP2A in hepatocellular carcinoma and its relationship with patient prognosis. Cancer Cell Int 22(1): 29, 2022. DOI: 10.1186/s12935-021-02439-0
150 Tang Y, Guo C, Chen C, Zhang Y: Characterization of cellular senescence patterns predicts the prognosis and therapeutic response of hepatocellular carcinoma. Front Mol Biosci 9: 1100285, 2022. DOI: 10.3389/fmolb.2022.1100285
151 Feng J, Wei X, Liu Y, Zhang Y, Li G, Xu Y, Zhou P, Zhang J, Han X, Zhang C, Zhang Y, Wang G: Identification of topoisomerase 2A as a novel bone metastasis-related gene in liver hepatocellular carcinoma. Aging (Albany NY) 15(22): 13010-13040, 2023. DOI: 10.18632/aging.205216
152 Du X, Xue Z, Lv J, Wang H: Expression of the Topoisomerase II Alpha (TOP2A) gene in lung adenocarcinoma cells and the association with patient outcomes. Med Sci Monit 26: e929120, 2020. DOI: 10.12659/MSM.929120
153 Guo W, Sun S, Guo L, Song P, Xue X, Zhang H, Zhang G, Wang Z, Qiu B, Tan F, Xue Q, Gao Y, Gao S, He J: Elevated TOP2A and UBE2C expressions correlate with poor prognosis in patients with surgically resected lung adenocarcinoma: a study based on immunohistochemical analysis and bioinformatics. J Cancer Res Clin Oncol 146(4): 821-841, 2020. DOI: 10.1007/s00432-020-03147-4
154 Kou F, Sun H, Wu L, Li B, Zhang B, Wang X, Yang L: TOP2A promotes lung adenocarcinoma cells' malignant progression and predicts poor prognosis in lung adenocarcinoma. J Cancer 11(9): 2496-2508, 2020. DOI: 10.7150/jca.41415
155 Yang X, Feng Q, Jing J, Yan J, Zeng Z, Zheng H, Cheng X: Identification of differentially expressed genes associated with lung adenocarcinoma *via* bioinformatics analysis. Gen Physiol Biophys 40(01): 31-48, 2021. DOI: 10.4149/gpb_2020037
156 Huang P, Gu Y, Guo L, Zou X, Yi L, Wu G: Bioinformatics analysis and screening of potential target genes related to the lung cancer prognosis. Med Princ Pract: 1, 2023. DOI: 10.1159/000533891
157 Wang Y, Wang R, Ma J, Wang T, Ma C, Gu Y, Xu Y, Wang Y: Identification of pivotal genes with prognostic evaluation value in lung adenocarcinoma by bioinformatics analysis. Cell Mol Biol (Noisy-le-grand) 69(8): 221-225, 2023. DOI: 10.14715/cmb/2023.69.8.34
158 Yin D, Zhang Y, Li H, Cheng L: Association of TOP2A and ADH1B with lipid levels and prognosis in patients with lung adenocarcinoma and squamous cell carcinoma. Clin Respir J 17(12): 1301-1315, 2023. DOI: 10.1111/crj.13717
159 Zhang L, Liu Y, Zhuang JG, Guo J, Li YT, Dong Y, Song G: Identification of key genes and biological pathways in lung adenocarcinoma by integrated bioinformatics analysis. World J Clin Cases 11(23): 5504-5518, 2023. DOI: 10.12998/wjcc.v11.i23.5504
160 Jiang H, Yuan F, Zhao Z, Xue T, Ge N, Ren Z, Zhang L: Expression and clinical significance of MPS-1 in hepatocellular carcinoma. Int J Gen Med 14: 9145-9152, 2021. DOI: 10.2147/IJGM.S334378
161 Li B, Gu X, Zhang H, Xiong H: Comprehensive analysis of the prognostic value and immune implications of the TTK gene in lung adenocarcinoma: a meta-analysis and bioinformatics analysis. Anim Cells Syst (Seoul) 26(3): 108-118, 2022. DOI: 10.1080/19768354.2022.2079718
162 Zhang Y, Chen Q, Huang T, Zhu D, Lu Y: Bioinformatics-based screening of key genes for transformation of tyrosine kinase inhibitor-resistant lung adenocarcinoma to small cell lung cancer. Front Med (Lausanne) 10: 1203461, 2023. DOI: 10.3389/fmed.2023.1203461